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RECEPTOR TRPC5 COMO POTENCIAL ALVO FARMACOLÓGICO NO TRATAMENTO DA SÍNDROME METABÓLICA

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São Luís - MA
AGOSTO/2023

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Tese de doutorado apresentada para exame de qualificação ao Curso de Doutorado do Programa de Pós-Graduação em Biodiversidade e Biotecnologia - Rede BIONORTE, na Universidade Ceuma, como requisito parcial para a obtenção do Título de Doutor em Biodiversidade e Biotecnologia.

Orientador (a):
Prof. Dra. Elizabeth Soares Fernandes.

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RECEPTOR TRPC5 COMO POTENCIAL ALVO FARMACOLÓGICO NO TRATAMENTO DA SÍNDROME METABÓLICA

Os desequilíbrios metabólicos induzidos pelo açúcar são um grande problema de saúde, uma vez que o consumo excessivo de sacarídeos tem sido associado a maiores taxas de obesidade em nível global. A sacarose, um dissacarídeo composto por 50% de glicose e 50% de frutose, é comumente utilizada na indústria alimentícia e encontrada em uma variedade de fast foods, restaurantes e alimentos processados. Somado a isso, a ingestão em excesso de sacarose pode modular diversas células, citocinas pró inflamatórias e receptores, como por exemplo os receptores de potencial transitório permeáveis ao Ca^{+2}, os quais têm sido apontados como importantes reguladores da inflamação, dor, depressão e do gasto energético. Entretanto, a relevância de alguns receptores desta família como TRPC4 e TRPC5 para a SM e/ou suas comorbidades permanece não esclarecida. O presente trabalho avaliou o efeito do bloqueador (ML204) do TRPC4/TRPC5 nos desequilíbrios metabólicos desencadeados pela exposição precoce à dieta enriquecida com sacarose (25%) em camundongos. Para isso, camundongos C57BL/6 com 21 dias de vida (após o desmame) foram divididos em 2 grupos, um alimentado com dieta normal (Nuvital®, n = 22) e outro alimentado com dieta rica em sacarose (Sacarose 25%, n = 22) durante 20 semanas. Ainda, na 20ª semana foram tratados com o ML204 (2mg/kg/dia S.C por 1 semana) ou DMSO 3% em salina (10 ml/kg/dia S.C por 1 semana) utilizado como controle. Animais alimentados com dieta rica em sacarose (DRS) apresentaram hiperglicemia, dislipidemia e índice de massa corporal aumentado. Ainda, exibiram acúmulo de tecido adiposo mesentérico com células adiposas de maior diâmetro e esteatose hepática em comparação com aqueles alimentados com dieta normal. Camundongos DRS também exibiram níveis aumentados de TNFα e VEGF adiposo, hepático e pancreático. A utilização do ML204 exacerbou hiperglicemia, dislipidemia, deposição de tecido adiposo, esteatose hepática e tecido adiposo e TNFα hepático em camundongos alimentados com DRS. Camundongos normais tratados com o bloqueador apresentaram maior esteatose hepática e número/diâmetro de células do tecido adiposo do que aqueles que receberam o veículo, mas não mostraram alterações significativas na inflamação do tecido, glicose e níveis lipídicos. Os resultados indicam que complexos formados por TRPC4/TRPC5 protegem contra os desequilíbrios

metabólicos causados pela ingestão de alto teor de sacarose, podendo funcionar como possíveis alvos terapêuticos em desordens metabólicas.
Palavras-chave: Dieta rica em sacarose; alterações metabólicas; esteatose hepática; acúmulo de gordura; TRPC5; TRPC4.

TRPC5 RECEPTOR AS A POTENTIAL PHARMACOLOGICAL TARGET IN THE TREATMENT OF METABOLIC SYNDROME

Sugar-induced metabolic imbalances are a major health problem, as excessive consumption of saccharides has been linked to higher rates of obesity globally. Sucrose, a disaccharide composed of 50% glucose and 50% fructose, is commonly used in the food industry and found in a variety of fast foods, restaurants and processed foods. Added to this, excessive sucrose intake can modulate several cells, pro-inflammatory cytokines and receptors such as the transient receptor potential channels, a family of receptors permeable to Ca^{+2} involved in processes such as inflammation, pain, depression and energy expenditure. However, the relevance of some receptors of this family such as TRPC4 and TRPC5 for MS and/or its comorbidities remains unclear. The present work evaluated the effect of the TRPC4/TRPC5 blocker (ML204) on metabolic imbalances triggered by early exposure to a diet enriched with sucrose (25%) in mice. For this, 21-day-old C57BL/6 mice (after weaning) were divided into 2 groups, one fed a normal diet (Nuvital®, n = 22) and the other fed a high-sucrose diet (25% Sucrose, n = 22) for 20 weeks. Still, in the 20th week they were treated with ML204 (2mg/kg/day S.C for 1 week) or 3% DMSO in saline (10 ml/kg/day S.C for 1 week) used as control. Animals fed a diet rich in sucrose (HS) showed hyperglycemia, dyslipidemia and increased body mass index. They exhibited accumulation of mesenteric adipose tissue with adipose cells of greater diameter and hepatic steatosis compared to those fed a normal diet. HS mice also exhibited increased levels of adipose, hepatic, and pancreatic TNFα and VEGF. The use of ML204 exacerbated hyperglycemia, dyslipidemia, adipose tissue deposition, hepatic steatosis and adipose tissue and hepatic TNFα in mice fed HS. Normal mice treated with the blocker showed greater hepatic steatosis and number/diameter of adipose tissue cells than those that received the vehicle, but did not show significant changes in tissue inflammation, glucose and lipid levels. The results indicate that TRPC4/TRPC5 complexes protect against metabolic imbalances caused by HS ingestion, and may function as possible therapeutic targets in metabolic disorders.

Key words: High sucrose diet; metabolic changes; hepatic steatosis; fat deposition; TRPC5; TRPC4.

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ARTIGO 1

LISTA DE ABREVIATURAS E SIGLAS

ANOVA	**Análise de Variância**
BAT	**Tecido adiposo marrom**
C57BL/6	**C57 black 6**
CCL-2	**Quimiocina CC ligante 2**
CEUA	**Comissão Ética no Uso de Animais**
DCNT	**Doenças crônicas não transmissíveis**
DCV	**Doenças Cardiovasculares**
dL	**Decilitro**
DM2	**Diabetes Mellitus tipo 2**
DMSO	**Dimetilsulfóxido**
DN	**Dieta Normal**
DNA	**Ácido desoxirribonucleico**
DOHaD	**Origens do desenvolvimento da saúde e das doenças**
DRS	**Dieta Rica em Sacarose**
EPM	**Erro padrão da média**
ERNS	**Espécies reativas nitrogênio**
EROS	**Espécies reativas de oxigênio**
GLUT1	**Transportador de glicose 1**
H&E	**Hematoxilina e eosina**
HDL	**Lipoproteina de alto peso molecular**
HO1	**Heme-oxigenase**
IDF	**Federação Internacional da Diabetes**
IL-10	**Interleucina-10**
IL-13	**Interleucina-13**
IL-17	**Interleucina-17**
IL-1β	**Interleucina-1 beta**
IL-4	**Interleucina-4**
IL-5	**Interleucina-5**
IL-6	**Interleucina-6**
IMC	**Índice de Massa Corporal**
kg	**Quilograma**
KO	**Knockout**
M1	**Macrófagos M1**
M2	**Macrófagos M2**
MCP-1	**Proteína quimiotática de monócitos 1**
mg	**Miligrama**
ml	**Mililitros**
ML204	**4-Methyl-2-(1-piperidinyl)-quinoline**
mmHg	**Milímetro de mercúrio**
mRNAs	**Ácido Ribonucleico Mensageiro**

NCEP-ATPIII	**National Cholesterol Education Program III**
NO	**Óxido nítrico**
O_2^-	**Superóxido**
PAI-1	**Plasminogen activator inhibitor-1**
PNS	**Pesquisa Nacional de Saúde**
RI	**Resistência à Insulina**
S.C	**Subcutâneo**
SM	**Síndrome Metabólica**
TNFα	**Fatores de Necrose Tumoral Alfa**
TRP	**Receptor de Potencial Transitório**
TRPA1	**Receptor potencial transitório anquirina 1**
TRPC	**Receptor de potencial transitório Canônico**
TRPC5	**Receptor de potencial transitório Canônico 5**
TRPM	**Receptor de potencial transitório Melastatina**
TRPML	**Receptor de potencial transitório mucolipina**
TRPP	**Receptor de potencial transitório polycistina**
TRPV1	**Receptor de potencial transitório vanilóide 1**
UFMA	**Universidade Federal do Maranhão**
VGEF	**Fator de crescimento endotelial vascular**
WAT	**Tecido adiposo branco**
WT	**Wild type**

SUMÁRIO

1. INTRODUÇÃO

A Síndrome metabólica, pode ser definida como um conjunto de disfunções metabólicas interconectadas que aumentam os riscos para o desenvolvimento de obesidade central, hiperglicemia, dislipidemia aterogênica, resistência à insulina, diabetes tipo 2 e doenças cardiovasculares, entre outras comorbidades – é considerada um alarmante problema de saúde pública afetando aproximadamente 25% da população mundial independente de gênero, etnia e desenvolvimento social (AGUILAR-SALINAS *et al*., 2019; BOVOLINI *et al*., 2021; BELETE *et al*., 2021). Seu manejo visa principalmente a redução do risco de doenças cardiovasculares (DCVs) e DM2, e inclui modificações no estilo de vida e uso de múltiplos medicamentos (GRUNDY 2005; ALTABAS 2016). Sabe-se que, países subdesenvolvidos, assim como o Brasil, mais de 60% da população consome altas quantidades de açucares (FISBERG *et al*., 2018).

Recentemente, dados da Pesquisa Nacional de Saúde (PNS/2019) apontam que, atualmente, no Brasil, 60,3% dos adultos apresentam excesso de peso, o equivalente a 96 milhões de pessoas. A maior prevalência é no público feminino (62,6%). A condição de obesidade, que engloba parte dos indivíduos com excesso de peso, já atinge 25,9% da população – cerca de 41,2 milhões de adultos, também com distribuição maior em mulheres (29,5%) do que em homens (21,8%). O problema do excesso de peso tem afetado também os mais jovens. Entre as crianças atendidas na Atenção Primária, em 2019, 14,8% dos menores de 5 anos e 28,1% das crianças entre 5 e 9 anos tinham excesso de peso, e dessas, 7% e 13,2% apresentavam obesidade, respectivamente. Quanto aos adolescentes acompanhados, em 2019, cerca de 28% e 9,7% apresentavam excesso de peso e obesidade, respectivamente. (Ministério da Saúde 2019).

Também, analisou-se a frequência de adultos com excesso de peso e obesidade em todas as capitais, onde as menores frequências de excesso de peso, entre homens, ocorreram em Salvador (47,2%), Vitória (50,6%) e Macapá (53%); e, entre mulheres, em Palmas (43,7%) e São Luís (44,4%). Dados relacionados a crescente de pacientes diabéticos, demonstram que o percentual de pessoas do gênero masculino de São Luís (MA) apresentou um aumento de 17% no diagnóstico de

diabetes tipo II, entre os anos de 2006 e 2017. Há cerca de 11 anos atrás, o número de homens que haviam sido identificados com a doença era de 4,7%, em contrapartida, o índice passou para 5,5%. Entretanto, apesar de demonstrar um maior percentual em 2006, o número de mulheres com diagnóstico de diabetes se manteve estável em 2019 (5,6%).

De forma geral, São Luís -MA, aparece como uma das capitais que tem o menor número de pessoas com a enfermidade, com 5,2%. (Vigitel Brasil 2019). Vale ressaltar que, o expressivo crescimento da síndrome metabólica está bastante relacionado ao consumo elevado de carboidratos, especialmente de açúcares de adição (sacarose e frutose) utilizados como edulcorantes em alimentos processados e refrigerantes (LENNERZ *et al*., 2018; WILCOX *et al*., 2021). No Estado do Maranhão, o consumo excessivo e regular destes açúcares atinge cerca de 14% da população adulta (CLARO *et al*., 2015).

Diversas alterações estão envolvidas na fisiopatologia da SM, tais como no metabolismo, mediadores inflamatórios e estresse oxidativo. Além disso, as alterações de lipídios e glicose, estão diretamente associados a um declínio na liberação de insulina, que é um dos fatores centrais ao desenvolvimento de um ambiente glicolipotóxico nas ilhas pancreáticas e no tecido adiposo (CHAIT *et al*., 2020; KARGAR *et al*., 2021). Este ambiente glicolipotóxico afeta a função mitocondrial, causando o aumento da produção de espécies reativas de oxigênio (EROS) e de nitrogênio (ERNS), produzidos em grandes quantidades por macrófagos em tecidos periféricos e pâncreas, e por células β-pancreáticas (COLAK *et al*., 2021). Por sua vez, uma dieta contínua e rica em glicose e ácidos graxos promove estresse no retículo endoplasmático, reduzindo assim, a capacidade de células β-pancreáticas de produzir insulina, contribuindo para a cronicidade da inflamação e do estresse oxidativo; e subsequentes danos ao DNA e proteínas, e à integridade lipídica celular, ocasionando morte celular, além disso, diferentes mecanismos fisiopatológicos têm sido identificados na SM, destacando as vias inflamatórias, hormonais e neuronais (BARROSO *et al*., 2019; COLAK *et al*., 2021).

Além disso, diferentes mecanismos patológicos têm sido identificados na SM, incluindo vias inflamatórias, hormonais e neuronais. Diferentes receptores e mediadores são expressos por estes neurônios, incluindo a superfamília de canais iônicos não seletivos para o Ca^{+2}, conhecidos como receptores de potencial transitório (TRP; do inglês *Transient Receptor Potential*). Os TRPs encontram-se expressos em diferentes tecidos neuronais e não-neuronais, incluindo aqueles com atividade metabólica como pâncreas, tecido adiposo, rim, fígado e músculo esquelético; e em vasos sanguíneos e células imunes (FERNANDES *et al*., 2012; SANTONI *et al*., 2018; SUN *et al*., 2021). Nesse contexto, evidências têm sugerido que a modulação de alguns receptores dessa família, tais como o receptor de potencial transitório vanilóide (TRPV1), receptor de potencial transitório anquirina (TRPA1) e receptor de potencial transitório Canônico (TRPC5) podem produzir efeitos benéficos em doenças de cunho inflamatório e distúrbios metabólicos, sendo assim, esses receptores podem ser utilizados como alvos farmacológicos para diversas patologias (KOIVISTO *et al*., 2012; NUMATA *et al*., 2016; HELLENTHAL *et al*., 2018). Este é um estudo novo, através do qual será possível obter conhecimentos sistemáticos acerca da relevância do receptor TRPC4/TRPC5 na síndrome metabólica e suas complicações, poderemos entender se esses receptores são essenciais para o estabelecimento e progressão da síndrome metabólica causada por alta ingestão de açúcares de adição, além de entender se podem moduladores (antagonistas) do TRPC4/TRPC5 serem utilizados para o tratamento da síndrome metabólica e suas comorbidades.

1.1 OBJETIVO GERAL

Avaliar a relevância do receptor TRPC5 isolado e formando complexo TRPC4/TRPC5 nos desequilíbrios metabólicos desencadeados pela exposição precoce à dieta enriquecida com sacarose em camundongos.

1.1.2 Objetivos Específicos

Identificar os principais pontos críticos dos TRPs relacionados a exposição precoce à dieta rica em sacarose;

Avaliar o efeito do bloqueio do TRPC5 e TRPC4/TRPC5, utilizando o ML204, nas alterações metabólicas causadas por dieta rica em sacarose;

Investigar os efeitos do bloqueio do TRPC5 e TRPC4/TRPC5, utilizando o ML204, no acúmulo de gordura, nos níveis de lipídios e glicose no sangue, induzido pela alimentação rica em sacarose em camundongos;

Investigar os efeitos do bloqueio do TRPC5 e TRPC4/TRPC5, utilizando o ML204, no processo inflamatório no tecido adiposo, fígado e pâncreas induzido pela dieta rica em sacarose.

2. REVISÃO BIBLIOGRÁFICA

2.1 SÍNDROME METABÓLICA: DEFINIÇÃO, CAUSAS E FISIOPATOLOGIA

Anteriormente conhecida como quarteto da morte, síndrome de Reaven, síndrome X e síndrome da Resistência à Insulina (ODA 2012), a SM é caracterizada por um conjunto de características que causam desregulação no metabolismo do organismo como um todo, acarretando um ambiente pró-inflamatório e pró-trombótico nos pacientes, levando ao aumento de fatores de risco para diversas patologías como a DM2 e DCV (MCCRACKEN *et al.,* 2018; BARROSO *et al.,* 2019).

Existem divergências em relação aos critérios para o diagnóstico da SM, sendo que essas inconformidades influenciam diretamente nos dados de prevalência da doença. Os critérios mais utilizados para o diagnóstico são os estabelecidos pelo Painel de Tratamento de Adultos do Programa Nacional de Educação do Colesterol III (NCEP-ATPIII) e pela Federação Internacional do Diabetes (IDF) (ALBERTI *et al.*, 2009; SUN *et al*., 2019).

Os critérios do NCEP-ATPIII envolvem cinco características: obesidade abdominal (circunferência de cintura >102 cm), níveis de triglicérides acima de 105 mg/dL, níveis baixos de HDL (Lipoproteína de alta densidade) menores que 40 mg/dL, pressão arterial maior que 130 x 85 mmHg e glicemia em jejum maior que 110 mg/dL. Para o diagnóstico de SM segundo o NCEP-ATPIII, o paciente deve apresentar três destas cinco características, mesmo se estiver em tratamento medicamentoso específico para estas condições (Expert Panel on Detection 2001; DO MONTE *et al.,* 2019).

Pelos critérios estabelecidos pela IDF, a obesidade abdominal (circunferência de cintura varia de acordo com gênero. No geral, maior que 90 cm para homens e 80 cm para mulheres) ou IMC superior a 30 kg/m², deve ser um dos critérios de diagnóstico, somado a duas das seguintes características: níveis de triglicérides acima de 150 mg/dL, níveis baixos de HDL (menor que 40 mg/dL em homens e 50 mg/dL em mulheres), pressão arterial maior que 130 x 85 mmHg e glicemia em jejum maior que 100 mg/dL, assim como estar em tratamento medicamentoso específico para estas condições (SANTOS *et al*., 2009; DO MONTE *et al*., 2019).

Além dos critérios apresentados, outros fatores hormonais, ambientais e comportamentais estão relacionados ao aumento dos casos de SM (AJIOHANI *et al.*, 2014; BARROSO *et al.*, 2019). Dentre eles, destacam-se o sedentarismo (GOMES *et al*., 2019; RODRIGUES *et al.*, 2021;), o tabagismo (CHIOLERO *et al.*, 2008; RODRIGUES *et al*., 2021), a hiperinsulinemia, comum em mulheres no período da pós-menopausa devido às quedas do estrógeno (GASPARD *et al.*, 2009; PREZOTTO *et al.*, 2022), e dieta rica em carboidratos e gorduras (LENNERZ *et al*., 2018; AGUILAR-SALINAS *et al.*, 2019). O risco aumenta com o agrupamento desses fatores, que estão associados à RI, sendo a obesidade e o aumento da circunferência abdominal o fator determinante na etiologia de todos os outros fatores (GRADIDGE *et al.*, 2016; HOFFMAN *et al.*, 2021).

A inflamação crônica e a resistência à insulina, principalmente induzida pela obesidade, são considerados os fatores mais críticos na patogênese da SM. A expansão do tecido adiposo com o aumento da quantidade e do conteúdo das células de gordura impede o aporte ideal de oxigênio no tecido, promovendo a hipóxia e, em muitos casos, leva à necrose dessas células (PATEL *et al.*, 2015; CHAIT *et al.*, 2020). O estresse oxidativo elevado está associado à disfunção dos adipócitos acarretando um quadro crônico de hipóxia (NETZER *et al.*, 2015; SUN *et al.*, 2019).

O estresse oxidativo é um fator de grande importância na evolução da SM (COLAK *et al*., 2021). Acredita-se que o aumento na liberação de ERO desregula a síntese e liberação de adipocinas (reduzindo as anti-inflamatórias: adiponectina e leptina; aumentando as pró-inflamatórias: IL-6 e resistina), potencializando a inflamação. O aumento da liberação desses reativos na gordura abdominal eleva o estresse oxidativo sistêmico (CHAIT *et al.*, 2020; COLAK *et al*., 2021).

Os macrófagos, residentes no tecido adiposo, têm sua polarização mediada pelo hormônio PAI-1 (Plasminogen activator inhibitor-1, secretado pelos adipócitos), em macrófagos do tipo M1 (considerados pró-inflamatórios). O influxo desses fagócitos no tecido adiposo, que encontra-se aumentada no estresse oxidativo, são os principais responsáveis pela liberação de mediadores ligados à RI (como TNF-α e IL-6), além de outros fatores como CCL-2 (quimiocina CC ligante 2), Interleucina-1β (IL-1β), resistina e espécies reativas derivados do óxido nítrico (COLLINS *et al.*,

2018). Os linfócitos assim como macrófagos, estão presentes em maiores quantidades no tecido adiposo de pessoas obesas, e desempenham importante papel na polarização dos fagócitos por meio da liberação de IL-4, IL-5 e IL-13, além de Interferon-gama (IF-γ) e IL-17 (GORDON *et al*., 2010; WANG & WU, 2018).

2.2 DESREGULAÇÃO DA ADIPONECTINA, ESTRESSE OXIDATIVO E INFLAMAÇÃO COMO MECANISMOS DA SÍNDROME METABÓLICA

2.2.1 Desregulação da Adiponectina

A adiponectina é uma adipocina secretada pelos adipócitos, descrita pela primeira vez em 1995 (SCHERER 1995). Embora as funções da adiponectina fossem desconhecidas naquela época, usando células de camundongos, este relato foi o primeiro a demonstrar a existência de uma ligação entre secreção de insulina, diferenciação de adipócitos e liberação de adiponectina, e a sugerir um papel para esta adipocina na regulação de carboidratos e metabolismo lipídico. Em 1996, a adiponectina humana foi descrita em dois estudos diferentes, que mostraram sua presença em tecido adiposo humano e amostras de plasma (MAEDA *et al.,* 1996; NAKANO *et al.,* 1996).

Nas últimas décadas, ficou claro que a adiponectina é um regulador essencial do metabolismo da glicose e dos lipídios e um grande influenciador do risco de desenvolvimento de obesidade, DM2, DCV e, portanto, de SM. Sabe-se agora que a adiponectina forma complexos de diferentes pesos moleculares. Digno de nota, o de alto peso molecular (HMW) mostrou ser o mais potente na redução dos níveis séricos de glicose em camundongos (PAJVANI *et al.,* 2004).

O mesmo estudo demonstrou que o complexo HMW é reduzido em camundongos diabéticos obesos e que se torna aumentado tanto em camundongos DT2 quanto em pacientes após tratamento com rosiglitazona – um agonista do PPARγ. Mais tarde, descobriu-se que a hipoglicemia induzida por adiponectina era independente dos níveis de insulina (COMBS *et al.,* 2001; BERG *et al.,* 2001) mas foi capaz de melhorar a sensibilidade à insulina (YAMAUCHI *et al*., 2001). Logo depois, foi demonstrado que a adiponectina atravessa a barreira hematoencefálica

e induz a expressão hipotalâmica do hormônio liberador de corticotrofina (CRH) anorexígeno, levando à perda de peso e aumento do gasto energético (YAMAUCHI *et al*., 2001; QI *et al*., 2004).

Os multímeros de adiponectina podem ser clivados em um fragmento contendo o domínio globular C-terminal, que tem efeitos potentes nas células musculares esqueléticas. A adiponectina completa e seus fragmentos podem exercer diferentes ações em diferentes tipos de (CEDDIA *et al.,* 2005; FANG *et al.,* 2005; FRUEBIS *et al.,* 2001; UJIIE *et al.,* 2005). Existem diferentes tipos de receptores da adiponectina, tipo 1 (AdipoR1) e 2 (AdipoR2). AdipoR1 é constitutivamente expresso em todas as células, especialmente no músculo esquelético, enquanto AdipoR2 é amplamente expresso no fígado (IWABU *et al.,* 2019). Ambos também são expressos em várias regiões do cérebro, incluindo hipotálamo, tronco cerebral, hipocampo e córtex (THUNDYIL *et al.,* 2012).

Um estudo de Bjursell e colaboradores investigou a contribuição de AdipoR1 e AdipoR2 para a homeostase do metabolismo energético usando camundongos knockout (KO) AdipoR1 e AdipoR2 alimentados com uma dieta rica em gordura (HFD). Eles demonstraram que homens AdipoR1KOs têm maior adiposidade e intolerância à glicose, resultando em ganho de peso e gasto energético, aumento de triglicerídeos hepáticos (TG) e leptina plasmática (um hormônio da saciedade produzido e secretado pelo tecido adiposo branco (WAT) (BJURSELL *et al*., 2007; CINTI *et al.,* 1997), além de maior expressão de AdipoR2 mRNA no tecido adiposo marrom (BAT), um tecido termogênico.

Por outro lado, o mesmo estudo demonstrou que os AdipoR2KOs são resistentes à obesidade, mesmo comendo mais do que os camundongos controle. Os mesmos KOs exibiram maior expressão de mRNA de CRH no hipotálamo, menos leptina e colesterol plasmáticos, menor TG hepático, maiores níveis plasmáticos e de adiponectina e maior tolerância à glicose e gasto energético. Curiosamente, AdipoR2KOs apresentou níveis reduzidos do mRNA para AdipoR1 no fígado e BAT (BJURSELL *et al*., 2007).

Estudos em humanos associaram hipoadiponectinemia com excesso de gordura intra-abdominal e múltiplos defeitos no metabolismo da glicose e energia na SM. A síndrome também

tem sido associada ao aumento dos níveis circulantes de citocinas (por exemplo, interleucina (IL)-6 e IL-1β) e moléculas de adesão solúveis (por exemplo, P-selectina e ICAM) (SALMENNIEMI *et al.*, 2004). O mesmo estudo sugeriu que a baixa produção de adiponectina é uma causa subjacente de dano endotelial e inflamação sistêmica de baixo grau na SM.

Os dados são apoiados por estudos anteriores mostrando que a hipoadiponectinemia aumenta o risco de doença arterial coronariana (DAC) em homens (KUMADA *et al.*, 2003) e dados de camundongos que mostraram que a adiponectina protege contra danos vasculares após lesão mecânica (MATSUDA *et al.*, 2002). Além disso, pacientes obesos com DAC têm níveis plasmáticos diminuídos de adiponectina e menor expressão de receptores de adiponectina em monócitos periféricos em comparação com aqueles sem DAC, enquanto macrófagos de pacientes com DAC apresentam liberação prejudicada de IL-10 após a incubação de adiponectina (KOLLIAS *et al.*, 2011).

2.2.2 Estresse Oxidativo

O estresse oxidativo é definido como o desequilíbrio entre as vias de produção e neutralização de ERO e ERN. Estudos já demonstraram a ligação entre o estresse oxidativo e as vias de inflamação na progressão da SM (FORRESTER *et al.*, 2018; CHECA e ARAN, 2020). A produção fisiológica de EROs (como ânion superóxido (O_2^-), radical hidroxila (OH), peróxido de hidrogênio (H_2O_2) e ácido hipocloroso (HClO) e ERN como óxido nítrico (NO) e ânion peroxinitrito ($ONOO^-$) ocorre através de diferentes vías enzimáticas endógenas (por exemplo, nicotinamida adenina dinucleotídeo fosfato oxidases (NOX), NO sintases (NOS), mieloperoxidase (MPO), xantina oxidase (XOs), entre outros.). Embora a sinalização de ERO e ERN contribua para diversos processos celulares (KLOTZ *et al*., 2002; CHECA e ARAN, 2020) sob estresse oxidativo, há aumento da disponibilidade dessas espécies levando a efeitos nocivos em vários estados de doença, inclusive na SM.

Por exemplo, O_2^- produzido por NOX ativa XOs induzindo oxidação de tetraidrobiopterina (BH4), desacoplamento endotelial de NOS e consequente redução da produção

e biodisponibilidade de NO, uma característica essencial da patogênese de DM2 e hipertensão (D'ORIA *et al.*, 2020). Outros efeitos celulares do estresse oxidativo envolvem danos a proteínas, lipídios de membrana e ácidos nucléicos. A lipoperoxidação induzida por OH e os danos ao DNA (avaliados pela formação de 8-hidroxi-2'-desoxiguanosina-8-OHdG) são marcadores bem estabelecidos de inflamação crônica na SM (VONA *et al.*, 2019).

Por outro lado, as vias antioxidantes atenuam a reatividade das EROs (ROY *et al*., 2017). As vias antioxidantes primárias incluem as enzimas superóxido dismutase (SOD), glutationa peroxidase (GPx) e catalase. Vias adicionais incluem glutationa redutase, tioredoxina (TRX) e glutaredoxina. Outras vias não enzimáticas compreendem glutationa reduzida (GSH), bilirrubina e compostos de baixo peso molecular de origem alimentar (por exemplo, vitaminas A, C, E, flavonoides, zinco e selênio) (VONA *et al.*, 2019). Dessa forma, as vias antioxidantes fornecem condições para a produção controlada de espécies oxidantes fisiologicamente relevantes (como o H_2O_2) e a manutenção da homeostase.

O estresse oxidativo também tem sido diretamente ligado à patogênese de doenças cardiovasculares, como hipertensão e resistência à insulina em DM2 (OGUNTIBEJU, 2019). Na SM, o estresse oxidativo é caracterizado principalmente pela diminuição da expressão e atividade das vias antioxidantes secundárias a uma diminuição nos níveis do fator 2 relacionado ao fator nuclear E2 (NRF2), em amostras de plasma de pacientes com SM (CHENG *et al*., 2011). Esses achados também estiveram presentes em modelos experimentais de obesidade (FOSTER *et al*., 2003).

A hipertensão está associada à redução da biodisponibilidade de NO e aumento da produção de ERO, seja por disfunção mitocondrial ou aumento da expressão de NOX em células endoteliais. O ânion peroxinitrito, produto da reação entre O_2^- e NO, também contribui para o controle disfuncional do tônus vascular sistêmico (SENONER e DICHTL, 2019). Além disso, a dislipidemia, a resistência à insulina, a hiperglicemia e outros fatores contribuem para a disfunção mitocondrial e aumentam a produção mitocondrial de O_2^- pelas células endoteliais, cardiomiócitos

e células β pancreáticas (BURGOS-MORÓN *et al.*, 2019) sendo estas últimas particularmente vulneráveis ao estresse oxidativo devido à baixa expressão de defesas antioxidantes nessas células.

Diversos mecanismos estão relacionados aos efeitos do estresse oxidativo na função das células β pancreáticas, incluindo a expressão alterada de micro-RNAs responsáveis pela regulação gênica das vias de sinalização redox (VEZZA *et al.*, 2021). A produção excessiva de EROs, juntamente com a hiperglicemia, contribui para a inibição da gliceraldeído-3-fosfato desidrogenase, que resulta no acúmulo de precursores da via glicolítica (como frutose-6-fosfato e gliceraldeído-3-fosfato). Nesse caso, a ativação subsequente de cascatas de poliol (por produtos de glicação avançada - AGEs) causa depleção de NADPH e biodisponibilidade reduzida de GSH (GIACCO e BROWNLEE, 2010).

Nesse caso, a ativação do fator nuclear-κB (NF-κB) e NOX promove estresse oxidativo e um estado pró-inflamatório que contribui para as complicações vasculares do DM2 devido à baixa biodisponibilidade de NO e alta expressão de moléculas de adesão celular (WAUTIER *el al.*, 1996). Além disso, a vasoconstrição aumentada induzida pela endotelina-1 e outros vasoconstritores endógenos (como prostaglandina H_2 e tromboxano A_2) prejudica tanto a função endotelial quanto a integridade da parede vascular, particularmente no nível da microcirculação (BERWICK *et al.*, 2012). Portanto, os AGEs desempenham um papel importante na delicada interface entre DM2 e DCVs (RAMASAMY *et al.*, 2008).

Conforme discutido anteriormente, o estresse oxidativo pode contribuir para a hipoadiponectinemia e inflamação e, portanto, para a obesidade. A obesidade é caracterizada por um estado pró-inflamatório sistêmico, principalmente devido ao desenvolvimento de resistência à insulina (HUTH *et al.*, 2016). De uma perspectiva celular, a função mitocondrial prejudicada e a biogênese causada por hiperglicemia e/ou hiperlipidemia prejudicam a via de sinalização da insulina (BOUCHER *et al.*, 2014).

Isso, além do tecido adiposo disfuncional, aumenta o estresse oxidativo ativando vias pró-inflamatórias nos adipócitos (LEE *et al.*, 2003) que estão entre os fatores etiológicos de DM2 e DCVs (FRANCESCHI e CAMPISI, 2014). Curiosamente, níveis circulantes aumentados de

tioredoxina (TRX) estão presentes em pacientes com DM2 (KAKISAKA *et al.*, 2002) e têm sido associados a maior risco de DCV em indivíduos com SM (MIWA *et al.*, 2006).

2.2.3 Inflamação

Além da desregulação da adiponectina e do estresse oxidativo, estudos forneceram evidências de que o progresso da disfunção metabólica está intimamente relacionado a um estado de inflamação crônica de baixo grau (YU *et al*., 2009; DALLMEIER *et al.*, 2012; RASTELLI *et al*., 2018) que é caracterizado principalmente pelo recrutamento de macrófagos pró-inflamatórios para o tecido adiposo. Os macrófagos aumentam a resposta inflamatória (WEISBERG *et al.*, 2003; LUMENG *et al*., 2007; PATEL e PATEL, 2015; COLLINS *et al.*, 2018) contribuindo para o acúmulo de lipídios ectópicos e o desenvolvimento de resistência à insulina (PATEL e PATEL, 2015).

Os macrófagos M1 e M2 desempenham um papel importante no tecido adiposo durante a inflamação de baixo grau (COLLINS *et al.*, 2018) por meio da produção e liberação de TNFα, IL-1β e IL-6 e IL-10, respectivamente (GORDON e MARTINEZ, 2010; GAO *et al.*, 2010). Os macrófagos M1 recrutados para as ilhotas pancreáticas causam disfunção das células β pancreáticas e apoptose (GAO *et al*., 2010). Além disso, a produção de citocinas pró-inflamatórias no tecido adiposo leva à hipertrofia dos adipócitos (LUMENG *et al*., 2007). A liberação local de FFA, especialmente ácidos graxos saturados, ativa o receptor toll-like 4 em macrófagos (LANCASTER *et al.*, 2018; ROGERO e CALDER, 2018) desencadeando a ativação de NF-κB e a expressão adicional de citocinas pró-inflamatórias (LI *et al*., 2018).

Os dados acima reforçam a importância do desequilíbrio inflamatório para as alterações do tecido adiposo na SM e suas comorbidades/complicações (YU *et al*., 2009). De fato, a inflamação do tecido adiposo também afeta outros tecidos e órgãos, como o fígado (BOUTARI *et al*., 2018; SHABALALA *et al.*, 2020) pâncreas (WAGNER *et al.*, 2021) e músculos (PETERSEN *et al.*, 2007) deposição de gordura nesses órgãos é particularmente deletéria (CHAIT *et al*., 2020).

Os macrófagos residentes no fígado (células de Kupffer) também podem ser polarizados em M1 e produzir TNFα como resultado de uma dieta rica em lipídios que, por sua vez, contribui para o aumento da liberação de glicose pela gliconeogênese, produção e armazenamento de lipídios pela inibição das lipases intracelulares (GAO, 2010). As complicações metabólicas associadas a um declínio na liberação de insulina levam à glicolipotoxicidade nas ilhotas pancreáticas e no tecido adiposo (KEANE *et al.*, 2015; FURUKAWA *et al*., 2017), desequilíbrio dos estados redox e disfunção mitocondrial (FURUKAWA *et al.*, 2017).

Uma dieta obesogênica promove estresse do retículo endoplasmático e disfunção das células β pancreáticas, com consequente redução da produção de insulina (KEANE *et al*., 2015). Essas alterações estão intimamente associadas ao aumento da inflamação, estresse oxidativo e danos subsequentes ao DNA, proteínas, lipídios celulares e, potencialmente, morte celular (TRAYHURN, 2005).

De fato, o dano hepático pode ser causado pela secreção de citocinas pró-inflamatórias (por exemplo, TNFα), (MAKKI *et al*., 2013) hipoadiponectinemia (IM *et al*., 2006; ABENAVOLI e PETA, 2014) e altos níveis de resistina e leptina (POLYZOS *et al*., 2011; BOUTARI *et al*., 2018; POLYZOS *et al*., 2016) no tecido adiposo. Aumento do acúmulo de lipídios hepáticos no fígado seguido por lipogênese *de novo* e redução da oxidação de ácidos graxos (JUNG e CHOI, 2014; IPSEN et al., 2018) leva a danos histológicos caracterizados como esteatose simples, esteato-hepatite não alcoólica ou cirrose, e até mesmo carcinoma hepatocelular em casos mais graves (ANGULO, 2002; POLYZOS e MANTZOROS, 2016).

Além dos macrófagos, as células T também desempenham um papel importante na SM, uma vez que o influxo de células $CD8^+$ precede o de macrófagos M1 no tecido adiposo, aumentando a inflamação e a resistência sistêmica à insulina. Camundongos sem células T encontram-se protegidos contra DM2 induzido por obesidade em camundongos alimentados com dieta rica em gorduras, que está associado a menor acúmulo de macrófagos e regulação negativa de citocinas/quimiocinas inflamatórias (MCP-1, IL-6, TNFα e IFNγ) em amostras de músculo esquelético e tecido adiposo (KHAN *et al.*, 2014).

Por outro lado, em outro trabalho, o recrutamento de células T e a regulação positiva de IFNγ ocorreram no WAT do epidídimo após o influxo de macrófagos (STRISSEL *et al.*, 2014). No geral, esses dados mostram a contribuição das células Th1 para a inflamação do tecido adiposo na SM. Além disso, as células Th17 contribuem para um fenótipo pró-inflamatório no tecido adiposo e resistência à insulina (BERTOLA *et al.*, 2012) enquanto as células Th2 são sugeridas para proteger contra a obesidade (MCLAUGHLIN *et al.*, 2014). Curiosamente, a porcentagem de células Th2 em amostras de tecido adiposo humano se correlaciona negativamente com inflamação sistêmica e resistência à insulina MCLAUGHLIN *et al.*, 2014).

2.3 DIETAS RICAS EM AÇÚCARES E GORDURAS NO DESENVOLVIMENTO DA SÍNDROME METABÓLICA

Diversos trabalhos já evidenciaram que intervenções nutricionais são eficazes na indução controlada de doenças metabólicas, tornando-as ferramentas essenciais na pesquisa experimental. As principais intervenções utilizadas em pesquisa são baseadas em dietas ricas em carboidratos ou gorduras, funcionando como indutoras de resistência à insulina, obesidade, DM2 e SM em modelos animais (LOMBARDO *et al.*, 1996; BUETTNER *et al.*, 2007; LIMA *et al.*, 2016; BURGEIRO *et al.*, 2017; FRANÇA *et al.*, 2020), assim como em humanos (MA *et al.*, 2015; STANHOPE, 2016; DINICOLANTONIO *et al.*, 2017). É válido ressaltar que existem diversos outros modelos experimentais utilizando compostos que podem induzir o quadro de diabetes e SM, onde podemos destacar o uso da estreptozotocina (STZ), que é um produto químico usado em animais de laboratório para indução de diabetes (VERÔNYCA *et al.*, 2022). Esta droga destrói as células β pancreáticas e leva à má síntese de insulina e, consequentemente, à hiperglicemia (VERÔNYCA *et al.*, 2022). Entretanto, com o intuito de mimetizar de forma mais real ao cotidiano dos indivíduos, os modelos experimentais de indução de distúrbios metabólicos baseado na dieta, apesar de demandar mais tempo, têm ganhado destaque.

A dieta rica em gordura, pode ser considerada como uma das intervenções nutricionais pioneiras na pesquisa científica, para a qual foi demonstrada a efetividade na indução de obesidade

e distúrbios metabólicos em roedores, que se assemelham à síndrome metabólica humana (BUETTNER *et al.,* 2007). A intervenção nutricional utilizando a dieta rica em gordura teve início na década de 1940, e posteriormente originou vários estudos que validaram a metodologia empregada, além de demonstrarem que a mesma pode induzir hiperglicemia e resistência à insulina, sendo uma excelente alternativa para estudar seus efeitos na fisiologia muscular, hepática, tecido adiposo, saciedade, além de diversos aspectos associados à doenças metabólicas (OAKES *et al.,* 1998; AHREN *et al.,* 1999; LINGOHR *et al.,* 2002; BUETTNER *et al.,* 2007).

Em estudos focados na obesidade, foi demonstrado que a alimentação prolongada com dietas ricas em gordura promove aumento de peso corporal em roedores suscetíveis quando comparados a animais alimentados com ração padrão (PECKHAM *et al.*, 1962). Ainda, nesse mesmo estudo, observou-se que a indução da obesidade é mais eficaz quando a dieta é iniciada em uma idade jovem e contínua por várias semanas (PECKHAM *et al.,* 1962).

De forma parecida, porém mais recente, alguns estudos vêm mostrando que o consumo em excesso em carboidratos, principalmente os açúcares de adição (sacarose e frutose), representa um importante fator nutricional e pode favorecer o balanço energético positivo no organismo do indivíduo, e desencadear o aumento nos níveis de glicemia, lipídeos, além do armazenamento dos depósitos de gordura corporal, que são fatores preditores para o desenvolvimento da obesidade central, resistência à insulina, diabetes e SM (BARKER *et al*., 1995; SIMENTAL-MENDIA *et al.*, 2008; FRANÇA *et al*., 2020; HOFFMAN *et al* 2021). Foi demonstrado que a exposição precoce a DRS foi capaz de induzir o acúmulo de gordura sem aumentar o peso corporal dos ratos (DE MELO et al., 2021).

Um estudo pioneiro, realizado em camundongos, demonstrou que, animais expostos a uma dieta com 25% de sacarose desde o desmame até a idade adulta, foi capaz de induzir disfunções metabólicas, como a SM e desenvolvimento de DHGNA (KARLA *et al*., 2018). Corroborando a isso, também foi demonstrado que a exposição de ratos desmamados por 60 dias a uma dieta rica com 25% de sacarose, com o mesmo teor calórico, aumentou a massa corporal em associação com o aumento do acúmulo de gordura nos depósitos subcutâneos e viscerais. Esses animais também

apresentavam hiperglicemia, hipertrigliceridemia, intolerância à glicose e sensibilidade à insulina prejudicada (SOUSA *et al.*, 2018).

Além da sacarose e gordura, alguns estudos exploram a utilização da dieta com alto teor de frutose, sendo esta, utilizada para avaliar alterações metabólicas e hepáticas, inclusive em modelos experimentais em camundongos C57Bl/6 (KENDALL *et al.*, 2006; JUN *et al*., 2012). Sendo que, o uso crônico pode alterar o metabolismo de carboidratos, desencadeando na hiperglicemia, hiperinsulinemia, hipertrigliceridemia, além do aumento da pressão arterial, elevação de marcadores pró-inflamatórios, tais como TNF e IL-6 e diminuição de adiponectina (SILVA et al., 2021).

A utilização de modelos experimentais que induzem SM por dietas ricas em sacarose, frutose e/ou ricas em gordura, são ferramentas que permitem desenvolver estudos em diversos tecidos e órgãos. Como foi evidenciado por Yamada-Obara e colaboradores, em modelo experimental em ratos, que uma dieta com alto teor de gordura e frutose por seis semanas antes do acasalamento e mantida durante o período de gestação e lactação, desencadeia na prole de 16 semanas, quadros de glomeruloesclerose, hiperglicemia e pressão arterial média elevada associada à redução da podocina e ao aumento da expressão do fator de crescimento transformador β1 nos rins (YAMADA-OBARA *et al.*, 2016). De forma similar, Panchal e colaboradores, demonstraram que após 16 semanas de dieta rica em gordura, ratos apresentaram aumentos progressivos no peso corporal, ingestão calórica, deposição de gordura abdominal e circunferência abdominal, além da intolerância à glicose, dislipidemia, hiperinsulinemia e aumento das concentrações plasmáticas de leptina e malondialdeído. Ainda, os animais apresentaram disfunção endotelial, inflamação, fibrose e aumento das ilhotas panceráticas. (PANCHAL *et al.*, 2011).

Estudos já demonstraram que o alto teor de açúcares na dieta pode ativar diretamente a síntese descontrolada de novos lipídeos. Estas alterações podem desencadear efeitos deletérios no metabolismo de lipídeos em diferentes tipos de órgãos, tais como fígado, músculo, pâncreas e tecido adiposo, além de está diretamente ligada com o desenvolvimento de esteatose hepática (DINICOLANTONIO *et al.*, 2017; IIZUKA, 2017; FRANÇA *et al*., 2020).

Também já foi mostrado que a exposição precoce de uma dieta rica em sacarose (DRS) é capaz de induzir o acúmulo de gordura sem aumentar o peso corporal dos ratos (DE MELO *et al.*, 2021), isso pode ser devido a frutose ser massivamente absorvida pelos adipócitos, onde é metabolizada em triglicerídeos e contribui para a hipertrofia dos adipócitos (HERNANDEZ-DIAZCOUDER et al., 2019). Além disso, nesse mesmo estudo, foi demonstrado que a DRS altera o metabolismo da glicose e causa resistência à insulina (DE MELO *et al.*, 2021). De forma parecida, estudos mostram que, peso, IMC, gordura visceral e glicemia são os parâmetros que são comumente afetados pela dieta rica em açúcar (SCHLESINGER et al., 2019; TAMMI et al., 2023).

2.4 RECEPTOR DE POTENCIAL TRANSITÓRIO E SÍNDROME METABÓLICA

Estudos indicam que as diversas alterações observadas na SM estão diretamente relacionadas ao desenvolvimento de um ambiente oxidativo tecidual e sistêmico (FURUKAWA *et al.*, 2017; COLAK *et al.*, 2021). Além disso, diversos receptores celulares estão envolvidos na SM, capazes de modular diversos mecanismos metabólicos, oxidativos, hormonais e inflamatórios, nesse cenário, destaca-se a família dos TRPs (Receptores de potencial Transitório), onde já existem estudos constatando a sua participação na transdução da dor, regulação do gasto energético e modulação do processo inflamatório (TABERNER *et al.*, 2015; KOIVISTO *et al.*, 2021).

Os canais TRPs são canais catiônicos polimodais que medeiam os influxos de Ca^{2+} através da membrana celular (RAMSEY *et al*., 2006). Influxos catiônicos através de TRPs despolarizam a membrana celular e ativam muitas respostas celulares. O desenvolvimento de agonistas, antagonistas e camundongos KO para TRPs ajudou a definir seus locais de expressão e funções fisiopatológicas ao longo das últimas décadas. Embora os TRPs tenham diferentes padrões de expressão, sua ampla distribuição fisiológica indica seu envolvimento com processos biológicos em diferentes células, tecidos e órgãos (WU *et al*., 2010; NILIUS, B.; SZALLASI, 2014; KOIVISTO *et al.*, 2022).

A família TRP de mamíferos é composta por 28 membros classificados em seis subfamílias: vanilóide (TRPV), anquirina (TRPA), canônica (TRPC), melastatina (TRPM), mucolipina (TRPML) e policistina (TRPP) (CLAPHAM *et al*., 2001; SAMANTA *et al*., 2018). Os TRPs são expressos em células neuronais e não neuronais e medeiam uma variedade de respostas, incluindo nocicepção, inflamação, tônus vascular, contratilidade celular, gasto de energia, entre outros.

Vários desses receptores têm sido amplamente estudados, como por exemplo o TRPV1, onde já foi evidenciado que são expressos em neurônios e em tecidos metabólicos, incluindo o tecido adiposo (BASKARAN *et al.,* 2017; ZHANG *et al.,* 2007) e o fígado (VRIENS *et al.,* 2004; LI *et al.,* 2012). O TRPV1 também é expresso em macrófagos M1 (LI *et al.,* 2012; LV *et al*., 2021) e células T (MACHO *et al.,* 1999; SAMIVEL *et al*., 2015; FOLEY, 2014) sugerindo um papel importante no processo inflamatório e na SM. Por outro lado, a expressão de TRPV1 em células β pancreáticas é controversa (AKIBA *et al*., 2004; DIAZ-GARCIA *et al.,* 2014).

Estudos vêm demonstrando que, a ativação do TRPV1, além de promover o estímulo de forma positiva à secreção de insulina e o gasto energético, ainda, promove redução do acúmulo de gordura, aumento da atividade da lipase e redução de triglicerídeos, além de causar vasorelaxamento e sensibilização periférica a esse hormônio (ZHU *et al*., 2011; BASKARAN *et al*., 2017). Além dos dados controversos sobre a expressão de TRPV1 nas células β pancreáticas (AKIBA *et al.,* 2004; DIAZ-GARCIA *et al.,* 2014) sua contribuição para a resistência à insulina não é clara. Camundongos propensos a diabetes sem inervação pancreática são protegidos do desenvolvimento de doença pancreática; esses dados levam à conclusão de que a ativação do TRPV1 está associada à patogênese do diabetes tipo 1 (RAZAVI *et al*., 2006).

Além disso, os camundongos TRPV1KO tiveram um tempo de vida mais longo do que os animais do tipo selvagem (WT), além de maior sensibilidade à insulina (RIERA *et al.,* 2014). De acordo, tanto a quimiodenervação dos neurônios TRPV1 quanto seu bloqueio induziram a secreção de insulina dependente de glicose em roedores (VON BANCHET *et al*., 2007; GRAM *et al.,* 2005; TANAKA *et al.,* 2011). Esses achados sugerem o envolvimento da ativação neuronal do

TRPV1 na resistência à insulina e na inflamação das ilhotas. Em contraste, outros estudos mostraram que camundongos TRPV1KO alimentados com alto teor de gordura apresentam maior resistência à insulina do que WTs nas mesmas condições dietéticas (LEE *et al*., 2015).

Interessantemente, a ingestão de baixas doses de capsaicina dietética, um ativador TRPV1, tem sido associada à melhora dos sinais clínicos de obesidade e DM2 (ÁVILA *et al.,* 2021; ZHANG *et al.,* 2021). Ainda, estes receptores são sensores de estresse oxidativo, sendo ativados por moléculas pró-oxidantes como o peróxido de hidrogênio e compostos lipofílicos como o 4-hidroxinonenal (ZHU *et al*., 2011; ZHANG *et al*., 2020). Nesse contexto, um importante papel como sensor de estresse oxidativo foi atribuído ao TRPV1, podendo este receptor ser ativado por produtos do estresse oxidativo como H_2O_2, e regular a produção destes mediadores (FERNANDES *et al.,* 2012; KEEBLE *et al*., 2009).

Além do envolvimento no estresse oxidativo, a literatura mostra sua participação na modulação de células inflamatórias, onde a expressão de TRPV1 em células T $CD4^+$ de camundongos foi confirmada e mostrou mediar a produção de diferentes citocinas (IL-4, IL-5, IL-6 e IL-17), associadas ao aumento da fosforilação de quinases e NF-κB (SAMIVEL *et al.,* 2015). Esses achados foram apoiados por dados de células Jurkat T após tratamento com o inibidor de TRPV1, BCTC, e de camundongos TRPV1KO sensibilizados com ovalbumina, pois tanto as células tratadas com inibidor quanto os animais com ablação gênica do canal resultaram em menos citocinas (FOLEY, 2014; SAMIVEL *et al.,* 2015).

O tecido adiposo desempenha um papel essencial na SM, influenciando os equilíbrios de glicose e lipídios. Existem diferentes tipos de tecido adiposo (branco, marrom e bege), e seu conteúdo celular, substâncias secretadas e localização determinam o desenvolvimento e a progressão da SM. É importante destacar que o tecido adiposo branco (TAB) armazena o excesso de energia como triglicerídeos, enquanto o tecido adiposo marrom (TAM) está envolvido no gasto de energia.

A diferenciação do TAB em um fenótipo semelhante ao TAM é conhecida como escurecimento do TAB e é caracterizada por adipócitos termogênicos bege, também chamados de

células “brite”. Os adipócitos TAM e bege contribuem para a redução da secreção de insulina e, portanto, para o controle do DM2, além da obesidade. Esses aspectos foram recentemente revisados (KAHN *et al*., 2019; CHAIT e DEN HARTIGH, 2020; CHENG *et al.,* 2021).

A expressão de TRPV1 foi demonstrada em pré-adipócitos 3T3-L1 cultivados e em amostras de tecido adiposo humano e de camundongos (ZHANG *et al.,* 2007; BISHNOI *et al.,* 2013; BASKARAN *et al.,* 2016; BASKARAN *et al.,* 2017). O primeiro estudo, em 2007 (ZHANG *et al.,* 2007) demonstrou que é reduzido a expressão de TRPV1 durante a adipogênese, e que a incubação de capsaicina previne essa resposta em células 3T3-L1, indicada por conteúdo reduzido de TG, menor expressão de PPAR-γ e síntese de ácidos graxos; os efeitos da capasaicina na adipogênese foram atenuados pelo knockdown do TRPV1.

A expressão de TRPV1 também foi diminuída no tecido adiposo visceral de camundongos obesos e na gordura visceral e subcutânea de pacientes obesos em comparação com controles magros (ZHANG *et al.,* 2007). A capsaicina dietética estimula a expressão da proteína de desacoplamento termogênico específica de BAT-1 (UCP-1) e o escurecimento de TAB em WT, mas não em camundongos TRPV1KO, aumentando a expressão de sirtuína-1 (BASKARAN *et al.,* 2016). Por sua vez, ocorre a desacetilação do PPARγ levando à redução da síntese lipídica e obesidade (BASKARAN *et al.,* 2016).

Um efeito semelhante foi observado para outro agonista de TRPV1, o monoacilglicerol, que mostrou aumentar a expressão de UCP-1 e prejudicar o acúmulo de gordura visceral em camundongos alimentados com dieta rica em gordura/alta sacarose (IWASAKI *et al.,* 2011). O papel do TRPV1 como um receptor termogênico em adipócitos também foi confirmado por um estudo recente no qual os progenitores de adipócitos TRPV1+-termogênicos foram caracterizados (SHAMSI *et al.,* 2021).

Vários relatos mostram que os TRPs também são relevantes para o restabelecimento da função hepática durante a SM. Do ponto de vista terapêutico, a melhoria do metabolismo mitocondrial é uma estratégia pertinente destinada ao tratamento da doença hepática gordurosa não alcoólica (DHGNA), pois o aumento do estresse oxidativo hepático está correlacionado com a

inflamação em dietas obesogênicas (SATAPATI *et al.*, 2015). Neste caso, a ativação do TRPV1 secundária à ingestão dietética de baixa dose de capsaicina preveniu o dano hepático observado na DHGNA por meio da regulação positiva da proteína desacopladora 2 (UCP-2) em camundongos (LI *et al.*, 2012; HU *et al.*, 2017).

Li e colaboradores descreveram a expressão do TRPV1 nos hepatócitos e os mecanismos desencadeados por sua ativação. Os efeitos observados compreendem a redução do acúmulo de lipídios e dos níveis de concentração de TG em WT, mas não em animais TRPV1KO (LI *et al.*, 2012). A regulação positiva de UCP-2 secundária à ativação de TRPV1 também foi associada a outros efeitos terapêuticos, como a reversão da disfunção endotelial induzida por hiperglicemia em camundongos. Tal mecanismo antioxidante via UCP-2 pode ser uma ligação multifacetada entre a ingestão dietética de capsaicina e seus efeitos terapêuticos em doenças metabólicas ou cardiovasculares (SUN *et al.*, 2013).

Outras funções hepáticas também podem se beneficiar da ingestão dietética de baixa dose de capsaicina, como o metabolismo das lipoproteínas. Embora tenha sido demonstrado que a capsaicina não reduz o acúmulo de LDL em macrófagos sensibilizados com TNFα, a ativação do TRPV1 aumentou a expressão do cassete de ligação do ATP (ABCA1 e ABCG1) via X receptor α do fígado, aumentando assim o efluxo de colesterol das células [254 **]** . Esses achados também são relevantes na fisiopatologia da aterosclerose, já que oxLDL é um biomarcador amplamente conhecido tanto da aterosclerose quanto da DHGNA (SUN *et al.*, 2013; ZHAO *et al.*, 2013).

De forma parecida, o TRPA1 é expresso essencialmente nos neurônios sensoriais nociceptivos, onde possui como função a detecção de produtos químicos pungentes encontrados em plantas tais como o isotiocianato de alila e cinamaldeído (ANDERSSON *et al*., 2008; TIAN *et al.*, 2020). O TRPA1 é amplamente expresso em todo o corpo, inclusive em tecidos metabólicos e células (RO *et al*., 2009; NILIUS *et al*., 2012; CAO *et al.*, 2012).

O TRPA1 pode ser ativado por uma variedade de moléculas produzidas e liberadas durante a fosforilação oxidativa, incluindo metilglioxal (JENSEN, 2013) 4-HNE, 15-desoxi-delta (12,14) - prostaglandina J_2 (15d-PGJ2) e H_2O_2 (TRAVERSO *et al.*, 1998). Estas moléculas, e

TRPA1, têm sido associadas com efeitos anti-hiperglicêmicos e anti-obesidade que são discutidos mais adiante neste documento.

Estudos já demonstraram que a ativação do TRPA1 por agonistas exógenos tem sido relacionada à diminuição dos níveis circulantes de glicose, da resistência à insulina, e do acúmulo de gordura, melhora da dislipidemia e aumento da termogênese; além de causarem sensibilização periférica à dor em modelo de diabetes (KOIVISTO *et al.,* 2012; JENSEN *et al.,* 2013; KOIVISTO *et al.,* 2021). Dados experimentais adicionais mostraram expressão reduzida de TRPA1 nas ilhotas de Langerhans obtidas de roedores com DM2 (KONG *et al.,* 2019). No entanto, outro estudo demonstrou que os efeitos deletérios da estreptozotocina (um composto usado para indução experimental de diabetes) nas células β são independentes da ativação do TRPA1 (ANDERSSON *et al.,* 2015).

Em um modelo de pancreatite crônica (induzida pela injeção de ácido trinitrobenzeno sulfônico), foi demonstrado o envolvimento de TRPA1 no desenvolvimento desta condição, pois TRPA1KOs apresentaram inflamação pancreática reduzida em comparação com camundongos WT (CATTARUZZA, F, *et al.,* 2013). Estudos com ativadores endógenos de TRPA1, como 4-HNE, apoiam ainda mais o envolvimento de TRPA1 na modulação dos níveis de glicose e resistência à insulina. O tratamento do músculo gastrocnêmio e das células musculares L6 com 4-HNE reduziu a sinalização da insulina e a captação de glicose induzida pela insulina nas células do músculo esquelético, aumentando o estresse oxidativo e a depleção de GSH (PILLON, N.J, *et al.,* 2012).

Além disso, este aldeído foi negativamente correlacionado com a sensibilidade à insulina em indivíduos obesos (GUO *et al.,* 2017). Nesse contexto, o complexo papel do TRPA1 na resistência à insulina sugere que a regulação da ativação do TRPA1 pode ser uma nova estratégia terapêutica, embora estudos adicionais sejam necessários para elucidar adequadamente essa via na SM. Também é possível que a expressão neuronal de TRPA 1, provavelmente no nervo vago, contribua para a termogênese como os agonistas do receptor cinamaldeído e isotiocianato de alilo,

ambos induzem a secreção de adrenalina e previnem o acúmulo de gordura e obesidade em ratos (WATANABE e TERADA, 2015).

O mesmo estudo mostrou a capacidade do cinamaldeído de ativar BAT e reduzir a gordura visceral em animais alimentados com dieta rica em gordura/alta sacarose. Dados de suporte demonstraram que o cinamaldeído diminui o ganho de peso e as quantidades de TG plasmático, ácidos graxos não esterificados e colesterol em camundongos com HFD (HUANG *et al*., 2011) e que a incubação de cinamaldeído com células 3T3-L1 diminui o acúmulo de TG e fosfolipídios, enquanto redução do PPARγ; esses efeitos foram bloqueados pelo antagonista TRPA1 AP-18 (HOI *et al.*, 2020).

A contribuição da ativação do TRPA1 para a termogênese tem sido apoiada não apenas por estudos com agonistas exógenos como o cinamaldeído, mas também por aqueles realizados com ativadores endógenos do canal, incluindo o 4-HNE. Altos níveis de 4-HNE foram detectados no tecido adiposo subcutâneo de indivíduos obesos (ELRAYESS *et al.*, 2017). A incubação de 4-HNE com adipócitos subcutâneos desencadeou a produção de ROS (H_2O_2) e enzimas antioxidantes (TRX, SOD e catalase), associada à redução do crescimento e diferenciação de pré-adipócitos (ELRAYESS *et al.*, 2017).

Os efeitos do cinamaldeído foram investigados no fígado de ratos DM2 e diabéticos gestacionais induzidos por dieta rica em gordura/alta sacarose (HOSNI *et al.*, 2017; ABDELMAGEED *et al.*, 2019). O tratamento intragástrico com cinamaldeído diminuiu significativamente a peroxidação lipídica hepática, esteatose e inflamação, e aumentou os níveis hepáticos de GSH e SOD em ratos com DM2. Essas mudanças foram associadas com maior sensibilidade à insulina (ABDELMAGEED *et al.*, 2019). Além disso, a administração oral de cinamaldeído controlou a hiperfagia e a intolerância à glicose em ratos com diabetes gestacional (HOSNI *et al.*, 2017) tais efeitos foram associados com níveis circulantes reduzidos de colesterol total, triglicerídeos, leptina e TNFα, e níveis mais altos de lipoproteína de alta densidade (HDL)-colesterol, adiponectina, glicogênio hepático e expressão de PPARγ, e a atividade de enzimas antioxidantes.

Por outro lado, a análise de amostras de fígado humano saudável por hibridização in situ demonstrou a expressão de TRPA1 no revestimento endotelial sinusoidal e nas células de Kupffer, mas não nos hepatócitos (BADR *et al.*, 2016). Assim, se os efeitos do cinamaldeído forem devidos à ativação do TRPA1, isso ocorreria por meio de células endoteliais e/ou de Kupffer, e isso deverá ser confirmado em pesquisas futuras.

Assim como o TRPV1 e TRPA1, o TRPC5 também podem ser ativados por produtos do estresse oxidativo. De forma interessante, o TRPC5 pode ser ativado tanto por moléculas pró-oxidantes (H_2O_2) quanto antioxidantes (tioredoxina), além de NO (PEREIRA *et al*., 2018; TAO *et al*., 2020). Nesse contexto, alguns pesquisadores já sugeriram que o TRPC5 parece estar envolvido na detecção de lipídios, EROS e espécies reativas de nitrogênio (LIU *et al*., 2008; WANG *et al.*, 2009; SUNGGIP *et al.*, 2018).

O TRPC5 pode formar homo e heterocomplexos funcionais com outros receptores da mesma família, como TRPC4 e TRPC1 (STRÜBING *et al.*, 2001; HOFMANN *et al.*, 2002) que exercem diferentes funções, desde a inflamação até o remodelamento vascular. Os complexos TRPC5 são amplamente expressos no sistema nervoso central (SNC) e em níveis mais baixos em outros tecidos e células (ZHOLOS, 2014). No contexto da SM, o TRPC5 tem um papel importante conectando os tecidos metabólicos e o cérebro. O TRPC5 pode ser ativado por uma variedade de moléculas, incluindo H_2O_2 (NAYLOR *et al.*, 2011) TRX reduzido (XU *et al*., 2008) e ácidos graxos (SUKUMAR *et al.*, 2012).

Ainda, vale enfatizar que o TRPC5 é encontrado especialmente na região cerebral, sendo passível de modificação covalente por meio de cisteínas reativas, funcionando como um sensor redox ao ser ativado por aplicação extracelular da proteína redox endógena, a tioredoxina, por peróxido de hidrogênio endógeno, óxido nítrico ou fosfolipídeos oxidados (TAKAHASHI *et al.*, 2012; PEREIRA *et al.*, 2018). Em um relatório inicial, TRPC5 foi encontrado expresso em níveis muito baixos em linfócitos T efetores em repouso de murinos, e foram modulados após a ativação dessas células (WANG *et al.*, 2009). Corroborando, já foi demonstrado que o TRPC1, mas não o TRPC4, é detectado nas células T. Esta foi a primeira evidência de que a ativação de complexos

TRPC5 pode contribuir para a supressão autoimune. Em macrófagos (células RAW 264.7), a inibição de TRPC5 por antagonismo com ML-204 ou silenciamento de RNA, causou polarização celular para um fenótipo M1 que foi caracterizado pelo aumento da secreção de citocinas pró-inflamatórias envolvendo a ativação de NF-κB (TNFα, IL-1β e IL-6) (TAO *et al.,* 2020).

Camundongos TRPC5KO alimentados com dieta rica em gordura tiveram maior número de macrófagos M1 infiltrando a aorta e maiores níveis séricos de TNFα e IL-6 (TAO *et al.,* 2020). Além disso, a deleção ou antagonismo de TRPC5 por ML-204 restaurou a fagocitose em macrófagos desafiados com LPS e TRX bacteriano (PEREIRA *et al.,* 2018). Essas evidências indicam um papel protetor para TRPC5 na inflamação e doenças cardiovasculares. Há poucos dados sobre a expressão pancreática de TRPC5 (UHLÉN *et al.,* 2015) e nenhum relato até o momento sobre o papel desse receptor na resistência à insulina.

Apesar disso, TRPC1 pode formar complexos com TRPC5 (STRÜBING *et al.,* 2001) e há evidências crescentes sobre a expressão pancreática de TRPC1 (UHLÉN *et al.,* 2015; MARABITA e ISLAM, 2017; FELS *et al*., 2016) bem como sobre sua função como regulador da tolerância à glicose e secreção de insulina (KROUT *et al.,* 2017; XU *et al.,* 2019). Ademais, o envolvimento dos TRPs na resistência à insulina remete primeiro aos TRPC4 e TRPM2, pois sua ativação leva à despolarização das células pancreáticas e ao influxo de Ca^{2+}, regulando assim a secreção de insulina por mecanismos distintos (QIAN *et al.,* 2002; TOGASHI *et al.,* 2006).

No entanto, a expressão sistêmica de outros TRPs pode ser alterada pela hiperglicemia, conectando concomitantemente o DM2 e as DCVs na SM. A existência de um eixo TRPC5-glicólise aeróbio também foi observada em células de câncer colorretal (WANG *et al.,* 2018). Além disso, TRPC5 foi encontrado para mediar dano celular neuronal e morte sob estresse metabólico, como privação de oxigênio-glicose (DATTILO *et al.,* 2008).

Portanto, espera-se que novos desenvolvimentos no campo sejam capazes de anular ou demonstrar a importância dos complexos TRPC5 na resistência à insulina e/ou seus papéis como sensores dos níveis de glicose. Complexos TRPC1/TRPC5 também foram identificados em células 3T3-L1 cultivadas e em amostras de tecido adiposo perivascular obtidas de camundongos e

humanos (SUKUMAR *et al.,* 2012; BISHNOI *et al.,* 2013). A ativação constitutiva desses complexos nos adipócitos maduros da gordura perivascular foi sugerida como um regulador negativo da adiponectina (SUKUMAR *et al.,* 2012).

O knockdown TRPC1/TRPC5 *in vitro* aumentou a geração de adiponectina em camundongos, disrupção de complexos contendo TRPC5 e aumento dos níveis de adiponectina independentemente da composição da dieta (ração ou HFD) (SUKUMAR *et al.,* 2012). Curiosamente, o mesmo estudo mostrou que os efeitos inibitórios dos complexos TRPC1/TRPC5 na adiponectina foram interrompidos pela exposição aos ácidos graxos ω-3 da dieta em células 3T3-L1 diferenciadas. Até agora, há informações limitadas sobre a expressão de membros da subfamília TRPC no fígado (UHLÉN *et al.,* 2015; BADR *et al.,* 2016) no entanto, os dados atuais não suportam um papel para TRPC5 no fígado na SM.

Em contrapartida, a ação protetora envolvendo o TRPC5 em camundongos com colestase já foi citada, pois animais TRPC5KOs tiveram uma proteção contra a doença, uma vez que apresentaram aumento do fígado atenuado, ácido biliar hepático reduzido e conteúdo lipídico, além de enzimas hepáticas, níveis de colesterol e triglicerídeos diminuídos (ALAWI *et al.*, 2017). Apesar de diversos mecanismos já terem sido identificados na SM, o tratamento desta síndrome nem sempre é efetivo. Assim, a elucidação de novas vias envolvidas na SM, principalmente em seus eventos inflamatórios e oxidativos, é de suma importância (ÁVILA *et al.,* 2021; ZHANG *et al.,* 2021).

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2.4.1 TRPC4/TRPC5 e ML204

A subfamília do TRPC de mamíferos é subdividida em quatro grupos, TRPC1, TRPC2, TRPC3/C6/C7 e TRPC4/C5, com base nas semelhanças de sequência. TRPC2, C3, C6 e C7 podem ser ativados diretamente por diacilgliceróis, incluindo um análogo sintético, 1-oleoil-2-acetil- *sn* -glicerol (OAG) **(**MILLER *et al.*, 2011). Em contrapartida, os canais TRPC4/C5 não são ativados pelo diacilglicerol, mas são facilitados pelo Ca 2+ interno e externo (SCHAEFER, 2000;

MILLER *et al*., 2011).

Sabemos que a identificação e utilização de agonistas e antagonistas exógenos são de extrema importância dentro do ambiente científico, porém, a caracterização funcional e identificação de ativadores ou bloqueadores específicos é bem complexa, como por exemplo, sabe-se que o SKF96365 e borato de 2-aminoetoxidifenil (2-APB), bem como lantânio e gadolínio, podem modular as funções TRPC4/C5, entretanto, esses compostos não são seletivos, e modulam uma diversidade de receptores celulares (MILLER *et al*., 2010; MILLER *et al.*, 2011).

Nesse sentido, os primeiros relatos do ML204 foram publicados e divulgados no PubChem (AID2247 e AID2256), onde foram detalhados os critérios de seleção de compostos ativos. Estudos de relação estrutura-atividade juntamente com caracterização biológica levaram à nomeação do CID 24829278 como um composto de Sonda de Bibliotecas Moleculares, denominado de ML204.

Estudos já descreveram que a utilização do ML204 (4-metil-2-piperidin-1-ilquinolina; cloridrato), como um potente e seletivo antagonista dos receptores TRPC4/TRPC5, que permite a sua utilização para avaliar a participação e os impactos desses receptores em diferentes patologias. (SCHAEFER, 2000; MILLER *et al.*, 2010; MILLER *et al.*, 2011). Ainda, nesses estudos supracitados, foi possível demonstrar que embora o ML204 também tenha alguns efeitos inibitórios fracos sobre receptores muscarínicos e outros receptores acoplados à proteína G, ele apresenta seletividade pelo menos 20 vezes maior para TRPC4/TRPC5 comparados aos outros receptores iônicos. Reforçando que, este nível de seletividade é muito superior a outros bloqueadores farmacológicos atualmente utilizados na pesquisa de canais TRPC e deve fornecer bloqueio específico de canais TRPC4/C5.

Além disso, ML204 apresentou estabilidade *in vitro*, com meia-vida de 2 horas e foi funcionalmente eficaz *in vivo* (SCHALDECKER *et al.*, 2013). Para analisa a seletividade do antagonismo do TRPC4/5 utilizando o ML204, um estudo realizado por Alawi e colaboradores, demonstraram em um modelo de artrite reumatóide induzida por adjuvante completo de Freund (CFA), que o tratamento crônico com ML204, aumentou a assimetria na sustentação de peso,

hiperalgesia secundária e concentrações de citocinas (interferon (IFN) -γ, TNFα e interleucina (IL) -10) (ALAWI *et al*., 2017).

Observamos também que, os estudos acerca dos agonistas relacionados ao TRPC4/C5 possuem uma maior acervo, além de serem melhores elucidados, como por exemplo, a (-)-Englerin A (EA), um extrato da planta da África Oriental *Phyllanthus engleri* foi identificado como um agonista de TRPC4/5, onde já foi atribuído o efeito anti-inflamatório e analgésico (DE SOUSA *et al.*, 2021). Ademais, a rosiglitazona, fármaco anti-diabético utilizado no tratamento de diabetes do tipo II, é um potente ativador in vitro do TRPC5, ação esta, independente da afinidade deste composto por PPAR-γ, seu alvo farmacológico previamente identificado (MAJEED *et al.*, 2011).

Além disso, o papel protetor dos complexos neuronais TRPC5 na SM é apoiado por dados obtidos de estudos sobre agonistas do GLP-1 e seus efeitos nos neurônios pró-opiomelanocortina (HE *et al.*, 2019; DONG *et al.*, 2021). De fato, as ações da liraglutida e da semaglutida nos neurônios pró-opiomelanocortina envolvem a ativação do TRPC5 *in vivo* e em fatias hipotalâmicas de camundongos. É digno de nota que, no hipocampo, as respostas dependentes de leptina não requerem expressão de TRPC5 (DHAR *et al.*, 2014).

2.4.2 Perspectivas Clínicas de Ativadores e Bloqueadores de TRPs na síndrome metabólica

Além de estudos não clínicos, os efeitos benéficos da modulação dos canais TRPV1, TRPA1 e TRPC5 na obesidade, DM2, aterosclerose e SM foram investigados em uma série de ensaios clínicos. Nestes, foram avaliados ativadores pungentes e não pungentes do TRPV1. Em um estudo, foram administrados capsaicina a 0,25% ou placebo em 24 indivíduos (12 homens e 12 mulheres; idade: 35±10 anos; IMC: 25,0±2,4 kg/m ^{2} ; faixa 20–30), a ingestão alimentar de 16 horas foi avaliada quatro vezes durante 2 dias consecutivos, foi observado que, a curto prazo, a exposição oral e gastrointestinal à capsaicina aumenta a saciedade e reduziu a ingestão de energia

e gordura; a redução mais forte com a exposição oral sugere um efeito sensorial da capsaicina (WESTERTERP-PLANTENGA *et al*., 2004).

Em outro relatório com 19 homens com sobrepeso ou obesos, um suplemento contendo capsaicina aumentou o gasto de energia em comparação ao placebo (BELZA e JESSEN, 2005). Essas descobertas foram apoiadas por estudos posteriores (BELZA *et al*., 2005; REINBACH *et al.,* 2009; BELZA *et al.,* 2009; JANSSENS *et al*., 2013; RIGAMONTI *et al.,* 2018). O uso de capsaicina 1h antes do exercício de baixa intensidade também melhorou a lipólise em voluntários saudáveis (SHIN e MORITANI, 2007).

Além disso, a capsaicina de *Capsicum frutescens* teve efeitos hipoglicemiantes em indivíduos saudáveis (CHAIYASIT *et al.*, 2009). Os capsinóides são substâncias não pungentes relacionadas à capsaicina (KOBATA *et al.,* 1998). Indivíduos com IMC entre 25,0 e 35,0 receberam óleo de capsinóide (6 mg/dia) obtido de *Capsicum anuum* L. variedade CH-19 Sweet ou placebo, os capsinóides diminuíram o peso corporal enquanto aumentavam a oxidação de gordura (SNITKER *et al.*, 2009). O mesmo estudo encontrou uma correlação entre a redução da gordura abdominal e as variantes genéticas TRPV1 Val585Ile e UCP-2-866 G/A.

Outro capsinóide, o dihidrocapsiato, causou um pequeno efeito termogênico em indivíduos saudáveis. O consumo de um suplemento contendo capsinóides de baixa dose (2 mg) levou ao aumento dos níveis plasmáticos de AGL (BLOOMER *et al.,* 2010) Consequentemente, os capsinóides *de C. anuum* aumentaram o gasto de energia ativando TAM em indivíduos saudáveis em comparação com o grupo placebo (YONESHIRO *et al.,* 2012; NIRENGI *et al.,* 2012). Os dados acima indicam o potencial da capsaicina para tratar a obesidade e a hiperglicemia. Por outro lado, embora promissores, os efeitos termogênicos dos capsinóides ainda precisam ser confirmados em estudos posteriores com indivíduos com sobrepeso e obesidade.

Cinamaldeído é um dos principais compostos encontrados em cascas de canela (RAO *et al*., 2014). Vários estudos investigaram os efeitos benéficos da canela no DM2. Em um estudo com 60 indivíduos com DM2 (30 mulheres e 30 homens), a ingestão de cápsulas de canela atenuou a glicose sérica, TG, colesterol total e lipoproteína de baixa densidade (KHAN *et al.,* 2003). De

acordo, os extratos ou suplementos de canela diminuíram os níveis de glicose plasmática e as concentrações de malondialdeído e melhoraram o perfil lipídico em indivíduos com sobrepeso a obesos (ROUSSEL *et al*., 2013; LIU *et al.,* 2015; GUPTA *et al.,* 2017; ZARE *et al.,* 2019) e hipoglicemia induzida em pacientes com DM2 (LU *et al.,* 2012) e indivíduos saudáveis (BEEJMOHUN *et al.,* 2014).

Por outro lado, o consumo de canela em pó ou suplemento não alterou a glicose plasmática ou o perfil lipídico sérico em pacientes com DM2 (SUPPAPITIPORN *et al*., 2006; TALAEI *et al.,* 2017). Um resultado semelhante foi observado em pacientes na pós-menopausa com DM2 (VANSCHOONBEEK *et al.,* 2006) e indivíduos saudáveis (MARKEY *et al.,* 2011). Curiosamente, a ingestão de canela em pó reduziu a pressão arterial e a hemoglobina glicada em pacientes com DM2 (AKILEN *et al.,* 2010). Embora as evidências coletadas desses estudos sejam controversas, elas chamam a atenção para novos estudos para apoiar o uso potencial de canela e compostos derivados no manejo da SM.

Nenhum ensaio clínico avaliando o impacto do TRPC5 na SM humana foi publicado até o momento. No entanto, o uso de inibidores TRPC4/TRPC5 para perda de peso, bem como para combater a obesidade, DM2, SM, DHGNA e esteato-hepatite não alcoólica foi publicado recentemente (números de acesso: WO/2018/146485; EP3579838; US20200345741). As ações antidiabéticas de liraglutida e semaglutida no hipotálamo requerem TRPC5, o que indica que esse canal é um alvo interessante para o desenvolvimento de novas terapias para SM.

No entanto, considerando que a SM é uma doença complexa, não é surpreendente que outros TRPs, além do TRPV1, TRPA1 e TRPC5, possam influenciar o equilíbrio entre o estresse oxidativo e a inflamação durante a progressão da doença. Por exemplo, TRPM2 é outro TRP ativado por EROs (especificamente, H_2O_2), que está envolvido na resistência à insulina (TOGASHI *et al*., 2006; UCHIDA e TOMINAGA, 2011). A expressão de TRPM4 e TRPM5 também foi descrita em ilhotas de Langerhans humanas, indicando ainda possíveis papéis com perspectivas clínicas para SM (COLSOUL *et al*., 2013).

Digno de nota, a expressão de TRPM2 é significativamente aumentada durante NAFLD, e sua ativação por ERO super produzida durante a doença desempenha um papel significativo na fisiopatologia, contribuindo para sua progressão (ALI *et al.*, 2021). Antioxidantes naturais como o saliroside (da *Rhodiola rosea*) e a curcumina são capazes de inibir a ativação do TRPM2 nos hepatócitos, resultando na redução da deposição de lipídios, diminuição da expressão de citocinas (IL-1β e IL-6) e proteção contra danos celulares (KHERADPEZHOUH *et al.*, 2016; ALI *et al*., 2021). Estas são descobertas iniciais e mais pesquisas no campo são importantes e merecem ser realizadas.

Desta forma, com o presente estudo, buscou adquirir e ampliar o conhecimento acerca do TRPC5 e suas funções na fisiopatologia da Síndrome metabólica, principalmente na inflamação, comportamento hedônico, adipogênese, esteatose e ganho de peso. Ressalta-se que compostos capazes de bloquear ou ativar estes receptores vêm sendo desenvolvidos para o tratamento de doenças de curso crônico, como a artrite reumatoide, obesidade, DM2 e SM. Assim, faz-se extremamente relevante a obtenção de informações relativas aos potenciais efeitos deletérios do uso repetido e prolongado destes compostos

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ARTIGO 01

An Overview of the TRP-Oxidative Stress Axis in Metabolic Syndrome: Insights for Novel Therapeutic Approaches

Abstract: Metabolic syndrome (MS) is a complex pathology characterized by visceral adiposity, in- sulin resistance, arterial hypertension, and dyslipidaemia. It has become a global epidemic associated with increased consumption of high-calorie, low-fibre food and sedentary habits. Some of its un- derlying mechanisms have been identified, with hypoadiponectinemia, inflammation and oxidative stress as important factors for MS establishment and progression. Alterations in adipokine levels may favour glucotoxicity and lipotoxicity which, in turn, contribute to inflammation and cellular stress re- sponses within the adipose, pancreatic and liver tissues, in addition to hepatic steatosis. The multiple mechanisms of MS make its clinical management difficult, involving both non-pharmacological and pharmacological interventions. Transient receptor potential (TRP) channels are non-selective calcium channels involved in a plethora of physiological events, including energy balance, inflammation and oxidative stress. Evidence from animal models of disease has contributed to identify their specific contributions to MS and may help to tailor clinical trials for the disease. In this context, the oxidative stress sensors TRPV1, TRPA1 and TRPC5, play major roles in regulating inflammatory responses, thermogenesis and energy expenditure. Here, the interplay between these TRP channels and oxidative stress in MS is discussed in the light of novel therapies to treat this syndrome.

Keywords: TRP channels; metabolic syndrome; energy metabolism; hypoadiponectinemia; reactive oxygen species; inflammation

1. Introduction

Metabolic syndrome (MS) is a complex pathology characterized by visceral adiposity, insulin resistance, arterial hypertension, and dyslipidaemia [1]. MS presents significant morbidity and mortality as it strongly increases the risk of developing different diseases, such as those affecting the cardiovascular system and type 2 diabetes (T2D) [2]. Its manage- ment is primarily aimed at reducing the risk for cardiovascular diseases (CVDs) and T2D, and includes lifestyle modifications and multiple drugs [3,4].

Abdominal obesity, insulin resistance and sedentary life-styles are major risk factors for MS [1]. These increase with ageing, by taking medicines which increase weight gain, by mitochondrial and endocrine dysfunctions, and genetic predisposition [3]. Although not the focus of the current review, the later findings on the genetic basis of MS have greatly contributed to further understanding the different underlying mechanisms and phenotypes of MS [5–7].

Energy metabolism is influenced by an intricate network of molecules released and receptors expressed within metabolic organs such as the pancreas, liver, adipose tissue and skeletal muscle, connecting the periphery to the brain (Figure 1). Hypoadiponectinemia, inflammation and oxidative stress [8–12] account for some of the mechanisms involved in MS establishment and progression, with a clear interplay between them. Different pathways are suggested to modulate these mechanisms. In this context, members of the transient receptor potential (TRP) family of non-selective Ca2+ channels may play an important role in MS by regulating inflammatory responses, thermogenesis and energy expenditure [13–16]. Herein, we discuss the mechanisms of MS and the roles of TRPV1, TRPA1 and TRPC5, known as oxidative stress sensors and regulators of inflammation, in MS. We also present the clinical perspectives of targeting these receptors for MS management.

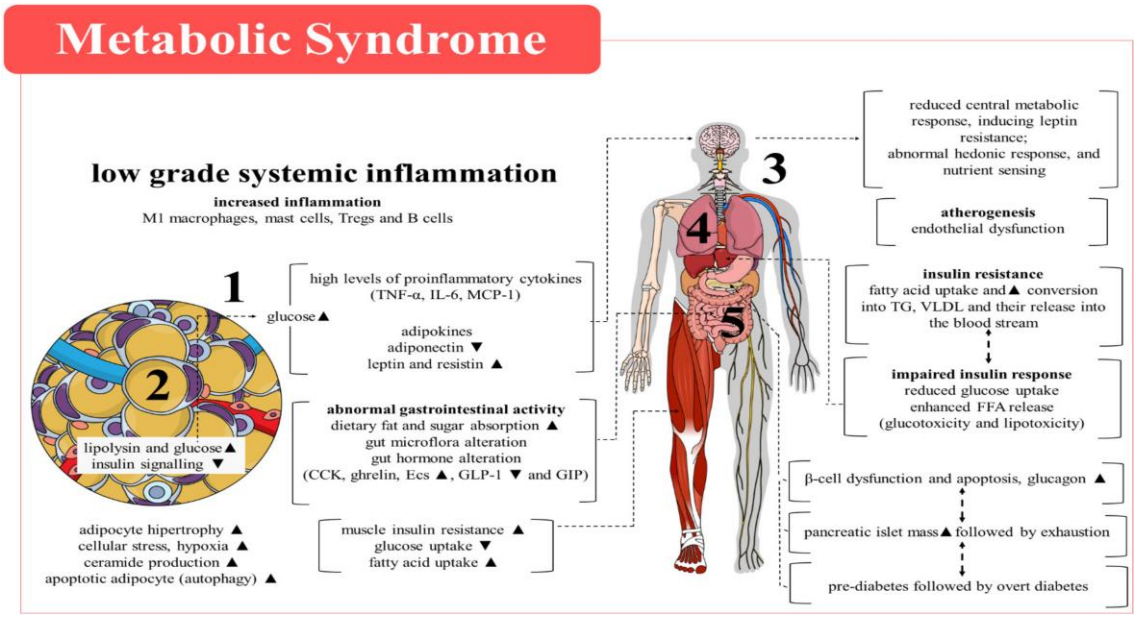

Figure 1. Mechanisms of metabolic syndrome (MS) pathophysiology. MS is a result of a metabolic imbalance which involves alterations in different tissues and a variety of molecules. (1) Insulin resistance is accompanied by (2) a low-grade inflammation in the adipose tissue characterized by reduction of adipokines such as adiponectin, enhanced levels of leptin and resistin, accumulation of inflammatory cells in the adipose tissue, paralleled with high levels of cytokines/chemokines and reactive oxygen species. Alterations of the central (hypothalamus and the brainstem) and peripheral mechanisms of hunger and satiety occur (3). All these events contribute towards (4) decreased energy expenditure, hyperglycaemia and dyslipidaemia, increasing the risk for type 2 diabetes and cardiovascular diseases. Nutrient absorption (5) and the gut microbiota play key roles in the modulation of MS, aiding the connection between the brain and metabolic tissues. TG—triglycerides; VLDL—very low-density lipoprotein; CCK—cholecystokinin; Ecs—estrogens; GLP-1—glucagon-like peptide-1; GIP—gastric inhibitor peptide; TNFα—tumour necrosis factor α; IL-6—interleukin-6; MCP-1—macrophage chemotatic protein-1.

2. Adiponectin Dysregulation, Oxidative Stress and Inflammation as Mechanisms of Metabolic Syndrome

2.1. Adiponectin Dysregulation

Adiponectin is an adipokine secreted by adipocytes, first described in 1995 [17]. Al- though adiponectin functions were unknown at that time, by using mouse cells, this report was the first to demonstrate the existence of a link between insulin secretion, adipocyte differentiation and adiponectin release, and to suggest a role for this adipokine in the regulation of carbohydrate and lipid metabolism. In 1996, the human adiponectin was described in two different studies, which showed its presence in human adipose tissue and plasma samples [18,19].

In the last decades, it has become clear that adiponectin is an essential regulator of glucose and lipid metabolism and a great influencer of the risk for developing obesity, T2D, CVD and, therefore, for MS.

It is now known that adiponectin forms complexes of different molecular weights. Of note, the one of high molecular weight (HMW) was shown to be the most potent in reducing serum glucose levels in mice [20]. The same study demonstrated that the HMW complex is reduced in obese diabetic mice and that it becomes increased in both T2D mice and patients following treatment with rosiglitazone—a PPARγ agonist. Later, adiponectin-induced hypoglycaemia was found to be independent of insulin levels [21,22] but was able to improve insulin sensitivity [23]. Soon after, it was shown that adiponectin crosses the blood- brain barrier and induces the hypothalamic expression of the anorexigenic corticotrophin- releasing hormone (CRH), leading to weight loss and enhanced energy expenditure [23,24].

Adiponectin multimers can be cleaved in a fragment containing the C-terminal glob-ular domain, which has potent effects on skeletal muscle cells. Full length adiponectin and its fragments may exert different actions on different cell types [25–28] by binding to the G-protein coupled adiponectin receptors type 1 (AdipoR1) and 2 (AdipoR2). AdipoR1 is constitutively expressed in every cell, especially in skeletal muscle, whilst AdipoR2 is greatly expressed in the liver [29]. They

are both also expressed in various brain regions including hypothalamus, brainstem, hippocampus, and cortex [30].

A study by Bjursell and collaborators [31] investigated the contribution of AdipoR1 and AdipoR2 to energy metabolism homeostasis by using AdipoR1 and AdipoR2 knockout (KO) mice fed with a high-fat diet (HFD). They demonstrated that male AdipoR1KOs have greater adiposity and glucose intolerance, resulting in weight gain and energy expenditure, increased liver triglyceride (TG) and plasma leptin (a satiety hormone produced and secreted by white adipose tissue (WAT) [32]) levels, in addition to higher AdipoR2 mRNA expression in brown adipose tissue (BAT), a thermogenic tissue. On the other hand, the same study demonstrated that AdipoR2KOs are resistant to obesity, even eating more than control mice. The same KOs exhibited increased expression of CRH mRNA in the hypothalamus, less plasma leptin and cholesterol, lower liver TG, greater plasma and adiponectin levels, and higher glucose tolerance and energy expenditure. Interestingly, AdipoR2KOs presented with decreased levels of AdipoR1 mRNA in the liver and BAT [31]. Similar to AdipoR1KOs, mice with adiponectin gene ablation fed with a high-fat/high- sucrose diet had severe insulin resistance [33]. Interestingly, mice lacking adiponectin fed with a normal diet presented delayed free-fatty acid (FFA) clearance, and higher plasma and adipose tissue tumour necrosis factor-α (TNFα) levels. Injection of a full-length adiponectin producer adenovirus reversed this phenotype in adiponectin KO mice.

Human studies have associated hypoadiponectinemia (Figure 2), with excessive intra-abdominal fat and multiple defects in glucose and energy metabolism in MS. The syndrome has also been linked to increased circulating levels of cytokines (e.g., interleukin (IL)-6 and IL-1β) and soluble adhesion molecules (e.g., P-selectin and ICAM) [34]. The same study suggested that low adiponectin production is an underlying cause of endothelial damage and low-grade systemic inflammation in MS. The data are supported by previous studies showing that hypoadiponectinemia increases the risk for coronary artery disease (CAD) in men [35], and data from mice that showed that adiponectin protects against vascular damage following mechanical injury [36]. In addition, obese patients with CAD have diminished plasma levels of adiponectin and lower expression of adiponectin receptors in peripheral monocytes in comparison with those without CAD, while macrophages from CAD patients present impaired release of IL-10 following adiponectin incubation [37].

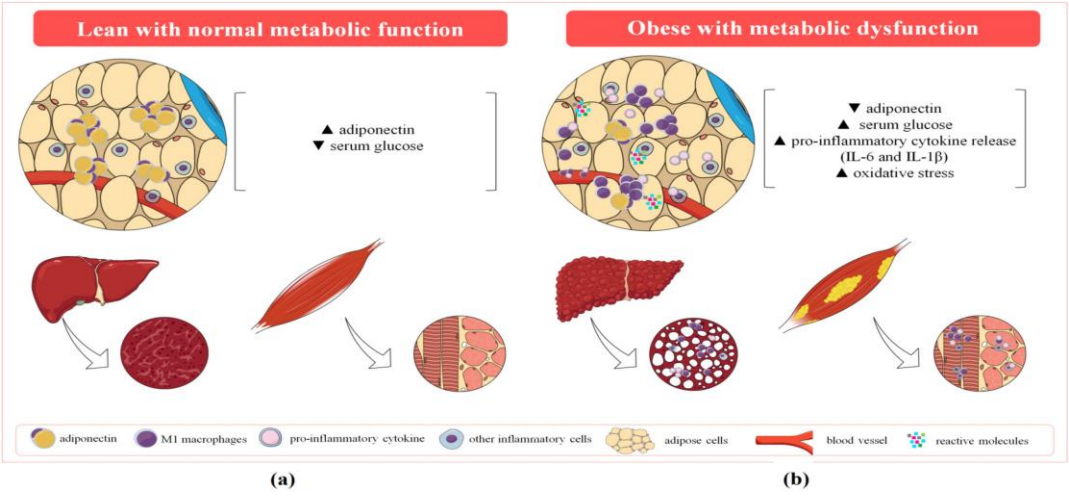

Figure 2. Fat tissue inflammation and adiponectin dysregulation in metabolic syndrome. (**a**) In lean individuals, adipose tissue contains few M2 macrophages and adipocytes produce high levels of adiponectin. Their insulin levels and sensitivity are regulated and result in normal glucose levels. (**b**) Individuals with metabolic dysfunction present with inflamed metabolic tissues with fat deposition and ROS production, which result in reduced cell viability and insulin resistance/high glucose levels.

Oxidative stress has been suggested as a cause of hypoadiponectinemia [38–40]. Indeed, exposure of pre-adipocytes (3T3-L1 cells) to oxidants such as hydrogen peroxide (H_2O_2), glucose oxidase or 4-hydroxynonenal (4-HNE), results in decreased expression and secretion of adiponectin. The low levels of this adipokine caused by oxidants are accompanied by increased production of pro-inflammatory cytokines (TNFα, IL-6) and chemokines (macrophage inflammatory protein-1; MCP-1) by adipocytes [40–43]. The contribution of oxidative stress to MS is discussed below.

2.2 Oxidative Stress

Oxidative stress is defined as the imbalance between the production and neutralizing pathways of reactive oxygen and reactive nitrogen-derived pro-oxidant species (ROS and RNS, respectively) in favour of these species. The link between oxidative stress and inflammation pathways highlights the burden of this condition in MS [44].

The physiological production of ROS (such as superoxide anion—O_2^-, hydroxylradical—OH, H_2O_2 and hypochlorous acid—HClO) and RNS (such as nitric oxide—NO and peroxynitrite anion—$ONOO^-$) occurs via different endogenous enzymatic pathways (e.g., nicotinamide adenine dinucleotide phosphate oxidases—NOX, NO synthases—NOS, myeloperoxidase—MPO, xanthine oxidase—XOs, amongst others.). Although ROS and RNS signalling contribute to diverse cellular processes [45,46], under oxidative stress, there is increased availability of these species leading to harmful effects in various disease states, including in MS. For example, O2− produced by NOX activates XOs inducing tetrahydrobiopterin (BH4) oxidation, endothelial NOS uncoupling and the consequent lowering of NO production and bioavailability, an essential hallmark of the pathogenesis of T2D and hypertension [47]. Other cellular effects of oxidative stress involve damage to proteins, membrane lipids, and nucleic acids. OH.—induced lipoperoxidation and DNA damage (as assessed by the formation of 8-hydroxy-2′-deoxyguanosine-8-OHdG), are well-established markers of chronic inflammation in MS [48].

On the other hand, neutralizing antioxidant pathways mitigate the reactivity of ROS [49]. Primary antioxidant pathways include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. Additional pathways include glutathione reductase, thioredoxin (TRX), and glutaredoxin. Other non-enzymatic pathways comprise reduced glutathione (GSH), bilirubin, and low molecular weight compounds of dietary origin (e.g., vitamins A, C, E, flavonoids, zinc,

and selenium) [48]. In this way, antioxidant path- ways provide conditions for controlled production of physiologically relevant oxidant species (such as H2O2) and the maintenance of homeostasis.

Oxidative stress has also been directly linked to the pathogenesis of CVDs such as hypertension, and insulin resistance in T2D [50]. In MS, oxidative stress is mainly characterized by the diminished expression and activity of antioxidant pathways secondary to a decrease in the levels of nuclear factor E2-related factor 2 (NRF2), in plasma samples from patients with MS [51]. These findings were also present in experimental models of obesity [52].

Hypertension is associated with reduced bioavailability of NO and increased ROS production either from dysfunctional mitochondrial or enhanced NOX expression in endothelial cells. The peroxynitrite anion, the product of the reaction between $O2^{-}$ and NO, also contributes to dysfunctional systemic vessel tonus control [53]. Furthermore, dyslipi- daemia, insulin resistance, hyperglycaemia, and other factors, contribute to mitochondrial dysfunction and enhance mitochondrial $O2^{-}$ production by endothelial cells, cardiomy- ocytes and pancreatic β-cells [54], the latter being particularly vulnerable to oxidative stress due to the low expression of antioxidant defences in these cells.

Diverse mechanisms are related to the effects of oxidative stress on pancreatic β-cell function, including altered expression of micro-RNAs responsible for the gene regulation of redox signalling pathways [55]. Excessive ROS production, together with hyperglycaemia, contributes to glyceraldehyde-3-phosphate dehydrogenase inhibition, which results in the accumulation of glycolytic pathway precursors (such as fructose-6-phosphate and glyceraldehyde-3-phosphate). In this case, the subsequent activation of polyol cascades (by advanced glycation end-products—AGEs) causes NADPH depletion and reduced bioavailability of GSH [56]. In this case, the activation of nuclear factor-κB (NF-κB) and NOX promotes oxidative stress and a pro-inflammatory status that contribute to the vascular complications of T2D due to the low NO bioavailability and high expression of cell adhesion molecules [57]. In addition, the enhanced vasoconstriction elicited by endothelin-1 and other endogenous vasoconstrictors (such as prostaglandin H2 and thromboxane A2) impairs both the endothelial function and vascular wall integrity, particularly at the microcirculation level [58]. Therefore, AGEs play an important role in the delicate interface between T2D and CVDs [59].

As previously discussed, oxidative stress (Figure 2) can contribute to hypoadiponectinemia and inflammation, and thus, to obesity. Obesity is characterized by a systemic pro-inflammatory status, mainly due to the development of insulin resistance [60]. From a cellular perspective, impaired mitochondrial function and biogenesis caused by either hyperglycaemia and/or hyperlipidaemia impairs the insulin signalling pathway [61]. This, in addition to dysfunctional adipose tissue, enhances oxidative stress by activating pro- inflammatory pathways in adipocytes [62], which are amongst the aetiological factors of T2D and CVDs [63].

Interestingly, increased circulating levels of TRX are present in T2D patients [64] and have been associated with higher risk for CVD in individuals with MS [65].

2.3. Inflammation

In addition to adiponectin dysregulation and oxidative stress (Figure 2), studies have provided compelling evidence that the progress of metabolic dysfunction is closely related to a state of low-grade chronic inflammation [66–68], which is primarily characterized by recruitment of pro-inflammatory macrophages to the adipose tissue. Macrophages enhance the inflammatory response [69,70], contributing to the accumulation of ectopic lipids and the development of insulin resistance [71]. M1 and M2 macrophages play an important role in adipose tissue during low-grade inflammation [72] through the production and release of TNFα, IL-1β, and IL-6, and IL-10, respectively [73,74]. M1 macrophages recruited to the pancreatic islets cause pancreatic β-cell dysfunction and apoptosis [74]. Furthermore, the production of pro-inflammatory cytokines within the adipose tissue leads to adipocyte hypertrophy [70]. The local release of FFA, especially saturated fatty acids, activates toll-like receptor 4 on macrophages [75,76], triggering the activation of NF-κB and the additional expression of pro-inflammatory cytokines [77]. These events continuously contribute to insulin resistance in the adipose tissue, liver, and skeletal muscle [78,79]. The above data reinforce the importance of inflammatory imbalance to the adipose tissue changes in MS and its comorbidities/complications [67]. Indeed, adipose tissue inflammation also impacts other tissues and organs such as the liver [80,81], pancreas [82] and muscles [83]. Fat deposition in these organs is particularly deleterious [10].

Liver resident macrophages (Kupffer cells) can also be polarized into M1 and produce TNFα as a result of a lipid-rich diet that, in turn, contributes to increased glucose release by gluconeogenesis, lipid production and storage by inhibiting intracellular lipases [74]. The metabolic complications associated with a decline in insulin release lead to glucolipotoxicity in the pancreatic islets and the adipose tissue [84,85], imbalance of redox states, and mito- chondrial dysfunction [85]. An obesogenic diet promotes endoplasmic reticulum stress and pancreatic β-cell dysfunction, with consequent reduction of insulin production [84]. These alterations are closely associated with increased inflammation, oxidative stress, and subse- quent damage to DNA, proteins, cellular lipid, and potentially cell death [86]. In fact, liver damage may be driven by the secretion of pro-inflammatory cytokines (e.g., TNFα) [87], hypoadiponectinemia [88,89], and high levels of resistin and leptin [80,90,91] in the adipose tissue. Increased hepatic lipid accumulation into the liver followed by de novo lipogenesis and reduction of fatty acid oxidation [92,93] leads to histological damage characterized as simple steatosis, non-alcoholic steatohepatitis, or cirrhosis, and even hepatocellular carcinoma in more serious cases [94,95].

Although the studies are still controversial [96–99], pancreatic fat may be associated with β-cell dysfunction and insulin resistance [100,101]. Importantly, sarcopenic obesity is directly related to additional weight gain [102] and poor physical function and ability [103].

In addition to macrophages, T cells also play a role in MS. Mice fed HFD present with higher numbers of CD8+ and smaller populations of CD4+ and regulatory T cells in the epididymal WAT in comparison with normal chow-fed mice [104]. CD8+ cell influx precedes that of M1 macrophages in the adipose tissue, increasing inflammation and systemic insulin resistance. In agreement, mice lacking T cells are protected against obesity- induced T2D in HDF-fed mice,

which is associated with less macrophage accumulation and down-regulation of inflammatory cytokines/chemokines (MCP-1, RANTES, IL-6, TNFα and IFNγ) in skeletal muscle and adipose tissue samples [105]. Conversely, in another report, T cell recruitment and IFNγ up-regulation occurred in epididymal WAT following macrophage influx [106]. Overall, these data show the contribution of Th1 cells to adipose tissue inflammation in MS. Additionally, Th17 cells contribute towards a pro- inflammatory phenotype in the adipose tissue and insulin resistance [107], whilst Th2 cells are suggested to protect against obesity [108]. Interestingly, the percentage of Th2 cells in human adipose tissue samples negatively correlates with systemic inflammation and insulin resistance [108].

3. Transient Receptor Potential Channels

3.1. General Overview of TRPV1, TRPA1 and TRPC5 Channels

TRP channels are polymodal cation channels that mediate Ca2+ influxes across the cell membrane [109]. Cationic influxes through TRPs depolarize the cell membrane and activate many cellular responses. The development of agonists, antagonists and KO mice for TRPs has helped to define their expression sites and pathophysiological functions throughout the last few decades. Although TRPs have different expression patterns, their wide physiological distribution indicates their involvement with biological processes in different cells, tissues, and organs [110–112]. The mammalian TRP family is composed of 28 members classified into six sub-families: vanilloid (TRPV), ankyrin (TRPA), canonical (TRPC), melastatin (TRPM), mucolipin (TRPML), and polycystin (TRPP) [113,114].

TRPs are expressed in both neuronal and non-neuronal cells and mediate a range of responses including nociception, inflammation, vascular tonus, cell contractility, energy expenditure, amongst others. These channels can be activated by a plethora of endogenous stimuli such as inflammatory mediators, lipids and oxidative/nitrosative stress products. As the focus of this review is to discuss the TRP-oxidative stress axis in different metabolic tissues in MS, the roles of TRPV1, TRPA1 and TRPC5 are presented.

TRPV1 (Figure 3a) was the first to be described and is the most extensively studied member of the TRP family [115,116]. It contains six transmembrane domains or sub-units (S1–S6) and a hydrophobic pore region between S5 and S6, in addition to intracellular domains—a long N-terminus with multiple ankyrin repeats and a short C-terminal re- gion [115]. These domains are now known to be essential as protein and compound- binding sites and, therefore, detrimental to the modulation of TRPV1 functions. Details on TRPV1 binding sites have been recently revised [117]. Fatty acid-derived products such as hydroxyeicosapentaenoic acid (12 (S)-HPETE) [118], 20-hydroxyeicosatetraenoic acid (20-HETE) [119], 9- and 13-hydroxyoctadecadienoic acids (9-HODE and 13-HODE) and oxidized forms [120], endocannabinoids such as anandamide [121], hydrogen sulphide (H2S; [122]), and ROS (H2O2; [123]), amongst others, are able to endogenously activate the receptor, either directly or by sensitization. TRPV1 is widely expressed

in neurones and also in metabolic tissues including the adipose [124,125] and liver tissues [126,127]. TRPV1 is also expressed in M1 macrophages [127,128] and T cells [129–131], already discussed herein, as a key inflammatory factor of in MS. On the other hand, TRPV1 expression in pancreatic β-cells is controversial [132,133].

TRPA1 (Figure 3b) also consists of six sub-units (S1–S6) and a hydrophobic pore region between S5 and S6 and has large intracellular N and C-terminal domains. A do- main containing five ankyrin repeats surrounds the coiled-coil region [134]. Key cys- teines necessary to channel activation by electrophiles are found within the pre-S1 re- gion [134]. TRPA1 is broadly expressed throughout the body including in metabolic tissues and cells [135–137]. TRPA1 can be activated by a variety of molecules produced and released during oxidative phosphorylation, including methylglyoxal [138], 4-HNE, 15-deoxy-delta(12,14)-prostaglandin J2 (15d-PGJ2) and H2O2 [139]. These molecules, and TRPA1, have been associated with anti-hyperglycaemic and anti-obesity effects which are further discussed herein.

TRPC5 (Figure 3c) is formed by a four-fold symmetric homotetramer, and each of the four monomers presents with a compact cytosolic domain and a transmembrane domain. The cytosolic domain is composed of the N-terminal region with an ankyrin domain and a region of seven α helices, whilst the C-terminal sub-domain contains a connecting helix and a coiled-coil domain. The transmembrane domain contains sub-units (S1–S6), a TRP domain, and several small helices, including a pore helix [140]. The presence of a disulphide bond at the extracellular side of the pore and a preceding small loop confer functionality to TRPC5 [140]. Of importance, as previously demonstrated for TRPV1 and TRPA1, which are able to functionally interact as dimmers (recently revised [141]), TRPC5 can also form functional homo and heterocomplexes with other receptors of the same family, such as TRPC4 and TRPC1 [142,143] that exert different functions, from inflammation to vascular remodelling. TRPC5 complexes are widely expressed in the central nervous system (CNS) and at lower levels in other tissues and cells [144]. In the context of MS, TRPC5 has an important role connecting metabolic tissues and the brain. TRPC5 can be activated by a range of molecules including H2O2 [145], reduced TRX [146], and fatty acids [147].

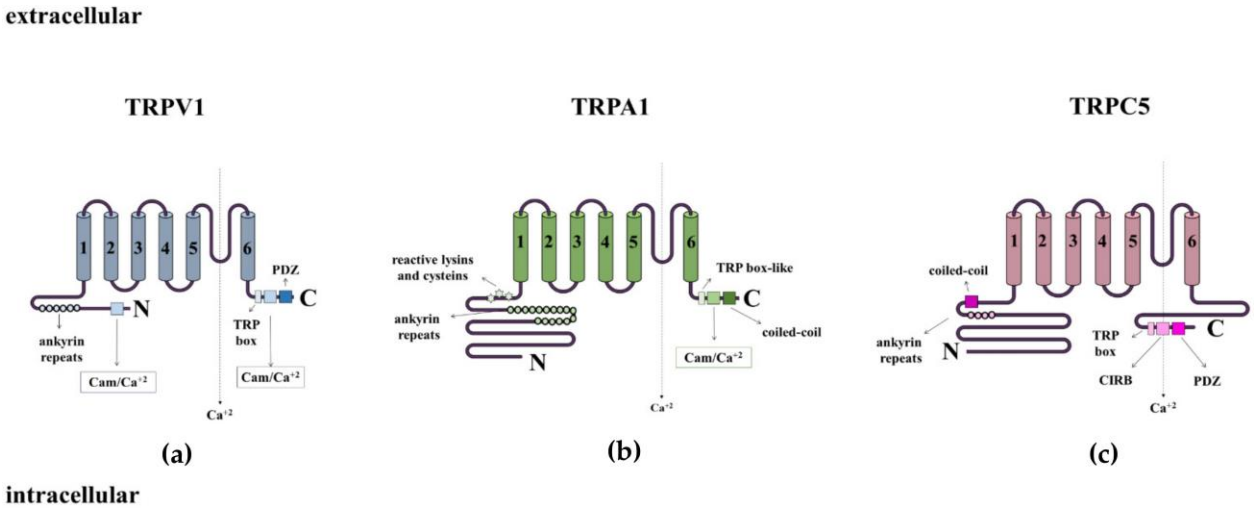

Figure 3. TRPV1, TRPA1 and TRPC5 structures. (**a**) TRPV1, (**b**) TRPA1 and (**c**) TRPC5 structures are composed of different domains including six transmembrane domains with a pore region, *N* and C- terminus, ankyrin repeats, coiled-coil, calmodulin (CaM)/Ca^{2+}-binding region, TRP-box, calmodulin (CaM)/inositol 1,4,5-trisphosphate (IP_3) receptor binding (CIRB), and PDZ domains.

The roles of TRPV1, TRPA1 and TRPC5 as mediators of oxidative stress and inflammation and, as modulators of MS are discussed below.

3.2. TRPs as Key Sensors of Oxidative Stress

TRP channels play essential roles in cellular function and disease [148]. Interestingly, specific TRPs are activated by ROS, amongst the several stimuli described to date. TRPM2 was the first TRP channel described as sensitive to ROS [149]. It is now known that TRPV1, TRPA1 and TRPC5 are not only oxidative stress sensors but also modulate oxidative stress pathways.

Reactive molecules, such as those involved in oxidative stress, are able to either directly activate or sensitize the TRP channels discussed herein. Evidence for the functional activation of these receptors by reactive molecules is listed in the Table 1. Different studies have demonstrated the ability of H2O2 to sensitize TRPV1 [123,150–152]. An initial report showed that H2O2 potentiates heat-induced membrane currents mediated by TRPV1 in HEK293T cells [150]. Next, this ROS was found to cause thermal hyperalgesia by TRPV1- dependent and independent mechanisms when intra-articularly injected in mice [151], and to potentiate apnoeic responses in rats by acting on both TRPV1 and TRPA1 when given as an aerosol [153]. H2O2 also induced increases in coronary blood flow, a response partially mediated by TRPV1 [123]. In the same study, H2O2 promoted the activation of intrinsic TRPV1-specific currents in isolated mouse coronary endothelial cells, which were blunted in endothelial cells lacking TRPV1. Interestingly,

the prolonged exposure of TRPV1 to H2O2 and reactive aldehydes, such as 4-HNE, impairs TRPV1 functions contributing to microvascular dysfunction in T2D [123,154]. 4-HNE-induced inhibition of TRPV1-mediated responses in coronary arterioles was suggested to be due to direct binding of this aldehyde to the channel [154]. H2O2 and O2− generation can be modulated by TRPV1, indicating a feedback loop between this channel and ROS production [155,156].

Table 1. Evidence for the functional activation of TRPV1, TRPA1 and TRPC5 by reactive molecules involved in metabolic syndrome.

TRP Channel	Reactive Molecule	Cell Type	Activation Mode	Ca^{2+} Influx	Electrophysiology
TRPV1	H_2O_2	HEK293T [123,150,152]	Sensitization	G	G
		Bovine aortic endothelial cells [123]	Sensitization	G	
TRPA1	H_2O_2	HEK293T [157–159]	Direct	G	
		DRG neurones [158–160]	Direct	G	
		Bladder neuronal afferents [161]	Direct		G
		CHO cells [160]	Direct	G	
	NO	HEK293T [159]	Direct	G	
		DRG neurones [159]	Direct	G	
	H+	HEK293T [159]	Direct	G	
		DRG neurones [159]	Direct	G	
	Aldehydes (4-HNE and 4-ONE)	HEK293T cells [157]	Direct	G	
		DRG and trigeminal ganglia neurones [157,160]	Direct	G	
		CHO cells [160,162]	Direct	G	
TRPC5	H_2O_2	HEK293T cells [145]	Direct	G	
	Reduced TRX	HEK293T cells [150]	Direct	G	
		Synoviocytes [150]	Direct	G	

As for TRPV1, TRPA1 is a well-documented oxidative stress sensor. The first evidence that the channel could be activated by reactive molecules demonstrated the ability of 4- HNE to evoke pain via TRPA1 activation on rodent nociceptive neurones. This event led to the release of substance P, causing neurogenic inflammation [157], and it was supported by further evidence [160]. In vivo and in vitro models showed that H2O2 triggers the neuronal activation of TRPA1 [160,163]. Oxidative stress can also activate TRPA1 on non-neuronal tissues and cells. For instance, 4-HNE induces the dilation of cerebral arteries [164] and increases of Ca2+ influx in pancreatic β-cells [137] following activation of this channel. Neurogenic vasodilatation is also mediated by TRPA1, a response which requires peroxynitrite generation [165].

TRPC5 is perhaps one of the most interesting TRP members with respect to oxidative stress signalling. TRPC5 can be activated by both oxidant (H2O2; [145]) and antioxi- dant (reduced TRX;

[146]) molecules; the latter shown to be a response dependent on TRPC1/TRPC5 complexes in non-neuronal cells. Interestingly, a recent report showed that eNOS-derived NO causes suppression of TRPC5 activity in endothelial cells [166]. Considering the reduced activity of eNOS and NO bioavailability in MS, it is possible that TRPC5 function in this syndrome is linked to regulation of blood vessel tonus and pressure control. TRPC5 is constitutively expressed in the brain and in metabolic tissues such as the adipose. Its contribution to energy metabolism is further discussed in this review.

Amongst the many cellular responses mediated by TRPs, the regulation and mainte- nance of inflammatory mechanisms have unique roles, given TRP permeability to Ca2+, which mediates transcription, translation, cellular division and apoptosis. In this way, ROS- based signalling mechanisms via TRPs are critical points worthy of deeper investigations in MS [48]. Different from TRPM2-redox activation by OH. (mainly produced in the Fenton reaction of iron-catalysed H2O2 decomposition), the main mechanism of TRPA1, TRPV1 and TRPC5 activation by ROS is a redox-sensitive pathway via cysteine disulphide forma- tion from proximal cysteine residues [167]. In fact, at least four cysteine residues have been described in the redox-sensitive mechanism of TRPA1 activation: Cys-421, Cys-621, Cys-641 and Cys-665 [158,163,168]. Cys-621 is the binding residue for 4-HNE in TRPV1 [154] and Cys-158 the binding residue for H2O2 in the same channel [152].

3.3. TRPs as Regulators of Inflammation

The roles of TRPV1, TRPA1 and TRPC5 in inflammation have been widely investigated in past years. Different pieces of evidence indicate these channels participate in inflam- matory events including cell migration, inflammatory mediator release and cell survival. Since both macrophages and T cells play a role in MS, this session focuses on the impact of these channels on T cell and macrophage responses.

The first indication that these channels are functional in inflammatory cells dates from the late 1990s. Incubation of capsaicin with activated human T cells caused Ca2+ mobilization [129]. TRPV1 expression in mouse CD4+ T cells was later confirmed and shown to mediate the production of different cytokines (IL-4, IL-5, IL-6, and IL-17), asso- ciated with increased phosphorylation of kinases and NF-κB [130]. These findings were supported by data from Jurkat T cells following treatment with the TRPV1 inhibitor BCTC, and from TRPV1KO mice sensitized with ovalbumin, as both the inhibitor-treated cells and the animals with gene ablation of the channel resulted in less cytokines [130,131]. TRPV1 expression was also confirmed in mouse CD11c+ dendritic cells and CD11b+F4/80+ macrophages [169]. Increased channel activation promoted higher secretion of cytokines (higher level of IL-6, IL-1β, TNFα, and IL-23) by dendritic cells [169]. TRPV1 was found to regulate macrophage and monocyte responses. In the absence of TRPV1, mouse macrophages are more susceptible to apoptosis, have impaired ability to perform phagocy- tosis and to produce ROS and NO, and release high levels of cytokines during bacteraemia associated with worsening of the disease in vivo [156]. In mouse cerebral malaria, the

lack of TRPV1 triggers less cerebral swelling, increased oxidative stress, and diminished production of cytokines [170]. These results indicate that, depending on the stimuli, the modulation of inflammation by TRPV1 can result in either protection against, or damage, in diseases. In fact, TRPV1 is highly expressed in M1 macrophages and its activation in these cells leads to inhibition of M1 polarization [128,171]. The inflammatory response is not modulated by TRPV1 only in microbial infections, but also in many different chronic diseases such as rheumatoid arthritis [172], colitis [169], rhinitis [130], and MS [173,174].

Human circulating leukocytes, Jukart T and mouse CD4+ T cells also express functional TRPA1 [175–177]. By using TRPA1 antagonists and KO mice, conflicting results have been found concerning the channel role in immune cells. Pre-treatment of murine splenic T cells with TRPA1 antagonists (A967079 and HC-030031) abolished T cell receptor-induced Ca2+ currents, as well as reduced T cell activation and cytokine release (TNFα, IFNγ and IL-2) by these cells [178]. Another report showed however, that TRPA1KO CD4+ splenic T cells present enhanced and prolonged T cell receptor-induced Ca2+ currents [176]. A compensatory role via TRPV1 was found to be involved in this response. In addition to T cells, monocytes and macrophages also express TRPA1. TRPA1 activation in cultured primary human monocytes triggers TNFα release and impairment of IL-10 production [179]. THP-1-derived macrophages express functional TRPA1 [179,180]. In these cells, TRPA1 was found to mediate the effects of lysophosphatidylcholine (an atherogenic lipid; [181]) on mitochondrial ROS production and membrane depolarization, IL-1β production and cell survival [180]. TRPA1 is also involved in the ATP actions on macrophages, contributing to mitochondrial damage, IL-1β secretion, and cell death [179]. Of note, ATP is an important molecule in atherosclerosis and hypertension [182,183]. These results infer that TRPA1 can contribute towards CVD in MS by regulating macrophage-mediated responses. Analysis of mouse atherosclerotic aortas indicated they express higher TRPA1 levels than control samples, especially in macrophages found in the atherosclerotic lesions [184]. TRPA1 blockade by HC-030031 or its genetic ablation resulted in larger lesions, hyperlipidaemia, and increased levels of pro-inflammatory mediators in the aorta (TNFα, IL-6, MCP-1 and MIP-2). The same study demonstrated that oxidized low-density lipoprotein directly activates TRPA1 and that channel activation protects against the formation of foam cells by reducing lipid accumulation [184]. These studies highlight a dual role (protective or deleterious) for TRPA1 in atherosclerosis.

In an initial report, TRPC5 was found to be expressed at very low levels in murine resting effector T lymphocytes, and to become up-regulated following activation of these cells [185]. TRPC5 mediated Ca2+ currents induced by the lectin galectin-1 produced by regulatory T cells; this response was abrogated by the TRP blocker SK&F96365 and receptor knockdown, and also in T cells from TRPC5KO mice. The same study showed that TRPC1 but not TRPC4 is detected in T cells. This was the first evidence that the activation of TRPC5 complexes can contribute to autoimmune suppression. In macrophages (RAW 264.7 cells), TRPC5 inhibition by antagonism with ML-204 or RNA silencing, caused cell polarization to a M1 phenotype which was characterized by increased secretion of pro-inflammatory cytokines involving NF-κB activation (TNFα, IL-1β and IL-6) [186]. TRPC5KO mice fed HFD had higher numbers of M1 macrophages

infiltrating their aorta and greater serum levels of TNFα and IL-6 [186]. In addition, TRPC5 deletion or antagonism by ML-204 restored phagocytosis in macrophages challenged with LPS and bacterial TRX [187]. These pieces of evidence indicate a protective role for TRPC5 in inflammation and CVD.

The above findings highlight the importance of TRPV1, TRPA1 and TRPC5 as modulators of inflammation in MS and are supported by studies performed with their endogenous agonists, including H2O2, 4-HNE and reduced TRX. H2O2 is suggested to act as a first mes- senger for different pro-inflammatory ligands including NO and AGEs [188], in addition to its role as second messenger in intracellular pathways which lead to the expression of pro-inflammatory mediators via redox-sensitive kinases and NF-κB activation [189–191]. A rapid increase of H2O2 following tissue damage also triggers fast leukocyte recruit- ment [192]. 4-HNE induces ciclooxigenase-2 expression in RAW 264.7 and peritoneal macrophages, in addition to leukocyte migration in mice, and via kinase activation [193]; these effects may contribute to the pro-inflammatory roles of prostaglandins. In accordance, 4-HNE activates NF-κB in vascular smooth muscle cells and 5-lipoxygenase production in murine macrophages [194,195]. Conversely, 4-HNE can cause inhibition of NF-κB activation as observed in monocytes, Jukart T and rat kupffer cells treated with the aldehyde [195–197]. These findings suggest that 4-HNE can be either pro or anti-inflammatory depending on the cell/tissue. An anti-inflammatory role has been attributed to TRX. Indeed, in vitro incubation of TRX-1 induces a M2 macrophage phenotype, and also reduces TNFα and MCP-1 generation by M1 macrophages [198]. The same study showed that TRX protects against atherosclerosis by shifting macrophage polarization to M2 in ApoE2.K1 mice with severe atherosclerotic lesions. The TRX-1-mimetic peptide CB3 reduced ROS production and NF-κB-mediated release of cytokines/chemokines (IL-1, IL-6, IL-1β and MCP-1) by cul- tured macrophages [199]. CB3 also presented atheroprotective effects in ApoE2.Ki mice fed HFD, which was associated with reduced levels of pro-inflammatory cytokines, increased production of anti-inflammatory proteins (adiponectin and IL-10) in the plasma, and a M2 macrophage phenotype in aortic lesions.

4. The Roles of TRPV1, TRPA1 and TRPC5 in MS

This section presents current data on the expression patterns (Figure 4; Table 2) and roles of TRPV1, TRPA1 and TRPC5 in the regulation of metabolic tissues, as well as in the connection between these tissues and the brain. Importantly, the combined expression of all the TRPs discussed herein contributes to regulate the functions of metabolic tissues and cells.

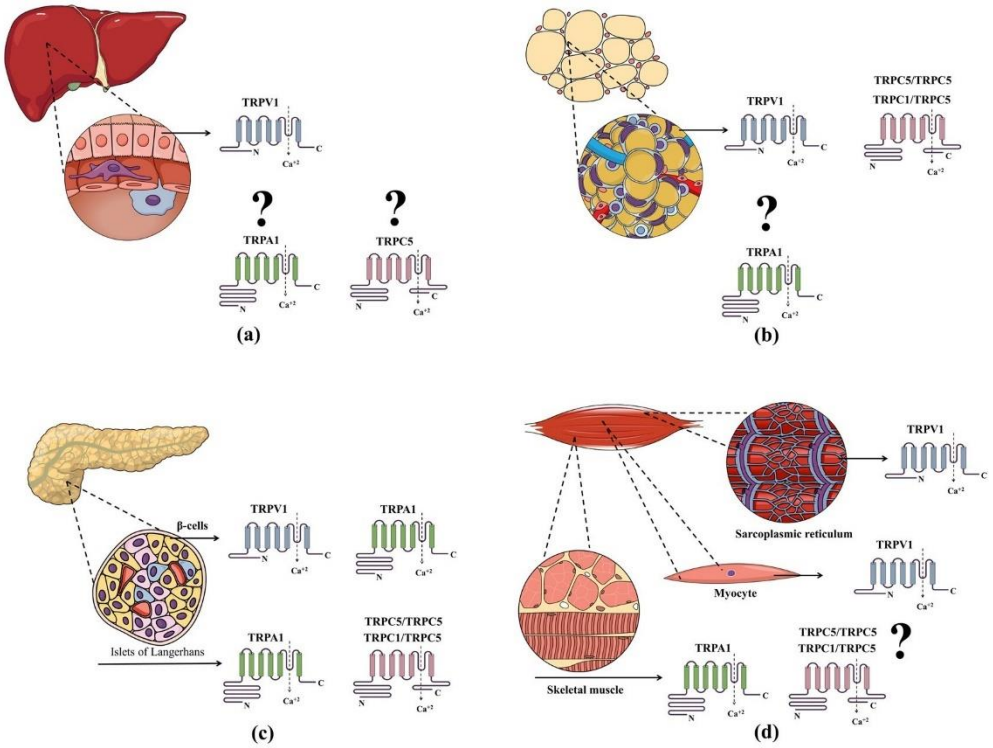

Figure 4. TRPV1, TRPA1 and TRPC5 expressions in metabolic tissues. (a) Liver, (b) adipose tissue, (c) pancreas and (d) skeletal muscle. All these TRPs are detected in the pancreas either as transcripts or functional proteins. TRPV1 is found in all metabolic tissues (liver, adipose tissue, pancreas and skeletal muscle). Additionally, TRPA1 and TRPC5 (either as homo or heterodimers) are expressed in the skeletal muscle and adipose tissue, respectively. The question tag (?) represents expressions yet to be confirmed: TRPA1 in the liver and adipose tissues, and TRPC5 in the skeletal muscle.

Table 2. Evidence for TRPV1, TRPA1 and TRPC5 expression on cells and in tissues involved in metabolic syndrome.

TRP Channel	Cell/Tissue	PCR/ qPCR	Immunostaining/ Immunofluorescence	Western Blot	Ca^{2+} Influx	Electrophysiology
TRPV1	adipose tissue/adipocytes [124,125,200,201]	G	G	G	G	
	liver [126,127]	G	G	G	G	
	M1 macrophages [128]		G		G	
	pancreatic β-cells/langerhans islets [132]	G	G	G		
	coronary endothelial cells [123]					G
	T cells [129–131]		G	G	G	G
	skeletal muscle [202–204]	G	G	G	G	
	pro-opiomelanocortin neurones [205]	G	G	G		G

Table 2. *Cont.*

TRP Channel	Cell/Tissue	PCR/ qPCR	Immunostaining/ Immunofluorescence	Western Blot	Ca^{2+} Influx	E ectrophysiology
TRPA1	pancreatic β-cells/langerhans islets [137,206]	G	G	G	G	G
	T cells [175–177]	G	G	G	G	G
	skeletal muscle cells [207]	G	G	G	G	G
	monocytes/macrophages [179,180]	G	G	G	G	
TRPC5	endothelial cells [166]				G	
	T cells [185]	G			G	
	M1 macrophages [186]	G		G		
	pancreas [208]	G				
	adipose tissue [147,200]	G	G	G	G	G
	pro-opiomelanocortin neurones [209–211]					G

4.1. Regulation of Insulin and Insulin Resistance

The involvement of TRPs in insulin resistance first remits to TRPC4 and TRPM2, as their activation leads to pancreatic cell depolarization and Ca2+ influx, thus regulating insulin secretion by distinct mechanisms [212,213]. However, the systemic expression of other TRPs may be altered by hyperglycaemia, concomitantly connecting T2D and CVDs in MS [214].

In addition to the controversial data regarding TRPV1 expression in pancreatic β- cells [132,133], its contribution to insulin resistance is unclear. Mice prone to diabetes lacking pancreatic innervations are protected from the development of insulitis and pan- creatic disease; these data lead to the conclusion that TRPV1 activation is associated with the pathogenesis of type-1 diabetes [215]. Furthermore, TRPV1KO mice had a longer life-span than wild-type (WT) animals, in addition to higher insulin sensitivity [216]. In agreement, both the chemo-denervation of TRPV1 neurones and its blockade induced glucose-dependent insulin secretion in rodents [172,217,218]. These findings suggest the involvement of neuronal TRPV1 activation in insulin resistance and islet inflammation. In contrast, other studies showed that TRPV1KO mice fed with HFD present with higher in- sulin resistance than WTs under the same dietary conditions [219]. Interestingly, the intake of low doses of dietary capsaicin, a TRPV1 activator, has been associated with improved clinical signs in obesity and T2D [220,221].

Pancreatic β-cells and other insulin-secreting cells express TRPA1 [133,137], after which activation of glucose-dependent insulin secretion by these cells is potentiated [137]. In vivo studies showed that the metabolic activity of TRPA1 involves glucose uptake stimulation, intestinal incretin hormone secretion, and inhibition of food intake [222–224]. It was also indicated that TRPA1 agonists such as cinnamaldehyde improve diabetes in vivo through glucose transporter (GLUT4) translocation in peripheral tissues [222]. Recently, it was demonstrated that the effects of endogenous catechol oestrogens on insulin secretion by pancreatic β-cells is mediated by TRPA1

activation, thus making of this receptor a link between oestrogen metabolism and metabolic diseases [225].

Additional experimental data showed reduced TRPA1 expression in the islets of Langerhans obtained from rodents with T2D [206]. However, another study demonstrated that the deleterious effects of streptozotocin (a compound used for experimental diabetes induction) on β-cells are independent of TRPA1 activation [226]. In a model of chronic pancreatitis (induced by the injection of trinitrobenzene sulfonic acid), it was demonstrated the involvement of TRPA1 in the development of this condition, as TRPA1KOs showed reduced pancreatic inflammation in comparison with WT mice [227]. In contrast, allyl isothiocyanate (a TRPA1 agonist) was able to enhance insulin sensitivity and glucose tolerance in mice fed HFD, and the effects are most probably related to the reversal of the impaired mitochondrial function [228]. Studies with endogenous activators of TRPA1 such as 4-HNE, further support the involvement of TRPA1 in the modulation of glucose levels and insulin resistance. Treatment of gastrocnemius muscle and L6 muscle cells with 4-HNE reduced insulin signalling and insulin-induced glucose uptake in skeletal muscle cells by increasing oxidative stress and depletion of GSH [229]. In addition, this aldehyde was negatively correlated with insulin sensitivity in obese subjects [230]. In this context, the complex role of TRPA1 in insulin resistance suggests that the regulation of TRPA1 activation could be a novel therapeutic strategy, although additional studies are needed to properly elucidate this pathway in MS.

There is little data on the pancreatic expression of TRPC5 [208] and no reports so far on the role of this receptor in insulin resistance. Despite that, TRPC1 can form com- plexes with TRPC5 [142], and there is growing evidence on the pancreatic expression of TRPC1 [208,231,232] as well as on its function as regulator of glucose tolerance and insulin secretion [233,234]. The existence of a TRPC5-aerobic glycolysis axis was also observed in colorectal cancer cells [235]. In addition, TRPC5 was found to mediate neuronal cell damage and death under metabolic stress such as oxygen-glucose deprivation [236]. Therefore, it is expected that further developments in the field will be able to overrule or demonstrate the importance of TRPC5 complexes in insulin resistance and/or their roles as sensors of glucose levels.

4.2. Regulation of Adypocytes

The adipose tissue plays an essential role in MS by influencing glucose and lipid balances. There are different types of adipose tissue (white, brown, and beige), and their cellular content, secreted substances and location determine MS development and progression. It is important to highlight that WAT stores excess energy as TGs, whilst the BAT is involved in energy expenditure. The differentiation of WAT into a BAT-like phenotype is known as browning of WAT and is characterized by thermogenic beige adipocytes also called “brite” cells. BAT and beige adipocytes contribute to reduction of insulin secretion and, therefore, to control T2D, in addition to obesity. These aspects have been recently reviewed [10,237,238].

TRPV1 expression was shown in cultured 3T3-L1-preadipocytes and in mouse and hu- man adipose tissue samples [124,125,200,201]. The first study, in 2007 [125], demonstrated that TRPV1 is down-regulated during adipogenesis, and that capsaicin incubation pre- vents this response in 3T3-L1 cells, indicated by reduced TG content, lower expressions of PPAR-γ and fatty acid synthase; capasaicin effects in adipogenesis were blunted by TRPV1 knockdown. TRPV1 expression was also decreased in the visceral adipose tissue of obese mice and in the visceral and subcutaneous fat of obese patients in comparison with lean controls [125]. Dietary capsaicin stimulates the expression of the BAT-specific thermogenic uncoupling protein-1 (UCP-1) and the browning of WAT in WT but not TRPV1KO mice, by increasing the expression of sirtuin-1 [201]. In turn, the deacetylation of PPARγ occurs leading to reduced lipid synthesis and obesity [201]. A similar effect was seen for another TRPV1 agonist, monoacylglycerol, shown to increase UCP-1 expression and to impair the accumulation of visceral fat in high fat/high sucrose diet-fed mice [239]. The role of TRPV1 as a thermogenic receptor in adipocytes was also confirmed by a recent study in which TRPV1+-thermogenic adipocyte progenitors were characterized [240].

Despite consuming equivalent energy and absorbing similar quantities of lipids to WTs, TRPV1KOs fed HFD gain less weight, present less adiposity and greater thermo- genesis [241]. On the other hand, in ageing mice fed HFD, the lack of TRPV1 promotes obesity due to altered energy balance and leptin resistance [219]. In another study with mice given HFD, no differences were noted between WT and TRPV1KO mice in regards to weight gain and adipose tissue mass [173]. It is possible that the differences between these studies are due to variations in the fat contents of HFD. Irrespective of this controversy, the above evidence indicates a promising clinical use of TRPV1 agonists such as capsaicin to preventing obesity by activating TRPV1. In agreement, capsaicin intake increases lipolysis in exercising individuals [242].

TRPV1 is not the only TRP channel to modulate thermogenesis. In this context, the alkamide trans-pellitorine found in Piper nigrum (black pepper) impairs lipid accumula- tion by reducing PPARγ levels in 3T3-L1 cells during the differentiation and maturation phases via the indirect activation of TRPV1 and TRPA1 [243]. This indicates a synergistic contribution of the functional expression of both channels in the regulation of energy expen- diture. Corroborating these findings, the incubation of cinnamaldehyde diminished TG and phospholipid content in 3T3-L1 preadipocytes by down-regulating PPARγ expression and increasing AMP-activated protein kinase levels [244,245]. TRPA1-independent pathways of thermogenesis and metabolic reprogramming were also reported for cinnamaldehyde; the compound was shown to promote these responses in mouse and human adipose cells by increasing UCP-1 and SOD expressions [245].

It is also possible that the neuronal expression of TRPA 1, probably in the vagus nerve, contributes to thermogenesis as the receptor agonists cinnamaldehyde and allyl isothiocyanate, both induce adrenaline secretion and prevent fat accumulation and obesity in rats [246]. The same study showed the ability of cinnamaldehyde to activate BAT and reduce visceral fat in animals fed high-fat/high-sucrose diet. Supporting data demon- strated that cinnamaldehyde decreases weight gain, and the quantities of plasma TG, non-esterified fatty acid, and cholesterol in mice with HFD [247], and also that incubation of cinnamaldehyde with 3T3-L1 cells decreases TG and

phospholipid accumulation, whilst reducing PPARγ; these effects were blocked by the TRPA1 antagonist AP-18 [244]

The contribution of TRPA1 activation to thermogenesis has been supported not only by studies with exogenous agonists such as cinnamaldehyde, but also by those performed with endogenous activators of the channel including 4-HNE. High levels of 4-HNE were detected in the subcutaneous adipose tissue of obese subjects [248]. Incubation of 4-HNE with subcutaneous adipocytes triggered the production of ROS (H2O2) and antioxidant enzymes (TRX, SOD and catalase), associated with reduced growth and differentiation of preadipocytes [248]. The down-regulation of adiponectin by 4-HNE has been previously discussed, and it is known to occur by degradation of adiponectin protein following incuba- tion with the aldehyde via the ubiquitin-proteasome system [249]. Of note, although 4-HNE reduces adipogenesis, its inhibitory effects on adiponectin may reflect in inflammation, and worsening of MS. Indeed, 4-HNE induced TNFα gene transcription in WAT samples of obese subjects [250]. Despite the interesting actions of cinnamaldehyde and 4-HNE in adipogenesis, the specific contributions to TRPA1 activation in this response is yet to be established by further studies employing strategies including KO mice, knockdown and antagonists for the channel.

TRPC1/TRPC5 complexes were also identified in cultured 3T3-L1 cells and in perivas-cular adipose tissue samples obtained from mice and humans [147,200]. The constitutive activation of these complexes in the mature adipocytes of the perivascular fat was suggested to act as a negative regulator of adiponectin [147]. In vitro TRPC1/TRPC5 knockdown increased adiponectin generation in mice, disruption of TRPC5-containing complexes and enhanced adiponectin levels irrespective of the diet composition (chow or HFD) [147]. Interestingly, the same study showed that the inhibitory effects of TRPC1/TRPC5 com- plexes on adiponectin were halted by exposure to dietary ω-3 fatty acids in differentiated 3T3-L1 cells.

4.3. TRPs and the Liver

Several reports show that TRPs are also relevant for the reestablishment of liver function during MS. From a therapeutic point of view, the improvement of mitochondrial metabolism is a pertinent strategy aimed for the treatment of non-alcoholic fatty liver disease (NAFLD), as enhanced hepatic oxidative stress is correlated with inflammation in obesogenic diets [251]. In this case, TRPV1 activation secondary to the dietary intake of low-dose capsaicin prevented the hepatic damage observed in NAFLD via uncoupling protein 2 (UCP-2) up-regulation in mice [127,252]. Li and collaborators [127] described TRPV1 expression on hepatocytes and the mechanisms triggered by its activation. The observed effects comprise reduced lipid accumulation and TG concentrations levels in WT, but not in TRPV1KO animals [127]. UCP-2 up-regulation secondary to TRPV1 activation was also associated with other therapeutic effects, such as the reversal of hyperglycaemia- induced endothelial dysfunction in mice. Such an antioxidant mechanism via UCP-2 may be a multifaceted link between the dietary intake of capsaicin and its therapeutic effects in either metabolic or cardiovascular diseases [253].

Other liver functions may also benefit from low-dose dietary intake of capsaicin, such as lipoprotein metabolism. Although it was demonstrated that capsaicin does not reduce oxLDL accumulation in TNFα sensitized macrophages, TRPV1 activation up-regulated ATP-binding cassette (ABCA1 and ABCG1) expression via liver X receptor α, thus enhanc- ing cholesterol efflux from the cells [254]. These findings are also relevant in the phys- iopathology of atherosclerosis, as oxLDL is a widely known biomarker of both atheroscle- rosis and NAFLD [253,254].

As demonstrated in mice receiving chronic dietary capsaicin, reduced inflammatory biomarkers and up-regulation of PPARδ secondary to TRPV1 activation takes place in WT but not in TRPV1KO animals with NAFLD [255]. Noteworthy, TRPV1 plays a substantial role in the obesity pathogenesis, with important consequences for hepatic health. TRPV1KO mice demonstrated a more pronounced hepatic steatosis when fed HFD, which was cor- related with reduced expression of PPARα and oxidation of fatty acids. In addition, the impaired glucose metabolism and hepatic health observed in TRPV1KO mice are some of the evidence confirming the significant relationship between TRPs and MS-related diseases, as recently described by Baskaran and collaborators [256].

However, the role of TRPV1 in other hepatic diseases may be in contrast with the results so far, thus evidencing the complexity of this matter. For example, the genetic depletion of TRPV1 did not blunt hepatic steatosis but prevented the hepatic injury in chronic alcoholic hepatic disease [257], thus evidencing different roles for TRPV1 in the pathogenesis of different hepatic diseases and making clear that TRPV1 activation is not an obvious pathway to be clinically explored, mainly in the case of MS patients with other comorbidities.

The effects of the cinnamaldehyde have been investigated in the liver of T2D and gestational diabetic rats induced by high fat/high sucrose diet [258,259]. Intragastric cinnamaldehyde treatment significantly decreased hepatic lipid peroxidation, steatosis and inflammation, and enhanced hepatic GSH and SOD levels in rats with T2D. These changes were associated with enhanced insulin sensitivity [258]. In addition, the oral administration of cinnamaldehyde controlled hyperphagia and glucose intolerance in rats with gestational diabetes [259]; such effects were associated with reduced circulating levels of total cholesterol, triglycerides, leptin and TNFα, and higher levels of high-density lipoprotein (HDL)-cholesterol, adiponectin, liver glycogen and PPARγ expression, and the activity of antioxidant enzymes. On the other hand, analysis of healthy human liver samples by in situ hybridization demonstrated the expression of TRPA1 in the sinusoidal endothelial lining and Kupffer cells, but not in hepatocytes [260]. Thus, if cinnamaldehyde effects are due to TRPA1 activation, this would occur via endothelial and/or Kupffer cells, and this is yet to be confirmed by future research.

So far, there is limited information on the expression of TRPC sub-family members in the liver [208,260]; however, the current data do not support a role for TRPC5 in the liver in MS. Nonetheless, TRPC5 was found to mediate cholestasis in mice, as TRPC5KOs protected against the disease once they presented attenuated liver enlargement, reduced hepatic bile acid and lipid

content, diminished liver enzymes, and decreased hepatic cholesterol, TG and phospholipid contents [261].

4.4. TRPs and Skeletal Muscle

The importance of the skeletal muscle to metabolic syndrome has been well docu- mented and discussed [262,263]. Skeletal muscle is considered the largest tissue of the body sensitive to insulin, and it is where most of the insulin-mediated glucose uptake by GLUT4 occurs [264]. This tissue is also a producer of myokines which include cytokines (IL-6), myostatin, myonectin, irisin, and musclin [265]. These are released during muscle contrac- tion, during exercise for example [266,267], and have endocrine and paracrine functions acting in other metabolic organs (liver, adipose tissue, and pancreas).

TRPV1 expression was first described in the rat skeletal muscle sarcoplasmic retic- ulum [202] and it was later confirmed in the human tissue as a target for endocannabi- noids [203]. The latter finding indicated that TRPV1 mediates the down-regulatory effects of these molecules on adiposity. This was supported by data from skeletal L6-cells in which the TRPV1 antagonist SB-366791 blocked the insulin-induced glucose uptake triggered by the endocannabinoid 2-arachidonoylglycerol [204].

In another study, functional TRPV1 was detected in mouse myocytes (C2C12 cells) and skeletal muscle [268]. Indeed, the in vitro incubation of capsaicin triggered Ca2+ in- flux, and increased glucose oxidation and ATP production in C2C12 cells; both responses were blocked by TRPV1 antagonists (5′-iodo-resiniferatoxin-α or SB-452533) [268,269]. Of note, glucose oxidation and ATP generation in C2C12 cells were suggested to happen independent of insulin [269]. In another report, capsaicin induced the up-regulation of TRPV1 and peroxisome proliferator-activated receptor-γ coactivator-1α (a regulator of lipid and glucose metabolism, mitochondrial biogenesis and muscle remodelling in my- ocytes, and enhanced mitochondrial biogenesis and ATP production in myotubes [268,270]. Analysis of the gastrocnemius muscle indicated that the myocytes of mice fed with z capsaicin-supplemented diet exhibited a similar phenotype to that observed in vitro [268]. In addition, the same study showed that capsaicin enhances exercise endurance whilst lowering the levels of blood lactic acid and TGs in WT but not TRPV1KO mice; similar data were gathered from mice over-expressing the receptor which also presented with greater numbers of oxidative muscle fibres. In another study, TRPV1KO mice fed HFD presented higher insulin resistance in WAT and BAT, but not in the skeletal muscle in comparison to WTs [219]. Overall, the results suggest that the activation of skeletal muscle-located TRPV1 contributes towards thermogenesis and enhanced insulin sensitivity; both responses are exacerbated by exercise.

Functional TRPA1 was identified in primary human myoblasts but became down-

regulated during differentiation to skeletal muscle cells [207]. Indeed, TRPA1 agonists such as allyl isothiocyanate induced Ca2+ currents in these cells that were blocked by the TRPA1 antagonists HC-030031 and A967079. The same study demonstrated that TRPA1 activation causes

myoblast migration and fusion, and suggested this receptor is an important sensor of muscle damage and inflammation and, therefore, contributes to muscle repair.

A functional role in the maintenance of skeletal muscle force during sustained repeated contractions was shown for TRPC1 [271]. TRPC1 activation also annuls the beneficial ef- fects of exercise on obesity-associated T2Din mice [233]. In addition, the activation of TRPC1/TRPC4 complexes is key to myogenesis and skeletal muscle differentiation [272]. On the other hand, the expression of TRPC5 and its function in the skeletal muscle is con- troversial. In fact, there is conflicting data on its expression on skeletal myoblasts [271,273]. Therefore, the possible roles of TRPC5 in MS via the skeletal muscle remain and deserve to be investigated.

4.5. Connecting Metabolic Tissues and the Central Nervous System

The CNS has an important role in the regulation of food intake and energy metabolism. After a meal, satiation signals are sent by the gastrointestinal tract to multiple centres in the CNS (hypothalamus and the brainstem), as well as adiposity signals about energy availability in the WAT. Then, humoral and neuronal outputs are sent from the CNS to the peripheral metabolic tissues in order to regulate energy metabolism. These aspects have been previously reviewed and discussed [274,275]. Herein, we present the current data that connect the CNS to the periphery in the regulation of energy metabolism via TRPs.

Evidence indicates that TPRV1 interacts with the CNS via appetite regulating hor- mones such as ghrelin (an orexigenic peptide found in the stomach [275], leptin, and the glucagon-like peptide-1 (GLP-1; an anorexigenic peptide hormone secreted by intestinal L-cells and pancreatic α-cells, and the brain [275–277]). Human data indicate that the acute TRPV1 activation increases GLP-1 and diminishes ghrelin levels in the plasma samples of individuals receiving a capsaicin-containing meal, as soon as 15 min after consumption, without altering energy expenditure [278]. Capsaicin effects on satiety are controversial with some studies indicating the compound reduces energy intake [279,280] and others showing no effects [278,281].

The stomach, especially the pyloric portion and duodenum, and the small and large intestines, express functional TRPA1 [282]. In the stomach, TRPA1 is expressed in ghrelin-producing cells. TRPA1 expression was also shown in the MGN3-1 cell line; this, when incubated with cinnamaldehyde, presents up-regulation of TRPA1 and insulin receptor mRNAs and reduced secretion of ghrelin. Cinnamaldehyde effects on ghrelin secretion were partially attenuated by TRPA1 antagonism with HC-030031. In vivo, the acute oral administration of cinnamaldehyde caused reduction in food intake in the initial 2h follow- ing treatment and delayed gastric emptying in WTs but not TRPA1KO mice. Repeated treatment with the compound did not affect food intake, but reduced body weights and fat mass, and improved insulin sensitivity in mice fed HDF [282]. The same mice presented increased expression of glucose transporters and of genes involved in fatty acid oxidation in WAT and BAT. TRPA1 involvement in ghrelin production was confirmed by another study in which intragastric β-eudesmol, an oxygenized sesquiterpene, increased food intake and plasma octanoyl ghrelin levels [283]. β-eudesmol also enhanced gastric vagal nerve

activity, a response diminished by different TRPA1 antagonists and deletion of TRPA1 receptor. Despite the conflicting results, the data show that TRPA1 regulates ghrelin secretion and food intake; however, the degree of regulation may depend on the TRPA1 agonist and the activated pathways.

Additionally, TRPV1 is functionally expressed on the intestinal cell line secretin tu-mour cell-1 (STC-1) and in mouse ileum samples known to produce GLP-1 [284]. In the intestinal cells, capsaicin stimulated the production of GLP-1 which was blocked by the TRPV1 antagonists capsazepine and 5′-iodo-resiniferatoxin-α. Intragastric capsaicin in- creased plasma GLP-1 levels following glucose challenge in WTs and in mice with T2D, a response impaired by treatment with 5′-iodo-resiniferatoxin-α or receptor ablation [284]. Hypothalamic pro-opiomelanocortin neurones are involved in food intake and express functional TRPV1 [205]. These neurones respond to GLP-1 release via the GLP-1 receptor, and are also the site of action of liraglutide, a GLP-1 analogue used in the treatment of T2D [285]. In a recent report, GLP-1 was suggested to activate TRPV1/TRPA1-dependent Ca2+ currents in GLP-1 receptor-expressing enteric neurones, and the subsequent release of substance P [286]. It is possible, therefore, that GLP-1 may elicit Ca2+ influx via TRPs in hypothalamic pro-opiomelanocortin neurones.

Mouse intestinal L cells and the small intestine express functional TRPA1, which responds to allyl isothiocyanate and polyunsaturated fatty acids in vitro [287]. Indeed, the Ca2+ currents elicited by these compounds were blocked by the TRPA1 agonist A-967079. Allyl isothiocyanate caused GLP-1 release from intestinal cells in a TRPA1-dependent manner, without altering glucose-induced secretion of GLP-1. GLP-1 secretion was abol- ished in TRPA1KO intestinal cells and in those treated with HC-033031 [288]. Additionally, TRPA1 was found to mediate AS1269574-induced GLP-1 production in intestinal cells (STC-1 cells) [288]. Noteworthy, AS1269574 is an agonist of G protein-coupled receptor 119 (GPR119), an important enteroendocrine sensor of dietary triglyceride metabolites ex- pressed in intestinal cells. Glucagon production triggered by AS1269574 though, is a direct result of GPR119 activation, with no involvement of TRPA1 [223]. The non-electrophilic small molecule GLP-1 secretagogue JWU-A021 produced TRPA1-dependent Ca2+ currents in STC-1 and primary intestinal cells, which were suppressed by the antagonists A967079 and HC030031 [223]. More recently, allicin, another dietary TRPA1 agonist, restored GLP-1 levels and insulin sensitivity in HFD-fed mice [289]. These data indicate that intestinal located TRPA1 mediates GLP-1 release.

Leptin activates its receptor on hypothalamic pro-opiomelanocortin neurones and causes the subsequent increase in the levels of the anorectic peptide α-melanocyte-stimulating hormone, whilst inhibiting neuropeptide Y (NPY) neurones [290–292]. High levels of this hormone are present in most obese subjects and animals [293,294]. This is suggested to be due to the necessity for high circulating levels of leptin to overcome resistance to its action and maintain energy homeostasis [295]. Leptin resistance and altered energy balance have been attributed to obesity in TRPV1-null mice fed HFD [219]. Treatment with leptin did not reduce food intake, and leptin-mediated hypothalamic signals were impaired in the TRPV1KO mice [219]. These animals were more obese and insulin-resistant than their counterparts. On the other hand, in another study, leptin

levels were raised in both TRPV1 WTs and KOs [173]. TRPV1 activation also enhanced the frequency of miniature excitatory synaptic currents in leptin receptor-containing neurones in stomach-associated brainstem dorsal motor nucleus of the vagus [296]. Evidence also indicates that TRPV1 receptor activity is diminished in the brainstem dorsal vagal complex of diabetic mice [297]. These data suggest that TRPV1 mediates the effects of leptin.

No reports have linked TRPA1 activation/expression to leptin signalling and its connection to the brain regions involved in hunger and energy expenditure. On the con- trary, TRPC5 has been indicated as an interesting target to regulating leptin responses. In fact, the neuronal deficiency of TRPC5 or its deletion in pro-opiomelanocortin neurones leads to obesity associated with decreased energy expenditure and higher food intake in mice [209]. The same study demonstrated that both leptin and serotonin 2C receptor- agonists exert their acute anorexigenic effects via TRPC5 activation. TRPC5 complexes also contribute to melanocortin neuronal activity, thus altering energy metabolism and feeding behaviour [209]. Moreover, the intracerebroventricular injection of insulin resulted in a similar response of energy expenditure via TRPC5 activation [298]. Both insulin and leptin were suggested to activate TRPC5 indirectly, following their binding to their specific receptors and downstream signalling (phosphatidylinositide-3 kinase and phospholipase Cγ activation) [298]. Since both TRPC1 and TRPC4 are functionally expressed in pro-opiomelanocortin neurones [298], it is possible that all TRPC5 complexes contribute to the metabolic responses mediated by these cells. The protective role of neuronal TRPC5 complexes in MS is supported by data obtained from studies on GLP-1 agonists and their effects on pro-opiomelanocortin neurones [210,211]. Indeed, both liraglutide and semaglu- tide actions on pro-opiomelanocortin neurones involve TRPC5 activation in vivo and in mouse hypothalamic slices. Of note, in the hippocampus, leptin-dependent responses do not require TRPC5 expression [299].

Interestingly, mitochondrial-derived ROS are produced by brain neuronal cells of different regions including the hypothalamus [300,301] and are involved in central glu- cose [302] and hypertriglyceridemia sensing [303]. Accordingly, H_2O_2 causes a marked increase in the firing of hypothalamic pro-opiomelanocortin neurones and decreased feed- ing in mice [304]. Considering the ability of TRP channels to sense this ROS, it is also possible they mediate ROS signalling in these neurones.

5. Clinical Perspectives

In addition to non-clinical studies, the beneficial effects of modulating TRPV1, TRPA1 and TRPC5 channels in obesity, T2D, atherosclerosis and MS have been investigated in a range of clinical trials.

In these, pungent and non-pungent activators of TRPV1 have been assessed. In a study, either 0.25% capsaicin or placebo were given to 24 subjects (12 men and 12 women) with body mass index (BMI) of 25.0, 30 min before meal. Oral capsaicin enhanced satiety and diminished calorie and fat intake [279]. In another report with 19 overweight to obese men, a supplement containing capsaicin increased energy expenditure in comparison to placebo [305]; these findings

were supported by further studies [306–310]. The use of capsaicin 1h prior to low intensity exercise was also shown to improve lipolysis in healthy volunteers [242]. Moreover, capsaicin from Capsicum frutescens had hypoglycaemic effects in healthy individuals [311]. Capsinoids are non-pungent capsaicin-related substances [312]. Individuals with BMI between 25.0 and 35.0 received capsinoid oil (6 mg/day) obtained from Capsicum anuum L. variety CH-19 Sweet or placebo, capsinoids decreased body weight whilst enhancing fat oxidation [313]. The same study found a correlation between reduction of abdominal fat and the genetic variants TRPV1 Val585Ile and UCP-2-866 G/A. Another capsinoid, dihydrocapsiate, caused a small thermogenic effect in healthy subjects [314]. Consumption of a supplement containing low dose capsinoids (2 mg) led to increased plasma levels of FFA [315]. Accordingly, C. anuum capsinoids increased energy expenditure by activating BAT in healthy subjects in comparison with the placebo group [316,317]. The above data indicate the potential of capsaicin to treat obesity and hyperglycaemia. On the other hand, although promising, the thermogenic effects of capsinoids are yet to be confirmed in further studies with overweight and obese individuals.

Cinnamaldehyde is a major compound found in cinnamon barks [318]. Several stud- ies have investigated the beneficial effects of cinnamon in T2D. In a study with 60 T2D subjects (30 woman and 30 men), intake of cinnamon capsules attenuated serum glucose, TG, total and low-density lipoprotein cholesterol [319]. In agreement, cinnamon extracts or supplements decreased plasma glucose levels and malondialdehyde concentrations, and improved lipid profile in overweight to obese individuals [320–323], and induced hypoglycaemia in T2D patients [324] and healthy subjects [325]. Conversely, cinnamon powder or supplement consumption did not alter plasma glucose or serum lipid profile in T2D patients [326,327]. A similar result was observed in postmenopausal patients with T2D [328] and healthy individuals [329]. Interestingly, cinnamon powder intake lowered blood pressure and glycated haemoglobin in patients with T2D [330]. Although the evi- dence gathered from these studies are controversial, they raise attention for further studies to support the potential use of cinnamon and derived compounds in the management of MS.

No clinical trials assessing the impact of TRPC5 in human MS have been published to date. Nonetheless, the use of TRPC4/TRPC5 inhibitors for cosmetic weight loss as well as to combat obesity, T2D, MS, NAFLD and non-alcoholic steatohepatitis was recently published (accession numbers: WO/2018/146485; EP3579838; US20200345741). Liraglutide and semaglutide antidiabetic actions in the hypothalamus require TRPC5, which indicates this channel is an interesting target for the development of novel therapies for MS.

Nonetheless, considering that MS is a complex disease, it is not surprising that other TRPs, in addition to TRPV1, TRPA1 and TRPC5, may influence the balance between oxida- tive stress and inflammation during disease progression. For instance, TRPM2 is another TRP activated by ROS (specifically, H_2O_2), which is involved in insulin resistance [213,331]. TRPM4 and TRPM5 expression were also described in human Langerhans islets, further indicating possible roles with clinical perspectives for MS [332]. Of note, TRPM2 expression is significantly enhanced during NAFLD, and its activation by ROS overproduced during the disease plays a significant role in

pathophysiology contributing to its progression [333]. Natural antioxidants such as saliroside (from Rhodiola rosea) and curcumin are both able to inhibit TRPM2 activation in hepatocytes, resulting in reduction of lipid deposition, dimin- ished expression of cytokines (IL-1β and IL-6) and protection against cell damage [333,334]. These are early findings and further research in the field is important and deserves to be pursued.

6. Conclusions

Most of the metabolic alterations comprised in MS are correlated with altered expres- sion of TRPs and are directly connected with the observed vascular dysfunction in T2D and obesity. Herein, the available information on the contribution of TRPV1, TRPA1 and TRPC5 to MS is discussed and summarized in Table 3.

TRP Channel	Endogenous Agonists	Expression Site	Role in MS
TRPV1	12 (*S*)-HPETE [118], 20-HETE [119], 9-HODE and 13-HODE [120], anandamide [121], H_2S [122], ROS (H_2O_2) [123]	Adipose tissue/adipocytes [124,125,200,201], liver [126,127], M1 macrophages [128], pancreatic β-cells/langerhans islets [132], coronary endothelial cells [123], T cells [129–131], skeletal muscle [202–204], pro-opiomelanocortin neurones [205]	Increase of insulin sensitivity [216,220,221], browning of WAT, reduction of lipid synthesis and obesity/adiposity [201,203,204,239], enhanced thermogenesis [240] and leptin sensitivity [219], reduction of lipid accumulation and TG [127], protection against endothelial dysfunction [253], increase of GLP-1 and attenuation of ghrelin production [278]
TRPA1	Methylglyoxal [138], 4-HNE, 15-deoxy-delta(12,14)-prosta-glandin J_2 (15d-PGJ_2) and H_2O_2 [139]	Pancreatic β-cells/langerhans islets [137,206], T cells [175–177], adipocytes [244,245], vagus nerve [246]	Macrophage-mediate responses in atherosclerosis [180,184], increase of insulin secretion [137,222–225] and sensitivity [228,258,259], reduction of insulin signalling and insulin-induced glucose uptake in skeletal muscle cells [229], weight loss and reduction of TG and cholesterol [244,247], attenuated adipogenesis [250], increased adipose tissue inflammation and ROS [248,250] reduction of ghrelin [282], production of ghrelin [288]
TRPC5	H_2O_2 [145], reduced TRX [146], and fatty acids [147]	Endothelial cells [166], T cells [185], M1 macrophages [186], pancreas [208], adipose tissue [147,200], pro-opiomelanocortin neurones [209–211]	Polarization of macrophages to M2 and protection against atherosclerosis [186], negative regulation of adiponectin [147], enhance of energy expenditure [209,298]

Overall, these channels are involved in the regulation of different pathways of MS, including hormone production, inflammation, and ROS generation at systemic levels and different metabolic tissues (adipose, pancreatic, hepatic and skeletal muscle), connecting those to the CNS. The different patterns of expression of these channels across tissues confer on them the ability to control a variety of cell functions. Non-clinical and clinical data clearly highlight the potential of ligands for these channels, especially natural compounds such as capsaicin/capsinoids and

cinnamaldehyde, to treating the various aspects of MS, from insulin resistance to atherosclerosis. Considering the multiple mechanisms underlying MS establishment and progression, it is possible that a combination of TRP ligands may confer better control of adiponectin release, ROS production, and inflammation in the disease. In this context, the dual roles of TRPs such as that of TRPA1 in atherosclerosis must be considered.

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ARTIGO 02

Analysis of the Effect of the TRPC4/TRPC5 Blocker, ML204, in Sucrose-Induced Metabolic Imbalance

Sugar-induced metabolic imbalances are a major health problem since an excessive con- sumption of saccharides has been linked to greater obesity rates at a global level. Sucrose, a disac- charide composed of 50% glucose and 50% fructose, is commonly used in the food industry and found in a range of fast, restaurant, and processed foods. Herein, we investigated the effects of a TRPC4/TRPC5 blocker, ML204, in the metabolic imbalances triggered by early exposure to sucrose- enriched diet in mice. TRPC4 and TRPC5 belong to the family of non-selective Ca+2 channels known as transient receptor potential channels. High-sucrose (HS)-fed animals with hyperglycaemia and dyslipidaemia, were accompanied by increased body mass index. mesenteric adipose tissue accumu- lation with larger diameter cells and hepatic steatosis in comparison to those fed normal diet. HS mice also exhibited enhanced adipose, liver, and pancreas TNFα and VEGF levels. ML204 exacerbated hyperglycaemia, dyslipidaemia, fat tissue deposition, hepatic steatosis, and adipose tissue and liver TNFα in HS-fed mice. Normal mice treated with the blocker had greater hepatic steatosis and adipose tissue cell numbers/diameter than those receiving vehicle, but showed no significant changes in tissue inflammation, glucose, and lipid levels. The results indicate that TRPC4/TRPC5 protect against the metabolic imbalances caused by HS ingestion.

Keywords: high sucrose intake; metabolic changes; fat deposition; hepatic steatosis; TRPC4 and TRPC5 channels

1. Introduction

The intake of high-content sugar foods and beverages from an early age has been linked to an increased risk of obesity, type II diabetes, and cardiovascular diseases, amongst other chronic pathological alterations [1–5]. Sucrose is a disaccharide composed of 50% glu- cose and 50% fructose commonly added to foods and drinks as a sweetener [6]. In humans, the long-term daily ingestion of sucrose has been linked to an increase in body weight, fat mass, hepatic steatosis, and cholesterol levels in overweight subjects [7,8]. In addition, studies with healthy- and normal-weight young male volunteers have demonstrated that high-sucrose (HS) diets augment glucose, low-density lipoprotein, and C-reactive protein quantities [9,10]. Similar observations have been made in rodents following HS diet [11–14]. This evidence demonstrates that HS causes important metabolic imbalances, which can result in chronic pathologies such as metabolic syndrome (MS), a major health problem which affects the global population at all ages [15,16].

Transient receptor potential channels are non-selective Ca+2 channels involved in a plethora of pathological and physiological roles [17–21]. First described in Drosophila melanogaster (for review see: [22–24]), it is now known that their expressions and acti- vation profiles on neuronal and non-neuronal cells can influence the protection against or the development of a range of chronic diseases in mammals, including pain [25,26], cardiovascular diseases [27,28], asthma [29,30], amongst others. Also, their contributions to MS have been explored within the last several decades, especially in regard to TRP vanilloid 1 (TRPV1) and TRP ankyrin 1 (TRPA1) channels [31,32]. On the other hand, information on the involvement of TRP canonical channels 4 (TRPC4) and 5 (TRPC5) in weight and metabolic regulations remains scarce and deserves further investigation. As TRPC4 and TRPC5 can form homo- and heterotetramers between themselves and also with TRPC1, their roles in metabolic homeostasis are rather complex and have been re-cently discussed [33]. Interestingly, TRPC4 activation was found to modulate insulin secretion by triggering pancreatic cell depolarisation and Ca2+ influx, and the disruption of TRPC1/TRPC5 signalling was demonstrated to result in an increased generation of adiponectin by adipocytes [34,35]. Recent studies have also demonstrated that the central actions of liraglutide and semaglutide, type II antidiabetic drugs associated with marked weight loss, on hypothalamic proopiomelanocortin (POMC) neurones require TRPC5 sig- nalling [36,37]. On the contrary, the use of TRPC4/TRPC5 inhibitors was requested for cosmetic weight loss and treatment of obesity, type II diabetes, MS, and hepatic steatosis (accession numbers: WO/2018/146485; EP3579838; US20200345741).

Herein, in order to obtain more information on the role of TRPC4 and TRPC5 in the metabolic alterations caused by HS diet, we used a dual TRPC4/TRPC5 blocker, ML204, and investigated its effects on body weight, hyperglycaemia, dyslipidaemia, fat tissue accumulation, and tissue inflammation, in comparison with mice fed a standard diet. The results indicate a protective role for TRPC4/TRPC5 against the metabolic imbalances caused by HS ingestion.

2. Results

2.1. High Sucrose Induces Increased Body Mass Index, Fat Accumulation, and Glycaemia

We initially investigated the effects of HS intake on body weight, BMI, fat mass, and glycaemia, parameters that are commonly affected by diet (for review see: [38,39]). Although only a modest increase in body weight at the 20th week was observed in animals fed HS diet in comparison with those receiving standard chow (Figure 1A; $p > 0.05$), HS ingestion led to a transient increase in BMI at the 4th week, which became sustained from the 18th week in comparison with animals receiving a standard diet (Figure 1B; $p < 0.05$). An analysis of the areas under the curves from the 18th to the 20th week demonstrated that there are no differences in body weight between groups ($p > 0.05$): 32.5 ± 9.8 (standard diet group) versus 34.7 ± 9.6 (HS diet group). In addition, an analysis of the areas under the curves from the week 18th to the 20th week confirmed the differences observed in Figure 1B between the BMIs of HS- and standard diet-fed mice as follows: 0.549 ± 0.02 (standard diet group) versus 0.653 ± 0.019 (HS diet group); $p < 0.05$. Hyperglycaemia was also noted from the 10th week in HS-fed mice (Figure 1D; $p < 0.05$) when compared to those receiving standard diet. On the other hand, Lee indexes were similar in those receiving either diets (Figure 1C; $p > 0.05$). The mesenteric fat was collected and weighed at the end of the 20th week as a measure of adipose tissue accumulation in the abdomen. HS diet-fed animals with a marked fat deposit increase in comparison to those receiving standard diet showed the following mean ± SEM values: 10.8 + 1.9 (standard diet group) versus 24.3 ± 1.8 mg of fat/g of body weight (HS diet group; $p < 0.05$).

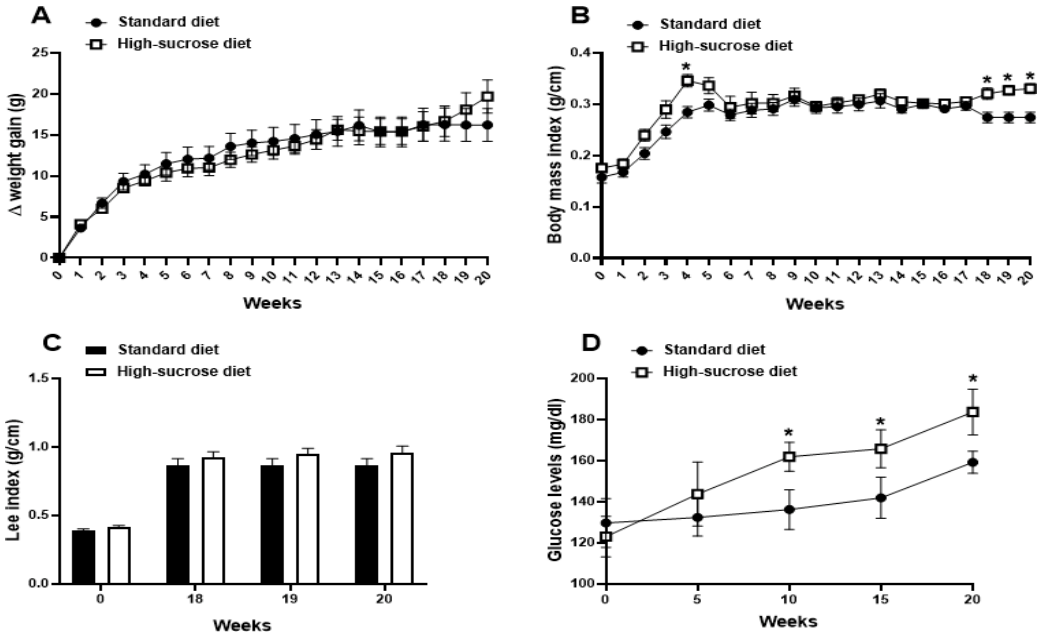

Figure 1. Effects of high-sucrose (HS) diet on body weight, body mass (BMI), and Lee indexes, and glycaemia. Animals received either HS or standard diet for 20 weeks (n = 6/group). Body weight gain (A) and BMI (B) were registered once a week. Lee index (C) was measured once a week from the 18th week, and blood glucose levels (D) were recorded at every 5 weeks. Glucose was measured in non-fasted animals. * $p < 0.05$, differs from the standard diet group.

2.2. ML204 Regulates Circulating Glucose and Lipid Levels

In order to assess the involvement of TRPC4/TRPC5 in the metabolic changes caused by a high sugar diet, animals receiving a standard or HS diet were treated with either ML204 or vehicle. Figure 2 depicts the effects of ML204 on HS- and standard diet-fed mice. Repeated treatment with ML204 did not affect body weight gain, nor body mass (BMI) and Lee indexes in animals fed any of the diets (Figure 2A–C; $p > 0.05$). In contrast, ML204 further increased hyperglycaemia and impaired glucose tolerance in HS-fed mice (Figure 2D,E; $p < 0.05$). Of notice, ML204 also induced an elevation of blood glucose and caused glucose intolerance in those receiving a standard diet (Figure 2D,E; $p < 0.05$).

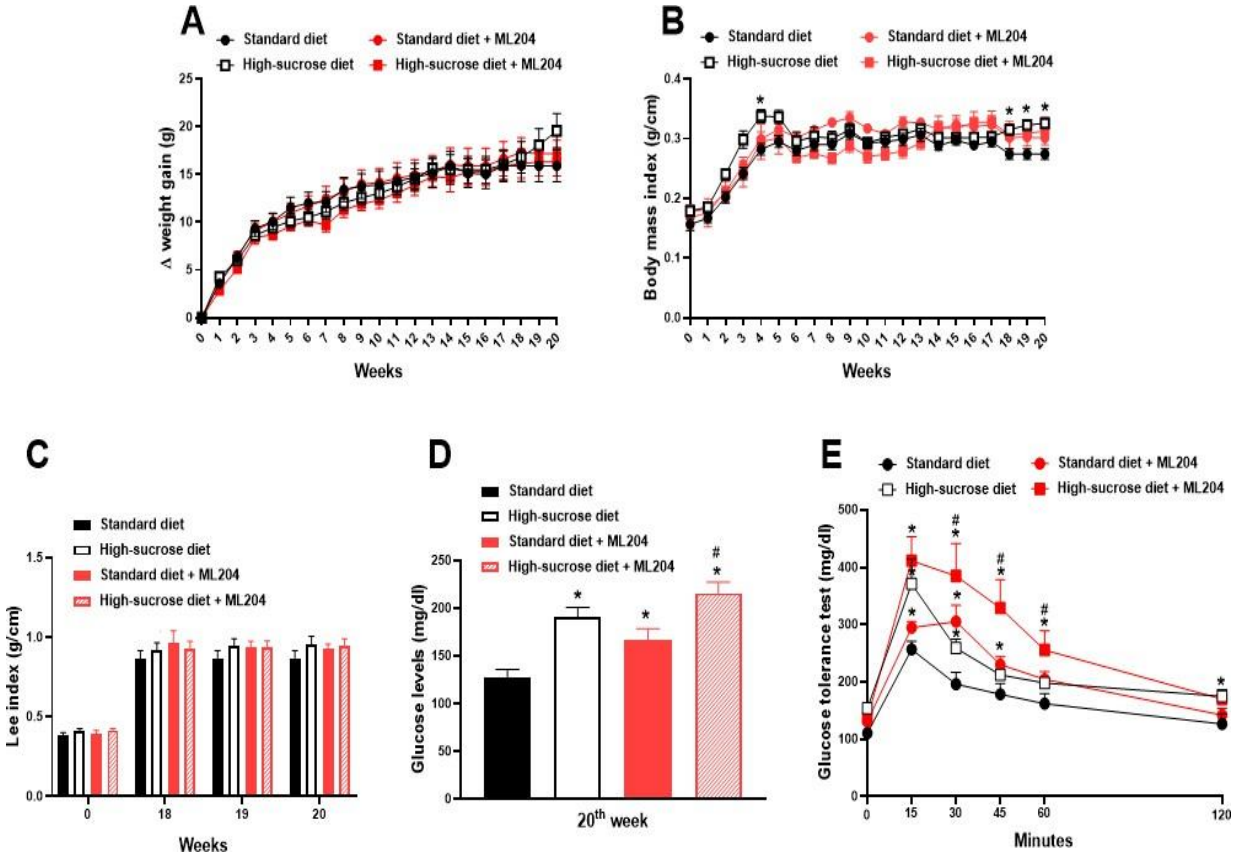

Figure 2. Repeated ML204 treatment increases blood glucose levels and impairs glucose tolerance. Animals received either a high-sucrose or standard diet for 20 weeks (n = 8/group). Body weight gain (A) and body mass index (BMI; (B)) were registered once a week. Lee index (C) was measured once a week from the 18th week. Blood glucose levels (D) were recorded at every 5 weeks and a glucose tolerance test (E) was performed at the 20th week. Glucose and glucose tolerance were measured in non-fasted and fasted animals, respectively. ML204 (2 mg/kg) or vehicle (3% dimethyl sulfoxide (DMSO) in phosphate-buffered saline (PBS)) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. * $p < 0.05$, differs from the standard diet group; # $p < 0.05$, differs from the high-sucrose diet control group.

Interestingly, ML204 did not alter triglyceride or cholesterol levels and neither the amount of mesenteric fat in standard diet-fed mice (Figure 3A,B; $p > 0.05$). Conversely, it caused hypertriglyceridaemia and exacerbated hypercholesterolemia in animals fed HS diet (Figure 3A,B; $p < 0.05$).

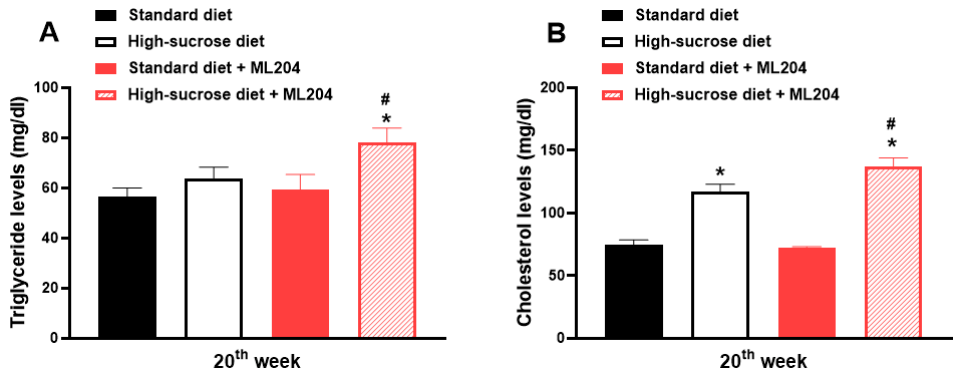

Figure 3. Repeated ML204 treatment causes hypertriglyceridaemia and exacerbates hypercholes- terolemia in animals fed a high-sucrose (HS) diet. Animals received either HS or standard diet for 20 weeks (n = 8/group). Triglyceride (**A**) and total cholesterol (**B**) levels were measured at the end of the 20th week. ML204 (2 mg/kg) or vehicle (3% DMSO in PBS) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. * $p < 0.05$, differs from the standard diet group; # $p < 0.05$, differs from the high-sucrose diet control group.

2.3. ML204 Increases High-Sucrose-Induced Adipose Tissue and Liver Inflammation by Modulating TNFα Production

Inflammation is an important event that contributes to metabolic imbalances; thus, tumour necrosis factor α (TNFα) and vascular endothelial growth factor (VEGF) levels (inflammatory mediators involved in obesity and glycaemia control (for review see: [33,40])) were evaluated in adipose tissue, liver, and pancreas samples obtained from animals fed either a standard or HS diet. HS diet-fed mice led to a greater release of these inflammatory mediators in adipose tissue and liver samples in comparison with those receiving standard diet, an effect which was further enhanced by ML204 injection (Figure 4A–D; $p < 0.05$). No differences were observed in regard to the pancreas levels of TNFα and VEGF between diets (standard diet versus HS diet) or

treatments (vehicle versus ML204) (Figure 4E,F); $p > 0.05$.

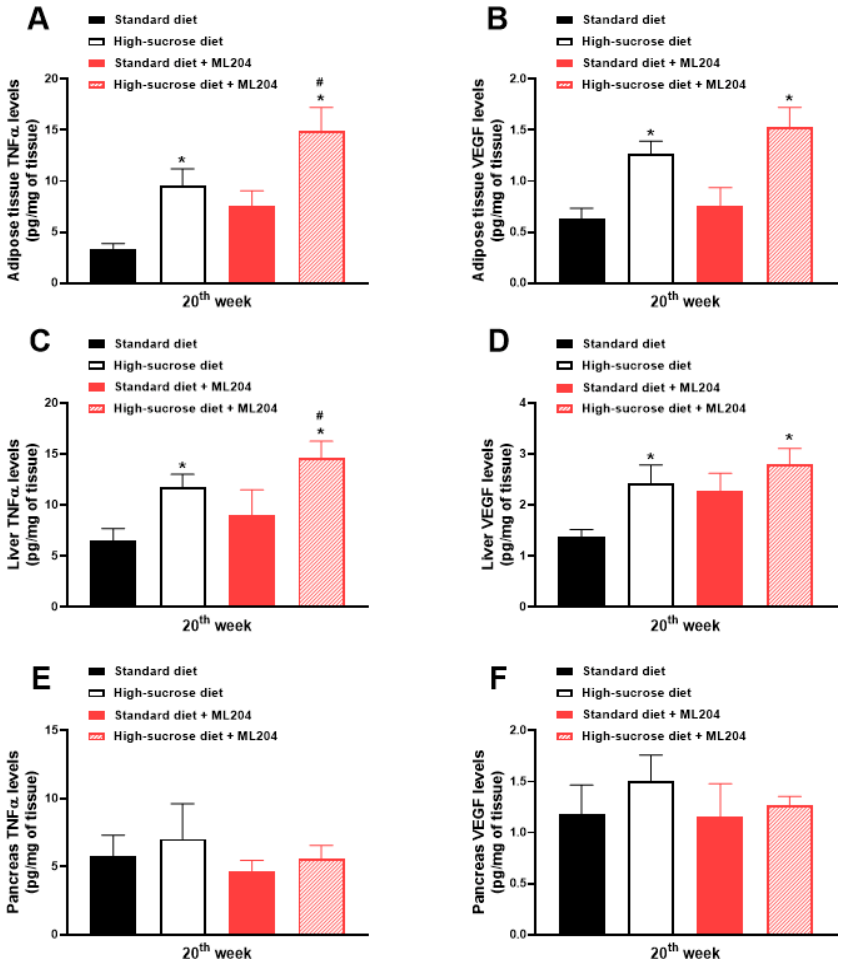

Figure 4. Repeated ML204 treatment enhances inflammation in the adipose and liver tissues of animals fed a high-sucrose (HS) diet. Animals received either HS or standard diet for 20 weeks (n = 8/group). TNFα was measured in (A) adipose tissue, (C) liver, and (E) pancreas. Adipose (B), liver (D), and pancreas (F) VEGF tissue levels. Samples were collected at the end of the 20th week. ML204 (2 mg/kg) or vehicle (3% DMSO in PBS) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. * $p < 0.05$, differs from the standard diet group; # $p < 0.05$, differs from the high-sucrose diet control group.

2.4. ML204 Enhances Adipocyte Area and Mesenteric Fat Accumulation in High-Sucrose-Fed Mice and the Size of Adipocytes in Those Receiving Standard Diet

The analysis of the mesenteric adipose tissue (Figure 5A–D; $p < 0.05$) indicates a greater fat accumulation in animals fed HS diet. The mice receiving HS diet presented with higher fat-to-body weight ratios, as well as with larger adipocyte areas and sizes (>50–100 μm) than those that received standard diet; $p < 0.05$. ML204 administration further enhanced fat weight and adipocyte area in HS-fed mice without affecting the size of their adipocytes (Figure 5B–D; $p < 0.05$). Interestingly, although no effects were observed for ML204 in regard to the fat weight and adipocyte areas of mice fed standard diet, the same animals presented a significant percentage of medium-sized cells (30–40 μm; $p < 0.05$) in comparison with vehicle controls.

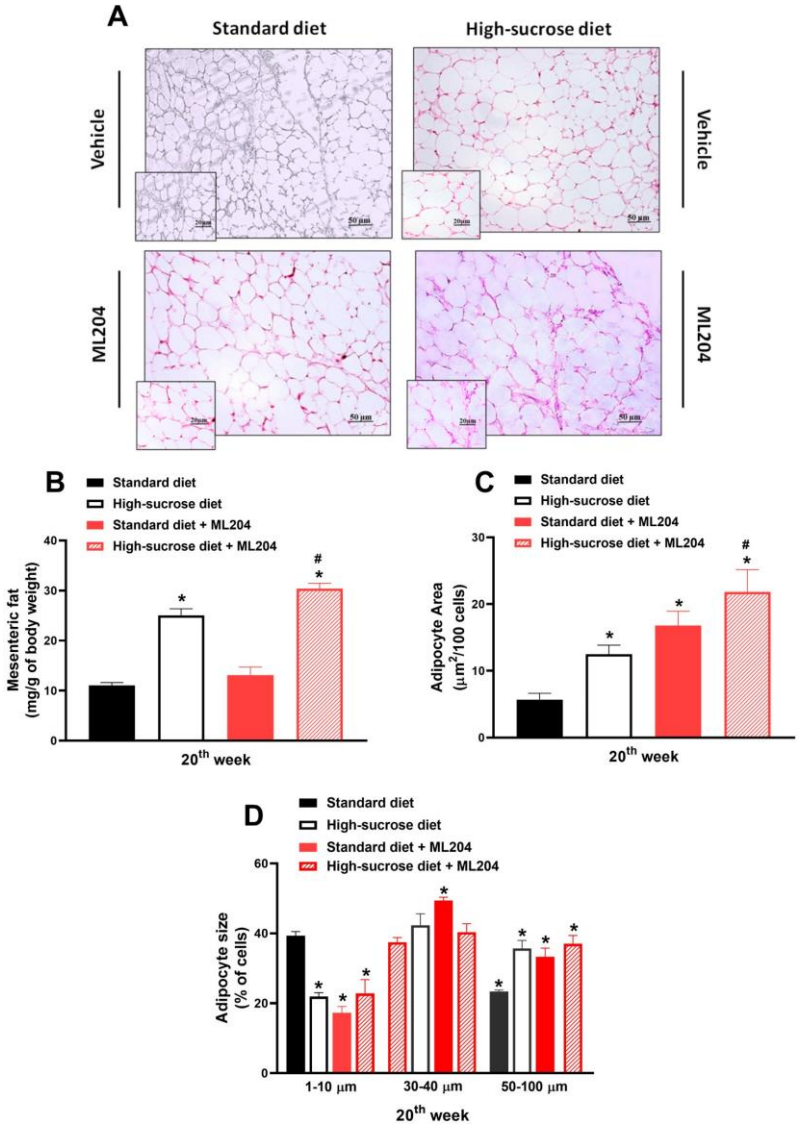

Figure 5. Repeated ML204 treatment causes fat accumulation in animals fed high-sucrose (HS) diet and the size of adipocytes in those receiving standard diet. (A) Representative H&E histology sections of adipose tissue (20 and 50 µm areas) from animals fed either HS or standard diet for 20 weeks (n = 8/group). Mesenteric fat/body weight ratios (B), adipocyte area (C), and size (D) measured at the end of the 20th week. ML204 (2 mg/kg) or vehicle (3% DMSO in PBS) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. Samples were stained by haematoxylin and eosin (H&E). * $p < 0.05$, differs from the standard diet group; # $p < 0.05$, differs from the high-sucrose diet control group.

2.5. Non-Alcoholic Fatty Liver Disease Activity Score Is Enhanced by ML204 in High-Sucrose-Fed Mice

We next investigated the effects of ML204 on non-alcoholic fatty liver disease NAFLD activity score (NAS). Figure 6A–C show that HS diet increases NAS by causing hepatic steatosis (red arrows), ballooning (orange arrows), and inflammatory cell influx (dark green arrows) to the tissue; $p < 0.05$. In a much lesser degree, ballooning and cell migration, but not steatosis are noted in standard-diet animals treated with ML204 (Figure 6; $p < 0.05$).

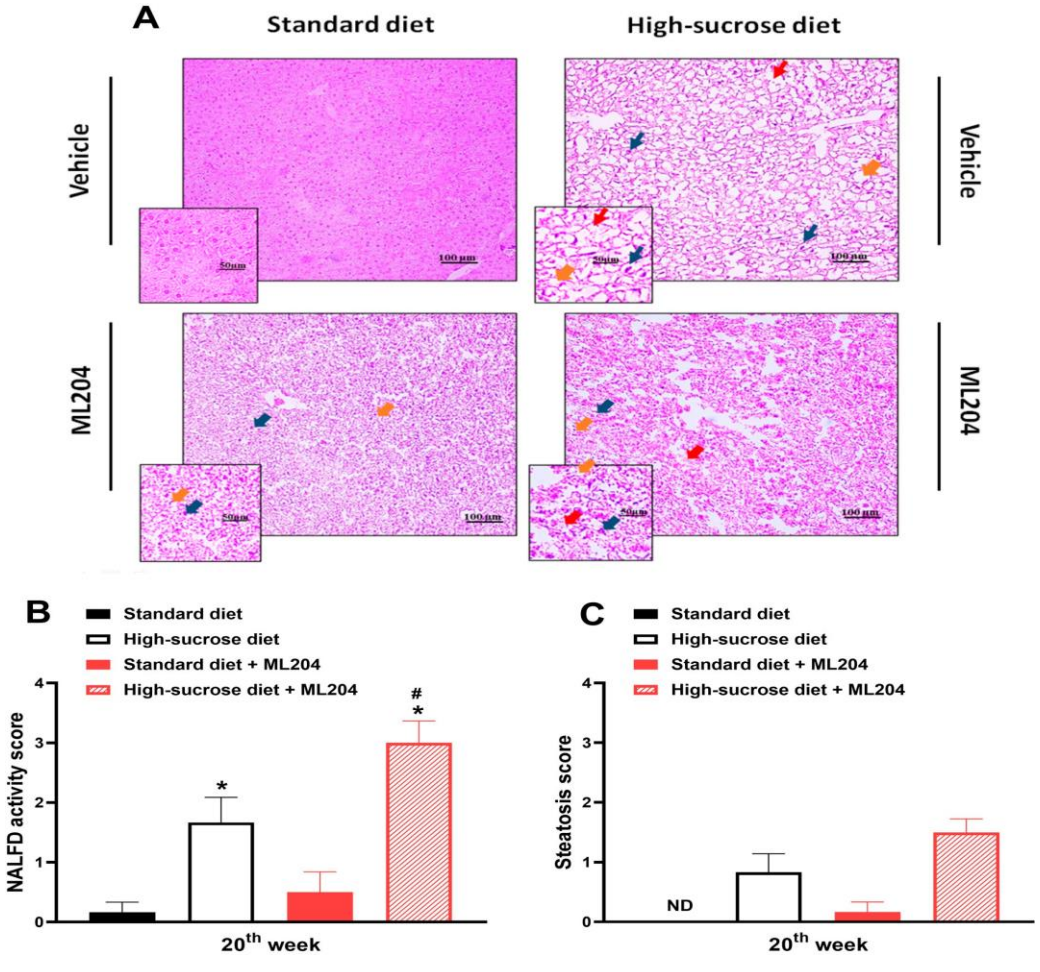

Figure 6. Repeated ML204 treatment increases non-alcoholic fatty liver disease (NALFD) activity score (NAS) in high-sucrose (HS)-fed mice. (A) Representative H&E histology sections of liver (50 and 100 µm areas) from animals fed either HS or standard diet for 20 weeks (n = 8/group). NAS (B) and steatosis score (C) were measured at the end of the 20th week. ML204 (2 mg/kg) or vehicle (3% DMSO in PBS) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. NAS was determined by the summation of hepatic steatosis (red arrows), ballooning (orange arrows), and inflammatory cell influx (dark green arrows) scores. Samples were stained by haematoxylin and eosin (H&E). * $p < 0.05$, differs from the standard diet group; # $p < 0.05$, differs from the high-sucrose diet control group.

3. Discussion

In the last several decades, foods and beverages containing high sugar levels became popular products found in the shelves of houses, restaurants, bars, and supermarkets all around the world. Diets rich in such products are now well-known to increase the risk for chronic diseases associated with metabolic imbalances, including obesity [38,41,42]), type II diabetes [42], and cardiovascular diseases [43], amongst other chronic pathological alterations, indicating that HS diets cause important metabolic changes, which can result in MS. This is particularly important considering the early age intake of HS [1–5]. Indeed, a recent analysis of the global scenario demonstrated that nearly 3% of children and 5% of the adolescent population present with MS [16]. Also, a drastic panorama has been noted in the adult population, with a 19.5% and 48.6% prevalence of MS amongst 20–39 year olds and those ≥60 years, respectively [15].

Herein, as expected [44–48], HS diet promoted a modest weight gain. Also in agree- ment, HS significantly increased BMI, hyperglycaemia, mesenteric fat deposition, glucose tolerance, hypercholesterolemia, and NAS score in comparison with mice receiving a stan- dard diet. In addition, HS-fed mice presented with adipose tissue and liver inflammation characterised by increased levels of TNFα, a cytokine involved in adipocyte hypertrophy, fat deposition, insulin resistance, and hyperglycaemia (for review see: [33]). Higher VEGF levels were also noted in both liver and adipose tissue samples from HS mice. Of note, VEGF production in the adipose tissue is suggested to play a protective role against hy- poxia, insulin resistance, and obesity, being an essential growth factor in the maintenance of metabolism homeostasis [49,50].

We show for the first time that when repeatedly administered to mice, ML204 ex- acerbates hyperglycaemia, dyslipidaemia, fat tissue deposition, hepatic steatosis, and adipose tissue and liver inflammation in HS-fed mice. The compound also affected normal mice, promoting hepatic steatosis and increasing adipose tissue cell numbers and diameter without causing tissue inflammation, or changing glucose and lipid levels.

We used a dual TRPC4/TRPC5 blocker, ML204, to further understand the roles of TRPC4 and TRPC5 in the metabolic alterations caused by HS diet. ML204 was first de- scribed as a potent and selective TRPC4/TRPC5 inhibitor in vitro [51,52]. Since then, accumulating evidence has demonstrated its ability to modulate inflammatory responses by regulating cytokine (TNFα, IL-1β, IL-6, and IL-10) production in vivo and in vitro, although reductions in or upregulations of these proteins seem to depend on the model used [53–55]. Importantly, inflammation, alongside oxidative stress (events in which these channels are shown to modulate) in metabolic tissues, are

important mechanisms of glucose and lipid imbalances, which can ultimately contribute to MS development and progression (for review see: [33]).

Knowledge from the last several decades has consistently pointed to the importance of TRP channels such as TRPV1 and TRPA1 in MS [31,32]. However, only recently, an emerging and complex role has been attributed to TRPC channels, especially TRPC5. This is mainly due to its ability to form not only homotetrameric, but also heterotetrameric complexes with other TRP channels (TRPC4 and TRPC1; for review see: [33]).

In this context, it is important to consider the contributions of both homo- and het- erotetramers containing TRPC5 in the regulation of metabolism. Whilst TRPC4 activation was shown to modulate insulin secretion, and TRPC1/TRPC5 signalling was suggested to regulate adiponectin release by adipocytes [34,35], TRPC4/TRPC5 inhibitors were re- cently patented for use in weight loss, type II diabetes, MS, and hepatic steatosis (accession numbers: WO/2018/146485; EP3579838; US20200345741). Also, TRPC5 was suggested as a key mediator for the central effects of the glucagon-like peptide-1 (GLP-1) receptor ago- nists liraglutide and semaglutide [34,35], used for type II diabetes and weight loss [56,57]. The above pieces of evidence indicate that TRPC5 contributions to metabolic homeostasis may require both central and peripheral actions, and depend on the tetramer activation. Nonetheless, the results clearly indicate that TRPC4/TRPC5 channels protect against the metabolic imbalances caused by HS ingestion.

4. Materials and Methods

4.1. Animals

Inbred male and female C57BL/6 mice (3 weeks old) from the Biological Service Unit of Universidade CEUMA were used. All the animals were housed under 12 h light/dark cycle, at a controlled environmental temperature (21 ± 2 ◦C) and humidity (60 ± 5%). All the experimental groups were matched for gender and body weight. All experiments followed the recommendations of the Brazilian guidelines on animal experimentation of the National Council for the Control of Animal Experimentation (CONCEA) and the ARRIVE guidelines [58]. All procedures were previously approved by the Animal Use Ethics Committee of Universidade CEUMA (protocol no 00081/18).

4.2. High-Sucrose-Induced Metabolic Disturbances

A total of 22 female and 22 male mice were used in the study. In order to standardise the model, mice received either normal or HS diet (3 male and 3 female mice/group), as previously described [59]. Either standard (Nuvital®, Nuvilab; Curitiba; Brazil; 3.52 kcal/g; composed of 55.4% carbohydrate (10% sucrose), 21% protein, and 5.2% lipids) or HS diet (3.48 kcal/g; composed of 65% carbohydrate (25% sucrose), 12.3% protein, and 4.3% lipids) was fed to the mice for 20 weeks. Both water and food were provided ad libitum. Body weights and body mass

indexes (BMI; body weight (g)/ nose-to-anus length (cm)) were registered for each mouse prior to and at every week, once a week post-diet. Analyses of AUCs were performed for body weight changes and BMIs between weeks 18 and 20. In parallel, the Lee index ($\sqrt[3]{}$body weight (g)/nose-to-anus length (cm) × 1000) [59]) was analysed at the 18th, 19th, and 20th weeks post-diet. Glycaemia was measured at baseline and at every five weeks from blood samples collected from the tail veils of restrained non- fasted animals by using a portable glucose meter and glucose strips (Accu-Chek Active®, Roche, Indianapolis, IN, USA).

To evaluate the effects of ML204, standard- and HS diet-fed mice received either vehicle (3% DMSO in PBS; v/v) or ML204 (2 mg/kg), subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. Body weights, body mass, and Lee indexes were measured at baseline, prior to and after ML204 treatment (between the 18th and 20th weeks), and evaluated as described above. Also, at the end of the 20th week, following 8 h of fasting, a glucose tolerance test was performed. Just before fasting, blood glucose levels were tested. Then, the animals were anaesthetised with ketamine and xylazine (75 mg/kg and 1 mg/kg, respectively). Blood samples were collected by cardiac puncture for analysis of the circulating quantities of triglyceride and cholesterol. Liver, mesenteric adipose, and pancreas tissue samples were collected for histology and inflammatory mediator production analysis (TNFα and VEGF).

4.3. Glucose Tolerance Test

For analysis of glucose tolerance, baseline blood glucose was measured in fasted mice. Then, animals received an intraperitoneal injection of glucose (2 g/kg; [60]). Next, glycaemia was measured from blood samples collected from the tail veil of restrained mice at 15, 30, 45, 60, and 120 min post-glucose administration in comparison to baseline by using a portable glucose meter and glucose strips (Accu-Chek Active®, Roche, Indianapolis, IN, USA).

4.4. Cholesterol and Triglyceride Quantifications

The blood collected at the end of the 20th week post-diet was centrifuged at 1300× g for 15 min, for serum separation. Serum levels of cholesterol and triglyceride were measured by using commercial kits according to manufacturer's instructions (Labtest, MG, Brazil). For this, 10 µL of the serum was used per reaction for each assay in duplicate. Samples were incubated at 37 ◦C for 10 min and then, the absorbances were read at 500 nm. The results are expressed as milligram per decilitre (mg/dL) of cholesterol or triglyceride.

4.5. TNFα and VEGF Tissue Levels

Approximately 100 mg of tissue was homogenised in 500 µL of PBS containing protease inhibitors (cOmplete™, EDTA-free Protease Inhibitor Cocktail; Sigma-Aldrich; São Paulo;

Brazil), by using a tissue lyser (6 cycles of 30 s each, 4000 r.p.m.; between cycles, samples were kept on ice for 20 s; TissueLyser LT; Qiagen; São Paulo, SP, Brazil). The homogenates were centrifuged at 1000 r.p.m., for 10 min, at 4 ◦C and the supernatants collected and used for the measurements of TNFα and VEGF in adipose tissue, liver, and pancreas samples by using pre-coated plates, as per the manufacturer´s protocol (Sigma-Aldrich; São Paulo, SP, Brazil). Protein content of each supernatant was determined by using BCA protein kit, according to manufacturer´s instructions (Sigma-Aldrich; São Paulo, SP, Brazil). For this, 100 µL per well of the supernatants was used for each assay in duplicate. Absorbances for each sample were compared to those of a standard curve of each inflammatory mediator. The results are expressed as picograms of sample per milligram (pg/mg) of tissue.

4.6. Histology

Portions of the liver and mesenteric adipose tissues were collected, washed in PBS, and infused with 10% formalin in PBS for 24 h. Then, the samples were embedded in paraffin for cutting. Tissue samples were deparaffinised in xylene followed by dehydration in a graded series of ethanol/water. Serial 10 µm (adipose tissue) and 5 µm (liver) sagittal sections were cut on a microtome. Samples were stained with haematoxylin and eosin (H&E) to allow for the observation of the general morphology of tissues by microscopy (Nikon Eclipse Ci-L; Nikon, Biolab; São Paulo; Brazil).

Two independent observers blinded to treatments scored the liver sections for steatosis (score 0–3), hepatocyte ballooning (score 0–2), and inflammation (score 0–3), according to NAS, and were modified [14]. The maximum possible score was 8, and the results are expressed as the mean of the scores attributed by each observer.

Four pictures from separate parts of each section of adipose tissue were taken. Then, the area of 100 cells was measured (ImageJ; bundled with Zulu OpenJDK 13.0.6.; Madison, WI, USA) and the percentage (%) of the different cell sizes was calculated [45]. All counts were performed by two different observers blinded to treatments.

4.7. Statistical Analysis

The results are presented as mean ± mean standard error (SEM). For multiple sta- tistical comparisons between groups, data were analysed by repeated measures analysis of variance (ANOVA), or one-way ANOVA, followed by the Bonferroni test with FDR correction. Unpaired t tests were used when appropriate. Histology scores were analysed using Kruskal–Wallis test followed by Dunn's test for multiple comparisons. All data were analysed in GraphPad Prism 6.0. (now Dotmatics; Woburn, MA, USA); $p < 0.05$ was considered significant. All n numbers are indicated on the graphs.

5. Conclusions

Although we were not able to dissect the expression sites in which activated TRPC4 and TRPC5 can influence metabolism changes, the data presented herein clearly demon- strated the importance of TRPC4/TRPC5 as protective channels against the metabolic imbalances caused by HS diet and highlights the need for further investigations in the field. Considering the complex roles of TRPC4 and TRPC5 either as homotetramers or heterotetramers, as well as of other heterotetramers formed between TRPC5 and TRPC1, for example, it is essential to highlight that the interpretation of data obtained from the use of TRPC5 activators, blockers, or genetically modified animals must always take into account such receptor interactions.

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CONCLUSÃO

O TRPC5 é um importante alvo farmacológico, devido vários estudos já evidenciaram esse receptor como um importante regulador da inflamação, dor, depressão e do gasto energético. Ainda, é atualmente conhecido como um alvo farmacológico adicional da rosiglitazona, um anti-diabético utilizado no tratamento da DMT2, bem como das ações da liraglutida e da semaglutida, medicamentos utilizados no tratamento da DMT2, neurônios pró-opiomelanocortina que também envolvem a ativação do TRPC5.

Embora o presente trabalho não tenha sido capaz de determinar os locais de expressão nos quais TRPC4 e TRPC5 podem influenciar alterações metabólicas, os dados aqui apresentados demonstram claramente a importância destes canais na proteção contra os desequilíbrios metabólicos causados pela dieta rica em sacarose e destacam a necessidade de mais investigações no campo. Considerando os papéis complexos de TRPC4 e TRPC5 como homotetrâmeros ou heterotetrâmeros, bem como de outros heterotetrâmeros formados entre TRPC5 e TRPC1, por exemplo, é fundamental destacar que a interpretação dos dados obtidos do uso de ativadores, bloqueadores de TRPC5 ou animais geneticamente modificados deve sempre levar em consideração conta tais interações com os receptores.

Sendo assim, os achados do presente trabalho servem como ponto de partida para estudos mais específicos, podendo contribuir no desenvolvimento de novos alvos terapêuticos capazes de tratar ou prevenir o desenvolvimento da SM, como o uso de agonistas mais específicos para o receptor TRPC5. Nesse contexto, novos estudos são necessários, uma vez que a ausência de sinalização via TRPC5 pode agravar infecções e seus efeitos anorexígenos ainda não são bem elucidados.

ANEXOS

ANEXO A

ARTIGO 1: An Overview of the TRP-Oxidative Stress Axis in Metabolic Syndrome: Insights for Novel Therapeutic Approaches

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Review

An Overview of the TRP-Oxidative Stress Axis in Metabolic Syndrome: Insights for Novel Therapeutic Approaches

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Abstract: Metabolic syndrome (MS) is a complex pathology characterized by visceral adiposity, insulin resistance, arterial hypertension, and dyslipidaemia. It has become a global epidemic associated with increased consumption of high-calorie, low-fibre food and sedentary habits. Some of its underlying mechanisms have been identified, with hypoadiponectinemia, inflammation and oxidative stress as important factors for MS establishment and progression. Alterations in adipokine levels may favour glucotoxicity and lipotoxicity which, in turn, contribute to inflammation and cellular stress responses within the adipose, pancreatic and liver tissues, in addition to hepatic steatosis. The multiple mechanisms of MS make its clinical management difficult, involving both non-pharmacological and pharmacological interventions. Transient receptor potential (TRP) channels are non-selective calcium channels involved in a plethora of physiological events, including energy balance, inflammation and oxidative stress. Evidence from animal models of disease has contributed to identify their specific contributions to MS and may help to tailor clinical trials for the disease. In this context, the oxidative stress sensors TRPV1, TRPA1 and TRPC5, play major roles in regulating inflammatory responses, thermogenesis and energy expenditure. Here, the interplay between these TRP channels and oxidative stress in MS is discussed in the light of novel therapies to treat this syndrome.

Keywords: TRP channels; metabolic syndrome; energy metabolism; hypoadiponectinemia; reactive oxygen species; inflammation

1. Introduction

Metabolic syndrome (MS) is a complex pathology characterized by visceral adiposity, insulin resistance, arterial hypertension, and dyslipidaemia [1]. MS presents significant morbidity and mortality as it strongly increases the risk of developing different diseases, such as those affecting the cardiovascular system and type 2 diabetes (T2D) [2]. Its management is primarily aimed at reducing the risk for cardiovascular diseases (CVDs) and T2D, and includes lifestyle modifications and multiple drugs [3,4].

Abdominal obesity, insulin resistance and sedentary life-styles are major risk factors for MS [1]. These increase with ageing, by taking medicines which increase weight gain, by mitochondrial and endocrine dysfunctions, and genetic predisposition [3]. Although not

the focus of the current review, the later findings on the genetic basis of MS have greatly contributed to further understanding the different underlying mechanisms and phenotypes of MS [5–7].

Energy metabolism is influenced by an intricate network of molecules released and receptors expressed within metabolic organs such as the pancreas, liver, adipose tissue and skeletal muscle, connecting the periphery to the brain (Figure 1). Hypoadiponectinemia, inflammation and oxidative stress [8–12] account for some of the mechanisms involved in MS establishment and progression, with a clear interplay between them. Different pathways are suggested to modulate these mechanisms. In this context, members of the transient receptor potential (TRP) family of non-selective Ca^{2+} channels may play an important role in MS by regulating inflammatory responses, thermogenesis and energy expenditure [13–16]. Herein, we discuss the mechanisms of MS and the roles of TRPV1, TRPA1 and TRPC5, known as oxidative stress sensors and regulators of inflammation, in MS. We also present the clinical perspectives of targeting these receptors for MS management.

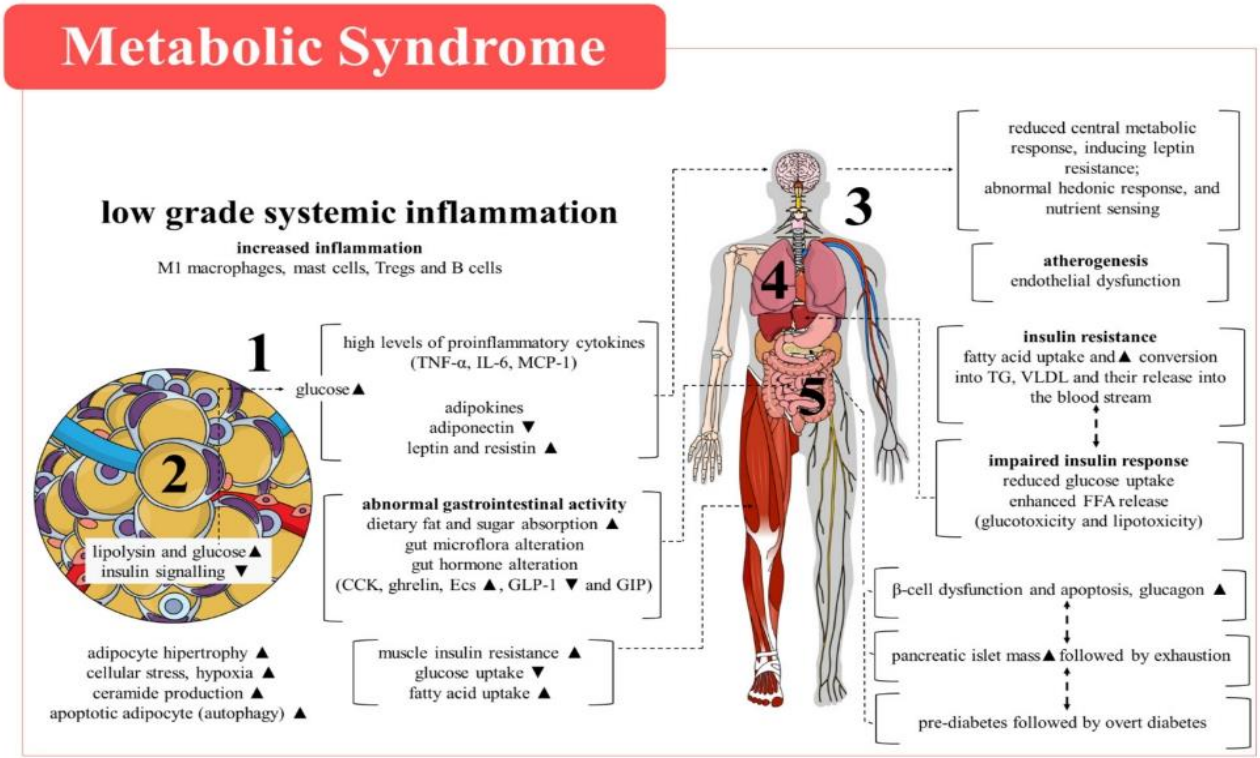

Figure 1. Mechanisms of metabolic syndrome (MS) pathophysiology. MS is a result of a metabolic imbalance which involves alterations in different tissues and a variety of molecules. (1) Insulin resistance is accompanied by (2) a low-grade inflammation in the adipose tissue characterized by reduction of adipokines such as adiponectin, enhanced levels of leptin and resistin, accumulation of inflammatory cells in the adipose tissue, paralleled with high levels of cytokines/chemokines and reactive oxygen species. Alterations of the central (hypothalamus and the brainstem) and peripheral mechanisms of hunger and satiety occur (3). All these events contribute towards (4) decreased energy expenditure, hyperglycaemia and dyslipidaemia, increasing the risk for type 2 diabetes and cardiovascular diseases. Nutrient absorption (5) and the gut microbiota play key roles in the modulation of MS, aiding the connection between the brain and metabolic tissues. TG—triglycerides; VLDL—very low-density lipoprotein; CCK—cholecystokinin; Ecs—estrogens; GLP-1—glucagon-like peptide-1; GIP—gastric inhibitor peptide; TNFα—tumour necrosis factor α; IL-6—interleukin-6; MCP-1—macrophage chemotatic protein-1.

2. Adiponectin Dysregulation, Oxidative Stress and Inflammation as Mechanisms of Metabolic Syndrome

2.1. Adiponectin Dysregulation

Adiponectin is an adipokine secreted by adipocytes, first described in 1995 [17]. Although adiponectin functions were unknown at that time, by using mouse cells, this report was the first to demonstrate the existence of a link between insulin secretion, adipocyte differentiation and adiponectin release, and to suggest a role for this adipokine in the regulation of carbohydrate and lipid metabolism. In 1996, the human adiponectin was described in two different studies, which showed its presence in human adipose tissue and plasma samples [18,19].

In the last decades, it has become clear that adiponectin is an essential regulator of glucose and lipid metabolism and a great influencer of the risk for developing obesity, T2D, CVD and, therefore, for MS.

It is now known that adiponectin forms complexes of different molecular weights. Of note, the one of high molecular weight (HMW) was shown to be the most potent in reducing serum glucose levels in mice [20]. The same study demonstrated that the HMW complex is reduced in obese diabetic mice and that it becomes increased in both T2D mice and patients following treatment with rosiglitazone—a PPARγ agonist. Later, adiponectin-induced hypoglycaemia was found to be independent of insulin levels [21,22] but was able to improve insulin sensitivity [23]. Soon after, it was shown that adiponectin crosses the blood-brain barrier and induces the hypothalamic expression of the anorexigenic corticotrophin-releasing hormone (CRH), leading to weight loss and enhanced energy expenditure [23,24].

Adiponectin multimers can be cleaved in a fragment containing the C-terminal globular domain, which has potent effects on skeletal muscle cells. Full length adiponectin and its fragments may exert different actions on different cell types [25–28] by binding to the G-protein coupled adiponectin receptors type 1 (AdipoR1) and 2 (AdipoR2). AdipoR1 is constitutively expressed in every cell, especially in skeletal muscle, whilst AdipoR2 is greatly expressed in the liver [29]. They are both also expressed in various brain regions including hypothalamus, brainstem, hippocampus, and cortex [30].

A study by Bjursell and collaborators [31] investigated the contribution of AdipoR1 and AdipoR2 to energy metabolism homeostasis by using AdipoR1 and AdipoR2 knockout (KO) mice fed with a high-fat diet (HFD). They demonstrated that male AdipoR1KOs have greater adiposity and glucose intolerance, resulting in weight gain and energy expenditure, increased liver triglyceride (TG) and plasma leptin (a satiety hormone produced and secreted by white adipose tissue (WAT) [32]) levels, in addition to higher AdipoR2 mRNA expression in brown adipose tissue (BAT), a thermogenic tissue. On the other hand, the same study demonstrated that AdipoR2KOs are resistant to obesity, even eating more than control mice. The same KOs exhibited increased expression of CRH mRNA in the hypothalamus, less plasma leptin and cholesterol, lower liver TG, greater plasma and adiponectin levels, and higher glucose tolerance and energy expenditure. Interestingly, AdipoR2KOs presented with decreased levels of AdipoR1 mRNA in the liver and BAT [31].

Similar to AdipoR1KOs, mice with adiponectin gene ablation fed with a high-fat/high-sucrose diet had severe insulin resistance [33]. Interestingly, mice lacking adiponectin fed with a normal diet presented delayed free-fatty acid (FFA) clearance, and higher plasma and adipose tissue tumour necrosis factor-α (TNFα) levels. Injection of a full-length adiponectin producer adenovirus reversed this phenotype in adiponectin KO mice.

Human studies have associated hypoadiponectinemia (Figure 2), with excessive intra-abdominal fat and multiple defects in glucose and energy metabolism in MS. The syndrome has also been linked to increased circulating levels of cytokines (e.g., interleukin (IL)-6 and IL-1β) and soluble adhesion molecules (e.g., P-selectin and ICAM) [34]. The same study suggested that low adiponectin production is an underlying cause of endothelial damage and low-grade systemic inflammation in MS. The data are supported by previous studies showing that hypoadiponectinemia increases the risk for coronary artery disease (CAD) in men [35], and data from mice that showed that adiponectin protects against vascular

damage following mechanical injury [36]. In addition, obese patients with CAD have diminished plasma levels of adiponectin and lower expression of adiponectin receptors in peripheral monocytes in comparison with those without CAD, while macrophages from CAD patients present impaired release of IL-10 following adiponectin incubation [37].

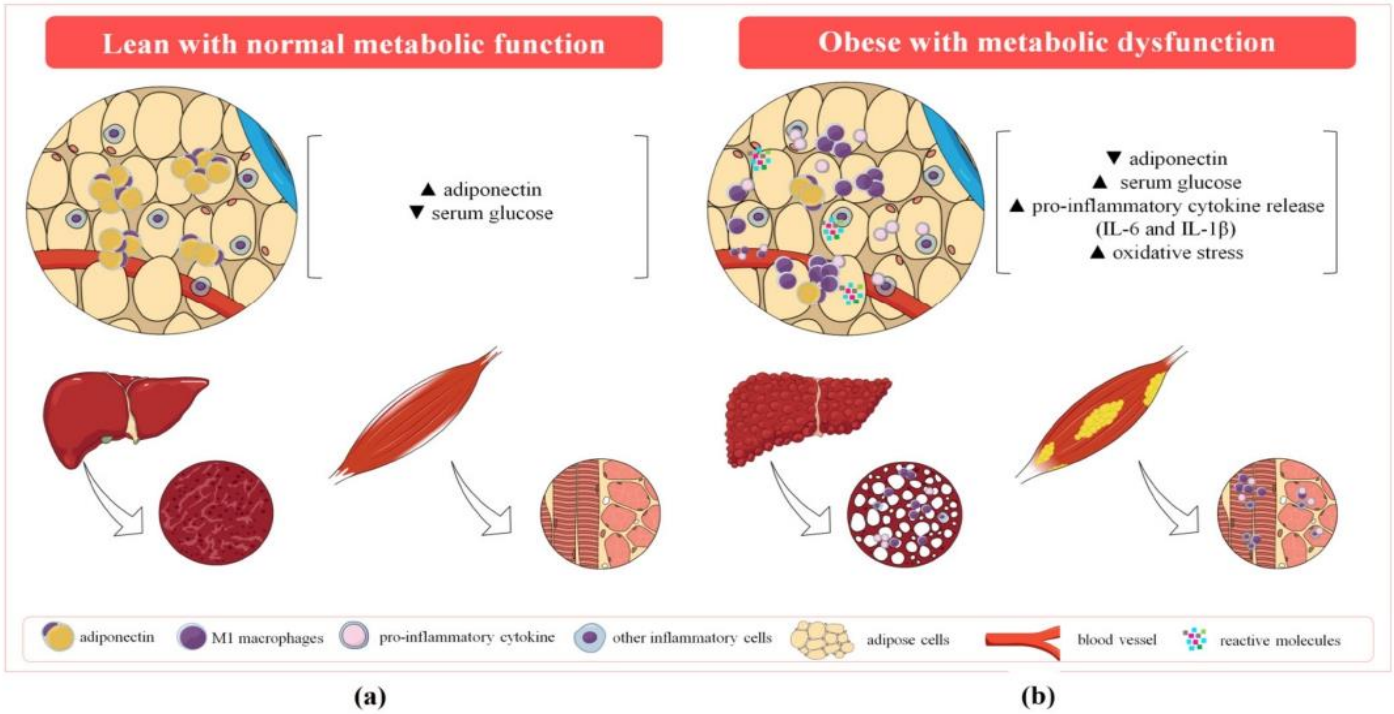

Figure 2. Fat tissue inflammation and adiponectin dysregulation in metabolic syndrome. (**a**) In lean individuals, adipose tissue contains few M2 macrophages and adipocytes produce high levels of adiponectin. Their insulin levels and sensitivity are regulated and result in normal glucose levels. (**b**) Individuals with metabolic dysfunction present with inflamed metabolic tissues with fat deposition and ROS production, which result in reduced cell viability and insulin resistance/high glucose levels.

Oxidative stress has been suggested as a cause of hypoadiponectinemia [38–40]. Indeed, exposure of pre-adipocytes (3T3-L1 cells) to oxidants such as hydrogen peroxide (H_2O_2), glucose oxidase or 4-hydroxynonenal (4-HNE), results in decreased expression and secretion of adiponectin. The low levels of this adipokine caused by oxidants are accompanied by increased production of pro-inflammatory cytokines (TNFα, IL-6) and chemokines (macrophage inflammatory protein-1; MCP-1) by adipocytes [40–43]. The contribution of oxidative stress to MS is discussed below.

2.2. *Oxidative Stress*

Oxidative stress is defined as the imbalance between the production and neutralizing pathways of reactive oxygen and reactive nitrogen-derived pro-oxidant species (ROS and RNS, respectively) in favour of these species. The link between oxidative stress and inflammation pathways highlights the burden of this condition in MS [44].

The physiological production of ROS (such as superoxide anion—O_2^-, hydroxyl radical—OH, H_2O_2 and hypochlorous acid—HClO) and RNS (such as nitric oxide—NO and peroxynitrite anion—$ONOO^-$) occurs via different endogenous enzymatic pathways (e.g., nicotinamide adenine dinucleotide phosphate oxidases—NOX, NO synthases—NOS, myeloperoxidase—MPO, xanthine oxidase—XOs, amongst others.). Although ROS and RNS signalling contribute to diverse cellular processes [45,46], under oxidative stress,

there is increased availability of these species leading to harmful effects in various disease states, including in MS. For example, O_2^- produced by NOX activates XOs inducing tetrahydrobiopterin (BH4) oxidation, endothelial NOS uncoupling and the consequent lowering of NO production and bioavailability, an essential hallmark of the pathogenesis of T2D and hypertension [47]. Other cellular effects of oxidative stress involve damage to proteins, membrane lipids, and nucleic acids. OH.—induced lipoperoxidation and DNA damage (as assessed by the formation of 8-hydroxy-2′-deoxyguanosine-8-OHdG), are well-established markers of chronic inflammation in MS [48].

On the other hand, neutralizing antioxidant pathways mitigate the reactivity of ROS [49]. Primary antioxidant pathways include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. Additional pathways include glutathione reductase, thioredoxin (TRX), and glutaredoxin. Other non-enzymatic pathways comprise reduced glutathione (GSH), bilirubin, and low molecular weight compounds of dietary origin (e.g., vitamins A, C, E, flavonoids, zinc, and selenium) [48]. In this way, antioxidant pathways provide conditions for controlled production of physiologically relevant oxidant species (such as H_2O_2) and the maintenance of homeostasis.

Oxidative stress has also been directly linked to the pathogenesis of CVDs such as hypertension, and insulin resistance in T2D [50]. In MS, oxidative stress is mainly characterized by the diminished expression and activity of antioxidant pathways secondary to a decrease in the levels of nuclear factor E2-related factor 2 (NRF2), in plasma samples from patients with MS [51]. These findings were also present in experimental models of obesity [52].

Hypertension is associated with reduced bioavailability of NO and increased ROS production either from dysfunctional mitochondrial or enhanced NOX expression in endothelial cells. The peroxynitrite anion, the product of the reaction between O_2^- and NO, also contributes to dysfunctional systemic vessel tonus control [53]. Furthermore, dyslipidaemia, insulin resistance, hyperglycaemia, and other factors, contribute to mitochondrial dysfunction and enhance mitochondrial O_2^- production by endothelial cells, cardiomyocytes and pancreatic β-cells [54], the latter being particularly vulnerable to oxidative stress due to the low expression of antioxidant defences in these cells.

Diverse mechanisms are related to the effects of oxidative stress on pancreatic β-cell function, including altered expression of micro-RNAs responsible for the gene regulation of redox signalling pathways [55]. Excessive ROS production, together with hyperglycaemia, contributes to glyceraldehyde-3-phosphate dehydrogenase inhibition, which results in the accumulation of glycolytic pathway precursors (such as fructose-6-phosphate and glyceraldehyde-3-phosphate). In this case, the subsequent activation of polyol cascades (by advanced glycation end-products—AGEs) causes NADPH depletion and reduced bioavailability of GSH [56]. In this case, the activation of nuclear factor-κB (NF-κB) and NOX promotes oxidative stress and a pro-inflammatory status that contribute to the vascular complications of T2D due to the low NO bioavailability and high expression of cell adhesion molecules [57]. In addition, the enhanced vasoconstriction elicited by endothelin-1 and other endogenous vasoconstrictors (such as prostaglandin H_2 and thromboxane A_2) impairs both the endothelial function and vascular wall integrity, particularly at the microcirculation level [58]. Therefore, AGEs play an important role in the delicate interface between T2D and CVDs [59].

As previously discussed, oxidative stress (Figure 2) can contribute to hypoadiponectinemia and inflammation, and thus, to obesity. Obesity is characterized by a systemic pro-inflammatory status, mainly due to the development of insulin resistance [60]. From a cellular perspective, impaired mitochondrial function and biogenesis caused by either hyperglycaemia and/or hyperlipidaemia impairs the insulin signalling pathway [61]. This, in addition to dysfunctional adipose tissue, enhances oxidative stress by activating pro-inflammatory pathways in adipocytes [62], which are amongst the aetiological factors of T2D and CVDs [63].

Interestingly, increased circulating levels of TRX are present in T2D patients [64] and have been associated with higher risk for CVD in individuals with MS [65].

2.3. Inflammation

In addition to adiponectin dysregulation and oxidative stress (Figure 2), studies have provided compelling evidence that the progress of metabolic dysfunction is closely related to a state of low-grade chronic inflammation [66–68], which is primarily characterized by recruitment of pro-inflammatory macrophages to the adipose tissue. Macrophages enhance the inflammatory response [69,70], contributing to the accumulation of ectopic lipids and the development of insulin resistance [71]. M1 and M2 macrophages play an important role in adipose tissue during low-grade inflammation [72] through the production and release of TNFα, IL-1β, and IL-6, and IL-10, respectively [73,74]. M1 macrophages recruited to the pancreatic islets cause pancreatic β-cell dysfunction and apoptosis [74]. Furthermore, the production of pro-inflammatory cytokines within the adipose tissue leads to adipocyte hypertrophy [70]. The local release of FFA, especially saturated fatty acids, activates toll-like receptor 4 on macrophages [75,76], triggering the activation of NF-κB and the additional expression of pro-inflammatory cytokines [77]. These events continuously contribute to insulin resistance in the adipose tissue, liver, and skeletal muscle [78,79]. The above data reinforce the importance of inflammatory imbalance to the adipose tissue changes in MS and its comorbidities/complications [67]. Indeed, adipose tissue inflammation also impacts other tissues and organs such as the liver [80,81], pancreas [82] and muscles [83]. Fat deposition in these organs is particularly deleterious [10].

Liver resident macrophages (Kupffer cells) can also be polarized into M1 and produce TNFα as a result of a lipid-rich diet that, in turn, contributes to increased glucose release by gluconeogenesis, lipid production and storage by inhibiting intracellular lipases [74]. The metabolic complications associated with a decline in insulin release lead to glucolipotoxicity in the pancreatic islets and the adipose tissue [84,85], imbalance of redox states, and mitochondrial dysfunction [85]. An obesogenic diet promotes endoplasmic reticulum stress and pancreatic β-cell dysfunction, with consequent reduction of insulin production [84]. These alterations are closely associated with increased inflammation, oxidative stress, and subsequent damage to DNA, proteins, cellular lipid, and potentially cell death [86]. In fact, liver damage may be driven by the secretion of pro-inflammatory cytokines (e.g., TNFα) [87], hypoadiponectinemia [88,89], and high levels of resistin and leptin [80,90,91] in the adipose tissue. Increased hepatic lipid accumulation into the liver followed by de novo lipogenesis and reduction of fatty acid oxidation [92,93] leads to histological damage characterized as simple steatosis, non-alcoholic steatohepatitis, or cirrhosis, and even hepatocellular carcinoma in more serious cases [94,95].

Although the studies are still controversial [96–99], pancreatic fat may be associated with β-cell dysfunction and insulin resistance [100,101]. Importantly, sarcopenic obesity is directly related to additional weight gain [102] and poor physical function and ability [103].

In addition to macrophages, T cells also play a role in MS. Mice fed HFD present with higher numbers of $CD8^+$ and smaller populations of $CD4^+$ and regulatory T cells in the epididymal WAT in comparison with normal chow-fed mice [104]. $CD8^+$ cell influx precedes that of M1 macrophages in the adipose tissue, increasing inflammation and systemic insulin resistance. In agreement, mice lacking T cells are protected against obesity-induced T2D in HDF-fed mice, which is associated with less macrophage accumulation and down-regulation of inflammatory cytokines/chemokines (MCP-1, RANTES, IL-6, TNFα and IFNγ) in skeletal muscle and adipose tissue samples [105]. Conversely, in another report, T cell recruitment and IFNγ up-regulation occurred in epididymal WAT following macrophage influx [106]. Overall, these data show the contribution of Th1 cells to adipose tissue inflammation in MS. Additionally, Th17 cells contribute towards a pro-inflammatory phenotype in the adipose tissue and insulin resistance [107], whilst Th2 cells are suggested to protect against obesity [108]. Interestingly, the percentage of Th2 cells

in human adipose tissue samples negatively correlates with systemic inflammation and insulin resistance [108].

3. Transient Receptor Potential Channels

3.1. General Overview of TRPV1, TRPA1 and TRPC5 Channels

TRP channels are polymodal cation channels that mediate Ca^{2+} influxes across the cell membrane [109]. Cationic influxes through TRPs depolarize the cell membrane and activate many cellular responses. The development of agonists, antagonists and KO mice for TRPs has helped to define their expression sites and pathophysiological functions throughout the last few decades. Although TRPs have different expression patterns, their wide physiological distribution indicates their involvement with biological processes in different cells, tissues, and organs [110–112]. The mammalian TRP family is composed of 28 members classified into six sub-families: vanilloid (TRPV), ankyrin (TRPA), canonical (TRPC), melastatin (TRPM), mucolipin (TRPML), and polycystin (TRPP) [113,114].

TRPs are expressed in both neuronal and non-neuronal cells and mediate a range of responses including nociception, inflammation, vascular tonus, cell contractility, energy expenditure, amongst others. These channels can be activated by a plethora of endogenous stimuli such as inflammatory mediators, lipids and oxidative/nitrosative stress products. As the focus of this review is to discuss the TRP-oxidative stress axis in different metabolic tissues in MS, the roles of TRPV1, TRPA1 and TRPC5 are presented.

TRPV1 (Figure 3a) was the first to be described and is the most extensively studied member of the TRP family [115,116]. It contains six transmembrane domains or sub-units (S1–S6) and a hydrophobic pore region between S5 and S6, in addition to intracellular domains—a long *N*-terminus with multiple ankyrin repeats and a short C-terminal region [115]. These domains are now known to be essential as protein and compound-binding sites and, therefore, detrimental to the modulation of TRPV1 functions. Details on TRPV1 binding sites have been recently revised [117]. Fatty acid-derived products such as hydroxyeicosapentaenoic acid (12 (S)-HPETE) [118], 20-hydroxyeicosatetraenoic acid (20-HETE) [119], 9- and 13-hydroxyoctadecadienoic acids (9-HODE and 13-HODE) and oxidized forms [120], endocannabinoids such as anandamide [121], hydrogen sulphide (H_2S; [122]), and ROS (H_2O_2; [123]), amongst others, are able to endogenously activate the receptor, either directly or by sensitization. TRPV1 is widely expressed in neurones and also in metabolic tissues including the adipose [124,125] and liver tissues [126,127]. TRPV1 is also expressed in M1 macrophages [127,128] and T cells [129–131], already discussed herein, as a key inflammatory factor of in MS. On the other hand, TRPV1 expression in pancreatic β-cells is controversial [132,133].

TRPA1 (Figure 3b) also consists of six sub-units (S1–S6) and a hydrophobic pore region between S5 and S6 and has large intracellular *N* and C-terminal domains. A domain containing five ankyrin repeats surrounds the coiled-coil region [134]. Key cysteines necessary to channel activation by electrophiles are found within the pre-S1 region [134]. TRPA1 is broadly expressed throughout the body including in metabolic tissues and cells [135–137]. TRPA1 can be activated by a variety of molecules produced and released during oxidative phosphorylation, including methylglyoxal [138], 4-HNE, 15-deoxy-delta(12,14)-prostaglandin J_2 (15d-PGJ2) and H_2O_2 [139]. These molecules, and TRPA1, have been associated with anti-hyperglycaemic and anti-obesity effects which are further discussed herein.

TRPC5 (Figure 3c) is formed by a four-fold symmetric homotetramer, and each of the four monomers presents with a compact cytosolic domain and a transmembrane domain. The cytosolic domain is composed of the *N*-terminal region with an ankyrin domain and a region of seven α helices, whilst the C-terminal sub-domain contains a connecting helix and a coiled-coil domain. The transmembrane domain contains sub-units (S1–S6), a TRP domain, and several small helices, including a pore helix [140]. The presence of a disulphide bond at the extracellular side of the pore and a preceding small loop confer functionality to TRPC5 [140]. Of importance, as previously demonstrated for TRPV1 and TRPA1, which

are able to functionally interact as dimmers (recently revised [141]), TRPC5 can also form functional homo and heterocomplexes with other receptors of the same family, such as TRPC4 and TRPC1 [142,143] that exert different functions, from inflammation to vascular remodelling. TRPC5 complexes are widely expressed in the central nervous system (CNS) and at lower levels in other tissues and cells [144]. In the context of MS, TRPC5 has an important role connecting metabolic tissues and the brain. TRPC5 can be activated by a range of molecules including H_2O_2 [145], reduced TRX [146], and fatty acids [147].

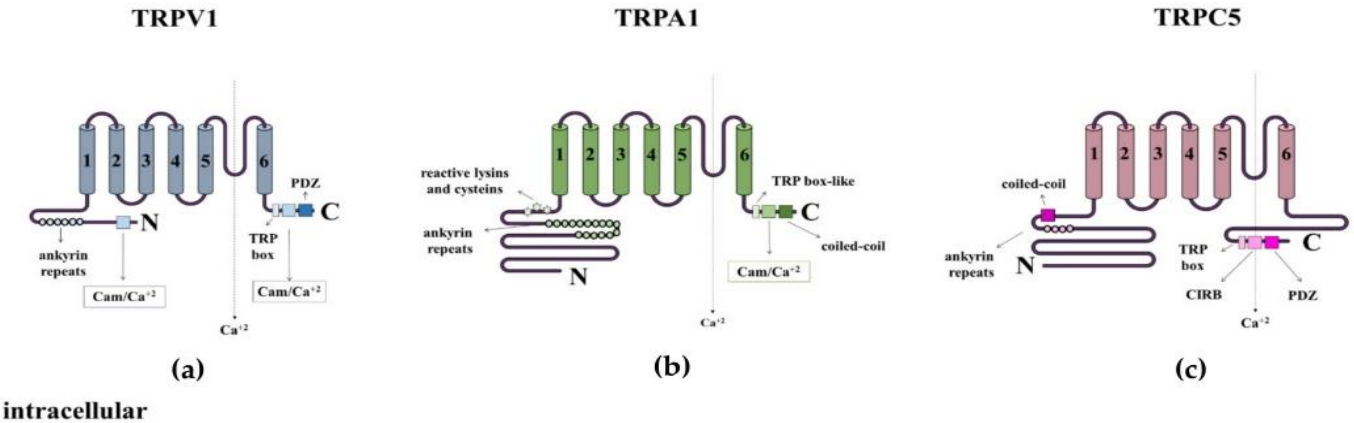

Figure 3. TRPV1, TRPA1 and TRPC5 structures. (**a**) TRPV1, (**b**) TRPA1 and (**c**) TRPC5 structures are composed of different domains including six transmembrane domains with a pore region, *N* and C-terminus, ankyrin repeats, coiled-coil, calmodulin (CaM)/Ca^{2+}-binding region, TRP-box, calmodulin (CaM)/inositol 1,4,5-trisphosphate (IP_3) receptor binding (CIRB), and PDZ domains.

The roles of TRPV1, TRPA1 and TRPC5 as mediators of oxidative stress and inflammation and, as modulators of MS are discussed below.

3.2. TRPs as Key Sensors of Oxidative Stress

TRP channels play essential roles in cellular function and disease [148]. Interestingly, specific TRPs are activated by ROS, amongst the several stimuli described to date. TRPM2 was the first TRP channel described as sensitive to ROS [149]. It is now known that TRPV1, TRPA1 and TRPC5 are not only oxidative stress sensors but also modulate oxidative stress pathways.

Reactive molecules, such as those involved in oxidative stress, are able to either directly activate or sensitize the TRP channels discussed herein. Evidence for the functional activation of these receptors by reactive molecules is listed in the Table 1. Different studies have demonstrated the ability of H_2O_2 to sensitize TRPV1 [123,150–152]. An initial report showed that H_2O_2 potentiates heat-induced membrane currents mediated by TRPV1 in HEK293T cells [150]. Next, this ROS was found to cause thermal hyperalgesia by TRPV1-dependent and independent mechanisms when intra-articularly injected in mice [151], and to potentiate apnoeic responses in rats by acting on both TRPV1 and TRPA1 when given as an aerosol [153]. H_2O_2 also induced increases in coronary blood flow, a response partially mediated by TRPV1 [123]. In the same study, H_2O_2 promoted the activation of intrinsic TRPV1-specific currents in isolated mouse coronary endothelial cells, which were blunted in endothelial cells lacking TRPV1. Interestingly, the prolonged exposure of TRPV1 to H_2O_2 and reactive aldehydes, such as 4-HNE, impairs TRPV1 functions contributing to microvascular dysfunction in T2D [123,154]. 4-HNE-induced inhibition of TRPV1-mediated responses in coronary arterioles was suggested to be due to direct binding of this aldehyde

to the channel [154]. H_2O_2 and O_2^- generation can be modulated by TRPV1, indicating a feedback loop between this channel and ROS production [155,156].

Table 1. Evidence for the functional activation of TRPV1, TRPA1 and TRPC5 by reactive molecules involved in metabolic syndrome.

TRP Channel	Reactive Molecule	Cell Type	Activation Mode	Ca^{2+} Influx	Electrophysiology
TRPV1	H_2O_2	HEK293T [123,150,152]	Sensitization	✓	✓
		Bovine aortic endothelial cells [123]	Sensitization	✓	
TRPA1	H_2O_2	HEK293T [157–159]	Direct	✓	
		DRG neurones [158–160]	Direct	✓	
		Bladder neuronal afferents [161]	Direct		✓
		CHO cells [160]	Direct	✓	
	NO	HEK293T [159]	Direct	✓	
		DRG neurones [159]	Direct	✓	
	H+	HEK293T [159]	Direct	✓	
		DRG neurones [159]	Direct	✓	
	Aldehydes (4-HNE and 4-ONE)	HEK293T cells [157]	Direct	✓	
		DRG and trigeminal ganglia neurones [157,160]	Direct	✓	
		CHO cells [160,162]	Direct	✓	
TRPC5	H_2O_2	HEK293T cells [145]	Direct	✓	
	Reduced TRX	HEK293T cells [150]	Direct	✓	
		Synoviocytes [150]	Direct	✓	

As for TRPV1, TRPA1 is a well-documented oxidative stress sensor. The first evidence that the channel could be activated by reactive molecules demonstrated the ability of 4-HNE to evoke pain via TRPA1 activation on rodent nociceptive neurones. This event led to the release of substance P, causing neurogenic inflammation [157], and it was supported by further evidence [160]. In vivo and in vitro models showed that H_2O_2 triggers the neuronal activation of TRPA1 [160,163]. Oxidative stress can also activate TRPA1 on non-neuronal tissues and cells. For instance, 4-HNE induces the dilation of cerebral arteries [164] and increases of Ca^{2+} influx in pancreatic β-cells [137] following activation of this channel. Neurogenic vasodilatation is also mediated by TRPA1, a response which requires peroxynitrite generation [165].

TRPC5 is perhaps one of the most interesting TRP members with respect to oxidative stress signalling. TRPC5 can be activated by both oxidant (H_2O_2; [145]) and antioxidant (reduced TRX; [146]) molecules; the latter shown to be a response dependent on TRPC1/TRPC5 complexes in non-neuronal cells. Interestingly, a recent report showed that eNOS-derived NO causes suppression of TRPC5 activity in endothelial cells [166]. Considering the reduced activity of eNOS and NO bioavailability in MS, it is possible that TRPC5 function in this syndrome is linked to regulation of blood vessel tonus and pressure control. TRPC5 is constitutively expressed in the brain and in metabolic tissues such as the adipose. Its contribution to energy metabolism is further discussed in this review.

Amongst the many cellular responses mediated by TRPs, the regulation and maintenance of inflammatory mechanisms have unique roles, given TRP permeability to Ca^{2+}, which mediates transcription, translation, cellular division and apoptosis. In this way, ROS-based signalling mechanisms via TRPs are critical points worthy of deeper investigations

in MS [48]. Different from TRPM2-redox activation by $OH^{\cdot}$ (mainly produced in the Fenton reaction of iron-catalysed H_2O_2 decomposition), the main mechanism of TRPA1, TRPV1 and TRPC5 activation by ROS is a redox-sensitive pathway via cysteine disulphide formation from proximal cysteine residues [167]. In fact, at least four cysteine residues have been described in the redox-sensitive mechanism of TRPA1 activation: Cys-421, Cys-621, Cys-641 and Cys-665 [158,163,168]. Cys-621 is the binding residue for 4-HNE in TRPV1 [154] and Cys-158 the binding residue for H_2O_2 in the same channel [152].

3.3. TRPs as Regulators of Inflammation

The roles of TRPV1, TRPA1 and TRPC5 in inflammation have been widely investigated in past years. Different pieces of evidence indicate these channels participate in inflammatory events including cell migration, inflammatory mediator release and cell survival. Since both macrophages and T cells play a role in MS, this session focuses on the impact of these channels on T cell and macrophage responses.

The first indication that these channels are functional in inflammatory cells dates from the late 1990s. Incubation of capsaicin with activated human T cells caused Ca^{2+} mobilization [129]. TRPV1 expression in mouse $CD4^+$ T cells was later confirmed and shown to mediate the production of different cytokines (IL-4, IL-5, IL-6, and IL-17), associated with increased phosphorylation of kinases and NF-κB [130]. These findings were supported by data from Jurkat T cells following treatment with the TRPV1 inhibitor BCTC, and from TRPV1KO mice sensitized with ovalbumin, as both the inhibitor-treated cells and the animals with gene ablation of the channel resulted in less cytokines [130,131]. TRPV1 expression was also confirmed in mouse $CD11c^+$ dendritic cells and $CD11b^+F4/80^+$ macrophages [169]. Increased channel activation promoted higher secretion of cytokines (higher level of IL-6, IL-1β, TNFα, and IL-23) by dendritic cells [169]. TRPV1 was found to regulate macrophage and monocyte responses. In the absence of TRPV1, mouse macrophages are more susceptible to apoptosis, have impaired ability to perform phagocytosis and to produce ROS and NO, and release high levels of cytokines during bacteraemia associated with worsening of the disease in vivo [156]. In mouse cerebral malaria, the lack of TRPV1 triggers less cerebral swelling, increased oxidative stress, and diminished production of cytokines [170]. These results indicate that, depending on the stimuli, the modulation of inflammation by TRPV1 can result in either protection against, or damage, in diseases. In fact, TRPV1 is highly expressed in M1 macrophages and its activation in these cells leads to inhibition of M1 polarization [128,171]. The inflammatory response is not modulated by TRPV1 only in microbial infections, but also in many different chronic diseases such as rheumatoid arthritis [172], colitis [169], rhinitis [130], and MS [173,174].

Human circulating leukocytes, Jukart T and mouse $CD4^+$ T cells also express functional TRPA1 [175–177]. By using TRPA1 antagonists and KO mice, conflicting results have been found concerning the channel role in immune cells. Pre-treatment of murine splenic T cells with TRPA1 antagonists (A967079 and HC-030031) abolished T cell receptor-induced Ca^{2+} currents, as well as reduced T cell activation and cytokine release (TNFα, IFNγ and IL-2) by these cells [178]. Another report showed however, that TRPA1KO $CD4^+$ splenic T cells present enhanced and prolonged T cell receptor-induced Ca^{2+} currents [176]. A compensatory role via TRPV1 was found to be involved in this response. In addition to T cells, monocytes and macrophages also express TRPA1. TRPA1 activation in cultured primary human monocytes triggers TNFα release and impairment of IL-10 production [179]. THP-1-derived macrophages express functional TRPA1 [179,180]. In these cells, TRPA1 was found to mediate the effects of lysophosphatidylcholine (an atherogenic lipid; [181]) on mitochondrial ROS production and membrane depolarization, IL-1β production and cell survival [180]. TRPA1 is also involved in the ATP actions on macrophages, contributing to mitochondrial damage, IL-1β secretion, and cell death [179]. Of note, ATP is an important molecule in atherosclerosis and hypertension [182,183]. These results infer that TRPA1 can contribute towards CVD in MS by regulating macrophage-mediated responses. Analysis of mouse atherosclerotic aortas indicated they express higher TRPA1 levels than control

samples, especially in macrophages found in the atherosclerotic lesions [184]. TRPA1 blockade by HC-030031 or its genetic ablation resulted in larger lesions, hyperlipidaemia, and increased levels of pro-inflammatory mediators in the aorta (TNFα, IL-6, MCP-1 and MIP-2). The same study demonstrated that oxidized low-density lipoprotein directly activates TRPA1 and that channel activation protects against the formation of foam cells by reducing lipid accumulation [184]. These studies highlight a dual role (protective or deleterious) for TRPA1 in atherosclerosis.

In an initial report, TRPC5 was found to be expressed at very low levels in murine resting effector T lymphocytes, and to become up-regulated following activation of these cells [185]. TRPC5 mediated Ca^{2+} currents induced by the lectin galectin-1 produced by regulatory T cells; this response was abrogated by the TRP blocker SK&F96365 and receptor knockdown, and also in T cells from TRPC5KO mice. The same study showed that TRPC1 but not TRPC4 is detected in T cells. This was the first evidence that the activation of TRPC5 complexes can contribute to autoimmune suppression. In macrophages (RAW 264.7 cells), TRPC5 inhibition by antagonism with ML-204 or RNA silencing, caused cell polarization to a M1 phenotype which was characterized by increased secretion of pro-inflammatory cytokines involving NF-κB activation (TNFα, IL-1β and IL-6) [186]. TRPC5KO mice fed HFD had higher numbers of M1 macrophages infiltrating their aorta and greater serum levels of TNFα and IL-6 [186]. In addition, TRPC5 deletion or antagonism by ML-204 restored phagocytosis in macrophages challenged with LPS and bacterial TRX [187]. These pieces of evidence indicate a protective role for TRPC5 in inflammation and CVD.

The above findings highlight the importance of TRPV1, TRPA1 and TRPC5 as modulators of inflammation in MS and are supported by studies performed with their endogenous agonists, including H_2O_2, 4-HNE and reduced TRX. H_2O_2 is suggested to act as a first messenger for different pro-inflammatory ligands including NO and AGEs [188], in addition to its role as second messenger in intracellular pathways which lead to the expression of pro-inflammatory mediators via redox-sensitive kinases and NF-κB activation [189–191]. A rapid increase of H_2O_2 following tissue damage also triggers fast leukocyte recruitment [192]. 4-HNE induces ciclooxigenase-2 expression in RAW 264.7 and peritoneal macrophages, in addition to leukocyte migration in mice, and via kinase activation [193]; these effects may contribute to the pro-inflammatory roles of prostaglandins. In accordance, 4-HNE activates NF-κB in vascular smooth muscle cells and 5-lipoxygenase production in murine macrophages [194,195]. Conversely, 4-HNE can cause inhibition of NF-κB activation as observed in monocytes, Jukart T and rat kupffer cells treated with the aldehyde [195–197]. These findings suggest that 4-HNE can be either pro or anti-inflammatory depending on the cell/tissue. An anti-inflammatory role has been attributed to TRX. Indeed, in vitro incubation of TRX-1 induces a M2 macrophage phenotype, and also reduces TNFα and MCP-1 generation by M1 macrophages [198]. The same study showed that TRX protects against atherosclerosis by shifting macrophage polarization to M2 in ApoE2.K1 mice with severe atherosclerotic lesions. The TRX-1-mimetic peptide CB3 reduced ROS production and NF-κB-mediated release of cytokines/chemokines (IL-1, IL-6, IL-1β and MCP-1) by cultured macrophages [199]. CB3 also presented atheroprotective effects in ApoE2.Ki mice fed HFD, which was associated with reduced levels of pro-inflammatory cytokines, increased production of anti-inflammatory proteins (adiponectin and IL-10) in the plasma, and a M2 macrophage phenotype in aortic lesions.

4. The Roles of TRPV1, TRPA1 and TRPC5 in MS

This section presents current data on the expression patterns (Figure 4; Table 2) and roles of TRPV1, TRPA1 and TRPC5 in the regulation of metabolic tissues, as well as in the connection between these tissues and the brain. Importantly, the combined expression of all the TRPs discussed herein contributes to regulate the functions of metabolic tissues and cells.

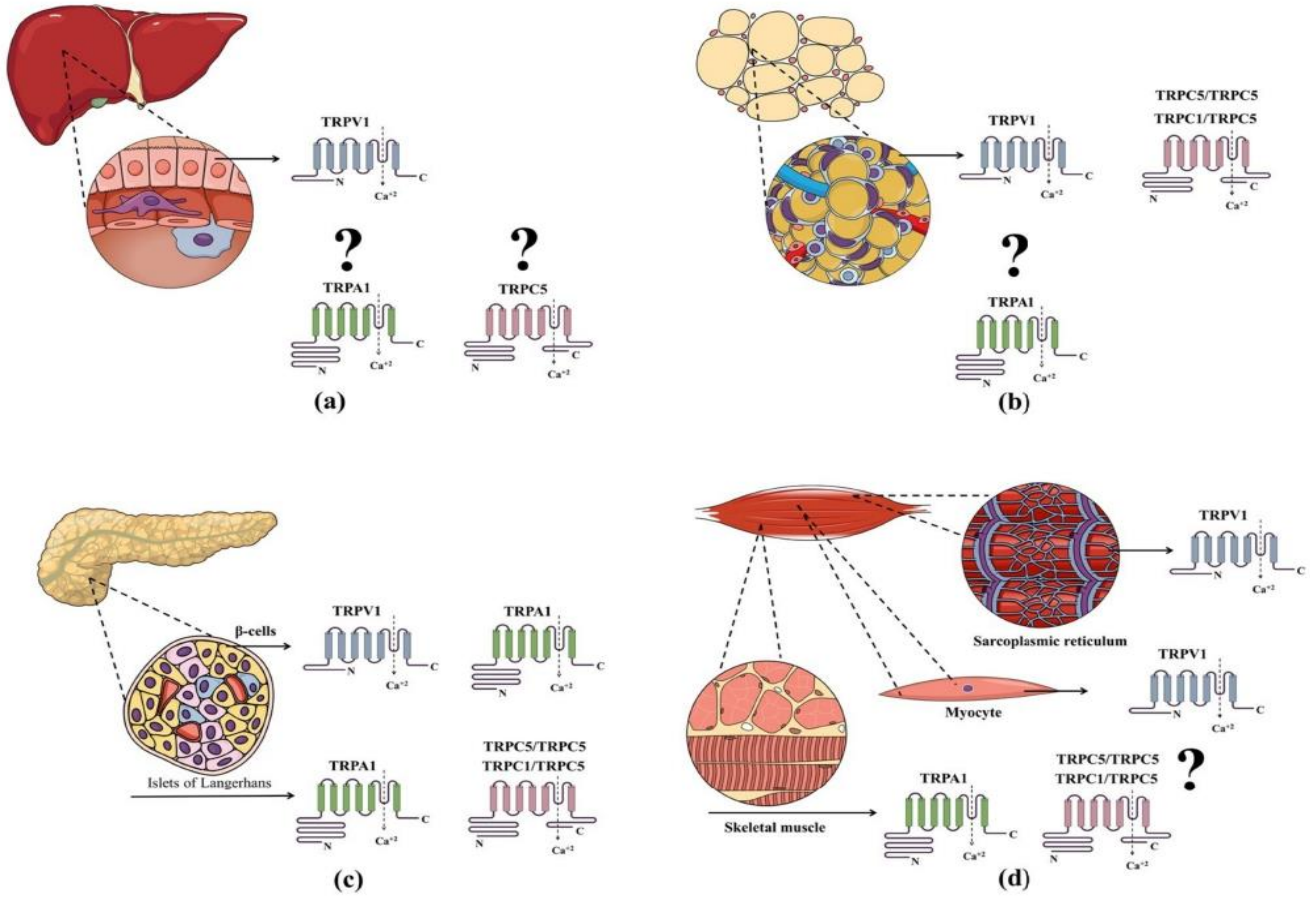

Figure 4. TRPV1, TRPA1 and TRPC5 expressions in metabolic tissues. (**a**) Liver, (**b**) adipose tissue, (**c**) pancreas and (**d**) skeletal muscle. All these TRPs are detected in the pancreas either as transcripts or functional proteins. TRPV1 is found in all metabolic tissues (liver, adipose tissue, pancreas and skeletal muscle). Additionally, TRPA1 and TRPC5 (either as homo or heterodimers) are expressed in the skeletal muscle and adipose tissue, respectively. The question tag (**?**) represents expressions yet to be confirmed: TRPA1 in the liver and adipose tissues, and TRPC5 in the skeletal muscle.

Table 2. Evidence for TRPV1, TRPA1 and TRPC5 expression on cells and in tissues involved in metabolic syndrome.

TRP Channel	Cell/Tissue	PCR/ qPCR	Immunostaining/ Immunofluorescence	Western Blot	Ca^{2+} Influx	Electrophysiology
TRPV1	adipose tissue/adipocytes [124,125,200,201]	✓	✓	✓	✓	
	liver [126,127]	✓	✓	✓	✓	
	M1 macrophages [128]		✓		✓	
	pancreatic β-cells/langerhans islets [132]	✓	✓	✓		
	coronary endothelial cells [123]					✓
	T cells [129–131]		✓	✓	✓	✓
	skeletal muscle [202–204]	✓	✓	✓	✓	
	pro-opiomelanocortin neurones [205]	✓	✓	✓		✓

Table 2. *Cont.*

TRP Channel	Cell/Tissue	PCR/ qPCR	Immunostaining/ Immunofluorescence	Western Blot	Ca^{2+} Influx	Electrophysiology
TRPA1	pancreatic β-cells/langerhans islets [137,206]	✓	✓	✓	✓	✓
	T cells [175–177]	✓	✓	✓	✓	✓
	skeletal muscle cells [207]	✓	✓	✓	✓	✓
	monocytes/macrophages [179,180]	✓	✓	✓	✓	
TRPC5	endothelial cells [166]				✓	
	T cells [185]	✓			✓	
	M1 macrophages [186]	✓		✓		
	pancreas [208]	✓				
	adipose tissue [147,200]	✓	✓	✓	✓	✓
	pro-opiomelanocortin neurones [209–211]					✓

4.1. Regulation of Insulin and Insulin Resistance

The involvement of TRPs in insulin resistance first remits to TRPC4 and TRPM2, as their activation leads to pancreatic cell depolarization and Ca^{2+} influx, thus regulating insulin secretion by distinct mechanisms [212,213]. However, the systemic expression of other TRPs may be altered by hyperglycaemia, concomitantly connecting T2D and CVDs in MS [214].

In addition to the controversial data regarding TRPV1 expression in pancreatic β-cells [132,133], its contribution to insulin resistance is unclear. Mice prone to diabetes lacking pancreatic innervations are protected from the development of insulitis and pancreatic disease; these data lead to the conclusion that TRPV1 activation is associated with the pathogenesis of type-1 diabetes [215]. Furthermore, TRPV1KO mice had a longer life-span than wild-type (WT) animals, in addition to higher insulin sensitivity [216]. In agreement, both the chemo-denervation of TRPV1 neurones and its blockade induced glucose-dependent insulin secretion in rodents [172,217,218]. These findings suggest the involvement of neuronal TRPV1 activation in insulin resistance and islet inflammation. In contrast, other studies showed that TRPV1KO mice fed with HFD present with higher insulin resistance than WTs under the same dietary conditions [219]. Interestingly, the intake of low doses of dietary capsaicin, a TRPV1 activator, has been associated with improved clinical signs in obesity and T2D [220,221].

Pancreatic β-cells and other insulin-secreting cells express TRPA1 [133,137], after which activation of glucose-dependent insulin secretion by these cells is potentiated [137]. In vivo studies showed that the metabolic activity of TRPA1 involves glucose uptake stimulation, intestinal incretin hormone secretion, and inhibition of food intake [222–224]. It was also indicated that TRPA1 agonists such as cinnamaldehyde improve diabetes in vivo through glucose transporter (GLUT4) translocation in peripheral tissues [222]. Recently, it was demonstrated that the effects of endogenous catechol oestrogens on insulin secretion by pancreatic β-cells is mediated by TRPA1 activation, thus making of this receptor a link between oestrogen metabolism and metabolic diseases [225].

Additional experimental data showed reduced TRPA1 expression in the islets of Langerhans obtained from rodents with T2D [206]. However, another study demonstrated that the deleterious effects of streptozotocin (a compound used for experimental diabetes induction) on β-cells are independent of TRPA1 activation [226]. In a model of chronic pancreatitis (induced by the injection of trinitrobenzene sulfonic acid), it was demonstrated the involvement of TRPA1 in the development of this condition, as TRPA1KOs showed reduced pancreatic inflammation in comparison with WT mice [227]. In contrast, allyl isothiocyanate (a TRPA1 agonist) was able to enhance insulin sensitivity and glucose

tolerance in mice fed HFD, and the effects are most probably related to the reversal of the impaired mitochondrial function [228]. Studies with endogenous activators of TRPA1 such as 4-HNE, further support the involvement of TRPA1 in the modulation of glucose levels and insulin resistance. Treatment of gastrocnemius muscle and L6 muscle cells with 4-HNE reduced insulin signalling and insulin-induced glucose uptake in skeletal muscle cells by increasing oxidative stress and depletion of GSH [229]. In addition, this aldehyde was negatively correlated with insulin sensitivity in obese subjects [230]. In this context, the complex role of TRPA1 in insulin resistance suggests that the regulation of TRPA1 activation could be a novel therapeutic strategy, although additional studies are needed to properly elucidate this pathway in MS.

There is little data on the pancreatic expression of TRPC5 [208] and no reports so far on the role of this receptor in insulin resistance. Despite that, TRPC1 can form complexes with TRPC5 [142], and there is growing evidence on the pancreatic expression of TRPC1 [208,231,232] as well as on its function as regulator of glucose tolerance and insulin secretion [233,234]. The existence of a TRPC5-aerobic glycolysis axis was also observed in colorectal cancer cells [235]. In addition, TRPC5 was found to mediate neuronal cell damage and death under metabolic stress such as oxygen-glucose deprivation [236]. Therefore, it is expected that further developments in the field will be able to overrule or demonstrate the importance of TRPC5 complexes in insulin resistance and/or their roles as sensors of glucose levels.

4.2. Regulation of Adypocytes

The adipose tissue plays an essential role in MS by influencing glucose and lipid balances. There are different types of adipose tissue (white, brown, and beige), and their cellular content, secreted substances and location determine MS development and progression. It is important to highlight that WAT stores excess energy as TGs, whilst the BAT is involved in energy expenditure. The differentiation of WAT into a BAT-like phenotype is known as browning of WAT and is characterized by thermogenic beige adipocytes also called "brite" cells. BAT and beige adipocytes contribute to reduction of insulin secretion and, therefore, to control T2D, in addition to obesity. These aspects have been recently reviewed [10,237,238].

TRPV1 expression was shown in cultured 3T3-L1-preadipocytes and in mouse and human adipose tissue samples [124,125,200,201]. The first study, in 2007 [125], demonstrated that TRPV1 is down-regulated during adipogenesis, and that capsaicin incubation prevents this response in 3T3-L1 cells, indicated by reduced TG content, lower expressions of PPAR-γ and fatty acid synthase; capasaicin effects in adipogenesis were blunted by TRPV1 knockdown. TRPV1 expression was also decreased in the visceral adipose tissue of obese mice and in the visceral and subcutaneous fat of obese patients in comparison with lean controls [125]. Dietary capsaicin stimulates the expression of the BAT-specific thermogenic uncoupling protein-1 (UCP-1) and the browning of WAT in WT but not TRPV1KO mice, by increasing the expression of sirtuin-1 [201]. In turn, the deacetylation of PPARγ occurs leading to reduced lipid synthesis and obesity [201]. A similar effect was seen for another TRPV1 agonist, monoacylglycerol, shown to increase UCP-1 expression and to impair the accumulation of visceral fat in high fat/high sucrose diet-fed mice [239]. The role of TRPV1 as a thermogenic receptor in adipocytes was also confirmed by a recent study in which TRPV1+-thermogenic adipocyte progenitors were characterized [240].

Despite consuming equivalent energy and absorbing similar quantities of lipids to WTs, TRPV1KOs fed HFD gain less weight, present less adiposity and greater thermogenesis [241]. On the other hand, in ageing mice fed HFD, the lack of TRPV1 promotes obesity due to altered energy balance and leptin resistance [219]. In another study with mice given HFD, no differences were noted between WT and TRPV1KO mice in regards to weight gain and adipose tissue mass [173]. It is possible that the differences between these studies are due to variations in the fat contents of HFD. Irrespective of this controversy, the above evidence indicates a promising clinical use of TRPV1 agonists such as capsaicin to

preventing obesity by activating TRPV1. In agreement, capsaicin intake increases lipolysis in exercising individuals [242].

TRPV1 is not the only TRP channel to modulate thermogenesis. In this context, the alkamide trans-pellitorine found in *Piper nigrum* (black pepper) impairs lipid accumulation by reducing PPARγ levels in 3T3-L1 cells during the differentiation and maturation phases via the indirect activation of TRPV1 and TRPA1 [243]. This indicates a synergistic contribution of the functional expression of both channels in the regulation of energy expenditure. Corroborating these findings, the incubation of cinnamaldehyde diminished TG and phospholipid content in 3T3-L1 preadipocytes by down-regulating PPARγ expression and increasing AMP-activated protein kinase levels [244,245]. TRPA1-independent pathways of thermogenesis and metabolic reprogramming were also reported for cinnamaldehyde; the compound was shown to promote these responses in mouse and human adipose cells by increasing UCP-1 and SOD expressions [245].

It is also possible that the neuronal expression of TRPA 1, probably in the vagus nerve, contributes to thermogenesis as the receptor agonists cinnamaldehyde and allyl isothiocyanate, both induce adrenaline secretion and prevent fat accumulation and obesity in rats [246]. The same study showed the ability of cinnamaldehyde to activate BAT and reduce visceral fat in animals fed high-fat/high-sucrose diet. Supporting data demonstrated that cinnamaldehyde decreases weight gain, and the quantities of plasma TG, non-esterified fatty acid, and cholesterol in mice with HFD [247], and also that incubation of cinnamaldehyde with 3T3-L1 cells decreases TG and phospholipid accumulation, whilst reducing PPARγ; these effects were blocked by the TRPA1 antagonist AP-18 [244]

The contribution of TRPA1 activation to thermogenesis has been supported not only by studies with exogenous agonists such as cinnamaldehyde, but also by those performed with endogenous activators of the channel including 4-HNE. High levels of 4-HNE were detected in the subcutaneous adipose tissue of obese subjects [248]. Incubation of 4-HNE with subcutaneous adipocytes triggered the production of ROS (H_2O_2) and antioxidant enzymes (TRX, SOD and catalase), associated with reduced growth and differentiation of preadipocytes [248]. The down-regulation of adiponectin by 4-HNE has been previously discussed, and it is known to occur by degradation of adiponectin protein following incubation with the aldehyde via the ubiquitin-proteasome system [249]. Of note, although 4-HNE reduces adipogenesis, its inhibitory effects on adiponectin may reflect in inflammation, and worsening of MS. Indeed, 4-HNE induced TNFα gene transcription in WAT samples of obese subjects [250]. Despite the interesting actions of cinnamaldehyde and 4-HNE in adipogenesis, the specific contributions to TRPA1 activation in this response is yet to be established by further studies employing strategies including KO mice, knockdown and antagonists for the channel.

TRPC1/TRPC5 complexes were also identified in cultured 3T3-L1 cells and in perivascular adipose tissue samples obtained from mice and humans [147,200]. The constitutive activation of these complexes in the mature adipocytes of the perivascular fat was suggested to act as a negative regulator of adiponectin [147]. In vitro TRPC1/TRPC5 knockdown increased adiponectin generation in mice, disruption of TRPC5-containing complexes and enhanced adiponectin levels irrespective of the diet composition (chow or HFD) [147]. Interestingly, the same study showed that the inhibitory effects of TRPC1/TRPC5 complexes on adiponectin were halted by exposure to dietary ω-3 fatty acids in differentiated 3T3-L1 cells.

4.3. TRPs and the Liver

Several reports show that TRPs are also relevant for the reestablishment of liver function during MS. From a therapeutic point of view, the improvement of mitochondrial metabolism is a pertinent strategy aimed for the treatment of non-alcoholic fatty liver disease (NAFLD), as enhanced hepatic oxidative stress is correlated with inflammation in obesogenic diets [251]. In this case, TRPV1 activation secondary to the dietary intake of low-dose capsaicin prevented the hepatic damage observed in NAFLD via uncoupling

protein 2 (UCP-2) up-regulation in mice [127,252]. Li and collaborators [127] described TRPV1 expression on hepatocytes and the mechanisms triggered by its activation. The observed effects comprise reduced lipid accumulation and TG concentrations levels in WT, but not in TRPV1KO animals [127]. UCP-2 up-regulation secondary to TRPV1 activation was also associated with other therapeutic effects, such as the reversal of hyperglycaemia-induced endothelial dysfunction in mice. Such an antioxidant mechanism via UCP-2 may be a multifaceted link between the dietary intake of capsaicin and its therapeutic effects in either metabolic or cardiovascular diseases [253].

Other liver functions may also benefit from low-dose dietary intake of capsaicin, such as lipoprotein metabolism. Although it was demonstrated that capsaicin does not reduce oxLDL accumulation in TNFα sensitized macrophages, TRPV1 activation up-regulated ATP-binding cassette (ABCA1 and ABCG1) expression via liver X receptor α, thus enhancing cholesterol efflux from the cells [254]. These findings are also relevant in the physiopathology of atherosclerosis, as oxLDL is a widely known biomarker of both atherosclerosis and NAFLD [253,254].

As demonstrated in mice receiving chronic dietary capsaicin, reduced inflammatory biomarkers and up-regulation of PPARδ secondary to TRPV1 activation takes place in WT but not in TRPV1KO animals with NAFLD [255]. Noteworthy, TRPV1 plays a substantial role in the obesity pathogenesis, with important consequences for hepatic health. TRPV1KO mice demonstrated a more pronounced hepatic steatosis when fed HFD, which was correlated with reduced expression of PPARα and oxidation of fatty acids. In addition, the impaired glucose metabolism and hepatic health observed in TRPV1KO mice are some of the evidence confirming the significant relationship between TRPs and MS-related diseases, as recently described by Baskaran and collaborators [256].

However, the role of TRPV1 in other hepatic diseases may be in contrast with the results so far, thus evidencing the complexity of this matter. For example, the genetic depletion of TRPV1 did not blunt hepatic steatosis but prevented the hepatic injury in chronic alcoholic hepatic disease [257], thus evidencing different roles for TRPV1 in the pathogenesis of different hepatic diseases and making clear that TRPV1 activation is not an obvious pathway to be clinically explored, mainly in the case of MS patients with other comorbidities.

The effects of the cinnamaldehyde have been investigated in the liver of T2D and gestational diabetic rats induced by high fat/high sucrose diet [258,259]. Intragastric cinnamaldehyde treatment significantly decreased hepatic lipid peroxidation, steatosis and inflammation, and enhanced hepatic GSH and SOD levels in rats with T2D. These changes were associated with enhanced insulin sensitivity [258]. In addition, the oral administration of cinnamaldehyde controlled hyperphagia and glucose intolerance in rats with gestational diabetes [259]; such effects were associated with reduced circulating levels of total cholesterol, triglycerides, leptin and TNFα, and higher levels of high-density lipoprotein (HDL)-cholesterol, adiponectin, liver glycogen and PPARγ expression, and the activity of antioxidant enzymes. On the other hand, analysis of healthy human liver samples by in situ hybridization demonstrated the expression of TRPA1 in the sinusoidal endothelial lining and Kupffer cells, but not in hepatocytes [260]. Thus, if cinnamaldehyde effects are due to TRPA1 activation, this would occur via endothelial and/or Kupffer cells, and this is yet to be confirmed by future research.

So far, there is limited information on the expression of TRPC sub-family members in the liver [208,260]; however, the current data do not support a role for TRPC5 in the liver in MS. Nonetheless, TRPC5 was found to mediate cholestasis in mice, as TRPC5KOs protected against the disease once they presented attenuated liver enlargement, reduced hepatic bile acid and lipid content, diminished liver enzymes, and decreased hepatic cholesterol, TG and phospholipid contents [261].

4.4. TRPs and Skeletal Muscle

The importance of the skeletal muscle to metabolic syndrome has been well documented and discussed [262,263]. Skeletal muscle is considered the largest tissue of the body sensitive to insulin, and it is where most of the insulin-mediated glucose uptake by GLUT4 occurs [264]. This tissue is also a producer of myokines which include cytokines (IL-6), myostatin, myonectin, irisin, and musclin [265]. These are released during muscle contraction, during exercise for example [266,267], and have endocrine and paracrine functions acting in other metabolic organs (liver, adipose tissue, and pancreas).

TRPV1 expression was first described in the rat skeletal muscle sarcoplasmic reticulum [202] and it was later confirmed in the human tissue as a target for endocannabinoids [203]. The latter finding indicated that TRPV1 mediates the down-regulatory effects of these molecules on adiposity. This was supported by data from skeletal L6-cells in which the TRPV1 antagonist SB-366791 blocked the insulin-induced glucose uptake triggered by the endocannabinoid 2-arachidonoylglycerol [204].

In another study, functional TRPV1 was detected in mouse myocytes (C2C12 cells) and skeletal muscle [268]. Indeed, the in vitro incubation of capsaicin triggered Ca^{2+} influx, and increased glucose oxidation and ATP production in C2C12 cells; both responses were blocked by TRPV1 antagonists (5′-iodo-resiniferatoxin-α or SB-452533) [268,269]. Of note, glucose oxidation and ATP generation in C2C12 cells were suggested to happen independent of insulin [269]. In another report, capsaicin induced the up-regulation of TRPV1 and peroxisome proliferator-activated receptor-γ coactivator-1α (a regulator of lipid and glucose metabolism, mitochondrial biogenesis and muscle remodelling in myocytes, and enhanced mitochondrial biogenesis and ATP production in myotubes [268,270]. Analysis of the gastrocnemius muscle indicated that the myocytes of mice fed with z capsaicin-supplemented diet exhibited a similar phenotype to that observed in vitro [268]. In addition, the same study showed that capsaicin enhances exercise endurance whilst lowering the levels of blood lactic acid and TGs in WT but not TRPV1KO mice; similar data were gathered from mice over-expressing the receptor which also presented with greater numbers of oxidative muscle fibres. In another study, TRPV1KO mice fed HFD presented higher insulin resistance in WAT and BAT, but not in the skeletal muscle in comparison to WTs [219]. Overall, the results suggest that the activation of skeletal muscle-located TRPV1 contributes towards thermogenesis and enhanced insulin sensitivity; both responses are exacerbated by exercise.

Functional TRPA1 was identified in primary human myoblasts but became down-regulated during differentiation to skeletal muscle cells [207]. Indeed, TRPA1 agonists such as allyl isothiocyanate induced Ca^{2+} currents in these cells that were blocked by the TRPA1 antagonists HC-030031 and A967079. The same study demonstrated that TRPA1 activation causes myoblast migration and fusion, and suggested this receptor is an important sensor of muscle damage and inflammation and, therefore, contributes to muscle repair.

A functional role in the maintenance of skeletal muscle force during sustained repeated contractions was shown for TRPC1 [271]. TRPC1 activation also annuls the beneficial effects of exercise on obesity-associated T2Din mice [233]. In addition, the activation of TRPC1/TRPC4 complexes is key to myogenesis and skeletal muscle differentiation [272]. On the other hand, the expression of TRPC5 and its function in the skeletal muscle is controversial. In fact, there is conflicting data on its expression on skeletal myoblasts [271,273]. Therefore, the possible roles of TRPC5 in MS via the skeletal muscle remain and deserve to be investigated.

4.5. Connecting Metabolic Tissues and the Central Nervous System

The CNS has an important role in the regulation of food intake and energy metabolism. After a meal, satiation signals are sent by the gastrointestinal tract to multiple centres in the CNS (hypothalamus and the brainstem), as well as adiposity signals about energy availability in the WAT. Then, humoral and neuronal outputs are sent from the CNS to the peripheral metabolic tissues in order to regulate energy metabolism. These aspects have

been previously reviewed and discussed [274,275]. Herein, we present the current data that connect the CNS to the periphery in the regulation of energy metabolism via TRPs.

Evidence indicates that TPRV1 interacts with the CNS via appetite regulating hormones such as ghrelin (an orexigenic peptide found in the stomach [275], leptin, and the glucagon-like peptide-1 (GLP-1; an anorexigenic peptide hormone secreted by intestinal L-cells and pancreatic α-cells, and the brain [275–277]). Human data indicate that the acute TRPV1 activation increases GLP-1 and diminishes ghrelin levels in the plasma samples of individuals receiving a capsaicin-containing meal, as soon as 15 min after consumption, without altering energy expenditure [278]. Capsaicin effects on satiety are controversial with some studies indicating the compound reduces energy intake [279,280] and others showing no effects [278,281].

The stomach, especially the pyloric portion and duodenum, and the small and large intestines, express functional TRPA1 [282]. In the stomach, TRPA1 is expressed in ghrelin-producing cells. TRPA1 expression was also shown in the MGN3-1 cell line; this, when incubated with cinnamaldehyde, presents up-regulation of TRPA1 and insulin receptor mRNAs and reduced secretion of ghrelin. Cinnamaldehyde effects on ghrelin secretion were partially attenuated by TRPA1 antagonism with HC-030031. In vivo, the acute oral administration of cinnamaldehyde caused reduction in food intake in the initial 2h following treatment and delayed gastric emptying in WTs but not TRPA1KO mice. Repeated treatment with the compound did not affect food intake, but reduced body weights and fat mass, and improved insulin sensitivity in mice fed HDF [282]. The same mice presented increased expression of glucose transporters and of genes involved in fatty acid oxidation in WAT and BAT. TRPA1 involvement in ghrelin production was confirmed by another study in which intragastric β-eudesmol, an oxygenized sesquiterpene, increased food intake and plasma octanoyl ghrelin levels [283]. β-eudesmol also enhanced gastric vagal nerve activity, a response diminished by different TRPA1 antagonists and deletion of TRPA1 receptor. Despite the conflicting results, the data show that TRPA1 regulates ghrelin secretion and food intake; however, the degree of regulation may depend on the TRPA1 agonist and the activated pathways.

Additionally, TRPV1 is functionally expressed on the intestinal cell line secretin tumour cell-1 (STC-1) and in mouse ileum samples known to produce GLP-1 [284]. In the intestinal cells, capsaicin stimulated the production of GLP-1 which was blocked by the TRPV1 antagonists capsazepine and 5′-iodo-resiniferatoxin-α. Intragastric capsaicin increased plasma GLP-1 levels following glucose challenge in WTs and in mice with T2D, a response impaired by treatment with 5′-iodo-resiniferatoxin-α or receptor ablation [284]. Hypothalamic pro-opiomelanocortin neurones are involved in food intake and express functional TRPV1 [205]. These neurones respond to GLP-1 release via the GLP-1 receptor, and are also the site of action of liraglutide, a GLP-1 analogue used in the treatment of T2D [285]. In a recent report, GLP-1 was suggested to activate TRPV1/TRPA1-dependent Ca^{2+} currents in GLP-1 receptor-expressing enteric neurones, and the subsequent release of substance P [286]. It is possible, therefore, that GLP-1 may elicit Ca^{2+} influx via TRPs in hypothalamic pro-opiomelanocortin neurones.

Mouse intestinal L cells and the small intestine express functional TRPA1, which responds to allyl isothiocyanate and polyunsaturated fatty acids in vitro [287]. Indeed, the Ca^{2+} currents elicited by these compounds were blocked by the TRPA1 agonist A-967079. Allyl isothiocyanate caused GLP-1 release from intestinal cells in a TRPA1-dependent manner, without altering glucose-induced secretion of GLP-1. GLP-1 secretion was abolished in TRPA1KO intestinal cells and in those treated with HC-033031 [288]. Additionally, TRPA1 was found to mediate AS1269574-induced GLP-1 production in intestinal cells (STC-1 cells) [288]. Noteworthy, AS1269574 is an agonist of G protein-coupled receptor 119 (GPR119), an important enteroendocrine sensor of dietary triglyceride metabolites expressed in intestinal cells. Glucagon production triggered by AS1269574 though, is a direct result of GPR119 activation, with no involvement of TRPA1 [223]. The non-electrophilic small molecule GLP-1 secretagogue JWU-A021 produced TRPA1-dependent Ca^{2+} currents

in STC-1 and primary intestinal cells, which were suppressed by the antagonists A967079 and HC030031 [223]. More recently, allicin, another dietary TRPA1 agonist, restored GLP-1 levels and insulin sensitivity in HFD-fed mice [289]. These data indicate that intestinal located TRPA1 mediates GLP-1 release.

Leptin activates its receptor on hypothalamic pro-opiomelanocortin neurones and causes the subsequent increase in the levels of the anorectic peptide α-melanocyte-stimulating hormone, whilst inhibiting neuropeptide Y (NPY) neurones [290–292]. High levels of this hormone are present in most obese subjects and animals [293,294]. This is suggested to be due to the necessity for high circulating levels of leptin to overcome resistance to its action and maintain energy homeostasis [295]. Leptin resistance and altered energy balance have been attributed to obesity in TRPV1-null mice fed HFD [219]. Treatment with leptin did not reduce food intake, and leptin-mediated hypothalamic signals were impaired in the TRPV1KO mice [219]. These animals were more obese and insulin-resistant than their counterparts. On the other hand, in another study, leptin levels were raised in both TRPV1 WTs and KOs [173]. TRPV1 activation also enhanced the frequency of miniature excitatory synaptic currents in leptin receptor-containing neurones in stomach-associated brainstem dorsal motor nucleus of the vagus [296]. Evidence also indicates that TRPV1 receptor activity is diminished in the brainstem dorsal vagal complex of diabetic mice [297]. These data suggest that TRPV1 mediates the effects of leptin.

No reports have linked TRPA1 activation/expression to leptin signalling and its connection to the brain regions involved in hunger and energy expenditure. On the contrary, TRPC5 has been indicated as an interesting target to regulating leptin responses. In fact, the neuronal deficiency of TRPC5 or its deletion in pro-opiomelanocortin neurones leads to obesity associated with decreased energy expenditure and higher food intake in mice [209]. The same study demonstrated that both leptin and serotonin 2C receptor-agonists exert their acute anorexigenic effects via TRPC5 activation. TRPC5 complexes also contribute to melanocortin neuronal activity, thus altering energy metabolism and feeding behaviour [209]. Moreover, the intracerebroventricular injection of insulin resulted in a similar response of energy expenditure via TRPC5 activation [298]. Both insulin and leptin were suggested to activate TRPC5 indirectly, following their binding to their specific receptors and downstream signalling (phosphatidylinositide-3 kinase and phospholipase Cγ activation) [298]. Since both TRPC1 and TRPC4 are functionally expressed in pro-opiomelanocortin neurones [298], it is possible that all TRPC5 complexes contribute to the metabolic responses mediated by these cells. The protective role of neuronal TRPC5 complexes in MS is supported by data obtained from studies on GLP-1 agonists and their effects on pro-opiomelanocortin neurones [210,211]. Indeed, both liraglutide and semaglutide actions on pro-opiomelanocortin neurones involve TRPC5 activation in vivo and in mouse hypothalamic slices. Of note, in the hippocampus, leptin-dependent responses do not require TRPC5 expression [299].

Interestingly, mitochondrial-derived ROS are produced by brain neuronal cells of different regions including the hypothalamus [300,301] and are involved in central glucose [302] and hypertriglyceridemia sensing [303]. Accordingly, H_2O_2 causes a marked increase in the firing of hypothalamic pro-opiomelanocortin neurones and decreased feeding in mice [304]. Considering the ability of TRP channels to sense this ROS, it is also possible they mediate ROS signalling in these neurones.

5. Clinical Perspectives

In addition to non-clinical studies, the beneficial effects of modulating TRPV1, TRPA1 and TRPC5 channels in obesity, T2D, atherosclerosis and MS have been investigated in a range of clinical trials.

In these, pungent and non-pungent activators of TRPV1 have been assessed. In a study, either 0.25% capsaicin or placebo were given to 24 subjects (12 men and 12 women) with body mass index (BMI) of 25.0, 30 min before meal. Oral capsaicin enhanced satiety and diminished calorie and fat intake [279]. In another report with 19 overweight to obese

men, a supplement containing capsaicin increased energy expenditure in comparison to placebo [305]; these findings were supported by further studies [306–310]. The use of capsaicin 1h prior to low intensity exercise was also shown to improve lipolysis in healthy volunteers [242]. Moreover, capsaicin from *Capsicum frutescens* had hypoglycaemic effects in healthy individuals [311]. Capsinoids are non-pungent capsaicin-related substances [312]. Individuals with BMI between 25.0 and 35.0 received capsinoid oil (6 mg/day) obtained from *Capsicum anuum* L. variety CH-19 Sweet or placebo, capsinoids decreased body weight whilst enhancing fat oxidation [313]. The same study found a correlation between reduction of abdominal fat and the genetic variants TRPV1 Val585Ile and UCP-2-866 G/A. Another capsinoid, dihydrocapsiate, caused a small thermogenic effect in healthy subjects [314]. Consumption of a supplement containing low dose capsinoids (2 mg) led to increased plasma levels of FFA [315]. Accordingly, *C. anuum* capsinoids increased energy expenditure by activating BAT in healthy subjects in comparison with the placebo group [316,317]. The above data indicate the potential of capsaicin to treat obesity and hyperglycaemia. On the other hand, although promising, the thermogenic effects of capsinoids are yet to be confirmed in further studies with overweight and obese individuals.

Cinnamaldehyde is a major compound found in cinnamon barks [318]. Several studies have investigated the beneficial effects of cinnamon in T2D. In a study with 60 T2D subjects (30 woman and 30 men), intake of cinnamon capsules attenuated serum glucose, TG, total and low-density lipoprotein cholesterol [319]. In agreement, cinnamon extracts or supplements decreased plasma glucose levels and malondialdehyde concentrations, and improved lipid profile in overweight to obese individuals [320–323], and induced hypoglycaemia in T2D patients [324] and healthy subjects [325]. Conversely, cinnamon powder or supplement consumption did not alter plasma glucose or serum lipid profile in T2D patients [326,327]. A similar result was observed in postmenopausal patients with T2D [328] and healthy individuals [329]. Interestingly, cinnamon powder intake lowered blood pressure and glycated haemoglobin in patients with T2D [330]. Although the evidence gathered from these studies are controversial, they raise attention for further studies to support the potential use of cinnamon and derived compounds in the management of MS.

No clinical trials assessing the impact of TRPC5 in human MS have been published to date. Nonetheless, the use of TRPC4/TRPC5 inhibitors for cosmetic weight loss as well as to combat obesity, T2D, MS, NAFLD and non-alcoholic steatohepatitis was recently published (accession numbers: WO/2018/146485; EP3579838; US20200345741). Liraglutide and semaglutide antidiabetic actions in the hypothalamus require TRPC5, which indicates this channel is an interesting target for the development of novel therapies for MS.

Nonetheless, considering that MS is a complex disease, it is not surprising that other TRPs, in addition to TRPV1, TRPA1 and TRPC5, may influence the balance between oxidative stress and inflammation during disease progression. For instance, TRPM2 is another TRP activated by ROS (specifically, H_2O_2), which is involved in insulin resistance [213,331]. TRPM4 and TRPM5 expression were also described in human Langerhans islets, further indicating possible roles with clinical perspectives for MS [332]. Of note, TRPM2 expression is significantly enhanced during NAFLD, and its activation by ROS overproduced during the disease plays a significant role in pathophysiology contributing to its progression [333]. Natural antioxidants such as saliroside (from *Rhodiola rosea*) and curcumin are both able to inhibit TRPM2 activation in hepatocytes, resulting in reduction of lipid deposition, diminished expression of cytokines (IL-1β and IL-6) and protection against cell damage [333,334]. These are early findings and further research in the field is important and deserves to be pursued.

6. Conclusions

Most of the metabolic alterations comprised in MS are correlated with altered expression of TRPs and are directly connected with the observed vascular dysfunction in T2D

and obesity. Herein, the available information on the contribution of TRPV1, TRPA1 and TRPC5 to MS is discussed and summarized in Table 3.

Table 3. Overall contribution of TRPV1, TRPA1 and TRPC5 to metabolic syndrome: a summary of endogenous agonists, expression sites and roles.

TRP Channel	Endogenous Agonists	Expression Site	Role in MS
TRPV1	12 (S)-HPETE [118], 20-HETE [119], 9-HODE and 13-HODE [120], anandamide [121], H_2S [122], ROS (H_2O_2) [123]	Adipose tissue/adipocytes [124,125,200,201], liver [126,127], M1 macrophages [128], pancreatic β-cells/langerhans islets [132], coronary endothelial cells [123], T cells [129–131], skeletal muscle [202–204], pro-opiomelanocortin neurones [205]	Increase of insulin sensitivity [216,220,221], browning of WAT, reduction of lipid synthesis and obesity/adiposity [201,203,204,239], enhanced thermogenesis [240] and leptin sensitivity [219], reduction of lipid accumulation and TG [127], protection against endothelial dysfunction [253], increase of GLP-1 and attenuation of ghrelin production [278]
TRPA1	Methylglyoxal [138], 4-HNE, 15-deoxy-delta(12,14)-prostaglandin J_2 (15d-PGJ_2) and H_2O_2 [139]	Pancreatic β-cells/langerhans islets [137,206], T cells [175–177], adipocytes [244,245], vagus nerve [246]	Macrophage-mediate responses in atherosclerosis [180,184], increase of insulin secretion [137,222–225] and sensitivity [228,258,259], reduction of insulin signalling and insulin-induced glucose uptake in skeletal muscle cells [229], weight loss and reduction of TG and cholesterol [244,247], attenuated adipogenesis [250], increased adipose tissue inflammation and ROS [248,250] reduction of ghrelin [282], production of ghrelin [288]
TRPC5	H_2O_2 [145], reduced TRX [146], and fatty acids [147]	Endothelial cells [166], T cells [185], M1 macrophages [186], pancreas [208], adipose tissue [147,200], pro-opiomelanocortin neurones [209–211]	Polarization of macrophages to M2 and protection against atherosclerosis [186], negative regulation of adiponectin [147], enhance of energy expenditure [209,298]

Overall, these channels are involved in the regulation of different pathways of MS, including hormone production, inflammation, and ROS generation at systemic levels and different metabolic tissues (adipose, pancreatic, hepatic and skeletal muscle), connecting those to the CNS. The different patterns of expression of these channels across tissues confer on them the ability to control a variety of cell functions. Non-clinical and clinical data clearly highlight the potential of ligands for these channels, especially natural compounds such as capsaicin/capsinoids and cinnamaldehyde, to treating the various aspects of MS, from insulin resistance to atherosclerosis. Considering the multiple mechanisms underlying MS establishment and progression, it is possible that a combination of TRP ligands may confer better control of adiponectin release, ROS production, and inflammation in the disease. In this context, the dual roles of TRPs such as that of TRPA1 in atherosclerosis must be considered.

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ANEXO B

ARTIGO 02 - Analysis of the Effect of the TRPC4/TRPC5 Blocker, ML204, in Sucrose-Induced Metabolic Imbalance

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Analysis of the Effect of the TRPC4/TRPC5 Blocker, ML204, in Sucrose-Induced Metabolic Imbalance

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Abstract: Sugar-induced metabolic imbalances are a major health problem since an excessive consumption of saccharides has been linked to greater obesity rates at a global level. Sucrose, a disaccharide composed of 50% glucose and 50% fructose, is commonly used in the food industry and found in a range of fast, restaurant, and processed foods. Herein, we investigated the effects of a TRPC4/TRPC5 blocker, ML204, in the metabolic imbalances triggered by early exposure to sucrose-enriched diet in mice. TRPC4 and TRPC5 belong to the family of non-selective Ca^{+2} channels known as transient receptor potential channels. High-sucrose (HS)-fed animals with hyperglycaemia and dyslipidaemia, were accompanied by increased body mass index. mesenteric adipose tissue accumulation with larger diameter cells and hepatic steatosis in comparison to those fed normal diet. HS mice also exhibited enhanced adipose, liver, and pancreas TNFα and VEGF levels. ML204 exacerbated hyperglycaemia, dyslipidaemia, fat tissue deposition, hepatic steatosis, and adipose tissue and liver TNFα in HS-fed mice. Normal mice treated with the blocker had greater hepatic steatosis and adipose tissue cell numbers/diameter than those receiving vehicle, but showed no significant changes in tissue inflammation, glucose, and lipid levels. The results indicate that TRPC4/TRPC5 protect against the metabolic imbalances caused by HS ingestion.

Keywords: high sucrose intake; metabolic changes; fat deposition; hepatic steatosis; TRPC4 and TRPC5 channels

1. Introduction

The intake of high-content sugar foods and beverages from an early age has been linked to an increased risk of obesity, type II diabetes, and cardiovascular diseases, amongst

other chronic pathological alterations [1–5]. Sucrose is a disaccharide composed of 50% glucose and 50% fructose commonly added to foods and drinks as a sweetener [6]. In humans, the long-term daily ingestion of sucrose has been linked to an increase in body weight, fat mass, hepatic steatosis, and cholesterol levels in overweight subjects [7,8]. In addition, studies with healthy- and normal-weight young male volunteers have demonstrated that high-sucrose (HS) diets augment glucose, low-density lipoprotein, and C-reactive protein quantities [9,10]. Similar observations have been made in rodents following HS diet [11–14]. This evidence demonstrates that HS causes important metabolic imbalances, which can result in chronic pathologies such as metabolic syndrome (MS), a major health problem which affects the global population at all ages [15,16].

Transient receptor potential channels are non-selective Ca^{+2} channels involved in a plethora of pathological and physiological roles [17–21]. First described in *Drosophila melanogaster* (for review see: [22–24]), it is now known that their expressions and activation profiles on neuronal and non-neuronal cells can influence the protection against or the development of a range of chronic diseases in mammals, including pain [25,26], cardiovascular diseases [27,28], asthma [29,30], amongst others. Also, their contributions to MS have been explored within the last several decades, especially in regard to TRP vanilloid 1 (TRPV1) and TRP ankyrin 1 (TRPA1) channels [31,32]. On the other hand, information on the involvement of TRP canonical channels 4 (TRPC4) and 5 (TRPC5) in weight and metabolic regulations remains scarce and deserves further investigation. As TRPC4 and TRPC5 can form homo- and heterotetramers between themselves and also with TRPC1, their roles in metabolic homeostasis are rather complex and have been recently discussed [33]. Interestingly, TRPC4 activation was found to modulate insulin secretion by triggering pancreatic cell depolarisation and Ca^{2+} influx, and the disruption of TRPC1/TRPC5 signalling was demonstrated to result in an increased generation of adiponectin by adipocytes [34,35]. Recent studies have also demonstrated that the central actions of liraglutide and semaglutide, type II antidiabetic drugs associated with marked weight loss, on hypothalamic proopiomelanocortin (POMC) neurones require TRPC5 signalling [36,37]. On the contrary, the use of TRPC4/TRPC5 inhibitors was requested for cosmetic weight loss and treatment of obesity, type II diabetes, MS, and hepatic steatosis (accession numbers: WO/2018/146485; EP3579838; US20200345741).

Herein, in order to obtain more information on the role of TRPC4 and TRPC5 in the metabolic alterations caused by HS diet, we used a dual TRPC4/TRPC5 blocker, ML204, and investigated its effects on body weight, hyperglycaemia, dyslipidaemia, fat tissue accumulation, and tissue inflammation, in comparison with mice fed a standard diet. The results indicate a protective role for TRPC4/TRPC5 against the metabolic imbalances caused by HS ingestion.

2. Results

2.1. High Sucrose Induces Increased Body Mass Index, Fat Accumulation, and Glycaemia

We initially investigated the effects of HS intake on body weight, BMI, fat mass, and glycaemia, parameters that are commonly affected by diet (for review see: [38,39]). Although only a modest increase in body weight at the 20th week was observed in animals fed HS diet in comparison with those receiving standard chow (Figure 1A; $p > 0.05$), HS ingestion led to a transient increase in BMI at the 4th week, which became sustained from the 18th week in comparison with animals receiving a standard diet (Figure 1B; $p < 0.05$). An analysis of the areas under the curves from the 18th to the 20th week demonstrated that there are no differences in body weight between groups ($p > 0.05$): 32.5 ± 9.8 (standard diet group) versus 34.7 ± 9.6 (HS diet group). In addition, an analysis of the areas under the curves from the week 18th to the 20th week confirmed the differences observed in Figure 1B between the BMIs of HS- and standard diet-fed mice as follows: 0.549 ± 0.02 (standard diet group) versus 0.653 ± 0.019 (HS diet group); $p < 0.05$. Hyperglycaemia was also noted from the 10th week in HS-fed mice (Figure 1D; $p < 0.05$) when compared to those receiving standard diet. On the other hand, Lee indexes were similar in those receiving either diets

(Figure 1C; $p > 0.05$). The mesenteric fat was collected and weighed at the end of the 20th week as a measure of adipose tissue accumulation in the abdomen. HS diet-fed animals with a marked fat deposit increase in comparison to those receiving standard diet showed the following mean ± SEM values: 10.8 ± 1.9 (standard diet group) versus 24.3 ± 1.8 mg of fat/g of body weight (HS diet group; $p < 0.05$).

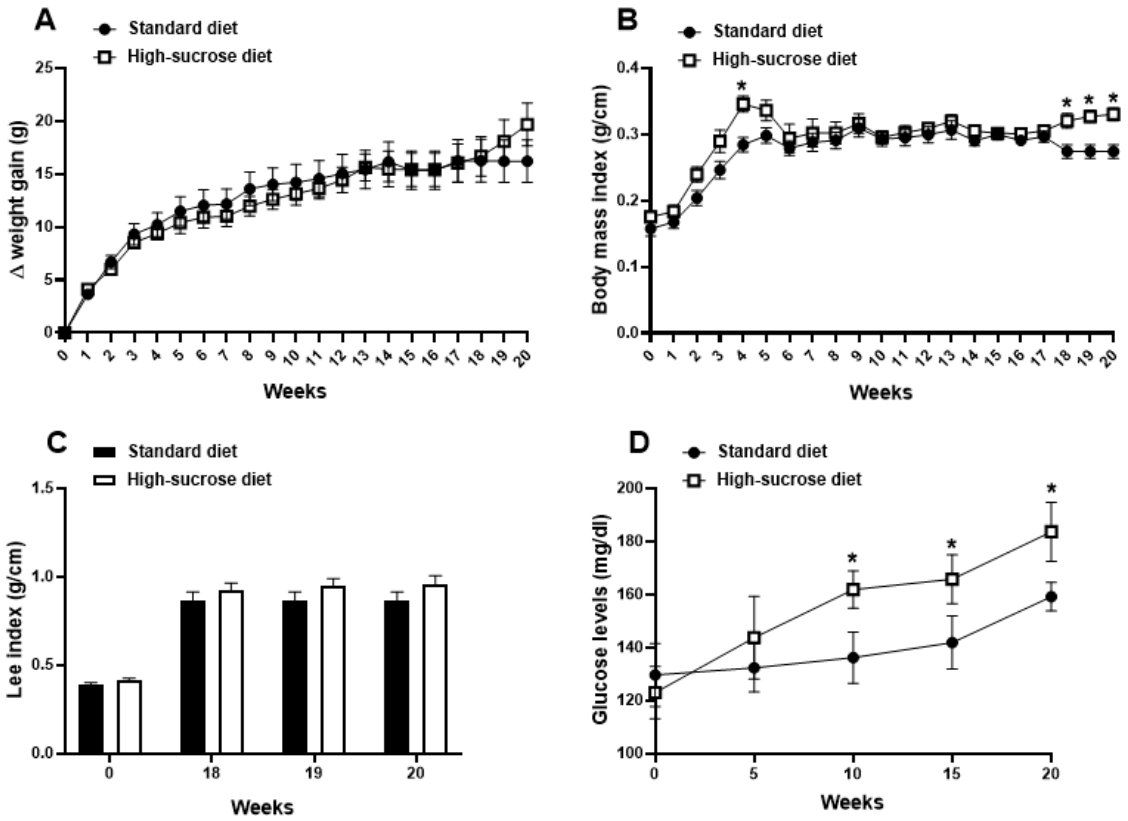

Figure 1. Effects of high-sucrose (HS) diet on body weight, body mass (BMI), and Lee indexes, and glycaemia. Animals received either HS or standard diet for 20 weeks ($n = 6$/group). Body weight gain (**A**) and BMI (**B**) were registered once a week. Lee index (**C**) was measured once a week from the 18th week, and blood glucose levels (**D**) were recorded at every 5 weeks. Glucose was measured in non-fasted animals. * $p < 0.05$, differs from the standard diet group.

2.2. ML204 Regulates Circulating Glucose and Lipid Levels

In order to assess the involvement of TRPC4/TRPC5 in the metabolic changes caused by a high sugar diet, animals receiving a standard or HS diet were treated with either ML204 or vehicle. Figure 2 depicts the effects of ML204 on HS- and standard diet-fed mice. Repeated treatment with ML204 did not affect body weight gain, nor body mass (BMI) and Lee indexes in animals fed any of the diets (Figure 2A–C; $p > 0.05$). In contrast, ML204 further increased hyperglycaemia and impaired glucose tolerance in HS-fed mice (Figure 2D,E; $p < 0.05$). Of notice, ML204 also induced an elevation of blood glucose and caused glucose intolerance in those receiving a standard diet (Figure 2D,E; $p < 0.05$).

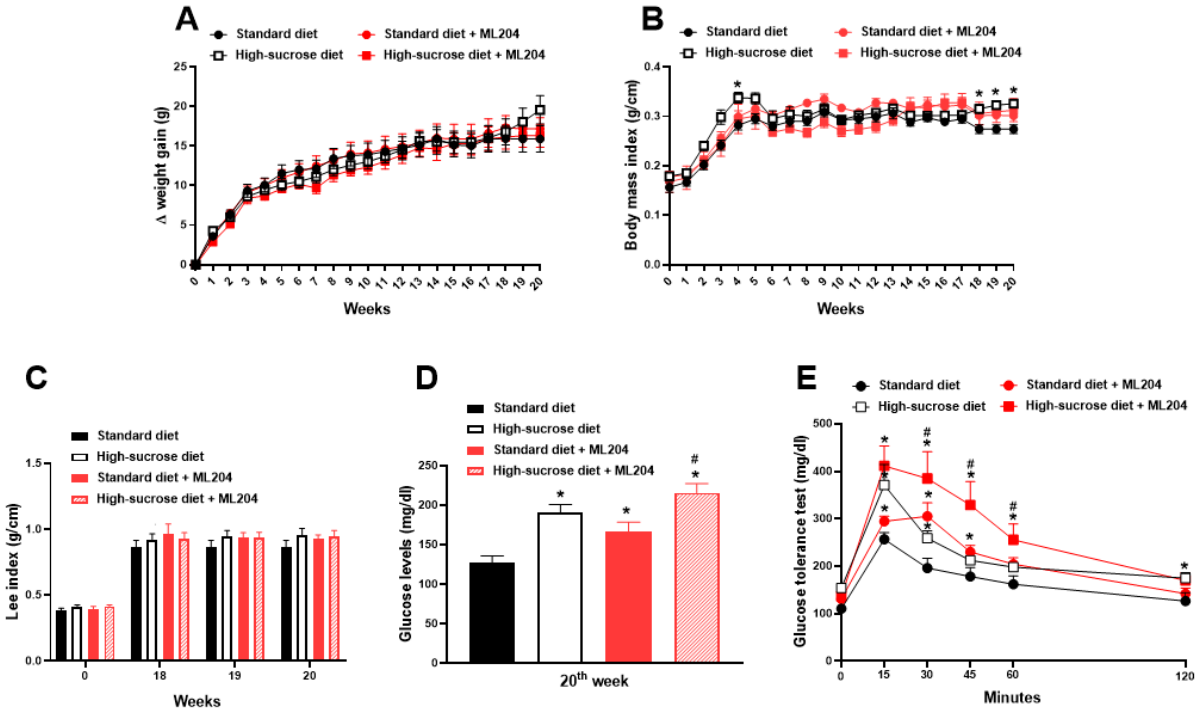

Figure 2. Repeated ML204 treatment increases blood glucose levels and impairs glucose tolerance. Animals received either a high-sucrose or standard diet for 20 weeks (n = 8/group). Body weight gain (**A**) and body mass index (BMI; (**B**)) were registered once a week. Lee index (**C**) was measured once a week from the 18th week. Blood glucose levels (**D**) were recorded at every 5 weeks and a glucose tolerance test (**E**) was performed at the 20th week. Glucose and glucose tolerance were measured in non-fasted and fasted animals, respectively. ML204 (2 mg/kg) or vehicle (3% dimethyl sulfoxide (DMSO) in phosphate-buffered saline (PBS)) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. * $p < 0.05$, differs from the standard diet group; # $p < 0.05$, differs from the high-sucrose diet control group.

Interestingly, ML204 did not alter triglyceride or cholesterol levels and neither the amount of mesenteric fat in standard diet-fed mice (Figure 3A,B; $p > 0.05$). Conversely, it caused hypertriglyceridaemia and exacerbated hypercholesterolemia in animals fed HS diet (Figure 3A,B; $p < 0.05$).

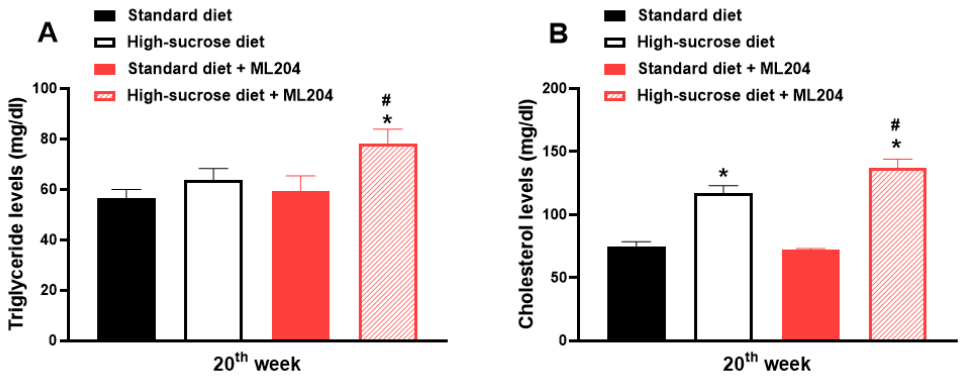

Figure 3. Repeated ML204 treatment causes hypertriglyceridaemia and exacerbates hypercholesterolemia in animals fed a high-sucrose (HS) diet. Animals received either HS or standard diet for 20 weeks (n = 8/group). Triglyceride (**A**) and total cholesterol (**B**) levels were measured at the end of the 20th week. ML204 (2 mg/kg) or vehicle (3% DMSO in PBS) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. * $p < 0.05$, differs from the standard diet group; # $p < 0.05$, differs from the high-sucrose diet control group.

2.3. ML204 Increases High-Sucrose-Induced Adipose Tissue and Liver Inflammation by Modulating TNFα Production

Inflammation is an important event that contributes to metabolic imbalances; thus, tumour necrosis factor α (TNFα) and vascular endothelial growth factor (VEGF) levels (inflammatory mediators involved in obesity and glycaemia control (for review see: [33,40])) were evaluated in adipose tissue, liver, and pancreas samples obtained from animals fed either a standard or HS diet. HS diet-fed mice led to a greater release of these inflammatory mediators in adipose tissue and liver samples in comparison with those receiving standard diet, an effect which was further enhanced by ML204 injection (Figure 4A–D; $p < 0.05$). No differences were observed in regard to the pancreas levels of TNFα and VEGF between diets (standard diet versus HS diet) or treatments (vehicle versus ML204) (Figure 4E,F); $p > 0.05$.

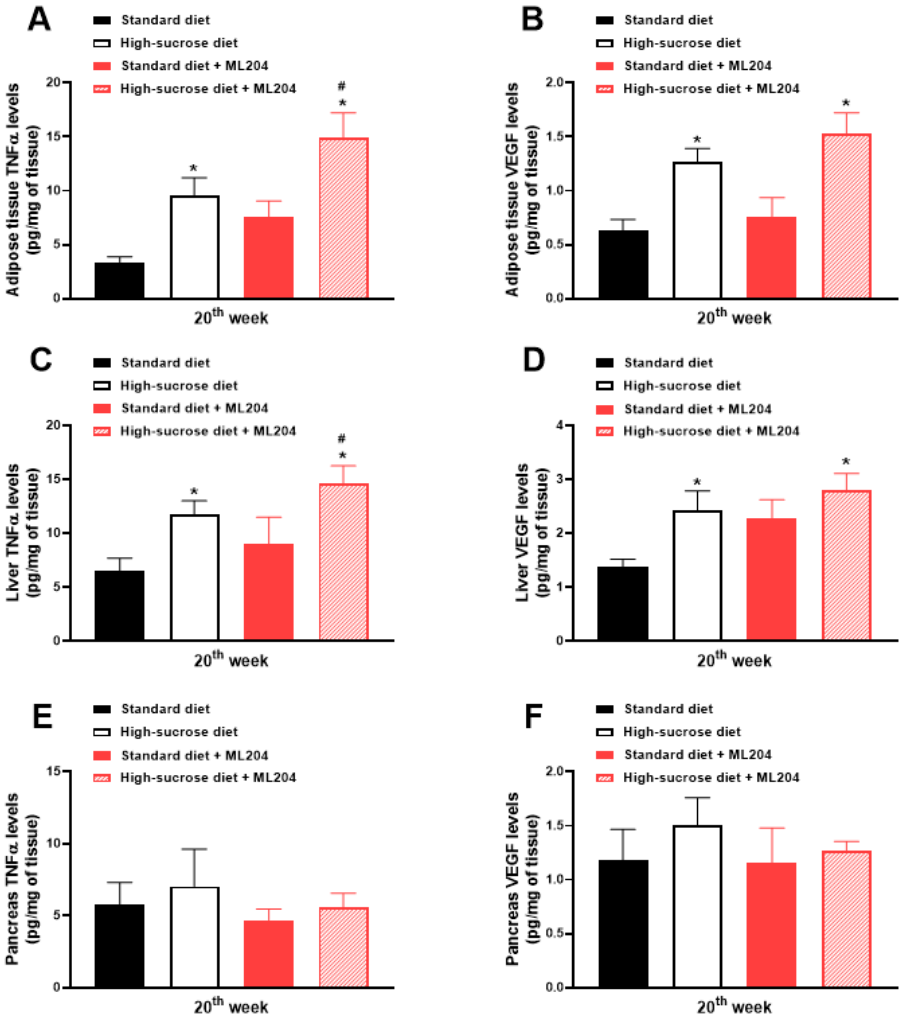

Figure 4. Repeated ML204 treatment enhances inflammation in the adipose and liver tissues of animals fed a high-sucrose (HS) diet. Animals received either HS or standard diet for 20 weeks ($n = 8$/group). TNFα was measured in (**A**) adipose tissue, (**C**) liver, and (**E**) pancreas. Adipose (**B**), liver (**D**), and pancreas (**F**) VEGF tissue levels. Samples were collected at the end of the 20th week. ML204 (2 mg/kg) or vehicle (3% DMSO in PBS) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. * $p < 0.05$, differs from the standard diet group; # $p < 0.05$, differs from the high-sucrose diet control group.

2.4. ML204 Enhances Adipocyte Area and Mesenteric Fat Accumulation in High-Sucrose-Fed Mice and the Size of Adipocytes in Those Receiving Standard Diet

The analysis of the mesenteric adipose tissue (Figure 5A–D; $p < 0.05$) indicates a greater fat accumulation in animals fed HS diet. The mice receiving HS diet presented with higher fat-to-body weight ratios, as well as with larger adipocyte areas and sizes (>50–100 μm) than those that received standard diet; $p < 0.05$. ML204 administration further enhanced fat weight and adipocyte area in HS-fed mice without affecting the size of their adipocytes (Figure 5B–D; $p < 0.05$). Interestingly, although no effects were observed for ML204 in regard to the fat weight and adipocyte areas of mice fed standard diet, the same animals presented a significant percentage of medium-sized cells (30–40 μm; $p < 0.05$) in comparison with vehicle controls.

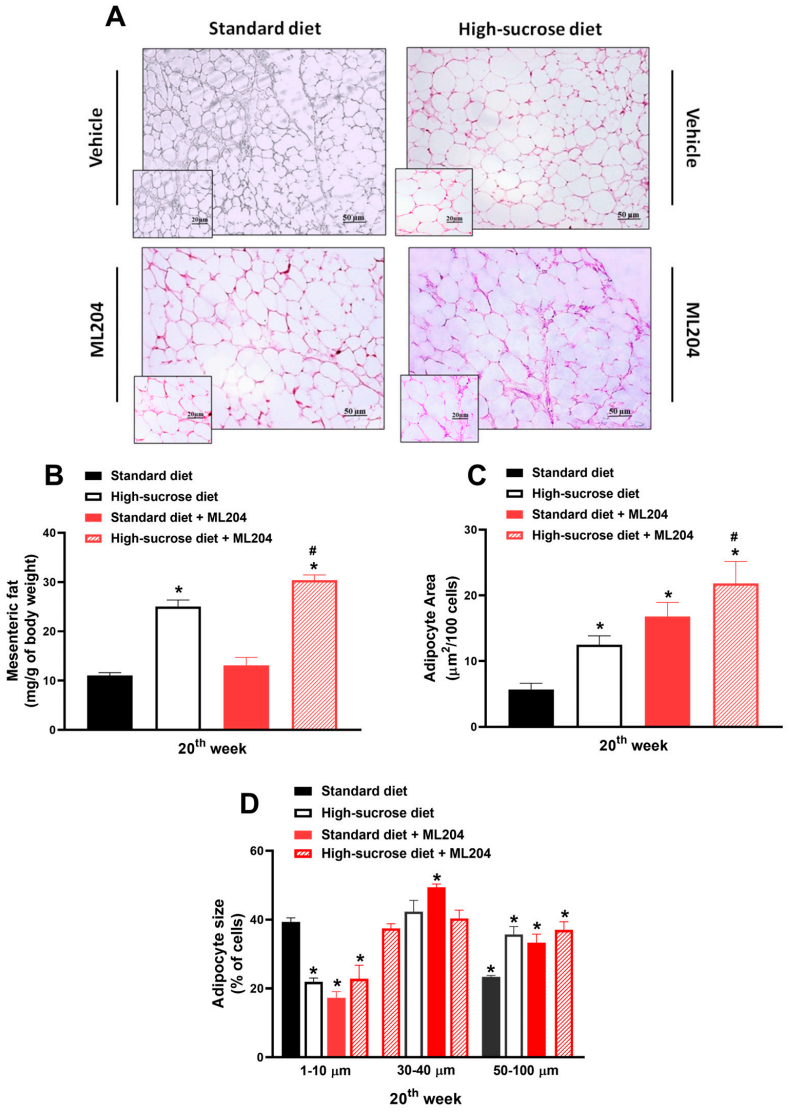

Figure 5. Repeated ML204 treatment causes fat accumulation in animals fed high-sucrose (HS) diet and the size of adipocytes in those receiving standard diet. (**A**) Representative H&E histology sections of adipose tissue (20 and 50 μm areas) from animals fed either HS or standard diet for 20 weeks ($n = 8$/group). Mesenteric fat/body weight ratios (**B**), adipocyte area (**C**), and size (**D**) measured at the end of the 20th week. ML204 (2 mg/kg) or vehicle (3% DMSO in PBS) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. Samples were stained by haematoxylin and eosin (H&E). * $p < 0.05$, differs from the standard diet group; $^{\#}$ $p < 0.05$, differs from the high-sucrose diet control group.

2.5. Non-Alcoholic Fatty Liver Disease Activity Score Is Enhanced by ML204 in High-Sucrose-Fed Mice

We next investigated the effects of ML204 on non-alcoholic fatty liver disease NAFLD activity score (NAS). Figure 6A–C show that HS diet increases NAS by causing hepatic steatosis (red arrows), ballooning (orange arrows), and inflammatory cell influx (dark green arrows) to the tissue; $p < 0.05$. In a much lesser degree, ballooning and cell migration, but not steatosis are noted in standard-diet animals treated with ML204 (Figure 6; $p < 0.05$).

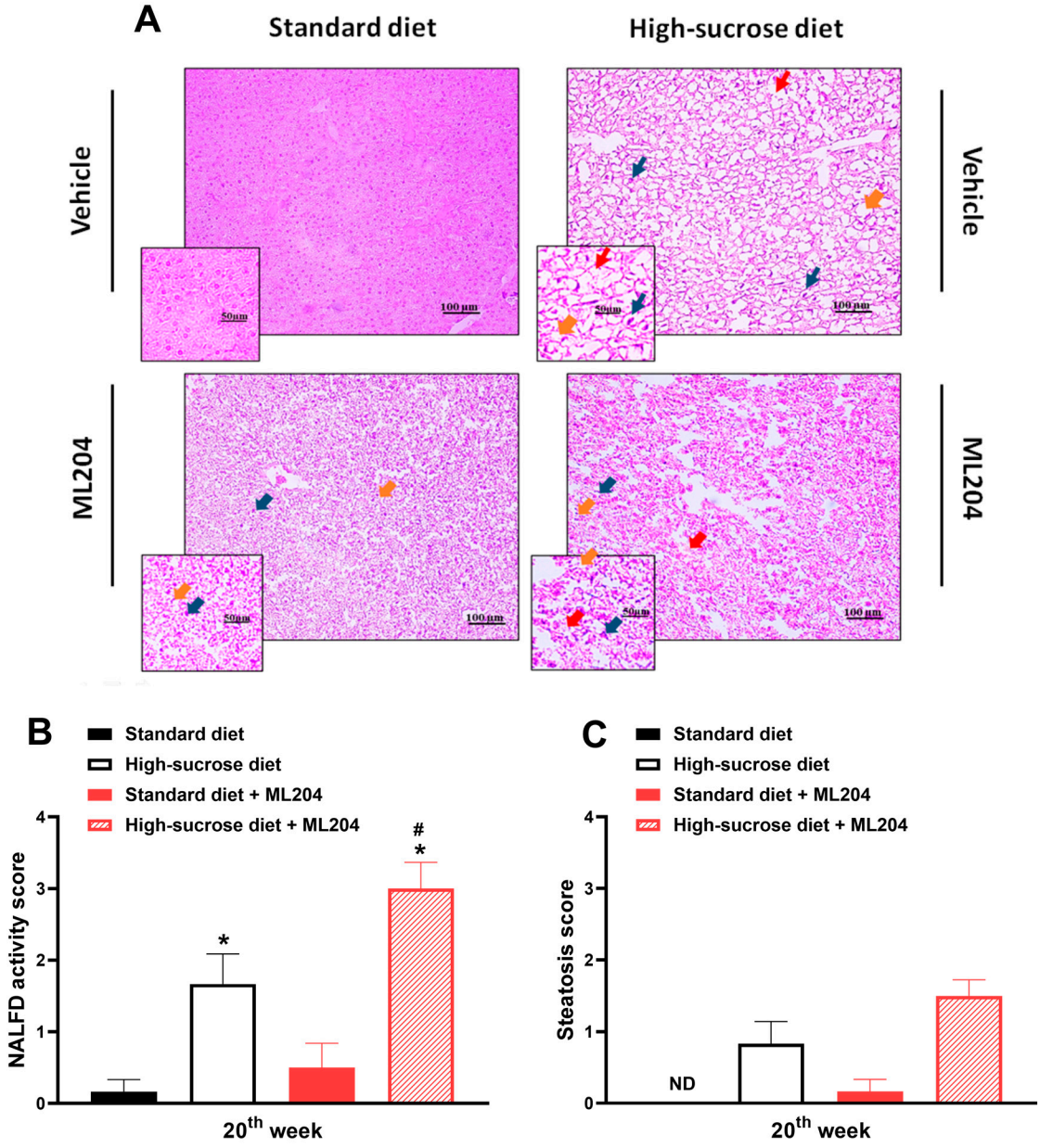

Figure 6. Repeated ML204 treatment increases non-alcoholic fatty liver disease (NALFD) activity score (NAS) in high-sucrose (HS)-fed mice. (**A**) Representative H&E histology sections of liver (50 and 100 μm areas) from animals fed either HS or standard diet for 20 weeks ($n = 8$/group). NAS (**B**) and steatosis score (**C**) were measured at the end of the 20th week. ML204 (2 mg/kg) or vehicle (3% DMSO in PBS) was administered subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. NAS was determined by the summation of hepatic steatosis (red arrows), ballooning (orange arrows), and inflammatory cell influx (dark green arrows) scores. Samples were stained by haematoxylin and eosin (H&E). * $p < 0.05$, differs from the standard diet group; $^{\#}$ $p < 0.05$, differs from the high-sucrose diet control group.

3. Discussion

In the last several decades, foods and beverages containing high sugar levels became popular products found in the shelves of houses, restaurants, bars, and supermarkets all around the world. Diets rich in such products are now well-known to increase the risk for chronic diseases associated with metabolic imbalances, including obesity [38,41,42]), type II diabetes [42], and cardiovascular diseases [43], amongst other chronic pathological alterations, indicating that HS diets cause important metabolic changes, which can result in MS. This is particularly important considering the early age intake of HS [1–5]. Indeed, a recent analysis of the global scenario demonstrated that nearly 3% of children and 5% of the adolescent population present with MS [16]. Also, a drastic panorama has been noted in the adult population, with a 19.5% and 48.6% prevalence of MS amongst 20–39 year olds and those $\geq$60 years, respectively [15].

Herein, as expected [44–48], HS diet promoted a modest weight gain. Also in agreement, HS significantly increased BMI, hyperglycaemia, mesenteric fat deposition, glucose tolerance, hypercholesterolemia, and NAS score in comparison with mice receiving a standard diet. In addition, HS-fed mice presented with adipose tissue and liver inflammation characterised by increased levels of TNFα, a cytokine involved in adipocyte hypertrophy, fat deposition, insulin resistance, and hyperglycaemia (for review see: [33]). Higher VEGF levels were also noted in both liver and adipose tissue samples from HS mice. Of note, VEGF production in the adipose tissue is suggested to play a protective role against hypoxia, insulin resistance, and obesity, being an essential growth factor in the maintenance of metabolism homeostasis [49,50].

We show for the first time that when repeatedly administered to mice, ML204 exacerbates hyperglycaemia, dyslipidaemia, fat tissue deposition, hepatic steatosis, and adipose tissue and liver inflammation in HS-fed mice. The compound also affected normal mice, promoting hepatic steatosis and increasing adipose tissue cell numbers and diameter without causing tissue inflammation, or changing glucose and lipid levels.

We used a dual TRPC4/TRPC5 blocker, ML204, to further understand the roles of TRPC4 and TRPC5 in the metabolic alterations caused by HS diet. ML204 was first described as a potent and selective TRPC4/TRPC5 inhibitor in vitro [51,52]. Since then, accumulating evidence has demonstrated its ability to modulate inflammatory responses by regulating cytokine (TNFα, IL-1β, IL-6, and IL-10) production in vivo and in vitro, although reductions in or upregulations of these proteins seem to depend on the model used [53–55]. Importantly, inflammation, alongside oxidative stress (events in which these channels are shown to modulate) in metabolic tissues, are important mechanisms of glucose and lipid imbalances, which can ultimately contribute to MS development and progression (for review see: [33]).

Knowledge from the last several decades has consistently pointed to the importance of TRP channels such as TRPV1 and TRPA1 in MS [31,32]. However, only recently, an emerging and complex role has been attributed to TRPC channels, especially TRPC5. This is mainly due to its ability to form not only homotetrameric, but also heterotetrameric complexes with other TRP channels (TRPC4 and TRPC1; for review see: [33]).

In this context, it is important to consider the contributions of both homo- and heterotetramers containing TRPC5 in the regulation of metabolism. Whilst TRPC4 activation was shown to modulate insulin secretion, and TRPC1/TRPC5 signalling was suggested to regulate adiponectin release by adipocytes [34,35], TRPC4/TRPC5 inhibitors were recently patented for use in weight loss, type II diabetes, MS, and hepatic steatosis (accession numbers: WO/2018/146485; EP3579838; US20200345741). Also, TRPC5 was suggested as a key mediator for the central effects of the glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide and semaglutide [34,35], used for type II diabetes and weight loss [56,57]. The above pieces of evidence indicate that TRPC5 contributions to metabolic homeostasis may require both central and peripheral actions, and depend on the tetramer activation. Nonetheless, the results clearly indicate that TRPC4/TRPC5 channels protect against the metabolic imbalances caused by HS ingestion.

4. Materials and Methods

4.1. Animals

Inbred male and female C57BL/6 mice (3 weeks old) from the Biological Service Unit of Universidade CEUMA were used. All the animals were housed under 12 h light/dark cycle, at a controlled environmental temperature (21 ± 2 °C) and humidity (60 ± 5%). All the experimental groups were matched for gender and body weight. All experiments followed the recommendations of the Brazilian guidelines on animal experimentation of the National Council for the Control of Animal Experimentation (CONCEA) and the ARRIVE guidelines [58]. All procedures were previously approved by the Animal Use Ethics Committee of Universidade CEUMA (protocol nº 00081/18).

4.2. High-Sucrose-Induced Metabolic Disturbances

A total of 22 female and 22 male mice were used in the study. In order to standardise the model, mice received either normal or HS diet (3 male and 3 female mice/group), as previously described [59]. Either standard (Nuvital®, Nuvilab; Curitiba; Brazil; 3.52 kcal/g; composed of 55.4% carbohydrate (10% sucrose), 21% protein, and 5.2% lipids) or HS diet (3.48 kcal/g; composed of 65% carbohydrate (25% sucrose), 12.3% protein, and 4.3% lipids) was fed to the mice for 20 weeks. Both water and food were provided ad libitum. Body weights and body mass indexes (BMI; body weight (g)/ nose-to-anus length (cm)) were registered for each mouse prior to and at every week, once a week post-diet. Analyses of AUCs were performed for body weight changes and BMIs between weeks 18 and 20. In parallel, the Lee index ($\sqrt[3]{}$body weight (g)/nose-to-anus length (cm) × 1000) [59]) was analysed at the 18th, 19th, and 20th weeks post-diet. Glycaemia was measured at baseline and at every five weeks from blood samples collected from the tail veils of restrained non-fasted animals by using a portable glucose meter and glucose strips (Accu-Chek Active®, Roche, Indianapolis, IN, USA).

To evaluate the effects of ML204, standard- and HS diet-fed mice received either vehicle (3% DMSO in PBS; *v*/*v*) or ML204 (2 mg/kg), subcutaneously, once a day, for 7 days starting at the beginning of the 19th week. Body weights, body mass, and Lee indexes were measured at baseline, prior to and after ML204 treatment (between the 18th and 20th weeks), and evaluated as described above. Also, at the end of the 20th week, following 8 h of fasting, a glucose tolerance test was performed. Just before fasting, blood glucose levels were tested. Then, the animals were anaesthetised with ketamine and xylazine (75 mg/kg and 1 mg/kg, respectively). Blood samples were collected by cardiac puncture for analysis of the circulating quantities of triglyceride and cholesterol. Liver, mesenteric adipose, and pancreas tissue samples were collected for histology and inflammatory mediator production analysis (TNFα and VEGF).

4.3. Glucose Tolerance Test

For analysis of glucose tolerance, baseline blood glucose was measured in fasted mice. Then, animals received an intraperitoneal injection of glucose (2 g/kg; [60]). Next, glycaemia was measured from blood samples collected from the tail veil of restrained mice at 15, 30, 45, 60, and 120 min post-glucose administration in comparison to baseline by using a portable glucose meter and glucose strips (Accu-Chek Active®, Roche, Indianapolis, IN, USA).

4.4. Cholesterol and Triglyceride Quantifications

The blood collected at the end of the 20th week post-diet was centrifuged at 1300× *g* for 15 min, for serum separation. Serum levels of cholesterol and triglyceride were measured by using commercial kits according to manufacturer's instructions (Labtest, MG, Brazil). For this, 10 µL of the serum was used per reaction for each assay in duplicate. Samples were incubated at 37 °C for 10 min and then, the absorbances were read at 500 nm. The results are expressed as milligram per decilitre (mg/dL) of cholesterol or triglyceride.

4.5. TNFα and VEGF Tissue Levels

Approximately 100 mg of tissue was homogenised in 500 µL of PBS containing protease inhibitors (cOmplete™, EDTA-free Protease Inhibitor Cocktail; Sigma-Aldrich; São Paulo; Brazil), by using a tissue lyser (6 cycles of 30 s each, 4000 r.p.m.; between cycles, samples were kept on ice for 20 s; TissueLyser LT; Qiagen; São Paulo, SP, Brazil). The homogenates were centrifuged at 1000 r.p.m., for 10 min, at 4 °C and the supernatants collected and used for the measurements of TNFα and VEGF in adipose tissue, liver, and pancreas samples by using pre-coated plates, as per the manufacturer´s protocol (Sigma-Aldrich; São Paulo, SP, Brazil). Protein content of each supernatant was determined by using BCA protein kit, according to manufacturer´s instructions (Sigma-Aldrich; São Paulo, SP, Brazil). For this, 100 µL per well of the supernatants was used for each assay in duplicate. Absorbances for each sample were compared to those of a standard curve of each inflammatory mediator. The results are expressed as picograms of sample per milligram (pg/mg) of tissue.

4.6. Histology

Portions of the liver and mesenteric adipose tissues were collected, washed in PBS, and infused with 10% formalin in PBS for 24 h. Then, the samples were embedded in paraffin for cutting. Tissue samples were deparaffinised in xylene followed by dehydration in a graded series of ethanol/water. Serial 10 µm (adipose tissue) and 5 µm (liver) sagittal sections were cut on a microtome. Samples were stained with haematoxylin and eosin (H&E) to allow for the observation of the general morphology of tissues by microscopy (Nikon Eclipse Ci-L; Nikon, Biolab; São Paulo; Brazil).

Two independent observers blinded to treatments scored the liver sections for steatosis (score 0–3), hepatocyte ballooning (score 0–2), and inflammation (score 0–3), according to NAS, and were modified [14]. The maximum possible score was 8, and the results are expressed as the mean of the scores attributed by each observer.

Four pictures from separate parts of each section of adipose tissue were taken. Then, the area of 100 cells was measured (ImageJ; bundled with Zulu OpenJDK 13.0.6.; Madison, WI, USA) and the percentage (%) of the different cell sizes was calculated [45]. All counts were performed by two different observers blinded to treatments.

4.7. Statistical Analysis

The results are presented as mean ± mean standard error (SEM). For multiple statistical comparisons between groups, data were analysed by repeated measures analysis of variance (ANOVA), or one-way ANOVA, followed by the Bonferroni test with FDR correction. Unpaired t tests were used when appropriate. Histology scores were analysed using Kruskal–Wallis test followed by Dunn's test for multiple comparisons. All data were analysed in GraphPad Prism 6.0. (now Dotmatics; Woburn, MA, USA); $p < 0.05$ was considered significant. All n numbers are indicated on the graphs.

5. Conclusions

Although we were not able to dissect the expression sites in which activated TRPC4 and TRPC5 can influence metabolism changes, the data presented herein clearly demonstrated the importance of TRPC4/TRPC5 as protective channels against the metabolic imbalances caused by HS diet and highlights the need for further investigations in the field. Considering the complex roles of TRPC4 and TRPC5 either as homotetramers or heterotetramers, as well as of other heterotetramers formed between TRPC5 and TRPC1, for example, it is essential to highlight that the interpretation of data obtained from the use of TRPC5 activators, blockers, or genetically modified animals must always take into account such receptor interactions.

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