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IGOR HENRIQUE RODRIGUES DE PAIVA

# AÇÃO DOS PREBIÓTICOS (FRUTOLIGOSSACARÍDEOS E GALACTOLIGOSSACARÍDEOS) SOBRE AS VIAS DE SINALIZAÇÃO DA NEUROINFLAMAÇÃO, ANSIEDADE E DEPRESSÃO EM MODELO ANIMAL DE OBESIDADE INDUZIDA POR DIETA

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Tese apresentada ao Programa de Pós-Graduação em Ciências Biológicas da Universidade Federal de Pernambuco, como requisito parcial para a obtenção do título de Doutor em Ciências Biológicas. Área de concentração: Biotecnologia

Orientadora: Profª. Drª. Christina Alves Peixoto

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Aprovada em / / .

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*Per scientiam aridam terram floret*

**RESUMO**

Estudos anteriores demonstraram que os prebióticos podem influenciar a composição da microbiota intestinal, consequentemente impactando a regulação do humor. Este estudo teve como objetivo avaliar os efeitos dos prebióticos, especificamente frutooligossacarídeos (FOS) e galactooligossacarídeos (GOS) na neuroinflamação, depressão e comportamento semelhante à ansiedade em um modelo animal de obesidade induzida por dieta rica em gordura (HFD). Inicialmente, os camundongos foram divididos em dois grupos: um grupo controle em uma dieta padrão (n = 15) e um grupo em uma HFD por 18 semanas (n = 45). Na 13ª semana, o grupo HFD foi subdividido em grupos experimentais: controle (n = 15), HFD (n = 15), HFD recebendo prebióticos (n = 15) e HFD recebendo fluoxetina (n = 15). A partir da 13ª semana, o grupo HFD + Prebióticos e HFD + Fluoxetina permaneceram tanto a dieta rica em gordura quanto nos seus respectivos tratamentos diluídos na água potável até a 18ª semana. Na 18ª semana, todos os camundongos foram submetidos a testes para avaliar o comportamento, incluindo o Teste de Suspensão da Cauda (TST), Teste de Natação Forçada (FST), Teste de respingo de sacarose (SST) e o Teste do Labirinto em Cruz (PMT), após os qual foram eutanasiados. Os camundongos do grupo HFD exibiram aumento no peso corporal, tamanho abdominal, glicemia, níveis de triglicerídeos, colesterol, insulina, índice HOMA (Homeostasis Model Assessment) e maior Interleucina (IL)-1β sérico em relação ao grupo controle. Esses camundongos obesos também apresentaram aumento no número de microglia e astrócitos, ativação da via TLR4 e níveis elevados de marcadores neuroinflamatórios como TNF-α, IL-1β e COX-2. Além disso, os camundongos obesos mostraram aumento na ativação da via IDO e diminuição nos níveis de receptores NMDA. Os marcadores de neurogênese e plasticidade sináptica, como PSD, SAP 102, CREB-p e BDNF, tiveram menores expressão proteica. O tratamento com FOS e GOS reverteu sintomas de depressão e ansiedade em camundongos submetidos à HFD. Essa melhora no comportamento resultou de uma redução na disbiose com um aumento nas bactérias produtoras de acetato *(Bacteroides acidifaciens* e *Bacteroides dorei*) e na permeabilidade intestinal, levando a uma diminuição na inflamação crônica periférica e central. Além disso, a modulação do eixo intestino-cérebro por FOS e GOS promoveu níveis elevados de acetato e GPR43 no cérebro. Este estudou mostrou que a suplementação com FOS e GOS melhorou o comportamento de animais obesos, reduzindo sintomas semelhantes a ansiedade e depressão mediante a modulação da microbiota, redução da inflamação e neuroproteção.

Palavras-chaves: Ansiedade; Depressão; Microbiota Intestinal; Neuroinflamação; Prebióticos

## ABSTRACT

Previous research has shown that prebiotics can shape the gut microbiota composition, thereby influencing mood regulation. This study investigated the effects of prebiotics, specifically fructooligosaccharides (FOS) and galactooligosaccharides (GOS), on neuroinflammation, depression, and anxiety-like behaviors in mice fed a high-fat diet (HFD). Initially, mice were divided into two groups: a control group on a standard diet (n = 15) and an HFD group (n = 45) for 18 weeks. At the 13th week, the HFD group was further subdivided into three experimental groups: HFD only (n = 15), HFD with prebiotics (n = 15), and HFD with fluoxetine (n = 15). From the 13th week, the HFD + Prebiotics group received FOS and GOS alongside the HFD, while the HFD + Fluoxetine group received fluoxetine via drinking water. In the 18th week, behavioral assessments were conducted using the Tail Suspension Test (TST), Forced Swimming Test (FST), Sucrose Preference Test (SPT), and Plus Maze Test (PMT), followed by euthanasia for further analyses. Mice on the HFD showed increased body weight, abdominal size, blood glucose, triglycerides, cholesterol, insulin, HOMA index, and serum IL-1β levels. They also exhibited heightened microglial and astrocytic activity, activation of the TLR4 pathway, and elevated neuroinflammatory markers such as TNF-α, IL-1β, and COX-2. The obese mice displayed increased IDO pathway activation, reduced NMDA receptor levels, and lower expression of neurogenesis and synaptic plasticity markers, including PSD, SAP 102, CREB-p, and BDNF. Treatment with FOS and GOS alleviated depression and anxiety symptoms in HFD-fed mice by mitigating dysbiosis, increasing acetate-producing bacteria (e.g., *B. acidifaciens* and *B. dorei*), and improving intestinal permeability. This led to a decrease in chronic peripheral and central inflammation. Furthermore, the modulation of the gut-brain axis by prebiotics resulted in higher acetate and GPR43 levels in the brain, reduced pro-inflammatory cytokines, and enhanced neuronal proliferation and survival pathways in the hippocampus and prefrontal cortex.



Keywords: Anxiety; Depression; Gut microbiota; HFD; Neuroinflammation; Prebiotics

## LISTA DE ILUSTRAÇÕES

**SUMÁRIO**

## 1. INTRODUÇÃO

A predisposição ao desenvolvimento de transtornos de humor, incluindo ansiedade e depressão, é influenciada por uma interação complexa entre fatores genéticos e ambientais. Dentre os fatores ambientais, destaca-se o impacto significativo de uma dieta rica em gorduras (em inglês, *High Fat Diet* - HFD) (Li et al., 2022). A busca por antidepressivos e ansiolíticos com início de ação mais rápido é essencial para melhorar a adesão ao tratamento. e reduzir os prejuízos associados ao atraso terapêutico. Contudo, os antidepressivos atualmente disponíveis apresentam limitações, com 10 a 30% dos pacientes com depressão mostrando resistência ao tratamento, caracterizada pela ausência de resposta positiva após o uso de diferentes classes de medicamentos em doses e períodos adequados (Beyer et al., 2024).

A ingestão de uma dieta rica em gorduras está associada tanto a alterações metabólicas quanto a transtornos psiquiátricos. Estudos sugerem que a disfunção da neurotransmissão serotoninérgica no hipocampo pode ser um elo entre a HFD e a depressão (Hersey et al., 2021). Camundongos alimentados com HFD exibiram comportamentos depressivos relacionados ao acúmulo de lipídios nas células microgliais e à remodelação neuronal no hipocampo (HC) (Zhuang et al., 2022). Mais investigações são necessárias para esclarecer os mecanismos subjacentes a esses comportamentos.

Interessantemente, além de comportamentos semelhantes à depressão em camundongos submetidos a HFD, o consumo de HFD contribui para distúrbios metabólicos, como obesidade, hiperinsulinemia e hiperglicemia (Lam et al., 2021). O Peptídeo semelhante ao glucagon-1 (em inglês, *Glucagon-like Peptide-1* – GLP-1) e seus análogos têm mostrado potencial terapêutico para tratar depressão e ansiedade (Anderberg et al., 2016; Y. K. Kim et al., 2020). Em modelos de camundongos, HFD resultou em menores níveis de GLP-1 plasmático (Anini & Brubaker, 2003), além de acelerar a degradação desse hormônio pela enzima dipeptidil peptidase-4 (DPP-4), reduzindo sua biodisponibilidade no sistema nervoso central (Lietzau et al., 2022). Além disso, o desbalanço do metabolismo lipídico provocada pelo consumo de HFD pode desempenhar um papel fundamental no surgimento de comportamentos depressivos e ansiosos. Investigações também estabeleceram uma conexão entre os níveis de lipídios no sangue e as vias fisiopatológicas associadas à depressão, conforme destacado por So e colaboradores (2021).

A hipótese da depleção de monoaminas sugere que um desequilíbrio na neurotransmissão de 5-hidroxitriptamina (5-HT), por exemplo, pode desencadear a depressão (Elhwuegi, 2004). Contudo, revisões questionam esta teoria, indicando que

uma redução isolada de 5-HT pode não ser suficiente para justificar a fisiopatologia, sugerindo a existência de outros fatores (Jesulola et al., 2018; Slavich & Sacher, 2019). Estudos em humanos e roedores mostraram correlações entre obesidade, estado inflamatório elevado e depressão (McLachlan et al., 2023; Yu et al., 2023). Em camundongos alimentados com HFD, níveis elevados de citocinas pró-inflamatórias foram associados a mudanças na neuroplasticidade em regiões cerebrais como o córtex pré-frontal e o hipocampo, influenciando os transtornos de humor (Fulton et al., 2022).

O triptofano é um aminoácido essencial que atua como precursor na síntese de serotonina. No entanto, determinadas condições podem desviar sua rota biossintética para vias catabólicas. Por exemplo, o triptofano é convertido em N-formilquinurenina pela indoleamina 2,3-dioxigenase (IDO) e, em seguida, em L-quinurenina (KYN), que é transformada em 3-hidroxiquinurenina (3-HK) e, posteriormente, em ácido quinolínico (QUIN). Citocinas pró-inflamatórias e lipopolissacarídeos (LPS) podem ativar a via IDO (Réus et al., 2015), resultando na redução dos níveis de 5-HT e no aumento de subprodutos neurotóxicos, como o quinolonato (QUIN), que atua como agonista dos receptores N-metil-D-aspartato (NMDA), promovendo excitotoxicidade neuronal. Essa cascata inflamatória e neurotóxica contribui para a disfunção sináptica e está associada aos mecanismos fisiopatológicos da depressão e ansiedade (Braidy e Grant , 2017).

Evidências acumuladas sugerem que a homeostase da microbiota intestinal está intimamente relacionada à função cerebral, promovendo o conceito do eixo intestino-cérebro. Três mecanismos principais são identificados: regulação da resposta imunológica, influência no metabolismo [como ácidos graxos de cadeia curta (em inglês, *Short Chain Fatty Acids* – SCFAs)] e efeitos na sinalização neuronal (Morais et al., 2021). Dietas HFD causam disbiose, diminuindo a diversidade microbiana e comprometendo a função da barreira intestinal, permitindo a entrada de LPS na circulação e desencadeando neuroinflamação por meio da ativação de Receptores Semelhantes à Toll (em inglês, *Toll Like Receptors* – TLRs) microgliais (Fiebich et al., 2018). Intervenções como prebióticos e probióticos têm mostrado potencial para restaurar o equilíbrio intestinal, influenciando positivamente o comportamento e condições neurológicas (Ansari et al., 2023). FOS e GOS são frequentemente usados para estimular o crescimento de bactérias benéficas, apresentando efeitos sobre ansiedade e depressão em modelos animais (Burokas et al., 2017). Pesquisas anteriores demonstraram que FOS e GOS podem melhorar a cognição em camundongos obesos por meio da modulação da via IRS/PI3K/AKT (de Paiva et al., 2023). No entanto, ainda faltam estudos clínicos que explorem o uso de prebióticos em modelos de HFD para depressão e ansiedade. Neste trabalho, investigamos os mecanismos do tratamento com FOS e GOS na melhora desses comportamentos em um

modelo de obesidade induzida por dieta em camundongos C57BL/6.

## 2. OBJETIVOS

### 2.1 OBJETIVO GERAL

Avaliar os efeitos dos frutoligossacarídeos e galactoligossacarídeos na modulação da neuroinflamação e cognição em modelo experimental de obesidade induzido por dieta em camundongos C57BL/6 adultos.

### 2.2 OBJETIVOS ESPECÍFICOS

Em um modelo obesidade induzido por dieta, investigar os efeitos do FOS e GOS sobre diversos parâmetros neurocomportamentais, metabólicos e moleculares, tais como:

a) O comportamento semelhante à depressão e à ansiedade nos camundongos, mediante a testes comportamentais padronizados, como o teste do nado forçado e o labirinto em cruz elevado;

b) Disbiose da microbiota intestinal do cólon, investigando a abundância relativa de principais espécies bacterianas por meio de técnicas de sequenciamento do 16S rRNA.

c) O perfil lipídico, com quantificação das dos triglicerídeos, colesterol total e suas frações no soro dos camundongos, por métodos bioquímicos;

d) As principais vias da neuroinflamação no hipocampo e córtex pré-frontal, por meio da quantificação de marcadores inflamatórios como TNF-α, IL-1β e COX-2 por meio de técnicas de biologia molecular e histológicas.

e) A expressão de marcadores de plasticidade sináptica no hipocampo e córtex pré-frontal, tais como BDNF e p-CREB, por meio por análise de western-blot e imunohistoquímica.

## 3 JUSTIFICATIVA

A obesidade é uma condição crônica cuja prevalência tem aumentado significativamente em todo o mundo nos últimos anos, especialmente devido a dietas hipercalóricas, consumo excessivo de alimentos ultraprocessados e o isolamento social da COVID-19, a qual agravou maus hábitos alimentares e aumentou os casos de depressão e ansiedade. A Organização Mundial de Saúde (OMS) afirma que, em 2025, a estimativa é de que 2,3 bilhões de adultos ao redor do mundo estejam acima do peso, sendo 700 milhões de indivíduos com obesidade (OMS., 2022). No Brasil, quase metade dos adultos (48%) terá obesidade até 2044, e mais 27% terão sobrepeso – assim, dentro de 20 anos, três quartos dos adultos brasileiros terão obesidade ou sobrepeso. Hoje, 56% dos adultos brasileiros têm obesidade ou sobrepeso (34% com obesidade e 22% com sobrepeso) (World Obesity, 2024).

Estudos demonstram uma relação direta entre o consumo de dietas hiperlipídicas e desenvolvimento de transtornos de humor. Essa relação pode ser explicada, em parte, pelo aumento da inflamação crônica decorrente da obesidade, que causa neuroinflamação em várias estruturas cerebrais e impacta negativamente o sistema límbico. Evidências crescentes sugerem que o eixo microbiota-intestino-cérebro desempenha um papel fundamental na regulação das funções cerebrais, particularmente no processamento emocional, comportamento e cognição. A microbiota intestinal é crucial para o neurodesenvolvimento, influenciando a expressão gênica em regiões críticas do cérebro. Fatores como idade, sexo, uso de antibióticos e alimentação afetam sua composição, e a manutenção do equilíbrio da microbiota contribui para a homeostase e a integridade do organismo.

Nesse contexto, os prebióticos têm demonstrado resultados promissores em modelos animais de depressão. Prebióticos, como FOS e GOS, promovem o crescimento de bactérias benéficas que ajudam a modular a inflamação e a melhorar as funções cerebrais por meio do eixo microbiota-intestino-cérebro. No entanto, ainda é pouco explorada a utilização de prebióticos na prevenção e tratamento de neuroinflamação e em condições de depressão e ansiedade comórbidas à obesidade. Esses achados apontam para a necessidade de mais estudos que investiguem como a modulação da microbiota pode ser uma abordagem terapêutica eficiente em casos de obesidade e suas complicações associadas.

# 4 REFERENCIAL TEÓRICO

## 4.1 OBESIDADE: DEFINIÇÃO, FISIOPATOLOGIA E NEUROINFLAMAÇÃO

As doenças não transmissíveis (DNTs) são responsáveis por mais de 70% das mortes prematuras em nível global. As DNTs associadas à nutrição inadequada têm um impacto significativo na mortalidade no Brasil, representando 71% de todas as mortes. As DNTs associadas à nutrição inadequada, como doenças cardiovasculares, diabetes tipo 2, cânceres – especialmente de cólon e obesidade, têm um impacto significativo na mortalidade no Brasil (Brasil. Ministério da Saúde, 2021). Dentre elas, a obesidade se destaca por reduzir a expectativa de vida em até 5 a 20 anos (Who., 2017). De acordo com a Organização Mundial da Saúde (OMS), a obesidade e o sobrepeso correspondem a um acúmulo excessivo de gordura corporal que pode afetar negativamente tanto a saúde física quanto a psicológica (Who, 2019). Contudo, essa definição não reflete toda a complexidade etiológica que caracteriza o fenótipo da obesidade (Hruby e Hu, 2015).

Segundo um relatório da OMS divulgado em 2022, 2,5 bilhões de adultos com 18 anos ou mais estavam acima do peso, incluindo mais de 890 milhões de adultos que viviam com obesidade. Isso corresponde a 43% dos adultos com 18 anos ou mais (43% dos homens e 44% das mulheres) que estavam acima do peso; um aumento em relação a 1990, quando 25% dos adultos com 18 anos ou mais estavam acima do peso. A prevalência de sobrepeso variou por região, de 31% na Região do Sudeste Asiático da OMS e na Região Africana a 67% na Região das Américas (WHO, 2022). No Brasil, a Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Telefonia (VIGITEL), conduzida pelo Ministério da Saúde, registrou um aumento de 96% na prevalência de obesidade nos últimos 15 anos, com os índices subindo de 11,8% em 2006 para 22,4% em 2021(Brasil. Ministério da Saúde, 2022).

A obesidade pode levar ao desenvolvimento de várias comorbidades, incluindo complicações respiratórias (Peters et al., 2018; Xanthopoulos & Tapia, 2017), hipertensão e outras doenças cardiovasculares (Csige et al., 2018; Piché et al., 2018), diabetes mellitus tipo II (Al-Goblan et al., 2014), alguns tipos de câncer (Iyengar et al., 2016) e distúrbios psiquiátricos (Rajan e Menon, 2017). Além disso, a obesidade e suas doenças associadas representam um grande fardo para os indivíduos, sociedade e economia, gerando custos elevados para os sistemas de saúde pública, além de aumentar a morbidade e a mortalidade (Nilson et al., 2020).

O diagnóstico é previsto principalmente pelo Índice de Massa Corporal (IMC), calculando pela relação entre peso (kg) e altura ao quadrado (m²). De acordo com os

critérios da OMS, os valores do IMC são categorizados da seguinte forma: eutrofia (18,5–24,9 kg/m²), sobrepeso (25,0–29,9 kg/m²), obesidade grau I (30,0–34,9 kg/m²), obesidade grau II (35,0–39,9 kg/m²) e obesidade grau III (≥ 40 kg/m²) (Who, 2019). No entanto, um relatório mais recente orienta que o IMC deve ser utilizado apenas como um indicador populacional de risco à saúde, não sendo adequado para avaliação individual. A confirmação do excesso de adiposidade deve ser feita por métodos diretos de medição da gordura corporal, quando disponíveis, ou por pelo menos um parâmetro antropométrico (como circunferência da cintura, razão cintura-quadril ou razão cintura-altura), além do IMC, utilizando métodos validados e pontos de corte apropriados para idade, gênero e etnia. Em casos de IMC acima de 40 kg/m², a adiposidade excessiva pode ser presumida sem necessidade de confirmação adicional. Indivíduos com obesidade confirmada devem ser avaliados para obesidade clínica, cujo diagnóstico exige evidências de disfunção de órgãos ou tecidos associadas à obesidade (Rubino et al., 2025).

A obesidade é uma doença multifatorial, e o principal fator para seu desenvolvimento é o desbalanceamento entre o consumo excessivo de calorias e sua baixa utilização (Blüher, 2019). Fatores intrínsecos, como o genótipo do indivíduo, juntamente com fatores extrínsecos, especialmente a dieta, podem contribuir para o surgimento da obesidade. Vários estudos clínicos e pré-clínicos identificaram formas monogênicas de obesidade, mas se sabe que também pode ser desencadeada por causas poligênicas (Hinney et al., 2010). Alterações genéticas que afetam a obesidade incluem modificações na expressão da leptina (LEP), um hormônio crucial no controle do apetite (ZHANG et al., 1994). Mutações no gene da LEP e em seu receptor (LEPR) estão diretamente associadas ao desenvolvimento de obesidade grave (Wasim et al., 2016). Além disso, outras alterações genéticas que interferem no sistema regulador do apetite incluem a pró-opiomelanocortina (POMC), o receptor de melanocortina 4 (MC4R), a carboxipeptidase (CPE), o receptor neurotrófico de tirosina quinase tipo 2 (TrkB) e o fator neurotrófico derivado do cérebro (BDNF), além dos fatores epigenéticos (Thaker, 2017).

Diversos fatores extrínsecos, como aspectos ambientais e sociais, podem contribuir para um balanço energético positivo, favorecendo o desenvolvimento da obesidade. Entre esses fatores, destacam-se a alimentação emocional (Frayn et al., 2018), a privação de sono (Chaput e Dutil, 2016), efeitos adversos de medicamentos (Schwartz et al., 2004), o estresse (Razzoli et al., 2017) e o consumo excessivo de alimentos ricos em gordura (Moyer et al., 2016). O aumento do consumo da dieta ocidental, caracterizada por altos níveis de açúcar / gordura saturada e baixa ingestão de fibras, também está associado ao desenvolvimento de outras comorbidades, como doenças cardiovasculares (Dehghan et

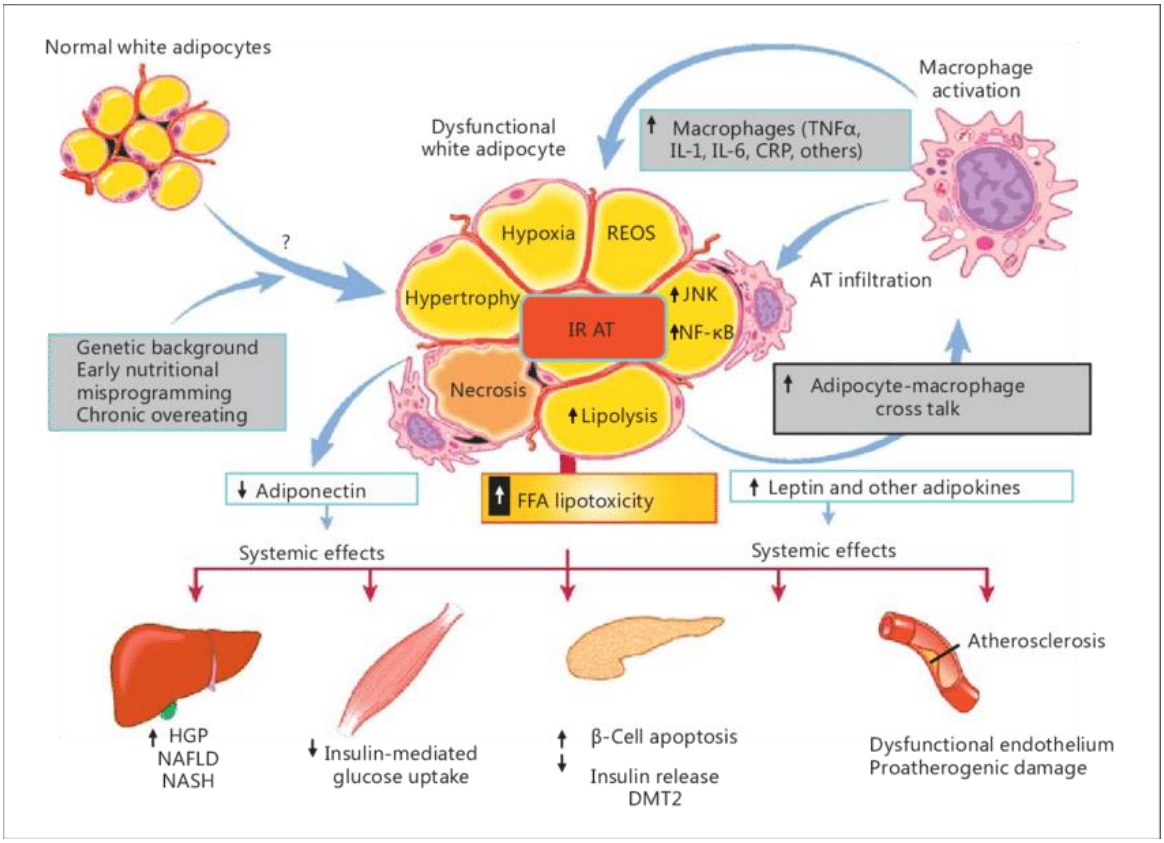
al., 2017), diabetes tipo II (Heydemann, 2016) e doenças neuropsiquiátricas como depressão e ansiedade (Liang et al., 2021)

O tecido adiposo tem sido amplamente estudado no contexto da obesidade, principalmente devido ao entendimento crescente de suas funções nos últimos anos. Localizado em várias regiões do corpo, o tecido adiposo pode ser classificado em subcutâneo, visceral e depósitos especializados, como nos linfonodos. Ele apresenta dois tipos celulares principais: o tecido adiposo marrom (TAM) e o tecido adiposo branco (TAB). O TAM, que se encontra principalmente em recém-nascidos e mamíferos hibernantes, desempenha a função de regular a temperatura corporal (Junqueira e Carneiro, 2017). Já o TAB, que antes era visto apenas como um simples reservatório de energia e protetor mecânico, é reconhecido como um regulador crucial de diversos processos fisiológicos e metabólicos, indo além de sua função de armazenamento de gordura (Fain, 2010; Kershaw e Flier, 2004).

O TAB é responsável pela secreção de hormônios específicos, conhecidos como adipocinas, que desempenham funções essenciais tanto no metabolismo quanto na regulação imunológica (Ouchi et al., 2011). Dessa forma, a obesidade deixa de ser vista apenas como uma doença metabólica, passando a ser considerada também uma doença inflamatória crônica de baixo grau (Jong et al., 2014; Trayhurn e Wood, 2004). Embora o gatilho exato que desencadeia o processo inflamatório ainda não seja completamente compreendido, sabe-se que a deposição excessiva de ácidos graxos no TAB leva à hipertrofia das células adiposas, desencadeando uma série de eventos que resultam em um estado pró-inflamatório no organismo (Horwitz e Birk, 2023).

A hipóxia e o estresse oxidativo no TAB parecem ser fatores-chave que desencadeiam a maior expressão de genes pró-inflamatórios, como os de Fator de Necrose Tumoral alfa (em inglês, Tumor Necrosis Factor Alpha - TNF-α), Interleucina-6 (IL-6), Interleucina 1 beta (IL-1β) e Proteína C Reativa (PCR) (Lee et al., 2014). Esse processo contribui para a transformação do TAB em um tecido inflamatório, exacerbando o quadro de obesidade conforme ilustra a figura 1. Além disso, ácidos graxos, que se acumulam nas células adiposas, também desempenham um papel regulador na secreção de diversas citocinas em células T, ampliando ainda mais a resposta inflamatória (Garcia et al., 2023). Portanto, a obesidade não é apenas uma questão de acúmulo de gordura, mas envolve uma complexa interação entre o TAB, os ácidos graxos e a regulação do sistema imunológico.

**Figura 1**. A inflamação do tecido adiposo branco e suas consequências neuroendócrino-metabólicas.




Legenda: Uma combinação de predisposição genética, dieta inadequada e estilo de vida sedentário pode promover o aumento hipertrófico da massa do tecido adiposo branco, acompanhado pela infiltração de macrófagos. Esse processo resulta em um padrão anormal na produção e liberação de adipocinas. O aumento na liberação de leptina derivada do TAB compromete a sensibilidade dos tecidos à insulina, caracterizando a resistência à insulina (IR). AT: Adipose tissue (tecido adiposo); REOS: Reactive Oxygen species (Espécies reativas de oxigênio); IL: Interleucina; TNF:Tumoral Necrose Factor (Fator de Necrose Tumoral); FFA: Free Fat Acid (Ácido Graxo de Cadeia Livre); DMT2: Diabetes Mellitus type 2 (Diabetes melitus tipo 2); NASH: Nonalcoholic steatohepatitis (Esteatohepatite não alcoólica); NAFLD: Non-alcoholic fatty liver disease (Doença hepática gordurosa associada ao metabolismo).

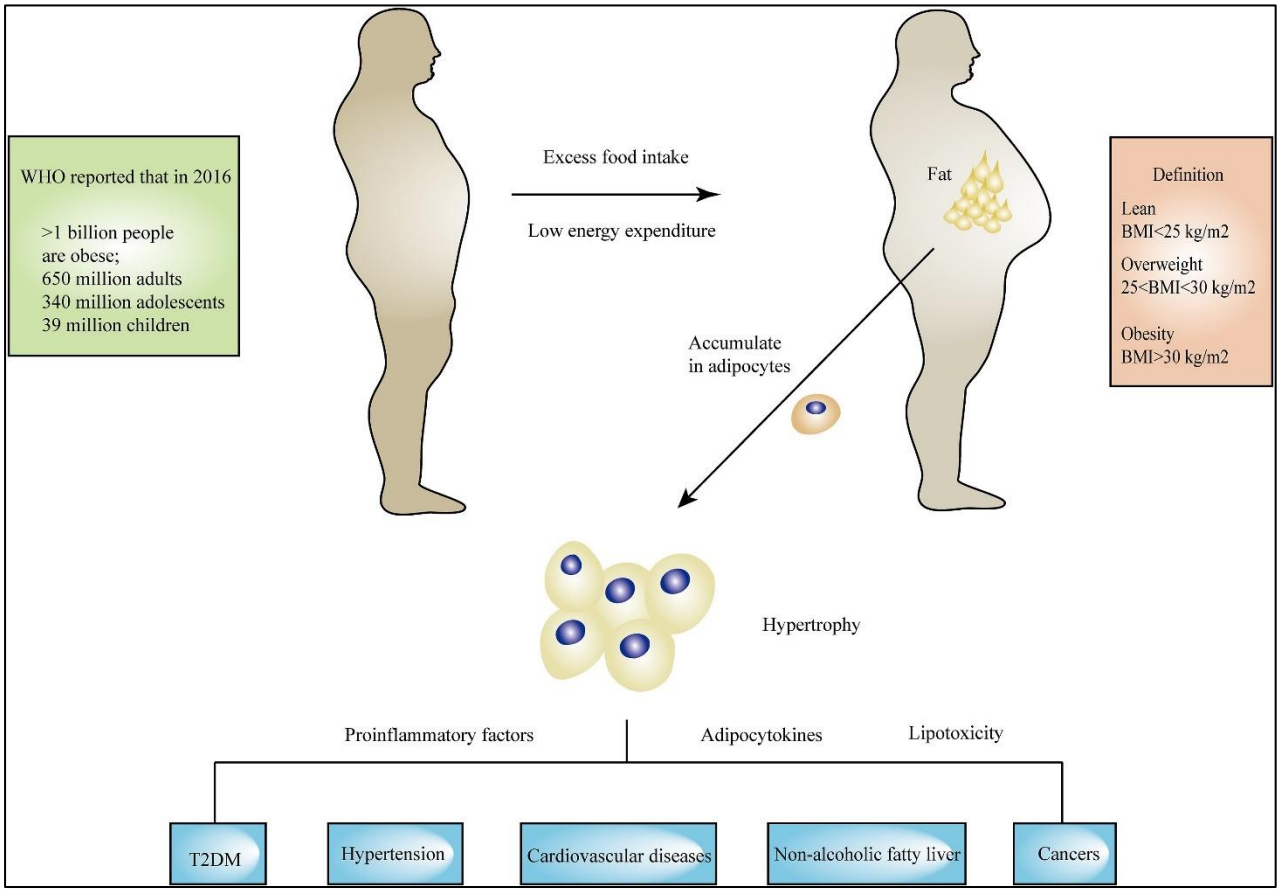
Fonte: Pagano et al., (2017)

O recrutamento de macrófagos para o TAB, tanto em modelos animais quanto em humanos, contribui significativamente para o aumento do estado inflamatório sistêmico (Rosenbaum et al., 2008; Ross et al., 2003). No TAB, observa-se uma mudança no fenótipo dos macrófagos, que de M2, com propriedades anti-inflamatórias, se transformam em M1, um perfil mais pró-inflamatório, com a secreção exacerbada de TNF-α durante a obesidade (Lumeng et al., 2007). Esse processo é acompanhado pela redução na

produção de adipocinas anti-inflamatórias, como a adiponectina, que desempenha papéis importantes no controle do apetite e na modulação da inflamação (Pyrzak et al., 2010). O declínio da adiponectina contribui para a manutenção e agravamento do estado inflamatório crônico observado na obesidade, formando um ciclo vicioso que exacerba os efeitos prejudiciais da doença.

A condição inflamatória crônica associada à obesidade tem repercussões alarmantes na saúde, estando diretamente relacionada ao surgimento de várias comorbidades, como diabetes tipo 2, câncer e doenças cardiovasculares, que afetam a qualidade de vida e pioram o prognóstico dos pacientes obesos conforme mostra a figura 2 (Csige et al., 2018; Iyengar et al., 2016).

**Figura 2**. Visão geral da obesidade, definição de obesidade e suas comorbidades




**Legenda**: A prevalência global de sobrepeso ou obesidade aumentou em 27% na idade adulta e 47% na infância durante 33 anos. Este número ainda está aumentando, e a OMS estima que aumentará ainda mais. A obesidade é um fator de risco para várias doenças, notadamente diabetes mellitus tipo 2, doença hepática gordurosa associada ao metabolismo, doença cardiovascular e alguns tipos de câncer. BMI: Body Mass Index (Indice de Massa corporal).

**Fonte**: Jin et al., (2023)

O aumento das citocinas pró-inflamatórias, como o TNF-α, contribui para o desenvolvimento da resistência à insulina, um dos principais fatores para o aparecimento do diabetes tipo 2 (Ruan & Lodish, 2003). Além disso, o TNF-α acelera o processo de aterosclerose, favorecendo a expressão de moléculas de adesão do endotélio (Antuna-Puente et al., 2008). A IL-6, produzida também no tecido adiposo branco, está intimamente ligada à resistência insulínica, pois diminui a produção de adiponectina e seus receptores (Fantuzzi, 2005), e pode ainda estimular o crescimento de neoplasias, como no caso do câncer de próstata, onde ativa o receptor de androgênio, promovendo a sobrevivência e proliferação tumoral (Tindall e Lonergan, 2011). Além disso, a IL-6 aumenta a produção de PCR pelo fígado, agravando ainda mais o estado inflamatório da obesidade (Memoli et al., 2007).

A obesidade, além de desencadear um processo inflamatório periférico, também influencia esta condição no sistema nervoso central. As citocinas pró-inflamatórias periféricas têm a capacidade de atravessar a barreira hematoencefálica (BHE) e alcançar diversas estruturas como hipocampo, córtex pré-frontal, amígdala e hipotálamo mediobasal, onde se localizam receptores específicos para esses mediadores inflamatórios (Sun et al., 2022). Esse processo pode estimular a ativação do fator nuclear kappa B (NF-κB) no hipotálamo, aumentando a permeabilidade da BHE e intensificando a entrada de citocinas e células inflamatórias no cérebro (Araujo et al., 2005; Lu et al., 2009). No tecido cerebral, as citocinas pró-inflamatórias ativam algumas vias neuroendócrinas, como o eixo Hipotálamo-Pituitária-Adrenal (HPA), afetando a função e o metabolismo de neurotransmissores, além de modificar a plasticidade neural, o que pode prejudicar funções do sistema límbico (Capuron e Castanon, 2011).

Em modelos animais obesos ou alimentados com dietas hiperlipídicas, a produção de mediadores inflamatórios pelas células gliais, especialmente pela micróglia, é acentuada. A micróglia, principal tipo de macrófago residente no cérebro, desempenha funções protetoras, como a poda sináptica e o recrutamento de monócitos circulantes para conter danos teciduais (Gu et al., 2014; Nimmerjahn et al., 2005; Stentz e Kitabchi., 2006). No entanto, a ativação crônica ou desregulada da micróglia pode se tornar prejudicial, agravando o estado inflamatório cerebral e contribuindo para o desenvolvimento de distúrbios neurológicos (Tremblay et al., 2011). Assim, a obesidade não apenas afeta o sistema metabólico, mas também tem impactos significativos na saúde cerebral, evidenciando a complexidade e a gravidade dessa condição.

Portanto, a obesidade transcende a definição simplista de acúmulo excessivo de gordura corporal, representando uma doença multifatorial com implicações metabólicas, inflamatórias e neurológicas. Sua prevalência crescente e os impactos profundos na saúde

física e mental sublinham a urgência de abordagens integradas para prevenção e tratamento, considerando fatores genéticos, ambientais e sociais. Compreender os mecanismos subjacentes à obesidade, como a interação entre tecido adiposo, inflamação e sistema nervoso central, é essencial para o desenvolvimento de estratégias terapêuticas mais eficazes.

## 4.2 ANSIEDADE E DEPRESSÃO: FISIOPATOLOGIA ALÉM DOS NEUROTRANSMISSORES

O transtorno depressivo maior (TDM) é uma condição mental amplamente disseminada, afetando cerca de 264 milhões de pessoas globalmente, o que o posiciona como o segundo maior responsável pela taxa de morbidade no mundo (Chan et al., 2024). Estima-se que ocorram aproximadamente 800.000 suicídios anuais, o que destaca o TDM como um desafio de grande magnitude para a saúde pública (Ruderfer et al., 2019). O TDM é marcado por uma disforia persistente, retardo psicomotor, insônia, anedonia, ideação suicida e uma redução significativa no bem-estar geral (Varghese et al., 2024). Além do TDM, os transtornos de ansiedade são condições psiquiátricas amplamente presentes e incapacitantes, afetando aproximadamente 10% da população mundial anualmente (WHO, 2017). Os transtornos de ansiedade são caracterizados por sintomas como preocupação excessiva, medos relacionados a situações sociais e de desempenho, ataques de pânico inesperados ou desencadeados, ansiedade antecipatória e comportamentos de evitação (Szuhany e Simon, 2022). A perda global de produtividade devido a transtornos de ansiedade e depressão é de aproximadamente US$ 1 trilhão por ano, um impacto que tende a crescer ao longo do tempo (Doran e Kinchin, 2017).

Atualmente, os inibidores da recaptação de monoaminas são a classe de antidepressivos/ansiolíticos mais frequentemente prescrita (Miyazaki et al., 2018). No entanto, um grande desafio com esses medicamentos é o considerável atraso entre o efeito farmacológico inicial na função dos neurotransmissores monoaminérgicos (que pode levar vários dias) e a redução na gravidade dos sintomas clínicos (geralmente entre 3 a 8 semanas) (Liu et al., 2017). Interessantemente, metade dos pacientes depressivos apresentam uma melhora significativa com o uso de antidepressivos, podendo apresentar uma resposta clínica restrita e variável. Além disso, sabe-se que cerca de um terço das pessoas com transtorno depressivo maior (TDM) tem um prognostico ruim, desenvolvendo a chamada depressão resistente ao tratamento (DRT). Nesta condição, o paciente não apresenta uma melhora satisfatória mesmo após o uso adequado de dois antidepressivos diferentes. Neste caso, pode-se atribuir a ineficácia do medicamento, intolerância aos efeitos colaterais ou outros fatores

ligados ao paciente e à própria doença. A resistência ao tratamento é um dos grandes problemas enfrentados pela psiquiatria já que está relacionada com a piora da qualidade de vida, maior taxa de suicídio e mais custos a saúde pública. Neste contexto, é importante pesquisas que visem novos psicofármacos mais eficientes e de ação mais rápida (Aleksandrova et al., 2017).

A teoria das monoaminas sugere que a depressão e ansiedade sejam causadas por um desequilíbrio nos neurotransmissores monoaminérgicos, como serotonina, noradrenalina e dopamina, no cérebro. De fato, o desbalanço do metabolismo dos neurotransmissores pode desempenhar um papel fundamental na etiologia da depressão e ansiedade (Li et al., 2021). A serotonina (5-HT), amplamente distribuída por todo o sistema nervoso, está associada a diversos transtornos de saúde mental, como depressão, fobias e ansiedade, quando em níveis deficientes(De-Miguel & Trueta, 2005). Nas últimas décadas, a hipótese da 5-HT tem sido central nas pesquisas sobre as causas subjacentes desses dois transtornos, com estudos sugerindo que pacientes deprimidos apresentam baixos níveis de 5-HT no cérebro e alterações nos receptores de serotonina (Maes et al., 2009). Além disso, a dopamina (DA), outro neurotransmissor crucial no sistema nervoso central, também desempenha um papel significativo na regulação do comportamento e na fisiopatologia da depressão. A dopamina atua como precursor da epinefrina e da norepinefrina (NE), e sua transmissão está intimamente relacionada ao desenvolvimento da depressão, com vários estudos mostrando que pacientes depressivos têm níveis elevados de transporte de DA, o que aumenta a eficiência dos neurônios pré-sinápticos na recaptação desse neurotransmissor (Duval et al., 2021; Salamone et al., 2022). Apesar de a teoria das monoaminas oferecer uma explicação para muitos casos de transtornos de ansiedade e depressão, ela não é totalmente abrangente nem justifica os casos de pacientes refratários aos tratamentos clássicos para esses transtornos. Outros mecanismos podem ajudar a compreender melhor a ansiedade e depressão, tais como a hiperatividade do eixo hipotálamo-hipófise-adrenal (HPA) (Heim et al., 2008), citocinas inflamatórias e metabólitos endógenos (Felger e Lotrich, 2013) e, adicionalmente, o microbioma intestinal, o qual desempenha um papel crítico na depressão ao afetar o eixo intestino-cérebro (Evrensel e Ceylan, 2015).

O estresse e os desafios agudos são fatores que podem desencadear o desenvolvimento do TDM e ansiedade. O papel do eixo HPA na resposta ao estresse é amplamente reconhecido, sendo essencial para a regulação dessa resposta nos mamíferos. Assim, alterações no eixo HPA durante a depressão podem refletir o impacto do estresse e influenciar a manifestação dos sintomas depressivos (Tan et al.,

2021). O estresse provoca a liberação do hormônio liberador de corticotropina (CRH) pelo hipotálamo, o que leva à produção de hormônio adrenocorticotrófico (ACTH) pela hipófise, resultando em um aumento na secreção de glicocorticoides pelas glândulas adrenais. Esses glicocorticoides, por sua vez, se ligam aos seus receptores em diversos tecidos-alvo, incluindo o eixo HPA, onde atuam como inibidores do feedback, reduzindo a produção de ACTH na hipófise e de CRH no hipotálamo (Sukhareva, 2021). Na ansiedade, o eixo HPA se torna hiperativo em resposta ao estresse, o que resulta em condições como hipercortisolemia, perda de ritmicidade e níveis elevados de cortisol (Hinds e Sanchez, 2022). Distúrbios no eixo HPA, induzidos pelo estresse, têm sido associados à depressão devido ao aumento da produção de cortisol e à inibição insuficiente do feedback regulatório do receptor de glicocorticoide (Keller et al., 2016). Além disso, níveis elevados de cortisol têm sido relacionados à gravidade da depressão, especialmente nos casos de depressão melancólica (Mickey et al., 2018). Pacientes com depressão que não conseguem normalizar o eixo HPA após o tratamento tendem a apresentar piores resultados clínicos e prognósticos (Nandam et al., 2020). Contudo, estudos anteriores indicaram que tratamentos direcionados à regulação do eixo HPA, como os antagonistas do receptor de glicocorticoide, não são eficazes em aliviar os sintomas depressivos (Aubry, 2013). Interessantemente, estudos pré-clínicos sugerem que uma dieta rica em gorduras durante a gestação e a lactação impacta significativamente a atividade do eixo HPA na prole adulta, tanto em situações de repouso quanto sob estresse. As alterações induzidas pelo consumo materno de HFD não apenas influenciam a resposta ao estresse na vida adulta, mas também podem contribuir para o desenvolvimento de um fenótipo mais suscetível a distúrbios comportamentais e outros problemas de saúde na fase adulta (Lin et al., 2015; Niu et al., 2019; Sasaki et al., 2014).

Embora a disfunção do eixo HPA e os níveis elevados de cortisol desempenhem um papel importante na fisiopatologia da depressão e da ansiedade, outros fatores também são essenciais para entender os mecanismos subjacentes à doença, como as neurotrofinas e a neurogênese. As evidências de redução dos níveis das neurotrofinas em várias áreas do cérebro, como o hipocampo, em pacientes com depressão, apoiam a hipótese de que a diminuição de fatores neurotróficos que regulam a plasticidade no cérebro adulto pode contribuir para o desenvolvimento da depressão (Park e Poo, 2013; Reichardt, 2006). Muitos estudos têm se concentrado no BDNF, que desempenha papéis cruciais em diferentes funções do sistema nervoso, como plasticidade sináptica, diferenciação, manutenção, crescimento neuronal e reparo (Binder e Scharfman, 2004). A teoria neurotrófica da depressão propõe que níveis reduzidos de BDNF no hipocampo estão relacionados à depressão induzida por estresse, e que esses níveis podem ser

elevados com o uso de antidepressivos (Martinowich et al., 2007). Além disso, descobriu-se que agentes que modulam o sistema BDNF produzem efeitos semelhantes aos dos antidepressivos (Zhang et al., 2019). Pesquisas crescentes indicam que os níveis de BDNF estão reduzidos no sangue periférico de pacientes com depressão, conforme observado em estudos post-mortem, e alguns relatos sugerem que o tratamento antidepressivo pode normalizar essa diminuição (Bocchio-Chiavetto et al., 2010; Satomura et al., 2011). Além disso, investigações em cérebros humanos post-mortem indicaram o envolvimento do BDNF na fisiopatologia de transtornos relacionados à ansiedade (Carola et al., 2008). Há também evidências de que a interação entre o BDNF e seu receptor está associada à depressão resistente ao tratamento (Satomura et al., 2011). A depleção de BDNF parece prejudicar a neurogênese, contribuindo para o desenvolvimento do TDM, e o tratamento antidepressivo pode atenuar os sintomas dessa condição ao aumentar os níveis de BDNF no cérebro. Neste contexto, estudos pré-clínicos têm demonstrado que o consumo de uma dieta rica em gorduras está fortemente associado à redução dos níveis de BDNF em regiões-chave do cérebro, como o hipocampo e o córtex pré-frontal. Esse efeito é mediado pela ativação da neuroinflamação, resultando em comportamentos semelhantes à depressão e ansiedade, além de déficits cognitivos significativos enquanto tratamentos que se baseiam no aumento da expressão de BDNF conseguem reverter os sintomas depressivos e ansiosos (Li et al., 2022; Zuo et al., 2024).

Interessantemente, nas últimas duas décadas, a hipótese de que a inflamação desempenha um papel importante na patogênese e fisiopatologia da depressão e ansiedade se tornou cada vez mais relevante (Peirce e Alviña, 2019). Estudos revelaram que a depressão é mais prevalente em pacientes com doenças autoimunes ou infecciosas em comparação com a população geral (Jeon e Kim, 2017). Além disso, indivíduos sem diagnóstico de depressão podem manifestar sintomas depressivos quando expostos a citocinas, sendo que os antidepressivos ajudam a aliviar esse desconforto (Miller e Raison, 2016). Os marcadores inflamatórios periféricos não apenas influenciam o estado de ativação imunológica no SNC, impactando o comportamento, mas também podem servir como indicadores biológicos para avaliar a eficácia de terapias antidepressivas e ansiolíticas (Haroon et al., 2018). Em estudo longitudinal prospectivo, Li e colaboradores demonstraram que os níveis de TNF-α eram mais elevados em pacientes com TDM antes do tratamento em comparação com controles saudáveis. Após o tratamento com venlafaxina, observou-se uma redução significativa nos níveis de TNF-α, sendo que essa diminuição foi ainda mais pronunciada no grupo de pacientes que responderam positivamente ao tratamento (Li

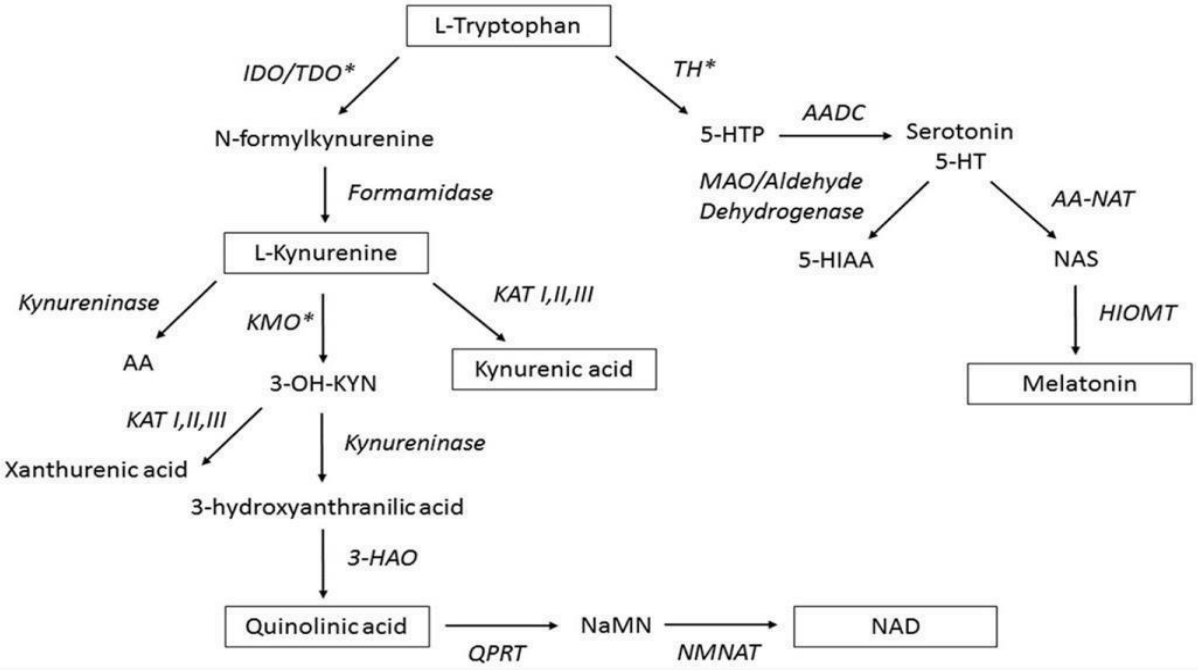
et al., 2013). Além disso, Syed e colaboradores descobriram que os marcadores inflamatórios em pacientes com depressão não tratados eram mais elevados. Entretanto, o tratamento antidepressivo reduziu a produção de citocinas inflamatórias e aumentou os níveis das anti-inflamatórias (Syed et al., 2018). Uma revisão sistemática e meta-análise sugeriu que os inibidores de citocinas, como os anticorpos monoclonais, podem ter efeito antidepressivo ao bloquear a ação das citocinas (Bavaresco et al., 2020). Um desequilíbrio entre citocinas pró-inflamatórias e anti-inflamatórias pode, assim, contribuir para a fisiopatologia da depressão.

O desequilíbrio entre citocinas pró-inflamatórias e anti-inflamatórias e o impacto da inflamação no SNC não se limitam à modulação de neurotransmissores e hormônios, mas também afetam as células gliais, como a micróglia e os astrócitos, que desempenham papéis cruciais na fisiopatologia da depressão e da ansiedade (Wang et al., 2022; Zhang et al., 2010). A ativação dessas células gliais em resposta à inflamação pode alterar a homeostase do SNC, afetando a comunicação neuronal, a plasticidade sináptica e a resposta ao estresse, agravando os sintomas depressivos e ansiosos. Estudos têm mostrado que a microglia, ao ser ativada, libera citocinas pró-inflamatórias que podem exacerbar a neuroinflamação, enquanto os astrócitos desempenham um papel fundamental na modulação do ambiente neuronal, afetando tanto a função sináptica quanto a neurogênese (Li et al., 2021; Prinz e Priller, 2014). Um estudo conduzido por Weng e colaboradores observou um aumento no número de microglia no córtex pré-frontal (PFC) de camundongos tratados com LPS por via intraperitoneal, o que também esteve associado ao agravamento do comportamento depressivo dos animais além do aumento expressão dos genes IL-1, IL-6 e TNF-α no PFC dos camundongos (Weng et al., 2019). Além disso, um estudo pré-clínico relatou que os a ativação dos astrócitos estão envolvidos na patogênese da inflamação induzida por estresse, associando-os aos sintomas depressivos e ansiosos (Virmani et al., 2021). A ativação da micróglia e do astrócito, por meio da liberação excessiva de fatores pró-inflamatórios e citotocinas, pode assim contribuir para o desenvolvimento gradual de comportamentos depressivos, destacando a relação entre a neuroinflamação e a manifestação de sintomas depressivos (Sochocka et al., 2016). Evidências sugerem que a ativação da micróglia é um fator crucial na desregulação da homeostase energética, agravando a resistência à insulina. Logo após a introdução de uma dieta rica em gordura, a micróglia hipotalâmica sofre alterações morfológicas e funcionais em resposta ao excesso de gorduras saturadas. Astrócitos e micróglia respondem rapidamente a sobrecarga inflamatória, desencadeando inflamação e exibindo gliose, possivelmente como uma tentativa de prevenir lesões neuronais (García-Cáceres et al., 2013; Maldonado-Ruiz et al., 2017). No entanto, a exposição crônica à dieta rica em

gordura pode sobrecarregar a capacidade protetora da glia, tornando os danos e perdas neuronais inevitáveis. Um exemplo disso é a inflamação hipotalâmica prolongada induzida pela HFD, que leva ao aumento da gliose, associado ao aumento da apoptose neuronal no hipotálamo (Mendes et al., 2018). Assim, a interação entre a inflamação periférica e a resposta das células gliais no SNC oferece uma nova perspectiva para entender os mecanismos subjacentes à depressão e à ansiedade, e para o desenvolvimento de terapias mais eficazes.

Por fim, o excesso de citocinas pró-inflamatórias, tais como IL-1β e TNF-α, pode induzir a síntese da indoleamina 2,3-dioxigenase em células do sistema imunológico, como macrófagos e células dendríticas, o que altera consideravelmente a biossíntese das monoaminas, como serotonina e dopamina, que são essenciais para a regulação do humor e da função cognitiva (Xu et al., 2015). Além disso, a superexpressão da IDO redireciona o triptofano (Try) da via biossintética da serotonina para a produção de outros catabólitos do triptofano (denominados TRYCATs), que têm propriedades neuroativas associadas a sintomas depressivos (Raison et al., 2010). A figura 3 ilustra os principais destinos do triptofano no cérebro.

**Figura 3**. Rotas metabólicas do Triptofano




**Legenda**: Dependendo das necessidades do organismo e do estado inflamatório, o Try pode ser direcionado para a síntese de serotonina, que pode, posteriormente, ser convertida em melatonina. No entanto, quando a IDO estar superexpressa, o triptofano pode ser convertido em catabólitos, alguns dos quais possuem efeitos neurotóxicos. IDO: indoleamina 2,3-dioxigenase; TDO: triptofano 2,3-dioxigenase; KAT: quinurenina aminotransferase; KMO: quinurenina 3-monooxigenase; 3-OH-KYN: 3-

hidroxiquinurenina; 3-HAO: 3-ácido hidroxiantranílicooxigenase; QPRT: fosfolibosiltransferase de quinolinato; NaMN: mononucleotídeo de nicotinamida; NMNAT: nicotinamida mononucleotídicaadeniltransferase; NAD:Nicotinamida adenina dinucleótido; TH: triptofano-hidroxilase; 5-HTP: 5-hidroxi- L-triptofano; AADC: L-aminoácido aromáticodescarboxilase; 5-HT: 5-hidroxitriptamina; 5-HIAA: ácido 5-hidroxiindoleatico; MAO: monoamina oxidase; AA-NAT: N- acetiltransferase de aralquilamina; NAS: N-acetilserotonina; HIOMT:hidroxindol O- metiltransferase.

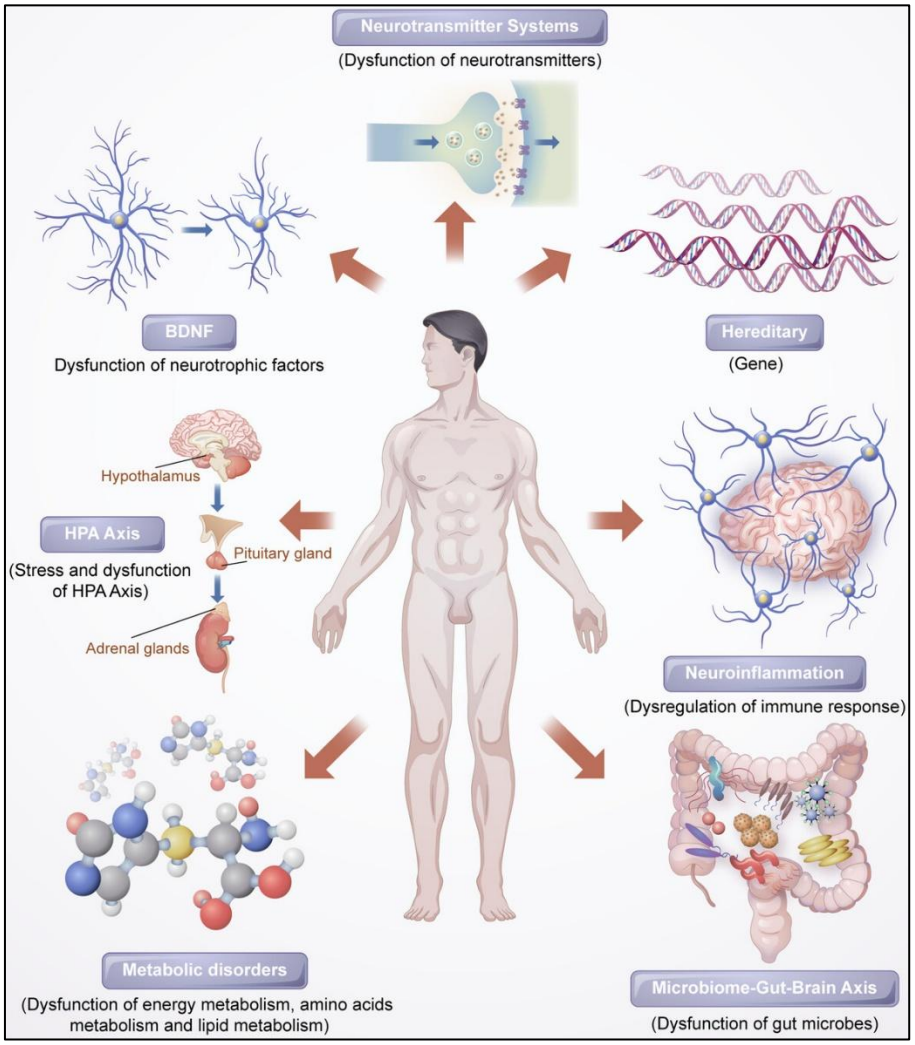
**Fonte**: Chaves Filho et al., (2018)

A 3-hidroxiquinurenina e o ácido quinolínico são dois exemplos de TRYCATs que, quando presentes em excesso, podem induzir a morte neuronal, como demonstrado em estudos sobre doenças neuropsiquiátricas e neurodegenerativas (Gulaj et al., 2010; Stone et al., 2012). De forma interessante, Gibney e colaboradores (2013) observaram que o processo neuroinflamatório foi capaz de induzir uma redução no BDNF, um aumento na expressão da IDO e uma ativação desregulada da micróglia no hipocampo de camundongos. Esses achados sugerem que a ativação da IDO, especialmente no hipocampo, tem um papel central na mediação dos efeitos no humor induzidos por citocinas. A ingestão excessiva de uma dieta rica em gordura pode elevar os níveis sanguíneos de LPS, e já foi relatado que indivíduos obesos apresentam concentrações de lipopolissacarídeo mais altas do que os indivíduos magros (Trøseid et al., 2013). Esse aumento contribui para o estado inflamatório crônico associado à obesidade, o que pode resultar em uma maior expressão da IDO e, consequentemente, um aumento na quantidade de TRYCATs (André et al., 2014). Assim, espera-se que a presença sistêmica de LPS seja um fator responsável pelos transtornos de humor tanto em animais quanto em humanos (Deng et al., 2012; Grigoleit et al., 2011; Stevens et al., 2018; Sulakhiya et al., 2016; Yin et al., 2023).

Essa influência da inflamação periférica sobre o cérebro pode ocorrer, em parte, por meio da modulação de neurotransmissores essenciais ao funcionamento neural. Nesse cenário, o glutamato, como principal neurotransmissor excitatório, desempenha um papel essencial na plasticidade sináptica e no humor (Zaghmi et al., 2022). Estudos sugerem que a depressão está intimamente ligada ao sistema glutamatérgico, com níveis elevados de glutamato observados no sangue e no cérebro de pacientes deprimidos (Chen et al., 2022; Li et al., 2019). Além disso, distúrbios na subunidade do receptor N-metil-D-aspartato (NMDAR) foram identificados como uma característica da depressão, e a inibição da função do NMDAR tem mostrado efeitos antidepressivos, além de proteger os neurônios do hipocampo contra alterações morfológicas induzidas pelo estresse (Gray et al., 2015; Musazzi et al., 2013). Além disso, alguns

antidepressivos têm efeitos semelhantes ao afetar a via AMPAR, sugerindo que a modulação do sistema glutamatérgico é uma estratégia promissora no tratamento da depressão (Gould et al., 2008).

**Figura 4**. As possíveis vias de sinalização da inflamação




**Legenda**: A depressão está relacionada a vários fatores, como desequilíbrios oxidante-antioxidante, disfunção mitocondrial e inflamação. A deficiência de serotonina e o estresse desempenham papéis críticos em sua etiologia. O eixo HPA, responsável pela resposta ao estresse, e a redução de fatores neurotróficos, como no hipocampo, contribuem para a doença. Além disso, distúrbios metabólicos e a interação entre microbiota-intestino-cérebro também influenciam o humor e o comportamento, impactando a atividade cerebral. BDNF: Brain-derived neurotrophic fator (Fator Neurotrófico Derivado do Cérebro); HPA Axis: Hypothalamic-pituitary-adrenal axis (Eixo Hipotálamo-Hipófise-Adrenal).

**Fonte**: (Tian et al., 2022)

Uma das conexões importantes entre a obesidade, depressão e ansiedade é a interação entre os fatores biológicos, comportamentais e ambientais. A obesidade é

frequentemente associada a condições psiquiátricas, como depressão e ansiedade, criando um ciclo vicioso no qual o desenvolvimento de uma condição pode agravar a outra (Jorm et al., 2003; Lorena et al., 2021). Estudos demonstram que a obesidade pode afetar a função do eixo HPA (Bose et al., 2009), aumentar a inflamação sistêmica e alterar a função do SNC (Lorena et al., 2021), fatores estes frequentemente envolvidos tanto na fisiopatologia da depressão quanto da ansiedade. Além disso, a ativação da neuroinflamação e a disfunção nas células gliais, como microglia e astrócitos, podem exacerbar a condição, promovendo alterações no comportamento e na resposta ao estresse (Ramirez et al., 2016; Stein et al., 2017). A obesidade pode, portanto, agravar os sintomas desses transtornos psiquiátricos, ao passo que a depressão e a ansiedade podem contribuir para comportamentos alimentares desregulados, perpetuando o ciclo de obesidade e agravamento dos sintomas de depressão e ansiedade (Amiri S; Behnezhad S, 2019).

## 4.3 EIXO MICROBIOTA-INTESTINO-CÉREBRO E SUA INFLUÊNCIA NA DEPRESSÃO E ANSIEDADE

Os seres humanos hospedam milhões de microrganismos, presentes tanto nas superfícies do corpo quanto nas cavidades. A interação entre humanos e microrganismos proporciona benefícios mútuos e é ecologicamente classificada como simbiose (Martin B; Schwab E, 2012). Diversas comunidades microbianas colonizam o trato respiratório, gastrointestinal e genital, desempenhando funções especializadas e com organização distinta (Lozupone et al., 2012). O termo mais apropriado para designar essas comunidades é "microbiota", já que expressões como "flora" ou "microflora" originalmente se referiam a plantas (Pace, 2009).

A microbiota intestinal adulta é composta por mais de 100 trilhões de microrganismos, sendo a maioria pertencente ao domínio das bactérias, com predominância de colonização no cólon ($10^{11}$ - $10^{12}$ células/ml) (Bermon et al., 2015). O intestino grosso, em especial o colón, é considerado a região mais favorável do trato gastrointestinal para o desenvolvimento de espécies microbianas, já que o estômago e o intestino delgado apresentam fatores que dificultam o crescimento desses organismos, como a presença de suco gástrico e sais biliares (Guarner e Malagelada, 2003). Estima-se que a microbiota intestinal humana seja composta por, pelo menos, 1000 espécies bacterianas conhecidas, responsáveis pela codificação de mais de 3 milhões de genes, o que corresponde a um número 100 vezes maior do que os genes do genoma humano (Bermon et al., 2015; Ley et al., 2006).

Estudos moleculares revelaram que os principais táxons da microbiota intestinal

humana e de camundongos são Firmicutes, Bacteroidetes, Proteobacteria e Actinomycetes, correspondendo a 64%, 23%, 8% e 3% dessa microbiota, respectivamente. Mais de 90% dos táxons bacterianos pertencem a dois grandes filos: Bacteroidetes e Firmicutes (Ley et al., 2006; Zupancic et al., 2012). Além disso, análises de amostras fecais humanas identificaram táxons filogeneticamente relacionados ao filo Archaea, como o *Methanobrevibacter smithii (Arumugam et al., 2011)*. Também fazem parte dessa microbiota organismos eucariotos, como fungos, e até mesmo vírus, o que contribui para sua elevada diversidade (Qin et al., 2010). Alterações na composição dessa microbiota estão associadas a mudanças nas funções microbianas, podendo levar ao desenvolvimento de diversas doenças, como será discutido posteriormente.

Por se tratar de uma relação simbiótica, os microrganismos hospedados no colón recebem continuamente um suprimento de água e nutrientes, enquanto, em contrapartida, proporcionam diversos benefícios à saúde humana (Bäckhed et al., 2005). Esses benefícios, por exemplo, não são observados em camundongos livres de microrganismos, conhecidos como germ-free, que apresentam diferenças fisiológicas e anatômicas significativas em relação a animais com microbiota. Essas diferenças incluem maior necessidade nutricional, alterações no peso de órgãos como o coração, menor espessura da parede intestinal, menor número de linfonodos, entre outras (Bamola et al., 2017). A microbiota intestinal pode influenciar a homeostase de várias regiões do corpo, incluindo o SNC, com evidências sugerindo que ela pode modificar funções cerebrais levando a neuroinflamação. Neste sentido, o eixo intestino-cérebro é uma via de comunicação bidirecional complexa entre esses dois órgãos, envolvendo diversos intermediários, como hormônios, citocinas imunológicas e até sinais neurais (Rhee et al., 2009). Esse eixo é composto por fibras e neurônios do Sistema Nervoso Autônomo (SNA), pelo eixo HPA e pela microbiota intestinal. Os benefícios proporcionados pela microbiota podem ser agrupados em três principais funções: metabólicas, protetoras e neurotróficas (Silva et al., 2020).

A microbiota intestinal desempenha um papel crucial na metabolização de componentes não digeríveis, como certos polissacarídeos. No intestino distal, os microrganismos fermentam esses carboidratos, resultando na produção de etanol, gases (como $H_2$, $CO_2$ e $CH_4$) e, principalmente, SCFA (Morrison e Preston, 2016; Ríos-Covián et al., 2016). Os principais SCFA produzidos são acetato (2 carbonos), propionato (3 carbonos) e butirato (4 carbonos), que, além de serem metabolizados pelos colonócitos, exercem importantes efeitos metabólicos no organismo (Bloemen et al., 2009). Esses ácidos graxos são capazes de regular o metabolismo hepático de

lipídeos e glicose (Den Besten et al., 2015; Nishina e Freedland, 1990) e de reduzir os níveis de insulina por meio da ativação do Receptor de Ácidos Graxos Livres 2 (Free Fatty Acid Receptor 2 e 3 - FFAR2/3) também conhecidos por receptores acoplados a proteína G (GPR – 41, 43 e 109) (Silva et al., 2020). Os SCFA também têm a capacidade de exercer efeitos neuroendócrinos, auxiliando no controle do apetite e do consumo alimentar (Byrne et al., 2015; Chambers et al., 2015). Além disso, já se sabe que esses ácidos graxos podem regular o sistema imunológico e a resposta inflamatória de diversas maneiras, como por meio da inibição da ativação do NF-κB e da desacetilação das histonas (HDAc)(Arpaia et al., 2013; Lührs et al., 2002).

A relação entre microbiota e imunidade está bem estabelecida e envolve várias vias importantes de sinalização. Além dos SCFA mencionados anteriormente, a microbiota desempenha um papel crucial na prevenção da invasão de diversos agentes patogênicos, como o *Clostridium difficile* (Hooper e Macpherson, 2010; Lawley et al., 2009). Isso ocorre devido à competição pela região da borda em escova no intestino e à oferta de nutrientes aos microrganismos. Além disso, algumas bactérias produzem substâncias antimicrobianas, como as bacteriocinas, que inibem o crescimento de outros microrganismos (Dobson et al., 2012). Interessante, a microbiota intestinal também desempenha um papel importante na proliferação das células epiteliais intestinais, visto que, em camundongos germ-free, as criptas intestinais são menores e apresentam menos células-tronco quando comparados aos animais normais (Sommer et al., 2015; Von Frieling et al., 2018). Os microrganismos também podem regular o desenvolvimento das células imunológicas T CD4+ para produzirem um perfil de citocinas Th17 nos folículos linfóides intestinais (Ivanov et al., 2008). Por sua vez, animais germ-free apresentam os órgãos linfóides subdesenvolvidos, o que os torna mais suscetíveis a infecções (Fiebiger et al., 2016). Os SCFA produzidos da microbiota ativam células neuroendócrinas intestinais que produzem peptídeos reguladores do apetite como o GLP-1 (e o PYY (Peptídeo YY)) (De Silva A; Bloom S, 2012).

Além da sinalização intestinal, a microbiota consegue influenciar a fisiologia cerebral, afetando a atividade de neurônios e células da glia tanto do intestino como do SNC por meio de várias conexões. O processo inflamatório intestinal ativa as células gliais entéricas (EGCs), que compartilham similaridades com astrócitos e, após ativação, liberam citocinas pró-inflamatórias, como TNF-α, IL-1β e óxido nítrico (Seguella e Gulbransen, 2021). Além disso, o intestino inflamado de pacientes com barreira epitelial intestinal prejudicada está relacionado à diminuição dos níveis de Fator Neurotrófico Derivado da Glia produzido pelas EGCs, o que está associado à

redução da proteína juncional desmossômica desmogleína 2, aumento de p38 MAPK e citoqueratinas (Meir et al., 2019). Essas citocinas ativam o nervo vago, o qual atua como principal mediador entre as inervações extrínsecas do intestino e o cérebro, além de encaminhar fibras parassimpáticas para o trato gastrointestinal (Beiroa et al., 2014; Foster et al., 2017). Esta ativação do nervo vago modula o eixo HPA, estabelecendo uma conexão entre a inflamação intestinal e a resposta neuroendócrina ao estresse. O eixo HPA é uma via importante porque prepara o organismo fisicamente para situações de estresse. Entre suas várias funções, ele pode influenciar o trato gastrointestinal, afetando a permeabilidade intestinal e a inflamação (Czimmer et al., 2006; Zheng et al., 2013). No entanto, a ativação excessiva desse eixo está associada à perturbação da microbiota (Weerth, 2017) e alterações cerebrais (Jacobson, 2014). Por fim, a microbiota intestinal contribui para a regulação do eixo cérebro-intestino por meio do controle das citocinas inflamatórias (Desbonnet et al., 2008), sensibilização do nervo vago (Bravo et al., 2011) e, como já mencionado, pela produção ou regulação de compostos neuroendócrinos (Burokas et al., 2017). Consequentemente, a alteração da microbiota leva a modificação da sinalização desse eixo está associada a doenças metabólicas, como obesidade e diabetes (Lartigue et al., 2011; Grasset et al., 2017) e a transtornos neuropsiquiátricos, como depressão e ansiedade (Cryan e O'Mahony, 2011; Grenham et al., 2011).

Disbiose é definida como uma alteração na estrutura das comunidades microbianas residentes, acompanhada por uma diminuição na diversidade microbiana e um aumento de microrganismos patogênicos em relação à microbiota de indivíduos saudáveis (Petersen C; Round J, 2014). Diversos estudos demonstraram modificações na estrutura da microbiota em doenças inflamatórias intestinais, como a colite ulcerativa (Aas et al., 2003), diabetes (Karlsson et al., 2013), asma (Abrahamsson et al., 2014) e transtornos neuropsiquiátricas, como o autismo, depressão e ansiedade (Grochowska et al., 2018). Há vários fatores que podem causar a alteração da microbiota, incluindo a genética do indivíduo, infecções, terapias medicamentosas (especialmente com antibióticos) e dieta (Jumpertz et al., 2011; Kau et al., 2011; Penders et al., 2006).

O consumo de dietas ricas em gorduras já mostrou modificar a estrutura da microbiota intestinal em humanos e modelos experimentais. Um exemplo disso é a alteração na proporção entre os filos *Firmicutes* e *Bacteroidetes*. Estudos documentaram que uma dieta hiperlipídica (35% a 45% de gordura) resulta em uma diminuição dos *Bacteroidetes* e um aumento dos *Firmicutes* (Hildebrandt et al., 2009; C. Zhang et al., 2012). Além disso, dietas ricas em lipídios reduzem a diversidade

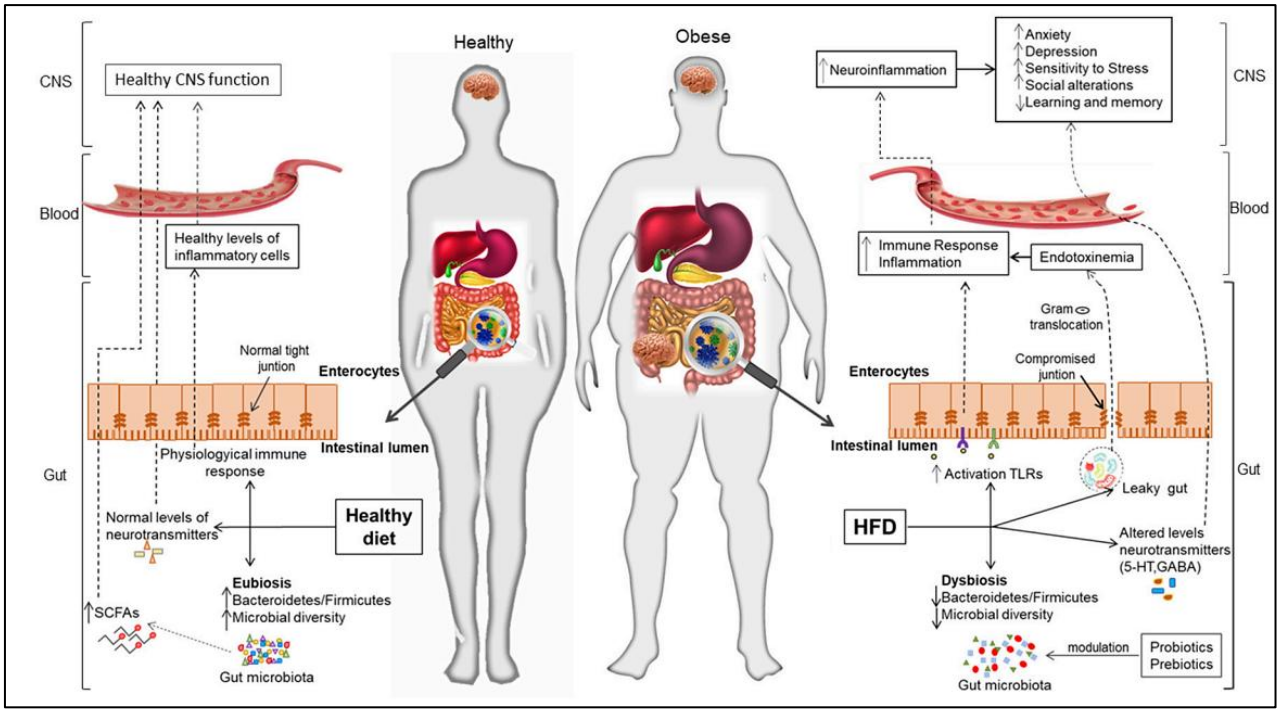
microbiana em comparação com animais alimentados com dietas normais (Parks et al., 2013). Em humanos, a composição dietética também pode alterar a estrutura microbiana, aumentando a razão *Firmicutes/Bacteroidetes* e a diversidade (David et al., 2014; Di Filippo et al., 2013). Além das modificações mencionadas, as dietas ocidentais têm sido associadas ao aumento da permeabilidade intestinal por meio de mecanismos já descritos na literatura. Lam e colaboradores (2012) relataram que o consumo de uma dieta rica em gordura em camundongos C57BL-6 resultou em uma diminuição na expressão das proteínas de junção estreita no cólon proximal. Da mesma forma, Cani e colaboradores (2008) mostraram que dietas obesogênicas levavam à diminuição das proteínas da zona de oclusão e das junções apertadas (do inglês, *tight junctions*). A redução dessas proteínas pode ser regida por um processo de feedback negativo relacionado ao aumento das citocinas pró-inflamatórias na disbiose (Al-Sadi et al., 2010; Ye et al., 2006). Adicionalmente, a disbiose intestinal, leva à redução dos SFCAs, a qual está diretamente relacionada à diminuição da expressão de proteínas das junções intercelulares das células epiteliais intestinais, como a ocludina, a claudina e a zonula occludens (ZO-1). Esse comprometimento estrutural favorece o aumento da permeabilidade intestinal, permitindo a translocação de microrganismos e seus produtos para a circulação sistêmica, o que pode contribuir para processos inflamatórios e doenças associadas à disfunção da barreira intestinal (Ma et al., 2022).

Em função do impacto das dietas hiperlipídicas no desenvolvimento de bactérias Gram-negativas, observa-se um aumento nos níveis de LPS no plasma de animais obesos (Kim et al., 2012). O LPS pode ser facilmente translocado para a circulação sistêmica, sendo reconhecido pelos TLR-4 tanto no intestino quanto na periferia, o que induz a ativação da via de sinalização NF-κB, responsável pela síntese de citocinas e quimiocinas pró-inflamatórias (Hawkesworth et al., 2013). Níveis elevados de LPS desempenham um papel chave no desenvolvimento de doenças crônicas, condição conhecida como endotoxemia metabólica (Cani et al., 2008; Ghanim et al., 2009). O TLR-4 também é expresso na micróglia no SNC, e sua ativação leva à produção de citocinas pró-inflamatórias como TNF-α e IL-1β, resultando em efeitos deletérios previamente mencionados (Beutler, 2000; Mrak e Griffin, 2005). A inflamação causada pelo LPS está diretamente relacionada, também, ao desenvolvimento de transtornos neuropsiquiátricos, como a depressão e ansiedade (André et al., 2014; Lee et al., 2018; Stevens et al., 2018).

Em resumo, a microbiota intestinal desempenha um papel crucial na regulação do eixo intestino-cérebro e na manutenção da saúde geral. Sua alteração, conhecida como

disbiose, frequentemente resultante de fatores de estilo de vida, como dietas não saudáveis e estresse, está fortemente associada à obesidade e suas consequências adversas para o humor. Padrões alimentares saudáveis, como dietas ricas em fibras e vegetais, aumentam a diversidade da microbiota intestinal e promovem a integridade epitelial intestinal, a homeostase imunológica e a função normal do SNC por meio do eixo intestino-cérebro. Por outro lado, dietas ocidentais, ricas em açúcares simples e gorduras saturadas, tendem a reduzir a diversidade microbiana, promover inflamação e contribuir para a síndrome do intestino permeável. Esse padrão alimentar facilita a translocação de componentes bacterianos Gram-negativos, o que aumenta a inflamação periférica e gera neuroinflamação, resultando em alterações no SNC. Esse processo está bem ilustrado na figura 5, que exemplifica o impacto das dietas ocidentais na microbiota intestinal e nas consequências para o sistema nervoso.

**Figura 5.** Relação entre a microbiota intestinal e o eixo intestino-cérebro na obesidade e nos transtornos mentais relacionados.




**Legenda:** A microbiota intestinal desempenha um papel crucial na modulação do eixo intestino-cérebro e na manutenção da saúde humana. No entanto, a disbiose, que pode ser causada por fatores como dietas inconvenientes, é fortemente associada à obesidade e aos seus efeitos prejudiciais sobre o humor e a cognição. Dietas hiperlipídicas alteram a diversidade microbiana, promovem inflamação por meio da ativação do TLR-4 e comprometem a integridade epitelial intestinal, facilitando a translocação de toxinas bacterianas como o LPS. Esse processo intensifica ainda mais o estado inflamatório da obesidade, resultando em neuroinflamação e alterações cognitivas. Por outro lado, dietas ricas em fibras aumentam a diversidade da microbiota intestinal, contribuindo para a preservação da integridade do epitélio intestinal, a manutenção da imunidade normal e o equilíbrio saudável

do SNC. Activation= Ativação; Altered levels of neurotransmitters = Niveis alterados de neurotransmissores; Dysbiosis =Disbiose; Enterocytes= Enterócitos; Eubiosis = Eubiose; GABA= Ácido gama-aminobutírico; Gut microbiota = Microbiota intestinal; Healthy CNS Function= Função saudável do SNC; Healthy levels of inflammatory cells = Níveis saudáveis de células inflamatórias; Healthy diet = Dieta Saudável; Intestinal lumen= Lúmen intestinal; Microbial diversity= Diversidade microbiana; Modulation= Modulação Normal tight juntion= Tight juntion normal; Normal levels of neurotransmitters = Níveis normais de neurotransmissores; Physiologycal imune response= Resposta imune fisiológica; Prebiotics= Prebióticos, Probiotics= Probióticos; SCFA (Short Chain Fat Acids) = Ácidos graxos de cadeia curta; 5-HT = 5-hidroxitriptamina,

**Fonte:** AGUSTÍ, A. et al. 2018

De maneira geral, a dieta hiperlipídica está vinculada ao desenvolvimento tanto da obesidade quanto da disbiose, e ambos estão correlacionados ao aumento dos processos inflamatórios sistêmicos. Como demonstrado anteriormente, há uma conexão entre o intestino e o cérebro por meio de vias neurais, endócrinas e imunológicas, que, quando desreguladas, podem afetar estruturas cerebrais como hipocampo e córtex pré-frontal, as quais estão ligadas ao humor. Nesse contexto, a modulação da microbiota alterada, por meio de intervenções não farmacológicas, pode ser uma estratégia eficaz para reduzir a inflamação, auxiliando na prevenção e no tratamento de disfunções cognitivas e outras comorbidades associadas à obesidade. Em particular, é importante considerar elementos nutricionais com propriedades imunorreguladoras.

## 4.4 SOLUÇÕES NATURAIS E ACESSÍVEIS: COMO OS PREBIÓTICOS MODULAM A SAÚDE?

A microbiota desempenha um papel importante na regulação da imunidade, contribuindo para esclarecer a etiopatogenia e, até mesmo, atenuar os sintomas clássicos de doenças neurodegenerativas e comportamentais, como ansiedade, depressão e doença de Alzheimer (DA), entre outras (Collins et al., 2012). Além disso, diversos microrganismos presentes em alimentos podem interagir com o microbioma e com células do organismo, causando tanto efeitos benéficos quanto prejudiciais (Arora et al., 2013). Dentre esses microrganismos, destacam-se os probióticos, conhecidos por seus impactos positivos no organismo. De acordo com a Associação Científica Internacional para Probióticos e Prebióticos (ISAPP), probióticos são definidos como microrganismos vivos que, quando consumidos em quantidades adequadas, promovem benefícios à saúde do hospedeiro (Gibson et al., 2017).Essa ideia se baseia nas observações de Élie Metchnikoff em 1907, que associou o consumo de produtos lácteos fermentados à melhoria da saúde em populações de aldeias búlgaras (Mackowiak,

2013).

Diversas espécies de bactérias são utilizadas como probióticos, sendo as mais comuns pertencentes aos gêneros *Bifidobacterium* (Ray et al., 2014) e *Lactobacillus* (Shokryazdan et al., 2014). Já o principal tipo de leveduras, destaca-se *Saccharomyces boulardii* (Kelesidis e Pothoulakis C, 2012). Estudos relatam inúmeros benefícios associados ao uso de probióticos, incluindo a redução da intolerância à lactose (Oak e Jha, 2019), melhoria da asma (Mennini et al., 2017), controle de disbiose (Ducatelle et al., 2015) e auxílio no manejo de doenças crônicas como diabetes e obesidade, por meio de mecanismos epigenéticos (Sun e Buys, 2016; Tonucci et al., 2017; Vähämiko et al., 2019).

De forma semelhante aos probióticos, a definição de prebióticos foi inicialmente proposta por Gibson e Roberfroid no final do século XX, caracterizando-os como componentes alimentares não digeríveis pelo organismo humano, mas que oferecem benefícios à saúde ao serem metabolizados por bactérias específicas do cólon (Gibson e Roberfroid, 1995). Em 2004, Gibson e colaboradores (2004) estabeleceram três critérios essenciais para que um composto seja considerado prebiótico: ser resistente à acidez gástrica, à ação de enzimas humanas e não ser absorvido no trato gastrointestinal. Além disso, ele deve ser fermentado pela microbiota intestinal e promover o crescimento ou a atividade de bactérias benéficas. Posteriormente, observou-se que os prebióticos também podem ser aplicados em outras regiões do corpo, como pele e vagina, onde exercem efeitos positivos (Ouwehand et al., 2010; Reid, 2012). Em 2017, a ISAPP redefiniu o conceito de prebióticos como "*um substrato utilizado seletivamente por microrganismos do hospedeiro, conferindo benefícios à saúde*" (Gibson et al., 2017). Entre os prebióticos mais relevantes destacam-se os mananoligossacarídeos (MOS), xiloligossacarídeos (XOS), inulina, oligossacarídeos do leite humano (HMO), com ênfase especial nos Frutooligossacarídeose Galactooligossacarídeos (Gibson et al., 2017).

A maioria dos prebióticos são de origem vegetal (Campbell et al., 1997) sendo o FOS encontrados em frutas, legumes e vegetais como Alcachofra de Jerusalém (10-15% do peso seco), Batata yacon (3-19% do peso seco), Chicória (5-10% do peso seco), Alho (3,6-6% do peso seco), Alho-poró (2,4-8,0% do peso seco), Aspargos (2-3% do peso seco), Cebola (1,1-7,5% do peso seco) e Trigo (1-4% do peso seco) (Macedo et al., 2020). Estas concentrações podem várias conforme o estágio de maturação do alimento e o tipo de preparo (cru, cozido ou fervido). No entanto, para obter os benefícios associados aos prebióticos relatados na literatura, como melhora na saúde intestinal e redução de inflamação, seria necessário consumir quantidades

elevadas de alimentos diariamente, o que é inviável. Em contrapartida, suplementos concentrados enriquecidos com prebióticos têm sido uma alternativa eficaz para atingir as quantidades adequadas. Por isso, a indústria alimentícia já consegue produzir e vender a forma isolada de alguns prebiótico, como o FOS.

A obtenção comercial dos frutooligossacarídeos pode ser realizada a partir de fontes vegetais, por meio de extração direta ou por hidrólise enzimática da inulina. A inulina, presente em diversas plantas como a chicória e o alho-poró, é frequentemente utilizada devido à sua abundância e capacidade de ser transformada em FOS por ação de enzimas específicas. Esse processo é amplamente empregado na indústria alimentícia para a produção de ingredientes com propriedades prebióticas, que contribuem para a saúde intestinal. Neste caso, a síntese de FOS ocorre pela transfrutosilação de resíduos de sacarose, mediada pelas enzimas frutosiltransferases ou β-frutofuranosidases (Blanch et al., 2011). A estrutura dos produtos dessa reação depende da origem das enzimas utilizadas na síntese, as quais podem ser produzidas por fungos como *Aureobasidium pullulans*, *Aspergillus niger*, *Aspergillus japonicus*, *Aspergillus foetidus*, *Aspergillus oryzae*, *Aspergillus sydowi*, *Fusarium oxysporum*, *Penicillium rugulosum* e *Scopulariopsis brevicaulis*, por leveduras como *Saccharomyces cerevisiae* e por bactérias como *Bacillus macerans* (Antošová e M. Polakovlc, 2001).

Por sua vez, os galactooligossacarídeos são oligossacarídeos derivados da galactose e estão incluídos na categoria de oligossacarídeos não digeríveis (Non Digestible Oligosaccharides - NDO). Esses compostos possuem aprovação como aditivos alimentares FOSHU (Foods for Specified Health Use) - Órgão regulamentar de saúde Japão (Sanz Valero, 2009). Comercialmente, o GOS consiste em uma mistura de diferentes espécies de oligossacarídeos, podendo ser produzido por meio de uma reação de transgalactosilação entre lactose e a enzima β-galactosidase. Durante esse processo, os subprodutos gerados incluem glicose e galactose (Sanz Valero, 2009). A reação ocorre pela transferência de um resíduo de açúcar da porção glicona do substrato para outra molécula de lactose. Caso a transferência ocorra para uma molécula de água, o resultado será uma reação de hidrólise (Akiyama et al., 2001). A composição final do GOS comercial geralmente apresenta mais de 55% de oligossacarídeos, cerca de 20% de lactose, 20% de glicose e uma quantidade residual de galactose, sendo disponibilizado tanto em forma líquida quanto em pó (C. S. Chen et al., 2002). Diversas empresas como a Nestlé®, BIOLIGO® e Bimuno®, produzem o GOS a fim de que possam ser incluídos em alimentos como iogurte, pães, cereais e bebidas (Grimaldi et al., 2016). Prebióticos se destacam dos probióticos por estimularem diversas espécies benéficas, sendo mais eficazes em casos de disbiose

multiespécie (Gibson et al., 2004).

Os FOS e GOS são classificados como prebióticos bifidogênicos devido à sua capacidade de estimular o crescimento de bactérias anaeróbias do gênero *Bifidobacterium* tanto em humanos quanto em animais (Liu et al., 2017; Mao et al., 2018; Martinez et al., 2013; Wingen et al., 2007). Além disso, esses compostos favorecem o desenvolvimento de bactérias gram-positivas produtoras de ácido lático, como *Lactobacillus spp.* (Goderska et al., 2008). A fermentação desses prebióticos por bactérias dos gêneros mencionados reduz o pH do cólon, inibindo o crescimento de bactérias patogênicas (Arboleya et al., 2016; Orrhage K; Nord C, 2000). De maneira geral, os FOS e GOS apresentam benefícios que vão além do trato gastrointestinal, impactando positivamente o sistema imunológico, o metabolismo ósseo e lipídico (Reid et al., 2017; Savignac et al., 2016; Soleimani et al., 2012; Vulevic et al., 2013; Weaver et al., 2011).

Além dos efeitos periféricos, os probióticos também demonstram a capacidade de influenciar positivamente o SNC. Nesse contexto, Dinan, Stanton e Cryan (2015) introduziram o termo "psicobióticos" para descrever probióticos que oferecem benefícios à saúde mental. De forma semelhante, os prebióticos, ao promoverem o crescimento de bactérias benéficas, também podem ser classificados como psicobióticos (Sarkar et al., 2016). A literatura destaca diversos prebióticos com atividade psicobiótica, como a inulina (Smith et al., 2015), XOS (Chunchai et al., 2018), oligossacarídeos de leite humano, como a sialilactose (Oliveros et al., 2018; Sakai et al., 2006), e, principalmente, FOS e GOS(de Paiva et al., 2023).

Diversos estudos pré-clínicos sugerem que a administração de prebióticos nas fases iniciais do desenvolvimento pode gerar efeitos neurológicos positivos na vida adulta, mediando esses benefícios por meio da redução de processos pró-inflamatórios e de ações diretas no SNC. Por exemplo, Williams e colaboradores (2016) demonstraram que ratos neonatos tratados com GOS entre 19 e 53 dias apresentaram maior expressão da subunidade N2A do receptor N-metil-d-aspartato (NMDAR), BDNF e sinaptofisina (SYN) no hipocampo, favorecendo a neurotransmissão e a plasticidade sináptica. Resultados semelhantes foram observados por Savignac e colaboradores (2013) que relataram maior expressão de BDNF e subunidades NMDAR (NR1 e NR2) no hipocampo e córtex frontal de camundongos alimentados com FOS e GOS por cinco semanas. Além disso, estudos apontam uma conexão entre a administração de GOS e alterações hormonais periféricas. A suplementação de GOS em ratos aumentou os níveis plasmáticos do hormônio intestinal PYY, sugerindo que a elevação da expressão de BDNF no cérebro pode ser mediada por esse hormônio. Mais recentemente, Gronier

e colaboradores (2018) identificaram que a ingestão de GOS por três semanas em ratos Sprague-Dawley aumentou as respostas neuronais ao NMDA e mitigou os danos causados pelo antagonista farmacológico do receptor NMDA, HA-966, promovendo um efeito pró-cognitivo associado ao NMDA.

Chen e colaboradores (2017) demonstraram que o FOS aumenta as concentrações de neurotransmissores como acetilcolina, serotonina e adrenalina, além de atenuar danos na região CA1 do hipocampo, reduzindo déficits cognitivos em modelos animais com DA. Em outro estudo com camundongos APP/PS1, Sun e colaboradores (2019) observaram que o tratamento com FOS por seis semanas melhorou a cognição, avaliada pelo desempenho no Labirinto Aquático de Morris, um efeito associado ao aumento dos níveis de SYN e da proteína de densidade pós-sináptica (em inglês, *Postsynaptic Density protein 95* - PSD-95), importantes para a plasticidade sináptica. Além disso, Burokas e colaboradores (2017) demonstraram que o tratamento com FOS e GOS por 3 semanas em camundongos C57BL/6 reverteu comportamentos semelhante a depressão e ansiedade em um modelo de estresse crônico, com redução dos níveis plasmáticos de corticosterona, aumento da expressão dos receptores de BDNF, GABAB1 e do GABAB2 no hipocampo, além de diminuição da expressão do receptor glicocorticoide no hipotálamo. No córtex pré-frontal, os prebióticos reduziram os níveis plasmáticos de triptofano e elevaram os níveis de serotonina

Diante das evidências apresentadas, os prebióticos, em especial FOS e GOS, emergem como alternativas naturais e acessíveis para a modulação da microbiota intestinal, impactando positivamente não apenas a saúde gastrointestinal, mas também a função imunológica, metabólica e neurológica. A associação de FOS e GOS apresenta uma maior capacidade de estimular seletivamente o crescimento de microrganismos benéficos, como Lactobacilos e Bifidobactérias, e influenciar a comunicação entre o intestino e o cérebro reforça seu papel como aliados na promoção da saúde mental e na prevenção de doenças crônicas. Embora o consumo de prebióticos através da alimentação seja um caminho viável, evidências científicas sobre seu impacto específico na depressão e ansiedade quando comórbidas à obesidade são extremamente escassas. Considerando a complexa interação entre o eixo intestino-cérebro e os mecanismos metabólicos envolvidos, pesquisas futuras nessa área podem oferecer novas perspectivas e esperança para o desenvolvimento de abordagens complementares no tratamento de pacientes que apresentam essas comorbidades. A investigação desses efeitos pode contribuir para estratégias terapêuticas mais integrativas, promovendo benefícios tanto para a saúde mental quanto para o equilíbrio

metabólico desses indivíduos.

# 5 RESULTADOS E DISCUSSÃO

Os resultados dessa tese estão apresentados na forma de artigo.

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## Prebiotics modulate the microbiota–gut–brain axis and ameliorate anxiety and depression-like behavior in HFD-fed mice

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ABSTRACT

Previous research has demonstrated that Prebiotics can influence the composition of the gut microbiota, consequently impacting mood regulation. This study aimed to assess the effects of Prebiotics, specifically Fructooligosaccharides (FOS) and Galactooligosaccharides (GOS) on neuroinflammation, depression, and anxiety-like behavior in a mouse model fed a high-fat diet (HFD). Initially, mice were divided into two groups: a control group on a standard diet (n = 15) and a group on an HFD for 18 weeks (n = 45). By the 13th week, the HFD group was further divided into experimental groups: Control (n = 15), HFD (n = 15), HFD receiving Prebiotics (n = 15), and HFD receiving Fluoxetine (n = 15). From the 13th week onward, the HFD + Prebiotics group received both the high-fat diet and a combination of FOS and GOS, while the HFD + Fluoxetine group received Fluoxetine in their drinking water. In the 18th week, all mice underwent tests to evaluate behavior, including the Tail Suspension Test (TST), Forced Swimming Test (FST), Sucrose Preference Test (SPT), and the Plus Maze Test (PMT), after which they were euthanized. Mice on the HFD exhibited increased body weight, abdominal size, blood glucose, triglyceride levels, cholesterol, insulin, HOMA index, and higher serum IL-1β. These obese mice also displayed an increased number of microglia and astrocytes, activation of the TLR4 pathway, and elevated levels of neuroinflammatory markers like TNF-α, IL-1β, and COX-2. Moreover, obese mice showed increased activation of the IDO pathway and decreased levels of NMDA receptors. Additionally, markers of neurogenesis and synaptic plasticity, such as PSD, SAP 102, CREB-p, and BDNF, were lower. Treatment with FOS and GOS reversed symptoms of depression and anxiety in mice subjected to HD. This improvement in behavior resulted from a reduction in dysbiosis with an increase in acetate-producing bacteria (*B. acidifaciens* and *B. dorei*) and intestinal permeability, leading to a decrease in chronic peripheral and central inflammation. Furthermore, the modulation of the gut-brain axis by FOS and GOS promoted elevated acetate and GPR43 levels in the brain and a reduction in the levels of pro-inflammatory cytokines, positively impacting signaling pathways of neuronal proliferation and survival in the hippocampus and prefrontal cortex.

### 1. Introduction

The susceptibility to developing mood disorders, including anxiety disorders and depression, is determined by a combination of genetic and environmental factors. Among these environmental factors, high-fat diet (HFD) has an important influence (Li et al., 2022). The identification of faster-acting antidepressants holds significant importance in enhancing adherence to treatment regimens and mitigating the detrimental consequences of delayed intervention. An insufficient therapeutic response is observed with currently available antidepressants; 10–30 % of individuals with depression show treatment resistance, which refers to the absence of positive results after trying different classes of pharmacological agents at appropriate dosages and periods (Al-Harbi, 2012). Moreover, there exists an elevated risk of suicide during acute-phase antidepressant treatment of undergoing antidepressant treatment (Simon et al., 2006).

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The intake of a diet rich in fats is connected to both metabolic dysfunction and psychiatric disorders. Research has indicated the possibility that the disruption of serotonergic neurotransmission in hippocampus could be responsible for the coexistence of HFD and depression (Hersey et al., 2021). Additionally, the depressive behavior displayed by HFD-fed mice is related to an escalation in lipids' buildup in microglial cells and the reshaping of neurons in the hippocampus (HC) (Zhuang et al., 2022).Further exploration is required to gain a more profound understanding of the mechanisms underpinning depressive behaviors resulting from the consumption of an HFD.

Other studies have demonstrated the impact of consuming an HFD on metabolic disturbances such as obesity and hyperglycemia and behavior resembling depression in mature Wistar rats. Moreover, mice fed HFD showed depression-like symptoms, and there was a notable rise in insulin levels (Lam et al., 2021). Both GLP-1 and its analogs hold therapeutic promise for addressing depression and anxiety reviewed by Anderberg et al., 2016; Kim et al., 2020). HFD-fed C57BL/6 led to a reduction in plasma GLP-1 levels (Anini & Brubaker, 2003). Additionally, the high-fat diet increased the swift degradation of GLP-1 by dipeptidyl peptidase-4 (DPP-4), making it less probable for substantial quantities of active gut-derived GLP-1 to reach the central nervous system (CNS)(Lietzau et al., 2022). Moreover, the disruption of lipid metabolism brought about by HFD consumption could play a pivotal role in the emergence of depressive and anxiety behaviors. Investigations have also established a connection between blood lipid levels and the pathophysiological pathways associated with depression, as highlighted by So et al. (2021).

The theory of monoamine depletion postulates that an imbalance in 5-hydroxytryptamine (5-HT) neurotransmission could contribute to the onset of depression (Elhwuegi, 2004). Nevertheless, several reviews have challenged this notion, demonstrating that a reduction in 5-HT alone might not be sufficient to exacerbate depression. This points to the existence of other underlying causes of depression (Jesulola et al., 2018; Slavich & Sacher, 2019). Investigations conducted in both humans and rodents have revealed a correlation between obesity, heightened inflammation, and depression (McLachlan et al., 2023; H. Yu et al., 2023). Indeed, prolonged elevation of cytokine levels in mice consuming an HFD has been linked to specific changes in neuroplasticity within certain brain regions, like the prefrontal cortex (PFC) and hippocampus, ultimately contributing to mood disturbances, as reviewed by Fulton et al (2022).

Tryptophan is converted into N-formyl kynurenine through the action of IDO and subsequently into L-kynurenine (KYN), which is catabolized into 3-hydroxykynurenine (3-HK) by kynurenine-3-monooxygenase (KMO) and transformed into 3-hydroxy anthranilic acid (3-HAA) by Kynureninase (KYNU). The 3-HAA is metabolized into quinolinic acid (QUIN) by 3-hydroxy anthranilate 3,4-dioxygenase (HAAO). Proinflammatory cytokines and lipopolysaccharides (LPS) can potentially trigger the activation of the IDO pathway (Réus et al., 2015). The elevated levels KYN and its harmful byproducts like QUIN. Concurrently, IDO activation is connected to a reduction in 5-HT levels. Activation of the IDO pathway by neuroinflammation leads to excitotoxicity through N-methyl-D-aspartate (NMDA) receptors through QUIN, which is associated with the underlying mechanisms of depression (reviewed by Braidy & Grant, 2017). Consequently, the activation of the IDO pathway could lead to a decrease in 5-HT levels and death of neurons.

Accumulating evidence suggests that gut microbiota homeostasis is closely related to brain function, promoting the gut–brain axis concept. There are three recognized mechanisms of the gut microbiota: modulation of the immune response (such as inflammatory response), impacts on metabolism, including short-chain fatty acid – SCFA (like acetate, butyrate, and propionate), hormones, neuropeptides, and neurotransmitters; and direct effects neuronal signaling (reviewed by Morais et al., 2021). The interaction between the microbiota, the gut, and the brain occurs bidirectionally. HFD may lead to a reduction in beneficial bacterial load and alters microbial diversity, causing dysbiosis, which disrupts gut barrier function, thus allowing LPS to enter the bloodstream, known as metabolic endotoxemia (Cani et al., 2008; Torres-Fuentes et al., 2017). LPS can bind to microglial surface Toll-like receptors (TLRs), activating signal transduction and ultimately triggering NF-κB activation. This process prompts the expression of proinflammatory molecules, such as IL-1β and TNFα, which can enter within HC and PFC, contributing to neuroinflammation (reviewed by Fiebich et al., 2018).

Strategies to maintain intestinal balance have gained prominence, mainly through interventions such as prebiotic or probiotic supplementation (Arora et al., 2013; Slavin, 2013). These approaches hold promise for influencing brain function, behavior, and the progression of neurological conditions (reviewed by Ansari et al., 2023). Among these strategies, supplementing with prebiotics to enhance gut microbial diversity emerges as a particularly safe option with minimal side effects (Gibson et al., 2004). The gut microbiota can convert some prebiotics into lactate and SCFAs, (Yao et al., 2022), which have been associated with improvements in obesity and chronic inflammation (Zhu et al., 2015). Furthermore, SCFAs have the potential to affect brain neurological functions through immunological and endocrine pathways (reviewed by Hernández et al., 2019). Fascinatingly, treatment of germ-free mice with SCFAs resulted in the restoration of changes in microglial cell structure and the reversal of cellular immaturity (Erny et al., 2015).

Fructooligosaccharides (FOS) and Galactooligosaccharides (GOS) are commonly combined in dietary fiber supplements to promote the growth of beneficial bacteria and promoted the improvement of anxious and depressive-like behaviors akin in a chronic stress model, as well as the restoration of impaired cognition (Burokas et al., 2017; reviewed by Paiva et al., 2020). Our previous research demonstrated that FOS and GOS could enhance cognitive function in obese mice by modulating the IRS/PI3K/AKT pathway (de Paiva et al., 2023). However, the application of prebiotics for addressing depression and anxiety in an HFD model is an avenue that has not yet been thoroughly explored, lacking reported clinical trials. Moreover, the effects of prebiotics and the mechanisms underlying their actions remain incompletely understood. In this study, we used an anxiety and depression-like mice model by employing a HFD and treatment with FOS and GOS to explore the mechanisms behind depression and anxiety.

## 2. Material and methods

### 2.1. Animals and experimental protocol

We used 60 male C57BL/6 mice. The animals were supplied from the central animal facilities of the Aggeu Magalhães Institute, Brazil. They were housed in standard cages in a temperature-controlled room (22 ± 1 °C) with a 12 h light/dark cycle and water ad libitum. All experimental procedures were conducted following the internationally accepted principles for the Care and Use of Laboratory Animals and were approved by the Aggeu Magalhães Institute Animal Welfare Committee (license 135/2018). C57BL/6 mice are used in many research areas, including obesity, diabetes, and metabolic syndrome.

At eight weeks of age, the wild-type mice were randomly divided into four groups for each mouse strain (n = 15 per group) and fed either standard chow (AIN-93 M; normolipid diet, ND) or a high-fat diet (HFD) for eighteen weeks. The ND contained 14 % protein, 77 % carbohydrate, and 9 % lipids, and the HFD contained 14 % protein, 33 % carbohydrate, 53 % lipids, and 0.5 % NaCl. Both diets were manufactured by Prag Soluções (Jaú, SP, Brazil). All animals were weighed at the beginning and end of the diet period and the trial included in HFD group only mice with a body mass exceeding 30 g. Mice fed the HF diet received prebiotics (FOS/GOS group) or Fluoxetine (Fluoxetine group) from the 13th week until the final week of the experiment. On the 18th day, the animals underwent behavioral tests, and subsequently, they received intraperitoneal injection of lidocaine (5 %) and thiopental (0.05 g/ml)

for euthanasia. Blood serum, intestinal, and brain tissues were also collected and stored at −80 °C for further analyses. All mice in the experiment were fed ad libitum. This experiment was performed 2 times (Fig. 1).

### 2.2. Treatment

The mice in the HFD + FOS/GOS group received 0.3 g of FOS (Molecular Weight. 1963.7 g/mol – Fosvita ®) and 0.4 g of GOS (Molecular Weight average. 950 g/mol - Bimuno®) diluted daily in the weekly drinking water, whereas the mice in the HFD + Fluoxetine group received 20 mg/kg (translational dose) administered daily in drinking water for six weeks. Previous studies have demonstrated that the administration of combined prebiotics in the drinking water exhibits more significant effects than when administered individually (Burokas et al., 2017; de Paiva et al., 2023). Before treatment, the trial included only mice with a body mass exceeding 30 g, excluding two animals.

### 2.3. Sucrose splash test (SST)

The experimental procedure involves the application of a 10 % sucrose solution onto the dorsal fur of a mouse. Subsequently, we record the latency (the time elapsed between the application of the solution and the initiation of grooming), the grooming duration and the total distance traveled over a 5-minute observation period. These metrics are manually coded to serve as indicators of self-care and motivational behaviors. Reduced grooming behavior is regarded as a potential marker for depression-like tendencies in mice (adapted from Isingrini et al., 2010).

### 2.4. The Tail Suspension Test (TST)

The TST serves as a behavioral assay in mice, valuable for the preliminary evaluation of potential antidepressant medications and the examination of other interventions anticipated to influence behaviors linked to depression (Can et al., 2012). Mice were inverted, positioned approximately 40 cm above the ground, with a tape affixed 1 cm from the tail tip. This arrangement restricted escape or gripping nearby surfaces. "Immobility" referred to instances when the animal remained motionless, and its body hung vertically. Immobility duration was recorded during the final 5 min of the 6-minute test period.

### 2.5. The Forced Swim Test (FST)

The FST is a rodent-based behavioral measure employed to assess antidepressant drugs, the efficacy of novel compounds in antidepressant treatment, and experimental manipulations targeting the induction or prevention of depressive-like states (Can et al., 2012). Briefly, individual mice were placed in a transparent container filled with water (22–25 °C), and their mobility associated with escape behavior was tracked over six minutes. In the FST context, "immobility" was defined as the absence of movement, apart from essential adjustments for body balance and keeping the head above water. Focus was directed toward the final five minutes due to the initial high activity of most mice, with potential treatment effects possibly not manifesting within the initial minute. Video surveillance was employed, and immobility time was measured through on-screen stopwatch software (Xnote Stopwatch, dnSoft Research Group). Animals were acclimated to the testing environment for one hour before testing.

### 2.6. Elevated Plus Maze Test (EPM)

The EPM, a rodent evaluation, is employed to identify anxiolytic pharmacological agents. This plus-maze, constructed from plywood, consists of two enclosed arms (21.5 × 7.5 × 20 cm) and two open arms (21.5 × 7.5 cm), extending from a central platform measuring 7.5 × 7.5 cm. The rodent is placed at the center of the plus-maze, positioned 38 cm above the ground, and its conduct is observed and documented within each arm. The assay capitalizes on rodents' instinctive aversion to open spaces, hypothesized to mirror their inherent fear of heights and predation. Reduced time spent in open arms and increased time in enclosed arms indicate anxiety-like behavior (Komada et al., 2008).

### 2.7. Biochemical analysis

Animal weights and average food consumption (grams per week) were assessed. All animals were fasted (6 h) before euthanasia and blood collection. The blood underwent centrifugation at 2300 relative centrifugal force (RCF) for 15 min. The serum obtained was then dispensed into a 96-well ELISA plate, where enzymatic systems were utilized to determine glucose levels (Labtest Diagnótica S.A®, MG, Brazil - Ref. 133), triglycerides (Labtest Diagnótica S.A®, MG, Brazil - Ref. 87), cholesterol (Labtest Diagnótica S.A®, MG, Brazil - Ref. 76), insulin (Elabscience, China), TNFα, IL-1β (Abcam, catalog number ab100705), Serotonin (Thermo Fisher, catalog number ab133053) and serum GLP-1 (Thermofischer, catalog number BMS2194). To measure the acetate concentration in HC and PFC, 10 μL content solutions were analyzed with an acetate assay kit (Bioassay Systems, USA) and the Fluoroskan Ascent FL (Thermo Labsystems, China) spectrofluorometer according to

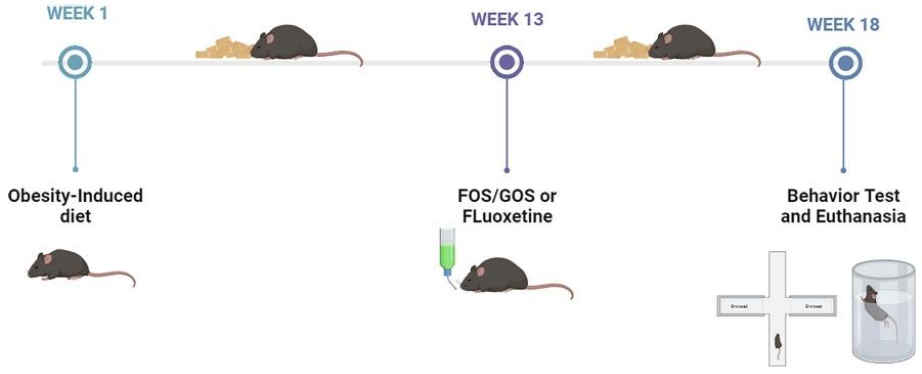


**Fig. 1.** Experimental schedule. 60 adult male mice were fed a high-fat diet for 18 weeks for diet-induced obesity. In the 13th week, the animals were treated with 0.3 g of FOS and 0.4 g of GOS/day/mice or 20 mg/Kg of Fluoxetine for six weeks. In the end (18th week), the animals were subjected to the Elevated plus-maze, Sucrose Splash, Tail suspension, and Forced swimming test and then euthanized. The hippocampus, Prefrontal cortex, colon, feces, and serum were collected. This experiment was performed 2 times.

the manufactory Turer's instructions. The resulting data were expressed as mean ± standard deviation using GraphPad Prism V6.0.

### 2.8. Immunohistochemistry

Following euthanasia, mice underwent transcardial perfusion with 20 ml of saline, followed by 4 % paraformaldehyde (PFA) in 0.1 M phosphate-buffered saline (PBS) at pH 7.2 (40 ml). Subsequently, the mouse brains were extracted and post-fixed overnight in a solution of 4 % paraformaldehyde (Sigma-Aldrich) in 0.1 M phosphate-buffered saline (PBS) at pH 7, which was prepared using monobasic heptahydrate and dibasic sodium phosphate from Sigma-Aldrich. Samples (consisting of 4 animals per group) were dehydrated through a series of ethanol washes from Insofar Chemical Co. (RJ, Brazil), clarified in xylene, and then embedded in purified paraffin from Merck (USA). Coronal sections, each 5 μm thick, were obtained using an RM 2035 microtome (Reichert S, Leica), mounted on glass slides, rehydrated, and subjected to treatment with 20 mM citrate buffer at pH 6.0 at 100 °C for 30 min. A 3 % hydrogen peroxide (H2O2) solution was used to block endogenous peroxidase activity, and unspecific epitopes were blocked with 3 % bovine serum albumin (BSA, fraction V) (Miles, Naperville, IL, USA) for 1 h at room temperature. Primary polyclonal antibodies employed for the hippocampal and prefrontal cortex labeling included: GFAP (Novus Biological, catalog number NB300-141) at a 1:1000 dilution, Iba1 (Wako, catalog number 016–20001) at a 1:500 dilution, TNF-α (Abcam, catalog number Ab34674) at a 1:100 dilution. Primary monoclonal antibodies used for hippocampal labeling included: COX-2 (Abcam, catalog number ab15191) at a 1:100 dilution, and pCREB (Cell Signaling, catalog number #9198) at a 1:500 dilution. All primary antibodies were incubated with the tissue sections overnight at 4 °C. After washing, the sections were incubated with a biotin-conjugated secondary antibody for 1 h (DakoCytomation, Biotinylated Link Universal HRP; catalog number: K0690, CA, USA). Labeling was visualized using 3,3′-diaminobenzidine (DAB) as a chromogen, followed by counterstaining with Carrazi's hematoxylin, and the sections were mounted in Entellan (Merck, catalog number: 1079610100, USA). Negative controls were established using commercial isotype-specific immunoglobulins at the same dilution. The stained areas from 8 images per group (2 images X 4 animals) were quantified using GIMP 2.6.11 software (GNU Image Manipulation Program software, CNET Networks, Inc. Australia), and statistical analyses were conducted using the values obtained from these measurements.

### 2.9. Immunofluorescence

Samples (consisting of 4 animals per group) were fixed in a solution of 4 % paraformaldehyde overnight, dehydrated through a series of ethanol washes, and embedded in paraffin. Sections, each 5 μm thick, were prepared using an RM 2035 microtome (Reichert S, Leica) and mounted on glass slides, rehydrated, and subjected to heat-induced antigen retrieval using 20 mM citrate buffer at pH 6.0 at 100 °C for 30 min. Subsequently, the sections were permeabilized using 0.5 % Triton X-100 and blocked with 3 % BSA and 0.2 % Tween 20 in Tris-buffered saline for 1 h. The slides containing prefrontal cortex regions, specifically the ventromedial, were then incubated overnight with primary antibody anti-pCREB (Cell Signaling, catalog number #9198) at a 1:500 dilution. After incubation with primary antibodies, the slides were subsequently incubated with a secondary polyclonal antibody conjugated to Alexafluor 546 (Alexa, catalog number A10040) specific to rabbit immunoglobulin at a 1:100 dilution for 1 h. Following this step, the slides were washed and mounted in Prolong Gold Antifade fluorescent medium (Life Technologies, catalog number: P36930). Analysis of the slides was carried out using an inverted fluorescence microscope from Zeiss MicroImaging GmbH, which was equipped with a camera (Zeiss AxioCam MRM) and image analysis capabilities. The stained area sections were quantified from 8 images per group (2 images from each of the 4 animals) using GIMP 2.6.11 software (GNU Image Manipulation Program software, CNET Networks, Inc. Australia). Statistical analyses were then performed using the values obtained from these measurements.

### 2.10. Western blot analysis

Sample total proteins were extracted, and 20 μg of proteins from each lane underwent separation via gel electrophoresis. Subsequently, the separated proteins were transferred onto a nitrocellulose membrane (Millipore, USA). The membrane was incubated with a blocking solution (BSA 5 %) to mitigate nonspecific antibody binding. After blocking, the membrane was incubated with a primary antibody as detailed in Table 1. Following this, the membrane was exposed to a secondary antibody, which was conjugated to an enzyme. The protein of interest was visualized using a chemiluminescence imaging system (Tanon-5200, Tanon, China) and Pierce ECL western blot substrate (Thermo, USA). The relative intensities of the immunoreactive bands were quantified through ImageJ software.

### 2.11. 16S rRNA gene sequence-based microbiota analysis

Following euthanasia, fecal contents were collected from each group (6 mice/group) and subjected to processing. Total DNA extraction was performed using magnetic beads, as outlined by Christoff et al., 2017. For bacterial identification, sequencing libraries were prepared utilizing the V3/V4 region of the 16S rRNA gene with 341F primer (CCTACGGGRSGCAGCAG) (Y. Wang & Qian, 2009) and 806R primer

**Table 1**
List of antibodies used for Western Blot.

| Antibody | Host | Dilution | Manufacturer |
|---|---|---|---|
| Anti-Indoleamine 2,3-dioxygenase (IDO) | Mouse | 1:500 | Millipore (MAB5412) |
| Anti-Kynurenine 3-monooxygenase (KMO) | Rabbit | 1:500 | Proteintech (10698-1-AP) |
| Anti-3-hidroxiantranilato 3,4-dioxigenase (HAAO) | Rabbit | 1:1000 | Invitrogen (Pa5115337) |
| Anti-GluR2 (GluA2) | Rabbit | 1:1000 | Alomone labs (AGC-005) |
| Anti-NMDAR1 (GluN1) | Rabbit | 1:500 | Alomone labs (AGC-001) |
| Anti-NMDAR2A (GluN2A) | Rabbit | 1:500 | Alomone labs (AGC-002) |
| Anti-BDNF | Rabbit | 1:250 | Alomone labs (ANT-010) |
| Anti-AKT (phospho T308) | Rabbit | 1:500 | Abcam (ab38449) |
| Anti-PI3K p85 alpha (phospho Y607) | Rabbit | 1:500 | Abcam (AB182651) |
| Anti p-CREB | Rabbit | 1:500 | Cell Signaling (#9198) |
| Anti-PSD-95 | Rabbit | 1:1000 | Alomone labs (#APZ-009) |
| Anti-SAP 102 | Mouse | 1:500 | Biolegend (832001) |
| Anti-TLR4 | Rabbit | 1:1000 | Abcam (ab13556) |
| Anti-p-NF-κB p65 (Ser536) | Rabbit | 1:1000 | Cell signaling (#3033) |
| Anti-MCP-1 | Rabbit | 1:1000 | Abcam (ab7202) |
| Anti-TRAP/CD40L | Rabbit | 1:1000 | Abcam (ab65854) |
| Anti-Malondialdehyde | Mouse | 1:1000 | ThermoFisher (ma527560) |
| Anti-Occludin | Mouse | 1:500 | Santa Cruz (Sc-133256) |
| Anti-Zo-1 | Rat | 1:200 | Santa Cruz (sc-33725) |
| IL-1β | Rabbit | 1:500 | Genway (gwb-bbp232) |
| TNF-α | Rabbit | 1:1000 | Abcam (ab6671) |
| Anti-MyD88 | Rabbit | 1:1000 | Abcam (ab2064) |
| Anti-IκB-α | Rabbit | 1:1000 | Santa Cruz (sc-371) |
| Anti-GPR43 | Rabbit | 1:1000 | Thermofisher (13535R) |

(GGACTACHVGGGTWTCTAAT) (Caporaso et al., 2012). The prepared samples were then sequenced using the MiSeq system (Illumina, USA) with the standard Illumina primers provided in the manufacturer's kit. Raw data from the MiSeq underwent processing using a pipeline developed by Neoprospecta (Christoff et al., 2017). The Illumina FASTQ files underwent primer trimming, and their accumulated errors were evaluated (Phred < 20). Clusters with abundances below 2 were eliminated. Taxonomic classifications were assigned using a 16S rRNA reference sequence database set at a 99 % identity level (Christoff et al., 2017) using blastn v.2.6.0+ (ALTSCHUL et al., 1990). The resulting oligotype tables, akin to traditional OTU (Operational Taxonomic Unit) tables, were employed for calculating alpha-diversity metrics using R (version 4.1.0) and the Phyloseq package. Relative abundance plots were generated using R (version 4.1.0).

### 2.12. Statistical analysis

The statistical data analysis was performed using the program Graphpad prism v 6.01. The parametric data were analysed using ANOVA-one way followed by Tukey's post-test. The data were represented by mean ± SD, and probability values lower than 0.05 were considered significant. In the context of microbiome statistical analysis, we assessed Alpha diversity using the Hill diversity series (Hill, 1973), where different values of q were employed: q = 0 represents richness, q = 1 corresponds to Shannon's entropy, and q = 2 signifies the Reciprocal Simpson index. To discern variations in taxonomic profiles among the experimental groups, we conducted beta diversity analysis via Principal Coordinate Analysis (PCoA). The PCoA was executed on log-ratio transformed data using the Bray–Curtis dissimilarity metric. These analytical procedures were carried out within the R environment utilizing the vegan package.

## 3. Results

### 3.1. The treatment with FOS and GOS improves body and biochemical parameters

In this study, we employed a diet-induced obesity model. During the last week of the experiment, the HFD group exhibited a significantly higher ($p < 0.05$) average weight (44.12 g ± 1.45) than the control group (29.1 g ± 2.06) (Fig. 2). However, by the end of the experiment, both the HFD + FOS/GOS and control groups had significantly ($p < 0.05$) lower weights (33.32 g ± 2.16) compared to the HFD group. Throughout the experimental period, we closely monitored the food intake of mice in all three groups. However, no significant changes in either food intake or body weight were observed in any of the groups (data not shown). The animals in the HFD group displayed a significantly ($p < 0.05$) higher waist circumference (10.12 cm ± 1.33) than the control group (7.2 cm ± 0.32). Notably, the HFD + FOS/GOS group exhibited a significantly ($p < 0.05$) lower waist circumference (8.44 cm ± 0.7) compared to the HFD group.

In the HFD group, there was a notable a significantly ($p < 0.05$) increase in blood glucose levels (220.3 mg/mL ± 31.44) compared to the control group (138.4 mg/mL ± 30.1). However, when mice were treated with FOS/GOS, blood glucose levels (165.3 mg/mL ± 30) were significantly ($p < 0.05$) restored and approached those of the control group.

Similarly, mice on an HFD exhibited significantly ($p < 0.05$) elevated total cholesterol (185.45 mg/mL ± 23.24) and triglyceride levels (195.78 mg/mL ± 15.14) compared to the control group (101.7 mg/mL ± 11.45 and 80.78 mg/mL ± 9.1). Nevertheless, the administration of FOS and GOS resulted in a significant ($p < 0.05$) reduction in both triglyceride (130.45 mg/mL ± 20.14) and cholesterol (122 mg/mL ± 21.44) levels when compared to the HFD group. Also, our data showed that HFD group presented significant ($p < 0.05$) levels of insulin (304. pg/mL ± 52.36) and HOMA-IR (3.86 ± 0.75), when compared to

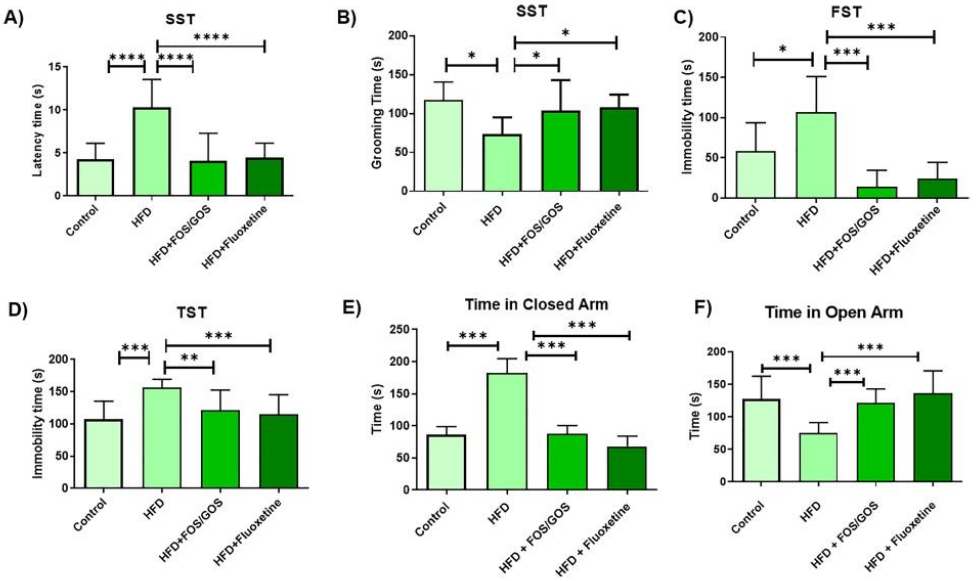


**Fig. 2.** Assessment of behavior following Prebiotics and Fluoxetine treatment. Analysis of anxiety and depression-like behavior (Immobility). A) Latency time (in seconds) in the sucrose splash test. B) Grooming time (in seconds) in the sucrose splash test. C) Immobility time (in seconds) in the forced swim test. D) Immobility time (in seconds) Tail suspension test. E) Time in the closed arm time on elevated plus maze test. F) Time in the open arm on elevated plus maze (n = 15). Analysis of variance (ANOVA), Holm-Sidak multiple comparisons test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

control group (130.33 pg/mL ± 33.56 and 0.96 ± 0.37), respectively. However, the treatment with FOS/GOS significantly ($p < 0.05$) reverted the insulin levels and resistance in obese mice (129.36 pg/mL ± 20.15 and 1.146 ± 0.12, respectively. Similarly, Fluoxetine reduced the insulin levels and HOMA-IR (180.9 pg/mL ± 21.32 and 1.89 ± 0.45, respectively). In turn, the GLP-1 stimulates insulin secretion and inhibits the glucagon secretion. Here, we observed that HFD group showed significant serum GLP-1 levels (25.12 pg/mL ± 3.9) ($p < 0.05$) compared to the control group (50.9 pg/mL ± 15.45). On the other hand, FOS/ GOS group has a significant increase of GLP-1 levels (49.36 pg/mL ± 3.9) compared to HFD group ($p < 0.05$).

We observed a significant increase in the concentration of lipopolysaccharide (LPS) in the HFD group (0.68 μg/mL ± 0.03) compared to the control group (0.19 μg/mL ± 0.018) ($p < 0.05$), indicating an increase in intestinal permeability. Impressively, treatments with prebiotics (0.25 μg/mL ± 0.15) and Fluoxetine (0.53 μg/mL ± 0.1) led to a significant decrease in serum LPS concentration in the HFD group ($p < 0.05$). Furthermore, animals in the HFD group displayed a significantly higher concentration of IL-1β in their serum (32.75 pg/mL ± 3.15) ($p < 0.05$), indicating a systemic inflammatory response. In contrast, the serum expression of this cytokine in groups treated with prebiotics (8.52 pg/mL ± 3.65) and Fluoxetine (27.66 pg/mL ± 3.96) was significantly lower than in the HFD group ($p < 0.05$).

The serotonin hypothesis suggests that reduced activity in serotonin pathways is a contributing factor in the development of depression (Cowen & Browning, 2015). In this study, the HFD group exhibited significantly reduced brain 5-HT levels (6.97 ng/mL ± 0.32) compared to the control group (9.45 ng/mL ± 0.6) ($p < 0.05$). Nevertheless, treatment with FOS/GOS and Fluoxetine significantly reversed the low serotonin levels in the brains of obese animals ($p < 0.05$) (Table 2).

**Table 2**
A) Effect of Prebiotics treatment in reducing HFD-induced body weight gain and improves and biochemical parameters. Weight, Abdominal Length, serum biochemical parameters (glucose, Triglycerides, total cholesterol and fractions, insulin, GLP-1 and IL-1β) were evaluated in 18th week of the experiment. Analysis of variance (ANOVA), Holm-Sidak multiple comparisons tests ($n = 30$ per group). Different letters mean significant statistical difference ($p < 0.05$).

| | Control | HFD | HFD + FOS/GOS | HFD + Fluoxetine |
|---|---|---|---|---|
| Body weight (g) | 29.10 ± 2.06 [a] | 44.12 ± 1.45 [b] | 33.32 ± 2.16 [a] | 41.42 ± 3.24 [b] |
| Abdominal Length (cm) | 7.2 ± 0.36 [a] | 10.12 ± 1.33 [b] | 8.44 ± 0.7 [a] | 9.58 ± 1.1 [b] |
| Glucose (mg/mL) | 138.4 ± 30.1 [a] | 220.3 ± 31.44 [b] | 165.3 ± 30 [a] | 188.2 ± 30.34 [b] |
| Cholesterol (mg/mL) | 101.7 ± 11.45 [a] | 185.45 ± 23.24 [b] | 122 ± 21.44 [a] | 179.45 ± 12.4 [b] |
| Triglyceride (mg/mL) | 80.78 ± 9.1 [a] | 195.78 ± 15.14 [b] | 130.45 ± 20.14 [a] | 174.45 ± 12.66 [b] |
| HDL (mg/mL) | 52.45 ± 7.41 [a] | 125 ± 14.12 [b] | 80.5 ± 22.4 [a] | 135.89 ± 15.45 [b] |
| LDL (mg/mL) | 20.19 ± 5.42 [a] | 59.11 ± 7.38 [b] | 15.75 ± 5.92 [a] | 47.42 ± 10.11 [b] |
| Insulin (pg/mL) | 130.33 ± 33.56 [a] | 304 ± 52.36 [b] | 129.36 ± 20.15 [a] | 180.9 ± 21.32 [a] |
| HOMA-IR | 0.92 ± 0.37 [a] | 3.86 ± 0.75 [b] | 1.145 ± 0.12 [a] | 1.89 ± 0.45 [a] |
| GLP-1 (pg/mL) | 50.9 ± 15.45 [a] | 25.12 ± 4.11 [b] | 49.36 ± 3.9 [a] | 27.55 ± 5.3 [b] |
| LPS (μg/mL) | 0.19 ± 0.018 [a] | 0.68 ± 0.03 [b] | 0.25 ± 0.15 [a] | 0.53 ± 0.1 [b] |
| IL-1β (pg/mL) | 13.45 ± 2.45 [a] | 32.75 ± 3.15 [b] | 8.52 ± 3.65 [a] | 27.66 ± 3.96 [b] |
| 5-HT – Brain (ng/mL) | 9.45 ± 0.6 [a] | 6.97 ± 0.32 [b] | 8.3 ± 0.92 [a] | 8.76 ± 0.45 [a] |

### 3.2. High-fat diets induce anxious and depression-like behaviors, which are reversed by treatment with FOS and GOS

The results from the SST demonstrated that the HFD group showed significantly ($p < 0.0001$) longer latency times (10.33 s ± 3.2) and decreased grooming (73.5 s ± 22.4) compared to healthy animals (4.3 s ± 1.8 and 116.8 s ± 23.2), indicating that these animals exhibited apathy. However, treatment with FOS and GOS significantly ($p < 0.0001$) reduced this behavior, improving latency (4 s ± 3.2) and grooming (103.39 s ± 30.9). The results from the FST and TST confirm that obese mice exhibited behavior akin to depression, as they displayed longer periods of immobility (106.6 s ± 44.39 and 153.6 s ± 12.75, respectively) compared to the control group (58.13 s ± 35.34 and 107.4 s ± 28.14) ($p < 0.05$). However, the administration of FOS/GOS and Fluoxetine significantly reduced the immobility times in the FST (13.59 s ± 20.58 and 23.5 s ± 20.8) and TST (121.1 s ± 31.66 and 114.8 s ± 30.7), respectively (Fig. 2).

Furthermore, in the EPM, it was observed that obese animals spent a longer time in the closed arm (182.7 s ± 22.6) ($p < 0.001$) compared to the control group. Additionally, the HFD group exhibited a significant ($p < 0.001$) decrease in the time spent in the open arm (75.31 s ± 15.8), indicative of behavior resembling anxiety (Fig. 2E-F). Treatment with FOS/GOS led to a significant reduction in the time spent in the closed arm (88.07 s ± 12.7) ($p < 0.001$) and a significantly increased time in the open arm (121.1 s ± 21.61) ($p < 0.001$), indicating an anxiolytic effect (Fig. 5C-D). Treatment with Fluoxetine yielded similar results ($p < 0.001$) (Fig. 2).

### 3.3. Obese animals show increased expression of pro-inflammatory cytokines in HC and PFC

Activation of TLR4 leads to the release of pro-inflammatory cytokines such as NF-κB, TNF-α, and IL-1β through the involvement of MyD88 (Kawai & Akira, 2007). In obese animals, there is a notable increase in protein expression levels of TLR4 (279 % ± 6.21 and 150.3 % ± 29), MyD88 (83 % ± 4.77 and 260 % ± 32.6), p-IkB-α (115 % ± 9.9 and 68 % ± 6.6) p-NF-κB (97.33 % ± 22.88 and 135.7 % ± 3.5), TNF-α (145.3 % ± 22.31 and 134.3 % ± 7.8), and IL-1β (95.33 % ± 27.31 and 125.3 % ± 12) in HC and PFC, respectively, compared to control animals. However, treatment with FOS/GOS significantly ($p < 0.05$) reduces the expression of these inflammatory markers, such as TLR4 (144 % ± 23 and 88 % ± 27.77), MyD88 (58.2 % ±4.4 and 153.7 % ± 36.5), p-IkB-α (60.33 % ± 5 and 34.33 % ± 2) p-NF-κB (54.8 % ± 10.29 and 99.75 % ± 5.1), TNF-α (100.7 % ± 9.4 and 71 % ± 11.33), and IL-1β (71 % ± 6.6 and 57 % ± 8.5) thereby contributing to a reduction in hippocampal neuroinflammation (Fig. 3). The overall effect of the Fluoxetin treatment was less effective compared to the prebiotics.

Similarly, the immunohistochemistry analysis demonstrated significantly elevated TNF-α levels in the HC and PFC of the HFD group (695.6 ± 163.3 and 720.6 ± 127.3) compared to the control group (253.8 ± 213.8 and 23 ± 11.95) ($p < 0.05$). Conversely, both the HFD + FOS/GOS (398.3 ± 114 and 185.9 ± 10.59) and HFD + Fluoxetine (312.5 ± 127.8 and 155.3 ± 17.32) groups exhibited a noteworthy reduction in TNF-α expression compared to the HFD group ($p < 0.05$) (Fig. 4).

Moreover, the consumption of a high-fat diet significantly increased the expression of COX-2 in both dentate gyrus (DG) and ventromedial prefrontal cortex (vmPFC) (352 ± 64.29 and 52.5 ± 8.2) when compared to the control group (18.78 ± 6.58 and 11.63 ± 7.52), indicative of PFC and hippocampal neuroinflammation. In contrast, treatment with prebiotics (20.71 ± 6.48 and 18 ± 6.85) and Fluoxetine (25.8 ± 7.2 and 22.13 ± 5.31) led to a significant reduction in COX-2 levels in the hippocampus and PFC ($p < 0.05$) (Fig. 5).

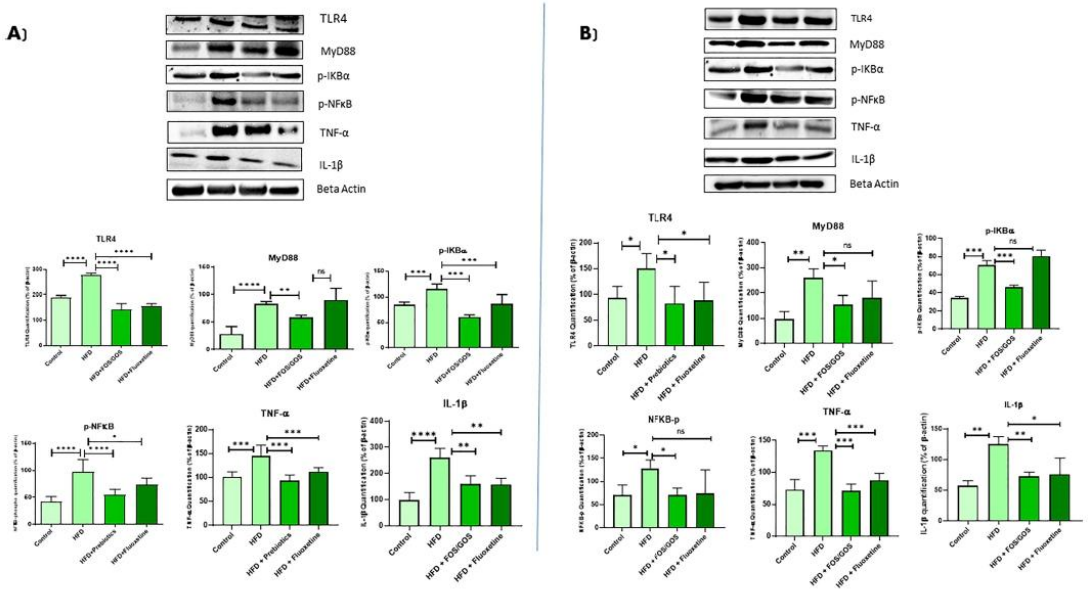


**Fig. 3.** Increased neuroinflammation in the hippocampus as a driver of anxiety and depressive-like behavior by HFD, which was modulated by prebiotics. Representative images of western blot bands and Western blot quantification of TLR4, MyD88, p-IKB-Aα, p-NFκB, TNF-α, IL-1β, and β-actin in A) HC, and B) PFC (n = 6/group). One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis. Values are presented as mean ± SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** p<;0.0001.

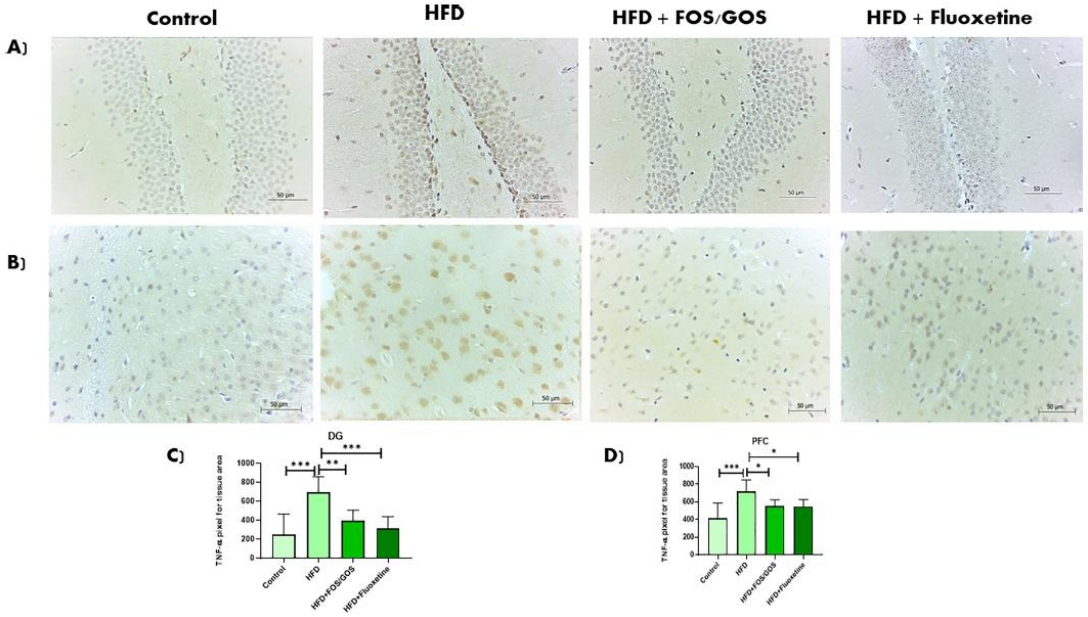


**Fig. 4.** Prebiotics reduced TNF-α levels in HC and PFC in HFD-fed mice. Immunohistochemistry for TNF-α in A) dentate gyrus (HC) and B) Ventromedial prefrontal cortex. Quantification of TNF-α (n = 16 images/group) in C) dentate gyrus (mean ± SD) and D) Ventromedial prefrontal cortex. One-way ANOVA followed by Tukey's post hoc test. *: $p < 0.05$; **: $p < 0.01$. ***: $p < 0.001$.

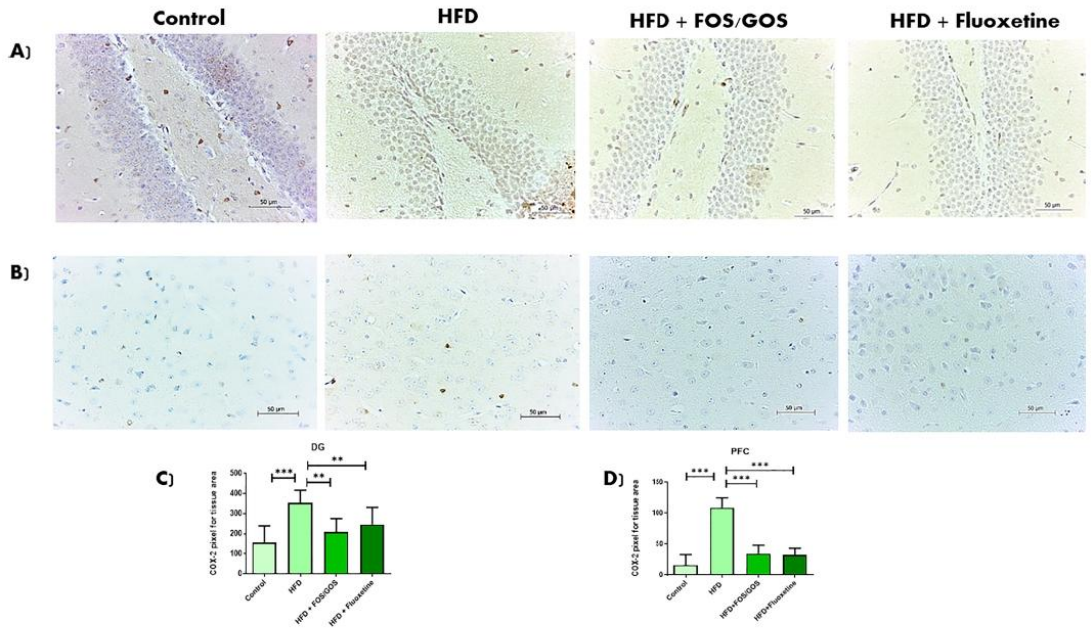


**Fig. 5.** Prebiotics decreased COX-2 levels in HC and PFC in HFD-fed mice. Immunohistochemistry for TNF-α in A) dentate gyrus (HC) and B) Ventromedial prefrontal cortex. Quantification of COX-2 (n = 16 images/group) in C) dentate gyrus (mean ± SD) and D) Ventromedial prefrontal cortex. One-way ANOVA followed by Tukey's post hoc test. *: $p < 0.05$; **: $p < 0.01$. ***: $p < 0.001$.

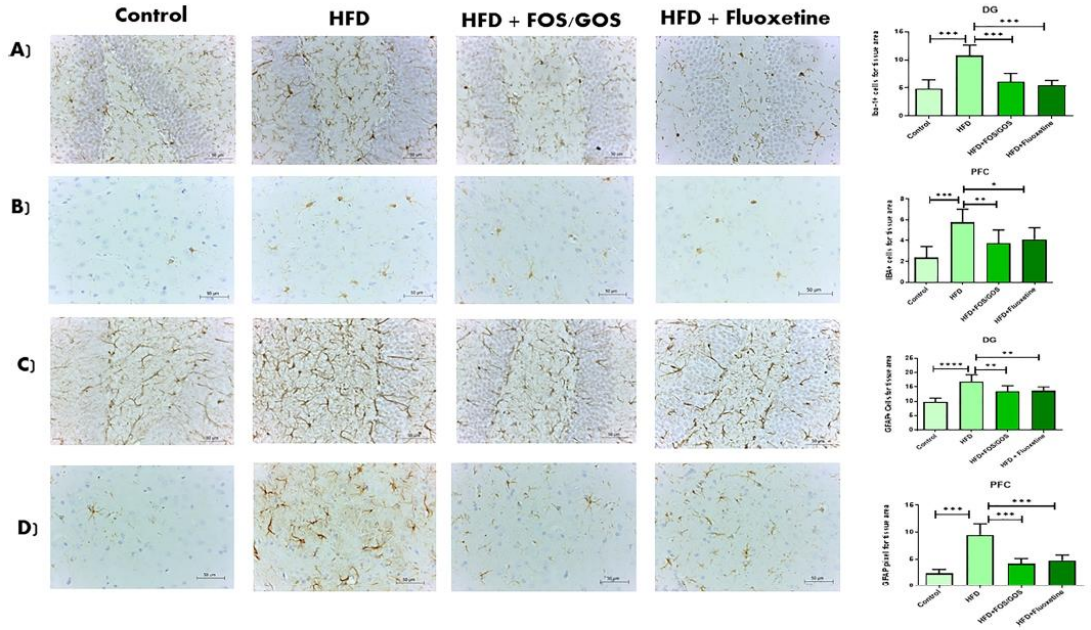


**Fig. 6.** Prebiotics reduced gliosis in the dentate gyrus and ventromedial prefrontal cortex in HFD-fed mice. Immunohistochemistry for Iba1: A) HC, and B) Ventromedial prefrontal cortex. Immunohistochemistry for GFAP + cells in C) HC and D) Ventromedial prefrontal cortex (mean ± SD). Quantification of Iba + and GFAP + cells (n = 8 images/group) (Right panels). One-way ANOVA followed by Tukey's post hoc test. *: $p < 0.05$; **: $p < 0.01$. ***: $p < 0.001$.

### 3.4. FOS and GOS treatment reduced gliosis in the hippocampus and prefrontal cortex in obese mice

In the DG and vmPFC of control animals, a baseline presence of Iba1 + cells was observed (4.8 cells ± 1.53 and 2.3 cells ± 1) (Fig. 5). In contrast, the HFD group exhibited a significant increase in Iba1 + cell expression ($p < 0.001$) with a count of 10.78 cells ± 1.8 (DG) and 5.7 cells ± 1.2 cells (vmPFC). However, treatment with Prebiotic induced a Iba1 + cells reduction ($p < 0.01$), with a count of 6.11 cells ± 1.4 (DG) and 3.7 ± 1.2 vmPFC. Similarly, Fluoxetine treatment also resulted in a reduction of Iba1 + cells ($p < 0.01$) (5.44 cells ± 1.4 in DG, and 4.1 cells ± 1.1 in vmPFC) (Fig. 6).

Astrocytes express the glial fibrillary acidic protein (GFAP), and an increase in GFAP is associated with astrocytes activation, a condition often referred to as reactive gliosis (RG). Within the dentate gyrus and vmPFC, mice in the control group displayed a basal number of GFAP + cells (9.7 cells ± 1.3 and 2.3 cells ± 0.7, respectively). In contrast, mice in the HFD group exhibited a significantly higher count of GFAP + cells in DG (16.88 cells ± 2.41), and in vmPFC (9.5 cells ± 2) compared to the control group ($p < 0.001$). However, treatment with FOS/GOS significantly reduced reactive astrogliosis in the DG (13.38 cells ± 1.9), and in the vmPFC (4.12 ± 1) ($p < 0.01$). Fluoxetine treatment also significantly reduced the number of GFAP + cells in the DG (13.63 cells ± 1.4), and in the vmPFC (4.7 cells ± 1) ($p < 0.05$) (Fig. 6).

### 3.5. Prebiotic intervention decreases IDO pathway activation and excitotoxicity in HC and PFC

Here, we investigated whether treatment with FOS/GOS reduces the expression of enzyme indoleamine-2,3-dioxygenase (IDO) and TryCATS, and whether they could be related to the excitotoxicity caused by decreased expression of glutamate receptors. In HC and vmPFC, the obese animals had significantly higher expression of IDO (131.2 % ± 9.6 and 122.3 % ± 4.9, respectively), KMO (124 % ± 2.6 and 106.6 % ± 5, respectively), and HAAO (142.3 % ± 3.5 and 106.3 % ± 4.7, respectively) compared to the control group ($p < 0.01$), indicating that IDO pathway activation. However, the HC and vmPFC of FOS/GOS group showed significantly reduced levels of IDO (101 % ± 3.3 and 74.5 % ± 7.2, respectively), KMO (79 % ± 3.9 and 52.33 % ± 13, respectively), HAAO (61.33 % ± 3.4 and 50.67 % ± 11, respectively). Similarly, the HC and vmPFC of the Fluoxetin treated group present reduced levels of IDO (99.67 % ± 10 and 34 % ± 6.5 respectively), KMO (79.33 % ± 3.7 and 55.67 % ± 14.67, respectively), HAAO (109.7 % ± 8.3 and 77.33 % ± 27.98, respectively).

In relation to the glutamatergic receptors, the HC and PFC of HFD fed mice showed significative differences in the expression of GluA2R (72.67 % ± 4.9 and 92.5 ± 10.1, respectively), GluN1 (73.6 % ± 5 and 94 ± 11.1, respectively), and GluN2A (108 % ± 2.8 and 84 % ± 7.5, respectively) compared to the control group ($p < 0.01$). In contrast, treatment with FOS/GOS significantly counteracted these changes in the levels of GluA2R (107.3 % ± 5 and 85.5 % ± 4.2), GluN1 (106.3 % ± 3.6 and 146 % ± 11.46), and GluN2A (98.8 % ± 5.1 and 120.7 % ± 10.5) in the HC and vmPFC, respectively, when compared to the HFD group ($p < 0.01$). Fluoxetine treatment had minor impact on modifying the glutamatergic receptors in HFD-fed mice (Fig. 7).

### 3.6. Therapeutic intervention with FOS and GOS improves synaptic plasticity via AKT/PI3K/CREB

The signaling pathway involving protein kinase B (Akt), cAMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF) represents a highly promising therapeutic target for addressing the development of neurodegenerative and neuropsychiatric diseases. On a mechanistic level, the interaction between BDNF and the TRKB receptor initiates the phosphorylation of the Akt/PI3K pathway, which, in turn, activates CREB and subsequently triggers the transcription of specific genes, including BDNF, to foster neuroprotection (Zarneshan et al., 2022). In turn, BDNF can increase the expression of specific postsynaptic proteins, such as postsynaptic density-95 (PSD-95) (Hu et al., 2011). Here, we observed that animals in

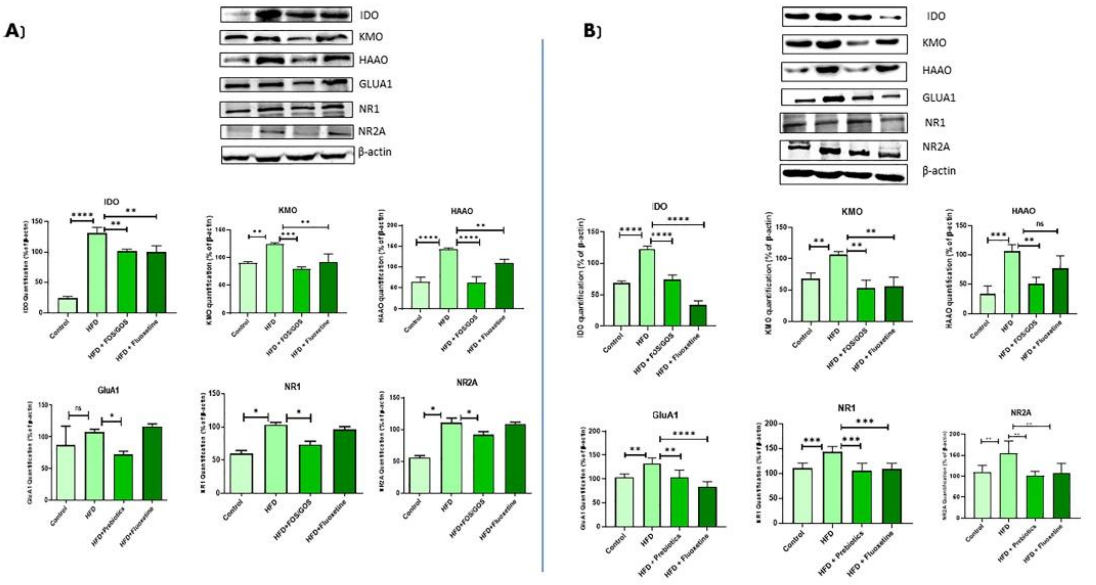


**Fig. 7.** Prebiotic treatment decreased activation of IDO pathway and ameliorated NMDA receptors in A) hippocampus and B) prefrontal cortex. Representative images of western blot bands and western blot quantification of IDO, KMO, HAAO, GluA2, GLUN1 and GLUN2A (n = 6/group). One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis. Values are presented as mean ± SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** p<;0.0001.

the HFD group exhibited a significant ($p < 0.01$) reduction in protein levels of BDNF (44 % ± 4.5 and 57.67 ± 6), p-AKT (56.75 ± 12.42 and 49.33 ± 6), p-PI3K (38 % ± 1.1 and 33 ± 1.1), p-CREB (52.6 ± 9.4 and 36.67 ± 5.5), PSD-95 (35.33 % ± 5.5 and 62 % ± 5), and SAP 102 (62 % ± 5 and 68.67 % ± 6) in HC and PFC, respectively, compared to the control group. Interestingly, treatment with prebiotics significantly reversed the damage caused by a high-fat diet by increasing the levels of BDNF (73 % ± 15.87 and 99 % ± 10.15), p-AKT (102.8 % ± 20.66 and 77.67 % ± 14 %), p-PI3K (64.5 ± 5.1 and 59.67 % ± 4.5), p-CREB (103.3 % ± 6.1 and 89 % ± 1.7), PSD-95 (54.67 % ± 4 and 101 % ± 5.2), and SAP 102 (111 % ± 5.8 and 116.30 % ± 30.8), both in HC and in vmPFC ($p < 0.05$) (Fig. 8). Fluoxetine treatment had similar impact on increased the AKT/PI3K/CREB pathway in HFD-fed mice (Fig. 8).

Similarly, immunohistochemistry and immunofluorescence confirmed the data regarding pCREB expression. Indeed, in the dentate gyrus and prefrontal cortex, we observed that the HFD group exhibited significative ($p < 0.001$) reduced CREB phosphorylation (2967 ± 825.2 and 3112 ± 580, respectively) compared to the control group (5976 ± 1512 and 7617 ± 1480, respectively). However, treatments with prebiotics significantly increased CREB phosphorylation in HC and PFC (4866 ± 831 and 5191 ± 692.4, respectively) and fluoxetine (5117 ± 908 and 5117 ± 908.5, respectively) (Fig. 9).

### 3.7. The treatment with FOS and GOS reduces the intestinal inflammation and permeability caused by the HFD

The Western diet promotes intestinal inflammation and contributes to the development of a leaky gut syndrome, facilitating the passage of components from Gram-negative bacteria, which, in turn, elevates peripheral inflammation and leads to neuroinflammation as well as other changes in the central nervous system (reviewed by Agustí et al., 2018). We observed that obese animals exhibited significant higher expression of TLR4 (126.3 % ± 7.7), p-NFKB (113.7 % ± 3), MCP-1 (106.8 % ± 10.56), CD40L (115.8 % ±. 2.6), and MDA (121.8 % ± 2.8) in distal colon compared to the control group. However, prebiotic treatment decreased the expression of TLR4 (86 % ± 6.5), p-NFKB (70 % ± 14), MCP-1 (54.33 % ± 15), CD40L (54 % ± 23.34), and MDA (82.75 % ± 15.17), thus reducing intestinal inflammation and oxidative stress (Fig. 10).

Moreover, in the HFD group, intestinal inflammation caused by TLR4 activation led to a significant decrease in tight junction proteins such as occludin (68 % ± 5) and ZO-1 (54.67 % ± 2) compared to healthy control animals. In contrast, FOS and GOS, but not Fluoxetine, significantly increased the expression of occludin (99 % ± 7.9) and ZO-1 (84.33 % ± 4.9) compared to obese mice (Fig. 10).

### 3.8. Prebiotics treatment attenuated the gut microbiota dysbiosis induced by HF diet

Our prior research has indicated that a prolonged HFD results in an imbalance in the composition of the gut microbiota referred to as microbial dysbiosis (de Paiva et al., 2023). To investigate the microbiota alteration promoted by FOS and GOS treatment in HFD-fed mice, we conducted an analysis of the gut microbiota profiles following six weeks of exposure to a long-term HF diet, with or without the administration of FOS and GOS, using 16S rRNA sequencing. We did not observe differences in the average proportion of Bacteroidetes and Firmicutes in long-term obese mice in comparison to the control group. However, treatment with prebiotics promoted an increase in Bacteroidetes and a decrease in Firmicutes (see Fig. 11) compared to the HFD group. Furthermore, we did not detect significant differences in bacterial diversity among the four experimental groups, as indicated by metrics such as Exponential Shannon, Richness, and reciprocal Simpson indices (see Fig. 12). In contrast, beta diversity analyses, represented by principal coordinate analysis (PCoA, Fig. 13D), revealed substantial distinctions in species diversity, composition, and abundance within the gut microbiota of the HFD + FOS/GOS group compared to the other groups. The intervention with FOS and GOS led to a significative reduction in the relative abundance of *Faecalibaculum rodentium* (Fig. 13A) and led to significative higher relative abundance of

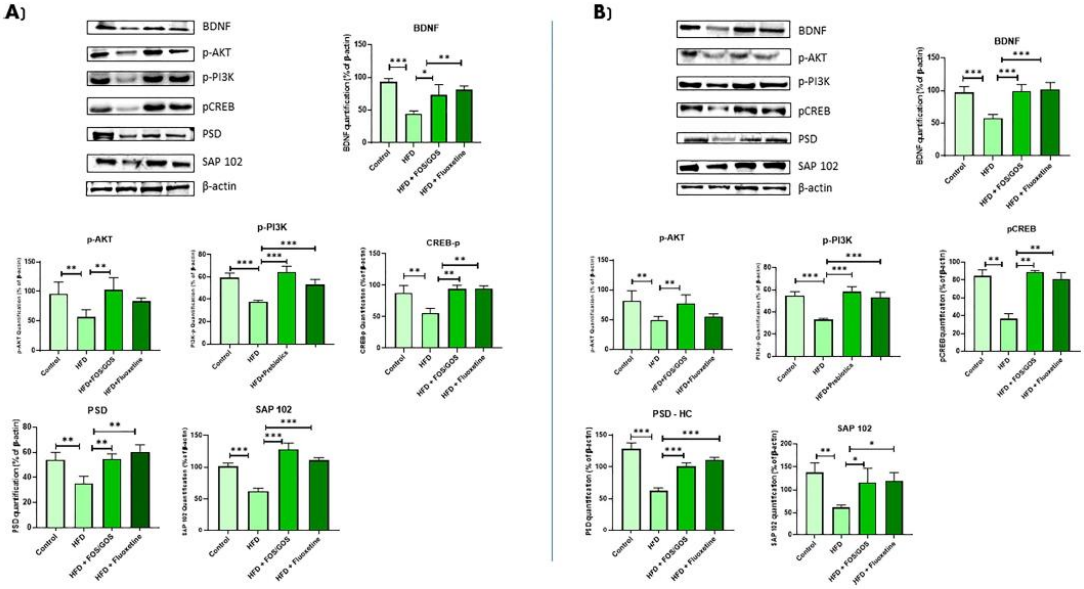


**Fig. 8.** FOS and GOS increased activation of BDNF pathway in A) hippocampus and B) prefrontal cortex of HFD mice. Representative images of western blot bands and western blot quantification of BDNF, p-AKT, p-PI3K, p-CREB, PSD-95 and SAP 102 (n = 6/group). One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis. Values are presented as mean ± SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** p<;0.0001.

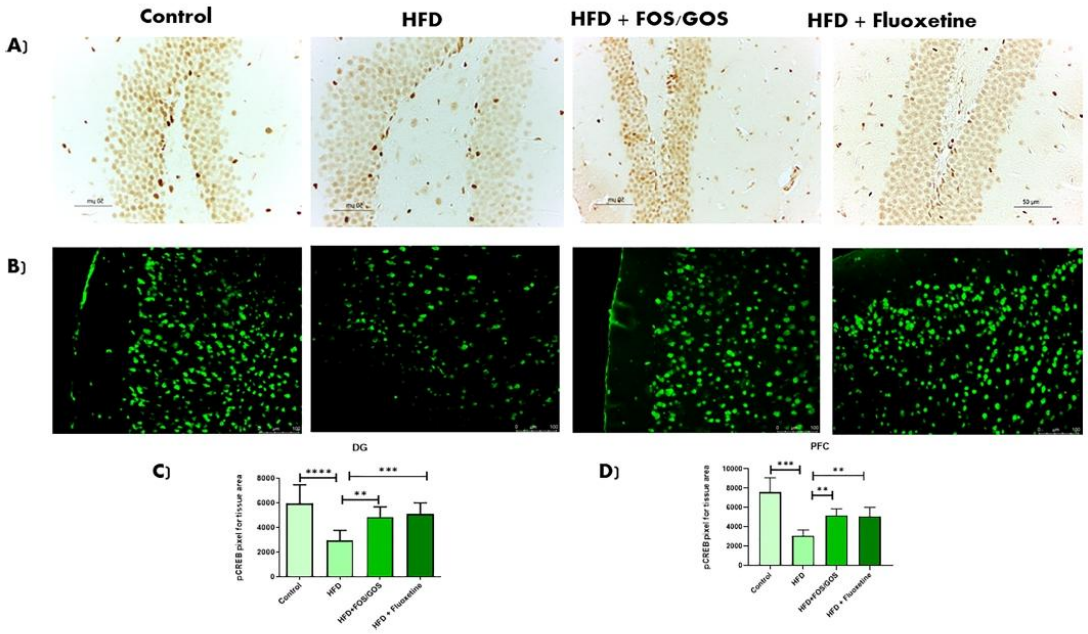


**Fig. 9.** Prebiotics increased the expression of pCREB in obese mice. A) Immunohistochemistry for BDNF in the dentate gyrus and B) Immunofluorescence for pCREB in the ventromedial prefrontal cortex group. C) Pixel quantification (n = 16 images/group), (mean ± SD) in C) HC and D) PFC. One-way ANOVA followed by Tukey's post hoc test. *: $p < 0.05$. **: $p < 0.01$. 400x.

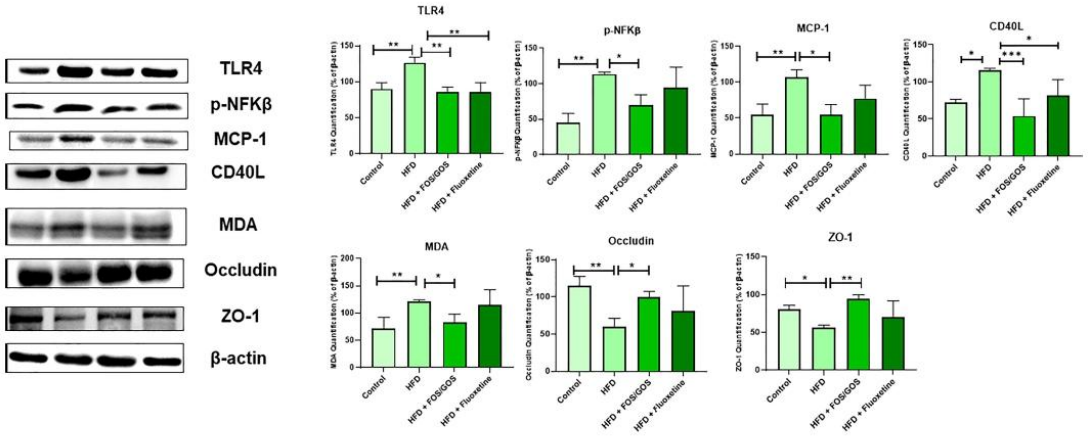


**Fig. 10.** HFD increased the inflammation and leaky gut. Representative images of western blot bands and western blot quantification of TLR4, p-NFKB, MCP-1, CD40L, MDA, occludin and ZO-1 in distal colon (n = 6/group). One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis. Values are presented as mean ± SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** p<;0.0001.

*Bacteroides acidifaciens* (Fig. 13B) and *Bacteroides dorei* (Fig. 13C).

### 3.9. Prebiotic treatment increased GPR43 expression and acetate concentration

In order to investigate whether acetate produced by *B. acidifaciens* and *B. dorei* could be involved in the anti-inflammatory effects in the hippocampus and prefrontal cortex, we evaluated acetate levels in the distal colon, HC and PFC. Obese animals showed significant ($p < 0.01$) lower concentrations of acetate in the hippocampus (54.34 mM ± 1.8) and prefrontal cortex (44.78 mM ± 5) compared to control animals (133.1 mM ± 1.8 and 77.71 mM ± 11.2, respectively). However, the administration of FOS and GOS significantly increased ($p < 0.01$) acetate levels in the HC (81.25 mM ± 8) and PFC (65.63 mM ± 4.8) compared to the HFD group. Moreover, we evaluated the expression of the acetate-binding receptors GPR43 in HC and PFC. Mice fed with HFD

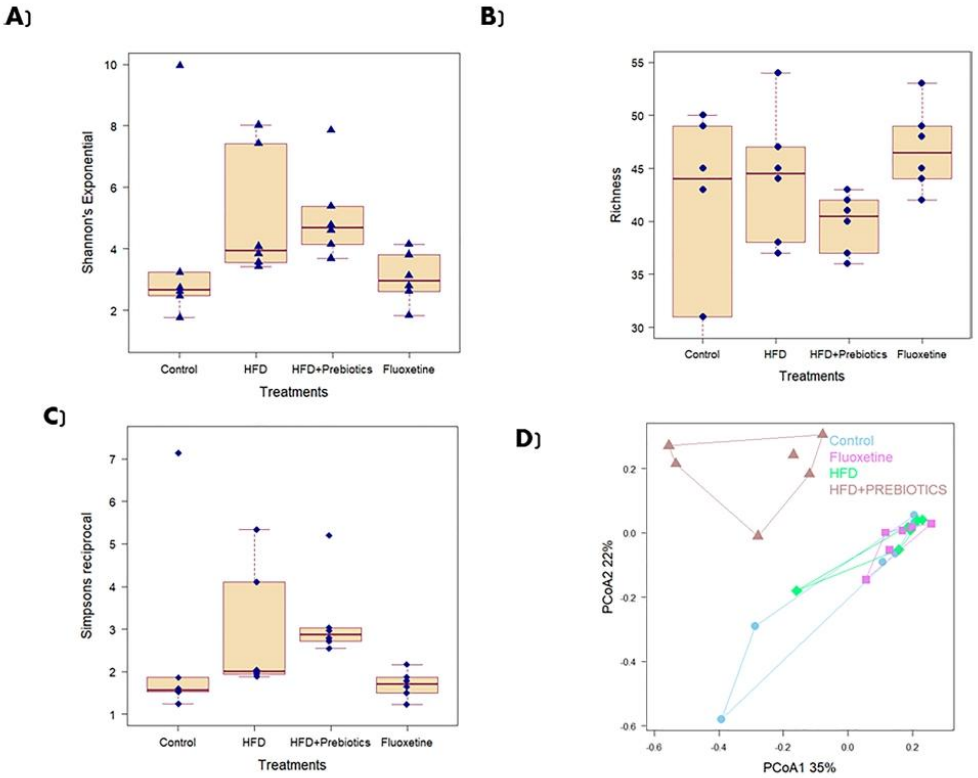


**Fig. 11.** FOS and GOS treatment modulated phylum profile in HFD-fed mice. A) Relative abundance at the phylum (n = 6 cecal content/group). B) Relative abundances of Firmicutes (n = 6 cecal content/group). C) Relative abundances of Bacteroidetes (n = 6 cecal content/group) (n = 6 cecal content/group). One-way ANOVA followed by Tukey's multiple comparison tests was used for statistical analysis. * $p < 0.05$; *** $p < 0.001$.

showed a reduced expression of GPR43 in distal colon (45.33 % ± 20.5), HC (84 % ± 8.5), and PFC (33.33 % ± 5.7) compared to the control group (127.3 % ± 8; 123.5 % ± 7.7; 77 % ± 5.4, respectively) ($p < 0.05$). In contrast, FOS and GOS neutralized this effect by inducing significantly higher expression of GPR43 ($p < 0.05$) in distal colon (110 % ± 19.83), HC (136 % ± 2.8), and PFC (81 % ± 20) compared to the obese mice. No significant differences were observed in acetate levels in the fluoxetine-treated group, as well as in the expression of GPR43 in the hippocampus (see Fig. 14).

## 4. Discussion

The present study demonstrated that a high-fat diet, composed of 60 % of caloric intake from fats, resulted in systemic inflammation associated with intestinal inflammation and permeability. Furthermore, our results showed that the HFD induced a significant impact on body composition, lipid metabolism, and glucose regulation.

According to previous observations, metabolic endotoxemia in obesity leads to low-grade inflammation, triggering insulin resistance by activating intracellular proinflammatory pathways (Rorato et al., 2017). The present results showed, in contrast, that FOS and GOS treatment prevented abnormal weight gain, LPS translocation, increased lipidic profile serum, and insulin resistance. A study performed Yu and cols showed that the administration of FOS in C57BL/6 mice ameliorated cholesterol imbalance caused by a diet rich in sugar and lipids (Yu et al., 2019). A recent study showed that treatment with FOS in C57BL/6 mice with NASH (non-alcoholic steatohepatitis) improved the metabolic profile and reduced genes associated with lipid inflammation and metabolism (such as, ACC1, PPARγ3, IL-1β, and IL-6) (Huang et al., 2023). In turn, GOS modulated the lipid profile in the serum (including TG, CT, HFD, and LDL) and prevented weight gain in Sprague Dawley rats fed a high-fat diet (Kong et al., 2022). Additionally, the GOS treatment for 14 days exhibited anti-inflammatory effects in a model of dextran sulfate sodium-induced colitis, reducing the expression of inflammatory markers such as COX-2, IL-1β, TNF-α, and MCP-1 (Dai et al., 2018). Furthermore, a study realized by Merino-Aguilar and cols showed that the FOS-Fraction from the Roots of *P. decompositum* administration in male Wistar, fed high-fructose corn syrup, inhibited fat synthesis and reduced the expression of pro-inflammatory cytokines, such as IL-6, IFNγ, and IL-1β, contributing to the improvement of systemic inflammatory (Merino-Aguilar et al., 2014). Recently, we reported that the administration of FOS and GOS prevented weight gain and improved biochemical profiles in C57Bl/6 mouse HFD-fed (glucose, triglycerides, and total cholesterol) (de Paiva et al., 2023).

The primary objective of our study was to investigate the influence of an HFD on the biological processes involved in the development of depression- and anxiety-related behaviors. Our findings revealed that HFD induces behavioral deficits akin to those seen in chronic stress models of depression, including heightened anxiety and anhedonia (Burokas et al., 2017; Liu et al., 2015; Taksande et al., 2013). These behavioral alterations are likely linked to increased activation of TLR4, elevated expression of inflammatory cytokines, and disturbances in

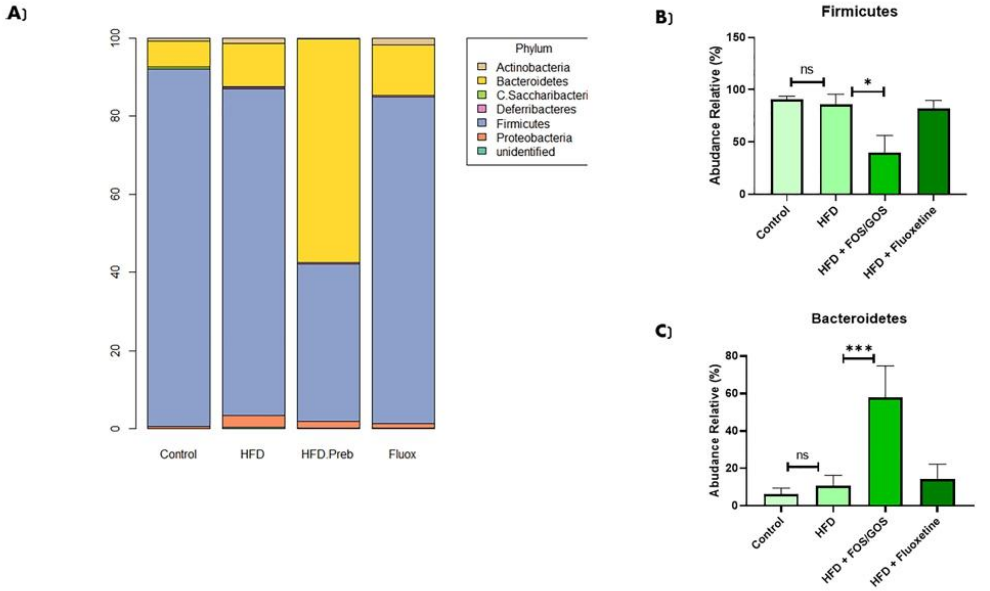


**Fig. 12.** FOS and GOS treatment modulated gut microbiota composition. A) Shannon exponential index. B) alpha diversity: Richness index. C) Reciprocal Simpson index. D) Principal Coordinates analysis (PCoA). Alpha diversity indexes were determined by ANOVA one-way followed by Tukey's post hoc test. Values are presented as mean ± SD (n = 6 cecal content/group). Different letters mean significant statistical difference ($p < 0.01$).

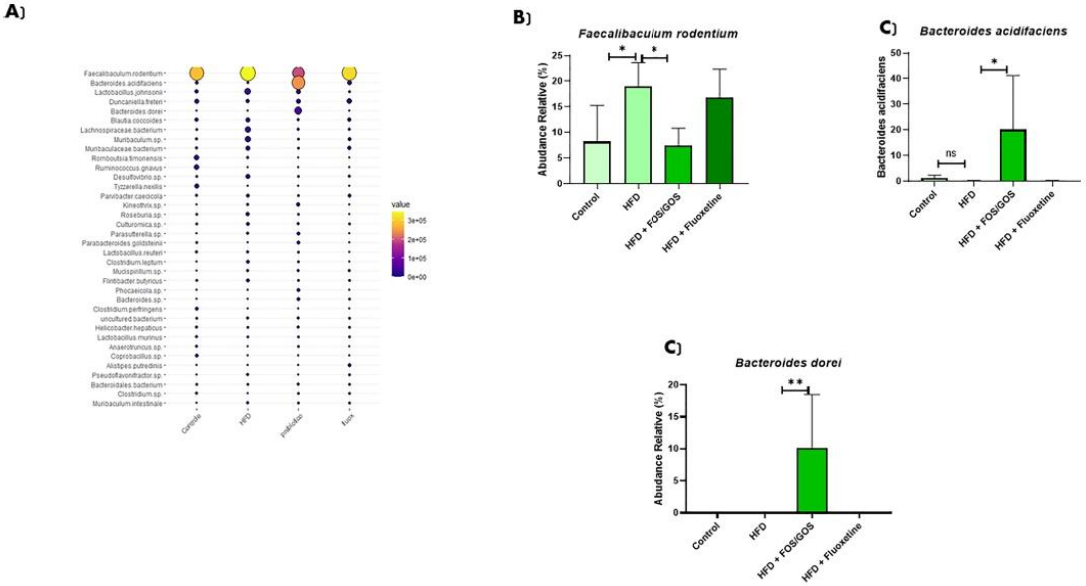


**Fig. 13.** Effect of Prebiotics treatment on species of the intestinal microbial community in HFD-fed mice. A) Relative the abundance at the species levels. B) Relative abundance of *Faecalibaculum rodentium* levels. C) Relative abundance of *Bacteroides acidifaciens* levels. C) Relative abundance of *Bacteroides dorei* levels. One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis. * $p < 0.05$; ** $p < 0.01$.

neurogenesis and neurotrophin signaling in the hippocampus and prefrontal cortex. Pro-inflammatory cytokines, such as IL-1β and TNF-α can reach the brain through specific receptors present in BBB or passively through the circumventricular organs. Damaged neurons and glial cells can release DAMPs, which activate TLR4 and the subsequent cascade of pro-inflammatory cytokines through either the MyD88-dependent or

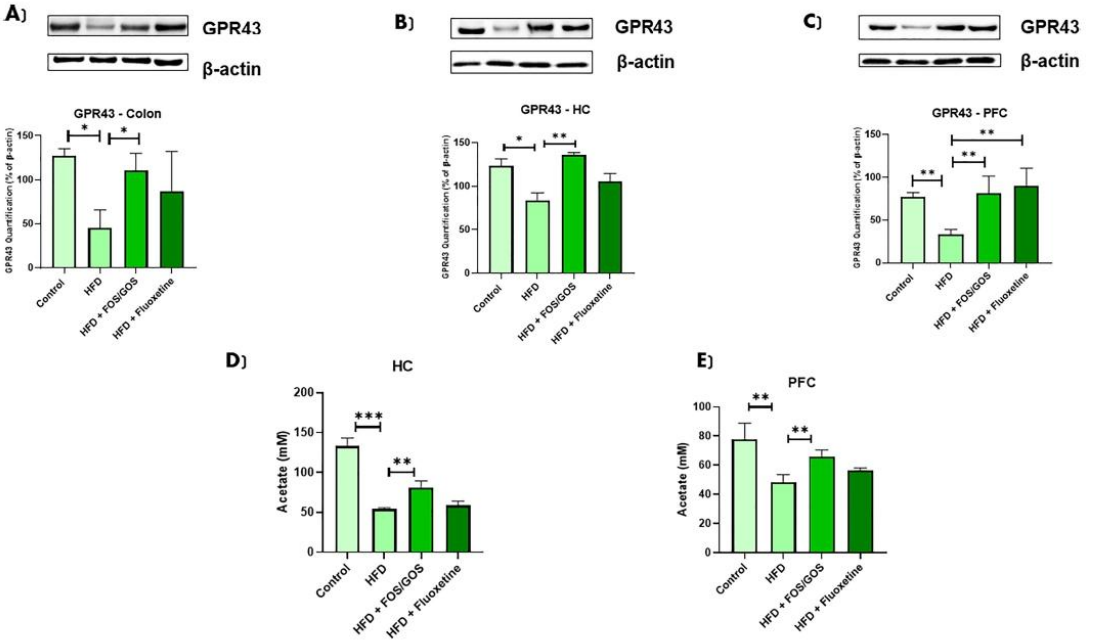


**Fig. 14.** A). FOS/GOS increased the GPR43 expression and acetate levels. Representative images of western blot bands and western blot quantification of GPR43 in distal colon (A), HC (B), and PFC (C). Quantification of acetate levels in HC (D) and PFC (E). One-way ANOVA followed by Tukey's multiple comparison test was used for statistical analysis (n = 4). * $p < 0.05$; ** $p < 0.01$.

other independent pathway (Kumar, 2019; Li et al., 2021). Indeed, several studies have provided evidence that the activation of TLR4 within brain tissues is a pivotal factor contributing to cognitive impairment, anxiety, and depressive behaviors (Kang et al., 2016; Mohammed et al., 2020; Obadia et al., 2022).

Fructooligosaccharides (FOS) and Galactooligosaccharides (GOS), the two most prevalent prebiotics, besides promoting the growth of beneficial bacteria, are also related to the improvement of anxiety and depression like-symptoms (Burokas et al., 2017; Paiva et al., 2020). Here, the treatment with FOS and GOS reduced depressive and anxious symptoms in obese mice, likely due to the decrease in TLR4 expression and the inhibition of the TLR4/MyD88/NF-κB pathway activation. Similarly, a study conducted by Shujuan Zhang and cols (2023) demonstrated that the TLR4-MyD88-NF-κB pathway may be involved in the gut-brain mechanism through which both FOS and GOS alleviate neuroinflammation in Alzheimer's disease (Zhang et al., 2023). Moreover, another recent study showed that inulin supplementation modulated the TLR4/MyD88/NF-κB signaling pathway, alleviating the neuroinflammatory responses and reducing depression and anxiety-like symptoms (Wang et al., 2023).

Increased cyclooxygenase activity is a well-established characteristic of neuroinflammation, with the inducible form COX-2 assuming a dominant role within the Central Nervous System (CNS). In pathological conditions, the prefrontal cortex and hippocampus present an overexpression of COX-2, which increases the production of pro-inflammatory cytokines such as IL-1ß, IL-6, and TNF-α (Chen et al., 2017). Indeed, elevated levels of pro-inflammatory cytokines can result the depletion of tryptophan and decreased serotonin levels. This cascade of events may contribute to the onset of depressive symptoms, potentially culminating in depression (Reviewed by Zádor et al., 2021). Here, we demonstrate that a long-term high-fat diet promoted an increase in COX-2 expression in the hippocampus and prefrontal cortex, as findings from other recent studies (Masetto Antunes et al., 2022; Wang et al., 2021). However, after 6 weeks of FOS and GOS administration, the COX-2 expression in the vmPFC and HC significantly decreased. Other studies have reported that other prebiotics, such as inulin, were also capable of reducing COX-2 expression in the HC and PFC (Farabegoli et al., 2023; Haas et al., 2020).

Multiple lines of evidence from both animal models and human studies suggest that both short-term and long-term consumption of high-fat diets leads to changes in glial function within various brain regions, including the hippocampus, prefrontal cortex, amygdala, and hypothalamus (Butler et al., 2020; Hao et al., 2016; Valdearcos et al., 2019). The increased presence of microglia and astrocytes is linked to the development of symptoms resembling depression in animal models (Wang et al., 2022; Zhou et al., 2019). Our findings provide further evidence in line with earlier research, indicating that the activation of microglia and the regulation of inflammatory cytokines through TLR4-NF-κB play a role in the development of anxiety and depression associated with obesity (Rebai et al., 2021; Wu et al., 2021). Other findings have also reported that prebiotics such as inulin and xylooligosaccharides regulate glial cells in obese mice exposed to an HFD, improving cognition and depression behavior (Chunchai et al., 2018, 2020).

Pro-inflammatory cytokines can activate the enzyme indoleamine-2,3-dioxygenase (IDO), which has been demonstrated to play crucial roles in various depression and anxiety models. Kynurenine metabolites, such as 3-hydroxy-kynurenine (3-OH-KYN) and QUIN exert detrimental effects on brain function. Moreover, QUIN may result in the excessive stimulation of hippocampal N-methyl-D-aspartate (NMDA) receptors, ultimately leading to apoptosis and hippocampal atrophy. These processes highlight the intricate relationship between inflammation, IDO, and the toxic effects of kynurenine metabolites in the context of depression (Huang et al., 2023). Excessive activity or abnormal

expression of NMDA receptors can lead to excitotoxic neuronal damage, which has been associated with the pathogenesis of various human brain disorders, including mood disorders (Chang et al., 2008). Several prior studies confirmed that both short-term and long-term consumption of an HFD activates IDO in various brain structures, such as the hippocampus, which is associated with depressive and anxious symptoms (André et al., 2014; Del Rio et al., 2016; Gainey et al., 2016). Here, the present results confirm these previous observations, in which the increase in COX-2 and pro-inflammatory cytokines, such as TNF-α and IL-1β, could mediate the activation of the IDO pathway. This is the first study to demonstrate that the utilization of prebiotics, FOS and GOS, can modulate the IDO pathway, reducing the HC and PFC expression of IDO, KMO, and HAAO, however, more studies are necessary to confirm the efficacy of prebiotics in modulating the KYN pathway.

There is a growing body of evidence indicating that impaired glutamatergic neurotransmission, particularly through NMDA receptors, plays a role in the pathogenesis of major depressive disorder (Amidfar et al., 2019). HFD can disrupt the homeostasis of these receptors, leading to symptoms like anxiety and depression (Yilmaz et al., 2011). Our findings offer proof that a HFD led to a reduction in the expression of GLUN1 and GLUN2A in the hippocampus and prefrontal cortex. Nevertheless, our study revealed that the impact of obesity on NMDAR activity in the hippocampus and prefrontal cortex can be improved by administering FOS and GOS. Maintaining NMDAR activity at a balanced physiological level is crucial for neuroprotection and HFD. A study conducted by Gronier and cols (2018) demonstrated that the administration of B-GOS® for 3 weeks led to increased cortical NMDAR responses in male Sprague Dawley rats. Another study pointed out that the impact of GOS on central NMDAR signaling components was more significant than that of FOS in both the HC and PFC regions in Sprague Dawley rats (Savignac et al., 2013).

BDNF and its receptor, tropomycin receptor kinase B (TrkB), play a crucial role in the development of depression and anxiety. Inflammation induced by LPS leads to depression-like symptoms by affecting the BDNF-TrkB signaling in the prefrontal cortex and hippocampus (Zhang et al., 2016). The TrkB activation promotes the increase of the transcription factor CREB via Akt/PI3K, which enhances the synthesis of endogenous BDNF. Therefore, proteins like Akt, BDNF, and CREB can be considered central indicators of neuro-regeneration and potential therapeutic targets, as they support neurogenesis and the survival of neurons. Interestingly, the Akt/CREB/BDNF dysregulation may has a critical role in pathophysiology of depression and the mechanisms that underlie the effects of antidepressant drugs (Reviewed by Lindholm & Castrén, 2014). In this study, we report that obese animals have reduced levels of BDNF, AkT, PI3K, and p-CREB. In contrast, the administration of FOS and GOS reverses these effects caused by the high-fat diet. Other studies have demonstrated that prebiotic intervention with FOS and GOS increased the expression of BDNF in the HC and PFC in other experimental models, improving symptoms resembling depression and anxiety (Burokas et al., 2017; McVey Neufeld et al., 2019; Savignac et al., 2013).

HFD promotes the growth of gram-negative bacteria, which leads to a subsequent rise in LPS levels in the intestinal lumen and the activation of TLR4/MyD88/P-NFκB pathway, triggering the inflammation onset. This pro-inflammatory condition in the intestines contributes to leaky gut syndrome and facilitates the translocation of Gram-negative bacterial components (reviewed by Fiebich et al., 2018), which heightens the peripheral inflammatory responses, resulting in neuroinflammation and alterations in the CNS (Agustí et al., 2018). Here, HFD induced changes in the gut microbiota of mice, leading to increased inflammation by the TLR4 signaling pathway, a process associated with increased levels of pNF-κB, MDA, MCP-1, and CD40L. As a previously study performed by Kim and cols showed that HFD triggered inflammation in the colon by TLR4 activation and increasing of NF-κB, iNOS, COX-2. Additionally, the HFD led to a decrease in the expression of tight junction-associated proteins, specifically claudin-1 and occludin, in the colon (Kim et al., 2012). However, our data showed the administration of FOS and GOS reduced the expression of TLR4 and its downstream cascade in the intestine of mice fed an HFD while increasing the levels of junction proteins, such as ZO-1 and occluding, counteracting the leaky gut. Other authors suggested that FOS mitigates the deleterious effects of LPS through modulation of TLR4 and pro-inflammatory transcription factors (Wu et al., 2017).

Considering that the composition of the gut microbiota is affected by a diet that promotes obesity, as well as by conditions of depression and anxiety, we investigated the effects that FOS and GOS on the gut-brain axis. The increase in the relative abundance of the Bacteroidetes phylum and a decrease in Firmicutes is one of the characteristics found in the feces of patients with depression and anxiety (Liu et al., 2023), as well as in mice that received transplantation of fecal microbiome from depressed patients (Zhang et al., 2022). In contrast, here, animals treated with prebiotics showed a significant increase in Bacteroidetes and a decrease in Firmicutes, which were associated to anxiolytic and antidepressant effects. Furthermore, it is also important to note that beta diversity, but not alpha diversity, of the microbiota increased in response to prebiotic treatment. Similar findings in the literature have been described (Burokas et al., 2017). However, the effect on microbiota diversity is inconsistent in the literature (Tran et al., 2019; Zhang et al., 2021). The present study showed that changes occurred at lower taxonomic levels, such as in the species *F. rodentium, B. dorei, and B. acidifaciens* in obese animals. *Bacteroides dorei* plays an important role in brown adipose tissue metabolism and the suppression of pro-inflammatory immune responses (Hu et al., 2023), while the administration of *B. acidifaciens* is related to the improvement of obesity and diabetes in mice, reducing insulin levels and increasing GLP-1(Yang et al., 2016).

Our data on serum GLP-1 and body weight measure suggest that treatment with FOS/GOS induced the production of intestinal microbiota-derived acetate which may act by binding to the G-protein coupled receptor 43 (GPR43) on enteroendocrine colonic cells, responsible for the acetate-mediated effect in GLP-1 and PYY secretion, hormones involved in the modulation of food intake, energy homeostasis, and body weight (reviewed by Ulven, 2012). Thus, the anti-obesity properties of prebiotics seem to be strongly associated with the control of satiety hormones, acting through anti-obesity mechanisms such as increasing GLP-1 levels and reducing the population of some microorganisms, including Firmicutes (reviewed by Cerdó et al., 2019). Moreover, accordingly to other authors, acetate can directly mediate immunomodulatory effects (M2 macrophages and T cells), which may improve adipose tissue and its function toward homeostasis (reviewed by Hernández et al., 2019).

Acetate beneficially influences energy metabolism through the functionality of intestinal hormones such as GLP-1 and PYY, affecting appetite, lipid oxidation and release of pro-inflammatory cytokines. Furthermore, SCFAs have the potential to affect brain neurological functions through immunological and endocrine pathways (reviewed by Hernández et al., 2019). Interestingly, our results also showed elevated acetate levels and GPR43 expression in HC and PFC of FOS + GOS treated-mice, indicating a possible role of acetate-bacteria producers, *B. acidifaciens* and *B. dorei*, in the anti-inflammatory and neuroprotective effects in the CNS, which may contribute to the improvement of the depressive and anxious behaviors by W. Huang and cols (2021). Hsiao and cols also demonstrated that the oral treatment with the human commensal *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates stereotypic and anxiety-like features of ASD (Hsiao et al., 2013). Additionally, a recent study demonstrated that treatment with indole acetic acid exerts anti-depressive effects on an animal model of chronic mild stress by increasing the proportions of intestinal bacterial genera, including other Bacteroides species (Chen et al., 2022).

Our results also demonstrated that FOS and GOS decreased the abundance of *F. rodentium*, which may be related to depressive and

anxious behavior in obese animals, confirming previous observations by others authors. A study conducted by Wang and cols showed that the relative abundance of *F. rodentium* in mice undergoing fecal microbiota transplantation (FMT) from mice subjected to chronic social defeat stress was significantly associated with anhedonia-like behavior (Wang et al., 2021).

## 5. Conclusion

Disturbance in the balance of the microbiota-gut-brain axis contributes to the emergence of mood and anxiety disorders disorders (Lee & Kim, 2021; Margolis et al., 2021). This study revealed that therapeutic intervention with FOS and GOS reversed symptoms of depression and anxiety in mice subjected to HD. This improvement in behavior resulted from a reduction in dysbiosis with an increase in acetate-producing bacteria and intestinal permeability, leading to a decrease in chronic peripheral and central inflammation. Furthermore, the modulation of the gut-brain axis by FOS and GOS promoted a reduction in the levels of pro-inflammatory cytokines, positively impacting the indoleamine 2,3-dioxygenase, NMDA, BDNF and CREB receptor pathways, which play fundamental roles in neuronal proliferation and survival in the hippocampus and prefrontal cortex.

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## CRediT authorship contribution statement

**Igor Henrique Rodrigues de Paiva:** Writing – original draft, Methodology, Investigation, Conceptualization. **Laís Macedo Maciel:** Methodology. **Rodrigo Soares da Silva:** Methodology. **Ingrid Prata Mendonça:** Methodology. **José Roberto Botelho de Souza:** Methodology, Formal analysis. **Christina Alves Peixoto:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## 6. CONSIDERAÇÕES FINAIS

No presente estudo, a intervenção com FOS e GOS promoveu melhorias significativas no comportamento dos animais obesos, revertendo sintomas associadas à obesidade, como comportamento semelhante a depressão e a ansiedade. Essa melhora foi atribuída ao aumento de bactérias acetogênicas, como produtoras de acetato, que desempenham papel crucial na restauração do equilíbrio do eixo microbiota-intestino-cérebro. O tratamento reduziu a disbiose intestinal e a permeabilidade da barreira intestinal, diminuindo a inflamação crônica periférica e central, o que impactou positivamente a neuroinflamação.

Além disso, a administração de FOS e GOS resultou na modulação de vias moleculares relacionadas à plasticidade sináptica e neuroproteção. Houve redução dos níveis de marcadores pró-inflamatórios (como TNF-α, COX-2, TLR4 e CASP-3), que estão superexpressos na obesidade, e da imunoexpressão de marcadores gliais, como Iba-1 e GFAP, atenuando a microgliose e astrogliose no hipocampo. Paralelamente, o tratamento promoveu a fosforilação do CREB, aumentou a expressão de BDNF, NeuN e NGF, e restaurou os marcadores de plasticidade sináptica e neurogênese, como Ki67.

Essas alterações refletiram em uma melhora funcional nos testes comportamentais: os animais tratados com prebióticos apresentaram maior número de alternâncias no labirinto em T, evidenciando a recuperação da memória de trabalho, e menor latência nos testes de aprendizado espacial. Assim, o FOS e GOS demonstraram não apenas promover a neuroproteção, mas também restaurar a função cognitiva, sendo potenciais aliados no tratamento de distúrbios cognitivos e emocionais associados à obesidade.

## 7. SÚMULA CURRICULAR

**• Identificação**

Nome e profissão: Igor Paiva, Biomédico.

Laboratório: Laboratório de Ultraestrutura – IAM / FIOCRUZ – PE

**• Produção Científica**

**Artigo 1**. da Silva, R. S., de Paiva, I. H. R., Mendonça, I. P., de Souza, J. R. B., Lucena-Silva, N., & Peixoto, C. A. (2024). **Anorexigenic and anti-inflammatory signaling pathways of semaglutide via the microbiota–gut—brain axis in obese mice**. Inflammopharmacology, 1–20. https://doi.org/10.1007/S10787-024-01603-Y/METRICS

**Artigo 2**. de Paiva, I. H. R., da Silva, R. S., Mendonça, I. P., de Souza, J. R. B., & Peixoto, C. A. (2024). **Semaglutide Attenuates Anxious and Depressive-Like Behaviors and Reverses the Cognitive Impairment in a Type 2 Diabetes Mellitus Mouse Model Via the Microbiota-Gut-Brain Axis.** Journal of Neuroimmune Pharmacology : The Official Journal of the Society on NeuroImmune Pharmacology, 19(1). https://doi.org/10.1007/S11481-024-10142-W

**Artigo 3**. de Paiva, I. H. R., da Silva, R. S., Mendonça, I. P., Duarte-Silva, E., Botelho de Souza, J. R., & Peixoto, C. A. (2023). **Fructooligosaccharide (FOS) and Galactooligosaccharide (GOS) Improve Neuroinflammation and Cognition By Up-regulating IRS/PI3K/AKT Signaling Pathway in Diet-induced Obese Mice**. Journal of Neuroimmune Pharmacology, 1, 1–21. https://doi.org/10.1007/S11481-023-10069-8/FIGURES/13

**Artigo 4.** Duarte-Silva, E., Oriá, A. C., Mendonça, I. P., de Melo, M. G., Paiva, I. H. R., Maes, M., Joca, S. R. L., & Peixoto, C. A. (2022). **Tiny in size, big in impact: Extracellular vesicles as modulators of mood, anxiety and neurodevelopmental disorders**. Neuroscience and Biobehavioral Reviews, 135. https://doi.org/10.1016/J.NEUBIOREV.2022.104582

**Artigo 5.** Duarte-Silva, E., Oriá, A. C., Mendonça, I. P., Paiva, I. H. R., Leuthier dos Santos, K., Sales, A. J., de Souza, J. R. B., Maes, M., Meuth, S. G., & Peixoto, C. A. (2024). **The Antidepressant- and Anxiolytic-Like Effects of the Phosphodiesterase Type-5 Inhibitor Tadalafil are Associated with the Modulation of the Gut-Brain Axis During CNS Autoimmunity**. Journal of Neuroimmune Pharmacology : The Official Journal of the Society on NeuroImmune Pharmacology, 19(1). https://doi.org/10.1007/S11481-024-10148-4

**Artigo 6.** Mendonça, I. P., de Paiva, I. H. R., Duarte-Silva, E. P., de Melo, M. G., da Silva, R. S., do Nascimento, M. I. X., & Peixoto, C. A. (2022). **Metformin improves depressive-like behavior in experimental Parkinson's disease by inducing autophagy in the substantia nigra and hippocampus**. Inflammopharmacology, 30(5), 1705–1716. https://doi.org/10.1007/S10787-022-01043-6

**Artigo 7.** Mendonça, I. P., Paiva, I. H. R. de, Duarte-Silva, E. P., Melo, M. G. de, Silva, R. S. da, Oliveira, W. H. de, Costa, B. L. da S. A. da, & Peixoto, C. A. (2022). **Metformin and fluoxetine improve depressive-like behavior in a murine model of Parkinsońs disease through the modulation of neuroinflammation, neurogenesis and neuroplasticity**. International Immunopharmacology, 102. https://doi.org/10.1016/J.INTIMP.2021.108415

**Artigo 8.** Paiva, I. H. R. de, Maciel, L. M., Silva, R. S. da, Mendonça, I. P., Souza, J. R. B. de, & Peixoto, C. A. (2024). **Prebiotics modulate the microbiota-gut-brain axis and ameliorate anxiety and depression-like behavior in HFD-fed mice**. Food Research International (Ottawa, Ont.), 182. https://doi.org/10.1016/J.FOODRES.2024.114153

**Artigo 9**. Silva, R. S. da, Mendonça, I. P., Paiva, I. H. R. de, Souza, J. R. B. de, & Peixoto, C. A. (2023). **Fructooligosaccharides and galactooligosaccharides improve hepatic steatosis via gut microbiota-brain axis modulation**. International Journal of Food Sciences and Nutrition, 74(7), 760–780. https://doi.org/10.1080/09637486.2023.2262779

- **Participação em eventos, congressos, exposições e feiras**

I) 2021

- Capacitação no **Uso e Manejo de Animais de Laboratório em formato de ensino a distância, coordenado pela Central de Bioterismo** do Instituto de Ciências Biomédicas (USP) (CH: 50h)

- Minicurso online sobre **Introdução a procedimentos experimentais em animais de laboratório** promovido pelo Biotério do IAM/Fiocruz-PE (CH: 10h)

- Participação como membro titular da banca examinadora do trabalho de conclusão do Curso de Ciências Biológicas intitulado **"Tadalafil exerce efeitos antidepressivos através da modulação da morte e proliferação celular e neurotransmissão glutamatérgica em modelo murino de encefalomielite autoimune experimental (EAE)"**.

- Apresentação do trabalho intitulado "O Eixo A Influência Dos Prebióticos Sobre a Ansiedade e Depressão em Casos Clínicos" promovido pelo Núcleo de Estudos em Neurociências vinculado ao Departamento de Biofísica e Radiobiologia da Universidade Federal de Pernambuco, totalizando uma carga horária de uma (01) hora e sendo premiado com o 1º LUGAR.

II) 2022

- Ministrante da Oficina com o tema de **Acesso venoso e arterial** como parte integrante do II Workshop Formatec de Ciências Mortuárias (CH:10h).

- Participante do curso de **Avaliação Antropométrica na Prática Clínica** (CH: 10h).

- Apresentação do trabalho **Avaliação da memória da cognição e ativação astrocítica em camundongos C57BL/6 wild type e LDL -/-** submetido na 10ª Semana de Biociências e Biotecnologia em Saúde e realizado em formato presencial na modalidade Apresentação Oral.

- Apresentação do trabalho **Frutooligossacarídeo e Galactooligossacarídeo melhoram neuroinflamação, cognição e comportamento semelhante a depressão em modelo animal de obesidade** submetido na 10ª Semana de Biociências e Biotecnologia em Saúde e realizado em formato presencial na modalidade Apresentação Oral.

- Apresentação do trabalho **Avaliação dos efeitos dos prebióticos (fruto-oligossacarídeos e galacto-oligossacarídeos) no metabolismo lipídico hepático em modelo animal,** submetido no 1ª Congresso de Fisiologia e Patologia e realizado em formato presencial na modalidade Apresentação Poster.

- Encontro de Neuroimunomodulação (NIM) na qualidade de APRESENTADOR de trabalhos de pesquisa apresentados na modalidade oral e banner.

- Palestrante sobre o tema "Punção venosa: Como perder o medo e realizar uma coleta sem erros? promovida pela UNINABUCO.

- Apresentação do trabalho **"Herdabilidade genética como fator de risco e expressão gênica variável na esquizofrenia",** submetido no VI Simpósio do Complexo Hospitalar da Universidade de Pernambuco, tendo como tema central, "Saúde Digital: desafios e oportunidades" e realizado em formato presencial na modalidade Apresentação Oral.

- Participação como membro titular da banca examinadora do trabalho de conclusão do Curso de Ciências Biológicas intitulado **“Análises dos efeitos imunomodulatórios da Dietilcarbamazina (DEC) no encéfalo de modelo murino de Hepatite Autoimune Experimental”.**

- Participação como membro titular da banca examinadora do trabalho de conclusão do Curso de Ciências Biológicas intitulado **“O papel dos genes CD80 e CD86 na Tireoidite de Hashimoto”.**

**-** Professor de Química, do projeto de extensão GRADAÇÃO (Pré-Vestibular da Inclusão), de maio a setembro de 2020, com carga horária de 60h.

- Participação do curso básico de Leitura de Lâminas - da morfologia a liberação (CH: 10h).

- Participação do Curso "NEUROBIOLOGIA DOS TRANSTORNOS MENTAIS" (CH: 40h).

III) 2023

- Apresentação do trabalho **Potenciais biomarcadores para transtornos psiquiátricos: uma revisão de literatura,** submetido na XXVIII Semana de Biomedicina: *Scientia et Evolutio* e realizado em formato presencial na modalidade categoria vídeo-pôster.

- Apresentação do trabalho **Quimiorresistência e o direcionamento terapêutico para o perfil metabólico de células cancerígenas,** submetido na XXVIII Semana de Biomedicina: *Scientia et Evolutio* e realizado em formato presencial na modalidade categoria vídeo-pôster.

- Participação como membro titular da banca examinadora do trabalho de conclusão de Residência intitulado **“Residência em Atenção ao Câncer e Cuidados Paliativos”.**

**-** Ministrante do minicurso **"Interpretação de Hemograma"** no II WeBiom - Webinar de Biomedicina da UFPE, de forma online, contabilizando a carga horária de 4 horas.

**-** Coorientação do trabalho de conclusão de Residência intitulado “Ação Do Frutoligossacarídeo e Galacto-Oligossacarídeo sobre a Depressão Comórbida em modelo animal de obesidade.

- Palestrante na XXIX Semana da Biomedicina - Saúde e Desenvolvimento, com o tema “Influência do eixo microbiota-instetino-cérebro no desenvolvimento de doenças neuropsiquiátricas.

IV) 2024

- Apresentação do trabalho **"Prebióticos melhoram o metabolismo lipídico e inflamação periférica no tecido adiposo via GPR43 em camundongos obesos",** submetido na 12ª Semana de Biociências e Biotecnologia em Saúde e realizado em formato presencial na modalidade Apresentação Banner.

- Apresentação do trabalho **"Frutooligossacarídeo e galactooligossacarídeo inibem a neuroinflamação hipotalâmica por meio da regulação da via de sinalização irs/pi3k/akt em modelo animal diabetes tipo 2 induzido por dieta",** submetido na 12ª Semana de Biociências e Biotecnologia em Saúde e realizado em formato presencial na modalidade Apresentação Banner.

- Participação como suplente do trabalho de conclusão do Curso de Ciências Biológicas intitulado **“Efeitos de prebióticos sobre o comprometimento motor, neurodegeneração e neuroinflamação em modelo experimental de doença de parkinson”.**

- Apresentação do trabalho **"Semaglutida atenua comportamentos semelhantes a ansiedade e a depressão e reverte o comprometimento cognitivo em um modelo de camundongo com diabetes mellitus tipo 2 por meio do eixo microbiota-intestino-cérebro",** submetido na 12ª Semana de Biociências e Biotecnologia em Saúde e realizado em formato presencial na modalidade Apresentação Banner.

- Curso/evento **Biossegurança** (2ª Oferta) oferecido pela Fundação Oswaldo Cruz, por meio da Unidade Fiocruz Pernambuco com duração de 50 hora(s).

- Parecerista do Programa Institucional de Bolsas de Iniciação Científica do edital 01/2024 da Afya – Faculdade de Ciências Médicas.

- Apresentação do trabalho **"Análogos de GLP-1 na doença de Parkinson: Uma revisão",** submetido na IV Congresso de Neurofisiologia na modaliAas, J., Gessert, C. E., & Bakken, J. S. (2003). Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *36*(5), 580–585. https://doi.org/10.1086/367657


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# ANEXO 1 – CERTIFICADO CEUA/IAM 135/2018

Ministério da Saúde

FIOCRUZ
**Fundação Oswaldo Cruz**
Instituto Aggeu Magalhães

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

### Letter of IACUC Approval

We certify that the project entitled **"AÇÃO DOS PREBIÓTICOS (FRUTO-OLIGOSSACARÍDEOS E GALACTOOLIGOSSACARÍDEOS) E SUA ASSOCIAÇÃO COM A FLUOXETINA SOBRE AS VIAS DE SINALIZAÇÃO DA NEUROINFLAMAÇÃO, COGNIÇÃO E DEPRESSÃO EM MODELO ANIMAL DE OBESIDADE"** (IACUC protocol number nº **135/2018**), coordinated by **Christina Alves Peixoto** follows strictly the ethical principles in animal research and is in accordance with the Brazilian federal law 11.794/2008. The project was approved by the Institutional Animal Care and Use Committee (IACUC) of the Aggeu Magalhães Institute/Oswaldo Cruz Foundation and is valid until february 2022. It is the responsibility of the Principal Investigator to notify the IACUC of any proposed changes regarding the work described within this project. The Principal Investigator agrees that no such changes will be implemented until approved by the IACUC/IAM.

| **Number of animals approved** | |
|---|---|
| **Species/Strain/Breed** | **Number of animals/Weight/Age/Sex** |
| Inbred Mouse C57BL6 LDL r-/- | 150 (20 gr/ 8-10 weeks / females) |
| **Total** | **150** |

Recife (PE, Brazil), February, 06, 2019

Mª Edileuza Felinto de Brito
IACUC Vice Chair/IAM

Maria Edileuza Felinto de Brito
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## ANEXO 2 – ARTIGO 2 PUBLICADO NO DOUTOURADO

Journal of Neuroimmune Pharmacology
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RESEARCH

# Fructooligosaccharide (FOS) and Galactooligosaccharide (GOS) Improve Neuroinflammation and Cognition By Up-regulating IRS/PI3K/AKT Signaling Pathway in Diet-induced Obese Mice

**Igor Henrique Rodrigues de Paiva[1,2] · Rodrigo Soares da Silva[1] · Ingrid Prata Mendonça[1,2] · Eduardo Duarte-Silva[1,3] · José Roberto Botelho de Souza[4] · Christina Alves Peixoto[1,5]**

Received: 6 January 2023 / Accepted: 12 May 2023


**Abstract**
Increasing evidence has indicated that prebiotics as an alternative treatment for neuropsychiatric diseases. This study evaluated the prebiotics Fructooligosaccharides (FOS) and Galactooligosaccharides (GOS) on the modulation of neuroinflammation and cognition in an experimental model of mice high-fat diet fed. Initially, mice were distributed in the following groups: (A) control standard diet (n = 15) and (B) HFD for 18 weeks (n = 30). In the 13th week, the mice were later divided into the following experimental groups: (A) Control (n = 15); (B) HFD (n = 14); and (C) HFD + Prebiotics (n = 14). From the 13th week, the HFD + Prebiotics group received a high-fat diet and a combination of FOS and GOS. In the 18th week, all animals performed the T-maze and Barnes Maze, and were later euthanized. Biochemical and molecular analyzes were performed to assess neuroinflammation, neurogenesis, synaptic plasticity, and intestinal inflammation. Mice fed HFD had higher blood glucose, triglyceridemia, cholesterolemia, and higher serum IL-1β associated with impaired learning and memory. These obese mice also showed activation of microglia and astrocytes and significant immunoreactivity of neuroinflammatory and apoptosis markers, such as TNF-α, COX-2, and Caspase-3, in addition to lower expression of neurogenesis and synaptic plasticity markers, such as NeuN, KI-67, CREB-p, and BDNF. FOS and GOS treatment significantly improved the biochemistry profile and decreased serum IL-1β levels. Treatment with FOS and GOS also reduced TNF-α, COX-2, Caspase-3, Iba-1, and GFAP-positive cells in the dentate gyrus, decreasing neuroinflammation and neuronal death caused by chronic HFD consumption. In addition, FOS and GOS promoted synaptic plasticity by increasing NeuN, p-CREB, BDNF, and KI-67, restoring spatial learning ability and memory. Moreover, FOS and GOS on HFD modulated the insulin pathway, which was proved by up-regulating IRS/PI3K/AKT signaling pathway, followed by a decreasing Aβ plate and Tau phosphorylation. Furthermore, the prebiotic intervention reshaped the HFD-induced imbalanced gut microbiota by modulating the composition of the bacterial community, markedly increasing Bacteroidetes. In addition, prebiotics decreased intestinal inflammation and leaky gut. In conclusion, FOS and GOS significantly modulated the gut microbiota and IRS/PI3K/AKT signaling pathway, decreased neuroinflammation, and promoted neuroplasticity improving spatial learning and memory.

**Keywords** Cognition · Obesity · Neuroinflammation · Gut Microbiota · Prebiotics

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## ANEXO 3 – ARTIGO 2 PUBLICADO NO DOUTOURADO

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RESEARCH

# Semaglutide Attenuates Anxious and Depressive-Like Behaviors and Reverses the Cognitive Impairment in a Type 2 Diabetes Mellitus Mouse Model Via the Microbiota-Gut-Brain Axis

Igor Henrique Rodrigues de Paiva[1,2] · Rodrigo Soares da Silva[1,2] · Ingrid Prata Mendonça[1,2] · José Roberto Botelho de Souza[3] · Christina Alves Peixoto[1,4]

Received: 9 August 2023 / Accepted: 14 July 2024


**Abstract**

Newly conducted research suggests that metabolic disorders, like diabetes and obesity, play a significant role as risk factors for psychiatric disorders. This connection presents a potential avenue for creating novel antidepressant medications by repurposing drugs originally developed to address antidiabetic conditions. Earlier investigations have shown that GLP-1 (Glucagon-like Peptide-1) analogs exhibit neuroprotective qualities in various models of neurological diseases, encompassing conditions such as Alzheimer's disease, Parkinson's disease, and stroke. Moreover, GLP-1 analogs have demonstrated the capability to enhance neurogenesis, a process recognized for its significance in memory formation and the cognitive and emotional aspects of information processing. Nonetheless, whether semaglutide holds efficacy as both an antidepressant and anxiolytic agent remains uncertain. To address this, our study focused on a mouse model of depression linked to type 2 diabetes induced by a High Fat Diet (HFD). In this model, we administered semaglutide (0.05 mg/Kg intraperitoneally) on a weekly basis to evaluate its potential as a therapeutic option for depression and anxiety. Diabetic mice had higher blood glucose, lipidic profile, and insulin resistance. Moreover, mice fed HFD showed higher serum interleukin (IL)-1β and lipopolysaccharide (LPS) associated with impaired humor and cognition. The analysis of behavioral responses revealed that the administration of semaglutide effectively mitigated depressive- and anxiety-like behaviors, concurrently demonstrating an enhancement in cognitive function. Additionally, semaglutide treatment protected synaptic plasticity and reversed the hippocampal neuroinflammation induced by HFD fed, improving activation of the insulin pathway, demonstrating the protective effects of semaglutide. We also found that semaglutide treatment decreased astrogliosis and microgliosis in the dentate gyrus region of the hippocampus. In addition, semaglutide prevented the DM2-induced impairments of pro-opiomelanocortin (POMC), and G-protein-coupled receptor 43 (GPR43) and simultaneously increased the NeuN + and Glucagon-like Peptide-1 receptor (GLP-1R+) neurons in the hippocampus. Our data also showed that semaglutide increased the serotonin (5-HT) and serotonin transporter (5-HTT) and glutamatergic receptors in the hippocampus. At last, semaglutide changed the gut microbiota profile (increasing Bacterioidetes, Bacteroides acidifaciens, and Blautia coccoides) and decreased leaky gut, improving the gut-brain axis. Taken together, semaglutide has the potential to act as a therapeutic tool for depression and anxiety.

**Keywords** Diabetes mellitus 2 · Depression · Cognition · Anxiety · Gut microbiota · Semaglutide

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