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INFLUÊNCIA DA DISLIPIDEMIA PARENTAL SOBRE A SAÚDE INTESTINAL, PARÂMETROS BIOQUÍMICOS, SOMÁTICOS E COMPORTAMENTAIS DA PROLE

João Pessoa - PB
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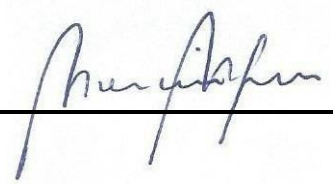

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“Porque dEle, por Ele e para Ele, são todas às coisas; glória, pois, a Ele eternamente.” Rm 11,36

RESUMO

A programação fetal é a influência permanente da exposição a estímulos no período crítico do desenvolvimento sobre a estrutura e função do corpo, devido à sua plasticidade e sensibilidade às mudanças ambientais. Este trabalho avaliou os efeitos da alimentação hiperlipídica dos reprodutores e sua influência sobre a saúde intestinal, parâmetros bioquímicos, somáticos e comportamentais dos filhotes do início da vida até a idade adulta. Foram utilizados 40 ratos Wistar com ± 90 dias, randomizados em quatro grupos de acordo com a dieta dada aos reprodutores: pais e mães controle (PC/MC, n = 10); pais alimentados com dieta hiperlipídica e mães controle (PH/MC, n = 10); pais alimentados com dieta controle e mães com dieta hiperlipídica (PC/MH, n = 10); pais e mães alimentados com dieta hiperlipídica (PH/MH, n = 10). O consumo alimentar e a massa corporal foram verificados semanalmente. Do nascimento até o desmame foram verificados os parâmetros de desenvolvimento reflexo e somático da prole. O comportamento tipo ansioso foi avaliado utilizando o teste de campo aberto e labirinto em cruz elevado nos reprodutores e filhotes aos 30 e 90 dias. Coletou-se amostras de fezes para análise de grupos bacterianos fecais e de ácidos orgânicos, os órgãos para análise histológica e sangue para análises do perfil lipídico e glicêmico. Filhotes PH/MC apresentaram retardo na maturação somática nos parâmetros de erupção dos dentes inferiores, o PH/MH teve surgimento dos pelos epidérmicos retardado e antecipação da abertura do conduto auditivo. O grupo PH/MC apresentou retardo na preensão palmar, endireitamento, geotaxia negativa, mas antecipou resposta ao susto. Os filhotes PH/MH, 30 e 90 dias tiveram aumento do número de bolos fecais e maior tempo de *rearing*, *freezing* e *grooming*, menor tempo em braços abertos e maior em braços fechados, característicos de comportamento tipo ansioso em roedores. Quanto ao peso corporal, PH/MC, PC/MH e PH/MH, apresentaram baixo peso ao nascer com ganho de peso excessivo ao longo do tempo (30 a 90 dias) e hiperfagia (PH/MH). Filhotes, PH/MC, PC/MH e PH/MH apresentaram em média altos níveis de CT (308 mg/dL), LDL (70 mg/dL) e redução de HDL (49 mg/dL. Os reprodutores machos alimentados com a dieta hiperlipídica e os filhotes (90 dias) PH/MH apresentaram menor contagem de *Lactobacillus* e *Bifidobacterium*; com aumento de *Bacteroides* e *Enterobacteriaceae*. Reprodutores com dieta hiperlipídica diminuíram a concentração do ácido propiônico fecal, enquanto nos filhotes PH/MC e PC/MH (90 dias) houve aumento. A prole (30 dias) PH/MH teve menor concentração de ácidos graxos poli-insaturados cerebrais (48.11±0.55g/100g). As fêmeas alimentadas com dieta hiperlipídica tiveram marcação focal e intensa e a prole PH/MC e PH/MH apresentaram marcações pronunciadas, multifocais e intensas para NF-kB no córtex cerebral, inclusive com maior área de marcação o que são indicativas de processo inflamatório. Uma dieta hiperlipídica dos pais afeta negativamente o desenvolvimento intrauterino e pós-natal, a adiposidade, a saúde metabólica e intestinal, e o neurodesenvolvimento da prole de machos, sendo ainda mais ansiogênica quando ambos reprodutores seguem o mesmo padrão alimentar.

Palavras-chave: ansiedade, ácidos graxos, bactérias intestinais, dieta hiperlipídica, maturação reflexa, NF-kB

ABSTRACT

Foetal programming refers to the enduring impact of exposure to stimuli during critical periods of development on the body's structure and function, owing to its plasticity and sensitivity to environmental changes. This study assessed the effects of a high-fat diet in parental rats and its influence on the intestinal health, biochemical, somatic, and behavioural parameters of their offspring from early life to adulthood. Forty Wistar rats, approximately 90 days old, were randomised into four groups based on the diet provided to the parents: control fathers and mothers (CF/CM, n = 10); fathers fed a high-fat diet and control mothers (HF/CM, n = 10); control fathers and mothers fed a high-fat diet (CF/HM, n = 10); and both parents fed a high-fat diet (HF/HM, n = 10). Food intake and body mass were monitored weekly. From birth to weaning, reflex and somatic development parameters of the offspring were recorded. Anxiety-like behaviour was evaluated using the open field test and elevated plus maze in both parents and offspring at 30 and 90 days. Faecal samples were collected for analysis of bacterial groups and organic acids, organs were collected for histological analysis, and blood samples were taken for lipid and glycaemic profiling. Offspring in the HF/CM group exhibited delayed somatic maturation, particularly in the eruption of lower incisors. The HF/HM group showed delayed epidermal hair emergence and earlier auditory canal opening. The HF/CM group also displayed delays in palmar grasp, righting reflex, and negative geotaxis, but showed an earlier startle response. At 30 and 90 days, HF/HM offspring demonstrated increased faecal boli number and more time spent rearing, freezing, and grooming, with reduced time in open arms and increased time in closed arms of the elevated plus maze, indicative of anxiety-like behaviour in rodents. Regarding body weight, HF/CM, CF/HM, and HF/HM groups exhibited low birth weight followed by excessive weight gain (30 to 90 days) and hyperphagia (HF/HM). HF/CM, CF/HM, and HF/HM offspring showed elevated average levels of total cholesterol (TC) (308 mg/dL), LDL cholesterol (70 mg/dL), and reduced HDL cholesterol (49 mg/dL). Male breeders fed a high-fat diet and 90-day-old HF/HM offspring had lower counts of *Lactobacillus* and *Bifidobacterium*, with increased *Bacteroides* and *Enterobacteriaceae*. High-fat diet breeders showed reduced faecal propionic acid concentration, whereas HF/CM and CF/HM offspring (90 days) had increased levels. At 30 days, HF/HM offspring had lower concentrations of cerebral polyunsaturated fatty acids (48.11±0.55g/100g). Females on a high-fat diet exhibited focal and intense labelling, while HF/CM and HF/HM offspring showed pronounced, multifocal, and intense NF-kB labelling in the cerebral cortex, indicating inflammatory processes. A parental high-fat diet negatively impacts intrauterine and postnatal development, adiposity, metabolic and intestinal health, and neurodevelopment in male offspring, being even more anxiogenic when both parents follow the same dietary pattern.

Keywords: anxiety, fatty acids, intestinal bacteria, high-fat diet, reflex maturation, NF-kB

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LISTA DE ABREVIATURAS E SIGLAS

ABCA1 - ATP-binding Cassette Transporter (Transportador de Cassete de Ligação de ATP)

AIN - American Institute of Nutrition

AIN-93G – American Institute of Nutrition Rodent Diets – 93 Growing (Dietas para Roedores do Instituto Americano de Nutrição – 93 Crescimento)

ANOVA – Análise da Variância

APOB - Apolipoproteína B

APOE - Apolipoproteína E

BDNF - Brain-derived Neurotrophic Factor (Fator Neurotrófico Derivado do Cérebro)

CA – Circunferência Abdominal

CONCEA – Conselho Nacional de Controle de Experimentação Animal

CT – Circunferência Torácica

CT – Colesterol Total

CTL – Controle

DAC – Doença do Aparelho Circulatório

DCNT – Doenças Crônicas Não Transmissíveis

DCV – Doenças Cardiovasculares

DHA - Docosahexaenoic Acid (Ácido Docosaexaenoico)

DLP – Dislipidêmica

DNA – Deoxyribonucleic Acid **(**Ácido Desoxirribonucleico)

EPA - Eicosapentaenoic Acid (Ácido Eicosapentaenoico)

FAO – Food and Agriculture Organization of the United Nations (Organização das Nações Unidas para a Alimentação e a Agricultura)

FOS - Frutooligossacarideos

GAPDH - Gliceraldeído-3-fosfato Desidrogenase

GLUT-1 - Glucose Transporter 1 (Transportador de Glicose 1)

GOS - Galacto-oligossacarídeo

HC - Hipercolesterolemia

HDL – High-density lipoprotein (Lipoproteína de Baixa Densidade)

HE – Hematoxilina-Eosina

HeFH - Hipercolesterolemia Familiar Heterozigótica

HF - Hipercolesterolemia Familiar

HFD – High Fat Diet (Dieta com alto teor de gordura)

HoFH - Hipercolesterolemia Familiar Homozigótica

IL-6 – Interleucina 6

IMC – Índice de Massa Corporal

LANEX - Laboratório de Nutrição Experimental

LDL – Low-density lipoprotein (Lipoproteína de Baixa Densidade)

LDLR – Low-Density Lipoprotein Recepetor (Receptor de Lipoproteina de Baixa Densidade)

LPS – Lipopolissacarídeo

LXRα - Liver X Rreceptor Alpha (Receptor Alfa do Fígado)

miRNA – micro RNA

MUFA - Ácidos Graxos Monoinsaturados

OMS – Organização Mundial Da Saúde

PCR - Proteína C-reativa

PUFA - Ácidos Graxos Poli-insaturados

RNA - Ribonucleic acid (Ácido Ribonucleico)

SBC – Sociedade Brasileira De Cardiologia

SFA - Ácidos Graxos Saturados

SREBP2 - Sterol Regulatory Element-binding Protein 2 (Proteína de Ligação ao Elemento Regulador de Esterol 2)

TGL – Triglicerídeos

TLR4 - Toll-like Receptor 4 (Receptor tipo Toll 4)

TNF-α – Tumour Necrosis Factor Alpha (Fator de Necrose Tumoral Alfa)

TTG - Teste de Tolerância à Glicose

TTI - Teste de Tolerância à Insulina

UFC – Unidade Formadora de Colônias

UFPB - Universidade Federal do Paraíba

UFPE - Universidade Federal do Pernambuco

VET – Valor Energético Total

VLDL – Very Low-Density Lipoprotein (Lipoproteína de Muita Baixa Densidade)

SUMÁRIO

INTRODUÇÃO

A vida intrauterina desempenha um papel importante na determinação da saúde em longo prazo dos indivíduos, uma vez que fatores maternos e/ou paternos, como injúrias nutricionais, hormônios, alterações metabólicas e função placentária, podem afetar o desenvolvimento do feto e levar à resultados de saúde positivos ou negativos (Cao-Lei *et al.*, 2021; George *et al.*, 2019; Kabaran; Besler, 2015).

Estudos epidemiológicos resultaram na abordagem das origens desenvolvimentistas da Saúde e da Doença (DOHaD), que sugere que doenças não transmissíveis, como doenças cardiovasculares e diabetes tipo 2, originam-se no período perinatal e no início da vida (Barker, 2004). Esse fenômeno é conhecido como programação metabólica, estudos têm demonstrado que a má ou supernutrição durante a vida perinatal é associado a um risco aumentado de doenças crônicas mais tarde na vida, moldando a trajetória de saúde das gerações atuais e futuras (Barbosa *et al.*, 2016; Bodden; Hannan; Reichelt, 2020; Grilo *et al.*, 2021; Kaspar *et al.*, 2020; Ojeda *et al.*, 2021).

O número de pessoas acometidas por doenças crônicas não transmissíveis, vem crescendo rapidamente nas últimas décadas, tais doenças são associadas ao estilo de vida, como má alimentação, onde se prioriza o consumo de comidas ricas em açúcar, sal e gorduras saturadas (Cunha *et al.*, 2021). Nesse contexto, a dislipidemia, constitui um dos principais fatores de risco para doenças cardiovasculares, sendo um grupo heterogêneo de distúrbios no metabolismo lipídico, em que tais alterações são potencialmente capazes de afetar o desenvolvimento fetal durante a gestação (Bezerra *et al.*, 2018b; De Araújo *et al.*, 2020).

Estudos prévios identificaram fortes associações entre padrões alimentares maternos e alterações durante a vida fetal e neonatal com consequente maior predisposição para o desenvolvimento de doenças cardiovasculares, obesidade, resistência à insulina, diabetes na vida adulta, além de alterações no metabolismo lipídico e no funcionamento intestinal da prole (De Araújo *et al.*, 2020; Guimarães *et al.*, 2017; Pinheiro *et al.*, 2019). Modificações em parâmetros comportamentais na prole também foram observadas em modelo animal devido a alterações no padrão alimentar materno (Cao-Lei *et al.*, 2021; Dieberger *et al.*, 2018). Estudos com primatas e com roedores sugerem que a exposição pré-natal e/ou pós-

natal a uma dieta rica em lipídios, fonte de colesterol e de ácidos graxos saturados e trans pode resultar em maior suscetibilidade à ansiedade na prole, que também pode variar de acordo com a maturação do cérebro (Silva *et al.*, 2021a; Thompson *et al.*, 2017).

As dietas ocidentais são conhecidas também por desencadear alterações robustas e duradouras na microbiota intestinal e essa população dinâmica de micro-organismos participa de diversas funções fisiológicas (Bolte *et al.*, 2021; Ecklu-Mensah; Gilbert; Devkota, 2022). Estudos não clínicos e clínicos indicam fortemente que a alteração da microbiota intestinal pode prejudicar a função cerebral, e que várias condições estão associadas à colonização microbiana intestinal neonatal alterada, podendo afetar a barreira intestinal e a maturação imunológica, e em última análise, contribuir para o desenvolvimento de distúrbios neurológicos (Avolio *et al.*, 2019a; Mohajeri *et al.*, 2018; Noronha *et al.*, 2019a, 2019b).

Tais alterações são mediadas pelo eixo intestino-cérebro que é definido como uma complexa rede de comunicação bidirecional entre o sistema nervoso gastrointestinal e o sistema nervoso central, compreendendo o sistema nervoso entérico, o sistema nervoso autônomo, hormônios e neurotransmissores, bem como a microbiota intestinal. Esta interação multifacetada é essencial para a regulação das funções gastrointestinais e neuropsicológicas, desempenhando um papel fundamental na homeostase e no bem-estar do organismo (Carabotti *et al.*, 2015; Cryan *et al.*, 2019).

Estudo prévio realizado por nosso grupo de pesquisa demonstrou alterações no desenvolvimento intestinal dos filhotes oriundos de mães dislipidêmicas tais como: diminuição da contagem de *Bifidobacterium* spp. e *Lactobacillus* spp. e aumento das contagens de *Bacteroides* spp. nas fezes, além de danos nas vilosidades intestinais e níveis séricos elevados de colesterol total, triglicerídeos, VLDL, vistos a curto e longo prazo de forma diferenciada em machos e fêmeas (Pinheiro *et al.*, 2019). Embora a conexão entre a dieta de uma mãe e a saúde a curto e longo prazo de sua prole venha sendo estudada em detalhes (De Vasconcelos *et al.*, 2023; Guimarães *et al.*, 2017; Pinheiro *et al.*, 2019; Vieira *et al.*, 2023), a compreensão sobre como a saúde dos filhos pode ser afetada pela dieta paterna permanece limitada. A transmissão paterna de doenças resultantes da exposição de células germinativas masculinas a fatores ambientais, como sub e supernutrição, está recebendo atenção crescente devido ao surgimento de novos mecanismos para explicar os

efeitos mediados pela paternidade, como o estudo epigenético (Mcpherson; Lane, 2020; Potabattula *et al.*, 2019; Raad *et al.*, 2019; Watkins *et al.*, 2018).

Seguindo esta linha, o nosso grupo pretende nesta tese, continuar avaliando potenciais impactos de uma dieta hiperlipídica paterna e materna, desta vez focando nas respostas do consumo continuado de tal dieta pelos ratos reprodutores sobre função intestinal, parâmetros bioquímicos, somáticos e comportamentais da prole, mais especificamente no acompanhamento do peso corporal e consumo alimentar; avaliação dos parâmetros murinométricos e índice de adiposidade; avaliação do comportamento tipo ansioso, maturação reflexa e somática; quantificação de ácidos graxos cerebrais; análise de perfil lipídico e da tolerância à glicose e insulina; análise histológica intestinal e cerebral incluindo quantificação de NF-kB, contagem de bactérias e quantificação de ácidos orgânicos fecais.

2. REFERENCIAL TEÓRICO

2.1 Dieta materna e paterna, programação fetal e epigenética

A alimentação é algo que interfere na fisiologia humana durante toda vida, quer seja proporcionando saúde ou não. No início da vida, fatores ambientais são fundamentais no desenvolvimento fetal, dentre tais fatores, destaca-se a nutrição. A influência da nutrição materna já é amplamente estudada na literatura, tanto durante o período gestacional, bem como no período lactacional.

Estudos experimentais com ratas Wistar, mostraram que as que se alimentaram com dietas dislipidêmicas, ricas em colesterol e ácido graxo saturado e trans, são capazes de influenciar no surgimento de hipertensão arterial, disbiose intestinal, inflamação intestinal e dislipidemia nos filhotes a longo prazo (Guimarães *et al.*, 2017; Pinheiro *et al.*, 2019). Um número crescente de estudos evidencia que a dieta paterna influencia na saúde dos filhos, e tal interferência passa pelo impacto que os fatores ambientais causam na qualidade do esperma, no desenvolvimento pós-fertilização e suas consequências na fisiologia da prole (Lucas; Watkins, 2017; Watkins *et al.*, 2018).

Modelos animais têm sido utilizados para investigar a possível transferência de informação de herança epigenética paterna de uma geração para a seguinte, a fim de excluir qualquer influência confusa dos efeitos gestacionais sobre os tecidos somáticos durante o desenvolvimento embriológico (Kaspar *et al.*, 2020). Usando esses tipos de modelos, foi relatado que o estado nutricional do pai prejudica o metabolismo da prole, o que implica fortemente que os espermatozoides carregam informações que são influenciadas pelo fator dietético (Li *et al.*, 2016).

Estudo em humanos realizado por com 1190 adolescentes e mais 1060 pais e 1089 mães mostrou a relação entre obesidade dos pais e o desenvolvimento de sobrepeso/obesidade em adolescentes no período pós-puberdade (Notara *et al.*, 2019). Outro estudo conduzido no Brasil verificou a relação entre a obesidade paterna e/ou materna e o desenvolvimento de obesidade nos filhos, foram utilizados 1816 pré-adolescentes e adolescentes, idade mínima de 10 anos, e foi verificado que existia uma maior influência paterna nos filhos, do que nas filhas (Donelly; Materleto, 2018).

Estudos com modelos animais, também têm verificado a relação entre a nutrição paterna e a programação fetal. Animais submetidos a uma dieta com baixa ingestão proteica foi associado a uma predisposição de complicações cardíacas nos filhotes, por alterações epigenéticas verificado no esperma dos pais, metilações nos genes *Adcy5*, *Plcb*, and *Prkcb* relacionados a disfunção cardíaca por diminuição na expressão da sinalização do transportador de cálcio (Watkins *et al.*, 2018). Outro estudo com ratos pais que receberam uma dieta hiperlipídica mostrou que tal dieta foi capaz de reprogramar o epigenoma de células espermáticas, afetando o fenótipo metabólico da prole até a segunda geração, mostrando que a expressão alterada do miRNA let-7c no espermatozoide coincide com o nível elevado de tecido adiposo da prole, podendo também alterar o metabolismo dos mesmos (Barbosa *et al.*, 2016).

Estudo com camundongo também verificou a relação do IMC paterno com o desenvolvimento da obesidade na prole. Foi observada uma correlação específica de gênero entre a metilação do DNA de *Dmr Meg3-Ig*, *Hif3a* e *Dmr0* de *Igf2* no sangue do cordão umbilical da prole e do IMC paterno, indicando que a obesidade paterna pode influenciar a programação de metilação do DNA no esperma e também afetar o epigenoma da próxima geração, descobertas que se correlacionam com pesquisas anteriores realizadas em humanos (Potabattula *et al.*, 2019). Estudos mostram que dietas paternas podem afetar até a segunda geração reprogramando transgeracionalmente o metabolismo de maneira específica em cada tecido, afetando o desenvolvimento e a saúde das gerações futuras, sendo assim, a compreensão de como se dá essa via de transmissão genética de doenças é fundamental para que haja prevenção de doenças e promoção de saúde (Barbosa *et al.*, 2016; Fullston *et al.*, 2012).

Outras alterações que a dieta hiperlipídica pode vir a desencadear, consistem em danos genômicos (oxidação dos ácidos nucléicos, como DNA), causados pelo estresse oxidativo que tal dieta induz no organismo. Tais danos se não reparados, podem vir a interferir na replicação e transcrição do DNA, levando a um acúmulo de mutações, que podem resultar em: carcinoma, distúrbios genéticos e metabólicos; podendo inclusive ser transmitidos às próximas gerações (Del Bo' *et al.*, 2019; Remely *et al.*, 2017a, 2017b; Setayesh *et al.*, 2019).

2.2 Dislipidemia

2.2.1 Hábitos alimentares não saudáveis e dislipidemia

As gorduras alimentares são nutrientes que fazem parte das necessidades diárias para o bom funcionamento do organismo, elas estão presentes na produção hormonal, são ótimas fontes de energia, auxiliam no transporte de enzimas lipossolúveis, compõe na formação de enzimas, química neuronal e estruturas celulares (Riordan *et al.*, 2018). Sua ingestão é de suma importância para o corpo humano, porém o consumo excessivo na sua conformação saturada é a causadora de algumas patologias, dentre elas, a dislipidemia (Chiu; Williams; Krauss, 2017).

A dislipidemia é uma condição caracterizada por um estado de alterações lipídicas anormais nos níveis de TGL (triglicerídeos), colesterol e/ou de fosfolipídios no organismo (Hunter; Hegele, 2017). Entre os fatores de risco conhecidos de dislipidemia, incluindo fatores genéticos, anormalidades hormonais e fatores de estilo de vida, a dieta é considerada um dos mais importantes, que desempenha um papel fundamental no desenvolvimento e manutenção da dislipidemia (Kim; Joung; Shin, 2019).

De acordo com a Sociedade Brasileira de Cardiologia (SBC) as dislipidemias podem ser classificadas genotipicamente em mono ou poligênicas, ou ainda fenotipicamente por meio de análises bioquímicas de colesterol total, HDL, triglicerídeos e LDL, em que são subdividas em quatro grupos, hipercolesterolemia isolada, hipertrigliceridemia isolada, hiperlipidemia mista ou baixos níveis de HDL, desempenhando importante papel na avaliação do risco de evento coronariano agudo na população em geral (Xavier *et al.*, 2013). O aumento na ingestão de calorias totais na dieta acompanhado por uma alta ingesta de gorduras saturadas são importantes fatores causais no desenvolvimento da dislipidemia, como as principais fontes de tais gorduras temos leites e derivados, produtos cárneos, frituras e gorduras animais como banha de porco (Breetha; Tr, 2018).

Existem inúmeras evidências que demonstram a associação entre a alimentação e níveis lipídicos no sangue, alguns estudos indicam que a ingestão dessas gorduras saturadas e colesterol estão associados diretamente a alterações dos níveis de lipídeos no sangue, como elevação LDL e triglicérides, enquanto o consumo de vegetais e frutas está inversamente associado a esses níveis de lipídios no sangue (Kim; Joung; Shin, 2019). Mesmo que para

fins terapêuticos, alguns estudos com crianças e adolescentes que fazem uso da dieta cetogênica clássica, utilizadas para tratamentos de epilepsia e para portadores de deficiência no GLUT-1, mostraram que tal dieta é capaz de causar alterações nas frações lipídicas do sangue com aumento nos níveis de LDL e triglicerídeos. Nessas dietas a proporção na distribuição dos macronutrientes é de 4g de lipídios para 1g de carboidratos e proteínas, (Azevedo De Lima *et al.*, 2017; Güzel *et al.*, 2016; Klepper *et al.*, 2016). Outro estudo com 64 adultos (homens e mulheres) com hábitos alimentares não saudáveis, dieta com aproximadamente 35% de carboidratos, 25% de proteínas e 40% de gorduras sendo 20% delas saturadas, mostrou a relação direta da ingesta de ácidos graxos saturados com a dislipidemia e aumento no risco aterogênico (Chiu; Williams; Krauss, 2017).

2.2.2 Hipercolesterolemia familiar

Hipercolesterolemia (HC) é amplamente caracterizada como excesso de colesterol, na forma de lipídios, na corrente sanguínea, definido a partir de uma concentração total de colesterol sérico de 240 mg/dL ou superior. Pode ser causada por múltiplos fatores genéticos e ambientais, como dieta, estilo de vida e história familiar (Soslowsky; Fryhofer, 2016; Taylor; Cheema; Soslowsky, 2017).

Especificamente, a hipercolesterolemia familiar (HF) é herdada de ambos ou de um dos progenitores e resulta numa atividade reduzida ou disfuncional dos receptores lipídicos de baixa densidade (LDL) (Marks *et al.*, 2003). Subsequentemente, a incapacidade de absorção ou degradação dos lipídeos no fígado conduz a uma concentração de colesterol no soro marcadamente elevada, tão elevada como 1000 mg/dL, significativamente superior à concentração de colesterol saudável de 200 mg/dL. A forma homozigótica da hipercolesterolemia familiar (HoFH) tem uma prevalência de um em um milhão, enquanto a hipercolesterolemia familiar heterozigótica (HeFH) afeta uma em cada 500 pessoas em todo o mundo (Klose *et al.*, 2014; Taylor; Cheema; Soslowsky, 2017).

Os pacientes com HF têm colesterol LDL-hiper-letal desde o nascimento e a aterosclerose progride desde a juventude, resultando em um alto risco de DAC (Doença do Aparelho Circulatório). Os homens com HeFH não tratados de 30 a 50 anos de idade, e mulheres de 50 a 70 anos de idade, respectivamente, muito provavelmente desenvolverão DAC, como infarto do miocárdio e angina pectoris (Harada-Shiba *et al.*, 2018a;

Nordestgaard *et al.*, 2013). Na verdade, foi relatado que o risco de DAC é 13 vezes maior em HeFH não tratado do que em não HF. Na prática médica para pacientes com HF, a realização de diagnóstico precoce e tratamento adequado, bem como a triagem familiar (triagem em cascata) é muito importante para prevenir a morte prematura, já que a própria hipocolesterolemia-LDL é assintomática (Harada-Shiba *et al.*, 2018b).

O diagnóstico de HF baseia-se em cinco critérios: história familiar, história clínica de doença arterial coronariana, exame físico de xantomas e arcos corneanos, colesterol LDL muito alto em medidas repetidas e/ou mutação causativa detectada pela genética molecular. As causas secundárias de hiperlipidemia devem ser excluídas, determinando-se que as enzimas hepáticas, a função renal e os hormônios tireoidianos são normais e que não há hiperglicemia ou albuminúria (Nordestgaard *et al.*, 2013).

Todos os indivíduos com HF e suas famílias devem ser submetidos a educação intensiva visando o manejo do estilo de vida, incluindo intervenções sobre tabagismo, dieta e atividade física. Um nutricionista deve apoiar a implementação de uma dieta saudável com o envolvimento de toda a família. Um registro completo dos hábitos alimentares deve ser obtido, e as recomendações para uma dieta saudável devem ser individualizadas (Broekhuizen *et al.*, 2012; De Backer *et al.*, 2019).

Alimentos funcionais conhecidos por reduzir o colesterol LDL, como esteróis e estanóis de plantas, podem ser considerados coadjuvantes no tratamento da HF. O consumo de estanóis dietéticos, em crianças com HF, mostrou eficaz na redução de 20% de LDL-c principalmente quando associado com estatinas (Vuorio; Kovanen, 2018). Um estudo *in-vitro* utilizando o 6-gingerol (6-GN), composto do gengibre, foi capaz de diminuir o colesterol total celular e os níveis de colesterol livre por meio da regulação positiva de LDLR (Receptor de LDL) pela ativação de SREBP2 (Sterol regulatory element-binding protein 2), bem como da regulação positiva dos genes relacionados ao efluxo de colesterol LXRα (Liver X receptor alpha) e ABCA1 (ATP-binding cassette transporter) (Li *et al.*, 2018). A adesão à dieta Mediterrânea, também tem sido utilizado como uma ferramenta terapêutica no tratamento da HF, um estudo com adultos mostrou que consumo de gorduras poli e monoinsaturadas oriundas da dieta mediterrânea foi capaz de reduzir os níveis de LDL, bem como de marcadores inflamatórios como ApoB (Apoliproteina B) e PCR (Proteína C-reativa) (Antoniazzi *et al.*, 2021).

O principal objetivo do aconselhamento nutricional é evitar o excesso de peso e reduzir a quantidade de alimentos e bebidas com colesterol alto, gordura saturada e conteúdo de transfusão. Exercício físico regular deve ser implementado. Em adultos com HF, a avaliação da função cardiovascular é aconselhável antes de iniciar qualquer programa de exercícios significativo (Cicero *et al.*, 2019; Nordestgaard *et al.*, 2013).

2.2.3 Modelos experimentais para estudo da hipercolesterolemia

Para a indução da hipercolesterolemia em modelos animais, é usual a utilização dietas contendo em sua composição, colesterol e ácido cólico, as quais variam de rações comerciais suplementadas com níveis substancialmente diferentes de colesterol, assim como modificações nas porções de lipídeos e carboidratos (Vinué; Herrero-Cervera; González-Navarro, 2018). Ratos e camundongos, quando alimentados com uma dieta normal, com baixo teor de gordura, não desenvolvem aterosclerose naturalmente. Além disso, estas espécies, devido a um sistema metabólito bastante eficiente no que tange a mobilização e o metabolismo do colesterol, tendem a responder brandamente a dietas hipercolesterolêmicas, desenvolvendo hipercolesterolemia leve e apenas estrias gordurosas no arco aórtico (Getz; Reardon, 2017; Vinué; Herrero-Cervera; González-Navarro, 2018).

Desta forma, destaca-se o surgimento de camundongos geneticamente modificados, os quais solucionaram muitos problemas relacionados ao estudo experimental da hipercolesterolemia e aterosclerose (Poledne; Jurčíková-Novotná, 2017). Os camundongos com deleção gênica de apolipoproteína E (apoE-/-) ou do receptor de LDL (LDLr-/-) são amplamente empregados na atualidade e ambos fornecem uma ferramenta prática para o estudo da hipercolesterolemia e suas consequências (Arshad *et al.*, 2019; He *et al.*, 2019).

O camundongo LDLr-/-, desenvolvido em 1991 por Ishibashi e colaboradores, é reconhecido como um modelo de hipercolesterolemia familiar humana (Arshad *et al.*, 2019; He *et al.*, 2019). O camundongo LDLr-/- apresenta hipercolesterolemia, caracterizada por níveis moderados de colesterol LDL quando submetidos a uma dieta padrão, podendo desenvolver lesões ateroscleróticas em longo prazo. Contudo, quando estes são alimentados com dieta rica em colesterol, tornam-se severamente hipercolesterolêmicos com o desenvolvimento de intensa aterosclerose aórtica e xantomas subcutâneos (Ishibashi *et al.*, 1993; Nordestgaard *et al.*, 2013; Soslowsky; Fryhofer, 2016).

Algumas características deste modelo animal podem trazer vantagens para sua utilização, tais como: (1) semelhança à condição humana de hipercolesterolemia familiar, causada por mutações no gene para o receptor de LDL; (2) o perfil de lipoproteínas plasmáticas, que se assemelha ao de humanos, estando a maior parte do colesterol confinado na fração LDL; e (3) o grau de dislipidemia intermediário, desenvolvendo lesões menos avançadas do que os camundongos apoE-/- (Getz; Reardon, 2017). Estudos com ratos Wistar no qual a dieta continha 45% de gordura oriunda de gordura hidrogenada do coco, ou até mesmo com dietas hipolipídicas (~12% de gordura, fonte de óleo de milho) mas que tinha na sua composição a adição de colesterol sigma (1%) e ácido cólico (0,25% - 0,5%), já foi possível constatar uma elevação nos níveis séricos de CT e de LDL-c nesses animais com 30 dias de indução (Andreadou *et al.*, 2020).

Importante salientar que a maioria dos estudos que induzem dislipidemia em modelos animais não trazem a quantificação do perfil de ácidos graxos presentes na dieta, mas basicamente os percentuais de lipídios e os ingredientes fontes destes lipídios (Quadro 1).

Quadro 1: Modelos de indução de dislipidemia em animais

ANIMAL	INGREDIENTES/ COMPOSIÇÃO	DURAÇÃO (SEMANAS)	DISTÚRBIOS PROVOCADOS	REFERÊNCIA
Wistar Fêmeas	20% de proteína, 32% de lipídio (68% saturado, 16% monoinsaturado, 16% de ácido graxo poli-insaturados) e 49% de carboidrato, fornecendo assim 4,2 kcal/g.	6 semanas (gestação e lactação)	Filhotes oriundos das mães que receberam a dieta ocidentalizada: elevação da glicemia, ↑ LDL, TGL e Colesterol Total, ↓ HDL; ↑ Peso corporal; Elevação da pressão sistólica e da frequência cardíaca.	(Vidal-Santos *et al.*, 2017)
Wistar Machos	40% lipídio +35% sacarose +17,5% frutose	2 e 6 semanas	Esteatose hepática, desregulação das vias de metabolismo de colesterol no fígado (diminuição nos níveis de proteínas captadoras de LDL-C), aumento nos níveis plasmáticos de Colesterol Total.	(St-Amand *et al.*, 2020)
Sprague-Dawley Machos	39% lipídio +33% sacarose	4 semanas	Aumento nos níveis de colesterol e proteínas inflamatórias no hipocampo; elevação nos níveis de proteína precursora de amilóide, presenilina 1 e nicastrina (proteínas relacionadas a doenças neurodegenerativas como Alzheimer)	(Spagnuolo *et al.*, 2020)
Sprague-Dawley Machos	39% lipídio +33% sacarose	4 semanas	Resistência insulínica; ↑ TGL e Colesterol Total; ↑ Peso corporal, ↑ inflamação hepática, homeostase redox alterada.	(Mazzoli *et al.*, 2019)
Wistar Machos	45% lipídio (15% banha de porco, 1,2% colesterol, 0,2% ácido cólico)	8 semanas	↑CT, ↑TGL, ↑ Peso corporal, Esteatose hepática, ↓ HDL	(Li *et al.*, 2019a)
Wistar Machos	60% de lipídio	8 semanas	↑CT, ↑TGL, ↓ HDL, aterosclerose, osteoporose	(Sabry *et al.*, 2021)

2.2.4 Lipídios e metabolismo

Nos organismos vivos já se tem relatado 180.000 variações diferentes da família lipídica (LI *et al.*, 2019c). As funções dos lipídios nos seres vivos incluem sinalização celular, armazenamento de energia e agem como componentes de bio-membranas ou precursores de hormônios esteroides, também participam do processo de apoptose celular, transdução de sinal, infecção e resposta imune. Fortes evidências mostram que o metabolismo de certos lipídios está intimamente associado à resistência à insulina (RI), diabetes, câncer, Alzheimer e doenças cardiovasculares (Harari *et al.*, 2017; Kitessa; Abeywardena, 2016; Li *et al.*, 2019b; Waldeyer *et al.*, 2017).

Os lipídios têm como suas maiores fontes, os óleos vegetais e as gorduras animais, sendo parte constituinte em diversos produtos alimentícios. Os hábitos alimentares da cultura ocidental, como a ingestão *fast-foods* ricos em sal, açucares e gorduras, são fatores que influenciam para o surgimento de tais desordens metabólicas, sendo que os ácidos graxos saturados, muitas vezes, contribuem com a maior parte da fração lipídica dos alimentos da dieta moderna (Pinheiro *et al.*, 2019).

Hoje, já se sabe que esses ácidos graxos possuem uma capacidade diferenciada dos outros, mono e polinsaturados, em ativar TLR4 (Figura 1), um receptor do sistema imune inato, o que é capaz de gerar uma resposta inflamatória que prejudica a sinalização anorexígena no hipotálamo (Rogero; Calder, 2018). Dessa forma, a dieta hiperlipídica rica em ácidos graxos saturados não é apenas capaz de contribuir para o maior consumo calórico em decorrência de sua maior palatabilidade, mas também por meio de alterações em importantes vias moleculares, dentre elas a que envolve a regulação do apetite. Além disso, tais ácidos graxos estão envolvidos com o desenvolvimento das comorbidades associadas à obesidade, como o desenvolvimento de esteatose hepática não alcoólica e resistência à insulina (Figueiredo *et al.*, 2017).

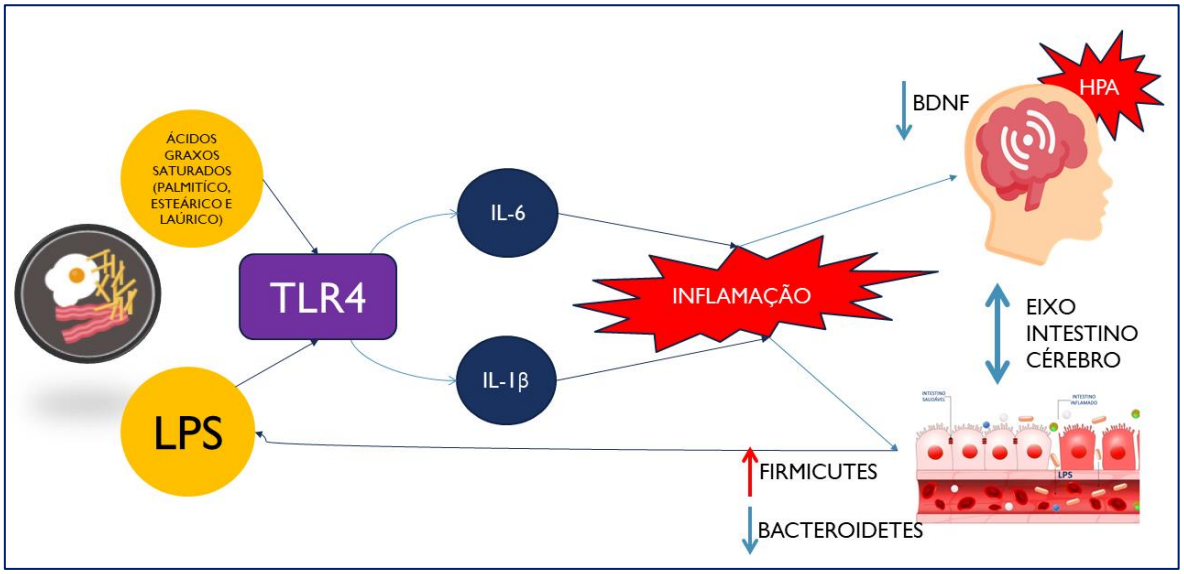

Figura 1 – Mecanismo de ativação da via inflamatória TLR4 e sua ação no eixo intestino-cérebro. Fonte: adaptado de Rogero; Calder (2018). Legendas: LPS – lipopolissacarídeos, TLR4 – *Toll like receptor 4* (receptor Toll like 4), IL-6 – interleucina 6, IL-1B – interleucina 1 beta, BDNF - *Brain-derived neurotrophic fator* (Fator neurotrófico derivado do cérebro), HPA - *hypothalamic-pituitary-adrenal axis* (Eixo hipotálamo-hipófise-adrenal)

Estudos com modelos animais vem mostrando a relação entre dietas hiperlipídicas e alterações fisiológicas como indução de obesidade, resistência insulínica, hipertensão, alteração na função intestinal, disbiose, dislipidemia, doenças cardiovasculares, danos cerebrais, esteatose hepática, etc (Arshad *et al.*, 2019; Bezerra *et al.*, 2018c; Chiu; Williams; Krauss, 2017; Guimarães *et al.*, 2017). Um estudo com ratos Wistar alimentados com uma dieta que tinha em sua composição 30% de gordura, 5% de colesterol e 2% de ácido cólico, foi capaz de induzir a hipercolesterolemia e formação de placas de ateroma, outro estudo utilizou o mesmo percentual em gorduras porém com redução na quantidade de colesterol com 1,25% e 0,5% de colato de sódio, alimentados por 3 semanas, foi observado níveis elevados de colesterol livre, alteração no metabolismo de esfingomielinas e de fosfatidilcolinas, indução de esteatose hepática (Lee *et al.*, 2017; Tu *et al.*, 2017).

Um outro estudo recente com camundongos C57Bl/6J, mostrou que a ingestão de uma dieta hiperlipídica em apenas um dia foi o suficiente para ocasionar o branqueamento da gordura marrom no organismo; além de aumento de resistência insulínica e diminuição da termogenicidade dessa gordura, ocorrendo redução na captação de glicose e triglicerídeos e consequentemente diminuição na oxidação mitocondrial (Kuipers *et al.*, 2019a). Estudo

com ratos Wistar, mostrou que uma dieta hiperlipídica por 9 semanas foi capaz de induzir o comportamento do tipo ansioso, causando também danos na memória desses animais (Ajayi *et al.*, 2021).

Estudos com ratas Wistar alimentadas com dietas com altas concentrações de ácidos graxos saturados e colesterol, durante gestação e lactação, mostraram que tal alimentação teve influência sobre a função intestinal, metabolismo, alterações comportamentais relacionadas com ansiedade (Guedine *et al.*, 2018; Pinheiro *et al.*, 2019). Há também estudos com ratos no período infantil ou juvenis que mostraram relação entre a alimentação hiperlipídica e danos no hipocampo, deficiência cognitiva e de memória (Arcego *et al.*, 2016; Khazen *et al.*, 2019).

As atuais diretrizes dietéticas visam limitar a ingestão de gordura saturada em grande parte devido à sua capacidade de aumentar os níveis de colesterol LDL (LDL-C) e presumivelmente o risco de doença cardiovascular (DCV), particularmente os ácidos mirístico (14: 0) e palmítico (16: 0), correlacionados com níveis plasmáticos aumentados de partículas maiores de LDL, mas não das partículas menores de LDL ou de apo B (Chiu; Williams; Krauss, 2017; Chowdhury *et al.*, 2014). Diminuir a ingestão de gorduras saturadas e potencializar o consumo de gorduras mono e poli-insaturadas se torna uma boa estratégia para a melhora da saúde, como a ingestão do óleo de peixe, que pode promover o desenvolvimento das células cerebrais, melhorar o aprendizado e a memória e prevenir doenças neurodegenerativas, por ser fonte de ômega 3, EPA e DHA, (Kerdiles; Layé; Calon, 2017; Zhang; Xu; Wang, 2019). Estudos demonstraram que a ingestão direta de EPA e DHA é eficaz para aumentar os níveis de EPA e DHA no coração, fígado, cérebro e soro ocasionando um efeito protetivo nesses órgãos (Miller *et al.*, 2016; Wu *et al.*, 2017).

2.3 Eixo intestino-cérebro

O eixo intestino-cérebro é uma via de comunicação bidirecional entre o microbioma intestinal, o intestino e o cérebro, onde sinais endócrinos, neuroendócrinos e inflamatórios gerados pela microbiota intestinal e células especializadas dentro do intestino podem, em princípio, afetar o cérebro. Por sua vez, o cérebro pode influenciar a composição e função microbiana através de mecanismos endócrinos e neurais (Martin *et al.*, 2018; Mayer *et al.*, 2014).

Durante o processo evolutivo, as bactérias que colonizavam plantas e animais estabeleceram com esses meios uma relação mutualística, um complexo microrganismo-hospedeiro. Essa interação foi capaz de modular genotipicamente e fenotipicamente gerando assim uma co-dependência fisiológica culminando numa promoção de saúde e bem-estar ao hospedeiro (Ochoa-Reparaz; Kasper, 2016).

Os nutrientes de uma dieta da podem influenciar diretamente o intestino no que tange a composição e diversidade microbiana intestinal, que por sequência afetará na produção dos ácidos graxos de cadeia curta (AGCC) após o metabolismo microbiano, pode modular a conexão intestinal. Alguns desses AGCC derivados de micróbios são absorvidas e chegam ao cérebro através da circulação sistêmica e/ou do nervo vago, alterando a sensação bem-estar ou de estresse no indivíduo. Da mesma forma, o cérebro pode modular o microbioma diretamente através do efeito de substâncias neuroativas liberadas no lúmen intestinal afetando a expressão gênica e o comportamento dos micróbios, ou indiretamente por meio de alterações do ambiente microbiano intestinal (Horn *et al.*, 2022; Martin *et al.*, 2018; Shi *et al.*, 2020).

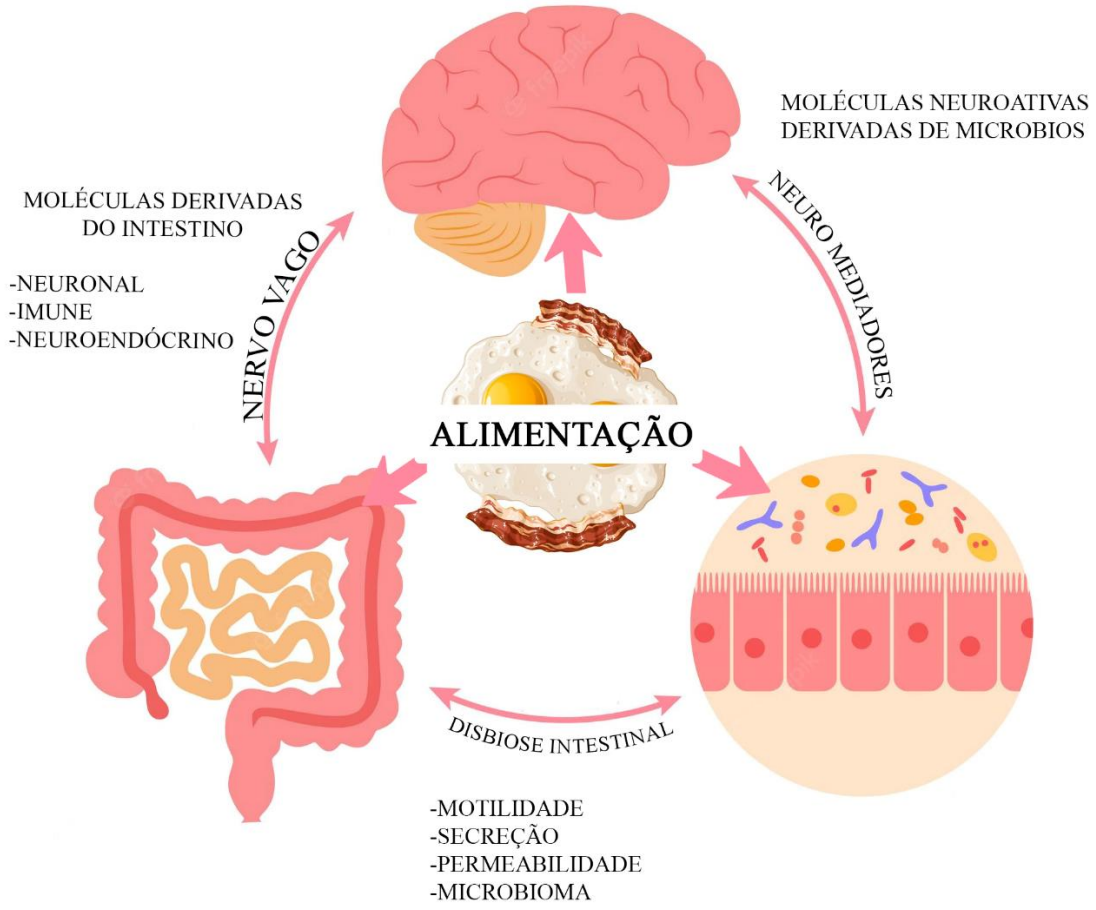

Figura 2 – Interação do eixo intestino-cérebro-microbioma. Fonte: adaptado de Martin *et al.* (2018).

No organismo humano é bem fundamentado a importância de uma boa saúde intestinal e sua influência no processo digestivo, no metabolismo e no sistema imunológico. Cada vez mais a literatura tem mostrado a influência da microbiota intestinal nos aspectos cognitivos, humorais bem como comportamentais a ponto de ser chamado por alguns pesquisadores de "o segundo cérebro", tamanha é sua influência na saúde humana (Ochoa-Reparaz; Kasper, 2016). Um estudo duplo-cego, randomizado, controlado por placebo com 22 pessoas, verificou que o uso de probióticos (*Bifidobacterium longum* R0175, *Lactobacillus helveticus* R0052 e *Lactobacillus plantarum* R1012) foi eficaz na redução do estresse nos indivíduos mediante ressonância magnética. Estes probióticos foram capazes de regular áreas do cérebro conhecidas por serem responsáveis pelas emoções e resposta ao estresse incluindo regiões dos giros cingulados orbitais laterais e ventrais (Șchiopu *et al.*, 2022).

Estudos com ratos obesos, mostram que tais animais tiveram uma redução na quantidade e diversidade de microrganismos na região do colón, correlacionando uma redução de Bacteroidetes e expressão de BDNF (fator neurotrófico derivado do cérebro) no hipocampo, ocasionando uma disfunção cognitiva e de memória nos animais por meio da diminuição das sinapses cerebrais na região hipocampal (ShiI *et al.*, 2020; Zhang *et al.*, 2019). Estudos em ratos, com cepas de Lactobacillus sp. (*Lactobacillus rhamnosus* GG e *Lactobacillus plantarum* IS-10506), demonstraram uma correlação positiva nos níveis de BDNF no cérebro desses animais, favorecendo o bom desenvolvimento e funções cerebrais (Orlando *et al.*, 2020; Ranuh *et al.*, 2019).

Uma alimentação rica em gordura saturada, pobre em fibras foi capaz de ocasionar redução na produção de ocludina em modelos animais, uma proteína responsável pelas tight-junctions, causando uma degradação da barreira mucosa do cólon e endotoxemia por LPS (Pan *et al.*, 2021; Zhou *et al.*, 2021). Uma via de reverter seria por meio de alteração da fonte de gordura ingerida, estudos com modelos animais, ratos Sprague-Dawley, demonstraram que a utilização de gorduras poli-insaturadas fora capaz de diminuir os níveis de LPS a nível sistêmico e hepático, tendo como fontes dessas gorduras os óleos de perila e de krill (Son *et al.*, 2021, 2022).

2.3.1 Influência da alimentação sobre a função intestinal e ansiedade

A alimentação moderna com alto teor de gorduras e açúcar são conhecidas por desencadear alterações duradouras na microbiota intestinal, tal população dinâmica de bactérias participam de funções fisiológicas, que vão desde a nutrição à imunidade, rupturas nesse equilíbrio podem vir a causar doença no ser humano, incluindo o comprometimento neuropsiquiátrico (Bruce-Keller *et al.*, 2017). Diversos estudos clínicos e experimentais vêm mostrando como o processo de disbiose intestinal impacta na função cerebral do organismo (Alonso; Guarner, 2013; Bested; Logan; Selhub, 2013; Bruce-Keller *et al.*, 2015, 2017; Kang *et al.*, 2014; Luna; Foster, 2015; Lyte, 2013), dentre as alterações ocorridas, tem-se as mudanças comportamentais relacionadas a ansiedade.

A ansiedade tem repercussões em nível intestinal por alterar não somente a composição da microbiota intestinal, levam a um nível elevado de bactérias gram-negativas e seus produtos como o LPS e peptideoglicanas, bem como modifica a produção de neurotransmissores no lúmen intestinal como GABA, 5-HT, dopamina e noradrenalina (Chen *et al.*, 2020; Han *et al.*, 2020; Jiang *et al.*, 2018; Zhang *et al.*, 2022). Um estudo com 133 adultos, entre 25 e 45 anos de idade, sem antecedentes de distúrbios emocionais, mostrou uma relação inversa entre níveis de ansiedade e contagem de colônias de *Bifidobacterium* nas mulheres. Nos homens também foi observada uma relação inversa entre níveis de depressão e a população de *Lactobacillus*. A partir destes resultados, os autores sugerem que mudanças na microbiota podem influenciar alterações nos estados de humor, e essas mudanças podem se manifestar de maneiras distintas entre os gêneros (Taylor *et al.*, 2019).

Pesquisas com ratos e camundongos têm confirmado a influência da alimentação na saúde intestinal e cerebral. Um estudo experimental mostrou que camundongos alimentados com dieta hiperlipídica indutora de obesidade, tiveram o desenvolvimento de um processo de disbiose levando também a deficiência cognitiva e desenvolvimento de comportamento ansioso. Tais alterações podem ocorrer devido ao potencial inflamatório que a alimentação teve na elevação dos níveis de LPS, TNF-α e da população de Proteobácterias. Adicionalmente, também foi observada diminuição da expressão do BDNF que é responsável pela plasticidade neuronal na região do hipocampo e seus níveis reduzidos estão relacionados a tais alterações cerebrais (Jeong; Jang; Kim, 2019).

Por outro lado, modificações na dieta, como introdução de hábitos saudáveis podem auxiliar na promoção de saúde tanto intestinal como neuronal. A exemplo da utilização de probióticos (*Lactobacillus* sp. e *Bifidobacterium* sp.) e prebióticos (FOS – Fruto-

oligossacarídeo e GOS - Galacto-oligossacarídeo) que podem auxiliar na redução de níveis de ansiedade e mudanças positivas no humor (Agusti *et al.*, 2018; Avolio *et al.*, 2019b; Jang *et al.*, 2019; Moya-Pérez *et al.*, 2017; Szklany *et al.*, 2019). Assim como a utilização de compostos fenólicos oriundos frutas, que devido capacidade de inibir o crescimento de bactérias patogênicas e/ou aumentar a população de bactérias probióticas, pode auxiliar na melhora de quadros de depressão, ansiedade e obesidade (Matarazzo; Toniato; Robuffo, 2018).

E quanto mais cedo for a mudança para hábitos saudáveis na alimentação melhor será para o desenvolvimento cognitivo e prevenção de doenças cerebrais. Estudos mostram que desde a gestação, a saúde intestinal materna tem influência sobre a saúde neuronal nos filhotes, bem como o leite materno influência no desenvolvimento de comportamentos ansioso nos filhotes (Degroote *et al.*, 2016a; Guedine *et al.*, 2018). Um estudo com ratos Fischer f344 com 24 dias de vida, mostrou que esses animais alimentados no início da vida durante 4 semanas com prebiótico e com nutrientes encontrados no leite materno, teve a capacidade de melhorar o desenvolvimento cerebral, sua plasticidade e regulação emocional. A dieta estimulou o crescimento de bactérias probióticas intestinais (*Lactobacillus* spp.) e aumentou significativamente a expressão de miRNA para o BDNF no córtex pré-frontal, que está diretamente relacionado a plasticidade neuronal (Mika *et al.*, 2018).

3. MATERIAL E MÉTODOS

3.1 TIPO DE ESTUDO E ENSAIO BIOLÓGICO

Esta pesquisa trata-se de um estudo experimental, não clínico, envolvendo animais. Foram utilizadas fêmeas primíparas da linhagem Wistar para obtenção de neonatos, provenientes do Biotério de criação da Universidade Federal do Pernambuco (UFPE). Todos os procedimentos a seguir foram conduzidos de acordo com as Diretrizes para o Cuidado e Uso de Animais Experimentais e com as Diretrizes da Pesquisa Animal: Relatórios de Experimentos *In Vivo (Animal Research: Reporting of In Vivo Experiments -ARRIVE guidelines*), sendo aprovado pela Comissão de Ética no Uso de Animais (CEUA) sob o número 9877041019 (Anexo A). Os animais foram mantidos no Laboratório de Nutrição Experimental (LANEX) da Universidade Federal da Paraíba, em condições-padrão: temperatura de 21 ± 1°C, com ciclo claro-escuro não invertido (de 12 h; com início da fase clara às 07 h), umidade de ± 55%, tendo livre acesso a água.

3.2 ANIMAIS E DIETA

Foram utilizados 40 ratos (20 machos e 20 fêmeas) *Wistar* com ± 90 dias de idade, mantidos em gaiolas coletivas com água e ração *ad libitum*, temperatura 21 ± 1 °C, umidade relativa entre 50 e 55 % e ciclo claro/escuro de 12 h. Os ratos foram randomizados em quatro grupos de acordo com os tratamentos dietéticos dados aos ratos reprodutores, sendo cada grupo com 5 machos e 5 fêmeas, assim descritos: pais e mães controle (PC/MC, n = 10); pais alimentados com dieta hiperlipídica e mães controle (PH/MC, n = 10); pais alimentados com dieta controle e mães com dieta hiperlipídica (PC/MH, n = 10); pais e mães alimentados com dieta hiperlipídica (PH/MH, n = 10).

Os pais foram aleatoriamente designados para receber uma dieta controle ou uma dieta hiperlipídica começando com 50 dias de idade e continuando por 6 semanas. As fêmeas primíparas foram alimentadas com ração comercial até os 90 dias de idade. Com uma semana antes dos 90 dias de idade as fêmeas foram divididas em grupos com dieta controle ou dieta hiperlipídica. Os machos alimentados com controle (dieta AIN93) ou hiperlipídica foram postos para acasalar individualmente fêmeas primíparas com ±90 dias de vida e com peso acima de 200 g para gerar descendentes; idade no qual também se iniciou o período de

indução da dislipidemia materna. Para evitar desequilíbrios nutricionais pós-natais, as ninhadas foram padronizadas para 8 filhotes no 3° dia em cada grupo.

Após o desmame, ao 21º dia de vida, todos os filhotes machos (n=10) foram separados por grupo em gaiola coletiva tipo caixa (4 animais/gaiola), de polietileno (40 x 30 x 30 cm) e assoalho coberto com maravalha e passaram a receber dieta controle e água *ad libitum.*

Ambas as dietas foram analisadas quanto à microbiologia de acordo com a metodologia descrita pela *American Public Health Association* (1985) e quanto ao teor de ácidos orgânicos (Coelho *et al.*, 2018b) e ácidos graxos (Meireles *et al.*, 2021) por cromatografia líquida de alta eficiência. A dieta controle foi elaborada com base nas recomendações do Instituto Americano de Nutrição (AIN-93G) que temo óleo de soja como fonte de lipídios; enquanto a dieta hiperlipídica teve a fonte lipídica modificada para além do óleo de soja, gordura vegetal, banha de porco e colesterol sintético (Tabela 1).

O peso corporal e o consumo alimentar dos ratos e filhotes machos foram aferidos semanalmente durante todo o experimento, utilizando-se balança eletrônica digital (Toledo, prix III, São Bernardo do Campo, Brasil).

A eutanásia e coleta de sangue, fezes, cérebro e intestino foram realizadas nos machos após o acasalamento; nas mães após a lactação e no 30° e 90° dia de vida dos filhotes. Os testes comportamentais da prole começaram na 8ª semana de idade, quando atingiram a maturidade sexual (Guedine *et al.*, 2018).

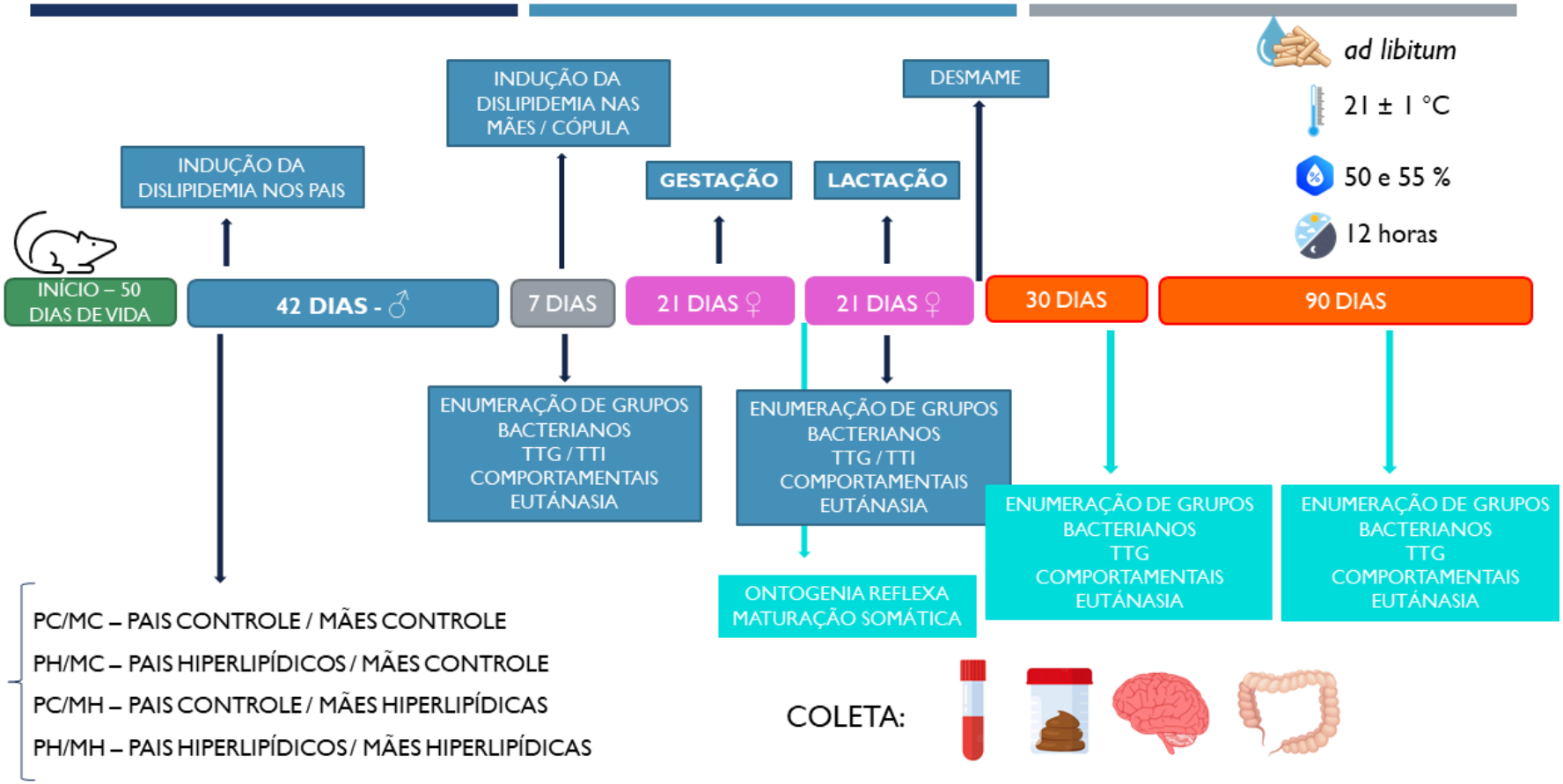

Figura 3 – Desenho do estudo do ensaio biológico – visão global

Tabela 1 - Ingredientes, macronutrientes, valor energético, ácidos graxos e orgânicos das dietas AIN93G e ricas em gordura usadas no experimento.

Ingredientes (g/100 g)	**Dietas**	
	Controle – AIN93G	**Hiperlipídica**
Amido de milho	39.75	33.09
Amido Dextrinizado	13.20	15.50
Sacarose	10.00	6.00
Fibra	5.00	5.00
Caseína	20.00	19.86
L-cistina	0.30	0.30
Bitartarato de colina	0.25	0.25
Mistura Mineral AIN 93G	3.50	3.50
Mistura de vitaminas AIN 93	1.00	1.00
t-BHQ	0.14	0.14
Óleo de soja	7.00	3.00
Banha	-	6.00
Gordura vegetal não hidrolisada	-	5.00
Ácido cólico	-	0.50
Colesterol	-	1.00
Valor total de energia (kcal/g)	3.96	4.34
Carboidratos (kcal %)	63.58	50.32
Proteínas (kcal %)	20.20	20.06
Lipídios (kcal %)	15.91	31.82
Ácidos graxos (g/100g)		
Octanoic acid C8:0	0.05±≤0.01	n.d.
Ácido cáprico C10:0	0.11±0.03	0.08±≤0.01
Ácido láurico C12:0	0.17±0.03	0.13±≤0.01
Ácido pentadecanóico C15:0	0.08±0.01	0.31±0.01*
Ácido palmítico C16:0	10.03±0.04	27.95±0.03*
Ácido 14-metil hexadecanóico C17:0	n.d.	0.30±0.01
Ácido heptadecanóico C17:0 (Margárico)	0.11±0.03	1.04±0.01*
Ácido estearato C18:0 (esteárico)	5.86±0.30	40.69±0.09*
Ácido nãoadecanóico C19:0	n.d.	0.19±0.02*
Ácido eicosanóico C20:0 (araquídico)	0.49±≤0.01	0.60±0.01*
18-metilnonadecanoato C21:0	n.d.	0.76±≤0.01
Ácido docosanóico C22:0 (benênico)	0.47±0.02	0.24±0.05*
Ácido tetracosanóico C24:0 (Lignocérico)	0.16±0.03	n.d.
Total de ácidos graxos saturados (AGS)	**17.53**	**72.29**
Ácido trans-9-hexadecenóico C16:1 t9	0.34±0.02	2.03±0.02*
Metil hexadec-9-enoato C17:1	0.15±0.06	n.d.
Ácido trans-11-octadecenóico C18:1 t11 (Vaccênico)	n.d.	0.05±≤0.01
Ácido octadecenóico C18:1 ω 9 (Oleico)	20.25±0.41	2.27±0.06*
Ácido Cis-11-Octadecenóico (cis Vaccênico)	n.d.	0.05±≤0.01
Ácido Cis-13-Eicosenoico C20:1 ω7	0.21±0.01	0.35±0.01*
Total de ácidos graxos monoinsaturados (MUFA)	**21.25**	**4.75**

Ácido Cis-9,12-Octadecadienóico C18:2 ω6c (Linoleico)	54.52±0.44	n.d.
Ácido trans-9,12-octadecadienóico C18:2 ω6t	n.d.	20.85±0.23
ácido 9,12,15-octadecatrienóico C18:3 ω3 (linolênico)	6.70±0.04	1.69±0.06*
Ácido Cis-11,14-Eicosadienoico C20:2 ω6 (Dihomolinoleico)	n.d.	0.30±0.02
Ácido 5,8,11,14-Eicosatetraenoico C20:4 ω6 (Araquidônico)	n.d.	0.12±0.01
Total de ácidos graxos poliinsaturados (PUFA)	**61.22**	**22.96**
Ácidos orgânicos (µmol/g)		
Cítrico	0.68±0.04	0.73±0.05
Málico	2.52±0.05	2.04±0.02*
Tartárico	0.80±0.03	0.88±0.01*
Ácidos orgânicos totais (µmol/g)	**4.00**	**3.65**

*Adaptado de Reeves; Nielsen; Fahey, (1993). ** Rhoster – Indústria e Comércio Ltda. ***t-BHQ: terc butil hidroquinona.

3.3 ONTOGÊNESE REFLEXA E DESENVOLVIMENTO DE PARÂMETROS FÍSICOS E SOMÁTICOS

Foram medidos diariamente desde o 1º de vida até o 21º, os comprimentos do eixo crânio látero-lateral (distância entre os dois ouvidos), eixo anteroposterior da cabeça (distância entre focinho e a articulação da cabeça-pescoço), nasoanal (distância entre o focinho e o ânus) com um paquímetro de 0,01 mm de precisão.

A ontogênese reflexa foi avaliada diariamente do 1º ao 21º dia de vida, das 13h às 15h. A reação esperada foi considerada positiva quando se repetiu por três dias consecutivos, sendo o 1º dia do aparecimento considerado o dia da consolidação. O tempo de observação para cada parâmetro foi de 10 segundos. As avaliações seguiram o modelo experimental estabelecido por Smart e Dobbing (1971) (Quadro 2).

Quadro 2. Indicadores para avaliação da Ontogenia Reflexa.

Reflexo	**Estimulo**	**Resposta**
Desaparecimento da Preensão Palmar (DPP)	Percussão leve na palma da pata dianteira direita de cada animal com um bastonete metálico.	Flexão rápida dos dedos

Recuperação Postural de Decúbito (RPD)	O animal é colocado em decúbito dorsal sobre uma superfície plana e lisa.	Retorno ao decúbito ventral apoiado sobre as quatro patas.
Colocação Espacial Desencadeada pelas Vibrissas (CPV)	O animal é suspenso pela cauda e suas vibrissas tocam levemente borda de uma superfície plana.	As patas dianteiras são colocadas sobre a mesa, realizando movimentos de marcha.
Aversão ao Precipício (AV)	O animal é colocado com as patas dianteiras na extremidade de uma superfície plana e alta, de maneira que ele detecte o precipício.	O animal desloca-se para um dos lados e caminha em sentido contrário à borda.
Geotaxia Negativa (GN)	O rato é colocado no centro de uma rampa inclinada com a cabeça voltada para baixo.	O corpo gira em um ângulo de 180°, posicionando a cabeça em sentido ascendente.
Resposta ao Susto (RS)	Estímulo sonoro intenso e agudo.	Retração das patas, com imobilização rápida e involuntária do corpo.
Recuperação do Decúbito em Queda Livre (RDQL)	Segurado pelas quatros patas a uma altura de 30 cm, o rato é solto sobre um leito de espuma sintética.	Recuperação da posição durante a queda livre sobre a superfície apoiada pelas quatro patas.

Fonte: Smart; Dobbing, 1971

Do 1º dia até o 21º de vida pós-natal, os filhotes foram examinados sempre no mesmo horário (13h às 15h), de modo a determinar o dia em que a maturação somática foi completa (Quadro 3).

Quadro 3. Indicadores de Maturação Somática.

Maturação Somática	**Resposta**
Abertura do Pavilhão	Desdobramento completo do APA para a posição ereta. Nesta

Auricular (APA)	avaliação, a maturação é considerada positiva quando os dois pavilhões estiverem desdobrados.
Abertura do Conduto Auditivo (ACA)	Considerou-se positivo a ACA no dia em que os orifícios auriculares direito e esquerdo encontraram-se abertos, podendo ser visualizados.
Erupção dos Dentes Incisivos Superiores (EDIS)	É registrado o rompimento da gengiva quando ambos os incisivos estavam expostos.
Erupção dos Dentes Incisivos Inferiores (EDII)	É registrado o rompimento da gengiva quando ambos os incisivos estavam expostos.
Abertura dos Olhos (AO)	A resposta é considerada positiva quando os dois olhos estão abertos, com presença de movimento reflexo das pálpebras.
Aparecimentos dos Pelos Epidérmicos (APE)	Seu aparecimento é confirmado quando se detecta a presença da pelugem, para tal teste desliza-se gentilmente os dedos sobre a epiderme do animal.
Comprimento da Cauda (CC)	O animal é colocado sobre uma régua milimetrada, sendo a cauda delicadamente mantida bem estendida, desde a base até a extremidade.

Fonte: Smart; Dobbing, 1971

3.4 AVALIAÇÃO DO COMPORTAMENTO TIPO ANSIOSO

Os testes para avaliação do comportamento tipo ansioso pelos ratos foram conduzidos durante o ciclo claro, filmados utilizando câmera IP (marca D-Link, modelo IP2P Wireless, Shenzen, China) e analisados de forma cega pelos pesquisadores envolvidos. Para a avaliação da ansiedade foi utilizado o teste de campo aberto, cujo aparato é utilizado para avaliar o comportamento de ansiedade e a atividade exploratória, a fim de verificar os efeitos de ambientes não familiares sobre o estado emocional de ratos (Hall, 1934; Seibenhener, M.L., Wooten, 2015). O aparato consiste em uma arena com formato circular com 90 cm de diâmetro e paredes com 50 cm de altura., uniformemente iluminado.

Cada animal foi observado durante 10 minutos, no ciclo claro; sendo avaliados os parâmetros: ambulação (número de cruzamentos dos segmentos pelo animal com as quatro

patas), número de comportamentos de levantar-se (*rearing*), tempo de comportamentos de autolimpeza (*grooming*) e defecação (registrada por meio do número de bolos fecais).

Um dia após o teste do campo aberto, foi realizado o teste utilizando o labirinto em cruz elevado (LCE), cujo modelo é validado do ponto de vista farmacológico, bioquímico e comportamental como teste de ansiedade no rato. O LCE é um teste fundamentado na aversão natural de roedores a espaços abertos e altos e no conflito de aproximação-esquiva (Lister, 1990; Bradley *et al.*, 2007). O LCE é um aparato composto por dois braços fechados e dois braços abertos perpendiculares aos primeiros, uma área central, sendo este elevado do solo.

O rato foi colocado no centro do aparato com o focinho voltado para o braço fechado direito. Durante 5 minutos foi analisado por meio de filmagem, a frequência de entradas nos braços fechados e abertos (considera-se uma entrada quando o animal entrar com as quatro patas no braço), o tempo gasto em cada braço e no centro do aparato. Além disso, também foi contabilizada a quantidade de mergulhos de cabeça (quando o animal colocar o focinho ou a cabeça no braço aberto e explorar o precipício).

3.5 TESTE DE TOLERÂNCIA À GLICOSE (TTG) E À INSULINA (TTI)

Depois do término de todos os testes comportamentais foi realizado o TTG, após um jejum de 6 horas, a glicemia inicial foi aferida por meio de incisão na cauda do rato (tempo 0). Foi administrado uma solução de glicose a 50 % na dose de 1 mg/g, aferindo-se a glicemia nos tempos 15, 30, 60, 90 e 120 minutos.

No dia posterior ao TTG, foi realizado o TTI na condição basal após administração intraperitoneal de insulina regular (Novolin® R, Novo Nordisk, Bagsvaerd, Dinamarca), equivalente a 0,75 UI/kg, aferindo-se a glicemia nos tempos 0, 30, 60, 90 e 120 minutos. A glicemia foi aferida utilizando glicosímetro (marca Accu-check, modelo Performa, Jaguaré, SP, Brasil) (Kothari *et al.*, 2017).

3.6 DETERMINAÇÃO DOS PARÂMETROS MURINOMÉTRICOS E EUTANÁSIA

Os parâmetros murinométricos foram aferidos antes da eutanásia, sendo eles: o Peso corporal, Comprimento naso-anal, Comprimento da cauda, Circunferências abdominal (CA; cm), Torácica (CT; cm) e calculado o Índice de Massa Corporal (IMC; g/cm^2) (Novelli *et*

al., 2007). A eutanásia foi realizada por decapitação em guilhotina (EB271, Insights, Ribeirão Preto, Brasil), de acordo com a (BRASIL, 2013) nº 13 de 2013 do CONCEA para coleta de sangue e órgãos como o cérebro, intestino e testículos.

Foram coletadas as gorduras viscerais, gonadal e subcutânea, pesadas e armazenado para as análises histológicas. A soma da massa desses depósitos de gordura é considerada gordura total. O índice de adiposidade foi calculado pela seguinte fórmula: (GT/PT x 100), sendo GT a gordura total, e PT o peso total no dia da eutanásia (Nascimento *et al.*, 2011).

3.7 ANÁLISES BIOQUÍMICAS

Foram realizadas as dosagens de colesterol total (CT), Triglicerídios (TG) e lipoproteína de alta densidade (HDL), lipoproteína de baixa densidade (LDL) e lipoproteína de muito baixa densidade (VLDL). As análises foram realizadas utilizando kits comerciais (Labtest, Minas Gerais, Brazil), seguindo as recomendações do fabricante, utilizando analisador automático Labmax 240 premium (Labtest, Belo Horizonte, Brasil).

3.8 AVALIAÇÃO HISTOLÓGICA DE ÓRGÃOS

O intestino (cólon) e o cérebro (córtex pré-frontal) dos machos e fêmeas reprodutores e dos filhotes, bem como os testículos dos machos reprodutores foram destinados para as análises histológicas, sendo fixados em formol tamponado a 10 % e processados de acordo com a técnica histológica de rotina. As lâminas obtidas foram coradas através da técnica de Hematoxilina de Harris e Eosina, realizando a montagem entre lâmina e lamínula com resina sintética (Entellan-Merck) para análise em objetivas crescentes e fotografadas em aumento total de 40x em microscópio óptico comum (Motic BA 200, Kowloon, Hong Kong).

No cérebro foram avaliadas as arquiteturas estruturais dos órgãos e a presença, característica e intensidade de possíveis infiltrados inflamatórios. No intestino, foi avaliada à ocorrência de hiperemia, exsudato inflamatório, hemorragia, vasodilatação, necrose, preservação epitelial, além de hipertrofia e hiperplasia da camada muscular lisa (Batista *et al.*, 2018).

Foram realizados também, análises quantitativas de morfometria intestinal dos animais. As análises morfométricas para a quantificação da razão entre vilosidade e cripta

intestinal, foram realizadas utilizando HE através de analisador de imagem Zeiss Imaging Processing Software (KS 300, Zeiss, Alemanha). De cada material, foram selecionados 25 campos de cada lâmina histológica contendo amostras histológicas de forma aleatória, usando-se a objetiva de 10x. Esses campos foram capturados através do analisador de imagens. Para obtenção das imagens, utilizou-se objetiva de 10x para fotomicrografia do cólon e 40x para fotomicrografia cerebral.

3.9 ENUMERAÇÃO DOS GRUPOS BACTERIANOS SELECIONADOS

As amostras fecais foram homogeneizadas em água peptonada (100 mg/mL) e depois diluídas em série (cinco diluições). Alíquotas (20 µL) das respectivas diluições foram inoculadas pela técnica de inoculação de microgotículas (Miles *et al.*, 1938) em placas de Petri estéreis contendo ágar para contagem de *Lactobacillus spp*. (Man, ágar Rogosa e Sharpe-MRS, Himedia, Índia), *Bifidobacterium spp*. (ágar *Bifidobacterium*, Himedia, Índia), família *Enterobacteriaceae* (ágar MacConkey, Himedia, Índia), Escherichia coli (ágar azul de metileno eosina, Himedia, Índia) ou *Enterococcus spp* (ágar Bile Esculin-BHE, Himedia, Índia). Placas de cultura para *Lactobacillus spp*. e *Bifidobacterium spp*. foram incubados em condições anaeróbicas (Anaerobic System Anaerogen; Oxoid Ltd, Wade Road, Reino Unido) a 37 ° C durante 48 h. *Enterobacteriaceae*, *Enterococcus* e *Escherichia coli* foram contadas após 24 horas de incubação a 37 °C em condições aeróbias. Após a incubação, as colônias características nos meios de cultura seletivos foram contadas e os números de células viáveis (Unidades Formadoras de Colônias - UFC) foram expressos como Log 10 UFC/g de fezes (Batista *et al.*, 2018).

3.10 ANÁLISE ESTATÍSTICA

O poder estatístico de 0,80 (80%) foi obtido estimando-se vinte ratos Wistar adultos, fêmeas (cinco fêmeas por grupo), vinte ratos Wistar adultos machos (cinco machos por grupo) e quarenta filhotes (dez filhotes por grupo). A normalidade das medidas foi avaliada através do teste de Kolmogorov-Smirnov. Para o tratamento de dados não paramétricos utilizou-se o teste de Mann-Whitney para duas amostras e o de Kruskal-Walls para comparações múltiplas. Os dados paramétricos foram analisados via análise de variância (ANOVA) para comparações múltiplas e pós teste de Tukey, utilizando o nível de

significância de 5%. Para todos os testes comportamentais foram analisados pelo teste de Mann-Whitney e foram expressos como média, mediana e percentis 25% e 75%. Para todas as análises foi adotado nível de significância de 5% ($p \leq 0,05$). Os resultados foram analisados no software estatístico GraphPad Prism 8.0 (versão para avaliação, GraphPad Software Inc. La Lolla, CA, USA).

4. RESULTADOS

Os resultados desta tese estão apresentados em forma de dois artigos originais apresentados nos apêndices I e II.

O primeiro artigo apresentado no apêndice I se intitula "**Does parental diet alter the neurobehaviour and reflex and somatic parameters of the offspring?**". Os resultados desse estudo mostram que um padrão dietético hiperlipídico rico em colesterol, ácidos graxos saturados e trans, podem trazer como consequência, um impacto no desenvolvimento físico da prole nos primeiros 21 dias de idade, com atrasos em alguns parâmetros somáticos, como surgimento dos pelos epidérmicos, revelando que a influência da dieta dos pais pode se estender desde os primeiros estágios de vida.

Além da parte somática, foi encontrado também atrasos na ontogenia dos reflexos em ratos cujos pais consumiram a dieta hiperlipídica, implicando no desenvolvimento do sistema nervoso dos filhotes e impactando na sua capacidade de realizar funções reflexas essenciais. Outro resultado importante foi a manifestação de comportamento ansioso em ratos aos 30 dias de idade, nascidos dos pais e mães que se alimentaram da dieta hiperlipídica quando comparados aos outros demais grupos.

Além disso, houve uma redução no número de corpos neuronais e na porcentagem de ácidos graxos poli-insaturados no cérebro da prole aos 30 dias de vida. Tais resultados sugerem que a dieta dos pais teve impacto no neuro comportamento da prole que pode ter implicações em curto prazo para a saúde mental. No que diz respeito à saúde metabólica, a prole de pais que receberam a dieta hiperlipídica, apresentou níveis elevados de colesterol total (CT) e lipoproteína de baixa densidade (LDL), bem como uma redução significativa na lipoproteína de alta densidade (HDL). Essas alterações no perfil lipídico estão associadas a um maior risco de doenças cardiovasculares e metabólicas em curto e longo prazo.

O segundo artigo apresentado no apêndice II se intitula "**High-fat parental diet alters somatic, biochemical, neurobehavioural and gut health parameters in adult offspring**"

Os resultado desse trabalho indica que filhotes aos 90 dias de idade, a prole de pais submetidos à dieta hiperlipídica demonstraram hiperfagia, ganho de peso corporal, desenvolvimento de comportamento ansioso, caracterizado por um aumento na defecação e no tempo gasto em *grooming* no campo aberto, bem como um tempo mais prolongado nas áreas fechadas do labirinto em cruz. Além disso, houve mudanças significativas na contagem

de bactérias fecais dos filhotes. *Lactobacillus* e *Bifidobacterium*, bactérias benéficas para o intestino, diminuíram, enquanto as contagens de *Bacteroides* e *Enterobacteriaceae*, bactérias associadas a desequilíbrios intestinais, aumentaram. Essas alterações na microbiota fecal podem ter implicações para a saúde intestinal e metabólica a longo prazo. Os níveis de colesterol total (CT) e lipoproteína de baixa densidade (LDL) estavam significativamente elevados nos filhotes nascidos de pais submetidos à dieta hiperlipídica, enquanto os níveis de lipoproteína de alta densidade (HDL), que é benéfica para a saúde cardiovascular, estava reduzidos, sugerindo um maior risco de doenças cardiovasculares e metabólicas na vida adulta.

Além disso, os filhotes do grupo em que ambos os pais se alimentaram com a dieta hiperlipídica mostraram alterações graves na mucosa intestinal, incluindo perda do revestimento epitelial e atrofia das vilosidades. Estes resultados são indicativos de danos significativos no sistema digestivo, o que pode afetar a absorção de nutrientes e a saúde intestinal. Um achado notável foi a intensa marcação para NF-kB no córtex cerebral, um marcador de inflamação, na prole dos grupos em que somente o pai ou ambos (pais e mães) se alimentaram da dieta hiperlipídica. Este resultado sugere que a dieta dos pais pode ter desencadeado uma resposta inflamatória no cérebro da prole quando adultos jovens, mesmo estes tendo se alimentado do desmame até os 90 dias de idade de uma dieta controle ou normolipídica, o que pode estar relacionado a uma série de problemas de saúde mental em longo prazo.

5. CONSIDERAÇÕES FINAIS

Como resultado das pesquisas conduzidas nesta tese, ficou evidente que a dieta hiperlipídica dos pais tem um impacto significativo e abrangente na saúde e no comportamento de sua prole ao longo de diferentes estágios de desenvolvimento. Os resultados apresentados nos dois artigos originais, contidos nos apêndices I e II, destacam de maneira inequívoca as consequências adversas dessa dieta.

Desde os primeiros dias de vida até a idade adulta, a prole exposta à dieta hiperlipídica dos pais enfrentou desafios somáticos, neurológicos e metabólicos substanciais. Essas implicações incluem atrasos no desenvolvimento somático, modificações nos reflexos e no sistema nervoso em curto prazo; além da manifestação de comportamento ansioso, desequilíbrios na microbiota intestinal tanto em curto quanto em longo prazo e um aumento significativo nos níveis de colesterol principalmente em curto prazo, o que se traduz em um maior risco de doenças cardiovasculares e metabólicas.

Adicionalmente, os resultados indicam que a dieta dos pais pode desencadear uma resposta inflamatória no cérebro de seus filhotes, mesmo quando estes são alimentados com uma dieta normal após o desmame e ao longo da vida. Essa inflamação cerebral pode ter implicações sérias na saúde mental em longo prazo.

Em conjunto, os resultados da tese indicam que a nutrição dos pais desempenha um papel crucial na saúde e no bem-estar de sua descendência. Elas sublinham a importância de promover uma dieta saudável e equilibrada não apenas para os indivíduos adultos, mas também como uma medida preventiva para garantir um futuro mais saudável para as gerações futuras, conforme evidenciado pelos resultados robustos obtidos neste estudo.

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ARTIGO I

DOES PARENTAL DIET ALTER THE NEUROBEHAVIOR AND REFLEX AND SOMATIC PARAMETERS OF THE OFFSPRING?

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Does parental diet alter the neurobehaviour and the reflex and somatic parameters of the offspring?

Abstract

A high-fat diet is associated with several diseases and it can trigger changes in the metabolism and neurobehaviour of the offspring when consumed by the parents. This study investigated the effects of a high-fat diet (HFD) consumed by the parents on the biochemical, somatic parameters, reflex ontogeny, fatty acids, brain histology, and anxiety-like behaviour in rat offspring. Breeders were randomly divided into 4 groups (n=10 rats/group): NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF = both breeding rats fed a HFD. The following analysis were performed: somatic development, physical maturation, postnatal ontogeny (T0 to T21), open field and elevated plus maze test, glucose tolerance test, lipid profile, brain fatty acid and histology (T30). The NF/HF and HF/HF groups presented a delay in the appearance of somatic growth, and the HF/NF and NF/HF groups presented a delay in reflex ontogeny. The NF/HF and HF/HF groups showed anxiety-like behaviour compared to the NF/NF and HF/NF groups. The HF/HF group showed an increase in the TC (439.28±71.88 mg/dL) and LDL levels (151.11±28.72 mg/dL), and a reduction in HDL (36.84±18.93 mg/dL) together with the HF/NF and NF/HF groups. HF/HF offspring showed an increase in the adiposity index, a reduction in neuronal bodies and in the cerebral polyunsaturated fatty acid percentage. This study demonstrates that parental HFD during the preconception and pregnancy/lactation periods compromised the offspring's neurobehavioural and somatic development, as well as causing metabolic disorders in early life.

Keywords: anxiety, adiposity index, brain, fatty acids, lipoprotein, ontogeny.

Introduction

Pregnancy comprises a period of major physiological and metabolic changes in the female body to form a new life1. Adequate foetal and postnatal development is influenced by

maternal nutrition, so nutritional stimuli, particularly during the foetal growth and development period, modulate long-term health and disease risks 2,3.

Lipids structurally compose the nervous system, stimulate their development, differentiation and even regulate the migration of neuronal cells 4,5. The quality and proportions of fatty acids from lipid sources in the maternal diet during this period of intrauterine neurodevelopment is an important factor for cognitive development, somatic maturation, and reflexes 6,7. In addition, postnatal locomotor performance involves a concomitant integration between the nervous and muscular systems, with an orderly and hierarchical development that begins with immature reflex responses and progresses to obtaining a functional movement pattern 8.

Although maternal nutrition plays a fundamental role in the physical growth of offspring, as well as in behavioural development, an inadequate supply of nutrients can negatively influence brain development, resulting in changes in its structure and functionality 9. In this context, the western food pattern is currently characterized by high consumption of saturated and trans fatty acids, ultra-processed foods and fast foods which result in developing dyslipidaemia and other chronic noncommunicable diseases 10, which can also affect their descendants (BOURDY *et al.*, 2021; CLAUSS *et al.*, 2022; PARADIS *et al.*, 2017; RADFORD-SMITH; ANTHONY, 2023; VIDAL-SANTOS *et al.*, 2017; ZIELIŃSKA *et al.*, 2022).

Maternal diets which are unbalanced in the omega-3 and omega-6 proportions during pregnancy and early postnatal life (for example), are causes of fatty acid remodelling in the brain that compromise neuronal morphology(HORMAN *et al.*, 2020; MADORE *et al.*, 2020; STANFORD *et al.*, 2018), affecting cognitive and locomotor ability, as well as the development of behaviours related to anxiety and depression in the successive generation, thereby affecting mental health 20,21.

In parallel, the father's diet and lifestyle can also influence the development of the offspring 19. Previous studies with parents fed Westernized diets, high-fat diets, or low-protein diets, for example, have shown that the offspring developed cardiovascular diseases, hypertension, weight and adiposity gain, glucose intolerance, hypertriglyceridemia, epigenetic alterations22,23, as well as neurobehavioural changes 24–26. Paternal diet and maternal

health influence the development of anxious-like behaviour, such as diets rich in saturated fats like palmitic acid, which may be related to the activation of inflammatory pathways such as toll-like receptor 4 (TLR4), causing epigenetic changes in response to these environmental signals; these also have repercussions on the dysregulation of neurohormones production, such as serotonin and dopamine, leading to implications for stress reactivity in adulthood [27–29]. However, there is a gap in the literature on paternal and maternal consumption of a high-fat diet, mainly rich in cholesterol, saturated and trans fatty acids, its metabolic implications and on the neurobehaviour and development of the offspring during childhood. Therefore, the aim of this study was to investigate the effects of a high-fat diet consumed by the parents on biochemical and somatic parameters, reflex ontogeny, fatty acids and brain histology, and anxiety-like behaviour in rat offspring.

Materials and Methods

Experimental design

This study followed an experimental protocol in accordance with the ethical recommendations of the Animal Research guidelines: Reporting of In Vivo Experiments: the ARRIVE Guidelines (DU SERT *et al.*, 2020) and was approved by the Ethics Committee on the use of Laboratory Animals (CEUA) of the Federal University of Paraíba under protocol no. 9877041019. A total of 40 Wistar rats (20 males and 20 females) were used with ± 90 days of age, kept in collective cages with water and feed *ad libitum*, temperature 21 ± 1 °C, relative humidity between 50 and 55% and light/dark cycle of 12h/12 h (light phase 7 a.m.). The rats were randomized into four groups according to the dietary treatments given to the breeding rats, each group with 5 males and 5 females, not inbred, as follows: NF/NF- males and females breeding rats fed a normal-fat diet; HF/NF - breeding males fed a high-fat diet and females fed a normal-fat diet; NF/HF - breeding males fed a normal-fat diet and females fed a high-fat diet; and HF/HF- breeding male and female rats fed a high-fat diet.

The respective diets were offered to both males in the period before mating and to females during pregnancy and lactation, and consumed the diets for the same period of days (6

weeks). Only male breeders were randomly assigned to receive a normal-fat diet (NFD) or a high-fat diet (HFD) starting at 50 days of age and continuing for 6 weeks. Males (at 90 days of age) fed with NFD or HFD were put to mate individually with females who were also 90 days old, weighing between 200 and 210 g, also fed with NFD or HFD to generate offspring. The males and females were arranged in 1:1 proportion and fed a normal fat diet during the 07 days of mating.

The NFD offered was made with soybean oil as a lipid source and based on the recommendations of the American Institute of Nutrition (AIN) 31, and the HFD (Rhoster®, São Paulo, Brazil) showed changes in the lipid source with soy oil, cholesterol, hydrogenated vegetable fat and lard being added (Table S1). The litters were standardised for 8 offspring on the 3rd day in each group to avoid postnatal nutritional imbalances 31–33.

After weaning, all male offspring were separated into their respective groups in a collective cage (4 rats/cage) on the 21st day of life and received a control diet and water *ad libitum* until they were 30 days old. The study design is illustrated in Fig. 1.

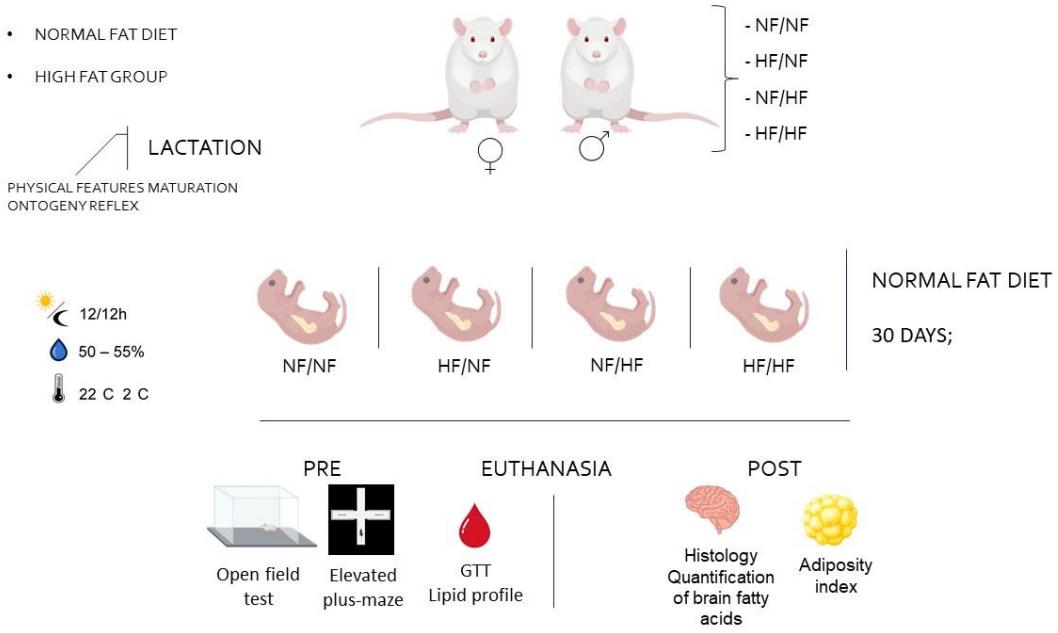

Fig. 1. Study design. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and

females fed a HFD; and HF/HF group = both breeding rats fed a HFD. GTT= glucose tolerance test.

Body weight and food consumption of breeding rats were measured weekly throughout the experiment. These measurements were performed daily for rats aged 30 days from weaning using a digital electronic scale (Toledo, prix III, São Bernardo do Campo, Brazil).

Reproductive performance and birth parameters

The following data were recorded for each group: number of mated females, number of pregnant females, litter size, presence of stillbirths, litter weight and birth weight. The following indices were also calculated: female fertility index (number of pregnant females/number of mated females × 100), gestation index (number of females with live offspring/number of pregnant females × 100), live birth index (number of offspring born alive/total number of offspring born × 100), viability index (number of live offspring on day 4 of postnatal), and weaning index (number of live offspring at day 21/number of live offspring born × 100) 34–36.

Somatic growth

Somatic growth was assessed by measuring body weight and length, as well as medio-lateral and anteroposterior head axes measurements37. These measurements were performed for each pup from the post-natal day (PND) 1 to PND 21 between 12:00 p.m. and 2:00 p.m. The body weight was measured with an electronic scale (Toledo, prix III, São Bernardo do Campo, Brazil) with a sensitivity of 0.01 g. The longitudinal body growth (distance between the snout and the base tail), as well as medio-lateral head axis were measured with a digital calliper (Stainless Hardened, Guarulhos, Brazil 0.05 mm precision).

Somatic maturation

The physical features 37 were observed and performed daily from PND 1 to PND 21 between 12:00 p.m. and 2:00 p.m. during the suckling period. The following physical features were observed: unfolding of the external pinnae of both ears to the fully erect position (EU); auditory conduit opening (ACO) — internal auditory conduit opening of both ears; incisor eruption — eruption of superior incisors (ESI), eruption of inferior incisors (EII); and eye

opening (EO) — when any visible break in the covering membrane of both eyes was detected and appearance of epidermal hair (AEH). Maturation age of a particular feature was defined as the day when it occurred for the first time 37,38.

Reflex ontogenesis

Reflexes were daily assessed between 12:00 p.m. and 02:00 pm from PND 1 to PND 21. When the expected reflex response was repeated for three consecutive days, the response was considered day 1 37. Palm grasp (PG) disappearance was evaluated, as well as the following reflexes: Righting reflex (R), Vibrissae placement (VP), Cliff avoidance (CA), Negative geotaxis (NG), Auditory startle (AS) and Free-fall righting (FR). The maximum observation time was 10 s.

Test to assess anxiety-like behaviour in offspring

Behavioural tests were performed on the offspring at 30 days of age. The open field test was used to evaluate anxiety, which is an apparatus to test anxiety behaviour and exploratory activity to verify the effects of unfamiliar environments on the emotional state of rats (HALL, 1934; SEIBENHENER; WOOTEN, 2015). The apparatus consists of a square arena (60 x 60 x 60 cm) with six crossed lines forming 6 quadrants measuring 20 x 20 cm, uniformly illuminated, filmed and analyzed blindly by the researchers involved.

Each animal was observed for 10 min, and the following parameters were evaluated: ambulation (number of crossings of the segments by the animal with all four paws), number of rearing behaviours, grooming behaviour time (grooming) and defecation (recorded by half the number of faecal bolus).

Next, the elevated plus maze test was performed one day after the open field test, a pharmacologically, biochemically, and behaviourally validated model as an anxiety test for rats. It is a test based on the natural aversion of rodents to open and high spaces and on approach-avoidance conflict 41,42. The apparatus is composed of two closed arms and two open arms perpendicular to the first ones, as well as a central area which is elevated from the ground.

The animal was placed in the centre of the apparatus with their snout facing the right closed arm. The frequency of entries in the closed and open arms (an entry is considered when the animal enters with all four paws in the arm), the time spent in each arm and in the centre of the apparatus were analysed for 5 min. In addition, the number of head dives (when the animal places its snout or head on the open arm and explores the cliff) was also counted and analyzed blindly by the researchers involved.

Glucose tolerance test and lipid profile in offspring

The glucose tolerance test (GTT) was performed two days later after the end of all behavioural tests after a 6-h fast. Initial glycaemia was measured by means of an incision in the rat's tail (time 0). A 25% glucose solution was administered at a dose of 2 g of glucose/kg of body weight, and blood glucose was measured at 15, 30, 60, 90 and 120 min using an Accu-Chek® Performa glucometer (Roche Diagnóstica Ltda., Santo Amaro, Brazil).

Next, total cholesterol (TC), triglycerides (TG) and high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) measurements were performed using commercial kits (Bioclin Quibasa, Belo Horizonte, Brazil) to evaluate the lipid profile. The analyses were performed following the manufacturer's recommendations with subsequent reading in a spectrophotometer (Biotek Instruments, Santa Clara, USA) at wavelengths of 505 nm (TG), 500 (TC), 546 nm (LDL), and 500 nm (HDL). The very low-density lipoprotein (VLDL) quantity was calculated by the TG/5.

Euthanasia, murinometric parameters and collection of biological materials

Murinometric parameters were evaluated immediately before euthanasia as follows: thoracic circumference (TC) (immediately anterior to the hind paw), abdominal circumference (AC) (immediately behind the foreleg), body weight and naso-anal length using inextensible tape measure, all measured in cm. The Body Mass Index (BMI) was calculated from the body weight (g) /length² (cm²) 43 and the Lee Index (LI) was calculated by the cube root of the body weight (g) divided by the nasoanal length (cm) 44

The offspring were euthanized at PND 30 by guillotine decapitation (EB271, Insights, Ribeirão Preto, Brazil) to collect blood, adipose tissue, and brain. The blood was collected in sterile tubes and centrifuged (1,040 x g / 10 min) to obtain the serum for lipid profile

analysis. The brain was removed and stored at -20 ºC until the day to analyse the fatty acid profiles.

Visceral, gonadal, and subcutaneous fats were collected, weighed, and then discarded. The adiposity index was calculated by the following formula: (GT/PT x 100), where GT is total fat, and PT is total weight on the day of euthanasia 45.

Quantification of brain fatty acids

The lipid extract of the brain was obtained by the method of Folch *et al.* (1957) 46. Then, methyl esterification was performed following the methodology in Hartman and Lago (1973) 47 to determine the fatty acid profile of the extract.

Methyl esters were analysed by a GCMS-QP2010 gas chromatograph (Shimadzu, Kyoto, Japão) coupled to a Durabound DB-23 capillary column with dimensions of 30 m × 0.25 mm and 0.25 mm, which was used with helium as the carrier gas (Flow rate of 1 mL/min). The injector and detector temperature were set at 230 °C and the column temperature at 90 °C. The elution gradient in the column was from 90 to 150 °C (10 °C/min), from 150 to 200 °C (5 °C/min), and from 200 to 230 °C (3 °C/min) in a total time of 34 min 48. Next, 1.0 μL aliquots of esterified extract were injected in a Split/Splitless injector. The chromatograms were recorded using the Galaxie Chromatography Data System program. The fatty acid results were quantified by integrating the areas of the methyl esters and are expressed in percentage by area.

Histological analysis in brain

Tissue samples from the brain (prefrontal cortex) were fixed in 10% phosphate-buffered formalin, embedded in paraffin, and sectioned into 4 μm slices. H&E staining was performed following the standard protocol for morphology assessment. The images of the slides were analysed in a crescent objective and photographed in total magnification of 40x optical microscope (Motic BA 200, Santa Monica, USA), evaluating the structural architecture of the brain.

Statistical analysis

A statistical power of 0.80 (80%) was obtained by estimating 20 females adult Wistar rats (five females per group), 20 male adult Wistar rats (five males per group) and 40 pups (ten pups per group). The minimally detectable effect size was 1.0, and the significance level was 0.05. The results for the analysis of weight, glucose tolerance test (GTT), lipid profile, murinometric parameters, adiposity index, brain fatty acids and fertility rate were expressed as mean ± SD (standard deviation) and analysed by Two-Way Analysis of variance (ANOVA) followed by Tukey's test. These data are presented as the means ± standard deviation. Reflex ontogeny, somatic growth and physical feature maturation were expressed as median values for the day (Min-Max) and analysed by the Mann-Whitney test. Data regarding consumption were analysed by One-Way ANOVA followed by Tukey's test. All behavioural tests were analysed by the Mann-Whitney test and were expressed as mean, median and 25% and 75% percentiles. A significance level of 5% was adopted for all analyses ($p \leq 0.05$). The results were analysed in the GraphPad Prism 8.0 statistical software program (version for evaluation). Principal Component Analysis (PCA), was employed as a multivariate analysis technique in the study. The methodology was applied to analyse the relationships between specific variables, contributing to a deeper understanding of the data and aiding in the interpretation of the research results.

Results

Effects of diet on reproductive performance in female rats and birth parameters

The HFD caused a reduction in the reproductive performance of rats (Table 1) by reducing the female fertility index ($p \leq 0.0001$), a reduction in the rate of live births ($p \leq 0.05$), and a lower litter weight compared to NFD dams ($p \leq 0.0001$).

Table 1

Effects of high-fat diet on the reproductive performance of female rats.

	Diets	
Parameters	**NFD**	**HFD**
Mated females/Pregnant females (n)	11/10	13/10
Female fertility index (%)	91.65 ± 8.78	77.38 ± 6.27*

Gestation index (%)	100	100
Litter size	10.50 ± 1.58	9.51 ± 2.41
Stillborn (n)	1	2
Live birth index (%)	91.43	84.76*
Litter weight (g)	54.10 ± 10.01	43.53 ± 4.02*
Birth weight (g)	5.70 ± 0.30	5.01 ± 0.27
Viability index (%)	100	96.25
Weaning index (%)	100	96.25

Data expressed as mean ± standard deviation. Analysis by t- test, p ≤0.05. * = different from NFD.NFD= normal-fat diet; HFD= high-fat diet.

Somatic growth

All offspring in which at least one of the breeders received the HFD diet (HF/NF, NF/HF and HF/HF) showed significant changes in relation to control regarding somatic characteristic, ($p \leq 0.05$) (Fig. 2). The HF/NF group presented greater length in relation to the other groups ($p \leq 0.0001$) from the 13th day (Fig. 2a), as well as the smallest tail length from the 7th day of life, and the NF/HF group from the 10th day onwards ($p \leq 0.0001$) (Fig. 2b).

The mediolateral length for the skull axes (Fig. 2c) in the NF/HF group presented a smaller dimension in relation to the other groups from the 4th day of life ($p \leq 0.001$). Moreover, the HF/NF group had a smaller anteroposterior axis in relation to the other groups from the 1st day after birth (Fig. 2d), while the NF/HF group also presented a smaller dimension from 7th day ($p \leq 0.001$).

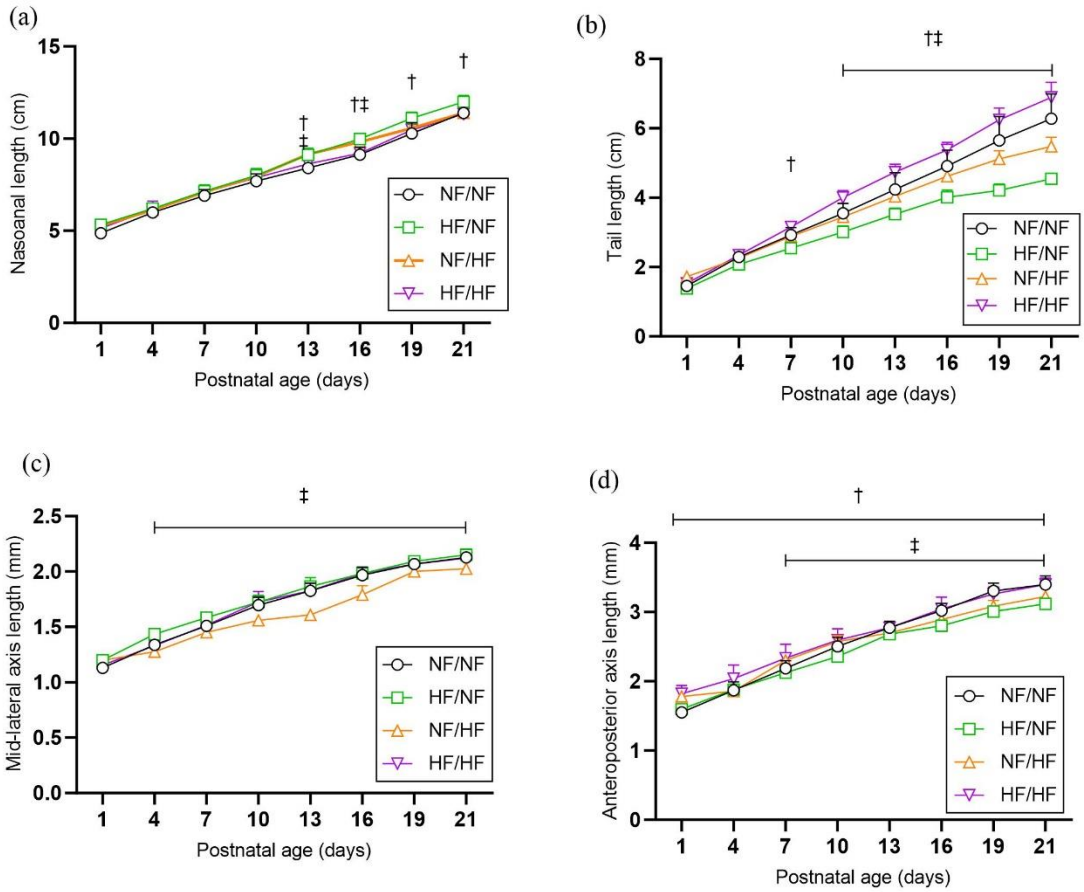

Fig. 2. Body nasoanal length (a) and tail length (b); medio-lateral (c) and anteroposterior (d) head axes of rat pups from breeders fed a high-fat diet (HFD) or fed a normal-fat diet (NFD). Data expressed as mean and standard deviation of the mean. †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; p≤0.05. Two-way ANOVA test, followed by Tukey post-test. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Physical feature maturation and reflex ontogenesis testing

The offspring of the breeders from the NF/HF and HF/HF groups showed a delay in some maturation features like in the appearance of epidermal hairs ($p \leq 0.01$), as well as a delay in the eruption of the lower incisors in the HF/NF group ($p \leq 0.01$); however, there was earlier auditory canal opening in the HF/HF group (in which both breeders received the HFD) in relation to the other groups (Table 2).

Likewise, reflex ontogeny of offspring in which at least one of the breeding parents were

fed HFD showed delay in most reflexes ($p \leq 0.05$) such as: righting in HF/NF and NF/HF groups, auditory startle in the NF/HF group, and palm grasp in the HF/NF group. Negative geotaxis appeared early in the HF/NF offspring when compared to the other groups ($p \leq 0.05$). The reflexes of cliff avoidance, free-fall righting and vibrissae placement were not altered by the breeder's diet (Table 3).

Table 2
Maturation age (days) for physical features of rat pups from breeders fed a high-fat diet (HFD) or a normal-fat diet.

Parameters	**Groups**			
	NF/NF	**HF/NF**	**NF/HF**	**HF/HF**
Ear unfolding	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)
Auditory conduit opening	12 (10-13)	12 (12-13)	13 (10-13)	11 (11-12) *†‡
Epidermic hair appearance	4 (4-5)	4 (4-5)	6 (6-7) *†	7 (6-7) *†
Eyes opening	14 (13-15)	14 (1315)	15 (13-15)	14 (13-15)
Eruption of superior incisors	9.5 (9-10)	9 (8-10)	8.5 (8-10)	9 (9-10)
Eruption of inferior incisors	7 (6-8)	9 (7-10) *	6 (6-7) †	6 (6-7) †

Data expressed as median values (minimum-maximum), N=15. Analysis by Kruskal-Wallis test. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; p≤0.05. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Table 3
Reflex maturation age (days) for physical features of rat pups from breeders fed a high-fat diet (HFD) or a normal-fat diet.

	Groups

Parameters	NF/NF	HF/NF	NF/HF	HF/HF
Palm grasp	5 (4-6)	11 (6-13) *	4.5 (2-9) †	6 (3-6) †
Righting	4 (3-6)	11 (10-11) *	7.5 (7-12) *	4 (3-6) †‡
Vibrissae placing	9 (7-11)	9 (6-10)	6 (5-11)	9 (5-11)
Cliff avoidance	5.5 (4-7)	4 (3-6)	6 (5-6)	6 (4-7)
Negative geotaxis	18 (16-19)	17 (16-17)	19 (16-20) †	18 (16-19) †
Auditory startle	12 (11-13)	12 (12-13)	12 (12-14)	11 (10-11) *†‡
Free-fall righting	13.5 (11-14)	13 (11-15)	14 (11-15)	12 (11-14)

Data expressed as median values (minimum-maximum), N=15. Analysis by Kruskal-Wallis test. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; p≤0.05. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Assessment of anxiety-like behaviour in offspring rats

The offspring in which both breeders received the HFD diet (HF/HF) showed higher defecation rates rats (Fig. 3b), rearing (Fig. 3c), and longer freezing (Fig. 3d) and grooming times (Fig. 3e) ($p \leq 0.05$) in the open field test for the anxiety behaviour in the offspring. The rats in which only male breeders or only female breeders receiving the HFD diet (HF/NF and NF/HF, respectively) had a higher ambulation number (Fig 3a) compared with the NF/NF group ($p \leq 0.05$).

The offspring from mothers who ingested the HFD diet (NF/HF) had less time in open arms in the elevated plus maze test compared with the HF/NF and HF/HF groups; and the HF/HF group had less time in the open arms compared to the HF/NF group (Fig 3i). The NF/HF group presented the longest time in the closed arms, (Fig 3h) in comparison to the NF/NF group ($p \leq 0.05$). The offspring where both parents received the HFD diet (HF/HF) had a greater number of entries in the centre of the apparatus (Fig. 3k) ($p \leq 0.05$).

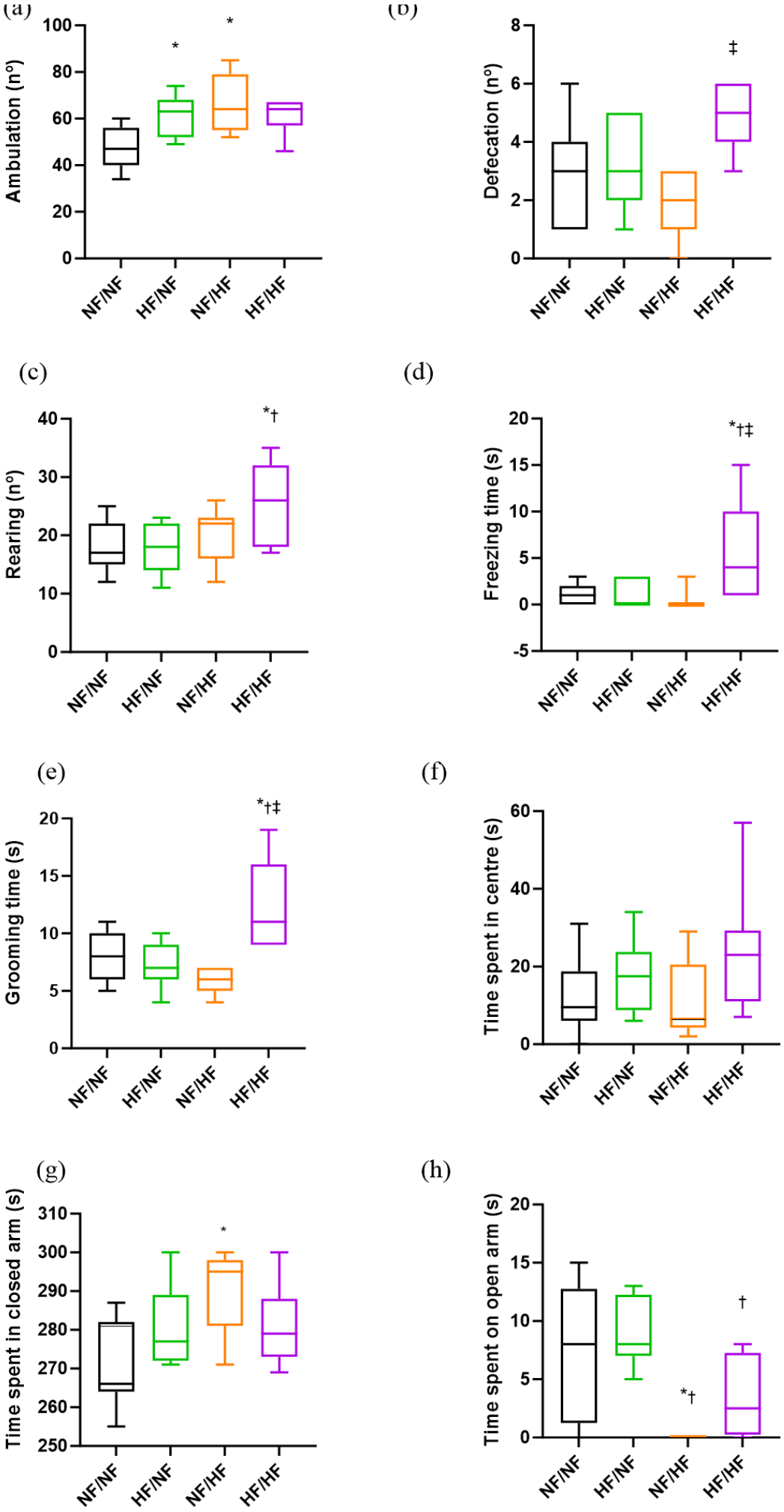
(a)
Ambulation (n°)
100
80
60
40
20
0
*
*
NF/NF
HF/NF
NF/HF
HF/HF
(b)
Defecation (n°)
8
6
4
2
0
‡
NF/NF
HF/NF
NF/HF
HF/HF
(c)
Rearing (n°)
40
30
20
10
0
*†
NF/NF
HF/NF
NF/HF
HF/HF
(d)
Freezing time (s)
20
15
10
5
0
-5
*†‡
NF/NF
HF/NF
NF/HF
HF/HF
(e)
Grooming time (s)
20
15
10
5
0
*†‡
NF/NF
HF/NF
NF/HF
HF/HF
(f)
Time spent in centre (s)
60
40
20
0
NF/NF
HF/NF
NF/HF
HF/HF
(g)
Time spent in closed arm (s)
310
300
290
280
270
260
250
*
NF/NF
HF/NF
NF/HF
HF/HF
(h)
Time spent on open arm (s)
20
15
10
5
0
*†
†
NF/NF
HF/NF
NF/HF
HF/HF

Fig. 3. Assessment of anxiety-like behaviour in 30-day-old rat pups from breeders fed a high-fat diet (HFD) or a normal-fat diet (NFD). Data expressed as mean and standard deviation of the mean. *significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; p≤0.05. One-way ANOVA test, followed by Tukey post-test. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Food intake and body weight

The weight of the offspring on the day of birth was similar among the groups, but all offspring from the HFD parents had lower weight at 21 days old in relation to the NFD parents ($p \leq 0.001$) (Fig.4a). All offspring from HFD groups had lower weight at 30 days old compared to the NFD ($p \leq 0.001$), but the HF/NF group had lower weight compared to the NF/HF and HF/HF groups ($p \leq 0.0001$) (Fig.4a). Furthermore, the offspring in which both parents consumed the HFD diet (HF/HF group) had a higher feed intake than the other groups ($p \leq 0.0001$) during the period from weaning (21 days old) to euthanasia (30 days old) (Fig.4b).

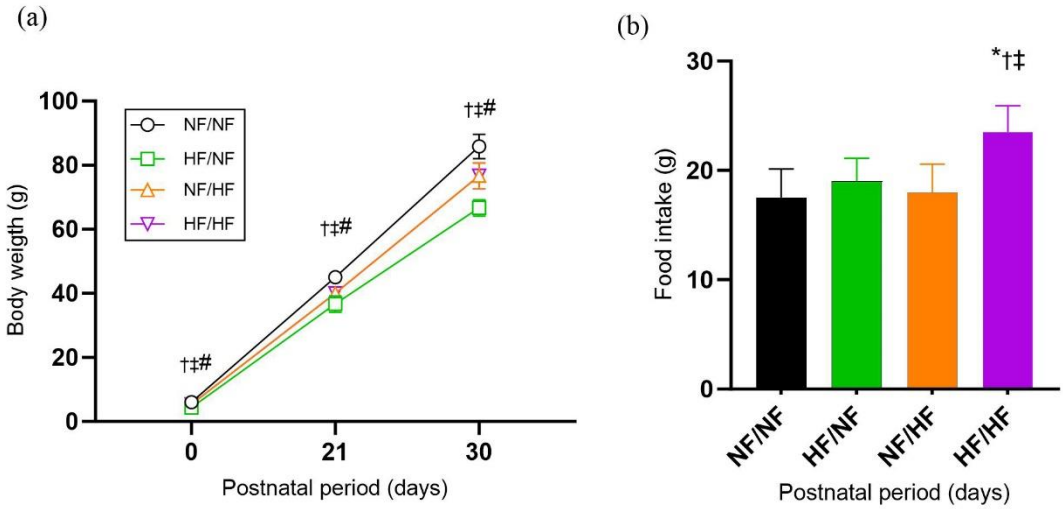

Fig 4. Body weight and food intake of rat pups from breeders fed a normal-fat diet (NFD) or a high-fat diet (HFD). Data expressed as mean and standard deviation of the mean. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; #significant difference compared to HF/HF $p \leq 0.05$. Two-way ANOVA test, followed by Tukey post-test. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD;

NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Somatic parameters and organs and brain weight

There was no difference between the groups regarding the somatic parameters of the 30-day-old pups (Table 4). The HF/NF and NF/HF groups had lower relative brain weight ($p \leq 0.05$); while the HF/HF offspring in which both parents received the high fat diet and the HF/NF offspring in which only the male sires received the high fat diet had a higher adiposity index compared to the NF/HF and NF/NF groups ($p \leq 0.05$).

Table 4. Somatic parameters and normalized weight of the organs of offspring at 30 days old.

Variables	**Groups**			
Offspring 30d	**NF/NF (n=10)**	**HF/NF (n=10)**	**NF/HF (n=10)**	**HF/HF (n=10)**
Murinometry				
Length (cm)	17.87±0.83	15.25±0.27	15.81±0.46	16.37±0.52
BMI (g/cm2)	0.45 ±0.03	0.43±0.02	0.39±0.04	0.48±0.03
Lee's index	0.25 ±0.02	0.28±0.02	0.24±0.02	0.29±0.03
TC (cm)	11.50±0.53	10.0±0.65	10.06±0.73	10.87±0.64
AC (cm)	11.62±0.74	11.50±0.60	11.56±0.82	14.0±0.53
Adiposity index (%)	0.70±0.20	1.03±0.29*‡	0.53±0.04†	1.11±0.04*‡
Organ weight (g)				
Brain	1.86±0.50	1.39±0.60*	1.14±0.01*†	1.51±0.06*†‡

Data expressed as mean ± standard deviation, two-way ANOVA test followed by the Bonferroni post-test. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; $p \leq 0.05$. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Assessment of lipid and glycaemic parameters of offspring

The HFD offered to the breeders caused changes in glycaemia levels in all offspring in which at least one of the parents ingested this diet, especially in the NF/HF group which had levels

well below the control group (NF/NF) at all times of blood glucose checks (Fig 5a) ($p \leq 0.05$). The HFD also caused an increase in TC levels in all experimental groups (HF/NF, NF/HF and HF/HF) in comparison to NF/NF (Fig 5c) ($p \leq 0.05$), an increase in LDL in offspring in the NF/HF and HF/HF groups ($p \leq 0.05$), and a decrease in HDL in the HF/NF, NF/HF and HF/HF compared to the NF/NF group ($p \leq 0.05$).

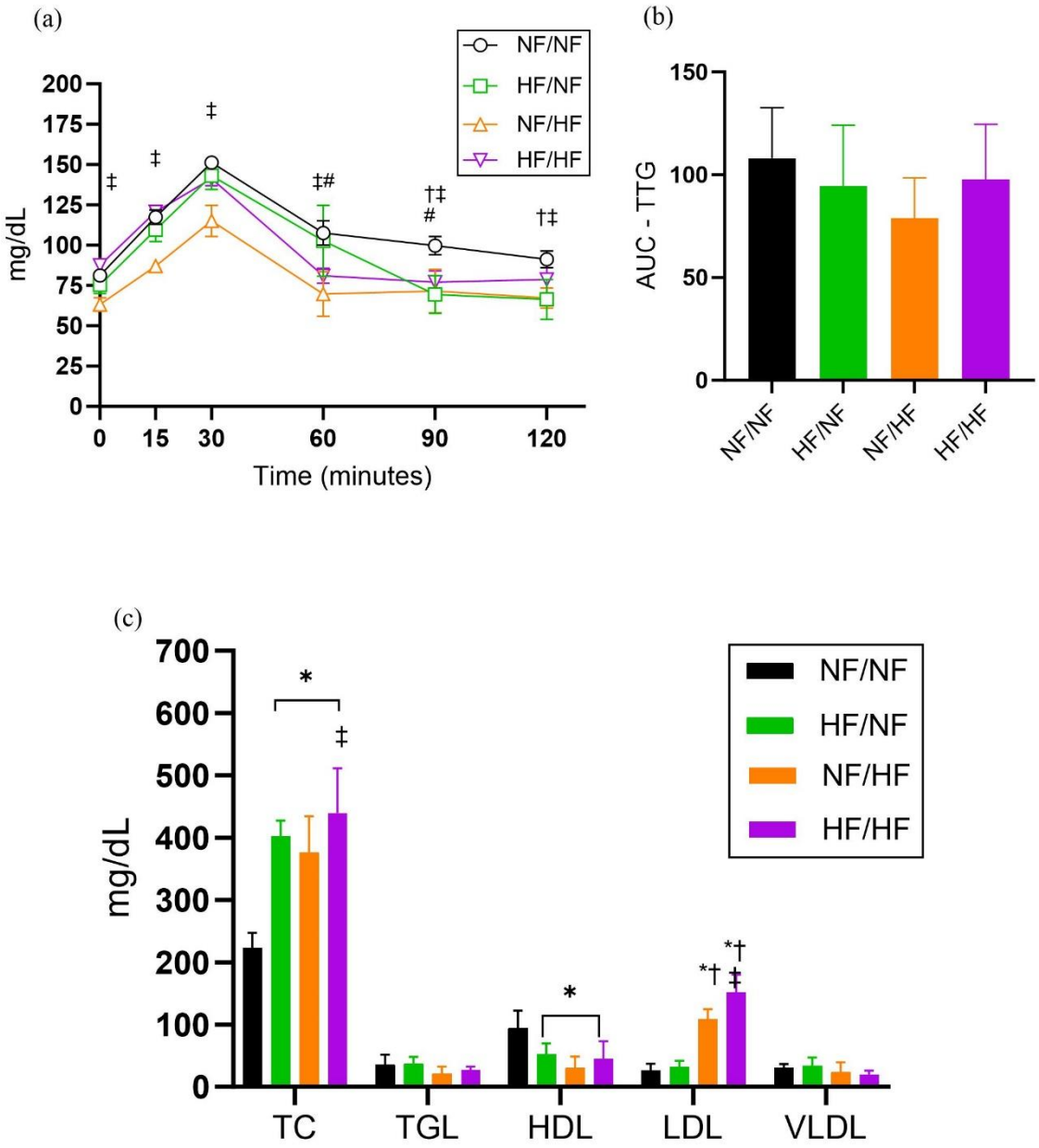

Fig.5. Lipid profile and glucose tolerance test in rat pups at 30 days old from breeders fed a high-fat diet (HFD) or a normal-fat diet (NFD). *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; $p \leq 0.05$. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Composition of fatty acids in brain of offspring

The brains of offspring in which both parents were fed the HFD (HF/HF group) showed high levels of saturated fatty acids (caprylic and capric) ($p \leq 0.0001$). Lauric acid was found in similar amounts in the NF/NF and NF/HF groups ($p \leq 0.0001$). Myristic acid was only quantified in the control group (NF/NF), while pentadecanoic and margaric acids were only quantified in the HF/NF group. High levels of nervonic acid and reduced levels of linoleic acid were observed for mono and polyunsaturated acids, respectively, in the HF/HF group in relation to the others ($p \leq 0.0001$) (Table 5).

Table 5. Composition of fatty acids in offspring brains at 30 days old.

	Groups			
Fatty Acids (FA) (g 100g $^{-1}$)	**NF/NF**	**HF/NF**	**NF/HF**	**HF/HF**
Saturated FA (SFA)				
Caprylic acid C8:0	2.56 ± 0.11	n.d.	3.09 ± 0.11	16.79 ± 0.22*‡
Capric acid C10:0	2.68 ± 0.16	n.d.	2.87 ± 0.13	15.68 ± 0.33*‡
Lauric acid C12:0	2.24 ± 0.11	n.d.	2.42 ± 0.11	n.d.
Myristic acid C14:0	2.60 ± 0.16	n.d.	n.d.	n.d.
Pentadecanoic acid C15:0	n.d.	2.05 ± 0.11	n.d.	n.d.
Margaric acid C17:0	n.d.	2.63 ± 0.22	n.d.	
Total	**10.08**	**4.67**	**8.39**	**32.48**
Monounsaturated FA (MUFA)				
Nervonic acid C24:1 ω9	3.54 ± 0.22	n.d.	n.d.	20.21 ± 0.22*
Total	**3.54**	**n.d.**	**n.d.**	**20.21**

Polyunsaturated FA (PUFA)				
Linoleic acid C18:2 ω6	86.94 ± 0.05	95.33 ± 0.33	91.42 ± 0.55	48.11 ± 0.55*†‡
Total	**86.94**	**95.33**	**91.42**	**48.11**

Data expressed as mean ± standard deviation, ANOVA two-way test followed by the Bonferroni post-test. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; $p \leq 0.05$. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Brain histology

The parenchyma of the central nervous tissue (prefrontal cortex) has neurons with a regular size and distribution of both cell bodies and stroma compatible with normality in the NF/NF group (Fig. 6a) and HF/NF group (Fig. 6b). On the other hand, there is a focal reduction in the size of neuronal cell bodies in the cortex of the NF/HF group (Fig. 6c), when compared to the NF/NF or HF/NF groups (black arrow). Finally, there is an intense and diffuse reduction in the size of neuronal cell bodies in the cortex of the HF/HF group (Fig. 6d) when compared to all other experimental conditions (black arrows).

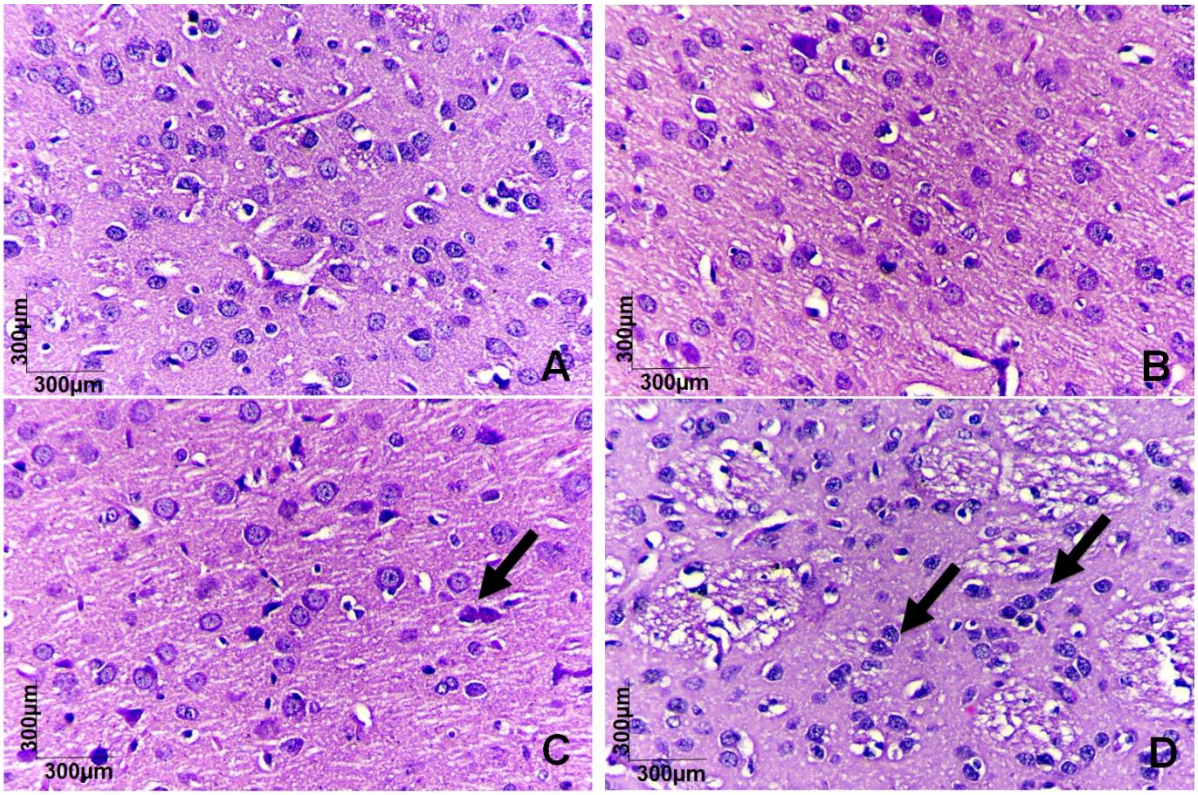

Fig 6. Histology in the brain (cortex) in rat pups at 30 days old from breeders fed a high-fat diet (HFD) or a normal-fat diet (NFD). (A) NF/NF = both breeding rats fed a normal-fat diet (NFD); (B) HF/NF = breeding males fed a HFD and females fed a NFD; (C) NF/HF = breeding males fed a NFD and females fed a HFD; and (D) HF/HF group = both breeding rats fed a HFD.

The principal components analysis of the offspring revealed that the groups from parents fed a high fat diet presented results correlated with anxiety-like behaviour, dyslipidaemia, and saturated fatty acid, being verified in a potentiated way in the HF/HF group (Fig. 7). Principal components 1 and 2 together account for 36.15% and 22.64%, respectively.

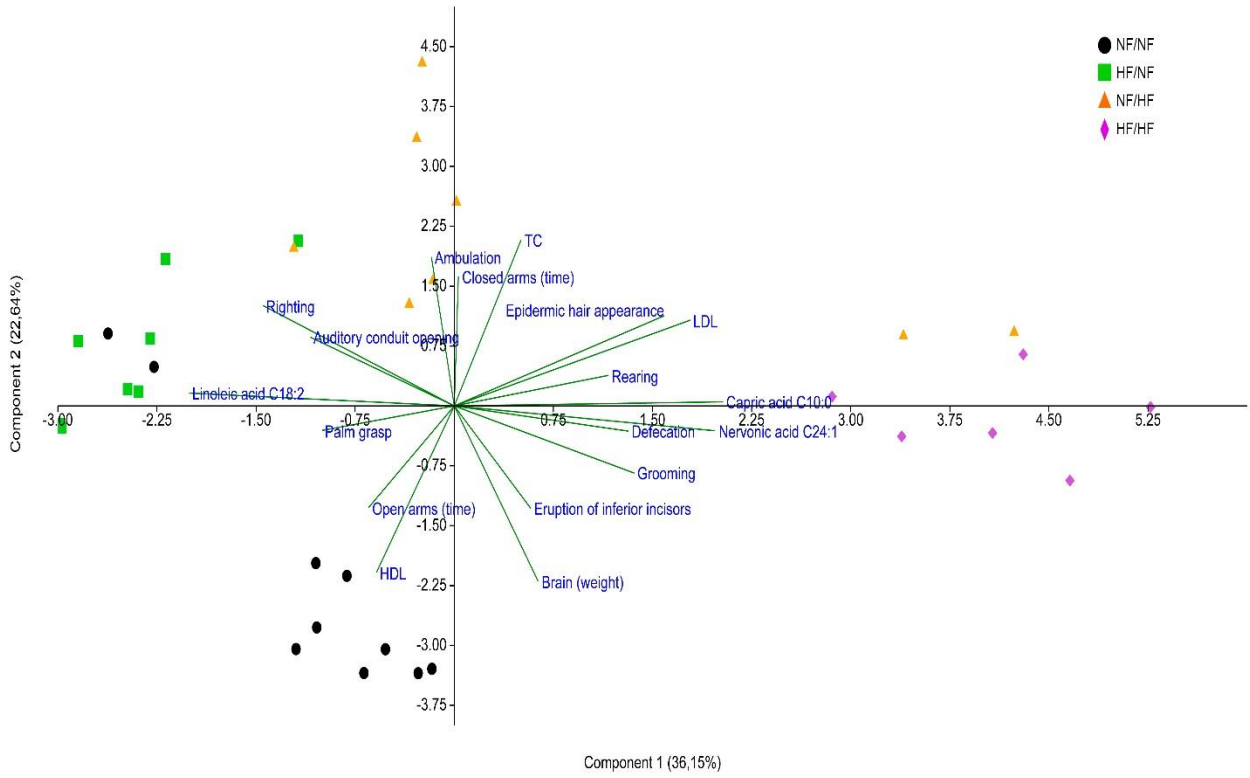

Fig.7. Principal component analysis biplot of parental diets and biological parameters of offspring. NF/NF= males and females breeding rats fed a normal-fat; HF/NF = breeding males fed a high-fat diet and females fed a normal-fat; NF/HF= breeding males fed a normal-fat and females fed a high-fat diet and HF/HF= males and females breeding rats fed a high-fat diet.

Discussion

In this study we have demonstrated the different repercussions of a parental diet rich in cholesterol, saturated and trans fatty acids on the reproductive performance of females; weight gain, lipid and glucose parameters, somatic and reflex development of offspring during lactation, as well as on the anxious-like behaviour, somatic parameters, and cortex histology of the offspring at 30 days of age. For decades, studies have focused on the effects of maternal diet on these parameters 32,49,50, however, there is increasing evidence of the repercussions of the paternal diet on the offspring 24,27,51–53, such as anxiety-like behaviour, as seen in our study, as well as damage to cognition and memory, dysbiosis,

glucose intolerance, cardiovascular disease, obesity, and decreased fertility in male offspring (DIMOFSKI *et al.*, 2021; KORGAN *et al.*, 2022a; RAAD *et al.*, 2021; SERTORIO *et al.*, 2022; WATKINS; SINCLAIR, 2014; ZHOU *et al.*, 2018).

Our findings regarding poor reproductive performance from HFD-fed females was also seen in a study with female rats exposed to a high-fat diet (45% fat) for 6 weeks which showed reduced reproductive capacity of such females56. Other studies with a longer high-fat feeding time (9 weeks) have also shown that such a feeding pattern can cause a reduction in the reproductive capacity of rats57,58. Such results may be related to the fact that hypercaloric diets (i.e. high fat diets) are associated with a decrease in the quantity and quality of oocytes as one of the consequences of inflammation caused by excess free fatty acids in the body (GAMBINERI *et al.*, 2019; MAREI *et al.*, 2020; RAVISANKAR *et al.*, 2021; WU *et al.*, 2015). Excessive consumption of saturated fatty acids cause changes in the lipid composition of the endoplasmic reticulum membrane, compromising its capacity to retain calcium, which in turn alters cytoplasmic homeostasis, leading to the induction of apoptotic pathways in oocytes (CHEN *et al.*, 2019; FU *et al.*, 2011). Additionally, the changes in metabolic levels caused by HFD, such as hyperinsulinemia, lead to poor follicular vascularization and an increase in anti-Mullerian hormone (AMH), making the follicles more resistant to the FSH action, resulting in inhibition of follicular maturation (DEWAILLY *et al.*, 2020; DI BERARDINO *et al.*, 2022). The high-fat diet used in this experiment was able to change the weight of the offspring from the genitors who fed on it32.

The low weight throughout lactation and at 30 days old of the HF/HF, HF/NF and NF/HF groups may be related to the inflammatory process, in which inflammatory cytokines are able to cross the placenta, resulting in serious consequences for intrauterine life, such as foetal, neonatal, and foetal growth in postnatal development 67–69. We can also attribute the low weight gain to a decrease in sucking related to changes in neuronal systems responsible for postnatal development, bringing harm to the suction stimulus of these neonates, reflecting on their low weight throughout the lactation period67,70,71. On the other hand, this same inflammatory process has the power to alter the neuroendocrine control of satiety, causing an increase in food consumption, as seen in pups in which both parents (male and female breeding) were fed a high-fat diet 70.

In addition, the offspring from HFD parents (HF/NF, NF/HF and HF/HF) presented altered development in the somatic parameters in the first days of life, such as reduced cranial axes and body length. Recent experimental studies have demonstrated the influence of prenatal and early postnatal maternal nutrition on the body and cranial growth of the offspring; in this context, the offspring of dams fed a high-fat had reduced cranial axes and reduced body length 72–74. There are no studies in the literature that show the relation between paternal diet and alteration in the dimensioning of cranial axes, but Lecomte *et al.*75 verified that a paternal obesity-inducing diet in Sprague-Dawley rats could reduce the production of hormones related to growth in the offspring, such as somatomedin C (IGF-1) and the growth hormone (GH), indicating a possibility of cranial reduction in these animals.

The alterations in the mammary glands and damage in the lactogenesis caused by the high-fat diet from the inflammatory process is one of the causes of the cranial reduction in offspring caused by poor nutrition in dams76. The accumulation of lipids in the secretory cells prevents the full supply of breast milk, causing the supply of proteins such as beta casein and beta lactalbumin to be impaired 77, as well as the HFD diet itself altering the production of such proteins, interfering in the reduction percentage of protein in breast milk78,79.

Our study was able to show that parental feeding was able to change some metabolic parameters such as the lipid profile, in which the offspring in which at least one of the breeders was fed with HFD had an increase in TC and LDL levels and a reduction in HDL, thus configuring dyslipidaemia in offspring(MENDELSON *et al.*, 2016; PINHEIRO *et al.*, 2019), which can lead to diseases such as arterial hypertension, atherosclerosis and stroke (CVA) (CHIU; WILLIAMS; KRAUSS, 2017; DE ARAÚJO *et al.*, 2020; GUIMARÃES *et al.*, 2017), as well as at the metabolic level, such as insulin resistance and type 2 diabetes mellitus(AKHAPHONG *et al.*, 2022; WADA *et al.*, 2020). Our results did not show alterations in the glycaemia of the offspring in the oral glucose tolerance test, although the literature demonstrates that the offspring of mothers who were fed a high-fat diet showed high glycaemia in the long-term related to the inflammatory process caused by the high consumption of cholesterol, acids saturated and trans fatty acids (AKHAPHONG *et al.*, 2022; CHIU; WILLIAMS; KRAUSS, 2017; PINHEIRO *et al.*, 2019).

Our results regarding the somatic parameters and reflex ontogeny of the offspring corroborate what Silva *et al.*74 found, namely that the maternal high-fat diet can produce different effects on the development of the offspring, anticipating some reflexes and delaying others. This may be because HFD itself can provide other fatty acids besides saturated and trans-fatty acids, such as w-3 and w-6 fatty acids, as we quantified in the diets used in this experiment. Our results showed a higher concentration of linoleic fatty acid in the brains of NF/NF, HF/NF and NF/HF pups compared to the HF/HF group, which aid in the neuronal myelination process, causing some reflexes to manifest quickly in these groups such as palmar pressure, negative geotaxis, and cliff avoidance (LABROUSSE *et al.*, 2018; QUEIROZ *et al.*, 2019), which was noticed in the NF/HF and HF/NF groups that presented high concentrations of this fatty acid in the brain and had some reflexes developed in advance.

On the other hand, the HF diet itself can provide lipotoxicity through the lipid peroxidation process, activating pro-inflammatory cascades and oxidative stress, thereby affecting the neurodevelopment of the offspring. Moreover, the pro-inflammatory saturated fatty acids present in HFD such as capric and caprylic fatty acids which are predisposing factors to this neuronal delay 74,77,86, as seen in the HF/HF group.

Studies show that nervonic acid is part of the group of important fatty acids in the brain myelination process, especially in the early stages of brain development; however, high levels such as those presented in our study showed the relationship between these brain levels of nervonic acid and psychotic diseases, such as depression. Nevertheless, other studies do not corroborate these results, as they present data which show an inverse relationship of low nervonic acid levels with depression and Alzheimer's disease, for example, justified by the demyelination process that occurred with the decrease in brain concentration of nervonic acid (KAGEYAMA *et al.*, 2018, 2021; LI *et al.*, 2019b).

Our study showed that the consumption of high-fat diet by both (the breeding fathers and mothers) worsened some typical parameters of anxious-like behaviour in the offspring in the open field and elevated plus maze tests. The offspring of the HF/HF group had an increase in the number of faecal boluses, rearing and longer grooming time in the open field test 39,41. Anxious animals tend to defecate and groom themselves more often 90,91. In fact,

the quality of the consumed fats, low consumption of polyunsaturated fatty acids and the high consumption of saturated and trans fatty acids is a preponderant factor for developing anxiety 92, because the low ingestion of unsaturated as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can cause alterations in neurohormone production, such as gamma-aminobutyric acid (GABA), dopamine and serotonin, affecting brain function and may lead to anxiety-like behaviour 50,86,93.

HFD diets alter brain metabolism in both parents and offspring, which at the cortical level, leads to a reduction in the number of energy-related molecules such as creatine/phosphocreatine and lactate due to oxidative stress, decreased mitochondrial oxidative capacity, and reduced brain-derived neurotrophic factor (BDNF) in the cerebral cortex, leading to neuronal atrophy which was seen in the NF/HF and HF/HF offspring 94. This neuronal loss also results in a reduction in the production of neurotransmitters, such as GABA, inducing an anxious/depressive type of behaviour seen in both humans and in experimental models, resulting in a negative impact on neuronal plasticity and low serotonin (5-HTP) levels, as seen in female rats fed HFD 95,96.

Our study presents some limitations which may be evaluated in future studies for better understanding of the repercussions of the parental HFD diet on the offspring, such as: evaluation of key enzymes in lipid metabolism and of genes affected by mutations in spermatozoa and parental eggs, as well as the analysis of inflammatory markers in brain tissues and sexual organs of parents and offspring.

In summary, the present study demonstrated that the intake of a high-fat diet during preconception by fathers and/or during pregnancy/lactation by mothers compromises neurobehavioral development, resulting in anxiety-like behaviour, in addition to causing a reduction in in the size of neuronal cell bodies and modification in the composition of brain fatty acids of the offspring. At the metabolic level, it was also verified that when both parents (paternal and maternal) ingest the same high-fat diet, there is a potentiation of changes in lipid metabolism, causing hyperphagia, weight gain and increased body adiposity in the offspring, which can cause the genesis of several non-transmissible chronic diseases. However, further studies are needed to better elucidate the neurological, metabolic, and epigenetic mechanisms involved in this process in the offspring in the short-term.

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Conflict of Interest

The authors declare no competing interests.

Authorship

R.O.P., J.K.B.S. and JSA: Conceptualization; Data curation; Methodology; Visualization; Investigation, Writing- Original draft preparation; Editing and Writing- Reviewing.. R.O.P, A.C.A.V., M.L.R.B. G.A.C.; M.B.S.B, A.N.V.A., A.M.T.M.C., and A.F.A.: Validation; Data curation; Formal analysis. JSA: Funding acquisition, Project administration and Supervision.

Supplementary material

For supplementary material/s referred to in this article, please visit: https://doi.org/

Table S1 - Ingredients, macronutrients, energy value and fatty and organic acids of normal- and high-fat diets consumed by male and female breeding and by offspring up to 30 days of age.

	Diets	
Ingredients (g/100 g)	**NFD**	**HFD**

Maize starch	39.75	33.09
Dextrinized Starch	13.20	15.50
Sucrose	10.00	6.00
Fibre	5.00	5.00
Casein	20.00	19.86
L-cystine	0.30	0.30
Choline bitartrate	0.25	0.25
Mineral Mix AIN 93G	3.50	3.50
Vitamin Mix AIN 93	1.00	1.00
t-BHQ	0.14	0.14
Soybean oil	7.00	3.00
Lard	-	6.00
Non-hydrolyzed vegetable fat	-	5.00
Cholic Acid	-	0.50
Cholesterol	-	1.00
Total energy value (kcal/g)	3.95	4.34
Carbohydrates (kcal %)	63.78	51.52
Proteins (kcal %)	20.26	18.74
Lipids (kcal %)	15.96	31.85
Fatty Acids (FA) (g/100g)		
Octanoic acid C8:0	0.05±≤0.01	n.d.
Decanoic acid C10:0	0.11±0.03	0.08±≤0.01
Dodecanoic acid C12:0	0.17±0.03	0.13±≤0.01
Pentadecanoic acid C15:0	0.08±0.01	0.31±0.01*
Hexadecanoic acid C16:0 (Palmitic)	10.03±0.04	27.95±0.03*
14-Methyl hexadecanoic acid C17:0	n.d.	0.30±0.01
Heptadecanoic acid C17:0 (Margaric)	0.11±0.03	1.04±0.01*
Stearate acid C18:0 (Stearic)	5.86±0.30	40.69±0.09*

Nonadecanoic acid C19:0	n.d.	0.19±0.02*
Eicosanoic acid C20:0 (Arachidic)	0.49±≤0.01	0.60±0.01*
18-Methylnonadecanoate C21:0	n.d.	0.76±≤0.01
Docosanoic acid C22:0 (Benhenic)	0.47±0.02	0.24±0.05*
Tetracosanoic acid C24:0 (Lignoceric)	0.16±0.03	n.d.
Total of saturated fatty acids (SFA)	**17.53**	**72.29**
Trans-9-Hexadecenoic acid C16:1 t9	0.34±0.02	2.03±0.02*
Methyl hexadec-9-enoate C17:1	0.15±0.06	n.d.
Trans-11-Octadecenoic acid C18:1 t11 (Vaccenic)	n.d.	0.05±≤0.01
Octadecenoic acid C18:1 ω 9 (Oleic)	20.25±0.41	2.27±0.06*
Cis-11-Octadecenoic acid (*cis* Vaccenic)	n.d.	0.05±≤0.01
Cis-13-Eicosenoic acid C20:1 ω7	0.21±0.01	0.35±0.01*
Total of monounsaturated fatty acids (MUFA)	**21.25**	**4.75**
Cis-9,12-Octadecadienoic acid C18:2 ω6c (Linoleic)	54.52±0.44	n.d.
Trans-9,12-Octadecadienoic acid C18:2 ω6t	n.d.	20.85±0.23
9,12,15-Octadecatrienoic acid C18:3 ω3 (Linolenic)	6.70±0.04	1.69±0.06*
Cis-11,14-Eicosadienoic acid C20:2 ω6 (Dihomolinoleic)	n.d.	0.30±0.02
5,8,11,14-Eicosatetraenoic acid C20:4 ω6 (Arachidonic)	n.d.	0.12±0.01
Total of polyunsaturated fatty acids (PUFA)	**61.22**	**22.96**
Organic acids (µmol/g)		
Citric	0.68±0.04	0.73±0.05
Malic	2.52±0.05	2.04±0.02*
Tartaric	0.80±0.03	0.88±0.01*
Total organic acids (µmol/g)	**4.00**	**3.65**

NFD= normal-fat diet, AIN-93G diet proposed by American Institute of Nutrition (AIN) (Reeves *et al.*, 1993); HFD= high-fat diet (Rhoster Industry and Commerce Ltda); t-BHQ: tert-butylhydroquinone. n.d.= not detected.

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ARTIGO II

HIGH-FAT PARENTAL DIET ALTERS SOMATIC, BIOCHEMICAL, NEUROBEHAVIOURAL AND GUT HEALTH PARAMETERS IN ADULT OFFSPRING

(**Submetido ao periódico:** Journal of Affective Disorders. **Fator de impacto:** 6.6 - **Qualis**: A1)**.**

High-fat parental diet alters somatic, biochemical, neurobehavioural and gut health parameters in adult offspring

ABSTRACT

Background: Foetal programming refers to the process by which a stimulus, occurring in the critical period of development, has permanent effects on the structure and functions of the organism, due to plasticity and sensitivity to changes in the environment. The present study aims to evaluate the influence of parental high-fat diet (maternal and paternal) on the somatic, neurobehavioral, biochemical, and gut health parameters in adult rat offspring. *Methods*: Breeding males and females were fed a normal-fat (NFD) or high-fat (HFD) diet and their male offspring were divided into 4 groups according to the dietary pattern. The offspring in which both HFD breeders showed hyperphagia, body weight gain, development of anxious-like behaviour with increased defecation, grooming time in open field, longer time in closed arms in plus maze, decrease in *Lactobacillus* and *Bifidobacterium* counts,

increase Bacteroides and *Enterobacteriaceae* counts, high levels of TC and LDL and reduction of HDL. HF/HF offspring showed loss of epithelial lining and villi atrophy in the intestine. HF/NF and HF/HF pups showed an intense area marking for NF-kB. Parental HFD can potentiate the harmful effect on some parameters related to gut-brain axis, and biochemical in the offspring of rats in the long term.

Keywords: anxiety, faecal bacteria, lipid profile, NF-kB, organic acids

Abbreviations: AC: abdominal circumference; AIN: American Institute of Nutrition; ANOVA: analysis of variance; ARC: arcuate nucleus; BMI: body mass index; CCK: cholecystokinin; CEUA: Ethics Committee on Animal Use; CFU: colony forming units; CT: circumference thoracic; DNA: deoxyribonucleic acid; DOHaD: developmental origins of health and disease; FA: Fatty Acids; GTT: glucose tolerance teste; HDL: high-density lipoprotein; HE: haematoxylin and eosin; HF/HF: males and females breeding rats fed a high-fat diet; HF/NF: breeding males fed a high-fat diet and females fed a normal-fat diet; HFD: high fat diet; HPLC: high-performance liquid chromatography; IL-6: interleukin 6; ITT: insulin tolerance teste; LPL: lipoprotein lipase; LPS: lipopolysaccharide; MUFA: monounsaturated fatty acids; NF/HF: breeding males fed a normal-fat and females fed a high-fat diet; NF-kB: nuclear factor kappa B; NF/NF: males and females breeding rats fed a normal-fat diet; NFD: normal fat diet; NPY: Neuropeptide Y; PUFA: polyunsaturated fatty acids; SCFA: short chain fatty acids; SD: standard deviation; SFA: saturated fatty acids; TC: total cholesterol; TF: total body fat; TG: triglycerides; TLR: toll like receptor; TNF-alpha: tumoral necrose factor alpha; TW: total body weight; VLDL: very low-density lipoprotein; 5-HT: 5-hydroxytryptamine.

1. Introduction

Modern life associate to unhealthy habits have been brought negative consequences to human health that can impact future generations. According to the Developmental Origins of Health and Disease (DOHaD), adverse situations in early life during in embryonic development can program the pattern of health and disease throughout the life of the offspring, such reorganization is also known as foetal programming (Barker 1986). Among these, maternal high-fat diets rich in cholesterol, saturated fatty acids, omega-6 and trans polyunsaturated fatty acids have impacted metabolic changes such as insulin resistance, diabetes, dyslipidaemia, hypertension, non-fatty liver disease, obesity, and changes in faecal bacteria and health intestinal tract of the offspring, even in the long term (Akhaphong *et al.*, 2022; Guimarães *et al.*, 2017; Liu *et al.*, 2022; Pinheiro *et al.*, 2019; Wada *et al.*, 2020).

Previous studies report that high-fat maternal diet causes intestinal dysbiosis by increasing Firmicutes to the detriment of Bacteroidetes decrease, which in turn can cause systemic inflammation in the offspring's body associated with an increase in circulating endotoxin, lipopolysaccharide (LPS) levels (Wang *et al.*, 2021; Xie *et al.*, 2018a).

This chronic systemic inflammation, as well as changes in the profile of metabolites such as organic acids caused by intestinal dysbiosis, has also been related to neurobehavioural changes in adult individuals, such as anxiety and depressive-like behaviours, Alzheimer's disease, and attention deficit hyperactivity disorder (Bruce-Keller *et al.* 2017; Cavalcanti *et al.* 2021; da Silva *et al.* 2021).

Recent studies have demonstrated that these SCFAs can cross the blood-brain barrier and interact with specific receptors in the central nervous system, influencing neuronal function, brain inflammation, neurotransmitter synthesis, and blood-brain barrier integrity. In addition to the production of organic acids, the intestinal bacteria themselves play an essential role in modulating neurobehaviour. These bacteria can influence the synthesis and release of neurotransmitters, such as serotonin, which play a crucial role in mood and behaviour regulation (Silva *et al.*, 2020; Soares *et al.*, 2021; Vieira *et al.*, 2023). Such relation is explained by the gut-brain axis that allows a bidirectional communication between these organs through different metabolic pathways and nerve fibres (Degroote *et al.*, 2016; P. Zhang *et al.*, 2019).

Furthermore, several inflammatory mechanisms may be involved in the association between high-fat diet intake and behavioural damage. Studies have shown that prolonged intake of high amounts of saturated fats can lead to dysbiosis, promoting the growth of potentially pathogenic bacteria such as those of the Clostridium genus, which produce SCFAs such as butyric acid. Prolonged activation of NF-kB in the central nervous system can precipitate a chronic inflammatory state, negatively affecting neuronal homeostasis and contributing to neurobehavioral disorders such as anxiety and depression (Santos *et al.* 2020; Vieira *et al.* 2023; Silva *et al.* 2021).

In parallel, some studies show that fathers fed diets rich in saturated fatty and trans fatty acids also influence the emergence of epigenetic changes capable of resulting in the occurrence of insulin resistance, dyslipidaemia, obesity, decreased sperm number, low

fertility in adult offspring and even changes in kidney function in the offspring of adult rats (AIZAWA; TOCHIHARA; YAMAMURO, 2022; CHOWDHURY *et al.*, 2016; OSHIO *et al.*, 2020).

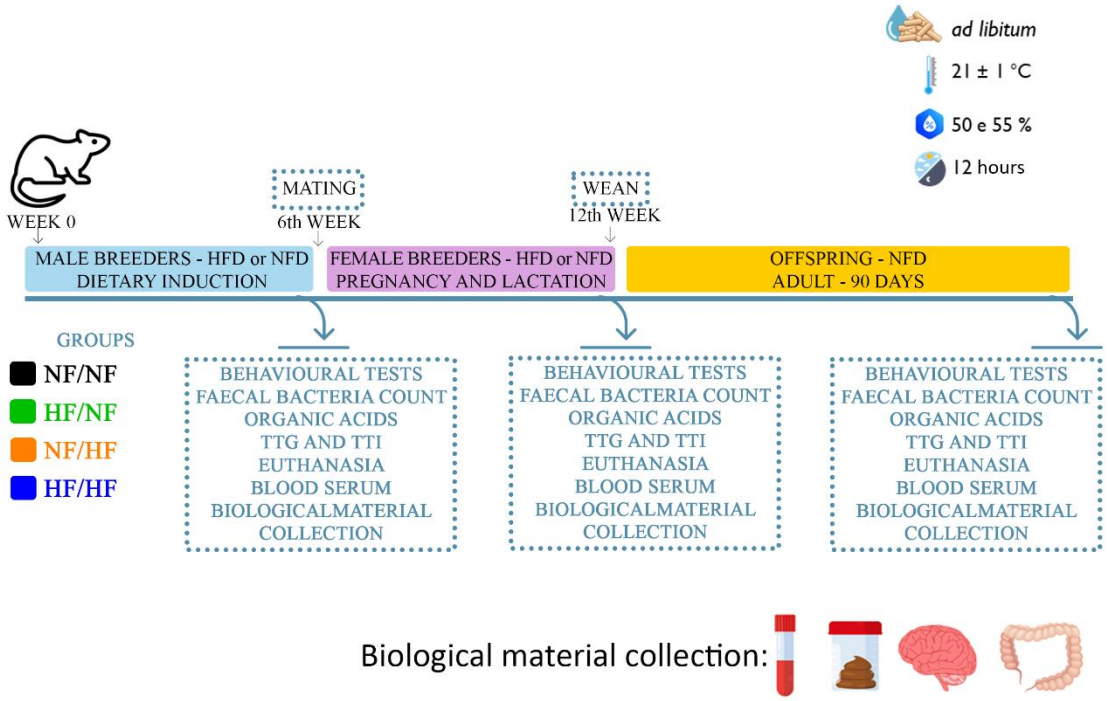
In this scenario, there is a gap in the literature on the outcomes caused by the consumption of a high-fat parental diet, that is, maternal and paternal diets on adult offspring. Therefore, the main objective of this research was to investigate and understand the relationship between the effects of high-fat parental diet on somatic, biochemical, neurobehavioural and intestinal health parameters in the offspring of adult Wistar rats.

2. Material and Methods

2.1 Experimental design

The experimental protocol of this study is in accordance with the ethical recommendations of the Animal Research guidelines: Reporting of In Vivo Experiments: the ARRIVE Guidelines(DU SERT *et al.*, 2020) and was approved by Ethics Committee on Animal Use (CEUA) of the Federal University of Paraíba under protocol n. 9877041019. Forty Wistar rats (20 males and 20 females) aged ± 90 days were used, kept in collective-type cages with water and food *ad libitum*, temperature 21 ± 1 °C, relative humidity between 50 and 55 % and light/dark cycle of 12 h (light phase 7 a.m.). The rats were randomized into four groups according to the dietary treatments given to the breeding rats, each group was composed of 5 males and 5 females, not inbred, as follows: NF/NF- males and females breeding rats fed a normal-fat diet; HF/NF - with breeding males fed a high-fat diet and females fed a normal-fat diet; NF/HF - breeding males fed a normal-fat diet and females fed a high-fat diet and HF/HF- males and females breeding rats fed a high-fat diet (Fig. 1).

Fig 1. Biological assay overview.



Male rats were randomly assigned to receive either a normal fat diet (NFD) or a high fat diet (HFD) starting at 50 days of age and continuing for 6 weeks. At 90 days old, males fed NFD or HFD were placed to mate individually with females weighing 200g in minimum and ±90 days old to generate offspring. The dams also fed NFD or HFD during pregnancy and lactation.

As a control diet or normal-fat diet (NFD) the AIN-93 diet proposed by the American Institute of Nutrition (AIN) was used (Reeves *et al.*, 1993) and the HFD diet was modified and produced by Rhoster Indústria e Comércio Ltd. Both diets were analysed for microbiology, for the content of organic acids (Coelho *et al.*, 2018) and fatty acids (Meireles *et al.*, 2021) by high performance liquid chromatography (Table S1). The diets were also analyzed microbiologically to ensure acceptable standards for consumption (Table S2).

Table S1 - Ingredients, macronutrients, energy value and fatty and organic acids of normal- and high-fat diets consumed by male and female breeding and by offspring up to 90 days of age.

	Diets	
Ingredients (g/100 g)	**NFD**	**HFD**
Maize starch	39.75	33.09

Dextrinized Starch	13.20	15.50
Sucrose	10.00	6.00
Fibre	5.00	5.00
Casein	20.00	19.86
L-cystine	0.30	0.30
Choline bitartrate	0.25	0.25
Mineral Mix AIN 93G	3.50	3.50
Vitamin Mix AIN 93	1.00	1.00
t-BHQ	0.14	0.14
Soybean oil	7.00	3.00
Lard	-	6.00
Non-hydrolyzed vegetable fat	-	5.00
Cholic Acid	-	0.50
Cholesterol	-	1.00
Total energy value (kcal/g)	3.95	4.34
Carbohydrates (kcal %)	63.78	51.52
Proteins (kcal %)	20.26	18.74
Lipids (kcal %)	15.96	31.85
Fatty Acids (FA) (g/100g)		
Octanoic acid C8:0	0.05±≤0.01	n.d.
Decanoic acid C10:0	0.11±0.03	0.08±≤0.01
Dodecanoic acid C12:0	0.17±0.03	0.13±≤0.01
Pentadecanoic acid C15:0	0.08±0.01	0.31±0.01*
Hexadecanoic acid C16:0 (Palmitic)	10.03±0.04	27.95±0.03*
14-Methyl hexadecanoic acid C17:0	n.d.	0.30±0.01
Heptadecanoic acid C17:0 (Margaric)	0.11±0.03	1.04±0.01*
Stearate acid C18:0 (Stearic)	5.86±0.30	40.69±0.09*
Nonadecanoic acid C19:0	n.d.	0.19±0.02*
Eicosanoic acid C20:0 (Arachidic)	0.49±≤0.01	0.60±0.01*
18-Methylnonadecanoate C21:0	n.d.	0.76±≤0.01
Docosanoic acid C22:0 (Benhenic)	0.47±0.02	0.24±0.05*
Tetracosanoic acid C24:0 (Lignoceric)	0.16±0.03	n.d.
Total of saturated fatty acids (SFA)	**17.53**	**72.29**
Trans-9-Hexadecenoic acid C16:1 t9	0.34±0.02	2.03±0.02*
Methyl hexadec-9-enoate C17:1	0.15±0.06	n.d.
Trans-11-Octadecenoic acid C18:1 t11 (Vaccenic)	n.d.	0.05±≤0.01
Octadecenoic acid C18:1 ω 9 (Oleic)	20.25±0.41	2.27±0.06*
Cis-11-Octadecenoic acid (*cis* Vaccenic)	n.d.	0.05±≤0.01
Cis-13-Eicosenoic acid C20:1 ω7	0.21±0.01	0.35±0.01*
Total of monounsaturated fatty acids (MUFA)	**21.25**	**4.75**
Cis-9,12-Octadecadienoic acid C18:2 ω6c (Linoleic)	54.52±0.44	n.d.
Trans-9,12-Octadecadienoic acid C18:2 ω6t	n.d.	20.85±0.23
9,12,15-Octadecatrienoic acid C18:3 ω3 (Linolenic)	6.70±0.04	1.69±0.06*
Cis-11,14-Eicosadienoic acid C20:2 ω6 (Dihomolinoleic)	n.d.	0.30±0.02
5,8,11,14-Eicosatetraenoic acid C20:4 ω6 (Arachidonic)	n.d.	0.12±0.01
Total of polyunsaturated fatty acids (PUFA)	**61.22**	**22.96**
Organic acids (µmol/g)		
Citric	0.68±0.04	0.73±0.05

Malic	2.52±0.05	2.04±0.02*
Tartaric	0.80±0.03	0.88±0.01*
Total organic acids (µmol/g)	**4.00**	**3.65**

NFD= normal-fat diet, AIN-93G diet proposed by American Institute of Nutrition (AIN) (Reeves *et al.*, 1993); HFD= high-fat diet (Rhoster Industry and Commerce Ltda); t-BHQ: tert-butylhydroquinone. n.d.= not detected.

Table S2 - Microbiological analysis of diets consumed by male and female breeding and their 90-day-old offspring.

Microbiological analysis	**Diets**	
	NFD	**HFD**
Total coliforms (NMP/g)	<3,0	<3,0
Total mesophiles	Absence	Absence
Thermotolerant coliforms (NMP/g)	<3,0	<3,0
*Salmonell*a spp.	Absence	Absence
Molds and Yeasts	Absence	Absence

NFD= normal-fat diet, AIN-93G diet proposed by American Institute of Nutrition (AIN) (Reeves *et al.*, 1993); HFD= high-fat diet for maintance phase (Rhoster Industry and Commerce Ltda).

To avoid postnatal nutritional imbalances, litters were standardized to 8 offspring on day 3 in each group. After weaning, on the 21st day of life, male offspring were separated by group in a collective box-type cage (4 animals/cage) and were fed a control diet (AIN-93) and water *ad libitum*. Body weight and food consumption (difference between feed offered and tailing) of rats breeders and male offspring were measured weekly throughout the experiment, using a digital electronic scale (Toledo, prix III, São Bernardo do Campo, Brazil).

2.2 Somatic parameters

Somatic parameters were evaluated immediately before euthanasia, in breeding males and females and in Offspring at 90 days old, as follows: thoracic circumference (CT) (immediately behind the foreleg), abdominal circumference (AC) (immediately anterior to the hind paw), body weight and naso-anal length, using inextensible tape measure, all measured in cm. The Body Mass Index (BMI) was calculated from the body weight (g) /length² (cm²) (Novelli *et al.*, 2007) and the Lee Index was calculated by the cube root of the body weight (g) divided by the nasoanal length (cm) (Bernardis and Patterson 1968).

Visceral, gonadal, and subcutaneous fats were collected to characterize total fat, weighed, and discarded. The adiposity index was calculated using Equation 1 (Nascimento *et al.*, 2011):

Adiposity index= (TF/TW) x 100 Equation 1

In which: TF = total body fat and TW = total body weight

2.3 Anxious-like behavior tests

Behavioural tests using open field and elevated plus maze were performed on males breeders it was carried out after mating, in female breeders after lactation phase and in offspring at 90 days old by two trained evaluators. The experiments were filmed using an IP camera (D-Link brand, model IP2P Wireless, Shenzhen, China) attached to the support installed in each of the apparatus and analyzed blindly by the researchers involved.

. Each apparatus used was meticulously cleaned with 10 % ethyl alcohol before and after exposure of each rat.

For the evaluation of anxiety, the open field test was used, which is an apparatus to test anxiety behaviour and exploratory activity, to verify the effects of unfamiliar environments on the emotional state of rats (SEIBENHENER; WOOTEN, 2015). The apparatus consists of a square arena (60 x 60 x 60 cm), with six crossed lines forming 6 quadrants measuring 20 x 20 cm, uniformly illuminated.

Each animal was observed for 10 min, and the following parameters were evaluated: ambulation (number of crossings of the segments by the animal with all four paws), number of rearing behaviours, time of grooming behaviours (grooming) and defecation (recorded by half the number of faecal boluses).

One day after the open field test, the test was performed using the elevated plus maze, a pharmacologically, biochemically, and behaviourally validated model as an anxiety test in the rat. It is a test based on the natural aversion of rodents to open and high spaces and on approach-avoidance conflict (BRADLEY; CURRY; DEVERS, 2007; LISTER, 1990). The apparatus is composed of two closed arms and two open arms perpendicular to the first ones, a central area, which is elevated from the ground.

The rat was placed in the centre of the apparatus with the snout facing the right closed arm. During 5 min, the frequency of entries in the closed and open arms (an entry is considered when the animal enters with all four paws in the arm), the time spent in each arm and in the centre of the apparatus were analysed. In addition, the number of head dives (when the animal places its snout or head on the open arm and explores the cliff) was also counted.

2.4 Faecal bacterial counts and organic acids

In the final week before euthanasia, enumeration of selected bacterial groups and quantification of fecal organic acids were carried out on both breeding males and females as well as offspring.

Faecal samples were homogenized in peptone water (100 mg/mL) and then serially diluted (five dilutions). Aliquots (20 uL) of the respective dilutions were inoculated by the microdroplet inoculation technique (Miles *et al.*, 1938) into sterile Petri dishes containing agar for counting *Lactobacillus* spp. (Man, Rogosa and Sharpe-MRS agar, Himedia, India), *Bifidobacterium* spp. (*Bifidobacterium* agar, Himedia, India), *Enterobacteriaceae* family (MacConkey agar, Himedia, India), *Escherichia coli* (Methylene Blue Eosin Agar, Himedia, India) or *Enterococcus* spp (Bile Esculin Agar-BHE, Himedia, India). Culture plates for *Lactobacillus* spp. and *Bifidobacterium* spp. were incubated in anaerobic conditions (Anaerobic System Anaerogen; Oxoid Ltd, Wade Road, UK) at 37 °C for 48 h. *Enterobacteriaceae, Enterococcus* and *Escherichia coli* were counted after 24 h of incubation at 37 °C under aerobic conditions. After incubation, the characteristic colonies in the selective culture media were counted and the numbers of viable cells (Colony Forming Units - CFU) were expressed as Log 10 CFU/g of faeces (Batista *et al.*, 2023).

The organic acids (including acetic, butyric, formic, lactic, propionic, and succinic acids) present in fecal samples were quantified through high-performance liquid chromatography (HPLC) using a 1260 Infinity LC system (Agilent Technologies Agilent Technologies, Santa Clara, California, USA) in conjunction with a PDA detector (G13315D; Agilent Technologies, Santa Clara, California, USA). The analysis utilized an Agilent Hi-Plax H column (300 x 7.7mm) with 8.0 μm particle size, shielded by a PL Hi-Plax H guard column (5 x 3mm). Column temperature was maintained at 50°C. Each sample was diluted in filtered ultrapure water (0.45μm pore membrane), injected with a 10 μL volume, and run at a flow rate of 0.5mL/min for 20 minutes. The mobile phase consisted of 4.0mm H_2SO_4 (Merck,

Darmstardt, Germany) in ultrapure water (Scientific Mars System, São Paulo, SP, Brazil) (COELHO *et al.*, 2018a).

HPLC peaks were identified by comparing their retention times to organic acid standards. Quantification was based on average peak areas from triplicate injections, with detection at 210 nm using a DAD. All compounds displayed calibration curves with $R^2 > 0.995$. The limits of detection and quantification for all compounds were LOD≤ 0.042 g/L and LOQ ≤0.131 g/L. Data were processed using the Agilent Technologies OpenLAB CDS ChemStation EditionTM (Agilent Technologies, Santa Clara, California, USA) program and reported in μmol/g (BATISTA *et al.*, 2018; COELHO *et al.*, 2018a).

The acetic, butyric, propionic, succinic acid, lactic and malic acids standards were acquired from Vetec (Rio de Janeiro, RJ, Brazil) and the formic acid standard was acquired from Sigma-Aldrich (St. Louis, MO, USA), all with a purity of ≥ 99%.

2.5 Glucose and Insulin tolerance test

Glucose and insulin tolerance tests were performed after behavioural tests and three days before euthanasia of the parents or offspring. In both tests, blood glucose was measured using a glucometer (Accu-check brand, Performa model, Jaguaré, SP, Brazil). The glucose tolerance teste (GTT) was performed, after a 6-h fast, the initial blood glucose was measured through an incision in the rat's tail (time 0). Then, oral glucose solution (2g glucose/kg weight) was administered, and blood glucose was measured at 15, 30, 60, 90 and 120 min.

On the day after GTT, insulin tolerance test (ITT) was performed with the normally fed rats, after intraperitoneal administration of regular insulin (Novolin® R, Novo Nordisk, Bagsvaerd, Denmark), equivalent to 0.75 IU/kg, for measuring blood glucose at times 0, 15, 30, 60, 90 and 120 min. (Kothari *et al.*, 2017).

2.6 Euthanasia and collection of biological materials

At the end of the experiment, the rats were fasted for 6 h and were then euthanized by beheading using a guillotine (EB271, Insights, Ribeirão Preto, Brazil). On the euthanasia day, the rats' blood was collected and centrifuged (1,040 *x g* / 10 min/25ºC). The serum was collected and stored at - 80 °C for further analysis. Faeces, brain, and intestine were also

collected from breeding males after mating, breeding females after lactation and on the 90th day of the offspring's life.

2.7 Lipid profile

To evaluate the lipid profile, measurements of total cholesterol (TC), triglycerides (TG) and high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were performed in serum. The analyses were performed using commercial kits (Bioclin Quibasa, Minas Gerais, Brazil) following the manufacturer's recommendations.

2.8 Histological analysis

The colon and cortex of breeding males, females, and offspring underwent histological analysis. These tissues were fixed in 10% buffered formalin and processed using standard histological techniques. Slides were prepared and stained with Harris Hematoxylin and Eosin, mounted with synthetic resin (Entellan®-Merck, Darmstadt, HE, Germany), and examined at 100× total magnification under an optical microscope (Motic BA 200, Kowloon, Hong Kong).

In the cortex, we assessed organ structure and the presence, characteristics, and intensity of potential inflammatory infiltrates. In the colon, we evaluated hyperemia, inflammatory exudate, hemorrhage, vasodilation, necrosis, epithelial preservation, as well as hypertrophy and hyperplasia of the smooth muscle layer (BATISTA *et al.*, 2018).

Quantitative analyses of intestinal morphometry were conducted to determine the villus-to-intestinal crypt ratio using HE staining and a Zeiss Imaging Processing Software image analyzer (KS 300, Zeiss, Germany).

Cortex sections underwent NF-κB immunohistochemical analysis. Antigenic recovery was achieved using a 0.1% citrate retriever buffer solution [pH 6.0] (EasyPath Diagnostics®, Brazil, REF EP-12–20,558) through a high-temperature method, followed by overnight incubation with monoclonal antibodies against NF-kB (Cloud Clone, Ref. CLOU-PAB8 24RA01–200 U) at a 1:100 dilution at 4 °C. Slides were processed using biotinylated goat anti-mouse and anti-rabbit antibodies (DAKO En Vision+ Dual Link System – HRP, Ref. K4061, California, US) and developed with diaminobenzidine (DAB – Easy Path

Diagnostics, REF. EP-12–20,541, São Paulo, Brazil). Counterstaining was done with Harris's hematoxylin, followed by dehydration, clearing, and coverslip mounting.

The area of immunohistochemical staining was calculated using algorithms within the KS300 software program (Zeiss, Jena, Germany). Black-stained pixels in each image were selected to generate a binary image with area measurements in μm2. All chemicals used were of analytical grade.

2.9 Statistical analysis

The normality of measurements was assessed using the Shapiro-Wilk test. The results were expressed as mean ± SD (standard deviation) and analysed in the GraphPad Prism 8.0 statistical software (version for evaluation). Weight, food intake, GTT, insulin ITT, lipid profile, somatic parameters, faecal bacterial counts, and faecal organic acids the results, were analysed by Two Way ANOVA (analysis of variance) followed by Tukey test. The behavioural parameter from breeders data were analysed in pairs via the Student's t test and from offspring were analysed by One Way ANOVA, except for the parameters of number of entries and time spent in the open and closed arms of the elevated plus maze test, which were analysed by the Mann-Whitney. All behavioural test results were expressed as mean, median and 25% and 75% percentiles. The GraphPad Prism 8® package (GraphPad Software Inc. La Lolla, CA, USA) was used for the statistical analyses. For all analyses, a significance level of 5% ($p \leq 0.05$) was adopted.

3. Results

3.1 Food intake

Regarding food consumption, during pregnancy the HFD breeding females consumed less feed ($p \leq 0.01$) (Fig.2a), however the dietary lipid (Fig.2b) intake was higher in the HFD group ($p \leq 0.001$), such results made the total energy intake (Fig.2c) showed no significant difference ($p \leq 0.05$). In breeding females during the lactation period (Fig.2d-f), as well as in breeding males (Fig.2g-i), there was no difference in the consumption in grams of the diet, but the lipid and total caloric intake was higher in the rats that ingested HFD ($p \leq 0.001$). In

the offspring, the rats which at least one of the parents consumed the HFD diet had higher the total consumption in grams (Fig.2j), lipid (Fig.2k) and energy intake (Fig.2l) in relation to control ($p \leq 0.01$), however the HF/HF presented much higher lipid and energy intake in relation to all other groups ($p \leq 0.001$) (Fig.2k-l).

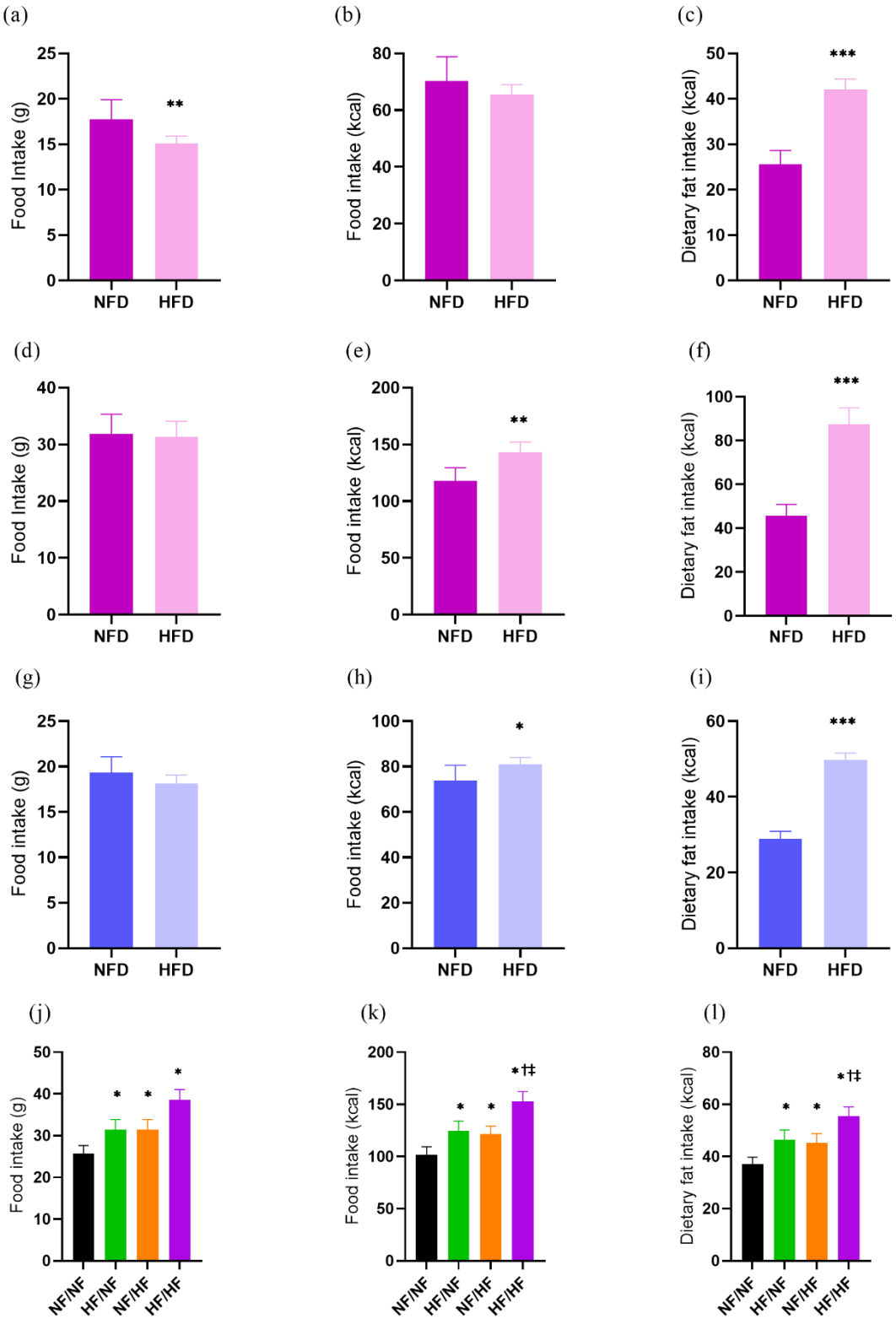


Fig 2. Food consumption of breeding females during gestation (a-c), lactation (d-f) and males before matting (g-h) both fed a normal-fat diet (NFD) or high fat diet (HFD).and their adult offspring (j-l). Data expressed as mean and standard deviation of the mean. †significant

difference compared to HF/NF; ‡significant difference compared to NF/HF; p≤0.05. Two-way ANOVA test, followed by Tukey post-test. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD, and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Somatic parameters

As for the somatic parameters, it was seen that there was a significant gain in body weight in the breeding males that received the HFD (*p≤0.001*) and in the offspring of the HF/HF group, coming from males and females breeding HFD (*p≤0.001*), in the other parameters in all groups there were no significant differences (Table 1).

Table 1 Somatic parameters of male and female breeding both fed NFD or HFD and their respective adult offspring.

Variables	**Groups**			
Female breeders	**NFD**		**HFD**	
Somatic parameters				
Weight (g)	240±0.98		240±17.02	
Length (cm)	21.08±0.20		21.25±0.27	
BMI (g/cm^2)	0.62±0.03		0.54±0.03	
Lee's Index(g/cm^3)	0.25±0.01		0.26±0.02	
TC (cm)	13.50±0.32		13.05±0.44	
AC (cm)	16.33±0.52		15.42±0.49	
Adiposity index (%)	4.01±1.12		3.03±0.54	
Male breeders	**NFD**		**HFD**	
Somatic parameters				
Weight (g)	345.83±14.29		380.83±10.21***	
Length (cm)	24.4±0.91		21.83±0.41	
BMI (g/cm^2)	0.63±0.02		0.71±0.07	
Lee's Index (g/cm^3)	0.26±0.01		0.34±0.03	
TC (cm)	15.67±0.52		16.5±0.55	
AC (cm)	16.67±0.61		18.67±0.41	
Adiposity index (%)	3.05±0.69		2.96±0.54	
Offspring 90d	**NF/NF**	**HF/NF**	**NF/HF**	**HF/HF**
Somatic parameters				
Weight (g)	337.86±19.97	340.71±20.29	333.57±26.25	359.28±27.29*†‡
Length (cm)	19.43±0.78	22.42±0.53	22.67±0.44	23.30±0.67
BMI (g/cm^2)	0.74±0.05	0.64±0.03	0.63±0.03	0.61±0.03
Lee's Index (g/cm^3)	0.34±0.03	0.27±0.01	0.63±0.03	0.61±0.03

TC (cm)	15.14±0.38	15.86±0.90	14.71±0.49	15.43±0.53
AC (cm)	17.93±0.84	18.14±0.38	17.04±0.29	17.94±0.73
Adiposity index (%)	2.96±0.35	4.00±0.64*‡	2.50±0.22	4.04±0.51*‡

Data expressed as mean ± standard deviation, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, results to breeders obtained from the ANOVA two-way test followed by the Bonferroni post-test. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; p≤0.05. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD, and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD. TC = Thoracic Circumference, AC = Abdominal Circumference; BMI = Body Mass Index

Effects of high-fat diet on anxious-like behaviour

In the open field test, HFD breeding females showed a decrease in ambulation (Fig. 3a), and an increase in freezing time (Fig. 3d) (p≤0.01), in the HFD breeding males there was a decrease in rearing numbers (Fig. 3h) and increase in grooming time (Fig. 3j) (p≤0.01). The Offspring in groups HF/NF, NF/HF and HF/HF had an increase in grooming time (Fig 3o) (p≤0.001), groups NF/HF and HF/HF had an increase in the number of faecal boluses (Fig. 3l) (p≤ 0.01), and only the HF/NF group had a reduction in ambulation within the apparatus (Fig 3k) (p≤0.01).

In the elevated plus maze test, the HFD breeding females showed no significant difference in any of the analyzed parameters (Fig.4 a-f) (p>0.05), whereas the HFD breeding males had less time spent in the open arms (Fig.4 j) and more time in the closed arms (Fig.4k) (p≤0.001). The offspring of groups HF/NF, NF/HF and HF/HF had a greater number of entries in the closed arms (Fig. 4 n) (p≤0.001), groups HF/NF and NF/HF had a greater number of entries in the centre of the apparatus (Fig. 4 o) (p≤0.001). As for the time spent in the apparatus, the Offspring from groups NF/HF and HF/HF spent more time in the closed arms (Fig.4 q) (p≤0.01), and only the NF/HF group showed more time spent in the centre (Fig.4 r) (p≤0.01).

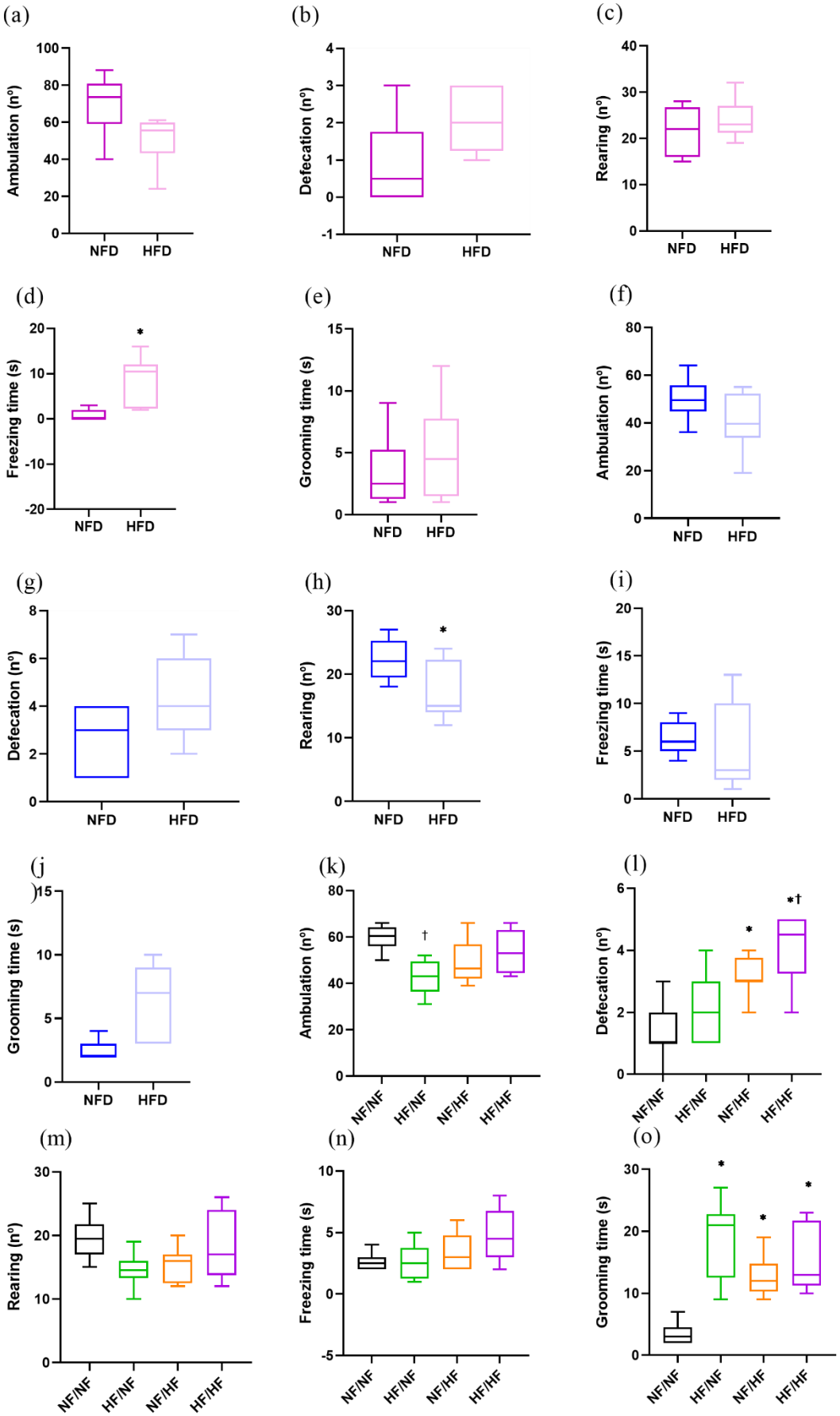

(a)
Ambulation (nº)
NFD
HFD
(b)
Defecation (nº)
(c)
Rearing (nº)
(d)
Freezing time (s)
*
(e)
Grooming time (s)
(f)
(g)
(h)
(i)
(j)
(k)
†
NF/NF
HF/NF
NF/HF
HF/HF
(l)
*†
(m)
(n)
(o)

Fig 3. Behavioural parameters evaluated in the open field test of rats of breeding females (a-e) and males (f-j) both fed a normal-fat diet (NFD) or high fat diet (HFD), and their adult offspring (k-o). Data expressed as mean and standard deviation of the mean. *significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; $p \leq 0.05$. One-way ANOVA test, followed by Tukey post-test. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

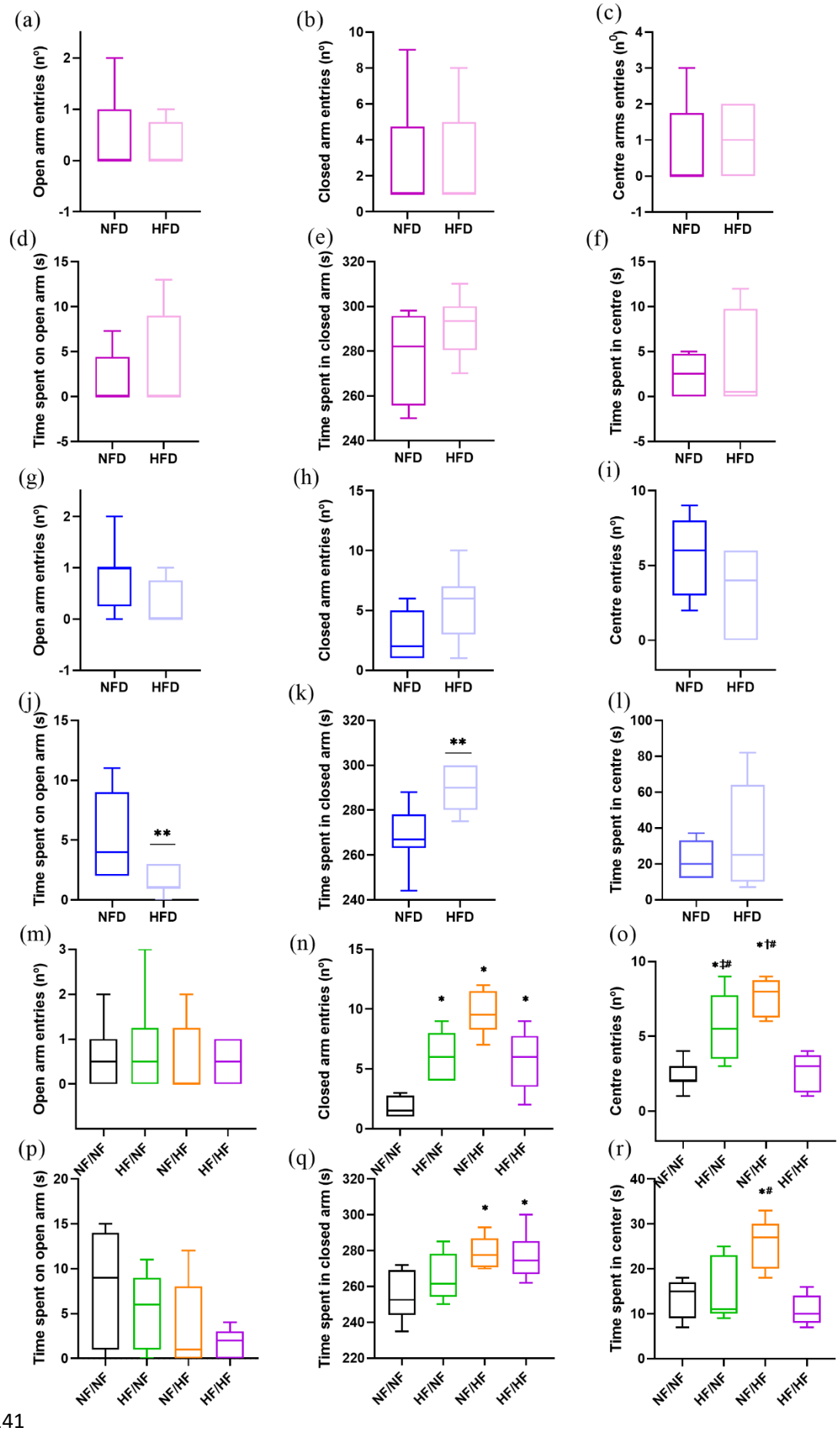

(a)
Open arm entries (nº)
NFD
HFD
(b)
Closed arm entries (nº)
(c)
Centre arms entries (nº)
(d)
Time spent on open arm (s)
(e)
Time spent in closed arm (s)
(f)
Time spent in centre (s)
(g)
(h)
(i)
Centre entries (nº)
(j)
**
(k)
(l)
(m)
NF/NF
HF/NF
NF/HF
HF/HF
(n)
*
(o)
*‡#
*†#
(p)
(q)
(r)
*#

Fig 4. Behavioural parameters evaluated in the elevated plus maze test of rats of breeding females (a-f) and males (g-l) both fed a normal-fat diet (NFD) or high fat diet (HFD).and their adult offspring (m-r) Data expressed as mean and standard deviation of the mean. *significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; p≤0.05. One-way ANOVA test, followed by Tukey post-test. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Effects of high-fat diet on bacterial count and organic acid in the faeces of the breeders and offspring

HFD breeding females had higher counts of *E. coli*, Enterobacteriaceae and Bacteroides (p≤0.001) (Table 2). The HFD breeding males also had an increase in the bacterial count of E. coli, Enterobacteriaceae and Bacteroides (p≤0.001), as well as a reduction in the count of *Lactobacillus* and *Bifidobacterium* (p≤0.001). The HF/HF offspring had a reduction in *Lactobacillus, Bifidobacterium* counts (p≤0.01) and an increase in Enterobacteriaceae and Bacteroides counts (p≤0.001) (Table 2).

Regarding the quantification of faecal organic acids (Table 2), in the HFD breeding females there was a decrease in the amount of acetic and propionic acids (p≤0.001), with no significant difference in the other acids. The HFD breeding males showed a reduction in the amounts of lactic, formic, and propionic acids (p≤0.001). In the offspring, HF/NF had a higher concentration of faecal lactic acid, HF/HF had a higher concentration of faecal formic acid compared to the other groups and in NF/NF in relation to HF/NF and NF/HF (p≤0.001). Acetic acid was more abundant in the faeces of Offspring in HF/NF compared to all groups and in NF/HF compared to groups NF/NF and HF/HF (p≤0.001). In turn, propionic acid was found in greater amounts in the faeces of the Offspring in NF/NF when compared to the other groups, as was also observed in the HF/NF group in relation to the NF/HF and HF/HF groups (p≤0.001) (Table 2).

Table 2 - Bacterial counts and organic acid amounts in the faeces of male and female breeding both fed NFD or HFD and their respective adult offspring.

Variables	Groups			
Female breeders	**NFD**		**HFD**	
Bacterial count (CFU/g)				
Lactobacillus	5.87±0.55		5.67±0.21	
Bifidobacterium	5.67±0.64		5.49±0.47	
Escherichia coli	5.72±0.42		7.67±0.34***	
Enterobacteriaceae	5.49±0.54		8.22±0.29***	
Bacteroides	5.25±0.22		7.75±0.53***	
Organic acids (µmol/g)				
Citric acid	0.11±0.08		0.22±0.21	
Latic acid	35.57±7.82		32.27±2.01	
Formic acid	1.11±0.97		3.32±0.92	
Acetic acid	6.25±0.13		2.15±0.28***	
Propionic acid	85.08±0.93		25.63±1.31***	
Total	**128.12**		**63.59**	
Male breeders	**NFD**		**HFD**	
Bacterial count (CFU/g)				
Lactobacillus	8.02±0.11		7.34±0.28***	
Bifidobacterium	7.44±0.20		6.75±0.10***	
Escherichia coli	6.19±0.32		6.96±0.15***	
Enterobacteriaceae	5.65±0.12		7.76±0.14***	
Bacteroides	6.20±0.35		6.86±0.07***	
Organic acids (µmol/g)				
Citric acid	4.79±2.68		0.87±0.05	
Latic acid	32.25±2.43		4.02±0.99***	
Formic acid	50.87±6.29		2.06±0.76***	
Acetic acid	5.37±0.32		3.42±0.11	
Propionic acid	69.83±4.06		28.02±2.11***	
Total	**163.11**		**38.39**	
Offspring 90d	**NF/NF**	**HF/NF**	**NF/HF**	**HF/HF**
Bacterial count (CFU/g)				
Lactobacillus	7.73±0.21	7.53±0.22	7.713±0.39	7.24±0.30*‡
Bifidobacterium	9.21±0.36	7.65±0.26	8.02±0.47	6.87±0.18*†‡
Escherichia coli	5.74±0.18	6.29±0.47*	6.63±0.38*	6.37±0.39*
Enterobacteriaceae	5.36±0.26	5.91±0.29*	5.69±0.26	6.55±0.04*†‡
Bacteroides	5.85±0.18	5.91±0.25	6.19±0.36	6.61±0.61*†‡
Organic acids (µmol/g)				
Citric acid	1.11±0.05	0.65±0.21	0.63±0.03	2.11±0.12
Latic acid	1.92±0.23	24.05±1.76*‡#	2.89±2.02	4.58±1.13
Formic acid	9.97±1.79†‡	1.28±0.08	1.71±0.61	76.72±7.83*†‡
Acetic acid	4.49±0.23	17.39±0.59*#	10.84±1.35*#	3.20±0.73

Propionic acid	156.52±6.32$^{\dagger\ddagger\#}$	107.24±5.58$^{*\ddagger\#}$	68.66±5.72	50.45±4.82
Total	**174.01**	**150.61**	**84.73**	**137.06**

Data expressed as mean ± standard deviation, * p ≤0.05, ** p ≤0.01, *** p ≤0.001, results obtained from the ANOVA two-way test followed by the Bonferroni post-test. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; # significant difference compared to HF/HF p≤0.05. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Effects of high-fat diet on glucose and insulin tolerance in breeders and offspring

The HFD breeding females did not show significant changes in GTT (Fig.5 a) (p>0.05) and in the ITT at time 90 min there was an increase in glycemic levels (Fig.5 b) (p≤0.01), in breeding males there was a single change in glycemic levels in the GTT at time 30 min (Fig.5 c) (p≤0.01). Regarding the Offspring, in the GTT only the NF/HF group presented low glycemic levels compared to all other groups (Fig.5 e) (p≤0.01) In the ITT the NF/HF group continued to present low glycemic levels at all times compared to NF/NF and HF/HF, and the HF/NF group at the times 30 min, 60 min and 90 min compared to NF/NF and HF/HF groups (Fig.5 f) (p≤0.01).

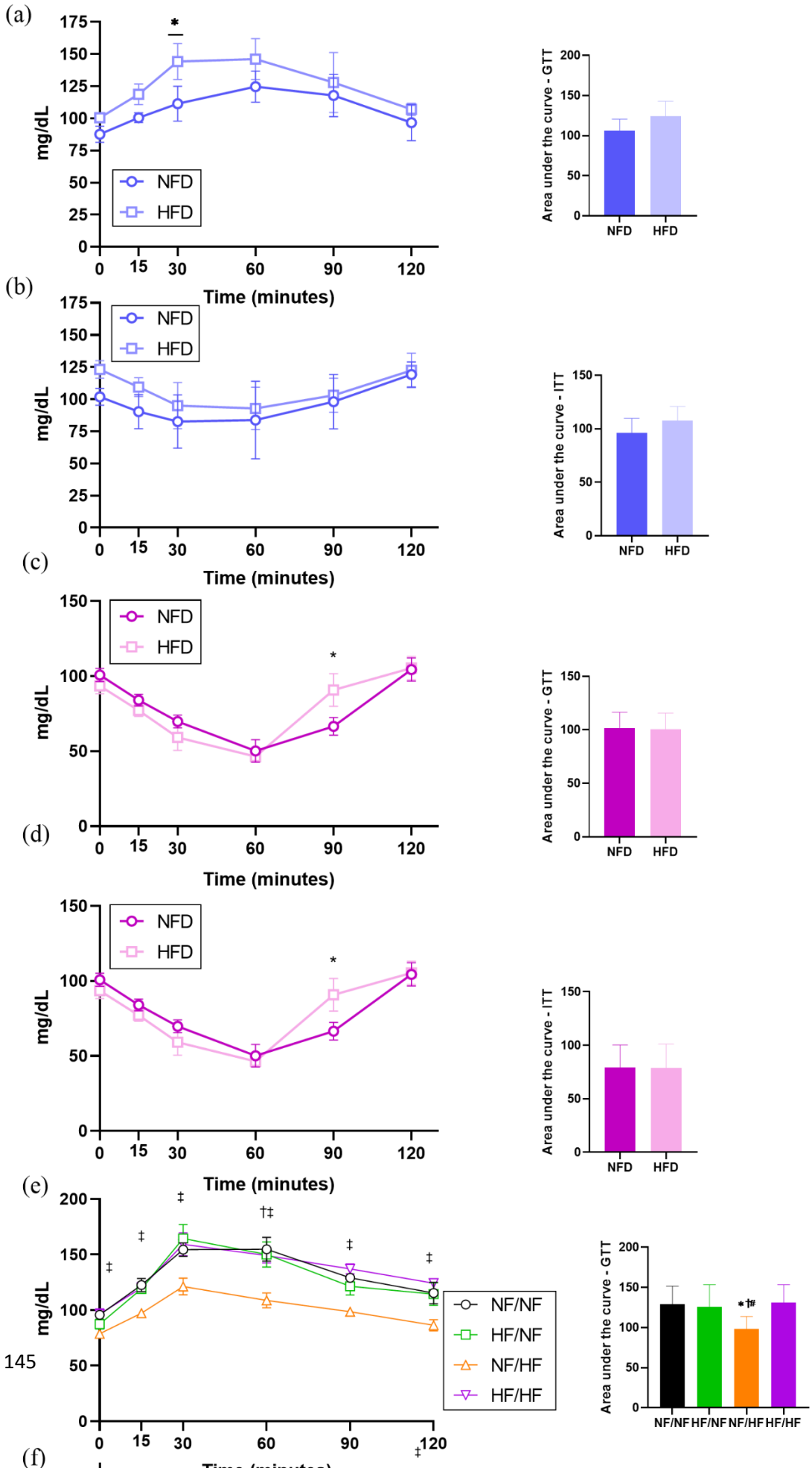

(a)
mg/dL
Time (minutes)
NFD
HFD
Area under the curve - GTT
(b)
mg/dL
Time (minutes)
NFD
HFD
Area under the curve - ITT
(c)
mg/dL
Time (minutes)
NFD
HFD
Area under the curve - GTT
(d)
mg/dL
Time (minutes)
NFD
HFD
Area under the curve - ITT
(e)
mg/dL
Time (minutes)
NF/NF
HF/NF
NF/HF
HF/HF
Area under the curve - GTT
NF/NF HF/NF NF/HF HF/HF
(f)

Fig 5. Analysis of glucose and insulin tolerance test of breeding females (a, b) and males (c, d) both fed a normal-fat diet (NFD) or high fat diet (HFD) and their adult offspring (e, f). Data expressed as mean and standard deviation of the mean. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; #significant difference compared to HF/HF $p \leq 0.05$. Two-way ANOVA test, followed by Tukey post-test. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Effects of a high-fat diet on the lipid profile of breeding rats and offspring

The HFD breeding females and males showed high levels of TC and LDL and a reduction in HDL (Fig.6 a-b) ($p \leq 0.001$), whereas in the offspring (Fig.6 c) groups HF/NF and HF/HF showed high TC levels ($p \leq 0.001$) in relation to the other groups, as for HDL, the offspring of groups HF/NF, NF/HF and HF/HF had low levels ($p \leq 0.001$), and only the HF/HF group showed an increase in LDL levels in relation to the other groups ($p \leq 0.001$) (Fig.6 c).

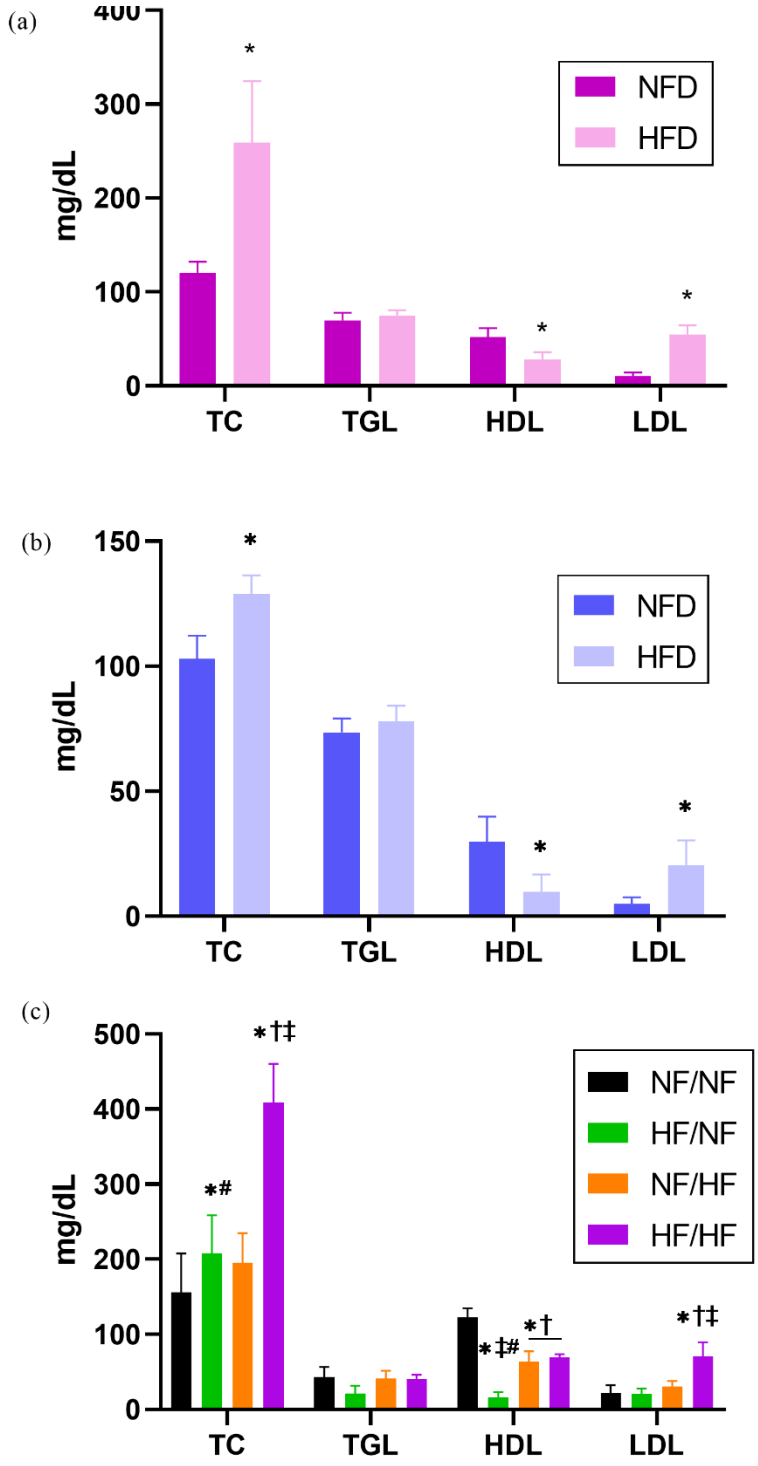


Fig 6. Lipid profile of breeding females (a) and males (b) fed a normal-fat diet (NFD) or high fat diet (HFD) and their adult offspring (c). Data expressed as mean and standard deviation of the mean. *Significant difference compared to NF/NF; †significant difference compared to HF/NF; ‡significant difference compared to NF/HF; #significant difference compared to HF/HF $p \leq 0.05$. Two-way ANOVA test, followed by Tukey post-test. NF/NF = both breeding rats fed a normal-fat diet (NFD); HF/NF = breeding males fed a HFD and

females fed a NFD; NF/HF = breeding males fed a NFD and females fed a HFD; and HF/HF group = both breeding rats fed a HFD.

Effect of high-fat diet on intestinal and brain parenchyma

In the various experimental situations observed, NFD father (Fig. 7a), HFD father (Fig. 7b), NFD mother (Fig. 7c), HFD mother (Fig. 7d), NF/NF (Fig. 7e), HF/NF (Fig. 7f) and NF/HF (Fig. 7g) tissue preservation is observed. However, in animals from group HF/HF (Fig. 7h), an inflammatory process with loss of epithelial lining is observed (black arrow). The morphometry of the breeders that were fed with HFD (Fig. 7i), had an atrophy of the intestinal villi, the same was verified in the pups of the groups HF/NF, NF/HF, HF/HF (Fig. 7j).

Regarding the NF-kB marker, NFD male (Fig. 8a), HFD male (Fig. 8b) or NFD female (Fig. 8c) breeders an absence of marking is observed. However, in the HFD female breeder (Fig. 8d) focal and intense marking is observed. In the offspring, focal marking is observed in the NF/NF (Fig. 8e) and NF/HF (Fig. 8g) groups. The rats in group HF/NF (Fig. 8f) and HF/HF (Fig. 8h) show more pronounced, multifocal, and intense markings (arrowheads), indicative of an inflammatory process. In the morphometry of the cerebral prefrontal cortex, the inflammatory areas of the NF-kB marking, it was verified that the breeding females (Fig. 8i) and the groups of pups HF/NF, NF/HF, and HF/HF (Fig. 8j) presented a larger area with the brown marking of the NF-kB.

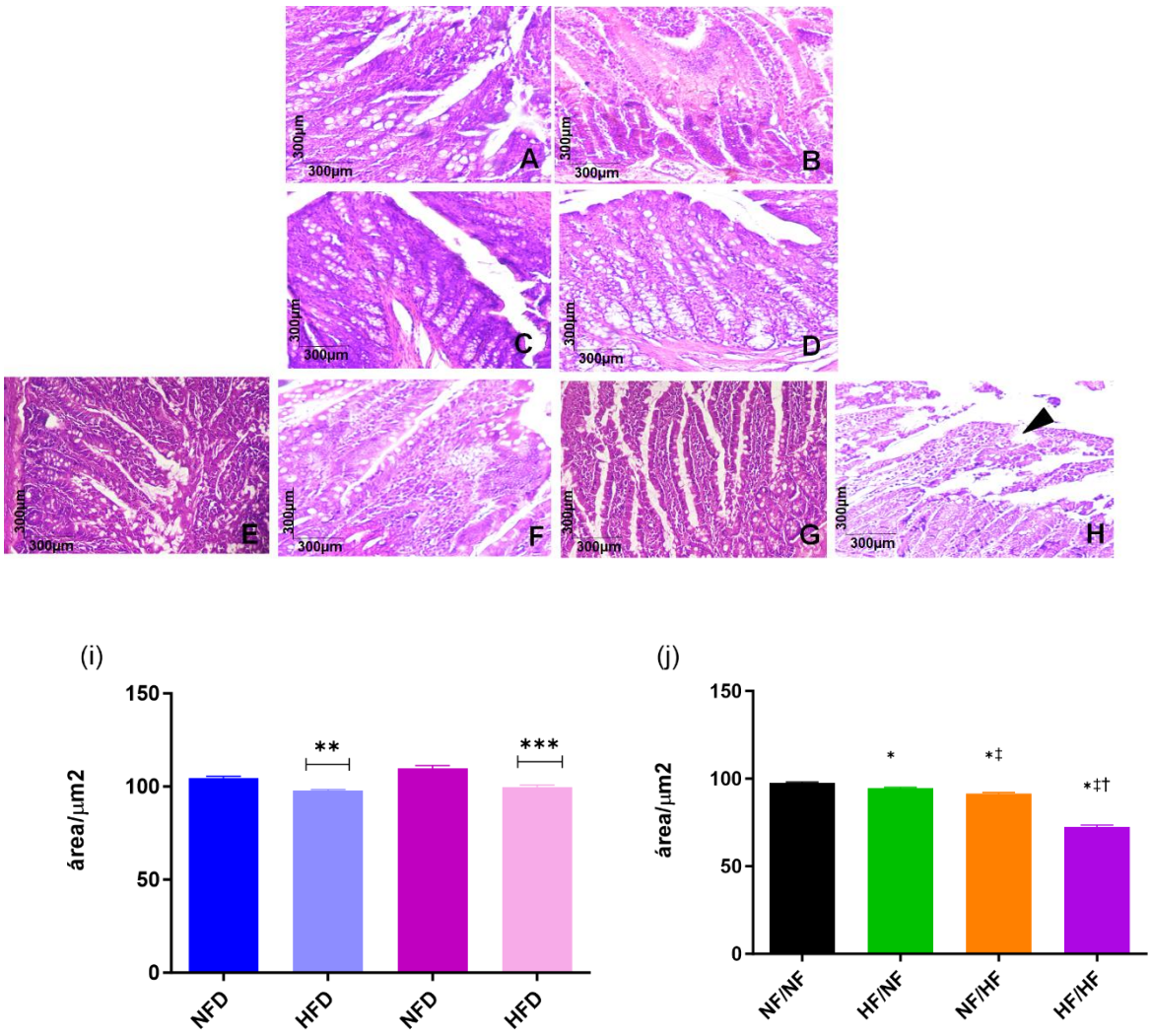


Fig 7. Histology (a-h) and morphometry (i-j) of the colon in breeders rats and offspring at 90 day old, from breeders fed a high-fat diet (HFD) or fed a normal-fat diet (NFD). (a) fathers NFD, (b) fathers HFD, (c) mothers NFD and (d) mothers HFD. Offspring (e) NF/NF= males and females breeding rats fed a normal-fat; (f) HF/NF = breeding males fed a high-fat diet and females fed a normal-fat; (g) NF/HF= breeding males fed a normal-fat and females fed a high-fat diet and (h) HF/HF= males and females breeding rats fed a high-fat diet. (i) morphometry of the breeders and (j) morphometry of the offspring. Data expressed as mean and standard deviation of the mean. *significant difference compared to NF/NF; ‡significant difference compared to HF/NF; #significant difference compared to NF/HF $p \leq 0.05$. Arrow = Inflammatory process with loss of epithelium lining

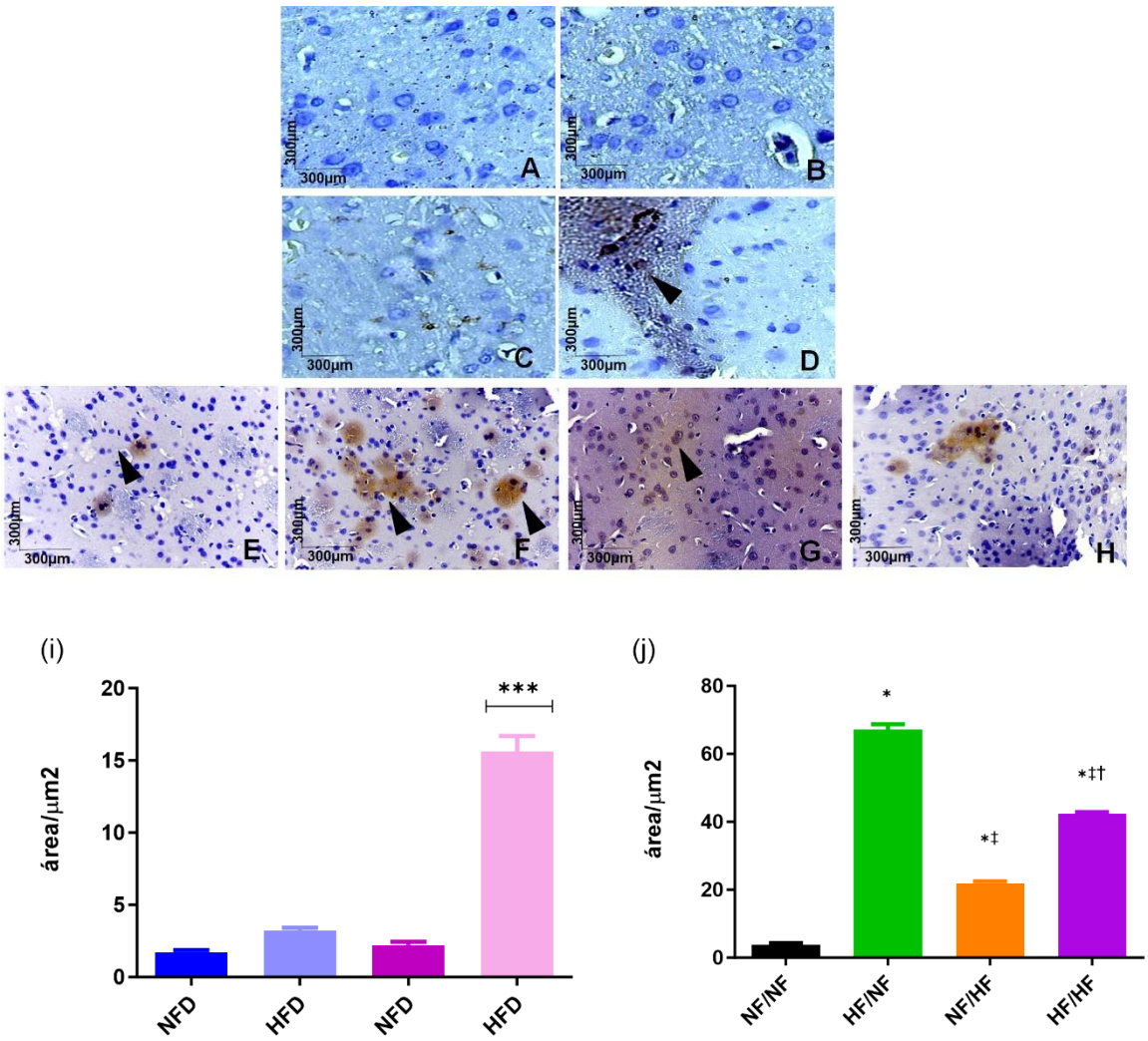


Fig 8. Immunohistochemical reaction for NF-κB in cortex in breeding rats and offspring at 90 day old, from breeders fed a high-fat diet (HFD) or fed a normal-fat diet (NFD). (a) fathers NFD, (b) fathers HFD, (c) mothers NFD and (d) mothers HFD. Offspring (e) NF/NF= males and females breeding rats fed a normal-fat; (f) HF/NF = breeding males fed a high-fat diet and females fed a normal-fat; (g) NF/HF= breeding males fed a normal-fat and females fed a high-fat diet and (h) HF/HF= males and females breeding rats fed a high-fat diet. (i) morphometry of the breeders and (j) morphometry of the offspring. Data expressed as mean and standard deviation of the mean. *significant difference compared to NF/NF; ‡significant difference compared to HF/NF; #significant difference compared to NF/HF $p \leq 0.05$. Arrow = focal marking.

Discussion

Our results demonstrate that such a dietary pattern of male and female breeders can modulate parameters related to the gut-brain axis of offspring, such as anxiety-related behavioural

worsening, alteration in the faecal bacterial counts which may favor intestinal dysbiosis, changes in the quantification of organic acids in the faeces of offspring rats fed high-fat even in young adulthood. In fact, the high-fat diet has been shown to influence the physiology of numerous metabolically relevant tissues.(Pinheiro *et al.*, 2019; Watanabe *et al.*, 2018; P. Zhang *et al.*, 2019).

We found a high consumption of the diet in offspring in which at least one of the breeders was fed a high fat diet, being enhanced in the HF/HF group, that indicating that the consumption of a diet rich in fat in the preconception period and during pregnancy may have generated this behavioral pattern of hyperphagia in the HF/HF offspring. A previous study reported that puppies whose breeding females were fed a high-fat diet showed changes in the gene expression of dopaminergic receptors (D2 and D3) that altered their mesolimbic reward system, causing such puppies to develop changes in food control to seek dopamine release and consequently of pleasure in eating, culminating in hyperphagia (Fukuhara *et al.*, 2019; Santos *et al.*, 2021).

In relation to body weight, it was observed that high-fat diet (HFD) consumption did not significantly affect weight gain in breeding females, whereas in breeding males, it led to considerable weight gain. Recent research suggests that females possess protective mechanisms against hyperphagia and weight gain, attributed to estradiol's modulation of intestinal hormones like cholecystokinin (CCK), peptide-1, and amylin, which have anorectic effects by reducing leptin signaling, resulting in decreased energy intake. This mechanism is not observed in males, where HFD consumption leads to weight gain due to hyperphagia. (Huang *et al.*, 2020).

The high food intake seen in groups HF/NF, NF/HF, and HF/HF suggests that a maternal diet high in saturated, trans, and cholesterol fats may disrupt the development of hypothalamic neuronal circuits, particularly in the hypothalamic arcuate nucleus (ARC), resulting in hyperphagia. This dietary pattern leads to a preferential differentiation of neurons into orexigenic neurons, including those expressing Neuropeptide Y (NPY), which stimulates hunger. (Desai *et al.*, 2016, 2020; Lemes *et al.*, 2018).

We demonstrated that breeding parents and offspring, especially those in the HF/HF group, had elevated levels of TC and LDL, and low levels of HDL in relation to control group. The

maternal HFD diet increases the accumulation of fetal fat, increasing the activity of placental lipoprotein lipase (LPL) and the increase in the gene expression of placental lipid transporters, favouring dyslipidaemia in the offspring the effects of paternal exposure to HFD before conception also impair the lipid metabolism of the offspring, as was seen in the HF/NF group of our study, an offspring with high levels of CT and low levels of HDL(CALABUIG-NAVARRO *et al.*, 2017; DE PAULA SIMINO *et al.*, 2017; PINHEIRO *et al.*, 2019).

Recent studies show that HFD can cause epigenetic changes that lead to disturbances in the lipid metabolism of the offspring. And this is justified by the gene transmission that occurs through the altered paternal genetic load, which in the process of sperm formation can be transmitted to offspring and induce changes in the gene expression of genes related to lipid metabolism (Aizawa *et al.*, 2022; Masuyama *et al.*, 2016; Zhang *et al.*, 2017). Thus, paternal influence can potentiate the harmful effects of poor diet in offspring for two generations, but more studies are needed to elucidate these changes that impact gene expression and triglyceride metabolism in offspring (MASUYAMA *et al.*, 2016b).

Our results showed that breeding parents and offspring, especially those in the HF/HF group, had elevated levels of TC and LDL, and low levels of HDL in relation to control group. The maternal HFD diet increases the accumulation of foetal fat, increasing the activity of placental LPL and the increase in the gene expression of placental lipid transporters, favoring dyslipidaemia in the offspring (Calabuig-Navarro *et al.*, 2017; Easton & Regnault, 2020; Qiao *et al.*, 2015; Wang *et al.*, 2021).

On the other hand, in our study, the HFD was not able to change glucose and insulin tolerance parameters, either in breeding parents or offspring, which may be related to what was observed by Ji *et al.* 2019 who demonstrated that the consumption of high-fat diets may command the pancreas to produce more HFD-dependent β cells as a compensatory effect and a mechanism regulated by the TLR4 and TLR2 pathways.

Regarding anxious-like behaviour in breeders, changes in some parameters can be verified that indicate that HFD increases anxious-like behaviour in rodents, as seen in the reduction of ambulation and increase in freezing time in females, and a decrease in the numbers of rearing and increased grooming, a behaviour that is typical of anxious rodents (Deal *et al.*,

2020). In our results, it was possible to verify that the dietary pattern rich in saturated fats can cause an inflammatory process at the level of the cerebral cortex, verified by the by intense labeling for NF-kB in this region. In turn, reduction in the size of the dendrites, as well as the process of neuronal demyelination, can affect the transmission of the nervous impulse, compromising the communication between the neurons (BORDELEAU *et al.*, 2021, 2022; CAVALIERE *et al.*, 2019b; TAN; NORHAIZAN, 2019), which may result in neuromotor and behavioural alterations such as anxiety-like behaviour, observed both in breeding females and in offspring from fathers and mothers fed HFD (APRYATIN *et al.*, 2017, 2019).

The consumption of saturated fatty acids, such as palmitic acid found in substantial quantities in HFD, which is linked to activation of the Toll like receptor 4 pathway, triggering a cascade of events that includes increased activity of the IKK-β/NF-κB and JNK/AP-1 signaling pathways, which is an inflammatory pathway responsible for increasing the production of pro-inflammatory cytokines, such as IL-6, TNF-alpha, which, upon reaching the nuclei of anxiety regulation found in the hypothalamus, increase this anxiogenic behavior in rodents (Rogero & Calder, 2018; Santamarina *et al.*, 2019; Souto *et al.*, 2020). There is evidence that consumption of these diets during adulthood can cause neuroinflammation, affecting brain regions associated with neurodevelopment and emotional behavior. Furthermore, studies also suggest that maternal consumption of these diets may impact the predisposition to inflammation to the next generation, affecting male and female offspring at distinct stages of life(Vasconcelos *et al.*, 2023; Silva *et al.*, 2021; Vieira *et al.*, 2023). Furthermore, damage to the genetic material of breeding males fed HD, caused by the inflammation generated, can also influence mood regulation, through the genetic transmission of damaged DNA, and especially if the parents already have anxiety in their clinical history (KORGAN *et al.*, 2022a).

In the offspring, some parameters indicate anxious-like behavior in those coming from breeders that ingested HFD, such as a longer grooming time in these offspring (HF/NF, NF/HF and HF/HF) in the open field test, and a longer time and entries in the closed arms in the elevated plus maze test. Some studies show that maternal nutrition influences this behaviour due to neuroinflammation generated by poor eating habits, also seen in adult rats, and by changes in the modulated serotonergic system pathway of intrauterine life caused by

the reduction of the immunoreactivity of serotonin receptors (5-HT) in the prefrontal cortex. Recent studies with maternal diet have shown that such anxious behaviour can persist into the second generation (Cavalcanti *et al.*, 2021; Deal *et al.*, 2020; Silva *et al.*, 2021).

Neurobehavioural changes such anxious-like behaviour caused by the HFD diet seem to be closely related to imbalances in the gut microbiota, via the gut-brain axis (CÂNDIDO *et al.*, 2017). We observed in the breeding males and females, and in the Offspring from group HF/HF, which the number of *Bifidobacterium* was reduced, and the *Escherichia coli* is increased as are *Enterobacteriaceae* and *Bacteroides*, the latter having an affinity for saturated fat as a metabolic substrate (ALLAIN *et al.*, 2021; AMABEBE *et al.*, 2020; HASSAN *et al.*, 2019; WANG *et al.*, 2021a)

Our research group has already shown that dams fed with HFD caused damage to the intestinal parenchyma, caused by an inflammatory process, decrease in intestinal villi and, consequently, and alteration in the bacterial faecal counts of the offspring with a reduction in the count of *Lactobacillus* and *Bifidobacterium* and an increase in potentially pathogenic bacteria (*Enterobacteriaceae* and *Bacteroides spp*.), even when they are fed with a healthy diet along of life (PINHEIRO *et al.*, 2019). Previous studies showed that 3-week-old offspring from breeding females fed with HFD developed long-term inflammatory bowel disease, due to an increase in pro-inflammatory cytokines such as IL-6, an alteration microbial composition in faeces with the increase in the *Firmicutes*/*Bacteroidetes* ratio and damage to tight junction formation (Liu *et al.*, 2022; Xie *et al.*, 2018a).

Experimental studies have also shown that dysbiosis induced by diets rich in saturated and trans fatty acids can decrease the amount of short-chain fatty acids affecting the intestinal barrier.(Garcia-Larsen *et al.*, 2018; Yao *et al.*, 2021)

Propionic acid, quantified in breeding females and males and in the offspring of the HF/HF group (both breeding males fed on HFD) is because this SCFA, together with the butyrate is widely used as a substrate for gluconeogenesis in enterocytes and at the hepatic level (Koh *et al.*, 2016). The low levels of acetic acid observed in breeding rats and in the offspring of the HF/HF group can relate to the reduced count of *Bifidobacterium*, which are the producers of acetate (Izumi *et al.*, 2019; Nagpal *et al.*, 2019). Low acetate levels may also be linked to hyperphagia, and increased weight seen in the HF/HF offspring, as acetic acid can bypass

the blood-brain barrier activating neurons in the hypothalamus that induce satiety (Frost *et al.*, 2014).

Organic acids play a key role in gut-brain axis signaling, human studies show a positive correlation between high faecal propionic acid levels in anxious behaviour, particularly in young people (Huang *et al.* 2021; On Wah *et al.* 2019).

Our study showed that HFD, being a highly inflammatory diet, can cause intestinal damage, such as the reduction of intestinal crypts, decreasing the area of villi, both in breeding mothers fed with HFD, as well as in breeding fathers, as well as in offspring. from both breeders who fed the same diet, showing that both intrauterine development and gene transmission can influence the intestinal development of the offspring. In breeders, they are characterized by the deposition of dead cells of the intestinal epithelium within the crypts. In the offspring, the inflammatory process caused by excess saturated and trans fatty acids, caused damage to the development of the organ in intrauterine life, reducing the intestinal absorptive area (DAI *et al.*, 2020; GOHIR *et al.*, 2019; XIE *et al.*, 2018b; ZHENG *et al.*, 2023).

The evaluation of inflammatory markers in the sexual organs of the parents, as well as the analysis of epigenetic changes in the brain tissues and sexual organs of the parents and children can be considered limitations of our study to better understand some of the repercussions of the parental HFD diet on the offspring.

We conclude that fetal programming can be affected by pre- and post-conceptional high-fat parental nutrition, and that this dietary pattern caused increased adiposity, in addition to dyslipidaemia, anxiety-like behaviour and changes in intestinal bacteria counts, with potential involvement of acids. organic and NF-kB. Such observed changes remain in the offspring in the long term and were enhanced in offspring in which both breeders (males and females) were fed an HFD diet.

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Conflict of Interest

The authors declare no competing interests.

Authorship

R.O.P., J.K.B.S. and JSA: Conceptualization; Methodology; Visualization; Investigation, Writing- Original draft preparation. R.O.P., M.M., J.K.B.S. and JSA: Editing and Writing-Reviewing. R.O.P, A.C.A.V., M.L.R.B., N.L.S., H.C.C., D.S.S., H.M.A.N., and A.F.A.: Validation; Data curation; Formal analysis. JSA and M.M: Funding acquisition; J.S.A.: Project administration and Supervision.

Supplementary material

For supplementary material/s referred to in this article, please visit: https://doi.org/

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ANEXO

Universidade Federal da Paraíba

Comissão de Ética no Uso de Animais
Reitoria

CERTIFICADO

Certificamos que a proposta intitulada "Influência da dislipidemia paterna sobre a função intestinal, parâmetros bioquímicos e comportamentais na prole", protocolada sob o CEUA nº 9877041019 (ID 000902), sob a responsabilidade de **Jailane de Souza Aquino** *e equipe; Rafael Oliveira Pinheiro; Juliana Kessia Barbosa Soares; Mariana Campos Lins* - que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino - está de acordo com os preceitos da Lei 11.794 de 8 de outubro de 2008, com o Decreto 6.899 de 15 de julho de 2009, bem como com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi **aprovada** pela Comissão de Ética no Uso de Animais da Universidade Federal da Paraíba (CEUA/UFPB) na reunião de 06/12/2019.

We certify that the proposal "Influence of paternal dyslipidemia on intestinal function, biochemical and behavioral parameters in offspring", utilizing 40 Heterogenics rats (males and females), protocol number CEUA 9877041019 (ID 000902), under the responsibility of **Jailane de Souza Aquino** *and team; Rafael Oliveira Pinheiro; Juliana Kessia Barbosa Soares; Mariana Campos Lins* - which involves the production, maintenance and/or use of animals belonging to the phylum Chordata, subphylum Vertebrata (except human beings), for scientific research purposes or teaching - is in accordance with Law 11.794 of October 8, 2008, Decree 6899 of July 15, 2009, as well as with the rules issued by the National Council for Control of Animal Experimentation (CONCEA), and was **approved** by the Ethic Committee on Animal Use of the Federal University of Paraíba (CEUA/UFPB) in the meeting of 12/06/2019.

Finalidade da Proposta: Pesquisa (Acadêmica)

Vigência da Proposta: de 11/2019 a 09/2022 Área: Nutrição

Origem:	Unidade de Produção Animal IPeFarM						
Espécie:	Ratos heterogênicos	sexo:	Machos e Fêmeas	idade:	40 a 45 dias	N:	40
Linhagem:	Rattus Norvegicus - Wistar			Peso:	85 a 95 g		

Local do experimento: Laboratório de Nutrição Experimental, LANEX (Departamento de Nutrição/Centro de Ciências da Saúde - DN/CCS/UFPB) está sendo credenciado e tem como responsável técnico o veterinário prof. Eulampio José da Silva Neto. Foi anexado no sistema do CEUA-UFPB a Anotação de Responsabilidade Técnica (ART) do médico veterinário acima citado, emitida pelo Conselho Regional de Medicina Veterinária do Estado da Paraíba.

João Pessoa, 09 de dezembro de 2019

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