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LUANA BARRETO MEICHTRY

ADIÇÃO DE GORDURA SATURADA E GORDURA VEGETAL HIDROGENADA NA DIETA INDUZ COMPORTAMENTOS TIPO - DEPRESSIVO E ANSIOSO EM *Drosophila melanogaster*

Uruguaiana, RS, Brasil

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Dissertação apresentada ao programa de Pós-graduação Stricto Sensu em Bioquímica da Universidade Federal do Pampa (UNIPAMPA), como requisito parcial para obtenção do grau de **Mestra em Bioquímica**.

Orientadora: **Profa. Dra. Marina Prigol**

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Área de concentração: Bioquímica toxicológica

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RESUMO

Atualmente há um elevado consumo de alimentos ricos em ácidos graxos (FA) saturados e transterificados. Esse consumo inadequado está associado a desordens metabólicas e neurológicas, podendo aumentar a vulnerabilidade a doenças como ansiedade e depressão. Um modelo para estudo de doenças humanas é o de *Drosophila melanogaster*, conservando vias metabólicas, sinalizadoras e comportamentais dos humanos. Diante disso objetivou-se avaliar se a adição de gordura saturada e gordura vegetal hidrogenada na dieta induziria comportamento mimético à depressão e ansiedade em *Drosophila melanogaster*. As moscas foram expostas a dietas contendo gordura vegetal hidrogenada (HVF) nas concentrações de Gordura vegetal hidrogenada substituta (SHFV), HVF 10% e HVF 20%, e Banha (L) nas concentrações de Banha substituta (SL), L 10% e L 20%, durante 7 dias. Avaliou-se a mortalidade, o peso corporal e a ingestão alimentar das moscas, além disso, foram analisados comportamentos miméticos a ansiedade (através dos testes de limpeza e claro/escuro) e depressão (através do teste de natação forçada). Além disso, foi avaliado o comportamento agressivo das moscas, assim como, a atividade locomotora e a capacidade de escalada (através dos testes de campo aberto e geotaxia negativa, respectivamente). Por fim, os níveis de serotonina (5HT) foram dosados na cabeça das moscas. Observou-se que altas quantidades de HVF e L na dieta podem causar uma diminuição na expectativa de vida e influenciar parâmetros comportamentais. As moscas alimentadas com dieta HVF em todas as concentrações apresentaram comportamento semelhante à depressão, ansiedade e, além disso, um maior número de eventos agressivos quando comparados à dieta regular (RD). Já as moscas expostas a dieta L apresentaram comportamento semelhante à depressão em todas as concentrações, não apresentando comportamento semelhante à ansiedade. Porém, houve aumento na agressividade em moscas expostas a L 20%. Além disso, houve uma redução nos níveis de 5HT nas moscas expostas a HVF 10%, HVF 20%, SL, L 10% e L 20%. Conclui-se que a *D. melanogaster* pode servir como um modelo ideal para a compreensão de distúrbios psiquiátricos e que o tipo de FA ofertado na dieta pode influenciar nesses distúrbios, demonstrando o impacto da composição dos FAs nas vias neurais, podendo influenciar na sinalização de neurotransmissores como o 5HT aqui avaliado, e dessa forma, causar alterações comportamentais.

Palavras-chave: Metabolismo de lipídios, composição dietética, distúrbios psiquiátricos, serotonina.

ABSTRACT

Currently there is a high consumption of foods rich in saturated and transesterified fatty acids (FA), this inadequate consumption is associated with metabolic and neurological disorders, and may increase vulnerability to diseases such as anxiety and depression. A model for the study of human diseases is that of Drosophila melanogaster, conserving metabolic, signaling and behavioral pathways with humans. The aim of this study was to evaluate whether the addition of saturated fat and hydrogenated vegetable fat in the diet would induce mimetic behavior to depression and anxiety in Drosophila melanogaster. The flies were exposed to hydrogenated vegetable fat (HVF) at the concentrations of Substituted hydrogenated vegetable fat (SHFV), HVF 10% and HVF 20%, and Lard (L) in the concentrations of substituted lard (SL), L 10% and L 20% for 7 days. The mortality, body weight and dietary intake of flies were evaluated. In addition, anxiety mimetic behaviors (through cleaning and light / dark tests) and depression (through forced swimming test) were analyzed. In addition, we evaluated the aggressive behavior of the flies, as well as the locomotor activity and the climbing ability through the open field and negative geotaxis tests, respectively. Lastly, serotonin (5HT) levels were dosed. It was observed that high amounts of HVF and L in the diet can cause a decrease in life expectancy and influence behavioral parameters, and that flies fed HVF diet at all concentrations presented behavior similar to anhedonia, anxiety and, in addition, a greater number of aggressive events when compared with the regular diet (DR). On the other hand, the flies exposed to the SL diet showed behavior similar to anhedonia in all concentrations, not presenting behavior similar to anxiety. However, there was an increase in aggressiveness in flies exposed to L 20%. In addition, there was a reduction in 5HT levels in flies exposed to HVF 10%, HVF 20%, SL, L 10% and L 20%. It is concluded that D. melanogaster can serve as an ideal model for the understanding of psychiatric disorders and that the type of AF offered in the diet can influence these disorders, demonstrating the importance of the composition of the FAs in the neural pathways, which may influence the signaling of neurotransmitters such as the 5HT assessed here, and thus, cause behavioral changes.

Keywords: Lipid metabolism, dietary composition, depression, membrane permeability.

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LISTA DE ABREVIATURAS E SIGLAS

FA: Ácido graxo

PUFA: Ácido graxo poliinsaturado

EPA: Ácido eicosapentaenoico

DHA: Ácido docosahexaenoico

ARA: Ácido araquidônico

RD: Dieta regular

HVF: Gordura vegetal hidrogenada

SHVF: Gordura vegetal hidrogenada substituta

L: Banha

SL: Banha substituta

5HT: Serotonina

ACSL: Ácido graxo de cadeia longa – CoA sintetase

OMS: Organização mundial da saúde

SUMÁRIO

1. INTRODUÇÃO

A alimentação está diretamente relacionada à homeostasia do organismo. Sabe-se que, quanto mais natural é o alimento a ser consumido, melhor é sua qualidade nutricional (NICOLAU; DE CASTRO, 2018), porém, atualmente o consumo de alimentos prontos, conhecidos como industrializados aumentou consideravelmente pela população. Esse tipo de alimento pode trazer malefícios à saúde, visto que, muitos desses, tendem a ter valores elevados de gorduras saturadas e gorduras do tipo trans (LAM; ADAMS, 2017; CHANG et al., 2018; MONTEIRO et al., 2018).

Esses tipos de gorduras, além de serem prejudiciais sobre fatores metabólicos, causando, alterações nos níveis de triglicerídeos, glicose, obesidade e o surgimento de doenças cardiovasculares, também podem estar associadas ao desenvolvimento de desordens cerebrais, podendo alterar as membranas neurais e dessa forma, afetar a neurotransmissão sináptica (LABOUESSE et al., 2013; HAYGERT et al., 2018).

Além disso, a ingestão inadequada de gordura pode estar relacionada ao surgimento de desordens psicológicas, como por exemplo, transtornos de ansiedade e depressão (LIN; HUANG; SU, 2010; BAZINET; LAYÉ, 2014). Tais transtornos são responsáveis por atingir grande parte da população mundial, sendo considerados incapacitantes e em casos mais graves, podendo acarretar na morte do indivíduo afetado (GANGWISCH et al., 2015; JACKA et al., 2015).

Diante disso, é de grande importância a compreensão dos mecanismos de tais desordens, sendo assim, há uma grande busca por modelos alternativos e eficazes que possam discutir a fisiologia humana, os quais tornem possível o estudo de tais desordens psicológicas, sendo esse modelo de fácil acesso e manejo, para que posteriormente, se tornem mais acessíveis as investigações para a descoberta de novos fármacos (MORALES, 2008).

Um modelo que tem sido altamente utilizado para estudos de desordens humanas é o de *Drosophila melanogaster*, tendo em vista que esse modelo compartilha com os humanos inúmeros genes, conserva vias metabólicas e sinalizadoras. Além disso, há conservação a nível comportamental e de seus mecanismos moleculares, incluindo ritmos circadianos, aprendizagem, memória e sono (NICHOLS, 2006; BENTON, 2008; PANDEY; NICHOLS, 2011). Esse modelo é considerado útil para estudar o metabolismo lipídico e homeostasia, já que assim como os humanos, em *Drosophilas* os lipídios também desempenham papéis importantes ao organismo (ATELLA; MAJEROWICZ; GONDIM, 2012). Diante disso, objetivou-se avaliar se a adição de gordura saturada e gordura vegetal hidrogenada (HVF) na dieta induziria comportamento mimético à depressão e ansiedade em *Drosophila melanogaster.*

2. OBJETIVOS

2.1 Objetivo geral

Avaliar os efeitos da adição de gordura saturada e gordura vegetal hidrogenada na dieta sobre os comportamentos miméticos a depressão e ansiedade em *Drosophila melanogaster*.

2.2 Objetivos específicos

- Avaliar a mortalidade de moscas expostas a diferentes concentrações de HVF e banha (L);

- Analisar o consumo alimentar e peso corporal de moscas expostas a diferentes concentrações de HVF e L;

- Investigar a influência na atividade locomotora de diferentes concentrações de HVF e L nas moscas;

- Avaliar os efeitos das dietas ricas em gordura em diferentes concentrações sobre os parâmetros comportamentais semelhantes a ansiedade e depressão nas moscas.

- Analisar o efeito das dietas HVF e L em diferentes concentrações no comportamento agressivo das moscas;

- Investigar o efeito das dietas HVF e L em diferentes concentrações sobre os níveis de 5HT na cabeça das moscas.

3. REVISÃO BIBLIOGRÁFICA

3.1. Consumo Alimentar

O consumo de alimentos é essencial a vida pois auxilia na manutenção e equilíbrio energético, proporcionando a homeostasia do organismo (GARLAPOW et al., 2015). Uma dieta equilibrada tem grande importância em quase todas as principais categorias de doenças, indo desde as desordens metabólicas, até mesmo doenças mentais (OPIE et al., 2015; KINGSBURY et al., 2016).

Através de uma alimentação saudável é possível haver a prevenção e controle de riscos para desordens como, diabetes tipo 2, hipertensão, obesidade, colesterol elevado, doenças cardiovasculares e doenças neurodegenerativas, estando associadas também à redução do risco de mortalidade por todas as causas, como também, ao início da doença (MATTEI et al., 2018; SCHWINGSHACKL; BOGENSBERGER; HOFFMANN, 2018). Além disso, uma alimentação equilibrada e fracionada em horários coerentes durante o dia, pode trazer benefícios ainda maiores ao organismo de cada indivíduo, mostrando dessa forma, que os alimentos e a forma como são consumidos, são extremamente essenciais ao funcionamento adequado do nosso corpo (KARATZI et al., 2015; LARSSON et al., 2016).

Em relação aos benefícios, existem alimentos funcionais, que podem trazer vantagens à saúde, tendo potencial antioxidante (BENZIE; CHOI, 2014), anti-inflamatório (GRIFFITHS et al., 2016) entre outras propriedades, podendo até mesmo reduzir o risco de doenças mentais, como a ansiedade e a depressão, um exemplo desses alimentos são os ácidos graxos (FAs) poli-insaturados, onde há evidências que tais tipos de FAs podem ser incorporados nas membranas da estrutura do sistema nervoso central, atuando no aumento e fluidez dessas membranas e assim, facilitando o transporte de serotonina, entre outras funções. Da mesma forma, os FAs monoinsaturados, que podem melhorar a ligação da serotonina em seus receptores (LOGAN, 2005; BERTOLI et al., 2015).

Salienta-se que doenças mentais podem tornar-se as maiores contribuintes para gastos em saúde pública, podendo custar até mais que doenças cardiovasculares, câncer, diabetes e doenças respiratórias crônicas. Embora a intervenção nutricional relacionada a doenças mentais sejam medidas de saúde pública, ainda existe uma limitação quanto a implementação, devido à falta de pesquisas relacionadas a quais intervenções seriam mais conformes e em qual tipo de população seriam mais eficazes positivamente (HOERR; FOGEL; VAN VOORHEES, 2017).

No entanto, assim como os alimentos podem trazer benefícios a saúde, quando estes são consumidos de maneira não adequada, podem ser prejudiciais ao organismo, podendo acarretar em desordens no metabolismo (HEINDEL et al., 2017), dentre essas desordens, podem estar presentes, as alterações metabólicas, como, diabetes 2 (SCHWINGSHACKL; BOGENSBERGER; HOFFMANN, 2018), obesidade (TURNBAUGH, 2017), hipercolesterolemia, doenças cardiovasculares (ADRIOUCH et al., 2017) e também desordens psicológicas, como, ansiedade (ZEMDEGS et al., 2016) depressão (GANGWISCH et al., 2015; JACKA et al., 2015; LANG et al., 2015), e até mesmo danos ao sistema psicomotor (LEVENTAKOU et al., 2016).

Segundo a OMS doenças crônicas estão diretamente relacionadas à alimentação inadequada, onde estudos relatam uma redução no consumo de alimentos saudáveis e substituição destes por alimentos industrializados e/ou refeições prontas (LAM; ADAMS, 2017). Hoje em dia a maioria das pessoas procuram alimentos visando a praticidade, durabilidade e atratividade destes, deixando assim, de lado os nutrientes os quais deveriam dar maior importância.

Esses alimentos, também chamados de “Fast food”, geralmente além de ser pobre em nutrientes, contém componentes que podem ser prejudiciais à saúde quando consumidos em excesso, como, elevado teor de açúcar, elevado teor de gordura e elevado teor de sal, conhecidos por constituírem a “tríade sagrada” (DE ROSA; LA CAVA; MATARESE, 2017). Além do mais, esses alimentos geralmente contém um elevado teor de corantes artificiais, intensificadores de sabor e aditivos, fazendo com que tenham hiperpalatabilidade, além de terem maior durabilidade e praticidade em seu preparo, fazendo assim com que sejam mais atrativos ao consumidor

(BIELEMANN et al., 2015; MOUBARAC et al., 2017; CHANG et al., 2018; MONTEIRO et al., 2018). Inclusive, a sua apresentação e marketing promovem o aumento do consumo desses alimentos, tornando-os ainda mais interessante para o consumidor.

Salienta-se que segundo evidências a substituição de alimentos naturais para alimentos industrializados está associado a maior risco para várias doenças não transmissíveis relacionadas a dieta (MONTEIRO et al., 2018). Acrescentando-se que, esses alimentos podem ser considerados uma ameaça substancial à saúde, visto que, muitos desses, tendem a ter teores mais elevados de FAs, sendo esses, ácidos graxos saturados e FAs do tipo trans (LAM; ADAMS, 2017).

Na indústria alimentícia, as gorduras têm um papel fundamental na produção de alimentos, contribuindo no sabor, palatabilidade, textura e aroma, sendo desta forma, indispensáveis no processo de industrialização de grande parte de alimentos e assim, estando presente o dia-a-dia dos consumidores (VACLAVIK; CHRISTIAN 2013).

3.2. Consumo de ácidos graxos

Os lipídios são extremamente importantes na nossa dieta, por vários motivos, dentre eles, são fontes de energia para nosso corpo, auxiliam na absorção de alguns nutrientes lipossolúveis, por exemplo, algumas vitaminas lipossolúveis, são compostos bioativos e também, podem ajudar a melhorar o sabor de alguns alimentos (PEHLIVANOĞLU et al., 2018).

Em nosso organismo, os lipídios são responsáveis por desenvolver diversas funções, como, dar permeabilidade a membrana celular, formando a bicamada lipídica, são componentes da membrana nuclear e retículo endoplasmático, podem ser esteróis, podem apresentar funções estruturais e sinalizadoras, participam na síntese de hormônios. Além do mais, podem auxiliar no crescimento corporal e também no metabolismo e prevenção de doenças ósseas. Sendo assim, existem uma ampla variedade de lipídios que são necessários para diferentes funções (DOWHAN; BOGDANOV, 2002; MACRI et al., 2012; MURO; ATILLA-GOKCUMEN; EGGERT, 2014).

Porém, isso não significa que a ingestão de gorduras pode ser ilimitada. Diante disso, a organização mundial da saúde (OMS) objetivou a recomendação de ingestão diária de lipídios de 15 a 30% da energia total. No entanto, deve-se tomar cuidado ao tipo de lipídio a ser consumido, tendo em vista que, existe uma ampla variedade de lipídios e que estes podem trazer benefícios, assim como, ser prejudiciais à saúde dependendo da composição e quantidade a ser ingerida. Devido a isso, a OMS determina que a ingestão de FA saturado seja inferior a 10% e a de FA do tipo trans inferior a 1% do valor de energia total, sendo o restante compostos por ácidos graxos do tipo insaturado.

3.2.1. Ácido graxo saturado

O FA do tipo saturado é um lipídio composto por ligações carbono-carbono, ou seja, não possuí dupla ligação. R-COOH representa sua fórmula geral, onde o grupamento R é representado por um hidrocarboneto de cadeia linear. Esse tipo de FA geralmente é encontrado na natureza possuindo estrutura não ramificada e um número par de átomos de carbono, (RATNAYAKE; GALLI, 2009). Os alimentos ricos nesse tipo de FA incluem, carne vermelha e suína, laticínios ricos em gordura e alimentos processados (KENNEDY et al., 2009).

Existe uma ampla base de estudos que associa o alto consumo desse tipo de gordura ao aparecimento de doença cardiovascular, isso devido ao aumento das concentrações de colesterol LDL no sangue (SIRI-TARINO et al., 2010). Além disso, estudos mostram uma associação no aumento de marcadores pró-inflamatórios em modelos animais e linhagens celulares aos quais tiveram maior exposição aos FAs saturados, evidenciando dessa forma, um estado inflamatório provocado pela gordura (MU; MUKAMAL; NAQVI, 2014; SANTAREN et al., 2017). Ainda, o consumo desse FA, é associado ao aparecimento de diabetes 2, contribuindo para o desenvolvimento da síndrome metabólica além de um aumento no peso corporal (LUNDMAN et al., 2007; KENNEDY et al., 2009; FOROUHI et al., 2014).

Esse tipo de FA é altamente encontrado em produtos industrializados, os quais são consumidos largamente pela população, então, devido a vários estudos relacionados aos malefícios causados pela elevada ingesta, as indústrias de alimentos tiveram que obter uma forma de reduzir a quantidade de gorduras saturadas nos alimentos, consequentemente reduzindo o teor de gordura total dos mesmos. Assim, ocorreu uma reformulação desses produtos, sendo os FAs saturados substituídos por FAs do tipo trans (LIST; MARANGONI, 2017).

3.2.2. Ácido graxo trans

Os FAs trans são definidos como isômeros geométricos de FAs monoinsaturados e poli-insaturados com pelo menos uma dupla ligação na configuração trans. Este tipo de FA sempre fez parte da dieta humana, estando presente de forma natural em produtos de origem animal, no entanto, devido a modificações frequentes nos padrões de alimentação e avanços industriais houve um aumento na utilização e consumo desse tipo de gordura (COSTA; BRESSAN; SABARENSE, 2006; IQBAL, 2014).

Porém, assim como a gordura saturada, a gordura trans também tem um efeito negativo a saúde, podendo provocar uma série de desordens como, aumento na concentração de colesterol LDL e triglicerídeos, pode promover disfunção endotelial e síntese de gordura hepática e ainda, reduzir os níveis de HDL no sangue, resultando em um risco ainda maior de desenvolver doença cardiovascular (LIU et al., 2017). Está também associada a dislipidemia, câncer, diabetes, inflamação e aumento na mortalidade por todas as causas (RAATZ et al., 2018).

O processo de hidrogenação dos FAs provoca a perda da atividade metabólica dos FAs naturais, dentre os efeitos dessa alteração metabólica está o aumento do risco de doenças cardiovasculares, além disso, existem estudos relacionados a efeitos negativos a saúde materno-infantil, afetando o crescimento intrauterino, retardo no desenvolvimento cerebral e maiores riscos de pré-eclâmpsia (ASCHERIO; WILLETT, 1997; COSTA; SEMMA, 2002; BRESSAN; SABARENSE, 2006).

Devido aos diversos efeitos negativos a saúde, as legislações de diferentes países empregaram restrições sobre a utilização de gorduras trans na produção de alimentos (RATNAYAKE et al., 2014), diante disso, a OMS recomenda que o consumo máximo deste tipo de gordura não deva ser superior a 1% das calorias totais. Já o Instituto de medicina determinou que não há um nível considerado seguro para a ingestão de gorduras trans industriais (LIU et al., 2017).

3.2.3. Ácidos graxos e distúrbios neurológicos

Estudos relatam que os macronutrientes desempenham um papel importante nas vias neurais, as quais estão envolvidas na regulação da homeostasia energética e hedônica (TULLOCH et al., 2015). O consumo de determinados alimentos altamente palatáveis, pode afetar de diferentes formas o cérebro, podendo modificar a sinalização e até mesmo todo o mecanismo comportamental. Um exemplo de diferentes alterações, encontra-se durante o consumo elevado de determinados tipos de gordura.

Existem estudos que têm mostrado que a ingestão de dietas ricas em gordura pode causar alterações tanto metabólicas, quanto no sistema nervoso central, onde são responsáveis por induzir a adaptações neuronais, prejudicando também, funções cognitivas (LABOUESSE et al., 2013). No entanto, as alterações neurais são mais evidentes dependendo do tipo de gordura a ser consumida (TULLOCH et al., 2015).

Em 1990, GREENWOOD realizou um dos primeiros estudos relacionados a aprendizado e memória em ratos alimentados com 20% de gordura saturada provinda de banha de porco, onde houve comprometimento em todos os parâmetros avaliados, demonstrando que o cérebro é sensível à disponibilidade dietética dos FAs e que à medida que o perfil de FAs no sistema nervoso central era alterado, o desempenho em tarefas cognitivas diminuía.

O tipo de FA consumido na dieta é de grande importância para as membranas neurais, pois são ligados aos fosfolipídios, regulando as propriedades físico-químicas da membrana, como, estrutura, fluidez e permeabilidade. Participa de funções importantes como regulação das funções proteicas da membrana, por exemplo, atividade enzimática, ligação ao receptor, interações proteína-membrana, entre outras (FUNARI; BARCELÓ; ESCRIBÁ, 2003). No entanto, a composição lipídica da membrana pode ser alterada de acordo com FAs consumidos na dieta (ZIEGLER et al., 2015).

Existem FAs que são essenciais para a saúde cerebral, como por exemplo os FAs poli-insaturados de cadeia longa (LCPUFA), onde auxiliam no desenvolvimento e funcionamento do sistema cerebral (INNIS, 2008; BAZINET; LAYÉ, 2014; JANSSEN; KILIAAN, 2014;). A bicamada lipídica consiste em fosfolipídios tendo como principais componentes DHA, ARA e EPA, dessa forma, uma deficiência na ingestão desse tipo de FA está associado a desordens cerebrais, estando relacionadas até mesmo ao aparecimento de sintomas de ansiedade e depressão (LIN; HUANG; SU, 2010; BAZINET; LAYÉ, 2014).

No momento em que há a deficiência de FAs importantes para a composição da membrana, estes, podem ser substituídos por outros provindos da dieta, porém, isso pode acarretar em possíveis problemas. Um exemplo está quando há um alto consumo de FA do tipo trans, este tipo de ácido graxo pode ser incorporado na membrana e consequentemente alterar a sua fluidez, uma vez que o FA do tipo trans encontrado em industrializados, é um FA modificado pelo processo de hidrogenação, onde ele passa a ser sintético e não mais natural. Com isso, a presença desse FA pode alterar os fosfolipídios, influenciando assim a permeabilidade da membrana (GINTER; SIMKO, 2016).

Neste contexto, a fluidez da membrana irá determinar a quantidade e o tipo de substância que irá ultrapassá-la, da mesma forma irá controlar os sinais a serem transmitidos através da mesma, então, o consumo inadequado de FAs pode ter como consequência, alteração na plasticidade e neurotransmissão sináptica (GINTER; SIMKO, 2016; HAYGERT et al., 2018).

Um dos neurotransmissores que podem ter sua sinalização afetada é o 5HT, este, quando alterado, é associado a distúrbios neuropsiquiátricos, estando relacionado a transtornos de humor como ansiedade e depressão, onde em um estudo com roedores, a substituição de FAs importantes por outros, provocou a redução na liberação de 5HT estimulada (CHALON, 2006) e em demais estudos essa diminuição esteve relacionada ao aparecimento de sintomas de ansiedade e depressão (CARVER; JOHNSON; JOORMANN, 2009; ZEMDEGS et al., 2016).

3.3. Ansiedade e depressão

Segundo a OMS, distúrbios psicológicos afetam grande parte da população mundial, tornando-se uma das maiores causas de incapacidade da população. Pesquisas recentes têm mostrado que fatores externos como a alimentação, podem tornar-se influentes para o aparecimento e agravamento de tais morbidades, podendo modular biomarcadores associados ao desenvolvimento de mudanças no humor, sendo a ansiedade e depressão os transtornos relacionados ao humor que mais atingem a população mundial (GANGWISCH et al., 2015; JACKA et al., 2015; LANG et al., 2015).

A depressão é responsável por diminuir a qualidade de vida em grande parte da população mundial, gerando incapacidade e podendo causar até mesmo a morte dos indivíduos afetados (EBERT et al., 2018), essa desordem tem como sintomas característicos humor triste, anedonia e insônia (BEARD et al., 2016), além disso, pode causar alterações físicas e cognitivas (PRATT; BRODY, 2014). Normalmente, pacientes que se encontram em estado depressivo, geralmente apresentam ansiedade associada ao transtorno (DUNNER et al., 2003).

A ansiedade geralmente é uma consequência de eventos adversos na vida. Tendo como sintoma a tendência de imaginar e fixar a possibilidade de vivenciar cenários futuros adversos (MILOYAN et al., 2018). No entanto, o transtorno de ansiedade pode trazer prejuízos à saúde, uma vez que o indivíduo pode ter sintomas de preocupação excessiva, sendo esta inapropriada e persistente, muitas vezes sem um motivo objetivo, além do mais, pode ser acompanhada de sintomas físicos como, taquicardia, tremor, fadiga, agitação, além de, dificuldade de concentração, dentre outros, sendo considerado, assim como a depressão, um distúrbio incapacitante (LADER, 2015).

Apesar de existir uma ampla gama de medicamentos fornecidos para o tratamento de tais desordens psicológicas, nem sempre esses medicamentos são eficazes, podendo ser acompanhados de efeitos colaterais desagradáveis, além de atrasos para começar o efeito desejável podendo ocasionar até mesmo na desistência no tratamento pelo indivíduo afetado (DALY et al., 2018; (BANDELOW et al., 2015).

Diante disso, é de extrema importância a compreensão do mecanismo de tais doenças humanas e a busca por modelos alternativos e eficazes que possam discutir a fisiologia humana, sendo esse modelo de fácil acesso e manejo, para que futuramente sejam mais alcançáveis as técnicas experimentais, obtendo-se um maior acesso para pesquisa e tornando maior a possibilidade para descoberta de novos fármacos alternativos, e assim, proporcionar uma qualidade de vida melhor (MORALES, 2008; BANDELOW et al., 2015).

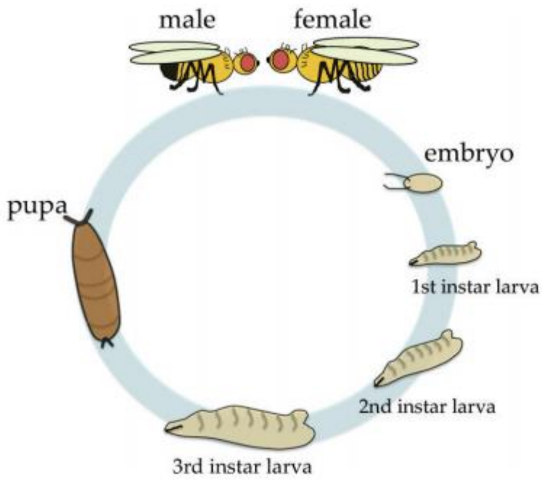
3.4. Modelo *Drosophila melanogaster*

O modelo *Drosophila melanogaster* é altamente utilizado para compreensão dos mecanismos de doenças humanas. Esse modelo e os humanos compartilham inúmeros genes, conservam vias metabólicas e sinalizadoras e ainda, há crescente evidência de conservação a nível comportamental e de seus mecanismos moleculares, incluindo ritmos circadianos, aprendizagem, memória e sono (NICHOLS, 2006; PANDEY; BENTON, 2008; NICHOLS, 2011).

Além do mais, a *Drosophila* é um modelo de fácil manipulação, profílica, de baixo custo, fácil criação e tolerante a diversas condições, além de ser invertebrado, ou seja, não é necessário ter aprovação pelo comitê de ética para posterior utilização, dessa forma, tornando-se mais fácil o acesso a sua utilização (NICHOLS 2006).

O ciclo completo da *Drosophila* tem duração em torno de 10 dias à uma temperatura de ± 25°C. Para desenvolvimento completo embrionário a mosca deve passar por 3 estágios larvais antes da pupação, onde as larvas comem e crescem e se desenvolvem. Ao completar a metamorfose, uma mosca adulta eclode (Allocca & Bellosta, 2018).

Figura 1. Ciclo de vida da *Drosophila melanogaster*



Fonte: Allocca & Bellosta, 2018.

Nos últimos anos, a *Drosophila* surgiu como um modelo útil para estudos do metabolismo lipídico e homeostasia energética. Nos insetos, assim como nos vertebrados, os lipídios desempenham papéis importantes no organismo, como, formação de importantes reservas energéticas, são constituintes de estruturas celulares, atuam como hormônios, sendo fundamentais em algumas situações de grande demanda metabólica (ATELLA; MAJEROWICZ; GONDIM, 2012).

Em comparação aos mamíferos, a *Drosophila* compartilha anatomia de órgãos e tipos celulares envolvidos no metabolismo de lipídios e homeostasia. Na mosca, os lipídios são armazenados na forma de triacilglicerol e éster de colesterol, sendo acumulados no corpo gordo da *Drosophila*, sendo este semelhante aos adipócitos de mamíferos (KÜHNLEIN, 2011; LIU; HUANG, 2013). Sendo assim, a *Drosophila* pode servir como modelo útil para estudos de doenças metabólicas, como lipodistrofia e obesidade. Assim como para estudos da homeostasia metabólica em relação aos nutrientes consumidos, por exemplo, diabetes e obesidade induzidas por alto teor de gorduras ou alto teor de açúcares (LIU; HUANG, 2013).

Além disso, nosso grupo de pesquisa demonstrou em estudo recente que a exposição a uma dieta rica em gordura causa alterações metabólicas e comportamentais em *Drosophila melanogaster*, como, aumento no estresse oxidativo, redução da sobrevivência, alterações nos níveis de glicose e triglicerídeos, redução na atividade locomotora e redução da atividade da enzima acetilcolinesterase (TRINDADE DE PAULA et al., 2016).

Assim como a maior parte dos eucariotos, a *Drosophila* é capaz de fazer síntese de FAs saturados não essenciais através da acetil-CoA carboxilase e FA sintetase, porém, assim como a maior parte dos animais, a mosca é isenta de enzimas que produzam o ácido alfa-linoleico (C18:2) e alfa-linolênico (C18:3), precisando adquiri-los através da alimentação, sendo estes, os mais abundantes encontrados na *Drosophila*.

Curiosamente, diferente dos humanos, a mosca não possui FAs de cadeia longa com mais de 20 carbonos, dessa forma, quando consumidos, eles são divididos em moléculas menores contendo até 20 carbonos (VRABLIK; WATTS, 2013; SHEN et al., 2010; ZIEGLER et al., 2015). Dessa forma, assim como os vertebrados, a *Drosophila* também precisa adquirir FAs essenciais através da dieta para obter um bom funcionamento do organismo, assim como, do sistema nervoso central, podendo a deficiência desses FAs, acabar gerando disfunções sinápticas e consequentemente, alterando a neurotransmissão (BAZINET; LAYÉ, 2014).

A neurociência na *Drosophila* é cada vez mais compreendida, onde é possível estudar os mecanismos do controle genético sobre o comportamento, mecanismos celulares e também relacionados aos circuitos, uma vez que no cérebro adulto da *Drosophila* encontra-se cerca de 100.000 neurônios tratáveis (ITO et al., 2013). Seu cérebro utiliza neurotransmissores, canais e módulos semelhantes como aqueles em cérebro de mamífero, além de já existirem sugestões de que as moscas são capazes de formar uma espécie de memória de trabalho e tomada de decisões simples, tornando possível a compreensão de mecanismos comportamentais (KAZAMA, 2015).

Estados emocionais podem ser compartilhados entre humanos e animais, podendo ser avaliados conforme testes bioquímicos e também comportamentais (MOHAMMAD et al., 2016). Em um estudo realizado anteriormente por nosso grupo de pesquisa, foi possível observar comportamentos semelhantes a desordens como anedonia e ansiedade em um modelo de *Drosophila* expostas a diferentes tipos de estresse, demonstrando que a mosca pode ser considerada um modelo eficiente para estudo de desordens psicológicas causadas por fatores externos (ARAUJO et al., 2018).

No entanto, tendo em vista que tais desordens podem ser avaliadas nesse modelo, e que o tipo de FA consumido na dieta pode ser responsável por alterações na neurotransmissão e com isso levar a distúrbios psicológicos, há uma deficiência de estudos que relacionem ambos parâmetros concomitantemente nesse modelo.

4. MANUSCRITO CIENTÍFICO

Os resultados os quais fazem parte desta dissertação apresentam-se sob a forma de manuscrito científico, o qual encontra-se aqui estruturado sob o título: "Addition of saturated fat and vegetable hydrogenated fat in the diet induces depressive and anxiety-like behaviors in *Drosophila melanogaster*". Os itens Materiais e Métodos, Resultados, Discussão e Referências Bibliográficas, encontram-se inseridos no próprio manuscrito. O manuscrito apresenta-se na forma que será submetido a revista "Metabolism".

Addition of saturated fat and vegetable hydrogenated fat in the diet induces depressive and anxiety-like behaviors in *Drosophila melanogaster*

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Abstract

Aim: Evaluate the effects of the addition of saturated fat and hydrogenated vegetable fat in the diet on depressive and anxiety-like behaviors in *Drosophila melanogaster.*

Methods: The flies (both genders) were exposed to experimental diets containing hydrogenated vegetable fat (HVF, containing a high concentration of trans fat) in the concentrations of SHVF, HVF 10% and HVF 20%, and Lard(L, containing high saturated fat content) in the concentrations of SL, L 10% and L 20%, during a period of 7 days. Mortality, body weight and dietary intake of these flies were analyzed. In addition, were analyzed anxiety-like behavior (evaluated through the grooming and light/dark tests) and depressive-like (evaluated by the forced swim test). In addition, the aggressive behavior of the flies was evaluated. To verify that the tests did not have interference due to motor damage, we evaluated the locomotor activity and climbing capacity of the flies through the test of open field and negative geotaxis, respectively. Lastly, the levels of serotonin (5HT) were dosed in the head.

Results: Our results showed that high amounts of HVF and L in the diet can cause an increase in mortality of flies, and that the inappropriate consumption these fats may influence behavioral parameters. We observed that flies fed with HVF diet at all concentrations had similar behaviors to depression, anxiety and a greater number of aggressive events when compared with regular diet (RD). The L flies showed depressive-like behavior in all concentrations but did not present anxiety-like behavior. However, there was an increase in the number of aggressive events in flies exposed to L 20%. Regarding the 5HT levels, there was a significant reduction in the flies exposed to SHVF 10%, HVF 20%, SL, L 10% and L 20% compared with the RD group.

Conclusion: This work shows that *Drosophila melanogaster* can serve as valuable model for understanding psychiatric disorders and that the type of AF offered in the diet can influence these disorders. Demonstrating the importance of the composition of the FAs in the neural pathways, being able to influence the signaling of neurotransmitters, such as 5HT and thus, cause behavioral changes.

Keywords: Metabolism, cell membrane, dietary composition, psychological disorders, serotonin.

Abbreviations: FA: fatty acid; PUFA: polyunsaturated fatty acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; ARA: arachidonic acid; RD: regular diet; HVF: hydrogenated vegetable fat; SHVF: hydrogenated vegetable fat substitute; L: Lard; SL: Lard substitute 5HT: Serotonin; ACSL: long-chain-fatty-acid-CoA synthase

1. Introduction

The consumption of foods is essential due be the main font of energy demand, being related to the homeostasis of the organism. However, any imbalance in the caloric intake can be cause negative consequences to the metabolism. Currently, the world population has a high consumption of industrialized foods [1], these, go through a type of processing with the intent of, increase taste, palatability, consistency, odor, durability, among others, for what become more pleasant to consumer. However, these foods can be considered a substantial threat to health, since, many of these, tend to be more elevated in saturated fat and trans fat [2].

The high consumption of saturated fat is associated to the appearance of cardiovascular diseases, due to increase of the concentrations of LDL cholesterol in the blood [3]. For this reason, the food industries had to obtain a form to reduce the amount of saturated fat in the foods, consequently reducing the total fat content of the very, thus making are formulation of these products where the saturated FA were replaced per trans FA [4].

The trans FA are defined with geometric isomers of monounsaturated and polyunsaturated FA with at least a double bond in the trans configuration. This type of FA always did part of the human diet, being present of natural form in products of animal origin, however, due to frequents modifications in the feeding patterns and industrial advances there was an increase in the use and consumption of this type of fat [5,6]. However, as well as the saturated fat, the trans fat also has a negative effect to health. The hydrogenation process of FA provoke the loss of metabolic activity of the naturals FA, among the effects of that metabolic alteration it is the increased risk of cardiovascular diseases [6, 7].

Furthermore, it is associated to the development of neurological problems, where this type of fat can end up incorporating in the neural lipid bilayer, being able to cause changes in neurotransmission, thus, increasing vulnerability to psychological diseases, such as anxiety and depression. These psychological disorders are responsible per affect millions of people in the world, can cause even in death [8, 9]. According to OMS in the next years these disorders may reach second place related to the main causes of diseases in the world, being the depression an of the disease considered more incapacitating.

Thus, it is extremely important the understanding to the mechanism of such human disease, for what posteriorly become easier the search per alternative treatments, aiming at reducing the damage caused by such disorders. Usually, the model of rodents is widely used for understanding psychiatric disorders [10], however, increases gradually the access scarcity to these animals. On this, it is of great importance the search for alternative experimental models and effective that can discuss human physiology, being easy to access and manage, enabling the understanding of mechanisms of disease in humans, going from metabolic changes, even to neurological disorders, for posteriorly become more achievable the experimental techniques for discovery of new alternative drugs [11].

On this, a model that has been bringing promising results related to understanding human diseases is the of *Drosophila melanogaster*. This model and the humans share innumerable genes, conserve metabolic and signaling pathways and, besides that, there are growing evidence of conservation to behavior level and of their molecular mechanisms, including circadian rhythms, learning, memory, and sleep [12, 13]. Besides that, is a useful model for studies of lipid metabolism and energy homeostasis, being that in the insects, as well as in the vertebrates, lipids play important roles in the organism [14, 15].

Furthermore, is an effective model for evaluation of behavioral diseases related to neuroscience, since nearly 75% of the genes causing human diseases have a functional homolog in the fly [15]. In view of these factors, it is of great interest evaluate the effect of the addition of saturated fat and hydrogenated vegetable fat in the diet relating to mimetic behaviors of the depression and anxiety in the fruit fly *Drosophila melanogaster*.

2. Materials and methods

2.1. Materials and Fly Culture Conditions

The HVF (rich in trans FA) was produced by Coamo® (Paraná, Brazil) purchased in free market and the L (rich in saturated FA) was produced by Alibem® (Santa Rosa, Brazil) purchased from a local supermarket. Sodium Dodecyl Sulfate (SDS; Cat. L3771), Sucrose (S5016) and Hepes Minimum 99.5% (Titration, H3375) were acquired from Sigma-Aldrich® (São Paulo, SP, Brazil).

Drosophila melanogaster (Harwich strain) was obtained from the National Species Stock Center, Bowling Green, OH, USA. The flies were maintained in incubators BOD, light photoperiod of 12 h (25°C ± 1°C; 60 % of humidity), fed on fed in standard media of the laboratory containing: corn flour (76.59%), sugar (7.23%), wheat germ (8.51%), salt (0.43%), powdered milk (7.23%) and Nipagin (antifungal agent). The flies progenitors were maintained in this environment medium until mating and egg laying, after, the adults were removed and flies of hatched used in the treatments (approximately 3 days old).

2.2. Fat and diet composition

Fat content of diets was determined by the gravimetric method of [16] and used to determine the FA composition of diets. Fats were saponified in methanolic Potassium hydroxide solution and esterified in methanolic sulfuric acid solution [17]. Methyl ester FA were analyzed using an Agilent Technologies gas chromatograph (HP 6890) equipped with a DB-23 capillary column (60 m x 0.25 mm x 0.25 µm) and flame ionization detector. The temperature of the injector port was set at 250°C and the carrier gas was nitrogen (0.6 mL/minute). After injection (1 µL, split ratio 50:1), the oven temperature was hold at 150°C for 1 minute, the it was increased to 240°C at 4°C/minute and hold at this temperature for 12 minutes. Standard FA methyl esters (37-component FAME Mix and PUFA number 2 from Sigma, Saint Louis, MO, USA) were run under the same conditions and the subsequent retention times were used to identify the FA. FA were expressed as percentage of the total FA identified.

2.3. Experimental protocol

Were used adult flies (both genders) aged 1 to 4 days, these were submitted to treatment which had a duration of 7 days. The time of exposure in the diets and the addition of fat concentration in the diet was determined according to a work performed with fat previously by our research group [18]. Therefore, the flies were divided in 7 groups: (1) Regular diet (RD) containing: corn flour, sugar, wheat germ, salt, powdered milk, agar, (2) SHVF (values of fat of the regular diet were replaced by hydrogenated vegetable fat in the same proportion), (3) HVF 10% (regular diet with 10% hydrogenated vegetable fat) (4) HVF 20% (regular diet with 20% hydrogenated vegetable fat), (5) SL (Lard) (values of fat of the regular diet were replaced by lard in the same proportion), (6) L 10% (regular diet with 10% lard), (7) L 20% (regular diet with 20% lard), where the values percent of fat were added to regular diet, according to Table 1.

The values of macronutrients contained in the diets were calculated through the ADSNutri program using values referring to the Brazilian food composition table values given in Table 1.

2.4. *In vivo* assays

2.4.1. Mortality and body weight

The mortality rate of the flies was monitored daily being accounted the number of death flies to every 24 hours until the end of treatment. The flies were transferred for fresh foods for every 2 days. Also, was analyzed the body weight at the beginning and end of the seven days of treatment. Approximately, 150 flies per group were used for these analyses, and the total number of flies results from the sum of 3 independent experiments.

2.4.2. Negative geotaxis

The climbing ability, used to analyze if there is locomotor damage in the flies, was evaluated according to the negative geotaxis test described by [19]. The flies were transferred separately for test tubes (length of 10 cm, diameter 1.5 cm) soon, the flies were beats softly in the bottom of the tube and was timed how long that for each fly took to climb 8 cm of the tube. Was used one total of 15 flies per group, where each fly was tested 5 times in at 1 minute intervals. The data were analyzed according to mean between the times. Were realized 3 independent experiments per group.

2.4.3. Open fiel test

The open field behavior test was realized according to the method already described by [20] with some modifications. Each fly was positioned in an arena of 9 cm of diameter, divided into squares (1 cm x 1 cm) covered by a Petri dish. The exploratory activity was evaluated through the movement of the flies and the traveled distance during the time of 60 seconds was calculated analyzed the number of squares that the fly crossed. About 20 flies were used for each group, totaling 4 independent experiments.

2.4.4. Forced Swim Test

The behavior test was realized according described by [21] with adaptations by [22]. Was used a platform measuring 45 x 12 mm^2, completed with 4 mL of 0.04% SDS, the flies were placed individually on the platform, after, were observed during 3 minutes the following factors: time for first latency, total immobility time, total swimming time and numbers of swim attempts. All these times were timed manually, in this test were evaluated 30 flies individually per experimental group, totaling 3 independent experiments. Was characterized as depression-like behaviors the flies that remained per for more time immobile to the situation. For the validation of the test, after the evaluation time, the flies were removed of the platform of swim and placed to a napkin of paper, where was observed the capacity of recuperation of the fly, the flies that were incapable of walk normally were excluded from the final analysis.

2.4.5. Grooming

The analysis of grooming was realized according to with [23] with modifications. About of 6 flies were placed in an arena individually and allowed to acclimate for 1 minute, where each fly was tested twice in at 1 minute intervals, were evaluated how much time the flies passed realizing the cleaning act, during a total time of 2 minutes. The cleaning activity is a normal behavior performed by animals, but when performed excessively, can serve with a useful measure in behaviors in that there is the presence of stress and anxiety in wild and laboratory animals, being observed mainly with a mere to anxiety response [24, 25, 26]. The data were analyzed according to with the mean between the times, were used one total of 24 flies per group, totaling 4 independent experiments.

2.4.6. Light/Dark Exploration Test

This test was evaluated according described by [21], with adaptations. Was used a box of 6 x 1 cm, divided in a light compartment (16W) and other dark compartment, the parts light and dark of the box were divided where there was a gateway for that the fly could choose in which side of the box would like to stay. Six flies per group were placed individually in the light compartment of the box, after a period of adaptation, the amount of time spent in the dark compartment was registered. The fly was considered in the dark or light sections of the box when the head and at least half of the body were located within those sections. The *Drosophilas* are phototaxis, that is, are more active during the daytime, were there is clarity, so, expect that remain in the light side of the box when in normal conditions, thus a larger exposure to the dark side of the box is evaluated as anxiety-like behavior [22]. Were evaluated a total of 24 flies per group, totalizing 4 independents experiments.

2.4.7. Aggression assay

The aggressiveness was evaluated according to the method of [27] adapted by [22]. Pairs off male flies were placed in a circular arena with a radius of 45 mm and a height of 12 mm, in the center of the arena contained a paper soaked with a drop of sucrose 5%. The males were placed in the arena and after a time of adaptation were observed the aggressive events during the time of 5 minutes, was contabilized as aggression the following factors: leg extension from one fly to another resulting in physical contact, chase, fast loading approach that leads to direct orientation, wing raising in response to proximity/approach of another fly, and high box impact interaction involving the front legs of both flies. Were utilized 10 pairs off male flies per group for evaluation. Totalizing 30 pairs per group in a total of 3 independents experiments. The score corresponded to the number of encounters aggressive among experimental flies.

2.5. *Ex vivo* assays

2.5.1. Food consumption

The food intake was analyzed according to [28]. Flies of 1 - 7 days were used for analysis. About 5 flies per group were placed in a diet containing 0.5% of blue dye (FD & C Blue Dye no. 1) added to their respective groups of treatments. The flies were allowed to feed for 30 minutes, and after were transferred for eppendorfs and anesthetized. The bodies were homogenized in 200 µL of distilled water, after, was performed centrifugation to 12,370 rpm per 2 minutes. The absorbance of the supernatant was then measured at 625 nm using a spectrophotometer. A total of 20 flies were used per group, totalizing 4 independent experiments.

2.5.2. 5HT levels

Levels of 5HT were determined by high-performance liquid chromatography (HPLC) [29]. The flies were anesthetized (40 flies per group) the heads were removed homogenized with 100 µL of sodium phosphate buffer (0.1 M, pH 7.4) containing 1 mM ethylenediamine tetraacetic acid (EDTA) and centrifuged at 25,000 × g for 10 minutes at 4 ° C, where the supernatant was used as the sample. Three independent experiments were performed using a total of 120 flies per group for the analysis.

2.6. Statistical analysis

The results were evaluated by one-way ANOVA, followed by the post hoc Tukey test. The percent mortality was determined using the Mantel-Cox log-rank test. Differences between groups were considered significant when $p < 0.05$. GraphPad Prism software version 6 (San Diego, CA, USA) was used to perform these analyses.

3. Results

3.1. Evaluation of mortality rates of flies exposed the different high-fat diets

The mortality analysis revealed that flies exposed to SHVF, HVF 10%, HVF 20%, SL, L 10% and L 20% had a significant increase in the mortality percentage ($p < 0.05$) when compared with the RD group (Fig. 2).

3.2. Evaluation of the food intake and body weight of flies exposed the different high-fat diets

According one-way ANOVA there was no significant difference in dietary intake [$F_{(6, 21)} = 1.476$, $p = 0.2344$] as well as in body weight [$F_{(6, 14)} = 2.315$, $p = 0.0918$] in the groups when compared with the RD according shown table 2.

3.3. Effect of different high-fat diets on 5HT levels

The one-way ANOVA showed that there was a significant difference in 5HT levels in head between the groups [$F_{(6, 14)} = 11.00$, $p = 0.0001$]. Post hoc analysis revealed that there was a significant reduction of the 5HT neurotransmitter in HVF exposed flies at concentrations of 10% and 20%, and in flies exposed to L at all concentrations when compared with the RD group, as shown in Figure 3.

3.4. Effect of different high-fat diets in the depression like behavior

The one-way ANOVA analysis showed that there was a significant difference in latency of first immobility between the groups evaluated [$F_{(6, 14)} = 9.993$, p =

0.0002] as well as in total immobility time [$F_{(6, 14)} = 18.59$, $p < 0.0001$]. The Post hoc analysis revealed that there was a decrease in latency of first immobility (Fig. 4A) and an increase in total immobility time (Fig. 4D) in flies exposed to both HVF and L rich diets at all concentrations when compared with the RD group. Likewise, the one-way ANOVA analysis showed that was a significant difference in total swimming time [$F_{(6, 14)} = 17.55$, $p < 0.0001$] and also in the number of swimming [$F_{(6, 14)} = 11.35$, $p = 0.0001$] compared with RD group. According Post hoc analysis there was a decrease in the total swimming (Fig. 4B) time and also in the number of swimming (Fig. 4C) attempts in the groups exposed to both the high fat diets at in all concentrations when compared with the DR group.

3.5. Effect of different diets in the anxiety-like behavior.

The one-way ANOVA analysis showed that there was significant difference in the grooming test [$F_{(6, 21)} = 15.23$, $p < 0.0001$] and in the light / dark test [$F_{(6, 21)} = 17.15$, $p < 0.0001$] between groups when compared with RD. Post-hoc analysis showed that the flies exposed to the HVF diet at all concentrations had higher cleaning activity when compared with the control group (Fig. 5A). Likewise, the flies exposed to the SHVF diet at all concentrations remained more on the dark side of the box (Fig. 5B), when compared with the RD group. The flies exposed to the diets composed of SL did not show significantly different on grooming time and time in the dark compartment, compared with the RD group, in both analyzes.

3.6. Evaluation of exploratory and locomotor performance on the open field test and geotaxis negative

The one-way ANOVA analysis revealed that there was not a significant difference in the negative geotaxis test [$F_{(6, 14)} = 4.023$, $p = 0.0150$] and in the open field test [$F_{(6, 21)} = 1.209$, $p = 0.3406$] when compared with RD group. Post-hoc analysis showed that the climbing ability of flies was similar in all experimental groups (Fig. 6A). Likewise, there was no significant difference in relation to the exploratory behavior of the flies (Fig. 6B).

3.7. Effect of different diets on Aggressive Behavior

The one-way ANOVA analysis showed that there was significant difference in the between the groups in the aggression test [$F_{(6, 14)} = 17.47$, $p < 0.0001$] when compared with the control group. The post-hoc analysis showed that the groups exposed to the SHVF diet in all evaluated concentrations increased the number of aggressive episodes in the flies when compared with the RD group (Fig. 7). However, in groups exposed to diet SL there was an increase in the number of aggressive episodes only in the group with the highest fat concentration (20%).

4. Discussion

In this study we evaluated the effects of the consumption of diets with different percentages of two types of fats usually consumed of elevated form the by population. Our intention was to discover the influence of these different diets on the emergence of behavioral changes related to neuropsychological disorders in the Drosophila melanogaster model. Our findings showed that a diet with high-fat content can contribute to the development of behaviors disturbances, which were observed in parameters evaluated. However, not having locomotor impairment of the flies. Curiously, the chronic consumption of the different diets wasn't related to the increase in the body weight, however, there was a decrease in the life expectancy these flies.

It was observed that diet with different concentrations of fat decreased the lifetime of the flies. Referring to this, the life expectancy is highly related to an adequate balance of the nutrients offered in the diet, given that, a poor adequacy in caloric intake can cause damages to the body. These damages can be observed when there is an excess in the consumption of lipids, being able to contribute to the appearance of metabolic disorders, increasing the generation of reactive species of oxygen leading to the development of diseases. In addition, the high-fat diet is associated with obesity, as well as being a contributor to premature senescence, leading to a reduction in the life expectancy of living organisms [30, 31]. Moreover, in a study conducted previously by our research group, a diet rich in fat was able to cause changes in the homeostasis of the organism, thereby decreasing the rate of survival of the flies [18].

However, not only the amount of fat offered in the diet has its importance, but also the fatty acid composition of this fat, since different lipids play important roles both in metabolism and in health and brain structure [32]. Thus, inadequate intake of fatty acids can lead to consequences not only related to metabolism, but also to psychiatric disorders [33].

The cell membrane, composed of a phospholipid bilayer, is responsible for several functions, such as protecting and giving permeability the cell, serving as a barrier to entry and exit of certain substances. However, the lipid composition of the membrane can be altered according to the type of FA consumed in the feed [34]. In our study, we observed that the composition of fatty acids offered in the diet, has a deficiency of essential fatty acids necessary for cerebral health, as discussed later.. Thus, both the amount of free polyunsaturated fatty acids (PUFAs) and the amount of PUFAs bound to diacylglycerol and triacylglycerol in the brain may depend on the FAs obtained from the diet [34]. An adequate offer of long chain PUFAs is very important for good brain health [33, 35].

In our study, there is a deficiency of α-linolenic acid in the dietary composition of the diet offered to flies. This fatty acid also plays an important role in brain composition, since, a study conducted in rats, demonstrated that an α-linolenic deficient diet causes an increase in the incorporation of trans isomers into brain structures [36]. In our study, the trans FA was found of form high in HVF-enriched diets, since the recommended is that the amount of trans fat does not exceed 1% of the intake [37]. When there is an incorporation of this type of FA in the membrane, this can be prejudicial, considering that trans FA obtained through industrialized foods, is synthetic and not natural, being modified by the hydrogenation process. In this context, the presence of FA type trans may disorder the phospholipids, influencing in permeability of the membrane [38].

In addition to these changes, prolonged deprivation of omega-3 fatty acids and their replacement by others also impairs cerebral monoamines system, where in a rodent study omega-3 PUFA deprivation increase the 5-HT synaptic basic 5-hydroxytryptamine, but decreased the release of stimulated 5-HT [39]. Briefly, substitution of lipid content in cerebral membranes may affect synaptic plasticity and neurotransmission [8].

Since monoamine systems are directly related to mood disorders, we chose to evaluate 5-HT neurotransmitter levels in the head of flies exposed to experimental diets. Like most eukaryotes, *Drosophila* can synthesize nonessential saturated fatty acids through acetyl-CoA carboxylase and fatty acid synthetase, but like most animals, the fly is free of enzymes that produce alpha-linoleic acid (C18: 2) and alpha-linolenic acid (C18: 3), needing to acquire them through by feeding, being these, the most abundant in the fly. In addition, unlike humans, the fly does not have long chain fatty acids with more than 20 carbons, thus, when consumed they are divided into smaller molecules [34, 40, 41].

Considering that fatty acids PUFAs are essential for *Drosophila*, being related to the better functioning of the nervous system, the lack of these fatty acids can end up generating synaptic dysfunctions, consequently, altering the neurotransmission. Given that, neurotransmission can be changed as a result of the poor ingestion of fatty acids. In our study we evaluated the levels of the 5HT neurotransmitter in the flies exposed to the experimental diets, this, was found to be significantly reduced in flies that received the HVF diets at concentrations of 10 and 20%, as well as in flies that received the L, L 10% and L 20% when compared with the RD group. This neurotransmitter participates in important functions in the body, especially functions related to mood [42, 43].

According to OMS, psychological disorders affect most of the world population, becoming one of the major causes of population incapacity. In recent studies in rodents, is possible to observe that the high-fat diet is responsible for reducing the neurogenesis and hippocampal volume. Thus, being responsible for the development of neurological disorders such as memory loss, anxiety disorders, and depression [9, 44].

In our study, flies exposed to the HFV and L diets at all concentrations had depression-like behaviors, observed in the forced swimming test. Such findings are according to a study carried out with rodents, where a diet rich in fat caused behaviors similar to depression, also evaluated through the forced swim test [45].

Depressive-like behavior may also be related to the reduction of 5HT levels in the head found here, given that, 5HT neurons project widely throughout the brain to innervate key regions involved in depression and anxiety, being according to other studies, where the vulnerability to these disorders is related to the low serotoninergic function [42, 43].

Normally, patients that are found in state depressive, usually can to present anxiety associated with the disorder [46]. Therefore, we evaluated the behavioral state with similarity to anxiety, where our results showed that flies exposed to the HVF diet at all concentrations had similar behaviors to anxiety, observed in the grooming and light / dark tests.

Besides that, a study realized with rats shows an incorporation of trans FA in the brain of animals (0,30%), causing the modification of the activity of Na + K + -ATPase and so, alterations in the parameters related to anxiety and memory of animals [47]. These results are according with realized studies in rodents exposed to high-fat diets to long-term, where it is evaluated the effects related to psychological disorders, where is observed that rats exposed to these diets had behaviors like anxiety and anhedonia, without affecting the locomotor activity [48, 49].

In the same way, we evaluated the locomotor activity and climbing ability of the flies, performed in the open field and negative geotaxia tests respectively. In our results no locomotor declines were observed in the flies, being considered a positive and fundamental result, because that way, become valid the previous tests related to anxiety and depression, since there will be no influence of locomotor damage on the flies [22].

According to behavioral changes, we evaluated the aggressive behavior of flies, where a greater number of aggressive events were observed in flies exposed to HVF at all concentrations, already in flies exposed to L, a higher number of aggressions could be observed only in the L 20% group. This increase in the number of aggressions may be related to the altered levels of 5HT found here.

Aggressive behavior is considered of great importance in several factors such as food defense, companion, progeny, among others. However, there is a considerable increase in the number of aggressive episodes in patients with behavioral disorders, being associated with a reduction in 5HT levels [27, 50]. In this sense, low serotoninergic function allows the brain areas related to emotion and mood to be more active, intensifying actions and emotions, the which could explain a larger episode of combat events found here [51].

Furthermore, the effects of a high-fat diet on aggressive behavior can be mediated by innumerable factors, going from body weight even to changes in cell membrane structure, since dietary FA can be incorporated into the lipid bilayer, altering their fluidity and cellular functionality, can lead to possible changes in the release of neurotransmitters responsible for mood, such as the neurotransmitter 5HT evaluated here [52, 53].

It is concluded that D. melanogaster can serve as an useful model for the understanding of psychiatric disorders and that the type of AF offered in the diet can influence these disorders, demonstrating the importance of the composition of the FAs in the neural pathways, which can influence the signaling of neurotransmitters such as the 5HT assessed here, and thus, cause behavioral changes.

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Figures legends:

Fig. 1. Experimental design of the study.

Fig. 2. Effect of different diets, Regular diet (RD), Hydrogenated vegetable fat (HVF), in concentrations of SHVF, HVF 10% and HVF 20%, besides Lard (L) in concentrations of SL, L 10% and L 20%, in the mortality percent of Drosophila melanogaster flies. Were used a total of 150 flies per group, totaling the sum of 3 independent experiments. The values are shown as mean + SD. The measure of life time was determined comparing the curves of mortality of Mantel-Cox log-rank tests, being. * indicates significant difference in relation to RD ($p<0.05$).

Fig. 3. Effect of the different diets, Regular diet (RD), Hydrogenated vegetable fat (HVF), in concentrations of SHVF, HVF 10% and HVF 20%, besides Lard (L) in concentrations of SL, L 10% and L 20%, in 5HT levels in the head of the *Drosophila melanogaster* flies. To evaluate the 5HT levels, were used a total of 120 flies per group, totaling the sum of 3 independent experiments. The values are shown as mean + SD. The significance was determined by one-way analysis of variance (ANOVA), followed by Tukey test. * indicates a significant difference in relation to RD group ($p<0.05$).

Fig. 4. Effect off different diets, Regular diet (RD), Hydrogenated vegetable fat (HVF), in concentrations of SHVF, HVF 10% and HVF 20%, besides Lard (L) in concentrations of SL, L 10% and L 20%, in forced swim test in *Drosophila melanogaster* flies. A) Latency to first immobility, B) Bout duration, C) Number of bout, D) Immobility time. Were used a total of 30 flies per group, totaling the sum of 3 independent experiments. The values are shown as mean ± SD. The significance was determined by one-way analysis of variance (ANOVA), followed by Tukey test. * indicates a significant difference in relation to RD group ($p<0.05$).

Fig. 5. Effect off different diets, Regular diet (RD), Hydrogenated vegetable fat (HVF), in concentrations of SHVF, HVF 10% and HVF 20%, besides Lard (L) in concentrations of SL, L 10% and L 20%, in the anxiety-like behavior in *Drosophila melanogaster* flies. A) Grooming test, B) light and dark test. Were used a total of 18 flies per group for each test, totaling the sum of 3 independent experiments. The values are shown as mean + SD. The significance was determined by one-way analysis of variance (ANOVA), followed by Tukey test. * indicates a significant difference in relation to RD group ($p<0.05$).

Fig. 6. Effect of the different diets, Regular diet (RD), Hydrogenated vegetable fat (HVF), in concentrations of SHVF, HVF 10% and HVF 20%, besides Lard (L) in concentrations of SL, L 10% and L 20%, in the locomotive ability test in *Drosophila melanogaster* flies. A) Negative geotaxis test, B) Open field test. To evaluate the ability to scale were used a total of 15 flies per group, similarly were used a total of 15 flies per group to evaluate the locomotor damage, totaling the sum of 3 independent experiments. The values are shown as mean + SD. The significance was determined by one-way analysis of variance (ANOVA), followed by Tukey test. * indicates a significant difference in relation to RD group ($p<0.05$).

Fig. 7. Effect off different diets, Regular diet (RD), Hydrogenated vegetable fat (HVF), in concentrations of SHVF, HVF 10% and HVF 20%, besides Lard (L) in concentrations of SL, L 10% and L 20%, in aggressive behavior of *Drosophila melanogaster* flies. To evaluate the aggressive behavior, were used a total of 30 flies per group, totaling the sum of 3 independent experiments. The values are shown as mean + SD. The significance was determined by one-way analysis of variance (ANOVA), followed by Tukey test. * indicates a significant difference in relation to RD group ($p<0.05$).

Figures

Fig. 1.

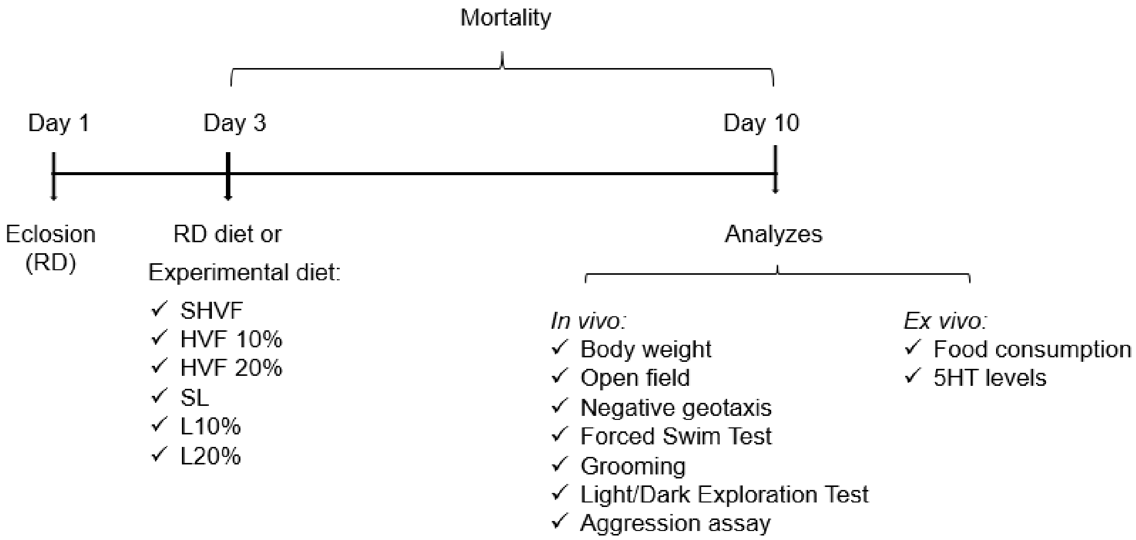


Fig. 2.

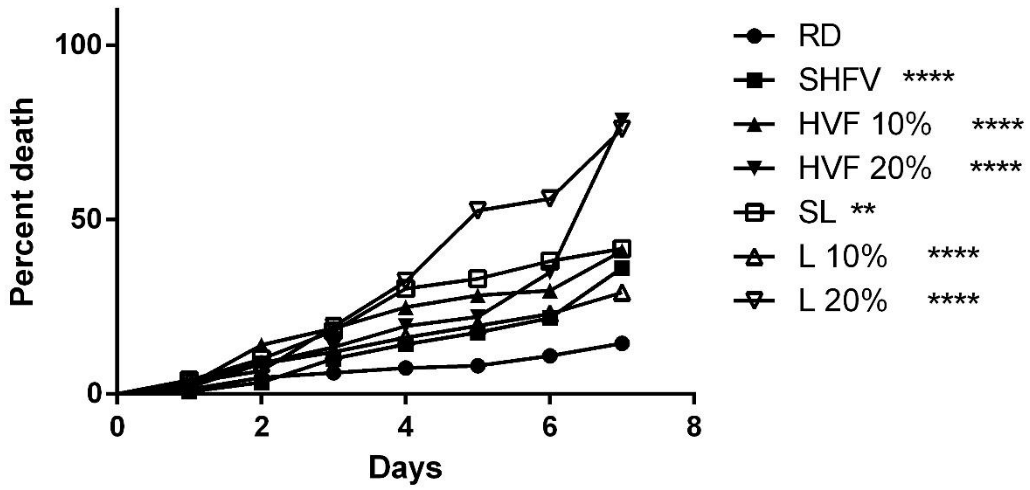
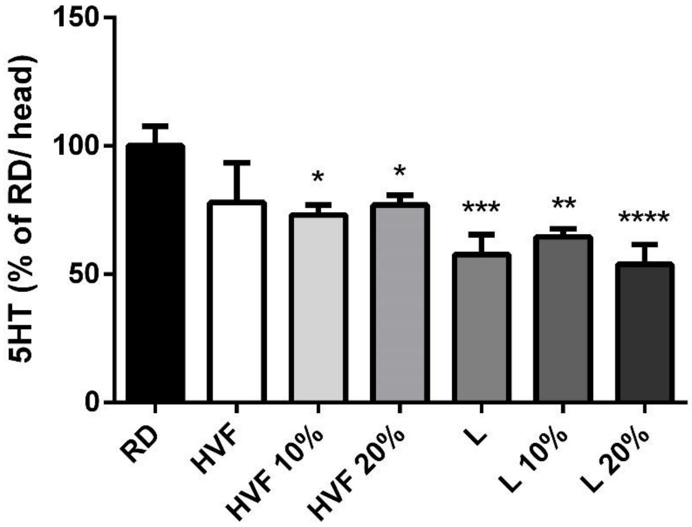


Fig. 3.


150
100
50
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5HT (% of RD/ head)
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*
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RD
HVF
HVF 10%
HVF 20%
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L 10%
L 20%

Fig. 4.

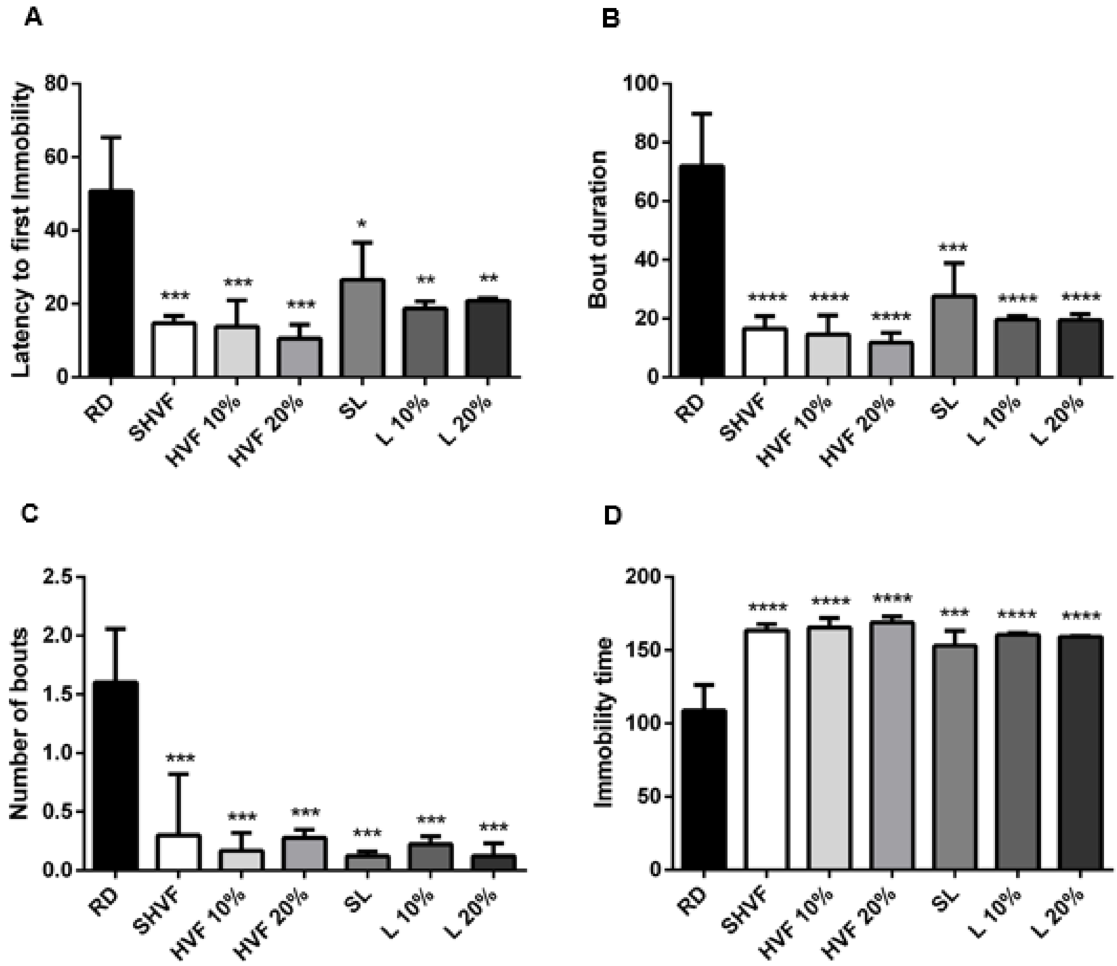
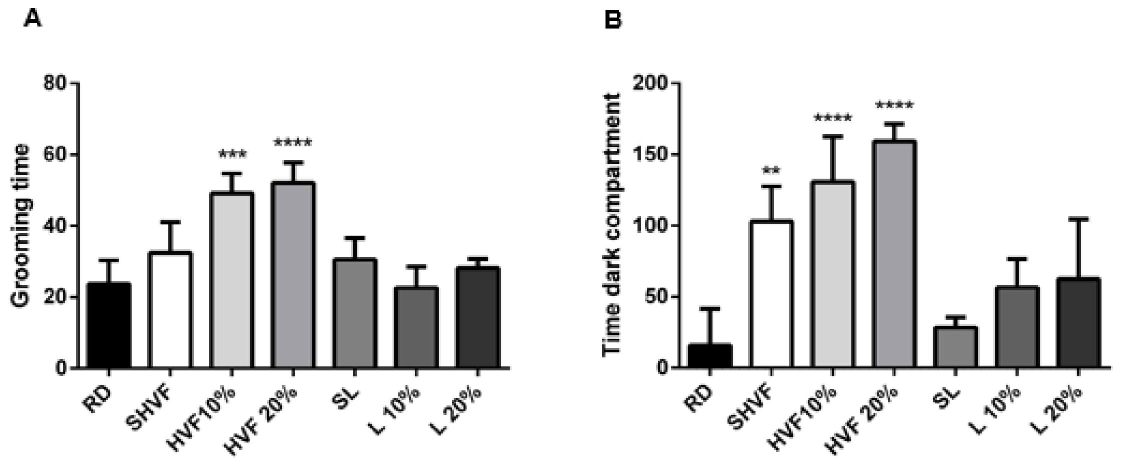

A
B
C
D
Latency to first Immobility
Bout duration
Number of bouts
Immobility time
RD
SHVF
HVF 10%
HVF 20%
SL
L 10%
L 20%

Fig. 5.


A
Grooming time
80
60
40
20
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HVF10%
HVF 20%
SL
L 10%
L 20%
B
Time dark compartment
200
150
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RD
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Fig. 6.

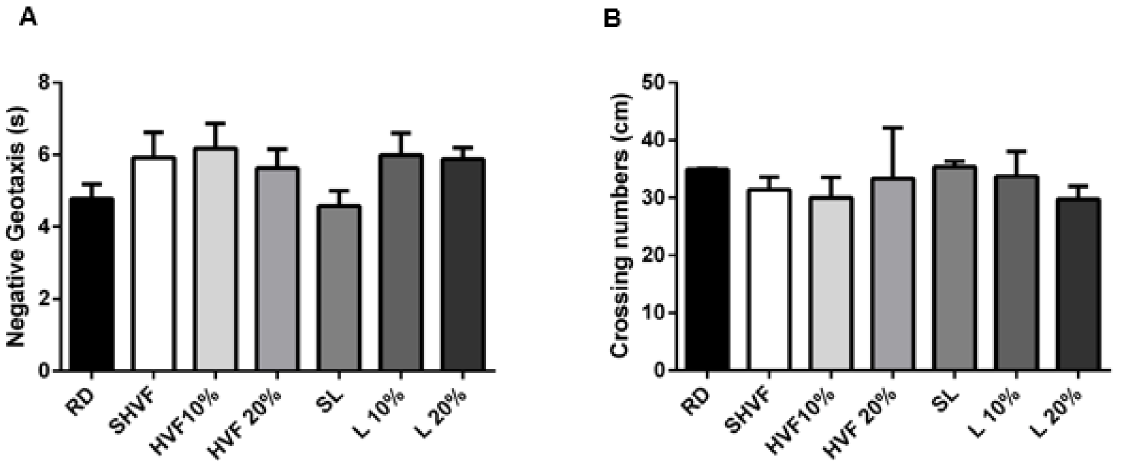
A
Negative Geotaxis (s)
8
6
4
2
0
RD
SHVF
HVF10%
HVF 20%
SL
L 10%
L 20%
B
Crossing numbers (cm)
50
40
30
20
10
0
RD
SHVF
HVF10%
HVF 20%
SL
L 10%
L 20%

Fig. 7.

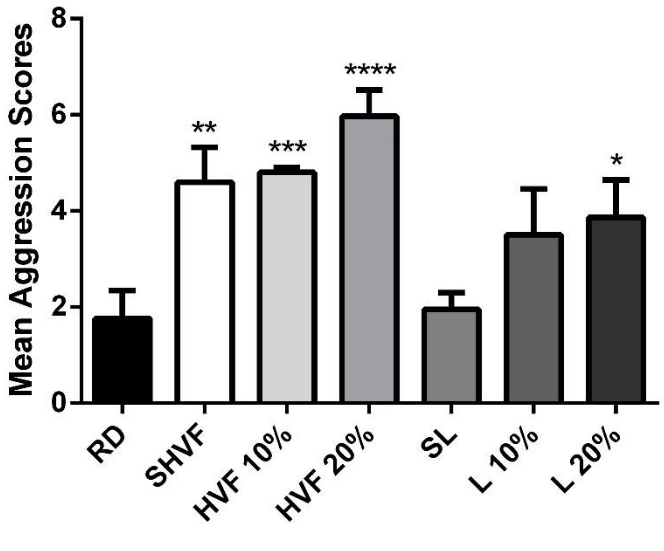

Table 1. Composition of the HVF Diet and L Diet

	RD	SHFV	HFV 10%	HFV 20%	SL	L 10%	L 20%
Total (kcal/g)	**3,67**	**3,64**	**4,16**	**4,56**	**3,64**	**4,16**	**4,56**
Carbohydrates (%)	**79,44**	**80,34**	**63,81**	**12,87**	**80,34**	**63,81**	**12,87**
Fibers (%)	6,44	6,31	6,44	6,44	6,31	6,44	6,44
Proteins (%)	**11,4**	**10,79**	**9,21**	**7,70**	**10,79**	**9,21**	**7,70**
Total Fat (%)	**9,1**	**8,86**	**26,97**	**38,97**	**8,86**	**26,97**	**38,97**
C10:0	0,12	0,02	0,16	0,18	0,02	0,15	0,16
C12:0	0,18	0,02	0,22	0,25	0,01	0,19	0,20
C14:0	0,63	0,02	0,63	0,63	0,11	0,85	1,00
C16:0	2,70	1,53	5,65	7,63	1,99	6,72	9,42
C16:1n7	0,09	0,02	0,09	0,09	0,15	0,41	0,63
C17:0	0,04	0,06	0,06	0,07	0,07	0,09	0,13
C17:1n5	0,00	0,00	0,00	0,00	0,02	0,04	0,07
C18:0	0,81	1,29	3,66	5,57	0,95	2,84	4,21
C18:1n9t	0,16	1,12	2,81	4,59	0,03	0,24	0,28
C18:1n9c	2,05	3,52	9,69	14,82	3,33	9,24	14,08
C18:1n7	0,08	0,29	0,71	1,13	0,21	0,53	0,84
C18:2n6t	0,00	0,08	0,19	0,32	0,00	0,00	0,00
C18:2n6c	2,09	0,88	2,98	3,57	1,79	5,13	7,18
C18:3n3	0,15	0,03	0,15	0,15	0,09	0,28	0,38
C20:1n9	0,02	0,00	0,02	0,02	0,06	0,17	0,26
C20:3n6	0,00	0,00	0,00	0,00	0,01	0,03	0,05
C20:4n6	0,00	0,00	0,00	0,00	0,02	0,05	0,09

Table 2. Food consumption and body weight of flies

	Food consumption	Body Weight
RD	115.7 ± 18.44	100,6 ± 2,60
SHVF	105.1 ± 27.69	92,71 ± 27,27
HVF 10%	75.32 ± 12.21	63,26 ± 19,02
HVF 20%	74.04 ± 12.30	143,0 ± 62,02
SL	98.65 ± 11.61	159,2 ± 22,78
L 10%	113.7 ± 18.29	101,2 ± 31,00
L 20%	59.71 ± 20.18	-12,11 ± 55,77

Values are expressed by (%) of the RD, as mean and

Supplementary material

Table 1. Fatty acid composition of the HVF and L

Fatty acids composition	% Fatty acids composition in lard	% Fatty acids composition in trans
C10:0	0,16	0,22
C12:0	0,08	0,23
C14:0	1,25	0,00
C16:0	22,52	16,50
C16:1n7	1,81	0,00
C17:0	0,32	0,11
C17:1n5	0,23	0,00
C18:0	11,38	15,95
C18:1n9t	0,40	14,81
C18:1n9c	40,27	42,76
C18:1n7	2,53	3,53
C18:2n6t	-	1,08
C18:2n6c	17,05	4,98
C18:3n3	0,76	0,00
C20:1n9	0,81	0,00
C20:3n6	0,16	-
C20:4n6	0,29	-

5. CONCLUSÕES

A partir dos resultados obtidos nesse estudo, pode-se concluir que dietas contendo HVF e L em diferentes concentrações, reduzem a expectativa de vida das moscas, além de causar alterações em comportamentos miméticos a ansiedade e depressão, estando relacionado a um número maior de eventos agressivos. Além do mais a ingestão dessas gorduras causa uma redução nos níveis do neurotransmissor 5HT, podendo este estar relacionado aos resultados comportamentais aqui observados. Diante disso, pode-se considerar o modelo de *Drosophila melanogaster* útil para o entendimento de distúrbios comportamentais relacionados a serotonina e que a composição dos FAs ofertados na dieta pode influenciar no surgimento desses distúrbios, podendo estar relacionado a alteração na composição e permeabilidade da membrana neural.

6. PERSPECTIVAS

Com base nos resultados obtidos neste estudo, é necessário um aprofundamento nos demais mecanismos envolvidos nas alterações aqui encontradas, sendo assim, pretende-se realizar as seguintes avaliações:

- Avaliar demais neurotransmissores interligados aos comportamentos analisados;

- Realizar avaliação neurológica;

- Analisar os parâmetros oxidativos;

- Avaliar possíveis alterações no metabolismo energético;

- Avaliar os níveis das enzimas envolvidas na síntese de FAs;

- Realizar a busca por fármacos alternativos para tratamento de tais alterações.

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