Fatty acids role on obesity induced hypothalamus inflammation: from problem to solution – A review

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Abstract

Background

Obesity has currently reached a worldwide pandemic level, playing a central role in the development of non-communicable diseases and in health care burden. The available drugs for obesity have not achieved the required level of clinical effectiveness and have been associated with severe health side effects. Recent investigations suggest that obesity is more complex as it is associated with altered brain functions.

Scope and approach

In this review the hypothalamus inflammation was presented as playing a major role in obesity development and progression. The role of diet, namely western pattern diet was presented as one of the major responsible for such inflammation focusing on saturated fatty acids role, since they bind to toll-like receptor 4 (TLR4) triggering inflammatory processes. In contrast, the anti-inflammatory ability of polyunsaturated fatty acids was described and the potential of using conjugated fatty acids use in antiobesogenic therapies specifically aiming hypothalamic inflammation was, for the first time, postulated.

Key findings and conclusions

Promising hypothalamic anti-inflammatory effects of omega-3 fatty acids, mediated by G protein receptor 120 (GPR120), have been extensively described and present promising results in diet induced obesity studies. Besides, several *in vivo* and *in vitro* studies have demonstrated beneficial effects of conjugated linoleic acid (CLA) and conjugated linolenic acid (CLNA) isomers on aspects related to immune function and inflammation, also presenting an anti-inflammatory effect. Moreover, they were successfully described to decrease peripheral obesity effects. Nevertheless, few studies have addressed specifically the effect of those isomers on obesity induced hypothalamic inflammation and further investigations are warranted.

Keywords. obesity; hypothalamic inflammation; omega-3; conjugated linoleic acid; conjugated linolenic acid; anti-inflammatory effect

Abbreviations. α-Linolenic Acid (ALA); α-Melanocortin Stimulating Hormone (α-MSH); Adrenocorticotropin (ACTH); Agouti-related Protein (AgRP); AMP-activated Protein Kinase (AMPK); Arcuate Nucleus (ARC); Blood brain barrier (BBB); Body mass index (BMI); Cardiovascular (CVD); Central Nervous System (CNS); c-Jun N-terminal Kinase (JNK); Conjugated Linoleic Acid (CLA); Conjugated Linolenic Acid (CLNA); Docosahexaenoic Acid (DHA); Eicopentaenoic Acid (EPA); European Medicines Evaluation Agency (EMA); Endoplasmic Reticulum (ER); Fatty Acid (FA); Food and drug administration (FDA); G Protein Receptor (GPR); Growth Hormone Secretagogue Receptor (GHSR); High Fat Diet (HFD); Insulin Receptor Substrate (IRS); Kilodalton (kDa); K-opioid Receptor (KOR); Leptin Receptor (LepRb); Linoleic Acid (LA); Linolenic Acid (LNA); Lipopolysaccharide (LPS); Long-chain polyunsaturated Fatty Acid (LC-PUFA); Polyunsaturated fatty acids (PUFA); Long-chain Saturated Fatty Acid (LC-SFA); Magnetic resonance imaging (MRI); Medium Chain Fatty Acids (MCFA); Melanocortin Receptor (MCR); Monounsaturated Fatty Acid (MUFA); Neuronal X-Box Binding Protein (XBP); Neuropeptide Y (NPY); Nitric Oxid Synthase (iNOS); Nuclear factor-kappa B (NFkB); Organisation for Economic Co-operation and Development (OECD); Palmitoleic Acid (PA); Paraventricular nuclei (PVN); Peroxisome Proliferator-activated Receptor (PPAR); Propiomelanocortin (POMC); Pro-convertase 2 (PC2); Punicic Acid (PUA); Reactive oxygen species (ROS); Saturated Fatty Acids (SFA); Supressor of Cytokine Signaling (SOCS); Targeting Rapamycin (mTOR); TGF-β Activated Kinase (TAK); TGF-β Activated Kinase Binding Protein (TAB); Toll-like Receptor (TLR); Trans Fatty acids (TFA); Transforming Growth Factor (TGF); Unfolded Protein Response (UPR); White Adipose Tissue (WAT); World Health Organization (WHO).

Introduction

Worldwide Obesity Pandemic

The World Health Organization (WHO) (2020b) defines overweight and obesity *"*as abnormal or excessive fat accumulation that may impair health*"*, which can be triggered by high and imbalanced food intake plus a sedentary lifestyle. Although both are preventable, WHO data reported that in 2016 more than 1.9 billion adults (≥18 yrs.;

39% of world's population) were overweight and over 650 million were obese (13% of world's population). Recent data about this worldwide pandemic are concerning; according to WHO both obesity and overweight are now on the rise in low- and middle-income countries, particularly in urban settings. Nevertheless, a recent study assessing the trajectory of obesity of children and adolescents have shown that the rising trends in children's and adolescents' body mass index (BMI) have plateaued, since 2000, in many high-income countries (but remaining at high levels). The authors have reported, though, that from 1975 to 2016 children's and adolescent's age-standardised mean BMI increased globally (0.32 kg/m^2 for girls and 0.40 kg/m^2 for boys per decade) ((NCD-RisC), 2017). Furthermore, regarding children under the age of 5, 38 million were reported to be overweight or obese in 2019, while from ages 5 to 19 the overweight/obesity prevalence reached 340 million in 2016 (World Health Organization (WHO), 2020b). According to Organisation for Economic Co-operation and Development (OECD) latest projections, it is expected that obesity rates continue to increase until at least 2030 (OECD, 2017). Moreover, obesity and overweight are recognized as the second metabolic factor, after blood pressure alterations, involved in the development of non-communicable diseases, such as cardiovascular (CVD), cancer, chronic respiratory diseases and diabetes. According to the most recent data, CVD accounts for most non-communicable disease deaths – 17.9 million people annually (representing 31% of all global deaths) (World Health Organization (WHO), 2018). Besides, the associated health deficits have high socioeconomic costs: in Europe, CVD is the leading cause of mortality (3.9 million deaths/year) with an estimated burden of €210 billion/year (Wilkins et al., 2017). Diabetes is other comorbidity known to be associated with obesity, and it is estimated to affect 60 million people in the European Region. Moreover, diabetes was directly responsible, in 2016, for an estimated 1.6

million deaths (World Health Organization (WHO), 2020a). According to recent projections, the diabetes absolute global economic burden will increase to US$ 2.1 trillion by 2030 (Bommer et al., 2018). The magnitude of this health problem as well as the difficulties with existing weight-loss therapies emphasizes the need for different approaches and for a better and more complete understanding of the problem. Additionally, and despite the huge progression made over the last years, the overweight and obesity prevalence rates continue to increase, suggesting that additional elements must be involved in the pathogenesis of this disease.

Obesity Effects on Peripheral Tissues

In mammals, the adipose tissue is comprised by, at least, two kinds of adipose tissue: the white adipose tissue (WAT) and the brown adipose tissue (BAT) - which is not going to be deepened in this review. WAT is considered as the main site of energy storage in mammals and birds and mechanical insulation roles are commonly attributed to this tissue. It is composed by adipocytes that are held together by a poorly vascularized and innervated connective tissue, where sympathetic innervation has been described (Caron et al., 2018; Gómez-Hernández et al., 2016). Such tissue is in fact, distributed over the entire body and recently, has been described as a highly dynamic organ, which is involved in a wide range of physiological and metabolic processes. Indeed, WAT is an endocrine organ: white adipocytes secrete several major hormones together with a diverse range of other signal proteins and factors (Trayhurn & Wood, 2004). Consequently, it can affect the function of many systems as adipocytes are known to secrete more than 600 bioactive factors – collectively known as adipokines (Trayhurn & Wood, 2004) -, in addition to fatty acids (FAs), lipids and their metabolites (Lehr et al., 2012). There is a wide diversity of adipokines in terms of protein structure

and of putative function. In fact, adipokines include classical cytokines (as TNF-α, IL-6 and IL-8), growth factors and proteins of the alternative complement system (e.g. adipsin acylation-stimulating protein), as well as proteins that are involved in several homeostatic processes, namely in vascular haemostasis, regulation of blood pressure, lipid metabolism, glucose homeostasis, angiogenesis, and acute-phase and stress responses (Trayhurn & Wood, 2004). It has been reported that the production of these secreted proteins by adipose tissue is increased in obesity (Longo et al., 2019). Diet excess and obesity itself produce an accumulation of lipids in adipocytes, triggering cellular stress and the activation of c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NFkB) pathways, resulting in raised circulating levels of several acute-phase proteins and inflammatory cytokines suggesting a state of chronic low-grade inflammation that has been linked to insulin resistance and to metabolic syndrome (Gómez-Hernández et al., 2016; Longo et al., 2019). Studies performed in patients subjected to bariatric surgery, suggested that those levels are reduced after weight loss (Rao, 2012). Thus, in view of the wide secretion and distribution of these molecules in different tissues, the secretion of adipokines by WAT was hypothesized to rely on an extensive communication system between this tissue and other tissues and organs, including the brain. Supporting this hypothesis, co-culture studies demonstrated that there is a cross-talk between white adipocytes and the brain (Turtzo et al., 2001), through leptin and the sympathetic nervous system (Rayner & Trayhurn, 2001). Moreover, as reviewed by Parimisetty et al., (2016) central nervous system (CNS) has receptors for adipokines and they may either cross the blood brain barrier (BBB) or modify BBB physiology by acting on it building cells. Therefore, has been suggested that adipokines can regulate neuroinflammation and oxidative stress, the two recognized processes involved in neurodegeneration. Despite such evidence, the role of WAT,

namely the effect of adipokines on the pathophysiology of the CNS remains poorly described.

Brain Imbalance Triggered by Obesity and the Diet Effect

Several of the available drugs (most of them working through CNS pathways reducing appetite or enhancing satiety) for obesity have not achieved the required level of clinical effectiveness and the ones that are sufficiently effective, have been associated with severe health side effects. Data from recent meta-analyses studies showed that the overall placebo-subtracted weight reduction (%) with the use of antiobesogenic drugs for at least 12 months ranges from 2.9 to 6.8% (Tak & Lee, 2020). Although side effects are widely dependent on the individual, the most common ones are associated with increased blood pressure, tachycardia, insomnia, alterations on sexual behaviour, malabsorption or carcinogenic effects (Gómez-Hernández et al., 2016; Müller et al., 2018; Srivastava & Apovian, 2018). For instance, orlistat, a Food and drug administration (FDA) and European Medicines Evaluation Agency (EMA) approved anti-obesity drug that decreases fat absorption, reported the following side effects (incidence of 5% and at least twice that of placebo): flatulence, oily spotting, faecal urgency, fatty/oily stool, oily defecation, increased defecation and faecal incontinence and other adverse effects such as nephrotoxicity, hepatotoxicity, nephrolithiasis and pancreatitis (Srivastava & Apovian, 2018). Moreover, since the FDA's adoption of stricter regulations and proof of clinical efficacy, a couple of recently approved anti-obesity drugs have been removed from the U.S. market for safety concerns: sibutramine (Meridia) was approved between 1997 and 2010. The concerns were related with elevated risk of CVD events in patients at high risk for CVD when given sibutramine. The rates of nonfatal myocardial infarction and nonfatal stroke were 4.1 and 2.6% in the

sibutramine group and 3.2 and 1.9% in the placebo group, respectively (James et al., 2010). Lorcaserin (Belviq) use was approved between 2012 and 2020. A re-analysis of a safety clinical trial showed an increased incidence of certain cancers. According to the data provided, a greater number of participants who received lorcaserin compared to placebo were reported with multiple primary cancers (n=20 vs. 8), total cancers (n=520 vs. 470), metastases (n=34 vs. 19), and cancer deaths (n=52 vs. 33) (Sharretts et al., 2020). In Europe, for example, the application for lorcaserin by the EMA was withdrawn in May 2013 after the EMA stated that the weight-loss benefits of lorcaserin did not outweigh its risks, which included the potential to increase the frequency of psychiatric disorders and valvulopathy (Haslam, 2016). In view of the diversity of the side effects observed it is expectable that the targeted pathways – related with satiety promotion - are important in a wide range of tissues and not just in those that are directly implicated in the regulation of energy balance and obesity (Dietrich & Horvath, 2012).

As discussed in the *Obesity effects on peripheral tissues* section, it has been suggested that energy balance is maintained by adipose tissue-brain crosstalk, and energy imbalance results in an accumulation of excessive calories in the form of triglycerides in adipose tissue, leading to overweight and obesity (Zhou & Rui, 2013).

Nonetheless, in the last decade, research focused on the humoral, neuronal and molecular mechanisms involved in the regulation of hunger and satiety, unravelled the fundamental role performed by CNS, especially by hypothalamus in coordinating these processes (Jais & Brüning, 2017). Hypothalamic lesion studies in rats have described specific areas in this region as central regulators of feeding (Hetherington, 1944; Hetherington & Ranson, 1940, 1942). Moreover, certain hypothalamic lesions led to the cessation of feeding and subsequent death by starvation (Anand & Brobeck, 1951a,

1951b). Indeed, this research demonstrated that obesity is far more complex than initially thought as it is associated with altered brain functions. In a study by Jastreboff et al. (2016) using functional Magnetic resonance imaging (MRI), it was observed that after drinking a cherry flavoured glucose-sweetened beverage, obese adolescents presented decreased brain perfusion in prefrontal cortex (associated to decision making) and an increased perfusion in hypothalamus (homeostatic appetite regions of the brain). The authors have demonstrated that study subjects have impaired prefrontal executive control responses, which seems to be related to glucose and fructose overconsumption, consequently increasing weight gain. Food intake is a complex process that is controlled by several molecules, namely neurotransmitters - dopamine, GABA, norepinephrine, serotonin -, peptides and amino acids. Dopamine has attracted increased interest due to its role in regulating food intake. Interestingly, Wang et al. (2001) showed that in obese human subjects, the availability of dopamine D2 receptor (D2R) was decreased in proportion to their Body Mass Index. The authors suggested that since dopamine modulates motivation and reward circuits, the dopamine deficiency observed in obese individuals may perpetuate their pathological eating, since they are less sensitive to reward stimuli. In other study, Johnson and Kenny (2010) associated the downregulation of striatal D2R found in obese rats, to drug addiction mechanisms. Indeed, the authors reported that similar changes in reward homeostasis are induced by addiction drugs, such as cocaine or heroin, and excessive food consumption, triggering similar compulsive behaviours. Consequently, common hedonic mechanisms may underlie both obesity and drug addiction. In fact, these similarities gave rise to the hypothesis of food addiction. Furthermore, Kuhn et al. (2013) showed that in a mice model, the intake of hydrogenated vegetable oil containing 11.72% of trans fat resulted in higher preference for amphetamine and it was associated with withdrawal signs, such

as anxiety and fear. In consequence, the authors proposed that chronic consumption of foods rich in trans fatty acids (TFA) can modify factors related to drug preference. In addition, TFA presence in diet during the development and growing periods can exacerbate both withdrawal symptoms as well as brain oxidative status. Such alterations were thought to arise from the health condition; however, studies focusing on diet effects demonstrated that in fact it can be fostered by nutrients alone. Feeding trans α-linolenic acid (ALA) to Wistar rats up to 21 months decreased the dopamine levels (neurotransmitter associated to attention, motivation and emotion) by 95% in hippocampus. Indeed, it was observed that the isomerization of dietary ALA can induce a "deficiency-like" status that results in modifications of the levels of endogenous dopaminergic neurotransmitters (Acar et al., 2003). In addition, Wistar rat offspring whose mothers were fed with a hydrogenated vegetable oil (rich in TFA) during gestation and lactation showed modification of spatial memory. Although only slight brain incorporation of dietary TFA was observed, it was enough to modify behavioral and biochemical parameters on the experimental animals (A. S. Souza et al., 2012). Thus, by focusing on food addiction problem it is easily understood how most obese people are unable to regulate their food intake and relapse towards their elevated body weight after repeated dieting and exercising attempts. This cycle of overconsumption, dieting and relapsing has been compared to the cycle of drug intoxication, abstinence and relapse observed in drug addiction (Volkow et al., 2017). Such perspective explains, along with all the socioeconomical and lifestyle conditionings, how the present strategies are ineffective and how obesity, although preventable, is on the rising. Considering all the discussed points, perhaps we should start considering the direct effect of diet, precisely nutrients in obesity; not only its role on adipose tissue but also if such nutrients can have a direct impact on brain.

Western Pattern Diet

Western pattern diet is associated with high-glycemic/high-insulinemic carbohydrates, including refined cereals, corn, potatoes and sugars (particularly sucrose and fructose), dairy products, and considerable amounts of proteins. Moreover, this kind of diet is also characterized by high levels of fat, namely saturated fatty acids (SFAs) and TFAs. In contrast, low levels of omega-3 FAs and other long-chain polyunsaturated fatty acids (LC-PUFAs) are present (Abramova et al., 2019; Kopp, 2019). According to the Food and Agriculture Organization of the United Nations (FAO), dietary fats include all fats and oils that are edible, produced from plants or animals. Dietary fats consist mainly of triglycerides, which can be split into glycerol and FAs. FAs constitute the main components of these lipids and are required as a source of energy, and for metabolism and structure (Food and Agriculture Organization of the United Nations, 2021).

FAs are classified present a carbon aliphatic chain and a single carboxyl group and are classified as saturated and unsaturated. SFAs contain only single carbon–carbon bonds in the aliphatic chain. They are important as sources of energy and as components of cell membranes. These FAs are not considered essential since the human body is able to synthetize them. Unsaturated fatty acids (one or more carbon–carbon double bonds), are subdivided into monounsaturated (MUFA) - one carbon–carbon double bond in the aliphatic chain- and polyunsaturated fatty acids (PUFAs) – two or more carbon-carbon double bond in the aliphatic chain (Moghadasian & Shahidi, 2017). The term ‘trans fat’ typically refers to edible fats that contain TFAs. These FAs have at least one double bond in the *trans* configuration, as opposed to the more common *cis* configuration, (Lichtenstein, 2016).

As recently reviewed by Dragano et al., (2020) FAs are known to cross the BBB and enter the cells of the CNS where they are converted into long chain fatty acid-Coenzyme A (LCFA-CoA) and further metabolized by β-oxidation or incorporated into phospholipids. The exact mechanisms through which this transport occur are not fully characterized, but passive diffusion, translocation by carrier proteins (cluster of differentiation 36 (CD36) and FA transport proteins (FATP)-1 and -4) are the commonly accepted mechanisms.

On the other hand, sugar overconsumption has been widely associated with obesity and some studies related reduction in sugar consumption with a slowing down of the USA annual rate of increase of obesity (Faruque et al., 2019). Therefore, since the current western diet often provides considerable amounts of sugar and SFA and TFA, it may represent a threat for health (A. S. Souza et al., 2012).

The Effect of Saturated Fatty Acids in Brain: Hypothalamic Inflammation

The effect of a high fat diet (HFD) in obesity animal models has been largely reported. In comparison with control diet, HFD presents increasing levels of endoplasmic reticulum (ER) stress proteins (pJNK, pPERK, peIF2α, GPR94 and GPR78), leading to accumulation of unfolded proteins due to high cellular demands. In response, affected cells activated a complex signalling system known as the unfolded protein response (UPR) to preserve cell integrity. This signalling system induces the production of inflammatory cytokines (TNF-α, IL-1, iNOS and IL-6) (Cavaliere et al., 2018; Nam et al., 2017), resulting in elevated levels of hypothalamic inflammation markers after HFD consumption. Consequently, these results point out to the existence in the brain of mechanisms to precisely recognize fatty acids. Toll-like receptors (TLR) 2 and 4, in the hypothalamus, are recognized binding sites for LC-SFA. Indeed, studies have shown

that diet also significantly increases the expression level of TLR gene expression (Nam et al., 2017). Most of the studies were focused on TLR 4, which is expressed in macrophages, dendritic cells, adipocytes, hepatocytes, muscles, and in the hypothalamus. Indeed, Milanski et al. (2009) showed that LC-SFA activate predominantly TLR 4 resulting in the induction of the mentioned ER stress, which ultimately leads to inflammatory pathways activation in the hypothalamus, by cytokine expression Furthermore, a loss-of-function mutation and inhibition of TLR4 protects mice from diet-induced obesity. As reviewed by (Li et al., 2020) TLR4 activation by SFAs has been demonstrated in cultured adipocytes, monocytes/macrophages, hepatocytes, endothelial cells, and skeletal muscle cells. However, the direct binding of SFAs to TLR 4 has been challenged (Erridge & Samani, 2009) and it is thus, possible that SFA interact with TLR 4 indirectly through fetuin A (Pal et al., 2012). Although, SFAs, including palmitic and stearic acid, can activate TLR 2 and TLR 4-dependent signaling pathways, MUFAs and PUFAs, particularly omega-3 PUFAs, do not and might instead protect against SFA-induced TLR activation (Valdearcos et al., 2015). Such hypothesis is going to be further discussed in *Using PUFA as Antiobesogenic Drugs.*

Besides, it has been reported that HFD elevates the markers of hypothalamic inflammation within 24 hours, in contrast with inflammation in peripheral tissues, which is a slow process taking weeks or months to develop (Thaler et al., 2012). A recent study has shown that after 3 days of HFD no changes in inflammation-related proteins was observed, but instead many proteins associated with cellular stress were found to be changed in response to this diet. Thus, such results suggest that oxidative stress in neurons may precede and ultimately cause HFD-induced hypothalamic inflammation (McLean et al., 2019). In fact, SFAs have not only been associated with

inflammatory processes, but they have been showing to promote hypothalamic apoptosis (Moraes et al., 2009; Nobunaga et al., 2014) or alterations in the cell volume distribution of proopiomelanocortin (POMC), resulting from defective regulation of hypothalamic POMC, and orexin-producing neurons (Lemus et al., 2015; G. F. P. Souza et al., 2016). These results suggest that, in both humans and rodent models, an HFD-induced obesity is associated with dysregulation in important brain areas for energy homeostasis. This is highly relevant since CNS energy homeostasis, as depicted in figure 1, is largely controlled by the fine balance between the two distinct subpopulations of neurons in the hypothalamus arcuate nucleus (ARC), namely the ones co-expressing orexigenic neuropeptides (agouti-related protein [AgRP] and neuropeptide Y [NPY]), and those producing anorexigenic neuropeptides α-melanocyte stimulating hormone (α-MSH) - a product of POMC precursor protein processing - and cocaine and amphetamine-regulated transcript (CART), whose peptides are neuromodulators involved in feeding, drug reward, stress, cardiovascular function, and bone remodeling (Lemus et al., 2015; Schneeberger et al., 2014). NPY/AgRP and POMC neurons in the ARC control energy homeostasis and coordinate the response to changes in metabolic statues, namely nutrient and hormonal fluctuations (Lemus et al., 2015; Valdearcos et al., 2015). AgRP and POMC, together with downstream target neurons, which express melanocortin receptor (MCR) 3 and 4, a family of G protein receptors (GPRs), are the core of melanocortin system. For instance, NPY acts on Y1 and Y5 receptor in the paraventricular nucleus of the hypothalamus to stimulate food intake and reduce basal energy expenditure (Lemus et al., 2015). α-MSH is an endogenous MCR 3 and 4 agonist, consequently generating an anorexigenic output by suppressing appetite and enhancing thermogenesis. On the other hand, AgRP is an antagonist of these receptors counteracting the anoretic effect of α-MSH, namely on

food intake and body weight (Ramírez & Claret, 2015; Valdearcos et al., 2015). Through NPY/AgRP and POMC neurons, the hypothalamus can exert control over other groups of neurons. This action ultimately leads to a regulation on efferent CNS outputs that regulate energy balance and fuel homeostasis in the rest of the body.

[Figure 1 near here]

The problem with hypothalamic ER stress mediated by obesity is related with its possible interference with the proper synthesis and processing of POMC. A defective POMC processing prevents the release of α-MSH in response to leptin, leading to leptin resistance (discussed in *Hypothalamic leptin resistance* section). Additionally, pro-convertase 2 (PC2), responsible for catalyzing the conversion of adrenocorticotropin (ACTH) into α-MSH, was found to be reduced by ER stress, consequently leading to the reduced α-MSH levels in diet induced obesity (Ramírez & Claret, 2015). Moreover, studies found a direct correlation between HFD feeding, in an obesity context, and POMC neurons apoptosis. Indeed, Moraes et al. (Moraes et al., 2009) reported that an HFD alters the expression of 57% of genes associated with neuronal apoptosis, proving the effect of dietary fats in inducing the hypothalamic neuronal cell death. However, HFD administration was shown to reduce the number of POMC neurons, but not NPY neurons, leading to an imbalance in energy homeostasis. The reduced number of POMC neurons was demonstrated not only to be a consequence of obesity, but also to be involved in the onset of obesity development. An hypercaloric (high-carbohydrate, high-fat) environment induces mitochondrial stress in POMC neurons, a consequence of a persistent elevation of microglial (principal resident immune cells of the brain) reactivity which results in TNF-α secretion. Indicating, that the HFD induced inflammation along with ER stress, plays a major role in the functional impairment of

hypothalamic POMC neurons and ultimately generating an additional pathogenic drive towards impaired energy homeostasis and obesity (Yi et al., 2017).

Moreover, an *in vitro* study carried out in embryonic mouse hypothalamic cell lines concluded that palmitate significantly increased mRNA levels of NPY and pro-apoptotic proteins (CHOP) associated to ER stress (Dalvi et al., 2017). These changes observed in the ARC neuron population, and the consequent energy homeostasis imbalance, seems to be involved in the main challenge of the anti-obesity therapies: patients that rapidly regain weight after finishing of treatment. When mice fed a HFD were administered with the neurocytokine ciliary neurotrophic factor (CNTF) the effects were a 20% body weight loss, neurogenesis of both POMC and NPY cells and increment of pSTAT3, a component of the leptin-activated signaling cascade in leptin receptor–containing cells of the hypothalamus (Kokoeva et al., 2005). However, if animals were treated with antimitotic drug Ara-C to prevent the proliferation of neural cells, body weight increased almost immediately after ending the intervention, reaching the starting value in 15 days and surpassing it in 20% by the end of the study (35 days).

In addition, recent research has shown that HFD induces chaperone-mediated autophagy (CMA) in the hypothalamus in short-term feeding. Prolonged exposure to this type of diet leads to CMA impairment (Portovedo et al., 2020). CMA is an important process since it regulates protein quality control and other cellular homeostasis mechanisms. In consequence, in the CNS, CMA is responsible for neuron protection against injuries and chronic neurodegeneration. Specifically, palmitate (a SFA) is able to directly activate CMA in hypothalamic neurons (Portovedo et al., 2020). The authors reported that HFD leads to early modifications in CMA machinery in the hypothalamus. Although such relation was not yet proved, this is highly relevant since

CMA HFD induced impairment may lead to an absence of misfolded and oxidized proteins degradation, resulting in hypothalamus dysfunction and neurodegeneration.

Hypothalamic Insulin Resistance

Insulin executes important roles in hypothalamus since it suppresses food intake and improves glucose metabolism. When there is a disruption of such effects a condition known as hypothalamic insulin resistance arises. Insulin signalling in some hypothalamic cell types, is stimulated by insulin in CNS. For instance, in neurons insulin signalling is initially mediated by insulin receptor (IR) activation, which results in electrophysiological and/or transcriptional changes in neurotransmitters (Ono, 2019). Besides, insulin (through IR) plays an important role in astrocyte's glucose transport from peripheral blood to CNS (Fernandez et al., 2017; García-Cáceres et al., 2016).

It is recognized that the obesity induced inflammation closely connects obesity to the development of both glucose intolerance and insulin resistance, a central component of type 2 diabetes (Geng et al., 2015). The HFD induced low level hypothalamic inflammation, namely through the expression of several proinflammatory cytokines and inflammatory responsive proteins, is accompanied by increased activation of intracellular serine kinases JNK and NFkB, a transcription factor that regulates the expression of proinflammatory genes, including cytokines (such as IL-1 and TNF-α), chemokines and adhesion molecules (Lawrence, 2009). The problem arises since the activation of intracellular kinases such as JNK and IkB kinase β (IKKβ), which act as intermediaries for proinflammatory signalling, induces phosphorylation of insulin receptor substrate (IRS) on its serine residues, inhibiting phosphorylation of its tyrosine residues (Rorato et al., 2017; Tanti & Jager, 2009). Importantly, the phosphorylation of those IRS-1 tyrosine residues, upon activation of the IR, constitutes a critical step in the

transmission of the insulin signal to downstream effectors and biological outcomes. In contrast to tyrosine phosphorylation, the induced serine phosphorylation blunts insulin signalling promoting insulin resistance. Reactive oxygen species (ROS) have also been related with insulin resistance. Under normal circumstances, hypothalamic insulin triggers the transient production of ROS to enhance insulin signalling. In obesity and diabetes, a ROS overproduction is reported, which will induce inflammation, consequently disrupting insulin signalling (Kjaergaard et al., 2018; Ono, 2019).

Hypothalamic Endoplasmic Reticulum Stress

The ER homeostasis can be altered by strong and prolonged cellular disturbance, leading to the accumulation of potentially toxic unfolded or misfolded proteins in ER lumen. In such conditions, to restore adequate ER performance, a set of stress-responsive signaling pathways, referred to as the unfolded protein response (UPR), is activated. If normal ER function is not restored the UPR sustained activation can lead to cell death by the activation of autophagic programs or apoptosis (Ramírez & Claret, 2015).

HFD diet exposure in rodent models has been showing to affect the mRNA expression of hypothalamic ER stress related UPR markers. Consequently, the UPR markers seemed to be a sensitive sensor of fatty acid availability as well as nutrient load (Belegri et al., 2017). Recently, palmitic acid (SFA) was demonstrated to increase the mRNA expression of the ER stress markers - Chop, Grp78, and the Bax/Bcl2 ratio - along with cellular neuroinflammation markers - mRNA levels of pro-inflammatory cytokines Il6, TNF-α, and Il1b, TLR-4 receptor, and the proinflammatory transcription factor NFkB, in mHypoA-POMC/GFP-2 neurons (POMC expressing neurons) (Tse & Belsham, 2018) . In a different study, other SFAs besides palmitic acid, such as lauric

and myristic acids, increase ER stress mRNA expression of Atf4, Atf6, Xbp1, Bip and Chop in mHypoE-N43/5 (S. Park et al., 2020). In fact, it has been suggested that lipid overload, especially SFAs, cause hypothalamus ER stress by inducing alterations in the ER membrane composition and its biophysical properties. Those variations, are sensed by UPR transducers, such as the ER membrane protein Ire1 and PKR-like kinase (PERK), an ER transmembrane kinase (Promlek et al., 2011; Volmer et al., 2013). A close relationship between ER stress and obesity was described for the first time by using dietary (HFD-induced) and genetic models (*ob/ob*) of murine obesity. The authors observed an increased phosphorylation of PERK in the obesity models. As a consequence, the phosphorylation of translation initiation factor 2 (eiF2) by PERK, was also increased (U. Ozcan et al., 2004). Indeed, eiF2 is an important factor for protein translation, and phosphorylation of its serine residue (Ser51) has inhibitory effect on protein translation. Therefore, the phosphorylation of both PERK and eIF2 is a key indicator of ER stress (Yilmaz, 2017).

Under normal conditions, NFkB, remains inactive in the cytoplasm through the action of its inhibitor, the IκB inhibitory protein (IκBα). Activation of IKKβ through phosphorylation induces IκBα phosphorylation (its substrate), which results in ubiquitination and ultimately proteasomal degradation. This action releases NFkB to translocate into the nucleus resulting in the transcription of its target genes (Zhang et al., 2008). Obesity induced ER stress was found to be both an upstream intracellular mediator and downstream event of the hypothalamic IKKβ/NFkB activation. Indeed, the benefits observed by suppressing ER stress in the CNS resemble the ones observed from suppressing IKKβ/NFkB. IKKβ/NFkB in the hypothalamic neurons was found to respond to the metabolic signals that are produced by overnutrition and that are a cause of multiple neuronal disease pathways (Zhang et al., 2008). Moreover, the NFkB

pathway activation is mediated by myeloid differentiation primary response 88 (Myd88) activation, through TLR4. In a recent study, an astrocyte specific Myd88 knockout mice fed a HFD or injected with SFAs showed ameliorated hypothalamic reactive gliosis and inflammation. Furthermore, the Myd88 expression in hypothalamic astrocytes was also increased in the mice subjected to the treatment. These results suggested an important role of Myd88 on mediating HFD signals for inflammation (Jin et al., 2020). Such results suggest that in obesity and overnutrition, ER stress and IKKβ/NFkB in the hypothalamus enhance each other leading to energy imbalance and consequently disease.

In conclusion, excessive nutrients, namely SFA, leads to UPR signaling in hypothalamus and consequently to inflammation and crosstalk with innate and adaptive immunity. Besides, high levels of SFA cause resistance to the action of key metabolic hormones, such as leptin and ghrelin, which are important players in the neuroendocrine control of energy homeostasis (Cui et al., 2017). Interestingly, contrarily to SFA, studies have shown that expression of ER stress markers was not affected when cells were treated with the MUFA oleic acid (S. Park et al., 2020).

Hypothalamic Leptin Resistance

As previously mentioned, adipose tissue secretes a variety of humoral factors – adipokines -, which regulate nutrient metabolism. Some adipokines, like leptin, serve as signals related to body energy storage and availability to the brain (Frederich et al., 1995; Maffei et al., 1995). The brain, particularly the hypothalamus, senses and integrates these signals and maintains energy homeostasis and body weight by controlling feeding behavior and energy expenditure (Zhou & Rui, 2013).

493 The gene product of the obese gene (*ob)* locus was first described by Ingalls et
494 al. (1950). Defects in *ob* gene were later associated with a marked increase in adipose
495 tissue mass as part of a syndrome that resembled morbid obesity in humans (Coleman,
496 1978). The *ob* gene product was finally described as leptin, a 16-kilodalton (kDa)
497 protein produced by the adipose tissue and defined as being able to reduce body fat in
498 mice. Its absence in obese mice leads to a massive increase in body fat (Halaas et al.,
499 1992; Maffei et al., 1995). Later, Wiesner et al. (1999) proposed a release of the leptin
500 from the brain into the blood. Such mechanism suggested an intrinsic brain source of
501 leptin. Leptin expression in the rat hypothalamus was found to be downregulated by
502 prolonged food restriction, like what has been previously observed in WAT. However,
503 this downregulation could not be abolished by refeeding, indicating that leptin
504 expression by prolonged fasting/refeeding is affected in a different way than in adipose
505 tissue (Sucajtys-szulc et al., 2009). Recently, a conditioned place preference test was
506 used to assess the effect of leptin on the preference of leptin-deficient *ob/ob* mice for
507 HFD. In this study conditioned place preference for HFD is higher among *ob/ob* mice
508 than among wild-type mice. Moreover, leptin replacement was shown to decrease the
509 reward value of HFD and sucrose independently of obesity. Such results suggested that
510 leptin reduces food intake by suppressing the hedonic feeding pathway in *ob/ob* mice
511 (Shimizu et al., 2017).
512 Leptin receptor (LepRb) is known to be expressed in various sites in the brain,
513 namely on choroid plexus, ventral tegmental area, the ARC and paraventricular nuclei
514 (PVN), and the ventromedial and dorsolateral hypothalamus. Importantly, mice with
515 hypothalamic deficiency of LepRb developed early-onset obesity (Ring & Zeltser,
516 2010). These results indicate that leptin can act directly on LepRb in the CNS,
517 informing various parts of the brain about the amount of peripherally stored energy

(Campfield et al., 1995; Gorska et al., 2010). Through the binding and activation of its brain receptor - LepRb -, leptin can decrease food intake while increasing energy expenditure. One of the most surprising features regarding leptin in obese individuals was that its circulating levels are abnormally high in these situations. This situation corresponds to a state defined as hyperleptinemia. Studies in both humans and mice, showed that indeed brain leptin transport is impaired in those subjects (Banks et al., 1999; Caro et al., 1996; El-Haschimi et al., 2000). It has been speculated that hyperleptinemia leads to leptin resistance (Knight et al., 2010). Indeed, leptin resistance is defined by the reduced ability of leptin to suppress appetite and weight gains (Zhou & Rui, 2013). However, over the past 10 years and as reviewed by Zhou and Rui (2013), other mechanisms besides hyperleptinemia have been proposed to explain leptin resistance, including impairment in leptin transport, leptin signaling and in the leptin-targeted neuronal circuits. Thus, defects in LepRb signaling cascades components, such as reduction of LepRb cell surface levels, upregulation and downregulation of negative and positive regulators, respectively, result in leptin resistance (Coppari & Bjorbaek, 2012; Morris & Rui, 2009). Although the core biological mechanisms behind leptin resistance and how it can be induced by overnutrition are currently unknown, HFD-related inflammation have been reported to have a role on leptin resistance (Son et al., 2019). On one hand, activation of the hypothalamic IKKβ/NF-κB pathways was shown to induce leptin resistance, as summarized in figure 2, whereas inhibition of hypothalamic IKKβ protects against obesity in mice. A recent review by (Dragano et al., 2016) , discussed the role of cytokine signaling 3 (SOCS3), a core inhibitor of insulin and leptin signaling, as an important mechanism involved in the appearance of leptin resistance in hyperleptinemic states. Indeed, in HFD-fed mice SOCS3 inhibitory pathway is altered and its expression basal levels were higher than in control groups and

were no longer responsive to leptin injection (Mainardi et al., 2017). The involved molecular mechanisms may include the control of IKKβ/NFκB over SOCS3 (Zhang et al., 2008). On the other hand and regarding ER stress, Ozcan et al. (2009) demonstrated that deletion of an important regulator of ER homeostasis, neuronal X-box binding protein 1 (XBP-1), lead to hypothalamic ER stress and consequently to leptin resistance in the XBP-1 knockout mice (*XNKO* mice). The leptin levels in XNKO mice dramatically increased (not proportionally to the body weight) at the early phases of HFD feeding. Therefore, these results might suggest that contrary to what was initially thought, in HFD, the induced ER stress and/or IKKβ/NFκB activation could be a reason for the development of leptin resistance, independently of prolonged leptin action and even before the onset of adiposity and hyperleptinemia.

[Figure 2 near here]

Hypothalamic Ghrelin Resistance

Ghrelin is a 28 amino acid peptide hormone acting on the brain to stimulate appetite. It is secreted by endocrine X/A-like cells present in the stomach mucosa, intestinal mucosa, ARC of the hypothalamus, the pituitary and other tissues. Besides, it is produced in the pancreatic islets, acting as an autocrine/ paracrine growth factor (Date et al., 2002; Khatib et al., 2015; Seim et al., 2013). It was first discovered by Kojima in (1999) as the ligand of growth hormone secretagogue receptor type 1a (GHSR1a). Acylation of ghrelin is required for its binding to GHSR and for its endocrine, metabolic and orexigenic actions. Ghrelin binds to GHSR, and the starvation signals to the brain, are transmitted to NPY and AgRP neurons of the ARC via the vagal afferent pathway, therefore stimulating appetite (Cui et al., 2017). Thus, when nutrient availability is low, levels of ghrelin increase, and after consumption of a meal, ghrelin levels are decreased.

Some investigations point out that ghrelin can be also produced in the hypothalamus, specifically in the ARC (Perello et al., 2012). GHSR is highly expressed in the hypothalamic cell populations that regulate feeding and body weight, such as ARC AgRP- and NPY-expressing neurons and VMH neurons expressing AMP-activated protein kinase (AMPK) (Guan et al., 1997; Nogueiras et al., 2004; Tannenbaum et al., 1998; Willesen et al., 1999).

As commented above, obesity is associated to alterations in the hypothalamic neuron population, low physical activity and ghrelin resistance. Unexpectedly for an orexigenic hormone, a positive energy balance induces ghrelin resistance in humans and rodent models and obesity is associated with reduced secretion and plasma levels of ghrelin (Otto et al., 2001, 2005; Perreault et al., 2004; Tschöp et al., 2001). Nonetheless, diet-induced hypothalamic inflammation results in the reduction of *Ghsr* expression in nodose ganglion and hypothalamus of mice, causing impaired transmission of gastric-derived ghrelin signals to the hypothalamus (Naznin et al., 2015). Ghrelin resistance has been demonstrated to be reversible following reversal of the HFD-induced inflammation and obesity phenotypes (Naznin et al., 2018). The diet-induced hypothalamic inflammation is thus demonstrated to have a high impact on ghrelin resistance. The HFD-induced ghrelin resistance mechanisms may also involve ER stress, the AMPK pathway or targeting rapamycin (mTOR) and k-opioid receptor (KOR) (Cui et al., 2017). Perez-Tilve et al. (2011) demonstrated that ghrelin resistance in response to HFD can occur rapidly and is almost independent from the length of the nutritional intervention. Short-term exposure (12 hours) to HFD is enough to alter the orexigenic effects of ghrelin. Nonetheless, the capacity of ghrelin to modulate lipogenesis in WAT is unaffected by HFD, indicating that different neuronal circuitries mediate ghrelin-specific regulation of food intake and lipid metabolism (Cui et al.,

2017). However, contradictory results were demonstrated by Briggs et al. (2014): ghrelin resistance in NPY/AgRP neurons occurs by 3 weeks of HFD feeding in mice. These authors observed that leptin-deficient genetically obese mice (*ob/ob*) are still ghrelin sensitive but become ghrelin resistant when leptin is administered through an intracerebroventricular injection. These results indicated that ghrelin resistance occurs because of increased plasma leptin (hyperleptinemia) associated with weight gain, instead of acute exposure to an HFD. Nevertheless, the exact mechanism by how leptin prevents ghrelin's effects on NPY neurons remains unknown. These observations reinforce the need for further studies to completely understand the HFD role in ghrelin resistance.

Potentialities of Using Polyunsaturated Fatty Acids as Antiobesogenic Drugs

Omega-3 Receptors in Brain and the Anti-inflammatory Process

PUFAs are unsaturated fatty acids with two or more double bonds and their classification depends on the position of the first double bond relative to the methyl-end group. Therefore, they can be subdivided into two groups: omega-6 (meaning that the double bound is 6 carbon atoms away from the terminal methyl group) and omega-3 FAs (meaning that the double bound is 3 carbon atoms away from the terminal methyl group). Omega-3 and omega-6 PUFAs are synthesized from the essential fatty acid ALA (C18:3 *c*9,*c*12,*c*15) and linoleic acid (C18:2 *c*9,*c*12), respectively. These precursors, ALA and linoleic acid, cannot be synthesized in the human body. However, humans may synthesize EPA and DHA in very small amounts from ALA (Moghadasian & Shahidi, 2017).

Considering the SFA hypothalamic effect presented here and framed within the homeostatic processes, it may be expected that other FAs could be also recognized by

specific receptors. In fact, G protein receptor 120 (GPR120), highly expressed in adipocytes and macrophages, is known to bind some FAs. Indeed, some PUFAs, such as the omega-3 fatty acids, ALA, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are established activators of GPR120 (Oh et al., 2010). As illustrated in figure 3, activation of GPR120 by DHA recruits β-arrestin 2 and the resulting GPR120-β-arrestin 2 complex is internalized. Both the TNF-α and TLR4 proinflammatory pathways, which have been discussed in this review, coincide at the step where TGF-β activated kinase 1 (TAK1) interacts with TGF-β activated kinase 1 binding protein 1 (TAB1). This interaction mediates downstream inflammatory processes by activation of NFkB and JNK. In fact, the internalized GPR120-β-arrestin 2 complex interacts with TAB1, thereby inhibiting the TAB1 interaction with TAK1 and in effect, inhibiting the downstream -proinflammatory pathways (Talukdar et al., 2011). Oh Da et al. (2010) reported that DHA stimulation of GPR120 inhibits both TLR 2/3/4 and the TNF-α proinflammatory cascade. Moreover, these authors observed that GPR120 stimulation specifically inhibits TAK1 phosphorylation and activation. Therefore, GRP120 activation provides a common mechanism for the inhibition of both TLR and TNF-α signaling. Wellhauser & Belsham (2014) have studied the gene expression levels of proinflammatory cytokines in rHypoE-7 hypothalamic neuronal cells, upon exposure to TNF-α treatment in the presence or absence of DHA, and they concluded that translational and transcriptional inflammatory response triggered by TNF-α exposure resulted in abundant GPR120 expression levels, since it is functionally responsive to DHA. Nevertheless, the inflammatory state was prevented by DHA pretreatment, since GPR120 was activated thereby reducing the inflammatory response to TNF-α. Moreover, disruption of endogenous levels of GPR120 significantly abrogated the anti-inflammatory effects of DHA, therefore identifying GPR120 as the main mediator of

omega-3 FA actions on the inflammatory status of the studied cell model (Wellhauser & Belsham, 2014). Moreover, intracerebroventricular infusion of a GPR120 agonist in mice resulted in reduction of food intake and lower rewarding effects of high fat/high sucrose diet (lever-pressing test) (Auguste et al., 2016). Importantly, a deleterious mutation inhibiting GPR120 signaling activity was described in obese subjects. Consequently, the discovery of this mutation gives evidence that the GPR120 activity is also physiologically relevant in humans, since it increases the risk of obesity in European population (Ichimura et al., 2012).

Using PUFA as Antiobesogenic Drugs

Omega-3

Recently, omega-3 has also demonstrated neurogenesis activities (preferentially in POMC neurons) when administered as fatty acids (intracerebroventricular injection) or assayed in diets using Swiss mice (Nascimento et al., 2016). Indeed, PUFAs were observed to increase hypothalamic neurogenesis to levels similar or even higher than the ones induced by the brain-derived neurotrophic factor (BDNF), a well-described factor responsible to induce hypothalamic neurogenesis (Nascimento et al., 2016). Interestingly authors associated the neurogenic activities to GPR40 and not to GPR120, as previously discussed. In fact, GPR120 was found to be expressed predominantly in microglial whereas GPR40 in POMC and NPY neurons. Indeed, in a study performed by Dragano et al. (2017) the use of GPR120 and GPR40 agonists showed that while the first acted predominantly reducing hypothalamic inflammation, the latter acted by reducing body mass and increasing POMC expression. Such results suggest that the combined activation of both receptors in the hypothalamus may result in better metabolic outcomes.

Moreover, lard substitution by fish oil (rich in omega-3 FAs) in the feeding of male Wistar rats resulted in reduction of inflammation and apoptosis markers. In this work, utilization of fish oil led to lower body weight gain compared with lard, as well as decreased phosphorylation of AMPK (decrease activation) (Viggiano et al., 2016). Indeed, AMPK, a serine/threonine kinase activated by phosphorylation, acts as a central nutrient sensor involved in glucose uptake and lipogenesis among other metabolic functions, contributing to homeostasis (Mihaylova & Shaw, 2011). In another study by Pimentel et al. (2012) HFD enriched with either soy (rich in omega-6 FAs) or fish oil were compared by evaluating insulin hypophagia and hypothalamic signaling after insulin injection. In contrast to what was found in the soy rich diet, fish oil supplementation showed a decreased in the TRAF6, TNF-α and IL-6 hypothalamic proinflammatory mediators' levels, while showing increased anti-inflammatory cytokine IL-1 levels. Besides, the fish group showed normal fat pad weight and leptin levels, as well as improved blood lipid profile. In addition, reduced levels of corticosterone, a feature that is known to favor insulin sensitivity, were detected in the fish group. In a recent study, evaluating the potential of fish oil in the reversion of a depression induced state in rats, Dang et al. (2018) observed that interestingly, fish oil supplementation attenuated the induced abnormal behavior and brain inflammatory response. Furthermore, fish oil supplementation also restored the neurochemical disturbance associated with induced depression. It suppressed the expression of proinflammatory mediators and oxidative stress by inhibiting NFkB and the inducible isoform of Nitric oxide synthases (iNOS). Thus, the well-studied anti-inflammatory effect of omega-3 FAs of marine origin EPA and DHA is thought to involve the inhibition of the phosphorylation of the inhibitory subunit of NFkB – IκB – trapping, as a result, NFkB in its active trimeric state on the cytosol. These effects are thought to be

690 mediated by membrane bound GPR120 (Calder, 2013). Table 1 (1a and 1b) summarizes
691 results found in several studies that reinforce the possible beneficial effect of dietary
692 omega-3 fatty acids on neuroinflammatory diseases, such as obesity.
693 [Table 1a and 1b near here]

694 *Conjugated Linoleic Acid*

695 Conjugated linoleic acid (CLA) corresponds to a group of positional and geometric
696 isomers of linoleic acid (LA; *cis*-9, *cis*-12-octadecadienoic acid; *c*9,*c*12). Although a
697 number of CLA isomers are found in food, the primary research focus is on the two
698 main isomers: *cis*-9, *trans*-11 (*c*9,*t*11) and *trans*-10,*cis*-12 (*t*10,*c*12). In fact, naturally
699 occurring CLA primarily consists of the *c*9,*t*11 isomer (>80%) present in food, such as
700 beef, milk, and dairy products, since it is produced by rumen bacteria from LA
701 (Yeonhwa Park, 2009). As reviewed by Rodríguez-Alcalá et al. (2017) several
702 biological activities have been attributed to CLA: it has been shown to reduce cancer in
703 several animal models; to reduce atherosclerotic lesions in rabbits and hamsters; and to
704 reduce total cholesterol, triacylglycerides, low density lipoprotein-cholesterol (LDL-
705 cholesterol) and increased high density lipoprotein-cholesterol (HDL-cholesterol) in a
706 number of animal models. Furthermore, the anti-obesity effects of CLA are well studied
707 in different animal models since it has shown to increase lean body mass and to reduce
708 body fat mass. Although its effect on peripheral tissues, such as adipocyte tissue has
709 been widely assessed, and its ability to reduce body fat in animals was first reported in
710 1995 (Y Park et al., 1995), several other beneficial health effects have been attributed to
711 it. In a study aimed at assessing the effect of CLA on ameliorating colitis, it was found
712 that CLA exerted anti-inflammatory properties by repressing TNF-α expression and
713 NFkB activation, while inducing the expression of the immunoregulatory cytokine

714 transforming growth factor β1 (TGF-β1). The anti-inflammatory CLA action was
715 reported to be mediated by PPAR (Peroxisome proliferator-activated receptor) γ and δ
716 induction. Indeed the loss of the PPAR γ gene in the colon was found to cancel the
717 beneficial effects of CLA in induced colitis (Bassaganya-riera et al., 2004). PPAR (α,
718 β/δ and γ) are nuclear receptors that translate nutritional and/or pharmacologic stimuli
719 into changes in gene expression. They were originally described as components of
720 adipocyte gene expression differentially regulating lipid homeostasis (P Tontonoz et al.,
721 1994; Peter Tontonoz et al., 1994). In further studies, PPARs were shown to be
722 involved in the regulation of inflammation, immunity and epithelial cell differentiation
723 (Bassaganya-riera et al., 2004; Cunard et al., 2002; R. A. Gupta et al., 2003; Jones et al.,
724 2002; Natarajan & Bright, 2002; Y. L. Wang et al., 2002). Some *in vitro* studies
725 concluded that dietary PUFA and their metabolites are endogenous PPAR γ ligands
726 (Hwang, 2000). CLA has been previously demonstrated as being able to activate PPAR
727 γ eliciting *in vivo* effects consistent with PPAR γ activation, namely on the reduction of
728 the inflammatory response (Yang & Cook, 2003; Yu et al., 2002).
729 The beneficial effect of CLA on several peripheral tissues is well documented,
730 namely on reducing body fat (Yeonhwa Park & Pariza, 2007; Whigham et al., 2007).
731 However, its incorporation in brain has been detected only in few cases and at very low
732 concentrations (Alasnier et al., 2002). The above-discussed anti-inflammatory and anti-
733 proliferative activities linked to CLA could impact positively neurological diseases,
734 including obesity, where inflammatory response contributes to the pathogenesis. Fa et
735 al. (2005) have found that indeed, CLA isomers *c*9,*t*11 and *t*10,*c*12 are actively
736 incorporated and metabolized in rat brain and in *in vitro* astrocytes cultures. Since it is
737 known the presence of PPARs in different brain areas, the beneficial effect of CLA
738 could be achieved through specific PPAR-mediated differentiation pathways. Moreover,

739 after intracerebroventricular administration of CLA, Cao and collaborators reported that
740 food intake was inhibited in rats (Cao et al., 2007). This effect was shown to be related
741 with decreased mRNA expression of NPY and AgRP. Importantly, such inhibition was
742 not repeated by other unsaturated FA, indicating a CLA-specific action. Besides,
743 promising results have been shown regarding decreased serum leptin levels in rats
744 following CLA treatment (Y.-M. Wang et al., 2005; Yanagita et al., 2005). In fact, acute
745 and chronic activation of CNS PPAR γ led to positive energy balance and restored
746 leptin sensitivity in HFD fed rats (Ryan et al., 2011). Nevertheless, as demonstrated in
747 Table 2, despite the promising results that have emerged over the last few years
748 regarding a potential beneficial effect of CLA in the brain, few studies have specifically
749 targeted the antiobesogenic effect of CLA isomers on CNS, especially on hypothalamic
750 inflammation. Actually, some contradictory results have been reported: when *t*10,*c*12
751 CLA was added to cell cultures it increased PPAR γ gene expression and activation,
752 NFkB activation and expression of TNF mRNA. Although there was an upregulation of
753 PPAR γ, the studied CLA isomer acted in a proinflammatory manner (Calder, 2013).
754 However, in the presence of lipopolysaccharide (LPS), the NFkB activation was
755 decreased and so were the TNF mRNA levels. In the presence of such inflammatory
756 stimulus, *t*10, *c*12 CLA acted in an anti-inflammatory manner (Kim et al., 2011). These
757 results suggest that indeed FAs may present different actions depending on the exact
758 conditions that prevail. In a study performed by Wargent and collaborators (2005)
759 treatment of leptin-deficient genetically obese mice (*ob/ob*) with CLA showed to
760 initially decrease but subsequently increase insulin sensitivity, suggesting that in short
761 term another mechanism, namely the reduction of adipocyte number and consequently
762 plasma adiponectin concentration, may decrease insulin sensitivity. Therefore, although
763 recent research, as shown in this review, have evaluated the role of some CLA isomers,

764 there is still the need to better understand isomer-specific effects of CLA. Besides, some
765 safety concerns and contradictory results regarding the use of CLA in humans increase
766 the need for further investigations (Yeonhwa Park & Pariza, 2007).
767 [Table 2 near here]
768

Conjugated Linolenic Acid

Conjugated alpha linolenic acid (CLNA) isomers refers to a mixture of different linoleic acid (LNA) conjugated isomers occurring naturally in milk fat and meat of ruminants, but are mostly found in vegetable oils. Punicic acid (PUA) (C18:3 *c*9,*t*11,*c*13) is mostly found in pomegranate (*Punica granatum*) seed oil (≈70g of PUA/100g of fat) (Fontes et al., 2017). CLNA isomers share similarities with CLA, such as carbon composition, atomic arrangement and the number of carbon double bonds (Melo et al., 2014), and some works suggest that they can exert similar effects to CLA at lower doses. An effective dose of CLA in humans is 3 g/day (Ip et al., 1994) while for CLNA is 2-3 g/day (Shinohara et al., 2012). Thus, as reviewed by Fontes et al. (2017) similar biological activities to CLA have been attributed to CLNA: some studies reported a cytotoxic effect of CLNA isomers on different human tumor cell lines and antioxidant activity since a reduction in lipid peroxidation was observed. Moreover, CLNA isomers have also been described to exert positive effects on body weight.

It is important to consider that the naturally occurring agonists of PPARs remain largely unknown. Due to the similarities found between punicic acid (PUA), omega-5 octadecatrienoic acid and the mentioned *c*9, *t*11 CLA isomer, the possibility of PUA being also a PPAR activator was hypothesized. Indeed, PUA specifically activates PPAR α and γ in adipocyte cells in a dose-dependent manner (Hontecillas et al., 2009). Moreover, dietary PUA was found to decrease fasting plasma glucose concentrations, improve the glucose-normalizing ability, suppress NFkB activation, TNF-α expression and upregulated PPAR α and γ responsive genes in both skeletal muscle and WAT in mice. In addition, loss of PPAR γ impaired the ability of dietary PUA to improve glucose homeostasis and suppress inflammation (Hontecillas et al., 2009). Moreover, PUA was found to ameliorate HFD induced obesity and insulin resistance in mice, by

improving peripheral insulin sensitivity without affecting liver insulin (Vroegrijk et al., 2011). In a similar way to what was found for CLA, the beneficial effect of PUA is known for the peripheral tissues, namely adipose tissue. A commercial source of PUA - Xanthigen - was able to significantly suppress 3T3-L1 adipocyte differentiation and lipid accumulation. This effect was attributed to a decrease in PPAR γ expression levels (Lai et al., 2012). This is relevant since PPAR γ is a regulator of adipogenesis and it is necessary for adipocyte differentiation (Rosen et al., 1999; P Tontonoz et al., 1994).

[Table 3 near here]

A research work determined that CLA is converted into CLNA in rat brain (Fa et al., 2005). The neuroprotective potential of pomegranate seed oil (a known source of PUA) in HFD induced-obese mice was reported as shown in table 3 (Amri et al., 2017). Indeed, in a study aiming to assess the effect of pomegranate seed oil (source of PUA) on BV-2 microglial cells activation, the authors demonstrated that the pomegranate seed oil did not suppressed the intracellular oxidant generation and did not influenced the intracellular distribution of cholesterol. But the morphology of activated cells was affected. The authors suggested that pomegranate seed oil may have an immunomodulation and cytoprotecting potential in BV-2 cells comparable to omega-3 PUFAs (Račková et al., 2014). However, considering that the effect of CLNA isomers on brain is largely unknown and although some promising results have emerged regarding assays on adipocytes cells showing a potential antiobesogenic role, there is the need of further investigations, specifically on human subjects, as well as the potential adverse health effects.

[Figure 3 near here]

Conclusion

Although preventable, obesity and overweight are still associated with worrying

819 rates worldwide. The current drugs and therapies available are not sufficient to tackle
820 such problem. One of the major reasons has been associated with brain dysregulation
821 induced by HFD, intimately associated with western pattern diet. In fact, brain
822 inflammation, specifically hypothalamus inflammation, has been linked to obesity
823 development and progression. Indeed, SFAs by binding to TLR4, trigger inflammatory
824 processes. The ultimate consequence is the production of inflammatory cytokines,
825 which result in elevated levels of hypothalamic markers after HFD consumption. In this
826 review, it was demonstrated that dietary obesity can be largely prevented by inhibiting
827 IKKβ/NFkB. Indeed, the well-studied anti-inflammatory effect of omega-3 FAs of
828 marine origin EPA and DHA is thought to involve the inhibition of the NFkB pathway.
829 Other PUFAs may show similar potential and this review explored for the first time, the
830 CLA potential in reverting the pro-inflammatory action of SFA in hypothalamus.
831 Indeed, CLA has been recognized for its anti-inflammatory role in peripheral tissue.
832 There are some *in vitro* and *in vivo* studies already showing its potential at a
833 hypothalamic level. Additionally, due to structural similarities with CLA isomers,
834 CLNA (PUA isomer) was hypothesized has also having a potential beneficial effect on
835 reverting hypothalamus inflammation. Indeed, a small number of studies with PUA
836 revealed anti-inflammatory actions mediated by PPARs. Nevertheless, regarding the
837 obesity induced hypothalamic inflammation process, despite some promising results,
838 there is still the need to further clarify CLA, and specially CLNA isomers' anti-
839 inflammatory actions in hypothalamus. Considering such potential, we believed that
840 new routes of research need to be established to explore such capability.

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Conflicts of interest

The authors declare no conflict of interest.

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1583 **Table 1a**

Studied FA/Source	Experimental model	Study Objective	Main Results	Reference
Saturated FAs - Lauric acid (C12:0), Palmitic acid (C16:0) and Stearic acid (C18:0)- and polyunsaturated FAs -DHA (C22:6(n-3)).	Primary astrocytes derived from Sprague-Dawley rats	Effect of long-chain fatty acids on inflammatory signaling in cultured astrocytes.	Palmitic acid, lauric acid and stearic acid, trigger the release of TNF-α and IL-6 from astrocytes. DHA acts in a dose-dependent manner to prevent the actions of palmitic acid on inflammatory signaling.	(S. Gupta et al., 2012)
Flax seed oil (rich in C18:3), Olive oil (rich in C18:1) and omega-3 and omega-9 fatty acids	Male Wistar rats and Male Swiss mice	Evaluate the effects of unsaturated fatty acids on hypothalamic inflammation in obesity.	Unsaturated fatty acids can act either as nutrients or directly in the hypothalamus, reverting diet induced inflammation and reducing body adiposity. omega 3 and omega 9 fatty acids activate signal transduction through GPR120.	(Cintra et al., 2012)
Soy oil (omega-6 PUFAs) and fish oil (omega-3 PUFAs)	Male Wistar rats	Effect of high-fat PUFA diets on the expression of proteins involved in inflammatory pathways in hypothalamus and other organs (muscle and tissue).	Soy diet induced local stimulation of the NFkB pathway. Fish diet diminished hypothalamic levels of TRAF6 and of the inflammatory cytokines TNF-α and IL-6, along with enhanced anti-inflammatory IL-10 cytokine levels.	(Gustavo Duarte Pimentel et al., 2013)
Soy bean oil (omega-6 PUFAs), fish oil (omega-3 PUFAs) and hydrogenated vegetable fat (saturated and *trans* FA)	Female Wistar rats	Influence of soybean oil, fish oil and hydrogenated vegetable fat on preference parameters for amphetamine.	Only fish oil did not show any anxiety-like symptoms or increased locomotion; it was related to lower oxidative damages to proteins and increased catalase activity in striatum and hippocampus.	(Kuhn et al., 2013)
DHA	rHypoE-7 rat hypothalamus cells	GPR120 activation at the level of individual neurons upon exposure to TNF-α in the presence or absence of DHA.	DHA pretreatment prevents the inflammatory state and this effect was inhibited by the reduction of endogenous GPR120 levels.	(Wellhauser & Belsham, 2014)
Omega-3 FAs	Sprague-Dawley rats and hypothalamic cells from obese rats	Effect of omega-3 fatty acids on brain derived neurotrophic factor (BDNF) gene expression.	Omega-3 FAs in vivo assays showed to reverse the negative effect that obesity has on BDNF gene expression: decreased in serum total cholesterol and TAG. In vitro omega-3 FAs present an increase in BDNF expression.	(Abdel-maksoud et al. 2016)
DHA	Male Swiss albinus mice	Potential of omega-3 PUFAs, in diet or by local injection, to induce hypothalamic neurogenesis.	Omega-3 PUFAs increase neurogenesis in the hypothalamus, accompanied by reduction of apoptosis markers, increased responsiveness to leptin, and reduced body mass gain.	(Nascimento et al., 2016)

1584 **Table 1b**

Studied FA/Source	Experimental model	Study Objective	Main Results	Reference
Fish oil (omega-3 PUFAs)	Male Wistar rats	Potential of PUFA beneficial effects being mediated by AMPK in the hypothalamus	Substitution of saturated by unsaturated fatty acids diet (omega-3) has beneficial effects on modulation of hypothalamic inflammation and function in obesity.	(Viggiano et al., 2016)
	Male Spraque-Dawley rats	Effects of fish oil supplementation on induced behavioral changes, inflammatory cytokine expression and oxidative reactions in frontal cortex and hippocampus.	Fish oil supplementation attenuated the induced abnormal behavior, the brain inflammatory response, the induced oxidative reactions and neural apoptosis. It restored the neurochemical disturbance.	(Dang et al., 2018)
Krill oil (omega-3 PUFAs) and Buttermilk fat globule membranes (BMFC)	Wistar rats	Effect of dietary bioactive phospholipid concentrates of krill oil and/or BFMC on insulin signaling, mitochondrial activity and biogenesis, and synaptic signaling in the hippocampus and cortex.	Dietary supplementation with krill oil and BFMC improves peripheral and central insulin resistance, the energy state within neurons and facilitates both mitochondrial and protein synthesis, necessary for synaptic plasticity.	(Tomé-carneiro et al., 2018)
Fish oil	Male Swiss mice	Evaluate the effects of omega-3 on inflammation, oxidative stress, and energy metabolism parameters in the brain of mice subjected to HFD-induced obesity model.	Omega-3 treatment partially reversed the changes in the inflammatory and in the oxidative damage parameters and attenuated the alterations in the antioxidant defense and in the energy metabolism.	(Mello et al., 2019)
DHA	Male C57BL/6J mice	Determine the beneficial central effects and mechanism of DHA (by intracerebroventricular injection(icv)) in HFD fed mice.	DHA	(Cheng et al., 2020)
Fish oil (equal amounts of DHA and EPA)	Male C57Bl/6J mice	Study the effects of omega-3 PUFA supplementation on energy homeostasis, anxiodepressive behavior, brain lipid composition, and gliosis in the diet-induced obesity.	Fish oil supplementation also defended against the anxiogenic and depressive-like effects of HFD. Brain lipids, particularly anti-inflammatory PUFA, were diminished by HFD, whereas FO restored levels beyond control values.	(Demers et al., 2020)

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1586 **Table 2**

Studied FA	Experimental model	Study Objective	Main Results	Reference
*c*9,*t*11 and t10,c12 CLA isomers	Female Sprague-Dawley rats and in vitro culture of astrocytes	Accumulation and metabolism of CLA in the brain.	CLA isomers were incorporated and metabolized in rat brain	(Fa et al., 2005)
	Sprague-Dawley rats	Hypothalamic effect of CLA by intracerebroventricular injections.	CLA can inhibit food intake by decrease the expression of NPY and AgRP.	(Cao et al., 2007)
	Female Long Evans rats	Effect of oral administered CLA on CNS vasculature.	CLA administration significantly reduces angiogenesis in the cerebellum by decrease in pro-angiogenic growth factors and their receptors.	(Sikorski et al., 2008)
	Male mice Jcl:ICR strain	Effect of CLA Triacylglycerol oil on brain endocannabinoid content (EC).	CLA influences brain EC system by reducing the amount of 2-AG in the cerebral cortex.	(Tsuyama et al., 2009)
	Male ICR mice	Effect of *t*10, *c*12 CLA on energy intake and body weight composition is confounded by dietary fat concentration and involves hypothalamic appetite controlling mechanisms.	The Hypothalamic proopiomelanocortin (POMC) and AMP-activated protein kinase α2 elevated mRNA expression was suppressed due to CLA treatment.	(So et al., 2009)
	Male ICR mice	Effect of dietary CLA brain lipids incorporation in appetite-regulation neuropeptide expression and reductions in feed intake and body fat.	No CLA isomer was detected in the brain neither any change in brain lipid profile	(Shelton et al., 2012)
	Mice	Effects of dietary CLA intake on CNS autoimmunity.	CLA supplementation suppresses CNS autoimmunity and reduced CNS inflammation	(Fleck et al., 2018; Klotz et al., 2015)
CLA isomers not specified	Neural Stem cells	Effect of CLA on neural stem cell differentiation.	CLA promotes neuronal cells differentiation and arrests cell cycle by activating cyclin dependent kinase inhibitors.	(Okui et al., 2011)

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1589 **Table 3**

Studied FA/Source	Experimental model	Study Objective	Main Results	Reference
Pomegranate seed oil (omega-5 fatty acids source)	BV-2 microglial cells	Effect of Pomegranate seed oil (omega-5 rich oil, including punicic acid) in immunomodulation and cytoprotection of BV-2 microglia cells.	No notable suppression of the intracellular oxidant generation and no influence the intracellular distribution of cholesterol. But affected the morphology of activated cells.	(Račková et al., 2014)
Pomegranate extracts	High-fat-high fructose diet induced-obese rat	Investigate beneficial effects of Pomegranate seeds oil, leaves, juice and peel on brain cholinesterase activity, brain oxidative stress and lipid profile.	Neuroprotective effects of pomegranate extracts by inhibition of cholinesterase and the stimulation of antioxidant capacity	(Amri et al., 2017)

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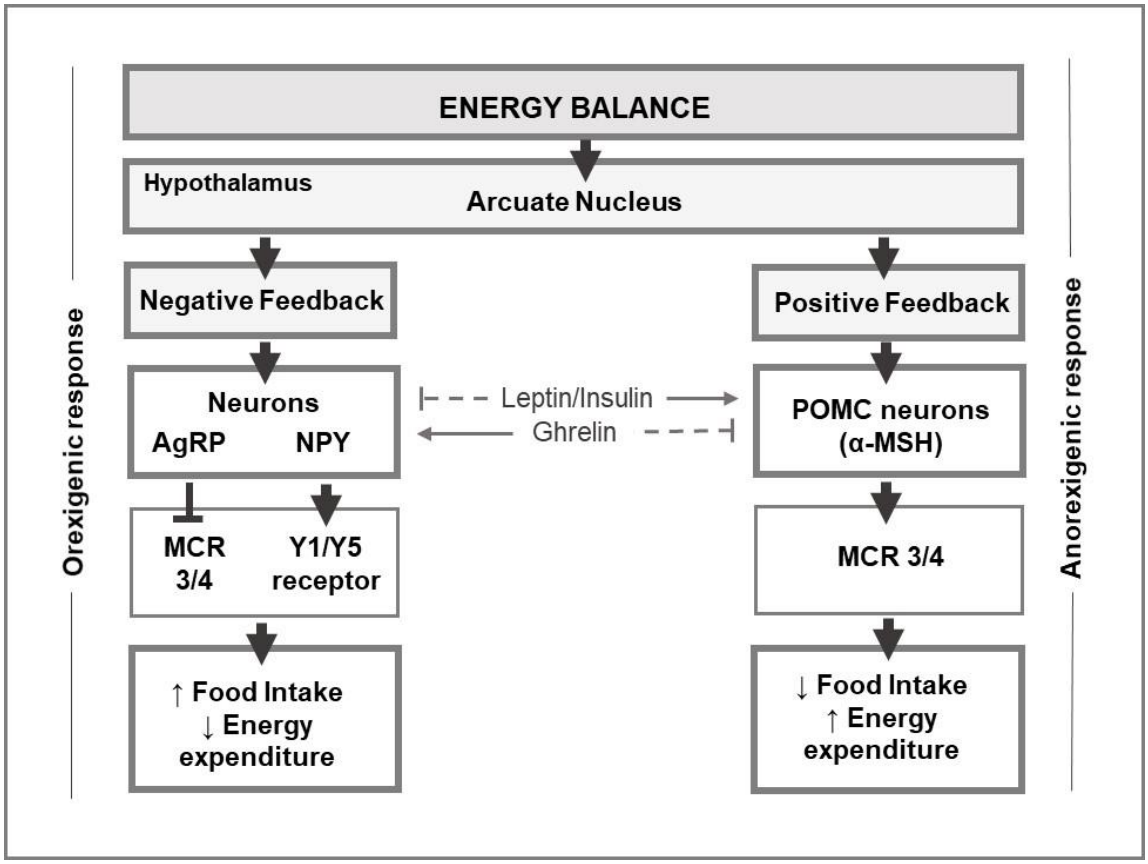
phosphorylation and activation, by interacting with TAB1 (Osborn & Olefsky, 2012). Regarding both CLA and CLNA isomers, several studies have reported their anti-inflammatory potential in adipose tissue, which is mediated by PPARs. Nevertheless, regarding the obesity induced hypothalamic inflammation process, despite some promising results, there is still the need to further clarify CLA, and specially CLNA isomers' anti-inflammatory actions in hypothalamus. Since it is known the presence of PPARs in different brain areas, the beneficial effect of those fatty acids in hypothalamus, specifically, is hypothesized as being modulated through specific PPAR-mediated differentiation pathways.

1632 **Figure 1**.



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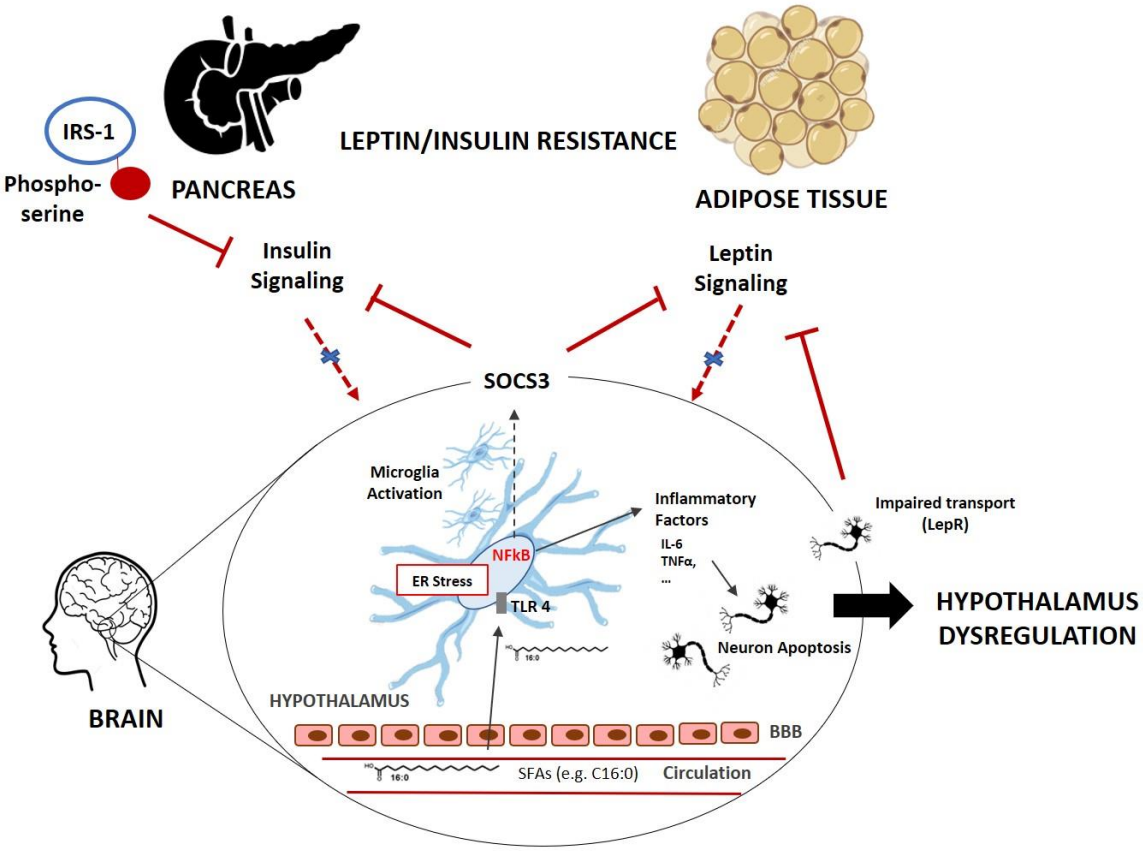
1635 **Figure 2.**



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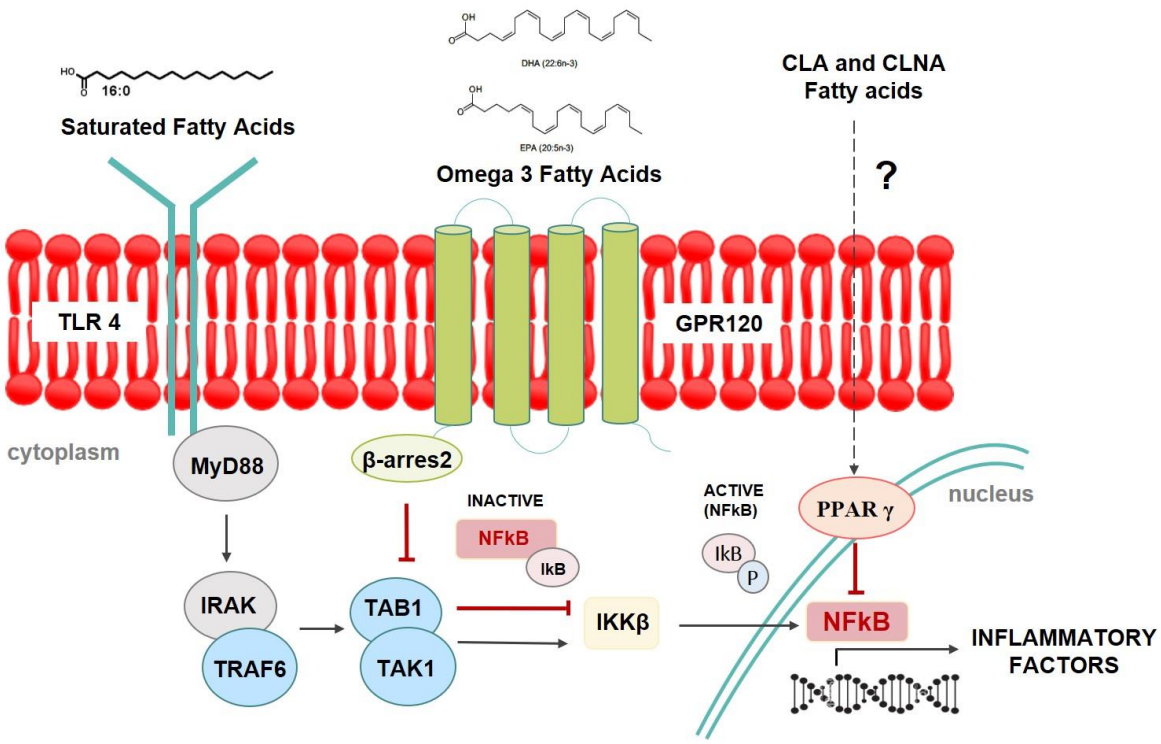
1638 **Figure 3.**



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