Role of bioactive lipids on obesity

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Abstract

Obesity continues to be one of the major global challenges in the present century and its incidence nearly tripled between 1975 and 2016. It is estimated that obesity rates are going to increase further by 2030. The available drugs for obesity have not achieved the required level of clinical effectiveness and have been associated with severe health side effects. Diet has been widely recognized as playing a central role in such disorder. Although high-fat diets are often blamed for increased obesity rates, fats are diverse and respond differently *in vivo*. Saturated fatty acids bind to toll-like receptor 4 (TLR 4) triggering inflammatory processes in brain, adipose tissue and liver. Besides, saturated fatty acids are responsible for increased lipid storage in adipose tissue leading to an accumulation of lipids in adipocytes. In contrast, medium-chain fatty acids, monounsaturated and polyunsaturated fatty acids are related with body weight reduction and a protective potential of both peripheral tissues and brain, in part related with their anti-inflammatory capability.

Keywords

Bioactive lipids; obesity; saturated fatty acids; medium-chain fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; inflammation; insulin resistance

Abbreviations

α-linolenic acid (ALA); α-melanocyte stimulating hormone (α-MSH); 11-β-hydroxysteroid-dehydrogenase type 1 (11β-hsd1); Acetyl-CoA carboxylase (ACC); Acyl-CoA synthetase (ACS); Agouti-related protein (AgRP); AMP-activated protein kinase (AMPK); Arcuate nucleus (ARC); Blood-brain barrier (BBB); Body mass index (BMI); Brown adipose tissue (BAT); Cardiovascular disease (CVD); Carnitine palmitoyltransferase-1 (CPT1); Central nervous system (CNS); Conjugated linoleic acid (CLNA); Conjugated linolenic acid (CLNA); Cluster of differentiation 36 (CD36); C-reactive protein (CRP); cyclic adenosine monophosphate (cAMP); Docosahexaenoic acid (DHA); Docosapentaenoic acid (DPA); Eicosapentaenoic acid (EPA); European Medicines Evaluation Agency (EMA); Endoplasmic reticulum (ER); Fatty acid binding protein (FABPpm); Fatty acid synthase (FAS); Fatty acid transport proteins (FATPs); Food and Drug Administration (FDA); High fat diet (HFD); Hormone-sensitive lipase (HSL); Insulin receptor substrate (IRS); Kilocalories (kcal); Linoleic acid (LA); Long-chain saturated fatty acids (LC-SFAs); Lipopolysaccharide (LPS); lipoprotein lipase (LPL); Low-density lipoprotein (LDL); Long-chain triglycerides (LCTGs); Malonyl-CoA descarboxilase (MDC); Medium-chain saturated fatty acids (MC-SFAs); Medium-chain triglycerides (MCTGs); Mitofusins 1 and 2 (Mfn1 and Mfn2); Monounsaturated fatty acids (MUFAs); Neuropeptide Y (NPY); Non-alcoholic steatohepatitis (NASH); White adipose tissue (WAT); World Health Organization (WHO); Oleoylethanolamide (OEA); Organization for Economic Co-operation and Development (OECD); Palmitic acid (PA); Palmitoylethanolamide (PEA); Peroxisome proliferator-activated receptor (PPAR); Polyunsaturated fatty acids (PUFAs); Propiomelanocortin (POMC); protein kinase A (PKA); Reactive oxygen species (ROS); Saturated fatty acids (SFAs); TGF-β activated kinase 1 (TAK1); TGF-β activated kinase binding protein 1 (TAB1); Toll-like receptor (TLR); Triglycerides (TGs); Tumor necrosis factor (TNF); Unfolded protein response (UPR)

1. Introduction

1.1. What is obesity?

Overweight and obesity are defined by world health organization (WHO) as an "abnormal or excessive fat accumulation that may impair health". Both overweight and obesity in adults are classified by assessing body mass index (BMI). It is a simple index of weight-for-height that is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). For adults, WHO defines overweight as a BMI greater than or equal to 25, while obesity corresponds to a BMI greater than or equal to 30. Although great efforts and advances have been made regarding obesity, especially in developed countries, it is still one of the major global challenges in the present century. In fact, according to WHO data obesity nearly tripled between 1975 and 2016 (World Health Organization (WHO), 2020). Moreover, according to an Obesity update by Organisation for Economic Co-operation and Development (OECD) it is estimated that obesity rates are going to increase further by 2030 (OECD, 2017). Worryingly, epidemiologic studies have identified high BMI as a risk factor for an expanding set of chronic diseases, including cardiovascular diseases (CVD), diabetes mellitus, chronic kidney disease, many cancers and an array of musculoskeletal disorders, as reviewed by (Afshin et al., 2017). To decrease the impact of such comorbidities associated to obesity, at least 5% of body weight should be reduced. It was expected that with lifestyle changes this goal may be achieved in a few months, instead most patients usually recover weight in the long-term.

1.2. Limitations of current anti-obesity drugs and therapies

As reviewed by Rubio et al. (Rubio, 2014) the use of drugs in obesity treatment is considered to have an efficacy placed between the lifestyle changes efficacy, which accounts for 5 to 10% of weight loss, and bariatric surgery the most efficient treatment, with 20 to 30% weight loss. Thus, the authors stated that according to the Food and Drug Administration (FDA) for a drug to be considered effective in obesity treatment it should be responsible for a difference in weight as compared to a >5% after 1 year of treatment. Data from recent meta-analyses studies showed that the overall placebo-subtracted weight reduction (%) with the use of anti-obesogenic drugs for at least 12 months ranges from 2.9 to 6.8% (Tak & Lee, 2020). Although some anti-obesity drugs present promising results, the associated side-effects continue to be one of the major drawbacks regarding the developed and available drugs (Table 1). Indeed, although side effects are widely dependent on the individual, the most common are those associated with increased blood pressure, tachycardia, insomnia, alterations on sexual behaviour, malabsorption of nutrients or carcinogenic effects (Gómez-Hernández et al., 2016; Müller et al., 2018; Srivastava & Apovian, 2018). For instance, orlistat, an anti-obesity drug approved by FDA and European Medicines Evaluation Agency (EMA) decreases fat absorption by 30% through inhibition of gastric and pancreatic lipases, but 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 adoption by FDA of stricter regulations and requirements of proof of clinical efficacy, a couple of recently approved anti-obesity drugs have been removed from the United States' 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 (James et al., 2010). The utilization of Lorcaserin (Belviq) was approved between 2012 and 2020. A re-analysis of a safety clinical trial, during from 6 months to 2.5 years, showed an increased incidence of certain cancers. According to the data, 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 was withdrawn in May 2013 after the EMA stated that the weight-loss benefits of lorcaserin did not justify its risks, which included the potential to increase the frequency of psychiatric disorders and valvulopathy (Haslam, 2016).

2. The role of bioactive lipids on obesity

In the last few years, new policy strategies devised to fight obesity have emerged. The rapid increasing rate of obesity can be greatly attributed to a combination of excess intake of energy and reduced physical activity. An important factor that has contributed to the rapid increase in cases of obesity among the population is the change in dietary patterns of individuals, mainly characterized by increased consumption of energy dense foods, rich in sugar and saturated fatty acids (SFAs), combined with a sedentary lifestyle (Costa & Rosado, 2012). Thus, diet has been widely recognized as playing a central role in such disease. It is feasible to reduce the risk of obesity through modifications of daily diet. For instance, high-fat diets (HFDs) are often blamed for increasing obesity rates; however, fats are diverse and respond differently *in vivo*. Lipids have been commonly recognized as important players in obesity and their different roles are going to be further discussed.

2.1. Lipid metabolism

2.1.1. Lipid metabolism in brain and obesity

Early studies from the 1950's have suggested the existence of neuronal hypothalamic populations able to sense the energy status of the body and respond to this status by controlling hunger/caloric intake and energy expenditure (Dragano, Monfort-Pires, et al., 2020; KENNEDY, 1950; MILLER et al., 1950), suggesting a role of brain in appetite regulation and therefore in obesity. Later, studies have demonstrated that indeed there are fatty acid membrane receptors that act through other signaling mechanisms to control the energy homeostasis (Dragano, Monfort-Pires, et al., 2020; Elizondo-Vega et al., 2019; Milligan et al., 2017), providing some insights on the action of these molecules on brain mechanisms and clarifying their role on obesity induced-neuroinflammation.

In summary and as reviewed by (Dragano, Monfort-Pires, et al., 2020) brain is rich in PUFAs but essential fatty acids are transported into the brain from the circulation. This transport is made through the blood-brain barrier (BBB) and once they arrive to the brain these fatty acids are converted into long-chain fatty acid-Coenzyme A (LCFA-CoA) and are later either metabolized by β-oxidation or incorporated into phospholipids. The mechanisms through which fatty acids pass through BBB are not yet fully understood. Nevertheless, some evidences suggest that they can pass by passive diffusion or be translocated by carrier proteins, being the cluster of differentiation CD36 and fatty acid transport proteins (FATP)-1 and 4 the most recognized ones (Bruce et al., 2017; Dragano, Monfort-Pires, et al., 2020; Le Foll et al., 2009). Besides its role on fatty acid uptake from BBB, the receptor CD36 is also suggested to be involved in many lipid sensing responses in hypothalamus neurons (Magnan et al., 2015; Moullé et al., 2014).

After entry into neurons, long-chain fatty acids are esterified by LCFA-coA synthase to form LCFA-CoA. Studies have demonstrated that this process is indeed important for the inhibition of food intake during systemic increases in lipid availability, since long-chain fatty acids produce an increase in LCFA-CoA levels and generate a metabolic signal of energy surplus (Lam et al., 2005). Intracellular LCFA-CoAs are translocated into mitochondria via carnitine palmitoyltransferase-1 (CPT1) where they undergo β-oxidation. In neurons of arcuate nucleus (ARC), mitochondrial CPT1c activity is regulated by the availability of malonyl-CoA. Under normal physiological conditions, CPT1 activity is inhibited by increased malonyl-CoA

concentration, and hypothalamic malonyl-CoA levels closely correlate with nutritional status. Thus, increased levels of malonyl-CoA may act as a signal of energy surplus that regulates orexigenic and anorexigenic neuropeptide release to suppress food intake and increase energy expenditure (Dragano, Monfort-Pires, et al., 2020). Moreover, malonyl-CoA levels depend on the equilibrium of acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and malonyl-CoA descarboxilase (MDC). Being the activities of ACC and MDC directly regulated by phosphorylation via AMP-activated protein kinase (AMPK); when AMPK its active it phosphorylates and inhibits ACC, decreases FAS mRNA expression and activates MCD. Thus, AMPK activation reduces malonyl-CoA levels and the flux of substrates through the fatty acid biosynthetic pathway. The decreased malonyl-CoA levels stimulate the CPT1, which promotes access of LCFAs-CoA into the mitochondria and increased fatty acid oxidation (Dragano, Monfort-Pires, et al., 2020).

When there is increased and sustained availability of fatty acids, the hypothalamic nutrient-sensing system is dysregulated, and the pool of long-chain fatty acids increase and there is an augmented uptake by the brain. This enhanced uptake results in rising LCFA-CoA levels in the hypothalamus, which has a negative impact on regulation of food intake and energy expenditure (Dietrich & Horvath, 2013; Karmi et al., 2010).

2.1.2. Lipid metabolism in adipose tissue and obesity

As reviewed by (Kojta et al., 2020) over 95% of dietary fat is accumulated in adipose tissue and is stored in the form of triglycerides (TGs). When there are increased energy requirements the stored TGs are hydrolyzed during the lipolysis process, releasing both free fatty acids and glycerol. In consequence, lipolysis is an important metabolic process in the adipose tissue (Arner, 2005).

In summary, the binding of β-adrenergic receptor agonists β1 and β2, conjugated with adenyl cyclase leads to an increased production of cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA) (Anthonsen et al., 1998). Then, these two proteins phosphorylate hormone-sensitive lipase (HSL), which results in the decomposition of TGs with the action of triglyceride lipase, hydrolyzing TGs to diglycerides. HSL then decomposes diglycerides to monoglycerides (Wolf, 2005). When there is an increase in the supply of energy substrates, there is accumulation of their excess in adipose cells in lipogenesis process. Such process is regulated by insulin, which increases the activity of lipoprotein lipase (LPL) stimulating the hydrolysis of TGs in circulating plasma, in combination with albumins, chylomicrons or VLDL, allowing free fatty acids to enter the cell. This process is mediated by transporters/receptors such as cluster of differentiation 36 (CD36) protein, fatty acid transport proteins (FATPs) and fatty acid-binding protein plasma membrane (FABPpm). Through the action of Acyl-CoA synthetase (ACS), an enzyme that converts free fatty acids to acetyl-CoAs, acyl-CoAs is used as a substrate for *de novo* synthesis of other lipids, including TGs (Beale et al., 2004; Tordjman et al., 2003).

Under normal physiological conditions, adipose tissue can store excess energy as a result of hypertrophy – increased size of cells - and/or hyperplasia – increased number of cells. The problem in obesity is that hypertrophic adipocytes become resistant to the antilipolytic effect of insulin and have a reduced ability to accumulate lipids. When the adipocyte storage capacity is exceeded, fat accumulates in cells such as muscle and liver cells, leading to insulin resistance (Sethi & Vidal-Puig, 2007). In obesity there is an increased plasma concentration of free fatty acids from adipose tissue, leading to an intense uptake by tissues which are involved in the regulation of glucose homeostasis, such as skeletal muscles, liver and pancreas. This increased fatty acid uptake leads to intracellular lipid accumulation since mitochondria is not able to oxidize them. This leads to lipotoxicity, which favors reduction in insulin sensitivity (Belfort et al., 2005).

2.2. Long-chain saturated fatty acids role on obesity development

2.2.1. Effect of long-chain saturated fatty acids in hypothalamus

The continuously increasing prevalence of obesity pave the way for the development of several studies aiming to understand the role of different dietary lipids on the onset and development of such disease. Recent studies reported that HFD is responsible for inducing inflammatory actions both on central nervous system (CNS) and peripheral tissues, such as adipose tissue. Indeed, it has been suggested that while peripheral inflammation develops as a consequence of obesity, hypothalamic inflammation develops early after a HFD consumption, prior to weight gain; studies have reported that within 1 to 3 days of HFD consumption inflammatory markers are evident in *in vivo* models, such as rats and mice (Thaler et al., 2012). For instance, Nam and collaborators (Nam et al., 2017) reported that an HFD induces increased expression of genes related to immune responses, while down-regulating genes related with neuronal differentiation and synaptic transmission, suggesting a neurotoxic role of such diet. These effects ultimately lead to a worsened cognitive performance in HFD-mice when comparing to mice on normal diet. Moreover, other studies have actually suggested that there is an induced neuronal injury in key brain areas for body weight control (Thaler et al., 2012). The inflammatory potential of such diet was associated with a persistent increase of microglia reactivity (principal resident immune cells of the brain) and consequent tumor necrosis factor (TNF)-α secretion, which ultimately induces mitochondrial stress in Propiomelanocortin (POMC) neurons, contributing to the development of obesity (Yi et al., 2017). This is highly relevant since CNS energy homeostasis is largely controlled by the fine balance between the two distinct subpopulations of neurons in the hypothalamus ARC, 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. NPY/AgRP and POMC neurons intervene the ARC control energy homeostasis and coordinate the response to changes in metabolic status, namely nutrient and hormonal fluctuations (Lemus et al., 2015; Valdearcos et al., 2015). SFAs, specifically, have been associated with hypothalamic inflammation and their entry in the CNS, in a diet induced-obesity context, have been described as the potential nutritional trigger of hypothalamic inflammation (Argente-Arizón et al., 2015; Valdearcos et al., 2014). For instance, palmitic acid (PA) (C16:0) has been demonstrated to induce proinflammatory actions in microglia cells (Duffy et al., 2015; Valdearcos et al., 2014; Z. Wang et al., 2012). The main route of action of SFAs has been suggested to be through NFkB– a transcription factor involved in the expression of proinflammatory genes- pathway induction (Duffy et al., 2015; Z. Wang et al., 2012). In fact, SFA, specifically, act through toll-like receptor 4 (TLR 4), which determines both the activation of inflammatory pathways, insulin resistance as well as other important features of obesity, such as endoplasmic reticulum (ER) stress (Milanski et al., 2009).

For instance, obesity and precisely fat overconsumption is known to cause hypothalamic insulin resistance. In summary, insulin exists in the CNS, playing important regulatory roles in the hypothalamus, and it is responsible to suppress food intake and to improve glucose metabolism. The disruption of both these signaling processes is a result of insulin resistance, that is known to be caused by obesity and the overconsumption of saturated fat. Obesity induces brain insulin resistance, which blunts the suppressive action of insulin on food intake, thus inducing more severe obesity leading to a vicious cycle. Besides, as reviewed by (W. Chen et al., 2017) insulin resistance has been described as the common link between obesity and the development of type 2 diabetes. In a prospective study (Facchini et al., 2001) performed on 208 healthy and nonobese individuals, it was identified insulin resistance as a strong predictor of both type 2 diabetes and other diseases such as hypertension, cancer, coronary heart disease and stroke. Moreover, IkB kinase β (IKKβ) and JNK are major players in the inflammation pathway, and

they have been suggested to play important roles on insulin resistance (Ono, 2019). The HFD induced low level of hypothalamic inflammation (*i.e.* chronic) accompanied by increased activation of intracellular kinases JNK and NFkB, through IKKβ (Lawrence, 2009). The problem with the obesity-induced low grade inflammation is related with the activation of the intracellular kinases: JNK and IKKβ, which induces phosphorylation of the insulin receptor substrate (IRS) on its serine residues, inhibiting phosphorylation on its tyrosine residue, which is critical to the transmission of the insulin signal to downstream effectors and biological outcomes (Rorato et al., 2017). It was recently reported that one day of HFD feeding is enough to blunt the suppressive effects of hypothalamic insulin on liver glucose production (Ono et al., 2008). Moreover, at the same time there is a decrease in the tyrosine phosphorylation of insulin receptor substrate protein (IRS)-1, inhibiting the insulin signal transduction in hypothalamus (Ono, 2019).

Other relevant consequence of obesity and saturated fat diet is leptin resistance. More than 20 years ago, in 1978, leptin and its receptors were identified as key regulators of body weight and energy homeostasis (Coleman, 1978). Later, in 1999, a release of the leptin from the brain into the blood was proposed (Wiesner et al., 1999). Leptin is important since it presents an anorexigenic effect, meaning that minor increases in leptin concentration reduces appetite and leads to a decrease in body weight. However, in obesity there are abnormally high levels of leptin, a state described as hyperleptinemia. Several studies in both humans and mice, showed that the brain leptin transport is impaired in those subjects (Banks et al., 1999; Caro et al., 1996; El-Haschimi et al., 2000) thus, the anorexigenic effect is decreased, leading to leptin resistance development (Knight et al., 2010). Indeed, it is commonly accepted that a decrease in tissue sensitivity to leptin, commonly referred as leptin resistance, leads to the development of obesity and other metabolic disorder, such as the mentioned insulin resistance and dyslipidemia (Gruzdeva et al., 2019). The exact mechanisms behind leptin resistance, especially in hypothalamus, are not fully characterized but it is suggested that may include mutations in genes encoding both leptin (*ob* gene*)* and its receptors, as well as proteins involved in self-regulation of leptin synthesis and BBB permeability. Deterioration of leptin-receptor function accompanied by hypothalamic inflammation and ER stress are also suggested mechanisms of leptin resistance. Indeed, activation of the hypothalamic IKKβ/NFkB pathways was shown to induce leptin resistance, while the inhibition of IKKβ protects against obesity in mice (Son et al., 2019).

Moreover, SFAs obtained from diet - *e.g.* PA (S. Park et al., 2020; Tse & Belsham, 2018), lauric (C12:0) and myristic acid (C14:0) (S. Park et al., 2020)-, have been showing to affect the mRNA expression of hypothalamic ER stress marker in both *in vitro* models (neuronal cells) (S. Park et al., 2020) and rodent models (Belegri et al., 2017), suggesting that such markers may be sensitive sensors of fatty acid availability and nutrient load. Obesity-induced ER stress was found to be both an upstream intracellular mediator and downstream event of the hypothalamic IKKβ/NFkB activation (Zhang et al., 2008). ER stress occurs when the ER homeostasis is altered by strong and prolonged cellular disturbance, leading to the accumulation of potentially toxic unfolded or misfolded proteins in ER lumen. In order to restore the normal function, a set of stress-responsive signaling pathways, 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).

2.2.2. Effect of long-chain saturated fatty acids in peripheral tissue

2.2.2.1. Adipose tissue

In mammals, adipose tissue can be divided into two major types: brown (BAT) and white adipose tissue (WAT). Regarding BAT, in newborns this tissue is important in regulation of energy expenditure by thermogenesis. In adults, the amount of BAT is inversely correlated to BMI suggesting a potential role in metabolism (Curat et al., 2004). On the other hand, WAT,

considered the main site of energy storage, is currently seen as an active and important participant in regulating physiological and pathological processes, such as immunity and inflammation (Karastergiou & Mohamed-Ali, 2010). WAT is considered as the largest endocrine organ and 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; Conti et al., 2019; Gómez-Hernández et al., 2016). Indeed, macrophages are components of this tissue and important regulators of its activities. Moreover, there is cross-talk between lymphocytes and adipocytes, which implies immune regulation (Fantuzzi, 2005). Adipose tissue also produces a variety of factors, like adipokines, such as leptin, adiponectin, and resistin, as well as pro-inflammatory (*e.g.* TNF-α and IL-6) and anti-inflammatory cytokines and chemokines (Lafontan, 2005). 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 lipids and their metabolites (Lehr et al., 2012).

In the last few years, several studies have demonstrated that consumption of western diets, namely the high presence of SFAs can be considered a pro-inflammatory factor itself and an association between this type of diet and the presence of obesity, hepatic steatosis and type 2 diabetes have been extensively described (Calder et al., 2011; Cnop, 2008; Johnson et al., 2008; Ravaut et al., 2021; Vaittinen et al., 2017). Thus, similarly to what was described for CNS, in condition of chronic positive energy balance – like what happens in SFA-induced obesity -, adipose tissue undergoes profound modifications including adipocyte expansion, induction of hypoxia and mitochondrial function alteration, which ultimately leads to tissue remodeling, inflammation and metabolic dysfunction (Conti et al., 2019; Longo et al., 2019). Such events result in severe changes in the immune response and consequently, in the development of a pro-inflammatory profile. The meta-inflammation - a chronic low-grade inflammatory state – is growingly associated with adipose tissue in an obesity context and is considered a characteristic feature of metabolic syndrome: there is secretion of inflammatory adipokines mainly from adipose tissue, including leptin, IL-6 and TNF-α. Besides, the meta-inflammation state along with the reduction on the production of adiponectin, a significant predictor of cardiovascular mortality, which is associated with impaired fasting glucose, leading to type-2 diabetes development, metabolic abnormalities, coronary artery calcification, stroke and cancer (Conti et al., 2019; Ellulu et al., 2017).

The SFA diet excess itself, characteristic of obesity is responsible for increasing lipid storage in adipose tissue. Such process results in an accumulation of lipids in adipocytes. This leads adipocytes to develop larger lipid droplets and therefore to contain more TGs. The increased intracellular TG pool leads to increased leptin secretion by adipocytes (Johnson et al., 2008; Ravaut et al., 2021). Besides, this accumulation triggers cellular stress as well as the activation of pro-inflammatory pathways such as JNK and NFkB (as discussed in the previous section) (Ellulu et al., 2017). This process raises the circulating levels of several acute-phase proteins and inflammatory cytokines resulting in the mentioned chronic low-grade inflammation state (Gómez-Hernández et al., 2016; Longo et al., 2019). An increasing number of studies had suggested that lipids, specifically fatty acids play an important role in obesity development and in the interplay between excessive adiposity and development of associated comorbidities (previously enumerated) (Conti et al., 2019; Masoodi et al., 2015). Indeed, the type of fatty acids stored in adipose tissue critically affects tissue functions, since fatty acids can directly or indirectly modify immune and inflammatory responses, by acting on cell surface and intracellular receptors (such as TLR 4, as discussed in the previous section) that control cell signalling and gene expression (Ralston et al., 2017; Rocha et al., 2017). Recent studies have shown that overeating SFAs (*e.g.* PA) promotes greater visceral fat storage (associated with metabolic disease) when comparing to unsaturated fatty acids. The authors showed that there is a link between SFAs in visceral adipose tissue and *HSD11B1*, a gene responsible for the expression of

11-β-hydroxysteroid-dehydrogenase type 1 (11β-hsd1), which is a major regulator of cortisol (important in body fat distribution regulation) activity (Petrus et al., 2015).

Among the mentioned adipokines secreted by WAT, leptin is one of the hormones presenting a direct link to body fat and obesity. In a study aiming to identify the association of leptin gene (*ob*) expression in visceral and subcutaneous adipose tissue with fatty acid intake in adults, it was reported that dietary intake of SFA is positively associated with both subcutaneous and visceral adipose tissue leptin gene expression (Rostami et al., 2017). In peripheral tissues, leptin is highly relevant since it is involved in several physiological processes, such as angiogenesis, hematopoiesis, bone formation, wound healing, immunocompetence or lipid and carbohydrate metabolism regulation as well as nutrient intestinal absorption (Sáinz et al., 2015). Leptin resistance in obesity has been suggested to be initiated by activation of inflammatory signals. As reviewed by (Sáinz et al., 2015), inflammatory factors, such as TNF-α and IL-1a as well as lipopolysaccharide (LPS), are known to increase circulating leptin concentrations in both rodents and humans. Since NPY neurons and leptin interact to maintain an homeostasis in order to regulate body-fat mass and energy level at both CNS and adipocyte level, early studies showed that leptin is involved in the regulation of lipolysis (Frühbeck et al., 1997, 1998; Sáinz et al., 2015) – defined as the hydrolytic cleavage of ester bonds in TGs, resulting in the generation of fatty acids and glycerol (Schweiger et al., 2014). In fact, the lipolytic effect observed in adipocytes from lean mice was lower than from *ob/ob* mice (Frühbeck et al., 1998). Moreover, recent studies have demonstrated that leptin induces intracellular signaling in preadipocytes and adipocytes promoting adipogenesis and modulating the secretion of inflammatory mediators (increase TNF-α production in 3T3-L1 cells) contributing to the inflammatory profile characteristic of obesity (Palhinha et al., 2019). Thus, impaired regulation of leptin response, due to leptin resistance, may lead to the development of more and bigger adipocytes – WAT expansion - and contribute to the accumulation of excessive fat mass found in obese state.

In addition, the excessive lipid accumulation in adipose tissue, ectopic accumulation (defined as steatosis) appears in other tissues like liver and muscle. These adipocytes release free fatty acids into the blood stream through the action of the CD36, the plasmatic fatty acid binding protein (FABPpm) and the fatty acid transport proteins (FATPs). The circulating free fatty acids are captured by other organs, especially the mentioned ones (liver and muscle) leading to steatosis (Ravaut et al., 2021).

2.2.2.2. Liver

Besides adipose tissue, liver plays a major role in homeostasis regulation and is important for the maintenance of nutrient metabolism. Since leptin regulates hepatic gluconeogenesis and insulin sensitivity, defects in leptin action impairs hepatic function leading to hyperglycemia, hyperinsulinemia and hyperlipidemia (Sáinz et al., 2015). Morbidly obese patients have a prevalence of more than 90% of changes in liver histology, namely hepatic steatosis (also known as fatty liver disease - which is characterized by the presence of an increased liver due to a higher concentration of triglycerides in hepatocytes). In fact, non-alcoholic fatty liver disease is a prevalent condition associated with obesity and insulin resistance, which is becoming the most common form of liver disease worldwide (Araujo Martins, 2016).

The problem in obesity is that the increase of fatty acids in hepatocytes leads to a higher synthesis of TGs. Consequently, the liver is not able to export them efficiently being accumulated in the hepatocytes (liver parenchymal cells), which leads to a non-alcoholic steatohepatitis-like phenotype, characterized by hepatic steatosis (S.-N. Wang et al., 2010). Besides, this high production of TGs is also associated with ER stress on hepatic cells, which ultimately leads to hepatocyte lipoapoptosis (Eriksson et al., 1986). Moreover, the accumulation of LC-SFAs leads to the formation of toxic lipids such as ceramides, known to modulate signaling pathways

involved in regulating glucose metabolism, triglyceride synthesis, apoptosis, and fibrosis (Li et al., 2020; Unger, 2002). Such lipids induce lipotoxicity, which ultimately leads to ER stress and inflammation (Ravaut et al., 2021). Besides, since macrophages are recruited to the adipose tissue, they induce the secretion of other proinflammatory cytokines amplifying the already existing inflammatory state. Thus, such cytokines are continuously and abundantly released by adipose tissue and reach the liver through the portal vein circulation. Afterwards, they stimulate the secretion of C-reactive protein (CRP), an important marker of inflammation, the progression of hepatic insulin resistance and hepatic steatosis in obese individuals. Moreover, the direct contact of visceral fat with the proinflammatory cytokines contributes to the progression of insulin resistance (Araujo Martins, 2016; Ravaut et al., 2021).

2.3. The anti-obesity potential of fatty acids

2.3.1. Medium-chain fatty acids

As previously discussed, SFAs, specifically LC-SFAs, have been associated with detrimental effects on insulin sensitivity and cardiovascular health, among others. However, this has been recently challenged and the specific type of SFA appears to be relevant in such issue. Indeed, SFAs with medium chain length, such as hexanoic (C6:0), octanoic (C8:0), capric (C10:0) and lauric acid (C12:0) have been considered relevant in metabolic research (Lundsgaard et al., 2021). Medium-chain TGs (MCTGs) contain medium-chain fatty acids (MCFAs) esterified to the glycerol backbone and are usually completely hydrolyzed to yield the corresponding free fatty acids by lipases present in the gastrointestinal tract (Aluko, 2012). MCTGs are rapidly metabolized and less likely to be stored in the adipose tissue, resulting in a promising tool for weight control (Costa & Rosado, 2012). Indeed, they may counteract fat deposition in adipocytes by increasing thermogenesis and satiety (Dulloo, 2011). Human intervention trials showed that MCTGs reduce blood TGs levels, inducing thermogenesis and not contribute to weight gain since they are not deposited in the adipose tissue. Besides, MCTGs obtained through diet are also shown to reduce blood levels of several types of low-density lipoprotein (LDL) as well as LDL-cholesterol to greater extent than traditional oil that contained long-chain TGs (LCTGs). Thus, it has been suggested that MCTGs may be useful in preventing and treatment of obesity. Besides, they were shown to activate HSL and down-regulate FAS, which results in increased lipolysis and reduced fat accumulation, respectively in WAT. Furthermore, MCTGs are able to upregulate LPL, the major enzyme responsible for lipolysis (Aluko, 2012). Recently, a study aiming to evaluate the anti-obesity potential of MCTGs and LCTGs with different contents of MCFAs (10 to 30%) in C57BL/6J mice showed that a diet with 30% of these TGs shows significant decreases in body weight and fat mass in comparison to control mice fed and obesity-inducing high fat rapeseed oil diet (Zhou et al., 2017). Besides weight loss, reduction of blood glucose, serum TGs, total cholesterol, insulin, liver weight and liver TG were improved, showing the great potential in obesity treatment. As reviewed by Dulloo et al. (Dulloo, 2011) studies in both animals and humans have shown increased energy expenditure and lipid oxidation with MCTGs, specifically caprylic acid (C8:0) and capric acid (C10:0), compared with LCTGs. Increased satiety, resulting in reduced food intake, is another possible benefit from the fast oxidation of MCTGs through the formation of ketones (Dulloo, 2011; Poppitt et al., 2010). Recently, it was demonstrated that in humans fed HFD, the substitution of a fraction (≈ 30 g) of LC-SFAs with MC-SFAs is enough to prevent the LC-SFAs-induced impairments by rescuing insulin action: prevents whole body insulin resistance and impaired insulin-stimulated muscle glucose uptake. Moreover, the MCFAs diet increased basal fatty acids oxidation, maintained glucose metabolic flexibility, increased non-oxidative glucose disposal related to lower starting glycogen content and increased glycogen synthase activity, together with increased muscle lactate production (Lundsgaard et al., 2021). Considering their positive role on insulin and glucose metabolism, MCFAs have been explored due to their possible beneficial role on type 2 diabetes. Some studies have shown that by increasing MCFA/LCFA ratio the HFD-induced type 2 diabetes is mitigated. Such process is thought to be associated with reversing rubicon - a negative regulator of late-stage autophagosome maturation- protein accumulation in both mouse livers and HepG2 cells protecting it from the consequent autophagy impairment, ER stress and apoptosis (M.-E. Wang et al., 2017). Therefore, these studies have been highlighting the importance of carbon chain length in obesity-induced effects, not only the saturation of the consumed fatty acids.

Nonetheless, a literature review of the clinical studies between 2000 and 2010 regarding MCTGs on satiety, body composition and energy expenditure showed that from 14 studies only 6 showed a decrease in body mass, with consequent loss of weight. Only one showed positive effects on satiation and four showed an increase in energy expenditure. Therefore, the effects of

such fatty acids on obesity are still inconclusive and further studies with standardized amounts of MCTGs are required (Costa & Rosado, 2012).

2.3.2. Monounsaturated fatty acids

Interestingly, when comparing the impacts of SFAs and unsaturated fatty acids inverse effects are often reported. While SFAs present a pro-inflammatory action, unsaturated fatty acids present an anti-inflammatory profile. Considering unsaturated fatty acids, much is known regarding polyunsaturated fatty acids (PUFAs), namely omega-3, and favorable effects on health. Monounsaturated fatty acids effects (MUFAs) are less documented, but throughout the years more and more evidence have linked MUFAs to anti-inflammatory actions (Ravaut et al., 2021; Rocha et al., 2017). Recently, (Magtanong et al., 2019) have demonstrated that exogenous MUFAs potently inhibit the oxidative cell death process of ferroptosis - unique modality of cell death, driven by iron-dependent phospholipid peroxidation. The authors suggested that such protective effect is associated with the suppression of lipid reactive oxygen species (ROS) accumulation at the plasma membrane and decreased levels of phospholipids containing oxidizable PUFAs. Besides, higher MUFA consumption increases MUFA levels and therefore reduces both SFA and PUFA throughout the body modulating the lipid pool through nutrition (Raatz et al., 2018; Ravaut et al., 2021). Mediterranean diet is associated with high consumption of MUFAs from fish, olive oil, fruits and vegetables and whole grains. Fat corresponds to one third of total kilocalories (kcal) absorbed with 60% MUFA and 20% SFA (Ravaut et al., 2021). Several reports have associated this diet with beneficial effects on obesity (Estruch & Ros, 2020). In a study aiming to assess the effects of substituting a high-SFA diet with a high-MUFA or Mediterranean diet on 60 diabetics with mild abdominal obesity, the authors reported that both MUFA and Mediterranean diets did not affect insulin sensitivity but improved serum lipids when comparing to a high SFA diet (Bos et al., 2010). Moreover, in a study with 82 overweight and obese subjects by switching to a Mediterranean diet, while maintaining their energy intake, their blood cholesterol was reduced and caused multiple changes in their microbiome - higher levels of *Faecalibacterium prausnitzii* (fibre degrading bacteria) and of genes for microbial carbohydrate degradation linked to butyrate metabolism and a decrease of the potentially proinflammatory *Ruminococcus gnavus* - and metabolome - lower plasma and urinary carnitine levels and protein degradation products. The authors state that such changes in the intestinal microbiome are towards a state that promotes both metabolic and cardiovascular health (Meslier et al., 2020). Moreover, it has been suggested that the adherence to a Mediterranean diet at an early age (4 years old) may be associated with a lower risk of developing overweight, obesity and abdominal obesity at 8 years old (Notario-Barandiaran et al., 2020). As mentioned, the beneficial effects of Mediterranean diet are highly associated with MUFA consumption. The effect of a MUFA rich diet, olive oil based, on a preclinical animal model of HFD-induced metabolic syndrome (mice with leptin deficiency and with a knockout on the LDL receptor – induced dyslipidemia) showed that when compared against a SFA-HFD a MUFA rich diet reduces both TGs and free fatty acids levels, adipocyte hypertrophy, infiltration of macrophages that also presented an anti-inflammatory phenotype. On the other hand, MUFA diet induces the expression of the gene encoding peroxisome proliferator-activated receptor (PPAR)-γ and the production of anti-inflammatory cytokines IL-10 and IL-4 (Montserrat-de la Paz et al., 2019). Importantly, PPAR α, β/δ and γ are nuclear receptors that translate nutritional and/or pharmacologic stimuli into changes in gene expression and are involved in the regulation of inflammation, immunity and epithelial cell differentiation. (Bassaganya-riera et al., 2004; Cunard et al., 2002; Jones et al., 2002; Natarajan & Bright, 2002; P Tontonoz et al., 1994; Peter Tontonoz et al., 1994; Y. L. Wang et al., 2002; Zakaria, 2014). Regarding MUFAs anti-inflammatory potential, it was shown in a study aiming to address the impact of the omega-7 palmitoleic acid (C16:1 n-7) MUFA on atherosclerosis in mice that palmitoleic acid supplementation reduces the expression of IL-1β and TNF-α corresponding genes (Yang et al., 2020).

Besides adipose tissue, the beneficial effect of a MUFA rich diet on liver steatosis was also assessed in C57BL/6 mice: when comparing to a SFA group, the MUFA group showed lower plasma TGs levels, level of steatosis, plasma IL-6 levels, and TLR 4 expression. Moreover, MUFA group showed lower weight gain and insulin resistance (Tamer et al., 2020). In addition, the possible beneficial effect of MUFAs (oleic acid and palmitoleic acid) in pancreatic β-cells was determined by comparing with a SFA – PA – effect. The authors observed that oleic acid can reverse PA effect and has a partial protective role on lipotoxicity induced by PA since it relieves PA-induced ER stress. In addition, palmitoleic acid is able to improve insulin release and has more relevant effects upon intracellular calcium regulatory pumps (important for insulin release) (Acosta-Montaño & García-González, 2018).

Additionally, the possible beneficial role of MUFAs on brain, was recently assessed both *in vitro* and *in vivo*, using microglia cells (BV-2 cell line) and C57BL/6J mice, respectively. In both models using an olive oil source, MUFAs enhanced the microglia polarization towards the anti-inflammatory phenotype, while SFAs polarize microglia to a pro-inflammatory profile (Toscano et al., 2020). Such results suggest a possible positive impact of olive oil MUFAs (particularly oleic acid) on neuroinflammatory diseases, and consequently on obesity.

Interestingly, it has been suggested that the MUFA palmitoleic acid downregulates NFkB pathway through PPAR γ stimulation (de Souza et al., 2018). Nonetheless, *in vivo* studies have shown that palmitoleic acid interacts with GPR120 receptor and that its activation is responsible for the resolution of PA-induced inflammation (Hirasawa et al., 2005; Ichimura et al., 2012). Thus, it has been suggested that MUFAs can inhibit NFkB through direct binding of PPARs or GPR120, inhibiting its activation by SFAs (Ravaut et al., 2021).

Thus, the positive effect of a MUFA-rich diet on obesity is highly related with the PPAR- and GPR-120 - mediated anti-inflammatory potential, in adipose tissue and brain respectively, by inhibiting NFkB pathway.

2.3.3. Polyunsaturated fatty acids

Briefly, PUFAs are unsaturated fatty acids with two or more double bonds. They are classified in two groups, omega-3 and omega-6, according to the position of the first double bound relative to the methyl-end group. Omega-3 fatty acids have the double bound 3 carbon atoms away from the terminal methyl group and omega-6 have their first double bound 6 carbons away. Omega-3 and omega-6 fatty acids are synthesized from the essential fatty acid α-linolenic acid (ALA; C18:3 *c*9,*c*12,*c*15) and linoleic acid (LA; C18:2 *c*9,*c*12), respectively. These precursors, ALA and LA, cannot be synthesized in the human body and have to be obtained through diet (Moghadasian & Shahidi, 2017).

On the other hand, conjugated fatty acids (CFAs) represent PUFAs with conjugated double bonds, usually found in a mixture of positional and geometric isomers (Teneva-Angelova et al., 2018). Dietary CFAs triggered great interest in the last decades with isomers of conjugated linoleic acid (CLA) and conjugated linolenic acid (CLNA) being the target of numerous studies due to their bioactive potential (Andrade et al., 2017; Hennessy et al., 2016).

2.3.3.1. Omega-3

As discussed for the MUFAs, several *in vivo* studies using rodent models have shown that substitution or supplementation of a HFD rich in SFA by fish oil (rich in PUFAs, specifically omega-3 fatty acids) has several beneficial effects in both adipose tissue and hypothalamus. Omega-3 PUFAs are essential nutrients derived from either marine or vegetable sources. The most relevant omega-3 are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which have a marine origin, since they can be found in oily fish, such as salmon, tuna, mackerel, anchovy

and sardines. Although ALA (the vegetable derivative) can be converted in EPA and DHA, the conversion rate is not enough and a dietary intake of omega-3 PUFAs from their marine sources is needed (Martínez-Fernández et al., 2015a). Their important role on obesity-induced effects is going to be discussed in the next sections.

2.3.3.1.1. Hypothalamus

In the brain, PUFAs are largely esterified to the phospholipid cell membranes of neurons, glial cells and endothelial cells (Nadjar et al., 2016). As reviewed by (Ouyang et al., 2020) PUFAs account for 35% of total lipids in adult brain. Arachidonic acid (an omega-6 fatty acid) and DHA, which make up 50% and 40% of brain PUFAs, respectively, are important to brain development and maintenance of the brain structure and function. In healthy humans, PUFAs can cross the BBB at physiological concentrations by passive diffusion or via a selective protein mediated transport process by fatty acid transport proteins and fatty acid binding proteins, and cross the plasma membrane, followed by intracellular transport.

Regarding obesity-induced hypothalamus inflammation, (Pimentel et al., 2012) demonstrated that fish oil supplementation decreased levels of hypothalamic pro-inflammatory mediators (*i.e.* TNF-α and IL-6) and higher levels of anti-inflammatory cytokine IL-1. Besides, the fish supplementation led to normal leptin levels, and improved blood lipid profile. Further studies aiming to assess the effect of lard substitution by fish oil in the feeding of Wistar rats, reported both the reduction of inflammation and apoptosis markers. Besides, the use of fish oil was also associated with lower body weight gain (Viggiano et al., 2016). Such relevant anti-inflammatory effects on hypothalamus, similarly to what was previously discussed for MUFAs, is thought to be mediated through GPR120 receptor. In fact, some PUFAs, mostly omega-3 fatty acids - ALA, DHA and EPA – are proved activators of GPR120 (Oh et al., 2010). It has been suggested that activation of GPR120 by these omega-3 fatty acids leads to the recruitment of β-arrestin 2 – ubiquitously expressed proteins known for being a canonical G-protein coupled receptor (GPCR) signaling partner. A GPR120- β-arrestin 2 complex is formed and is internalized. Such complex interacts with TGF-β activated kinase binding protein 1 (TAB1), inhibiting its interaction with another protein, the TGF-β activated kinase 1 (TAK1). This inhibition is highly relevant since their interaction mediates downstream inflammatory processes by activating NFkB and JNK pathways. Thus, GPR120 activation by omega-3 fatty acids inhibits pro-inflammatory pathways activation, reverting the inflammatory action of SFAs via TLR 4 receptor (Talukdar et al., 2011). Furthermore, Oh Da et al. (2010) reported that DHA stimulation of GPR120 inhibits both TLR 2/3/4 and the TNF-α proinflammatory cascade. Moreover, Wellhauser and Belsham (Wellhauser & Belsham, 2014) 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. Those authors 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. The positive effects of omega-3 fatty acids on both weight management and their anti-inflammatory potential have attracted great interest on obesity therapies development. Recently, male C57BL/6J mice were used as the model to determine the beneficial central effects and mechanism of DHA (by intracerebroventricular injection) in HFD fed mice. The authors reported that DHA administration reduced both energy intake and body weight gain. Moreover, it ameliorated the HFD-induced hypothalamic inflammation and improved the central leptin's action in regulating hepatic lipid metabolism (Cheng et al., 2020). Using the same *in vivo* model, other study observed that fish oil supplementation also protects mice against the anxiogenic and depressive-like effects of HFD (Demers et al., 2020). Importantly, besides reversing the changes in the inflammatory state, omega-3 treatments are also

able to reverse the oxidative damage parameters and attenuate the alteration in the antioxidant defense and in the energy metabolism (Mello et al., 2019). Some *in vitro* studies have also reported relevant results in microglia cell lines: DHA was able to reverse LPS inflammatory effects in N9 microglia cells (Chang et al., 2015; De Smedt-Peyrusse et al., 2008) and is responsible for a reduction in ROS production (oxidative stress) in BV-2 microglia cells (Corsi et al., 2015). All these results have been showing that omega-3 fatty acids, especially EPA and DHA, present a complete action tackling the obesity-induced effects on hypothalamus, addressing both hypothalamic inflammation and the neuronal damage in key brain areas for body weight control.

The PUFA beneficial effect on obesity-induced hypothalamic inflammation is thought to be closely related with their role on inhibiting IKKβ/NFkB pathway by GPR120 activation (Salsinha et al., 2021).

2.3.3.1.2. Adipose tissue

As already discussed and reviewed by (Martínez-Fernández et al., 2015b) some studies have reported that omega-3 PUFAs are able to significantly decrease body weight and fat mass. Nevertheless, others reported that a significant action on body weight cannot be found. Instead, omega-3 fatty acids only act by reducing fat depots. On the other hand, there are some studies where no change on body weight or fat mass is observed.

Accordingly, a high-dose of omega-3 PUFA supplementation (4 g/day) was provided for 3 months to insulin resistance patients with obesity. The omega-3 supplementation was able to modulate significant changes in plasma fatty acid profile, adipose tissue and systemic inflammation. Moreover, significant improvement of insulin-stimulated glucose disposal was also reported (Hernandez et al., 2021). Besides, a wide-range of studies have reported a TG-lowering property which are highly supported by human trials (Martínez-Fernández et al., 2015a). Furthermore, favorable effects on glucose metabolism and insulin sensitivity (Martínez-Fernández et al., 2015a). EFSA has recognized the beneficial effects of omega-3 fatty acids and it recommends dietary intakes of 250 and 500 mg/day of EPA and DHA for European adults based on cardiovascular risk considerations. This is highly relevant considering the role of obesity on the development of comorbidities, such as CVD (European Food Safety Authority, 2012).

The effects of omega-3 PUFAs specifically on adipose tissue have been documented regarding a regulation on adipocyte inflammation, differentiation and apoptosis, effects on lipid storage and mobilization, on mitochondrial biogenesis and adipose tissue browning and adipokines production (Martínez-Fernández et al., 2015a). Similarly to what happens in hypothalamus cellular models, EPA and DHA attenuate inflammatory activation of *in vitro* human adipocytes (Ferguson et al., 2019). Some studies reported that EPA and DHA were shown to be able to regulate adipocyte differentiation by inhibiting its differentiation and proliferation processes (C.-Y. Chen et al., 2020). Besides, a direct relation with *Ppar γ* gene regulation has been suggested and it was demonstrated that at least part of the action mediated by these fatty acids occurs through PPAR γ (Song et al., 2017).

Other well-known effect of omega-3 fatty acids on adipose tissue is related with their effect on lipid storage and mobilization. It is important to consider that the accumulation of TGs in adipocytes is a result of a balance between lipolysis - hydrolytic cleavage of ester bonds in TGs, resulting in the release of fatty acids and glycerol (Schweiger et al., 2014) - and fatty acid oxidation and lipogenesis - *de novo* lipogenesis is the process by which carbon precursors of acetyl-CoA are synthesized into fatty acids (Tsiloulis & Watt, 2015). The TGs storage in adipocytes can be a result of dietary fatty acid uptake or *de novo* fatty acid biosynthesis (Martínez-Fernández et al., 2015a). Omega-3 supplementation has been showing to be able to modulate hepatic *de novo* lipogenesis. Omega-3 fatty acids (EPA and DHA) both *in vivo* and *in vitro*

showed to decrease hepatic lipogenesis and increase fatty acid oxidation and plasma glucose concentration (Green et al., 2020). In WAT, omega-3 PUFAs action on lipogenesis has been related with their modulatory action on specific lipogenic enzymes. Indeed, in 3T3-L1 adipocytes there was a suppression of lipid droplets formation in the presence of EPA when compared to either SFA or MUFA. EPA was demonstrated to suppress PPAR γ, Cidea – a protein highly localized in lipid droplets important for fatty acid esterification and lipid mobilization - and D9D/SCD1 – a desaturase required to convert SFA to MUFA that participate in lipid metabolism in adipocytes - gene expressions, while maintaining the expression of lipolytic genes: LPL and HSL (Manickam et al., 2010). Other study, assessing the impact of omega-3 EPA, docosapentaenoic acid (DPA) and DHA on lipid droplets formation in 3T3-L1 adipocytes have reported that all three PUFAs significantly reduced lipid droplets formation and the metabolic disorder marker, SCD1. DHA significantly increased lipolysis and ATGL gene and protein expression but reduced the gene expression of three proteins that are related with lipid droplets formation: the mentioned Cidea, Perilipin-A and Caveolin-1 (Barber et al., 2013). *In vivo* studies using rats, reported that fish oil supplementation for 2 weeks in rats fed with high sucrose diet suppress FAS (involved in the *de novo* biosynthesis of fatty acids) mRNA levels in BAT (Sebö ková et al., 1996). These studies support the importance of omega-3 PUFAs in downregulating lipogenic genes expression and consequently decreasing lipogenesis and fat accumulation.

As discussed in previous sections, insulin resistance is strictly linked to inflammatory pathways. This inflammatory state is intimately associated with ER stress, ROS production and mitochondrial function impairment (Lepretti et al., 2018). Importantly, the association between adipose tissue mitochondrial dysfunction and the progression of obesity and type 2 diabetes has been proved. Indeed, the lipid oversupply from chronic overfeeding, characteristic of obesity, has been linked to a negative effect on several organelles, namely ER and mitochondria. There is a reduction in the abundance of adipocyte mitochondrial number and an impaired mitochondrial function which leads to reduced fatty acid β-oxidation and therefore fat accumulation (Martínez-Fernández et al., 2015a). Moreover, since mitochondrial dysfunction is intrinsically connected to ER stress a role in insulin resistance has also been suggested. Mitochondrial morphology is highly variable, and it is maintained through a dynamic balance between fusion – regulated by mitofusins 1 and 2 (Mfn1 and Mfn2) - and fission processes, which allow mitochondria to redistribute in a cell, exchange contents and repair damaged mitochondria. Omega-3 PUFA present a positive modulatory effect on Mfn2, which may be related with the induction of fusion processes linked to amelioration of mitochondrial function (Lepretti et al., 2018). Even when compared to oleic acid, DHA maintained a healthy mitochondrial structure under induced inflammation on primary adipocytes while oleic acid led to elongated mitochondria with a thin thread like structures in adipocytes exposed to LPS (Bou et al., 2020). In summary, omega-3 fatty acids, opposing to SFAs, stimulate mitochondrial function and fusion processes reducing ROS production, they are also able to attenuate ER stress. Moreover, they present a positive modulatory effect on Mfn2 which may explain the induction of fusion processes that are linked to amelioration of mitochondrial function and maintenance of mitochondria associated ER membrane (MAM) integrity, which is responsible for efficient communication between these organelles exchanging calcium ions, lipids and other metabolites to maintain cellular metabolism and integrity. This is highly relevant since both processes are important for insulin sensitivity (Lepretti et al., 2018).

Besides, several evidences suggest that omega-3 PUFAs can counteract the adipokine dysregulation that occurs in obesity (Martínez-Fernández et al., 2015a) as summarized in table 2.

2.3.3.2. Conjugated linoleic acid (CLA)

CLA is a group of positional and geometric isomers of LA (C18:2 *c*9,*c*12). The most relevant isomers are the C18:2 *c*9,*t*11 (rumenic acid) and C18:2 *t*10,*c*12 due to their positive health benefits. Naturally occurring CLA primarily consists of the *c*9,*t*11 isomer (>80%) present in food, such as beef, milk, and dairy products, since it is produced by rumen bacteria from LA (Yeonhwa Park, 2009).

The ability of CLA isomers to reduce body fat mass in *in vivo* models was first reported in 1995 (Y Park et al., 1995) and later confirmed by several studies (Yeonhwa Park & Pariza, 2007; Whigham et al., 2007). As reviewed by Shen and McIntosh (Shen & McIntosh, 2016) the C18:2 *t*10,*c*12 CLA isomer is the major responsible for CLA's antiobesity effects and its antiobesity mechanisms are thought to include decrease adipogenesis and lipogenesis, increased lipolysis and fatty acid oxidation, inflammatory signaling, adipocyte apoptosis, increased energy expenditure and browning. Moreover, maternal supplementation 10 days prior to mating and throughout pregnancy/lactation of CLA to a HFD showed beneficial effect in adult male offspring namely on physiological, metabolic and adipogenic markers. Interestingly, the maternal CLA supplementation was shown to be sufficient to prevent the programmed obesity and metabolic impairment induced by HFD (Segovia et al., 2017). In addition, maternal supplementation of CLA is also responsible for a reduction in TGs levels related to a reduction of FAS, acetyl-CoA carboxylase (ACC) and glucose-6-phosphate dehydrogenase enzyme activities. A reduction of lipogenesis was also found in the liver of the offspring. Such results reinforce the positive role of CLA on obesity-induced effects, namely the programming effect of CLA on the lipid metabolic pathways leading to a preventive effect on the TGs accretion in adipose tissue and liver of male rat offspring (Lavandera et al., 2017). These effects were partially related with a decrease in adipocyte size and cell number by alteration of transcription of key adipogenic genes and adipose cellularity in adipocytes isolated from specific pathogen-free chicken. Indeed, C18:2 *c*9,*t*11 CLA isomer was shown to downregulate the expression of LPL – a fat metabolism-related gene - and acyl-coenzyme A binding domain containing 5 (ACBD 5) genes (Kumari Ramiah et al., 2017).

These beneficial effects attributed to CLA isomers are intrinsically linked to their anti-inflammatory potential. For instance, the ameliorating effect of CLA on colitis, was found to be related with its anti-inflammatory action on TNF-α and NFkB pathways. Recently, the C18:2 *t*10,*c*12 isomer was the one showing an homogenous reduction of the studied pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β), which suggests a more balanced and efficient physiological activity and possible a better protective potential (Dipasquale et al., 2018). As discussed for MUFAs, the anti-inflammatory CLA action was reported to be mediated by PPAR γ and δ induction (Bassaganya-riera et al., 2004; Dipasquale et al., 2018). CLA has been previously demonstrated as being able to activate PPAR γ eliciting *in vivo* effects consistent with PPAR γ activation, namely on the reduction of the inflammatory response (Yang & Cook, 2003; Yu et al., 2002). Besides PPARs, some *in vitro* studies have reported that CLA isomers may activate some GPRs receptors, namely GPR120 and GPR40, and thus such receptors may mediate some of their intracellular action in WAT (Shen & McIntosh, 2016).

CLA isomers incorporation in brain has been detected in few cases at very low concentrations (Alasnier et al., 2002; Murru et al., 2021), specifically C18:2 *c*9,*t*11 and C18:2 *t*10,*c*12 were demonstrated to be actively incorporated in rat brain and *in vitro* astrocyte cultures (Fa et al., 2005). After intracerebroventricular administration of CLA, (Cao et al., 2007) reported that food intake was inhibited in rats. This effect was shown to be related with decreased mRNA expression of NPY and AgRP. Besides, promising results have been shown regarding decreased serum leptin levels in rats following CLA treatment (Y.-M. Wang et al., 2005; Yanagita et al., 2005). In fact, acute and chronic activation of CNS PPAR γ led to positive energy balance and restored leptin sensitivity in HFD fed rats (Ryan et al., 2011). Recently, CLA was demonstrated to bind to PPAR α, a nuclear receptor key regulator of fatty acid metabolism and inflammatory

responses. Thus, it was suggested that after their incorporation, CLA isomers are metabolized into brain tissue (mouse brain) where they induce the biosynthesis of endogenous PPAR α ligands palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), possibly through positive feedback (Murru et al., 2021). As reviewed by (Murru et al., 2021) OEA and PEA are natural ethanolamides of oleic acid and PA, respectively. OEA reduces food intake and body weight gain in obese rats, stimulates lipolysis and fatty acid oxidation, reduces the content of TGs in both liver and adipose tissue. Since PPARs, specifically PPAR α, are important regulators of inflammatory responses, CLA anti-inflammatory actions in CNS are possibly connected to the activation of such factors. Indeed, PPAR α anti-inflammatory action is mediated through its repressive action on many activated transcription factors, such as NFkB, among others. Moreover, CLA may also be able to ameliorate oxidative stress by increasing peroxisomal β-oxidation acting as well as an antioxidative factor. Despite the promising results that have emerged over the last few years regarding a potential beneficial effect of CLA in the brain, few studies have specifically targeted the anti-obesogenic effect of CLA isomers on CNS, especially on hypothalamic inflammation. Since it is known the presence of PPARs or GPRs (GPR120 and GPR40) in different brain areas, the beneficial effect of CLA could be achieved through specific PPAR-mediated differentiation pathways or as reported for omega-3 through GPR120 action.

Nevertheless, caution is necessary when assessing the possible anti-obesogenic role of CLA isomers since contradictory results have been reported. For instance, in a study where C18:2 *t*10,*c*12 CLA was added to cell cultures although it increased PPAR γ gene expression it acted in a proinflammatory manner since it upregulated NFkB and TNF gene expression (Calder, 2013). But other studies reported that when in the presence of a inflammatory stimulus, such as LPS, the same CLA isomers acted on an anti-inflammatory manner (Kim et al., 2011). Moreover, in *in vivo* studies in genetic leptin-deficient obese mice CLA increased insulin sensitivity (Wargent et al., 2005). Thus, further studies are required to fully characterize the anti-obesogenic effects of CLA isomers, especially its role on hypothalamus obesity-induced inflammation.

2.3.3.3. Conjugated linolenic acid (CLNA)

CLNA isomers is the general term to refer to a mixture of different ALA conjugated isomers, which occur naturally in both milk fat and meat of ruminants and predominantly in vegetable oils. Punicic acid (PUA) (C18:3 *c*9,*t*11,*c*13), the most recognized and studied CLNA isomer, is mostly found in pomegranate (*Punica granatum*) seed oil, with approximately 70 g of PUA per 100 g of fat (Fontes et al., 2017). CLNA isomers are described to be able to exert similar effects as CLA, but at smaller doses 2-3g/day (Shinohara et al., 2012), while an effective dose for CLA is 3 g/day (Ip et al., 1994).

An antiobesogenic role has also been discussed for CLNA isomers, specifically PUA, in adipose tissue. Vrogrijk and colleagues (Vroegrijk et al., 2011) reported that PUA can improve peripheral insulin sensitivity without affecting liver insulin. Moreover, using a commercial source of PUA, xanthigen, 3T3-L1 adipocyte differentiation and lipid accumulation was suppressed due to a decrease in PPAR γ expression levels. The authors hypothesized that PPAR γ being a regulator of adipogenesis and being necessary for differentiation, a decrease in its expression is beneficial in adipocyte cells (Lai et al., 2012). Nevertheless, other studies have reported that PUA specifically activates both PPAR α and γ in WAT in mice. Such activation is responsible for the improvement of glucose homeostasis and suppression of inflammation, namely NFkB activation and TNF-α expression (Hontecillas et al., 2009). Supplementation of diet with 1% pomegranate seed oil (with PUA) showed to not affect abdominal WAT and serum lipid levels compared with the control diet. Nevertheless, this supplementation was sufficient to decrease the hepatic TG accumulation in obese, hyperlipidemic rats. The authors attributed this suppression, at least in part, to suppression of Δ-9 desaturation, a key step in the membrane-bound stearoyl-CoA

desaturase synthesis of MUFA from SFA (Arao et al., 2004). Furthermore, a reduction on LDL cholesterol (40% reduction) and total cholesterol (24% reduction) as well as TGs reduction was reported by pomegranate seed oil oral supplementation in rats (Shagholian et al., 2019).

Regarding CLNA action on CNS, specifically on hypothalamus inflammation, very few studies have addressed such possibility. It was suggested that CLA is converted into CLNA in rat brain (Fa et al., 2005). Another study demonstrated that pomegranate seed oil (a source of PUA) affected the morphology of activated microglia cells (BV-2 cells). The authors suggested an immunomodulation and cytoprotecting potential comparable to omega-3 PUFAs, important for neuroinflammatory disease such as obesity (Račková et al., 2014).

Although some promising results have emerged regarding assays on adipocytes cells showing a potential anti-obesogenic role, there is the need of further investigations of CLNA effects on both peripheral tissues and brain, specifically on human subjects, as well as the potential adverse health effects.

3. Conclusion

Despite the advances regarding obesity, especially in developed countries, it continues to be considered a global pandemic. There are some anti-obesity drugs which present promising results, however they are often associated with severe side-effects and new strategies and approaches are required to tackle this problem.

For instance, diet has been widely seen as an important player in the development of obesity; HFD are often associated and blamed for the increasing obesity rates. Nevertheless, fats are diverse and generate different responses *in vivo*. On one hand, SFAs act on a pro-inflammatory manner through TLR 4 to activate inflammatory pathways resulting in insulin resistance and ER stress both in adipose tissue and CNS. Moreover, the SFA diet excess, which is characteristic of obesity increases lipid storage in adipose tissue, which results in accumulation of lipids in adipocytes. This leads adipocytes to develop larger lipid droplets and therefore to contain more TGs, increased leptin secretion, cellular stress and the activation of pro-inflammatory pathways such as JNK and NFkB. On the other hand, other fatty acids such as MCFAs, MUFAs and PUFAs have been associated to positive effects on obesity. Indeed, MCTGs are rapidly metabolized and less likely to be stored in the adipose tissue, resulting in a promising tool for weight control. They may counteract fat deposition in adipocytes by increasing thermogenesis and satiety. In addition, the positive effect of a MUFA and PUFA-rich diet on obesity is highly related with the PPAR- and GPR-120-mediated anti-inflammatory potential, in adipose tissue and brain respectively, by inhibiting NFkB pathway. Furthermore, the effects of omega-3 PUFAs on adipose tissue have been documented regarding a regulation on adipocyte inflammation, differentiation and apoptosis, effects on lipid storage and mobilization, on mitochondrial biogenesis and adipose tissue browning and adipokines production. Similarly to what happens in hypothalamus cellular models, EPA and DHA attenuate inflammatory activation of *in vitro* human adipocytes. Beneficial effects attributed to omega-3, CLA and CLNA isomers (Figure 1) are intrinsically linked to their anti-inflammatory potential mediated by PPARs or GPRs receptors (namely GPR120 and GPR40) inhibitory action on NFkB pathway. Although some promising results have been reported, there is the need of further investigations of CLA and CLNA effects on both peripheral tissues and brain, specifically on human subjects, as well as the potential adverse health effects.

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5. Conflicts of interest

The authors declare no conflict of interest.

6. List of Tables

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8. References

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Table 1 – Summary of the developed drugs for obesity treatment, their mechanisms of action and associated side effects. (FDA) Food and Drug Administration; (EMA) European Medicine Agency.

Anti-obesity drug	Mechanism of action	Side effects	Status	Reference
Orlistat	Decreases fat absorption by inhibition of gastric and pancreatic lipases.	Flatulence, oily spotting, faecal urgency, fatty/oily stool, oily defecation, increased defecation, faecal incontinence, hepatotoxicity, nephrolithiasis and pancreatitis.	Approved by FDA since 1998 and EMA since 1999.	(Srivastava & Apovian, 2018)
Sibutramine	It works by preventing the neurotransmitters serotonin and noradrenaline from being taken back up into nerve cells in the brain. The increased levels of neurotransmitters in the brain help patients to feel full after a meal, and this helps to reduce their food intake.	Elevated risk of cardiovascular disease events at patients at high risk for cardiovascular disease.	Approved by FDA between 1997 and 2010. Approved by EMA from 1999 to 2010. Removed from the market.	(EMA, n.d.; James et al., 2010)
Lorcaserin/Belviq	It imitates the effects of serotonin on 5-HT2C receptors, which include an increased sense of fullness after a meal and reduced hunger before meals, thereby reducing food consumption.	Incidence of certain cancers.	Approved by FDA between 2012 and 2020. It was withdrawn by EMA from the European market in 2013.	(EMA, 2013; Haslam, 2016; Sharretts et al., 2020)
Fenfluramine	Used as an anoretic drug. When combined with a norepinephrine stimulant, phentermine, it became part of the anti-obesity medication Fen-phen.	Cardiovascular complications, including heart valve disease, pulmonary hypertension, and cardiac fibrosis.	Approved by FDA in 1973 and withdrawn in 1997.	(Xu et al., 2019)
Phentermine	Appetite suppression and basal energy expenditure increase.	Dry mouth, insomnia, dizziness, palpitations, constipations, irritability, mood changes, its use is contraindicated in patients suffering from anxiety, cardiovascular diseases, hyperthyroidism or glaucoma.	Approved by the FDA in 1959. Restricted to short-term use.	(Apovian et al., 2015; Dragano, Fernø, et al., 2020)
Rimonabant/Zimulti	Acts as a CB1 receptor inverse agonist (functional antagonist)-anoretic effect.	Severe mood disorders, like anxiety and depression.	Approved by EMA in 2006 and withdrawn in 2009. Withdrawn by FDA in 2007.	(Samat et al., 2008)
Liraglutide	GLP-1 receptor mono-agonist. Plays a role in the central regulation of feeding through its effects on arcuate nucleus and nucleus tractus solitarius.	Gastrointestinal adverse events: nausea, diarrhea, constipation, vomiting.	Approved by EMA in 2009 and FDA in 2010.	(Dragano, Fernø, et al., 2020)
Diethylpropion/Amfepramone	Indirect-acting sympathomimetic agents that act by releasing noradrenaline from presynaptic vesicles in the lateral hypothalamus. The increase in noradrenaline concentration results in the stimulation of β2-adrenergic receptors and a consequent inhibition of appetite.	Dizziness, dry mouth, difficulty sleeping, irritability, nausea, vomiting, diarrhea, constipation.	Approved by the FDA in 1959. Restricted to short-term use. Withdrawn from the European market by EMA in 2000.	(Ioannides-Demos et al., 2011)
Phendimetrazine	Activity similar to amphetamines that stimulates the central nervous system and elevates blood pressure most likely mediated via norepinephrine and dopamine metabolism. Causes stimulation of the hypothalamus. Reduces food intake	Insomnia, dry mouth, constipation, hyperpyrexia, mydriasis, chest pain, arrhythmias, delirium, rhabdomyolysis.	Approved by the FDA in 1959. Restricted to short-term use.	(Dragano, Fernø, et al., 2020; Kwiker et al., 2006)
Benzphetamine	Sympathomimetic and central nervous system stimulant. Similar action to amphetamines.	Insomnia, dry mouth, elevation of mood, nausea, vomiting, palpitation.	Approved by the FDA for short-term use.	(Dragano, Fernø, et al., 2020; PATEL et al., 1963)

Table 2 - Effect of omega-3 on adipokines regulation in obesity.

Adipokine	Biological importance	Obesity effects	Effect of omega-3	Reference
Adiponectin	It is an insulin-sensitizing adipokine that regulates glucose and lipid metabolism: reduces lipogenesis and promotes fatty acid oxidation. Stimulates mitochondrial biogenesis and has important anti-inflammatory properties.	Obesity effects reduce adiponectin levels, contributing to insulin resistance and cardiovascular disorders.	Omega-3 PUFAs are regulators of adiponectin production by adipocytes. Beneficial actions on insulin sensitivity, fatty acid oxidation and inflammation.	(Bahreini et al., 2018; Martínez-Fernández et al., 2015b; Oster et al., 2010; Siriwardhana et al., 2012; Turer & Scherer, 2012; Yadav et al., 2013)
Leptin	Regulation of food intake and appetite, insulin signaling, energy expenditure and immune system.	Obesity causes hyperleptinemia, resulting in leptin resistance causing disturbance of body weight regulation.	Regulation of leptin production. Nevertheless, omega-3 effects on leptin are highly dependent on the dose and duration of the treatment as well as the composition of the dietary fish oil and the metabolic state of the subjects on leptin production.	(Ahima et al., 1996; Havel, 2004; La Cava & Matarese, 2004; Martínez-Fernández et al., 2015b; Murata et al., 2000; Sáinz et al., 2015)
Apelin	Apelin is an adipokine with potential anti-diabetic, anti-obesity and cardioprotective properties.	Apelin circulating levels are upregulated in hyperinsulinemic obese subjects.	Modulatory effects on apelin: stimulatory effect on its levels.	(Bertrand et al., 2013; Boucher et al., 2005; Castan-Laurell et al., 2011; Lorente-Cebrián et al., 2010; Martínez-Fernández et al., 2015b)

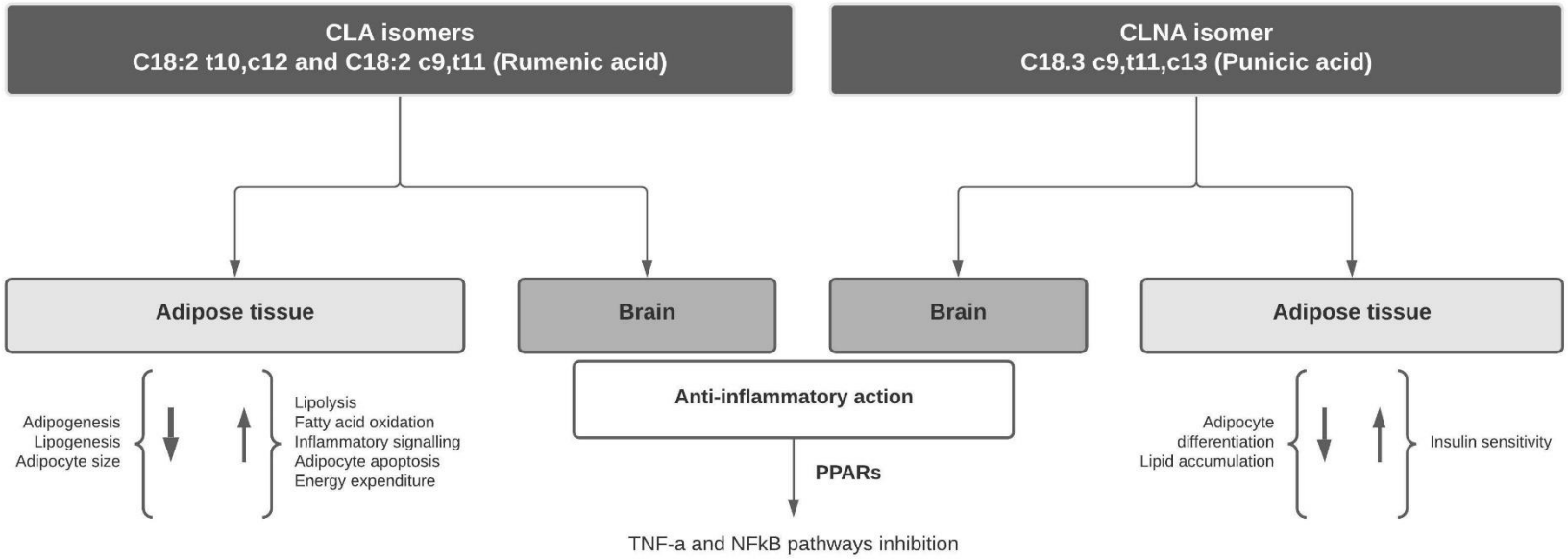

Figure 1 - Conjugated fatty acids role on obesity: Schematic representation of conjugated linoleic acid and conjugated linolenic acid anti-obesity properties in both peripheral tissues, specifically adipose tissue, and brain.