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Review

Understanding the appetite modulation pathways: The role of the FFA1 and FFA4 receptors

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ABSTRACT

Pharmaconutrition is an area of current interest, especially concerning the advances in the pharmacology of nutrient-sensing receptors, as have been accomplished in the last 20 years. The family of free fatty acid (FFA) receptors is composed of four members, sequentially named as FFA1 to FFA4, which are activated by the short to long-chain fatty acids. The affinity of the FFA1 and FFA4 receptors for the omega-3 polyunsaturated fatty acids prompted pre-clinical and clinical investigations regarding their involvement in metabolic diseases. The main studies have been focused on the receptors' expression analyses, the featuring of knockout mice, and the assessment of selective synthetic ligands. These clearly have indicated a relevant role for FFA1 and FFA4 in the peripheral and central circuits for the regulation of energetic metabolism. This review article aimed to discuss the relevance of the FFA1 and FFA4 receptors in appetite-related complications, mainly related to obesity, cancer cachexia, and anorexia in the elderly, emphasizing whether their pharmacological modulation might be useful for the management of these disorders.

1 General overview

The origin of the word *appetite* comes from old French term *apetit*, from Latin's *appetitus*, *appetere* (to strive after, long for), or *ad* + *petere* ("to seek"), and it is defined by "any of the instinctive desires necessary to keep up an organic life". In other words, appetite is defined as the desire of eating. The mechanisms of appetite are crucially regulated due to the importance of eating for the organism, being influenced by

Abbreviations: ALA, α-linolenic acid; A-MSH, α-melanocyte-stimulating hormone; AgoPAMs, Agonist also capable of acting as positive allosteric modulators; AgRP, Agouti-related protein; AKT, Protein kinase B; β3-AR, β-3 Adrenergic receptor; BDNF, Brain-derived neurotrophic factor; BNST, Bed Nucleus of the Stria Terminalis; CART, Cocaine-amphetamine regulated transcript; cAMP, Cyclic adenosine 3′,5′-monophosphate; CNS, Central nervous system; CGPR, Calcitonin gene-related peptide; CKK, Cholecystokinin; DAG, Diacylglycerol; DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid; FFA, free fatty acids; FFA1, Free fatty acid receptor 1; FFA2, Free fatty acid receptor 2; FFA3, Free fatty acid receptor 3; FFA4, Free fatty acid receptor 4; FDA, Food & Drug Administration; FOXO, Forkhead brox protein O; FTO, Fat mass and obesity-associated gene; GABA, γ-aminobutyric acid; GLP-1, Glucagon-like peptide-1; GLP-2, Glucagon-like peptide-2; GPR40, G-coupled protein receptor 40; GPR41, G-coupled protein receptor 41; GPR43, G-coupled protein receptor 43; GPR120, G-coupled protein receptor 120; 5-HT, 5-hydroxytryptamine; IP_3, Inositol trisphosphate; IGF-1, Insulin-like growth factor-1; i.c.v., Intracerebroventricular; IL-6, Interleukin-6; LH, Lateral hypothalamus; mTOR, Mammalian target of rapamycin; MC3R, Melanocortin receptor 3; MC4R, Melanocortin receptor 4; MCH, Melanin-concentrating hormone; MUFA, Mono-unsaturated fatty acid; NPY, Neuropeptide Y; NST, Nucleus of the solitary tract; NF-kB, Nuclear factor kappa-light-chain-enhancer of activated B cell; PBN, Para-brachial nucleus; PVN, Paraventricular hypothalamus; PTHrP, Parathyroid hormone-related protein; PYY, Peptide tyrosine tyrosine; PGC1α, Peroxisome proliferator-activated receptor gamma coactivator 1-α; PLC, Phospholipase C; PIP_2, Phosphatidylinositol 4,5-bisphosphate; PI3K, Phosphoinositide 3-kinase; PRDM16, PR domain containing 16; POMC, Proopiomelanocortin; PUFA, Polyunsaturated fatty acid; SMAD2, Mothers against decapentaplegic homolog 2; SMAD3, Mothers against decapentaplegic homolog 3; TRIF, Adaptor protein TIR-domain-containing adaptor inducing interferon-β; TNF, Tumor necrosis factor; Tab1, Transforming growth factor-β-activated kinase 1; Tak1, Transforming growth factor beta-activated kinase 1; UCP-1, Uncoupling protein-1; ZAG, Zinc-α2-glycoprotein.

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behavioral, psychological, environmental, and neuroendocrine factors [1]. Appetite is implicated in contrasting life-threatening conditions, such as obesity, cachexia, and anorexia, reflecting the importance of understanding this essential regulatory process [2].

According to the World Health Organization (WHO), overweight and obesity are defined as an abnormal or excessive fat accumulation that present a high risk to health [3]. Most importantly, in the last 50 years, obesity has become a pandemic, due to a global increase between the years of 1975 and 2016 [4]. Obese patients often display several complications that negatively impact on the overall quality of life and on healthcare costs [5]. Similarly, cachexia displays negative impacts over the life of patients, nevertheless, with an opposite phenotype. This disorder is defined as a multifactorial syndrome that is characterized by an ongoing skeletal muscle loss (with or without fat loss) that cannot be fully reversed by conventional nutritional therapy, leading to a progressive functional impairment [6]. Several conditions are associated with cachexia development, such as cancer, chronic kidney disease, chronic heart failure, congestive obstructive pulmonary disease, sepsis, trauma, AIDS, and aging [7–9]. More recently, it was observed that critical COVID-19 patients have displayed cachexia features, such as anorexia and muscle loss [10].

According to the United Nations, the world's population, with more 65-year old, will increase by approximately 79% by 2040 [11]. Notably, appetite loss is a common feature in this type of population [12]. The anorexia of aging is characterized by a multifactorial condition, which is associated with reduced hedonism, alterations in external cues, diminished release of the appetite-related hormones, hypothalamic inflammation, and an unbalanced melanocortin system [9,13].

In the past 20 years, the pharmacology of nutrient-sensing receptors has been widely explored [14]. One remarkable example of this type of receptors is the free fatty acid receptor family. This class of G protein-coupled receptors is composed of four receptors, namely FFA1, FFA2, FFA3, and FFA4 [15]. They respond to a wide range of free fatty acids (FFAs), demonstrating the importance of these molecules to homeostasis [16]. All of these four receptors are widely distributed throughout different tissues and organs, most importantly, in the sites related to metabolism control [17]. However, the modulation of these receptors has also been linked to other situations, such as pain, cancer, bone loss, and other inflammatory processes [18–20].

The authors decided to discuss the potential roles of FFA1 and FFA4 in these appetite-related conditions, as both are long-chained fatty acid-sensing receptors, and on account of the existing beneficial effects of the omega-3 fatty acids on obesity, together with the lack of data on cachexia and aging anorexia. In virtue of their metabolic similarities, it was possible to raise several hypotheses on how these receptors could help in these conditions. Additionally, due to these metabolic similarities and the challenge of treating each condition, the authors chose to discuss these three appetite-related conditions. Thus, this review discusses the role of the free fatty acid receptors on the control of appetite, besides their promising participation in the modulation of appetite-related disorders, such as obesity, cancer cachexia, and aging anorexia.

2. The peripheral and central mechanisms of appetite regulation

Food intake is regulated by two different systems that are intimately connected: the homeostatic and hedonic systems [21]. The homeostatic controlling mechanism is initiated at the hypothalamus, more precisely at the arcuate nucleus (ARC) of the hypothalamus. Importantly, the ARC is located near the area postrema and the median eminence, which are circumventricular organs. Significantly, the blood–brain barrier is strategically permeable as a result of the high quantity of permeable capillaries of these circumventricular organs, allowing peripheral substances to reach the ARC [2,22]. Amongst them, leptin and ghrelin are neuroendocrine hormones that are essential for appetite regulation. Leptin is produced by the adipose tissue, stomach, skeletal muscle, and hypophysis [23,24]. This hormone has a well-established effect that regulates the energy balance. When released by the gastrointestinal tract, its paracrine effect is even more substantial, by modulating the nutrient absorption and gut motility. Additionally, leptin has an endocrine role in fasting, or the refeeding after fasting [25]. Alternatively, ghrelin is also released from the enteroendocrine cells, but it mediates hunger [26]. The vagal nerve pathway connects the enteric nervous system to the central nervous system (CNS), regulating the appetite and food intake. Throughout this pathway, there are several receptors for the different gut peptides, such as leptin and ghrelin, but also for cholecystokinin (CKK), glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY), and 5-hydroxytryptamine (5-HT), which are all implicated in the regulation of hunger and satiety [27].

The homeostatic system is primarily controlled by a subset of neurons that are located at the ARC, with distinct characteristics [26]. The anorexigenic neurons express proopiomelanocortin (POMC) and the cocaine-amphetamine regulated transcript (CART). The POMC cleavage leads to the production of the α-melanocyte-stimulating hormone (α-MSH), which binds to the two receptors located at the paraventricular nucleus, these being the melanocortin receptors 3 and 4 (MC3R and MC4R). The two receptors lead to an appetite inhibition and an increased energy expenditure. Alternatively, the orexigenic neurons are characterized by expressing the Agouti-related protein (AgRP), neuropeptide Y (NPY), and γ-aminobutyric acid (GABA), which are responsible for increasing the food-seeking behavior and food intake when the organism is in an energy deficit. These neurons project to different brain regions, such as the lateral hypothalamus (LH), the paraventricular hypothalamus (PVN) terminals in the oxytocin-expressing neurons, as well the bed nucleus of the stria terminalis (BNST). Markedly, both of the anorexigenic and orexigenic neurons express leptin receptors, although they respond in contrasting ways [1,2,28]. A novel mechanism of appetite regulation was described by Campos et al., showing that the calcitonin gene-related peptide (CGRP)-expressing parabrachial neurons modulate the food intake. Furthermore, these CGRP-neurons are innervated by the AgRP-neurons, nevertheless, these AgRP-neurons when activated inhibit the CGRP-neurons, thus inducing hyperphagia and delayed satiety [29].

The hedonic system is an extremely complex signaling pathway that is related to the reward effect of food. The mesolimbic dopamine signaling-LH-cortex axis is considered an important circuit for the consumption of palatable food, which is associated with the rewarding effect. This particular axis is triggered by drug addiction, although, palatable and energy-dense foods promote a similar dopamine signaling [21]. In addition, regions, such as the amygdala, are also crucial for the hedonic system, due to the importance of this region regarding negative and positive emotions, as well as behavioral patterns [30]. Furthermore, the gustatory sensory information enters the brain by the nucleus of the solitary tract (NST), then continuing to the parabrachial nucleus (PBN) and the LH. At the LH, there are two classes of neurons expressing orexin and the melanin-concentrating hormone (MCH), respectively, and both are related to an increased food intake [2]. Further, the activation of the orexin receptors by orexin stimulates not only the food intake, but also the reward that is associated with food, drug addiction, and sleep/arousal regulation [28]. Moreover, oxytocin plays a vital role in the sensing of energy abundance or deficiency, as well as the reward effect of food [31]. Importantly, the homeostatic system is linked to the hedonic system, promoting a connection of appetite regulation, palatable food-seeking behavior, reward, and the consciousness of these processes [1,32].

Satiety is mainly regulated by the gut-secreted hormones, such as CCK and GLP-1. The release of CCK occurs in the presence of food, and it stimulates different aspects of the digestive system, such as pancreas functioning and gallbladder contraction. Additionally, CCK also mediates satiety by activating the CCK receptors throughout the CNS. As for GLP-1, this hormone is considered an incretin, being released after meal cessation. This hormone binds to its receptor in the pancreas, stimulating an insulin release. The GLP-1 receptor (GLP-1R) is widely

expressed in the brain, mainly at the hypothalamus. Above all, GLP-1 activates the POMC/CART anorexigenic neurons and indirectly inhibits, via GABAergic signaling, the AgRP/NPY neurons, resulting in the reduction of food intake and food-seeking behavior [33].

Regarding appetite control, the peripheral and central mechanisms work in an organized manner during homeostasis. Even so, in different circumstances, this signaling orchestra can be jeopardized, resulting in unfavorable outcomes. Thus, to explore the additional targets implicated in appetite control is a theme of current interest.

3. FFA receptors

The FFAs are essential components of the cell membranes. They participate in the synthesis of other signaling molecules and act as an energy source [16,17]. According to the International Union of Pure and Applied Chemistry (IUPAC), natural fatty acids commonly have a chain of 4 to 28 carbons (usually unbranched and even-numbered), which may be saturated or unsaturated [34]. Essentialy, fatty acids are not found in a free state in nature, but usually, they exist combined with glycerol in the form of triglycerides. Equally, the lipoprotein lipase (LPL) can be activated to hydrolyze the catalysis of triglycerides, releasing these free fatty acids from glycerol; however, in a tissue-specific manner [35]. In the organism, FFAs are only found after the processes of ingestion, digestion, and the absorption of the dietary lipids [16].

In the early 2000s, it was discovered that the FFAs could stimulate cell signaling themselves, acting as natural agonists of four G protein-coupled receptors, initially denoted as GPR40, GPR41, GPR43, and GPR120 [36–38]. Afterward, they were renamed as the free fatty acid receptors FFA1 (GPR40), FFA2 (GPR43), FFA3 (GPR41), and FFA4 (GPR120) [39]. The genes encoding FFA1, FFA2, and FFA3 were identified in 1997, being located at chromosome 19q13.1 in humans [40]. By 2008, FFA1, FFA2, and FFA3 composed the free fatty acid receptor class, while considering an overall sequence homology of 30 to 50% [39]. Nevertheless, they diverge regarding their ligands. FFA1 is activated by medium- to long-chain fatty acids, alternatively, FFA2 and FFA3 are activated by the short-chain fatty acids [36,37]. As for FFA4, the initial exclusion of this G protein-coupled receptor from this class was due to the low homology with the other free fatty acid receptors [39]. However, FFA4 and FFA1 are pharmacological targets for similar molecules, such as the omega-3 polyunsaturated fatty acids [41–43]. FFA4 was only included in the free fatty acid receptor class five years later in 2013 by the International Union of Basic and Clinical Pharmacology (IUPHAR) [43].

3.1. FFA1 receptor

The FFA1 receptor was deorphanized in 2003, resulting in the identification of the medium- to long-chained fatty acids as natural agonists of this receptor [36]. Among all of the molecules that can activate the FFA1 receptor, it is noteworthy to mention the polyunsaturated fatty acids, such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and α-linolenic acid (ALA) [36,41,44]. These molecules are the most potent activators (DHA > EPA > ALA) of this receptor. It was previously reported that the FFA1 signaling occurs via three types of G proteins, G_q, G_i, and G_s, resulting in different signaling cascades: the activation or inhibition of cAMP, or the activation of the PLC/IP_3/DAG pathway, leading to an increase of intracellular [Ca^{2+}], which can be observed in Fig. 1 [15]. Regarding the localization of the FFA1 receptor in the organism, it is expressed in cells and organs of great importance to metabolism control, such as pancreatic β-cells, monocytes, osteoblasts, osteoclasts, CNS, and the enteroendocrine cells [16].

The first mechanism described for the FFA1 receptor was the potentiation of glucose-dependent insulin release by the pancreatic β-cells [36]. Noteworthy, the FFA1 stimulation induces an incretin secretion when the long-chain fatty acids reach the intestines. These incretins, such as GIP, GLP-1, PYY, and CCK, when they are released to the bloodstream and the enteral nervous system, evoke outcomes, such as a decreased food intake and gastric emptying [45].Regardless, while

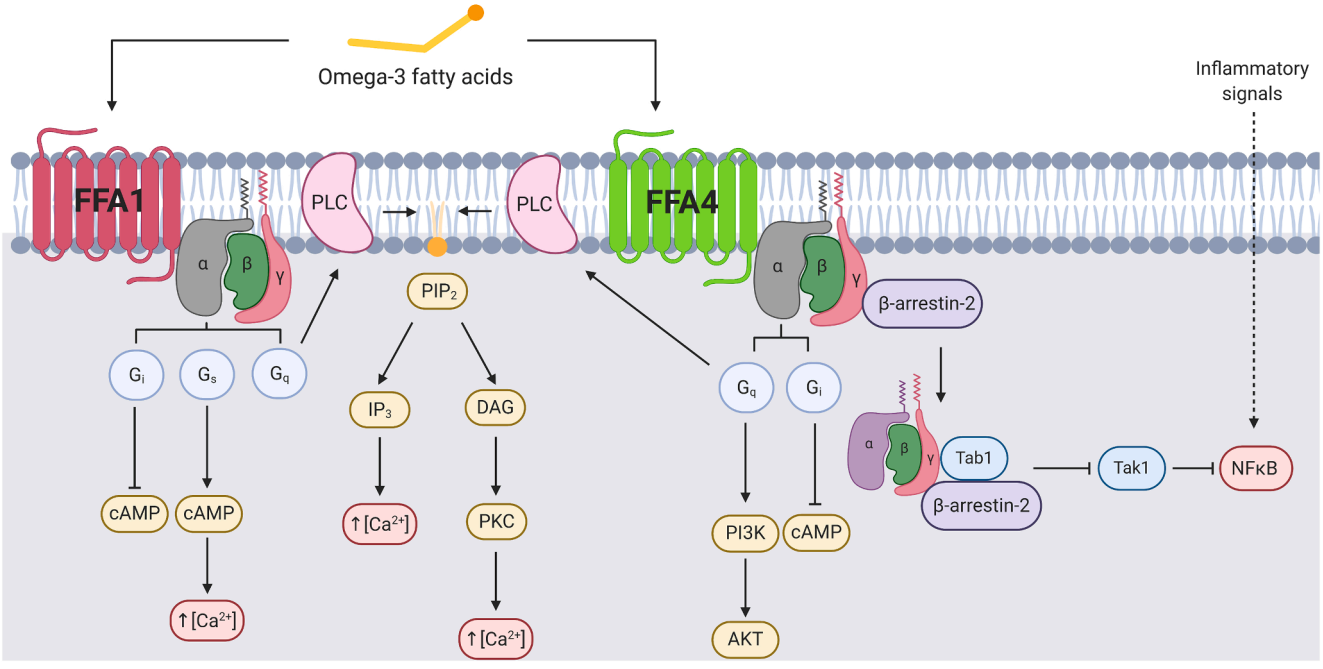

Fig. 1. Mechanisms of the FFAs receptors when activated by the omega-3 fatty acids. The FFA1 receptor signaling, as a result of the omega-3 fatty acid activation, occurs through G_q, G_i, and G_s protein activation, resulting in different signaling cascades: activation or inhibition of cAMP, or activation of the PLC/IP_3/DAG pathway, leading to an increase of intracellular [Ca^{2+}]. As for the FFA4 receptor, the binding of the omega-3 fatty acids leads to $G_{q/11}$, and G_i protein activation, or β-arrestin-2 recruitment and the formation of complex FFA4/β-arrestin-2/Tab-1, subsequently blocking the pro-inflammatory signaling pathways. cAMP: Cyclic adenosine 3′,5′-monophosphate; PLC: Phospholipase C; DAG: diacylglycerol; PIP_2: phosphatidylinositol 4,5-bisphosphate; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; Tab1: Transforming growth factor-β-activated kinase 1; Tak1: Transforming growth factor beta-activated kinase 1. Created with BioRender.com.

the insulin secretion is mediated by FFA1-G_q signaling, the incretin secretion by the enteroendocrine cells is co-mediated by G_s and G_q [36,46]. Primarily, these mechanisms have been widely investigated in an attempt to identify novel treatments for diabetes and obesity.

Emerging evidence reveals that the FFA1 receptor plays a pivotal role in the CNS, most importantly in pain management, psychiatric conditions, overall behavior, and metabolic homeostasis control [36,47–49]. FFA1 is widely expressed in the brain, with high expressions in the hippocampus, hypothalamus, caudate nucleus, medulla oblongata, substantia nigra, spinal cord, the subgranular and subventricular zones, CA1, and the cortex [47,50]. FFA1-deficient mice have displayed increased noradrenaline levels in the brain, exhibiting depressive- and anxious-like behavior, with impaired maternal care and emotional functions, indicating a relevant role for this receptor in affective aspects [49,51]. Alternatively, the activation of brain the FFA1 receptors by DHA, or by the synthetic partial agonist GW9508, restored the cognitive deficits that are associated with obesity and diabetes, and led to brain-derived neurotrophic factor (BDNF) upregulation [52].

The FFA1 receptor is co-localized with NPY and the POMC-expressing neurons, proposing a role for FFA1 in appetite control. Despite that, the mice that were fed with standard chow and treated with the synthetic partial agonist GW9508, presented similar food intakes when compared with the control group. Conversely, the diet-induced obese mice under the synthetic partial agonist GW9508 treatment displayed diminished chow consumption [50]. It was previously demonstrated the that omega-3 fatty acids triggered POMC-neurogenesis via the FFA1 receptor activation in obese mice, confirming the participation of the brain FFA1 receptors in appetite regulation [53]. Notwithstanding, most evidence regarding FFA1 and food intake is related to its ability to stimulate an incretin secretion that can either sensitize the vagal nerve, or reach the hypothalamus directly by the blood-brain barrier. In the light of these pieces of evidence, the FFA1 receptor is strongly accounted for as an important pharmaconutritional target for the management of metabolic disorders that directly tackle appetite control.

3.2. FFA4 receptor

The gene encoding FFA4 receptor was described by Fredriksson et al. in 2003, which is located in human chromosome 10q23.33 [54]. Two years later, this G protein-coupled receptor was deorphanized by Hirasawa et al., demonstrating its activation by medium- to long-chain fatty acids. Hirasawa et al. reported that the FFA4 receptor, when activated, participated in the GLP-1 secretion of enteroendocrine cells, implying that this receptor is a potential pharmacological target for obesity or eating disorders [38]. The glucose lowering effects that are secondary to the FFA4 receptor activation seem to be driven by GLP-1 secretion [55]. Further evidence has reported that FFA4 is one of the leading players in other situations, such as adipogenesis, non-shivering thermogenesis, by inducing the browning of the white adipocytes, and the inflammation resolution mechanisms [56–58]. This receptor has been demonstrated as being expressed in the enteroendocrine cells, osteoblasts, osteoclasts, macrophages, the brown, beige, and white adipocytes, hypothalamus, retina, and the skeletal muscle [42,57,59–61]. It was previously reported by Oh et al. that the FFA4 receptor signals in the adipocytes and macrophages were by distinct pathways. In the adipocytes, the glucose uptake is mediated by $G_{q/11}$ protein activation, while in the macrophages, the anti-inflammatory effects rely upon β-arrestin-2 recruitment and the formation of the complex FFA4/β-arrestin-2/Tab-1, subsequently blocking pro-inflammatory signaling pathways (Fig. 1) [42]. Likewise, some studies have reported that the FFA4 receptor also signals through G_s and G_i, impairing the ghrelin secretion by inhibiting cAMP, contrasting with the previous theory that the FFA4 receptor is only signaled via $G_{q/11}$ (Fig. 1) [55,62].

Strikingly, the human FFA4 receptors exist in two variants, the short isoform with 361 residues, and a long isoform containing 16 additional residues in intracellular loop 3. However, other mammals only express the short isoform [58,63]. These additional amino acids exert an essential role in functions of this receptor, due to the importance of this intracellular loop in G protein and β-arrestin-2 recognition [64]. Nevertheless, the β-arrestin-2 recruitment and FFA4 internalization is a mechanism that is conserved between both isoforms. The presence of these additional amino acids inhibits the G-protein activation, demonstrating that the long FFA4 isoform fails to signal through the G protein-mediated calcium mobilization (Fig. 1) [63].

The FFA4 receptor is widely expressed in the K-cells, the somatostatin-containing D cells, and the L-cells [62,65]. The activation of FFA4 by dietary lipids in the stomach is related to the inhibition of ghrelin secretion, leading to appetite dampening [62]. Furthermore, the FFA4 receptors are expressed mainly in the K-cells of the upper small intestine, and they are responsible for secreting CCK, GIP, and GLP-1, promoting responses, such as a reduced food intake and gastric emptying [66]. For instance, the FFA4 receptor is also highly expressed in the L-cells of the colon, where it stimulates the secretion of GLP-1, GLP-2, and PYY [38,65,67].

The mechanisms regarding the FFA4 receptor roles in the gut and its effects on incretin secretion are well described. However, there is scarce clinical evidence on this matter. Thought-provokingly, different from the FFA1 receptor, the role of FFA4 in the CNS remains unclear. Recent evidence has demonstrated that this receptor is expressed in the hypothalamus, microglia, and pituitary gland, yet information regarding the FFA4 expression in other brain regions is still unclear [50,60,68]. It was previously reported that the central activation of FFA4 acutely reduced the food intake and anxiety in mice, suggesting that the FFA4 receptor activation might control appetite and behavioral deficits under normal conditions [69]. Conversely, other studies have reported that the FFA4 receptor does not participate directly in the appetite control mechanism, but its activation leads to a hypothalamic inflammation reduction [50,60]. Taking into account the evidence cited above, the FFA4 receptor, as well as the FFA1 receptor, might be considered as promising therapeutic targets for managing metabolic conditions, by probably modulating hypothalamic inflammation and an unbalanced incretin secretion.

4. FFA receptors and their role in appetite-related disorders

The FFA receptors, such as FFA1 and FFA4, have been extensively investigated as potential pharmacological targets for metabolic diseases, such as obesity and diabetes. Importantly, conditions such as anorexia and cachexia are equally harmful, while at the same time, the role of the FFA receptors in these situations have been poorly investigated. In the next sections, the known facts regarding the FFA receptors and obesity will be discussed, and possible roles for both receptors will be proposed for cachexia and anorexia of aging management regarding appetite control.

4.1. Obesity

Obesity is recognized as a multifactorial chronic disease due to socioeconomic and biological factors. It develops mainly due to a long-term imbalance between energy intake and energy expenditure [5]. Noteworthy, one of the mechanisms observed in obese individuals is an unstable incretin secretion, such as leptin and ghrelin secretions, leading to the reduction of the vagal afferent signaling and the development of leptin resistance [70,71]. Furthermore, the hedonic system, which is linked to the reward system, has a pivotal role in obesity pathophysiology [33].

Obesity is mainly treated with non-pharmacological strategies, by promoting a negative energy balance via alterations of the dietary patterns, and the introduction of regular physical exercises. Nowadays, different nutritional strategies are widely used, with the intent to promote weight loss, such as high-protein and low-carbohydrate diets.

These diets are associated with an increase of the satiety hormones, such as GIP and GLP-1, reducing the ghrelin secretion and increasing protein-induced thermogenesis [72,73]. When this is considered, despite their extensive employment by dietitians and physicians, their long-term efficacy is questionable [74]. On the other hand, ketogenic or very-low-carbohydrate diets have proved beneficial effects on diabetes, cardiovascular parameters, and body weight [75]. Bariatric surgery is a non-pharmacological strategy that is widely used in severely obese patients, who are not responding to dietary interventions [76]. These patients that are submitted to bariatric surgery display significant long-term weight losses and normalized glycemia. The effects occur due to diminished ghrelin and an increased CCK, GLP-1, and PYY secretion, during the initial post-operative period. All the same, it is not clear if these alterations are due to incretin secretion modulation, except for improvement of the post-prandial glycemia, which is evoked by the increased GLP-1 secretion [77]. So far, the Food & Drug Administration (FDA) has approved six medications for obesity management, which are described in Table 1 [78]. Most of these medications display appetite suppression as a common clinical effect.

The fat mass- and obesity-associated gene (FTO) was identified as a strong genetic factor associated with obesity, demonstrating that carriers of this gene and its obesity-related variants display impaired satiety responsiveness; consequently, an increased energy consumption [79]. Worthy of note, high-risk individuals display postprandial activation of the satiety-related brain regions when visualizing caloric dense foods. These same individuals are declared less satiated, with preferred high-fat products, and they devour more calories [80]. In addition, mice that lacked the FTO gene showed similar characteristics to the dopamine receptor-knockout mice, demonstrating that the FTO gene might be related to reward functions [81]. Furthermore, a clinical study has demonstrated that the presence of the FTO rs9939609 variant influences food craving, and it is directly associated with a food-seeking behavior, in response to the unfavorable conditions [82]. Another variant of the FTO gene, rs1421085, inhibits adipocyte differentiation to the beige adipocytes. This variant induced the production of white adipocytes, promoting lipid storage and body weight gain [83]. The presence of the FTO gene proves even more that obesity is a multifactorial condition. Nonetheless, patients and health professionals must not face the presence of this gene as a life sentence. The individuals who were submitted to a hypocaloric diet and exercise displayed body weight and fat loss, irrespective of the FTO gene [84].

Regarding the FFA receptors, the intestinal expression of the FFAs receptors can be modulated by the presence of obesity, indicating that these receptors are essential for an obese pathophysiology. It has been demonstrated previously that the increased expression of human intestinal mRNA FFA4 was correlated with an elevated BMI. On the contrary, the FFA1 expression was unaltered in the same individuals [85]. Furthermore, both of the FFA1 and FFA4 receptors are upregulated in the colon of obese mice [86]. In this same report, the mice that were submitted to bariatric surgery presented inverse outcomes that were related to the FFA receptors. The FFA1 mRNA expression was upregulated, while the FFA4 expression was downregulated. The authors suggested that this occurred due to their diet and not because of the surgical procedure. As for their expressions in the CNS, both FFA1 and FFA4 are constitutively expressed in the appetite-related regions, such as the hypothalamic neurons expressing AgRP and POMC. Yet, this expression was not modulated by the presence of obesity [50]. As for the relationship between the FFA receptors and the FTO gene, the evidence is practically null. One experimental study investigated maternal obesity and its effect on low birth weight in pigs due to placenta alterations. This study demonstrated a downregulation of the FFA4 protein expression and FTO gene in low birth weight placentas, suggesting an essential role of both markers in impaired fetal growth associated with maternal obesity [87].

Investigating the modulation of the FFA receptors in obesity is still recent, as depicted in Table 2. The synthetic activation of FFA1 led to a reduction of food intake and body weight via GLP-1 secretion, or via the afferent vagal nerve, suggesting that the peripheral activation of this receptor can modulate the central responses related to appetite control [88,89] Nonetheless, in a mouse model of obesity and diabetes, the DHA-treated mice displayed a FFA1-dependent cognitive recovery, yet DHA failed to reduce the body weight gain [52].

Regarding the obesity-related hypothalamic alterations, the FFA1 receptor has been scarcely investigated, all the same, it is possible to suggest some mechanisms of action (Figs. 2 and 3). The synthetic central activation of FFA1 reduced the body weight gain and increased the POMC mRNA expression in obese mice [50]. In spite of this previous report, the FFA1 receptor's role in the CNS has been mostly investigated in other situations, such as pain, depression, and other behavioral impairments [47,49,52,90]. Markedly, hypothalamic FFA1 signaling inhibits the chronic inflammatory pain via the β-endorphin release from the POMC-neurons [90]. Intriguingly, the pharmacological combination of bupropion and naltrexone is based on their ability to modulate the POMC-neurons and the β-endorphin secretion, leading to a reduced food intake [91]. As for addiction behaviors, the combination of bupropion and naltrexone modulated the addictive behavior of high fructose corn syrup in self-administering rats. Notwithstanding, the authors have postulated that the result could not be attributed to motor activity alterations or high fructose corn syrup palatability. Still, the results support the use of this combination in obesity management. Explicitly, the combination of both drugs lead to a D_2R, POMC, and BDNF mRNA overexpression [92]. Furthermore, a case-control clinical study in binge eating disorders demonstrated that the combination of bupropion and naltrexone decreased binge eating, the craving for carbohydrates, grazing, and it diminished food addiction [93]. Similarly, it was previously demonstrated that β-endorphin knockout mice displayed an increased body weight gain when receiving a cafeteria diet [94]. On the other hand, a previous report showed that exogenous β-endorphin could antagonize α-MSH, promoting a food intake [95].

The activation of the FFA4 receptors leads to an incretin secretion, and this represents an attractive strategy for the treatment of obesity. As seen in Table 2, the modulation of incretins in experimental models leads to FFA4 activation and appetite control. Noteworthy, PUFA-enriched diets lead to lower ghrelin levels and higher CCK levels, accompanied by lower hunger ratings, suggesting that the FFA receptors might be involved in appetite-suppressing forces [96]. Previous studies have also demonstrated that flaxseed oil-enriched diets decreased body weight gain and food intake, accompanied by an inhibition of low-grade inflammation that is associated with obesity [59,60,97]. When considering all this information, it is reasonable to propose that the FFA4 agonists might not be used solely, but as adjuvants, in the treatment of obesity.

Table 1
FDA-approved medications for obesity management.

Active principle	Trade name	Pathway	Outcome	Reference
Phentermine	Adipex-P®	POMC-neuron activation	↓Appetite	[148]
Lorcaserin	Belviq®	Selective 5-HT_{2C} agonist	↓Appetite	[149]
Phentermine + Topiramate	Qsymia®	Synergism between the POMC-neurons and the GABA-A receptors	↓Appetite	[150]
Naltrexone + Bupropion	Contrave®	POMC-neurons activation, ↑noradrenaline, ↑dopamine, and ↓β-endorphin	↓Hunger	[151]
Orlistat	Xenical®	through gastric- and pancreatic- lipase inhibition	↓Dietary fat absorption	[152]
Liraglutide	Saxenda®	GLP-1 agonist	↓Appetite	[153]

Table 2
Effects of the FFA1 and FFA4 receptors on obesity.

Receptor	Treatment scheme	Function	Species	Experimental model	Outcomes	Mechanism(s) of action	Reference
FFA1	AgoPAM (Cmpd A; 30 mg/kg, orally)	Synthetic agonist	Mice	Diet-induced obesity (DIO)	↓ Food intake ↓Body weight	GLP-1 secretion	[88]
FFA1	T-3601386 (1, 3, 10 mg/kg; orally)	Synthetic agonist	Rats	DIO	↓Food intake	Afferent vagal nerve stimulation	[89]
FFA1	DHA (10 ng/μl, i.c.v.)	Endogenous agonist	Mice	Obesity and diabetes	↑Cognition ≈ Body weight	FFA1 activation	[52]
FFA4	ALA (100 nmol/g, into gastro)	Endogenous agonist	Mice	Not applicable	CCK secretion	FFA4 activation	[66]
FFA1/ FFA4	Not applicable	Not applicable	Rats	DIO and Diet-induced obesity resistant (DR)	Hyperphagia	↑ FFA1 expression ↑FFA4 expression ↓ CCK, PYY, and GLP-1	[154]
FFA4	ALA (2 Perilla oil capsules, twice a day)	Endogenous agonist	Humans	Obesity	≈ Body weight	↓IL-6 and ↓TNF	[97]
FFA4	GW9508	Synthetic partial agonist	Mice	Cold-induced browning	Browning of the adipose tissue	↑UCP-1, ↑PGC-1α, ↑PRDM16	[57]
FFA4	Omega-3	Endogenous agonist	Mice	DIO	↓Body weight and adiposity ↓Food intake	↓Hypothalamic inflammation ↑POMC and ↑CART expression	[60]
FFA4	TUG1197 (1 mM; i.c.v; twice a day for 6 days)	Synthetic agonist	Mice	DIO	≈ Body weight ≈ Caloric intake	↓Hypothalamic inflammation	[50]
FFA1	TUG 905 (1 mM, i.c.v.; twice a day for 6 days)	Synthetic agonist	Mice	Obesity	↓Body weight	↑POMC mRNA expression	
FFA1/ FFA4	GW9508 (1 mM; i.c.v; twice a day for 6 days)	Synthetic partial agonist	Mice	DIO	↓Energy efficiency ↑Food intake	↓Hypothalamic inflammation	
FFA4	GPR120 III (acutely 0.1 and 1 μM i.c.v.; repeated 0.1 μM, i.c.v.)	Synthetic agonist	Mice	DIO	Acutely: ↓Food intake Repeated treatment: ≈Food intake ≈Body weight	FFA4 acute activation	[69]

AgoPAMs: Agonist capable of acting as a positive allosteric modulator; ALA: α-linolenic acid; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; FFA1: free fatty acid receptor 1; FFA4: free fatty acid receptor 4

Remarkably, one of the most important mechanisms of the FFA4 receptors regarding obesity management is the ability to promote browning of the adipose tissue [57]. Moreover, a fish oil-enriched diet that was associated with a high-fat diet resulted in an increased body temperature and lean body mass, leading to the decreased food intake and fat mass loss [98]. These effect might depend on the upregulation of the thermogenesis mediators, such as UCP-1, PGC1α, and β3-AR, as well as the IL-6 and TNF gene expression downregulation [99]. When considering the data mentioned above, the peripheral effects of the FFA4 receptor might modulate food intake, consequently affecting body weight. In spite of that, these actions seem to occur through the anti-inflammatory pathways and the non-shivering thermogenesis mechanisms. One can presume that these anti-inflammatory and browning effects can synergize with an incretin secretion, followed by vagal afferent nerve stimulation, with the subsequent activation of the hypothalamic anorexigenic neurons.

When regarding the brain FFA4 receptors in obesity, the data is somewhat scarce (Table 2). Emphatically, Cintra et al. demonstrated that the dietary omega-3 fatty acids, as well as the omega-3 i.c.v treatment, rescued obesity-associated neuroinflammation, accompanied by body weight and food intake reductions [60]. Most importantly, another study demonstrated that the FFA4 receptors are expressed in the hypothalamic microglia of mice [50]. Worthy of attention, microglia participates in appetite control. Obese animals when submitted to high-fat diets display microglial activation, suggesting that this is a consequence of overeating, not a mechanism of action of obesity pathophysiology [100]. Further, microglia ablation leads to a decreased food intake and body weight, regardless of the sickness response. In the absence of microglia, the POMC-expressing neurons induce hyperactivation of the paraventricular thalamus after the feeding stimulus, followed by food intake suppression. This anorexigenic circuitry also modulates the neurons that are present in the arcuate nucleus of the hypothalamus, reducing leptin signaling and the POMC-neurons, while increasing the density of the AgRP and NPY neurons [101]. Uniquely, the FFA4 receptor upregulation in microglia seems to be tied to inflammation, which was observed in the microglia of mice that were submitted to focal ischemic brain injury. This same study demonstrated that the omega-3 fatty acids prevented brain injury by blocking the inflammatory processes via the FFA4/β-arrestin-2 process, followed by the inhibition of apoptosis via the neuronal PI3K/AKT singling pathway [102]. Due to the above-mentioned evidence, this FFA4 central modulation can be an interesting target for obesity modulation, when related to neuroinflammation (Figs. 2 and 3).

4.2. Cancer cachexia

Cancer cachexia is considered a paraneoplastic syndrome, which negatively impacts the energy balance, the skeletal muscle, and the fat tissue, inducing a significant weight loss. Due to this, cachexia strongly impairs the quality of life and the responsiveness to treatment, leading to increased mortality [6]. Moreover, cachectic patients display sickness behavior and anorexia, enhancing their critical state [103]. It is estimated that 50–80% of cancer patients develop cachexia, and up to 20% of cancer deaths are related to the syndrome [7].

Cancer-related cachexia is triggered by the interaction between the cancer cells and the host, characterizing a high inflammatory state [104]. Pro-inflammatory cytokines and other molecules are secreted by this interaction and they promote responses in different parts of the organism [105]. Under normal conditions, body weight loss would activate the AgRP-neurons, consequently inducing the food intake [2]. In cachexia, the pro-inflammatory cytokines inhibit this mechanism through POMC-neurons activation, leading to a reduced food intake and an increased energy expenditure [106].

Serotonin also seems to be an essential neuroendocrine factor in cachexia. Hypothalamic inflammation elevates the serotonin levels, which subsequently activate the POMC-anorectic pathways and inhibit the NPY secretion [107]. In two animal models of cachexia, the brain serotonin levels differed according to their food intake. This was while the C26-mice displayed and maintained the food intake, with decreased brain serotonin levels. The LLC-mice presented a marked reduction of

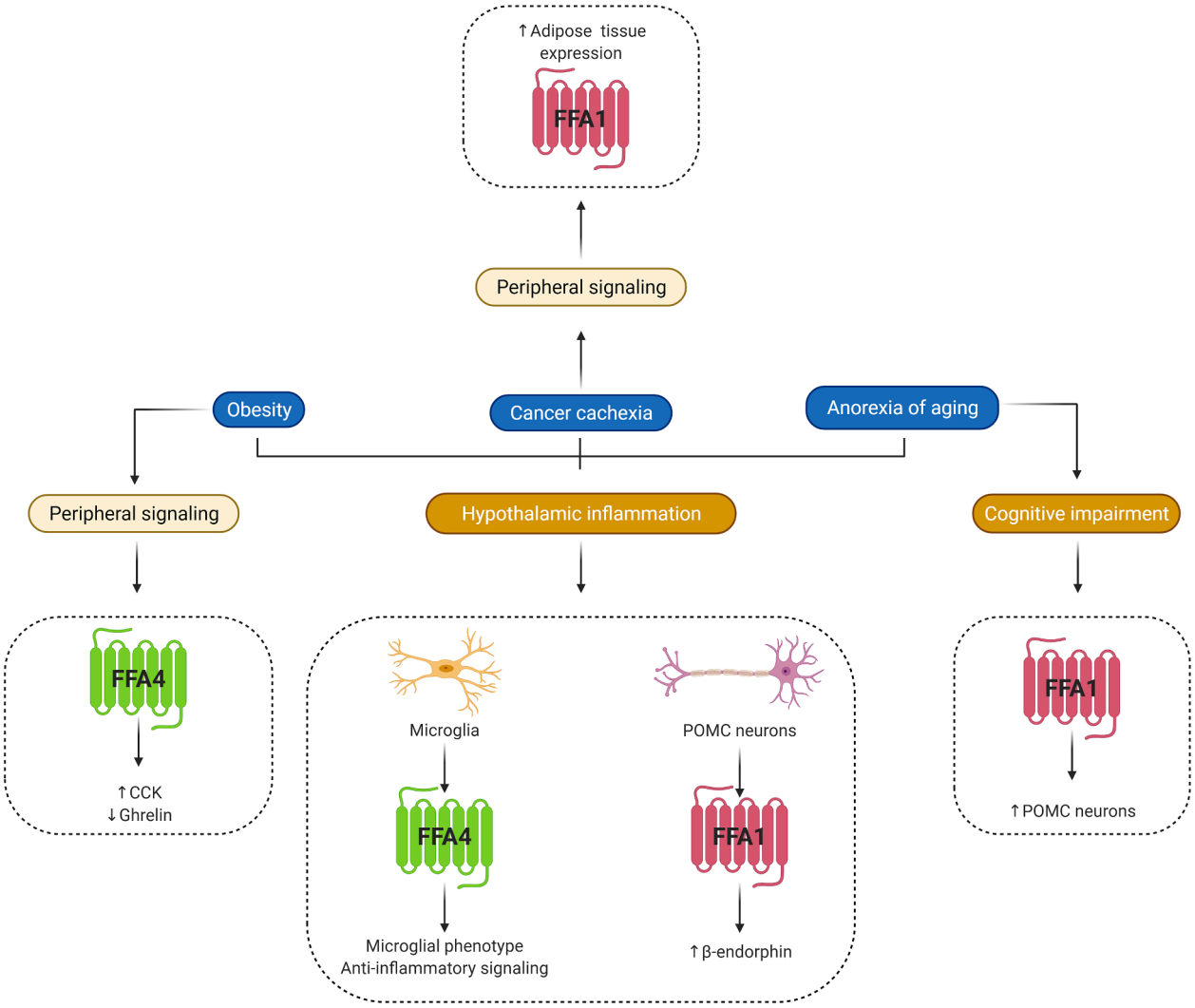

Fig. 2. The role of the FFA receptors in appetite-related disorders. Obesity, cancer cachexia, and anorexia of aging share hypothalamic inflammation as a common pathophysiological mechanism. In the hypothalamus, the FFA4 receptors are expressed in the microglia and through their activation, exert anti-inflammatory actions and might modulate the microglia phenotype. The FFA1 receptor is expressed in the POMC-neurons and when activated, stimulates the release of β-endorphin, which can modulate the appetite sensation. However, both receptors have peripheral signaling roles in obesity and cancer cachexia, by modulating the incretin signaling and the adipose tissue. Furthermore, in the anorexia of aging, the cognitive impairment is intimately related to appetite loss, and the activation of the FFA1 receptor induces neurogenesis and cognitive repair. Created with BioRender.com.

food intake, accompanied by high levels of serotonin [108]. In a clinical study, the cachectic patients presented decreased levels of circulating tryptophan. Regardless, anorexia was not evaluated in these patients [109]. Of note, Molfino et al. strongly suggested that the hypothalamic serotonin levels contributed to the catabolic outcomes of cancer cachexia [110]. The role of serotonin in cancer cachexia remains unraveled and this might be the link for sickness behavior that is associated with cachexia.

Microglial activation might play an active role in cachexia-anorexia. The adaptor protein, TIR-domain-containing adaptor inducing interferon-β (TRIF), is an essential signaling molecule that is involved in the Toll-like receptor activating pathways, and it is crucial for microglia function in disease states [111]. Previous research has demonstrated that TRIF is important for sickness behavior and cancer cachexia development, with the absence of this signaling molecule when attenuated with cancer cachexia [112]. Additionally, another study demonstrated that microglial ablation exacerbated the cachectic effects [113]. Furthermore, the PBN neurons expressing CGRP display a pivotal role in cancer-associated anorexia. In an LLC-cachexia model, the inhibition of this specific set of neurons led to appetite and sickness behavior improvements [114].

Nowadays, it is well established that the management of cancer cachexia must rely on a multitargeted approach [115]. The guidelines of the American Society of Clinical Oncology (ASCO) for the management of cancer cachexia recommend dietary interventions. Notwithstanding, there is no specific pharmacological intervention that is considered as standard, highlighting that there is no FDA-approved drug for cancer cachexia [116]. As for pharmacological recommendations, megestrol acetate is the most frequent pharmacological alternative for cachexia. Even so, this drug only stimulates the appetite, unaltering the systemic inflammation, and thus, not impeding the other cachexia-associated complications [117]. Regarding the multitargeted strategies in cachexia, MENAC (Multimodal Intervention for Cachexia in Advanced Cancer Patients Undergoing Chemotherapy) is a phase III randomized controlled trial (NCT02330926) that is under development, aiming to prevent cachexia progress, by combining oral nutritional supplements, ibuprofen, and exercise during an anti-cancer therapy in pancreatic and lung cancer patients [118]. Essentially, cancer cachexia remains an unmet medical need mainly due to its plurality of clinical characteristics, and its treatment requires further research, discussion, and novel

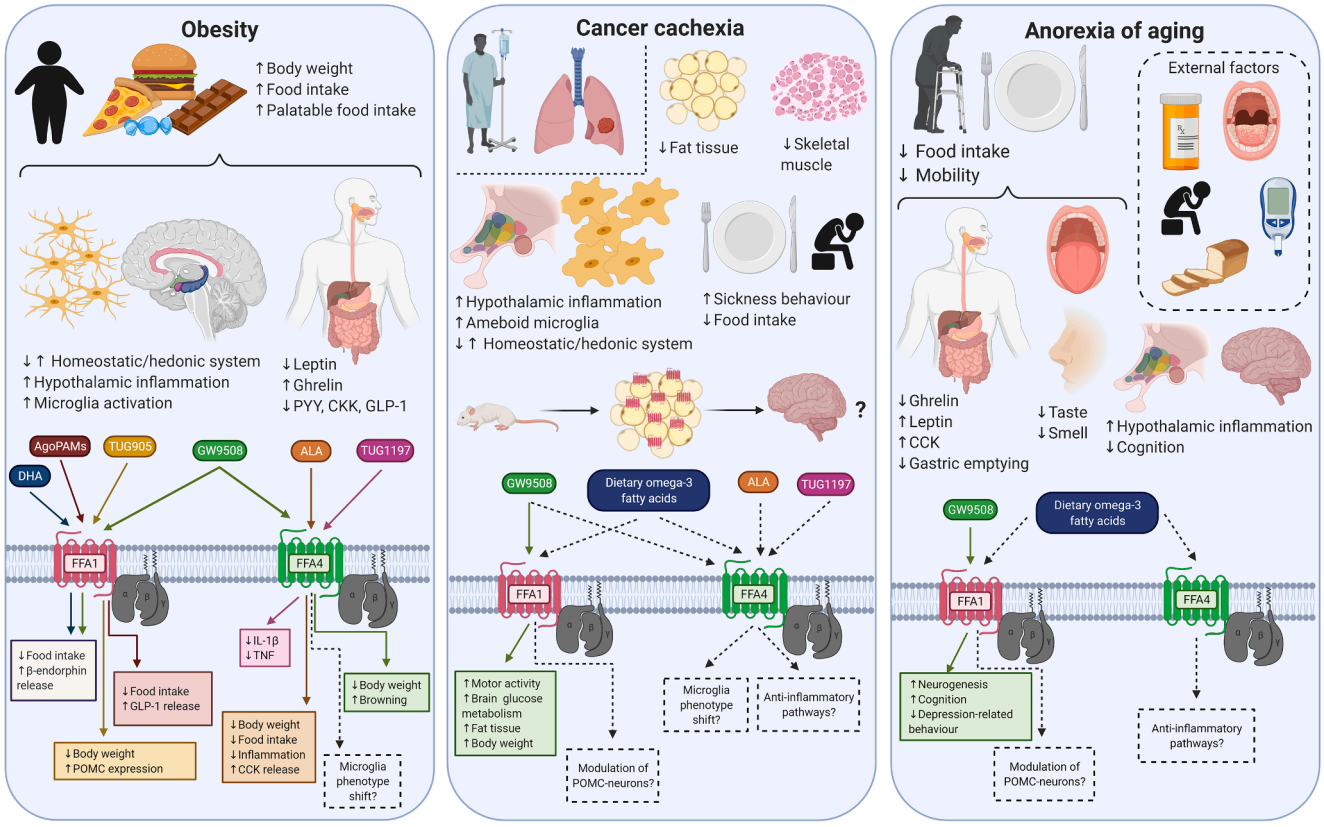

Fig. 3. The known and possible mechanisms of the FFA receptors activation in obesity, cancer cachexia, and the anorexia of aging. Obesity is a consequence of an unbalance between the energy intake and the energy expenditure, leading to an unstable homeostatic and hedonic system, hypothalamic inflammation, and microglia activation. Peripherally, the release of leptin, PYY, CKK, and GLP-1 is impaired, and the ghrelin release is augmented. The activation of the FFA1 receptors by synthetic and endogenous ligands demonstrated a diminished food intake and a body weight decrease, through the upregulation of the POMC-neurons, the activation of the anti-inflammatory pathways, the incretin secretion, the browning of the adipose tissue, and this could be the through microglia phenotype shift. Cachectic cancer patients display fat and skeletal muscle loss, hypothalamic inflammation, ameboid microglia morphology, and unbalanced hedonic and homeostatic systems, leading to an impaired quality of life, increased sickness behavior, and anorexia. The FFA1 receptor is upregulated in cachectic mice's adipose tissue, but this effect on the CNS is unknown. The activation of FFA1 using the synthetic agonist GW9508 leads to decreased cachexia-related outcomes. However, the FFA receptors' central effects in cachexia are still unknown and can be beneficial through the POMC-neurons and microglia phenotype modulation. The elderly population can suffer from the anorexia of aging, a multifactorial condition related to polypharmacy, depression, comorbidities, poor dentition, and poor nutrition. The development of anorexia of aging is related to impaired gastric emptying and the decreased ability to taste and smell. Furthermore, this population can display hypothalamic inflammation and impaired cognition. The activation of the FFA1 receptors concerning neurogenesis and cognitive repair can benefit anorexic people; however, by activating both of the FFA receptors in the anorexia of aging is still unknown but can be beneficial through similar mechanisms that are suggested in cancer cachexia management. AgoPAMs: Agonist capable of acting as a positive allosteric modulator, a synthetic full FFA1 agonist; ALA: α-linolenic acid, an endogenous ligand; DHA: Docosahexaenoic acid, an endogenous ligand; EPA: Eicosapentaenoic acid, an endogenous ligand; TUG905: 3-{2-fluoro-4-[({3-[4-(3-methanesulfonylpropoxy)-2-methylphenyl]phenyl}methyl)amino]phenyl}propanoic acid, a benzylamine selective FFA1 agonist; GW9508: 3-(4-{[(3-phenoxyphenyl)methyl]amino}phenyl) propanoic acid, a partial FFA1 agonist; TUG1197: 2-(3-fluoro-5-pyridin-2-yloxyphenyl)-3H-1,2-benzothiazole 1,1-dioxide, a selective FFA4 agonist; FFA1: free fatty acid receptor 1; FFA4: free fatty acid receptor 4. Created with BioRender.com.

strategies.

The omega-3 fatty acids display protective effects in cancer-associated complications and they are usually employed as anti-cachectic agents; however, the mechanisms involved are still not fully known [119]. A recent review discussed the known evidence regarding the omega-3 fatty acids in cachexia treatment, concluding that the effects of these molecules go beyond their anti-inflammatory properties [120]. All the same, given that omega-3 fatty acids are endogenous ligands of the FFA receptors and their link to cancer cachexia has not yet been investigated, looking into their role in this syndrome seems to be an attractive alternative.

It is widely known that the FFA receptors are important players in metabolic diseases. Given that cancer cachexia is considered as a chronic metabolic disease, why are the FFA receptors not considered as pharmacological targets for this condition? The FFA1 and FFA4 receptors are expressed in tissues that are involved in cachexia, such as in the adipose tissue, skeletal muscle, brain, and bones [47,56,59,121]. Particularly, a recent study from the current research group demonstrated that the FFA1 receptor is involved in cancer cachexia. This conclusion was based on the enhanced FFA1 immunopositivity in the adipose tissue of cachectic mice. The repeated systemic treatment with GW9508, a synthetic FFA1 partial agonist, also improved several cachexia-related outcomes, such as locomotor activity, adipose tissue loss, splenomegaly, and abnormal brain glucose metabolism. Nonetheless, the study did not evaluate food consumption, which remains to be investigated [122]. Since this review has aimed at discussing appetite modulation, the reviewers will focus on how these receptors could modulate cancer cachexia-anorexia.

Obesity and cachexia display mechanistic similarities, despite their phenotypical differences. An obese individual presents low-grade inflammation, while a cachectic patient has a higher inflammatory rate. Both of these conditions develop hypothalamic inflammation, a hallmark for appetite disruption [123,124]. There are a few studies that can help to suggest possible central FFA1/FFA4-related mechanisms for

cancer cachexia (Table 3, and Figs. 2 and 3). Of particular interest, the role of microglia in metabolic conditions has been recently explored. Microglia activation or ablation can either induce or inhibit the food intake, suggesting that the role of these cells in appetite modulation is complex [100]. Principally, activated microglia can present different phenotypes, like M1, the pro-inflammatory phenotype, and M2, the anti-inflammatory and pro-resolution phenotype [125]. Mouse hypothalamic microglia express the FFA4 receptors, which after stimulation by a synthetic agonist, or the dietary omega-3 fatty acids, can trigger anti-inflammatory responses via the FFA4/β-arrestin-2 pathway [50,60]. It is still unknown if the activation of microglial FFA4 can change the microglia phenotype, or whether the pro-inflammatory, or the anti-inflammatory microglia phenotypes participate in cancer cachexia. As for the FFA1 receptor, the hypothalamic microglia participation is unknown, probably due to the absence of this receptor in these cells [50]. The FFA1 receptor is mainly expressed in the hypothalamic POMC-expressing neurons and it is related to other mechanisms that might not involve the glial cells directly. Having said that, in a spinal nerve ligation-induced neuropathic pain model, FFA1 was detected in the microglia and astrocytes of the spinal cord of rats [126], suggesting that the astrocytic FFA1 expression might be induced by pathological stimuli.

As already discussed in this review, the FFA1 receptors are expressed in the POMC-neurons of mice, and in pain models, these neurons through the FFA1 activation, secrete β-endorphin [90]. The neural process of hunger and pain converge in the PBN, and activities of the hunger-associated hypothalamic AgRP-neurons reduce the pain responses in the PBN through NPY signaling. This mechanism has demonstrated that those mice in pain had a reduced food intake, while the fasting mice displayed less pain, during the behavioral assessments [127]. This mechanism is linked to an evolutionary matter, so hungry animals feel less pain to survive. Regardless of that, how could FFA1 modulate anorexia? Going in a different direction, maybe the blockage of this receptor can modulate the AgRP-neurons and increase the appetite by inhibiting the POMC-neurons. Anyway, what probably matters regarding cancer anorexia management through the FFA1 is not merely activating or blocking the receptor, but how this receptor responds to the disease.

As depicted in Table 3, the FFA4 receptor is expressed in the gonadotrophs of 24-h fasting mice [68]. Despite the relationship between the gonadotropins and fasting, there is no evidence linking this hormone to cancer anorexia. Furthermore, the central activation of FFA4 induced the anxiolytic effects, which are likely dependent on the modulation of the anti-inflammatory pathways or the microglia activation, although the authors did not evaluate the further mechanisms [69]. In the light of abovementioned evidence, both the FFA1 and FFA4 receptors might well be essential players in cancer-cachexia management, mainly by modulating the central mechanisms that are involved in this syndrome, which lead to the anorexia and sickness behavior.

4.3. Aging-associated anorexia

Aging is defined as a plethora of physiological alterations that occur in an organism through adult life, leading to function impairment and increased vulnerability; consequently, decreasing the survival (Fig. 3) [128]. According to the WHO, the global life expectancy in 2016 was 72 years. Provocatively, global average life expectancy increased by 5.5 years between 2000 and 2016, demonstrating the fastest growth since 1960 [129]. A significant syndrome that affects the elderly is the anorexia of aging. This condition is defined as a multifactorial syndrome that can lead to malnutrition, sarcopenia, reduced physical performance, slow gait speed, impaired mobility, and a poor quality of life [130]. Conversely, all of these effects might to be considered the causes of anorexia aging development, and not the consequences. Despite several medications that have been tested to stimulate the appetite in older individuals, none of them are usually employed in clinical practice. Aging-associated anorexia seems to respond better to non-pharmacological and multi-professional approaches, such as nutritional therapy, physical therapy, psychotherapy, and maintaining and reinforcing the social and family support [131].

Aging induces several alterations that are associated with the patterns of peptide release, resulting in an impaired antral stretch and acid secretion, accompanied by delayed gastric emptying [132]. The release of peptides, such as CCK, leptin, and ghrelin, is altered in older individuals, prolonging satiety [133,134]. Older individuals can also display alterations in smell and taste, impairing the food intake; consequently, the nutritional status [12]. Moreover, similar to the metabolic diseases, aging can lead to an inflammatory state, inducing hypothalamic inflammation, and with an unbalance of the melanocortin system [13]. A testosterone decline is directly linked to the anorexia of aging. The reduction of this hormone is associated with higher leptin levels and reduced ghrelin levels, with an unbalanced AgRP/CART-neurons signaling [135]. The anorectic state of the elderly population is also affected by external factors that are not related to the appetite-associated molecular pathways. This population can display depression, loneliness, and/or poor cooking skills [136]. Additionally, polypharmacy, multimorbidity, poor dentition, poor cognition, and low food variability also impact on this particular population (Fig. 3) [137].

Aging-related anorexia is associated with cognitive decline and other aging-associated diseases [12]. Importantly, DHA is a major component of grey matter, decreasing its quantity through life [138,139]. Moreover, brain DHA in Alzheimer's patients is even lower [140]. In preclinical studies of Alzheimer's disease, the activation of the FFA1 receptor by GW9508 has been beneficial for cognitive impairment that is associated with this disease [141]. In the clinical scenario, elderly patients with a low intake of the omega-3 fatty acids have displayed enhanced cognition when receiving an omega-3 fatty acid supplementation [142]. Furthermore, an observational study that followed 2612 multi-ethnic older women and men throughout an average of 4.5 years observed that those with a higher intake of dietary EPA and DHA

Table 3
Probable mechanisms of the FFA1 and FFA4 receptors in cancer cachexia.

Experimental model	Treatment scheme	Function	Outcomes	Hypothetical mechanisms of action	References
LLC-induced cachexia mouse model	GW9508 (8 mg/kg, s.c.; every other day)	Synthetic partial agonist	↑Locomotor activity ↑Adipose tissue ↑Brain glucose uptake ↑FFA1 upregulation	Central and/or peripheral FFA1 activation	[122]
Pancreatic cancer cachexia mouse model	Not applicable	Not applicable	Microgliosis Ameboid microglia	Microglia expresses FFA4; modulation of this receptor could modulate these effects	[113]
Pain mouse model induced by CFA	DHA (50 mg/mouse, i.c.v.) GW9508 (1.0– 25 mg/mouse, i.c.v.)	Endogenous agonist and partial synthetic agonist	FFA1-induced analgesia through β-endorphin release	Central FFA1 activation	[90]
24-h fasting (mice)	Not applicable	Not applicable	↑FFA circulating levels	↑FFA4 expression in gonadotrophs	[68]

DHA: Docosahexaenoic acid; FFA1: free fatty acid receptor 1; FFA4: free fatty acid receptor 4.

presented a lower risk of developing Alzheimer's disease [143].

Aging is associated with impaired neurogenesis, which could also harm the appetite balance. As for the role of the FFA receptors in this process, the activation of the FFA1 receptor, through omega-3 fatty acid sensing, can induce the neurogenesis associated with the BDNF expression (Figs. 2 and 3) [53]. More recently, Engel et al. demonstrated that an FFA1 activation induces neurogenesis through the BDNF and p38 pathways; however, through the i.c.v. administration of synthetic ligands [144]. Compellingly, it has been demonstrated that plasma BDNF is a biomarker for brain DHA enrichment [145]. All of the evidence mentioned above suggests that BDNF, the omega-3 fatty acids, and the FFA receptors are linked in neurological functions.

Regarding the FFA4 receptor, there is no evidence connecting this receptor to cognitive functions or impairments, which could lead to modulation of the appetite in the elderly population. Notably, in a subarachnoid hemorrhage model in rats, the omega-3 fatty acids rescued the inflammatory parameters through the FFA4/β-arrestin-2 pathway [146]. In any case, the analysis of expression and the activation of the FFA4 receptor was performed by using the whole brain, and the authors did not discriminate the brain regions. As already discussed in the previous sections of this review, the FFA4 receptor might play a role in appetite control by the modulation of neuroinflammation, what might indicate a relevant role for this receptor in aging-related brain complications (Fig. 2).

5. Conclusion

The use of the omega-3 fatty acids has only now being accepted in the medical community as a pharmacological asset [147]. The FFA1 and FFA4 receptors are endogenous pharmacological targets for the omega-3 fatty acids and when activated, they exert beneficial effects. Since their discovery, an expressive number of synthetic ligands have been in development to treat the metabolic diseases, such as obesity and diabetes. Unfortunately, none of these molecules have reached the clinical setting. Clinically, the only way to modulate these receptors is through an omega-3 supplementation, but the dosage required for this purpose is still unknown. Due to the increase of life expectancy, the ability to learn how to manage conditions, such as cancer cachexia and anorexia of aging, are essential. Both syndromes are metabolically similar to diabetes and obesity; after everything, the role of the FFA receptors in these conditions remains unknown. When considering that this family of receptors is slightly young in pharmacology, and that the idea of pharmaconutrition is even more recent, the study of the FFA1 and FFA4 receptors is crucial for understanding the precise role of these receptors in health and disease. The potential effects of the FFA1 and FFA4 ligands in the management of appetite alterations are depicted in Fig. 3. When contemplating the low adverse effects of an omega-3 fatty acids intake, it is tempting to predict fewer collateral events for the FFA1 and FFA4 synthetic ligands, which represents an advantage for using these drugs in the clinical setting, for the management of appetite-related disorders. Be that as it may, each ligand must be evaluated for safety and pharmacokinetics, which might be a limitation, as was observed for Fasiglifam (TAK-875), an FFA1 agonist that was associated with drug-induced liver injury inherent to its chemical nature.

CRediT authorship contribution statement

Raquel D.S. Freitas: Writing - original draft, Writing - review & editing. **Maria M. Campos:** Writing - review & editing.

Declaration of Competing Interest

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

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