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Neuropeptide receptors as potential pharmacological targets for obesity

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ABSTRACT

Obesity is a chronic multifactorial disease, characterized by an excessive accumulation of adipose tissue. It is usually the result of excessive food intake and/or low energy expenditure. Obesity can be triggered by lifestyle, nutritional, genetic, environmental, hormonal and psychological factors. Several strategies are used to treat obesity, including dietary reeducation, with balanced food intake, increased physical exercise, in order to promote energy expenditure and to overcome the insufficiency in weight reduction by other strategies, and administration of drugs. However, these medications are associated to undesirable side effects, resulting in a high withdrawal rate. Several studies have been focused on the development of compounds that act in the hypothalamic region where the center of the regulation of hunger and satiety is located. Some of them target the activity of endogenous peptides, such as ghrelin pancreatic polypeptide, peptide YY and neuropeptide Y, as well as their receptors. This review addresses the importance of understanding the neuropeptide/peptide hormones and their receptors for the development of novel anti-obesity compounds that may aid in weight reduction as a promising alternative for the treatment of obesity.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine receptors; AgRP, agouti-related peptide; ARC, arcuate nucleus; BMI, body mass index; CART, cocaine and amphetamine-regulated transcript; CNS, central nervous system; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; GALP, galanin-like peptide; GLP-1, glucagon-like peptide-1; GPCRs, G-protein coupled receptors; LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; MCR, melanocortin receptors; NPY, neuropeptide Y; OX1, orexin 1; OX2, orexin 2; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PVN, paraventricular nucleus; PYY, Peptide YY; RYGB, Roux-en-Y gastric bypass; TAG, triacylglycerol; TM, transmembrane helices; TRH, thyrotropin-releasing hormone; VMH, ventromedial hypothalamus; α-MSH, melanocyte-stimulating hormones.

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1. Introduction

Obesity is a multifactorial disease that can be considered one of the major public health problems, due to its high prevalence worldwide, being characterized as a global pandemic (Ng et al., 2014; Popkin et al., 2012; Swinburn et al., 2011). Obesity is characterized by excessive weight and abnormal or excessive fat accumulation, which can cause the development of several diseases (WHO, 2000), such as type 2 diabetes, insulin resistance, hypertension, cardiovascular diseases (Kopelman, 2000), hyperlipidemia, osteoarthritis, sleep apnea, non-alcoholic hepatic steatosis

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(Guh et al., 2009), and psychiatric disorders (Scott et al., 2008). In addition, there is strong evidence of increased cancer rates attributed to obesity (Wolin et al., 2010). Therefore, obesity can cause physical and psychological harm, leading to high morbidity and mortality rates (Bray & Tartaglia, 2000; Kissbah & Krakower, 1994; Padwal et al., 2003; Rexrode et al., 1997; Rimm et al., 1995; Visscher et al., 2001).

One of the main methods used to assess nutritional status is the body mass index (BMI), which divides the body weight (kg) by the square of the height (m^2) (WHO, 2000). This parameter may be used to rank adults as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–25 kg/m^2), overweight (BMI 25–30 kg/m^2), class I obesity (BMI 30–35 kg/m^2), class II obesity (BMI 35–40 kg/m^2) and class III obesity (BMI ≥ 40 kg/m^2) (WHO, 2000). However, when used alone, BMI yields an inaccurate analysis, mainly due to the inability to distinguish lean mass and disposition of body fat. The association with other nutritional parameters, such as waist circumference, waist hip ratio (WHR), skinfold measurements and, more recently, bioimpedance, ensures a higher effectiveness in the diagnosis of the health status of those patients (Cieślińska-Swider, 2015; Shulman, 2000).

Other very important aspects correlated with obesity are the sensorial characteristics, such as taste, sight and smell, which are conditioning the decision of preference or rejection of a given food or drink. It is known that foods with a high fat and sugar content present a greater palatability and, consequently, a higher preference for consumption, which is directly correlated with the weight gain (Mccrickerd & Forde, 2016; Mela, 2006; Sorensen et al., 2003). These factors have contributed substantially to the increasing incidence of obesity around the world. Satiety can be characterized by the satisfactory state and feeling of well-being after food intake, thereby reducing the consumption of food. However, hunger or the desire to eat may be characterized by a sensory response, which results in appetite (Blundell, 1991), generating food intake (Harrold et al., 2012). The hypothalamus is considered one of the main regulators of long-term energy balance and food intake, interfering with the increase or reduction of weight (Berthoud et al., 2017).

Other aspects, such as the imbalance of physiological mechanisms, may be inherently associated with increased weight and, consequently, obesity (Narayanaswami & Dwoskin, 2017) (Fig. 1). As an example, individuals who have a variant in the obesity FTO gene exhibit shorter post-prandial satisfaction and increased consumption of food, when compared to non-carriers of this gene variant (Fenwick et al., 2018). Other genetic factors also have a considerable influence on the etiology of obesity. Variation in the DNA sequence, specifically in a single gene, can lead to monogenic Prader-Willi syndrome (PWS), Bardet-Biedl syndrome, Alström syndrome, Albright hereditary osteodystrophy (AHO) or non-syndromic monogenic obesity, which includes inactivation or deficiency in transcription of leptin (LEP), leptin receptor (LEPR), neurotrophic type 2 receptor tyrosine kinase (NTRK2), pro-opiomelanocortin (POMC) or melanocortin receptor-4 (MC4R), resulting in hyperphagia and consequent extreme obesity (Pigeyre et al., 2016). However, polygenic obesity is the most usual form of this condition, being interconnected with environmental, cultural, social, economic and biological factors (Qasim et al., 2018).

In addition, another perspective influenced by weight increase is a reduction in the production of short chain fatty acids (SCFA), caused by intestinal dysbiosis. Intestinal dysbiosis consists of the unbalance of the composition of the intestinal microbiota, as well as the imbalance of its function (Llorente & Schnabl, 2015). These molecules have the ability to interact with G-protein coupled receptors (GPCRs), reducing the accumulation of body fat, insulin resistance in muscle and liver, in addition to prolonging satiety (Boulangé et al., 2016).

In short, the array of diverse elements, including increased consumption of industrialized meals such as fast foods, which generally have exacerbated calorific value by being rich in saturated lipids and sugars, associated with sedentary lifestyles, leads to a positive energy balance and, consequently, to fat accumulation (Cecchini & Warin, 2016; Cieślińska-Swider, 2015). According to a report recently published by WHO (WHO, 2016), the incidence of obesity has tripled in the last four decades, accounting for 650 million obese people and 1.25 billion overweight. A projection from the Centers for Disease Control and Prevention (CDC) (2014) estimates that in 2050 the prevalence of obesity will be 60% and 40% in men and women, respectively.

The control of the balance between hunger and satiety is carried out mainly by the peripheral nervous system (PNS) and central nervous system (CNS), prioritizing the hypothalamus, but also includes the adipose tissue itself, gastrointestinal tract, pancreas, liver and other organs (Narayanaswami & Dwoskin, 2017). Signaling molecules or hormones (in the most generic sense of the term), several of them of peptide nature, are produced by these tissues and are responsible for the regulation of long-term energy homeostasis (Narayanaswami & Dwoskin, 2017). The necessary information can be transmitted to the hypothalamus through hormones released during the digestive process, resulting in satiety and restriction of appetite (Geliebter, 1988; Stanley et al., 2005).

Other very important aspects to be correlated with obesity are cognitive modifications (Preiss et al., 2013) and memory difficulties (Chunchai et al., 2018). Some studies have analyzed the association of brain white mass reduction with a high BMI, implying that hypercaloric feeding is correlated with cognitive changes and neurological disorders (Manchanda & Kaur, 2017). According Cifre et al. (Cifre et al., 2018), congenital deficiencies, difficulty in reasoning and memory limitations were observed in individuals with a high fat diet, leading to an increase in oxidative stress, consequently worsening neuronal apoptosis. Some mechanisms may be directly related to obesity and cognitive changes, such as intestinal-brain axis communication, evidencing the influence of excess adipose tissue and the development of neurodegenerative diseases (Anstey et al., 2011).

In general, satiety can be characterized by the satisfaction state and feeling of well-being after food intake, thereby reducing the consumption of food. Hunger, or the desire to eat, may be characterized by a sensory response, which results in appetite (Blundell, 1991), generating food intake (Harrold et al., 2012). The hypothalamus is considered as one of the main regulators of long-term energy balance and food intake, interfering with the increase or reduction of weight (Berthoud et al., 2017). This relationship between energy balance and food intake has been strongly related to the intestine, where some hormones such as cholecystokinin (CKK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and pancreatic polypeptide (PP) are secreted (Hellström, 2013; Perry & Wang, 2012), activating the neural centers and resulting in signs of satiety after food intake (Holzer et al., 2012; Hussain & Bloom, 2013). It is known that some parts of the brain emit peripheral signals, being related to energy homeostasis, and consequently to food intake (Goldstone et al., 2014). Energy homeostasis and the sensation of pleasure in food intake are directly correlated and can be activated through the remembrance of foods that cause pleasure, thus activating the complex of energy compensation in the brain (Goldstone et al., 2009; Morris & Dolan, 2001; Stice et al., 2013).

A complex system involving receptors, hormones and neuropeptides may stimulate satiety or hunger, with key involvement of arcuate nucleus neurons (ARC), which are located in the region of the third ventricle, including an extension of the hypothalamus (Steele et al., 2013). The detection of nutrients occurs in several central nervous system (CNS) areas, with different neuronal populations being considered as first regulators of energy homeostasis (Berthoud & Morrison, 2008; Stanley et al., 2005). Some of the satiety factors generated in the gut arrive at the CNS through communication between different neurons, which are received through the brainstem, by passive or active transport. Signals can be sent through the vagal afferent fibers, generating communication between neurons and peripheral regions (Chambers et al., 2013). These mechanisms, controlled by different neuroendocrine systems, have not yet been fully elucidated, but provide a promising pathway for the treatment and control of obesity and related diseases.

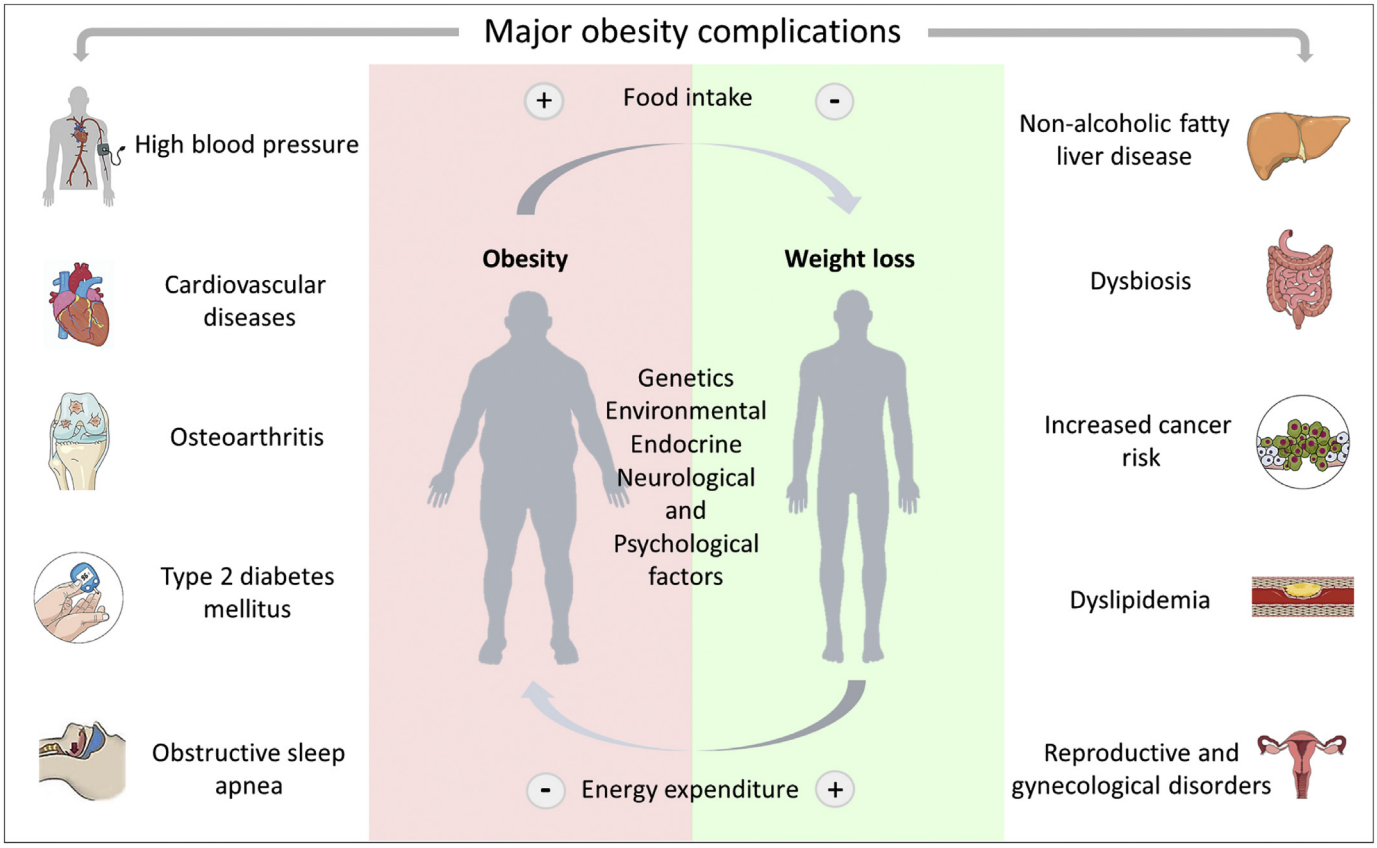

Fig. 1. Main internal and external factors that may lead to obesity. The imbalance between food intake and energy expenditure is the basis for excessive weight gain, triggering other diseases.

Strategies to combat obesity have been widely sought over the years, thus achieving lifestyle changes and weight loss of up to 10% in the first half of treatment, providing substantial reduction in the occurrence of the metabolic syndrome in obese individuals (Kushner, 2014). However, these measures are not always effective over a long period of treatment and may cause a recurrence of the previous weight. Other treatment strategies are commonly practiced, including cognitive-behavioral therapies (CBT), in order to aid in the improvement of eating behavior and self-control (Södersten et al., 2017), as well the use of drugs that may aid in weight reduction and bariatric surgeries.

In general, currently available treatments for obesity control include diets, physical exercise, anti-obesity drugs and surgical procedures, but they frequently do not provide the desired efficacy and fail to fulfill patient expectations (Glandt & Raz, 2011). Thus, it is necessary to develop new therapies to fight obesity. A growing number of studies have evidenced the importance of developing more potent agonists and antagonists bioinspired by neuroendocrine-related peptides, as a hope for more effective treatment with prolonged effects against obesity. In this review, we discuss neuropeptides and peptide hormones, along with their respective receptors involved in regulating appetite, as potential targets for developing new therapeutic alternatives for treating obesity and minimizing its complications. The approach proposed here differs from the studies already described, due to the specific questions regarding the development and applicability of bioinspired compounds that act towards neuropeptides, using them as potential anti-obesity drugs.

2. Neuroendocrine regulation of hunger and satiety

The relationship between satiety and food intake, as already pointed out, are two different aspects that are regulated by the CNS. Thus, other regions of CNS and peripheral tissues pass information to the hypothalamic centers, and thus regulate the organism's homeostasis (Berthoud & Morrison, 2008; Boughton & Murphy, 2013). Communication between the hormonal and neural systems and the nutrients present in the organism is established between several organs, such as liver, intestine and pancreas, as well as adipose tissue and brainstem, converging in the hypothalamus, which monitors energy/food intake and homeostasis (Fig. 2) (Hussain & Bloom, 2013).

The hypothalamus can be divided into several regions that participate in these pathways; namely, the arcuate and paraventricular nucleus (ARC and PVN, respectively), the lateral hypothalamic area (LHA) and the ventromedial and dorsomedial nuclei (VMH and DMH, respectively) (Boughton & Murphy, 2013). The ARC is the primary nutrient-sensing center within the hypothalamus, reacting for example to the intracellular concentration of ATP, then promoting a neuronal response according to the stimulus received (Banks, 2006; Blouet & Schwartz, 2010; Minokoshi et al., 2004; Mobbs et al., 2005). This region encompasses the two populations of neurons that are key to regulating food intake: satiety inducing neurons, called anorexigenic, which co-express proopiomelanocortin (POMC) and the cocaine and amphetamine-regulated transcript (CART), and the neurons inducing appetite, called orexigenic, which co-express the neuropeptide Y (NPY) and the agouti-related peptide (AgRP) (Berthoud & Morrison, 2008; Delgado et al., 2017; Hahn et al., 1998). The PVN region is highly important because it integrates signals from various regions of the CNS, as well as the hypothalamic-pituitary-thyroid axis, which is the main production region of the thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (Arora & Anubhuti, 2006; Fekete et al., 2000; Sawchenko & Swanson, 1983). The LHA region, previously classified as a feeding center, is one of the regions most susceptible to NPY and has a large number of neurons expressing orexins A and B (Bakos et al., 2016; Schwartz et al., 2000; Stanley et al., 1993). The VMN region is identified as a satiety center, so it is a primary target of leptin, the

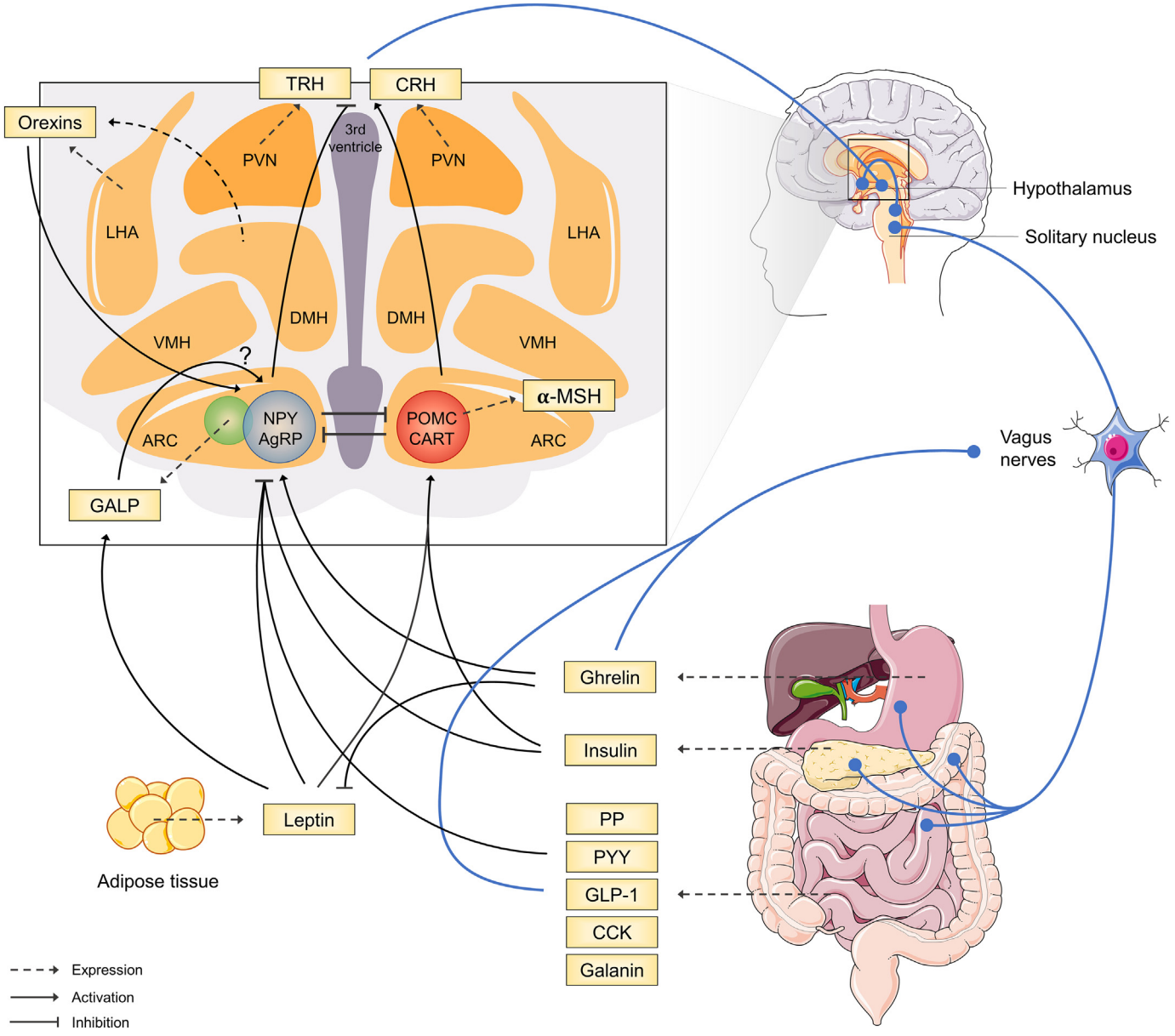

Fig. 2. Food intake and energy control signaling pathways. The hypothalamus is the main controller of these pathways, with different subunits participating by expression or being targeted by neuropeptides and peptide hormones involved. These subunits include the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventromedial hypothalamic nucleus (VMH), dorsomedial hypothalamic nucleus (DMH) and lateral hypothalamic area (LHA). Communication of solitary nucleus (SN) with hypothalamus is essential to translate the stimuli that are received from the gastrointestinal tract. ARC is responsible for food intake control, stimulating the orexigenic agouti-related peptide (AgRP) and neuropeptide Y (NPY) neurons, and consequently, stimulating appetite. Countering this effect are the proopiomelanocortin (POMC), through metabolization to α-melanocyte stimulating hormone (α-MSH), and cocaine and amphetamine-regulated transcript (CART) neurons, which have an anorexigenic effect (appetite suppressive action). When food intake occurs, signals of satiety are emitted and levels of leptin, insulin and glucagon-like peptide-1 (GLP-1) increase, inducing an anorexigenic activity. At the gastrointestinal tract level, pancreatic polypeptide (PP), peptide YY (PYY) and cholecystokinin (CCK) are the main responsible molecules that, through the vagus nerve, communicate these signals to the brain. Although, when leptin, insulin and GLP-1 levels decrease, orexigenic signals are stimulated, by releasing ghrelin (secreted in the stomach) and galanin (expressed in the gastrointestinal tract), which will thereby promote food intake and reduction of energy expenditure.

most important satiety related hormone, which down-regulates food intake (Arora & Anubhuti, 2006; Berthoud & Morrison, 2008; Burdyga et al., 2006; Schwartz et al., 2000). Communication of ARC with other hypothalamic regions is not unilateral. It can be controlled and regulated by the different signals received. These signals can be originated in the brainstem, which communicates through the solitary nucleus (SN) with the pituitary gland, which thus acts to control energy expenditure through the hypothalamus-pituitary-thyroid axis, the rhombencephalon, which receives endocrine signals, and the vagus nerve, connected to the gastrointestinal tract (Ricardo & Koh, 1978; Waterson & Horvath, 2015; Williams et al., 2001).

2.1. NPY/AgRP and POMC/CART neurons

Neurons are essential to maintain the body's energy homeostasis, not only because they express peptides and proteins in response to the stimulus received, but also because they are the "command center" of all information (Delgado et al., 2017). In obese individuals, neural progenitor cell (NPCs) proliferation and inhibition of neurogenesis are observed, showing the importance of this region in the maintenance of the energy balance (Sousa-Ferreira et al., 2014; Waterson & Horvath, 2015). As previously described, these neurons can be divided into anorexigenic and orexigenic (Waterson & Horvath, 2015). This

classification considers the neuropeptides they induce expression, signals that are promoted and their target pathways (Table 1).

Focusing on anorexigenic neurons, it has been shown that POMC and CART are co-expressed in the ARC (Vaisse et al., 2000; Vaisse et al., 1998). Melanocortin 3 and 4 receptors (MC3R and MC4R, respectively) are present mainly in the ARC, but are also expressed in the PVN and VMH regions. Both are essential for pathway activation, with related mutations being associated with obesity (Boughton & Murphy, 2013; Harrold et al., 1999; Valassi et al., 2008). The POMC protein is actually the precursor of melanocyte stimulating hormones (MSHs, also known as melanotropins), including α, β and γ forms, as well as other relevant peptides, namely adrenocorticotrophic hormone (ACTH, also known as corticotropin), β-endorphin, corticotropin-like intermediate peptide (CLIP), lipotropins (β and γ) and Met-enkephalin. Among all these signaling molecules, α-MSH is the actual promoter of anorexigenic neuron signaling (Arora & Anubhuti, 2006; Fekete et al., 2000). As for CART, which is co-expressed in 90% of POMC neurons in the ARC, it is also involved in sensory processing, stress and endocrine regulation (Arora & Anubhuti, 2006; Koylu et al., 1998).

In contrast, NPY/AgRP neurons are responsible for an orexigenic response, leading to peptide hormones and neuropeptides that promote food intake (Horvath et al., 1997; Stanley et al., 2005). NPY is the most potent orexigenic molecule, with 90% of neurons co-expressing AgRP. In addition to activating "starvation" pathways, both molecules act as inhibitors of anorexigenic neurons, promoting expression of γ-aminobutyric acid (GABA) and AgRP, by being an α-MSH receptor agonist (Roseberry et al., 2004; Waterson & Horvath, 2015). In the case of obesity, both NPY and AgRP are positively balanced, stimulating food intake (Stanley et al., 2005; Valassi et al., 2008).

In short, anorexigenic and orexigenic neurons are essential to control long-term energy balance and homeostasis of food intake at the hypothalamus level, promoting a specific stimulus according to those received from the body (Waterson & Horvath, 2015).

2.2. Hypothalamic peptides

The corticolimbic system integrates the amygdale, hippocampus and prefrontal cortices (Hussain & Bloom, 2013). The system provides body emotional and cognitive support (Kelley et al., 2005) and long-term energy homeostasis (Williams & Bindra, 2014). The corticolimbic system processes non-homeostatic factors, such as energy reward, mediated by the environment. Thus, the communication between the corticolimbic and hypothalamus systems directly integrates into the food intake, allowing environmental factors to coordinate energy homeostasis (Hussain & Bloom, 2013).

In the ARC, there is also the expression of galanin-like peptide (GALP), an orexigenic peptide homologous to galanin (Kageyama et al., 2005; Ohtaki et al., 1999). The prevailing hypothesis for its function is that GALP participates in the inhibition of POMC pathways, directly or indirectly promoting an effect on NPY/AgRP neurons (Boughton & Murphy, 2013; Lang et al., 2015). In addition, GALP is

Table 1
Peptides involved in the neuroendocrine response to food intake and satiety, classified according to their signaling effect.

Peptides	Function	Site of synthesis	Site of action	References
Anorexigenic				
POMC (cleaved to α-MSH, the active molecule)	Energy balance; Increase on O_2 consumption; Regulation of thyroid axis.	ARC	Hypothalamus (ARC, PVN, VMH)	(Schwartz et al., 2000) (Arora & Anubhuti, 2006)
CART	Energy homeostasis; Sensory processing; Stress and endocrine regulation.	ARC	Hypothalamus (ARC, PVN, VMH)	(Schwartz et al., 2000) (Stanley et al., 2005)
GLP-1	Glycemic homeostasis; Delay of gastric emptying; Reduction of orexigenic signaling (act in NPY/AgRP neurons).	L cells of small intestine	Communication through vagus nerve and solitary nucleus with hypothalamus	(Turton et al., 1996) (D'Alessio et al., 1995)
Insulin	Sensible to adiposity; Blood glucose regulation; Activate POMC/CART neurons; Inhibits NPY/AgRP neurons.	β-cells of pancreatic islets	Hypothalamus	(Schwartz et al., 1992) (Arora & Anubhuti, 2006)
Leptin	Sensible to energy stored in adipocytes; Control food intake; Inhibition of NPY/AgRP neurons; Activation of POMC/CART neurons.	Adipose tissue	Communication through vagus nerve with hypothalamus	(Zhang et al., 1994) (Schwartz et al., 1996) (Tolle et al., 2003)
PYY_{3-36}	Direct inhibition NPY/AgRP neurons; Energy homeostasis; Inhibition of gastrointestinal motility and pancreatic hormone release.	L cells of the gastrointestinal tract	Communication through vagus nerve and solitary nucleus with hypothalamus	(Larhammar, 1996) (Larsson et al., 1975)
PP	Inhibition gastric emptying; Gallbladder contraction; Prevention of intestinal secretions (water and electrolytes); Inhibition of gastrointestinal motility and pancreatic hormone release.	F-cells of pancreatic Langerhans islets; Exocrine pancreas; Distal gastrointestinal tract.	Communication through vagus nerve and solitary nucleus with hypothalamus	(Larhammar, 1996) (Tough et al., 2006) (Schwartz et al., 1978)
CCK	Reward, memory and anxiety behavior regulation; Food intake regulation by decrease of meal size.	Duodenal and ilium cells	Communication through vagus nerve and solitary nucleus with hypothalamus	(Schick et al., 1994) (West et al., 1984)
Orexigenic				
NPY	Activation of starvation pathways (food intake regulation); Inhibition of anorexigenic response; Promotion of GABA expression; Inhibition of sexual behavior.	ARC	Hypothalamus (ARC, PVN, VMH)	(Horvath et al., 1997) (Van den Top et al., 2004) (Roseberry et al., 2004)
AgRP	Activation of starvation pathways (food intake regulation); Inhibition of anorexigenic response (antagonist of melanocortin receptors).	ARC	Hypothalamus (ARC, PVN, VMH)	(Horvath et al., 1997) (van den Top et al., 2004) (Valassi et al., 2008)
GALP	Inhibition of POMC pathways; Participation on energy homeostasis (directly regulated by insulin and leptin).	ARC	Hypothalamus (ARC, PVN, VMH)	(Kageyama et al., 2005) (Ohtaki et al., 1999)
Galanin	Signaling hunger pathways (energy homeostasis); Physiological mechanisms (modulates insulin release); Depression, anxiety and neuropathic pain regulation.	Intestine; Central nucleus of amygdala; PVN.	Communication through vagus nerve and solitary nucleus with hypothalamus; PVN.	(Kaplan et al., 1988) (Tatemoto et al., 1983) (Fang et al., 2012, 2013)
Ghrelin	Signaling hunger pathways (energy homeostasis); Activates NPY/AgRP neruons; Control of weight gain and long-term energy; Modulates leptin activity; Regulation of glucose homeostasis and gastrointestinal motility.	Stomach (X/a-like endocrine cells); Intestine; Pancreas; Liver; Hypothalamus.	Communication through vagus nerve and solitary nucleus with hypothalamus; ARC.	(Cummings et al., 2001) (Kojima et al., 1999) (Wren, 2008)

regulated by leptin and insulin, showing the complexity of its activity in energy homeostasis (Fraley et al., 2004; Johansson et al., 2008).

The hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid hormones CRH and TRH, respectively, are produced in the PVN region (Fekete et al., 2000; Morley, 1987; Rivier et al., 1983). CRH has been associated with anorexia, due to the high stimulation of energy expenditure and high fat oxidation, being the expression induced by leptin (Arora & Anubhuti, 2006; Valassi et al., 2008). As for TRH, the release of this hormone is stimulated by anorexigenic neurons (more precisely, by α-MSH) and inhibited by orexigenic neurons, promoting a reduction in food intake (Morley, 1987; Schwartz et al., 2000; Stanley et al., 2005). The TRH is also regulated by leptin, inhibiting its expression, participating in the pathways of energy homeostasis (Valassi et al., 2008).

Finally, in the LHA region of the hypothalamus known as the feeding center, orexins A and B and the melanin concentrating hormone (MCH) are all expressed (Bakos et al., 2016; Sakurai et al., 1998). Orexins A and B are two small peptides that act through their G-coupled receptors (OX1R and OX2R) directly in the positive pathway between the NPY/AgRP neurons and, indirectly, acting on the inhibition of the POMC/CART neurons (Sakurai et al., 1998; Smart et al., 2000; van den Top et al., 2004). MCH plays a key role in energy homeostasis interacting with populations of ARC neurons, with their concentration increasing significantly during fasting (Arora & Anubhuti, 2006; Qu et al., 1996). The receptor of this hormone in the brain (MCH-1) is a potential target for anti-obesity medication, mainly due to the absence of serious side effects (Borowsky et al., 2002; Schwartz et al., 2000; Stanley et al., 2005).

2.3. Gastrointestinal tract and adipose tissue hormones

The gastrointestinal tract plays a substantial role in the control of food consumption and, consequently, in energy homeostasis (Wolfe & Boylan, 2014). In the different organs and tissues, the expression of peptide hormones promotes a hypothalamic response, mainly in anorexigenic and orexigenic neurons (Wilding, 2002). One of the most important hormones associated with energy balance is leptin, an anorexigenic peptide expressed by adipose tissue, which acts by sensing potential energy stored primarily as triacylglycerol in adipocytes and by controlling food intake (Stanley et al., 2005; Valassi et al., 2008; Zhang et al., 1994). Leptin can modulate the activity of several organs, being influenced by other circulating peptides, such as ghrelin or galanin (Maffei et al., 1995; Wilding, 2002). Leptin acts on the inhibition of NPY/AgRP neurons and the activation of POMC/CART neurons, both directly (there are receptors for leptin in both neuron populations) and for controlling the expression of other peptides involved in the different hypothalamic pathways (Elias et al., 1999; Kristensen et al., 1998; Schwartz et al., 1996). Insulin is produced by pancreatic islet β cells and, unlike leptin, has its concentration increased immediately after food intake (Schwartz et al., 1992; Stanley et al., 2005). In addition to its well-known direct regulation of glucose, glycogen and lipid metabolism, insulin has also an important direct action in ativating anorexigenic POMC/CART neurons and inhibiting orexigenic NPY/AgRP neurons, similarly to leptin.

In contrast to the anorexigenic effects of leptin and insulin, ghrelin is a potent orexigenic acylated peptide hormone, produced primarily in the stomach, but also at lower concentrations in intestine, pancreas, liver and hypothalamus (Berthoud & Morrison, 2008; Burdyga et al., 2006; Kojima et al., 1999; Stanley et al., 2005). Being known as the hunger hormone (Cummings et al., 2001), ghrelin controls weight gain and long-term energy balance (Cowley et al., 2003; Wren, 2008). In fact, concentration of ghrelin is inversely proportional to adiposity signs. Thus, the concentration of ghrelin is reduced in individuals with obesity and, consequently, elevated in lean individuals (Tolle et al., 2003; Valassi et al., 2008).

There are a large number of intestinal peptide signals that trigger a CNS response at the energy homeostasis level, including CCK, GLP-1, galanin, PP and PYY (Arora & Anubhuti, 2006; Berthoud & Morrison, 2008; Valassi et al., 2008; Wren, 2008). The latter two will be described in more detail in the following sections. All these peptides act on signaling pathways, from satiety to the hypothalamus through communication of the vagus nerve *via* the gut-brain axis (Table 1) (Bakos et al., 2016; Hussain & Bloom, 2013).

CCK is mainly produced by the duodenum and jejunum, being released locally after ingestion of nutrients, and also participating in other pathways associated with reward, memory and anxiety behavior (Gibbs et al., 1973; Schick et al., 1994; Stanley et al., 2005). Its action is essentially focused on reducing size and meals duration, being unable to act to reduce food consumption for a long time (Raybould et al., 2006; West et al., 1984).

GLP-1 is a peptide hormone that is synthesized by L cells of the small intestine after food intake, participating in glycemia homeostasis (Berthoud & Morrison, 2008; D'Alessio et al., 1995). In addition, it is involved in delayed gastric emptying and reduced orexigenic signaling of NPY/AgRP neurons, contributing to energy homeostasis (Hussain & Bloom, 2013; Turton et al., 1996). Its short time in circulation makes GLP-1 undesirable for the development of drugs for obesity (Valassi et al., 2008).

Galanin is a peptide hormone classified as orexigenic (Tatemoto et al., 1983). It may also be present in the hypothalamic region, more precisely in the PVN region (Fang et al., 2012, 2013; Lang et al., 2015), participating in several processes, such as depression, anxiety (Karlsson & Holmes, 2006; Picciotto, Brabant, Einstein, Kamens, & Neugebauer, 2010) and feeding (Corwin et al., 1993; Crawley, 1999). Galanin may be a potential marker of type 2 diabetes mellitus in pregnant women, as well as contribute to energy homeostasis through CNS connection. Nevertheless, the role of galanin in feeding is still controversial (Fang et al., 2013; Genders et al., 2018; Zhang et al., 2014).

3. Conventional drug treatment in obesity

Anti-obesity drugs can be divided into suppressants of appetite or digestion and absorption of nutrients (Table 2) (Kushner, 2014). Phentermine (2-methyl-1-phenylpropan-2-amine) was approved in 1959 as an anti-obesity treatment, with a short-term administration profile (Sweeting et al., 2014). This drug blocks norepinephrine reuptake and increases its secretion (George et al., 2014). The adverse reactions commonly reported by individuals using phentermine are insomnia and dry mouth (Yanovski & Yanovski, 2014). In addition, some reports point to more serious side effects, such as increased blood pressure, tachycardia and palpitations (Sweeting et al., 2014).

Sibutramine, used primarily as an antidepressant, works by blocking the reuptake of serotonin and norepinephrine, increasing satiety (McNeely & Goa, 1998). This drug was approved by the US Food and Drug Administration (FDA) in 1997 (Lean, 1997; Nisoli & Carruba, 2000) and has been used for >10 years on the treatment of obesity (Dedov et al., 2018). Valsamakis et al. (2004) state that sibutramine can reduce about 5% of body weight, reducing parameters such as waist circumference, triacylglycerols and insulin sensitivity, as well as producing anti-inflammatory effects reducing leptin levels and increasing adiponectin. These data corroborate Glandt and Raz studies (Glandt & Raz, 2011), indicating that treatment with this drug resulted in weight loss of, on average, 4.3 kg, compared with placebo. However, undesirable side effects have been described, such as insomnia, increased blood pressure, constipation, dry mouth and nausea. In addition, it is contraindicated in cardiac conditions, due to the increased occurrence of myocardial infarction and stroke (Rucker et al., 2007).

Another important drug is orlistat ((S)-((S)-1-((2S,3S)-3-hexyl-4-oxooxetan-2-yl)tridecan-2-yl) 2-formamido-4-methylpentanoate), approved by the FDA in 1999 (Filippatos et al., 2008). It acts by inhibiting pancreatic lipase, improving blood glucose indices, as well as reducing total cholesterol (CT) and low-density lipoprotein (LDL) values (Beg et al., 2015; Kim et al., 2013). Cholesterol is used for an annual period,

Table 2
Conventional medicines for weight loss. Mechanisms of action and side effects.

Molecule	Licensing year	Other name	Indication	Action mechanism	Adverse side effects	References
Phentermine	1959 (FDA)	Adipex-P, Ionamin	Anti-obesity	Mediated through sympathetic pathways, stimulates norepinephrine secretion	Increased blood pressure, insomnia, increased heart rate, headache, anxiety, dry mouth, may cause addiction, recommended short-term use	(Baretić, 2012; Sweeting et al., 2014; Yanovski & Yanovski, 2014)
Fluoxetine	1987 (FDA)	–	Major depression	Blocks the reuptake of serotonin; increases sensitivity to leptin; reduces weight gain	Insomnia, nausea, blurred vision, mental tension, vomiting	(Castrén & Rantamäki, 2010; Kessler et al., 2003; O'Leary et al., 2009; Scabia et al., 2018)
Sertraline	1991 (FDA)	Zoloft	Depression	Blocks the reuptake of serotonin	Increased risks of developing congenital malformations during the first three months of pregnancy	(Bérard et al., 2015; Olvey & Skrepnek, 2008)
Sibutramine	1997 (FDA)	Meridia	Anti-obesity	Blocks the reuptake of serotonin and norepinephrine	Insomnia, increased blood pressure, constipation, dry mouth, nausea	(Glandt & Raz, 2011; Lean, 1997; McNeely & Goa, 1998; Nisoli & Carruba, 2000; Rucker et al., 2007)
Orlistat	1999 (FDA)	Xenical	Anti-obesity; Reduces appetite and energy expenditure;	Inhibition of pancreatic lipase	Abdominal bloating, fecal incontinence, steatorrhea, deficient absorption of liposoluble vitamins	(Filippatos et al., 2008; Li et al., 2005; Rucker et al., 2007; Zhi et al., 2003)
Rimonabant	2006 (Europe)	–	Anti-obesity, decreased food intake	Cannabinoid receptor type 1 (CB1R) antagonist	Depression, suicidal thoughts, increased anxiety	(Baretić, 2012; Chhatwal et al., 2005; Di Marzo & Matias, 2005; Di Marzo & Szallasi, 2008; Haller et al., 2002; Navarro et al., 1997; Patel & Hillard, 2006; Rinaldi-Carmona et al., 2004; Rodgers et al., 2005)
Phentermine/Topiramate	2012 (FDA)	QsymiaT	Anti-epileptic; Anti-obesity	Blocks Na^+ channels; increases GABA receptor activity	Vomiting, excessive weight loss, dizziness, insomnia, paranesthesia, dry mouth, constipation, suicidal thoughts and increased heart rate	Halpern & Mancini, 2017; Garvey et al., 2012; FDA, 2012b; Colman et al., 2012
Lorcaserin	2012 (FDA)	Belviq	Anti-obesity	Activates serotonin 5-HT_{2C} receptors in hypothalamus and GLP-1 receptors	Nausea, dizziness, headache, fatigue, constipation, dry mouth	(Bray & Ryan, 2014; Fidler et al., 2011; Jackson et al., 2014; O'Neil et al., 2012; Smith et al., 2010)
Liraglutide	2014 (FDA) 2014 (Europe)	Saxenda	Anti-obesity	Analog of long-acting GLP-1, acts by activating the GLP-1 receptor, in order to slow down gastric emptying. Furthermore, it decreases ghrelin secretion through vagus nerve signaling	Nausea, fatigue, vomiting, dizziness, dyspepsia, abdominal pain, diarrhea, hypoglycemia, constipation, headache, increased lipase	(Jackson et al., 2014; Nonogaki & Suzuki, 2014; Nonogaki et al., 2014; Davies et al., 2015; Wadden et al., 2013; Fujioka, 2015; Christou et al., 2016)
Naltrexone/bupropion	2014 (FDA)	Contrave	Anti-obesity, depression, anxiety, alcohol dependence	Stimulates POMC; Increases satiety and energy expenditure	Dizziness, dry mouth, vomiting, nausea, constipation, excessive weight loss	(Greenway et al., 2009; Greenway et al., 2010; Halpern & Mancini, 2017)

reducing weight by an average of 2.9 kg when compared with placebo, in addition to lowering blood pressure, waist circumference, total cholesterol and occurrence of type 2 diabetes (Rucker et al., 2007). On average, 10% of patients experienced adverse effects, including abdominal bloating, fecal incontinence and steatorrhea. Further deficiencies in absorbing the liposoluble vitamins A, D, E and K have also been described, with patients needing their supplementation (Li et al., 2005).

Rimonabant, marketed in Europe in 2006, has an inverse agonist action on the cannabinoid-1 receptor (CB1R) (Brethauer et al., 2014; Chambers et al., 2007; Kang & Park, 2012; Ward & Raffa, 2011). Even though it leads to a significant weight reduction in patients, side effects such as suicidal thoughts, depression (Di Marzo & Szallasi, 2008; Ducobu & Sternon, 2005) and anxiety (Ioannides-Demos et al., 2011), led to its withdrawal from the market in 2008, and to the absence of FDA approval (Di Marzo & Szallasi, 2008; Ducobu & Sternon, 2005).

In 2012, FDA approved the use of another anti-obesity drug, an association of phentermine and topiramate (FDA, 2012b). Phentermine acts through the activation of α-MSH release (Fleming et al., 2013), while topiramate (2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate), commonly used for the treatment of epilepsy, acts as an anti-obesity drug in the long-term period, as a GABA agonist (Lee et al., 2003; Wilding et al., 2004). Adverse reactions include dizziness, insomnia, paranesthesia, dry mouth, constipation, suicidal thoughts (Colman et al., 2012; FDA, 2012b; Garvey et al., 2012) and increased heart rate (Halpern & Mancini, 2017). In addition, topiramate is contraindicated in cases of pregnancy, due to increase probability of developing fissures in the fetus (Margulis et al., 2012).

After 13 years of orlistat use, lorcaserin ((1*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine), a selective agonist of one of serotonin (the 5-HT2c receptor) was approved in 2012 by the FDA, becoming an important anti-obesity drug. According to (Martin et al., 2011), lorcaserin has no side effects on the activation of 5-HT2A and 5-HT2B, two other serotonin receptors. This drug activity is associated with the activation of POMC/CART neurons, causing a reduction in appetite (Lam et al., 2008). The approval of this drug was based on a 10 mg dose administered twice a day, for individuals with BMI ≥ 30 kg/m^2, along with a hypocaloric diet and physical exercise (FDA, 2012a). In addition, these individuals should have at least one obesity-associated disease, such as hypertension, dyslipidemia or type 2 diabetes mellitus (FDA, 2012a).

In 2014, the FDA approved the combination of naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) and bupropion (3-chloro-N-tert-butyl-β-keto-α-methylphenethylamine) for the treatment of obesity (FDA, 2014a). Naltrexone blocks the opioid receptors involved in the negative feedback, subsequently generating the activation of

POMC signaling (Billes et al., 2014). Bupropion acts by stimulating POMC production, in order to release α-MSH and activate the MC4R receptors, leading to appetite suppression and increased energy expenditure (Cowley et al., 2001; Ibrahim et al., 2003; Kelly et al., 1990). Previously, bupropion was commonly used to control depression and nicotine dependence (Dwoskin et al., 2006). This anti-obesity medication may have adverse effects such as dizziness, vomiting, headaches, dry mouth, insomnia, constipation, diarrhea and risk of suicidal thoughts (FDA, 2014a; Nissen et al., 2016).

Liraglutide is commonly administered for the type 2 diabetes mellitus treatment, which has an effect analogous to GLP-1 (FDA, 2010). However, FDA approved liraglutide as an anti-obesity drug, as well as for other weight-related diseases, including diabetes, dyslipidemia and hypertension (FDA, 2014b). Liraglutide was approved for obesity treatment in 2014 in the USA and later in 2015 in Europe (Fujioka, 2015). It acts by increasing GLP-1 levels, reducing appetite, aiding in reducing binge eating (Heppner et al., 2015), and consequently leading to weight loss (Jensterle et al., 2015). The most commonly reported side effects are vomiting, nausea and gastrointestinal disorders (Astrup et al., 2012; Wadden et al., 2013).

Currently, other drugs used to control neurological/psychiatric disorders (bupropion and fluoxetine) are being administered to fight obesity, without formal approval approval for this purpose (Glandt & Raz, 2011). Fluoxetine and sertraline act by blocking serotonin reuptake, being firstly indicated as antidepressants. However, some studies point to significant weight loss associated with these drugs, through the control of food consumption, as well as the intensification of energy expenditure (Leombruni et al., 2008; Wise, 1992).

Bariatric surgery may be considered when treatments above do not exhibit satisfactory results. The most commonly prescribed surgical procedures include gastric banding, sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB). Besides the advantage of achieving a weight-loss of up to 25% (Kushner, 2014), sleeve gastrectomy and RYGB increase the secretion of insulin, PYY and GLP-1 after meals, inducing appetite suppression (Gribble et al., 2018). However, surgery and post-operative risks, eating disorders such as bulimia and anorexia, schizophrenia and depression are possible side effects (Kushner, 2014).

Obviously, it is difficult to have drugs for obesity treatment, since many of them have been withdrawn from the market due to several side effects, which generate substantial preoccupation about obese individuals health (Connolly et al., 1997; Di Marzo & Despres, 2009; James et al., 2010). These side effects can be attributed to a high dosage treatment, because low doses often do not present significant effects on weight reduction (Wilding, 2017). In general, the mechanism of action of these already commercialized drugs focus on the control of appetite, reducing the absorption of nutrients. However, this may lead to energy compensation and exacerbated consumption of food with a high caloric index (Rajeev et al., 2016; Rodgers, 2017). In addition, (Hurt et al., 2014) indicate that the cases of cardiovascular diseases caused by pharmacotherapy are a great concern in obesity treatment.

The combination of two compounds with anti-obesity activity may be a satisfactory alternative for the regulation of energy appetite and homeostasis, potentiating treatment efficacy. Multi-therapy, as it is called, is given in lower doses when compared with monotherapy, which also tends to reduce the adverse effects of these drugs (Verhaegen & van Gaal, 2017). Therefore, with all the problems related to the side effects of drugs used for the treatment of obesity, some compounds were developed based on the mechanisms of action of drugs already marketed. D3 GSK588089 can be cited at this level, although this compound did not show effectiveness in phase 1 trials (Dodds, 2012; Nathan, 2012). Taranabant and otenabant, agonist and antagonist, respectively, of the CB1 cannabinoid receptor, showed adverse effects similar to those of rimonabant (Aronne, 2010; Aronne, 2011; Proietto, 2010), already withdrawn from the market (as mentioned in this section).

Studies such as that of (De Noronha et al., 2017), focused on the development of compounds that act directly on the hypothalamus, may lead to promising therapies, as they inhibit appetite and present anxiolytic properties, as the hypothalamus is one of the centers responsible for body homeostasis. This is corroborated by (Coulter et al., 2018), which state that promising compounds to be used as anti-obesity drugs will focus on activities in the peripheral mechanisms, which may decrease appetite and reduce adverse side effects.

Another treatment strategy for obesity recently indicated is hormonal therapy, through the administration of leptin, GLP-1, PYY and PP among others. However, these compounds present some negative points, such as short half-life and reduced efficacy (Colon-Gonzalez et al., 2013; Ravussin et al., 2009; Roth et al., 2008).

In addition, some compounds of multiple organisms, such as glucagon, GLP-1 and glucose-dependent insulinotropic polypeptide, have been tested to provide weight-reduction effectiveness as satisfactory as that achieved by bariatric surgery. These multiagonist or polyagonist compounds have a superior effect compared to those already marketed, but higher rates are needed to intensively evaluate their effects (Brandt et al., 2018).

4. The PP-fold neuropeptide family

Neuropeptides include a family called pancreatic polypeptide-fold (PP-fold neuropeptides family) (Table 3) (Berglund et al., 2003), representing a large group of molecules that perform substantial functions in the peripheral brain regions. These neuropeptides are reported in the regulation of various mechanisms, which include influence on appetite, behavior and inflammation, essential for body homeostasis (Lang et al., 2015; Pinter et al., 2014). In addition, they may perform a fundamental role in the CNS, being responsible for cellular communication, acting on the mechanisms of thermoregulation, water and food intake, circadian cycle and sexual behavior (Burbach, 2011; Catalani et al., 2017; Cervia & Casini, 2013).

In order for PP, PYY and NPY to act as appetite regulators, activation of GPCRs is essential (Pinter et al., 2014). Among seven existing receptors, only five are expressed in mammals (Sundstrom et al., 2013), all belonging to the GPCRs family (Lundell et al., 1995). These receptors are named Y1, Y2, Y4, Y5 and Y6, but the latter has no function in humans (Bromee et al., 2006). According to different authors (Gehlert, 1998; Lee & Miller, 1998), the Y3 receptor has reduced activity for PYY when compared to NPY. In contrast, Y3 has a higher activity profile with CXC type 4 chemokines, thereby being considered a member of the chemokine family and not of neuropeptides (Alexander et al., 2013). There is a difference of affinity levels between these peptides and receptors: PP binds with superior compatibility to the Y4 receptor, PYY can be considered the agonist with greater affinity for the Y2 receptor (Alexander et al., 2011; Cox, 2007a; McGowan & Bloom, 2004) and, finally, NPY binds with high affinity to Y1, Y2 and Y5 (Alexander et al., 2013).

The first pharmacokinetic analysis of PP was made in 23 healthy volunteers. These subjects received pure bovine PP (BPP) by infusion that

Table 3
PP-fold neuropeptide family sequences and tissues of their first isolation.

Neuropeptide	Sequence	Isolation	Reference
PP	YPSKPDNPGEDAPAEDLARYYSALRHYINLITRQRY	Avian pancreas	(Kimmel et al., 1975)
PYY	YPIKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY	Porcine intestine	(Tatemoto & Mutt, 1980)
NPY	YPSKPDNPGEDAPAEDLARYYSALRHYINLITRQRY	Porcine brain	(Tatemoto, 1982)

was given at doses of 1, 3 and 5 pmol/kg/min over 60 min. At the end of each infusion, blood was collected and among other analyzes, plasma BPP concentration was determined by radioimmunoassay. As a result, it was observed BPP levels rapidly decrease in circulation after endogenous administrations, with a half-life of 7 min (Adrian et al., 1978). After food intake, generally the PP concentration in the plasma increases (Adrian et al., 1976; Adrian et al., 1977; Adrian et al., 1978). The study by Adrian et al. (Adrian et al., 1976) observed that healthy young subjects had increased plasma PP concentration after meal with 830 cal (44 g fat, 28 g protein and 79 g carbohydrate) and remained elevated for 6 h. The results show 164 pmol/L of PP in the plasma 30 min after the meal and 80–1 pmol/L 6 h after the meal (Adrian et al., 1976). In another study, PP levels were also increased in healthy subjects after a high protein diet (70 g smoked pork loin and 20 g white bread) (Marco et al., 1980).

Central administration of NPY is correlated with the food intake stimulus (Stanley & Leibowitz, 1984). Food intake appears to be increased after injecting NPY into PVN, both in young animals and in older animals, including the lowest administered dose (0.05 nmol). In addition, elderly rats consumed more water and less food for 30, 90 and 240 min after NPY injection (Pich et al., 1992). To date, studies have correlated the effects of NPY with the Y1, Y2, Y4, and Y5 receptors (Kanatani et al., 1996; Widdowson et al., 1997; Schaffhauser et al., 1997; O'Shea et al., 1997; Marsh et al., 1998; Flynn et al., 1999; Kanatani et al., 2000; King et al., 2000). Thus, it is suggested that the effects of NPY on food intake are mediated by receptors combination (Stanley et al., 2005).

Regarding PYY, pharmacokinetics was evaluated in healthy subjects fasted by 3 PYY doses infusion (0.06, 0.19, and 0.57 pmol/kg/min) noticing that plasma PYY values decreased after infusion discontinuation (Adrian et al., 1986). In summary, it is necessary that more studies focus on the kinetics of neuropeptides after food intake so that it is possible to elucidate and compare roles in the health-disease process.

In this review, a special focus will be given to PP, PYY and NPY as potential leads for drug development against obesity. These three appetite-related peptides have a more target-restricted activity in the body, when compared with other molecules such as insulin, ghrelin, POMC or α-MSH, which may increase the possibility of acting exactly on the regulation of appetite and thus bring less interference to other physiological mechanisms.

4.1. Pancreatic polypeptide (PP)

PP, with 36 amino acid residues, belongs to a family of peptides with neural and endocrine activity (Michel et al., 1998) (Gehlert, 1998; Schwartz, 1983), being almost exclusively expressed in the digestive system (Holzer et al., 2012). The understanding of PP activity is still scarce (Kim et al., 2014). PP is secreted by the F-cells of pancreatic Langerhans islets, exocrine pancreas and distal gastrointestinal tract, being released in the bloodstream (Ekblad & Sundler, 2002; Larsson et al., 1975). PP acts on gallbladder contraction, pancreatic release and gastrointestinal motility (Kojima et al., 2007), whereas in the large intestine it is expressed at a minimal level, depending on the amount of food ingested (Adrian, 1978; Adrian et al., 1976; Cox, 2007b).

The mean baseline PP concentration in blood is 54 ± 4 pg.mL^{-1}, and it may vary according to age and gender, presenting higher levels in men (Floyd et al., 1978; Lonovics et al., 1981). However, plasma PP levels show variations throughout the day, being lower in the morning and higher during the night (Suzuki et al., 2012). Blood levels peak occurs 15 min after food intake, remaining elevated for 90 min and, according to some authors, even up to 6 h (Adrian et al., 1976; Kojima et al., 2007; Yeomans et al., 2016). The release of PP and other anorexigenic hormones can also be associated with physical exercise, mainly due to their effects on appetite and energy consumption (McIver et al., 2018). PP, through the vagus nerve, is also able to inhibit gastric emptying, which can be a possible explanation for its ability to act as an appetite suppressant (Field et al., 2010; Murphy & Bloom, 2006). In eutrophic individuals, intravenous administration of PP may provide a 25% reduction in food intake over a 24 h period (Batterham et al., 2003a,b). PP can be considered a potential indicator of visceral fat and, consequently, an indicator for cardiovascular risk (Stefan et al., 2008).

The body sensory responses related to the preference or rejection of certain foods are directly associated with the cephalic physiological responses (CPRs), which are initiated just before or at the beginning of food intake (Smeets et al., 2010). This way, cephalic signals emit messages about the food being ingested through the vagus nerve (Laughton & Powley, 1987), by releasing PP, initiating the cephalic phase (Schwartz, 1983). Foods high in protein and fat content were shown to induce higher cephalic signs, when compared to carbohydrate-rich foods (Crystal & Teff, 2006). This can be attributed to the sensory characteristics of foods rich in proteins and fats, which may lead to higher activity through the vagal nerve, consequently promoting a higher response to satiety during the cephalic phase (Smeets et al., 2010). However, this correlation between PP and the cephalic phase still needs to be further explored (Smeets et al., 2010).

Y4 receptors, through signaling in the parasympathetic vagus nerve, mediate PP activities related to food consumption and digestion (Field et al., 2010; Small & Bloom, 2005). PP activity on the Y4 receptor can occur in two specific regions, SN and the hypothalamus, both involved in involuntary responses (Dumont et al., 2007; Tasan et al., 2009). Through the Y4 receptor, PP may prevent intestinal secretion of several constituents (electrolytes and water) (Tough et al., 2006) and inhibit intestinal peristalsis (Fujimiya & Inui, 2000). There are several regions responsible for mediating PP effects in balancing food intake, such as brainstem, PVN, VMH and the third ventricle of the hypothalamus (Asakawa et al., 2003). PP acts similarly to GLP-1, being secreted into the bloodstream after food ingestion (Adrian et al., 1977; Katsuura et al., 2002), acting in several regulatory processes, such as gastric acid elimination after gastric emptying and the reduction of pancreatic secretion (Hazelwood, 1993; McTigue & Rogers, 1995). PP elimination from the digestive tract is greatly reduced during fasting, while at the time of digestion this release becomes faster. PP release levels in the brain are directly correlated with blood glucose and hypoglycemia indices, which may suggest an influence on the energy balance, as well as on the feeding behavior (Katsuura et al., 2002). In a study developed by (Sam et al., 2015), PP plasma levels were measured in obese individuals. This analysis demonstrated an association between PP levels and cholesterol, alanine transaminase (ALT), serum triacylglycerol (TAG), total cholesterol (TC) and blood pressure. These correlations may indicate that PP is an important hepatic and visceral fat indicator and may be considered a biomarker for cardiovascular diseases risk. PP may also be released after food intake, leaving the pancreatic islets innervating the vagal nerve, reaching the hypothalamus, and thus transmitting its anorexigenic effects (Schwartz et al., 1978). Even with the PP and Y4 receptor relationship being well characterized, PP binds also to all other Y receptors (Michel et al., 1998).

4.2. Peptide YY (PYY)

PYY is a 36 amino acid residue peptide, expressed in the digestive system (Holzer et al., 2012; Michel et al., 1998) and secreted through the gastrointestinal tract L cells (ileum, colon and rectum), acting as an appetite suppressant (Adrian et al., 1985). According to some studies, it is possible to point out that PYY also acts in food intake decrease through a direct intestine-brain communication (Batterham et al., 2002; Chaudhri et al., 2006; Karra & Batterham, 2010), exerting an energy homeostasis role (Konturek et al., 2005; Konturek et al., 2004). In addition, PYY acts on gastrointestinal motility inhibition and in pancreatic hormone release (Yang, 2002; Pfluger et al., 2006). Reduced PYY levels have been correlated with elevated BMI and obesity (Batterham et al., 2002). PYY is present in three-fold higher concentrations in the lower gastrointestinal tract, namely the ileum and colon (Adrian et al.,

1985; Le Roux & Bloom, 2005), being secreted through L cells for about 30 min immediately after food intake (Cox, 2007a, 2007b; Ekblad & Sundler, 2002; Greeley et al., 1989; McGowan & Bloom, 2004; Ueno et al., 2008). Therefore, PYY release may be controlled through food consumption, as well by the parasympathetic nervous system, inflammatory mediators and intestinal hormones (Ballantyne, 2006; Coskun et al., 2013; Cox, 2007b).

PYY release may occur even before food reaches the gut, indicating the existence of a neuronal mechanism directly related to the vagus nerve (Cox, 2007b; Fu-Cheng et al., 1997). This communication implies the participation of an activity-regulated cytoskeleton-associated protein, through a translation of the environmental effects. Due to this and to the fact that PYY encodes the genes related to this protein, a release is necessary to occur before food ingestion (Crespo et al., 2014; Hallden et al., 1999). Nevertheless, PYY release can occur through other mechanisms, such as secretion of gastric acid, cholecystokinin, bile acids and fatty acids (Feltrin et al., 2006; McGowan & Bloom, 2004). There are two PYY subtypes in circulation: PYY_{1-36} (the full-length peptide) and PYY_{3-36} (fragment with residues 3 to 36). The latter is generated through enzymatic cleavage of the PYY_{1-36} first two N-terminal amino acid residues, tyrosine and proline (Grandt et al., 1994; Mentlein et al., 1993). This change in the PYY structure occurs in parallel with a modification in the stimulated receptors (Cox, 2007b; McGowan & Bloom, 2004; Mentlein et al., 1993). Y1, Y2 and Y5 receptors have high binding affinity for PYY_{1-36}. However, the circulating form, PYY_{3-36}, has higher affinity binding to the Y2 receptor and is in a reduced ratio to Y5 (Cox, 2007b; McGowan & Bloom, 2004; Mentlein et al., 1993). PYY_{3-36} has higher appetite suppressant activity, when compared to PYY_{1-36} (Chelikani et al., 2004). In addition, several studies have reported that PYY_{3-36} promotes greater satiety in rats and humans (Batterham et al., 2002; Batterham et al., 2003a,b), with weight reduction after chronic admission (Pittner et al., 2004; Vrang et al., 2006). In the fasting state, PYY_{3-36} levels are lower than those of PYY_{1-36}, in contrast to the postprandial period, where the trend is inverted (Grandt et al., 1994).

Inhibition of intestinal activity mediated by PYY_{1-36} and PYY_{3-36} tolerates Y1 interference. Y1 receptors can act through enterocytes, myenteric/submucosal neurons and endothelial cells, whereas Y2 receptors act through submucosal and medullary neurons, extrinsic fibers of the primary afferent nerve; finally, Y4 receptors exert their function through enterocytes (Cox, 2007a, 2007b; Wang et al., 2010). Y1 and Y2 receptors mediate the gastric secretion inhibition that occurs after food intake in the brainstem and stomach (Yang, 2002). The stimulation caused by PYY_{3-36} in order to increase gastric pressure does not require the vagus nerve to activate the Y2 receptor (Janssen et al., 2012). According to Cox (2007b), short chain fatty acids are responsible for releasing PYY, which may result in inhibition of gastrointestinal motility, as well as in electrolyte elimination blockage. In general, PYY can act as an intestinal barrier, providing gut protection after food intake. This protection aims to delay gastric emptying and the motility of the intestine, assisting in the absorption of nutrients (Cox, 2007b; Lin et al., 1996; Nightingale et al., 1996; Pironi et al., 1993; Van Citters & Lin, 2006). (Batterham et al., 2003a,b) analyzed the PYY levels in blood samples from obese and non-obese individuals, during fasting. They observed that PYY levels in the obese group (10.2 ± 0.7 pmol/L) were lower than for the control group (16.9 ± 0.8 pmol/L). After food intake, PYY levels increased for the two groups analyzed, but the indices were lower for obese individuals (14.4 ± 1.2 pmol/L) when compared with non-obese individuals (23.5 ± 0.9 pmol/L). After 210 to 360 min, PYY was quantified again, yielding lower values for obese individuals (562.0 ± 44.6 pmol/h/L) when compared with control (841.4 ± 34.9 pmol/h/L). In conclusion, these data point out the relevance of PYY activity in weight control. Another study (Cox et al., 2010) pointed out the importance of PYY in diabetes and obesity control mediation, since it has the ability to act together with GLP-1, also secreted by the intestinal L cells. These cells also need GPCRs to provide the release of glucagon and PYY, in order to increase glucose tolerance. According to a study by (Steinert et al., 2010), the synergism between PYY and GLP-1 enables satiety and reduction in food ingestion. Thus, a direct relationship of plasma PYY bioavailability with satiety, and consequently with the effects of obesity, can be evidenced.

4.3. Neuropeptide Y (NPY)

NPY is a multifunctional 36-amino acid residue peptide (Malva et al., 2012; Reichmann & Holzer, 2016) that has been directly correlated with obesity, because of its ability to increase appetite and decrease energy expenditure (Billington et al., 1991; Raposinho et al., 2001; Szreder et al., 1994). Tatemoto et al. isolated NPY for the first time in 1982, from swine brain (Tatemoto et al., 1982). NPY can be considered as the most common brain neuropeptide (Sajdyk et al., 2004), performing a substantial role in food intake, energy balance, circadian cycling and cognitive sense (Eaton et al., 2007; Morin, 2013; White, 1993; Zhang et al., 2011). In addition, NPY also has a direct relationship with stress response, showing anxiolytic properties (Heilig, 2004; Sajdyk et al., 2004). The food intake balance is mainly controlled in distinct hypothalamic regions, as already mentioned (Berthoud & Morrison, 2008; Zheng & Berthoud, 2008). However, NPY may be present in several other regions, such as the hippocampus, amygdala and cerebral cortex (Eaton et al., 2007; Holzer et al., 2012; Kask et al., 2002; Wettstein et al., 1995). As discussed by (Greenwood et al., 2011), due to the great abundance of NPY in the CNS and its large number of functions, it is uncertain that a direct antagonism is effective for obesity treatment. Considering this, there is a problem in targeting only NPY seeking a hyperphagic effect without any side effect.

The NPY brain receptors widely abundant in the CNS are Y1 and Y2. However, Y4 and Y5 receptors, located in distinct regions, such as the hypothalamus, thalamus and amygdala, can also be targeted by NPY (Eaton et al., 2007; Kask et al., 2002; McGowan & Bloom, 2004; Tasan et al., 2009). In the PNS, NPY is expressed in sympathetic ganglia, which correlates with norepinephrine when nerve stimulation occurs (Ekblad et al., 1984). The main effect of NPY is stimulating appetite, despite other behavior and metabolism-related functions (Wisialowski et al., 2000). Afferent signals, such as insulin and leptin, may regulate NPY synthesis in the ARC, as well its release in PVN. Of the 5 GPCRs recognized, Y5 can be considered the receptor that has the greatest affinity to NPY related to food intake, especially on appetite stimulus (Marsh et al., 1998; Pedrazzini et al., 1998). In a study by (Cabrele et al., 2000), the first NPY analogue peptide with selectivity for the Y5 receptor was developed by insertion of two modified amino acid residues: Ala31 and Aib32 (2-aminoisobutyric acid). The insertion of the modified Aib amino acid residue was important to promote α-helix stability (Demizu et al., 2012). Through cell culture assays, it was possible to see that modified NPY had a substantial interaction with Y5 receptor, with an IC_{50} (half-maximal inhibitory concentration) of 6 nM, whereas it was 500 nM for Y1/Y2 and 1000 nM for Y4. That way, the NPY [Ala31, Aib32] peptide presents a favorable pharmacological profile for selective Y5 agonist, possibly being a candidate for the study of biological functions correlated with Y5 (Cabrele et al., 2000). To potentiate selectivity for Y5 receptor, the same authors designed another NPY analogue that presented selectivity 3-fold higher than native NPY and 25-fold higher than NPY [Ala31, Aib32]. These activities were also visualized in *in vivo* studies, showing an intense correlation of NPY with food consumption and, consequently, with obesity.

5. GPCRs and their relevance in obesity

G-protein coupled receptors comprise a superfamily of integral membrane proteins, constituted of transmembrane helices (TM) and intra/extracellular loops that have long been described as key players in the regulation of cell signaling processes (Cooke et al., 2015). In this context, GPCRs have been extensively studied as targets for cancer

(Lynch & Wang, 2016), diabetes (Mancini & Poitout, 2015), heart failure (Kamal et al., 2017) and obesity therapies (Collet et al., 2017). Several reports have shown that drugs acting on GPCRs represent approximately 27% of all drugs commercialized nowadays (Hauser et al., 2017). Consequently, the impact on the global economy by GPCR-based drugs is remarkable, surpassing the mark of US$800 billion in accumulated sales, as estimated from 2011 to 2015 (Hauser et al., 2017). Interestingly, despite over 800 proteins classified as human GPCRs, drugs have only been developed for <10% of them, thus revealing the huge effects of those drugs targeting GPCRs already in the market (Heifetz et al., 2015).

GPCRs are classified as one of the largest families constituted by membrane proteins found in humans to date (Hauser et al., 2017). This protein family has been divided into six main classes according to evolutionary homology studies (Fredriksson et al., 2003), including A (rhodopsin), B1 (secretin), B2 (adhesion), C (glutamate), F (frizzled) and taste 2 classes (Pándy-Szekeres et al., 2017). Currently, crystallographic structures for three (A, C and F) out of the six GPCR classes have been determined (>40 unique receptors, mainly from class A) (Heifetz et al., 2016). These advances in the structural biology field, for instance, have allowed researchers to determine the location of GPCRs orthosteric sites, usually found in the extracellular portion of receptors, and GPCRs allosteric sites, most likely deeply inserted into the transmembrane helical section (Cooke et al., 2015). Currently, >140,000 GPCR ligands have been identified for diverse GPCR binding sites, including allosteric and cryptic pockets, rendering them difficult to study by crystallographic methods (Heifetz et al., 2015). In addition to that, GPCRs are known for their highly dynamic structural arrangement during signal transduction, which varies depending on the attached ligand, type of modulation and coupling with intracellular effectors (Miao & McCammon, 2016). To overcome these obstacles, accurate computational methodologies, including molecular modeling, docking and dynamics, have been established (Vass et al., 2016). Moreover, these approaches have assisted GPCR molecular interaction fingerprint studies, leading to ligand binding mode prediction, structure/activity relationship (SAR) elucidation and virtual screening for novel GPCR-based drugs (Vass et al., 2016).

In the obesity context, reports have shown that seven GPCR-targeted agents were in clinical trials in December 2017 (Hauser et al., 2017). In terms of comparison, this same study revealed that 27 agents related to diabetes and targeting GPCRs were in clinical trials, followed by 23 anticancer agents (Hauser et al., 2017). In addition, fewer than five GPCR-based drugs for obesity have been approved, whereas >40 are under this same status for hypertension, allergies and as analgesics (Hauser et al., 2017). This reality, along with the high death risk associated with obesity worldwide, highlights the importance of novel drugs development for obesity treatment, with some of them developed focusing on the activation/blocking of hypothalamic receptors (Table 4). With that in mind, Heifetz et al. (Heifetz et al., 2013) proposed fighting obesity based on the design, synthesis and screening of a library of sugar-based compounds, to generate melanin-concentrating hormone-1 receptor (MCH-1R) antagonists. MCH-1R belongs to class A of GPCRs and acts in diverse regions of the CNS, including metabolic regulation and feeding behavior (Saito & Maruyama, 2006). In that work, they used the VAST (Versatile Assemble on State Templates) technology to initially obtain 490 compounds, among which ACL21823 presented moderate antagonistic potential against MCH-1R. Further structural studies were carried out, with ACL21823 being used as a template for virtual enrichment experiments and structure-based virtual screening, leading to the identification of 10 promising chemotypes, including the variants EOAI3367472 and EOAI3367474, which acted as MCH-1R antagonists at nanomolar levels (Heifetz et al., 2013). Robust computational studies have also been performed to investigate the influence of site-direct mutagenesis in the interaction of orexin receptors (class A GPCRs) with antagonists. Heifetz et al. (Heifetz et al., 2012), for instance, carried out a series of molecular modeling and dynamics studies, revealing that even slight amino acid residue substitutions in the TM3, from orexin receptors OX1 and OX2, drastically changed the structural conformation of these receptors, as well as antagonist binding affinities and selectivity. Moreover, these studies allowed authors to design two novel orexin, named EP-109-0092 (OX1 selective) and EP-009-0513 (OX2 selective).

Melanocortin receptors (MCR), including MC1R, MC3R and MC4R, are also members of the GPCR family (class A), and are mainly related to energy homeostasis and somatic growth. MC4R, more specifically, is known for playing a crucial role in food intake and body weight (Gautron et al., 2015). Several works have reported that mutations in the *MC4R* gene are associated with the most severe cases of obesity, classified as morbid obesity (Mergen et al., 2001). Interestingly, *in vivo* studies using *MC4R* knockout mice have also shown that weight regulation is most likely associated with quantitative variation in *MC4R* expression (Huszar et al., 1997). In this context, drugs that act as MC4R agonist have attracted great attention as obesity therapies. Among them, Setmelanotide is a cyclic peptide agonist of MC4R that has shown remarkable results in phase II clinical trials and, recently, has initiated phase III trials (Hauser et al., 2017).

It is known that GPCRs mediate the activation of different biological pathways, depending on the ligand and effector protein they interact with. Among the ligands described in the literature, long-chain fatty acids (LCFAs; carbon length over 12) have attracted attention due to their influence in diabetes and obesity (Guardado-Mendoza et al., 2009). Diverse GPCR family members, including GPR40, GPR41, GPR41 and GPR120, have been shown to act as LCFAs receptors (Yonezawa et al., 2013). The enteroendocrine cells substantially express GPR120, which also acts on different physiological processes, including regulation of appetite and adipogenesis (Hirasawa et al., 2005). In a robust study, (Ichimura et al., 2012) evaluated the influence of GPR120 dysfunction both in mice and humans. In that work, GPR120-deficient mice were fed with high-fat diet, resulting in obesity, glucose intolerance and changes in adipogenesis regulation. Similar findings were reported in humans, where obese individuals presented high levels of expression of GPR120 in adipose tissue, thus providing accurate data on the relevance of GPR120 in human and rodent energy balance (Ichimura et al., 2012). Interestingly, another study (Cartoni et al., 2010) reported that both GPR40 and GPR120 are involved in the mediation of taste preference for fatty acids, and that further studies in this field are encouraged for the development of non-caloric molecules mimicking fat taste to combat obesity.

Apart from MCH-1, MCR and GPR, the GPCR family members Y1, Y2, Y4 and Y5 receptors are substantially expressed in the hypothalamus, providing energy balance for the organism. The Y class receptors are commonly coupled to G_0 and G_i proteins, leading to inhibition of adenylate cyclase, cytosol cyclic adenosine monophosphate (cAMP) levels (Cabrele & Beck-Sickinger, 2000), and regulation of Ca^{2+} and K^+ channels (Holliday et al., 2004). Interestingly, several studies have shown that Y receptors play a crucial role in obesity *via* interaction with NPY, which is greater when involving Y1 and Y5 receptors, as presented above (Gerald et al., 1996; Wyss et al., 1998). The Y1 receptor, for instance, may be related to the amount of food ingested, as observed by (Kanatani et al., 2000). In that work, animals presenting mutations in Y receptors (Y1 and Y5) responded differently to NPY presence. As a result, it was observed that $Y1^{-/-}$ single knockout animals had a substantial reduction in appetite; whereas $Y5^{-/-}$ animals did not present a satisfactory alteration (Kanatani et al., 2000). Interestingly, according to another study (Stafford et al., 2008), the Y1 receptor has a direct influence on the reduction of the very-low-density lipoproteins (VLDL) and TAG levels in rats. These data are of great relevance, as hepatic VLDL-TAG rates are directly related to obesity, as well as to the triggering of cardiovascular diseases (Talayero & Sacks, 2011). In addition to Y1 receptors, it has been mentioned that Y2 receptors are mainly expressed pre-synaptically, following their activation by PYY_{3-36}. Consequently, there is a reduction in the release of neurotransmitters, including NPY

Table 4
Agonists and antagonists of GPCRs and their obesity-related effects.

Compounds	Receptor activity		Type of analysis	Function of the developed compounds	Reference
	Agonist	Antagonist			
ACL21823 EOAI3367472 EOAI3367474	–	MCR-1R	*In silico*	Analysis for prediction and validation of the antagonists	(Heifetz et al., 2013)
EP-109-0092	–	OX1 selective	*In silico*	Analysis of binding affinities and selectivity	(Heifetz et al., 2012)
EP-009-0513	–	OX2 selective	*In silico*	Analysis of binding affinities and selectivity	(Heifetz et al., 2012)
Setmelanotide	MC4R	–	Knockout mice	Weight regulation is most likely associated to quantitative variation in MC4R expression in MC4R	(Hauser et al., 2017)
PEGylated [K30(PEG2)] $hPP_{2–36}$	–	Y4	Knockout mice	Decreases fear and possible anxiety behavior in Y4	(Verma et al., 2016)
[2-(dimethyl-1-oxo-4*H*-1*H*-xanthen-9-yl)-5,5-dimethyl-cyclohexane-1,3-dione]	–	Y5	Mice	The compound did not change the weight; however, the Y5 receptor is directly related to the obesity treatment	(Ishihara et al., 2006)
D-Trp^{34}NPY	Y5	–	Mice	Oral and intracerebroventricular administration increased weight and adipose tissue, causing hyperleptinemia and hypercholesterolemia	(Mashiko et al., 2003)
Spironolactone	–	Y5	DIO mice	Reduction of body weight and insulin resistance	(Mashiko et al., 2008)
MK-0557	–	Y5	Obese patients	Double-bind, randomized, placebo-controlled study showed reduction of weight	(Erondu et al., 2006)

and GABA by orexigenic ARC activity, thus resulting in a state of satiety and indirectly influencing obesity (Loh et al., 2015).

Y4 receptors are very differentiated in the CNS, with substantial expression in the hypothalamic region and SN (Dumont et al., 2007; Tasan et al., 2009). A study (Pedragosa-Badia et al., 2014) characterized the Y4 receptor structure, as well as the Y4R-human PP complex interaction. Results demonstrated that Tyr2.64, Asp2.68, Asn6.55, Asn7.32 and Phe7.35 are the most relevant amino acid residues of the receptor for activation by PP. In addition, it was possible to observe that TM2, TM6 and TM7 are the main interaction and activation regions of the receptor. These findings may help in the design of agonists or antagonists bioinspired by the PP, potentiating their activity. Moreover, other works have also reported the direct correlation between the Y4 receptor and behavioral changes, anxiety and fear. For instance, (Verma et al., 2016) showed that, using a peptide derived from PP and selective for Y4, the PEGylated [K30 (PEG2)] hPP2–36, it was possible to observe substantial reduction of fear, blocking the expression of orexins through the inhibition of orexin-expressing neurons. In addition, these authors further pointed out that feeding-related research may be interesting for anxiety control.

Studies performed with Y1, Y2 and Y4 receptors have assessed whether these receptors are directly involved in obesity syndrome. (Lin et al., 2006), for example, reported the combined depletion of Y1, Y2 and Y4 in mice, generating four different genotypes and relating them with the overexpression of NPY. Among their findings, it could be observed that hyperphagia, hypogonadism and obesity induced by NPY were persistent in the single-, double- and triple-knockout mice ($Y1^{-/-}$, $Y2^{-/-}$, $Y2Y4^{-/-}$ and $Y1Y2Y4^{-/-}$, respectively). In that study, under specific conditions, it was concluded that Y1, Y2 and Y4 are not involved in obesity syndrome prevention (Lin et al., 2006).

The Y5 receptor is substantially expressed in the hypothalamic region in two different compositions, presenting 445 or 455 amino acid residues, depending on the inclusion (or not) of 10 amino acid residues at the N-terminal region (Nguyen et al., 2012; Parker & Herzog, 2000). However, not interfere in Y5 receptors function (Rodriguez et al., 2003), nor in their ability to interact with NPY, PYY or small PPs (Gerald et al., 1996). Diverse studies have been carried out to correlate Y5 with weight control. Schaffhauser et al., for instance, showed that, when NPY induces hunger, Y5 is the fundamental receptor associated with food intake. This receptor has also been involved as a promoter in the onset of obesity cases, as well as type 2 diabetes and insulin resistance (Schaffhauser et al., 1997). Moreover, in another study (Marsh et al., 1998), Y5-specific antagonists were developed to provide weight-reducing activity in animals with diet-induced obesity (DIO). In addition, (Ishihara et al., 2006) observed that Y5 antagonists may contribute to weight reduction in obese individuals. These data corroborate those described by (Fukasaka et al., 2018), which cites the Y5 receptor as a potential target for the development of novel promising compounds to be used as drugs for the treatment of obesity.

The Y5 receptor/food intake relationship has gained great attention over the years (Mashiko et al., 2003), for instance, studied the chronic impact of 3,3-dimethyl-9-(4,4-dimethyl-2,6-dioxocyclohexyl)-1-oxo-1,2,3,4-tetrahydroxanthene (d-Trp^{34}NPY) Y5 agonist in mice. The concentration of d-Trp^{34}NPY administered was shown to be directly correlated with food intake and adipose tissue. D-Trp^{34}NPY also induced an increase of total cholesterol, HDL and TAG, as well as insulin and leptin in plasma (Mashiko et al., 2003). Years later, some of the same authors (Mashiko et al., 2008) also analyzed the antagonistic effect of spironolactone on Y5 receptor and its influence on body weight gain, using wild-type and DIO animals (Mashiko et al., 2008). Spironolactone acts by blocking the action of NPY, with impact on the fat mass of the animals, as well as decreasing insulin resistance; however, no impact on the lean mass was reported. Thus, as insulin resistance is directly linked to the amount of body fat, the decrease of this resistance may be correlated with the loss of fat mass presented by the animals (Mashiko et al., 2008). In a study by (Erondu et al., 2006), it was possible to analyze the anti-obesity activity of a Y5 receptor antagonist, MK-0557 (trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azobenzofuran-1(3H),10-cyclohexane]-4-carboxamide), after a very-low calorie diet (VLCD). MK-0557 was administered orally to obese individuals, at a concentration of 1 $mg.day^{-1}$; however, these individuals did not present significant weight reduction. Moreover, they also point out that NPY is an essential molecule for energy homeostasis, with Y5 receptor being a promising component for the elaboration of new drugs that may help weight reduction. More recently, Y5 receptor knockout obese (Y5KO) mice were analyzed to verify if the anorexigenic neurons activity of $PYY_{3–36}$ is antagonized by the Y5 receptor (Shi et al., 2017). Y5KO mice received a high fat diet for 12 weeks, followed by $PYY_{3–36}$ administration and measurement of body weight, blood glucose and food intake for 3 weeks. These findings highlight the potential of combination

therapy using $PYY_{3–36}$ and Y5R in order to increase food intake, because Y5R may antagonize the appetite suppressant activity associated to $PYY_{3–36}$. In addition, it highlights the importance of Y5R in energy homeostasis and, consequently, in food intake (Shi et al., 2017).

Some studies (*e.g.*, Omori et al., 2012; Tamura et al., 2012a, 2012b, Tamura et al., 2013) highlight the development of Y5 receptor antagonist compounds, with potent appetite reduction activity *in vivo*. In addition, (Tamura et al., 2013) further note that the antagonist tested for 21 days also did not cause behavioral change in DIO animals. However, these compounds are still under development. In summary, there is still a need for additional research on the development of antagonists for the Y5 receptor (Fukasaka et al., 2018).

6. Conclusion and prospects

This review addresses obesity related problems, was well as the comorbidities associated, such as cardiovascular and autoimmune diseases, type 2 diabetes mellitus and even different types of cancer. Commonly used medication may cause several undesirable side effects, which compromise the long-term treatment, leading to a high dropout rate and, consequently, energy compensation and weight recovery. Several peptides are involved in the regulation of appetite, including the PP-fold neuropeptides family. They have a specific route of action in the hypothalamus, which may provide greater effectiveness in their mechanism of action. Thus, the PP-fold neuropeptides family has become a promising option for the development of new anti-obesity compounds due to their ability to act on specific hypothalamic receptors, reducing food consumption. These hypothalamic receptors, when active or inactive, transmit a message to the body, providing the sensation of hunger or satiety. Several studies have already demonstrated the importance of this approach and its potential efficacy in *in vivo* tests, using diet- induced obesity animal models. Therefore, appetite-related peptides may exert a more effective action to provide energetic homeostasis, concomitantly assisting in the treatment of obesity.

Conflicts of interest statement

All authors declare that there is no conflict of interests.

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