Effectiveness of pharmacotherapy in obesity treatment

Targeting the central nervous system and peripheral hormones

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Abstract

The prevalence of overweight and obesity has reached epidemic proportions over the last decades. Worldwide, more than 1.9 billion adults are overweight, of which over 650 million are obese; 39% and 13% of the total adult world population respectively. Obesity causes and exacerbates a wide spectrum of physical and mental conditions. Effective treatment of the disease has therefore been called for; however, finding a solution seems to be extremely difficult. There is a treatment gap between poor efficacy lifestyle modifications and invasive bariatric interventions, which pharmacotherapy could possibly overcome. We highlight the important role of the central nervous system and peripheral hormones, in feeding behaviour and energy homeostasis. The aim of the present essay was to answer the question whether targeting the central nervous system and peripheral hormones with pharmacotherapy is effective in the treatment of obesity. It can be concluded that steps are being made in the right direction regarding the use of pharmacotherapy in obesity treatment. Although there currently is not a single pharmacological drug effective in treating obesity when given as monotherapy, even a minor reduction of 5 – 10% in body weight already improves overall fitness and comorbidities. Further studies should focus on polytherapy, where multiple drugs are given in conjugation.

***Keywords*:** obesity, pharmacotherapy, central nervous system, peripheral hormones, feeding behaviour, energy homeostasis

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1. List of abbreviations and relevant definitions

2-AG	2-arachdonoylglycerol
ACTH	adrenocorticotrophic hormone
AgRP	agouti-related peptide
α-MSH	α-melanocyte-stimulating hormone
AP	area postrema
ARC	arcuate nucleus
BAT	brown adipose tissue
BDNF	brain-derived neurotrophic factor
BMI	body mass index
CART	cocaine- and amphetamine-regulated transcript
CB	cannabinoid
CCK	cholecystokinin
CLIP	corticotropin-like intermediate lobe peptides
CNS	central nervous system
CRH	corticotrophin-releasing hormone
D	dopamine
DMN	dorsomedial nucleus
DPPIV	dipeptidyl-peptidase IV
DVN	dorsal motor nucleus of the vagus nerve
FDA	Food and Drug Adminstration
GABA	inhibitory γ-aminobutyric acid
GC	glucocorticoids
GHS	growth hormone secretagogue
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GOAT	ghrelin O-acyltransferase
HbA1c	haemoglobin A1c
HPA	hypothalamic-pituitary-adrenal
HPT	hypothalamic-pituitary-thyroid
LHA	lateral hypothalamic area
MC	melanocortin
MCH	melanin-concentrating hormone
ME	median eminence
NAc	nucleus accumbens
NPY	neuropeptide Y
NTS	nucleus of tractus solitarius
OB	leptin
OX	orexin
PC	prohormone convertase
POMC	pro-opiomelanocortin
PP	pancreatic polypeptide
PVN	paraventricular nucleus
PYY	peptide tyrosine tyrosine
SF1	steroidogenic factor 1
SIM1	transcription factor single minded 1
TRH	thyrotropin-releasing hormone
TrkB	tropomyosin receptor kinase B
VMN	ventromedial nucleus
VTA	ventral tegmental area
WAT	white adipose tissue
WHO	World Health Organization

2. Introduction

Overweight and obesity are medical conditions in which a person has excess body fat, to the extent that it increases the risk of developing serious health problems (WHO, 2018). The most commonly used criterium for being classified as obese, is the body mass index (BMI). This parameter is calculated by dividing body weight in kilograms, by the square root of height in meters. A BMI between 18.5 – 25 kg/m^2 is generally described as healthy. Someone with a BMI between 25 – 30 kg/m^2 is classified as overweight, and a BMI ≥30 kg/m^2 is considered obese. Different body weight classifications are used in children, whereas body composition changes significantly during childhood, varying with age and sex. A BMI between the 85th – 95th percentile for corresponding age and sex is seen as overweight in children, and anywhere above the 95th percentile is considered obese (Sahoo et al, 2015).

One of the major flaws of using BMI as a parameter for obesity, is that it does not distinguish between different tissues. Body composition depends on the distribution of muscle-, fat- and bone mass. Trained athletes for example, tend to have relatively more muscle- than fat mass. It is therefore common in this group to see high BMI's, with an overestimation of obesity (Provencher et al, 2018). Another measure which should be taken into account is abdominal obesity, which is measured by waist circumference. There is a strong correlation between increased waist circumference and the risk of developing health problems. In Caucasians, an increased risk is expressed with a waist circumference of ≥94 cm in men and ≥80 cm in women (Alberti et al, 2006; Kanazawa et al, 2005).

The prevalence of overweight and obesity has reached epidemic proportions over the last decades. Worldwide, more than 1.9 billion adults are overweight, of which over 650 million are obese; 39% and 13% of the total adult world population respectively (WHO, 2018). This disease is not only limited to adults, as over 381 million children and adolescents are either overweight or obese. Worldwide obesity has nearly tripled since 1975, independent of age, sex, geographical locality, ethnicity or socioeconomic status (Chooi et al, 2019). Where obesity once used to be a luxury problem mainly seen in high-income countries, prevalence is nowadays increasing in both the developed- and developing world. Future predictions and trends on the progression of obesity do not look bright, as it is predicted that the number of patients will continue to rise even further in the upcoming years (NCD Risk Factor Collaboration, 2016; Pineda et al, 2018).

Obesity causes and exacerbates a wide spectrum of physical and mental conditions. Most of these conditions express themselves in the metabolic syndrome, which represents a cluster of metabolic abnormalities, including hypertension, type 2 diabetes mellitus, dyslipidaemia and cardiovascular diseases. Reproductive disorders, certain types of cancer, sleep apnoea and psychological problems are also linked to obesity. Ultimately, obesity increases the risk of premature mortality (Kyrou et al, 2018). Effective treatment of obesity has therefore been called for; however, finding a solution seems to be extremely difficult. First line treatment of obesity is lifestyle modification. Although it is possible to lose weight with lifestyle changes, both short- and long-term efficacy on weight loss is often poor (Franz et al, 2007). The most effective procedure in obesity treatment is bariatric surgery. Besides the promising and highly effective outcomes of bariatric surgery, there are some major downsides; postoperative complications may arise, and the procedure itself is often very invasive for the patient (Hope et al, 2018).

Pharmacotherapy could possibly overcome the treatment gap between poor efficacy lifestyle modifications and invasive bariatric interventions. We highlight the important role of the central nervous system (CNS) and peripheral hormones, in feeding behaviour and energy

homeostasis. The present essay aims to answer the question whether targeting the central nervous system and peripheral hormones with pharmacotherapy is effective in the treatment of obesity. We expect that none of the currently available pharmacological drugs will be effective to treat obesity when given as monotherapy. However, the results could be promising when given as polytherapy, together with lifestyle changes. This would open up possibilities for future research on obesity treatment, where pharmacological drugs could serve as a less invasive, yet effective, treatment option, in comparison to bariatric surgery.

3. Neuronal regulation of feeding behaviour and energy homeostasis

In order for the body to control and regulate food intake and energy expenditure, complex interactions and mechanism between the CNS and periphery have been integrated. These mechanisms are essential for maintaining whole-body energy homeostasis. Homeostatic control of feeding behaviour and energy expenditure is mainly driven by the hypothalamus and brainstem. They integrate signals and information about food intake and energy status, derived from peripheral organs, including the gastrointestinal (GI) tract, adipose tissue and pancreas (Wilson & Enriori, 2015). This crosstalk between signals from the periphery and brain is necessary for our current state of hunger or satiety (Clemmensen et al, 2017). The hypothalamus and brainstem have strong connections with other brain areas, such as the mesolimbic system, involved in rewarding and motivational aspects of eating (Lo Preiato et al, 2018).

3.1 Hypothalamus

The hypothalamus is found near the third ventricle at the base of the brain and is involved in a variety of fundamental biological processes, ranging from circadian rhythms and sleep, to control of body temperature and feeding behaviour (Saper et al, 2005; Zhao et al, 2017). The pituitary gland at the bottom of the hypothalamus links the nervous system to the endocrine circuits. Signals about food intake and energy status are integrated within the hypothalamus, which in turn drives anabolic and orexigenic (appetite-stimulating) or catabolic and anorexigenic (appetite-supressing) responses (Timper & Brüning, 2017). Distinct, but interconnecting nuclei, are found within the hypothalamus and include the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventromedial nucleus (VMN), dorsomedial nucleus (DMN) and lateral hypothalamic area (LHA). One of the major functions of these nuclei is responding to nutrient intake and fluctuations in energy status (Roh & Kim, 2016).

3.2 Arcuate nucleus

The ARC is a key player in regulating feeding behaviour and energy homeostasis (Myers & Olson, 2012). The nucleus is strategically located adjacent to the median eminence (ME). This circumventricular organ has a semi-permeable blood-brain barrier, allowing the influx of circulating hormones and nutrient signals from the bloodstream into the brain (Lechan et al, 2016; Rodríguez et al, 2010). This unique feature allows the ARC to accurately sense and integrate all these signals, while giving coordinated feedback responses in return. Lesion of the nucleus results in obesity (Olney et al, 1969).

3.3 Neurons of the arcuate nucleus

Two highly specialized subsets of neuronal populations with antagonistic properties can be distinguished within the ARC (Figure 1; Matafome & Seiça, 2017). These two branches of the melanocortin system are seen as first-order neurons, being able to rapidly sense circulating hormones and nutrient signals from the bloodstream. One neuronal population is localized medially in the ARC, co-expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP). These orexigenic neurons stimulate feeding upon activation (Broberger et al, 1997). The other population of neurons is localized laterally in the ARC, co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). These anorexigenic neurons inhibit feeding behaviour (Joly-Amado et al, 2014; Vrang et al, 1999). Both neuronal populations process the signals they receive and project them to second-order neurons in other nuclei of the hypothalamus, or to extrahypothalamic areas including the brainstem and spinal cord (Schneeberger et al, 2014).

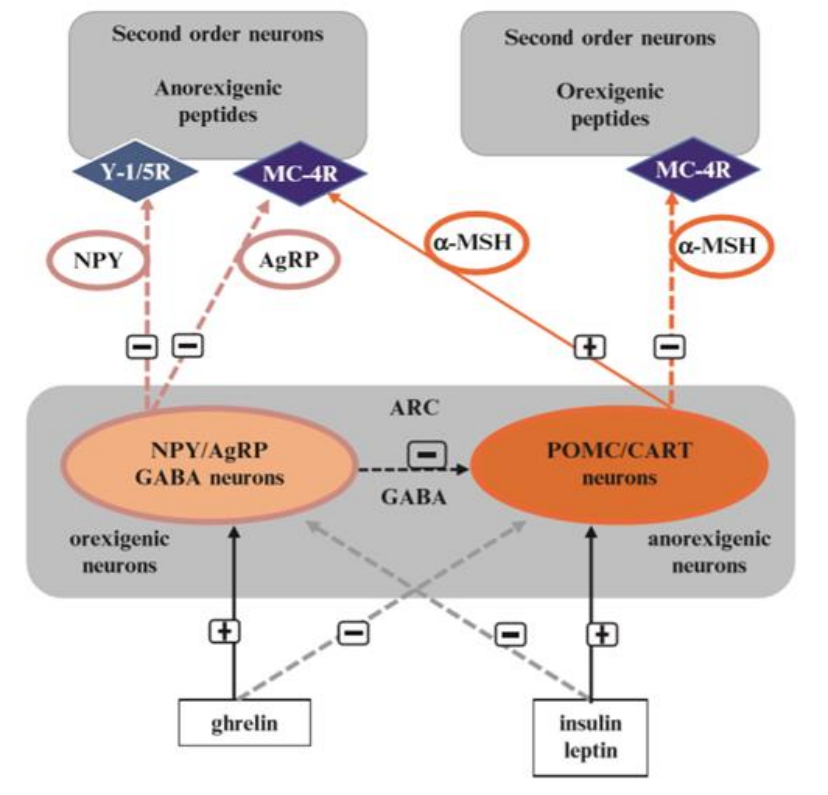

Figure 1. *Arcuate nucleus and its orexigenic and anorexigenic neuropeptide connections (Matafome & Seiça, 2017).*

3.4 NPY/AgRP neurons

NPY is widely expressed throughout the CNS, with the densest localization found in the ARC (Gehlert et al, 1987). NPY responds to fluctuations in energy status, whereas an increase in secretion is seen under fasting conditions (Mizuno et al, 1999). The neuropeptide exerts most of its effects through activation of G-protein-coupled receptor proteins. Five subtypes of NPY receptors have been identified, of which the Y1 and Y5 receptors stimulate food intake and decrease energy expenditure (Kienast et al, 2019; Yulyaningsih et al, 2011).

Adminstration or genetic overexpression of NPY results in hyperphagia and decreased energy expenditure, through inhibition of brown adipose tissue (BAT) thermogenesis, resulting in an obese phenotype (Ruohonen et al, 2012; Shi et al, 2013; Stanley et al, 1985; Yang et al, 2009; Zhang & Bi, 2015).

AgRP is exclusively expressed within the ARC, where fasting conditions enhance release of the neuropeptide (Cowley et al, 2001). AgRP is mainly released into the synaptic space of the PVN, where it acts as an inverse agonist to the G-protein-coupled melanocortin 3 and 4 (MC3/4) receptors. These melanocortin receptors are activated by POMC-derived, α-melanocyte-stimulating hormone (α-MSH), and antagonized by AgRP (Figure 2; Jackson et al, 2006; Reichenbach et al, 2013). Genetic overexpression or administration of the neuropeptide yields increased food intake and reduced energy expenditure, leading to obesity (Graham et al, 1997; Ilnytska & Argyropoulos, 2008; Small et al, 2003). AgRP neurons have connections to the mesolimbic system, attributing to an increased motivation to eat (Krashes et al, 2011). It has been reported that orexigenic effects of AgRP lasted for several days after administration (Hagan et al, 2000).

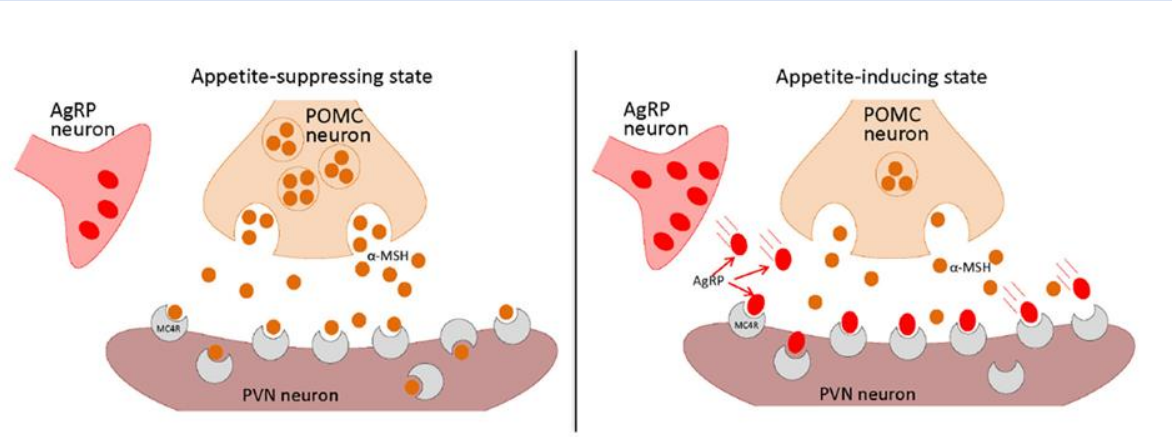

Figure 2. *Antagonistic interaction between AgRP and POMC-derived α-MSH for MC4 receptor binding at neurons of the PVN (Reichenbach et al, 2013).*

Besides NPY and AgRP, inhibitory γ-aminobutyric acid (GABA) is released from the orexigenic neurons. GABA inhibits activity of POMC/CART neurons (Figure 1). Output of GABA on these neurons is increased during fasting conditions, leading to an increase in food intake (Cowley et al, 2001). It has therefore been suggested that the orexigenic effects of GABA are accomplished by inhibition of the anorexigenic POMC/CART neurons, rather than actively activating an orexigenic pathway (Jeong et al, 2014; Waterson & Hovarth, 2015). It seems that NPY and GABA are mainly involved in acute feeding mechanisms, whereas AgRP does have a role in long-term regulation through its competition with α-MSH for the MC3/4 receptors (Wilson & Enriori, 2015).

3.5 POMC/CART neurons

The precursor polypeptide POMC is cleaved by prohormone convertase 1 and 2 (PC1/2) into multiple peptide hormones (Figure 3; Arnason et al, 2012), including α-MSH, corticotropin-

like intermediate lobe peptides (CLIP) and adrenocorticotrophic hormone (ACTH; Wardlaw, 2011). Release of α-MSH is increased during feeding conditions (Schwartz et al, 1997). The catabolic and anorexigenic effects of the neuropeptide are exerted by binding to MC3/4 receptors, which are highly expressed within the PVN (Krashes et al, 2016; Mountjoy, 2015; Sekar et al, 2017). There is an antagonistic interaction between α-MSH and AgRP for these receptors, as it was mentioned before (Figure 2). Binding of α-MSH to these receptors reduces food intake, while energy expenditure is enhanced (Könner et al, 2009). The role of MC3 receptors seems to be directed towards thermogenesis and BAT activity. Mice with MC3 receptor knockout became obese without an increase in food intake (Chen et al, 2000). Mutations of POMC or the MC4 receptor have been reported in both rodents and humans, leading to hyperphagia and an increased risk of developing obesity (Çetinkaya et al, 2018; Farooqi et al, 2006; Huszar et al, 1997; Iepsen et al, 2018; Krude et al, 2003).

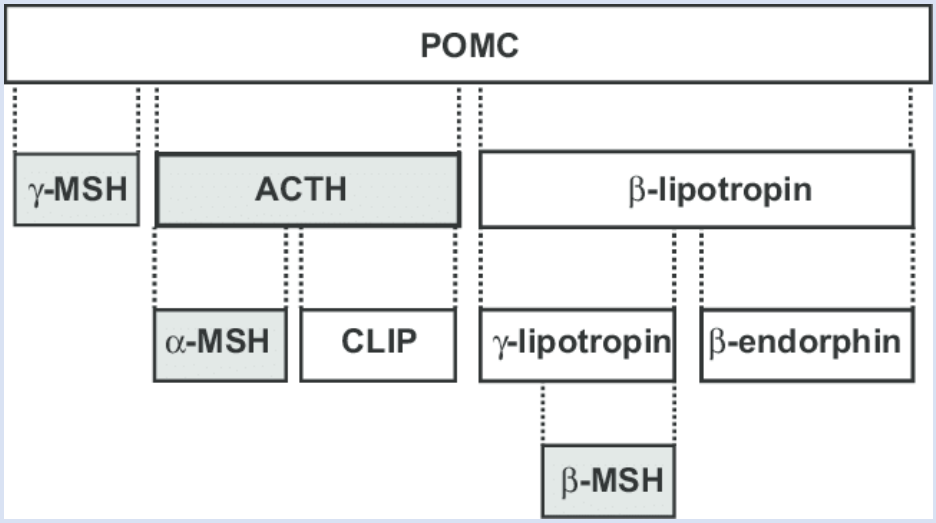

Figure 3. *Production of melanocortin peptides derived from POMC (Arnason et al, 2012).*

Most of the POMC neurons in the ARC co-express CART (Gilon et al, 2016). It is assumed that CART has metabolic properties, but to date no receptor to which the neuropeptide binds has been identified and the exact function remains unclear. A Leu34Phe missense mutation in proCART has been linked to hyperphagia, a reduced resting metabolic rate, and obesity in humans (del Giudice et al, 2006; Yanik et al, 2006). Blocking CART-activity with antibodies enhanced food intake (Lau & Herzog, 2014).

3.6 Paraventricular nucleus

Neurons of the PVN are described as second-order neurons. Signals from the ARC and other hypothalamic brain regions, such as LHA-derived orexin, are integrated by the neurons. The PVN is also connected to the nucleus of tractus solitarius (NTS), which is part of the brainstem, and expresses receptors for multiple hormones, including insulin, leptin and ghrelin (Jeong et al, 2014; Kirouac et al, 2005; López et al, 2007; Sutton et al, 2016; Wilson & Enriori, 2015). Hyperphagia, reduced energy expenditure and early onset of obesity were seen after lesions of the PVN (Leibowitz et al, 1981; Shor-Posner et al, 1986). Similar effects occurred with haploinsufficiency of transcription factor single minded 1 (SIM1), which is

critical in the development of the nucleus (Xi et al, 2013). These findings indicate that the neuropeptides secreted by the PVN have catabolic and anorexigenic properties. The PVN synthesizes and secretes thyrotropin-releasing hormone (TRH), corticotrophin-releasing hormone (CRH), and oxytocin (Abdalla, 2017; Rui, 2013).

It has been long known that CRH reduces food intake and stimulates energy expenditure (Richard et al, 2000). The hypothalamic-pituitary-adrenal (HPA) axis is regulated by CRH, trough the CRH-ACTH-GC system (Mastorakos & Zapanti, 2013; Toorie & Nillni, 2014; Toorie et al, 2016). CRH signals to the pituitary gland to release ACTH, which in turn increases the release of glucocorticoids (GC) from the adrenal gland (Figure 4; Everyday Health, 2019). GCs, including cortisol, are involved in stress management. It has been demonstrated that acute stress leads to a reduction in hunger, while chronic stress enhances food intake (Bartolomucci et al, 2009; Bellisle et al, 1990; Vicennati et al, 2011; Wardle et al, 2000; Willner et al, 1996). Chronic elevation of GCs has been linked to hyperphagia and obesity (Kovacs, 2013; Vale et al, 1981). A strong favour towards highly palatable foods under stressful conditions is directed by GCs (Francis et al, 2013; George et al, 2010).

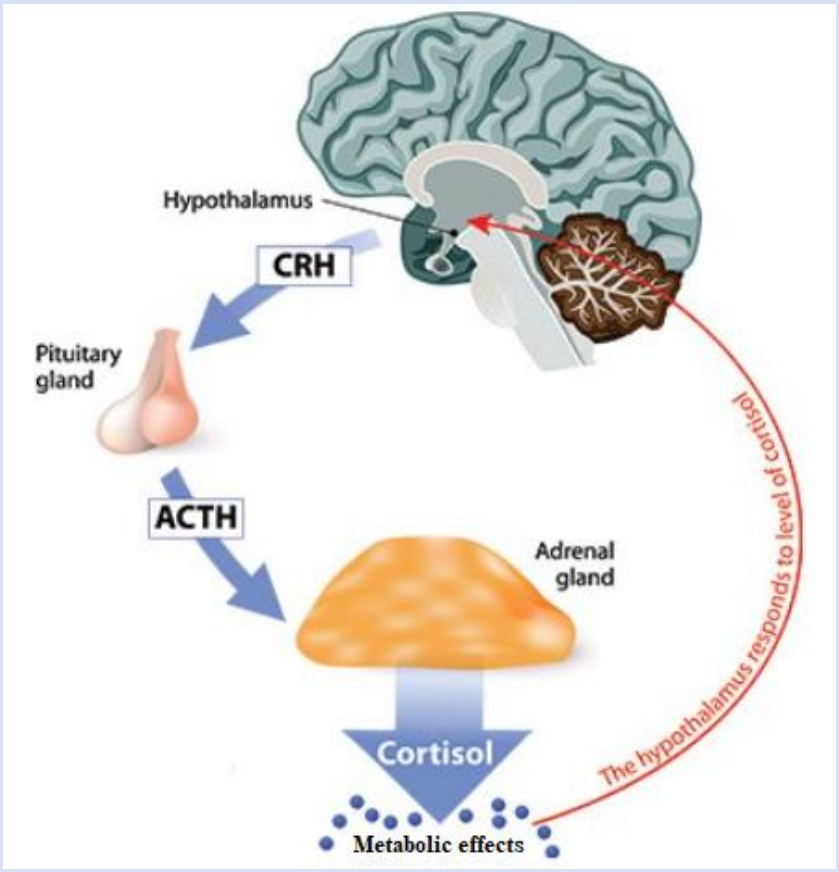

Figure 4. *Regulation of the HPA axis, through the CRH-ACTH-GC system (Everyday Health, 2019).*

TRH is involved in feeding behaviour, thermogenesis and locomotor activity. Expression of TRH is decreased under starving conditions (Abel et al, 2001). The neuropeptide inhibits activity of AgRP, while simultaneously exciting the activity of α-MSH (Fekete et al, 2000;

Fekete et al, 2001; Ghamari-Langroudi et al, 2010). TRH also modulates melanin-concentrating hormone (MCH) neurons in the LHA, subsequently reducing food intake (Zhang & van den Pol, 2012). Histamine, of which the release is stimulated by TRH, serves a role in body weight regulation. Blocking of the neurotransmitter or its receptors results in hyperphagia and obesity (Gotoh et al, 2007; Hegyi et al, 2004; Masaki et al, 2004). Another property of TRH is increasing metabolic rate, through stimulation of the hypothalamic-pituitary-thyroid (HPT) axis (Joseph-Bravo et al, 2015).

Oxytocin is involved in a variety of biological processes, including feeding behaviour and energy homeostasis (Lawson et al, 2017). The neuropeptide is released in different brain regions involved in energy metabolism, including the ARC, NTS, ventral tegmental area (VTA) and spinal cord (Maejimi et al, 2014; Sabatier et al, 2007; Sawchenko & Swanson, 1982; Shahrokh et al, 2010). Oxytocin inhibits food intake and stimulates thermogenesis (Chaves et al, 2013). A loss of function mutation in oxytocin is one of many possible genetic defects underlying Prader-Willi syndrome. Patients with this disease are characterized by constant hunger, often leading to obesity (Genetics Home Reference, 2020; Swaab et al, 1995).

3.7 Ventromedial nucleus

The VMN plays a role in energy homeostasis and is involved in processing and integrating signals of hunger and satiety. These signals mainly come from the adiposity hormones insulin and leptin (King, 2006; Routh, 2010). Lesion of the nucleus or deletion of leptin receptors within the nucleus leads to hyperphagia and early onset of obesity (Satoh et al, 1997). After lesion of the nucleus, insulinemia and glycemia became apparent (Berthoud & Jeanrenaud, 1979). A more recent study found that male rats did not become hyperphagic after lesion of the VMN, although they exhibited significant weight gain, attributed to metabolic changes (Dev et al, 2012).

A critical factor for postnatal development of the VMN is steroidogenic factor 1 (SF1). Deletion of SF1 disrupts thermogenesis and results in diet induced obesity (Choi et al, 2013; Kim et al, 2011; Majdic et al, 2002). Insulin and leptin stimulate synthesis of brain-derived neurotrophic factor (BDNF) in the VMN. This neuropeptide binds to tropomyosin receptor kinase B (TrkB), which is widely expressed within the hypothalamus (Cordeira & Rios, 2011; Kernie et al, 2000; Noble et al, 2011). Several catabolic and anorexigenic factors and receptors within the PVN are stimulated by BNDF, including CRH, oxytocin, urocortin and MC4 receptors (Jeanneteau et al, 2012). Absence or genetic defects to either BDNF or TrkB have been linked to hyperphagia and obesity (Rothman et al, 2012; Yeo et al, 2004).

3.8 Dorsomedial nucleus

The DMN plays a vital role in regulating a variety of biological processes, ranging from the circadian rhythm and fluid balance, to feeding behaviour and body weight regulation (Chou et al, 2003). High levels of α-MSH and NPY terminals, originating from the ARC, are found within the DMN (Broberger et al, 1998; Jacobowitz & O'Donohue, 1978). NPY expression is high under conditions requiring an increased energy demand, such as fasting conditions (Bi et al, 2003). Adminstration or genetic overexpression of NPY in the DMN causes hyperphagia and obesity (Yang et al, 2009; Zheng et al, 2013). NPY influences energy expenditure, through modulating BAT activity and thermogenesis (Bi et al, 2012). As expected,

knockdown of NPY in the DMN resulted in decreased food intake and reduced body weight. Moreover, was development of BAT promoted and impaired glucose tolerance in diet-induced obesity models reversed (Chao et al, 2011; Kim & Bi, 2016). The nucleus does also integrate peripheral signals from the GI tract and bloodstream, including adiposity and satiety signals. Destruction of the DMN results in hyperphagia and reduced locomotor activity, subsequently leading to obesity (Bernardis & Bellinger, 1986; Gooley et al, 2006; Li et al, 2016).

3.9 Lateral hypothalamic area

The LHA is involved in energy homeostasis, having impact on feeding behaviour, locomotor activity, and sleeping patterns (Brown et al, 2015). Whereas the PVN, VMN, and DMN are satiety centres, the LHA is a feeding centre, having an essential role in mediating orexigenic signals. The homeostatic and hedonic systems are connected through the LHA, which projects neurons to the mesolimbic reward system, implying its role in motivational eating behaviour (López et al, 2007; Harrold et al, 2012; Sobrino Crespo et al, 2014). Electrical stimulation of the nucleus induces feeding behaviour, even in well-fed animals (Stuber & Wise, 2016). Studies in rats revealed that lesion of the LHA caused them to lose motivation to eat and drink. Ultimately, self-inflicted starvation and dehydration caused these rats to die (Anand & Brobeck, 1951; Morrison et al, 1958). Lesion of the LHA results in hypophagia and weight-loss, together with severe muscle wasting (Carmichael & Braunstein, 2009). The peptides orexin and MCH are secreted by the nucleus.

Orexin, also called hypocretin, is present in two isoforms: orexin A and B. They bind to orexin 1 and 2 (OX1/2) receptors, both being widely expressed throughout the brain. Expression of orexin is increased during fasting conditions. Blood glucose levels influence these neurons, whereas they are stimulated during hypoglycaemia (Burdakov et al, 2013). MCH neurons, which are co-expressed within the LHA, are stimulated by orexin (Tsujino & Sakurai, 2009; van den Pol et al, 2004). Meal size is increased after activation of the OX1 receptors in the hindbrain, while projections to the VTA enhance food reward and sense of hunger (Parise et al, 2011). Similar findings were seen in studies where orexin was administrated; food intake and behavioural responses to food as a reward were promoted (Cason et al, 2010; Dube et al, 1999; Sakurai et al, 1998). Orexin knockout or impairment of orexin neurotransmission in the brain does not only cause hypophagia and obesity, but narcolepsy becomes apparent as well (Chieffi et al, 2017). This disease is characterized by periods of excessive sleepiness and involuntary sleep episodes during the day. Narcoleptic patients have an increased risk of becoming overweight or obese (National Institute of Neurological Disorders and Stroke, 2019).

Expression of MCH is increased during fasting conditions (Hu et al, 2008). MCH neurons project to the spinal cord and nucleus accumbens (NAc), the latter being a key component in the mesolimbic system. Chronic administration of MCH causes hyperphagia and a decrease in energy expenditure and body temperature, subsequently leading to obesity (Glick et al, 2009; Ludwig et al, 2001). Deficiencies to either the MCH gene or its receptors result in a lean phenotype in animals, because of reduced food intake (Shimada et al, 1998). Although MCH is able to bind to both the MCH1 and MCH2 receptor, their orexigenic activity is mainly mediated through MCH1 receptors. Mice with knockout of the MCH1 receptor became resistant to diet-induced obesity. These animals were also found to have increased energy expenditure and locomotor activity (Marsh et al, 2002).

3.10 Brainstem

Besides the hypothalamus, the brainstem is another key brain area involved in control of feeding behaviour and energy homeostasis (Figure 5; Suzuki et al, 2010). The dorsal vagal complex (DVC) in the brainstem senses circulating metabolites and hormones derived from peripheral organs, relaying them to the hypothalamus (Nillni, 2018). The DVC can therefore be described as the major neuronal connection between the gut and the brain. The dorsal motor nucleus of the vagus nerve (DVN), NTS, and area postrema (AP) are morphologically distinct areas within the DVC. The AP is comparable to the hypothalamic ME, in a sense that this organ also has a semi-permeable blood-brain barrier, allowing the influx of circulating hormones and nutrient signals from the bloodstream. Vagal signalling from the GI tract is an important afferent to the NTS, which receives information about luminal distension, nutrient content and locally produced peptides (Travagli et al, 2006). Gut hormones that are released upon food intake include CCK, GLP-1, and PYY. These hormones have receptor terminals of the vagus nerve (Roh & Kim, 2016). Hormonal signals are delivered to the hypothalamus via the NTS, where they induce satiety (Abbott et al, 2005; Yu & Kim, 2012). The role of the afferent vagus nerve in feeding behaviour has been demonstrated in multiple studies. Chronic or acute stimulation of the nerve led to a decrease in food intake and reduced body weight (Gil et al, 2011; Pilot & Grill, 2018; Yao et al, 2018; Ziomber et al, 2009).

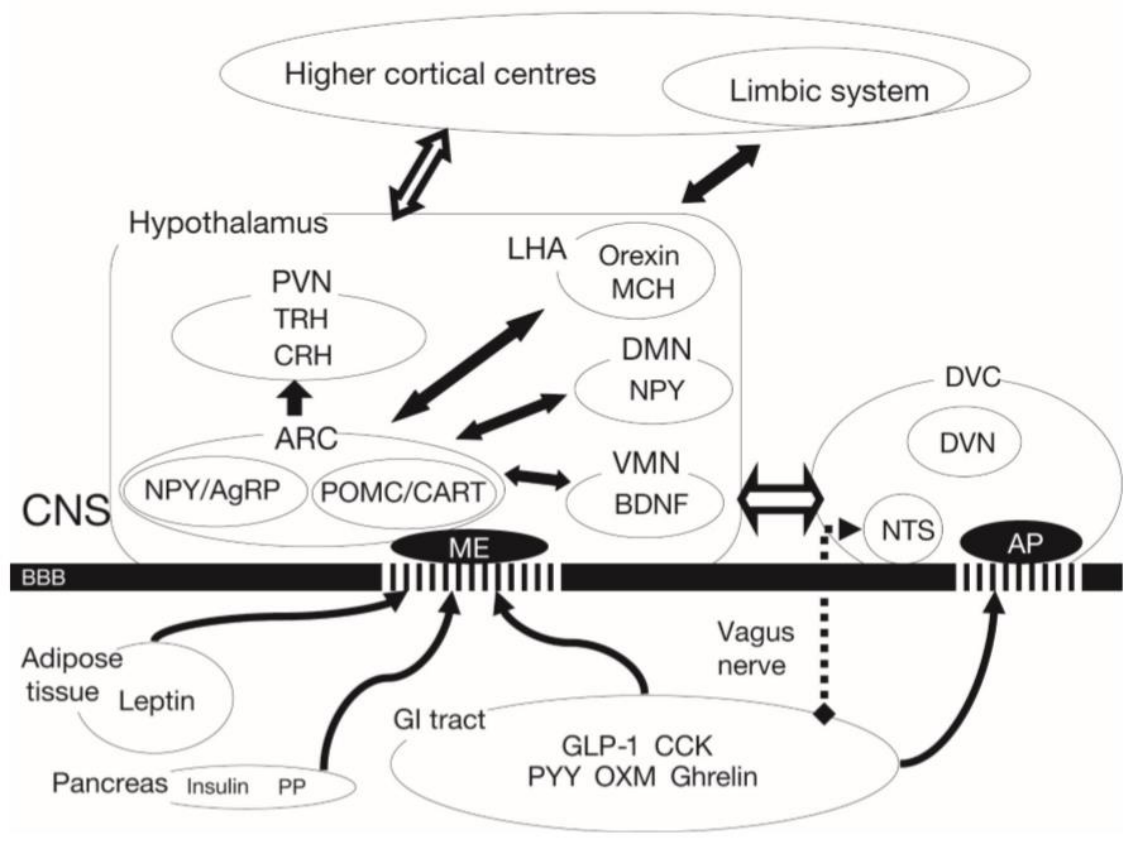

Figure 5. *Appetite regulation is under control of complex neuronal pathways with connections between the hypothalamus, brainstem and higher cortical centres (Suzuki et al, 2010).*

3.11 Hedonic reward system

The hypothalamus and brainstem mainly mediate homeostatic control of eating behaviour, while hedonic and reward feeding involves cognitive and emotional aspects of eating (Lo Preiato et al, 2018). Independent of current energy status, the desire to consume palatable food may override the physiological need to eat (Matafome & Seiça, 2017). Homeostatic and hedonic feeding circuits are closely integrated and connect to each other (Figure 5; Leigh & Morris, 2018; Yu et al, 2015). The hedonic circuits consist of complex interactions between mesolimbic-, opioid- and endocannabinoid systems, which interact with other brain areas including the amygdala, hippocampus, VTA and NAc. The LHA has direct effect on these pathways, as it is connected to neuronal circuits of both the VTA and NAc (Abdalla, 2017; López et al, 2007).

A central component of hedonic feeding is the mesolimbic dopaminergic system. Orexin and MCH, originating from the LHA, are projected to dopamine neurons. Dopamine and its dopamine 2 (D2) receptor are regulators of pleasure and emotion. Ingestion of palatable food elicits dopamine release from its neurons within the VTA, in turn activating neuronal pathways to the NAc and prefrontal cortex (Roseberrya et al, 2015; Yu & Kim, 2012). It is suggested that dopamine has a major role in the development of obesity in humans. An inverse correlation has been found between BMI and the presence of D2 receptors (Haltia et al, 2007; Volkow et al, 2011). Dopaminergic neuron activity influences feeding behaviour, through peripheral metabolic signals derived from adipose tissue and the GI tract (Hagan & Niswender, 2012; Hommel et al, 2006). Leptin for example, inhibits orexin and MCH activity, blunting their projections to dopamine neurons (Khanh et al, 2014). Ghrelin on the other hand, enhances hedonic food-related responses upon activation of its receptors in the VTA (Harrold et al, 2012; Malik et al, 2008). The exact relation between dopamine and energy expenditure is unclear. It is believed that dopamine can promote energy expenditure, but does this rather as a function of upcoming reward, than as a function of the energy cost itself. Reward-based decisions were of stronger influence than effort-based decisions (Beeler et al, 2012; Le Bouc et al, 2016; Walton & Bouret, 2019).

Another system involved in hedonic control of food intake is the endocannabinoid system. The two main endocannabinoids are 2-arachdonoylglycerol (2-AG) and N-arachidonoyl-ethanolamine (anandamide). These endogenous ligands for the cannabinoid (CB) receptors are produced from phospholipase D in the brain (Devane et al, 1992). Fasting conditions increase expression of endocannabinoids, while levels decrease after the ingestions of food (Kirkham et al, 2002). The specific receptors that they bind to are the CB 1 and 2 receptors. The CB1 receptor is predominantly expressed in tissues associated with energy homeostasis, including the hypothalamus, brainstem, and mesolimbic system, whereas the CB2 receptor is expressed on immune cells. The effects of endocannabinoids on energy homeostasis are therefore mediated through CB1 receptors (Cristino et al, 2014). Activation of this receptor leads to a preference of palatable food intake. Administration of endocannabinoids into the VMN causes hyperphagia, even in satiated rats (Jamshidi & Taylor, 2001; Mahler et al, 2007). Activation of the CB1 receptor on adipocytes and in the liver promotes lipogenesis and decreases energy expenditure (Gamage & Lichtman, 2012).

4. Peripheral hormones in feeding behaviour and energy homeostasis

Peripheral hormones and neurotransmitters are known to influence food intake and energy expenditure. They are either released and stimulated during fasting conditions, meal anticipation, or the actual luminal presence of nutrients (Suzuki et al, 2011). The GI tract, pancreas and adipose tissue release more than 20 different regulatory hormones and over 100 bioactive peptides (Lean & Malkova, 2016). These peripheral factors play critical roles in controlling and maintaining food intake and energy homeostasis. Moreover, are they involved in termination of meals and feelings related to hunger and satiety. There is a distinction between episodic and tonic signals (Figure 6; Blundell et al, 2012). Episodic signals are involved in short-term regulation of hunger and satiety and act mainly inhibitory, oscillating with eating patterns. Tonic signals influence long-term metabolic needs, and the amount of energy stored as fat mediates release (Halford & Blundell, 2000; Hopkins et al, 2016; Lo Preiato et al, 2018).

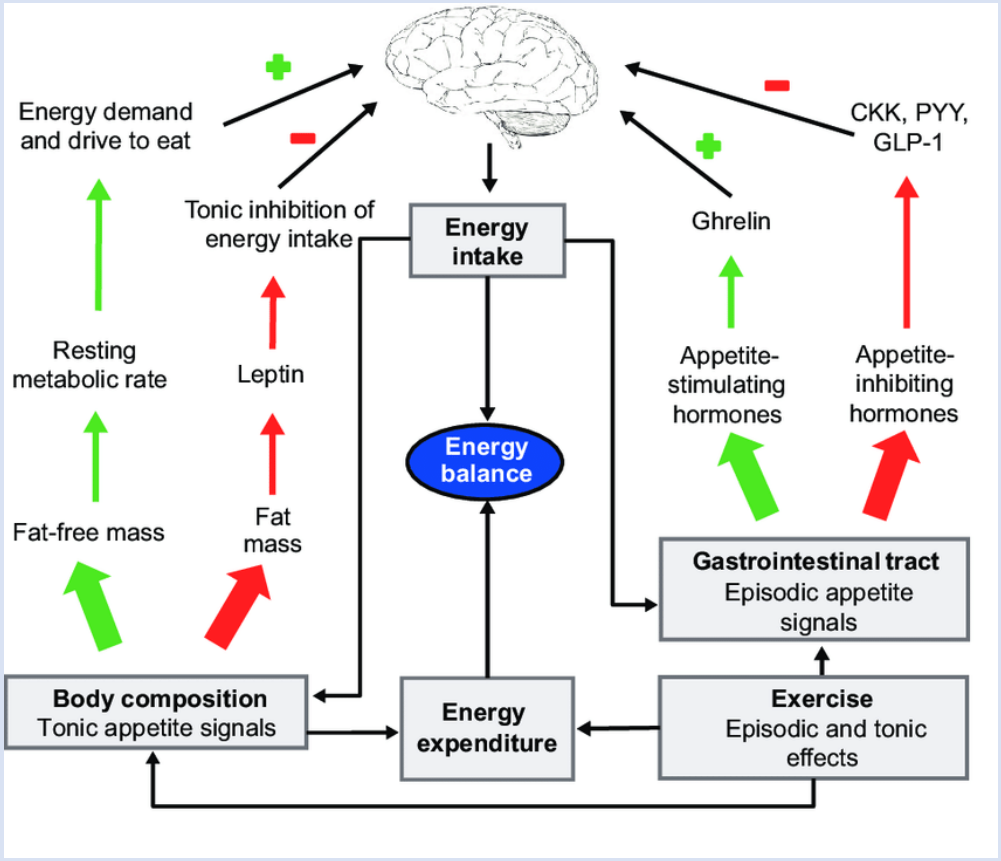

Figure 6. *Appetite regulation is under control of tonic and episodic signals (Blundell et al, 2012).*

4.1 Leptin

Leptin is one of the most important tonic appetite signals (Lo Preiato et al, 2018; Zhang et al, 1994). This hormone is mainly released from white adipose tissue (WAT), in proportion to fat stores in the body (van Swieten et al, 2014). Total fat mass and circulating leptin levels are correlated, indicating the role of the hormone in body weight maintenance. Leptin release

is stimulated in the presence of excess nutrient availability, supressing appetite. Fasting conditions on the other hand, decrease circulating leptin levels in order to stimulate appetite (Münzberg & Morrison, 2015; Sahu et al, 2003; Schwartz et al, 2000). Rising leptin levels postprandially, enhance energy expenditure, whereas fasting conditions inhibit sympathetic nerves activity, thyroid hormones action, and BAT thermogenesis (Hardwood, 2012; Pandit et al, 2017).

Leptin has three receptors to which it can bind; the short intracellular domain (OB-a), long form (OB-b) and secreted form (OB-c) receptors. OB-b receptors are highly expressed in the ARC, DMN, and VMN. Upon activation, the receptors are responsible for supressing appetite and stimulating energy expenditure through BAT thermogenesis (Fei et al, 1997; Parimisetty et al, 2016; Park & Ahima, 2015). Leptin receptors are expressed on both NPY/AgRP and POMC/CART neurons in the ARC, where leptin inhibits activity of NPY/AgRP neurons, reducing the release NPY, AgRP, and GABA. Conversely, leptin increases neuronal activity of POMC/CART neurons, stimulating the secretion of α-MSH (Münzberg 2010). As mentioned before, the results of these leptin mediated actions are a reduction in food intake and an increase in energy expenditure. Due to its projections to other nuclei, leptin activity in the ARC activates oxytocin, CRH, and TRH neurons in the PVN. In the LHA, inhibition of orexin and MCH neurons are the result of leptin derived projections from the ARC (Matafome & Seiça, 2017). Improved glucose and lipid metabolism are also attributed to leptin action in the hypothalamus (Minokoshi et al, 2012; Roh et al, 2016). Moreover, leptin is involved in the mesolimbic dopaminergic system, where it reduces food intake via D2 receptor signalling (Billes et al, 2012; Farooqi et al, 2007). The response to sweet taste is selectively suppressed through leptin signalling (Nakamura et al, 2008; Yoshida et al, 2015). Mutations to either leptin or the leptin receptor genes have been linked to obesity (Dubern & Clement, 2012; Montague et al, 1997; Wabitsch et al, 2015; Yupanqui-Lozno et al, 2019).

4.2 Ghrelin

Ghrelin, commonly dubbed as the hunger hormone, is the only known gut hormone with orexigenic properties (Kojima et al, 1999). The hormone is mainly synthesized and secreted by P/D1-type cells in humans, and X/A-like-type cells in rodents, found within the gastric oxyntic fundic mucosa (Kojima & Kangawa, 2010). Levels of the hormone peak before meal consumption, decline postprandially, and then gradually rise until the next preprandial peak (Cummings, 2006). All three macronutrients reduce ghrelin levels; however, the greatest postprandial satiety responses are elicited after consuming high-protein and high-fat meals (Rizi et al, 2018). Circulating hormones, recruited after food consumption, are also able to decrease ghrelin levels. The circulating hormones include CCK, PPY, and GLP-1 (Monteiro & Batterham, 2017).

In order for ghrelin to become biologically active, a few essential steps are required (Figure 7; Au et al, 2017). The 117-amino acid precursor peptide preproghrelin is cleaved into a 23-amino acid signal peptide and the 94-amino acid segment proghrelin. Proghrelin undergoes a unique posttranslational modification, in which the enzyme ghrelin O-acyltransferase (GOAT) catalyses octanoylation at the Ser3 position of the molecule. PC1/3 further cleaves octanoylated proghrelin, yielding the now biological active ghrelin and another fragment named obestatin (Gutierrez et al, 2008; Takahashi et al, 2009; Yang et al, 2008; Zhu et al, 2006). The major form of ghrelin in the circulation is des-octanoylated ghrelin, also called des-ghrelin. The exact function and role of this molecule in the body remains questionable. Des-ghrelin improves postprandial insulin levels and sensitivity (Callaghan & Furness, 2014;

Stoyanova, 2014). However, studies on the effect of des-ghrelin on appetite and body weight have shown diverse results (Chen et al, 2005; Toshinai et al, 2006).

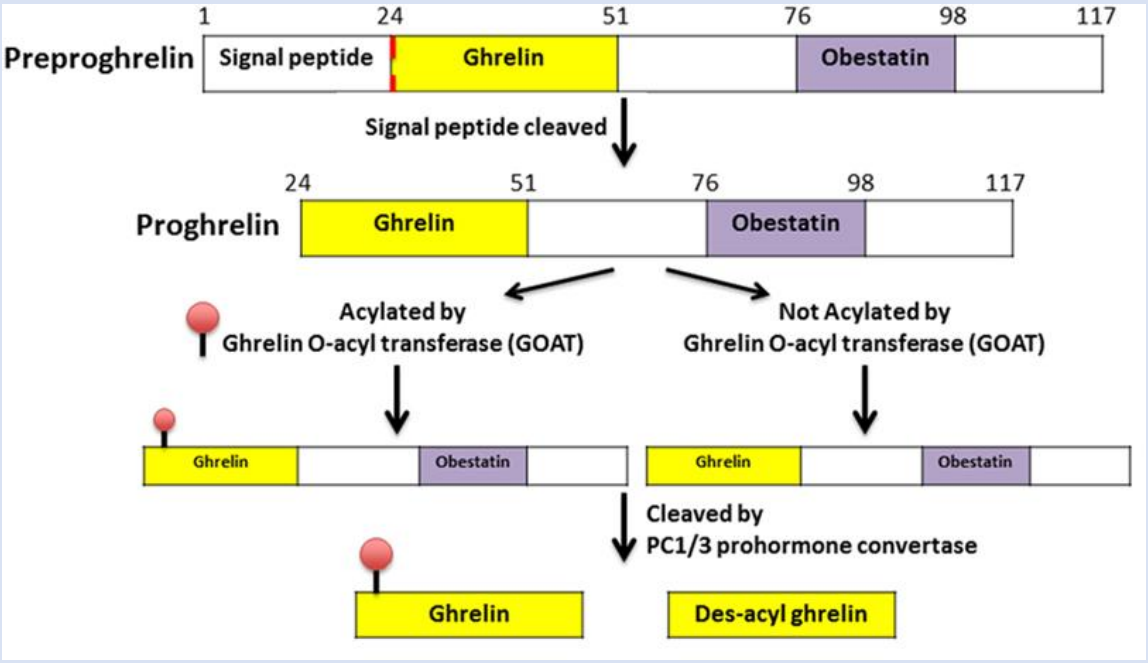

Figure 7. *Processing and acylation of ghrelin (Au et al, 2017).*

The only known receptor to which ghrelin can bind, is the growth hormone secretagogue (GHS) receptor type 1a. This receptor is widely expressed throughout different regions of the CNS, including the hypothalamus, pituitary gland, brainstem and mesolimbic circuits (Bailey et al, 2000; Cruz & Smith, 2008). A high expression of the receptor is found on NPY/AgRP neurons within the ARC. These neurons play an important role in mediating the orexigenic actions of the hormone. Ghrelin enhances enzymatic degradation of catabolic and anorexigenic α-MSH (Kwon Jeong et al, 2013). Activation of the GHS1a receptor increases food intake, decreases energy expenditure and promotes fatty acid storage in adipocytes (Lv et al, 2018; Mihalache et al, 2016; Perello & Raingo, 2014). Knockout of NPY/AgRP in mice abolished ghrelin's orexigenic effects on feeding behaviour (Chen et al, 2004). Ghrelin does also influence feeding behaviour through vagal afferent activity, where vagotomy blunted the orexigenic effects of the hormone (Arnold et al, 2006; Williams et al, 2003). Moreover, ghrelin stimulates food reward and dopamine release in the mesolimbic dopaminergic system, enhancing motivation to consume highly palatable foods (Abizaid et al, 2006; Dickson et al, 2011; Naleid et al, 2005; Skibicka et al, 2011; Skibicka et al, 2013).

4.3 Pancreatic polypeptide

Pancreatic polypeptide (PP) is mainly secreted from F cells, found in the pancreatic islets of Langerhans, and to a lesser extent from the colon and rectum (Hameed et al, 2009; Khandekar et al, 2015; Wren & Bloom, 2007). Levels of the polypeptide are low during fasting conditions and rise postprandially, in proportion to the number of calories ingested during a meal (Sobrino Crespo et al, 2014; Track et al, 1980). Low glucose levels, gastric

distension and physical activity also enhance the release of PP. Moreover, a variety of hormones enhance PP release, including motilin, gastrin and secretin (Field et al, 2008; Huda et al, 2006). Enhanced circulating levels of PP are sustained for several hours postprandially, suggesting that the peptide might serve a role as long-term regulator of feeding behaviour (Chaudbri et al, 2006; Choudhury et al, 2016; Mishra et al, 2016).

Although PP can bind to all Y receptors, it has the highest affinity for Y4 receptors, which are highly expressed in the hypothalamus and brainstem (Blomqvist & Herzog, 1997; Tasan et al, 2009). Binding of PP to the Y4 receptor decreases food intake, gastric emptying, and gallbladder motility, while energy expenditure is increased (Holzer et al, 2012; Lean & Malkova, 2016). It has been demonstrated in multiple studies that peripheral administration and transgenic overexpression of PP indeed lead to the aforementioned conditions, attributed to reduced hypothalmic expression of NPY and orexin, while simultaneously increasing BDNF (Batterham et al, 2003; Khandekar et al, 2015; Liu et al, 2008; Sainsbury et al, 2010; Ueno et al, 1999).

4.4 Peptide YY

Peptide tyrosine tyrosine (PYY) is a member of the pancreatic polypeptide-fold family, to which PP and NPY also belong (Wynne & Bloom, 2006). Members of this family share a similar structural homology, with tyrosine residues at both the N- and C-terminus (Tatemoto & Mutt, 1980). Two forms of PYY are found in the circulation. L cells of the ileum and colon mainly secrete PYY_{1-36}. The enzyme dipeptidyl-peptidase IV (DPPIV) mediates cleavage of the tyrosine-proline residue at the N-terminus of PYY_{1-36}, resulting in the major circulating form PYY_{3-36} (Eberlein et al, 1989; Grandt et al, 1993; Spreckley & Murphy, 2015). Levels of PYY in the circulation are low during fasting conditions and rise rapidly postprandially, with levels of the hormone being proportional to caloric intake and macronutrient content (Degen et al, 2005). Meals high in protein elicit greater PPY release compared to that of high-fat and -carbohydrate meals with similar calorie content (Lomenick et al, 2009). PYY levels peak around 60 – 90 minutes postprandially, and remain elevated for several hours (Adrian et al, 1985)

PYY binds to Y receptors: PYY_{1-36} has affinity to all Y receptors, whereas PYY_{3-36} has the highest affinity for Y2 receptors (Dumont et al, 1995; Keire et al, 2000). Y2 receptors are expressed in vagal afferents and in the brain. Especially the ARC has a high expression of these receptors, where they are located at presynaptic terminals of NPY neurons (Steinert et al, 2017). Release of NPY neurotransmitters is inhibited upon activation of the Y2 receptor (Stadlbauer et al, 2015). Increased satiety was seen after administration of PYY_{3-36}, which led to a reduction in food intake and body weight (Batterham et al, 2003; Karra et al, 2009; le Roux et al, 2006; Manning & Batterham, 2014; Stanley et al, 2004; Vrang et al, 2006). Although most studies have focused on feeding behaviour, there is evidence that PYY_{3-36} has beneficial effects on energy expenditure. Studies in both rodents and humans found that PYY_{3-36} increases energy expenditure and fat oxidation rates, but underlying mechanisms have yet to be described (Adams et al, 2006; Sloth et al, 2007; van den Hoek et al, 2007)

4.5 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is derived from the proglucagon gene, expressed in the intestine, pancreas, and brain. A variety of peptides are produced from glucagon after tissue-

specific posttranslational processing (Figure 8; Baggio & Drucker, 2007; Marathe et al, 2013; Rix et al, 2019). Cleavage of proglucagon by PC2 in α-cells of the pancreas yields glicentin-related pancreatic peptide (GRPP), glucagon, intervening peptide 1 (IP-1) and major proglucagon fragment (MPGF). Processing of proglucagon by PC1/3 in the intestine and brain results in GLP-1, GLP-2, oxyntomodulin (OXM), IP-2, and glicentin (Pocai, 2012). Two active forms of GLP-1 with similar bioactive and metabolic properties are known: GLP-1 (7-36)-amide and GLP-1 (7-37). Both forms of GLP-1 are synthesized and secreted by L-cells, located in the ileum and colon (Cho et al, 2014). Levels of the peptide hormone are low after periods of fasting. Secretion is increased in response to nutrient intake, with sugars and lipids eliciting the greatest response (Holst, 2007; Parker et al, 2010; Vilsbøll et al, 2003).

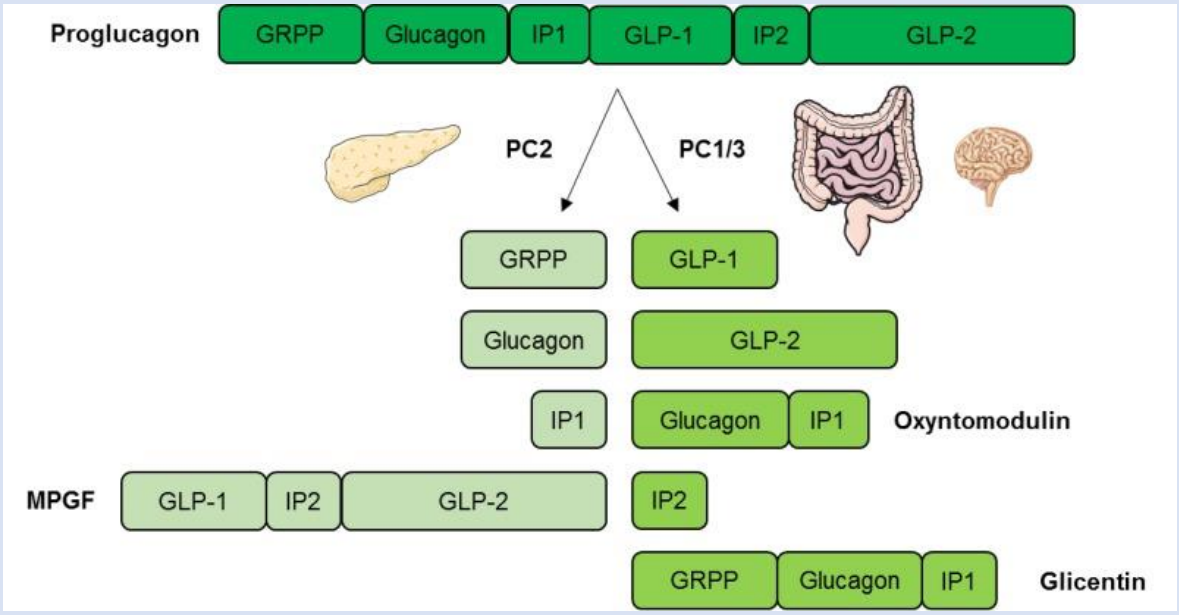

Figure 8. *Tissue-specific posttranslational processing mechanisms of proglucagon (Rix et al, 2019).*

GLP-1 binds to its G protein-coupled GLP-1 receptor. This receptor is part of the glucagon receptor family, and is expressed in peripheral tissues such as the GI tract and pancreas, as well as in different brain areas, including hypothalamic nuclei and neurons of the NTS in the brainstem (Matafome et al, 2017). The peptide hormone acts as incretin, which means that it enhances insulin secretion. GLP-1 is responsible for around 50 – 70% of postprandial insulin secretion after glucose consumption (Kim & Egan, 2008). Moreover, glucagon release is inhibited and gastric emptying delayed, the latter causing a deceleration of nutrient absorption (Campbell & Drucker, 2013; Deane et al, 2010). Some of the anorexigenic properties of GLP-1 could be explained by this delay of gastric emptying (Plamboeck et al, 2013). There is evidence that the hormone also acts anorexigenic by directly acting on feeding centres in the brain (De Silva et al, 2011). GLP-1 neurons project to the VTA and NAc in the brain, implying a role of the hormone in hedonic- and reward feeding (Harrold et al, 2012; Heppner & Perez-Tilve, 2015). Food intake is inhibited by GLP-1 in a dose-dependent manner, whereas administration of GLP-1 antagonists caused hyperphagia and weight gain (Barrera et al, 2011; Gutzwiller et al, 1999; Talsania et al, 2005). An increase in

BAT thermogenesis is seen after administration of GLP-1 (Geloneze et al, 2017; Lockie et al, 2012; Maciel et al, 2018).

4.6 Cholecystokinin

Cholecystokinin (CCK), reported as the first gut hormone to affect appetite and food intake, was discovered at the beginning of the twentieth century (Bayliss & Starling, 1902). The peptide hormone is produced and secreted by I cells in the duodenum and jejunum (Andreoli et al, 2018). Secretion of CCK into the circulation is seen postprandially, stimulated by the presence of nutrients in the lumen (Steinert et al, 2017). Proteins and lipids are the most potent stimulators of CCK secretion, whereas carbohydrates stimulate secretion to a lesser extent (Dockray, 2009). Fifteen minutes after consumption of a meal, plasma CCK levels already start to rise (Liddle et al, 1985).

CCK reduces food intake in both rodents and humans, by initiating satiety (Gibbs et al, 1973; Lieverse et al, 1995; Pi-Sunyer et al, 1982). Abdominal vagotomy blocked the effects of CCK on satiation vagotomy (Smith et al, 1981). Two receptor subtypes to which CCK can bind have been characterized; the CCK1 and CCK2 receptors. These receptors are expressed in vagal afferent fibres, projecting to the NTS in the brainstem, which in turn relay them to the hypothalamus (Corp et al, 1993). It appears that the CCK1 receptors on the vagal nerve, are mainly responsible for mediating the anorexigenic actions of CCK in regulating feeding behaviour (Dourish et al, 1989; Moran et al, 1997). Studies have shown that antagonists of the CCK1 receptor reversed inhibitory effects of CCK on food intake, meanwhile increasing feelings of hunger, leading to the consumption of more calories (Beglinger et al, 2001; Melville et al, 1992). Rats with a knockout of the CCK1 receptor had increased meal sizes and developed obesity in comparison to control animals (Moran & Bi, 2006).

5. Effectiveness of pharmacotherapy in obesity treatment

First line treatment of obesity is lifestyle modification, which consists of diet, exercise, and behaviour therapy (Wadden et al, 2012). Although it is possible to lose weight with lifestyle changes, both short- and long-term efficacy on weight loss is often poor (Franz et al, 2007). Due to metabolic adaptations within the body, sustainable weight loss is hard to maintain. Counter-regulatory alterations in hormonal pathways and mechanisms involved in feeding behaviour and energy homeostasis, result in regain of weight, despite continuing lifestyle changes (Sumithran & Proietto, 2013). A decrease in energy expenditure could last for at least 6 years after the initial weight loss (Fothergill et al, 2016; Hope et al, 2018).

The most effective procedure in obesity treatment is bariatric surgery; of which the Roux-en-Y gastric bypass, laparoscopic adjustable gastric band, and sleeve gastrectomy, are the most commonly performed bariatric surgery procedures (Ponce et al, 2016). These interventions are able to accomplish a significant reduction in body weight (Chang et al, 2014; Padwal et al, 2011). A follow-up study of patients that underwent Roux-en-Y gastric bypass, found that average weight loss after 12 years was 35 kg (Adams et al, 2017). Not only does bariatric surgery decrease body weight, it reduces rates of cardiovascular events, diabetes, cancer and mortality (Sjöström, 2013). Besides the promising and highly effective outcomes of bariatric surgery, there are some major downsides; postoperative complications may arise, and the procedure itself if often very invasive for the patient. Bariatric interventions cause alterations to the anatomy and physiology of the GI tract, making patients more susceptible to

developing nutritional deficiencies. This could lead to malnutrition, osteoporosis, anaemia and postprandial hypoglycaemia (Kang & Le, 2017; Lupoli et al, 2017). Moreover, might patients experience hormonal disturbance and dumping syndrome, characterized by diarrhea, nausea, and abdominal cramps (Jammah, 2015; Ramadan et al, 2016).

Pharmacotherapy could possibly overcome the treatment gap between poor efficacy lifestyle modifications and invasive bariatric interventions (Figure 9). Pharmacotherapy for obesity is directed at either; decreasing energy intake, increasing energy expenditure, modulating fat storage or adipocyte differentiation, or mimicking caloric restriction (Misra, 2013). Current pharmacological drugs only cause minor weight loss. The lipid inhibitor Orlistat for example, reduces dietary fat absorption, but serious adverse side effects include steatorrhea, faecal urgency, and faecal incontinence. Weight loss is small, with only a 3% reduction over the course of a year (Drew et al, 2007; Hope et al, 2018). In the chapter below we discuss how a variety of pharmacological drugs act on the CNS and peripheral hormones, and whether they are effective in treating obesity.

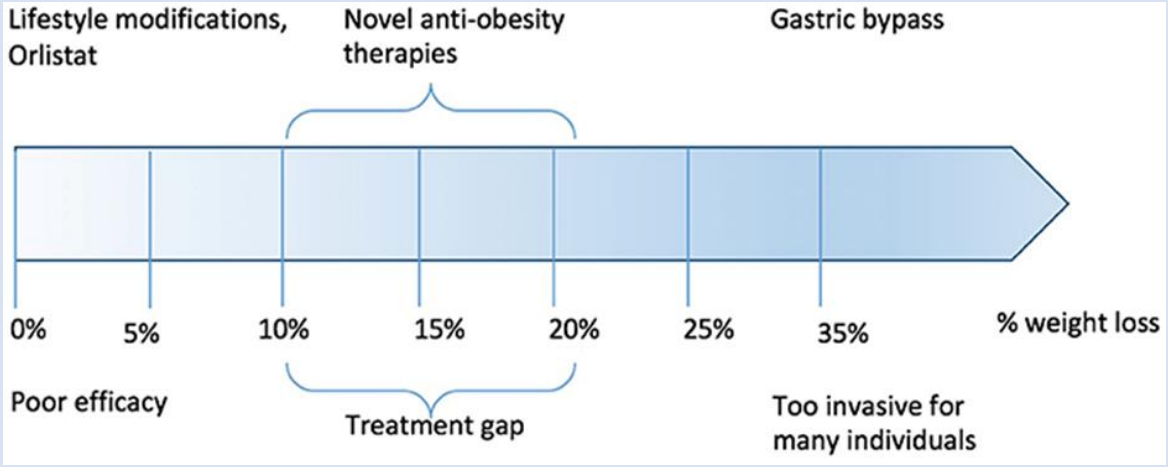

Figure 9. *Obesity therapy has a treatment gap between poor efficacy lifestyle modifications and invasive bariatric interventions (Hope et al, 2018).*

5.1 GLP-1 receptor agonists

Two injectable GLP-1 receptor agonists, namely Liraglutide and Exenatide, were initially approved by the FDA as treatment options for patients with type 2 diabetes mellitus (Yu et al, 2018). Endogenous GLP-1 has a short half-life of approximately 2 minutes. Once it enters the circulations, it is rapidly degraded by DPPIV. Therefore, using GLP-1 as pharmacological drug has little to no potential. Liraglutide and Exenatide are similar in structure to GLP-1, but are proteolysis-resistant, due to small molecular differences. This feature allows them to stay in the circulation for much longer; with Liraglutide having a half-life of over 13 hours (Howell et al, 2019).

Treatment dosage of Liraglutide in type 2 diabetes is 1.8 mg/day. A 20-week long trial in obese patients found that Liraglutide reduces body weight in a dose-dependent manner (Astrup et al, 2009). Dosages of 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg, reduced weight by 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg respectively, compared to a reduction of 2.8 kg in the placebo treated group. In another 56-week trial, individuals with a BMI of $\geq$30 kg/m^2 or $\geq$27 kg/m^2

with comorbidities, were given either 3.0 mg/day of Liraglutide or placebo. A significant reduction in body weight of 6.2% versus 0.2% was seen when patients were given the drug (Wadden et al, 2013). A short-term study in obese patients without diabetes, found that acute food intake and subjective hunger were suppressed at a daily dose of 3.0 mg, while gastric emptying was delayed (van Can et al, 2014). It appears that weight loss is mainly mediated through a reduction in appetite and food consumption, since no increases in energy expenditure were found. Although the dosage of 3.0 mg daily was well-tolerated in most patients, the prevalence of nausea, abdominal pain, vomiting, hypoglycaemia, and increases in lipase activity, was greater than 5% (Mehta et al, 2017; Steinberg et al, 2017).

A 35-week, randomized, double-blind, placebo-controlled, crossover study, investigated the effects of Exenatide on weight loss in obese women without diabetes (Dushay et al, 2012). A three-week washout period separated two treatment periods of 16 weeks each. Besides a significant reduction in waist circumference, patients treated with the drug lost on average 2.49 kg after 16 weeks, whereas there was an increase of 0.43 kg during placebo treatment (Figure 10). Major differences were found between individuals; 30% of the drug-treated individuals were high responders that lost over 5% of their body weight, whereas 31% of the patients were nonresponders who gained weight. Moreover, waist circumference decreased significantly in patients that did respond to the drug, which was demonstrated in another study as well (Su et al, 2016). A 6-month study of Exenatide in non-diabetic youth with extreme obesity, found a significant reduction in BMI, body weight, and fasting insulin levels, when compared to the placebo (Kelly et al, 2013). Although the drug is generally well-tolerated, common side effects that have an incidence of almost 40%, are nausea, vomiting, and diarrhea (Gadde et al, 2018).

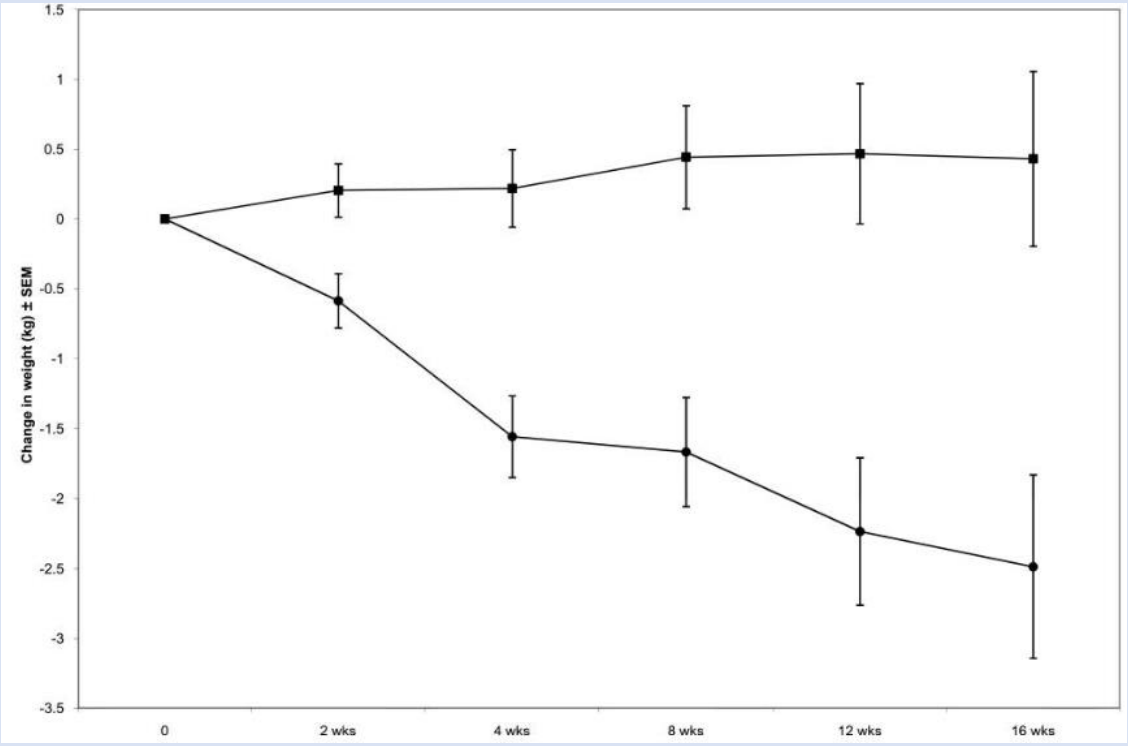

Figure 10. *Change in body weight during 16 weeks of Exenatide or placebo treatment (Dushay et al, 2012).*

5.2 Multiple ghrelin targets

Because of ghrelin's appetite-stimulating properties, blocking the hormone or its receptors has received a lot of attention in treating obesity (Delporte, 2012; Figure 11). Vaccination against ghrelin could potentially neutralize its effects. It was demonstrated in rats that vaccination with immunoconjugates of the hormone decreased feeding efficiency, adiposity, and body weight (Zorrilla et al, 2006). This led to the development of the ghrelin vaccine CYT009-GhrQb. A human trail in obese individuals found that the vaccine mounted a strong antibody response against ghrelin and was well-tolerated, but no effects were seen on weight loss (Colon-Gonzalez et al, 2013). Specific spiegelmers, substances able to inhibit peptide hormones, could neutralize ghrelin as well. Although the effects of spiegelmers in humans have yet to be determined, they did decrease food intake and body weight in diet-induced obese mice (Kobelt et al, 2006; Shearman et al, 2006).

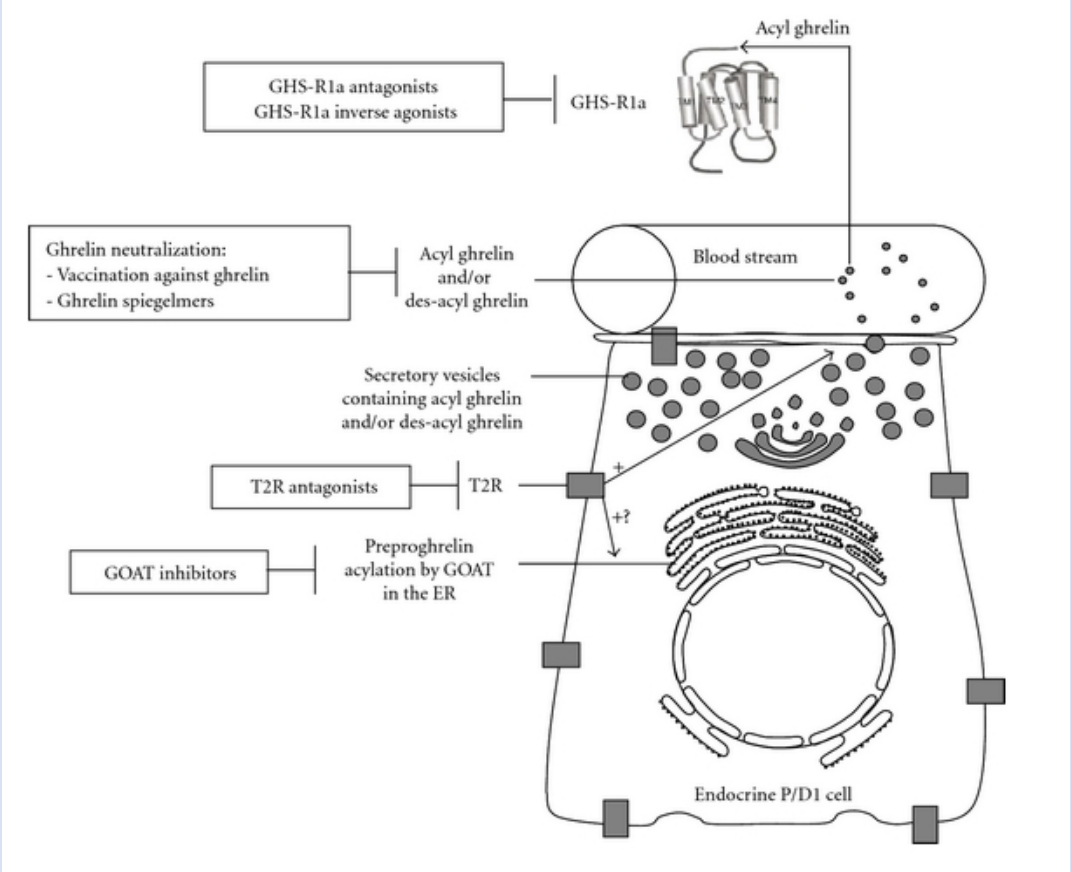

Figure 11. *Pharmacological drugs targeting ghrelin, GHS1a receptors, T2 receptors, and GOAT (Delporte, 2012).*

Another pharmacological target is inhibition of ghrelin signalling through GHS1a receptor antagonists or inverse agonists (Figure 11). Adminstration of the ghrelin receptor antagonist [D-Lys^3]-GHRP-6 decreased body weight, fat pad mass, and blood glucose levels in both lean and obese mice (Asakawa et al, 2003; Beck et al, 2004). Oral administration of another antagonist, YIL-870, reduced body weight in obese mice by 15%, due to reduced food intake, selective loss of fat mass and delayed gastric emptying (Esler et al, 2007). Several other

antagonists have been identified but whether they are effective in humans remains uncertain (Delporte, 2012; Schellekens et al, 2010). Since the GHS1a receptor has constitutive activity, inverse agonists might be more effective in promoting weight loss. The inverse agonist PF-05190457 was evaluated in healthy men (Denney et al, 2017). The drug blocked ghrelin activity and inhibited GH release in a dose-dependent manner. Gastric emptying was delayed by 30% and postprandial glucose levels were significantly reduced as well. Common adverse effects of the drugs were increased heart rate and somnolence.

Since ghrelin requires octanoylation by GOAT to become biologically active, this enzyme is another potential pharmacologic anti-obesity target (Figure 11). Ghrelin is the only known substrate of GOAT and, as such, inhibition would only affect octanoylation and no other physiological processes leading to undesired side-effects (Darling et al, 2015). Inhibition of GOAT could be achieved by the peptide GO-CoA-Tat. Intraperitoneal administration of GO-CoA-Tat increased insulin sensitivity and resistance to weight gain in mice (Barnett et al, 2010). Other rodent studies found a maximum reduction in food intake of 27% after treatment with the inhibitor (Taylor et al, 2015; Teuffel et al, 2015). These effects were attributed to reduced meal frequency, without changes in meal size. Before investigating the efficacy of GOAT inhibitors in humans, it has yet to be determined whether they cause long-term adverse events or are safe to use.

5.3 PYY_{3-36}

Multiple studies demonstrated that peripheral administration of PYY_{3-36} reduces food intake in obese patients. To investigate the effects of PYY_{3-36} on food intake, obese patients were given saline or an unspecified dosage of the drug, based on the surface area of the patient (Batterham et al, 2003). Ad libitum food intake at a buffet meal was observed, two hours after infusion. PYY_{3-36} infusion decreased caloric intake by 30%, which appeared to stay significantly reduced during the following 24 hours. Plasma levels of the hunger hormone ghrelin also decreased. Other studies demonstrated that the effects of PYY_{3-36} on food intake are dose-dependent, with dosages of 0.8 pmol/kg/min being the most successful and causing a 35% decrease (Degen et al, 2005; Sloth et al, 2007). Infusion of the drug improved postprandial insulin and glucose response, while increasing thermogenesis and lipolysis as well. The drug has a major drawback, whereas a significant number of patients withdrew from the study after experiencing serious nausea and reported to have lower ratings of well-being at the highest dosage. Continuous infusion is also impractical as a therapeutic strategy. Intranasal delivery of the drug has therefore been investigated. Patients did show a significant reduction in body weight after 12 weeks of therapy, but once again nausea appeared to be a drawback, with more than half of the patients withdrawing from the study (Gantz et al, 2007).

5.4 Dopamine reuptake inhibitor

Bupropion functions as reuptake inhibitor to norepinephrine and dopamine neurotransmitters, while also acting as antagonist to nicotinic receptors (Carroll et al, 2014; Fava et al, 2005). The drug is used as antidepressant to treat major depressive disorders and facilitates smokers to quit (Gadde & Xiong, 2007). In addition to the aforementioned properties, Bupropion has an appetite-supressing ability. In a 24-week long study, obese adults were counselled on lifestyle interventions, while given a placebo or either 300 or 400 mg/day of bupropion (Anderson et al, 2002). A significant greater number of patients lost at least 5 or 10% of their initial body weight at a daily dosage of 400 mg, in comparison to the placebo and dosage of

300 mg (Figure 12). Obese patients with depressive symptoms in another study were given either a placebo or 300 mg/day of Bupropion, and followed a caloric deficit of 500 kcal/day (Jain et al, 2002). Patients receiving the drug lost on average 4.4 kg after 26 weeks, whereas weight loss was 1.7 kg in the placebo treated group. Half of the patients who received the drug lost more than 5% of their initial body weight, compared to 28% in the placebo group. Depressive symptoms improved in both groups that lost at least 5% of their body weight. Overall, Bupropion was well-tolerated in both studies, without serious adverse events being linked to the drug.

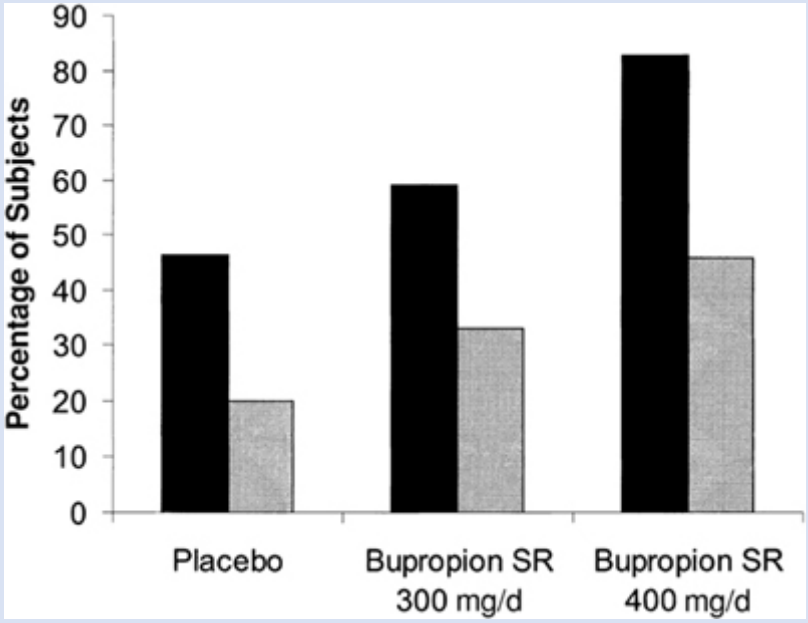

Figure 12. *Percentage of subjects losing ≥5% (dark bars) or ≥10% (light bars) of initial body weight after 24 weeks of treatment (Anderson et al, 2002).*

5.5 Selective CB1 receptor antagonist

SR141716, better known as Rimonabant, is a selective antagonist to the CB1 receptor. The drug was in clinical practice for weight loss, but has been withdrawn in 2008 due to serious psychiatric adverse effects (Sam et al, 2011). A one-year study on metabolic risk factors in overweight patients with dyslipidaemia found a significant reduction in body weight and waist circumference after treatment with a daily dosage of 20 mg of rimonabant (Després et al, 2005). It was also found in the study that HDL cholesterol levels were increased, while triglycerides were reduced. Another study in overweight and obese patients with type 2 diabetes found similar positive effects, alongside improvements in haemoglobin A1c (HbA1c) levels (Figure 13; Scheen et al, 2006). Multiple meta-analysis confirmed that a daily dosage of 20 mg of the drug, resulted in a clinically meaningful reduction in body weight and waist circumference, together with improvements in metabolic risk factors (Christensen et al, 2007; Christopoulou & Kiortsis, 2011; Curioni & André, 2006). Although Rimonabant has positive outcomes on weight loss, serious adverse events are common. Nausea was the most common side effect of Rimonabant, while more serious psychiatric adverse events included, anxiety, depression, and suicidal thoughts.

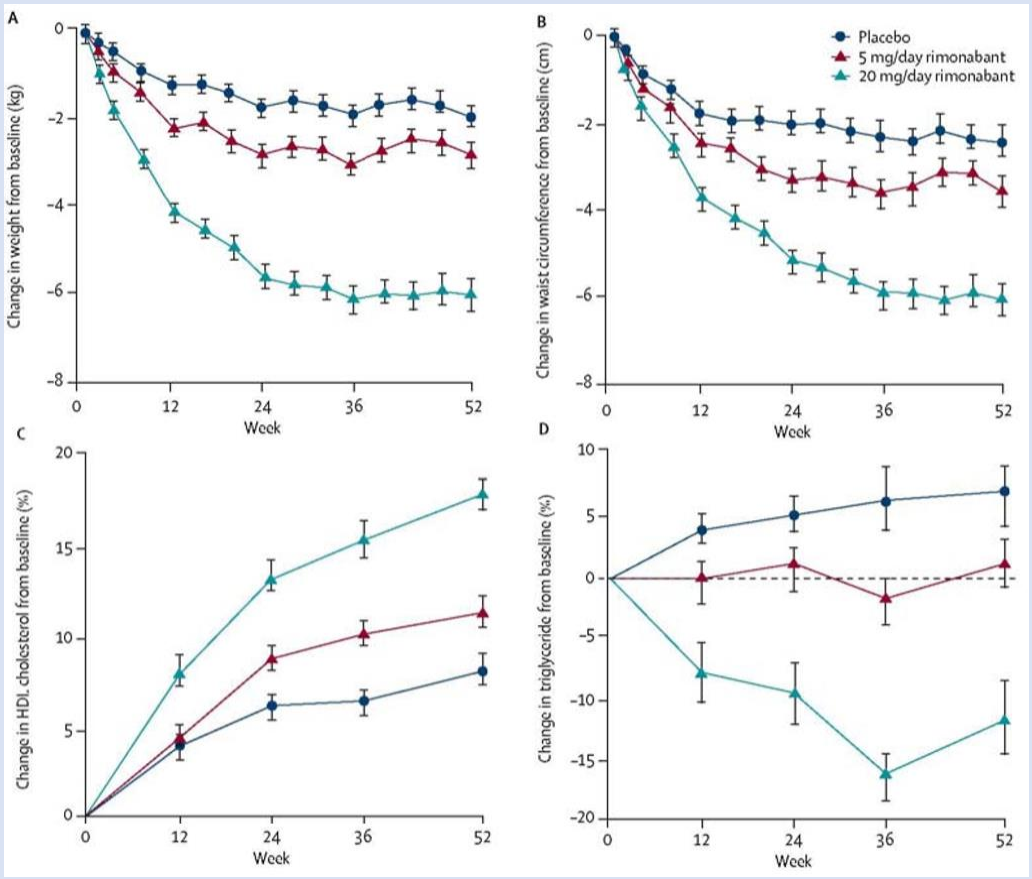

Figure 13. *Changes in (A) weight, (B) waist circumference, (C) HDL cholesterol, and (D) triglycerides (Scheen et al, 2006).*

5.6 NPY receptor antagonists

Both Y1 and Y5 receptors are anabolic and orexigenic, so neutralizing them with antagonistic pharmacological drugs could potentially aid in weight loss. Studies in rodents demonstrated that several antagonists to either of the receptors inhibit spontaneous food intake, fasted food intake, and free-feeding (Criscione et al, 1998; Kamiji & Inui, 2007; Kanatani et al, 1996; Kanatani et al, 2001; Wieland et al, 1998). Intraperitoneal administration of the Y5 receptor antagonist GW438014A, decreased weight gain rate and reduced fat mass in rats (Daniels et al, 2002). On the other hand, did oral administration of the drug not have any effect on food intake, due to poor oral bioavailability. The highly selective orally active Y5 antagonist MK-0557, was tested in overweight and obese patients in a 52-week trail (Erondu et al, 2006). Although the drug was well-tolerated and induced a significant reduction in body weight, this was not clinically meaningful. Another oral Y5 receptor antagonist, namely Velneperit (S-2367), was evaluated for efficacy and safety in obese patients (Srivastava & Apovian, 2018). Together with a low-calorie diet, the drug induced an average weight loss of 7.1 kg, versus 4.3 kg in the placebo treated group. Over half of the patients treated with the drug lost ≥5% of their initial body weight, together with improvements in waist circumference and lipid profiles. A clinical trial is investigating the combination of Velneperit with the lipid inhibitor Orlistat, but results have not been published yet (Shionogi Inc, 2018).

6. Discussion and Conclusion

In the present essay, we investigated the potential of pharmacotherapy to overcome the gap in obesity treatment between poor efficacy lifestyle modifications and invasive bariatric surgery. Our aim was to answer the question whether targeting the central nervous system and peripheral hormones with pharmacotherapy is effective in the treatment of obesity. It was found that a variety of pharmacological drugs appear to be effective in reducing body weight and improving metabolic risk factors. However, the positive outcomes were either small and not clinically meaningful, or they came with severe and serious adverse events, which hinders them from being given in clinical practice. This was in accordance to our hypothesis, which stated that there currently is no pharmacological drug effective to treat obesity when given as monotherapy.

Multiple studies have demonstrated that the CB1 receptor antagonist Rimonabant, the ghrelin inverse agonist PF-0519045, and the GLP-1 receptor agonists Liraglutide and Exenatide, have the potential to be effective in obesity treatment. These drugs did significantly reduce body weight and/or improve metabolic risk factors. A major drawback was that all of them came with serious adverse events, hindering them from being administrated to patients. The side effects that occurred were diverse; ranging from mild nausea and vomiting, to anxiety and suicidal thoughts. Long-term health consequences are unknown as well. When these adverse events can be inhibited or masked, without changing effectiveness of the drug itself, they offer numerous opportunities to be given as a treatment option in obese patients.

A variety of drugs did show promising effects on body weight and metabolic risk factors without serious adverse events, including the dopamine reuptake inhibitor Bupropion, and the NPY receptor antagonists MK-0557 and Velneperit. Although the promising effects of the pharmacological drugs were significant, they were not clinically meaningful. Yet, they are not useless and deserve further investigation. Although no single pharmacological drug is currently sufficient and effective in treating obesity itself, a minor reduction of 5 – 10% in body weight already produces clinically significant health benefits in obese patients. Minor weight loss improves overall fitness and comorbidities, such as cardiovascular disease, diabetes, and sleep apnoea (Bray, 2013; Ryan & Yockey, 2017).

Another group of pharmacological drugs that requires more research, are those that have not been investigated in humans but had positive outcomes on obesity in animal studies. The ghrelin antagonists [D-Lys^3]-GHRP-6 and YIL-870 both reduced body weight in obese mice. A decrease in fat pad mass was seen as well, together with improvements in blood glucose levels and delayed gastric emptying. The ghrelin pathway remains an interesting target in obesity treatment, whereas the peptide GO-CoA-Tat was able to inhibit the enzyme GOAT, which is required for octanoylation of ghrelin. GOAT inhibition in rodents reduced food intake, increased insulin sensitivity and made them resistant to weight gain, without any undesired side effects. Other rat studies found that intraperitoneal administration of the Y5 receptor antagonist GW438014A reduced fat mass and decreased weight gain rate.

Besides focussing on treating obesity with monotherapy, more attention should be paid to polytherapy. With this combination therapy, two or more pharmacological drugs are combined and given in conjugation. The major benefit is that this allows for the drugs to be administrated at lower dosages, which leads to less undesired side effects. Multiple drugs target different pathways and can act synergistic or additive to each other. Combination therapy has already proven to be successful in cancer treatment (Mokhtari et al, 2017). In obesity treatment, a few combinations have been investigated and demonstrated promising results when compared to monotherapy.

The anti-epileptic drug Topiramate and amphetamine derivate Phentermine were combined under the name Qnexa. Patients treated with the drug lost on average 14.7% body weight after 52 weeks of treatment, compared to 2.5% in the placebo treated group (Valentino et al, 2010). The drug also improved metabolic risk factors, including blood pressure, HbA1c levels, and triglycerides. Unlike monotherapy with Topiramate, did Qnexa not cause serious adverse events such as depression and suicidal thoughts. However, the FDA rejected the drug because of potential memory and concentration issues and risks for pregnant women (Motycka et al, 2011). A drug that has been approved by the FDA is Contrave, which is a combination of Bupropion and the opioid antagonist Naltrexone (Sherman et al, 2016). Four phase III studies found that patients treated with the drug achieved clinically significant weight loss in comparison to the placebo, caused by promoted satiety, reduced food intake, and enhanced energy expenditure (Apovian et al, 2013; Greenway et al, 2010; Hollander et al, 2013; Wadden et al, 2011).

Taken together, we can conclude that steps are being made in the right direction regarding the use of pharmacotherapy in obesity treatment. Although there currently is not a single pharmacological drug effective in treating obesity when given as monotherapy, even a minor reduction of 5 – 10% in body weight already improves overall fitness and comorbidities. A variety of drugs did show significant weight loss without undesired side effects, although this was not clinically meaningful. Yet, there were other drugs effective in reducing body weight and/or improve metabolic risk factors, despite serious adverse events. Further studies should focus on polytherapy, where multiple drugs are given in conjugation. This would allow for lower dosage and most likely less undesired side effects. We only described a handful of possible targets which pharmacological drugs could act on. The possibilities are endless and it is likely that in the near future, pharmacotherapy would serve as a less invasive, yet effective, treatment option, in comparison to bariatric surgery.

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