International Journal of Research
Available at https://pen2print.org/index.php/ijr/
e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 06 Issue 2
February 2019

Biochemical Mechanisms Involved in the Regulation of Appetite and Weight - Review

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Abstract

The overwhelming increase in the prevalence of overweight and obesity in recent years represents one of the greatest threats to the health of the developed world and part of the developing world. Among current treatments, gastrointestinal (GI) surgery remains the only approach capable of achieving significant weight loss results with long-term sustainability. As the obesity prevalence approaches epidemic proportions, the necessity to unravel the mechanisms regulating appetite and weight gain have garnered significant attention. It is well known that physical activity and food intake regulation are the two most important factors involved in body weight control. To regulate food intake, the brain must alter appetite. With this realization has come increased effort to understand the intricate interplay between enzymes, gut hormones (such as ghrelin, leptin, cholecystokinin, neuropeptide Y, glucagon-like peptide 1 etc.) and the central nervous system, and their roles in food intake regulation through appetite modulation. This review discusses the biochemical mechanisms involved in the regulation of appetite and body weight, and explores a suite of well characterized and intensely investigated enzymes, anorexigenic and orexigenic gut hormones, and their appetite-regulating capabilities. Indeed, some enzymes (such as fructose–1,6–bisphosphase and protease inhibitor), gut hormones and brain are involved in the perturbation of appetite and body weight.

Keywords: Appetite, weight, obesity, hormones

1. Introduction

Hunger and satiety are sensations. Hunger represents the physiological need to eat food. Satiety is the absence of hunger; it is the sensation of feeling full. There are several theories about how the feeling of hunger arises [1]. A healthy, well-nourished individual can survive for weeks without food intake, with claims ranging from three to ten weeks [2]. The sensation of hunger typically manifests after only a few hours without eating and is generally considered to be unpleasant. Hunger is also the most commonly used term to describe the condition of people who suffer from a chronic lack of sufficient food and constantly or frequently experience the sensation of hunger. When hunger contractions start to occur in the stomach, they are informally referred to as hunger pangs. Hunger pangs usually do not begin until 12 to 24 hours after the last ingestion of food. A single hunger contraction lasts about 30 seconds, and pangs continue for around 30 to 45 minutes, then hunger subsides for around 30 to 150 minutes [3]. Individual contractions are separated at first, but are almost continuous after a certain amount of time. Emotional states (anger, joy etc.) may inhibit hunger contractions [4]. Levels of hunger are increased by lower blood sugar levels, and are higher in diabetics [5]. They reach their greatest intensity in three to four days and may weaken in the succeeding days, although research suggests that hunger never disappears [6]. Hunger contractions are most intense in young, healthy people who have high degrees of gastrointestinal tonus. Periods between contractions increase with old age [3].

Appetite is the desire to eat food, sometimes due to hunger. Appealing foods can stimulate appetite even when hunger is absent [7]. Appetite exists in all higher life-forms, and serves to regulate adequate energy intake to maintain metabolic needs. It is regulated by a close interplay between the digestive tract, adipose tissue and the brain [8]. Appetite has a relationship with every individual's behavior. Appetitive and consummatory behaviors are the only processes that involve energy intake, whereas all other behaviors affect the release of energy [9]. When stressed, appetite levels may

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increase and result in an increase of food intake. Decreased desire to eat is termed anorexia, while polyphagia (or "hyperphagia") is increased eating. Dysregulation of appetite contributes to anorexia nervosa, bulimia nervosa, cachexia, overeating, and binge eating disorder [10]. *Bulik et al.*, [11] proposed that eating begins when we have an empty stomach. They suggested that the walls of an empty stomach rub against each other to produce what are commonly called "hunger pangs". However, observations of surgical patients indicated that there was more to the onset of eating than hunger pangs [12]. Removal of the stomach did not abolish hunger pangs, and these patients reported the same feelings of hunger and satiety that they had experienced before surgery [13]. The patients' stomachs had been removed because of cancer or large ulcers, and their esophagi had been attached directly to their small intestines. Although the patients ate small frequent meals because they had no stomachs to hold food, their reports of feelings of hunger and their total food intake were essentially normal [13].

2. Obesity

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health [14]. People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m^2, with the range 25–30 kg/m^2 defined as overweight [15]. Some East Asian countries use lower values. Obesity increases the likelihood of various diseases, particularly heart disease, type II diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis [14]. Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health [16]. It is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors [17]. BMI is closely related to both percentage body fat and total body fat [18]. In children, a healthy weight varies with age and sex. Obesity in children and adolescents is defined not as an absolute number but in relation to a historical normal group, such that obesity is a BMI greater than the 95th percentile. The reference data on which these percentiles were based date from 1963 to 1994, and thus have not been affected by the recent increases in weight [19]. BMI is defined as the subject's weight divided by the square of their height and is calculated as follows: $\frac{\textbf{Weight (kg)}}{\textbf{Height}^2\ (\textbf{m}^2)}$

Food intake is regulated by complex interactions between nutrients, hormones, neuropeptides and several different brain areas. The regulation of feeding can be divided into homeostatic and non-homeostatic feeding [20]. Homeostatic feeding controls energy balance by adjusting food intake to promote stability in the amount of energy stores. However, non-homeostatic or hedonic feeding can override this homeostatic pathway resulting in overeating. It has been postulated that this is caused by the rewarding (palatable) properties of food [21, 22].

3. Enzymatic Regulation of Appetite and Weight

3.1 Effect of Fructose-1,6-Bisphosphatase in Regulation of Appetite and Weight

Fructose-1,6-bisphosphatase (FBPase) is a regulatory enzyme in gluconeogenesis that is elevated by obesity and dietary fat intake [23]. Over recent years, excessive nutrient intake has been associated with rapidly increasing rates of obesity in both developed and developing societies. Body weight is maintained by a fine balance between food intake and energy expenditure [24]. Under normal conditions, energy homeostasis is maintained through a complex interaction between peripheral organs and the central nervous system (CNS). Many peripheral signals from white adipose tissue, the gut, and the pancreas are known to regulate body weight [25]. The CNS receives these signals and adjusts food intake and energy expenditure accordingly.

The gene expressing fructose-1,6-bisphosphatase (FBPase) is one of many genes upregulated in the liver by obesity and fat [26]. Even though FBPase is known as a regulatory enzyme in gluconeogenesis, a previous study showed that liver-specific FBPase transgenic mice with a physiologic threefold level of over expression had no change in whole-body glucose tolerance or endogenous glucose production [25]. Surprisingly, the mice consistently displayed an approximate 10% reduction in body weight compared with negative littermates, leading us to propose that liver FBPase may have a novel role in the control of body weight. Visinoni *et al.* [27]

investigated the potential regulatory role of liver FBPase by using transgenic mouse model that specifically over expresses FBPase in the liver. They reported that over-expression of this liver enzyme leads to the lean body weight phenotype in the transgenic mice by markedly reducing adiposity levels by 50%. Reductions in food intake rather than elevated energy expenditure were found to be the contributing factors. The appetite-stimulating neuropeptides, neuropeptide Y (NPY) and Agouti-related peptide (AgRP), were significantly suppressed, whereas the circulating satiety hormones, cholecystokinin (CCK), and leptin, rose significantly. Elevation of liver FAO via an increased flux through the hexosamine biosynthetic pathway (HBP) appears to be the key linking the increase in liver FBPase to reduced food intake and adiposity in our transgenic mouse [27].

3.2 Effect of Protease Inhibitors on Appetite and Weight

Restriction of energy intake remains the most effective way to lose weight and improve glucose control in individuals with obesity or diabetes. As such, obesity is normally treated by diet and exercise, but attempts to sustain significant weight loss by lifestyle intervention often fail [28]. Recent data suggest that the 2-year persistence rate with orlistat or sibutramine, the only FDA approved drug therapies for obesity, does not exceed 2% [29]. Therefore, novel therapeutics to reduce food intake and body weight with minimal adverse reactions is highly desirable. One way to improve dietary adherence rates in clinical practice may be to enhance satiety through the use of protease inhibitors. For a long time, plant protease inhibitors were considered as major anti-nutritional agents [30]. Their presence in many seeds and tubers in high amounts has caused much speculation as to whether these inhibitors have any role in the control of proteolysis during development of plant tissues. The idea that potato protease inhibitors would interfere with animal digestive processes subsequently led to the discovery of a many serine protease inhibitors capable of protecting plants from mammalian digestive enzymes [28].

Potato tuber is the source of potato protease inhibitor II (PI2) active in eliciting a satiety response and delayed gastric emptying in humans [31]. While several methods to isolate and purify PI2 have been developed over the years on a laboratory scale, all of them are laborious and expensive [30, 32, 33]. Potato protein recovery is also often complicated by interactions with non-protein components of potato tubers that lead to poor solubility and reduced biological activity of the protein fraction, thus hampering the potential therapeutic applications. Given the low yield and complexity of PI2 isolation, Slavko *et al*., [34] thought it was important to modify the extraction procedure and test the satiation activity of a crude potato protease inhibitor concentrate (PPIC) that contains several thermostable protease inhibitors, including PI2. As PPIC showed potential satiety-promoting activity *in vivo*, they also examined the mechanism of reduction of food intake following PPIC administration. It was suggested that PI2 promotes satiety by increasing circulating levels of cholecystokinin (CCK) similar to soybean trypsin inhibitor [29].

4. Hormonal Regulation of Appetite and Weight

4.1. Effect of Ghrelin in Regulation of Appetite and Weight

Ghrelin is often refers to as the "hunger hormone". It is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract which functions as a neuropeptide in the central nervous system. Besides regulating appetite, ghrelin also plays a significant role in regulating the distribution and rate of use of energy [35]. When the stomach is empty, ghrelin is secreted. When the stomach is stretched, secretion stops. It acts on hypothalamic brain cells both to increase hunger, and to increase gastric acid secretion and gastrointestinal motility to prepare the body for food intake. The receptor for ghrelin, the ghrelin/growth hormone secretagogue receptor (GHSR), is found on the same cells in the brain as the receptor for leptin, the satiety hormone that has opposite effects from ghrelin. Ghrelin also plays an important role in regulating reward perception in dopamine neurons that link the ventral tegmental area to the nucleus accumbens (a site that plays a role in processing sexual desire, reward, and reinforcement, and in developing addictions) through its colocalized receptors and interaction with dopamine and acetylcholine. Ghrelin is encoded by the GHRL gene and is presumably produced from the cleavage of the prepropeptide ghrelin/obestatin. Full-length preproghrelin is homologous to promotilin and

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both are members of the motilin family. Unlike the case of many other endogenous peptides, ghrelin is able to cross the blood-brain-barrier, giving exogenously-administered ghrelin unique clinical potential [36].

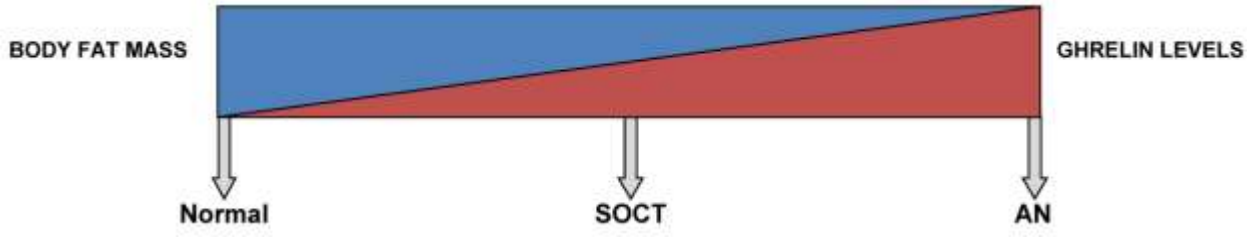

Figure 1: A gradient relationship between ghrelin levels and body fat mass in a normal, SOCT and anorexia nervosa (AN) patients.

Ghrelin has been linked to inducing appetite and feeding behaviors [37]. Circulating ghrelin levels are the highest right before a meal and the lowest right after. Injections of ghrelin in both humans and rats have been shown to increase food intake in a dose-dependent manner [35]. So the more ghrelin that is injected the more food that is consumed. However, ghrelin does not increase meal size, only meal number [37]. Ghrelin injections also increase an animal's motivation to seek out food, behaviors including increased sniffing, foraging for food, and hoarding food. Body weight is regulated through energy balance, the amount of energy taken in versus the amount of energy expended over an extended period of time. Studies have shown that ghrelin levels are negatively correlated with weight. This data suggests that ghrelin functions as an adiposity signal, a messenger between the body's energy stores and the brain [38]. When a person loses weight their ghrelin levels increase, which causes increased food consumption and weight gain. On the other hand, when a person gains weight, ghrelin levels drop, leading to a decrease in food consumption and weight loss [36]. This suggests that ghrelin acts as a body weight regulator, continuously keeping one's body weight and energy stores in check.

4.2. Effect of Leptin in Regulation of Appetite and Weight

Leptin is known as the "satiety hormone". It is a *hormone* made by *adipose cells* that helps to regulate *energy balance* by inhibiting hunger [39]. Leptin is opposed by the actions of the hormone *ghrelin*, the "hunger hormone". Both hormones act on receptors in the *arcuate nucleus* of the *hypothalamus* to regulate appetite to achieve *energy homeostasis*. In obesity, a decreased sensitivity to leptin occurs, resulting in an inability to detect satiety despite high energy stores [40]. Although regulation of fat stores is deemed to be the primary function of leptin, it also plays a role in other physiological processes, as evidenced by its multiple sites of synthesis other than fat cells, and the multiple cell types beside hypothalamic cells that have leptin receptors [39]. Leptin is produced primarily in the adipocytes of white adipose tissue. It is also produced by brown adipose tissue, placenta (syncytiotrophoblasts), ovaries, skeletal muscle, stomach (the lower part of the fundic glands), mammary epithelial cells, bone marrow, gastric chief cells and P/D1 cells. In humans, many instances are seen where leptin dissociates from the strict role of communicating nutritional status between body and brain and no longer correlates with body fat levels [41]:

- Leptin level is decreased after short-term fasting (24–72 hours), even when changes in fat mass are not observed.
- Leptin plays a critical role in the adaptive response to starvation.
- In obese patients with obstructive sleep apnea, leptin level is increased, but decreased after the administration of continuous positive airway pressure. In non-obese individuals, however, restful sleep (i.e., 8–12 hours of unbroken sleep) can increase leptin to normal levels.

- Serum level of leptin is reduced by sleep deprivation.
- Leptin level is increased by emotional stress.
- Leptin level is decreased by increases in testosterone levels and increased by increases in estrogen levels.
- Leptin level is chronically reduced by physical exercise.
- Leptin release is increased by dexamethasone.
- Leptin level is increased by insulin.
- Leptin levels are paradoxically increased in obesity.

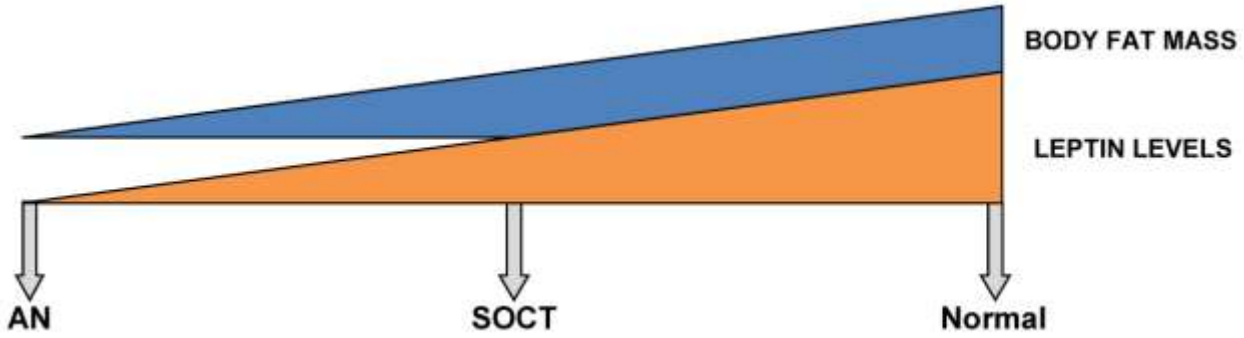

Figure 2: A Gradient Relationship between Leptin levels and Body Fat Mass in a Normal, SOCT and Anorexia Nervosa (AN) patients.

Although leptin reduces appetite as a circulating signal, obese individuals generally exhibit a higher circulating concentration of leptin than normal weight individuals due to their higher percentage body fat [39]. These people show resistance to leptin, similar to resistance of insulin in type 2 diabetes, with the elevated levels failing to control hunger and modulate their weight. A number of explanations have been proposed to explain this. An important contributor to leptin resistance is changes to leptin receptor signalling, particularly in the arcuate nucleus, however, deficiency of, or major changes to, the leptin receptor itself are not thought to be a major cause. Other explanations suggested include changes to the way leptin crosses the blood-brain-barrier (BBB) or alterations occurring during development [42].

4.3. Effect of Cholecystokinin in Regulation of Appetite and Weight

Cholecystokinin (CCK**)** is a peptide hormone of the gastrointestinal system responsible for stimulating the digestion of fat and protein [43]. Cholecystokinin, previously called pancreozymin, is synthesized and secreted by enteroendocrine cells in the duodenum, the first segment of the small intestine. Its presence causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively, and also acts as a hunger suppressant [44]. CCK is synthesized and released by enteroendocrine cells in the mucosal lining of the small intestine (mostly in the duodenum and jejunum), called I cells, neurons of the enteric nervous system, and neurons in the brain [43]. It is released rapidly into the circulation in response to a meal. The greatest stimulator of CCK release is the presence of fatty acids and/or certain amino acids in the chyme entering the duodenum. In addition, release of CCK is stimulated by monitor peptide (released by pancreatic acinar cells), CCK-releasing protein (via paracrine signalling mediated by enterocytes in the gastric and intestinal mucosa), and acetylcholine (released by the parasympathetic nerve fibers of the vagus nerve) [45]. Once in the circulatory system, CCK has a relatively short half-life [43].

As a peptide hormone, CCK mediates satiety by acting on the CCK receptors distributed

widely throughout the central nervous system. The mechanism for hunger suppression is thought to be a decrease in the rate of gastric emptying [46]. CCK also has stimulatory effects on the vagus nerve, effects that can be inhibited by capsaicin [44]. The stimulatory effects of CCK oppose those of ghrelin, which has been shown to inhibit the vagus nerve [44].

4.4. Effect of Neuropeptide Y in Regulation of Appetite and Weight

Neuropeptide Y (NPY) is a 36 amino acid peptide hormone that begins and ends with tyrosine (Y) residues [47]. NPY is expressed abundantly in several areas of the brain, exerting multiple biological effects. Within the hypothalamus, NPY is synthesized primarily by neurons found within a region known as the arcuate nucleus. These neurons extend to several different parts of the hypothalamus. The binding of NPY to receptors within one of the targeted regions (the periventricular nucleus) stimulates food intake in animal models. The repeated injection of NPY into the hypothalamus summarily results in obesity. In rodents, weight loss caused by caloric restriction ("dieting") stimulates NPY release in the periventricular nucleus [38].

Expression of hypothalamic NPY increases in response to fasting in rats [48]. Increased levels of the neuropeptide are also observed in two rather famous strains of mutant mice [*obesity* (*ob*/*ob*) and *diabetes* (*db*/*db*)]. The products of the *ob* and *db* genes constitute a hormone/receptor pair (leptin and the leptin receptor, respectively). These celebrity mice are unable to produce (*ob*/*ob*) or respond to (*db*/*db*) leptin, a peptide hormone produced by fat cells. Both types of mice are characterized by an early onset of severe obesity [47]. They eat excessively, show inappropriately low energy expenditure, and have an inherited form of diabetes. When leptin is administered to *ob*/*ob* mice, a remarkable turnaround is observed. The mice eat less, they become more active, their metabolic rates increase, and they lose a significant amount of weight. Consistent with all of these healthy changes, NPY levels of *ob*/*ob* mice fall markedly after introduction of ectopic leptin [49]. These and other observations strongly suggest that NPY is one target of the adipocyte-derived leptin. Early studies fueled a great deal of interest in leptin as a potential therapeutic for use in weight-loss regimens; however, it was quickly understood that reality is a bit more complex than that. Obesity in humans and in various rodent models as well, correlates strongly with higher levels of circulating leptin. This indicates that obesity is not usually due to an inability to produce leptin. Rather, weight problems may more often be attributed to a decreased sensitivity to the hormone [47].

4.5. Effect of Pro-Opiomelanocortin (POMC) in Regulation of Appetite and Weight

The biology of pro-opiomelanocortin (POMC) is complex and diverse. Smaller peptide fragments derived from the inert POMC precursor play a crucial role in integrating vital physiological functions, with POMC extensively processed in a highly tissue-specific manner to yield a range of peptides involved in a whole range of processes [50]. Historically, the most well-known roles for these peptides have been in skin pigmentation, adrenal steroid synthesis and inflammation. However, over the last decade, wealth of data has clearly shown that POMC-derived peptides, in particular those synthesized in neurons of the hypothalamus, play a critical role in controlling food intake and body weight [37, 51]. Building upon these fundamental insights into the regulation of body weight, there is now the potential for the development of rational, mechanistic-based therapies to treat perturbations in energy homoeostasis [51].

4.6. Effect of Glucagon-Like Peptide 1 in Regulation of Appetite and Weight

The delivery of nutrients to the gastrointestinal tract after food ingestion activates the secretion of several gut-derived mediators, including the incretin hormone glucagon-like peptide 1 (GLP-1). GLP-1 receptor agonists (GLP-1RA), such as exenatide and liraglutide, are currently employed successfully in the treatment of patients with type 2 diabetes mellitus. GLP-1RA improves glycaemic control and stimulates satiety, leading to reductions in food intake and body weight. Besides gastric distension and peripheral vagal nerve activation, GLP-1RA induce satiety by influencing brain regions involved in the regulation of feeding, and several routes of action have been proposed [52].

The CNS plays a major role in the maintenance of body weight and energy balance within a narrow range by regulating energy intake and energy expenditure [21, 22]. To regulate energy intake, signals, both neuronal and humoral, arising from peripheral organs involved in food intake, – digestion and – storage, such as the gut, pancreas, and adipose tissue, convey information on hunger and/or satiety to the brain. Gut-derived hormones, such as the orexigenic hormone ghrelin and the prandially secreted anorexigenic hormones cholecystokinin (CCK), peptide YY (PYY), oxyntomodulin (OXM) and glucagon-like peptide 1 (GLP-1), have been identified as players in the regulation of feeding by relaying meal-related information on nutritional status to the brain [21, 22].

5. Molecular and Genetic Regulation of Appetite and Weight

5.1. Brain Areas involved in Appetite and Weight Regulation

5.1.1. Hypothalamus

The hypothalamus, a small area of the brain located just below the thalamus, is the regulating center of appetite and energy homeostasis [53]. The hypothalamus consists of several interconnecting nuclei: the arcuate nucleus (ARC), paraventricular nucleus (PVN), lateral hypothalamic area (LHA), ventromedial nucleus (VMN), and the dorsomedial nucleus (DMN). The ARC of the hypothalamus is adjacent to the median eminence, a circumventricular organ having defective blood-brain-barriers (BBB) [54]. Thus, circulating hormones and nutrients can access the ARC without passing the blood-brain-barrier (BBB). Moreover, the ARC surrounds the third cerebroventricle. Hormones and nutrients in the cerebrospinal fluid can diffuse into the extracellular fluids of the ARC [55]. Due to these anatomical features, the ARC is considered to be a hypothalamic area primarily sensing peripheral metabolic signals. In the ARC, there are two distinct neuronal populations: one is a group of neurons coexpressing orexigenic neuropeptides, including neuropeptide Y (NPY) and agouti-related peptide (AgRP), and the other is a subset of neurons expressing anorexigenic neuropeptides, including proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). These neurons are first-order neurons where peripheral metabolic signals including leptin, insulin, ghrelin, and nutrients are primarily transferred. Anorexigenic monoamine serotonin also acts on POMC neurons through the 5HT-2C receptor to induce anorexia [53]. POMC neurons send axonal projections to the second-order neurons in other hypothalamic areas, the PVN, VMN, and LHA [55].

The α-melanocyte-stimulating hormone (α-MSH), an anorexigenic neuropeptide, is produced by the posttranscriptional processing of POMC and released from presynaptic terminals of POMC neurons. By binding to the melanocortin-3 and -4 receptor (MC3R, MC4R) on the second order neurons, α-MSH activates catabolic pathways: reduced food intake and enhanced energy expenditure. Targeted deletion of the MC4R in mice resulted in hyperphagia, reduced energy expenditure, and obesity [42]. In humans, MC4R mutations account for about 6% of severe early-onset obesity [55], supporting an important role for the central melanocortin system in the control of energy metabolism.

Endogenous melanocotin receptor antagonist AgRP is released from the terminals of ARC NPY/AgRP-producing neurons to the synaptic space on the second order neurons where it competes with α-MSH on MC3R and MC4R and antagonizes the effects of α-MSH [44]. Selective ablation of NPY/AgRP neurons in young mice resulted in a significant decrease in food intake and body weight, suggesting that these neurons are critical for promoting food intake and preventing weight loss. The PVN neurons synthesize and secrete neuropeptides that have a net catabolic action, including the corticotrophin-releasing hormone, thyrotropin-releasing hormone, somatostatin, vasopressin, and oxytocin. In addition, PVN sends sympathetic outflow to the peripheral metabolic organs, including liver and adipose tissue, resulting in increased fatty acid oxidation and lipolysis [56]. Destruction of PVN and haploinsufficiency of Sim1, a critical transcriptional factor in the development of PVN, caused hyperphagia and obesity, implying an inhibitory role for PVN in food intake and weight gain. The VMN mainly receives neuronal projections from the ARC, and projects their axons to the ARC, DMN and LHA, as well as brainstem regions. The VMN contains neurons that sense glucose and leptin. Moreover, anorexigenic neuropeptide, a brain-derived neurotrophic factor (BDNF), is produced in

the VMN. Destruction of the VMN caused hyperphagia and obesity, as well as hyperglycemia. Thus, the VMN is regarded as a pivotal area in generating satiety and maintaining glucose homeostasis. The DMN contains a high level of NPY terminals and α-MSH terminals originating from the ARC. Destruction of DMN also results in hyperphagia and obesity [57].

In contrast to PVN, VMN, and DMN, destruction of LHA leads to hypophagia and weight loss. Therefore, LHA has been considered to be a feeding center. LHA contains two neuronal populations producing orexigenic neuropeptides, the melanin concentrating hormone (MCH) and orexin, also called hypocretin. NPY/AgRP- and α-MSH-immunoreactive terminals from ARC neurons are in contact with MCH- and orexin-expressing neurons. Orexin-producing neurons are also involved in glucose sensing and the regulation of sleep-awake cycles [58]. Mice with orexin receptor 2 displayed canine narcolepsy. On the other hand, depletion of MCH or the MCH 1 receptor in mice attenuated body weight, suggesting that MCH acts as endogenous orexigenic molecules [58].

5.1.2. Brainstem

The brainstem is another key brain area involved in regulation of food intake and energy balance. Satiety signals from the gastrointestinal (GI) tract primarily relay to the solitary tract nucleus (NTS) through the sensory vagus nerve, a major neuronal link between the gut and the brain. Transaction of sensory vagal fibers resulted in increased meal size and meal duration, confirming that vagal afferents transfer satiety signals to the brain [38]. Like the ARC, the NTS is anatomically close to the circumventricular organ area postrema (AP). Therefore, the NTS is located in a perfect place for receiving both humoral and neural signals. Meanwhile, the NTS receives extensive neuronal projections from the PVN and *vice versa*, indicating that there is intimate communication between the hypothalamus and the brainstem. Similarly to hypothalamic neurons, NTS neurons produce glucagon-like peptide 1 (GLP-1), NPY, and POMC, as well as sensing peripheral metabolic signals. For instance, POMC neurons in the NTS show the signal transduction activated transcript 3 (STAT3) activation in response to leptin [56]. Thus, circulating hormones and nutrients may inform metabolic signals to the brain by acting on the hypothalamus and brainstem.

5.1.3. Midbrain

The brain rewarding system is involved in the control of hedonic feeding, i.e., the intake of palatable foods. Like other addition behaviors, the mesolimbic and mesocortical dopaminergic pathways are involved in hedonic feeding. Intake of palatable foods elicits a dopamine release in the ventral tegmental area (VTA), which in turn activates the neural pathways from the VTA to the nucleus accumbens (NA) via the medial forebrain bundles. Interestingly, hedonic feeding is modulated by metabolic signals. Leptin acts on the dopaminergic neurons in the VTA to suppress feeding [58]. Conversely, hedonic feeding can override satiety signals. Mice lacking a D_2 receptor were more sensitive to leptin [33].

5.2. Cocaine- and Amphetamine-Regulated Transcript in the Regulation of Appetite and Weight

The cocaine- and amphetamine-regulated transcript (CART) has been the subject of significant interest for over a decade. Work to decipher the detailed mechanism of CART function has been hampered by the lack of specific pharmacological tools like antagonists and the absence of a specific CART receptor(s). However, extensive research has been devoted to elucidate the role of the CART peptide and it is now evident that CART is involved in the regulation of diverse biological processes, including food intake, maintenance of body weight, reward and addiction, stress response, psychostimulant effects and endocrine functions [59].

Experiments conducted with acute administration of cocaine or amphetamine in rodents resulted in the up-regulation of a particular mRNA species in the striatum of the brain that was subsequently named “cocaine- and amphetamine-regulated transcript” (CART) and the encoded peptides are referred to as CART peptides [59, 60]. Importantly, CART mRNA levels were also found increased in the nucleus accumbens on post-mortem tissues from human victims of cocaine overdose. CART is transcribed as two alternatively spliced mRNAs that are of different lengths and hence produce pro-peptides of different lengths, called

proCART 1–89 and proCART 1–102 [60]. However, the mRNA splicing has no effect on the final peptide, as the active parts of the CART peptides are encoded by a sequence that lies downstream of the spliced region and is therefore identical in both pro-peptides [60, 61]. However, the proCART peptides contain several cleavage sites that allow post-translational processing by pro-hormone convertases in a tissue-specific manner [61]. This processing produces at least two known biologically active peptides, CART I (55–102) and CART II (62–102), each containing three potential disulphide bridges [60, 61, 62].

While the role of CART in controlling appetite and energy homeostasis in the human system might be somewhat different, in rodents, the neuronal network in which CART is involved to modulate energy homeostasis has been well-described. The expression of endogenous CART at brain regions involved in feeding regulation has been shown to be sensitive to the energy balance status and the genetic background of mice. In brief, fasting has been documented in various mammals to reduce CART mRNA levels at the hypothalamic PVN, Arc, perifornical region, as well as the nucleus accumbens shell (AcbSh) of the striatum, whilst refeeding restored the expression [63]. As a leptin-regulated neurotransmitter, the expression of CART mRNA and peptide levels at the Arc is described to be positively correlated with circulating leptin levels. This relationship between leptin and CART levels was less consistently demonstrated at the PVN and LHA, despite evidence supporting a pivotal role of CART-containing neurons projecting from the Arc to the second order neurons located in the PVN and LHA in producing anorexia [60, 62].

CART administration was able to eliminate the increase in feeding and deleterious weight gain caused by social isolation in rats, a consequence of the down-regulation of the hypothalamic CART-containing system in various hypothalamic feeding-related areas caused by this condition [64]. In the same study, whilst re-socialization of the isolation-reared rats restored the food intake, body weight, and hypothalamic CART-immunoreactivity back to controls levels, immune-neutralization of endogenous CART by i.c.v. CART antibody attenuated the restoration, confirming the important role of CART in feeding regulation under chronic psychological stress condition [64]. In addition to eliciting an anorectic response, gastrointestinal effects including inhibition of gastric acid secretion and gastric emptying have also been reported as a result from CART. Chronic overproduction of CART mRNA via viral approaches or continuous infusion of recombinant CART peptide transferred through i.c.v. cannulas into genetically (fa/fa) or diet-induced [65] obese rats induces hypophagic effects during fed states and reduced hyperphagia following fasting were also observed. Such reduction in energy intake was accompanied by suppression of body weight gain mainly due to decrease in lean mass, indicating the potential of CART in the long-term regulation of food consumption and body mass, under both normal condition and nutritionally induced obesity [65].

International Journal of Research
Available at https://pen2print.org/index.php/ijr/
e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 06 Issue 2
February 2019

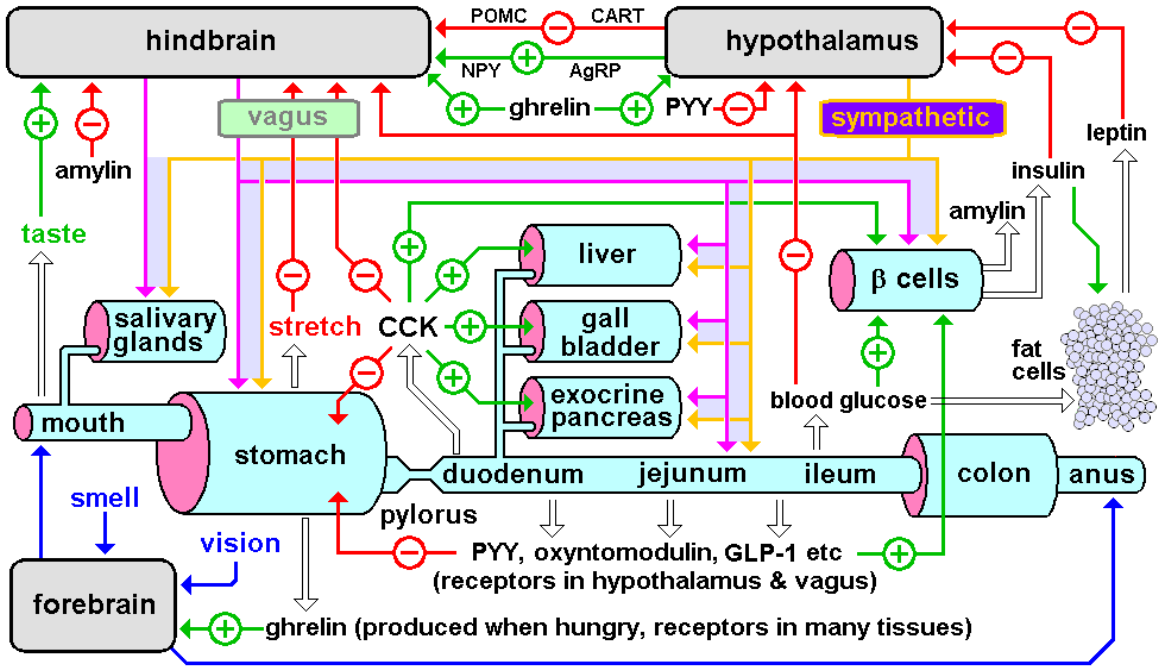

Figure 3: Schematic Representation of Regulation of Appetite

6. Conclusion

Given the growing epidemic of obesity, it has become increasingly important to understand the biochemical mechanisms involved in the regulation of appetite and body weight. Regulation of food intake and metabolism is maintained by complex pathways and neuronal circuits which themselves receive peripheral signals such as enzymes and hormones. Metabolically, important abdominal obesity with an excess of visceral fat accumulation results in altered release of adipokines, leading to CNS mediated skeletal muscle and hepatic insulin resistance. The central regulation of energy balance has become even more fascinating and complex with the characterization of mechanisms of action of NPY, the most abundant hypothalamic orexigenic factor. Much attention has recently centered on ghrelin, the only known circulating orexigen. Insulin resistance and compensatory hyperinsulinemia are independently associated with suppression of ghrelin that furthers our understanding of the variable expression of ghrelin in humans. With continued research, it should be possible to elucidate exactly how the associations among insulin resistance, hyperinsulinemia, and orexigens (NPY and ghrelin) participate in the more intricate web of factors that regulate appetite and body weight. Better understanding of the mechanisms involved in the regulation of energy metabolism will become a background for development of new therapeutic approaches against obesity, insulin resistance, metabolic syndrome, and other nutritional disorders.

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