Review Article

Central Nervous System Regulation of Appetite in Humans and Pet Animals

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Abstract

Weight gain leading to obesity in humans and their companion pet animals has become of national and international concern. This problem began centuries ago with the evolutionary, genomic and eipgenomic changes that came about when human populations shifted from hunters and gatherers to farmers. The resulting lifestyle and dietary changes also affected the domestication and diet of their animal companions, especially the dog, as well as the gut microbiota they share. Appetite is controlled in individuals by their feelings of bunger and satiety (the so-called appestat), and is regulated centrally through the hypothalamus and brain stem. The hypothalamus induces secretion of the hormones adiponectin (regulates insulin secretion and fatty acid oxidation), and leptin and ghrelin (the 'stop' and 'go' hunger hormones, respectively). Leptin comes from white adipose tissue cells and decreases appetite. The gut hormones like ghrelin, cholecystokinin, other pancreatic, neuro- and glucagon-like peptides, and oxyntomodulin are produced peripherally, and decrease appetite. Basically, these hormones act as signals for satiety, which regulates food intake. Leptin and serotonin function in separate systems to control appetite. The future success of appetite control for humans and pet animals will depend upon use of effective targeted pharmacological agents in conjunction with dietary modification and lifestyle changes.

ABBREVIATIONS

CNS: Central Nervous System; 5-HT: 5-Hydroxytryptamine; GI: Gastrointestinal; CCK: Cholecystokinin; NPYY: Neuropeptide YY; POMC: Pro-opiomelanocortin; MC-4: Melanocortin-4; CRF: Corticotrophin-releasing Factor; CART: Cocaine and Amphetamine-Regulated Transcript; PP: Pancreatic Polypeptide; GLP-1: Glucagon-Like Peptide

INTRODUCTION

There is a rising worldwide epidemic of obesity in humans and companion pet animals [1-5]. The World Health Organization forecasted that about 2.3 billion adults worldwide would be overweight and more than 700 million would be obese by 2015 [5]. Given their parallel evolutionary, dietary, and lifestyle adaptations, pet obesity has likewise become an epidemic [3]. A 2012 survey conducted by the Association for Pet Obesity Prevention revealed that 52.5% of dogs and 58.3% of cats were overweight or obese [4]. The most common endocrine disorders of dogs and cats are hypothyroidism and diabetes, respectively; both of which lead to obesity [3,6]. Banfield Pet Hospital's *State of Pet Health Report 2012* provides startling insight into the link between obesity and illness. The report, which analyzed data from more than two million dogs and 430 thousand cats, found that [6]:

- 42% of dogs with diabetes are overweight (and 40% of cats).

- 40% of dogs with arthritis are overweight (and 37% of cats).

- More than 40% of dogs with high blood pressure are overweight.

- 61% of hypothyroid dogs are overweight.

BACKGROUND

Evolution, genomic and epigenomic adaptations

Evolutionary changes over centuries along with the concurrent interactions between the genomic and epigenomic environments have had major influences on the microbiota of the gut in all mammals including humans [7-10]. As mammals evolved, so did their gut microbes; the host diet and phylogeny (evolutionary history) both influencing gut bacterial diversity which then became increased as one traverses from carnivores to omnivores to herbivores [7].

Ancient human populations shifted from hunters and gatherers to farmers, such that human lifestyles and diet changes also affected the domestication and diet of the dogs that accompanied them [7,9,11]. A bio cultural co evolution occurred

that affected both dog genes and human culture [9]. The genetic and epigenetic characteristics of the canine genome were transformed, so that dogs developed an increased number of *Amy2B* gene copies coding for pancreatic amylase. This allowed them to adapt more readily and thrive on an omnivorous diet rich in starches, in comparison to the strictly carnivorous diet of their ancestor, the wolf [9].

Intestinal microbiota

The estimated bacterial content of the mammalian Gitract is approximately 10^{14} bacteria [12,13]. Co-habiting family members and their dogs have been shown to share microbiota with one another [11]. Thus, direct and frequent contact with our cohabitant humans and animals could significantly shape the composition of the shared microbial environment [11]. While the shared gut microbiota logically could lead to the parallel consequences of weight gain and obesity in both species, this hypothesis is still unproven [8,13]. Additionally, indigenous microbiota within the GI tract can extract calories from the otherwise in digestible common polysaccharides found in daily diets [7]. Gut microbiota can also regulate the brain-gutaxis [8,10,12-17]. The gut microbiome can stimulate vagal sensory neurons, which is a major neural pathway that conveys information from the GI luminal contents to the brain and modulates GI motility and feeding behavior [5,13-20]. The gut microbiome can influence neuronal signaling to the brain through vagalaerent neurons [5,10,16-23].

Body fat regulating hormones and cytokines

As the number of fat cells in the body increases, the secretion of pro-inflammatory cytokines increases in parallel, thereby creating more chronic, systemic inflammation [24,25]. The fat regulating hormones are adiponectin and leptin [5,24-30]. Adiponectin is reduced in obesity and increased in response to fasting, whereas leptin has opposite effects [5,28]. Bio active peptides such as leptin, adiponectin, and pro-inflammatory cytokines secreted from the adipose tissue are called adipokines [23-26]. Serotonin (5-hydroxytryptamine; 5-HT) is biochemically derived from tryptophan and is mainly found in the gastrointestinal (GI) tract, platelets, and central nervous system (CNS) [26-29]. In coordination with the hypothalamus, 5-HT and the brain stem regulate appetite, eating behavior, energy balance and weight [27-31]. 5-HT also plays an important role in controlling carbohydrate (sugars, starches, and cellulose) intake [26,27].

Brain sites of appetite regulation

The hypothalamus and the brain stem are central sites of appetite regulation; the midbrain is also involved [5,14-18,31]. The hypothalamus and brain stem control carbohydrate metabolism [27]. In the canine study of de Lartigue and colleagues [23], leptin concentrations were high erin the obese group of dog's compared to those of the lean group. Adiponectin and cerebro spinal fluid 5-HT concentrations were high erin the lean group than in the obese group. Analysis of the microbiome revealed that the diversity of the microbial community was lower in the obese group. Microbes from the phylum *Firmicutes* (85%) were the pre dominant group in the gut microbiota of lean dogs.

However, bacteria from the phylum *Proteobacteria* (76%) were the predominant group in the gut microbiota of dogs in the obese group. Similar findings were recently published [8]. Whether dysbiosis induces the development of obesity or whether obesity causes the dysbiosis of gut microbiota in unknown [23]. Leptin is also capable of regulating the endogenous production of glucose both dependently and independently of the hypothalamus and brain stem [27].

Obesity Genes

Scientists have identified "obesity gene" variants in people, however many lean individual people and pets carry these obesity genes and never become overweight [25,32]. This means that the determining factor for becoming obese may be an individual's lifestyle [7,9,21,27].

One meta-analysis of data from more than 200,000 people who carry a specific gene predisposing them to obesity found that physically active adults who carried the obesity gene were nearly one-third less likely to become overweight or obese than those who didn't exercise [2]. Genetic predisposition does not mean that obesity is our destiny, or our dog's destiny [32,33].

This parallel between the spike in human obesity and obesity in companion animals has developed over the last half-century and is unsettling [3,4,32,33]. It appears to relate to the similar environmental and lifestyle changes that have occurred [2,3,9-12,21,27].

DISCUSSION

Brain regulation of appetite

Appetite: The desire to eat, is regulated by interaction between the digestive tract, adipose tissue and the brain [5,21-31]. During stress, appetite levels may increase, whereas dysregulation of appetite leads to anorexia nervosa, cachexia, bulimia, overeating and binge eating [20-23]. Regulation of eating in the sense of hunger or satiety is termed the appestat [18].

Hypothalamus: The hypothalamus is the main regulatory effect or organ of appetite, and controls the volume of food consumed [14-16,20-23,27,31]. It communicates with other CNS areas of the brain stem and reward-related limbic pathways of the midbrain [5,16,31]. The hypothalamus also acts as a sensor via numerous hormones, discussed below, and as a biological clock that stimulates hunger. Hunger occurs when the body's store of nutrients is depleted: short-term reservoir stores are carbohydrates; long-term reservoir stores are fat [18,31]. The glucose that regulates short-term control over appetite, and the lipostat controls long-term appetite through its cumulative effect over time [16,18]. The hypothalamus interprets and integrates the input of neural and humoral factors that result in the body's coordinated feeding and energy expenditure responses. Certain gut hormones including ghrelin, neuropeptide YY (NPYY), pancreatic polypeptide, glucagon-like-peptide 1 (GLP-1) and oxyntomodulin, play a physiological role in governing satiety through the hypothalamus [5,16,20,23].

Brain stem: The brain stem transfers information from the peripheral nervous system to the mid- and forebrain [5,16,20]. It directly connects with the gut by neuronal pathways and

regulates mechanical processes involving appetite and food intake such as chewing and swallowing [21]. The brain stem can organize certain aspects of feeding behavior without input from the hypothalamus [20]. It is also involved in regulation of energy balance. Satiety signals from the GI tract are relayed to the area postrema of the brain's fourth ventricle via the sensory vagus nerves [5,16,20].

Midbrain: The midbrain reward system partakes in control of hedonic feeding (intake of palatable foods) which can override satiety signals [5,20].

Peripheral regulation of appetite

The peripheral appetite regulatory mechanisms can be classified as adipostat factors and gut hormones [5,19-21,23]:

Adipostat factors: The hormone leptin was discovered in 1994; it is excreted by adipocytes in white adipose tissue. Leptin has a long half-life and circulates in plasma at concentrations proportional to an individual's fat mass, although women have much higher leptin concentrations than men [30]. Its effects are mediated by the hypothalamus in a fat regulation feedback loop, controlled by central and peripheral circadian clocks. The central circadian (hypothalamic) clock regulates weight control and long term energy balance. The peripheral circadian clock regulates leptin transcription in adipose tissue [16,23]. Circadian disruption is associated with obesity [34].

Obese individuals often have leptin resistance; and congenital leptin deficiency in mice and children results in obesity [21]. However, leptin resistance is not the only reason for obesity, as recent studies in mice have implicated circadian clock dysfunction [34]. Even chronic jet lag is sufficient to induce central leptin resistance independent of other risk factors [34]. Fertility is also affected. Insulin is secreted in response to meals and increases body stores of glycogen, fat and protein [20]. It plays a similar role to leptin, and causes obesity and diabetes; insulin-deficient animals are hyperphagic [26]. Both leptin and insulin are anorexigenic (anti-appetite stimulating) hormones. The brain regulates glucose flow from the liver [20].

Gut hormones: Post-prandial satiety is signaled by a gut sensor system [5,20]. GI hormones working with the liver transfer information to both the hypothalamus and brain stem [20]. Cholecystokinin (CCK) is the first gut hormone known to control appetite [23,24]. Digestive products in the gut lumen release this kinin from the proximal small intestine. The effects are mediated by the vagal nerve and result in anorexia [5,20,22,23]. Dietary fiber is anti-obesity and anti-diabetic; it induces neo gluco genesis when fermented by intestinal microbiota and this regulates energy homeostasis not only by metabolism of nutrients but also by the gut-brain neural network [20]. Ghrelin is the only known peripherally active appetite-stimulating (orexigenic) hormone, and relays hunger signals [5,20,21]. It is an endogenous growth hormone secretagogue, and novel orexigenic peptide that antagonizes leptin action through activation of the hypothalamic neuropeptide NPYY receptor pathway [5,20]. The major source of ghrelin is the stomach. It is a potent stimulator of food intake and growth hormone secretion. Plasma levels are inversely correlated with body weight. Blood levels rise during fasting and fall rapidly after a meal, so ghrelin output is regulated by caloric intake [21].

Pancreatic polypeptide (PP) and neuropeptide NPYY

These are anorectic gut hormones [5,16,20,22]. PP is found mostly in the pancreas, and its release is stimulated by food intake. It modulates gastric acid secretion and gastrointestinal motility; but inhibits pancreatic exocrine secretion and gallbladder contraction. NPYY, an appetite stimulator, is produced by gut endocrine cells, and is released post-prandially [16]. It is also a vasoconstrictor [5,16].

Glucagon-like peptide 1 (GLP-1) and oxyntomodulin

Both act as satiety signals. GLP-1 is cleaved from pro glucagon and released from the L-cells of the intestinal ileum and colon into the systemic circulation [5,20]. GLP-1 and its longer acting receptor agonists decrease food intake and have a strong incretin effect (increased stimulation of insulin) from oral glucose feeding [20,30]. Oxyntomodulin, also derived from pro glucagon, is co-secreted with GLP-1. It induces satiety, increases energy expenditure and decreases weight [5,20]. Both GLP-1 and oxyntomodulin are processed by the CNS, intestine and colon, and released in response to nutrient intake. They inhibit gastric acid secretion and reduce food intake [5,19,20]. Importantly, effective control of appetite expression remains a critical therapeutic target for weight management [1]. Current strategies utilize a combination of agents to target both homeostatic and hedonic control mechanisms [16,20].

Controlling Appetite

Leptin and 5-HT belong to separate systems for controlling appetite [28]. Satiation of hunger within and after meals is signaled by 5-HT in response to the pattern of an individual's food intake [27,29]. Circulating levels of the 5-HT precursor amino acid, tryptophan, along with certain macronutrients and peripheral satiety factors such as CCK and enterostatin control CNS 5-HT output. Hypothalamic 5-HT receptor systems inhibit NPYY, which is a potent stimulator of hunger and food intake. The hormone leptin, by contrast, provides a signal linking the status of adipose tissue with a number of important CNS circuits. Leptin itself stimulates CNS leptin receptors, which link with pro-opiomelanocortin (POMC) and melanocortin 4 (MC-4) receptors, leading to hypephagia and obesity. The effects of leptin may also be modulated by factors such as the corticotrophin-releasing factor (CRF), cocaine and amphetamine-regulated transcript (CART), orexins and galanin [16]. These separate 5-HT and leptin systems act as short-acting satiety signals (episodic in nature), and as a hormonal indicator of long-term (tonic) energy reserves, respectively [28].

Several mechanisms have been identified whereby certain pharmacological agents can induce changes in food intake, body weight and eventually in body composition [1]. Some of these drugs modify the appetite system as measured by subjective changes in feelings of hunger and fullness (indices of satiety), and are considered to be "appetite suppressants". Appetite suppressants act either via peripheral satiety peptide systems (such as CCK and enterostatin), or by altering CNS levels of various hypothalamic neuro peptides (NPYY, galanin, orexin and MC-4) or by changing levels of the key CNS appetite neurotransmitters such as 5-HT and noradrenaline [1].

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CONCLUSION

Both human and companion animal populations are facing increasing problems associated with weight gain and obesity. The control of appetite, also known as the appestat, requires a balanced interplay between the brain, digestive tract and adipose tissue, and is tightly regulated by the hypothalamus. The primary fat regulating hormones are adiponectin, serotonin, leptin and ghrelin. While the human and animal body also have so-called "obesity genes", the determining factors are most often related to their shared common environment and individual lifestyles. The future success of appetite control for humans and pet animals will depend upon use of effective targeted pharmacological agents in conjunction with dietary modification (less high glycemic carbohydrates and fat) and lifestyle changes (more exercise).

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