**Hypothalamic regulation of food intake and clinical therapeutic applications**

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**ABSTRACT**

Current estimates suggest that over 1 billion people are overweight and over 300 million people are obese. Weight gain is due to an imbalance between energy expenditure and dietary intake. This review discusses the hypothalamic control of appetite and highlights key developments in research that have furthered our understanding of the complex pathways involved. Nuclei within the hypothalamus integrate peripheral signals such as adiposity and caloric intake to regulate important pathways within the central nervous system controlling food intake and energy expenditure. Firmly established pathways involve the orexigenic NPY/AgRP and the anorexigenic POMC/CART neurons in the arcuate nucleus (ARC) of the hypothalamus. These project from the ARC to other important hypothalamic nuclei, including the paraventricular, dorsomedial, ventromedial and lateral hypothalamic nuclei. In addition there are many projections to and from the brainstem, cortical areas and reward pathways, which modulate food intake.

**Keywords**

Hypothalamus; obesity; appetite; arcuate nucleus; orlistat; sibutramine

**INTRODUCTION**

Current estimates suggest that over 1 billion people are overweight and over 300 million people are obese (1). Furthermore, 80% of obese adults have at least one or more co-morbidities including diabetes mellitus, hyperlipidaemia, hypertension, cardiovascular disease and have a significant increase in many forms of cancer (2). The increasing prevalence of obesity is partly attributable to a lack of exercise and partly to the availability of high calorie palatable food. In addition family, twin and adoption studies indicate that obesity is highly heritable, with the estimated genetic contribution ranging from 60-84% (3). The concept of a “thrifty phenotype” was contemplated in the 1950s and suggested that carriers of genes that enabled storage of energy more efficiently during periods of abundant food supply increased their...
odds of survival during famine. However this “thrifty genotype” becomes a disadvantage at times of abundant energy supply, resulting in obesity. A series of complex systems maintain energy homeostasis in order that sufficient energy is available and body weight remains stable. Central circuits in the brain rely on peripheral signals indicating satiety levels and energy stores, as well as higher cortical factors such as emotional and reward pathways. As illustrated in Figure 1, the hypothalamus is critical in the relaying of afferent signals from the gut and brainstem as well as processing efferent signals that modulate food intake and energy expenditure. The hypothalamus is subdivided into interconnecting nuclei, including the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventromedial nucleus (VMN), dorsomedial nucleus (DMN) and lateral hypothalamic area (LHA). Neuronal pathways between these nuclei are organised into a complex network in which orexigenic and anorexigenic circuits influence food intake and energy expenditure. The purpose of this review is to provide some clarity of this complex network and its role in appetite, highlighting areas of potential therapeutic targets for obesity.

HYPOTHALAMIC NUCLEI INVOLVED IN APPETITE CONTROL

Arcuate nucleus (ARC)

The ARC is a key hypothalamic nucleus in the regulation of appetite. In mice, lesions of the ARC result in obesity and hyperphagia (4). Its proximity to the median eminence and the fact that the ARC is not fully insulated from the circulation by the blood brain barrier means it is strategically positioned to integrate a number of peripheral signals controlling food intake (Figure 2). There are two major neuronal populations in the ARC implicated in the regulation of feeding. One population increases food intake and co-expresses neuropeptide Y (NPY) and agouti-related protein (AgRP). The second population of neurons co-expresses cocaine- and amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC) and inhibits food intake. Neuronal projections from these two populations then communicate with other hypothalamic areas involved in appetite regulation such as the PVN, DMN and LHA (5).

CART/POMC neurons

Cleavage of POMC by prohormone convertases PC1 and PC2 produces melanocortins which exert their effects through binding to G-protein coupled melanocortin receptors (MC-Rs). Five melanocortin receptors have been cloned however only the MC3-R and MC4-R are expressed in the brain (6). The MC4-R is highly expressed in the hypothalamus, most notably the PVN (6). Targeted deletion of the MC4-R in mice results in hyperphagia, reduced energy expenditure and obesity, underlying the importance of this receptor in appetite regulation (7). The role of the MC3-R remains less clear however MC3 receptor (Mc3r) knockout mice have a higher fat content and reduced lean body mass (8).

Melanocortin peptides, including α-MSH, released from ARC POMC neurons bind to downstream MC4-Rs to inhibit food intake (9). Consistent with this, knockout mice lacking all POMC derived peptides display increased food intake and weight gain (10). AgRP is the endogenous antagonist at the MC3-R and MC4-R (11) suggesting that melanocortinergic neurons may exert a “tonic” inhibition on feeding and permit increased energy expenditure, which is relaxed following AgRP antagonism of the MC3 and MC4-Rs, ultimately resulting in stimulation of feeding and a lower metabolic rate.
Severe recent studies have demonstrated the importance of the melanocortin system in regulating energy homeostasis in humans. MC4R mutations account for approximately 6% of severe early onset human obesity and as many as 90 different mutations have been associated with obesity (12). Homozygous mutations in the POMC gene in humans results in early onset obesity, adrenal insufficiency and red hair pigmentation (13).

The majority of POMC neurons in the ARC also co-express CART mRNA. Animal studies have shown that ICV administration of CART inhibits food intake, whereas ICV injection of CART antiserum increases food intake (14). However, preventing CSF flow between the 3rd and 4th ventricles by plugging the cerebral aqueduct abolishes the anorectic effect of CART following its administration into the 3rd ventricle (15). This suggests that the anorectic effects of CART occur through the hindbrain rather than the hypothalamus.

Interestingly, transgenic mice which are CART-deficient do not demonstrate significant alterations in feeding behaviour or body weight when fed a normal diet (16). In addition, recent studies have proposed that CART may also have an orexigenic role since CART injected directly into the VMN or ARC of fasted rats causes a significant increase in food intake at 1-2 hours (17). Similarly, twice daily intra-ARC injection of CART for one week in rats results in a 60% increase in food intake and CART overexpression using a CART transgene construct increases cumulative food intake and weight gain (18). This suggests that there may be distinct neuronal circuits within the hypothalamus in which CART can act as an orexigenic or anorexigenic signal.

**NPY/AgRP neurons**

Within the hypothalamus, NPY is an important regulator of body weight through its effects on food intake and energy expenditure. NPY acts at five different receptors (Y1-Y5 receptors), although NPY appears to exert its orexigenic effect predominantly via the Y1 and Y5 receptors. The majority of neurons expressing NPY in the hypothalamus are found within the ARC and most co-express AgRP (11,19). Ablation of NPY/AgRP neurons in young mice reduces food intake and body weight (20) whilst in adult rats, ICV injection of NPY potently stimulates food intake (21). NPY/AgRP...
neurons have extensive projections within the hypothalamus including the PVN, DMN and LHA which appear to be the main targets for the orexigenic effects of NPY (11,19,22). Approximately 20% of ARC NPY neurons innervate the PVN and DMN (22). Stimulation of this pathway leads to increased food intake through direct stimulation of Y1 and Y5 receptors in addition to AgRP antagonism of MC3 and MC4-Rs in the PVN.

Paraventricular nucleus (PVN)

Microinjection of almost all known orexigenic peptides into the PVN, including NPY and AgRP stimulate feeding (23,24). NPY/AgRP neurons from the ARC communicate with PVN neurons containing thyrotrophin releasing hormone (TRH) (25) which has been implicated in the control of energy balance, by contributions to both food intake and energy expenditure (26).

Lateral hypothalamic area (LHA)

The LHA receives neuronal projections from the ARC and contains the orexigenic neuropeptides melanin concentrating hormone (MCH) and orexins. NPY, AgRP and α-MSH immunoreactive terminals are extensive in the LHA and are in contact with MCH and orexin-expressing cells (27). MCH immunoreactive fibres also project to the cortex, brainstem and spinal cord (28).

In humans, two MCH receptors have been cloned in humans, Mchr1 and Mchr2 whereas in rodents only Mchr1 has been identified. Mchr1 knockout mice have increased energy expenditure, locomotor activity and are resistant to diet-induced obesity (29). In contrast, injection of MCH into the lateral ventricle of rats increases food intake and fasting increases the expression of Mch mRNA (30). Orexin A and B act via two receptors, OX1R and OX2R and ICV administration of these peptides increases food intake (31). However, subsequent studies have proposed that this may reflect associated heightened arousal and reduced sleep (32).

Dorsomedial nucleus (DMN)

Destruction of the DMN results in hyperphagia and obesity (33). The DMN contains a high level of NPY terminals (19) and α-MSH terminals originating in the ARC (34). α-MSH fibres also project from the DMN to the PVN terminating on TRH-containing neurons (35). In diet-induced obesity, obese agouti mice and Mc4r knockout mice, NPY mRNA expression is increased in the DMN (36,37).

Ventromedial nucleus (VMN)

Neuroimaging studies in humans have shown increased signal in the area of the VMN following an oral glucose load (38). The VMN contains a large population of glucose responsive neurons and receives NPY, AgRP and POMC neuronal projections from the ARC. Brain-derived neurotrophic factor (BDNF) is highly expressed in the VMN and lateral ventricle administration of BDNF reduces food intake and body weight (39). It is thought that ARC POMC neurons have a role in activating VMN BDNF neurons to decrease food intake (40).

ADIPOSKY SIGNALS ACTING ON THE HYPOTHALAMUS

Adipokines are secreted by adipose tissue and include leptin, adiponectin and resistin. They have been shown to act via the hypothalamus to affect food intake and energy expenditure (41). Leptin is secreted by adipocytes and circulates at concentrations proportional to fat mass. Rodents lacking leptin (ob/ob mice) or the leptin receptor (db/db mice and Zucker fa/fa rats) are obese and hyperphagic. In humans, the rare condition of leptin deficiency causes severe obesity which can be ameliorated by peripheral leptin administration (42).

Circulating leptin crosses the blood brain barrier and binds to the long form of the leptin receptor, Ob-Rb, in the hypothalamus (43). The Ob receptor is expressed widely within the hypothalamus but particularly in the ARC, VMN, DMN and LHA. Using viral mediated gene expression, chronic leptin over-expression in the ARC, PVN and VMN results in reduced food intake (44). In the ARC, Ob-Rb mRNA is expressed by both NPY/AgRP and CART/POMC neurons. Leptin directly activates anorectic POMC neurons and inhibits orexigenic AgRP/NPY neurons resulting in an overall reduction in food intake (45).

Circulating insulin rises in response to a glucose load and like leptin, circulating levels reflect fat mass. Insulin crosses the blood brain barrier via receptor-mediated transport. Insulin receptors are widely distributed in the brain particularly in hypothalamic nuclei involved in the regulation of food intake. Insulin has an anorectic effect when administered ICV or directly into the VMN, an effect which is reversed by insulin antibodies (46). The
precise mechanism by which insulin inhibits food intake is still unclear although administration of insulin into the 3rd ventricle of fasted rats increases ARC POMC mRNA expression and reduces food intake (47). This anorexigenic effect of insulin is blocked by melanocortin antagonists (47).

INTERACTIONS BETWEEN THE BRAINSTEM AND HYPOTHALAMUS

The hypothalamus is often regarded as the “gate keeper” of appetite signalling as it also receives input from the cortex, brain stem and the periphery (Figures 1 and 2). Similarly to the ARC, the area postrema of the brain stem also possesses an incomplete blood brain barrier. As such, peripheral satiety signals can also act directly on brainstem structures. Extensive reciprocal neuronal pathways exist between brainstem and hypothalamic appetite circuits to provide an alternative pathway through which circulating satiety factors can communicate with the hypothalamus (48,49). An additional major link between the gastrointestinal tract and the brain exists via the vagus nerve. Cell bodies of afferent fibers of the abdominal vagus nerve are located in the nodose ganglia, which project onto the brainstem. Here, the dorsal vagal complex (DVC) (consisting of the dorsal motor nucleus, the area postrema, and the sensory nucleus of the tractus solitarius (NTS)) contains projections to hypothalamic and higher centers (48,49).

GUT HORMONES

The gastrointestinal tract releases an array of peptide hormones that are sensitive to gut nutrient content. Furthermore, short-term feelings of hunger and satiety are believed to be partly mediated by co-ordinated changes in circulating gut hormone concentrations.

Cholecystokinin (CCK)

CCK was the first gut hormone demonstrated to have an effect on food intake. CCK is released post-prandially and in addition to local effects within the gut, inhibits food intake in rodents and humans (50,51). CCK1 receptor knockout rats and intraperitoneal delivery of CCK1 antagonists results in obesity, partly due to hyperphagia (52). The anorectic effects of peripherally administered CCK are thought to be mediated via CCK 1 receptors on vagal afferent fibres that relay to the brainstem. Interestingly, intraperitoneal CCK administration also increases c-fos expression in the DMN and PVN of the hypothalamus (53). Direct administration of CCK into the DMN decreases food intake and down-regulates NPY gene expression (53).

Glucagon like peptide-1 (GLP-1)

The pre-pro-glucagon gene is widely expressed in the enteroendocrine L cells of the intestine, pancreas and brainstem. It is cleaved by pro-hormone convertases 1 and 2 to produce mainly glucagon in the pancreas, and GLP-1, GLP-2 and oxyntomodulin in the CNS and intestine. GLP-1 is released into the circulation following a meal in proportion to the calories consumed and acts via the vagus nerve to inhibit food intake (54). Central administration of GLP-1 to rats inhibits food intake and activates c-fos expression in the ARC, amygdala and PVN (54,55). GLP-1 receptor mRNA is densely expressed in the ARC and over 60% appears to be co-localized with POMC neurons (56). Peripherally injected GLP-1 also induces expression of c-fos in the ARC and has an anorectic effect (57). However, this is thought to be mediated, in part, via the vagus nerve since vagotomy or ablation of the brainstem-hypothalamus pathways attenuates the anorectic effect of GLP-1 (57).

Oxyntomodulin

Like GLP-1, oxyntomodulin is secreted from intestinal L cells post-prandially and reduces food intake when administered peripherally or ICV to rodents (58). Peripheral administration of oxyntomodulin activates c-fos expression in the ARC and its anorectic effects can be blocked through the use of a GLP-1 antagonist (58). As a member of the secretin glucagon family of peptides, oxyntomodulin differs in producing a stronger inhibition of food intake than other members and has an anorectic action disproportionate to its binding to the GLP-1 receptor suggesting the possibility of an additional mode of action.

Ghrelin

Ghrelin is produced by the stomach and acts as an endogenous ligand on the growth hormone secretagogue (GHS) receptor. Although the majority of ghrelin is produced peripherally, there are ghrelin immunoreactive neurons within the hypothalamus that have terminals on hypothalamic NPY/AgRP, POMC and CRH.
neurons (59), as well as orexin fibres in the LHA (60). Ghrelin initiates hunger prior to a meal and stimulates food intake when injected directly into the PVN (61). Peripheral and central administration of ghrelin increases c-fos expression in ARC NPY/AgRP neurons and increases hypothalamic NPT mRNA expression (62). Although, ghrelin has potent actions on appetite, ghrelin null mice have normal appetite and body weight when fed a standard diet however do resist diet-induced obesity (63). This may be due to up-regulation of alternative systems controlling appetite or perhaps ghrelin has only short term effects on food intake, playing a smaller role in the overall regulation of appetite.

Nutrient Sensing

There is evidence that the hypothalamus can also sense nutrients and adjust food intake accordingly. When cellular energy stores are deplete, the enzyme adenosine monophosphate-activated protein kinase (AMPK) is activated in order to increase substrate uptake (68). In the ARC, activation of AMPK leads to increased food intake and body weight; an effect which is inhibited by both insulin and leptin (69). AMPK in the VMN also appears to play a key role in the detection of acute hypoglycaemia and initiation of the glucose counter-regulatory response (70). Acute hypoglycaemia also increases hypothalamic NPY and AgRP and reduces POMC expression (71). Other nutrients such as plasma long chain fatty acids and the amino acid leucine can regulate food intake via the hypothalamus. ICV administration of the long chain fatty acid, oleic acid inhibits food intake by reduction of ARC AgRP and POMC expression (72) and ICV administration of leucine reduces food intake in rats (73).

Peptide YY (PYY)

PYY3-36 is a member of the PP-fold family of peptides released by L-cells in the gut, into the circulation following a meal. The PP-fold family comprises NPY, PYY and pancreatic polypeptide (PP) although PYY3-36 is relatively selective for the Y2 receptor. Peripheral administration of PYY3-36 reduces food intake in rodents and humans and PYY knockout mice develop obesity (64,65). Although the exact mechanisms are unclear, the anorectic effects of PYY3-36 are thought to occur via the Y2 receptor since this is abolished in Y2 receptor knockout mice (64). The Y2 receptor is highly expressed on ARC NPY neurons and PYY3-36 may reduce food intake by inhibiting NPY release via autoinhibitory Y2 receptors. Interestingly vagotomy or lesioning of the brainstem-hypothalamic neuronal pathways abolishes the anorectic effects of peripheral PYY3-36 (57). This observation, combined with evidence for Y2 receptor expression in the NTS and nodose ganglion of the vagus nerve, has led to the proposal that PYY3-36 may regulate ARC neuronal activity indirectly via vagal-brainstem pathways.

Pancreatic polypeptide (PP)

The anorectic gut hormone PP is released from the pancreas into the circulation after a meal and like PYY, is released in proportion to calories ingested. Peripheral injection of PP to rodents and humans reduces food intake (66,67). Peripheral PP administration activates neurons in the area postrema of the brainstem, an area with a high density of Y4 receptors and reduces hypothalamic NPY and orexin mRNA expression (66). Like PYY, the reduction of food intake by intraperitoneal PP is abolished by vagotomy in rodents (66).

Reward mechanisms and hypothalamic appetite regulation

Reward mechanisms are thought to predominantly involve the mesolimbic system in the brain. Conditioned Taste Aversion (CTA) and lesioning experiments suggest the orbitofrontal cortex and amygdala are important in learning and experiencing food and its subsequent effect on food intake. MCH and orexin fibres in the LHA transmit and receive information from the cerebral cortex (28). In addition, the LHA receives an inhibitory input from the shell of the nucleus accumbens which in turn receives inputs from the prefrontal cortex (74).

Reward pathways utilise dopamine, opioids, serotonin and noradrenaline neuronal fibres which connect the hindbrain and midbrain to the hypothalamus and all are known to affect appetite when injected into hypothalamic nuclei. In addition, orexigenic NPY and anorexigenic POMC neurons in the ARC have projections throughout the brain including the serotonergic system in the raphe nuclei and areas involved in reward such as the amygdala.

There has been significant research looking at the role of endocannabinoids in appetite. Evidence to date suggests that endocannabinoids act as orexigenic signals via cannabinoid CB1 receptors in the CNS (75). CB1 receptors are expressed in key hypothalamic areas regulating appetite such as the PVN (75). Blocking
CB1 receptors inhibits food intake and causes weight loss in rodents (76). The weight-reducing effect of CB1 antagonists (e.g. rimonabant) has been used in the treatment of human obesity until recently.

**CLINICAL THERAPEUTIC APPLICATIONS**

The hypothalamic control of appetite is complex and relies not just on signalling pathways within the brain but also peripheral signals acting via the brainstem and reward circuitries. As such, there are multiple potential targets for developing anti-obesity agents. At present only two drugs are licensed by the Food and Drug Administration for long term therapy against obesity: orlistat and sibutramine. Orlistat is an inhibitor of pancreatic and gastrointestinal lipases preventing the absorption of dietary fat. The gastrointestinal side effects of diarrhoea and oily stools reduces compliance. Interestingly, a recent study has shown reduced plasma levels of CCK, PYY and GLP-1 following orlistat treatment in humans (77). Sibutramine is a serotonin and noradrenaline reuptake inhibitor and is contra-indicated in patients with hypertension. Both drugs result in very modest weight loss in clinical trials, perhaps between 4%-8%. Work is currently underway to identify novel treatments that act within the CNS to control appetite. MC4 receptor agonists (78) and drugs that modulate NPY (79) and serotonergic (80) signalling are currently being investigated however they have the disadvantage of affecting more functions than just appetite. Further, due to the complexity of neuronal circuits involved in appetite control, it is unlikely that targeting one specific pathway will result in prolonged and clinically relevant weight loss. The ability to modulate central pathways using peripherally administered physiological appetite regulating agents is more likely to be a successful, low side effect, approach. If we can mimic the success of bypass surgery by administering the responsible gut hormones we may be able to provide real hope for effective treatments for obese patients.

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