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# Physiological and neural controls of eating

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What and how much we choose to eat are influenced by a variety of factors. These include the palatability or taste of particular foods, what we have learned about specific foods through experience, social and cultural influences on what foods and what amounts of food are appropriate to consume, relative availability and the cost of specific foods and an interacting system of physiological controls that serve to both maintain adequate nutrition and limit intake to maximize our use of consumed nutrients. The recent obesity epidemic makes it clear that environmental influences can have a tremendous effect on overall energy balance. Obesity rates began to rise in the US in the 1970's and this can all be attributed to changes in the food environment. However, the changing food environment interacts with a set of physiologcal controls that are important in the meal to meal controls of eating.

In this review we will concentrate on the roles of three interacting physiological and neural systems important in feeding control (Figure 1). These are systems that mediate: 1) signals related to metabolic state and nutrient availability, 2) signals that arise during a meal that serve to end that meal and maintain as state of satiety and, 3) affective signals related to taste and nutritional consequences that serve to reinforce aspects of eating. We will also identify how these systems interact in the defense of overall energy balance.

## Nutrient Availability Signaling

Studies of rodent genetic obesity models had long suggested the importance of circulating factors in overall body weight control. Having identified two different mutations in mice that led to obesity, [1] led to parabiosis experiments involving two strains of obese (obese - ob/ob and diabetic - db/db) and normal mice in which the blood supply between two mice in a

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parabiotic pair was shared. The results led to the conclusion that ob/ob mice lacked a circulating satiety factor that, in its absence, results in greatly increased food intake and obesity while the db/db mouse produced the factor but lacked the ability to appropriately respond to that factor. Twenty years later, Friedman and colleagues cloned the ob gene and named the protein that it produced “leptin” from the Greek “leptos” meaning thin, as this was a factor that helped maintain a normal body weight [2]. Shortly thereafter the leptin receptor protein was identified as the product of the db gene [3, 4]. Leptin is primarily produced in white fat and circulating leptin levels correlate positively with the fat mass, increasing in circulation as animals or humans become obese [5]. Thus, leptin serves as a signal of the available stored energy.

The study of leptin’s actions has illuminated many of the brain circuits that contribute critically to the control of energy balance and provided a basis for understanding earlier lesion work demonstrating a role for hypothalamic nuclei in energy balance. Leptin receptors are expressed throughout the brain with a particularly high expression within hypothalamic nuclei and other brain regions with identified roles in energy balance [6]. Interactions of leptin with its receptors within these hypothalamic nuclei result in the activation or inactivation of hypothalamic pathways containing various peptides that when administered into the brain either stimulate or stop eating [7, 8].

A major hypothalamic site of leptin’s actions is the arcuate nucleus. The arcuate contains two distinct neuronal populations that express leptin receptors. The first are neurons that express the prepropeptide proopiomelanocortin (POMC). POMC is processed into multiple opioid and melanocortin peptides including the anorexigenic peptide α-MSH. Central administration of α-MSH or synthetic melanocortin agonists potently inhibits food intake [9, 10]. Leptin activates POMC neurons [11] resulting in both increased POMC expression [12] and α- MSH release at terminal sites [13]. Arcuate nucleus POMC expression decreases with food deprivation [14] and increases with overfeeding [15] suggesting a regulatory role for this peptide in overall feeding control. Important roles for melanocortin signaling in energy balance have been demonstrated in experiments examining the effects of POMC [16] and melanocortin-3 or melanocortin-4 receptor [17] knockouts. Furthermore, genetic mutations in various aspects of the melanocortin signaling pathway have been identified as monogenic causes of human obesity [18].

Leptin also interacts with arcuate neurons that express the orexigenic peptides, neuropeptide Y (NPY) and the endogenous melanocortin antagonists agouti related peptide (AgRP). Leptin inhibits neuronal activity in these cells, reducing NPY and AgRP release [13] and downregulates the expression of these peptides [7]. When leptin levels are low, in times of nutrient depletion or food restriction, the leptin inhibitory tone on NPY/AgRP neurons is diminished, activity in these neurons is increased and the orexigenic peptides NPY and AgRP are released. Lesions of these NPY/AgRP containing neurons in adulthood results in rapid starvation [19].

The feeding stimulatory actions of both NPY and AgRP have been well documented. Intracerebroventricular or direct hypothalamic injection of NPY potently stimulates feeding [20–23] and repeated or chronic NPY administration results in obesity. Cell bodies of

neurons expressing NPY are found in multiple hypothalamic nuclei including the arcuate and dorsomedial hypothalamic nuclei [24]. Chronic treatment with NPY or viral induced NPY overexpression [25, 26] can result in obesity.

AgRP is an endogenous melanocortin antagonist whose expression is limited to the NPY/AgRP expressing neurons within the arcuate nucleus. AgRP expression is upregulated in response to fasting [27]. AgRP or synthetic melanocortin antagonists increase food intake when administered into the brain and their effects are long lasting [9, 28]. GABAergic signaling is an additional important output of NPY/AgRP expressing neurons in their interactions with arcuate POMC neurons exerting an inhibitory tone on anorexigenic signaling [29] and on neurons in the midbrain parabrachial nucleus [30].

The hypothalamic paraventricular nucleus (PVN) and the perifornical area of the lateral hypothalamus (LH) are important projection sites for arcuate POMC and NPY/AgRP neurons. The PVN contains neuronal populations that mainly express anorexigenic peptides and thus the outputs from this nucleus serve to limit food intake. Leptin and/or melanocortins activate PVN neurons containing corticotrophin releasing factor [31–33], oxytocin [34] and gastrin-releasing peptide [35] and each of these peptides reduce food intake when centrally administered [36–38].

The perifornical region of the LH contains neurons expressing the orexigenic peptides orexin and melanin concentrating hormone (MCH). Prepro-orexin expression is increased in response to deprivation and decreased in response to leptin administration [39] and central orexin administration increases food intake [40]. Furthermore, administration of an orexin 1 receptor antagonist inhibits eating suggesting a role for endogenous orexin in food intake control [41]. MCH expressing cells are similarly located in the perifornical region of the lateral hypothalamus although they represent a distinct neuronal population. MCH expression is increased in response to fasting [42] and is decreased by leptin administration [43]. MCH administration increases food intake in a dose related fashion [44] and genetic overexpression of MCH results in obesity [45].

Although leptin is the adiposity signal that has received the most attention, insulin also acts in the hypothalamus as an adiposity signal. Insulin levels increase with increased adiposity, insulin is transported from the circulation into the brain and insulin receptors are localized to the hypothalamus with a high concentration in the arcuate nucleus [46]. Central insulin administration inhibits food intake [47] and has been shown to modulate activity in the leptin responsive arcuate circuit, decreasing NPY mRNA expression [48] and increasing activity in POMC neurons [49].

Arcuate neurons that respond to leptin and insulin have also been proposed to be responsive to alterations in the local concentrations of nutrients and in this way serve as sensors for both short and long term nutrient state [50]. For example, arcuate POMC neurons are activated [51] and NPY/AgRP expressing neurons can be either activated or inhibited by increasing glucose concentration [52]. However, the role of these glucose-induced alterations in electrophysiological activity in the control of eating is uncertain as brain glucose concentrations don’t necessarily reflect changes in circulating glucose or increase in

response to meals [53]. Hypothalamic neurons are also responsive to changes in the local concentration of fatty acids [54, 55] and intraventricular administration of a long chain fatty acid has been shown to reduce food intake [56]. These data have been interpreted to suggest a role for brain fatty acid concentrations as signaling nutrient availability [57]. Finally local hypothalamic administration of some amino acids has been shown to decrease food intake [58, 59]. However, whether such a mechanism is involved in signaling circulating protein availability has yet to be demonstrated.

While the hypothalamus has been a primary focus of the study of anorexigenic and orexigenic neuropeptide signaling, the neural pathways regulating energy balance are clearly distributed to multiple brain sites. For example, leptin receptors are expressed in the nucleus of the solitary tract (NTS) in the dorsal hindbrain [60]. Local leptin administration at this site reduces food intake and downregulation of NTS leptin receptors attenuates the ability of leptin to reduce food intake [61, 62]. Data such as these strongly support the view that the adiposity controls of food intake are distributed rather than simply localized to the hypothalamic arcuate nucleus [63, 64].

## Satiety Signaling

In people and many experimental models for the study of feeding control, eating is not a continuous activity but occurs in distinct bouts or meals. Meal initiation is determined by a variety of factors, especially food availability. During a meal, ingested nutrients contact a variety of receptors within the oral cavity and gastrointestinal tract resulting in neural and hormonal signals that contribute to the determination of meal size. Meal size can be highly variable and alterations in meal size appear to be a major determinant of overall food intake.

Taste plays a major role in both food choice and in the amount of a particular food that is consumed. The effects of taste on overall ingestion are best demonstrated under conditions in which the feedback from the gastrointestinal tract is minimized. Experimental paradigms that specifically assess the effects of taste or palatability on ingestion have been commonly used. The first of these is called “sham feeding” in which animals have an esophageal or gastric fistula so that consumed liquid nutrients drain out of the fistula and do not accumulate in the stomach or pass on to the intestine. Such a preparation was first employed by Pavlov [65]. Pavlov demonstrated that dogs with open esophageal fistulas did not develop satiety but continued to eat for hours. The sham feeding paradigm has demonstrated the important role of orosensory stimuli in ingestion. Increasing the concentration of sugar solutions or oil emulsions increases the amount consumed in a linear fashion over extensive concentration ranges [66–68]. Sham feeding does eventually stop and a number of processes have been proposed to contribute to the cessation of sham feeding including oral metering [69], habituation [70] and sensory specific satiety (decreasing pleasantness of a specific food as more is ingested) [71].

In normal ingestion, consumed nutrients contact gastrointestinal mechano- and chemosensitive receptors that provide feedback information that is important to the control of meal size. The potential range of feedback mechanism that could be operating to lead to meal termination is dependent upon the distribution of ingested nutrients during the meal.

During eating, gastric emptying is more rapid than following a meal [72, 73], meaning that prior to meal termination, ingested nutrients not only accumulate within the stomach but also come in contact with a significant portion of the small intestine. Thus, the stomach and the upper small intestine are potential sites for the generation of signals providing feedback on the nature and quantity of consumed nutrients.

The vagus nerve (X cranial nerve) is the major neuroanatomical link between the gastrointestinal tract and brain [74]. Vagal afferent fibers with cell bodies in the nodose ganglion innervate the digestive organs and project to the NTS in the dorsal hindbrain with a rough viscerotopic representation of the alimentary canal [75]. The response properties of vagal afferent fibers depend in part upon the target organ they innervate. Mechanosensitive gastric vagal afferents increase their firing in response to increasing gastric load volume [76]. Individual afferent fibers are differentially tuned such that there are differences in their dynamic range [77]. Some afferents reach their maximal activity at small intragastric volumes while others do not begin to respond until a significant gastric load is present. Gastric mechanoreceptive vagal afferent fibers do not respond directly to the nutrient character of the gastric contents. Firing rates are similarly increased by nutrient and non nutrient load volumes [78]. In contrast, duodenal vagal afferents are activated by both the volume and nutrient character of intestinal contents [79, 80]. Although gastric vagal activity is not directly responsive to intragastric nutrient character, gastric afferent responsivity can be altered by the presence of duodenal nutrients [81].

Alterations in vagal afferent activity may be stimulated by nutrient induced release of a range of GI peptides. For example, the brain/gut peptide cholecystokinin (CCK) is released by the duodenal presence of nutrient digestion products. Duodenal vagal afferents that express CCK receptors [82] are activated by local CCK administration and combinations of duodenal load and CCK combine to produce greater duodenal vagal afferent activity than either alone [83]. CCK also plays a role in the response of duodenal vagal afferents to duodenal nutrients [79]. CCK administration also results in increases in vagal gastric mechanoreceptive afferent activity similar to those produced by intragastric load [84] and, again, combinations of gastric load and CCK produce greater degrees of activity than either alone [84]. Experiments with CCK receptor antagonists have demonstrated that endogenous CCK plays a role in the response of duodenal afferents to nutrients [79].

Elimination of aspects of vagal afferent or peptide-induced feedback can result in significant alterations in meal patterns. For example, surgical vagal deafferentation results in the consumption of larger meals than those consumed by sham operated controls [85]. The number of meals consumed during the day is reduced in response to these meal size increases such that overall food intake is unchanged. Similar alterations in meal size also occur in response to the administration of CCK antagonists [86, 87].

A number of peripherally acting peptides with roles in the control of eating have been identified. The best characterized of these is the brain-gut peptide cholecystokinin (CCK). CCK is released from I cells in the upper intestine in response to the presence of intraluminal nutrients. Exogenously administered CCK was originally demonstrated to decrease food intake in rats [88] and this feeding inhibitory action of CCK and CCK

agonists has been demonstrated in a range of species including non-human primates and man [89, 90]. Exogenously administered CCK reduces meal size and results in an earlier appearance of a behavioral satiety sequence [91]. A role for CCK in the control of the size of individual meals was confirmed by experiments examining the effects of repeated, meal contingent, CCK administration. CCK consistently reduces meal size without producing a significant change in overall daily food intake [92].

As discussed above, CCK activates vagal afferents. Disruption of subdiaphragmatic vagal afferent signaling significantly blunts the ability of CCK to inhibit food intake [93–95]. A role for endogenous CCK in satiety is supported by data demonstrating that administration of CCK antagonists with specificity for the CCK-1 receptor result in increased food intake (178, 179). This increase is almost completely accounted for by an increase in the size of their first meal [87]. Alterations in meal patterns are also evident in rats lacking CCK-1 receptors - Otsuka Long Evans Tokushima Fatty (OLETF) rats [96]. OLETF rats are obese and hyperphagic. Characterization of their spontaneous solid or liquid food intake has revealed overall increases in daily food intake that are expressed through significant increases in the size of individual meals with an incomplete compensation in meal number [97].

Satiety actions for the pancreatic peptides glucagon and amylin have also been demonstrated. Eating rapidly elicits an increase in pancreatic glucagon secretion [98]. Glucagon is rapidly cleared from the circulation by the liver [98] and the liver appears to be the site of glucagon’s satiety action [99]. Hepatic-portal infusion of glucagon at meal onset elicits a dose related reduction in meal size [100] and the satiety action of requires the presence of other forms of ingestional consequences as glucagon does not affect intake during sham feeding [101]. The satiety action of pancreatic glucagon is vagally mediated as transection of the hepatic branch of the vagus blocks glucagon satiety [102]. A role for endogenous glucagon in the control of meal size is supported by data demonstrating the ability of hepatic portal infusions of glucagon antibody to increase meal size [103].

Amylin is co-secreted with insulin from pancreatic beta cells. Amylin plasma levels rise rapidly with meal onset and remain elevated for a significant period of time during and following meals. Exogenously administered amylin inhibits feeding in a dose dependent and behaviorally specific manner [104]. Amylin’s primary site of action is within the area postrema, a hindbrain structure lacking a blood brain barrier [105] although recent work has suggested actions in multiple brain areas to affect food intake [106]. A physiological role for endogenous amylin in feeding controls is supported by experiments demonstrating increases in food intake in response to administration of amylin antagonists [107].

Both peptide YY (3–36) [PYY(3–36)] and glucagon like peptide 1 (GLP-1) are secreted from intestinal L cells in response to the intraluminal presence of nutrients. In contrast to CCK, the secretion of PYY and GLP-1 is maintained following meal termination suggesting roles for these peptides in feeding control beyond the individual meal. Exogenously administered PYY 3– 36 has been shown to inhibit food intake in multiple species including man [108–110]. The feeding inhibitory actions of PYY are likely mediated through interactions with the inhibitory Y2 receptors on NPY/AgRP neurons [111] [108]. Further

supporting a brain site of action, PYY 3– 36 administration has been shown to modulate patterns of cortical and hypothalamic neuronal activation in human subjects consistent with its actions in inhibiting food intake [112].

Exogenously administered GLP-1 or long acting GLP-1 receptor agonists inhibit food intake. Meal contingent GLP-1 administration leads to earlier meal termination and thus reductions in meal size [113]. Prolonged GLP-1 infusions or administration of long acting GLP-1 analogs reduce overall and do so through reductions in meal size [114, 115]. Examinations of a role for endogenous GLP-1 in the controls of meal size have produced mixed results [116, 117] questioning whether meal stimulated intestinal GLP-1 release is involved in meal termiation under normal circmstances. Circulating GLP-1 is rapidly degraded by DDP-IV making it unlikely that feeding actions of the normally released peptide are mediated through endocrine mechanisms [118]. GLP-1 receptors are expressed in vagal afferent neurons and total subdiaphragmatic or specific afferent vagotomy has been demonstrated to significantly attenuate the satiety effects of intraperitoneally administered GLP-1 (199, 205). Thus, meal released GLP-1 may act on vagal afferent terminals in close approximation to the enteroendocrine L cells to affect food intake.

As well as deriving from the lower intestine, GLP-1 is also expressed in neurons within the NTS [119]. These neurons project extensively throughout the brain including to a variety of hypothalamic and reward sites [120]. Centrally administered GLP-1 inhibits food intake although the effects are site specific [121]. For example, GLP-1 administered into the amygdala not only reduces food intake but also induces a conditioned taste aversion while GLP-1 administration to hypothalamic, hindbrain or reward sites appears to have specific feeding inhibitory actions [121–124]. Whether gut released GLP-1 affects feeding through activation of specific brain targets has not been adequately investigated. However, GLP-1 and GLP-1 analogs have been demonstrated to readily cross the blood brain barrier [125] and thus, degradation resistant GLP-1 analogs or the high circulating levels found following bariatric surgery likely access central sites to inhibit food intake [126].

Unlike these peptides that limit food intake, ghrelin, a brain-gut peptide that is primarily synthesized in the stomach, stimulates food intake following either peripheral or central administration [127, 128]. Ghrelin synthesis and plasma ghrelin levels are increased by food deprivation and reduced by refeeding [127] and this pattern of release in relation to meals is consistent with a role for ghrelin in meal initiation [129]. Repeated exogenous ghrelin administration can result in obesity [130] and ghrelin antagonists have been show to reduce food intake supporting a role for the endogenous peptide in stimulating eating [131]. Arcuate NPY/AgRP containing neurons express ghrelin receptors [132] and peripheral or central ghrelin administration increases arcuate NPY expression [133–135] suggesting a hypothalamic site of action. However, ghrelin has also been show to increase food intake when administered in the hindbrain leading to the suggestion that ghrelin’s actions are distributed across multiple brain sites [133, 136]. Knockout of either ghrelin or its receptor protects against high fat diet induced obesity [137, 138] and the double knockout results in mice with a lean phenotype [139],

As well as being modulated by short term feeding status, plasma ghrelin levels are affected by long-term energy status or adiposity. Thus, ghrelin levels are lower in obesity and rise in response to weight loss [140]. Together with the short term effects of ghrelin on arcuate NPY, these data suggest a role for ghrelin that opposes that of leptin on overall arcuate signaling.

## Reward Signaling

As noted above, food choice and the amounts consumed are greatly affected by taste or palatability. The effects of palatability on ingestion have been shown to have both opioid and dopaminergic mediation. Opiate agonists increase, while antagonists decrease, eating and these effects on ingestion appear to occur through alterations in palatability. Morphine enhances the intake of preferred over nonpreferred diets [141] and enhances hedonic responses to sweet solutions [142]. In contrast, administration of the opioid antagonist naloxone specifically reduces the intake of a preferred diet while not affecting the intake of a nonpreferred diet in a choice paradigm [143].

A major site of action for opioids in modulating palatability is the nucleus accumbens (NAc). Microinjections of opioid agonists into the medial shell region of the NAc increase both ingestion and positive responses in a taste reactivity tests [144–146]. Furthermore, in a paradigm in which recently consumed tastes are less preferred, NAc injections of opioid agonists increase and antagonists decrease the consumption of a pre-fed flavor again suggesting modulation of palatability [147].

Dopaminergic mediation of palatability has also been documented. Dopamine agonists increase eating [148] and animals with severe neurotoxin induced dopamine depletions [149] or dopamine deficient through gene knockout [150] fail to independently consume food. Feeding increases extracellular dopamine within the NAc [151] and the increase is greater with the consumption of a highly palatable food [152] suggesting a role for mesolimbic dopamine in mediating food reward. Such increases can also be shown in response to sham feeding of sucrose or corn oil demonstrating that taste is a sufficient stimulus for increased NAc dopamine release [153, 154] suggesting that dopamine plays a critical role in the hedonic processing of orosensory stimuli.

Not only the taste but also the nutrient consequences of ingestion can serve to reinforce dietary choice. This is best demonstrated in experiments that pair a novel non-caloric taste with an intragastric nutrient infusion. Animals come to prefer a taste that has been associated with an intragastric nutrient. Although the phenomenon of flavor conditioning is well documented, its mediation is not well understood. Feedback pathways that mediate satiety do not appear to be involved [155]. In contrast to the mediation of palatability, nutrient conditioning does not appear to depend upon opioid mediation [156]. However, dopaminergic mediation is required as D1 receptor antagonists block or significantly attenuate the acquisition of preferences to a flavor paired with gastric nutrients [157, 158] and this appears to involve a separate population of dopaminergic neurons from those that encode palatability [159].

## Interactions Among Signaling Systems

While the controls of eating are dependent upon these seemingly separate systems, an important issue is where and how these systems interact to control meals and overall intake. A number of the clearest demonstrations of interactions involve the adiposity signal leptin. Both peripheral and central leptin administration reduce food intake and leptin's effects on eating are are expressed as reductions in meal size without changing meal frequency [160–162]. Leptin's actions in reducing meal size depend in part upon interactions with satiety signals. For example, administration of leptin at doses that are subthreshold for inhibiting eating when administered alone, enhance the satiating potential of peripheral CCK or an intragastric nutrient preload [163–165]. This action of leptin appears to depend upon its ability to enhance the NTS neural activation produced feedback satiety signaling. That is, leptin enhances the dorsal hindbrain representation of ascending vagal afferent feedback signals arising from CCK or gastric preload induced gastrointestinal stimulation [166]. Reducing leptin levels through food deprivation or exogenous NPY administration have the opposite result - the satiating potency of CCK is reduced [167, 168] and satiety related NTS activation is inhibited [166]. These actions of leptin may be a downstream consequence of leptin signaling in the arcuate nucleus or directly mediated at hindbrain sites since the NTS contains receptors for both leptin and NPY [169, 170].

Leptin may also decrease meal size by altering the reinforcing effects of ingestion. Leptin receptors are located on ventral tegmental area (VTA) dopamine neurons [171] as well as on lateral hypothalamic neurotensin neurons that project to the VTA and leptin can regulate the activity of VTA [172]. The outcome of such interactions impacts overall reward signaling. Thus, leptin reduces the rewarding efficacy of electrical brain self stimulation [173] and reduces conditioned place preferences to rewarding foods [174]. In contrast, ghrelin has been demonstrated to enhance the rewarding value of high fat diets as reflected in conditioned preferences [175]. Similar effect on reward pathways have been demonstrated for insulin [176]. Thus, adiposity signals serving as long term regulators of energy balance have multiple actions. Many of these may contribute to the controls food intake in ways that both modulate the negative feedback effects of ingestion while also affecting positive feedback. Together these actions result in the modulation of meal size that, over the long term, contribute to the maintenance of energy balance.

Satiety signals can also affect the efficacy of adiposity signals. For example, CCK has been demonstrated to enhance the ability of leptin to reduce food intake and decrease body weight over the longer term [177–179]. In addition, the satiety signal amylin alters leptin sensitivity, restoring responsivity to exogenous leptin in diet induced obese animals that are otherwise leptin resistant [180, 181]. Satiety signals can also affect reward processing. As noted above, GLP-1 receptors are found in both the VTA and the NAc and administration of GLP-1 or GLP-1 agonists to these brain areas reduces food intake and does so in ways consistent with reduced reward [123, 182]. Similarly, amylin receptor subunits are expressed in the VTA and amylin administration at this site reduces intake and dose so by modulating VTA dopaminergic signaling [183]. Amylin receptors are also expressed in the shell region of the NAc and amylin administration can reverse μ-opioid induced feeding through actions at this site [184].

Finally, alterations in reward signaling can modulate hypothalamic systems involved in feeding control. Palatable diet intake stimulated by NAc μ-opioid agonist administration depends upon activation of multiple hypothalamic sites and suppression of activity in these sites blocks this feeding [185]. Roles for both orexin and NPY in mediating the effects of NAc μ-opioid induced feeding have been demonstrated [186, 187].

## Summary

There are multiple physiological and neural systems involved in controlling eating. These systems derive from and control different aspects of ingestive behavior and its consequences. While adiposity, satiety and reward signaling have different primary sites of mediation within the brain, these are interacting systems that together modulate food intake. Some of the currently approved pharmacotherapies aimed at reducing eating and body weight target these signaling systems. For example, liraglutide, the active ingredient in Saxenda is a GLP-1 agonist compound targeting satiety signaling, Contrave contains the opioid antagonist naltrexone, targeting reward signaling and locaserin in Belviq is a serotonin agonist thought to act on POMC neurons that contribute to adiposity responses.

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## Synopsis

Multiple physiological and neural systems contribute to the controls over what and how much we eat. These systems include signaling involved in the detection and signaling of nutrient availability, signals arising from consumed nutrients that provide feedback information during a meal to induce satiation and signals related to the rewarding properties of eating. Each of these has a separate neural representation but important interactions among these systems are critical to the overall controls of food intake.

**Key Points**

- Multiple physiological and neural systems contribute to the controls over what and how much we eat.
- These systems include signaling involved in the detection and signaling of nutrient availability, signals arising from consumed nutrients that provide feedback information during a meal to induce satiation and signals related to the rewarding properties of eating.
- Each of these has a separate neural representation but important interactions among these systems are critical to the overall controls of food intake.

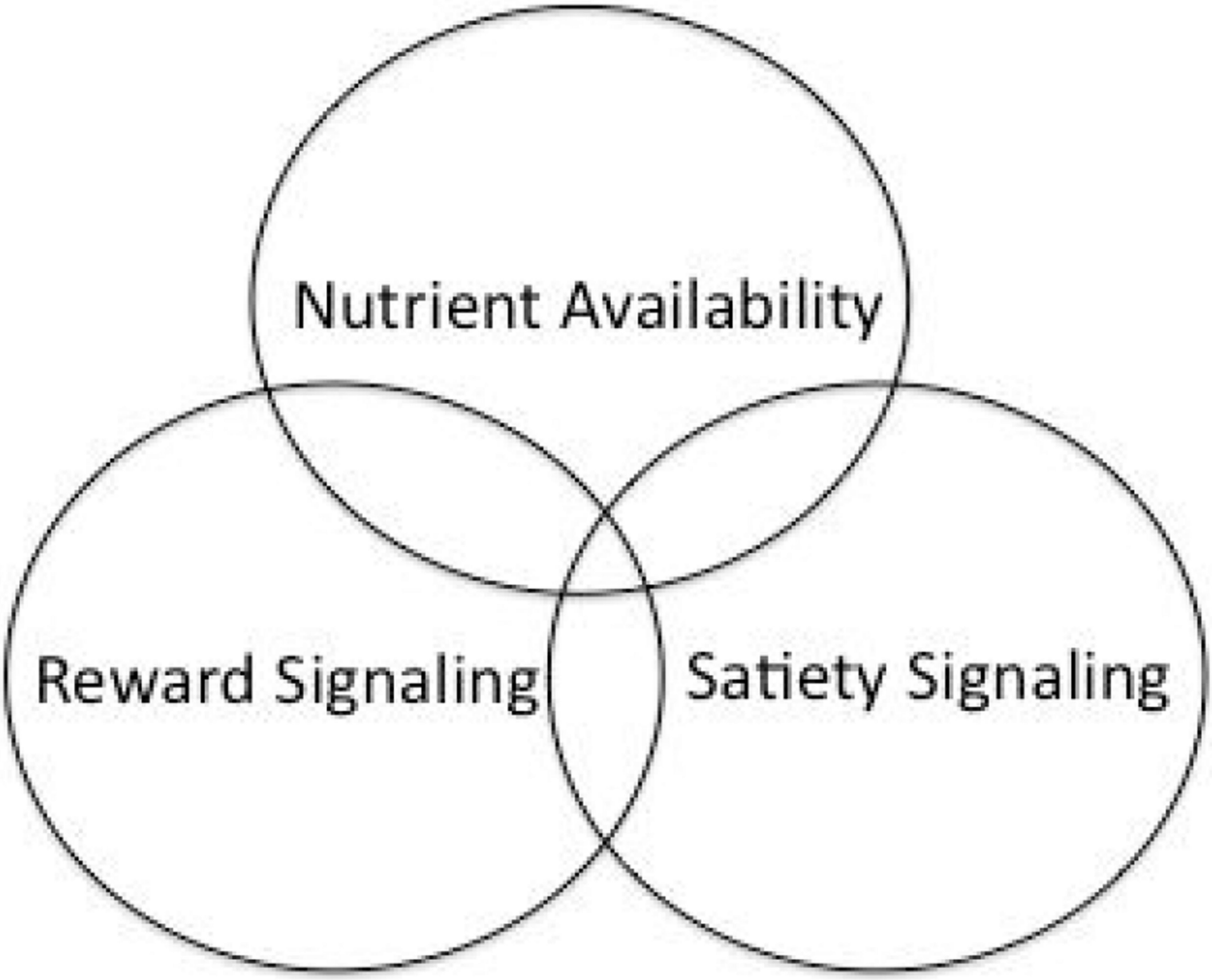


**Figure 1.**
Overall physiological controls of eating behavior