Satiety in Rats

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Abstract

Hunger and eating are fundamental parts of daily life, and dysfunctions in the system controlling them can cause significant health problems. This paper reviews some of the literature that has studied the different mechanisms involved in the hunger and satiety system in an attempt to provide a glimpse of what is currently known about the system. Many hormones and peptides have been implicated in the control of food intake, such as leptin, cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), and cocaine- and amphetamine-regulated transcript (CART). Numerous brain areas are involved in the system as well, including the nucleus accumbens (NAc) and nucleus of the solitary tract (NST). Both leptin and CCK have been found to affect the length of breaks between meals, however the interaction between the two has a much stronger suppressive effect on food intake. GLP-1 and its receptors respond to meal-related stimuli by reducing consumption. CART release is stimulated by leptin and CCK, and once it has been released it exerts effects similar to CCK on food intake and mediates the effects of leptin and CCK on short-term satiety as well. The NAc is involved in the reward aspect of food intake, and research on obesity treatments has found that drugs decreasing its effect on increasing food intake may be aid in the loss of body weight. The NST houses anorexigenic receptors that reduce food intake, and activation of these receptors by dietary proteins has been found to lower intake. The extensiveness of the literature and research on this system demonstrates just how complex it is; yet understanding how it works is essential to improve the health and quality of life of many individuals.
Satiety in Rats

Satiety is a process that, through many different mechanisms, terminates food intake when the body has consumed enough. It is a commonly studied subject because improper functioning of the satiety system can lead to a wide array of issues such as obesity or anorexia. The current review attempts to summarize what past research has found regarding some of the neuroanatomical and molecular mechanisms involved in satiety. Many brain areas are involved in the satiety process. The nucleus of the solitary tract (NST) contains glucoreceptors that detect the levels of nutrients in the body and sends signals to other brain areas to initiate feeding (Freberg, 2006). The lateral hypothalamus (LH) is involved in initiating feeding behavior. The arcuate nucleus is involved in the control of appetite, and the nucleus accumbens (NAc) is involved in the reward aspect of food intake. The ventromedial nucleus of the hypothalamus (VMH) controls the number of meals, while the paraventricular nucleus (PVN) controls meal size. Some of the molecular mechanisms involved in satiety are leptin, cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), and cocaine- and amphetamine-regulated transcript (CART).

Leptin is the product of the ob gene which functions as a feedback signal for regulating body weight and energy balance (Emond, Schwartz, Ladenheim, & Moran, 1999). It is released by white adipose tissue, and it has been found that increases in fat levels lead to higher leptin levels which decrease appetite and induce energy usage (Zorrilla, Inoue, Valdez, Tabarin, & Koob, 2005). This appetite-suppressing action is believed to be controlled by the long isoform of the leptin receptor in the periventricular sites in the hypothalamus and brainstem. Receptors in the arcuate nucleus have been implicated as well (Emond et. al, 1999). Leptin activates receptors (LRbs) in the hypothalamus by using a receptor-mediated transport system to cross the blood-brain barrier (Heldsinger, Grabauskas, Song, & Owyang, 2011). LRbs control feeding behavior.
and energy balance. Leptin interacts with meal-related signals, which heightens the anorexic response to gastrointestinal nutrients and satiety-related peptides (Williams, Baskin, & Schwartz, 2006).

Problems with the leptin system in rats have been found to lead to obesity (Zorrilla et. al, 2005). In obese \(ob/ob\) mice, exogenous leptin caused body weight and food intake to return to normal. This means that when there is a deficiency in the amount of leptin present in the body, obesity can develop, but when leptin is administered body weight and consumption go back to normal. A possible explanation for this is that leptin may increase the effectiveness of satiety signals during meals.

Cholecystokinin (CCK) is a short-term, meal-related, inhibitory signal that contributes to the inhibition of food intake (Kanoski, Walls, & Davidson, 2007). The effects of CCK are seen on the behavior that maintains the orosensory characteristics of food (Waldbillig & Bartness, 1982). It is secreted in response to nutrients, especially fat, entering the gut (Kanoski et. al, 2007). The satiety actions of CCK are controlled by low-affinity CCK-A receptors located on vagal afferent neurons, which are sensory neuron fibers of the vagus nerve that transmit information about different organs in the body (Heldsinger et. al, 2011). Unlike leptin, CCK acts both centrally and peripherally but does not cross the blood-brain barrier, which indicates that its actions are meal-related. In addition to reducing food intake, CCK release induced by fat in the small intestine also slows gastric emptying (Heldsinger et. al, 2012).

Glucagon-like peptide 1 (GLP-1) neurons are located principally and produced in the nucleus of the solitary tract (NST) (Dossat, Lilly, Kay, & Williams, 2011). GLP-1 receptors (GLP-1-Rs) are found in both the central nervous system (CNS) and the peripheral nervous system (PNS), so consumption is reduced when the receptors are activated in either system
(Williams, Baskin, & Schwartz, 2009). They are involved in food intake control and are activated by meal-related stimuli. Like CCK, GLP-1 may also activate vagal afferent fibers in the NST (Williams et. al, 2006). GLP-1 that is released from the gastrointestinal tract works in the physiological detection of satiety by the CNS (Dossat et. al, 2011), and this detection may occur before the onset of the sensation of fullness (Rodriquez et. al, 2000). The actions of GLP-1 lower blood glucose levels and food intake and eventually body weight as well (Williams et. al, 2006). GLP-1-R agonists aid in the treatment of diabetes and reduce appetite and body weight, and direct injections of GLP-1 in the PVN reduce food intake (Dossat et. al, 2011). An additional function of GLP-1 receptors may be inhibiting or reducing intake of potentially harmful foods or substances (Williams et. al, 2006).

Cocaine- and amphetamine-regulated transcript (CART) is an anorexigenic peptide in the nodose ganglia (NG), a part of the vagus nerve. It is expressed by vagal afferent neurons (VAN) and hypothalamic neurons and suppresses eating in rats (Heldsinger et. al, 2012). CART has also been found to mediate the actions of CCK and leptin regarding short-term satiety. CCK acts on VAN, increasing the expression of CART while decreasing the expression of orexigenic factors such as melanin concentrating hormone (MCH) (de Lartigue et. al, 2010). CART’s effect of reducing consumption has been seen when administered into the hypothalamus as well as the fourth ventricle.

The nucleus accumbens (NAc) is involved in the reward of food intake. Since this area is able to reinforce the intake of certain tastants, the motivation/reward pathways may play a role in the excessive intake of food (Katsuura, Heckmann, & Taha, 2011). Three different opioid receptors are located predominantly in the NAc, however the mu-opioid receptor (MOR) is thought to be the main receptor (Ignar et. al, 2011). Rats in which the MOR does not function are
found to have a reduced desire to eat and do not exhibit diet-induced obesity. Also, MOR are more active in diet-induced obese rats. MOR have been found to strongly increase consumption, even when rats are satiated, and it is believed that this effect is a result of increased palatability (Katsuura et. al, 2011). The increased intake of foods also depends on the nutrient content, because more high-fat foods are consumed. Also, MOR activity in the NAc activates other areas of the brain involved in food intake (Ignar et. al, 2011). This receptor is one of the focuses of research to decrease obesity. Antagonists have not been found to have very strong effects on MOR, however much more success has been achieved with inverse agonists in inhibiting its effects.

The nucleus of the solitary tract (NST) is involved in the initiation of food intake by sending signals to other parts of the brain after detecting nutrient levels in the body through glucoreceptors. Vagal afferents that run from the gastrointestinal tract to the NST also contribute to the actions of the NST (Wright et. al, 2011). Another type of receptor found in the NST is the NMDA receptor. Previous studies have found that the NMDA antagonists cause increases in the amount of food eaten during meals and delays the onset of satiety. When antagonists were administered directly into the NST meal size increased, but when the NST was destroyed this effect disappeared. Protein has been found to be a strong appetite suppressor (Bensaïd et. al, 2002). Studies have shown that increases in dietary protein lower consumption not because of a change in palatability or a conditioned taste aversion, but because of an enhancement of satiety (Picó, Oliver, & Sánchez, 2003). It is thought that information about dietary protein levels is processed in the same areas of the CNS that are involved in food intake and satiety, such as the NST (Darcel et. al, 2005).
The satiety system is very complex and involves many different structures and mechanisms in the body. Leptin and CCK are peptide hormones that are involved in the regulation of food intake. GLP-1 receptors also are located in the NST and are activated by meal-related stimuli. GLP-1 can reduce food intake and lower blood glucose levels from both the PNS and the CNS. These three mechanisms play an important role in the satiety process, and much research has been done to obtain knowledge about the specific ways that they reduce food intake.

**Leptin.** Many studies have been performed to investigate the role of leptin in satiety. Leptin is a peptide hormone that is known to regulate body weight and maintain energy balance. Levels of leptin in the body have been found to correspond with the amount of fat in the body.

In a study that used dose-response analyses and a meal definition of a break of five minutes after eating or drinking, the strongest effects of leptin were found in the length of breaks between meals (Zorrilla et. al, 2005). Acute intracerebroventricular (icv) leptin was found to have stronger effects on reducing the occurrence of spontaneous meals and breaks between meals than on the amount of food consumed during the meal. Leptin was also found to decrease the likelihood of another meal beginning after a meal was completed instead of causing a meal to end early. An example of how these effects can be manifested in humans is seen in reports of individuals with abnormal leptin levels claiming to feel “constantly hungry” and “demand food constantly.” Evidence that leptin is the true cause of these symptoms is seen in their elimination after leptin treatment. Also, changes in leptin levels between meals appear to be related to other factors involved in between meal breaks and the initiation of eating. These changes in leptin levels may be controlled by the stomach because gastric cells that secrete leptin are active during feeding. It appears that there are different modes of reducing appetite because intravenous (iv)
leptin gathers in the arcuate nucleus of the hypothalamus, whereas icv leptin spreads out among the periventricular structures.

Leptin has also been found to affect the actions of other mechanisms satiety, such as CCK and GLP-1. A study on the effects of centrally administered leptin on peripherally administered CCK in a meal context concluded that leptin greatly enhances the suppressive effects of CCK in wild type rats (Emond et. al, 1999). Leptin administered one hour before rats were given access to food greatly increased the magnitude of intake suppression caused by peripherally administered CCK. The combination of leptin and CCK also increased c-Fos expression in the periventricular nucleus (PVN), meaning there was more activity in that part of the brain as a result of the leptin+CCK administration. Also, high levels of c-Fos were found in the nucleus of the solitary tract (NST) only when leptin and CCK were administered together. Given the results of the study by Zorrilla and colleagues (2005), it could be hypothesized that the presence of CCK raises the levels of leptin in the satiety areas of the brain. Leptin levels also seem to correspond with CCK strength in some cases. If CCK is high, so is leptin, and if CCK is low, leptin is low as well. Therefore, future studies that examine the effects of leptin and CCK separately should make sure to include a combination condition to take into account their interaction. Another study that examined the effects of leptin on the suppression of food intake and reduced meal termination by GLP-1 showed that leptin levels affected the response of the satiety system to GLP-1-R stimulation (Williams et. al, 2006). The anorexic responses to both GLP-1 and Ex4, a GLP-1 agonist, were increased. Given this result, leptin resistance may lessen the food intake reduction caused by GLP-1. It was hypothesized that the brain areas involved in the interaction between leptin and GLP-1 were in the hindbrain and the area postrema. C-Fos activity was seen in both the hindbrain and the area postrema, but the activity was not found to
be mediated by leptin, for leptin pretreatment did not elicit any changes in those areas. In fact, leptin prevented Ex4 from activating those areas. The results suggested that the interaction between leptin and the GLP-1 agonist Ex4 may rely on an inhibitory response in the hindbrain, but their interaction must act on a different area in the brain.

These studies have shown that the primary effects of leptin are seen on the intermeal interval rather than on the amount of food consumed during a meal. Leptin also acts on other satiety mechanisms. When it is administered before CCK, intake suppression is stronger than it is when CCK alone is administered. Brain areas related to satiety are more active when both CCK and leptin are present in the body, indicating that CCK raises leptin levels in those areas. The intake suppression of GLP-1-R activation is also heightened when leptin is present. Overall, the findings of the studies suggest that leptin not only functions to increase breaks between meals but also interacts with other peptides or hormones that contribute to the process of satiety.

**Cholecystokinin (CCK).** CCK is another peptide hormone that reduces food intake. It acts in response to nutrients, mainly fat, entering the gut. CCK that is induced by fat consumption reduces food intake and also slows emptying of the stomach.

In a study that tested sucrose intake in response to different doses of CCK, it was found that the magnitude of the intake suppressing effect of CCK increases with the solution concentration (Waldbillig & Bartness, 1982). Another way to describe this change in effect is that as the solution becomes more food-like, the suppression induced by CCK becomes stronger. This indicates that CCK may have a physiological nature because its effects are connected to the food-like qualities of what is consumed. There is a strong association between sweet substances and caloric density, so the effect of CCK may be related to the caloric density of food, possibly
regulating meal size. Another way CCK may be involved in caloric regulation is through its effect on orosensory stimuli when released from the intestines, which induces satiety.

Because the satiety-related effects of CCK are more well-known than are the effects of other satiety mechanisms, CCK has been used to measure the effects of other mechanisms as well. One study in particular used CCK to compare its effects on the food intake and behavior of rats in their home cages to the effects on SB-334867, an antagonist of the orexin-A receptors in the lateral hypothalamus (Ishii et al., 2005). Orexin-A receptor activation occurs during fasting or when blood sugar is low, and consumption is increased. SB-334867, as an antagonist, induces a reduction in food intake. There have been hypotheses that the intake suppression caused by SB-334867 was simply due to sedation instead of actual satiety effects. However, the study found that SB-334867, like CCK, does not affect satiety behaviors. The study showed that CCK lengthens breaks between meals, reduces consumption, increases resting, and decreases other active behaviors as well. In other words, CCK can override the onset of natural satiety so that post-satiety behaviors are seen even if food is not consumed. Based on what was found in the previous study by Waldéllig and Bartness (1982), it can be concluded that CCK is released in response to consumed nutrients, and once enough of the nutrients have been ingested, satiety takes place and the behaviors described above are seen.

NMDA receptors, which can be found in the NST, have been found to be involved in the vagally-mediated reduction of consumption by hormones such as CCK (Wright et al., 2011). The results of a study observing the effect of NMDA antagonism on food intake suppression by CCK showed that fourth ventricle administration of NMDA antagonists inhibited the reduction of food intake by CCK administered intraperitoneally (ip). However, the same antagonists, when administered subcutaneously (sc) or ip, did not affect CCK action. This suggests that centrally
located NMDA receptors are very important in the control of food intake by CCK. However, vagal afferents express NMDA receptors as well, so it is difficult to conclude that the receptors located in the NST are responsible for attenuating the reduction in food intake induced by CCK. When central vagal afferent neurons located presynaptically to the NTS were destroyed, administration of NMDA antagonists had no effect on food intake, indicating that these neurons play a role in the reduction of food intake inhibition by CCK. Fourth ventricle administration of NMDA antagonists did increase activity in the NTS, however, which increased food intake, but not to the level of consumption that occurs in the absence of CCK.

Other food intake mechanisms have effects similar to CCK. In a study conducted to examine the role of the mu-opioid receptor (MOR) in the effects of the nucleus accumbens (NAc) on the intake of high-fat food, rats consumed more when MOR was stimulated in the NAc core (Katsuura et. al, 2011). However, activity related to palatability was found in both the core and the shell, suggesting that both areas are involved in taste reward. The intake of palatable foods was increased, but the intake of more neutral tastants was not affected. This is similar to the effects seen with CCK found by Waldbillig and Bartness (1982), in that CCK suppression became stronger as the solution became more food-like, however MOR stimulation increases intake and CCK suppresses it. Future studies could attempt to determine if there is a relationship or interaction between the two. Intake was increased by MOR stimulation regardless of caloric content, meaning that postingestive signaling is not necessary for MOR to act (Katsuura et. al, 2011). Evidence was also found that satiety signals are suppressed in addition to the changes in palatability. Inhibitory satiety effects such as licking rates and meal length are decreased with MOR stimulation.
These studies have shown that CCK may act in response to the caloric density of food that is ingested. The interaction of CCK with other receptors such as NMDA and MOR emphasizes the importance of CCK’s role in satiety. Given the involvement of CCK in the actions of several other mechanisms, studies should consider the effect of CCK in any study on satiety.

**Leptin+CCK interaction.** As has already been discussed, leptin and CCK have their separate functions: leptin regulates body fat and CCK helps with energy regulation (Kanoski et. al, 2007). However, when combined they cause an even stronger effect on the inhibition of food consumption. Their appetite suppression effects may be a result of effects on taste and reward, indicating the involvement of the nucleus accumbens (NAc) since it is the reward center for satiety. Since central administration of leptin did not affect food intake, it can be concluded that leptin’s reduction of food intake is not connected to its role in the production of satiety signals. It also indicates that satiety cues initiated by leptin may be dependent on where it acts or is released, because gastric tissue located in the stomach releases leptin in addition to adipose tissue. Previous studies have shown that adipose leptin may help regulate long term consumption and fat, whereas gastric leptin is involved in short term intake (Picó et. al, 2003). The effects of CCK were stronger than those of leptin alone but they were only seen when leptin was administered as well, demonstrating that the interaction of leptin and CCK is necessary for strong satiety cues (Kanoski et. al, 2007).

In a study that examined the pathways involved in the interaction between leptin and CCK and its effect on neuronal firing, it was found that the interaction between leptin and CCK increases neuronal activity more than either hormone does by itself (Heldsinger et. al, 2011). Evidence of the effect of CCK and leptin on the STAT3 gene, a transcription factor involved in
growth and immune function, was found in its increased phosphorylation. When STAT3 was silenced, the leptin and CCK interaction was eliminated, which is evidence that pSTAT3 regulates the closing of potassium (K+) channels involved in the interaction. In turn, leptin and CCK stimulate pP13K, which may increase the phosphorylation of STAT3. As has been found repeatedly in previous studies, leptin enhances the actions of CCK and increases the number of labeled neurons in the nucleus of the solitary tract (NST). In the NST, vagal afferent CCK feedback signals combine with leptin adiposity signals. However, the increase in pSTAT3 indicates that the nodose ganglia (NG, part of the vagus nerve) may be a primary area of leptin and CCK action. Considering the effects of leptin and CCK individually, both hormones are strengthened by their interaction: food intake suppression by CCK is strengthened and leptin is able to not only regulate feeding and energy, but also mediate short-term satiety. Heldsinger and colleagues (2011) also found that the interaction between CCK and leptin enhances the phosphorylation of STAT3 in the NG. The phosphorylation of this gene causes membrane depolarization and neuronal firing, which has been hypothesized to play a role in the release of neurotransmitters such as cocaine- and amphetamine-regulated transcript (CART).

Another study investigated the relationship between leptin resistance and reduced CCK sensitivity in diet-induced obese (DIO) rats (de Lartigue et al., 2012). It was found that in rats that lacked leptin signaling, there was no phenotypic change in the vagal afferent neurons (VAN), which is normally seen after feeding, and there was no inhibition of food intake by CCK. This indicates that VAN leptin resistance may be responsible for lipid- and CCK-controlled satiation and hyperphagia following high-fat consumption. The absence of satiety may be due to an inability to monitor or inaccurate monitoring of nutrients in the intestines, which can cause diet-induced hyperphagia and obesity. The results also show that leptin interacts with CCK and
can control the CCK signals in VAN. In obese rats, leptin injections did not cause phosphorylation of STAT3 in the arcuate nucleus and nodose ganglia. Usually, leptin and CCK work at the level of EGR1 (a transcriptional regulator that is associated with cell differentiation and neural activity) in VAN: leptin upregulates and CCK activates. The potentiation of CCK-induced protein synthesis in VAN by leptin is eliminated by EGR1. In DIO rats, CCK and leptin do not interact because leptin signals are absent. The CCK response is unchanged, but the enhancement of the response by leptin does not occur. This shows that leptin is necessary for CCK to function best. When leptin effects in VAN are absent, more CCK is required for satiation since leptin is not present to enhance the signal. Therefore, leptin resistance of VAN in DIO rats causes lower sensitivity to CCK and a change in VAN receptors that are involved in the regulation of food intake.

Cocaine- and amphetamine-regulated transcript (CART) is a peptide in the nodose ganglia (NG) that suppresses food intake. A study that investigated the role of leptin and CCK in CART release found that there is a synergistic interaction between vagal low-affinity CCK-A receptors (CCKARs) and leptin receptors (LRbs) which mediates CART release by the NG (Heldsinger et. al, 2012). CCKARs and LRbs were found on 18.7% of NG neurons and 63% of those neurons showed CART activity. This indicates that these neurons transmit the satiety signal caused by CCK and leptin. CART expression in neurons with CCKARs and LRbs shows that vagal afferent fibers release CART when the release of CCK and leptin is stimulated after a meal, which means that CART could function as a satiety signal in the nucleus of the solitary tract. It appears that there is a reciprocal relationship between leptin, CCK and CART. CART imitates the excitatory effects of CCK - it sustains and enhances them, leading to the inhibition of food consumption. It was also found that when CART expression was silenced in the NG, the
CCK/leptin satiety signal was eliminated, meaning that CART mediates leptin and CCK action on short-term satiety. De Lartigue and colleagues (2010) have also studied the relationship between CCK and CART. It was found that after CCK induces CARTp release, CARTp selectively has the same effects that CCK has on the expression of other receptors involved in satiety, and CCK action is inhibited if CART is blocked. The results indicate that the effects of CARTp alone are not strong enough to inhibit feeding after a long fast, but after a short term fast it can mildly reduce feeding. CARTp does, however, enhance the effects of CCK for an extended period of time.

The findings on the interaction between leptin and CCK show the complexity of the satiety system. Each hormone or mechanism involved in satiety has its separate function, but interactions are key to ensuring that the system works properly. Also, given that several different brain areas play a role, future studies could attempt to identify which specific aspect(s) of satiety each area controls.

**Glucagon-Like Peptide 1 (GLP-1).** GLP-1 has also been studied as a mechanism involved in the satiety process. It is a peptide produced by the nucleus of the solitary tract that is activated by meal-related stimuli and is involved in the control of food intake.

Dossat and colleagues (2011) performed a study to examine the nucleus accumbens (NAc) as a potential site for GLP-1 action. It was found that the GLP-1 projection to the NAc does play a physiological role in the control of food intake. Injections that had no effect in the lateral ventricle decreased food intake when injected into the NAc, but there was only an effect when it was injected into the core. Injections of Ex9, a GLP-1 antagonist, into the NAc increased consumption, which supports the idea that neuronal release of GLP-1 helps to limit food consumption. GLP-1 may have satiety effects when administered intracerebroventricularly (icv),
however it has a short half-life, which suggests that it naturally acts in the gut instead of the CNS because it would no longer be active by the time it made it to the CNS (Williams et. al, 2009). GLP-1-R agonists were found to cause reductions in meal size and lengthened breaks between meals. CCK was found to cause the same changes in feeding behavior, so it would be interesting in the future to compare the effects or roles of both CCK and GLP-1 or examine a possible interaction between them. Their effects of inducing satiety and weight loss are seen whether they are administered subcutaneously (sc) or (icv) (Rodriquez et. al, 2000). GLP-1-R agonists injected peripherally also may interact with feeding behavior mechanisms such as neurotransmitters. For example, Ex4 selectively lowers serotonin levels.

As discussed previously, GLP-1 also interacts with leptin. A study testing the effect of changes in leptin levels on the suppression effects of GLP-1-R found that leptin levels do affect the feeding response to GLP-1-R stimulation (Williams et. al, 2006). As a result, other agonists of the receptor cause stronger food intake suppression when leptin is present. This suggests that GLP-1-R agonists may only be mediated by GLP-1-R and may have their own mechanisms with which they interact as well. Lower sensitivity to GLP-1 has been found to contribute to weight gain. If low leptin levels decrease the effects of GLP-1, then it can be concluded that leptin resistance can reduce the ability of GLP-1-R to reduce food consumption, leading to weight gain.

GLP-1 clearly plays a role in the reduction of food intake, and a lack of its signaling can lead to weight gain. Similar to the other satiety mechanisms that have been discussed, GLP-1 does not act alone. Its effects are enhanced or weakened depending on leptin levels, so studies examining the effects of either leptin or GLP-1 should take their interaction into account before drawing conclusions.
Discussion

The food intake control system is of great interest to humans because consumption is a central part of daily life. Knowledge of how the system works is also important in regard to malfunctions of the system and problems such as eating disorders and obesity. It is known that many different parts of the body and brain are involved in regulating food intake, including the nucleus of the solitary tract, nucleus accumbens, and the vagus nerve. Hormones and peptides such as leptin, cholecystokinin, and glucagon-like peptide 1 are also involved.

Leptin was found to lengthen breaks between meals and increase the consumption suppression effects of other peptides and hormones, and CCK induced satiety behaviors such as longer breaks between meals and less physical activity. The interaction between leptin and CCK was found to have a much stronger inhibitory effect on food intake. GLP-1 was found to suppress food intake from the gut, and its effects can be strengthened by both leptin and CCK. The anorexigenic effects induced by VAN were found to be mediated by CART. CART release is induced by leptin and CART then enhances the food intake suppression effects of CCK. Studies showed that the NAc enhanced food intake because it is a source of reinforcement, however mu-opioid receptors (MOR) located in the NAc are a focus of obesity treatment research. Finally, the NST was found to be the location of NMDA receptors that reduce the suppressive effects of CCK. These functions only scratch the surface of what is known about and what remains to be discovered regarding the satiety system.

Studies have also been conducted to determine the effects of dietary protein on food intake. An increase in activity was found in several areas of the brain when rats were given high-protein diets, including the NST (Darcel et. al, 2005). The high levels of protein caused upregulation in the NST, which is the main area that receives gustatory information from the
vagus nerve. It regulates a number of food intake factors such as the ingestion of glucose, lipids, and amino acids, and satiety effects. The amygdala also is involved in feeding behaviors, and the results of the study showed that there is a reciprocal connection between it and the NST. Changes in the orosensory characteristics of the food did not reverse the food intake inhibition caused by high amounts of protein, indicating that it is the protein content that causes the satiety effects and not the sensory characteristics of the diet. Since this study did not obtain data about the specific mechanisms or receptors in the NST that are involved in the effect of protein, it would be interesting to investigate it in future studies. Given the results of the study by Wright and colleagues (2011) on the role of NMDA receptors in food intake reduction by hormones like CCK, studies could attempt to determine if protein has any effect on the NMDA receptors, since both have been linked to reduced food intake.

Given the knowledge that MOR are involved in increasing food intake, research on reducing obesity has made these receptors an area of focus. A low dose of GB1521498, an MOR inverse agonist, was found to act on MOR and maximally decrease consumption, supporting the conclusion that MOR is the receptor most involved in the regulation of food intake (Ignar et al., 2011). The diet-induced obese rats that received the drug lost weight, which indicates that the food intake suppression induced by GB1521498 causes a loss of fat mass. Since MOR are involved in the reward system for food intake, the drug was found to interfere with the food reward reinforcement that the receptor usually provides, which enhanced the onset of satiety. Given the effect of GB1521498 on food reward, describing its role as an enhancer of satiety is insufficient - it reduces the motivation to work for a reward. The rats still were able to press the lever, though, which shows that the drug inhibited only their motivation and not their ability to press it. However, this effect on reward motivation was only short-term, indicating that a
mechanism may exist that places a limit on this function but does not affect the onset of satiety induced by GB1521498. It was concluded that this drug has the potential to be an effective treatment for obesity.

As has been demonstrated by this review, the food intake and satiety system is quite complex. Many molecular and neuroanatomical factors are involved in inducing and reducing food intake, and these are of high interest in the science field, given the high rates of obesity and other eating problems and disorders. Research has reached a point where mechanisms have been found that can be manipulated in ways such as pharmacologically in order to decrease the prevalence of obesity and eating disorders. Knowledge of how the food intake and satiety system works can also help in the development of diets and lifestyle changes that will be maximally effective in controlling body weight and possibly reducing the number of fad diets that individuals buy into in an attempt to lose weight. There is still more to learn about the system, but studies have provided an abundance of knowledge that is invaluable to the health community and to the population in general.
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