The Cannabinoid System’s Role on Food Intake

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Abstract

The research presented here is important due to the increasing prevalence of obesity and obesity-related disorders in the United States and throughout the rest of the world. Researching ways through which appetite, or food seeking behavior, can be safely inhibited is an important step in the fight against obesity. The recent discovery of the cannabinoid system and the role it plays on food intake and the regulation of metabolism has prompted researchers to find means by which this system can be used to regulate appetite. For years, the stimulating effects of marijuana on appetite has been known, however, it was not until recently that researchers were able to isolate the compound responsible, Delta9-tetrahydrocannabinol (THC). The discovery of THC led to the discovery and further research on the cannabinoid system, the cannabinoid receptors, as well as the endogenous ligands of the cannabinoid system. These receptors, especially the CB1 receptor, are believed to play a role in the palatability and the rewarding sensory properties of food. Since it’s discovery, a myriad of specific cannabinoid receptor agonists and antagonists have been created in order to research the cannabinoid system’s exact role on metabolism. This information is being used to invent drugs to combat obesity. In fact, the drug rimonabant was made available in 2006; however, it was taken off the market due to deleterious side effects. Continuing research into the cannabinoid systems may play an important role in the search to find an effective means to combat the harmful effects of obesity. The present research reviews the current information available on the cannabinoid system and its effects on food intake.
The Endocannabinoid System’s Role on Food Intake

Marijuana has been used therapeutically and recreationally for centuries by a myriad of cultures. Different countries have instituted a number of different laws regarding marijuana’s legality and sale. For example, in the Netherlands marijuana may be bought and sold in “coffee shops”, while in China all marijuana is illegal to buy or sell. In the United States, marijuana has largely been restricted and highly regulated in the medical field. Despite the United States’ laws regarding marijuana and its efforts to regulate it, marijuana is still the most widely used drug in the United States (NHSDA, 1997). In 2012, the states of Colorado and Washington made a landmark vote, legalizing the recreational use of marijuana. Marijuana’s growing relevance in mainstream culture has prompted a renewed fervor of research into the possible therapeutic benefits the drug may offer.

Knowledge about marijuana, or Cannabis sativa, and its stimulatory effects on appetite has been around for centuries (Hollister, 1986). However, it was not until relatively recently that the natural compound in marijuana, Δ⁹-tetrahydrocannabinol (THC), was isolated. It was then that the anti-emetic, appetite-inducing, and psychotropic effects of marijuana were attributed to THC. THC has since been used to assuage vomiting and nausea in cancer patients as well as to prevent wasting syndrome in AIDS patients (Di Marzo & Matias, 2005).

In 1990, the first receptor for THC was isolated and characterized, called CB₁. The CB₁ receptor is a G-protein coupled membrane receptor (GPCR). This was supported by the fact that THC inhibits adenylyl cyclase and modulated the activity of calcium and potassium channels in neurons in a pertussis toxin-sensitive manner. The discovery of another cannabinoid receptor, the CB₂, receptor followed the discovery of the CB₁ receptor. CB₁ and CB₂ receptors can be found throughout the body, however, CB₁ receptors are found in larger concentrations in the central
nervous system, while CB$_2$ receptors are found in larger concentrations within the periphery, especially the immune system. In fact, the CB$_1$ receptor is the most abundant GPCR in the brain (Howlett, 2002).

The discovery of cannabinoid receptors in the 1990’s prompted the further discovery of endogenous ligands, or endocannabinoids. The first two endocannabinoids discovered were $N$-arachidonoyl ethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG). (Devane et al., 1992; Sugiura et al., 1995). These two endocannabinoids are hydrolyzed by the fatty acid hydrolase and monoacylglycerol to compounds that are inactive at cannabinoid receptors. Endocannabinoids act as mediators in different types of tissues which help to regulate the levels and functions of other mediators. Endocannabinoid regulation occurs when homeostasis changes within the cell, prompting endocannabinoids to interact with other mediators in order to return the cell to homeostasis (Di Marzo, Bifulco, & De Petrocellis, 2004). The cannabinoid receptors, the endocannabinoids and the enzymes catalyzing their biosynthesis and degradation comprise the endocannabinoid system (Di Marzo & Matias, 2005).

The cannabinoid system interacts with a wide range of other systems within the central nervous system such as the opioid system and areas involved in ingestion, such as the hypothalamus. The cannabinoid system regulates ingestion through interactions with gherlin, a signaling molecule in the stomach, as well as with the hypothalamus and areas within the hindbrain. Cannabinoid agonists and antagonists have the ability to induce hyperphagia and hypophagia, respectively.

Through interactions with the opioid system, the cannabinoid system also has the ability to modulate the sensory rewards relative to the intake of palatable foods. By stimulating the
cannabinoid system via cannabinoid agonists, organisms seem to increase food-seeking behavior as well as the ingestion of palatable food.

**Interactions Between the Cannabinoid System and Gherlin**

The cannabinoid system’s ability to regulate food intake begins with its interactions with ghrelin, the gastric peptide involved in signaling in the stomach. By stimulating the connections between the cannabinoid system and ghrelin, researchers have been able to induce hyperphagia. Conversely, by inhibiting signaling, researchers have also been able to induce hypophagia.

In 1999, ghrelin, a gastric-derived peptide was isolated. The discovery of ghrelin was a major step in understanding the mechanisms guiding energy homeostasis regulation (Kojima, 1999). It has been proposed that ghrelin is the link between signals from the stomach and the central nervous system. This link has been supported by research demonstrating the inhibitory effect of central and peripheral administration of rimonabant on the orexigenic and growth hormone releasing effect of ghrelin. In other words, when subjects have been administered rimonabant, researchers have found that effects of ghrelin are inhibited (Tucci, Rogers, Korbonits, & Kirkham, 2004). It has also been hypothesized that both the endocannabinoid system and ghrelin interact along the 5’ AMP-activated protein kinase (AMPK) pathway in the hypothalamus and periphery (van Thuijl, Kola, & Korbonits, 2008). Recent research by Senin et al. (2013) revealed that the peripheral blockade of the CB₁ receptor by the CB₁ antagonist, rimonabant, decreased food intake. However, this effect occurred only in food-deprived animals. Researchers attribute the decreased food intake to decreases in gastric ghrelin secretion induced by the activation of the mammalian target of rapamycin (mTOR) pathway in the stomach (Senin et al., 2013). mTOR is responsible for sensing the amount of energy, or energy supply, within the body. It is the component of two multi-protein complexes: mTOR complex 1 (mTORC1) and
mTOR complex 2 (mTORC2). mTORC1 is responsible for phosphorylating and modulating the activity of the serine/threonine ribosomal protein S6 kinase 1 (S6K1). S6K1 is responsible for phosphorylating and activating S6, which is a ribosomal protein involved in translation (Wullschleger, Loewith, & Hall, 2006).

In conclusion, previous research indicates that the cannabinoid system interacts with the gastric peptide, ghrelin, to mediate signaling between the central nervous system and the stomach. These interactions, occurring in the periphery and the hypothalamus, may stimulate or attenuate an organism’s food seeking behaviors. Interactions between ghrelin and the cannabinoid system are likely to occur along the AMPK and/or mTOR pathways. Further research may help elucidate these interactions.

**Interactions Between the Cannabinoid System and the Opioid System**

Recent studies have indicated a strong link between cannabinoid and opioid systems. The opioid system plays a significant role in reward processing, including the pleasure associated with eating and drinking (Cooper & Kirkham, 1993). In fact, Kirkham & Williams (2001) have conducted experiments revealing a synergistic effect on feeding when CB₁ and opioid receptor blockades have been administered. In this experiment, researchers administered low doses of the CB₁ antagonist, SR141716, as well as a low does of the general opioid receptor antagonist, naloxone. If administered alone in such a low dose, neither of these drugs would produce a marked reduction in food intake. However, both doses administered together yielded a significant decrease in food intake, exceeded the sum intake of either drug administered alone (Kirkham & Williams, 2001).

In a follow-up study conducted by Williams & Kirkham (2002), experimenters examined the ability of SR141714, naloxone, and dexfenfluramine to reverse the hyperphagia caused by
administration of THC. In this experiment, Williams & Kirkham (2002) administered oral doses of THC to pre-satiated Lister hooded rats. After being injected with THC, subjects were injected subcutaneously with either: SR141716, the CB2 antagonist SR144528, naloxone, or the serotonergic drug dexfenfluramine. Results revealed a marked decrease in food intake after administration of SR141716 and naloxone. Dexfenfluramine and SR144528, on the other hand, had no significant effect on food intake.

The hyperphagic effect of THC is primarily mediated by the CB1 receptor. CB1 receptors are found throughout the body; however, they are predominatly found in the central nervous system. In contrast, CB2 receptors are only found in the periphery of the body. In light of these results, feeding is directly influenced by CB1 receptors in the central nervous system, as shown by SR141716’s ability to attenuate hyperphagia induced by THC. These results also reveal that feeding is not directly associated with CB2 receptors, as shown by SR144528’s inability to counteract the effects of THC.

The opioid antagonist, naloxone, was able to successfully attenuate hyperphagia following administration of THC. These results indicate that opioids also play a role in food intake, interacting with the cannabinoid system. Even low doses on naloxone were able to successfully reduce food intake. This supports the notion that the opioid system is involved in food reward; opioid receptor agonists and antagonists increase and decrease food intake respectively. Previous studies have also indicated that opioid receptor antagonists diminish the pleasantness of normally palatable food, however, the rats in this experiment ate bland lab chow. Compared to controls, this food was insensitive to the anorectic effects of naloxone (Drewnowski et al., 1995) (Williams & Kirkham, 2002). Researchers attribute the ability of naloxone to attenuate THC-induced hyperphagia via interactions between the opioid and cannabinoid
systems. The enhanced anorexia of naloxone may reflect actions of the cannabinoid system, enhancing the rewarding properties of food. Researchers posit that this action may be directly mediated by the cannabinoid system, or indirectly through alterations in opioid functioning (Williams & Kirkham, 2002). The authors cite past evidence indicating that cannabinoids may play a role in increasing the synthesis and/or the release of opioids (Williams & Kirkham, 2002).

It is important to note that Williams & Kirkham (2002) offer another alternative for naloxone’s effect on food intake. Researchers posit that the anorexia shown in the results may be due to higher baseline levels of intake (Williams & Kirkham, 2002). In other words, observed hypophagia may have been due to subjects’ food consumption prior to the experiment, rather than naloxone’s interactions with the cannabinoid system.

Past evidence supports the results found in William & Kirkham’s (2002) experiment. In one experiment, naloxone successfully reversed the hyperphagic effects of the cannabinoid agonist CP-55, 940 of palatable solutions, beer and sucrose (Gallate et al., 1999). These interactions may be mediated by the functional relationship between the opioid and cannabinoid systems relative to reward processes and activity in the mesolimbic dopaminergic pathways (Williams & Kirkham, 2002). Stimulation of the cannabinoid system may also activate the opioid system through each system’s interconnections. Therefore, activating the cannabinoid system may yield an increased reward sensation to stimuli.

In conclusion, previous research has revealed a functional relationship between the cannabinoid and opioid systems. These two systems can interact to produce hyperphagia or hypophagia, probably through increasing or decreasing the reward value of food respectively. This is may be due to the cannabinoid system’s role in increasing the synthesis and/or the release of opioids within the brain.
Cannabinoids and Ingestion

_Cannabinoid agonists and antagonists_

For years, people have been cognizant of the appetite stimulating properties of marijuana, and specifically, THC. A myriad of research corroborates these findings. Williams, Rogers, & Kirkham (1998) conducted a study to determine the effects of orally administered THC on Lister hooded rats. Researchers allowed subjects access to a palatable wet mash diet for two hours before THC was administered. In other words, the rats were pre-satiated before administration of THC. Subjects were then orally treated with a sesame seed oil vehicle or THC. After one hour, subjects were allowed free access to standard rat chow, while researchers monitored intake over the course of twenty-four hours. During the first hours of testing, rats treated with THC at doses of 0.5, 1.0, and 2.0 mg/kg exhibited significant hyperphagia within the first hour of testing. Afterwards, treated rats compensated for increased food intake; total twenty-four hour food intake was similar in all conditions. Researchers observed that the 1.0 mg/kg dose had the most significant effect on food intake, followed by the 2.0 mg/kg dose. In a sense, administration of THC in different doses created a U-shaped curve effect. Marked hypophagia occurred following hyperphagia induced by the THC, in order to compensate for the quantity of food consumed. Food intake between five and 24 hours were similar across all conditions, indicating that a complete recovery had occurred.

This experiment reveals that, even after satiation, THC produced a marked increase in the amount of food consumed after one hour post-treatment. Researchers noted that the 2.0 mg/kg dose caused substantial motor incoordination, which may explain the reduction in food intake compared to the 1.0 mg/kg dose. Although the mechanisms through which hyperphagia occurs were not examined in this study, experimenters posit that THC may increase motivation by
enhancing the sensory or rewarding properties of food (Williams et al., 1998). This experiment corroborates the hypothesis that activation of the cannabinoid system produces hyperphagia.

While cannabinoid agonists, such as THC, seem to produce hyperphagia, evidence has suggested that the cannabinoid system does not play a role in the consumption of water. Verty, McFarlane, McGregor, & Mallet (2004) conducted a study in order to examine the interaction between CB₁ cannabinoid and oxytocin receptors in food and water intake. Oxytocin is a neurohypophyseal hormone that is involved in central and peripheral effects including feeding and osmoregulation (Verty et al., 2004). Researchers implanted cannulae into the lateral ventricles of male Wistar rats. Rats were injected with THC, oxytocin, or the CB₁ antagonist, SR 141716, and allowed free access to food and water for two hours. It is important to note that rats were not pre-satiated, however, rats had free access to standard laboratory chow before the onset of the experiment.

Results revealed that oxytocin, when administered alone, dose-dependently attenuated food and water intake compared to the vehicle solution. SR141716, when administered alone, also attenuated food intake, but did not affect water intake. When SR141716 and oxytocin were administered together, both were successful at attenuating both food and water intake, creating a synergistic effect. However, when THC and oxytocin were administered together, oxytocin was unable to attenuate the hyperphagia associated with THC.

These findings reveal that oxytocin and cannabinoid receptors interact relative to food intake. Both SR141716 and oxytocin, when administered together, were able to successfully attenuate both food and water intake. However, the mechanisms of interaction may be non-direct, as evidenced by the fact that oxytocin was unable to attenuate hyperphagia induced by the administration of THC. Results also reveal that the cannabinoid system has no affect on water
intake. This is supported by evidence in this study showing that SR141716 was unable to attenuate water intake (Verte et al., 2004). Therefore, while it seems that the cannabinoid system plays a functional role in food intake, it may not play a role in water intake.

While cannabinoid agonist have the ability to produce hyperphagia, studies of cannabinoid antagonists have shown that inhibiting the cannabinoid system produces hypophagia. In an experiment conducted by Werner and Koch (2003), researchers injected the CB1 antagonist, AM281, as well as the CB2 antagonist, AM630, into the lateral ventricle of male Lewis rats. Before administration, rats were deprived of food overnight, in order to examine the effects of cannabinoid antagonists on food-deprived subjects.

Results revealed that the CB2 antagonist, AM630, had no effect on reducing food intake. This finding corroborates the hypothesis that peripheral CB2 receptors do not play a direct role in food intake. However, the CB1 antagonist, AM281, successfully attenuated food intake at 0.5, 1, 2, 4, and 6 hours following administration (Werner & Koch, 2002). This experiment furthers the notion of differential placement of cannabinoid receptors throughout the body. CB1 receptors seem to be located in the central nervous system, providing a direct means by which to increase, or decrease, food intake. On the other hand, CB2 receptors seem to be dispersed throughout the periphery of the body. Evidence from this study and past studies provide support for the idea that CB2 receptors do not play a functional role in food intake. These findings also suggest that the cannabinoid system not only has the ability to increase food intake, but also the ability to decrease food intake. Food intake was attenuated, even after subjects were food-deprived for twenty-four hours. This provides further evidence that the cannabinoid system plays a functional role in food intake.
A similar study conducted by Chambers, Sharkey, & Koopmans (2004) also exhibited similar results. In this study, experimenters used the same CB1 antagonist, AM251, as did Werner and Koch (2002). Researchers intraperitoneally administered AM251 to moderately obese male Lewis rats. Vanilla-flavored Ensure Plus was used as food on account of its palatability. Subjects were injected and, after fifteen minutes, allowed free access to food. Food intake was observed at one, two, and three hours following administration of the drug.

Results revealed a significant reduction in food intake at all three time points, compared to control subjects. Also, researchers observed that AM251 caused a significant reduction in daily food intake for six days following systemic administration. These effects were dose-dependent; AM251 at a dose of 1.25 mg/kg significantly reduced food intake only on the day of administration. On the other hand, AM251 administered systemically at a dose of 2.5 mg/kg significantly attenuated food intake on the day of administration, as well as the following four days. Reduction in food intake was also accompanied by a significant loss in weight. In the control condition, rats actually gained weight over the course of the experiment, while rats in the experimental condition lost weight, or failed to gain weight, after doses of AM251 at 1.25 or 2.5 mg/kg (Chambers et al., 2004).

The experimental results support previous experiments showing that CB1 antagonists cause a significant reduction in food intake. AM251 was able to significantly attenuate food intake following administration, and at high doses, it significantly attenuated food intake for several days. While researchers could not explain why these effects lasted for so long, the results are still indicative of the ability of CB1 antagonists to modulate food intake.

In conclusion, evidence from past studies indicates that CB1 agonist and antagonists have the ability to induce hyperphagia or hypophagia, respectively. However, stimulation of the
cannabinoid system does not affect an organism’s water intake. These findings have occurred in subjects who were pre-satiated as well as subjects who were allowed free access to food during and prior to the experiment. In other words, satiation occurring prior to administration of cannabinoid agonists and antagonists does not seem to have much an effect on food intake, although it may lower overall intake. The mechanisms by which food intake is altered are CB₁ receptors that are located in the central nervous system. Conversely, CB₂ receptors located in the periphery do not seem to have an effect on food intake.

**Cannabinoids: Behavior and Palatability**

While numerous studies have confirmed the cannabinoid system’s ability to modulate food intake, scientists have been questioning the mechanisms by which this phenomenon occurs. Do CB₁ agonists increase hunger, increase the motivation to obtain food, or increase food’s palatability? Several studies have been conducted in order to examine the effects of cannabinoid stimulation and inhibition on food intake and food-motivated behavior.

**Motivation to Obtain Food**

Previous studies have indicated that cannabinoid agonists and antagonists may play a role in an organism’s drive to obtain food or not obtain food, respectively. For example, Barbano, Castane, Martin-Garcia, and Maldonado (2009) conducted a study in which experimenters observed THC’s effect on mice’s ability to obtain food in a fixed ratio 1 schedule of reinforcement. Mice first went through an acquisition period, in which mice were trained to press a lever to obtain food. Once the acquisition had been completed, defined as 80% stability, a foot-shock was paired contingent upon food delivery. Therefore, in order to obtain food, the rat must endure a shock. This was used in order to examine an organism’s drive to obtain food, even though food was paired with an aversive consequence. In the next phase of the experiment, mice
were intraperitoneally administered 1.0 mg/kg of THC. Thirty minutes after administration of THC, mice were placed in the operant condition chamber.

Results from this experiment revealed that THC had no effect on the operant performance of mice when trained to obtain standard food pellets associated with a shock. However, mice treated with THC significantly improved discrimination between reinforced and non-reinforced levers when pellets were either chocolate flavored or fat-enriched. In other words, mice treated with THC exhibited a significant decrease in the number of non-reinforced lever presses when receiving chocolate or fat-enriched pellets, compared to standard pellets. Researchers attributed the improved discrimination to THC’s ability to enhance the reinforcing properties of the pellets. Experimenters posit that THC may directly modulate operant performance to obtain high caloric food, regardless of whether it was chocolate or fat-enriched. Also, THC’s ability to decrease the aversive effect of the shock may be due to mice deviating attention from the shock in order to obtain food pellets (Barbano et al., 2009).

Barbano et al.’s (2009) experiment indicates that THC, a CB₁ agonist, enhances an organism’s drive to obtain food, specifically, high-caloric food. High-caloric food tends to be more palatable for organisms; more calories are associated with increased nutrients, which is evolutionarily adaptive. Therefore, this study indicates that the cannabinoid system may play a role in enhancing an organism’s drive to obtain high-caloric, palatable food.

A similar experiment conducted by Gallate, Saharov, Mallet, & McGregor (1999) exhibited similar results. In their study, experimenters examined rat’s motivation to obtain beer following administration of a CB₁ receptor agonist. Wistar rats were intraperitoneally administered either the CB₁ agonist, CP 55,940 or the CB₁ antagonist, SR141716, in a volume of 1 ml. Following administration, rats had access to two types of beer: light beer, and near-bear.
Each had a concentration of 2.7% and <.05% ethanol respectively. Rats also had access to a sucrose solution. Beer was used because previous experiments have shown that rats have an innate preference for beer. In order to examine food-reinforced behavior, experimenters used a “lick-based progressive ratio paradigm” to measure a rat’s motivation to obtain the solutions. The basis of a lick-based progressive ratio paradigm is that the rat must emit an ever-increasing number of licks in order for each successive fixed unit of beverage to be delivered.

Results revealed that the CB₁ receptor agonist, CP 55,940, significantly increased motivation to consume beer, as well as sucrose. Researchers note that the agonistic effect of CP 55,940 was seen across all types of beer, as well as the sucrose solution. In other words, CP 55,940 motivated rats to increase consumption of all types of solution, whether or not alcohol was contained within the solution (Gallate et al., 1999). These results indicate that CB₁ receptor agonists can augment an organism’s motivation to consume palatable solutions. In more general terms, this study, and previous studies, indicate that the cannabinoid system plays a role in an organism’s drive to consume palatable solutions.

If this is true, then experimenters would expect to see a significant reduction in motivation to consume palatable foods after administration of a CB₁ receptor antagonist. McLaughlin et al. (2006) conducted a study in order to investigate the behavioral effects of the CB₁ antagonist, AM 1387. McLaughlin et al. (2006) administered intraperitoneal doses of AM 1387 to food-deprived Sprague-Dawley rats. Subjects were food-deprived and AM 1387 was administered in 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 mg/kg doses thirty minutes prior to testing. Rats, depending on the condition, were placed in a cage containing high-fat, high-carbohydrate, or standard laboratory chow food. Food intake was defined as the difference between the weight of food, before and after testing.
Results revealed that AM 1387 significantly attenuated the consumption of all three types of food, with the most significant results trending towards the more palatable food groups, high fat and high-carbohydrate. Researchers are careful to note that these results are inconsistent with some studies indicating that CB₁ receptor antagonists, such as SR 141716A, do not significantly reduce food intake of palatable food compared with other, standard foods. However, AM 1387 was still able to significantly inhibit the consumption of standard foods, consistent with the effects of SR 141716A. AM 1387’s ability to attenuate the consumption of palatable food, unlike SR 141716A, may be due to differences in baseline intake, or scaling differences, rather than functioning of the CB₁ receptors. In any case, the study conducted by McLaughlin et al. (2006) is consistent with other studies showing the ability of CB₁ receptor antagonists to significantly reduce the intake of palatable foods compared to other foods (McLaughlin et al., 2006).

McLaughlin et al. (2006) also conducted a subsequent study in order to investigate the behavioral effects of the CB₁ receptor antagonist, AM 1387, on food-reinforced behavior. In this experiment researchers trained food-deprived mice on a FR1 schedule, in which each correct level pressing sequence was reinforced with food. Rats were intraperitoneally administered with AM 1387 at doses of either 0.25, 0.5, 1.0, 2.0, and 4.0 mg/kg thirty minutes prior to testing. Lever pressing and the rate of response was observed after injections had been administered. Data collected during the experiment indicated that AM 1387 significantly repressed food-reinforced behavior. Results revealed a significant suppression of the total number of responses, as well as the overall number of lever presses. These results are consistent with other findings, indicating an overall suppression of food-reinforced behavior after administration of CB₁ receptor antagonists (McLaughlin et al., 2006).
Taken together, these findings suggest that the cannabinoid system plays a role in an organism’s motivation to respond to food; this may also extend to palatable versus standard types of food. Experiments using CB₁ receptor agonists clearly show that stimulating the cannabinoid system leads to an overall increase in food intake, with some studies showing that the increased food intake may be more specific to palatable foods. On the other hand, studies also show that administration of a CB₁ receptor antagonist significantly attenuates food intake of standard food. Thus, it is reasonable to assume, that the cannabinoid system plays a significant role in an organism’s motivational state to find and obtain food.

*Ingestion of Food*

While some studies have been conducted in order to examine the role of the cannabinoid system relative to food-reinforced behavior, much of the studies involving the cannabinoid system have been conducted in order to examine its effects on palatable foods. One such study by Jarrrett, Limebeer, & Parker (2005) was conducted in order to determine the effect of THC on sucrose palatability. This experiment also observed the effects of the CB₁ receptor antagonist, SR 141716, relative to sucrose palatability as well.

In this study, male Sprague-Dawley rats were implanted with intraoral cannulae in order to receive the sucrose solution. THC in doses of 0.5 ml/kg, as well as SR141716 in doses of 2.5 mg/ml were intraperitoneally administered prior to each testing session. During each trial, sucrose solution was delivered at a rate of 1 milliliter a minute for five minutes while researchers observed and recorded the rat’s orofacial and somatic reactions. In the second experiment, both THC and SR141716 were administered in order to examine the CB₁ antagonists ability to attenuate the hyperphagia associated with THC.
Results collected from this study revealed that when THC was administered 120 minutes prior to intraoral infusion of sucrose solution, THC was able to significantly enhance palatability independent of sucrose concentration. However, this effect was not seen at 30 nor 60 minutes prior to intraoral fusion. The effect of THC was specific to this time interval; at 120 minutes post-injection, rats displayed significantly more ingestive responding compared to the control group, however, this effect was observed at no other time interval. The increased preference for sucrose solution after administration of THC was inhibited after administration of SR141716. However, researchers note, that SR141716 did not modify sucrose palatability on its own. Researchers explain this by saying that the CB1 receptor antagonist may not play a role in modifying the hedonic quality of the sucrose solution. However, the CB1 receptor agonist THC was able to modify the hedonic quality of the sucrose solution, perhaps indicating the cannabinoid system’s role in modifying palatability (Jarrett et al., 2005).

If CB1 receptor agonists have the ability to enhance palatability of foods, then it is reasonable to assume that CB1 antagonists should have the ability to downregulate palatable food intake. Dore et. al (2013) conducted an experiment in order to investigate the role of the cannabinoid system in compulsive eating. Researchers used male Wistar rats, which were continuously fed with either a regular chow diet, or intermittently with a chow diet for two days, as well as a palatable, high-sucrose diet for one day. Rats in the palatable diet condition exhibited increasing hypophagia when fed the regular chow diet, however, when rats were fed with a palatable diet, they exhibited increased hyperphagia.

After rats had been exposed to regular and palatable diets, researchers intraperitoneally administered with 0.3, 1, or 3 mg/kg and then placed subjects in a cage with either a regular or palatable diet depending on the condition. Results revealed that administration of the CB1
antagonist, SR141716 significantly decreased food intake across all conditions. However, SR141716’s effect was most prominent in rats that received palatable chow. The highest doses of SR141716 significantly reduced food intake of the palatable diet, compared to food intake of regular chow in other conditions. Along with this, researchers also observed marked reductions in weight gain caused by treatment of SR141716 (Dore et al., 2013).

While Jarrett et al. (2005) found that SR141716 was not able to significantly attenuate food intake by itself, these results are contradictory to Dore et al.’s (2013) findings, which suggest that SR141716 does have the ability to attenuate food intake. The discrepancies in the results may be due to the methodology of each experiment. In Jarrett et al.’s (2005) experiment, researchers administered SR141716 along with THC. This experiment also used a lower dose (0.5 and 2.5 ml/mg) compared to Dore et al.’s (2013) experiment (0.3, 1, or 3 mg/kg). The low dose of SR141716, combined with the administration of THC, may have attenuated the anorectic effect of SR141716. Also, SR141716 may not have been administered in high enough doses in Jarrett et al.’s (2005) experiment. In conclusion, it can be seen that CB1 receptor antagonists, when administered alone, have the ability to significantly reduce the amount of food intake. Specifically, CB1 receptor antagonists may have a preference for reducing the intake of highly palatable food.

In a study similar to Jarrett et al.’s (2005), researchers examined whether the CB1 receptor agonist, anandamide, could induce overeating via a specific action at central CB1 cannabinoid receptors. Williams and Kirkham (1999) conducted an experiment in which researchers used pre-satiated male rats to determine anadamide’s as well as SR141716’s effect on food intake. Three hours before nocturnal food intake tests, rats received subcutaneous injections of anandamide at doses of 0.5, 1.0, 5.0, and 10.0 mg/kg. Researchers then observed
food intake at one, two, and three hours following treatment. Results revealed that all doses of anandamide significantly increased food intake, with the most potent effect occurring following 1.0 mg/kg dose (William & Kirkham, 1999).

In a second experiment conducted by Williams and Kirkham (1999), SR141716 was administered subcutaneously at doses of 0.1, 0.5, and 1.0 mg/kg. Following SR141716’s administration, anandamide was administered subcutaneously thirty minutes later at a 1.0 mg/kg dose. Researchers then observed food intake at one, two, and three hours following treatment. Results revealed that SR141716 pretreatment successfully blocked anandamide-induced hyperphagia. The hyperphagic effect of anandamide was blocked by SR141716 at all doses, significantly decreasing food intake (Williams & Kirkham, 1999).

Williams and Kirkham’s (1999) results indicate that both CB1 receptor agonists and antagonists have the ability to increase and decrease food consumption, respectively. It seems that when drugs are administered together, whichever drug is administered first, the CB1 agonist or CB1 antagonist, has the most potent effect on food intake. In previous studies when CB1 antagonists have been administered before CB1 agonists, CB1 antagonists had the most pronounced effect on food intake. However, when CB1 agonists were administered before CB1 antagonists, the CB1 antagonist had the most pronounced effect on food intake. This is probably because cannabinoids administered first bind with cannabinoid receptors, blocking consecutive administrations. This is indicative of the notion that these drugs act competitively. In other words, both drugs have an affinity for the same binding site. When one drug binds with a binding site, further administrations are blocked.

Further evidence in support of the role the cannbinoid system plays on taste palatability are the results from an experiment conducted by Salamone et al. (2007). Salamone et al. (2007)
conducted a study in order to evaluate the CB$_1$ receptor inverse agonists, AM251 and AM1347, as well as rimonabant (SR141716) on palatable food intake. Researchers also investigated the role these drugs play on food-reinforced behavior.

Rats in this study were trained on a fixed ratio one and a fixed ratio five schedule of reinforcement. After acquisition, researchers administered the drugs rimonabant, AM251, and AM1347, depending on the condition in which the rat was placed. Results revealed that all three drugs significantly reduced food-reinforced behavior on both schedules of reinforcement. In addition, researchers observed the drugs effects on the intake of palatable foods: high-fat diet, high-carbohydrate diet, and a standard laboratory chow. Administration of all three drugs produced a dose-related suppression of food intake for all three diets. Further analysis indicated that there seemed to be no difference in attenuation of food intake between all three diet types. In other words, the CB$_1$ receptor inverse agonists did not play a selective role in the suppression of the more palatable foods, high fat and high carbohydrate lab chow. Researchers posit that these results may be due to differences in baseline consumption and scaling. In fact, when rats were pre-exposed to the three types of diets before testing, rats in the high-fat and high-carbohydrate group ate significantly more than rats in the standard laboratory chow group. These differences in baseline feeding may contribute to the insignificant results exhibited relative to suppression of palatable and standard types of food (Salamone, McLaughlin, Sink, Makriyannis, & Parker, 2007).

Salamone et al.’s (2007) study confirms the notion that CB$_1$ inverse agonists, similar to CB$_1$ antagonists, have the ability to suppress palatable food intake. While this experiment did not show significant differences in suppression between the three diet types, this result may be due to increased baseline feeding of rate in the palatable groups. In any case, it does seem that these
drugs have the ability to reduce food intake considerably. Results in this experiment also revealed that CB₁ inverse agonists suppress food-reinforced behavior. This result may be due to an inhibition of motivation to obtain food.

In light of previous research, it seems that the cannabinoid system plays a role in both food-seeking behavior as well as food consumption. This is supported by evidence that rats administered with CB₁ agonists are better able to discriminate between lever presses in order to obtain food, as well as consume more food when it is available. Conversely, administration of CB₁ receptor antagonists causes rats to significantly decrease motivation to consume food, as well as decrease overall intake. Furthermore, rats administered with CB₁ antagonists show marked reductions in weight as well.

Evidence from these studies also suggests that the cannabinoid system may play its most significant role on the intake of palatable food. Previous studies have shown that CB₁ receptor agonists and antagonists have the most pronounced effects on palatable food. For example, administration of SR141716 most significantly blocks the intake of palatable food compared to standard rat chow. In light of this information, it seems that the cannabinoid system may play a role in the reward circuitry in the brain. In other words, cannabinoids may increase the motivation to seek and consume palatable foods. This is supported by studies citing rats, administered with CB₁ agonists, prefer intake of high-sugar, high-carbohydrate, and high-fat food. Therefore, the cannabinoid system may “reward” an organism by increasing the natural rewards for seeking and consuming palatable foods, which are essential from an evolutionary standpoint.

Central Administration
While a multitude of studies have been conducted in order to investigate the systematic effect of CB₁ agonists and antagonists on food-reinforced behavior and food intake. There have also been studies, which have examined central administration of such drugs into certain areas of the brain. The benefits of these types of studies is that researchers are able to locate where, and how localized; CB₁ receptors are in the brain. These studies also bring to light any behavioral effects these drugs may have regarding food intake.

**Hindbrain**

Miller, Murray, Freeman, and Edwards (2004) conducted a study in order to investigate the effect of the CB₁ agonist, CP 55,940, on intake of palatable food when injected into the hindbrain. Researchers implanted bilateral cannulae into either the lateral or fourth ventricle of both male and female rats. Rats were previously trained to consume sweetened, condensed milk in order to avoid novelty-induced avoidance. Rats were injected with doses ranging between one and 100 nanograms, and fifteen minutes after injection, rats were presented with a tube of palatable tastant. Intake was measured at 30, 60, 120, and 180 minutes following presentation of food.

Results in this experiment reveal that the CB₁ agonist, CP 55,940 injected into the fourth and lateral ventricles facilitates the consumption of palatable food. This effect was seen over the three-hour period that the researchers observed the rats. However, the effect of CP 55,940 injected into the fourth ventricle was one thousand times lower compared to administration of CP 55,940 into the lateral ventricles. Researchers concluded that CP 55,940, when injected into the lateral ventricle, flows with the cerebrospinal fluid and activates feeding pathways in the hindbrain, such as the solitary tract (NTS) and the area postrema. Furthermore, it seems that female rats did not display the same sensitivity relative to feeding compared to male rats. In
other words, sex differences may exist relative to cannabinoid sensitivity. This effect was consistent with results in other studies; however, researchers note that more experiments should be conducted in order to investigate these sex differences (Miller et al., 2004).

Miller et al.’s (2004) results indicate that cannabinoid agonists, when injected into the hindbrain, significantly increase palatable food intake. This supports the idea that CB₁ receptors are located in areas within the hindbrain, specifically, areas associated with food intake. Lesion studies of these areas have also shown significant reductions in the intake of palatable food when these areas are damaged. Furthermore, due to results indicating enhanced intake of palatable food, these areas may be associated with the rewarding value of palatable diets. Miller, Murray, Freeman & Edward’s (2004) posit that the results shown in the study may be cannabinoid agonists acting on CB₁ receptors in the hindbrain, influencing both feeding and reward systems. This notion is supported by CP 55, 940’s significant effect of specifically palatable food intake. Dipartizio and Simansky (2008) conducted a study in order to investigate if central administration of endogenous cannabinoids stimulates feeding of palatable foods. In this study, male Sprague-Dawley rats were bilaterally implanted with cannulae aimed at the lateral parabrachial nucleus in the hypothalamus. Researchers chose to investigate the parabrachial nucleus because previous research had indicated the presence of CB₁ receptors and their mRNA’s in this region of the hypothalamus (Herkenham et al., 1991). After surgeries, subjects received AM251, 2-AG, or a saline control solution. Rats were then presented with three different types of diets: high fat and sucrose diet, sucrose diets, or a standard laboratory chow diet. Food intake was measured at 30 minutes, two, and four hours following administration. Histology was used following testing to ensure the proper placement of cannulae.
Results indicated that central administration of 2-AG significantly stimulated food intake of the high-fat and sucrose diet at thirty minutes. However, there were no differences between the experimental group and the control group at two and four hours. Researchers suggest that animals compensated for increased intake in the first thirty minutes. Researchers also note that there was an ‘inverted-U’ dose effect for 2-AG; the highest and lowest doses of 2-AG had no significant effect on food intake. AM251 was able to successfully block the hyperphagic effects of 2-AG. Researchers propose that the parabrachial nucleus of the hypothalamus, especially the parabrachial cannabinoid system, plays a functional role in modulating food intake. Specifically, it seems that cannabinoid receptors in the parabrachial nucleus can selectively enhance intake of foods deemed ‘pleasurable’ or palatable by an organism (Di Patrizio & Simansky, 2008).

**Nucleus Accumbens Shell**

Numerous studies have linked the nucleus accumbens in humans and other organisms to the role it plays in sensory reward process. Research conducted by Matyas et al. (2006) revealed CB$_1$ receptors located on GABAergic presynaptic axons in the nucleus accumbens shell. These receptors are often found near opioid receptors at the same synapses and in the same cells in the striatum (Pickel et al., 2004). In light of these findings, Mahler, Smith, and Berridge (2007) conducted a study in order to investigate the possibility that the CB$_1$ receptor agonist anandamide, when injected into the medial nucleus accumbens, enhances affective reactions to sweet and bitter tastants.

Mahler et al. (2007) surgically implanted cannulae into the medial nucleus accumbens shell. Rats either received intracerebroventricular injections of anandamide or a control solution, whereupon researchers would intraorally fuse either a quinine or sucrose solution. Researchers then observed rat hedonic, aversive, or neutral response patterns using taste reactivity video
scoring. A hedonic “liking” reaction was defined as the sum of lateral tongue protrusions, rhythmic tongue protrusions, and paw licks. The aversive “disliking” reaction was defined as the sum of gapes, headshakes, face washes, forelimb flails, and chin rubs.

Results from this experiment indicate that anandamide-induced stimulation of the medial shell of the nucleus accumbens enhances the palatability of sweet tastants. Anandamide microinjections more than doubled the total number of appetitive reactions. This effect occurred 15 minutes after the injection and persisted throughout the 45 minute testing session. However, anandamide-induced stimulation of the nucleus accumbens shell did not modify aversive reactions to the bitter tastant quinine. This result was observed concurrent with appetitive reactions to sucrose solutions on the same day. Researchers posit that endocannabinoid stimulation selectively enhances natural sensory rewards, such as sweet tastants. However, this phenomenon does not apply to unpalatable tastants such as quinine (Mahler et al., 2007).

A similar study, conducted by Soria-Gomez et al. (2007) observed food intake after stimulation of the nucleus accumbens shell via several types of endocannabinoids. Researchers bilaterally implanted cannulae into the nucleus accumbens shell of male Wistar rats. Subjects were administered either anandamide, 2-arachidonoylglycerol, or oleamide, and food intake was observed over the following four hours. In addition, researchers also administered the CB1 antagonist, AM251, to investigate its efficacy in blocking the hyperphagia associated with injections of endocannabinoids.

Results revealed that all of the endocannabinoids (anandamide, 2-arachidonoylglycerol, and oleamide) administered significantly stimulated food intake during the four hours following injections. Also, administration of the CB1 antagonist, AM251, successfully blocked the hyperphagia induced by all of the cannabinoids. However, AM251 was unable to significantly
decrease food intake when administered alone. In light of these results, researchers hypothesize that the administration of anandamide, or other endocannabinoid enhancers, into the nucleus accumbens shell increases food intake through the activation of CB1 receptors. Researchers say the observed effects of AM251, when administered concurrently with other cannabinoids, bolsters the notion that the effects seen in this experiment were due to activation of CB1 receptors. These cannabinoids activated the hypothalamic nuclei involved in regulating food intake, such as the ARC, DMH, and PVN. Researcher cite evidence, using Fos plumes, collected during the course of the study to support the activation of the hypothalamus. Researchers believe this supports the idea of a functional relationship between the hypothalamus and the nucleus accumbens shell (E Soria-Gomez et al., 2007).

Evidence from past studies has provided support for the notion that administration of cannabinoids into the nucleus accumbens shell significantly increases food intake. Specifically, this effect may be an enhancement of natural sensory rewards, such as palatable solutions. Conversely, there does not seem to be an enhancement of aversive tastants, such as quinine. These experiments provide support for interconnections between the nucleus accumbens and the hypothalamus, with endocannabinoids playing a role in both systems. The nucleus accumbens has been implicated in its role in sensory rewards. In these terms, it may be that stimulation of the endocannabinoid system, especially in the nucleus accumbens shell, causes increased reactivity to appetitive stimuli. Stimulation of the cannabinoid interconnections between the nucleus accumbens and the hypothalamus may motivate the organism to seek out and attain naturally rewarding stimuli. These systems may then enhance the natural “reward” associated with appetitive stimuli.

_Hypothalamus_
Numerous studies have implicated the hypothalamus’s involvement in regulating food intake. The notable properties of CB₁ agonists and antagonists relative to food intake make it reasonable to assume that there are numerous cannabinoid receptors in the hypothalamus that can heavily influence food intake.

In order to investigate the possible role anandamide plays in modulating food intake, Jamishidi & Taylor (2001) conducted a study in which researchers microinjected anadamide into the ventromedial hypothalamus in male albino Glaxo-Wistar rats. Experimenters targeted the ventromedial hypothalamus because previous research had indicated an increased number of cannabinoid receptor mRNA within this area of the hypothalamus. In this experiment, bilateral guide cannulae were implanted into the subject’s ventromedial hypothalamus. Researchers then injected anandamide, SR141716, or a saline solution into the hypothalamic region of the brain. Food intake was observed for three hours following drug administration. Histology was used after the experiment, in order to verify the correct placement of the cannulae.

In this experiment, rats injected with anandamide at doses of 25 and 150 nanograms indicated no significant changes in food intake compared to control groups. However, anandamide injected at a 50 nanogram dose revealed significant increase in food intake, generating an ‘inverted U’ shaped dose-response effect. The anandamide-induced hyperphagia was significantly attenuated following concurrent administration with SR141716. Researchers note that, in this study and similar ones, subjects were fed prior to testing (Jamishidi & Taylor, 2001).

Results from Jamishidi and Taylor’s (2001) study reveal the existence of CB₁ receptors within the ventromedial region of the hypothalamus. This result is supported by previous research, which found increased cannabinoid mRNA expression within this area of the
hypothalamus. These findings support the notion that there is a functional relationship between the cannabinoid system and the hypothalamus. In light of previous studies, it is possible to speculate from these results that the anandamide-induced hyperphagia may be due to stimulation of reward or rewarding behavior (Jamishid and Taylor, 2001). In this case, the natural reward that comes with consuming palatable food.

A similar study, conducted by Soria-Gomez et al. (2014), investigated the ability of AM251 to attenuate food intake following central administration into hypothalamic regions, as well as other central areas. Researchers implanted male Wistar rats with bilateral cannulae targeting the nucleus accumbens, lateral hypothalamus, paraventricular hypothalamic nucleus, or the caudate-putamen. All of these regions have been shown to be involved in food intake, except for the caudate-putamen, which is not directly involved in food intake. Subjects were fasted for twenty-four hours prior to treatment. Following AM251’s administration, researchers measured food intake for four hours.

Results from this experiment revealed no significant effect of central administration on food intake when AM251 was administered into the lateral hypothalamus and the caudate putamen. Conversely, administration of AM251 into the nucleus accumbens and the paraventricular hypothalamic nucleus significantly attenuated fasting-induced hyperphagia. These results, that administration of cannabinoids into the nucleus of accumbens modifies food intake, supports previous research conducted by Kirkham et al. (2002) and Soria-Gomez et al. (2007). Researchers contend that CB1 receptor blockade in the paraventricular hypothalamic nucleus yields hypophagia in free-fed subjects. Conversely, hyperphagia may be induced from pharmacological (ghrelin) or physiological (fasting) stimulation (E. Soria-Gomez et al., 2014).
Soria-Gomez et al.’s experiment (2014) shows that CB$_1$ receptors are present in the paraventricular hypothalamic nucleus. Numerous studies have implicated the hypothalamus’s role in regulating food intake. It seems that the cannabinoid system interacts with hypothalamic regions, which can stimulate or inhibit food intake. This effect may be specific to rewarding sensations, due to interactions via the cannabinoid system between the nucleus accumbens and the hypothalamus. Therefore, this interaction may yield an increased reward sensation for finding and eating food, especially palatable food.

Overall, it seems that CB$_1$ agonists and antagonist centrally administered into areas such as the hindbrain, hypothalamus, and nucleus accumbens produce hyperphagia and hypophagia, respectively. Results of central administration are similar to systemic administrations, in other words, it does not seem route of administration differs in behavioral effects. However, these studies show that CB$_1$ receptors are present in areas associated with feeding, such as the hypothalamus; and reward processes, such as the nucleus accumbens. This provides support for the argument that the endocannabinoids system interacts with the reward system as well as the homeostatic system. Thus, activation of the endocannabinoids system may modulate the natural sensory rewards of palatable foods.

**Conclusion**

In light of previous research, it seems that the cannabinoid system plays a functional role in food intake. This effect occurs through the endocannabinoids system’s interactions with homeostatic areas, such as the hypothalamus; and areas related to reward processes, such as the nucleus accumbens. Research has shown that the cannabinoid system interacts with the neuropeptide, ghrelin, associated with homeostatis; the endocannabinoid system also interacts with the opioid system, which has been implicated in reward processes. When activated the
cannabinoid system significantly increases food intake. Conversely, when inhibited, the cannabinoid system significantly reduces food intake. These effects occur through the endogenous cannabinoids such as anandamide and 2-AG. Also, these effects may be specific to palatable foods. Studies have shown that activation of the cannabinoid system increases consumption of palatable food, compared to standard foods. This action may be due to the activation of the cannabinoid system, or due to taste preference. More studies are needed to elucidate these findings.

Research has also indicated that the cannabinoid system has multiple receptors throughout much of the body and central nervous system. There are two types of cannabinoid receptors, CB1 and CB2 receptors, which are found in the central nervous system and the periphery, respectively. The focus of this review was on CB1 receptors, which reside largely in the central nervous system. These receptors are found in many areas of the brain associated with food intake, such as the hypothalamus, and reward, such as the shell of the nucleus accumbens. Therefore, it is possible to posit a functional connection between these two areas. In this case, activating the cannabinoid system would lead to an increased motivation to obtain palatable food. Palatable food, therefore, provides a rewarding sensation when it is sought out and consumed. These effects are largely a function of the cannabinoid system’s presence within areas like the hypothalamus and nucleus accumbens.

This research is important because it can be directly applied to combat the recent obesity trend that is presenting itself throughout the world. A myriad of data has supported findings indicating that pharmacological inhibition of the cannabinoid system leads to an overall decrease in food intake, even in subjects that have been fasting. In fact, at one point the drug rimonabant was put on the market as an anorectic, however, the drug had to be withdrawn due to it deleterious
side effects such as depression and suicidal thoughts. While many depression medication also have these similar side effects, people who took rimonabant showed significantly enhanced reactions. This may be due to the endocannabinoid system’s interactions with the opioid system.

Another reason research on the endocannabinoids system is important is marijuana’s emergence into mainstream society. In 2014, the states of Colorado and Washington legalized the use of recreational marijuana. While many see this as a major landmark, there are very few longitudinal studies on the effects of marijuana. One effect that may occur is to exacerbate the obesity problem that already exists. Research has shown that THC, the active psychoactive ingredient in marijuana, can induce substantial hyperphagia. Hence, if a large segment of the population starts using recreational marijuana, the obesity epidemic may grow further. The money from marijuana revenue may not be enough to offset the additional medical expenses of obesity.

Research on the cannabinoid system is still in its infancy. Much of the research conducted on cannabinoids has been conducted outside of the United States due to heavy restrictions. It is important that this research be continued because of the possible impact it could have on the world’s obesity epidemic as well as marijuana’s emergence into mainstream society.
Appendix

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Action</th>
<th>Behavioral Effect</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rimonabant</td>
<td>Antagonist</td>
<td>Hypophagia</td>
<td>Systemic</td>
</tr>
<tr>
<td>SR141716</td>
<td>Antagonist</td>
<td>Hypophagia</td>
<td>Systemic or Central</td>
</tr>
<tr>
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<td>Agonist</td>
<td>Hyperphagia</td>
<td>Systemic or Central</td>
</tr>
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<td>Systemic</td>
</tr>
<tr>
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<td>Antagonist</td>
<td>Hypophagia</td>
<td>Systemic or Central</td>
</tr>
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<td>AM1347</td>
<td>Inverse Agonist</td>
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</tr>
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</table>

*Table 1.* Table depicts all CB₁ agonists and antagonists used in this study, their action, behavioral effect, and whether each was administered systemically and/or centrally.
Works Cited


