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## Appetite-Regulating Hormones as a Tool for Combating Obesity and Feeding 10 Billion

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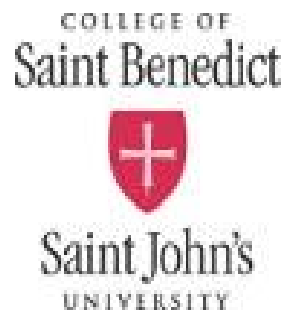
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# Appetite-Regulating Hormones as a Tool for Combating Obesity and Feeding 10 Billion

By

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This paper will focus on appetite-regulating hormones as a means for preventing overeating and obesity and as a solution for feeding the estimated future population of 10 billion.

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# Introduction

Obesity is a common disease that we see across developed nations. Obesity and overeating continue to impact the world and while its prevalence is increasing, future research is still needed. This disease is multifaceted but the most basic risk factors are lifestyle factors. The lifestyle factors that have the greatest impact are physical activity and food consumption. Those who do not exercise and consume excess calories are more likely to develop obesity. In fact, "... 90% of obesity in the United States could be abolished by walking an extra 2000 steps a day and reducing intake by [100 calories] per day" (Lean, 2005, p. 1340). Although these lifestyle choices play a role in obesity, there are other factors that can influence it.

Sleep is a factor that must also be considered in regards to obesity pathogenesis. People who sleep less during childhood are more likely to develop obesity (Lean, 2005). The specific mechanisms behind the effects of sleep deprivation have to do with cholesterol and appetite-regulating hormones. Those who sleep less have increased cholesterol levels and decreased leptin levels (Xing et al., 2020). Leptin is a hormone that plays a role in appetite suppression and will be discussed later. Both cholesterol and leptin are responsible for food intake and can lead to increased weight gain with altered levels, and therefore increased likelihood of developing obesity.

So far we have looked at the factors influencing obesity at the individual level, but there are other factors to consider such as influence from mother to child. During pregnancy, women who are obese or overweight are more likely to have children born with fetal macrosomia, or weighing more than 8 pounds (Savage et al., 2019). Therefore, there is a strong correlation

between maternal obesity and fetal obesity. Overweight women were 65% more likely to produce overweight children and obese women were 153% more likely to produce overweight children (Savage et al., 2019). The mechanisms behind this relationship between mother and offspring are still unclear, but provides insight into the complexity of the disorder.

These lifestyle factors have a biological impact on us and this can be seen in the stress response. When an individual is stressed, the fight-or-flight response is activated. The adrenal gland becomes activated and this releases glucocorticoids. Glucocorticoids in turn create glucose from non-carbohydrate sources for the use of energy in a process known as gluconeogenesis. However, a secondary effect of these corticoids has been found in the orexigenic pathway. In a study using rats, it was found that glucocorticoids activate the expression of Neuropeptide Y (NPY) (Morris, Beilharz, Maniam, Reichelt, & Westbrook, 2015). As will be discussed further later on, NPY is an appetite hormone that makes us feel hungry. The reasoning behind this may be due to the fact that when stressed we need energy as fuel for fight-or-flight. However, in the modern world our stressors differ from the stressors that society used to face. Majority of the stressors people are experiencing do not require fight-or-flight and therefore do not require more energy. The stress response evolved as a way to survive, but is actually becoming more harmful to us nowadays as we experience new stressors and therefore different biological requirements.

The reward pathway is a biological factor to also consider in regards to appetite regulation. One aspect of the pathway that food can impact is that of opioid receptors. Obesogenic foods, or foods that contribute to the development of obesity, can alter opioid receptors and change the “value” that is placed on foods (Morris et al., 2015). Therefore, when we eat obesogenic

foods, our brains view those foods as worth more. That will trigger the brain into craving those foods more, leading to overeating of those unhealthy foods and perhaps addiction.

Environmental cues have also been linked to appetite regulation. It has been determined that environmental cues, such as location of where food is purchased, can trigger food cravings (Morris et al., 2015). When eating palatable foods, people become more aware of the environmental cues around them. An association between the palatable food and the environmental stimuli occurs through pairings of the two. Therefore, people can become conditioned to want to eat more when presented with those same stimuli. Biologically, those environmental cues provide anticipation of a reward (food), which causes activation of brain structures involved in the reward pathway, one of those being the ventral tegmental area (VTA) (Morris et al., 2015). Activating this brain structure leads to food-seeking behavior. Psychological and biological underpinnings of environmental cues can alter the reward pathway, leading to overeating and obesity.

As the population continues to grow, the demand for food will continue to grow, but there is a limit to food availability. Also, the prevalence of obesity and overeating is increasing and is a problem that needs to be addressed. This is demonstrated by the fact that “the prevalence of obesity is already above the critical threshold of 15% set by the World Health Organization for epidemics needing intervention” (Lean, 2005, p. 1339). Moreover, by addressing this issue we also address the issue of food demand. If obesity and overeating are reduced, this provides increased food availability for others. By preventing excess food consumption, people are only eating what they need and therefore food is not being “wasted.” There are more food resources available for others. This idea provides a new solution to the problem of feeding 10 billion by

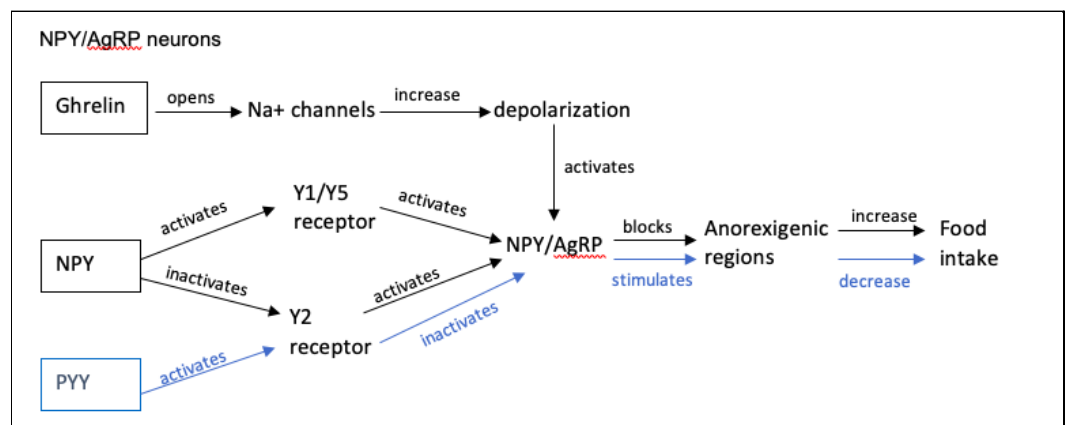
focusing on current issues. Therefore, the research in this paper will focus on appetite-regulating hormones as a means for preventing overeating and obesity and as a solution for feeding the estimated future population of 10 billion.

# Research

It is understood that obesity is multi-faceted, as some risk factors have been previously stated, so there will not be one single cure. However, one tool for future treatment that will be focused on in this paper is appetite-regulating hormones. There are many known hormones that exhibit effects on the consumption of food and as research continues, their relevance to society becomes more apparent. The most commonly researched hormones include ones that stimulate appetite or food intake and ones that suppress appetite or food intake.

Hormones that suppress appetite are known as anorexigenic agents. The hormones that will be discussed in this paper are leptin, peptide YY (PYY), and glucagon-like peptide 1 (GLP-1). Hormones that induce appetite are known as orexigenic agents. The hormones that will be discussed in this paper are ghrelin and neuropeptide Y (NPY). These hormones most commonly exhibit their effects on neurons within the brain, specifically within the hypothalamus. This region that these neurons are located within is the hypothalamic arcuate nucleus (Arc). This region includes two major pathways that are involved in the regulation of appetite. This includes the orexigenic NPY and agouti-related peptide (AgRP) neurons along with the anorexigenic neurons of pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons (Dailey & Moran, 2013).

Ghrelin mediates action of the NPY/AgRP neurons by opening of Na<sup>+</sup> channels (Hashiguchi



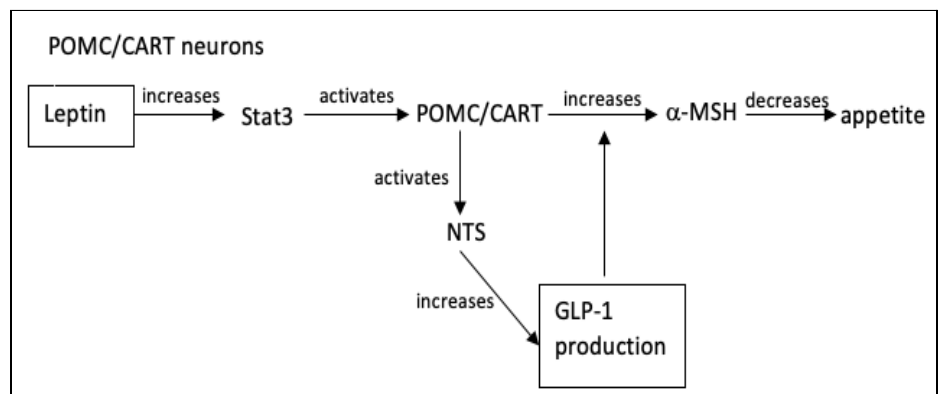
et al., 2017). While these channels remain open longer, sustained depolarization occurs which leads to increased activity of the NPY/AgRP neurons and inhibition of anorexigenic regions leading to increased food intake (Hashiguchi et al., 2017).

The other orexigenic agent NPY similarly works on these same neurons but through the activation of the Y1/Y5 receptor and inactivation of the Y2 receptor (Beck, 2006). This increases activity of the NPY/AgRP neurons which as stated previously leads to increased food intake. An anorexigenic agent has also been found to exhibit effects on the NPY/AgRP neurons. PYY is thought to be an agonist of the Y2 receptors that NPY inactivates (Holzer, Reichmann, & Farzi, 2012). By activating these receptors, the NPY/AgRP receptors are not activated and appetite is decreased.

The other anorexigenic agents act on the POMC/CART neurons. Leptin is one of the most potent hormones that inhibits food intake through the increased activation of the Stat3 protein (Morrison, 2009). This protein increases the activity of POMC/CART neurons leading to increased alpha-MSH in the paraventricular nucleus of the hypothalamus (PVN), ultimately leading to decreased appetite. GLP-1 exhibits similar effects through the regulation of alpha-MSH.

POMC/CART neurons hold projections onto the nucleus tractus solitarii (NTS) which is the location of GLP-1

producing cells. The stimulation of POMC/CART neurons leads to activation of the NTS and increased GLP-1





production and therefore increased alpha-MSH, which decreases appetite (Dailey & Moran, 2013). These pathways offer a possible target for future treatment and illustrate the most known and researched pathways that appetite regulating hormones are involved in. While there are more pathways involved and areas of contradicting evidence, these Arc neurons offer a baseline for future research.

Many of the causes of obesity and overeating come from the imbalance of these hormones. Like most areas of biology, these hormones are regulated by genetics and environmental factors. One cause of this imbalance may be due to the increased development of the world, which is pushing us to a more sedentary lifestyle. People are working long hours at desk jobs, sitting by the television for hours “bingeing”, and hours on social media. This change in cultural behavior is having a negative impact on the ability for our body to accurately regulate our food intake. Previous research has shown those who exercise were better able to control how much food they ate and their resulting weight loss due to feeding signals (Shakiba, Sheikholeslami-Vatani, Rostamzadeh, & Karim, 2019). These “feeding signals” are those appetite-regulating hormones. With dysregulation, which happens during sedentary behavior, there will be an increase in appetite-inducing hormones. This will cause an individual to eat more. Therefore, this change to a more sedentary lifestyle is going to magnify the obesity and overeating problem and requires a strategy to combat it.

Simply overeating and over consuming calories may lead to an imbalance of appetite hormones. Overeating leads to a positive feedback loop of more overeating. In a high fat diet, the body increases its levels of adipose tissue and this tissue is one of the main players in developing leptin resistance (Crujeiras et al., 2015). Leptin is an essential hormone for

suppressing appetite and therefore people that eat lots of high fat foods become immune to leptin. If they are not responding to leptin, then they feel hungry and will eat more. This positive feedback loop of overeating that comes from leptin resistance is why leptin dysregulation is thought to be one of the main factors in developing obesity.

Not only does overeating affect leptin, it also has an inverse effect on ghrelin. Ibrahim et al. (2018) found that an overeating diet in humans, whether it was a high-fructose corn syrup or whole wheat diet, led to increased ghrelin levels. Increasing ghrelin levels means that a person will feel more hungry, and therefore keep eating, creating a positive feedback loop. This imbalance in hormones causes an increase in behavior that will increase the likelihood of developing obesity.

So, it has been shown how an imbalance of these appetite-regulating hormones can occur and the consequences of this imbalance. The research shows that this imbalance can have a strong impact on our food consumption. In another study, rats who were injected with GLP-1 and PYY showed decreased sucrose consumption compared to control rats that received saline injections (Yamaguchi, Yasoshima, & Shimura, 2017). The two hormones the rats were injected with are anorexigenic which means they suppress hunger. The researchers experimentally controlled this imbalance of hormones and the results showed a response relative to the hormone's normal response. This shows us that these hormones play a key role in our eating habits, and also offers a possible treatment strategy for obesity and overeating.

A major player in the regulation of appetite hormones is genetics. Many genes have been found to be involved in the pathogenesis of obesity. One of the most commonly researched genes is the MC4R gene. This gene typically results in the addition of MC4 receptors which

allows for leptin to bind and decrease food intake. Many mutations in this gene can lead to the development of obesity. It has been discovered that “the severity of MC4 receptor dysfunction... can predict the amount of food ingested at a test meal by the subject...and correlates with the onset and severity of the obese phenotype” (Adan et al., 2006, pg. 819). Severity of obesity could be stimulated by the suppression of this MC4R gene, leading to decreased leptin levels. This indicates that genes associated with obesity, such as the MC4R, either suppressed or activated could lead to control of the appetite-regulating hormones, and thus subsequent food intake.

Historically, obesity treatments revolve around different drugs that do not target appetite-regulating hormones. Although most of these drugs were effective in weight loss, they had adverse side effects that forced them to be removed from the market. First were diet pills such as thyroxine which controlled metabolic rate. These aided in weight loss but caused hyperthermia in users (Jones and Bloom, 2015). Then there were amphetamine-mimetic anorectic agents. These agents activate the POMC neurons, which decreases appetite. However, these agents were highly addictive. Lastly, came the phentermine and fenfluramine period, known as the “phen-fen craze.” These were older drugs that proved to be highly effective when paired together, however there were valvular abnormalities that showed up in younger patients from its use (Jones and Bloom, 2015). One positive did come out of all the research in the 2000’s when the drug Orlistat was produced, which did not have extreme adverse side effects and was approved for long-term use (Jones and Bloom, 2015). Though research into appetite-regulating hormones is still fairly new, we can see the progression towards it through medication like the amphetamine-mimetic agents. Those agents were interacting with the

neurons involved with the appetite-regulating hormones even if the researchers did not know it at the time.

One possible treatment includes injections of appetite-regulating hormones. A study using rats investigated the effects of intranasal injection of leptin alongside a peptide (L-penetratin) that aids in crossing of the blood brain barrier (BBB) (Khafagy et al., 2020). An inability of leptin to cross the blood brain barrier is commonly believed to contribute to obesity. When leptin cannot cross the BBB it cannot exhibit effects on the hypothalamus and hunger signals are not suppressed. After the injection of leptin/L-penetratin intranasally they found that rats resulted in “appetite suppression with resultant reduction of risk factors... [and] eventually suppressed body weight increase” (Khafagy et al., 2020, pg. 406). A possible treatment option exists here as obese individuals experience decreased leptin sensitivity. If leptin could be injected with a peptide such as L-penetratin it could increase the amount of leptin that crosses the BBB and therefore increase leptin sensitivity.

Not only have injections of leptin shown promising results, but so have the anorexigenic hormones GLP-1 and PYY. Researchers found that when these hormones were combined and then injected into the abdomen of obese human volunteers, meal size and appetite decreased (Tan et al., 2017). Relative to other treatment options currently available, injections of these hormones also lead to larger increases in weight loss as individuals that were injected with the treatment saw a 32% reduction in food intake (Tan et al., 2017). The injection of anorexigenic hormones offers a treatment to obesity that would lead to a larger increase in appetite suppression and increased weight loss.

Monoamines are also a form of treatment that can be utilized to combat obesity.

Monoamines are neurotransmitters that transmit signals within the brain. One study using 32 healthy, overweight, and moderately obese men showed that tesofensine, a monoamine reuptake inhibitor, increased weight loss, decreased appetite, and increased fat oxidation (Sjödín et al., 2010). Tesofensine prevents the reuptake of dopamine, serotonin, and noradrenaline. Although the explanation for how these monoamines cause weight loss is unknown, one possible explanation is that these neurotransmitters lead to increased thermogenesis during sleep (Sjödín et al., 2010). Thermogenesis is using fat as a fuel source to produce heat. Therefore, the monoamines can possibly increase the amount of fat that is being burned for an individual, leading to increased weight loss.

The stress pathway has been shown to increase appetite and offers another target pathway for treatment. Previous research using rats have shown that “administration of synthetic glucocorticoid was shown to promote hyperphagia... Glucocorticoids also stimulate insulin secretion but affect food intake via the orexigenic neuropeptide, neuropeptide Y” (Morris et al., 2015, p.39). These stress hormones increase appetite-inducing hormones and act on neurons within the hypothalamus. Possible treatment could include blocking the receptors that these corticoids act on, which will be explained later under future research. Finding ways to naturally reduce stress such as through meditation and practicing mindfulness could perhaps reduce the number of these hormones present as well.

Regulation of food intake through controlling genes is another mechanism that has already been studied in obesity. Epigenetics is the modification of gene expression through changes in gene structure. It has been found that “methylation of a proximal region of LEP promoter

constitutes a significant determinant of leptin expression in human adult tissues” (Crujeiras et al., 2015, p.59). This means that silencing of the leptin occurs through methylation and activation of leptin occurs through demethylation. The authors describe that high-fat diets along with fetal programming can lead to the epigenetic modification of these genes that leads to changes in expression of the appetite suppressing hormones (Crujeiras et al., 2015).

Besides medically altering appetite-regulating hormones, there are also natural ways of regulating appetite hormones, with one of them being sleep. People that are sleep deprived have decreased leptin levels compared to those that are not ( $p < 0.01$ ) (Xing et al., 2020). Therefore, those that are sleep deprived feel less full and are more likely to overeat than those that are not sleep deprived. Thus, one natural way of decreasing overeating stems from individuals focusing on getting the correct amount of sleep every night. This will help maintain leptin levels and prevent overeating.

Diet is another natural treatment that heavily influences the risk of developing obesity. As stated previously high-fat and processed diets have been shown to lead to obesity. Changes in overall diet structure can have the opposite effect by increasing satiety and leading to changes in appetite hormones. A diet that is high in protein was shown to increase PYY and GLP-1 and decrease ghrelin in a randomized control study of obese humans (Wang, Yang, Lu, & Mu, 2014). The control of these hormones led to increased feeling of satiety and an overall reduction in food intake. Increasing intake of nutrients that are high in fiber and other nutrients may also promote satiety and lead to decreased risk of obesity.

Exercise offers a natural form of treatment for obesity and includes different forms of exercise such as resistance and endurance. A study conducted by Shakiba et al. (2019) showed

that resistance, endurance, and concurrent training (a mix of resistance and endurance) decreased ghrelin levels and increased PYY levels in humans. Therefore exercise, and physical activity of any sort, can alter the levels of appetite hormones in order to make people feel more full. This evidence provides a treatment strategy that is simpler in that it does not require any new medication. It just requires that people do some sort of physical activity, and this will help regulate the appetite hormones in the body to prevent overconsumption.

Looking further into exercise, temperature during exercise can also have an impact on hormone levels. Those who exercise in warmer environments showed increased leptin levels compared to those who exercised in colder environments (Mandic et al., 2019). Therefore, the effects of exercise on appetite and appetite hormones can be enhanced by exercising in a certain climate. Although exercise in any climate caused a change in hormone levels, the hot climate showed a statistically significant difference ( $p < 0.05$ ) (Mandic et al., 2019). Besides providing further evidence for the use of exercise in naturally moderating appetite hormones, it also provides evidence for what specific conditions during exercise can be most beneficial.

Various research has found contradictory evidence regarding the use of hormone therapy. One study using diabetic rats found that “glucocorticoid receptor blockade did not reverse diabetic hyperglycemia and suggested that normalization of the HPA axis and glucocorticoid signaling may not mediate the antidiabetic effects of leptin” (da Silva, Hall, & do Carmo, 2017, p.2). An alternate study performed by Udeen et al. (2003) looked at the effects of glucocorticoid injections on healthy women and found that injections of these steroid hormones led to increased weight gain. While both studies provide evidence of the controversial use of hormone

therapy, future research and studies will need to be conducted to find out the scope in which hormone therapy can and should be used.

There have been some areas of disagreement from the use of obesity treatment medications, and the adverse side effects that can come from them. For example Orlistat, which was the only drug that came out of the 2000's approved for long term use, can cause decreased absorption of fat-soluble vitamins and can even prevent the absorption of other medications (Jones and Bloom, 2015). Although these drugs may provide weight loss, they can induce other issues through their side effects. The disagreement lies on whether the benefits of the drugs outweigh the side effects of them.

The possibility for overuse of this appetite-regulating hormone therapy brings up a concern in its use. The methods that are suggested are for targeting overconsumption that leads to obesity. As mentioned previously, obesity is a complex disorder, and some forms of obesity do not stem from overeating. Therefore, these types of treatment strategy are not warranted. Also, this type of treatment should not be used for everyone and should be used with caution. Using appetite-suppressing hormones as injections or finding natural ways to induce them should only be used in the cases with overeating. This type of treatment could exacerbate issues with eating disorders and would have to be maintained closely in order to ensure correct use. Disagreement arises in more the ethical form of this treatment, as well as the fragility of its use and maintenance that it may require.

Since the use of appetite regulating hormones is a novel idea, understanding the long-term effects of it are still unknown. The current research shows that it can be an effective treatment in obesity and overeating. However, whether there are lasting effects on the body from its use



still requires some research. Also, as mentioned previously when talking about monoamines, there is still lack of clarity in the mechanics of the pathways. The relationship between monoamines and appetite regulating hormones is known, but the exact pathways and mechanisms of it are still unknown. Gaining more knowledge into the mechanics of this pathway, as well as others, will provide researchers a better understanding of the types of future treatments and research that should be focused on.

## Conclusion

Throughout this paper we have discussed the mechanisms behind how appetite-suppressing hormones regulate food intake and have applied this to obesity. We have examined current obesity treatments along with the contradicting evidence or results that they pose. Continued research on the pathways that these hormones act on could provide a new option for preventing obesity and overeating in the future. By increasing anorexigenic levels or decreasing orexigenic hormone levels, these hormones could be controlled to allow for proper nutrition and food intake relative to energy expenditure.

Ghrelin acts on the NPY/AgRP neurons through the opening of cation or sodium channels. A hormone or protein could be injected that blocks the opening of these channels, thus preventing the activation of those orexigenic neurons and decreasing appetite. NPY behaves similarly to ghrelin, thus a similar method could be used but instead blocking the Y1/Y5 receptors. The opposite could be done regarding the anorexigenic hormones. PYY decreases appetite through activating the Y2 receptor. Therapy could be applied through intake of PYY or through increasing the sensitivity of these receptors. Leptin and GLP-1 both act on POMC/CART neurons leading to increased alpha-MSH which leads to decreased appetite. Increasing the ability of these hormones to pass through the blood brain barrier, increasing receptor sensitivity, and increasing the overall amount of these hormones are all areas of future study for treatment. Future research into these ideas could provide valuable insight into the treatment of overeating and obesity.

By targeting overconsumption and obesity, less food will need to be consumed per individual. People will be able to eat according to their dietary demands, which as a population is

decreasing with time. Sedentary behavior and new work styles are decreasing the amount of food consumption that is required, and yet consumption is on the rise. By targeting obesity and meeting reasonable demands of food intake, more food would be available for the rest of the population. As the population grows and average food consumption is maintained, there would be decreased food demand, meaning more would be available to feed the rest of the population. While it is more difficult to increase the supply of food, decreasing the demand could bring forth a more reasonable alternative for providing enough food to feed the estimated future population of 10 billion.

The findings of this paper provide insight into future areas of research, one of those being antagonists. Ghrelin is known to be the main appetite hormone in stimulating hunger, so future research can look into ways of blocking ghrelin receptors and therefore decreasing hunger (Williams and Evans, 2020). The molecules that would block ghrelin receptors are known as antagonists and they prevent ghrelin from binding. Therefore, they prevent the effects that ghrelin normally has, like stimulating NPY and inhibiting the POMC neurons. This would decrease appetite and lead to decreased food consumption. Instead of focusing on modifying the levels of appetite regulating hormones, as was the focus of this paper, future research is looking into instead inhibiting parts of the pathway that the hormones act on.

Antagonistic medication could act on the other appetite-inducing hormone NPY. NPY inhibitors would deactivate NPY themselves, preventing NPY from inhibiting the POMC neurons (Williams and Evans, 2020). Similar to the ghrelin antagonists, blocking NPY prevents it from functioning normally in the pathway. As the POMC neurons are important in decreasing hunger,

by preventing its inhibition, hunger and consumption will decrease. As a result, future research into antagonists and inhibitors provides a new strategy into preventing overeating.

Instead of focusing on downregulating the appetite-inducing pathway, future research can also look into upregulating the appetite-suppressing pathway by using agonists. One idea is to create an MC4 receptor agonist, which would bind to the MC4 receptor and activate it thus leading to decreased food intake (Williams and Evans, 2020). As mentioned previously, MC4 receptors allow leptin to bind, leading to decreased appetite and food intake. Consequently, an agonist that activates the MC4 receptors would cause a decrease in food consumption and prevent overeating.

Similarly, the last possible avenue for future research that will be looked into are leptin analogues. Leptin analogues either closely resemble leptin and/or cause the body to create a response similar to that of leptin. Thus, these analogues in effect enhance the actions of leptin. They produce results similar to leptin and in cases where leptin production is mutated or decreased, these analogues can provide similar results leading to decreased hunger and preventing overconsumption. Modifying appetite-regulating hormone levels provides a great avenue into treatment for obesity and overconsumption. Even more, modifying the impacts of these hormones and the pathways in which they work could provide a new strategy into combating obesity and overconsumption, thus leading to increased food availability for those around the world.

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