The Impact of GLP-1 Receptor Agonists on the Brain's Addiction and Satiety Networks

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), with one of the most recognized being Ozempic, have increased in popularity for their abilities to help individuals with obesity or type 2 diabetes experience weight loss results. These medications mimic the GLP-1 hormone secreted by intestinal L-cells in response to the ingestion of a meal to slow gastric emptying, help regulate blood glucose levels, and promote feelings of fullness. A large aspect of their success in stimulating weight loss comes from their ability to bind to GLP-1 receptors in the hypothalamus, which stimulates satiety by activating neurons that produce satiety signals while inhibiting neurons that promote hunger, lowering overall food consumption and reducing appetite as a result. The impact that altering feeding networks in the brain can have on weight management illustrates the strong correlation between levels of food consumption and psychological aspects of hunger and fullness. While GLP-1 RAs are effective in providing weight loss results, they often come with adverse effects, such as nausea and headaches. Therefore, understanding the mechanisms behind GLP-1 RAs in the brain altering feeding behavior may help to develop future treatments that have a similar function in stimulating weight-loss but do not result in harmful side effects.

Increased Prevalence of GLP-1 RAS

Ozempic, one of the most well-known glucagon-like peptide-1 receptor agonist (GLP-1 RA) drugs on the market, has been referred to in the media as a "miracle drug" due to its ability to help individuals who have struggled with their weight for the majority of their lives finally achieve weight loss results. Obesity, defined as a BMI greater than or equal to 30, is a crucial issue in the United States. In 2017-2018, the age-adjusted prevalence of obesity in adults was 42.4%, increasing by 12% since 2000 (Hales et al., 2020). According to the National Institute of Diabetes and Digestive and Kidney Diseases, nearly one in three adults are overweight, and more than two in five adults are obese (NIDDK, n.d.). Obesity can have a serious impact on health, leading to heart disease, stroke, type two diabetes, musculoskeletal disorders, and certain cancers, which all contribute to premature death and substantial disability (World Health Organization, 2024). Therefore, obesity is a long-standing problem that severely endangers the health of a large portion of society. GLP-1 RAs, such as Ozempic, have been found to help individuals with obesity experience weight loss results, and a crucial reason for their success can be credited towards their ability to impact the appetite and satiety networks in the brain, altering feeding behavior.

In the past decade, many individuals have turned to GLP-1 RAs desperate for a solution to their struggle with weight. Use of these drugs has increased by 40-fold between 2017 and 2021, and six million Americans are now on either Ozempic or Mounjaro, which is another class of GLP-1 medication. From 2018 to 2023, 1,063,200 patients were prescribed a GLP-1 drug (Gratzl et. al, n.d.). An estimated nine million prescriptions were written in 2022, and roughly 2-3% of the United States population may now be taking one of these drugs (Logan, 2024). These statistics illuminate the increased prevalence of and dependency on GLP-1 RAs in recent years to combat weight issues.

Although GLP-1 RAs are commonly used for and understood as effective in stimulating weight-loss, there is a risk of experiencing side-effects when administered these medications. Several case reports have linked the use of these drugs with the occurrences of acute kidney injury, nausea, injection site reactions, headache, and nasopharyngitis (Filippatos et. al., 2014). Therefore, it is crucial to assess how GLP-1 RAs function in the brain to alter feeding behavior to eventually develop similar treatments that can suppress hunger and relay satiety signals to stimulate weight-loss without causing these harmful effects.

GLP-1 RA Mechanisms

GLP-1 RAs alleviate obesity by mimicking the action of glucagon-like peptide, a hormone secreted by the small intestine. Glucagon-like peptide triggers insulin, which is an essential hormone released from the pancreas that allows the body to use food for energy by lowering the amount of glucose in the blood (Cleveland Clinic, 2023). This extra insulin stimulated by a GLP-1 RA helps lower blood sugar levels, which is helpful for controlling type 2 diabetes and obesity. GLP-1 RAs also curb hunger by slowing the movement of food from the stomach into the small intestine, resulting in the body releasing less glucose from food into the bloodstream and allowing the individual to feel full faster and for longer. It is currently not completely understood why obese patients secrete less GLP-1 (Castro, 2022).

While these effects of GLP-1 RA drugs are crucial to their success in causing weight loss, the ability of GLP-1 RAs to influence the central nervous system's regulation of appetite and satiety is a major reason for their effectiveness. GLP-1 drugs exert their effects on glucose homeostasis and feeding behavior via indirect and direct pathways that the central nervous system mediates (Bloemendaal et. al., 2014). Hunger can be viewed as an addiction, as it is a learned behavior that eating is initially reinforcing by reversing an unpleasant bodily signal, such as changes in nutrient levels in the blood, changes in hunger hormones, and stomach contractions (Dagher, 2009). Altering and observing the brain's addiction and satiety networks can help an individual with a hunger or food addiction control their feeding behaviors. Therefore, a large reason for the effectiveness of GLP-1 drugs for weight loss is their ability to address the psychological factors that lead to obesity, impacting the brain's addiction and satiety networks in order to alter feeding behavior.

Regulation of Appetite and Satiety

Multiple parts of the hypothalamus, including the ventromedial nuclei, lateral hypothalamic area, and arcuate nucleus, work together to regulate appetite and satiety. Feelings of hunger and fullness involve complex interactions between hormones from the gastrointestinal tract to the hypothalamus. Ghrelin and leptin are two hormones that frequently signal to the hypothalamus to regulate sensations of hunger and satiety and to maintain energy homeostasis by balancing energy intake and expenditure. First, ghrelin, known as the hunger hormone, is produced by the gut and acts on the lateral hypothalamus. Ghrelin interacts with the growth hormone secretagogue receptor to promote feelings of hunger and food anticipation. Conversely, leptin, which is produced from adipose tissue, is the body's satiety signal and acts upon the arcuate nucleus, ventromedial nucleus, and lateral hypothalamus to promote stimulatory effects of satiety and inhibitory effects of hunger to coordinate the body's energy homeostasis. Together, ghrelin and leptin signals regulate sensations of hunger and satiety. Additional signals released from the gut,such as short-acting cholecystokinin and long-acting incretin, work to inhibit appetite in order to regulate energy homeostasis (Yeung and Tadi, 2023). In particular, GLP-1 drugs specifically mimic the long acting incretin-GLP signal to inhibit appetite. Glucagon-like peptide-1 (GLP-1) belongs to a family of hormones called incretins, which enhance the secretion of insulin. GLP-1 is synthesized and secreted by L-cells of the small intestine in response to food intake. It is also synthesized by a small population of neurons in the hunger center nucleus of the solitary tract (NTS) in the caudal brainstem, with the NTS projecting to areas in the hypothalamus and hindbrain, such as the arcuate nucleus, that express GLP-1 receptors (Barakat et al., 2024). When food is ingested, the vagus nerve relays satiety signals from GLP-1s that are secreted by L-cells to the GLP-1 receptors in the hypothalamus, with the purpose of controlling food intake. GLP-1 receptors in the hypothalamus stimulate fullness by activating neurons that produce satiety signals, such as pro-opiomelanocortin and cocaine and amphetamine-regulated transcript, while reducing food intake by inhibiting neurons that promote hunger, such as neuropeptide Y and agouti-related peptide (Baggio and Drucker, 2014).

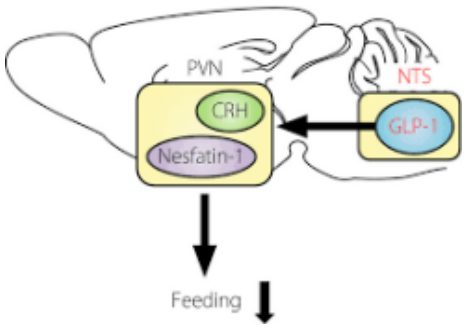

Figure 1. This model represents the interaction between GLP-1 sent from the NTS to GLP-1 receptors in the paraventricular nucleus within the hypothalamus, resulting in feeding suppression (Katsurada & Yada, 2016).

These results can also be observed when GLP-1 receptor agonists (GLP-1 RAs) are made to bind to GLP-1 receptors, mimicking the effects of GLP-1. GLP-1 RAs are administered subcutaneously, ensuring rapid absorption and peak concentration within hours. Post absorption, GLP-1 RAs exhibit a low volume of distribution and primarily remain in the bloodstream. These agents then selectively target GLP-1 receptors in various tissues involved in glucose regulation, with specific affinities for pancreatic cells and other metabolic control sites (Collins and Costello, 2024). In particular, by binding to GLP-1 receptors in the hypothalamus, GLP-1 RAs adapt the ability of GLP-1 to help control food intake and satiety.

Impact of GLP-1 RAS on Feeding Behavior Demonstrated

The effectiveness of GLP-1RAs on feeding behavior has been

demonstrated in multiple studies. For example, a study performed by Friedrichsen and colleagues in 2021 demonstrated the influence of GLP-1 RAs, specifically semaglutide, on feeding habits and hunger levels. A group of seventy two adults with obesity were randomized with either taking a once-weekly semaglutide of 2.4 milligrams or a placebo for twenty weeks. Gastric emptying was assessed following a standardized breakfast, in addition to energy intake during lunch being examined. Researchers also assessed participants' appetite ratings and responses from a "control of eating" questionnaire, which prompted participants to note their eating behaviors and feelings around food during the study. Results demonstrated that participants who took semaglutide experienced reduced hunger and food consumption and increased fullness and satiety compared to the placebo group. Their responses to the "control of eating" questionnaire indicated better self-control regarding eating and fewer and weaker food cravings compared to the placebo group responses. Body weight was reduced by 9.9% with semaglutide use and 0.4% with the placebo (Friedrichsen et al., 2021). Therefore, Friedrichsen and colleagues concluded that a once-weekly administration of semaglutide suppressed appetite, improved self-control regarding eating, and reduced food cravings, illustrating the effect of GLP-1 RAs on feeding behavior.

Since GLP-1 RAs are effective in altering feeding behavior and decreasing appetite, individuals who stop taking GLP-1 medications typically re-gain a majority of the weight they lost while taking the drug. This result is due to the secretion of GLP-1 and its binding to GLP-1 receptors both returning to pre-treatment levels once GLP-1 RAs are no longer administered, resulting in greater feelings of hunger and less satiety (Wilding et. al., 2022). This re-gaining of weight when administration of a GLP-1 RA is terminated demonstrates the ability of these medications to significantly alter feeding behavior and the regulation of satiety and hunger.

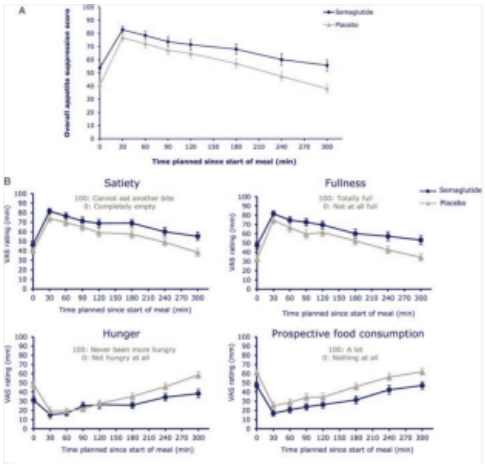

Figure 2. Results from the study performed by Blundell and colleagues, which randomized thirty subjects to a once-weekly dosage of semaglutide or placebo. Results show that overall appetite is lower and that satiety is higher in subjects who took the semaglutide (Blundell et. al., 2017).

Conclusion

The abilities of GLP-1 receptor agonists to mimic GLP-1 in individuals with less endogenous GLP-1 secretion, bind to GLP-1 receptors, and relay satiety signals to the hypothalamus to control feeding behavior, are what make these medications highly sought after by individuals seeking weight loss results. The impact of GLP-1 medications on the brain to alter feeding behaviors demonstrates that levels of food consumption is highly contingent on the ability of satiety signals to reach the brain. Therefore, GLP-1 RAs do not just work by slowing down gastric emptying to stimulate a feeling of fullness, but also directly impact the appetite centers in the brain by binding to GLP-1 receptors and relaying satiety signals. The direct impact of GLP-1 RAs on the brain by altering feeding behavior may be overlooked, but is demonstrated through the weight gain effects following termination of administration of the GLP-1RAs and subsequent increased appetite. Given that GLP-1 levels are lower in obese patients, future endeavors may seek to investigate the reasons for and mechanisms behind reduced secretion of GLP-1 in obese individuals. If the mechanisms behind the reduced GLP-1 secretion in obese patients are more fully understood, then treatments that target appetite centers and the reception of satiety signals in the brain may be developed that reduce the adverse withdrawal and weight-gain effects experienced when coming off GLP-1 RA medications. Trials on medications similar to GLP-1 RAs or that similarly target the appetite centers of the brain may also be conducted. Regardless, future research regarding medications that affect the appetite centers of the brain such as GLP-1RAs are limited to the difficulties of studying the in-vivo brain. By first fully understanding the complex mechanisms regarding satiety and feeding behavior in live individuals without invasive procedures, safer and more effective medications may be developed that permanently improve the quality of life for all.

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About the Author

Noreen is a freshman at the University of Illinois majoring in Neuroscience. She joined Brain Matters to investigate how the brain impacts the ways in which we interact with the world around us and stay updated on current research in the field. Noreen is interested in studying neurological diseases, hoping to further analyze and treat them as a physician in the future.