# What makes GLP1 receptor agonist drugs so effective for obesity?

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## Michael W. Schwartz, MD, discusses the effectiveness of GLP1 receptor agonist drugs, such as semaglutide and tirzepatide, in treating obesity as well as the role of gut-brain signaling in maintaining energy homeostasis

Over the past decade, the treatment of obesity and its closely related metabolic disorder, type 2 diabetes (T2D), has been revolutionized by the introduction of so-called GLP1 receptor agonist drugs. These drugs, which include semaglutide and tirzepatide, work by activating GLP1 receptors distributed throughout the body. While some of their effects involve peripheral tissues, the brain is the primary target for their anti-obesity action. Of particular importance are neurons that express the GLP1 receptor and are located in two key hindbrain areas: the area postrema (AP) and the nucleus of the solitary tract (NTS).

The names of these brain structures are less important than the vital role that they play as components of an ascending pathway that transmits information from the gastrointestinal (GI) tract to the brain. Upon food consumption, a variety of 'gut-brain' signals are conveyed along this pathway to inform the brain of the pending change in nutritional status; i.e., that nutrients are on their way into the body.

### Gut-brain signaling

Each time we consume a meal, a remarkable cascade of events is triggered, including changes of blood flow and heart rate, GI responses that collectively enable nutrient absorption into the bloodstream, metabolic processes that determine the fate of these circulating nutrients, and perceptual changes including both reduced hunger and increased satiety (or 'fullness'). Fundamental to the orchestration of these responses are gut-brain signals, which can be either neural or hormonal in nature.

On the one hand, the GI tract is richly supplied with sensory nerves (both autonomic and spinosensory) that are activated upon nutrient ingestion. On the other hand, hormones such as GLP1, CCK, and GIP are released during a meal from so-called 'enteroendocrine cells' distributed throughout the intestine. There is a fair amount of redundancy in the information communicated to the brain by these various signals, the net effect of which is to set in motion digestive, metabolic, cardiovascular, and perceptual changes noted above.

Under normal physiological conditions, the amount of GLP1 released into the circulation during a meal is probably insufficient to activate neurons located in the AP and NTS. But when GLP1R agonist drugs are administered at pharmacological doses, hindbrain

neurons that express the GLP1 receptor are robustly activated, and it is this effect that underlies the increased satiety and reduced hunger that they induce.

## Energy homeostasis

Gut-brain signaling is of fundamental importance to 'energy homeostasis', the physiological system that maintains stability in the amount of body fuel stored as fat. Most of us are not consciously aware of this system, but there is plenty of evidence of the important role it plays in our lives. To take but one example, consider a 30-year-old adult who weighs 75kg and, five years later, weighs 76kg – a fairly common scenario. If we assume that the 1kg weight increase is primarily fat, this amounts to a 9,000-kilocalorie surfeit over five years. Since such an individual can be expected to consume some five million kilocalories over these five years, however, we infer that the mismatch between calories consumed and calories expended amounts to just 0.2% (9,000 divided by five million).

Stated differently, calorie intake and expenditure over five years were matched to within 99.8% of each other in this example, a degree of precision that cannot be attributed to random chance. Instead, this outcome reflects the fidelity of the energy homeostasis system, which detects changes in the amount of body fuel stored as fat and, when they occur, triggers adaptive responses that promote homeostasis (aka, stability of the internal environment).

## The adaptive response to weight loss

While many inputs to the brain convey this information (termed 'adiposity negative feedback signals'), the hormone leptin plays an outsized role. Leptin is secreted by fat cells (adipocytes) in proportion to body fat content, but it is also highly sensitive to short-term changes in energy balance. During active weight loss, for example, circulating leptin levels drop rapidly, signaling to the brain that body fuel stores are under threat. In response, a series of behavioral, metabolic, and neuroendocrine responses are mounted both to limit further weight loss and to promote recovery of lost weight. Chief among these is an increase in the drive to eat, an effect that typically persists until lost weight has been regained.

Based on brain imaging (fMRI) studies, information regarding weight loss is broadcast widely throughout the brain. The origin of this response appears to be much more localized, however, residing in the brain's hypothalamus. This brain area is specialized to sense leptin and other circulating cues relevant to metabolic state, and neurons located in the hypothalamic arcuate nucleus (ARC) that detect and respond to changes in body fuel stores have been identified. The best studied among these are called AgRP neurons. Studies in animals have demonstrated not only that these neurons are activated during weight loss, but that this activation is required to drive the recovery of lost weight.

During weight loss, AgRP neurons are activated in part by reduced input from leptin, because leptin inhibits these neurons, and since leptin levels fall during weight loss. Whereas this type of regulation occurs over hours or days, AgRP neurons are also rapidly inhibited (within seconds or minutes) by most if not all gut-brain signals. Consequently, the activity of these neurons increases when food has not been consumed recently, but once the brain perceives that nutrients are on their way into the body (via gut-brain signaling), the adaptive response to weight loss (as exemplified by AgRP neuron activation) shuts off, at least temporarily. If the amount of food consumed is insufficient to fully replenish body fat stores, the neurons will again become hyperactive once the nutrients have been absorbed.

## Evidence that GLP1 receptor agonist drugs block the adaptive response to weight loss

So how does this background help to explain what makes GLP1RA drugs so effective? A key point is that in humans and other mammals, adaptive responses that promote recovery of lost weight (e.g., increased hunger, decreased satiety) are engaged once a threshold of ~5% weight loss has been crossed. Yet individuals taking GLP1RAs rapidly eclipse this weight loss threshold and, rather than experiencing the expected increase in hunger and decrease in satiety, they report the opposite. Even after weight loss of 10% or more, hunger scores remain low and satiety scores remain high, typically producing progressive weight loss that slows only after body weight has declined by at least 15%.

Moreover, recent work using fMRI in humans shows that these drugs block the normal, brain-wide activation response to weight loss. In fact, not only are these brain areas not activated by weight loss, but their activity is reduced to below normal levels. Taken together, these observations indicate that in addition to reducing food intake, GLP1RAs block the normal adaptive response to weight loss, which in turn increases the degree of weight loss that can be achieved.

## A role for the hypothalamus

How might these drugs block the adaptive response to weight loss? A large and growing literature indicates that projections from AP and NTS neurons into the hypothalamus are activated by GLP1RAs and other gut-brain signals. This activation response in turn inhibits AgRP neurons, and whereas this effect is usually transient (lasting only while ingested nutrients are processed), GLP1RA drugs are designed to activate GLP1 receptors maximally, for 24 hours a day, seven days a week.

Stated differently, GLP1RA drugs have co-opted the gut-brain signaling system’s ability to transiently inhibit the adaptive response to weight loss (exemplified by AgRP neuron inhibition). But because of how they are formulated, the inhibition that they induce is continuous, rather than transient. It is therefore not surprising that once the drug is stopped, adaptive responses are ‘re-awakened’, resulting in the rapid recovery of lost weight.

## Future treatment

To the extent that AgRP neurons are emblematic of all neurons that underlie the adaptive response to weight loss, we infer that sustained silencing of this important subset of neurons enables a much greater degree of weight loss than would otherwise be possible. We therefore anticipate that the future of obesity treatment will focus on the development of drugs that not only inhibit food intake but also suppress the adaptive response that normally constrains weight loss and promotes the recovery of lost weight.

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