What is GLP-1?

GLP-1 is a peptide hormone produced primarily in intestinal L-cells, as well as in microglia and specific neurons of the nucleus tractus solitarius. GLP-1 is secreted into the blood (1). GLP-1 production is regulated by blood glucose (blood sugar) levels, so elevated blood glucose levels cause an increase in GLP-1 secretion (1).

What is the function of GLP-1?

Preproglucagon (PPG) neurons, which innervate several important brain areas involved in the regulation of autonomic functions, are responsible for producing and secreting GLP-1 (2). As PPGs extensively innervate autonomic control centers, GLP-1 has many functions that are involved with the regulation of various autonomic physiological processes, including thermogenesis and energy balance (2). The main functions of GLP-1 are to stimulate insulin secretion and to inhibit glucagon secretion (3). These processes act to reduce blood glucose levels, effectively acting as a physiological regulator of appetite and food intake (3).

What physiological processes are affected by GLP-1?

When GLP-1 binds and activates its receptor, GLP-1R, several physiological processes are affected: energy balance regulation, anti-inflammatory cytokine production, resistance to neuroinflammation, and neurotransmitter production and action (1,3-5). Studies also suggest that GLP-1 may be able to attenuate several processes involved in the pathogenesis of depression (1, 6, 7).

Energy Balance

GLP-1 extensively affects energy balance regulation because GLP-1R activation reduces food intake and, subsequently, body weight (1,8). GLP-1 action has been demonstrated to improve postprandial glucose homeostasis by enhancing insulin secretion induced by the presence of food in the stomach. Thus GLP-1 has been a hormonal target of various Type 2 diabetes treatments (9).

Immunity

GLP-1 also affects immune processes, such as the production of anti-inflammatory cytokines (1). GLP-1 has been shown to promote the production of anti-inflammatory cytokines in adipose tissue, pancreatic tissue, and the brain (10-11). Studies have shown that GLP-1 reduces the expression of pro-inflammatory genes in human pancreatic islet cells, suggesting that GLP-1 may have a protective role against diabetes (12-13).

Neuroinflammation

In addition to its effects on energy balance regulation and the production of anti-inflammatory cytokines, GLP-1 has been shown to have a preventive effect on the progression of Alzheimer's disease pathology in rats (14). This protective action may result from a GLP-1-mediated attenuation of the neuroinflammation response (15).

Mood Regulation + Control

Importantly, research suggests evidence of GLP-1 activity and GLP-1Rs in areas of the brain involved in mood regulation and control (16). GLP-1 activity in these regions has been associated with increased production of dopamine, a neurotransmitter closely involved in depression pathology (17). Studies have demonstrated that GLP-1 can elevate the turnover of dopamine in the amygdala (17).

What are GLP-1 agonists?

GLP-1 agonists are drugs that are designed to mimic the action of the hormone GLP-1. GLP-1 agonists are commonly referred to as drug names like Semaglutide, Exendin-4, and Ozempic. When blood glucose levels start to rise after eating, GLP-1 agonists stimulate the body to produce more insulin, helping to lower blood glucose levels (18). GLP-1 agonists help control type 2 diabetes, but they also reduce gastric emptying (i.e. how quickly food moves from the stomach into the small intestine), appetite, and food intake by acting on GLP-1 receptors in the small intestine (19). As such, GLP-1 agonists can be used to control both type 2 diabetes and obesity (20).

How do GLP-1 agonists affect mood regulation?

While the weight-loss-related benefits of GLP-1 agonists can positively influence mood and improve self-image, GLP-1 agonists may also directly affect brain areas associated with emotional regulation. A 2015 study demonstrated that chronic central administration of a GLP-1 agonist, Exendin-4, significantly reduced depression-like behavior in rats (20). Another study demonstrated a significant reduction in anxiety and depression scores in diabetic patients receiving continuous 6-month treatment with a GLP-1 agonist (21). Interestingly, chronic GLP-1 receptor activation resembles the action of SSRIs, a class of antidepressant drugs that increase the signaling of serotonin (20). Like SSRIs, chronic GLP-1 receptor activation can both cause anxiety in early use which subsides with chronic exposure, and can cause improvement in depression symptoms (20). Additionally, a meta-analysis found that GLP-1 receptor agonists significantly reduced depression and anxiety symptoms in patients with type 2 diabetes compared to placebo (7).

Another study has identified four distinct actions taken by GLP-1 in the brain that may benefit depression and anxiety: a reduction of neuroinflammation that is associated with depression, an improved balance of serotonin and other neurotransmitters in the brain, stimulation of neurogenesis in the brain (i.e. the process of forming new neurons and neuronal connections), and prevention of cognitive decline, like memory loss, which is often seen in depression. (22).

These different mechanisms of action are responsible for the potential overall mood-related benefits of GLP-1 agonists, including improvement in anxiety and depression. It is important to remember that GLP-1 medications are not currently approved for the treatment of depression and anxiety, and their use for these conditions is still considered experimental.

What are the risks of using GLP-1 agonists?

There are some potential risks of using GLP-1 agonists to address depression and anxiety. A primary concern is the risk of GLP-1 agonists inducing gastrointestinal problems, such as nausea, vomiting, and diarrhea (23). This issue could be notably problematic for individuals with pre-existing gastrointestinal problems or eating disorders. Moreover, there is some indication that GLP-1 medications might elevate the susceptibility to pancreatitis, pancreatic cancer, and thyroid cancer although the current evidence is limited (24-25). Importantly, these potential side effects are associated with the use of GLP-1 agonists in general and no conclusive data is indicating an increased risk of such effects specifically among individuals with depression and anxiety.

Despite these potential risks, the overall safety profile of GLP-1 agonists appears to be favorable. The US Food and Drug Administration (FDA) has approved several GLP-1 agonists for the treatment of type 2 diabetes, and they are generally well-tolerated in clinical trials (26). Serious adverse events such as pancreatitis and pancreatic cancer are rare. A recent study indicated that adults with type 2 diabetes who use a GLP-1 receptor agonist for more than one year may have an increased risk for thyroid cancer (25).

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