Glucagon-Like Peptide 1 in the Brain: Where Is It Coming From, Where Is It Going?

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Glucagon-like peptide 1 (GLP-1) is likely best known by many readers of *Diabetes* because of the role it plays in insulin secretion. Indeed, GLP-1 receptor (GLP-1R) agonists have become important tools for glycemic control in the treatment of type 2 diabetes. In addition to its incretin effects, GLP-1 signaling plays a role in the control of feeding (1) and other motivated behaviors such as fluid intake (2) and drug taking (3,4). Although many of the effects of GLP-1 are known to be mediated at least in part by activation of central GLP-1Rs, the source(s) of endogenous GLP-1 that activate these receptors remain unclear. Complicating this issue is the fact that GLP-1 is produced both peripherally in the ileum, from which it is released into circulation, and centrally in limited regions of the brain that include the nucleus of the solitary tract (NTS) and the olfactory bulb (1,5) (Fig. 1).

To what extent peripherally versus centrally derived GLP-1 activates GLP-1Rs in the brain remains unclear. To date, indirect evidence has helped inform the field with regard to the source of endogenous GLP-1 relevant for the effect of GLP-1 on motivated behaviors. For instance, studies comparing GLP-1 and GLP-1 precursor gene expression after feeding or drinking found that feeding increased both plasma GLP-1 and preproglucagon (PPG) mRNA in the hindbrain, whereas drinking had no detectable effect on plasma GLP-1 but increased PPG mRNA in the hindbrain (6). Although this finding suggests that these actions of GLP-1 involve centrally produced GLP-1, peripherally derived GLP-1 acting at the brain could also be important.

In this issue of *Diabetes,* Holt et al. (7) approach the question of GLP-1 origin in feeding behavior using a mouse model that expresses Cre-recombinase under the control of the glucagon promoter. This allows them to target selectively cells in the hindbrain, specifically within the NTS, that produce GLP-1. Their studies provide important convergent evidence that GLP-1 of central origin is physiologically relevant for particular aspects of feeding. Specifically, the destruction or chemogenetic inhibition of these cells had no effect on feeding or body weight under ad libitum conditions but increased intake of a particularly large meal after a fast (7). Acute chemogenetic inhibition of these PPG cells also blunted the intake-reducing effect of stress (7).

A critical question is where the GLP-1–producing NTS neurons are projecting to exert these effects. Prior tracing studies have demonstrated that NTS PPG neurons project directly to several nuclei in the brain (8–11). This is especially interesting given that discrete sites in the brain can mediate specific subsets of GLP-1 responses. For example, GLP-1R activation in the arcuate nucleus of the hypothalamus is important for glycemic control but not feeding (12), whereas GLP-1R activation in areas including the ventral tegmental area of the mesolimbic reward system is important for energy balance control but does not induce the nausea/malaise that can occur with GLP-1R activation in other sites (8,13). Holt et al. (7) show compelling evidence that GLP-1–producing cells in the NTS provide GLP-1 to areas such as the hypothalamus, as destruction of the NTS GLP-1 cells caused marked reductions in hypothalamic as well as brainstem GLP-1 without any effect on blood GLP-1 (7). This suggests the importance of examining these areas as potential sites of action for the particular feeding effects of hindbrain GLP-1 neuron activation shown by Holt et al. (7). These findings align well with the aforementioned tracing work showing direct projections of NTS GLP-1 cells to hypothalamic sites such as the paraventricular nucleus (11). Further, these data complement prior studies indicating the presence of GLP-1–positive terminals in several areas of the brain (14,15), as well as findings demonstrating colocalization of GLP-1 in glutamatergic axon terminals (16). Collectively, the available data may point to a potential

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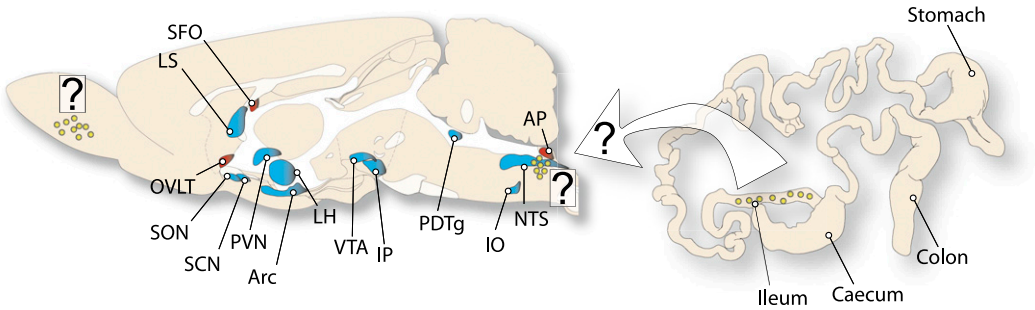

Figure 1— GLP-1 interactions with the brain. GLP-1–producing cells (yellow circles) are found in areas including the ileum, olfactory bulb, and hindbrain. GLP-1–responsive structures in the brain are far more distributed and include structures behind (blue) and outside of (red) the blood-brain barrier, a subset of which are represented in this schematic. Knowing which source of GLP-1 acts on which of the responsive structures is important in order to understand the role of endogenous GLP-1 in the control of the diverse effects of GLP-1; question marks highlight the lack of detail in current knowledge about the sources of GLP-1 to these and other GLP-1–responsive sites. The article by Holt et al. (7) offers an important step toward this understanding. AP, area postrema; Arc, arcuate hypothalamic nucleus; IO, inferior olive; IP, interpeduncular nucleus; LH, lateral hypothalamus; LS, lateral septum; OVLT, organum vasculosum of the lamina terminalis; PDTg, posterodorsal tegmental nucleus; PVN, paraventricular hypothalamic nucleus; SCN, suprachiasmatic nucleus; SFO, subfornical organ; SON, supraoptic nucleus; VTA, ventral tegmental area.

"transmitter-like" action of centrally produced GLP-1, although there is much work remaining to be done to fully understand the mechanisms of central neuronal GLP-1 release.

It is also important to note that particular GLP-1R populations in the brain may be activated via other routes of centrally produced GLP-1, such as volume transmission of GLP-1 through the ventricular system (17). An additional possibility is that circulating GLP-1 may be able to reach the brain either by crossing the blood-brain barrier (18) or by directly acting at circumventricular structures (19). In understanding the basic physiology of this system, and the way such knowledge may translate to our understanding of how U.S. Food and Drug Administration–approved GLP-1R agonists act in the body, it is critical to keep in mind that the long-acting GLP-1R agonists exendin-4 and liraglutide can penetrate the central nervous system and access blood-brain barrier–protected sites to influence GLP-1–mediated responses such as food intake and body weight (20), thus adding complexity to the puzzle. Although a systematic evaluation of all GLP-1–responsive sites and their roles in each of the diverse effects of GLP-1 will be a huge undertaking, it is a necessary step toward a complete understanding of GLP-1 and its actions. The findings of Holt et al. (7) published in this issue not only shed light onto the physiological relevance of centrally produced GLP-1 for energy balance control but also raise numerous intriguing follow-up questions.

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