Hindbrain contributions to anorexia

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FEEDING BEHAVIOR is the complex functional output of distributed neural networks, with critical components located at every level of the central neuraxis (1, 20). Nevertheless, the ability of any internal or external factor to modulate food intake ultimately depends on its ability to affect hindbrain neural circuits that control ingestive motor output. In this regard, anatomical, physiological, and behavioral data support the view that ingestive behavior outputs are modulated by neural signaling in the dorsal vagal complex (DVC), comprising the nucleus of the solitary tract, area postrema, and dorsal motor nucleus of the vagus. The DVC receives relayed and direct synaptic input from olfactory, glossopharyngeal, facial, trigeminal, vagal, and spinal visceroceptive afferents that convey information about the chemical and mechanical properties of food. Medial portions of the DVC contain fenestrated capillaries that provide local parenchymal access to blood-borne factors (e.g., toxins, cytokines, hormones, osmolytes) that affect food intake. DVC neurons are interconnected with brain stem central pattern generator, premotor, and motor nuclei that organize and execute ingestive movements such as licking, biting, chewing, and swallowing (3–5, 15, 17). DVC neurons also control parasympathetic outflow to the digestive tract (1). By determining the way in which ingesta are handled and metabolically processed, DVC circuits can help shape the visceroceptive landscape and thereby influence the occurrence and potency of many direct and indirect controls of food intake (14).

A relatively small number of neurons lying within the caudal DVC and adjacent reticular formation are immunoreactive for glucagon-like peptide-1 (GLP-1) (9). These discretely localized neurons give rise to axonal projections that terminate within multiple regions of the brain stem, hypothalamus, and limbic forebrain where GLP-1 receptors are coexpressed. Importantly, hindbrain GLP-1 neurons appear to provide the sole source of endogenous ligand for these receptors, whose neuronal anatomical localization suggests a potential functional role in the central control of food intake. Indeed, exogenous GLP-1 inhibits food intake in rats after central infusion into the lateral, third, or fourth ventricles. In each case the anorectic effect of synthetic peptide is reversed by pharmacological antagonism of central GLP-1 receptors (2, 7, 12, 16, 18). Whereas such studies clearly indicate that synthetic GLP-1 can interact with endogenous receptors to inhibit food intake, they do not reveal whether endogenous GLP-1 signaling mechanisms actually participate in feeding control.

This issue has been addressed, to some extent, by studies demonstrating that the majority of GLP-1-immunopositive neurons within the DVC are activated to express the immediate-early gene product c-Fos in experimental models of anorexia, including central administration of oxytocin (OT) (12), systemic administration of lithium chloride (LiCl), cholecystokinin octapeptide, or lipopolysaccharide (LPS) (11), and gastric balloon distension (19). Conversely, GLP-1 neurons do not express c-Fos in rats sated by voluntary consumption of a large meal (11), although food intake also is inhibited in this situation. Together these findings suggest that GLP-1 neurons are selectively activated by stimuli associated with visceral malaise and stress but not by stimuli associated with normal satiety. Moreover, the ability of central OT and systemic LiCl to inhibit food intake in rats is attenuated by pharmacological blockade of central GLP-1 receptors (10, 12, 13), evidence that endogenous GLP-1 signaling pathways are an important component of the neural circuits that mediate anorectic responses to these treatments. Similarly, Grill and colleagues (6) report in this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology that anorexia in rats after systemic LPS treatment is blunted significantly by pharmacological antagonism of central GLP-1 receptors, providing additional evidence for a specific role of GLP-1 signaling pathways in stress-induced anorexia. The authors also report that central antagonism of GLP-1 receptors by itself does not affect baseline food intake, thereby discounting a fundamental role for these pathways in normal satiety mechanisms.

A brain stem receptor site of action for GLP-1 to inhibit food intake has been suggested based on the anorectic effect of synthetic peptide infused into the fourth ventricle (7). However, synthetic GLP-1 also inhibits food intake when infused directly into the hypothalamus in small doses (8) that are subthreshold for inhibiting food intake when infused into the lateral, third, or fourth ventricles. Thus it appears that exogenously administered GLP-1 can act at multiple levels of the central nervous system to inhibit food intake. It is important to note, however, that previous studies have not examined potential sites of action for endogenously released GLP-1 to suppress feeding. Grill and colleagues report that the anorectic effect of LPS treatment in rats is attenuated by blockade of GLP-1 receptors that are accessible from the fourth ventricle. Conversely, when the cerebral aqueduct is occluded to prevent concurrent antagonism of hindbrain receptors, LPS anorexia is unaffected by blockade of GLP-1 receptors accessible from the third ventricle (6). As the authors point out, their results highlight a potential role of hindbrain GLP-1 receptors in the inhibition of feeding produced by LPS treatment and minimize potential roles for hypothalamic and other forebrain GLP-1 receptors in this behavioral response.

These new findings support the view that GLP-1 signaling pathways contained within the caudal brain stem contribute importantly to the anorectic effect of systemic LPS, an experimental model of acute inflammatory response and sickness behavior. Known direct and relayed projections from the DVC to somatic and autonomic motor nuclei provide potential routes by which brain stem GLP-1 signaling pathways might exert control over both the ingestion and digestion of food. The DVC is the major brain stem relay center for visceroceptive inputs to the brain and is also the recipient of direct descending projections from the hypothalamus and limbic forebrain. Thus the DVC and its remanant contributions to anorexia.

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dent GLP-1 neurons are well positioned to integrate interoceptive signals with cognitive/emotional state and thereby participate in context-specific modulation of food intake. The new data reported by Grill and colleagues invite continued focus on the DVC and its GLP-1-containing projections as integral components of the central neural circuits that shape ingestive behavior.

REFERENCES