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 visceral sensory afferents that convey information about the chemical and mechanical properties of food. Median 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 brainstem 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 visceral sensory 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 brainstem, 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 neuroanatomical 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. Thus it appears that endogenously 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 (6) report that the anorexic effect of LPS treatment in rats is attenuated 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 brainstem receptor site of action for GLP-1 to inhibit food intake has been suggested based on the anorexic 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 anorexic 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 anorexic 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 brainstem GLP-1 signaling pathways might exert control over both the ingestion and digestion of food. The DVC is the major brainstem relay center for visceral sensory inputs to the brain and is also the recipient of direct descending projections from the hypothalamus and limbic forebrain. Thus the DVC and its resi-
dient 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