RESEARCH HIGHLIGHT

GLP-1 appetite control via intestinofugal neurons

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The gut hormone glucagon-like peptide-1 (GLP-1) holds significant therapeutic interest for glycaemic and appetite control, but an endocrine role has been questioned, since GLP-1 is broken down rapidly in the bloodstream. A major new study by Zhang et al., identifies that a unique neuronal population within the enteric nervous system, whose axons leave the gut wall and activate sympathetic prevertebral neurons, links intestinal GLP-1 to gastric distension and acute appetite suppression, that characterizes a gastrointestinal behavior known as the "ileal brake".

Intestinofugal neurons (IFNs) comprise a unique population of intrinsic neurons in the gut wall because, unlike other enteric neurons, their axonal projections exit the gut. Most IFNs synapse with sympathetic neurons in abdominal prevertebral ganglia. In mice, rats and guinea pigs, IFNs have nerve cell bodies in the myenteric plexus. They are directly mechanosensitive, but also receive synaptic input from other enteric neurons.[1]

Extrinsic neural circuits linking distant gut regions are demonstrated in numerous studies of the intestino-intestinal and intestino-gastric reflexes. These reflexes inhibit gut motility following mechanical or chemical stimulation of distant gut regions. Two major circuits are implicated in these reflexes: long central circuits that include gastrointestinal spinal afferent neurons and sympathetic pre- and postganglionic neurons; and short peripheral circuits comprising IFNs and postganglionic sympathetic neurons that project back into the gut wall. The existence of IFNs was inferred by discovery of intestino-intestinal reflexes that operated through the short peripheral circuit[2] before their direct observation.[3]

Sympathetic reflex circuit activation under experimental conditions often required abrupt or noxious stimuli, raising need to establish their role in normal physiology. To this end, it was recently identified that a major firing pattern of the enteric nervous system, that triggers gut propulsion, is also fed out in parallel via IFN-sympathetic circuits[4] but the consequences of their efferent outputs remain to be established. Further, Muller et al.[5] provided evidence of a novel neural circuitry between IFNs and pancreas- and liver-projecting sympathetic neurons that mediated a CNS-independent glucoregulatory function that did not require glucagon-like peptide-1 (GLP-1).

The "ileal brake" is a behavior triggered by nutrients in the ileal lumen, causing inhibition of gastric and proximal intestinal motility, and is associated with acute appetite suppression.[6] Such coordination between distant gut segments exceeds the range of enteric neural circuits in the gut wall. Yet, no long-range mechanism has been confirmed. Candidate mechanisms included peripheral IFN-prevertebral sympathetic neuron reflex circuits and central vagal or spinal sensory reflexes. IFN circuits were considered more likely because the increasing proximo-distal gradient in IFN density along the small intestine mirrors the increasing potency of the ileal brake.[7]

GLP-1 has long been considered an ileal brake hormone whose receptor activation mimics effects of the ileal brake.[8] Rapid inactivation after release from intestinal L cells suggested that endogenous GLP-1 may act locally in the gut wall.[8] The exciting findings of Zhang et al. indicate that the ileal brake is indeed mediated by mucosal GLP-1, activating local IFNs that activate gastric sympathetic neurons in turn to evoke the gastric relaxation and acute inhibition of feeding that is characteristic of the ileal brake response.[9] Since GLP-1 receptors are prominent throughout the ileal myenteric and submucosal plexuses[8] it is possible that IFNs are activated both directly by GLP-1, and/or synaptically by evoked firing within the enteric network. Local actions on vagal pathways are also likely based on their GLP-1 receptor expression and the presence of vagal afferents in the ileum.[8] Interestingly, the abundance of subsets of IFNs was microbiome-dependent.[5] Thus, the findings of Zhang et al. raise the possibility that ileal brake function is modifiable by microbial colonization.[9]

A major obstacle to understanding IFN-sympathetic circuit function has been a lack of selective targeting methods for IFNs, since spatial, pharmacological and neurogenetic specificity is hampered by common transmitters, pathways and neurochemical expression profiles among IFNs, preganglionic sympathetic neurons, and other enteric neurons. Zhang et al.[9] cleverly overcame these obstacles, using combinations of focal viral transfection in the celiac ganglion, stomach and ileum. This enabled the specific ablation, activation, and inactivation of ileal IFNs with projections to celiac ganglion, to demonstrate their mediating role in the ileal brake reflex and the action of GLP-1 released from ileal L cells. Moreover, Zhang et al. demonstrate connectivity between ileal IFNs and gastric sympathetic neurons using rabies trans-synaptic tracing. In this way, the inputs and outputs of the IFN-sympathetic circuit were established; a method that might be used to map the full topography of entero-sympathetic circuits along the gastrointestinal tract.

The sympathetic effector arm of the ileo-gastric circuit described by Zhang et al. preferentially activated gastric myenteric neurons that expressed nitric oxide synthase to evoke gastric relaxation and appetite suppression. This is perhaps unexpected as a sympathetic mechanism, since the most common effect of

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noradrenaline on myenteric neurons is presynaptic inhibition of acetylcholine release from vagal or enteric nerve terminals, via α_2 adrenoreceptors. However, the ileal brake in rats was abolished by GLP-1 receptor antagonist or a combination of α and β adrenoreceptor antagonists, implicating adrenoreceptors other than α_2.[10]

A major finding of the study of Zhang et al. was the identification that spinal afferent pathways from the stomach monitored gastric volume and ultimately modulated neurons in the parasubthalamic nucleus to drive acute appetite suppression. Satiation is widely considered the domain of vagal afferent signaling, while spinal afferent pathways had been principally associated with nociception. The findings of Zhang et al. ignite a new paradigm for understanding of spinal afferents in normal physiological behavior. In fact, only recently, have the nerve endings of spinal afferents been identified in the stomach, some of which project directly into the mucosa, but they lack populations of low-threshold tension-sensitive intraganglionic laminar endings.[11] Thus, the specific type/s of volume-sensitive gastric spinal afferents activated by the ileal brake response now represent potential peripheral targets for acute appetite control.

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ADDITIONAL INFORMATION

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