RESEARCH HIGHLIGHT

Stressing out the intestinal microbiota via a brain-neuroglandular circuit

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A new study published in *Cell* identifies a stress-sensitive brain-neuroglandular circuit that regulates the intestinal microbiota and systemic host immunity. Chronic stress inhibits the duodenal gland activity, which drives intestinal dysbiosis and impaired host immunity to pathogens.

More than 2000 years ago, the Greek physician and philosopher Hippocrates coined the phrase "All diseases begin in the gut", reflecting the idea that human health and disease states in many tissues may be traced back to intestinal physiology, nutrition, and the complex microbial communities we now term the microbiota. This concept has remained a central theme of modern medicine. One example of this concept is the gut-brain axis, a bidirectional communication network that links the gut and the brain, that can influence both physical and mental health.[1] Recent research has demonstrated that changes in the composition of the intestinal microbiota are tightly associated with many pathological conditions ranging from autoimmunity, asthma, cardiovascular diseases, cancer to neurological disorders including autism and Parkinson's disease.[2]

Humans have co-evolved with the intestinal microbiota, leading to adaptations that enhance survival, such as the ability to digest complex carbohydrates or respond to dietary changes. Additionally, there is growing evidence indicating that psychological states impact systemic immunity by altering the gut microbiota especially mucosal-bacterial interactions. However, the mechanisms of how brain state may control intestinal tissue physiology, and the composition of the intestinal microbiota remain unclear.

In a recent publication in *Cell*, Chang et al.[3] provide experimental evidence highlighting the regulation of the composition of the intestinal microbiota by a novel brain-gut circuit (Fig. 1). The Brunner's gland (BG), which consists of mucus-producing cells, is an exocrine structure located beneath the epithelium within the upper bulbar duodenal submucosa. Chang et al. demonstrate that these glands are distinctly innervated by nerve terminals originated from the vagus nerve. Indeed, stimulation of BGs with the nutrient-responsive gut peptide cholecystokinin (CCK) induced robust calcium currents throughout the BG and mucus secretion revealed by intravital imaging. Importantly, vagotomy or gut-specific sensory vagal denervation abolished BG's responses to CCK, whereas vagal stimulation by electrical pulses was sufficient to induce calcium currents across the BG and mucus production. Moreover, Chang et al. demonstrated that this neuro-glandular circuit modulates the composition of the gut microbiota, with a specific regulation of the *Lactobacillus* species proliferation in both small and large intestines.

Since BGs were found to be critical for regulating the composition of the intestinal microbiota, Chang et al. went on to investigate their roles in regulating intestinal inflammation and infection. The authors designed a genetic approach to cell-specifically ablate BGs by generating triple mutant mice that express the diphtheria toxin receptor exclusively in BG cells. Surprisingly, genetic ablation and surgical resection of BGs led to reduced body weight, overactivated sympathetic tone, gastric bloating, and spleen contraction at baseline, indicating an ongoing immune response. Consequently, genetic ablation of BGs resulted in significantly increased mortality following exposure to enteric pathogen infection. Is this vulnerability to infection driven by alterations in the microbiota? Indeed, fecal microbiota transplantation experiments demonstrated that the enhanced mortality to pathogen infection is mediated by the altered microbiota upon BG ablation. Notably, probiotic or mucin administration reversed the abnormal sympathetic tone, the altered immune responses, and the increased mortality following intestinal pathogen infections in these BG-ablated animals, suggesting that mucus secretion by BGs that regulates *Lactobacillus* proliferation is critical for maintaining gut permeability, sympathetic tone, spleen morphology, and intestinal immune responses.

The dorsal motor nucleus of the vagus (DMV) located in the medulla oblongata of the brain stem plays a vital role in regulating parasympathetic functions in the innervating organs including receiving sensory information and sending motor signals to regulate digestive processes in the gastrointestinal tract.[4] In the present finding, Chang et al. detected cholinergic receptors in the BG, but not in epithelial mucous cells in the villus. By cell-specific chemogenetic activation or ablation of DMV vagal efferent neurons, they demonstrated that vagal cholinergic efferent neurons innervate BGs to stimulate mucus secretion and *Lactobacillus* proliferation. Moreover, polysynaptic retrograde pseudorabies virus labeling of vagal sensory fibers innervating the BG revealed that these nerve fibers originate from the paraventricular and parasubthalamic *hypothalami, locus coeruleus* and *insular cortices*, all of which are regions linked to autonomic control. Interestingly, this labeling also revealed the medial aspect of the central nucleus of the amygdala (CeA), a subcortical area

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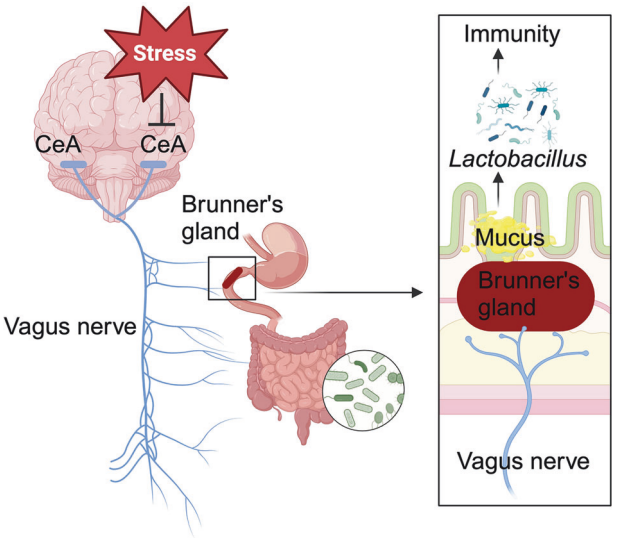


Fig. 1 A brain-neuroglandular circuit regulates the intestinal microbiota and host immunity. Stress-sensitive CeA neurons promote mucus production by BGs in the duodenum via the vagus nerve. Upon activation, BGs secrete mucus to promote *Lactobacillus* proliferation and subsequent immune responses to enteric pathogens. Chronic stress inhibits this brain-neuroglandular circuit thereby suppressing systemic immunity to pathogen infections. Figure created with BioRender.com.

within the temporal lobes that is implicated in emotional regulation and controls vagal innervation in the BG.

Previous research has shown that stress responses negatively regulate the intestinal microbiota.[5] We and others have also demonstrated that gut-innervating sensory neurons can modulate the composition of the intestinal microbiota via sensory neuropeptides to promote intestinal tissue protection.[6,7] Importantly, the intestinal microbiota has also been reported to influence neuronal activity and behavior,[8,9] highlighting the bidirectional communications between the gut microbiota and the brain. The remarkable findings reported by Chang et al. identify that stress-induced alterations in the microbiota are partially mediated by the CeA-DMV-BG circuitry. Acute stress or chronic stress caused a widespread inhibition of neuronal activity across CeA, indicating that the CeA-DMV-BG axis might be inhibited by exposure to stress. Consistently, stressed mice and non-stressed mice with CeA inhibition phenocopied BG-ablated mice with increased susceptibility to intestinal infection and abnormal spleen morphology and immune responses. In contrast, chemogenetic activation of CeA in stressed animals recovered the levels of *Lactobacillus*, limited bacterial infection, decreased gut permeability, normalized spleen morphology, and reactivated BG mucus secretion. Similarly, chemogenetic activation of DMV in stressed mice also recovered the abnormal gut phenotypes. In summary, Chang et al. demonstrated a novel circuit — how specific brain regions regulate the intestinal microbiota and immunity via peripheral parasympathetic nervous system innervating the duodenal glands.

The vagus nerve plays an important role in mediating cholinergic signaling that controls immune function and pro-inflammatory responses in the spleen.[10] In the most recent report by Chang et al., the mapping of vagally mediated, polysynaptic circuits connecting the CeA to BG extends our knowledge of brain-body circuits that have co-evolved between the nervous system and the intestinal microbiota. Chronic stress suppresses this neuro-glandular circuit and is associated with impaired mucus production, microbial dysbiosis marked by reduced probiotic bacteria *Lactobacilli,* and heightened vulnerability to infection. Targeting this newly identified local neuro-glandular circuit and other recently identified neuro-immune circuits[11,12] could lead to new therapeutic strategies for intestinal and extraintestinal inflammatory and infectious diseases.

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ADDITIONAL INFORMATION

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