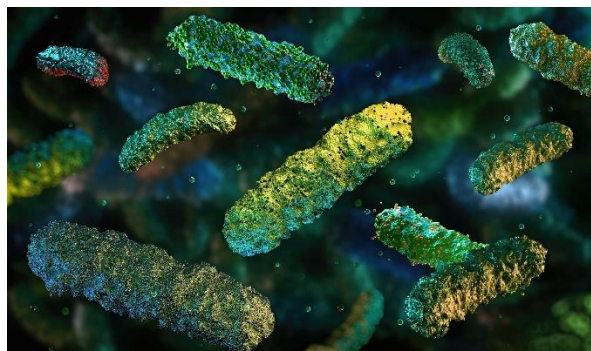


For Immune Regulation Brain Circuits Connecting Stress to Gut Bacteria Reveal New Pathways

Researchers showed that stress-sensitive neural circuits alter the [gut microbiome](#) by directly influencing duodenal glands.

Gut microbiomes promote nutrient digestion and protect against foodborne pathogens. Increasing evidence suggests that psychological states modulate immunity via changes in the host microbiome, suggesting a causal link between gut microbial homeostasis and [brain activity](#). Various preclinical and human studies have noted psychological states associated with altered microbiomes.

In non-human primates, stress induces significant reductions in beneficial bacteria accompanied by an increased susceptibility to opportunistic infections. Moreover, probiotic administration has been shown to augment physiological and emotional markers in rodent [anxiety](#) models. These effects of the brain states on the gut microbiome are believed to stem from alterations in mucosal-bacterial interactions. However, how brain states regulate mucosal secretion to influence the microbiome remains unknown.



Study and Results

In the present study, researchers explored the neuronal pathways that allow the brain to influence the mucosa-microbiome system. First, they investigated the effect of the vagus nerve and its connection to [Brunner's glands](#) (BGs), an exocrine structure confined to the duodenal submucosa. To this end, they generated *Glp1r[GCamp6]* mice with cell-specific expression of GCamp6 in BG cells and implanted them with an abdominal glass window for intravital imaging of calcium activity.

[Cholecystokinin](#) (CCK) was used to stimulate the BG via the vagus nerve. The researchers found that CCK administration led to robust calcium transients in the BG, inducing mucus secretion from BG cells. Next, this was repeated in mice with gut-specific sensory vagal denervation or subdiaphragmatic vagotomy (VGx). These interruptions in vagal transmission abolished BG responses to CCK. Further, after seven daily CCK injections, there was a notable proliferation of *Lactobacillus* species in cultures from large and small intestine tissues.

Importantly, BG resection abolished this CCK-induced *Lactobacillus* proliferation; sensory vagal denervation also abolished it. Further, the team confirmed that the vagal influence on mucus secretion was specific to BGs and did not involve epithelial mucous cells. Next, they performed single-nuclei sequencing of [ribonucleic acid](#) (RNA) transcripts from the proximal duodenal

tissue. They found that Muc6-expressing cells were the only cell type to co-express the muscarinic receptor M3 (Chrm3).

Administration of darifenacin (muscarinic receptor M3 blocker) abolished CCK-induced BG activation and reduced [Lactobacillus levels](#). Additionally, the researchers found that following CCK administration, the activation of the dorsal motor nucleus of the vagus (DMV) preceded surges in BG calcium signals. Further, selective ablation of DMV neurons abolished CCK-induced BG activation, mucosal secretion, and Lactobacillus growth.

Next, the researchers investigated whether BG ablation could result in intestinal barrier and immunological dysfunction. They generated [triple mutant mice](#) expressing diphtheria toxin (DTx) receptor (DTR) only in BG cells. Injecting DTx into the duodenal submucosa of these mice mimicked the effects of surgical BG resection of wild-type mice. While both approaches (surgical and cell-specific BG ablation) significantly reduced body weight, they also induced a higher preference for fiber-rich fatty food pellets.

Fos reactivity, the expression and activation of the Fos protein, which is a marker of neuronal activity in the brain, was markedly elevated in the celiac ganglia (CG) of BG-resected and BG-Dtx mice; besides, mice had severe gastric bloating and spleen contraction. However, celiectomies reversed splenic and gastric phenotypes in BG-Dtx mice. The researchers also tested the susceptibility of BG-DTx mice to gastrointestinal infection. These mice were infected with [Escherichia coli](#) EcAZ-2 strain, which increased EcAZ-2 counts in their excrement.

Further, infecting BG-DTx mice with *Staphylococcus xylosum* resulted in high mortality. Conversely, BG-saline control mice survived *S. xylosum* infection. Moreover, intestinal permeability was higher in BG-resected and BG-DTx mice, and after gut colonization, high levels of *S. xylosum* were detected in their [blood](#). Conversely, *S. xylosum* was not detected in control mice. Next, the team investigated whether mucin or probiotic administration could improve symptoms of BG ablation.

As such, BG-DTx and BG-saline mice underwent cecum infusions of a 12-strain probiotic cocktail (of Bifidobacteria and Lactobacilli) or neutral solutions. Probiotic administration reversed the sympathetic, lymphoid, and [splenic abnormalities](#) of BG ablation and also restored the body weight of BG-DTx mice. Notably, it decreased the mortality after *S. xylosum* infection and prevented *E. coli* proliferation. Mucin administration had similar effects on probiotics, reconstituting the intestinal barrier and Lactobacillus levels.

Next, the researchers explored the brain regions that regulate the [vagal parasympathetic fibers](#) innervating the BG.

They discovered that a brain region implicated in emotional regulation, the central nucleus of the amygdala (CeA), was connected to BG through the vagal but not sympathetic or spinal pathways. Finally, they investigated whether CeA-DMV-BG circuitry mediates the effects of stress. To this end, neuronal ensembles were first recorded in the CeA of mice exposed to acute or chronic restraint stressors. [Chronic restraint stress](#) induced widespread neuronal activity inhibition in the CeA. This effect was less pronounced with acute stress.

Moreover, chronic stress reduced Lactobacillus counts, and the chemogenetic inhibition of CeA reproduced this effect in non-stressed mice. In contrast, chemogenetic stimulation of CeA

induced robust [Lactobacillus growth](#) in chronically stressed mice. Besides, CeA inhibition and stress exposure together reproduced BG lesion-association phenotypes. Thus, stressed mice were more susceptible to gut infections and exhibited increased gut permeability and alterations in immune profile.

Notably, chemogenetic stimulation of CeA prevented infections, restored [spleen morphology](#), reduced gut permeability, and recovered Lactobacillus levels. Moreover, chemogenetic activation of DMV phenocopied these effects.

Conclusion

Together, the study identified a stress-sensitive neuroglandular circuit linking [brain states](#) to gut microbiome alterations. These emotion-related brain circuits regulate the BG via the vagus nerve, and the mucosal secretions from BG promote microbial growth, especially Lactobacilli. The researchers posit that mucin secretion from BGs serves as a crucial substrate for Lactobacillus growth, and that stress inhibits mucus secretion. Consequently, bacterial growth is suppressed, leading to lymphoid tissue abnormalities, increased gut permeability, and sympathetic overtone. Interestingly, probiotic administration was shown to alleviate these adverse effects.

Source:

<https://www.news-medical.net/news/20240811/Brain-circuits-connecting-stress-to-gut-bacteria-reveal-new-pathways-for-immune-regulation.aspx>