Microbiota modulates locomotion via vagus-dependent glucagon-like peptide-1 signaling

Tzu-Ting Lai[1,2], Wei-Li Wu[1,2,*]

1. Institute of Basic Medical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
2. Department of Physiology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background
Locomotor activity is a fundamental behavior that can be triggered by gut-driven motivation status to drive animals from one place to another. Gut-driven motivation is controlled by various gut hormones and transmitted through the vagus nerve terminal synaptically connecting the enteroendocrine cells. Gut microbiota is composed of a group of host-specific commensal microorganisms inhabiting the gastrointestinal tract. Recent studies suggest that the levels of the gut hormone can be driven by the colonization status of gut microbes, suggesting a complex interaction among gut bacteria, gut hormones, brain, and host behavior. Therefore, it is speculated that the gut microbiota modulates the locomotor activity via gut hormone signaling in a motivation-driven manner.

Aims & Objectives
Herein, we hypothesize that the vagus-dependent enteroendocrine signaling serves as a mediator for the gut microbiome to modulate locomotor behavior.

Methods
To assess the association among gut microbiome, gut hormone glucagon-like peptide-1 (GLP-1) levels, and locomotion in mice**,** we depleted the gut microbiome by administrating the cocktail of a broad-spectrum antibiotic (ABX) in the drinking water for C57BL/6J mice and tested for their locomotor activity. The brain, serum, and fecal samples were analyzed by immunohistochemistry staining, ELISA, and 16S rRNA sequencing, respectively. On the other hand, the vagus nerve is one of the promising neural connections bidirectionally innervating in the GI tract and the brain. The subdiaphragmatic vagotomy (SDV) was performed to understand the contributions of gut-associated vagal signaling involved in the microbiota-mediated GLP-1-induced locomotion alteration.

Results
We observed the ABX-treated mice displayed decreased locomotion and elevated sera gut hormone GLP-1. Antagonism of GLP-1 receptors in ABX mice rescued the deficiency locomotor phenotype. Next, subdiaphragmatic vagotomy (SDV) procedure successfully reversed the hypolocomotion in ABX mice, indicating the crucial role of the vagus nerve in the microbiota-mediated GLP-1 induced hypolocomotion. The expression of c-Fos, an immediate early gene associated with neuronal activity, was upregulated in the vagal ascending brain regions in the ABX mice after the locomotor test. We observed that deprived gut microbiota aberrantly activated neurons in the vagal afferent brain regions in response to locomotor behavior. Finally, we pinpointed several indigenous gut bacteria that might mediate the GLP-1 levels in the host by 16S rRNA sequencing of the fecal microbiota in antibiotic-treated mice. Colonizing the specific bacteria in germ-free and ABX mice suppressed the GLP-1 levels and restored their locomotor activity.

Discussion & Conclusion
The depletion of gut microbiota in mice impacts their locomotor activity through the upregulation of gut hormone GLP-1 levels. Moreover, the upregulation of GLP-1 relies on the vagal innervation in the gut and vagal afferent brain regions to decrease locomotion. The specific bacteria selected by antibiotic treatment is critical for the mediation of the circulating GLP-1 levels. Taken together, gut microbiota-mediated GLP-1 signaling impacts locomotor activity through specific microorganisms in the gut.