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Project Summary

Understanding the Mechanisms of Communication Between Immunity, the Gut Microbiota and the Brain in *Drosophila melanogaster*

Sleep loss are common in today's society. Insufficient sleep can have serious consequences on health affecting cardiovascular, immune and the central nervous system (CNS), among others. If we have a better understanding of sleep regulation mechanisms and the factors that influence it could lead to better treatment of sleep problems and comorbid conditions. In fact, illnesses in which sleep difficulties are common, as is the case in many psychiatric disorders, have also been associated with intestinal microbiota dysbiosis and changes in protein expression of the CNS. Although a brain-gut axis has been identified, the link between the gut microbiota and sleep is just beginning to be studied. In our recent work, we have found that rearing *Drosophila melanogaster* with broad-spectrum antibiotics produced a decrease in total sleep indicating the possibility that the intestinal microbiota could indeed have a relation with sleep regulation. Furthermore, when the microbiota was analyzed with 16S rRNA sequencing, we observed that flies that were sleep deprived showed a decrease in bacteria composition. However, when mutant flies with deficient sleep homeostasis (Pumilio knock down) are sleep deprived, the diminution in bacteria composition was not observed. Presently there are many gaps in our understanding involved in the brain-gut axis communication pathways. **Therefore, this study pursues to elucidate the mechanisms involved in the pathways of the brain-gut axis in particular the bidirectional communication between the gut microbiota and sleep regulation.** Of the 4 pathways that have been identified in the brain-gut axis (immunological, endocrine, afferent neuronal and a metabolic pathway), we propose that immunological and metabolic pathways could be of great importance. We know that the immune system plays an important role in maintaining intestinal microbiota homeostasis and that certain immune components produced in an immune response can promote sleep. Likewise, we propose that bacterial products could be of relevance in this communication. Studies have shown that there are bacteria that are able to produce γ-Aminobutyric acid (GABA), Serotonin (5-HT), and Acetylcholine (ACh) which are also neurotransmitters associated with sleep. **We therefore hypothesize that sleep homeostasis mechanisms involve interactions of the gut microbes and the innate immune system.** To test this hypothesis, we are proposing two specific aims in this study: 1) Identify bacterial gene products and neurotransmitters changes induced by chronic sleep deprivation, 2) Determine the role of Pumilio in the signaling pathway of the brain-gut axis.