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Linking the gut microbiota to a brain neurotransmitter

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Abstract

The past decade has yielded substantial evidence that the gut microbiome modulates brain function, including for instance behaviors relevant to anxiety and depression, pointing to a need to identify biological pathways involved. In 2013, Clarke and colleagues reported that the early life microbiome regulates the hippocampal serotonergic system in a sex-dependent manner, findings that opened up numerous lines of inquiry on the effects of the microbiome on neurodevelopment and behavior.

Keywords

microbiome; microbiota; gut-brain axis; stress; anxiety; serotonin

In the early 2000's, evidence was mounting for a link between the gut microbiome and stress-related behaviors. Based on long-standing associations of psychological stress with gastrointestinal disorders, Bailey and Coe [1] revealed that early life stress alters the composition of the gut microbiota in rhesus monkeys and that these changes in the microbiota correlate with anxiety-related behaviors and serum levels of stress hormones. Sudo et al. [2] further demonstrated that mice raised devoid of microbial colonization (germ-free) exhibit elevated stress hormone responses and decreased hippocampal levels of brain-derived neurotrophic factor (BDNF), a protein important for neurogenesis, compared to conventionally-colonized controls. These phenotypes were reversed by mono-colonizing germ-free mice with select gut bacteria, revealing a causal role for the gut microbiota in regulating stress responses. In subsequent years, several investigators, including Neufeld et al. [3], Diaz Heijtz et al. [4], Nishino et al. [5], and Davis et al. [6], extended these studies by examining various models including germ-free or antibiotic-treated mice, rats and zebrafish to demonstrate that changes in the gut microbiome alter stress-related behaviors across different organisms. To date, anxiety-associated changes in exploratory drive and risk avoidance have been the most frequently studied host behaviors in microbiota-gut-brain research.

While early work on microbial modulation of anxiety-related behaviors had revealed changes in stress hormones and brain BDNF levels, it seemed likely that additional neurotransmitter systems or modulators may be underlie microbial alterations in host

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behavior, and insights into such pathways were at the time lacking. In 2009, a metabolomics study by Wikoff et al. [7] revealed deficiencies in serum serotonin and elevated serum tryptophan in germ-free mice compared to conventional controls. This was later corroborated by additional research indicating that the gut microbiota regulates peripheral serotonin levels (Sjogren et al. [8], Yano et al. [9]). Serotonin is a hormone and excitatory neurotransmitter that is produced in large quantities in the gastrointestinal tract, but most prominently known for its central contributions to anxiety and depression. Whether microbial effects on the peripheral serotonergic system were similarly seen in the central serotonergic system had not been explored.

The study by Clarke et al. pioneered the efforts to examine effects of the microbiome on the brain serotonergic system [10]. It found that germ-free mice display increased levels of hippocampal serotonin, hippocampal 5-hydroxyindoleacetic acid (5-HIAA, serotonin's main catabolic product), plasma tryptophan, and decreased tryptophan metabolism to kynurenine, as measured by high-performance liquid chromatography. This was correlated with decreased expression of hippocampal BDNF. These latter findings corroborated previous studies [4, 7], by replicating GF-associated increases in peripheral tryptophan and decreases in hippocampal BDNF expression, respectively.

In addition to revealing a link between the gut microbiota and brain serotonin, the Clarke et al. study also highlighted the importance of considering sex in microbiota-gut-brain studies. At the time, many studies involving the microbiota examined consequences on the immune response particularly in female animals, leaving sexually dimorphic effects largely unconsidered. Prior reports of microbial effects on stress response and behavior similarly tended to be performed in animal cohorts of only one sex. Interestingly, in the Clarke et al. study, the microbiota-mediated changes in hippocampal serotonin, 5-HIAA, BDNF, and plasma tryptophan were observed only in male mice. This consideration aligned with existing evidence that regulation of the brain serotonergic system is sexually dimorphic (Llorente et al. [11]) and contributed to growing efforts to examine sex as a biological variable. Today, studies continue to probe for sex-specific effects of the microbiome on the host. Notably, Thion et al. [12] recently demonstrated that the absence of the microbiome has a sexually dimorphic impact both prenatally and postnatally on microglia function and maturation in mice.

The Clarke et al. study strengthened the notion that microbial effects on the brain may be dependent on critical periods of host development. To determine whether the neurochemical changes seen in germ-free mice could be corrected postnatally, the researchers colonized adult mice with a conventional microbiome (also referred to as conventionalization). This conventionalization corrected abnormalities in plasma levels of tryptophan and tryptophan metabolism through the kynurenine pathway, but had no effect on any of the observed hippocampal neurochemical phenotypes. This was consistent with prior work by Sudo et al. [2], which revealed that postnatal conventionalization of germ-free mice in adulthood fails to correct abnormalities in stress responses. Surprisingly, the altered anxiety-like behavior observed in germ-free mice was ameliorated by microbiota colonization despite no effects on brain serotonergic phenotypes. These results suggested that alterations in the brain serotonin system could be decoupled from altered stress-induced behavior as well as

peripheral serotonin metabolism. The work of Clarke et al. contributed to numerous lines of inquiry surrounding the role of the microbiome during neurodevelopment. Studies have since elucidated roles for the early-life microbiome in hippocampal neurogenesis, microglial maturation and neuronal myelination [13].

The several early behavioral studies conducted in microbiome-depleted animals have positioned the field to begin to consider not only *whether* the microbiome has effects on neurodevelopment and behavior, but importantly *how*. Advancements in integrating functional genomic and metabolomic data with mechanistic studies in animal models have allowed interrogation into how select bacterial species and microbially-derived products affect distinct immune, endocrine and neuronal pathways [13]. In addition, these studies have motivated the examination of microbiota-gut-brain interactions in systems more relevant to the human condition. In particular, Clarke et al. wrote, “The current study is limited by the common difficulty all germ-free studies have in directly translating the results to the clinical situation where no equivalent obliteration of the microbiota can be said to exist.” Approaches involving the transplantation of human-derived microbiomes into germ-free mice have recently allowed researchers to directly investigate the effects of human disease-associated microbes on host neurophysiology and behavior [14, 15]. Together, these developments better position the field to face the current challenge of dissecting the biological circuits that enable bidirectional communication between the gut microbiome and the brain. Though a formidable endeavor, detailed investigation into this line of inquiry will continue to push the field toward a better understanding of how our microbial symbionts influence human biology.

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