Effects of gut microbiota on the brain: implications for psychiatry

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It may be surprising to learn that the human gastrointestinal tract is home to 10^{14} bacterial organisms.[1] In fact, there are more bacteria in the gut than there are somatic cells in the body. These resident bacteria are referred to as commensal microbiota, and their arrival during the first few postnatal days sets up a symbiotic association that is necessary and crucial to normal physiology. This lifelong association is essential to host pathogen defence and plays an important role in nutrient uptake and metabolism.[2] Immunologists have been aware of this system and its importance to the development of the muscosal and systemic immune systems for a long time.[3,4] What is new and noteworthy is emerging evidence that gut microbiota influence behaviour and central nervous system (CNS) function.[5] This commentary provides a brief overview of research related to gut–brain communication in a context that allows neuroscientists and psychiatrists to take note and consider the role of microbiota in their research related to CNS function and behaviour.

Colonization of the gastrointestinal tract, predominantly the colon, begins at birth, continues in early development and remains throughout life. The early profile of microbiota is influenced by genetics and postnatal environmental exposure. Several bacterial phylotypes are distributed in the human gastrointestinal tract and, although each person's microbial profile is distinct, relative abundance and distribution along the gastrointestinal tract of these bacterial phylotypes is similar among healthy individuals.[6–8] Commensal flora serve several physiologic functions. Gut microbiota facilitate nutrient uptake and metabolism, providing us with otherwise inaccessible nutrients and vitamins.[9–11] Colonization and the presence of microbiota is important to the development, function and maintenance of a healthy gastrointestinal tract.[12–14] Interestingly, gut microbiota are also essential and necessary for the proper development of the mucosal and systemic immune systems,[3,4,15] an association we believe to be central when considering the impact that microbiota may have on the development and function of the brain.

Gastrointestinal research has for many years highlighted the importance of the "gut–brain axis," especially in relation to functional bowel disorders like irritable bowel syndrome, but much of this work has been focused on "top-down" control, or the examination of the impact that the brain can have on general gut function.[16,17] New work involving intestinal microbiota, the resident bacteria present in the healthy gastrointestinal tract, is indicating that events occurring in the gut also have an impact on the development and function of the CNS. Using the top-down approach, recent work has demonstrated that early life stress in a rodent, known to lead to altered stress reactivity later in life, in parallel leads to an altered profile of gut microbiota.[18] Gut microbiota are also known to influence energy balance and in turn, emerging evidence demonstrates the importance of gut microbiota to the pathophysiology of obesity.[19] Energy balance and food intake are centrally mediated processes; however, the direct link between gut microbiota and central feeding circuits has not yet been made. This is an example of the less-studied "bottom-up" control, which we believe will have an important impact on both the study and treatment of diseases that have been traditionally considered to be housed solely within the CNS.

Almost 50 years ago, Gustafsson[20–22] developed germ-free animals as a scientific tool.[20–23] These mice have no commensal intestinal microflora and, as such, exhibit an undeveloped immune system.[15,24–26] Germ-free mice have proven to be a useful tool for investigations into differences between adaptive and innate immunity. We propose that a vital pathway of communication from the gut to the brain is through the immune system and therefore suggest that experimentation in germ-free mice related to stress reactivity and related behaviours will provide answers to how intestinal microbiota influence CNS function.

A recent report found that compared with specific-pathogen-free mice, adult germ-free mice show an exaggerated stress response. Germ-free mice showed no difference in basal stress hormones but showed increased plasma

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corticosterone and adrenocorticotrophic hormone levels in response to restraint stress.[5] An additional interesting finding in this report was that colonization of the gut microbiota and the resultant constitution of the immune system at 6 weeks of age (adolescence) led to normalization of the stress axis; however, when mice were colonized in early adulthood (8 weeks of age or later), the altered stress response was persistent throughout adulthood. Our group extended this work and examined the behavioural phenotype of the germ-free mouse in early adulthood and observed a significant basal increase in open arm exploration in germ-free mice compared with specific-pathogen-free controls on the elevated plus maze (unpublished data). Retesting of the same mice after colonization with specific-pathogen-free microbiota showed that this altered anxiety-related phenotype was persistent. Therefore in the unstressed state, germ-free mice show less anxiety-like behaviour than specific-pathogen-free mice. This observation was surprising since Sudo and colleagues[5] demonstrated an exaggerated hypothalamic–pituitary–adrenal activation in response to restraint stress; however, it should be noted that the basal levels of stress hormones (corticosterone and adrenocorticotrophic hormone) in their germ-free mice were not elevated. Although preliminary in nature, these data are provocative and suggest the microbiota influence CNS development of stress reactivity and anxiety-like behaviour. Additional work using germ-free mice will provide an avenue to tease out the underlying mechanisms by which gut microbiota communicate with the CNS and influence behaviour.

Clinically, psychiatric illness does not stand alone. It is well recognized that many gastrointestinal disorders demonstrate a high comorbidity with psychiatric illness. This is particularly true for the functional bowel disorders such as irritable bowel syndrome and functional dyspepsia. Mood disorders are the most common of these psychiatric illnesses, with studies demonstrating that more than 50% of patients with irritable bowel syndrome also meet the criteria for mood disorders.[27] Indeed, antidepressants are one of the most common pharmaceutical interventions for irritable bowel syndrome. Whereas most clinical and preclinical studies have focused on top-down treatment options for primarily intestinal disorders, emerging work involving germ-free mice suggests treatment options for psychiatric diseases potentially being targeted to systems outside of the CNS. New directions in preclinical work considering the importance of microbiota in combination with clinical work examining the impact of antibiotics and probiotics on CNS development and function will inform us of the importance of bottom-up control to brain function. The results of work in this emerging area may provide novel targets for intervention in psychiatric illnesses.

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