Stress and the Microbiota-Gut-Brain Axis: An Evolving Concept in Psychiatry

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The concept of the gut influencing brain and behaviour has existed for almost 2 centuries. However, this gut-brain axis has been best appreciated and studied in the context of eating behaviour. Nonetheless, despite this concept being widely integrated into our everyday vernacular (gut feelings, gut instinct, gutted, gutsy, it takes guts, butterflies in one’s tummy), it was not until the advent of brain imaging that neuroscientists really began to appreciate the influence of this axis on modulating brain function and maintaining homeostasis, especially during stressful situations.

A new player has emerged in the past decade: the gut microbiota, which is now seen as a key regulator of the gut-brain axis. The gut is home to a diverse array of trillions of microbes (mainly bacteria but also archaea, viruses, and protozoa), which is 1.3 to 10 times the number of human cells. Advances in sequencing technologies show that the microbiota influences almost all aspects of human biology. Evidence of a crucial role for the microbiota in regulating stress-related changes in physiology, behaviour, and brain function has emerged mostly from animal studies. In 2004, Sudo and colleagues discovered that mice that grow up devoid of a microbiome (in a germ-free environment) have an exaggerated hypothalamic-pituitary axis response to stress; importantly, these researchers also found that this effect could be reversed by colonization with a specific bifidobacteria species. Converse findings soon emerged showing that stress (either early in life or in adulthood) changed the microbiota composition or depended on it to induce its deleterious effects.1-6 The concept that bacteria were required for normal brain development emerged soon afterward.7-12 Indeed, the microbiota is shown to regulate many key processes in the adult brain, such as neurogenesis13 and microglia activation.14 Thus, the ability to target the brain via the microbiome is viewed as a paradigm shift in neuroscience and psychiatry.15,16 Moreover, this research led to the concept of psychobiotics (bacteria with positive effects on mental health), coined by Dinan et al. in 2013.17 Animal studies again lead the way in showing that specific strains of bifidobacteria, lactobacilli, or bacteroides can have positive effects on the brain and behaviour.9,18-21 These studies are slowly being translated into research with healthy human volunteers.22-26 One immediate research goal is to elucidate the mechanisms underpinning the beneficial effects of specific bacterial strains. The role of microbiota composition as a susceptibility factor for various stressful insults, especially at key neurodevelopmental windows, is also emerging.27

Two articles in this special issue focus on the latter concept. Leclercq et al. focus on post-traumatic stress disorder (PTSD). There are limited clinical data implicating the microbiome in the susceptibility or treatment of PTSD. The authors review the available evidence and plausibly argue that there are converging pathways that enable the microbiome to gate susceptibility or resilience to stress in early life. Although the authors focus primarily on childhood trauma, the same logic would also apply to combat-associated or other forms of adult PTSD. In addition to gating stress susceptibility, the microbiome is primed to modify aspects of fear learning and extinction, amygdala-dependent processes thought to underpin PTSD at a neurobiological level. The fact that certain strains of bacteria are shown to enhance cognitive processes and affect fear learning in animal models also supports this concept.18,20,28-30 Additional research is needed, but this is an exciting area of pursuit.

McVey Neufeld et al. also examine stress susceptibility and resilience in adolescence, a particularly vulnerable period for environmental influences on brain function and development of psychopathology.31 The authors review evidence that the microbiota could be targeted to confer protection from insults to the brain and to ameliorate the negative effects of stressors at this vulnerable period. There is a

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growing interest in understanding the effects of microbiota perturbations at this life stage on behaviours relevant to stress and cognitive-related disorders. The use of microbiota-based strategies is in the early stages in all aspects of medicine, especially in psychiatry. The articles by Leclercq et al. and McVey Neufeld et al. highlight the promise of such an approach in treating stress-related disorders, especially at vulnerable time windows across the lifespan.

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