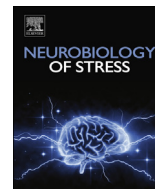




Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: <http://www.journals.elsevier.com/neurobiology-of-stress/>

Stress & the gut-brain axis: Regulation by the microbiome

Jane A. Foster^a, Linda Rinaman^{b,*}, John F. Cryan^{c,d}^a Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada^b Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, United States^c APC Microbiome Institute, University College Cork, Cork, Ireland^d Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland

ARTICLE INFO

Article history:

Received 15 December 2016

Received in revised form

16 February 2017

Accepted 2 March 2017

Available online xxx

ABSTRACT

The importance of the gut–brain axis in regulating stress-related responses has long been appreciated. More recently, the microbiota has emerged as a key player in the control of this axis, especially during conditions of stress provoked by real or perceived homeostatic challenge. Diet is one of the most important modifying factors of the microbiota–gut–brain axis. The routes of communication between the microbiota and brain are slowly being unravelled, and include the vagus nerve, gut hormone signaling, the immune system, tryptophan metabolism, and microbial metabolites such as short chain fatty acids. The importance of the early life gut microbiota in shaping later health outcomes also is emerging. Results from preclinical studies indicate that alterations of the early microbial composition by way of antibiotic exposure, lack of breastfeeding, birth by Caesarean section, infection, stress exposure, and other environmental influences – coupled with the influence of host genetics – can result in long-term modulation of stress-related physiology and behaviour. The gut microbiota has been implicated in a variety of stress-related conditions including anxiety, depression and irritable bowel syndrome, although this is largely based on animal studies or correlative analysis in patient populations. Additional research in humans is sorely needed to reveal the relative impact and causal contribution of the microbiome to stress-related disorders. In this regard, the concept of psychobiotics is being developed and refined to encompass methods of targeting the microbiota in order to positively impact mental health outcomes. At the 2016 Neurobiology of Stress Workshop in Newport Beach, CA, a group of experts presented the symposium “The Microbiome: Development, Stress, and Disease”. This report summarizes and builds upon some of the key concepts in that symposium within the context of how microbiota might influence the neurobiology of stress.

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* Corresponding author. Current address: Department of Psychology, Florida State University, Tallahassee, FL, United States

E-mail address: rinaman@psy.fsu.edu (L. Rinaman).

<http://dx.doi.org/10.1016/j.ynstr.2017.03.001>

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1. Introduction

The concept of the gut influencing brain and behaviour, and vice-versa, has perhaps been best appreciated and studied as it relates to the cephalic (preparatory) phase of digestion, visceral pain and malaise, and the ability of emotional stress to disrupt digestive functions. Nonetheless, despite wide integration of the “gut-brain” concept into our everyday vernacular (e.g., gut feelings, gut-wrenching, gut instinct, gutted, gutsy, it takes guts, butterflies in one’s stomach), neuroscientists have only recently developed adequate tools with which to reveal the bi-directional links between gut physiology and brain function, and to determine how these links operate under normal and stressful conditions. At the 2016 Neurobiology of Stress Workshop in Newport Beach, CA, a group of experts presented the symposium “The Microbiome: Development, Stress, and Disease”. This report summarizes and expands upon some of the key points from this symposium, focused on current understanding of how microbiota influence the neurobiology of stress.

The complex and multifaceted system of gut-brain communication not only ensures proper maintenance and coordination of gastrointestinal functions to support behaviour and physiological processes, but also permits feedback from the gut to exert profound effects on mood, motivated behaviour, and higher cognitive functions. The linkage between gut functions on the one hand and emotional and cognitive processes on the other is afforded through afferent and efferent neural projection pathways, bi-directional neuroendocrine signaling, immune activation and signaling from gut to brain, altered intestinal permeability, modulation of enteric sensory-motor reflexes, and entero endocrine signaling (Mayer et al., 2014a; Sherwin et al., 2016). Gut microbiota have emerged as a critical component potentially affecting all of these neuro-immuno-endocrine pathways (Carabotti et al., 2015; Bailey, 2014). For example, even short-term exposure to stress can impact the microbiota community profile by altering the relative proportions of the main microbiota phyla (Galley et al., 2014), and experimental alteration of gut microbiota influences stress responsiveness, anxiety-like behaviour, and the set point for activation of the neuroendocrine hypothalamic-pituitary-adrenal (HPA) stress axis (Carabotti et al., 2015; Golubeva et al., 2015; De Palma et al., 2015; Moussaoui et al., 2016; Crumeyrolle-Arias et al., 2014). Disease-related animal models such as mild and chronic social defeat stress also lead to significant shifts in cecal and fecal microbiota composition; these changes are associated with alterations in microbiota-related metabolites and immune signaling pathways suggesting that these systems may be important in stress-related conditions including depression (Bharwani et al., 2016; Aoki-Yoshida et al., 2016).

2. The gut microbiome

Within the past decade it has become clear that the gut microbiota is 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, yeasts, helminth parasites, viruses, and protozoa

(Lankelma et al., 2015; Eckburg et al., 2005; Gaci et al., 2014; Scarpellini et al., 2015; Williamson et al., 2016). The bacterial gut microbiome is largely defined by two dominant phylotypes, Bacteroidetes and Firmicutes, with Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia phyla present in relatively low abundance (Lankelma et al., 2015; Qin et al., 2010). Although the ratio of microbial to human cells has been recently revised downward (Sender et al., 2016), it is evident that microbial cells outnumber human cells. The total weight of these gut microbes is 1–2 kg, similar to the weight of the human brain (Stilling et al., 2014). Microbiota and their host organisms co-evolved and are mutually co-dependent for survival, and mammals have never existed without microbes, except in laboratory situations (Bordenstein and Theis, 2015).

In humans and other mammals, colonization of the infant gut is thought to largely begin at birth, when delivery through the birth canal exposes the infant to its mother’s vaginal microbiota, thereby initiating a critical maternal influence over the offspring’s lifelong microbial signature (Backhed et al., 2015; Collado et al., 2012; Donnet-Hughes et al., 2010). Advances in sequencing technologies are revealing that the early developmental microbiota signature influences almost every aspect of the organism’s physiology, throughout its life. The role of microbiota composition as a susceptibility factor for various stressful insults, especially at key neurodevelopmental windows, is rapidly emerging (Borre et al., 2014), and there is growing evidence that targeted manipulations of the microbiota might confer protection to the brain to ameliorate the negative effects of stress during vulnerable developmental periods.

3. Gut microbiota and stress-related behaviours

Several lines of evidence support the suggestion that gut microbiota influence stress-related behaviours, including those relevant to anxiety and depression. Work using germ-free (GF) mice (i.e., delivered surgically and raised in sterile isolators with no microbial exposure) demonstrates a link between microbiota and anxiety-like behaviour (Neufeld et al., 2011; Diaz Heijtz et al., 2011; Clarke et al., 2013). In particular, reduced anxiety-like behaviour in GF mice was shown in the light-dark box test and in the elevated plus maze (see (Luczynski et al., 2016a) for review). On the other hand, GF rats display the opposite phenotype, and are characterized by increased anxiety-like behaviour (Crumeyrolle-Arias et al., 2014). Interestingly, the transfer of stress-prone Balb/C microbiota to GF Swiss Webster (SW) mice has been shown to increase anxiety-related behaviour compared to normal SW mice, while transfer of SW microbiota to GF Balb/C mice reduced anxiety-related behaviour compared to normal Balb/C mice suggesting a direct role for microbiota composition in behaviour (Bercik et al., 2011a). Further, monocolonization of GF mice with *Lactobacillus plantarum* PS128 increased locomotor activity in comparison to control GF mice, a behavioural change that was associated with increased levels of dopamine, serotonin and their metabolites in the striatum (Liu et al., 2016a). Furthermore, antibiotic treatment during adolescence in mice altered microbiota composition and

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