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Review

What's bugging your teen?—The microbiota and adolescent mental health

Karen-Anne McVey Neufeld[a], Pauline Luczynski[a], Clara Seira Oriach[a,b], Timothy G. Dinan[a,b], John F. Cryan[a,c,*]

[a] APC Microbiome Institute, University College Cork, Ireland
[b] Department of Psychiatry, University College Cork, Ireland
[c] Department of Anatomy and Neuroscience, University College Cork, Ireland

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ABSTRACT

Human adolescence is a time of enormous developmental change, second only to infancy and early childhood in terms of brain shaping and growth. It is also a period in life when the young adult is faced with distinct environmental challenges and stressors. Interestingly, we now know that these external sources of stress all have an impact on the intestinal microbiota. Given that there is now a significant body of knowledge indicating a role for the microbiota-gut-brain axis in development and function of the brain, and potentially the emergence of psychiatric illnesses, we need to draw our attention to the intestinal microbiota in the adolescent. As psychiatric illnesses frequently first manifest during the teenage years it may be that the intestinal bacteria are playing an as yet unidentified role in disease pathogenesis. Identifying a role for the microbiota in psychiatric illnesses opens up an exciting opportunity for therapeutic advances via bacterial manipulation. This could prove to be a beneficial and novel avenue for treatment of mental illnesses in the developing teen.

Contents

Abbreviations: ACTH, adrenocorticotropic hormone; AH, afterhyperpolarization; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; ENS, enteric nervous system; GF, germ-free; HPA, hypothalamic-pituitary-adrenal; IBS, irritable bowel syndrome; MIA, maternal immune activation; PUFA, polyunsaturated fatty acid; VPA, valproic acid.

* Corresponding author at: APC Microbiome Institute, University College Cork, Ireland.
E-mail address: j.cryan@ucc.ie (J.F. Cryan).

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1. Introduction

As a society, we are well aware of the many and varied external sources of pressure adolescents face; from possible drug and alcohol exposure, to social issues involving peers, to changing habits related to eating and sleeping, to balancing workload and the seemingly inevitable associated stress. What we are likely less aware of is that teenagers face additional developmental influence from the inside – in the form of the commensal intestinal microbiota. In fact, we now know that collectively extrinsic factors and the internal microbial environment work in concert to exert defining effects on host anatomy, physiology and behavior (Cryan and Dinan, 2012; McVey Neufeld et al., 2013; Borre et al., 2014; De Palma et al., 2014; McVey Neufeld et al., 2016). In addition, emergence of psychiatric illness is often first seen during the adolescent period when environmental stressors frequently peak (Paus et al., 2008; O'Connor and Cryan, 2014). Intriguingly, for all of the external influencing factors listed above, lasting effects on the gut bacteria have been identified, leading to the hypothesis that mental illness emerging during adolescence could in part be mediated by the commensal intestinal microbiota (see Fig. 1).

The human gut houses 100 trillion bacteria, and the impact of our synergistic coexistence with these bugs on human development and function is only beginning to be appreciated (Backhed et al., 2005; Frank and Pace, 2008). A recent study examining the variation in microbiota in healthy adults has identified a human core microbiota that is globally observed, and is made up of 17 bacterial genera (Falony et al., 2016). In this review we will introduce the concept of the microbiota-gut-brain axis, a bi-directional axis of communication with broad implications for human physiology, health and disease. We will focus on the developing adolescent brain, its fragile balance between plasticity and vulnerability, and the role that this axis, and the intestinal microbiota particularly, may play in both its normal, healthy development and the pathophysiology of the psychiatric illnesses that frequently first manifest during this critical window. We will discuss studies examining the use of both pre- and pro-biotics; the latter are live bacteria that confer health benefits to the host and which only transiently inhabit the gut, and prebiotics are the indigestible foods (primarily carbohydrates), that selectively promote the growth of certain gut bacteria, thereby providing indirect health benefits to the host (Gibson and Roberfroid, 1995; Roberfroid, 2007). Finally, we will propose potential lines of inquiry for future research on therapeutics aimed at the treatment of psychiatric illnesses via the intestinal commensal microbiota.

2. Microbiota-gut-brain axis

The existence of a gut-brain axis has been acknowledged for decades, with both clinical and basic research identifying this bidirectional axis of communication as fundamental for both normal gastrointestinal function but also to the frequently co-morbid psychiatric and bowel diseases (Mayer, 2000). In the last decade, the concept of this axis has been extended to the "microbiota-gut-brain axis", a reflection of our increased understanding of the importance of the trillions of bugs residing and working in the human gut (Rhee et al., 2009; Bercik, 2011; Cryan and O'Mahony, 2011). Our relationship with the commensal bacteria is mutualistic – the bugs benefit from a rich and protected habitat, while we humans benefit as bacteria breakdown otherwise indigestible food products, providing us with previously inaccessible nutrients. We also gain as these beneficial bacteria provide a biofilm through which it is difficult for pathogenic bacteria to gain access. However, we are beginning to understand that this mutually beneficial relationship has further far-reaching consequences for optimal human health and well-being than previously considered, and that the benefits of a synergistic relationship with bacteria can extend to human mental health. Most interestingly, we now know that the microbiota influence the expression of host behavior and likely play a role in pathophysiology of psychiatric disease (Foster and McVey Neufeld, 2013).

Despite the fact that the concept of a microbiota-gut-brain axis is now well established both pre-clinically and clinically, exact mechanisms by which communication occurs are still under investigation. A number of systems are involved in this highway of information transfer, likely working in parallel to transmit information between the microbiota and the brain, with neural (both autonomic and enteric), immune, and endocrine pathways all engaged in the constant crosstalk (Cryan and Dinan, 2012; Foster and McVey Neufeld, 2013; El Aidy et al., 2015; Mayer et al., 2015).

The enteric nervous system (ENS) is a dedicated nervous system housed with the gastrointestinal wall that exists from the esophagus to the anus. While the ENS makes connections to the extrinsic nervous system, it is also capable of operating independently of the spinal cord and brain (Costa et al., 2000). Both the ENS and the vagal nerve have proven to be important in transmitting information regarding the intestinal microbiota from the gut to the brain, which is unsurprising when we consider that the first neural point of contact for the gut bacteria is the approximately 500 million neurons housed within the ENS and extending the full length of the gastrointestinal tract (Furness, 2006; Blackshaw et al., 2007). Pre-clinical studies carried out in mice have shown that the vagal nerve can be necessary for microbiota-gut-brain communication, but these findings seem to be dependent on the bacterial species in question. Both vagal dependence (Lyte et al., 2006; Bercik et al., 2011b; Bravo et al., 2011) and independence (Bercik et al., 2010, 2011a) have been demonstrated in rodent studies incorporating bacterial treatments with vagotomy.

The immune system is unquestionably involved in microbiota-gut-brain communication, but again the degree to which it is necessary for the transmission of specific information seems to depend upon the bacterial species under investigation. Early work has demonstrated that sub-clinical doses of pathogenic bacteria administered to mice could increase anxiety-like behavior in the absence of changes to peripheral cytokine levels (Lyte et al., 2006). A more recent study in immunocompromised animals demonstrated that B and T cell deficient Rag1 knockout mice, which have altered neurological and gut function, show normalization of some deficits following probiotic treatment (Smith et al., 2014).

Research using germ-free (GF) mice, animals raised and maintained in the total absence of bacteria, has provided perhaps the most persuasive evidence for a role of the microbiota in brain-gut signalling. GF animals show significantly altered immune, gastrointestinal, digestive, and metabolic function (for review see Luczynski et al., 2016). Moreover, the absence of microbes during development dramatically affects the brain-gut axis and central nervous system (CNS) circuitry and wiring, although exact mechanisms whereby these changes occur remain unknown. Indeed, GF animals show anxiolytic-like behavior (Diaz Heijtz et al., 2011; Neufeld et al., 2011; Clarke et al., 2013), reduced sociability (Desbonnet et al., 2014; Arentsen et al., 2015) and learning deficits (Gareau et al., 2011). GF mice also demonstrate heightened hypothalamic-pituitary-adrenal (HPA) axis reactivity following exposure to a stressor (Sudo et al., 2004), with stress hyperresponsivity known to induce CNS change. Most recently, it has been shown that GF animals have differences in brain structure, with hypermyelination observed in the prefrontal cortex (Hoban et al., 2016), and also marked differences in microglial cells (Erny et al., 2015). GF mice have more microglia throughout the brain compared to control mice, and these cells are clearly abnormal, with longer, more complex processes. In addition, the microglia of GF mice do not dis-