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Psychobiotics and Their Involvement in Mental Health

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Ingested prebiotic organic compounds stimulate the growth of intestinal probiotic bacteria [Saier and Mansour, 2005]. Pre- and probiotics represent important components in chains of complex biosynthetic and catabolic reactions that provide tremendous health benefits to the human or animal host organism [Singh et al., 2013; Vitetta et al., 2014]. These bacteria, which in part comprise the intestinal microbiome, do so by supplying nutrients such as short-chain fatty acids [Ohashi and Ushida, 2009] and precursors of enzyme cofactors including vitamin B_{12} [Capozzi et al., 2012]. They also successfully compete with potential pathogens [Corr et al., 2009] and stimulate host immune responses [Jirillo et al., 2012; Vitaliti et al., 2014]. They strongly influence either positively or negatively, depending on the bacterial types present, symptoms of numerous metabolic disorders including those responsible, in part, for the current obesity epidemic [Kotzampassi et al., 2014; Vitetta et al., 2014]. Therefore, not surprisingly, malnutrition in children has been shown to be associated with a lack of certain crucial gut bacteria [Subramanian et al., 2014]. It is now clear that the intestinal microbiome influences innumerable processes essential for the physical fitness of animals and humans.

The contribution of beneficial gut bacteria to human health is now scientifically well established [Shanahan et al., 2012]. The predominant well-studied probiotic bacteria are Firmicutes such as *Lactobacillus* species, Actinobacteria such as *Bifidobacterium* species and Bacteroidetes such as *Bacteroides* species. Several others, including Proteobacteria such as certain *Escherichia coli* strains, have also been shown to exhibit probiotic qualities. In fact, all of these microbes have beneficial consequences to the host organism. In only a few cases have the probiotic bacterial mechanisms of action been elucidated [Butel, 2014].

Since these bacteria influence so many aspects of human physiology, it should not be considered surprising that recent studies have revealed that they also have pronounced effects on brain function. Indeed, these bacteria produce tryptophan, a precursor of serotonin (5-hydroxytryptamine), tyrosine, a precursor of L-3,4-dihydroxyphenylalanine (DOPA) and dopamine, and other amino acids such as γ-amino butyric acid (GABA) and glycine, both of which serve as neurotransmitters in animals [Clarke et al., 2014b]. In fact, recent research has shown that the microbiota strongly influences brain activity and consequently behavior. It exerts effects on our moods, cognition and sensitivities to pain [Borre et al.,

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2014a]. While most of the mechanisms involved are still poorly defined, the molecular details of relevant processes are beginning to be understood.

For example, *Bifidobacterium breve*, in a strain-specific fashion, influences the compositions of brain fatty acids and lipids [Wall et al., 2012], altering and responding to changes in fatty acid metabolic rates [Barrett et al., 2012a]. Changes in phospholipid membrane compositions can alter neuronal sensitivities and neurotransmission in well-understood processes [Altrup et al., 2006].

Because of the emergence of 'mind-altering' probiotics relevant to psychiatry, a new term 'psychobiotics' has been coined to describe this exciting emerging field [Dinan et al., 2013]. A psychobiotic is defined as 'a live organism that, when ingested in adequate amounts, produces health benefits in patients suffering from a psychiatric illness' [Dinan et al., 2013]. The importance of bidirectional channels of communication between the brain and our microbiota is only now beginning to be realized. However, it is significant to note that these tiny microbes have been implicated in stress-related psychological disorders such as anxiety, autism and depression [Borre et al., 2014a; Dinan and Cryan, 2013]. In fact, it is already established that the gut microbiota, acquired during infancy, has an impact on the central nervous system and behavior from childhood on into adult life [Clarke et al., 2014a].

During fetal and early childhood development, probiotic organisms such as bifidobacteria and lactobacilli maintain a healthy balance between pro- and anti-inflammatory responses during their primary colonization stages [Vitaliti et al., 2014]. They play essential roles in the neuroimmune and neuroendocrine development of the host [Saulnier et al., 2013]. Microbially derived peptides and neuroactive mediators of neurotransmission (e.g. GABA, catecholamines and acetylcholine) induce synthesis and release of molecules by gut epithelial cells that modulate neural signaling [Bailey, 2014]. For example, while *Escherichia* and *Streptococcus* probiotic strains produce norepinephrine and serotonin, *Bifidobacterium* and *Lactobacillus* species release GABA and acetylcholine [Barrett et al., 2012b]. Different classes of nerve and immune cells express quantitatively different receptors for neurotransmitters [Lang and Bastian, 2007; Pannell et al., 2014], and consequently they respond differently to these compounds.

Neurotrophic factors produced by the gut microbiota trigger an immunogenic reaction in the infant, producing a mixture of local and systemic responses. Norepinephrine, for example, produces sympathetic proinflammatory effects at low-to-moderate systemic levels [Spengler et al., 1990], which in the presence of bacterial lipopolysaccharide, stimulate leukocytes to produce adrenocorticotropic hormone (corticotropin), a local peptide stress hormone [Harbour-McMenamin et al., 1985]. On the other hand, acetylcholine, produced by many probiotic bacteria, decreases proinflammatory cytokine release [Borovikova et al., 2000]. Bifidobacteria and lactobacilli lack bacterial lipopolysaccharide and adrenergic factors, thus decreasing the proinflammatory response during colonization. Changes in neuroplasticity can also occur depending on glial cell responses to GABA and serotonergic neurotransmitters [Pannell et al., 2014].

The gut microbiota has been shown to raise the levels of serotonin and serotonergic precursors in newborn mice during gut colonization [Clarke et al., 2013]. Aside from their psychological effects, these compounds depress indoleamine-pyrrole 2,3-dioxygenase, a proinflammatory enzyme, moderating hypothalamic-pituitary-adrenal production of cortisone and cortisone-related factors [Clarke et al., 2013]. The balance of pro-/anti-inflammatory pathways and the serotonergic regulatory mechanism operate synergistically, affecting appetite, sleep and mood, and modulating cortisol and cortisol-derivative release [Christmas et al., 2011]. Thus, the gut microbiota is likely to play a fundamental role in the interplay of neural, immune and hypothalamic-pituitary-adrenal development in young people [Dinan and Cryan, 2012].

It is not surprising that disruption of the human infant microbiota may lead to severe consequences. For example, extensive use of antibiotics has been shown to disrupt the microbial community in healthy infants, leading to microbial imbalance or dysbiosis. Alterations of the gut microbiota, especially in the formative years, have been implicated in altered brain development and plasticity. This can lead to changes in motor function and social behavior [Clarke et al., 2013; Diaz Heijtz et al., 2011; Sudo et al., 2004]. Moreover, breast-fed infants have a completely different microbial population than formula-fed babies with consequent health benefits that can last a lifetime [Goehring et al., 2014; Le Huerou-Luron et al., 2010].

The human animal is born with a surprisingly poorly developed nervous system compared to other mammals, including other primates. Very few (<10%) of the axonal nerve connections are established at birth relative to the human adult [Churchland and Sejnowski, 1988; Suhler and Churchland, 2011; Churchland, pers. commun.]. This serves as both a disadvantage (the human baby is far more altricial, being totally dependent on its mother) and

an advantage (it has a greater capacity to learn after birth during extensive neural development) [Churchland and Sejnowski, 1988]. It should not be surprising that development of the human microbiota occurs parallel to brain development and that the two normally develop in a mutually beneficial, cooperative fashion. Consequently, early-life perturbations in gut microbiota impact neurodevelopment, leading to the emergence of adverse mental health problems years later [Borre et al., 2014b].

The concept of parallel evolution, with complex microbial-neural interactions and interdependencies, opens up new therapeutic preventative approaches in early life to combat childhood and adult mental illnesses. Naturalistic medicine seeks to develop nutritional strategies to foster strong probiotic environments in patients, while the biotechnology industry investigates potential prebiotic drugs for practical applications [Dinan et al., 2013]. A detailed understanding of the evolutionary and physiological importance of the host-microbial system as a co-evolved ecosystem with interdependencies typical of complex, long-standing, multiorganismal systems must be emphasized. In this regard, it should be recalled that the adult human body contains roughly 10 times the number of bacterial cells as human cells [Macfarlane and Macfarlane, 1997]. The ecological, metabolic, physiological and psychological interrelationships are only now becoming fully recognized. This fertile field of study is ripe for further investigation.

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