GUT MICROBIOME AND NEUROCHEMICAL-BASED INTERACTIONS BETWEEN HOST, MICROBIOTA AND DIET: IMPLICATIONS FOR BEHAVIOR AND DISEASE

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The ability of the gut microbiome to influence various aspects of host health beyond more traditionally associated functions such as digestion of food is increasingly being recognized (Flint, 2012; Shreiner et al., 2015; Tuddenham and Sears, 2015). While interest over the past decade has grown dramatically, our understanding of the interface between the microbiome and host is still largely, but certainly not exclusively, based on *correlational* studies. Such correlational studies by definition do not demonstrate *causality*. Clearly, the need to identify the mechanisms by which the microbiome may influence the host remains paramount and an area for which the great bulk of research lies in the future.

This short review seeks to discuss one of those possible mechanisms by which the microbiota contained within the gastrointestinal system may impact host health, including behavior. It relies on the evolutionary relationship between the microbiota and host's neurophysiological system. This field of study has been termed microbial endocrinology. As will be discussed, the microbiota possesses the capacity to not only recognize neurochemicals produced by the host such as in response to stress, but also synthesize the same neurochemicals as produced by the host. The ability of the microbiome to produce and release neurochemicals that can influence the host, known as microbial endocrinology, provides for a mechanistic basis with which to examine the ability of stress to influence the health and behavior through the microbiome-gut-brain axis (Lyte, 2013a; Lyte and Cryan, 2014; Neuman et al., 2015).

MICROBIAL ENDOCRINOLOGY – CONCEPTUAL FRAMEWORK

Microbial endocrinology represents the intersection of two seemingly disparate fields, microbiology and neurobiology (Figure 1). The field of microbial endocrinology was founded in 1993 when the term was first coined (Lyte, 1993). Although the concept of microbial endocrinology was founded just over 2 decades ago, there has been published evidence by numerous investigators over the preceding six decades going back to 1930 that demonstrate the validity of uniting the fields of microbiology and neurobiology as a conceptual framework with which to understand interactions between the microbiota and the host, although at the time it was not conceived that a host-derived neurochemical could interact with a prokaryotic microorganism such as the infectious bacterium *Clostridium perfringens* (Lyte, 2010a).

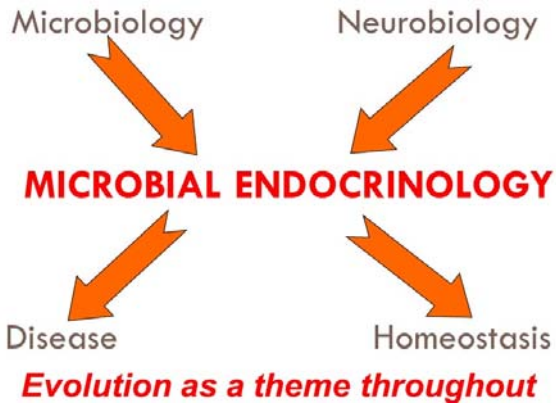

Figure 1. Conceptual basis of microbial endocrinology.

It is somewhat surprising to learn that what are often most thought of as exclusively mammalian in origin are in fact found widely disseminated throughout nature. This is expressly the case for a wide spectrum of neurochemicals extending from epinephrine to somatostatin (LeRoith et al., 1986; Lenard, 1992; Lyte, 2010a). A comprehensive analysis of the wide spectrum of neurochemicals and related cognate receptors that have been isolated form microorganisms highlights the presence in microorganisms of what are otherwise thought to be more commonly associated with mammalian systems (Roshchina, 2010). In general, the precise role of these neuroendocrine hormones in bacterial physiology is largely unknown. The diverse nature of these neurochemicals strongly suggests that from an evolutionary perspective the possession of what are normally considered to be specific to vertebrates implies that microorganisms have a means to recognize neurohormones within a vertebrate host and initiate changes in physiology that would prove advantageous to its survival.

ANATOMICAL ASSOCIATIONS THAT FOSTER MICROBIAL ENDOCRINOLOGY

The question must be asked if there is a spatial relationship between the gut microbiota and elements of the host nervous system that would enable interactions that are based on a shared neurochemistry. It is perhaps under-appreciated by most microbiologists that the gut is a highly innervated organ that possesses its own nervous system known as the enteric nervous system (ENS) that is in constant communication with the central nervous system (CNS) through nerves such as the vagus which directly connect portions of the gut to the brain (Figure 2).

The ENS is composed of over 500 million neurons. The extensive nature of this network is best shown in Figure 3 which demonstrates that the innervation extends not only to the tips of the villi themselves (Figure 3A) but also around the base of the crypts (Figure 3B) (Powley et al., 2011). It is through this ENS-vagus connection that information derived from elements of the ENS that innervate the gut is transmitted to the brain (Furness et al., 2014). Further contributing to the amount of information obtained in the gut are the luminal epithelial chemosensors, which can respond to and transmit information regarding bacterial metabolites such as neuroactive compounds that are contained within the luminal space (Breer et al., 2012). This gut-to-brain communication

has been the subject of intensive study for many years and is now recognized to play an important role in the ability of gut-related pathologies to also result in mental health–related issues such as depression (Foster and McVey Neufeld, 2013). The inclusion and recognition that microorganisms interact with elements of the ENS and thereby contribute to the information that is received by the brain concerning the physiological state of the gut has led to the relatively new field of study known as the microbiota-gut-brain axis (Lyte and Cryan, 2014).

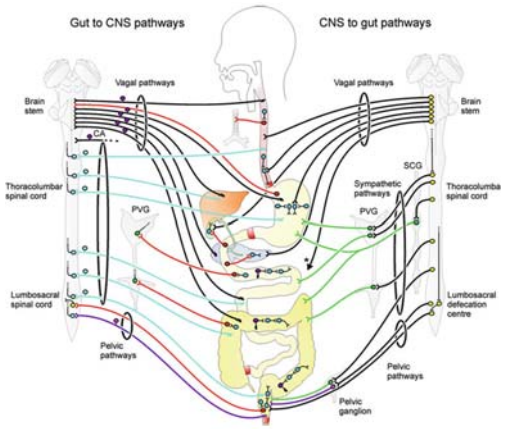

Figure 2. Innervation of gastrointestinal tract from Furness, 2014.

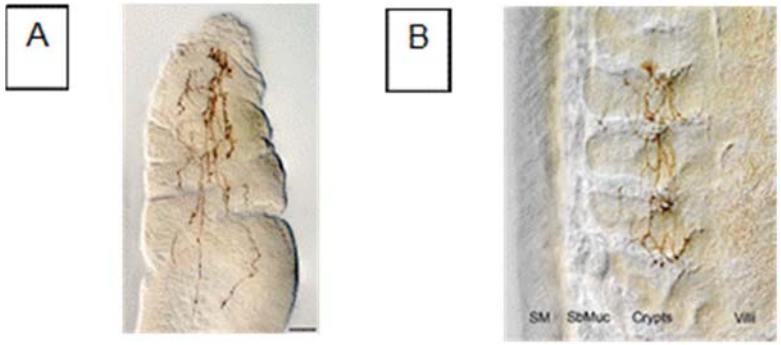

Figure 3. Presence of afferents in the intestinal villi (A) and crypts (B). From Powley, 2011.

Indeed, one of the most dramatic examples of how information that is gathered in the gut by components of the ENS can selectively influence the brain was shown following the interruption of the vagal nerve connection between the gut and brain by a procedure known as sub-diaphragmatic deafferentation (Klarer et al., 2014). Following this surgical procedure which involves transection of the vagus nerve, it was shown that specific behavioral responses of the animal, such as anxiety-like behavior or learned fear, could be selectively affected depending on whether the information from the vagal villus or the vagal crypt efferents were involved (Klarer et al., 2014). While this points out that “bottom-up” information collected by the components of the ENS have effects outside of the gut, left unanswered is the question of what in the lumen of the gut, namely the microbiota, may have on the information that is gathered by these ENS elements.

STRESS: THE PROTOYPICAL EXAMPLE OF MICROBIAL ENDOCRINOLOGY

To date, one of the most potent neurophysiological events that have been shown to influence host health, specifically susceptibility to infectious disease, and behavior is that of stress. Numerous studies have purported to show that stress can affect gut microbiota composition, influence microbiota-gut-brain communication, and result in behavioral alteration (Grenham et al., 2011; Cryan and Dinan, 2012; Collins et al., 2013). Both physical and psychosocial stress, as well as alteration of circadian rhythm, have been shown to alter microbiota community structure within the gut (Bailey et al., 2011; Bangsgaard Bendtsen et al., 2012; Thaiss et al., 2014).

There is a common evolutionary pathway in which stress-related neurochemicals first evolved in bacteria and, through lateral gene transfer, were acquired by mammals (Iyer et al., 2004). This means that a *mechanistic bi-directional* signaling pathway for these neurochemicals exists between gut microbiota and the host in response to stress as shown in Figure 4.

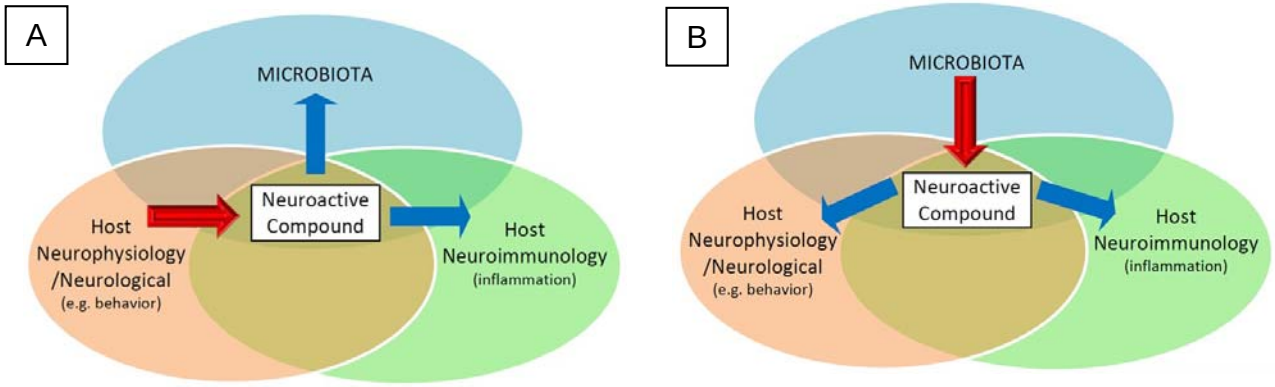

Figure 4. Bi-directional nature of microbial endocrinology in which neurochemicals produced by the host can influence the microbiota (A) and the very same neurochemicals produced by the microbiota can influence the host (B). The evolutionary-based neurochemical signaling pathway between microbiota and host means that a neurochemical(s) produced by the host can influence the microbiota (A) and at the same time a neurochemical(s) produced by the microbiota can, in turn, influence the host (B).

The microbiota community structure within the gut can rapidly change due to influx of host stress-related neurochemicals into the lumen. One of the principal classes of neurochemicals produced during periods of stress is the biogenic amines, notably the catecholamine family (dopamine, norepinephrine and epinephrine). Bacteria were first shown to be responsive to the catecholamines as reflected by changes in growth (Lyte and Ernst, 1992; Kinney et al., 1999; Roberts et al., 2002; Vlisidou et al., 2004), gene expression (Nguyen and Lyte, 1997; Anderson and Armstrong, 2006; Oneal et al., 2008) and transfer (Peterson et al., 2011). Release of catecholamines from neurotoxin-injured enteric neurons into the intestinal lumen result in the rapid alteration of microbiota

community from one dominated by Gram-positive taxa to one dominated by Gram-negative taxa (Lyte and Bailey, 1997). Further evidence of the association of neuronal activity to microbiota composition came from the observation that as injured nerves re-healed over a two week period, the microbiota community structure returned to normal (Lyte and Bailey, 1997). Remarkably, gut bacteria can also produce the very same neurochemicals produced by the host. For example, the *in vivo* production by gut bacteria of physiological levels of norepinephrine and dopamine capable of affecting host physiology has been observed (Asano et al., 2012). This further highlights the bi-directional nature of host-microbial interaction.

MICROBIAL ENDOCRINOLOGY AND INFECTIOUS DISEASE

The ability of infectious microorganisms to respond to neurochemicals and alter growth and virulence has now been reported by a number of groups (Lyte et al., 1997a; Kinney et al., 1999; Vlisidou et al., 2004; Nakano et al., 2007b; Bearson et al., 2008; Sandrini et al., 2010; Freestone et al., 2012; Sandrini et al., 2014). Although the mechanisms governing the ability of neurochemicals such as the biogenic amines to modulate the growth and production of virulence-related factors have not yet been completely elucidated, recent results have shown the ability of biogenic amines such as norepinephrine to induce transcriptional changes in mRNA transcript levels for a number of genes in a number of respiratory and intestinal pathogens as well as increase the rate of conjugative transfer between enteric bacteria (Nakano et al., 2007a; Oneal et al., 2008; Peterson et al., 2011).

From a clinical standpoint the ability of pharmacologically-relevant concentrations of neurochemicals, such as the catecholamines and related analogs (i.e. inotropes based on catecholamine structure such as dobutamine) have their greatest impact through the induction of biofilms. Early work demonstrated that dopamine and dobutamine, both used in the clinical intensive care setting for the support of cardiovascular and renal function, could induce biofilm formation from exceedingly low inocula of *Staphylococcus epidermidis* in physiologically-relevant plasma containing medium on materials used in the manufacture of indwelling medical devices (Lyte et al., 2003). Subsequent work has shown that catecholamines can induce the formation of biofilms by *Pseudomonas aeruginosa* which may provide a mechanistic explanation for its prevalence in ventilator-associated pneumonia (Freestone et al., 2012). Recent reviews have addressed the numerous and increasing number of studies which have examined the ability of neurochemicals to influence the pathogenesis of infectious disease through direct interactions with microorganisms, both prokaryotic and eukaryotic (Clemons et al., 2010; Lyte, 2015; Sandrini et al., 2015).

DIET AND BEHAVIOR – ROLE OF THE MICROBIOTA-GUT-BRAIN AXIS AND MICROBIAL ENDOCRINOLOGY AS A MEDIATING MECHANISM

The concept that bacteria in the gut can communicate with the brain thereby influencing behavior, and that the host nervous system can, in turn, influence the composition of the gut microbiota, has given rise to the concept of a microbiota-gut-brain

axis (Lyte and Cryan, 2014). An ever-growing number of studies have demonstrated the ability of bacteria to influence brain function for which a number of possible mechanistic routes have been proposed (Bravo et al., 2011; Lyte, 2011; Neufeld et al., 2011; Reid, 2011; Cryan and Dinan, 2012; Collins et al., 2013; Desbonnet et al., 2013; Lyte, 2013b; Wall et al., 2014). Due to shared neurochemicals between host and microbe, microbial endocrinology has been proposed as one of the mechanisms by which such reciprocal communication between brain (nervous system) and microorganisms in the gut can occur (Lyte, 2014b, a).

The ability of diet to alter the composition of the microbiome has been recognized for decades (for review see (Flint, 2012)). What is not known, however, is if diet-induced changes in the microbiome can directly and in a causal manner lead to changes in behavior via microbial endocrinology-based mechanisms. Such a proposal, that diet can influence bacteria to produce neurochemicals that interact with the ENS, or directly are absorbed into the portal circulation, would represent a new mechanism by which nutrition could impact the host and ultimately influence various aspects of behavior as well as food preferences and appetite. It should be noted that it has now been proposed that a positive feedback loop exists between the host's dietary preferences and the microbiome (Norris et al., 2013). The Norris et al. paper therefore represents one of the first proposals, along with that proposed earlier (Lyte, 2010b), that suggests that the nutritive state of the host and the microbiome influence one another through bi-directional microbial-based mechanisms that had not been previously envisioned as part of nutrition.

The presence of neurochemicals in plants and processed foods has long been recognized. For example, the source material used to demonstrate the biological role of the neurotransmitter acetylcholine in muscle contraction was obtained from the leaves of the common nettle before it was ever isolated from a vertebrate source (Roshchina, 2010). From a nutritional standpoint, these neurochemicals, which include the biogenic amines, have not been viewed as a significant dietary energy source. Their impact on health and well-being has in the past been primarily restricted to direct physiological or patho-physiological effects in the host such as following the consumption of foods containing vasoactive substances. The ability to demonstrate that the nutritional value of a particular food may extend beyond the more commonly accepted understanding of components such as carbon and nitrogen content (as well as protein content as typical examples) to that of providing a common signaling mechanism, namely neurochemicals, between the microbiome and host would add to our understanding how diet may affect the composition of the microbiota. That in turn would aid in deciphering the mechanisms by which the microbiota-gut-brain axis is capable of modulating behavior.

Figure 5 illustrates how the proposed neurochemical-based facets of diet and microbiome can interact to influence the microbiota-gut-brain axis and thereby influence cognitive processes that ultimately result in modulation of behavior. These involve microbial endocrinology-based pathways by which neurochemical compounds produced by both the host and the microbiota can serve as a mechanism by which the brain and behavior can be modulated within the microbiota-gut-brain axis (Lyte, 2013a).

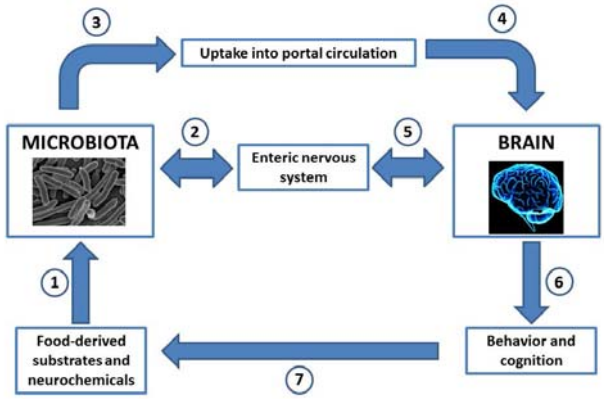

Figure 5. Microbial endocrinology-based pathways by which diet can influence the microbiota-gut brain axis. From Lyte, 2013a.

As shown in Figure 5, food ingested by the host contains both the substrates needed for neurochemical production by the host and the microbiota as well as fully functional neuroactive components (1). The microbiota in the gut is capable of either forming neurochemicals from the substrates present in the ingested food; or responding to the neuroactive food components themselves; or responding to neurochemicals secreted into the gut by components of the host enteric nervous system (2). Neurochemicals produced by the microbiota in the gut have two pathways by which to influence the host; they can either be taken up from the gut into the portal circulation (3) or they can directly interact with receptors found on components of the enteric nervous system which innervates the complete length of the gastrointestinal tract (2). Once in the portal circulation, microbiota-derived neurochemicals can influence components of the nervous system and ultimately the brain (4). Microbiota-derived neurochemicals can also influence components of the nervous system such as the brain through ENS-CNS communication (5). The result of either pathway (4) or (5) on the brain may result in an alteration of behavior or cognition (6) as well as food preferences and appetite (7) [82-85]. This should not be viewed as a one-way direction of only gut-to-brain since the brain may influence the composition of the microbiota through the specific release of neurochemicals into the gut lumen (2).

CONCLUDING STATEMENT

The ability of microorganisms to both produce and recognize the exact same neurochemicals that mammalian hosts (as well as plants and insects) produce offers a new mechanistic pathway by which to understand the ability of the microbiota to influence both behavior and disease.

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