Gut-Brain Communication: Major Mechanisms in Mental-Emotional Health and Disease

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> I strongly feel that it is the engagement of the gut and its microbiome that plays a major role in determining the intensity, duration, and uniqueness of our emotional feelings.
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This article will review the gut-brain axis via the vagus nerve and microbial metabolic products including endotoxin and short-chain fatty acids, hormones, neuropeptides, and adipokines. Two-way communication between the gut brain (enteric nervous system or ENS) and the central nervous system (CNS) is a continuous process which optimizes functioning in both systems. In addition, the gut microbiota can be thought of as a distinct organ, which initiates and modifies much of this cross talk. The gut microbiota includes oral, esophageal, gastric, small intestinal, and colonic flora. The microbiome (genome of the gut flora) consists of about four million genes.

The term *holobiome* is defined as the sum of the approximately 26,000 human and the resident microbial genes. Clearly, humans are getting a free ride by relying on the gut flora to modify our genetic functions. In fact, there are over 100 microbial genes for every one human gene. The metabolome - the sum of metabolic products produced by the microbiome – comprises close to half of the total metabolites in human blood. Leo Galland, MD puts it succinctly in his 2014 review article: "The gut microbiome can be viewed as an anaerobic bioreactor programmed to synthesize molecules which direct the mammalian immune system, modify the mammalian epigenome and regulate host metabolism" (Galland, 2014). The gut microbiome is essential for the maturation and development of the enteric nervous system. These effects include both density and proper activity of the enteric neurons.

Cross talk between the gut and brain occurs through the vagus nerve, the metabolome, and cytokines. The autonomic nervous system is the major anatomical connection between the enteric nervous system (ENS) and the central nervous system (CNS). The vast majority (90%) of the impulses are sensory from ENS to CNS. The shape and consistency of the bolus as well as the pressure of the bolus against the gut mucosa is transmitted through the vagus nerve. Additional information about food composition, levels of inflammation, and quality of the microbiota is transmitted. This feedback helps to fine-tune eating behavior, mood, blood glucose, digestive secretion, absorption, and gut motility via the production of serotonin and other neuropeptides by enteroendocrine cells (EECs). Taste receptors throughout the length of the gut respond to food and stimulate production of various neuropeptides that have local and distant effects. These receptors are located on EECs and dendritic cells scattered throughout the mucosa. For example, the stimulation of bitter receptors triggers release of ghrelin, which upregulates appetite when it reaches the CNS. Mechanoreceptors are stimulated by shearing forces as the bolus moves through the gut and stimulate the EECs to release serotonin, which modifies both vagal and ENS function. As Emeran Mayer, MD, states: "the gut is the NSA… the vagus nerve is the information highway for gut-brain traffic." The ENS optimizes motility, secretion, and mucosal blood flow as well as detecting toxins and irritants.

Microbial Lipopolysaccharides, Cytokines, and Inflammation

Remarkably, forty percent of the circulating metabolites in human blood are microbiota derived. Gut microbial metabolites, such as lipopolysaccharide (LPS or endotoxin), have major effects on vagal input to the CNS with wide-ranging effects on mood, cognition, intestinal permeability, and inflammation (Grigoleit, 2011). Lipopolysaccharide is a component of the outer membrane of gram negative bacterial cell walls. There are one million copies of LPS in each gram-negative microbe (Quig, 2016), and these are released from both growing and dead bacteria (Guerville, 2016). Release may also be triggered by antibiotic therapy. Adults have approximately one gram of total gut LPS (Erridge, 2007) (Bested,

2013). Locally, LPS is a significant stimulus of the zonulin pathway, which induces hyperpermeability. When absorbed into the portal vein, LPS has major effects on the liver; and, when excessive, LPS serum levels rise and have far reaching effects. LPS and inflammatory cytokines in serum can upregulate TNF alpha, IL-1B, and IL-6 in the brain (Quig, 2016). Clearly, intestinal bacteria do not need to cross the blood brain barrier in order to influence the CNS.

Not all bacterial LPS is the same. For example, Enterobacter-derived LPS may be 1000 times more potent than LPS derived from other gram negative bacteria (Mayer, 2016). The microbial balance affects body habitus, and obesity multiplies the volume of LPS. These levels may be two to three times higher in the obese population compared to lean individuals. LPS binding protein can be measured in serum and is considered a useful inflammatory marker.

How LPS Is Metabolized

In the neonate, LPS is bound and inactivated by a bacterial pattern recognition receptor CD14 found in human breast milk. CD14 is not detectable in commercial cow's milk or infant formula but is found in bovine colostrum. Lactoferrin in breast milk also binds to LPS (Guerville, 2016). After weaning, LPS binds to Toll-like receptor 4 (TLR-4) on intestinal epithelial cells. In addition, endosomal SIgA inactivates LPS, thereby reducing the NF-KB pathway and its cascade of proinflammatory cytokines: interferon, IL-6, TNF alpha (Boullier, 2009) (Fernandez, 2003). Mucins (from goblet cells) and antimicrobial peptides such as defensins (from Paneth cells) act on gram negative bacteria and, therefore, reduce exposure of intestinal epithelia to LPS. Defensins also alter the structure of developing bacterial cell walls to weaken the gram-negative microbes (Sass, 2010).

Intestinal alkaline phosphatase is a brush border enzyme secreted into blood and the intestinal lumen. It regulates lipid absorption, duodenal pH, and removal of LPS. Also, produced in the liver, phosphatase helps reduce LPS arriving via the portal vein. When LPS from gut bacteria is absorbed into the bloodstream at slightly higher levels, the alkaline phosphatase mechanism may not be adequate, and serum levels of LPS rise. The ensuing inflammatory cascade has emotional and cognitive effects. These effects may include anxiety, depression, and cognitive effects as well as visceral hypersensitivity (Grigoleit, 2011).

In addition to this LPS effect, adipose tissue in obese humans contains a tenfold increase in macrophages – 50% vs 5%. Increased systemic inflammation can trigger CNS inflammation by activating microglia (Hannestad, 2012). When CNS inflammation is initiated, it is difficult to turn off (Fenn, 2014). Inflamm-ageing is a term for the chronic inflammatory state affecting many tissues including the brain (Franceschi, 2000).

The ENS, Microbiome, and Neurotransmitter Synthesis

Gut bacteria strongly affect both the peripheral and central nervous systems by production of functionally active neurotransmitters: serotonin, dopamine, gamma-aminobutyric acid, acetylcholine, epinephrine (Bailey, 2011). Bacteria may synthesize neurotransmitters directly (e.g., gamma-amino butyric acid) or may modulate the synthesis of neurotransmitters (e.g., dopamine, norepinephrine, and brain-derived neurotropic factor).

The composition of the microbiota largely determines the levels of tryptophan in the systemic circulation and, indirectly, the levels of serotonin in the brain. Also, the composition of the microbiota determines the levels and nature of tryptophan catabolites, which in turn have profound effects on epithelial barrier integrity. This determines whether there will be an inflammatory or tolerogenic environment in the gut and other organs (Leclercq, 2016) (Galland, 2014).

Short Chain Fatty Acids – A Major Class of ENS to CNS Cross-Talk Molecules

Short-chain fatty acids (SCFAs) are produced by anaerobic bacterial fermentation of either dietary soluble fiber or intestinal mucin. Clostridia (Firmicutes phylum) are the most studied in this respect (Barcenilla, 2000), yet Lactobacillus and Bifidobacter species also produce butyrate by a "complex interspecies cross-feeding mechanisms" (Rios-Covian, 2015). The major SCFAs butyrate, propionate, and acetate are small organic acids with less than six carbon atoms. Measurement of fecal SCFAs may not fully represent concentrations in the colon because much of it is quickly taken up by colonocytes. In addition, new research is finding that certain Clostridia adhere tenaciously to the colonic mucin and are not often present in stool samples.

Butyrate is an energy source for colonocytes via beta oxidation. By this mechanism, butyrate decreases appetite and reduces the risk of immune-modulated disease by balancing inflammation. Butyrate is essential in neuroprotection and modulates microglial NF-KB signaling and optimizes apoptosis (Sun, 2016) (Ferrante, 2003). In addition to production by gut bacteria, significant quantities of butyrate are present in human breast milk as well as butter, full fat cow's milk, and most cheeses. Parmesan, as well as goat- and sheep-derived cheeses, may be especially rich in butyrate (Jaeggi, 2003).

A unique liver-specific transporter carries SCFAs into hepatocytes (Shin, 2007). Other SCFA transporters are present on the luminal aspect of enterocytes. Two types, monocarboxylate transporters and sodium coupled monocarboxylate transporters, are also located on brain neurons, astrocytes (Vijay, 2014), microglia (Moreira, 2009), oligodendrocytes (Lee, 2012), and the endothelia of the blood-brain barrier (Bergesen, 2002).

The effects of SCFAs in the gut and the brain are due to G protein coupling receptor signaling and inhibition of histone deacetylases, promoting gene expression in human cells (Stilling, 2016). SCFAs are absorbed into the systemic circulation and cross the blood-brain barrier. In the CNS, these fatty acids modulate the inflammatory cascade (Saint-Georges-Chaumet, 2015). A recent study suggests that butyrate is a major factor controlling the permeability of the blood-brain barrier via its effect on levels of the tight junction proteins claudin and occludin (Braniste, 2014).

Butyric acid is also partially responsible for the modest acidity of the colon (pH 5.7-6.7). Beta-hydroxybutyric acid and lactic acid are related molecules. A ketogenic diet induced by very low carbohydrate intake may raise the blood and cerebrospinal fluid content of beta-hydroxybutyric acid and mimic some of ➤

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the effects of butyric acid (Iriki, 2009). SCFAs are mediators of the cross talk among microbes, mitochondria, and the host. Along with microbially deconjugated secondary bile metabolites, the SCFAs react with receptors on EECs. This influences serotonin levels and therefore modulates colonic motility (Yano, 2015) (Reigstad, 2015), mood (anxiety), sleep, and pain sensitivity. Some of the signaling is also mediated by more direct vagal stimulation via 5 HT3 receptors (Fukumoto, 2003).

SCFAs, Microbes, Diabesity, and CNS Inflammation

Microbial metabolites including butyrate have crucial regulatory effects on the health of nearly every organ system (O'Mahony, 2015). In experimental animals on a high-fat diet, there is a reduction in obesity and insulin resistance after dietary supplementation with butyrate (Gao, 2009). This decrease in diabesity is likely due to down-regulation of the peroxisome proliferator-activated receptor gamma (den Besten, 2015). This down-regulation promotes a shift from lipid synthesis to lipid oxidation. The SCFAs butyrate and propionate have been shown to have the most significant effects on this mechanism (Lin, 2012). When visceral adiposity enlarges, it increases production of free fatty acids and adipokines, such as tumor necrosis factor-α (TNF-α), resistin, and interleukin-6 (IL-6), and decreases levels of insulin-sensitizing adiponectin. The adipokines stimulate the tenfold increase in the percentage of macrophages in the obese visceral fat. In turn, these macrophages produce pro-inflammatory cytokines, inducing more chronic inflammation, exacerbating insulin resistance and systemic and CNS inflammation. The insulin resistance and elevated glucose can contribute to neurodegenerative changes (Cherbuin, 2012). Following high carbohydrate meals, rapid fluctuations in blood glucose deplete serotonin, dopamine, B vitamins, and magnesium. These changes contribute to glycation, insulin resistance, depression, and neurodegeneration (Geroldi, 2005) (Perlmutter, 2013).

Dr. Steven Sandberg-Lewis has been a practicing naturopathic physician for nearly 40 years in the Pacific Northwest region of the USA and a professor at the National University of Natural Medicine (NUNM) in Portland, Oregon since 1985. In 2010, he co-founded the SIBO Center at NUNM, which is one of only four centers in the USA for Small Intestine Bacterial Overgrowth diagnosis, treatment, education and research. He lectures frequently at functional medicine seminars, presents webinars, and is frequently interviewed on issues of digestive health and disease. He is the author or co-author of several *Townsend Letter* award-winning articles and the author of the medical textbook *Functional Gastroenterology: Assessing and Addressing the Causes of Functional Digestive Disorders* (NCNM Press), now in its second edition. In 2014, he was named one of the "Top Docs" in Portland monthly magazines yearly healthcare issue and in 2015 was inducted into the OANP/NUNM Hall of Fame.

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