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Invited Review

Mood and gut feelings

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ABSTRACT

Evidence is accumulating to suggest that gut microbes (microbiota) may be involved in neural development and function, both peripherally in the enteric nervous system and centrally in the brain. There is an increasing and intense current interest in the role that gut bacteria play in maintaining the health of the host. Altogether the mass of intestinal bacteria represents a virtual inner organ with 100 times the total genetic material contained in all the cells in the human body. Surprisingly, the characterization of this extraordinarily diverse population is only just beginning, since some 60% of these microbes have never been cultured. Commensal organisms live in a state of harmonious symbiosis with each other and their host, however, a disordered balance amongst gut microbes is now thought to be an associated or even causal factor for chronic medical conditions as varied as obesity and inflammatory bowel diseases. While evidence is still limited in psychiatric illnesses, there are rapidly coalescing clusters of evidence which point to the possibility that variations in the composition of gut microbes may be associated with changes in the normal functioning of the nervous system. This review focuses on these data and suggests that the concept should be explored further to increase our understanding of mood disorders, and possibly even uncover missing links to a number of co-morbid medical diseases.

1. Introduction

Psychiatric disorders which are on the increase globally, already rank among the leading causes of disability, and are expected to take over first place within the next few years. Indeed, the World Health Report 2001 cites depression as causing the largest amount of disability worldwide (disability adjusted life years-DALYs) and in 2004 Ustun et al. stated that depression was the fourth leading cause of disease burden but represents the largest amount of non-fatal burden globally (WHO, 2001;Ustun et al., 2004). In addition, there is extensive epidemiological evidence to support the view that significant co-morbidity exists between many chronic medical and psychiatric diseases, especially mood disorders (Moussavi et al., 2007; Van Lieshout et al., 2008). The severity and prognosis of medical illness are substantially affected by the presence or absence of co-morbid depression. For example, depression is a significant risk factor for myocardial infarction (Rosengren et al., 2004) and its presence at the time of infarction predicts a greater than threefold increase in likely death from cardiac causes within 5 years (Lesperance et al., 2002). Individuals with depression also have higher rates of obesity, hypertension, dyslipidemia, metabolic syndrome and diabetes than the general population (Chengappa et al., 2004; Heiskanen et al., 2006).

Therefore, a better understanding of the biology of mood disorders is critically important not only to provide more effective treatment to patients with these conditions but also to those with chronic co-morbid medical illnesses.

Recent dramatic scientific advances in molecular biology and their application to the study of the human genome have produced much evidence to support the genetic basis of a number of chronic diseases. However, the results are fraught with difficulty of interpretation as well as the knowledge that most of these diseases are polygenic in origin. Indeed the solution to some of the conundra of causation of chronic diseases may lie in greater understanding of the consequences of gene-environment interactions (Cooper, 2003). As a result, the field of epigenetics is expanding explosively and is being applied to psychiatric disorders (Mill and Petronis, 2007; Tsankova et al., 2007).

We believe that one of the most significant areas that need to be investigated in terms of potential environmental factors contributing to both mood disorders and chronic diseases is the external

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milieu of microbes found in the intestine. In this review we highlight the evidence that is coming together to support the contention that the gut microbiome may be playing a role in neuronal development and plasticity, modulating pain perception and even behavior. This fertile area for exploratory research may shed some light on the causes of, and eventually offer novel therapeutic approaches to, mood disorders and the medical disorders that are often co-morbidly associated with them. (Fig. 1).

2. The gut microbiome

The human gut is sterile at birth. Immediately after birth, it is colonized by numerous types of microorganisms. In the first weeks of life, tremendous temporal and inter-individual variation is evident in the infant's microbial populations (microbiome). By 1 year of age, while babies retain their unique bacterial profiles, these converge toward a profile characteristic of the adult individual gastrointestinal tract (Palmer et al., 2007). While significant changes may occur in things such as disease, infections, stress, and diet in the intestinal microbiome, this tends to revert to that which was established in infancy if the external factors change. Traditional methods that rely on the isolation of microbes in culture, although invaluable to clinical microbiology, cannot address ecological questions because of the complexity of intestinal microbial communities. Indeed, by far the majority of these microbes are not readily cultured and are generally referred to as 'unculturable.' Recent advances in molecular-based technologies, however, now permit genetic analysis of complex microbial populations without

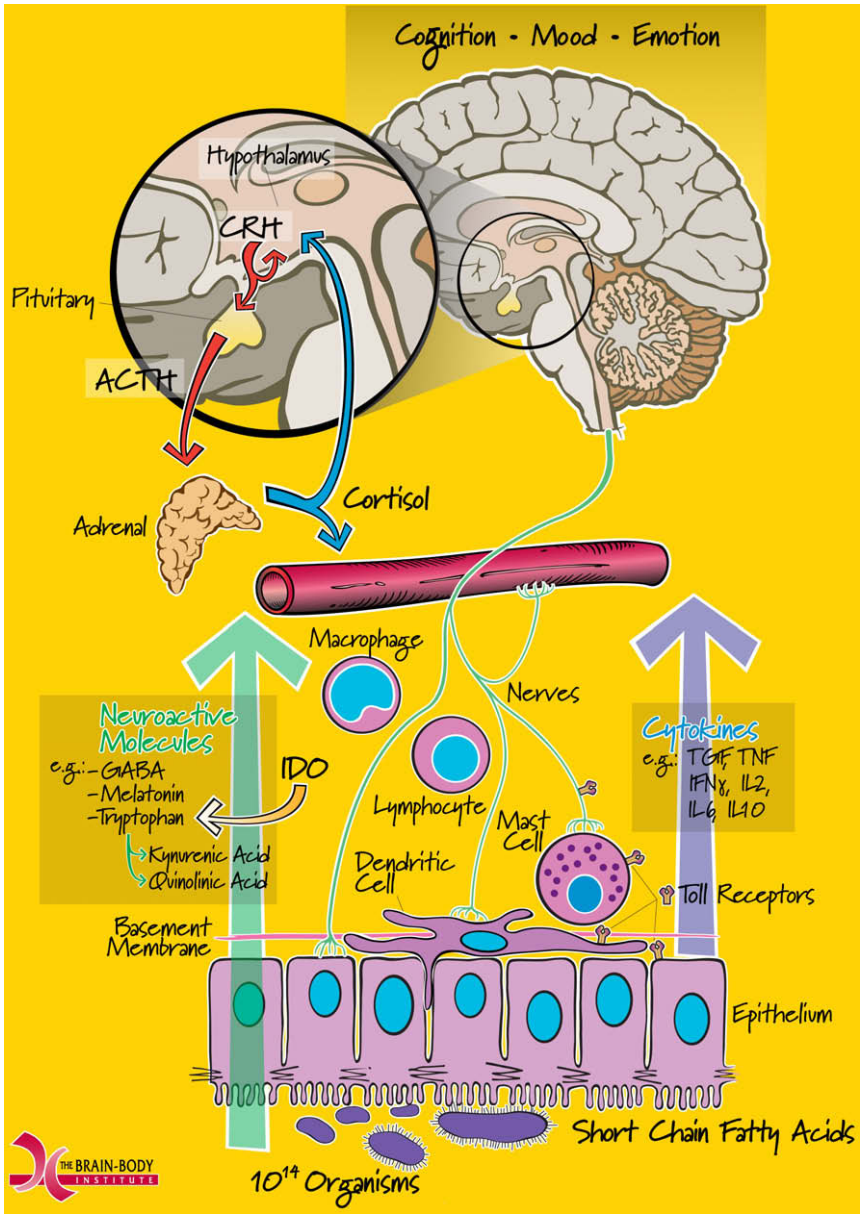

Fig. 1. Proposed mechanisms and pathways through which intestinal commensal microorganisms may influence the peripheral enteric and central nervous systems. The 10^{14} bacteria which together make up the intestinal microbiome are engaged in all the complex interactions with each other and the local tissue and in a balanced manner maintain normal homeostasis. They synthesize a vast array of biologically and neuroactive molecules including an almost complete array of neurotransmitters such as GABA, and through fermentation, a panoply of short chain fatty acids all of which have known and unknown effects on the nervous system. The direct and indirect effects of the intestinal microbiome on the intestinal epithelium, the local mucosal immune system and their cytokines, as well as the enteric nervous system, conspire to affect the afferent neuronal pathways to the brain. In turn, through complex interactional effects upon the HPA axis and especially CNS target structures affected by tractus solitarius activation in the brain stem, increasing evidence is pointing towards an influence by the intestinal microbiota upon cognition and mood.

the need for cultivation. As a result, gut microbiota have now been estimated to consist of at least 1800 genera and up to 40,000 species of bacteria based on the analysis of 16S ribosomal RNA. They have an estimated mass of 1–2 kg, number 100 trillion (Frank and Pace, 2008) and together possess 100 times the number of genes in the human genome (Kurokawa et al., 2007). Now that the human and many animal genomes have been unraveled, a significant worldwide effort is being invested in the characterization of the human microbiome (Kinross et al., 2008; Turnbaugh et al., 2007). While a limited number of metagenomic analyses of the human gut microbiome have been published already, much still needs to be done before we can compare individual analyses, or better still, look for abnormal patterns in disease. It should also be emphasized that almost all the work done so far in this area comes from analysis of fecal (and therefore largely colonic) samples, and very little information exists on the microbial content of the small intestine where considerable microbe-host biological interaction occurs.

3. Immune system and cytokines

The development of the intestinal immune system is largely dependent upon exposure to microorganisms (Umesaki et al., 1995). In germ free (GF) animals which have scanty lymphoid tissue and constitutively and are almost devoid of immune activity (Talham et al., 1999), association with certain individual selected microorganisms has been shown to be effective in generation of the complete repertoire of immune function. For example, colonization with the segmented filamentous bacterium was able to restore full functioning of the B and T cell compartments in the gut (Umesaki et al., 1995, 1999). In contrast, this was not achieved by colonization with a mixture of eight different bacterial strains (Schaedler's cocktail) (Talham et al., 1999). These findings illustrate the wide ranging biological importance of the indigenous intestinal microbiota. They also underscore the fact that the small intestine, often regarded as being relatively sterile (106 bacteria/g as opposed to the large bowel with 1014/g), has a major role to play in "inter-kingdom" signaling between the microbiome and the host (Hughes and Sperandio, 2008). While multiple pathways exist for bacteria to communicate with their host, one of them needs some emphasis: that of molecular pattern recognition by chemical structures (i.e., Toll-like receptors) on host cells. The ubiquitous distribution of these receptors on most structural as well as immune and inflammatory cells, includes neuronal localization (Rolls et al., 2007), thus allowing neurons to directly respond to bacterial and viral components. While the intestinal epithelium acts largely as a barrier to translocation of microorganisms into the internal milieu, the nervous system is prepared and capable of responding to such interactions. The reader should nevertheless recognize that many physiological ligands which are not related to microorganisms exist for Toll-like receptors.

Depression is associated with the presence of biomarkers of inflammation such as elevated IL-6, TNF and C reactive protein (Alesci et al., 2005). Similar elevated biomarkers of inflammation have also been seen in anxiety states and are in addition known to occur as a result of stress (Anisman and Merali, 2003). The temporal association between depression and inflammation has not been elucidated and we do not know whether such elevation is causally related to the development of depression and anxiety (Dantzer et al., 2008) or even whether it is in response to an as yet unknown infectious agent. The link between infectious diseases and psychiatric illness is not new. One has only to think of syphilis as an example of the host of central neurological deficits, including dementia, initiated through this infection. Lyme disease caused by another spirochaete, *Borrelia burgdorferii*, is associated with depressive symptoms in 26–66% of cases. (Fallon and Nields, 1994). While an infectious cause of mood disorders is not currently under mainstream discussion, elevated proinflammatory biomarkers of inflammation are themselves associated with so-called sickness behavior, a term used to describe behavioral changes secondary to inflammation caused by infections and fever such as disturbances of sleep, mood appetite, and fatigue (Hart, 1988). It is not clear whether peripherally produced inflammatory cytokines can directly affect brain function, although some can be transported into the brain (Banks, 2009) and specific receptors for cytokines exist within the CNS e.g., on circumventricular organs (Turrin and Rivest, 2004), and on endothelial cells (Quan and Banks, 2007; Schiltz and Sawchenko, 2003) Systemic cytokines have been shown to increase the permeability of the blood brain barrier (Boveri et al., 2006; Wong et al., 2004). Inflammatory cytokines have been shown to directly activate vagal afferents in the abdominal cavity and this type of activation is translated via the vagus nerve to the brain to induce a pyrexial response to endotoxin or infection (Hansen et al., 2001). The link between peripheral cytokines and CNS function is further supported by evidence that systemically injected inflammatory cytokines such as interferon alpha used in the treatment of hepatitis, or TNF and IL 1 used in the treatment of malignancies are associated with significant induction of depressive symptoms (Capuron et al., 2003; Fallon and Nields, 1994; Hauser et al., 2002) which can be prevented by antidepressant therapy (Musselman et al., 2001).

It has been suggested that the major pharmacological classes of antidepressant drugs may all work in part via the generation of perhaps the most potent immunoregulatory cytokine, IL-10, thereby suppressing inflammation and the CNS changes associated with depression (Maes, 2001). In this regard, it is interesting that the immunoregulatory effects of commensal organisms are also thought to occur through the generation of T regulatory cell populations and the synthesis and secretion of IL-10 (Ostman et al., 2006). Macpherson and Uhr (Macpherson and Uhr, 2004) showed that feeding of a commensal to GF mice resulted in local dendritic cell uptake and alteration of phenotype into one which promoted T reg production and IL-10 synthesis. We too have shown that feeding *Lactobacilli* spp. to conventional mice induces up-regulation of classic T reg production in the mucosal immune system, and subsequently in the spleen, from where wide spread systemic distribution occurs (Karimi et al., 2008). Ingestion of *Lactobacillus GG* has been suggested as a therapy in the management of atopic dermatitis and has been shown to up-regulate IL-10 in the plasma of patients (Pessi et al., 2000) suffering from this condition. While IL-10 has potent anti-inflammatory properties, it is also thought to act directly as an anti-nociceptive agent, indicating that it has broad neuro-immune effects (Duncker et al., 2008). Its effects on behavior remain unexplored, however, and it may be that the host response to the intestinal microbial balance may change the capacity and extent of regulation of inflammatory responses and in so doing may be intimately involved in the modulation of the expression of mood and behavior.

4. Role of gut microbiota in host metabolism

It is widely recognized that gut microbes are responsible for an enormous array of metabolic activities that include effects on the digestion of food and the production of a host of biologically active substances. Recent data suggest that gut microbiota also affect host metabolism, have an impact on energy storage and may therefore be an important environmental factor in the development of obesity and type 2 diabetes (Turnbaugh et al., 2006). These observations are relevant to the microbiome-psychiatric illness link because of the increased incidence of obesity and metabolic syn-

drome associated with mood disorders (Fagiolini et al., 2003; McElroy et al., 2002; Taylor et al., 2008). Furthermore, obesity itself is accompanied by an elevated serum inflammatory cytokine profile (Trayhurn and Wood, 2004). Fasting intestinal adipose factor (FIAF) is a circulating lipoprotein lipase inhibitor synthesized by intestinal epithelium in response to exposure to commensal gut microbiota and regulates the deposition of triglycerides in the liver and adipocytes, thus underlining the role of gut microbes as an important environmental factor influencing energy harvest and storage (Backhed et al., 2004). Other evidence demonstrating an important relationship between the gut microbiome and the development of obesity in humans has also been reported (Kinross et al., 2008; Turnbaugh et al., 2007) and confirmation of these findings is awaited.

5. Microbiota and the nervous system

While the role of gut microbiota in influencing brain and nerve function may not be strikingly obvious at first glance, recent research in several different disciplinary fields suggests that intestinal microbiota may be intimately and constitutively involved in modulation of both central and peripheral nerve function. A good example of this influence can be found in clinical medicine in hepatic failure. Hepatic encephalopathyis a commonly encountered medical condition consequent to hepatic failure, manifestations of which include impaired cognition, tremors, dementia and even coma. The gold standard of medical treatment is oral, non-absorbable antibiotics which work via reduction of urease producing bacteria, and therefore the production of ammonia and other neurotoxic metabolites (Strauss and da Costa, 1998). Recent research in several different disciplinary fields suggests that intestinal microbiota may be intimately and constitutively involved in modulation of both central and peripheral nerve function. For example, the reader is referred to a recent extensive review on the gut-brain axis (Collins and Bercik, 2009).

5.1. Microbiota and the hypothalamic–pituitary–adrenal (HPA) axis

An impaired HPA system is a well-known manifestation of depression and has also long been suggested as a causal factor in disease etiology: the "hypothalamic–pituitary–cortisol hypothesis"(Belmaker and Agam, 2008). Patients with depression often show elevated plasma cortisol levels, elevated corticotrophin releasing hormone (CRH) levels in the cerebrospinal fluid and increased levels of CRH messenger RNA and protein in limbic brain regions (Burke et al., 2005; Merali et al., 2004). In studies using dexamethasone to evaluate the sensitivity of the hypothalamus to feedback signals for the shutdown of CRH release, the normal cortisol-suppression is absent in about half of the most severely depressed patients (Carroll et al., 2007). Antidepressant-induced clinical remission is accompanied by reversal of some of these abnormalities (Holsboer, 2001).

Stress, also linked to perturbation of the HPA axis, is considered to be involved causally in mood disorders and has been shown to change the general composition of the gut microbiome (O'Mahony et al., 2008). Indeed the elucidation of the effects of stress on the microbiome has given rise to a new field in microbiology, termed 'Microbial endocrinology' (Freestone et al., 2008). Stress can promote the growth of pathogenic Escherichia coli O157:H7 (Freestone et al., 2008) via interaction with host epinephrine/norepinephrine and the quorum sensing molecule, QseC sensor kinase (Hughes and Sperandio, 2008). This signaling activates transcription of virulence genes in the bacteria and can be blocked specifically by adrenergic antagonists (Clarke et al., 2006). To begin to clarify the role of gut microbiota in HPA axis function, Sudo and colleagues (Sudo et al., 2004) compared the response of the HPA axis to stress in GF, specific pathogen free (SPF) and gnotobiotic mice that were mono-associated with a single bacterium. Restraint stress caused an exaggerated ACTH and corticosterone elevation in GF rather than SPF mice. This hyper-response of the HPA axis was reversed by mono-association with a single organism, *Bifidobacterium infantis*, which is a predominant bacterium in the infant gut and a commonly used probiotic organism (O'Mahony et al., 2005). Perhaps one of the most striking observations was that the microbe-induced reversal of the HPA axis set-point extended into adulthood, but only if bacterial colonization occurred before the animals reached 6 weeks of age. Colonization at 14 weeks of age was ineffective, suggesting a window of susceptibility to these effects of bacteria-host interaction. In a subsequent series of experiments, the levels of BDNF, norepinephrine and 5-HT in the cortex and hippocampus were significantly lower in GF mice than in SPF mice (Sudo, 2006). In this regard, conventional rats treated with the same bacterial species have also been shown to have a lower 5-HIAA concentration in the brain stem and a higher tryptophan concentration in the plasma than was found in the non-treated control animals (Desbonnet et al., 2008).

Taken together, these results clearly show that commensal bacteria have the capability to change not only the HPA axis but also other CNS molecules implicated in the pathophysiology of depression.

5.2. Gut microbiota and pain perception

Kamiya and colleagues (Kamiya et al., 2006) showed that oral feeding of a *Lactobacillus* species to anesthetized rats was capable of completely suppressing colonic distension induced pseudo-affective cardiac responses, reflecting inhibition of the perception of visceral pain. This treatment was also effective in reduction of electrical discharge in single fibres of the relevant dorsal root ganglia. Administration of the same *Lactobacillus* to conventional adult healthy rats consistently activated a calcium activated potassium channel in AH neurons of the enteric nervous system in the colonic myenteric plexus (Kunze et al., 2009). Moreover, work by Rousseaux et al. (2007) has shown that oral administration of specific *Lactobacillus* strains induces the expression of μ-opioid and cannabinoid receptors in intestinal epithelial cells and promotes analgesic functions similar to the effects of morphine, thus suggesting that gut microorganisms could influence our visceral perception. In this context, it has recently been reported that the somatic pain sensitivity of GF mice to inflammatory stimuli is lower than that of conventional mice, indicating that interaction with commensal microbiota is necessary for mice to develop inflammatory hypernociception (Amaral et al., 2008). These findings together indicate that gut microbiota can modulate the function of the nervous system responsible for visceral and even somatic pain perception. The mechanisms via which this happens are still unknown but a series of biological events initiated in gut epithelia upon exposure to microbiota, are thought to play an important role in this neuronal modulation.

5.3. Microbiota and animal behavior

The idea that gut bacteria may affect mood and behavior is supported by a series of elegant studies by Lyte and his colleagues (Gaykema et al., 2004, 2005, 2008; Lyte et al., 2006). They have shown that orally administered *Campylobacter jejuni,* in subclinical doses too low to elicit overt immune activation, result in anxiety-like behavior in mice. They also reported that areas of brainstem activation, such as the nucleus tractus solitarius and lateral parabrachial nucleus, participate, presumably via the vaug nerve pathway; in neural information processing that ultimately lead to autonomic, neuroendocrine and behavioral responses. This behav-

ior-microbiome link is also supported by results from our own lab; we have recently shown that GF mice exhibit anxiolytic behavior which was not reversible by conventionalization of flora in adulthood (Neufeld et al., 2008), and was accompanied by increased expression of transcripts for brain derived neurotrophic factor (BDNF) in the dentate gyrus. These types of experiments all support the suggestion that the gut microbiome may be intimately involved in the modulation not only of the peripheral but also aspects of the central nervous system including behavior.

The intestinal microbial balance may also be temporarily changed by an alteration in diet and the effects of the latter upon cognition and behaviour are well recognized. A recent study showed that a specific dietary manipulation positively affected memory and reduced anxiety-like behaviour (Li et al., 2009) Most importantly for this discussion, these changes were associated with significant increases in diversity of the microbiome as analyzed by the most up-to-date molecular methodology, (pyrosequencing).

6. Possible pathways involved in this signaling

The exact mechanisms whereby gut bacteria-induced local changes in gut epithelium and the enteric nervous system communicate with the brain and possibly alter its function and activity, remain to be elucidated. The underlying pathways are highly complex, and it is unlikely that only one common pathway or series of molecules is involved. Two possible pathways we feel may be implicated, however, are reviewed below.

6.1. Neurotransmitters

It is not widely appreciated that commensal organisms produce neuroactive molecules such as serotonin, melatonin, gamma-aminobutyric acid (GABA) catecholamines, histamine and acetylcholine (Iyer et al., 2004). As an example, GABA is made by many bacteria, especially *Lactobacilli,* and this property may well serve to protect the organism from the acid environment encountered in the stomach, since its synthesis involves proton exchange for the uptake of glutamate (Higuchi et al., 1997).

A recent publication by Wikoff et al. (2009) involving metabolomic assessment of plasma has shown that conventionalization of the microbiome of GF mice resulted in appearance of a 2.8-fold increase in serotonin and other neuroactive metabolites. This clearly indicates the significance of the direct or indirect effects of microbes on the development and function of the neuroendocrine system.

In addition, certain organisms including *Lactobacilli* are able to convert nitrate to NO, a potent regulator of both the immune and nervous systems while hydrogen sulfide (H2S) that is produced by some gut microbiota has been shown to modulate gut motility through action at the vanilloid receptor TRPV1 in capsaicin-sensitive nerve fibers (Schicho et al., 2006). *Lactobacilli* have also been shown to increase the activity of indoleamine 2, 3 dioxygenase (IDO), an enzyme involved in catabolism of tryptophan and formation of the neuroactive compounds kynurenic and quinolinic acid (Forsythe et al., 2007), Iyer and colleagues (Iyer et al., 2004) have proposed the interesting theory that the evolutionary history of prokaryotic genes encoding many of the enzymes involved in the synthetic and metabolic pathways of catecholamines, histamine, acetylcholine and GABA, is best described by scenarios that include late horizontal gene transfer from bacteria. This concept substantiates a growing body of evidence that bacteria produce small molecules which are formally involved in bacteria–bacteria communication and have now become involved in bacteria-host communication. The facts that some species of bacteria have a receptor-like molecule to take up GABA (Guthrie and Nicholson-Guthrie, 1989) and GABA and its receptor are found in host gut epithelia (Nakajima et al., 1996), suggest that GABA derived from gut microbiota may actually be involved in "inter-kingdom signaling" (Hughes and Sperandio, 2008), another aspect of which has previously been referred to with respect to stress-microbe interactions (Freestone et al., 2008). This would then occur in addition to bacteria–bacteria signaling and thereby participate in the modulation of the nervous system via actions on gut epithelial cells as well as upon the enteric nervous system.

While we emphasize GABA in this context, it is but one of many examples of the consequences of bacterial synthesis of neuroactive molecules which remain to be explored. An intriguing observation in this context is that of Tanida et al. (2005) who demonstrated that intraduodenal injection of live *Lactobacillus johnsonii* reduced blood pressure within minutes by changing autonomic neurotransmission via central histaminergic nerves through H3 receptors and involving the suprachiasmatic nuclei.

6.2. Short chain fatty acids

Short chain fatty acids (SCFAs) are the end products of anaerobic bacterial fermentation in the gastrointestinal tract. Under physiological conditions, their production is entirely dependent on commensal microbes, and there are only negligible amounts of SCFAs in GF mice (Hoverstad and Midtvedt, 1986). Butyric acid is produced by obligate anaerobic bacteria such as the *Clostridium* species and is also a prototype member of an emerging class of drugs, histone deacetylase inhibitors (Tsankova et al., 2007, 2006). Recent findings implicate epigenetic modifications in the etiology of mood disorders via chromatin remodeling and changes in histone acetylation (Tsankova et al., 2006). Schroeder et al. (2007) showed that systemic injection of butyrate induced histone hyperacetylation in the hippocampus and frontal cortex and exerted antidepressant like effects in mice that were associated with increased BDNF transcripts in the frontal cortex. Whether or not physiological levels of butyric acid in the intestinal lumen can have the same effects on the brain is undetermined but nevertheless intriguing. Butyrate has a profound effect on the enteric nervous system as well and could thereby affect the physiological functioning of the brain through the indirect control of the BDNF transcripts. Other SCFAs may be equally important in terms of their possible effects on brain functions. Propionic acid has also been suggested to have significant effects since intraventricular infusions of propionic acid induce irreversible behavioral changes which have been likened to those seen in autism (MacFabe et al., 2007). While these results are highly controversial, the relative balance of enteric fermentation metabolites such as SCFA on neural development and function, extending to behavior need to be further explored.

There is evidence, at least for omega-3 fatty acids, that SCFA may themselves alter the balance of intestinal microbiota. Mice on a diet containing fish oil had a threefold increase in quantities of bifidobacteria and reduced quantities of *Bacteroides* when compared to mice fed corn oil or beef fat-containing diets (Kuda et al., 2000). Seal oil, which is high in eicosapentanoic acid (EPA), has been shown to increase the adhesion of *Lactobacillus paracasei* to the intestines of piglets (Bomba et al., 2002). Conversely, treating human infants with *Bifidobacterium* for 7 months resulted in increased amounts of alpha-linolenic acid in plasma phospholipids (Kankaanpaa et al., 2002).

Some clinical studies have claimed to show beneficial effects of omega-3 fatty acids in various psychiatric disorders and, in particular, EPA and docosahexaenoic acid have been reported to have favorable effects on major depressive and bipolar disorders (Horrobin, 2002; Freeman et al., 2006). While the effects of omega-3 in depression are far from conclusive and even controversial,

(Owen et al., 2008) the bi-directional relationship between fatty acids and the gut microbiota and the potential impact of these factors on mood disorders and neuronal function warrant further investigation.

7. Microbe cell wall constituents

Many different microorganisms may have constitutive and modulatory effects on neuronal function. Commensal microbiota are also being widely consumed by the general public in the form of probiotics. Ingestion of *Saccharomyces boulardii*, one of these probiotic organisms, has been shown to alter the distribution of the regulatory calcium binding molecule calbindin in the enteric nervous system of conventional pigs (Kamm et al., 2004). The question thus arises as to any common mechanisms of action between different organisms with seemingly parallel effects on endocrine, neuronal and immune systems. Some of the anti-nociceptive effects previously discussed and accorded to a *Lactobacillus*, were also seen with heat killed or gamma-irradiated bacteria and even with conditioned medium obtained after culture of these bacteria (Kamiya et al., 2006). Such experiments clearly suggest that components of bacteria and/or secreted products can mimic the effects of the live organisms. Ingestion by rats of a mutant bacterium, *Lactobacillus plantarum* in which D-alanine was markedly reduced within a cell wall constituent, lipoteichoic acid, was more effective than treatment with the parent wild strain in terms of immunoregulatory effects (Grangette et al., 2005) as well as inhibition of perception of visceral pain (Duncker et al., 2008). Thus, it can be concluded, at least in this case, that bacterial cell wall structure, must in part, have been a determinant of the immune as well as the neuronal effects. Recently, ingestion of a cell wall complex carbohydrate from a commensal bacterium, *Borrelia fragilis*, has been shown by itself to reproduce a host of diverse immune and anti-inflammatory functions (Mazmanian et al., 2008), opening the door to the molecular elucidation of some of the mechanisms of action of commensal organisms. Extension of these types of findings to the exploration of nervous and behavioral functions can be anticipated now with great interest.

8. Conclusions and perspectives

It is rapidly becoming apparent that the gut microbiome plays a major role in the development and regulation of metabolic systems such as those governing energy production and fat metabolism, neuroendocrine systems such as the HPA axis and the development and function of the immune system. Moreover, evidence is beginning now to accumulate suggesting that intestinal commensals may also be involved in neural development both peripherally in the enteric nervous system and centrally in the brain, although the precise mechanisms remain still to be clarified. While extensive research needs to be conducted before definitive conclusions can be reached regarding the biological significance of gut microbiota on the functioning of the nervous system, we are confident this rapidly expanding frontier is opening up territory for exploration. Novel pathways of interest will also emerge and these include the fact that bacteria synthesize gases such as nitric oxide, hydrogen sulfide and carbon monoxide, all of which are themselves involved as neurotransmitters in the nervous system (Wang, 2002).Other bacterial products produced in large amounts in the gut by bacteria and not widely addressed in examination of factors affecting neuronal function include the polyamines, putrescine, spermine, spermidine, and cadaverine, all of which are synthesized by intestinal microbes but also play major roles in central nervous system functioning (Gilad and Gilad, 2003; Gilad et al., 1995).

The biological significance of these rapidly coalescing clusters of evidence point towards a possible role for GI commensal microbes in the modulation of nervous system function. We believe that this area holds considerable promise for future research inquiry. Most particularly it may have important lessons in furthering our understanding of mental health and illness and eventually offer new therapeutic approaches to mood disorders and some of their co-morbid medical illnesses. It may be that we need to change the focus from the brain and look at the role of the gut in what have traditionally been thought of as brain based disorders.

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