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Microbiome: A Potential Component in the Origin of Mental Disorders

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It is not surprising to find microbiome abnormalities present in psychiatric disorders such as depressive disorders, bipolar disorders, etc. Evolutionary pressure may provide an existential advantage to the host eukaryotic cells in that it survives in an extracellular environment containing non-self cells (e.g., bacteria). This phenomenon is both positive and negative, as with other intercellular processes. In this specific case, the phenomenal amount of information gained from combined bacterial genome could enhance communication between self and non-self cells. This can be coupled to both pathological processes and healthy ones.

In this review, we chose to examine potential associated disorders that may be coupled to the microbiome, from the perspective of their bidirectional communication with eukaryotic cells in the gut. Cognition, being the newest neural networking functionality to evolve, consumes a good amount of organismic energy, 30% of which arises from the gut flora. Furthermore, the mammalian gut is highly innervated and has a highly developed immune component, reflecting brain complexity.

The brain-gut axis uses similar molecular messengers as the brain, which affects bacterial processes as well. Thus, any modification of normal bacterial processes may manifest itself in altered behavior/cognition, originating from the gut. The origin of some disorders associated with this bidirectional communication may be harnessed to restore normal functioning.

MeSH Keywords: Microbiota – Physiology • Psychiatry – History • Depression – Microbiology • Fecal Impaction – Psychology

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1484 — — 79

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Neuropsychiatric Disorders

It is slowly becoming evident that neuropsychiatric disorders have a commonality in that they tend to exhibit, simultaneously, a proinflammatory phenomenon [1,2]. This proinflammatory event, which takes place in a microenvironment, may be part of a detection and repair process which becomes evident when a clinical condition brings it to a level of awareness. This proinflammatory state may be due to a number of stimuli, such as the presence of common immune and/or neural mediators at abnormal times and/or concentrations; which may be evidence for a normal intrinsic event that occurs as maintenance or surveillance, such as minor hypoxic events [3–5]. Certainly, such an event, even at the micro-environmental level, could result in the accumulation of degenerated neurons or activated immune cells such as microglia [6], and metabolic chemical residues such as proteins, glycated products, and lipid peroxidation. Indeed, if normally initiated, this proinflammatory state may not have the intrinsic ability to terminate itself, leading to a chronic state of activation, which could become progressively worse [1,7]. Clearly, any intervention which can be brought to bear would profoundly alter this negative cycle. Importantly, this phenomenon should be known to clinicians and be incorporated into their therapeutic strategies.

The incorporation of the gastrointestinal (GI) tract into brain modulation, initiating cognitive impairments, is novel and noteworthy. The gut, in the last 1.5 million years, has become extensively innervated and highly developed for immune surveillance, innate immunity, as well as neuroimmune communications [8,9]. In essence, evolutionary "cultivation" of autonomously functional strains of gut microflora enables prolonged health via regulatory effects at the whole organ level. Importantly, maintenance of normal microbiome components and regulatory activities may be functionally linked to bidirectional communication with host tissues and organs, thereby suggesting retention of common messenger molecules and homologous receptors.

Psychiatric Implications

A legitimate question emerges as to how does this endogenous symbiotic relationship of bacteria and eukaryotic cells become dysfunctional? Since many disorders increase as an individual ages (in plants as well as mammals), a wear and tear hypothesis emerges as well as chemical messenger-associated abnormalities hypothesis [10,11]. Accordingly, intrinsic responses to prolonged environmental stressors, i.e., overproduction of reactive oxygen species (ROS), have been observed to negatively alter ongoing intracellular biochemical and molecular processes [12,13]. Resultant adaptive responses of intrinsic strains of gut microflora appear to mediate necessary changes which underlie the maintenance of homeostatic cohabitation of prokaryotic and eukaryotic components of the gut. These adaptive processes may involve alterations in the intrinsic ratios of the existing subpopulations of gut microflora or the introduction of additional strains. The appearance of similar adaptive phenomena may also be functionally linked to significant dietary alterations.

Morphine Systems

Furthermore, we surmise the endogenous morphine systems may play a key role in gut, gut-brain, and bacterial communication. Opiate processes are noted because of their presence and influence on bacteria, gut, and neurovascular modulation [7,14–20]. In this regard, one may speculate that the pathway to the endogenous synthesis of morphine may be compromised since it involves dopamine as a major precursor, which is well established in psychiatric phenomena [21,22]. Morphine generally exerts a calming action on excitatory activity and behavior, including gut physiological actions [20,23]. Endogenous morphine selectively interacts with a mu-3 like receptor that is coupled to constitutive nitric oxide synthase (cNOS) that occurs in neural and gut tissues [7,20,24–28].

Morphine exerts cell membrane and mitochondrial membrane actions, which appear to be evolutionarily conserved, probably due to the mitochondrion's bacterial origin [29]. Thus, morphine-nitric oxide synthase (morphine-NOS) coupling to produce NO, is a mitochondrial regulating chemical messenger [22,29–34]. This newer coupling phenomena in eukaryotic cells probably supplemented the already present nitrite reductase driven NO generating system found in prokaryotic and eukaryotic cells, thus producing more NO for mitochondrial modulation in an aerobic environment [35–38]. Moreover, one can speculate that as NO accumulates at the cellular level, energy metabolism would start to diminish and if allowed to continue, more drastic physiological consequences would occur (e.g., constipation); interestingly, an ileus can occur via inducible nitric oxide synthase NO [11,39].

Antibiotics Validate Microbiome and Eukaryotic Bidirectional Communication and Significance in Psychiatric Disorders

As noted, operationally, stereo-selective conformational matching between bacteria and microbiome physiological complexes appears to support the conservation of a critically important set of chemical messengers required for existential regulation of homeostatic cellular processes. The manifestation of acute and/or chronic psychiatric conditions following antibiotic usage may provide unique insights into key etiological factors

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of major psychiatric syndromes that involve bidirectional communication between the microbiome and the brain [35,39]. Interestingly, one of the first descriptions of the use of antibiotics in understanding cellular processes occurred in 1980 in Prague [40]. This apparently conserved interaction may simply be based on two energy-rich requiring areas, namely, the brain and the gut metabolism [41,42], balancing the same phenomenon. A more global view indicates a potential window of opportunity for development of novel therapeutic agents targeting microbiome neuron immune components, and the influence this has on brain function as a significant causative factor in severe behavioral disorders.

Antibiotics, Probiotics, and Behavior

Some antibiotic-induced side-effects can be referred to as antibio-mania since some occur in neural tissues (antimicrobial-induced mania) [30,43]. For example, ciprofloxacin induces a small number of treated patients to develop psychosis [44–47] and once treatment stops, behavior returns to normal. Behavioral changes are not limited just to ciprofloxacin, but also occur with exposure to metronidazole [48], ofloxacin [49], trimethoprim-sulfamethoxazole [50], cotrimoxazole [51], procaine penicillin [52], and clarithromycin [53,54].

Microbes in the gut may also affect the activation state of white blood cells, which can enter the brain compartment and communicate with neurons in an abnormal state and numbers [6]. In the shared commonality of chemical communication with bacteria, antibiotic-induced interactions represent a critical factor in the micro-environmental and in organismic survival [39]. Thus, an enhanced microbial presence or a shift in their microbiome ratio, and an antibiotic presence, may induce behavior disorders. We speculate that in susceptible individuals and in individuals using these agents for extended periods of time, and when antibiotics are use at non-recommended doses, theses antibiotics may turn an acute stress response into one that is chronic and/or one that upsets the balance of bacteria in the gut thereby altering its excitation potential and thus impact the brain [55].

Recent reports have demonstrated that consumption of select probiotic agents may represent a novel treatment method for major depressive disorder using a preclinical rodent model [56,57]. The veracity of these observations is substantiated by another therapeutic treatment, which influences gut, brain-gut communication, e.g., fecal transplantation [57–59]. Depression-associated microbiota have been identified [60,61]. Interestingly, fecal transplantation, representing an old and economical methodology, can induce microbiome modifications in a new host's GI tract flora leading to behavioral changes, providing a new treatment for neurobehavioral disorders [59,62–67]. This 1,700 year old technique appears to be gaining in use because, as these reports indicate, it can be used to treat GI-associated maladies as well diseases such as Crohn's disease. It has recently gained credible status as a novel approach to treat metabolic autoimmune diseases as well as psychiatric disorders [59,62–71]. This approach has been reported to positively affect autism as well [72,73]. However, there are reports of inducing behavioral abnormalities, such as depression, via this treatment modality [8]. In summary, the literature demonstrates that the microbiome does affect host processes via, in all probability, common chemical messengers whose appearance and synthesis depends on normal ratios of specific bacteria, which can be modified via the microbiome environment, e.g., diet, stress via the CNS, etc.

Conclusions

A contemporary understanding of mental abnormalities is largely based on a search for genetic contexts that involve these disorders [74,75] and their interactions with the environment [75,76]. This approach is also reflected in current treatment guidelines. Davidson (2009) published an analysis of six sets of guidelines for treatment of depressive disorder from Europe and the Americas [77]. Current first-line treatment recommendations for moderate major depressive disorder include antidepressant monotherapy, psychotherapy, and a combination of both. Severe depression may require the combination of an antidepressant and an antipsychotic, electroconvulsive therapy, or the combination of an antidepressant and psychotherapy. Other medications play a very limited role in the treatment of depression. Most of the treatment guidelines rely on current pharmacotherapy; the issuance of lifestyle modifications is regarded as supportive therapy. However, current literature provides evidence for specific lifestyle choices and the alleviation of depressive symptoms [78,79]. In this regard, lifestyle issues targeting enhanced and appropriate bidirectional communication of the microbiome with the host tissue is also becoming very important in light of our understanding of the shared chemical messengers and signaling systems that appear to integrate gut-brain regulatory processes. Finally, the potential association of aberrant metabolic and communication processes in the microbiome to the etiology and persistence of psychiatric disorders may lead to the development of novel treatment strategies and therapeutic agents directly focused on re-establishing a functionally competent microbiome.

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