

Mitochondria, Microbiome and Their Potential Psychiatric Modulation

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Abstract

Pervasive developmental disorders, or autism spectrum disorders, are multifaceted and have a high rate of occurrence. Additionally, the origin of Autism appears to be multidimensional and largely unknown. Thus, it would appear novel approaches and concepts are needed in this area of scientific endeavor. In this regard, microbial cells harbored within the human gut and elsewhere are being studied to understand their multi-functional properties and their ability to affect physiological activities in their "host" organism. The communities of approximately 10 trillion microbial cells that live within the gut are involved in functions such as metabolism, nutrition and immune regulation. We and others surmise this microbiota can contribute to disruption of normal activities, causing harmful pathologies such as gastrointestinal complications, obesity, and diabetes and autism. They have the ability to trigger inappropriate immune activation, especially macrophages, which can travel from the gut and penetrate the blood brain barrier and communicate inappropriately with neural cells, altering behavior. Normally these immune cells can enter the brain and become microglia. However, being abnormally stimulated, many more can enter the brain, awakening the sentinel microglia and establishing a proinflammatory state, inducing hypoxia (altering mitochondrial performance). Thus, the microbiome has the potential to extend its influence into the brain, suggesting this may also take place within the parameters of normal activity. In part, the behavioral outcome of such an inappropriate invasion would depend on the region(s) penetrated, manifesting itself with a multidimensional behavioral profile such as occurs in autism.

Keywords: Gut; Microbiome; Mitochondria; Metabolic Syndrome; Autism

sclerosis), perinatal impairment, and autoimmune disorders. Genetic origins are currently the focus of intensive research [5].

Introduction

Pervasive developmental disorders (PDD), or autism spectrum disorders (ASD) have a high rate of occurrence and their origin appears to be multidimensional and largely unknown. PDD encompasses a class of disorders with the following characteristics: impairments in social interaction, imaginative activity, verbal and nonverbal communication skills and a limited number of interests and activities that tend to be repetitive [1,2]. Clearly, these comportments are a part of normal behaviors; however, in autism they are exaggerated or diminished in their expression levels, suggesting alterations in cellular communication.

PDD exhibits many subtypes: childhood autism; atypical autism; Rett's syndrome; other childhood disintegrative disorders; overactive disorder associated with mental retardation and stereotyped movements; Asperger syndrome; other pervasive developmental disorders and other pervasive disorders [3]. Thus, PDD confounds an accurate diagnosis. Given the central nervous system's (CNS) functional architecture, expression of the components of this disorder may manifest themselves alone or in combination to produce the final behavioral "output". Tsai [4] speculates the origin is in neurological abnormalities, whereas Trottier et al. [5] surmises a pathophysiologic process, arising from the interaction of an early environmental insult and/or a genetic predisposition. Volkmar [2] speculates that autism is one of the most heritable of all psychiatric conditions. In any event, a number of proposed causes have been suggested, including medical conditions (e.g., phenylketonuria, fragile X syndrome, and tuberous

Discussion

Given the multifaceted, complex nature of autism, we propose that the gut microbiome is playing a role in the initiation and sustainability of autism and, in part, can account for its complex behavioral manifestations, as well as providing insight into potential divergent origins. Others support this hypothesis as well [6-10]. Microbial cells harbored within the human gut and elsewhere are being studied to understand their multifunctional properties and their ability to affect physiological activities in their "host" organism. The community of approximately 10 trillion microbial cells that live within the gut are involved in functions such as metabolism, nutrition and immune regulation [11]. While the microbiota can contribute to these positive physiological conditions, they can also be disrupted, causing harmful pathologies such as gastrointestinal complications, obesity, and diabetes [11]. Furthermore, we surmise they have the ability to trigger inappropriate immune activation, especially in macrophages, in their immediate environment. These activated cells can then be transported to the brain via the vasculature. Normally these immune cells can enter the brain and become microglia [12]. If abnormally stimulated, many more can enter the brain, awakening the sentinel microglia and establishing a proinflammatory state [13]. Thus, the microbiome has the potential to influence the brain by stimulating these cells, which then travel to and enter this privileged environment.

Abnormal shifts in the ratios of the different components of the microbiome can also initiate various pathologies, adding to the trigger concept hypothesis. Though information regarding the various ratios

of the different populations of microbiota such as *Firmicutes*, *Bacteroidetes* and *Actinobacteria* are conflicting in studies, it can be determined that different ratios may contribute to obesity [11]. Not only does the composition of these gut microbiota affect obesity, but it also affects the obesity-associated condition of type 2 diabetes. A recent study using 16S rRNA compositional sequencing demonstrated a reduction of the class of microbiota *Clostridia* and also *Firmicutes* in a test group who had type 2 diabetes [11]. The microbiota *Bacteroidetes* and *Betaproteobacteria* were identified to be heightened compared to the control group. Other recent studies have been able to identify microbial markers illustrating an increase of opportunistic pathogens in the gut of type 2 diabetes patients.

Recent reports also have suggested that autism spectrum disorders (ASDs), e.g., behavioral symptoms, may increase if dietary and gut factors worsen over time. When factors such as hospitalization, early antibiotic exposure and perinatal infection occur, the risk of ASD increases, in all probability due to the gut microbiota being altered [14]. Another factor that may trigger ASD is the enteric short-chain fatty acids (SCFAs) that gut bacteria produce after dietary carbohydrates are fermented. One major SCFA that is known to be produced by ASD-associated gastrointestinal bacteria is propionic acid [14]. A recent study conducted on rodents administering propionic acid provides evidence that this SCFA can produce reversible behavioral changes, such as metabolic, neuroinflammatory, and epigenetic alterations, which are also identified in ASD [14]. Importantly, these alterations may be associated with mitochondrial dysfunction involving carnitine metabolism, as well as epigenetic modulation of the genes associated with ASD [8]. Taken together, the causes of ASDs are potentially influenced by environmental factors, which cause intestinal microbiota to become altered, suggesting novel prevention or treatment methods.

Mitochondria

Interestingly, many individuals who have ASD also exhibit mitochondrial dysfunctionality and gastrointestinal (GI) symptoms [14,15]. Individuals that have ASD and also mitochondrial disorders often do not exhibit primary genetic mutations. Without there being signs of genetic mutation, it is possible that mitochondrial disorder occurs due to a combination of environmental triggers and genetic susceptibilities. An unsuspecting trigger may be antibiotics, which affect the gut bacteria and mitochondria, especially due to this organelle's bacterial origin [16].

Mitochondria are very sensitive organelles that can be affected by both endogenous and exogenous environmental stressors that alter oxygen and glucose levels, and their performance [17]. These stressors include factors such as toxicants, immune activation, metabolic disturbances, and iatrogenic medications, which are also known to be correlated with ASD [15]. Due to both the mitochondria and ASD being affected by these common stressors, this further suggests causes of ASD [15]. It is also known that the mitochondria have an important role in ASD, where levels of enteric bacteria, such as *Clostridia* spp., are higher in children with ASD [15]. This bacterium produces short-chain fatty acid metabolites, which are known to be toxic to mitochondria, causing dysfunction.

If gut microbiome (GM) composition is as important as it appears to be, then it is possible that there is a therapeutic approach to manipulate the GM [9]. This could lead to the improvement of ASD symptoms, comorbidities, and potentially even gastrointestinal symptoms. Recent research has proposed a hypothetical approach to

test the relevance of GM to ASD [18]. There are many known treatments that potentially alter or reduce the composition of gut microbiome, such as antibiotics [18]. Certain treatments, such as fecal microbiota transplantation, probiotics, eating unprocessed and fermented foods can also replenish GM, presumably helping ASD individuals. Dietary treatments such as eating healthier foods or taking vitamins may also alter the composition of GM, and therefore, alleviate ASD symptoms [18-20].

Consolidation

We surmise that various types of stress, such as changes to the microbiome composition, antibiotics, etc., may create a local environment, e.g., neural, gut, etc., that is proinflammatory in nature [21-24]. This environment may also be initiated by hypoxia, which causes mitochondria to become dysfunctional, creating poorly functioning cells [13,16,17,25,26]. In susceptible individuals, if this state is not alleviated, it may become chronic, potentially leading to autism. As noted earlier, the stress-induced dysfunctional mitochondria may cause an immune response, e.g., abnormal macrophage excitation, penetration into the brain, activation of microglia and further brain stimulation via inappropriate release of chemical messengers, simply by having a hypoxic event, which the stressor initially causes [12,13,17,27]. Predicted entry points, e.g., choroid plexus, would provide widespread access to the privileged compartment and explain the diverse symptomology of autism.

The multifactorial etiology of autism opens the door to novel concepts. Epigenetic modifications, e.g., DNA methylation and histone modifications, certainly affect stereospecific regulatory processes of genetic outcomes. Siniscalco [8,9] and colleagues note that nutritional deficiencies and other chemical stressors appear to be epigenetic regulators, which affect individual health via affecting the gut microbiome. Preferential evidence favoring genetically driven etiological factors is compelling and is inherently complex, but perhaps underestimates the contribution of environmental determinants [2,28,29] such as the gut microbiome. Along these lines of evidence, neuroimaging studies have indicated the involvement of broad and developmentally interrelated neural systems, contradicting the notion of single core deficits [2]. We surmise this indeed is the case. However, given the complexity of autism, we may indeed be faced with a disorder that manifests itself from varying abnormal structures and brain areas, as well as triggering events. The tendency to "lump" all into a single event may be fatally flawed for autism. In this regard, we also surmise that inappropriately activated immune cells, e.g., macrophages, could and do wander into the brain, releasing common chemical messengers and that, in so doing, stimulate abnormal behavioral outcomes, e.g., autism-like [13]. This is possible because of common receptors on immune and neural cells, which is the hallmark of neuroimmunology. Importantly, what is causing this abnormal immune cell non-specific excitation may be the gut microbiome, which is constantly producing chemical messengers and other substances while potentially undergoing shifts in the ratios of its bacterial community [7,10,18,30,31]. Thus, one of the stressors may induce a state of inappropriate activation on a wide scale based on the numbers and kinds of bacteria present.

Conclusion

Recently, the hypothesis concerning the origination of autism has been expanded to include mitochondria, which is quite compelling in its ability to add to the explanation of the causes of the multitude of

widespread behavioral characteristics that occur in this disorder, as well as other psychiatric disorders [1,15-17]. Mitochondrion involvement represents an important eukaryotic cellular organelle involved with generating ATP, powering the cell's many reactions, normally without abrupt interruptions [15,17,25,26,32-34]. It is surmised that mitochondrial dysfunction, when it occurs, targets the CNS because of its intrinsic level of oxygen utilization, which allows for a rapid presentation of altered behavior. In so doing, diverse negative stimuli, e.g., trauma, antibiotics, hypoxia, etc., would damage neurons initiating neural and neuroimmune disorders, e.g., autism. Again, this could be done by gut microbiome alterations, which activate white blood cells, e.g., macrophages [13]. Indeed, if genetic susceptibilities are present, the target becomes more specific, as opposed to a more diffuse manifestation of a disorder. Given the universal presence of mitochondria at high levels in the CNS, it provides for a credible explanation for the complications and characteristics that emerge in autism [16,17]. We and others have recently surmised that there are very common links in specific disorders (Alzheimer's, Type 2 diabetes, atherosclerosis [6,17,21,35-37]), which can be centered around critical events, e.g., proinflammation, hypoxia, all of which can be found to involve energy metabolism, including gut microbial processes. This may be why behavioral manifestations of the disorder emerge, since they require high energy levels to sustain normal function. In essence, behavioral abnormalities of a particular kind, as noted earlier, serve as diagnostic indicators because they are at the forefront of the energy output processes. Further, this level of gut influence over bodily functions occurs because of the sheer number of bacteria and diverse bacteria, which taken together provides for a "strong" message to immune and neural cells. Here again, the macrophage may be central to this communication since being abnormally stimulated and releasing chemical messengers at the wrong time would evoke behavioral anomalies [13].

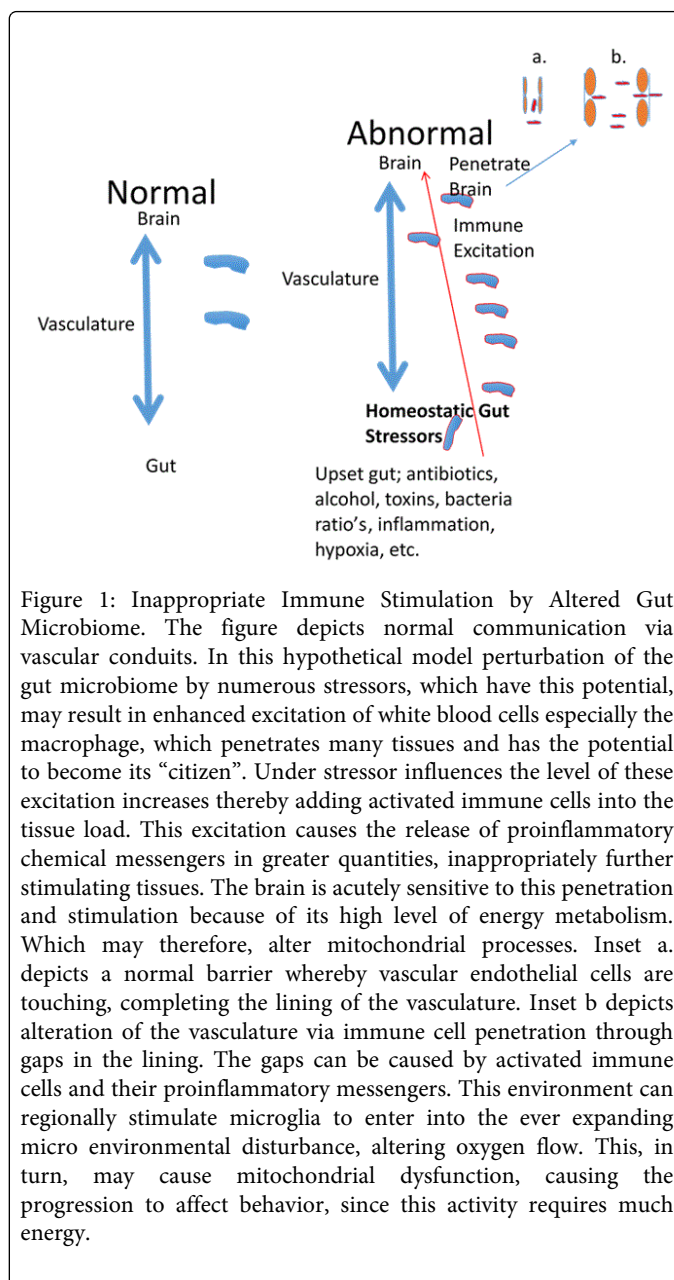


Figure 1: Inappropriate Immune Stimulation by Altered Gut Microbiome. The figure depicts normal communication via vascular conduits. In this hypothetical model perturbation of the gut microbiome by numerous stressors, which have this potential, may result in enhanced excitation of white blood cells especially the macrophage, which penetrates many tissues and has the potential to become its "citizen". Under stressor influences the level of these excitation increases thereby adding activated immune cells into the tissue load. This excitation causes the release of proinflammatory chemical messengers in greater quantities, inappropriately further stimulating tissues. The brain is acutely sensitive to this penetration and stimulation because of its high level of energy metabolism. Which may therefore, alter mitochondrial processes. Inset a. depicts a normal barrier whereby vascular endothelial cells are touching, completing the lining of the vasculature. Inset b. depicts alteration of the vasculature via immune cell penetration through gaps in the lining. The gaps can be caused by activated immune cells and their proinflammatory messengers. This environment can regionally stimulate microglia to enter into the ever expanding micro environmental disturbance, altering oxygen flow. This, in turn, may cause mitochondrial dysfunction, causing the progression to affect behavior, since this activity requires much energy.

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