**Neuro-entero-immunological Theory of Psychopathology in ADHD**

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**Key Words:**

Attention-Deficit/Hyperactivity Disorder (ADHD), Gut-Microbiota-Brain Axis, Pro/Pre-Biotics

**In this micro review, the literature and primary mechanisms of a novel theory for the psychopathology and etiology of Attention-Deficit/Hyperactivity Disorder (ADHD) is presented. The explanatory framework in this review’s presentation of ADHD etiology– the “autonomic dysregulation model of ADHD”– was first proposed in Sandgren and Brummer’s 2018 paper in the journal Medical Hypotheses1. There is now a paradigm shift in neuroscience toward an increasingly supported understanding of neurobiology in terms of not only the CNS, but also the so-called second brain residing in the enteric nervous system of the gut and its resident microbiota. Accordingly, more and more research is looking into the possible role of this second brain in the etiology and psychopathology of neurodevelopmental diseases like ADHD. This micro-review outlines a novel explanatory model, which, if further supported by more rigorous studies, has the potential for the development of novel psychiatric treatments via modulation of gut-microbiota dysbiosis with pro/pre-biotics, etc., as well as a theoretically promising avenue to disease prevention via intervention into the gut-microbiota during the neurodevelopmental window in which we believe ADHD is developed.**

**Introduction**

 The currently prevailing psychopathological theory of Attention-Deficit/Hyperactivity Disorder (ADHD) is neuropsychiatric in nature, conceptualizing the disorder as polygenic variations in the functioning of the monoamine neurotransmitter systems and alterations in neural network structures. This neuropsychiatric paradigm is slowly being joined by a neuroenteroimmunological perspective fed by the quickly expanding field of evidence for the bidirectional interplay of the gut-microbiota-brain, which is presently transitioning from preclinical research into human studies. A significant deviation from the previous tradition of thought, this theory emphasizes the role of environmental factors on the development and function of the BGM axis leading to phenotypic implications. The strength of a microbiota-derived etiologic model here is especially seen in its possible explanation to the long puzzling question of the wide variance in worldwide ADHD prevalence, as diet, gut microbiota composition, and other environmental factors vary so much in the world’s great heterogeneity of cultures and climates. Additionally, this model, if shown to be correct, opens up significant avenues for not only effective treatment of the disorder, but also possible prevention.

**Recent Progress**

**A Novel Hypothesis for ADHD Etiology: Autonomic Dysregulation Model**

 This explanatory model of ADHD suggests the autonomic dysregulation seen in ADHD is caused by an imbalanced, less rich and less diverse gut microbiota early in life, as well as perpetuated throughout adulthood1. This theory for the fundamental causes of ADHD relays how early life environmental differences lead to variations in microbiota composition responsible for the alterations in metabolic and immunologic functioning that causes the various symptoms of ADHD. During the early life periods of neurodevelopment, autonomic dysregulations lead to altered immunologic functioning, as well as altered metabolism and formation of pathophysiologically relevant monoamines such as dopamine, serotonin, and the neurotransmitter-derivative, tryptophan.

**Mechanisms of Autonomic Dysregulation**

*Altered metabolism and formation in the periphery as mediator of CNS GABA concentrations*

 Central to this neuroenteroimmunological theory of psychopathology in ADHD is the idea of a suboptimal (lowered/imbalanced) microbial inoculation in early life resulting in a dysbiotic gut microbiota development, altering not only early life neurodevelopment, but also the continued metabolic, and other, activity of gut microbiota throughout life. One possible mechanism of pathology in ADHD is reduced levels of the inhibitory neurotransmitter GABA, and this is gastroenterologically relevant as GABA is a common metabolic product of microbial fermentation2.

 MRS study has indicated reduced CNS levels of GABA in ADHD children3. It has been shown that the GABAergic system is responsive to both short- and long-term stress sensitivity in rodents, possibly mediated by the neuroactive steroid and neurosteroid hormones4. Additionally, a study on healthy rodents indicates emotional behavior and expression of GABA receptors in brain can be modulated by introduction of a probiotic. In accordance with these findings, it is possible an altered GABA metabolism or formation in the CNS may be caused by alterations in the periphery.

*Altered metabolism and formation in the periphery as mediator of CNS monoamines (dopamine, serotonin, norepinephrine) concentrations*

In line with predominating theories of ADHD pathology is the theory of decreased dopamine (DA) levels in the CNS1. Various studies have shown this insufficiency in DA concentrations may have its roots in the periphery5. A study comparing germ-free (GF) mice to control, wild-type gut microbiota possessing mice gives support to the hypothesis of peripheral mediation of DA, where GF mice demonstrated elevated turnover of monoamines such as dopamine, norepinephrine, and serotonin in the striatum, as well as altered expression of anxiety and plasticity-related genes in multiple brain regions6.

 In addition to the pathophysiological role of altered CNS dopamine levels in ADHD, serotonin has been implicated in the impulsivity and hyperactivity symptoms seen in the disorder7. Serotonin is widely established to be a central component of bidirectional communication of the gut-microbiota-brain axis8. In addition to the role of the gut in synthesis of the majority of the body’s serotonin, the gut also serves as the source of tryptophan, which crosses the blood-brain barrier into the CNS where it is used for further serotonin synthesis9. Important implications of these findings are suggested in the role of CNS serotonin modulation of learning and memory function via effects on dopaminergic, cholinergic, and GABAergic neurotransmission10. This is relevant to ADHD pathology and gastrointestinal immunologic functioning, as research has suggested serotonin signaling properties become altered following intestinal inflammation, resulting in decreased functioning and expression of serotonin-selective reuptake transporter11 (SERT). In vitro evidence has indicated decreased tryptophan transport in boys in combined type ADHD, possibly implying decreased serotonin levels in the brain12.

*Altered Immunologic functioning in ADHD*

 It has been suggested that chronic pro-inflammatory immune dysregulation, possibly resulting from genetic predisposition, mediates the pathogenesis of ADHD13. Evidence for this hypothesis is found in, among others, studies showing a significant prevalence of allergic diseases (asthma, urticarial, atopic dermatitis, allergic rhinitis) in individuals diagnosed with Attention-Deficit/Hyperactivity Disorder14. Higher intake of the probiotic fermented food, kimchi, omega-3 fatty acids, polyunsaturated fatty acids (PUFAs), and lower intake of fast food, were associated with lower odds of having ADHD15. Furthermore, immunologic dysregulation has been implicated in not only in the etiology of ADHD, but also in its on-going pathophysiology. As with Autism Spectrum Disorders, it has been suggested that sensitivities to certain foods, and their subsequent reactions, may act as antigens to induce more severe ADHD symptoms16. Interestingly, in one study, this food sensitivity-related allergic reaction was shown to be non-allergic or cell-mediated16 (non-IgE, non-IgG mediated).

**Discussion**

 These results seem to suggest potential avenues of therapeutic intervention acting on the very immunological dysfunction and neurotransmitter metabolism, which seems to be implicated in the etiology of the disorder. Even more exciting for the state of neuropsychiatry than additional therapeutic methodologies, is the prospect of preventative action via early life gut-microbiota inoculation of anti-inflammatory and monoamine-promoting probiotics and prebiotics. For a neurodevelopmental disorder with a growing prevalence in western societies, this novel explanatory model addresses an increasing societal burden, possibly marking the shift toward a future pediatric psychiatry empowered for the first time with a sort of psycho-vaccination.

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