Neuroinflammation in ASD

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Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction across multiple contexts and restricted, repetitive patterns of behavior, interests and activities. The maternal status of polyunsaturated fatty acids (PUFA) regulates microglial activity and neuroinflammatory pathways during a child's brain development. In children with ASD, the metabolism of PUFA is thought to be deficient or abnormal, leading to increased production of proinflammatory cytokines, increased oxidative stress and an imbalance in the formation and action of neurotransmitters. In addition, nutritional deficits in omega-3 PUFA may affect gut microbiota and contribute to ASD by the gut–brain axis.

ASD PUFA supplementation neuroinflammation gut microbiota gut–brain axis

1. Introduction

Autism spectrum disorder (ASD) is defined by the American Psychiatric Association as a complex neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction across multiple contexts and restricted, repetitive patterns of behavior, interests and activities, according to the Diagnostic and Statistical Manual for Mental Health, Fifth Edition (DSM-5) [1]. These symptoms must be present in the early developmental period and produce clinically significant developmental impairment in social, occupational or other important areas of current functioning [1][2][3].

The exact cause of ASD is unclear, but a combination of different risk factors and genetic and environmental factors is assumed [4]. The conventional perspective of ASD symptoms suggests that ASD is a genetic disorder that involves a complex genetic background [3][5]. Several research directions support the belief that a combination of complex neurobiological, environmental, immunological and genetic factors is crucial in the etiology of autism. Additionally, proinflammatory cytokines secreted by several types of different cells contribute to the pathogenesis of neuroinflammation [6].

Many patients with ASD have associated medical conditions such as anxiety, sleep disorders, metabolic disorders, eating disorders and gastrointestinal (GI) problems that have a significant impact on the quality of patients and their caregiver's lives [7]. Studies of immune dysregulations and GI problems within the neuroimmune system of patients with ASD are particularly interesting to many scientists [8].

The aim of this study was to review the possible role of neuroinflammation in the development and progression of ASD and the effects of omega-3 PUFA supplementation in children with ASD. Given that a wide range of symptoms

is related to ASD, the issues about the broad biological background of autistic symptoms and the potential beneficial effect of omega-3 PUFA supplementation are discussed.

2. Gut–Brain Axis (GBA) and ASD

The human gut contains up to 100 trillion microorganisms, including at least 1000 different types of (so far) known bacteria, that collectively affect the host's digestive, immune, metabolic and nervous systems [9][10]. The gut microbiome (microbiota) is mainly formed during the first months of life under the influence of various factors such as vaginal birth, host genome, formula feeding, antibiotic use, GI infections and stress [9][10][11].

A growing body of evidence supports the hypothesis that gut microbiota plays a vital role in neuroinflammation [12]. Communication along the microbiota–GBA mainly describes how signals from the gut microbiota influence brain function, as well as how brain messages impact microbiota activity and GI physiology [13]. Disturbances within the microbiota–GBA have been suggested as potential contributors to the occurrence and development of ASD. The balance of inflammatory cytokines is skewed, and intestinal permeability seems to be increased in children with ASD who display gastrointestinal symptomatology when compared to those children who did not [14]. Short-chain fatty acids (SCFA) are critical mediators in creating a link between the gut microbiota and the brain, as they cross the blood–brain barrier and directly affect changes in brain activity [13][15]. The three types of SCFA are acetic acid, valeric acid and propionic acid [16], and these SCFAs are important for the health and regulation of the small intestine membrane and the development of native and adaptive immune responses [10][11][17]. The pathway of the initial immune response is evoked by the production of bacterial toxins (e.g., *Clostridia* spp.) by the gut microbiota, which further evokes the immune response in the gut as well as in the bloodstream; and increased oxidative stress occurs in this type of immune response. Afterwards, oxidative stress on epithelial membranes increases intestinal permeability, resulting in bacterial translocation into lamina propria of mesenteric lymphoid tissue. Subsequently, mucosal immune cells, macrophages and dendritic cells release proinflammatory cytokines [10][11][18]. Proinflammatory cytokines then activate the vagus nerve or reach the brain (**Figure 1**) through the bloodstream, and in this way, they regulate the activity of microglia and the functioning of the Central Nervous System (CNS) [10][11][18]. Microglial cells are a type of macrophages that act as the first defense mechanism of the brain immune system, and these unique, resident, immune cells of the CNS monitor the CNS and synaptic discharges during normal neural development and represent the primary mediators of inflammation [6].

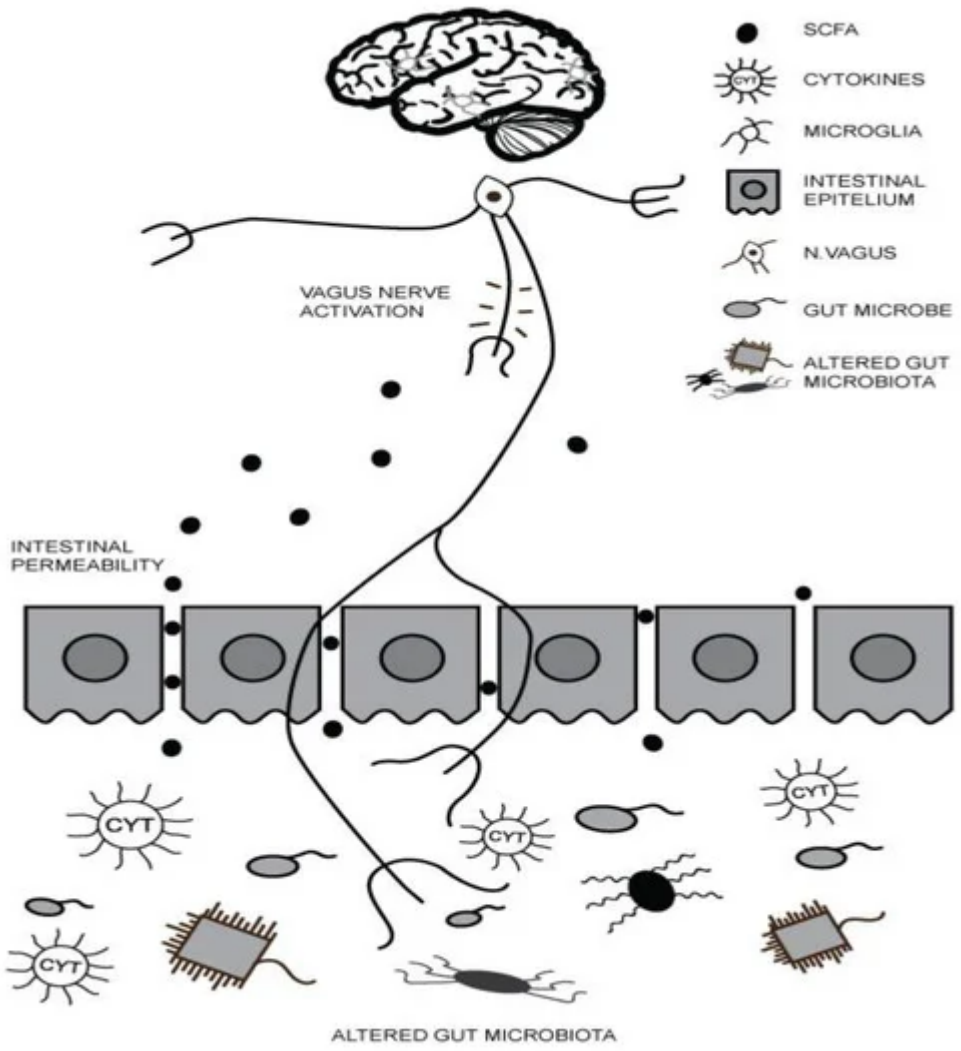

Figure 1. Altered gut microbiota and inflammatory processes in Autism Spectrum Disorder (ASD).

The gut microbiota exhibits important bidirectional interactions with the immune system. Many facets of immunity are dysregulated in ASD [8]. Neuroinflammation affects the composition of the microbiota and vice versa, and nutritional deficits in omega-3 fatty acids can be an important risk factor for ASD [17].

3. Maternal Inflammation during Pregnancy and ASD

Epidemiological studies indicate a strong association between maternal inflammation and the pathogenesis of ASD [17][18]. During pregnancy, pathogens are thought to increase the risk of neurodevelopmental disorders in the offspring depending on the timing of infection and the magnitude of the maternal immune response [17]. Pathogenic microbiota, bacterial metabolites and their components can stimulate the secretion of proinflammatory cytokines [9][19]. These maternal cytokines can cross the placental barrier and stimulate de novo synthesis of cytokines in the fetal brain, which makes the fetal brain sensitive to neurodevelopmental changes [17]. Additionally, placenta inflammation can induce a systemic fetal inflammatory response that contributes to white matter damage in the fetal brain. This type of inflammation also leads to neonatal brain damage [19]. The presence of various levels of

inflammatory cytokines has been found in blood, especially in monocytes, serum and plasma, as well as in the brain tissue and cerebrospinal fluid of patients with ASD, which leads to impairment in CNS immune capacity and enhanced activation of microglia in the brain [6][20]. Chronic microglial activation contributes to the development and progression of neurodegenerative disorders. Active microglia can induce the production of proinflammatory cytokines such as interleukin 1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α), which are typically intended to prevent further damage of the brain tissue. Abnormal microglia activation is sometimes toxic to neurons and other glial cells [6].

Many studies have confirmed the presence of activated microglia, accompanied by proinflammatory factors such as cytokines and chemokines in the brain and in cerebrospinal fluid in the dorsolateral prefrontal cortex of patients with ASD. Deficits in microglial activity during brain development lead to an increased number of immature synapses, and thus to the cognitive impairments and behavioral disorders typical for patients with ASD [17]. Inflammation that occurs in the form of elevated cytokine levels transmit across the blood–brain barrier and initiate a neuroinflammatory response that has been offered as an explanation for later neurodevelopmental complications, including cerebral palsy, autism, schizophrenia and cognitive impairments [19]. Although supplementation with PUFA can reduce inflammation and improve the balance between pro- and anti-inflammatory cytokines, the effects of PUFA on later neurodevelopmental complications are not clear.

The immunophenotypes that can be seen in patients with ASD are characterized by elevated proinflammatory status, i.e., elevated levels of cytokines and chemokines, including IL-1β, IL-6, interferon μ (IFN-μ), tumor necrosis factor α (TNF-α), subunit beta of interleukin 12 (also known as IL-12 subunit p40), MCP-1 (monocyte chemoattractant protein 1, cytokine also known as CCL-2), TGF-β (transforming growth factor-β) as well as hyperactive cellular immune responses [21]. However, immune abnormalities, including differentiating the immune/cytokine profile, are the result of the diet, lifestyle and genetic profile of each patient with ASD [8], and this makes it difficult to pinpoint the links between maternal inflammation, diet/supplementation and ASD changes in children [22].

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