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Review

Sodium Dysbiosis and Autism Spectrum Disorder

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ABSTRACT

Autism is a neurodevelopmental disorder whose cause and treatment are not clearly known, for which genetic and environmental factors are thought to play a role in its etiology. Although the importance of maternal diet in terms of fetus development is known, studies investigating the frequency of autism seen in offspring with the mother's diet are extremely limited. It is thought that the maternal diet influences cytokine responses and fetus development through modifying the immune system's microbiome composition. This article will examine potential mechanisms between dysbiosis and autism development due to high salt consumption.

Keywords: Autism spectrum disorder, dysbiosis, high salt.

Autism spectrum disorder (ASD) is one of the most common neurodevelopmental illnesses in children, characterized by a lack of social skills, as well as restricted and repetitive movements.[1] ASD is becoming more common by the day, with an annual increase of more than 1%. It affects one out of every 160 children globally, according to the World Health Organization (WHO), and the number of children diagnosed is rising every day.[2]

Despite the rising number of ASD cases, the disease's origin is still unknown. Autism is assumed to be caused by a variety of genetic, environmental, and neurological factors.[3] A previous large-cohort study (n=2,049,973) has shown that autism is approximately 50% hereditary.[4] The gut microbiota and immune system dysregulation may be major environmental, epigenetic variables in ASD cases, according to another recent study.[5]

In the maternal period, the hypothesis that activation/dysregulation in the immune system is associated with psychiatric diseases such as ASD and schizophrenia in children has recently attracted attention. A group of pregnant mice was given polycytidylic acid (Poly I:C) and maternal immune activation (MIA) during the maternal period in a mouse study. Another group was given lipopolysaccharides (LPS) on the 9th day of post-natal, and immune activation was achieved in the early period. In both sexes, but especially in male mice, early immune activation has been found to promote social problems and repetitive behaviors. Pro-inflammatory factors (TNF, IL6, IL1) increased in both groups at the same time, while anti-inflammatory factor expression reduced in male mice.[6]

Other environmental factors that contribute to the development of cognitive and psychiatric illnesses include obesity, a high-fat diet, and excessive salt consumption. Nitric oxide (NO), a mediator, is affected by high salt ingestion, endotel dysfunction, and vasodilators. When endotel function is compromised and not enough NO is released, the essential vasodilator activity is not detected, resulting in decreased cerebral blood flow and cognitive impairment. Although the underlying mechanism by which salt in the diet affects NO is unknown, it is well recognized that a decrease in cerebral blood flow produces neuronal dysfunction.[7]

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High salt consumption also causes dysregulation of the immune system. Increased salt consumption both increases the proliferation of pro-inflammatory immune cells and suppresses the functions of regulator immune cells. According to studies, a high-salt diet disrupts the Th17 (T helper 17 cells) axis by causing gut dysbiosis.[8]

AUTISM AND GUT DYSBIOSIS

More than 15,000 kinds of bacteria, weighing around 1 kilogram, live in the gut microbiome.[9] The gut microbiome's interaction with the nervous system has been the subject of extensive research in recent years. In addition to normal conditions, the gut microbiota impacts behaviour in neurological diseases such as autism.[10] There is a strong link between bacterial variety and personality traits, according to research. It has been reported that there are fewer 'proteobacteria' filum in the intestines of people with distraction, focus problems.[11] In addition to increased intestinal permeability, people with autism have more gastrointestinal problems like diarrhea and constipation, as well as higher levels of proinflammatory cytokines in their blood. These inflammatory molecules make their way to the brain, where they might activate the immune system. The effects of gut dysbiosis and associated dysregulation in the immune system on autism are noted.[12,13]

It's suspected that changes in the gut microbiome during pregnancy are linked to the development of autism in offspring. In recent research on this subject; Probiotic suplementation was performed on pregnant rats created by the MIA model, and it was shown that autism-like behaviors were rarer in the offspring of the group receiving probiotics compared to the group without suplementation.[14]

AUTISM AND IMMUNE DYSREGULATION

Th1 and Th2 cytokines increase in the immune system of people with autism, and there is a regulation issue in both innate and adopted immune systems, according to human and animal research.[15] This imbalance in inflammatory pathways is hypothesized to be linked to blood-brain barrier disruption and brain function.[16] In many studies, in individuals with autism; tumor necrosis factor-alpha (TNF-α), Interferon-gamma (IFN-γ), interleukin 6 (IL-6), interleukin 8 (IL-8) levels have been proven to increase.[17] An increase in interleukin-17 (IL-17) levels was found to be positively connected with autism levels in another investigation of children with autism.[18] When all of these findings are taken together, it appears that elevated levels of pro-inflammatory cytokines (IL-6, IL-8) and decreased levels of anti-inflammatory cytokines (IL-10) in autism may be linked to immune system overactivation.[19] In a recent meta-analysis study (n=1393 patients with autism, n=1094 controls), people with autism had levels of IFN, IL-6, TNF-, and IL-1 that were statistically substantially higher than the control group of the same age.[20]

Another study showing dysfunction in the immune system in autism has shown that antibodies of maternal origin negatively affect neuronal and glial development.[21] In autism, the existence of these antibodies has been linked to behavioral and cognitive impairment.[22] It has been clearly reported that these maternal antibodies are completely different from autoantibody functionally.[23,24] Although there is no direct evidence that differentiated maternal antibodies pass from mother to fetus and cause autism, IgG antibodies from mothers of children with autism were given to rhesus monkeys and showed a significant increase in stereotypical movements when compared to the placebo group.[25,26] In another study of mice with a similar method, antibodies taken in the mothers of children with autism were given to pregnant mice and proved to be changes in the behavior and socialization of the offspring compared to the group taken from the normal child's mother and injected into the mouse.[27] Maternal antibodies have been studied recently, and differences in binding affinities have been discovered. More specifically, it's not the first time we've been able to do that. Antibodies from mothers of children with autism have been shown to be more diverse and tend to bind to peptides that are not normally linked.[28]

A study examining the relationship between hereditary factors and dysfunction in the immune system found a history of autoimmune disease near the first degree of 37% of children with autism; this frequency is set at 6% in the control group.[29] Autism was found to be more common in children with a family history of type 1 diabetes, rheumatoid arthritis, autoimmune thyroid illness, or systemic lupus disease.[30,31]

Activation of the immune system has been linked to autism in several studies. Animal models displaying autism-like characteristics in offspring have been shown valid using immune stimulation

during the maternal period. For this reason, the number of studies investigating the relationship between the MIA model and autism has increased in recent years. Poly(I:C) causes the development of an autistic-like phenotype in children by elevating serum IL-6 levels, according to an autism model research conducted with Poly(I:C) injected on the 12th day of pregnancy.[32] In a recent study, it was discovered that, in addition to IL-6, an increase in IL-17 levels causes autism-like symptoms. In this study, it was also demonstrated that autism can be prevented by administering antibodies that cause autism and lower IL-17 levels, as well as that IL-17-specific receptors exist in the fetal brain.[33] In light of these findings, it was predicted that the binding of IL-17 with unique receptors during the development of the nervous system during the maternal period initiated various structural and behavioral anomalies.

HIGH SALT DIET, GUT DYSBIOSIS AND IMMUNE DYSREGULATION

Excess salt consumption remains a public health problem worldwide. According to the WHO, ischemic heart disease and stroke are the top 2 due to excessive salt consumption when looking at the causes of death worldwide.[34] At the same time, while there are small differences between societies around the world, salt consumption is above the recommended levels. Although the WHO recommends a daily salt intake of fewer than 5 grams, the global average is between 9 and 12 grams.[35] Salt in the diet has a number of negative impacts on the innate immune system. Extracellular hypertonicity produced by excessive salt ingestion is responded to by mononuclear phagocyte system (MPS) cells, while macrophages release vascular endothelial growth factor-C (VEGF).[36] This isn't the only effect of a hypertonic solution caused by excessive salt ingestion on macrophages. By activating pro-inflammatory macrophages (M1) and inducing inflammation, high salt concentration increases IL-1 levels.[37] Other effects of sodium-related hypertonicity include the activation of the mitogen-activated protein kinase (MAPK) signal pathway and an increase in different cytokine and chemokine expressions.[38] It also inhibits the function of anti-inflammatory macrophages (M2) that are responsible for high sodium cell repair.[39]

High salt consumption also implies that it has a positive impact on the immune system after it has been acquired through several channels. The first of these effects, elevated IL-1 levels, promotes Th17 cell development.[40] Furthermore, in naive CD4+T cells, elevated sodium concentration stimulates a variety of signaling pathways. In CD4+T cells, high salt phosphorizes the MAPK signal pathway and activates the NFAT5 pathway, which is a transcription factor. Furthermore, increased sodium levels produce an increase in serum/glucocorticoid regulated kinase 1 (SGK1).[41] Activation of SGK1 activates phosphorylation of the FOXO1 pathway. FOXO1 proteins, which are normally dephosphorylated, bind to IL-23 receptors and suppress transcription. Phosphorylated FOXO1 proteins bind to IL-23, thereby increasing the concentration of IL-23, an important stimulator in Th17 cell differentiation.[42] Furthermore, increased differentiation in Th17 cells caused by high salt consumption lowers endothelial NO levels, lowering blood flow and, in this situation, impairing cognitive function.[43]

In studies, it has been observed that high salt consumption causes significant changes in microbiome composition. The high-salt diet has been shown to cause a decrease in the species Lactobacillus, Oscillibacter, Clostridium cluster XIVa, an increase in the Parasutterella species. Similarly, this study demonstrated that gut dysbiosis mediated by salt ingestion resulted in an abnormal increase in IL-17 concentrations via Th17 cell development.[44,45]

AUTISM DUE TO MATERNAL SALT CONSUMPTION

In autism research, the maternal nutrition and gut microbiome are examined. The association between salt consumption and autism has not been thoroughly explained, despite the fact that factors connected with the maternal diet are routinely explored. Gut dysbiosis caused by excessive salt consumption in the mother has been proven to trigger both the innate and adaptive immune systems. As a result of dysbiosis, the differentiation of Th17 cells leads to excessive IL-17 production. This condition is associated with the development of various autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and thyroid.[46]

Research shows that the gut microbiome in the maternal period can be transferred to the fetus/newborn through placental blood circulation and breastfeeding.[47] High sodium taken by diet causes gut dysbiosis and dysregulation in the Th17 axis. IL-17 serum levels due to increased Th17 cell differentiation during pregnancy increase and

Table 1. Potential changes due to sodium hypertonicity

Effects on the innate immune system	Increase in pro-inflammatory cytokines with MAPK activation[39]
	Increased levels of IL-1 via proinflammatory cytokines of the M1 type[38]
	Decrease in M2 type macrophage activation[40]
Effects on the adaptive immune system	Th17 differentiation due to increase in IL-1 β levels[41]
	Decrease in NO levels with Th17 differentiation, impairment of cognitive functionb[44]
	Activation of the FOXO pathway due to activation of the SGK1 pathway[42,43]
Changes due to maternal dysbiosis	Increase in IL-17 levels transferred from mother to baby[48]
	IL-17 caused by deterioration of the blood-brain barrier, increased permeability and cytokine infiltration[49]
	Neuronal stem cell apoptosis as a result of ovarian activation of microglia with the increase of IL-17 receptors, decrease in the differentiation of neuronal stem cells[51,52]

MAPK: Mitogen-activated protein kinase; NO: Nitric oxide; SGK1: Serum/glucocorticoid regulated kinase 1.

are transferred to the fetus through placental circulation. When IL-17 reaches the developing fetal brain, blood can cause disorders in the development of the brain barrier. Increased permeability causes the damaged blood-brain barrier to function; various effectors, such as cytokines, can trigger molecular infiltration. Furthermore, proinflammatory cytokines produced as a result of the mother's altering microbiota are transferred to the fetus via placental circulation.[48] The altered microbial composition increases the intestinal permeability of the fetus, causing increased cytokine levels in circulation.[49] The expression of IL-17 receptors (IL-17R) is minimal under normal conditions,[50] but IL-17R expression in the fetal brain may increase due to IL-17 from placental circulation.[51] The fact that IL-17 is connected to its receptors and activated has a number of potential effects. The first is that activated IL-17R causes neuron loss by inhibiting neural stem cell differentiation. The second is that excessive microglia activation causes neural stem cell death and impaired neuronal development.[50] IL-17R activation can also activate Act1, which in turn can stimulate extracellular signal-regulated kinase (ERK) pathways. The ERK pathway is associated with important functions such as neural differentiation and plasticity on the nervous system.[52] The MAPK/ERK pathway has been shown to be overactive in autism in both human and animal studies.[53,54] Autism is hypothesized to be caused by IL-17 activation in the prenatal brain, depending on the pathways mentioned above. Furthermore, administering MIA modeled mice-specific antibodies or probiotics to IL-17 has been shown to reduce the indications of autism in offspring. Given the link between the maternal microbiota and autism, it's possible that increased salt intake during pregnancy causes autism in the offspring.[55] All mechanisms that develop due to sodium hypertonicity are summarized in Table 1.

Conclusion

Autism is a neurodevelopmental disorder that is becoming more common due to genetic, epigenetic, and environmental causes. The cause and treatment have not been fully clarified. Dysbiosis can be induced by dietary factors affecting the microbiome's composition, and studies have demonstrated that dysbiosis causes immune system dysregulation. However, the processes by which elements connected to the mother's nutrition affect the development of the kid throughout the maternity period have not been identified. In our country and around the world, people consume more salt than is suggested. High salt consumption alters immune system functioning and inflammatory state by causing dysbiosis in the gut microbiota. Neurodevelopmental illnesses such as autism are caused by immune system dysregulation during pregnancy. Gut dysbiosis induced by increased salt consumption during pregnancy and the problems it can cause are discussed in this article. To shed light on possible pathways, more human and animal research should be conducted.

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