

# Vitamin B6 and Magnesium in Autism Spectrum Disorders: Potential Mechanisms and Clinical Applications

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## Abstract

This review explores the potential mechanisms and clinical applications of vitamin B6 and magnesium in autism spectrum disorder (ASD). We analyze their synergistic effects on neurodevelopment, neurotransmission, and gut-brain-microbiome interactions, highlighting evidence from preclinical and clinical studies. While supplementation with these nutrients shows promise in ameliorating core ASD symptoms such as social deficits and repetitive behaviors, methodological limitations and heterogeneous outcomes warrant further investigation.

**Keywords:** Autism Spectrum Disorder, Vitamin B6, Magnesium, Neurodevelopment, Nutritional Intervention

Autism Spectrum Disorder (ASD) is a wide range of neurodevelopmental disorders characterized primarily by deficits in social communication, limited interests, and repetitive behavior patterns. In recent years, the prevalence of ASD has caught a lot of attention, gradually increasing over time [1][2]. According to a report from the Centers for Disease Control and Prevention (CDC) in 2020, about 1/36 in the U.S. ASD with boys being about 3.8 times more likely to have it than girls [3]. According to the National Health Commission's "Guidelines for Screening and Intervention Services for ASD in Children Aged 0-6 (Trial)," the prevalence of ASD among children in China is about 0.7% [4]. ASD severely impacts children's daily functioning and quality of life, and if effective intervention and treatment are not provided in a timely manner, it can impose a significant financial strain on families and society. The causes of ASD are complicated, with current research focusing on genetic and environmental factors, which interact and are widely believed to contribute to ASD [5]. Nutrients are a key environmental factor, participating in many metabolic and neurodevelopmental processes in the human body. Vitamin B6 is critically regulates in amino acid metabolism, neurotransmitter synthesis, and fatty acid metabolism [6][7]. Magnesium is an important mineral involved in energy production, protein synthesis, and cell signaling [8]. Research indicates that vitamin B6 and magnesium might work together to affect brain function and emotions [9][10]. In recent years, there has been increasing attention on the potential roles of vitamin B6 and magnesium in ASD.

This review aims to explore the role of vitamin B6 and magnesium in ASD, analyze the potential biological mechanism and clinical application value of ASD, and deeply study the research and application of ASD, which may provide new ideas and new methods for its treatment.

## 1. Biological Functions of Vitamin B6

### 1.1. Metabolic Pathways of Vitamin B6

The metabolic pathways of vitamin B6 primarily include three forms: pyridoxine, pyridoxal, and pyridoxamine, which are phosphorylated to produce the bioactive form pyridoxal-5'-

phosphate (PLP). As an important coenzyme, PLP participates in the catalytic reactions of over 160 enzymes, involving the metabolism of amino acids, carbohydrates, and neurotransmitters. The metabolism of vitamin B6 mainly occurs through two pathways: direct acquisition through food intake and endogenous synthesis. Particularly in nerve cells, a deficiency of PLP can lead to various pathological states. Research indicates that key enzymes in the metabolic pathway of vitamin B6, such as pyridoxal kinase, pyridoxal-5'-phosphate oxidase (PNPO), and phosphatases, play important roles in the biosynthesis and recycling of vitamin B6. Deficiencies in these enzymes can lead to insufficient PLP levels, thereby triggering the occurrence of neuro-related diseases [11][12].

### 1.2. Role of Vitamin B6 in the Nervous System and Neurodevelopment

Vitamin B6 plays a critical biological role in the nervous system, especially in neurotransmitter synthesis, where PLP acts as a cofactor for various enzymes involved in amino acid metabolism and neurotransmitter synthesis. Research shows that PLP is crucial in synthesizing gamma-aminobutyric acid (GABA) and monoamine neurotransmitters such as dopamine and norepinephrine, which are essential for maintaining neural function. In animal models, vitamin B6 deficiency is closely related to neuronal apoptosis, reduced neuronal connectivity, and impaired neurotransmitter synthesis. Additionally, vitamin B6 has antioxidant and neuroprotective functions, reducing oxidative stress damage to nerve cells [13][14].

The impact of vitamin B6 deficiency on neurodevelopment has been confirmed in multiple studies, indicating that a lack of vitamin B6 can lead to abnormal neurodevelopment during fetal and infant stages, potentially affecting cognitive abilities and social behavior, and may result in mental health issues such as depression and anxiety [15]. Furthermore, maternal deficiency in vitamin B6 during pregnancy is also considered related to an increased risk of autism spectrum disorder in children. Therefore, ensuring adequate intake of vitamin B6 for pregnant women and infants is crucial for promoting healthy neurodevelopment [16][17].

### **1.3. Vitamin B6 and the Gut-Brain-Microbiome Axis**

Gut microbiota is really important for keeping our bodies balanced. Reports indicate that gut microbiota are associated with many neuropsychiatric disorders, such as anxiety, depression, and epilepsy. In ASD patients, changes in gut microbiota have been observed, which are related to severe gastrointestinal issues. In recent years, fecal microbiota transplantation (FMT) has become a possible treatment to improve autism symptoms. Emerging evidence implicates gut microbiota in modulating vitamin B6 metabolism: fecal microbiota transplantation (FMT) restored mitochondrial function and improved social deficits in ASD mice, partially through vitamin B6 pathway regulation. One study assessed the effects of FMT on behavior and multi-omics characteristics in ASD model mice, showing an interaction between FMT and vitamin B6 metabolism, with improvements in social deficits post-FMT linked to the restoration of mitochondrial function and regulation of vitamin B6 metabolism. Additionally, supplementation with vitamin B6 improved social behavior in ASD mice. Further research indicates a connection between gut microbiota-regulated vitamin B6 metabolism and impaired fatty acid metabolism (suggesting mitochondrial dysfunction) in the context of ASD mouse models. Future studies should investigate the interactions between these pathways and their collective impact on improving social behavior in ASD [18].

Another animal study on ASD showed that the deficiency of vitamin B6 is crucial for gut microbiota-mediated ASD-like behavior in mice. The study found that gut microbiota has a novel role in regulating vitamin B6 and confirmed that gut microbiota-mediated vitamin B6 improved social deficits in ASD mice, while intraperitoneal injection of vitamin B6 also improved social deficits. Furthermore, ASD patients exhibited reduced dopaminergic activity in the prefrontal cortex, indicating that the dopamine levels in ASD mice are regulated by gut microbiota-mediated vitamin B6, thereby improving social deficits in ASD mice [19].

## **2. Biological Functions of Magnesium**

### **2.1. Metabolism and Physiological Functions of Magnesium**

Magnesium (Mg) is the fourth most abundant cation in the human body, participating in over 600 biochemical reactions as a cofactor for various enzymes. Magnesium is crucial for how our cells produce energy, protein synthesis, and the synthesis of DNA and RNA, which are essential for normal nervous system function [20]. It plays a critical role in nerve conduction, neuronal excitability, and synaptic plasticity [21]. Low magnesium levels may lead to impaired  $\gamma$ -aminobutyrate signaling and increase the risk of ASD [22]. Several studies have shown that serum magnesium levels are significantly lower than normal pediatric [23][24], so ensuring adequate magnesium intake is essential to maintain overall health.

### **2.2. Role of Magnesium in the Nervous System, Neurotransmission, and Synaptic Function**

Research shows that magnesium plays an important role in neurotransmission and synaptic function by participating in neurotransmitter release and regulating neuronal excitability. Magnesium is considered an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which can reduce excessive neuronal excitability, thereby protecting nerve cells from excitotoxic damage [25]. Additionally, magnesium's role in the process of neural signal transmission is also significant.

Magnesium ions, as an important electrolyte, play an indispensable role in both excitatory and inhibitory signal transmission in neurons. Studies have shown that magnesium can influence neurotransmitter release and neuronal membrane potential, thereby regulating neural signal transmission. For example, it affects the activity of NMDA receptors, thereby modulating glutamate transmission in the nervous system, which is essential for learning and memory processes. Furthermore, magnesium is involved in the activation of various enzymes, all of which are closely related to neural signal transmission. Low magnesium levels are believed to be associated with various neurological diseases, highlighting magnesium's importance in maintaining nervous system health [26]. Therefore, ensuring adequate magnesium intake is significant for maintaining neural function and preventing neurological diseases.

### **2.3. The Impact of Magnesium Deficiency on Neurodevelopment**

The impact of magnesium deficiency on neurodevelopment has drawn widespread attention. Research shows that magnesium plays a crucial role in the neurodevelopment of embryos and children. A deficiency of magnesium may lead to poor neuronal development, affecting the formation of neural networks, which can subsequently trigger cognitive and behavioral disturbances. Therefore, magnesium deficiency is associated with the occurrence of neurodevelopmental disorders (such as autism spectrum disorder and attention deficit hyperactivity disorder) [27]. In animal models, magnesium deficiency has been found to lead to increased neuronal apoptosis, which may affect the formation of neural networks related to later learning and memory abilities. Additionally, magnesium deficiency can impair neurotransmitter synthesis and release, potentially exacerbating neurodevelopmental disorders. Thus, promoting healthy neurodevelopment and ensuring adequate magnesium intake for children and pregnant women is essential [28]. Supplementation with magnesium may become an effective strategy for the prevention and intervention of neurodevelopmental issues.

### **2.4. The Relationship Between Magnesium Deficiency and Behavioral Abnormalities**

Magnesium deficiency is significantly correlated with various behavioral abnormalities, especially among ASD patients. Studies showed that serum magnesium level is negatively correlated with ABC scale total score and communication ability score [25], Skalny et al. In a study of magnesium content in children with ASD, they proposed that magnesium content in hair and urine may be an important predictor of neurodevelopmental disorders [29]. Magnesium deficiency may lead to nerve conduction disorders, which can cause anxiety, depression and other mood disorders [30]. Magnesium deficiency is thought to aggravate social interaction impairment and behavioral problems. The clinical studies have shown that children with ASD tend to be lower than the normal range, and some patients have improved behavioral and social [31] after magnesium supplementation. Moreover, magnesium is essential for emotional and behavioral stability, such as the balance of neurotransmitters such as glutamate and GABA play an important regulatory role [32], so magnesium supplementation may become an adjunct to ASD treatment and deserves further clinical research and exploration.

### **3. Interaction Between Vitamin B6 and Magnesium**

#### **3.1. The Synergistic Interaction Between Vitamin B6 (including its active form pyridoxal phosphate) and Magnesium**

Magnesium participates in the metabolism of vitamin B6, particularly in neurotransmission and enzyme activity. Research shows that magnesium deficiency may affect the bioavailability of vitamin B6 in the body. For example, magnesium facilitates the conversion of vitamin B6 to its active form, pyridoxal phosphate [33]. Additionally, the interaction between magnesium and vitamin B6 involves various enzyme-catalyzed reactions, which play important roles in amino acid metabolism and neurotransmitter synthesis and metabolism [6]. Insufficient magnesium can affect the activity of glutamate decarboxylase, a cofactor for vitamin B6, leading to the conversion of the excitatory neurotransmitter glutamate into the inhibitory neurotransmitter GABA, potentially exacerbating symptoms of anxiety and other neuropsychiatric disorders [10][11]. Therefore, adequate intake of vitamin B6 and magnesium is essential for maintaining normal nervous system function and overall health.

#### **3.2. The Importance of the Synergistic Effect of Vitamin B6 and Magnesium on Neurodevelopment**

Research has found that vitamin B6 plays a key role in the development and function of the nervous system, particularly during the growth, differentiation, and synapse formation of neurons. Magnesium promotes normal neurodevelopment by regulating neuronal excitability and synaptic plasticity [34]. Notably, deficiencies in both vitamin B6 and magnesium can lead to neurodevelopmental disorders, resulting in cognitive and behavioral issues. Some studies indicate that maternal deficiency in vitamin B6 and magnesium during pregnancy may lead to poor fetal neurodevelopment, affecting children's cognitive and behavioral development [16]. Additionally, adequate magnesium intake is believed to alleviate neurodevelopmental issues caused by vitamin B6 deficiency, demonstrating the interdependence and synergistic effects of both nutrients on neurodevelopment. Therefore, ensuring adequate intake of vitamin B6 and magnesium during early pregnancy and childhood is essential.

### **4. Current Status of Clinical Research**

#### **4.1. Research on Vitamin B6 in ASD Interventions**

The application of vitamin B6 in ASD interventions has garnered widespread attention. Recent studies indicate that vitamin B6, as a coenzyme, participates in various biochemical reactions, particularly in amino acid metabolism and neurotransmitter synthesis. Research has found that ASD patients often exhibit metabolic disorders of vitamin B6, and supplementation may improve their behavior and social skills [35]. An intervention study on children with ASD showed that vitamin B6 supplementation significantly reduced behavioral problems and improved children's social skills. However, long-term high-dose use of vitamin B6 may lead to side effects such as peripheral neuropathy, and its safety and efficacy need to be cautiously evaluated in clinical applications [36]. A small study on the IQ of ASD patients (n=8) found statistically significant benefits in IQ for the treatment group using vitamin B6 [37]. Another study measuring plasma total vitamin B6 levels explored the biochemical basis of vitamin B6 treatment, showing that after supplementation, 77% of ASD children had elevated plasma total vitamin B6 levels, which was believed to

be associated with improved behavior [38]. Research has found that maternal vitamin B6 deficiency during pregnancy alters the expression of genes related to the GABA system, indicating the important role of vitamin B6 in brain development [39]. However, some studies have shown no significant differences in social interaction, communication, compulsivity, impulsivity, or hyperactivity between the treatment and placebo groups after vitamin B6 intervention. The limitations of these studies include small sample sizes and poor reliability of assessment scales, necessitating further research.

#### **4.2. The Impact of Magnesium Supplementation on ASD Symptoms**

Research indicates that magnesium deficiency may be associated with the exacerbation of ASD symptoms, particularly in cases of magnesium deficiency, where its role in regulating emotions and cognitive function is more pronounced. A lack of magnesium may lead to excessive neural excitability, thereby worsening behavioral problems in ASD. Clinical studies show that magnesium supplements can improve social skills and emotional states in ASD patients, reducing anxiety and aggressive behaviors [40][41]. Additionally, the synergistic effects of magnesium with other vitamins and minerals are also considered an adjunctive approach to improving ASD symptoms, and ASD patients have begun receiving magnesium treatment. Among them, some studies have found that taking magnesium and vitamin B6 together works better.

#### **4.3. The Impact of Combined Supplementation on ASD Symptoms**

Several studies have explored the effects of combined supplementation of vitamin B6 and magnesium on ASD symptoms. Research has found that ASD patients often exhibit deficiencies in nutritional elements, with deficiencies in vitamin B6 and magnesium potentially related to the severity of their symptoms [42]. A study on children with ASD showed that supplementation with vitamin B6 and magnesium could improve their behavior and social skills, particularly in cases of nutritional deficiency [43][44]. Furthermore, combined supplementation may also influence the pathological mechanisms of ASD by improving gut microbiota function, thereby enhancing the overall quality of life for patients [43]. Therefore, as a potential adjunctive treatment, the combined supplementation of vitamin B6 and magnesium warrants further research and validation in the clinical management of ASD.

These two nutrients have potential positive effects on improving ASD symptoms, and the research results on vitamin B6 and magnesium in ASD interventions have been comprehensively analyzed. However, some studies have failed to confirm their efficacy, and this discrepancy may stem from differences in study design, sample sizes, individual participant differences, and measurement indicators. Moreover, current research has many limitations, including insufficient sample sizes, inadequate study designs, and a lack of long-term follow-up. These factors restrict our overall understanding of the roles of vitamin B6 and magnesium in autism spectrum disorder. Additionally, individual differences, genetic backgrounds, and environmental factors may also influence the efficacy of these nutrients, so patient-specific circumstances and needs should be considered when formulating intervention plans. Future research should further explore the mechanisms of action of vitamin B6 and magnesium in ASD treatment and evaluate their

combined effects with other therapies to provide more effective comprehensive treatment options for ASD patients.

Future investigations should explore the optimal supplementation doses, timing of interventions, and combinations with other treatment methods. Additionally, studies should be conducted on larger populations to validate the effects of these micronutrients on ASD. Furthermore, it is necessary to consider differences in genetic backgrounds, dietary habits, and lifestyles that may affect ASD, aiming for a more comprehensive understanding of the mechanisms of action of vitamin B6 and magnesium to guide clinical practice.

Current research findings suggest that as an adjunctive treatment strategy, supplementation with vitamin B6 may be considered as part of ASD management, and nutritional interventions should be combined with other treatment methods (such as behavioral therapy, pharmacotherapy, etc.) to form a multidimensional intervention system that maximizes the quality of life for patients. Therefore, future research should focus on assessing the effectiveness of comprehensive treatment plans while also considering the adaptability and feasibility of nutritional interventions for different individual groups. Additionally, healthcare professionals should timely adjust treatment plans to ensure that patients receive the best therapeutic outcomes while remaining attentive to the latest research findings.

In summary, studies on vitamin B6 and magnesium for autism are still getting started, and future in-depth studies will provide us with clearer insights, helping to improve how we treat patients.

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