Narrative Review Article

Role of Zinc and Shank Protein Family in Autism Spectrum Disorder

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ABSTRACT

Autism spectrum disorder (ASD) is a brain developmental disorder influenced by various genetic and environmental factors. Zinc, a trace element essential for cellular functions such as growth, wound healing, and immune support, also plays a novel role in brain development during pregnancy. During brain development, synoptic proteins have a major role in successful brain development. Shank is one of the synaptic proteins which are regulated by Zinc. Zinc and Shank are mostly involved in neurological disorders, especially in Autism. Much recent literature highlights the involvement of Zinc and Shank in neurological disorders, particularly ASD. In PubMed, there are nearly 250 articles published in association with Zinc and Autism spectrum disorder. Similarly, the zinc and shanks protein family are widely studied and there are 125 articles published in the ASD model. However, the crosstalk between zinc and shanks proteins has not been exclusively reviewed in the development of autism since last year. The purpose of this review is to highlight the fundamental role of zinc and shank proteins in the development of autism. The first part of the review focuses on the role of Zinc and Shank in the ASD brain, and the second part focuses on crosstalk between zinc and shank genes in the brain especially in ASD.

Keywords: Autism spectrum disorder, Zinc, Shank, postsynaptic density protein and DNA damage

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by heterogeneous repetitive behaviors. Over recent years, the prevalence of ASD has increased, yet there are no specific biomarkers or targeted medications to cure it (1). Despite extensive scientific research uncovering various mechanisms, novel elements continue to emerge in understanding autism's impact on brain development. Among these, zinc has gained attention as a key mediator in ASD-related neurodevelopmental processes (2). Zinc is the second most abundant metal in the human body and plays essential roles in both biology and chemistry. It is a vital nutrient involved in hundreds of enzyme-catalyzed reactions that support metabolism, nerve conduction, wound healing, and hormone secretion (3). As Zn^{2+}, it functions as a co-factor for approximately 300 enzymes and 2,000 transcription factors. Previous literature demonstrates that more than 10% of proteins require zinc binding for proper function, and Zn^{2+} influences their expression (18). One of Zinc's critical roles is in preserving genetic material. It stabilizes DNA and regulates gene expression, which is essential

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for normal cell development and division, especially during key growth phases such as infancy, puberty, and pregnancy. Zinc deficiency during these periods can result in stunted growth, impaired immune function, and reproductive issues (4). Additionally, zinc contributes to protein and cell membrane structure, wound repair, and the senses of taste and smell, influencing nearly every major body system (5). Shank proteins, which are regulated by zinc, are synaptic scaffolding proteins with significant roles in neurological function. The interaction between zinc and Shank proteins is particularly relevant in the context of ASD. However, the crosstalk between zinc and Shank proteins has not been comprehensively reviewed in relation to autism development until recently. This review focuses on the role of zinc and Shank in brain function and ASD, emphasizing their molecular interplay and its implications for neurodevelopment.

ROLE OF ZINC IN THE BRAIN

About 60 years ago, Frederich Timm developed a histochemical technique that enabled scientists to visualize zinc distribution in brain tissues. Subsequent studies using electron microscopy revealed a rich supply of free zinc concentrated in several brain regions, particularly within synaptic boutons, which are specialized structures at the ends of neurons responsible for signal transmission (9). This discovery suggested that zinc may play a role in synaptic communication (10).

Zinc is essential for brain function. It contributes to neurotransmission, sensory processing, and neuronal signaling. Depending on the cellular environment, zinc can initiate both pro-survival and pro-death pathways. It is involved in numerous signal transduction cascades that regulate neural activity and plasticity, and it is required to maintain healthy brain function (11). Stored in presynaptic vesicles, zinc is released during neuronal activity to support synaptic signaling. Transporters such as ZnT3 help maintain zinc homeostasis, and disruptions in this balance can lead to serious neurological consequences (12).

During brain injury or disease, elevated zinc levels can cause cellular damage. Excess zinc may accumulate in nearby cells, impair energy production, increase oxidative stress, and trigger apoptosis by inhibiting enzymes like GAPDH, which reduces NAD^+ and ATP levels (13). Zinc also activates proteins such as PKC and Erk-1/2 and enhances NADPH oxidase activity, contributing to neuronal harm (14). In some cases, zinc initiates cell death via the p75NTR pathway. On the other hand, deficiency can also lead to apoptosis through more conventional mechanisms (15). Imbalances in zinc levels are linked to various neurological disorders, including Alzheimer's, Parkinson's, Huntington's, and ALS (16).

Among these, Autism Spectrum Disorders (ASDs) have been extensively studied in relation to zinc deficiency. Children with ASD often exhibit low zinc levels, which can lead to the accumulation of toxic metals like mercury and disrupt metal-dependent biological systems (17). Zinc is found in high concentrations in brain regions such as the hippocampus, amygdala, cerebral cortex, and olfactory cortex, where it supports cognitive functions like learning, memory, and neurogenesis (24, 25). It also regulates neurotransmitters and neurotrophic factors (26, 27), and plays dual roles in neuroinflammation, acting through both pro-inflammatory and anti-inflammatory pathways (28).

During synaptic activity, Zn^{2+} is released with glutamate and interacts with receptors such as NMDA, GABAA, and AMPA (29). It is crucial for long-term potentiation (LTP), particularly in forming auditory fear memory (30), and activates glial cells that contribute to neuroinflammation (31). Zn^{2+} also influences the Shank protein family, which is vital for synaptic structure and function. Babaknejad *et al*. (2016) found significant differences in plasma zinc levels between autistic patients and controls, prompting further investigation into zinc's role in ASD (32). Zinc deficiency in autism is often linked to malabsorption in the intestinal mucosa, leading to DNA damage and impaired antioxidant defenses (33). Multiple studies have confirmed elevated zinc deficiency in children with ASD (34), including findings by Lakshmi P *et al*. (2011) and Conti *et al*. (2024), who reported that zinc deficiency exacerbates oxidative stress and metabolic disturbances (35, 36).

To explore this further, Sauer AK *et al*. (2022) developed a prenatal zinc-deficient mouse model to study ASD pathophysiology and mechanisms of zinc homeostasis during early development (37,38). Zinc regulates various postsynaptic proteins, and its deficiency may disrupt Shank scaffolding proteins, contributing to ASD onset. This review aims to explore the emerging crosstalk between zinc and Shank proteins in the context of neurological disorders, particularly ASD. Prior studies have shown that zinc modulates glutamatergic receptors such as NMDA, which in turn influence Shank proteins at the postsynaptic level.

ROLE OF SHANK FAMILY IN THE BRAIN

The neurotransmission is transmitted in the synaptic cleft between the pre and post synaptic neurons. For regulation of neuro chemicals transmission, pre and post synaptic proteins play a major role in the glutamatergic, cholinergic and GABAergic neurons. The pre-synaptic proteins such as SNARE, Munc-18 are essential for vesicle fusion. Likewise, post-synaptic proteins such as PSD-95, Shank and Homer are essential for synaptic transmission and plasticity. The group of post-synaptic proteins are called postsynaptic density (PSD). PSD is located mainly on dendritic spines under the postsynaptic membrane where many proteins present and function as receptors, scaffolding signaling enzymes (39). Numerous evidence demonstrates that dysfunction within the PSD leads to many neurological diseases such as schizophrenia and autism spectrum disorder, epilepsy and Alzheimer's diseases (AD) (40). Among PSD, Shank proteins belong to scaffold proteins which are involved in synaptic organization and signaling (41). Scaffold proteins mean bringing together multiple proteins and activating or facilitating specific reactions. Interestingly, Shank family proteins have many key features in synaptic locations. The Shank family has three genes such as Shank1, Shank2 and Shank3 and each has a different role. Shank deletion or mutations have been implicated in schizophrenia and Alzheimer's diseases. Besides, Shank gene has been observed in the human epithelial cancers acting as a potential oncogene. Nevertheless, shank gene role has been predominantly studied in the autism spectrum disorders with the novel interaction with Zinc in the developmental stage. There is not much review article available to summarize the crosstalk of Zinc and Shank genes in the ASD. Synaptic proteins have important roles in the brain circuits and development including shank 1, shank 2 and shank 3 proteins. Evidence strongly suggests that SHANK genes were first identified in neurodevelopmental disorders. Among ASD patients ~1% of all patients with disruption of the Shank gene family (42). The human genetic data demonstrates the association between different SHANK family and distinct cases of ASD, these three mutant mice carrying Shank1 and Shank2 deletion display certain ASD like phenotypes. The mice show repetitive behaviors, motor behavior, reduced social interaction and ultrasonic vocalization (43-46).

Shank proteins identified with ASD individuals who have mutations in Shank genes (47). Despite shank proteins directly involved in the development of ASD, the availability of shank proteins is different among the brain regions.

CROSSTALK BETWEEN ZINC AND SHANK PROTEINS IN ASD

Based on the literature clearly stated that Zn plays a significant role in the regulation of cell cycle, DNA replication and proteins (48). Zn deficiency alters the synaptic Shank scaffold protein changes synapse plasticity and maturation is associated with ASD (49). Lee *et al*. reported that social interaction behavior was improved by Shank2 Zn mobilization. (50). In the line of experiments, Fourie *et al*., demonstrated that Zn supplementation minimizes the autism-like repetitive behavior (51) through modulating NAMDAR (52). It is also notable that Zn supplementation improves alterations of Shank gene expression (53). Not only shank1, shank3 mutations also impact on lower Zn levels in the association between shank3 and zinc transporter expression (54). Since Zinc is highly enriched in the PSD, it shows a dominant effect on shank2/3 (55, 56). If zinc is available in the synaptic location where shank2/3 form in the PSD and increase the synaptic density (57). In another hand, zinc depletion likely reduced the postsynaptic density along with decrease with shank2/3 genes (58). This data strongly suggests that there is intensive action between zinc and shank genes to increase synaptic plasticity machinery of postsynaptic density. SHANK proteins, particularly SHANK2 and SHANK3, serve as critical scaffolding components within the postsynaptic density, orchestrating the assembly of synaptic signaling complexes. Their structural integrity and localization are highly dependent on zinc, which stabilizes SHANK domains and facilitates protein-protein interactions essential for synaptic maturation. Zinc dysregulation, whether due to environmental factors or altered expression of zinc-binding proteins like S100B, can impair SHANK function by disrupting zinc availability during key developmental windows (59). In individuals with SHANK mutations, this disruption is compounded, as the mutated proteins may already exhibit reduced stability or impaired binding capacity. Thus, zinc deficiency and SHANK mutations converge mechanistically by destabilizing synaptic architecture and impairing neuronal connectivity, contributing to neurodevelopmental phenotypes such as those observed in autism spectrum disorders. Zinc sulphate prevents cerebellar neuronal loss (60). However, Zn and shank

Table 1. Zinc-Shank interaction studies in ASD models

AuthorNear	Model	Main findings /Relevance to ASD
Hung AY *et al*., 2008	Mice model	Shank1 lacking/weaker synaptic transmission
Silverman JL *et al*., 2011	Mice model	Shank 1 null mice /deficits in autism relevant behaviors
Wohr M *et al*., 2011	Mice model	lacking shank1/ reduced ultrasonic vocalizations
Won H *et al*., 2012	Mice model	Zinc and Shank2 mutant/ restoring NMDA receptor function
Lee K*et al*., 2024	Mice model	Shank2 knockout/altering synaptic function
Zhang L*et al*., 2023	Mice model	Zinc water/ reduce repetitive behaviors
Al-Garni AM *et al*., 2025	Rat model	Zinc sulfate/ prevent degeneration in cerebellar cells

crosstalk not only in the brain, but also found in the gut through limiting Zn absorption in ASD (Table 1).

CONCLUSION

Centers for Disease Control and prevention of autism and developmental disabilities monitoring networks reported that 3.2% of children have been identified with ASD among eight years old in the USA as ASD based data 2022 (61). The prevalence of autism is co-occurring with depression, epilepsy and anxiety among males than females. Autism is a genetic disorder with neuronal developmental disorders resulting in dysfunction in social interactions and with repetitive behaviors. Hence, this review summarizes the key role of zinc and shank in the development of the autism spectrum disorder to understand the fundamental mechanisms to create new insights for ASD research and development. Researchers should consider the developmental disabilities and prevalence of autism to develop the therapeutic approach to minimize ASD development. Numerous literatures reported that zinc deficiency causes ASD in the reduction of Purkinje cells in the cerebellum. However, Zinc sulfate could be one of the significant therapeutics to prevent Purkinje cells in the cerebellum. Another study reported that Oxiracetam and zinc ameliorate autism like symptoms. Zinc Gluconate orally administration could improve tight junctional remodeling of the in ASD. Oxytocin intranasal administration ameliorates social behavioral deficits in ASD. There is evidence suggesting controlling ASD prevalence. The treatment for shank, deletion or mutation is the only way to control ASD prevalence. Among shank family, shank1 and shank 3 are involving the development of ASD. For example, shank1 deficiency could enhance performance in a learning task however in contrast loss of shank3 leading to behavioral abnormalities in ASD. Although improving the zinc level, shank family levels also must be studied. The cross talk between zinc and shank is vital part in the development of ASD, hence, researchers may improve the animal models to study the novel mechanisms to identify zinc and shank role in ASD model in the future.

Based on current literature, researchers must clarify the specific role of Shank family proteins in the development of mouse models. Zinc supplementation may help restore zinc balance; however, the precise requirements for zinc levels should be carefully evaluated in these models. As a chemical element, zinc can become toxic if its concentration exceeds physiological limits. Shank proteins facilitate postsynaptic signaling by supporting neurotransmitter activity. Although both zinc and Shank proteins contribute to postsynaptic function, behavioral outcomes ultimately depend on neurochemical release, particularly glutamate, which is mediated by NMDA receptors. Overactivation of NMDA receptors can lead to excessive glutamate signaling, resulting in repetitive behaviors or neuronal toxicity. Therefore, future research should focus on developing effective mouse models and therapeutic strategies to investigate the combined effects of zinc, Shank proteins, and NMDA receptor activity in the context of ASD development.

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CONFLICT OF INTERESTS

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