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Review Article

Role of the PI3K/Akt/mTOR Pathway in Autism Spectrum Disorder: Insights into Heavy Metal Toxicity

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Abstract

The review provides an in-depth understanding of the molecular mechanisms in heavy metal-induced neurotoxicity and the therapeutic use of natural products in ASD intervention. The PI3K/Akt/mTOR pathway has been linked to autism spectrum disorder characterized by a decline in social interaction and difficulties in communication as well as repetitive behaviors, which is pivotal in the disease pathogenesis and exacerbated by heavy metal toxicity. Heavy metals including lead, mercury, arsenic, and cadmium have been found to interfere with cellular processes, impairing neurodevelopment and resulting in abnormal signaling cascades, synaptic dysfunction, and neuronal damage through mechanistic induction of oxidative stress, inflammation, and mitochondrial dysfunction as well as disruption of metal homeostasis—all of which dysregulate the PI3K/Akt/mTOR pathway. Preclinical investigations have demonstrated that polyphenols, flavonoids, and herbal extract shows the potential to modulate the neuroprotective pathway, synaptic flexibility, and inflammation through antioxidant, anti-inflammatory, and metal binding properties that subdue heavy metal-induced neurotoxicity and restore regular PI3K/Akt/mTOR signaling. Further research is necessary to elucidate the precise mechanisms of action of these natural compounds and evaluate their clinical efficacy.

INTRODUCTION

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by deficits in social communication and interaction alongside restricted, repetitive patterns of behavior, interests, or activities [1,2]. These symptoms manifest early in a child's development, often within the initial two years of life, and cause significant impairment in social, occupational, or other areas of functioning. The stereotypical behaviors exhibited by those with ASD stem from perturbations in various regions of the brain, including the amygdala, cerebellum, hippocampus, and cerebral cortex, which disrupt typical neurodevelopmental processes [3,4]. Recent statistics indicate concerning rates of ASD, with one in every fifty-four American children now diagnosed along the spectrum. Genetic predispositions contribute greatly to disease susceptibility. However, environmental factors such as exposure to toxic heavy metals have increasingly become topics of intense investigation. Lead, mercury, cadmium, and arsenic pervade the environment and are well-established developmental neurotoxicants. Epidemiological data suggests links between prenatal and childhood heavy metal exposure and enhanced propensity for ASD [5,6]. These metals breach the placental and blood-brain barriers, accumulating at harmful concentrations in the brain to interfere with normal development. Additional non-hereditary risk modulators include older parental age, poor prenatal nutrition, antenatal infections, and certain medications or compound exposures during gestation. Maternally activated immunity due to infections while pregnant may also alter the offspring social behaviors [7]. This review explores the growing body of research on ASD etiology with emphasis on the roles of heavy metal intoxication and dysregulation of PI3K/Akt/mTOR signaling in disease pathogenesis. It also discusses the prospective application of select phytochemicals demonstrated to impede ASD progression.

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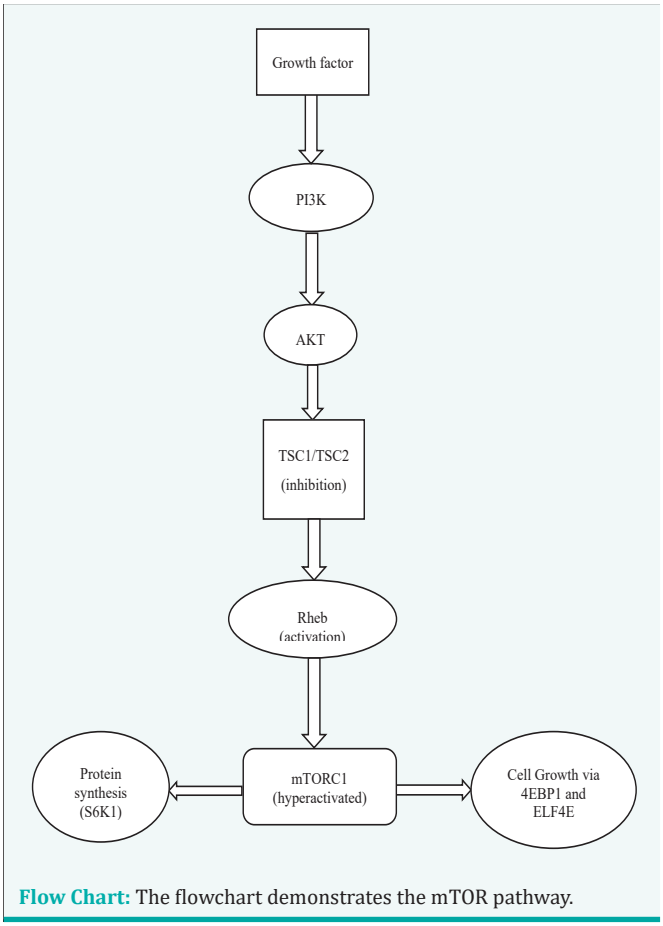
THE MTOR PATHWAY AND ITS COMPONENTS

The Mammalian Target of Rapamycin (mTOR) kinase was originally discovered in the yeast Saccharomyces cerevisiae, the ligands are essential for viability and are encoded by the TOR1 and TOR2 genes [8]. An antibiotic that is produced by the soil bacterium Streptomyces hygroscopicus, rapamycin, is known to specifically inhibit mTOR. Although rapamycin was discovered as an, initially synthesized antifungal agent it later exhibited immunosuppressive and anti-proliferative effects [9,10]. mTOR is widely expressed in mammalian cells and belongs to the Phosphatidylinositol Kinase-Related Kinase (PIKK) family [11] by binding directly with FK506-Binding Protein 12 (FKBP-12), rapamycin inhibits mTOR. There are two different protein complexes of mTOR: mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) [12–14]. mTORC1 plays a role in the sense of rapamycin and controls several key cellular processes including protein synthesis, autophagy, metabolism and cell growth [15-17]. mTOR-dependent regulation of autophagy mTORC1 is a protein complex consisting of at least some or all of the core components mTOR, RAPTOR (regulatory-associated protein of mTOR), mLST8 (also known as GβL), and PRAS40 (proline-rich Akt substrate 40kDa). mTORC2, on the other hand, is insensitive to rapamycin and regulates cytoskeletal organization, cell survival, and metabolism. The core components of mTORC2 are mTOR, RICTOR (Rapamycin-insensitive companion of mTOR), mLST8, mSIN1 (mammalian stress-activated protein kinase-interacting protein 1), and PROTOR [18] (Flow Chart).

The flowchart demonstrates the mTOR pathway, where growth hormones stimulate PI3K to AKT and then halt TSC1/TSC2; Rheb is also activated, which consequently activates mTORC1. As a result, mTORC1 regulates cellular functions including cell division and production of protein. Mutations or loss of TSC1/TSC2 function results in hyperactivation of mTORC1 and, importantly, has been associated with neurological diseases such as ASD. This hyperactivation disturbs the abnormal growth of synapses and neurons, which exacerbates the symptoms of autism.



Flow Chart: The flowchart demonstrates the mTOR pathway.

REGULATION AND ACTIVATION OF MTOR SIGNALING

mTOR signaling pathway components, TSC1, TSC2, PTEN and PI3K have been implicated to be associated with ASD phenotypes [19]. Ras homolog enriched in brain (RHEB) by mTORC1 is the more direct upstream factor that triggers mTORC1 activity in neurons. Inactivation of the TSC complex by mutations impairs its ability to activate autophagy, which can result in brain tumor formation. TSC complex repression of RHEB inhibits mTORC1, and preventing this inhibition gives rise to hyperactivation of mTORC1 [20,21]. Another regulatory molecule is PTEN, which further controls Akt activation and lipid signaling by degrading the PI3K mediator, whose misregulation also results in hyperactivity in both the mTORC1 and Akt pathways [22-24]. Inactive AMPK leads to activation via dephosphorylation of T172 and phosphorylation of Raptor, inhibiting mTORC1 formation because low cellular energy levels lead to the inhibition of TORC1 by AMPK [25]. However, when the concentration of cellular nutrition is high, mTORC1 is switched on and drives ribosome biogenesis, inhibition of autophagy or initiation of mRNA translation and some downstream events [25]. In contrast mTORC2 is not nutrient sensitive but growth factor dependent and has a critical role in cell motility, growth and proliferation [25,26]. The TSC1/TSC2 complex is a potent inhibitor of mTORC2 activity, and the activation of mTORC2 is essential for coordinating cytoskeletal dynamics and cellular metabolism. While Akt induces mTORC1 signaling and positively regulates mTORC1, it is phosphorylated by mTORC2 that in turn enhances the activity of mTORC1 and consequently inhibits autophagy [27].

PI3K/AKT/MTOR SIGNALING CASCADE

The PI3K/Akt/mTOR cascade signaling network is a critical transduction pathway that influences neurodevelopment by upregulating intracellular reactions from extracellular cues. It interferes with axon guidance, neural progenitor proliferation and neuronal differentiation [28]. This pathway is vital in the adult nervous system to modulate neurotransmitter release, maintain the morphology of dendritic spines and mediate plasticity. The activation of mTORC1 has been shown to facilitate the process of Long Term Potentiation (LTP) and subsequent synaptic strengthening through protein synthesis at synapses [29]. The PI3K/Akt/mTOR pathway also integrates extrinsic inputs, including neurotrophic factors and synaptic activity that can modulate synaptic transmission and neural connections. The PI3K/Akt/mTOR pathway involved in the regulation of autophagy comprises upstream signaling molecules of mTOR such as Phosphoinositide 3-kinases (PI3K) and protein kinase B (Akt/PKB). Activation of the kinase Phosphatidylinositol-3-OH-kinase (PI3K), downstream growth hormone or insulin binding to tyrosine kinase receptor, leads to phosphorylation of Phosphatidylinositol-4,5-bisphosphate (PIP2) and sequentially production of phosphatidylinositol 3,4,5-triphosphate [30-32]. PIP3 is a second messenger that draws Akt to the cell membrane where it can be phosphorylated by mTORC2 and PDK1 at Thr308 and Ser473, respectively [33]. This phosphorylation decreases the TSC complex's action against mTOR, advancing mTORC1 activity due to repression of TSC [34]. PTEN, a PI3K inhibitor, is a key negative modulator of this pathway because it dephosphorylates PIP3 to form PIP2 and thus also regulates the strength of the incoming signals [35].

THE ROLE OF PI3K/AKT/MTOR IN AUTISM SPECTRUM DISORDERS

ASD is linked to a variety of cellular changes and structural abnormalities in the brain's structure, including cortical dysgenesis, aberrant neuronal migration, bigger brain size, higher cell density, fewer Purkinje cells in the cerebellum, and microcephaly and macrocephaly [36]. Disruption of synaptic pruning, an essential process for brain development, is a prominent characteristic of ASD [36]. In ASD brains, there is a correlation between higher spine density and greater phosphorylation of mTOR and its downstream effector, ribosomal protein S6 [37]. The Akt/mTOR pathway increases synaptic Long-Term Potentiation (LTP), which is important for learning and memory formation [38]. In ASD models produced by valproic acid, mTOR activity inhibition enhances autophagy via the PI3K/Akt/mTOR pathway and enhances social interactions [38]. Numerous genetic studies have found multiple potential genes linked to ASD, including genome-wide association studies, Single Nucleotide Polymorphism (SNP) investigations, copy number variation screening, and whole-genome linkage analyses. Such downstream effectors of the Akt/mTOR signaling cascade as FMR1, PTEN, TSC1, and TSC2 are among the several potential genes [39]. Symptoms of Autism Spectrum Disorder are thought to arise in part because of the Akt/mTOR pathway's control over several neurodevelopmental processes [40].

IMPACT OF HEAVY METALS ON PI3K/AKT/MTOR SIGNALING IN ASD

The PI3K/Akt/mTOR pathway may be disrupted by heavy metal exposure, which could lead to neurodevelopmental defects linked to ASD, according to emerging research [41]. The inactivation of Akt and the dysregulation of mTOR in neural cells have also been connected to mercury exposure [41]. Research indicates that the pathophysiology of ASD may involve the involvement of heavy metal-induced disruption of the PI3K/Akt/mTOR pathway [42]. Animal models have been used in preclinical research to show that behavioral and neurobiological changes resembling ASD can be brought on by exposure to heavy metals such lead, mercury, cadmium, and arsenic during crucial stages of neurodevelopment [42]. For example, lead-exposed rodent models show abnormalities in communication, social interaction, and repetitive behaviors in addition to synaptic dysfunction and reduced neural connections [42]. Similarly, exposure to mercury causes oxidative stress,

inhibits synaptic plasticity, and alters neurogenesis, all of which lead to symptoms similar to ASD in animal models [43]. Exposure to cadmium and arsenic has also been demonstrated to disrupt neuronal growth, synaptic transmission, and neurotransmitter signaling, which may contribute to the behavioral anomalies linked to autism spectrum disorders [43].

INFLAMMATORY MECHANISMS IN ASD

Inflammation plays a vital role in the pathogenesis of autism spectrum disorder. Elevated amounts of inflammatory molecules like cytokines for instance interleukin-1 beta, interleukin-6, and interleukin-8 have been seen in the brain, cerebrospinal fluid, and peripheral blood of those with autism [44]. Moreover, increased autoantibodies, alterations in immunoglobulins, and shifts in immune cells such as T cells, B cells, monocytes, and natural killer cells regularly appear in autism patients [45]. Microglial activation, which boosts the expression of toll-like receptors and pro-inflammatory mediators, hastens neuronal harm through the PI3K/Akt/microglial pathway [45]. In these conditions, microglia take on a neurotoxic persona, generating proteases, nitric oxide, reactive oxygen species, and pro-inflammatory cytokines like tumor necrosis factor-alpha, interleukin-1 beta, interleukin-12, and interleukin-6, exacerbating neuronal damage [45]. Inflammatory signaling pathways in both the CNS and the PNS can affect synaptic function. The effects are mediated through components like microglia, cytokines, and their receptors, as well as Major Histocompatibility Complex Class I Molecules (MHCI) [46]. Microglia and astrocytes are essential for maintaining brain homeostasis by regulating synaptic morphology and plasticity. Several studies have demonstrated the critical function of neuroinflammation in ASD pathogenesis, showing different expressions of cytokines and chemokines in individuals with ASD [46]. Cytokines activate signal transduction pathways, including the JAK-STAT and PI3K/Akt/mTOR pathways, which regulate numerous cellular responses [47]. Emerging evidence also indicates microglial activation in the brains of individuals with ASD, with elevated plasma levels of the proinflammatory chemokine CCL5 (C-C motif ligand 5) observed in children with ASD [48]. Aberrations in the Akt/mTOR signaling pathway can affect cell growth and cytokine synthesis in the immune system, leading to adverse behavioral effects [49-52]. A study found that lead exposure was associated with increased oxidative stress markers and dysregulation of the PI3K/Akt/mTOR pathway in children with ASD [53]. Similarly, reports of elevated levels of mercury in individuals with ASD, which were correlated with alterations in the PI3K/Akt/mTOR pathway and increased oxidative stress have been reported [54]. Furthermore, a study demonstrated that exposure to arsenic led to activation of the PI3K/Akt/mTOR pathway and increased oxidative stress in a mouse model of ASD [54,55].

MITOCHONDRIAL DYSFUNCTION AND HEAVY METAL EXPOSURE IN ASD

Mitochondria play a pivotal role in cellular energy production, reactive oxygen species regulation, and programmed cell death [56,57]. Dysfunctions in these intracellular organelles have been implicated in the pathophysiology of autism spectrum disorder. Various heavy metals including mercury, lead, arsenic, and cadmium have a proclivity to bioaccumulate within mitochondria, disrupting their normal functioning and contributing to oxidative stress and cell injury in individuals with autism [58]. Notably, research has demonstrated that heavy metals can impair mitochondrial performance and exacerbate oxidative stress across diverse cell types, culminating in energy deficits and mitochondrial damage in autism. Specifically, mercury exposure has been thoroughly explored in relation to autism outcomes, with evidence indicating mercury's preferential sequestration within mitochondria where it impairs organelle function and exacerbates oxidative stress. Studies have also found a robust linkage between mitochondrial dysfunction and mercury exposure in children diagnosed with autism [59]. Similarly, lead exposure has been tied to oxidative stress and compromised mitochondrial functioning in autism as elevated lead levels correlated with higher markers of oxidative stress and reduced mitochondrial performance in affected children [60,61]. Furthermore, exposure to cadmium and arsenic has been displayed to provoke oxidative stress and impair mitochondrial function across various cell cultures and animal models [62,63].

EPIGENETIC DYSFUNCTION AND HEAVY METAL EXPOSURE IN ASD

Histone changes, DNA methylation, and non-coding RNAs are examples of epigenetic modifications that are essential for regulating gene expression and developmental processes. The pathophysiology of autism spectrum disease has been linked to the dysregulation of these systems [64]. Exposure to heavy metals has been shown to interfere with certain epigenetic processes, such as the PI3K/Akt/mTOR signaling cascade. For instance, differences in the DNA methylation patterns of autistic offspring have been related to lead exposure during pregnancy [65]. These alterations usually affect genes related to synapse function and neuronal progression, both of which are necessary for normal brain development. Exposure to mercury has also been linked to autism's epigenetic instability. Similarly, exposure to arsenic and cadmium has been displayed to alter microRNA manifestation and histone modifications, which change gene expression profiles associated with the pathophysiology of autism [66,67].

HEAVY METALS AND APOPTOSIS IN ASD

To maintain tissue homeostasis and healthy development, apoptosis, or programmed cell death, is necessary. ASD has been associated with dysregulation of apoptosis, and exposure to heavy metals has been demonstrated to impact apoptotic pathways, which are frequently regulated by the PI3K/Akt/mTOR pathway [68]. For example, studies have demonstrated that exposure to mercury increases the rate of neuronal apoptosis by activating the PI3K/Akt/mTOR pathway, which interferes with signals that are necessary for cell survival and death [69]. Similar to this, it has been shown that exposure to lead causes neuronal cells to undergo apoptosis via the PI3K/Akt/mTOR pathway, upsetting the delicate balance between pro-survival and pro-apoptotic signals and ultimately resulting in the death of the neuronal cells [70]. Through the PI3K/Akt/mTOR pathway, exposure to arsenic and cadmium has also been linked to apoptotic dysregulation in a variety of cell types, including brin cells [71,72].

PHYTOCONSTITUENTS IN THE TREATMENT OF ASD

Naturally occurring products have served as a source of molecules that have the potential for alleviating a wide range of conditions. Different phytoconstituents can target distinct cellular and molecular mechanisms, as well as oxidative stress, inflammatory, and apoptotic pathways, providing therapeutic effects in a range of neurodegenerative disorders [73]. By modifying the PI3K/Akt/mTOR pathway, plant bioactive compounds have shown tremendous potential in the treatment of ASD. Chrysophanol, also known as chrysophanic acid, derived from the plant Rheum palmatum has been evaluated for the neuroprotective effect in an experimental model of autism induced by propionic acid in rats [74]. According to the study, chrysosphanol prevented severe pathological alterations linked to autism, such as demyelination, and restored abnormal neurochemical levels [74]. In addition to enhancing learning, memory, and social interaction deficiencies, chyrsophanol also downregulated the PI3K/Akt/mTOR pathway in autistic mice. Despite promising preclinical results, additional clinical research is needed to establish the efficacy and pharmacological mechanisms of phytoconstituents in humans.

RECOMMENDATIONS AND CONCLUSION

PI3K/Akt/mTOR is the complex molecular mechanisms pathway in the pathogenesis of autism spectrum disorders, characterized by a deficit

in communication and social interaction. PI3K/Akt/mTOR pathway interacts with heavy metal toxicity offers important insights into the processes behind ASD .This knowledge could pave the way for novel therapeutic strategies aimed at mitigating the effects of environmental toxins, thereby improving outcomes for individuals with ASD. Further research is essential to delineate these complex interactions and to explore potential interventions that target this critical signaling pathway.

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