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Mitochondrial Dysfunction and mTOR in Autism Spectrum Disorders

Otizm Spektrum Bozukluklarında Mitokondriyal Disfonksiyon ve mTOR

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ABSTRACT

Autism spectrum disorders (ASD) are neurodevelopmental diseases that manifest themselves at early ages as insufficient social and communicative skills, repetitive sensory-motor behaviors and restricted interests, and peculiar combinations of these traits. Autism prevalence in wealthy nations is currently rising. Due to increasing numbers of diagnosis, studies on the genetic background of autism have gained momentum recently. Especially the research on mitochondrial dysfunction and mammalian target of rapamycin (mTOR) is important in that it might provide a great contribution to the ASD field for new treatment resources. .
Keywords: mTOR, mitochondrial dysfunction, autism spectrum disorders

ÖZ

Otizm spektrum bozuklukları (OSB), erken yaşam dönemlerinde kişilerde kendini sosyal iletişim becerilerinde yetersizlik, tekrarlayan sensori-motor davranışların yanı sıra kısıtlanmış ilgi alanları ile karakterize nörogelişimsel hastalıklardır. Otizm spektrum bozukluğunun dünya üzerindeki prevalansı yüksek gelirli ülkelerde artış göstermektedir. Bu artış dolayısıyla otizmin genetik altyapısına yönelik çalışmalar son dönemde hız kazanmıştır. Bu çalışmalardan mitokondriyal disfonksiyon ve mammalian target of rapamycin (mTOR) ilişkili olanları OSB tedavisinde yeni olanaklar sağlamak adına oldukça büyük bir potansiyel teşkil etmektedir.
Anahtar sözcükler: mTOR, mitokondriyal disfonksiyon, otizm spektrum bozuklukları

Introduction

Autism spectrum disorders (ASD) are a group of hereditary and heterogeneous neurodevelopmental diseases (Lord et al. 2020). According to DSM-5, the concept of the spectrum was created as the general nomenclature of pervasive developmental disorders (Autistic disorder, childhood integration disorder, Asperger's syndrome, and pervasive developmental disorder not otherwise specified) in DSM-IV. According to DSM-5, the Rett syndrome is no longer included in ASD. ASD has comorbidities that stem from single gene mutations (Hodges et al. 2020).

The most common gene mutations observed in ASD are those in Fragile X Syndrome (FMR1), Tuberous Sclerosis (TSC1, TSC2), Angelman Syndrome (UBE3A), Neurofibromatosis (NF1), Phelan-McDermid Syndrome (PTEN and SHANK3), and Rett Syndrome (MECP2) (Betancur 2011). Apart from these genes, rare mutations that occur in neurexin (NRXN1) and neuroligin (NLGN2/3) cause ASD (Jamain et al. 2003). Especially, TSC1, TSC2, NF1, and PTEN are closely related to mTOR. Tuberous sclerosis complex is an autosomal dominant disease caused by mutations of the TSC1 or TSC2 genes. Although the tuberous sclerosis complex also affects the skin, kidney, heart, and lungs, it increases the patient mortality rate the most by causing cognitive deficiencies (Crino et al. 2006). Neuropsychiatric disorders are seen in 90% of patients with tuberous sclerosis. ASD is the most frequently observed (61%) (Vignoli et al. 2015).

Chromosome 10 phosphatase and tensin homologous tumor suppressor gene (PTEN) catalyzes the dephosphorylation of the signal molecule phosphatidyl inositol 3,4,5 triphosphate (PI3K), which is involved in many critical cellular pathways (Chalhoub and Baker 2009). When PTEN is mutated, it causes many types of human cancers (Abdulkareem and Blair 2013). Mutations of PTEN are related to several neurological conditions, including cancer, epilepsy, megalocephaly, and ASD (Zhou and Parada 2012). Finally, neurofibromatosis type 1 is a single-gene patterned neurodevelopmental disorder caused by the mutation of the NF1 gene. NF1 mutation increases the probability of the formation of various tumors. In addition, cognitive impairments and autism-like

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symptoms occur in patients with neurofibromatosis type 1 compared with others (Molosh and Shekhar 2018). This study reports that gene mutations participate in ASD, their common pathway mTOR, and the treatment strategies modulating it.

Mitochondrial Dysfunction

In addition to producing more than 90% of the cellular energy molecule ATP, mitochondria have an essential role in carbohydrate, fatty acid, amino acid, and nucleotide metabolism in the cell. They are also responsible for programmed cell death, removal of reactive oxygen species, immune response, intracellular calcium ion balance, and even the maintenance of the gut microbiota. In addition to the primary role of mitochondria in bioenergetic and non-energy-dependent biological processes, it has been known that cellular, tissue, and organ functions are also dependent on mitochondrial regulation. Therefore, mitochondrial dysfunction has been associated with many diseases. Examples of these diseases are neurodegenerative and neurodevelopmental disorders. The increase in the diagnosis of neurodevelopmental ASD in recent years has accelerated studies in this field (Castora 2019). In these studies, the role of mitochondrial dysfunction in ASD was extensively investigated. Researchers focused on the factors that change the gut-microbiota-brain axis in the early stages of life. Maternal nutrition, the effect of branched amino acids, and environmental toxin exposure are some of these factors.

Gut Microbiota-Brain Axis

According to recent epidemiological, physiological, and genomic studies, some effects of the environment on human health are regulated microbially. All microorganisms found on various surfaces and body cavities of the human body are called microbiota. The microbiota includes several bacteria, archaea, bacteriophages, eukaryotic viruses, and fungi (Lynch and Pedersen 2016).

The gut microbiota also affects neurodevelopmental processes and brain functions. The first of these interactions is the gut and the extrinsic neural innervation of the brain (vagal and spinal fibers with efferent sympathetic and parasympathetic nerves extending to the gut from the brain) (Rude et al. 2019). In addition to this neural network, other routes that provide the connection between the gut and the brain are the neuroendocrine HPA (hypothalamic-pituitary, adrenal) axis, the immune system, the neurotransmitters and neuro regulators synthesized in the digestive tract microbiota, and the barrier pathways such as the intestinal-mucosal and blood-brain barriers. (Wang and Wang 2016). These connections are shaped from the fetal period to early childhood.

Along with neuronal migration, synaptic elimination, and myelination occur in the fetal brain. The mother's vaginal and fecal microbiota are transferred to the newborn at birth, leading to the newborn's gut microbiota colonization. Disruption of host microbiota-newborn interaction gives rise to various neurodevelopmental disorders (Jašarević et al. 2015a). Especially maternal oxidative stress might result in ASD because maternal stress can change the composition of the colonized microbiota. Altered colonization negatively affects the immunological and metabolic functions of the newborn. This situation is caused by the inability to meet the high metabolic energy need of the developing brain in this period due to digestive tract dysbiosis or the neuroinflammatory and immunological effects triggered by inflammation due to the changing microbiota composition (Borre et al. 2014, Gur et al. 2015, Jašarević et al. 2015b).

Maternal Gut Dysbiosis

The maternal gastrointestinal tract microbiome is crucial for fundamental processes like immune system maturation and neural development during fetal and early postnatal development. However, the mechanism that causes the neurodevelopmental effect of maternal diet has yet to be completely elucidated. Inflammation, epigenetic modification, and changes in the digestive tract microbiome are emphasized (Bilbo and Tsang 2010, Godfrey et al. 2017, al Nabhani et al. 2019,). For these reasons, neurotransmitters and their precursors, branched-chain amino acids (valine, isoleucine, and leucine), and short-chain fatty acids (acetate, propionate, and butyrate), have gained vital importance (Rivell and Mattson 2019). Branched-chain amino acids are essential amino acids ingested or produced by the microbiota and have a primary role in intercellular and inorganic nitrogen transfer (von Ehrenstein et al. 2019). According to some studies, branched-chain amino acids (BCAA) have functions beyond simple nutrition (Monirujjaman and Ferdouse 2014).

Unlike other amino acids, branched-chain amino acids (BCAA) are not metabolized in the liver, and oxidation of branched-chain amino acids occurs in peripheral tissues, primarily skeletal muscle, by branched-chain aminotransferase isozymes (Sweatt et al. 2004). In skeletal muscle, branched-chain amino acids are involved in

protein synthesis and degradation, hormonal regulation, and glucose homeostasis, besides PI3K-protein kinase B (AKT) and mTOR signaling pathways (di Gesù et al. 2021). BCAAs can also initiate mRNA translation (Kimball and Jefferson 2001). The mechanism involved in the arousal of protein synthesis by BCAAs is thought to be under the control of the mTOR signaling pathway (Hay and Sonenberg 2004). Of the three branched-chain amino acids, leucine is the one that most effectively increases mRNA translation. It has been demonstrated that leucine does this with the activation of eukaryotic translation initiation factor 4E binding protein (eIF4E-BP1) and ribosomal protein S6 kinase beta-1 (p70-S6 Kinase 1), which are the main effectors of the mTOR pathway.

Besides microbial metabolites, maternal obesity affects fetal development and programming as it can significantly alter the composition of the gastrointestinal tract microbiome of the mother and fetus (Calatayud et al. 2019, Jašarević and Bale 2019). Excessive consumption of energy-rich foods (especially fructose) causes obesity and metabolic syndrome, and the disruption of energy metabolism has other effects that are thought to cause ASD-like behaviors (Arnold et al. 2018, Mattson et al. 2018). Since these effects cause chronic activation of anabolic cellular pathways and prevent the shift of metabolic balance towards ketosis, they alter GABAergic signaling and neuronal excitation, causing neuronal hyperactivation (Rivell and Mattson 2019). In addition to hyperactivation, several studies show that prenatal stress causes synaptic plasticity and long-term potentiation (LTP)-related impairments.

LTP, Synaptic Signaling and ASD

Although no exclusive definition of LTP has been made, the broadest conceptual framework used to explain LTP describes it as a long-term strengthening of the synaptic connection after a short-term high-frequency stimulation. LTP types with different mechanisms exist, and the most studied LTP is located in the Schaffer collateral synapse, extending from the hippocampal CA1 region to CA3. According to the general opinion, the LTP here is independent of NMDA receptors and is stimulated presynaptically (Nicoll and Malenka 1995, Nicoll and Schmitz 2005).

Hippocampal synaptic plasticity is critical in learning and memory-related cellular mechanisms. (Bliss and Collingridge 1993, Morris 2003). For this reason, the effect of prenatal stress (PS) on hippocampal synaptic plasticity is investigated. In a study by Hui Zhang et al. (2017), bidirectional synaptic plasticity, namely LTP, and depression (DEP: LTP reversal), of Schaffer collaterals extending from the hippocampal CA1 to the CA3 region of a rat exposed to prenatal stress were measured. In addition, some behavioral tests were also performed. As a result of the measurements, it was revealed that LTP and DEP were inhibited, and PS decreased cognitive flexibility and increased anxiety-depression-like symptoms compared to the tests performed. It has also been determined that PS reduces the expression of postsynaptic density protein 95 (PSD95) and synaptic NMDA receptor subunits NR2A and NR2B. All this suggests that prenatal stress leads to ASD-like behaviors. Finally, exposure to environmental toxins causes ASD-like symptoms.

Environmental Exposures

The period in which exposure to pesticides, one of the environmental toxins, is accepted as a significant risk factor for comorbid intellectual disability in ASD is the first year of life (von Ehrenstein et al. 2019). Polychlorinated biphenyls (PCB) are pesticides frequently encountered in the environment and primarily used in coolers, capacitors, and transformers (Rude et al. 2019). PCBs were banned in the United States in 1977, but they continued polluting due to their presence in old buildings, and equipment, their long half-life, and the release of by-products into the environment (FernándezGonzález et al. 2011, Herrick et al. 2007, Robson et al. 2010). Although no PCB production occurred in Turkey, PCBs were imported and used in industrial products. According to a regional assessment conducted in 2010, several PCB contamination areas were identified in Turkey (Gedik and Imamoğlu 2010). PCB causes cognitive dysfunction in ASD through different mechanisms depending on the PCB type.

For instance, it is known that the PCB mixture Aroclor 1254 significantly reduces the protein and mRNA expression of GLT-1 (Struyska et al. 2012). PCB 95, on the other hand, increases neuronal dendritic growth in squirrels. Different studies on PCB 95 show that PCB 95 causes mTOR activation by increasing serine 2448 phosphorylation of the mTOR protein (Keil et al. 2018). Researchers also demonstrated that PCBs trigger inflammation in gut epithelia. Especially oral exposure to PCB-153 increases proinflammatory cytokine expression and intestinal permeability (Phillips et al. 2018). All these provide evidence for mTOR's effect on ASD.

mTOR and Synaptic Signaling

mTOR or FK506-binding protein 12-rapamycin-associated protein 1 (FRAP1) is a protein kinase, a member of the PI3K-dependent kinase family, encoded by the mTOR gene (Sabers et al. 1995). mTOR is critical in cellular functions such as lipid and protein synthesis, cell growth, and proliferation. In addition to these functions, mTOR is effective in neurodevelopmental processes like neuro-cortico-synaptogenesis, cell migration, and axon guiding (Gilbert and Man 2017). mTOR functions are affected by neuronal surface receptors and channels. These channels and receptors include molecules critical for the induction and maintenance of LTP and LTD, such as NMDA-R, AMPA-R, BDNF, and mGluR (Zheng and Gallagher 1992, Huber et al. 2001, Banko 2005, Hou 2004, Hou et al. 2006). mTOR is central to both these receptors and many signaling pathways, including molecules pyruvate dehydrogenase kinase 1 (PDK1), PI3K, Akt, and tuberous sclerosis complex (TSC1/2) (Tang and Schuman 2002, Hay and Sonenberg 2004, Schicknick et al. 2008, Costa-Mattioli et al. 2009, Slipczuk et al. 2009).

mTOR Complexes

mTOR interacts with various proteins to form two distinct complexes, mTORC1 and mTORC2. The hallmark of these complexes is that Raptor (Regulatory-associated protein of mTOR) is a component of mTORC1 while mTORC2 has the Rictor (Rapamycin-insensitive companion of mTOR). Since mTORC1 is effective in single-gene inherited ASD, it has been extensively studied on TSC1, TSC2, NF1, and PTEN. The consensus is that mTORC1 overactivation causes ASD, but the mechanisms have not been clarified yet. The most characterized function of mTORC1 is its regulation of two essential components of translational mechanisms, p70-S6 kinase 1 and 2 and eIF4E-BPs (Klann and Dever 2004). Although most studies on mTOR have focused on translation mechanisms, researchers try to enlighten the relationship between mTOR and synaptic signaling.

PTEN, TSC1/2, and NF1 with mTOR Hyperactivation in Synaptic Signaling

PTEN, TSC1, TSC2, and NF1 act on a crossing pathway as negative effectors of mTORC1 (Kelleher and Bear 2008). According to mouse models, mTOR hyperactivation induced by the PTEN mutation causes neuronal plasticity, growth, and proliferation anomalies in brain regions, including the hippocampus (Garcia-Junco-Clemente and Golshani 2014). PTEN deletion in CA3 neurons and hippocampal dentate granule cells (DG) causes morphologically distinct synaptic plasticity defects (Takeuchi et al. 2013). Some researchers are investigating the function of PTEN in hippocampal neurogenesis. Acute destruction of PTEN in the adult hippocampus results in neuronal hyperstimulation (Williams et al. 2015). Although the role of adult hippocampal neurogenesis in social interactions has not been clarified, it is thought to be remarkable in developing social skills in adolescence (Wei et al. 2011). In this context, an experiment on DG neurons of 4-week-old mice revealed that PTEN deletion negatively affects social skills (Amiri et al. 2012). Since limitation in social interactions is one of the main phenotypes of autism, the destruction of juvenile neurogenesis may contribute to ASD (Li et al. 2019).

In physiological conditions, the complex formed by tuberin encoded by TSC2 and hamartin encoded by TSC1 (TSC1/2) inhibits mTOR. An experiment performed in heterozygous mutant mice with the TSC2 gene caused mTOR hyperactivation (Ehninger et al. 2008). Concurrently, post-mitotic perturbation of TSC1 caused changes in neuronal morphology and decreased dendritic spine density (Tavazoie et al. 2005). In other TSC1/2 mutation-dependent mTORC1 over activation-based studies, besides neuronal morphological differences, synaptogenesis changes and excitation-inhibition imbalances were also observed (Henske et al. 2016). Since astrocytes and microglia are important in the development and function of synapses, it is thought that glia may be effective in the pathogenesis of ASD.

Studies on the pathogenesis of neurofibromatosis type1 and glia of mTORC1 have shown that RAS activates PI3K in embryonic fibroblast, astrocyte, and neurofibromatosis type 1 tumor cells of a mouse with a dysfunctional NF1 gene. In addition, mTORC1 inhibits tuberin via AKT, and its activity was increased by RAS (Dasgupta et al. 2005, Johannessen et al. 2005). Later, it was revealed that NF1 regulates glial cell proliferation and tumor growth, dependent on AKT/mTORC1 but independent of tuberin/Rheb, which is effective in mTOR activation (Banerjee et al. 2011). NF1 genetic function has been attributed to selective AKT hyperactivation of neural stem cell proliferation and gliogenesis in mutant mice and other studies in mouse-derived neural stem cell neurosphere cultures. On the other hand, AKT activation in stem cells is the result of differential Rictor expression (Lee et al. 2010). All these data suggest that mTOR/Rictor-regulated AKT activation plays a central role in neural stem cell proliferation and gliogenesis.

Treatment Strategies on mTOR Modulation

According to recent data, the significance of mTOR for the etiology of ASD is evident. For this reason, researchers have focused on developing mTOR modulatory treatment strategies. Among these strategies, mTOR inhibitors and gut microbiota mTOR modulations are promising. Since mTOR inhibition can prevent the abnormal signal transmission of various growth factors, it is thought that the emergence and development of diseases can be prevented by mTOR inhibition. First-generation mTOR inhibitors are rapamycin and rapamycin-derived drugs, while second-generation inhibitors contain various ATP-competing kinases. RapaLink-1, a third-generation mTOR inhibitor, has more effective therapeutic effects than rapamycin and mTOR kinases (Xu et al. 2020). These inhibitors, which alleviate the cognitive damage of ASD, have been studied principally in patients with tuberous sclerosis. In clinical trials of sirolimus performed in renal angiomyolipomas and lymphangioleiomyomatosis accompanying tuberous sclerosis, progress has been made in short-term memory and executive functions (Davies et al. 2011).

On the other hand, Everolimus reduced the frequency of seizures in patients with tuberous sclerosis and subependymal astrocytoma. In addition, an increase was observed in ASD-related quality of life scores after everolimus treatment (Franz et al. 2015, Krueger et al. 2010). Based on all these studies, it is thought that clinical conditions like FMR1, NF1, and PTEN mutation and increased mTORC1 activity-dependent macrocephaly autism syndrome may also benefit from mTOR inhibitors (Sato 2016).

Apart from pharmacological interventions for mTOR inhibition, studies aim to show that a nutritional routine that can eliminate prenatal stress in the etiopathogenesis of ASD may be neurodevelopmentally beneficial. In one of these studies, antigen-stimulated mast cell degranulation was used as a monitoring method, and the mTORC1 modulatory capacities of several amino acids were investigated (Wu et al. 2017). In addition to being a crucial component of the allergy response, mast cell activation is regulated by a series of complex intracellular signaling cascades that include the phosphorylation of main elements of the mTORC1 pathway (p70 S6K, 4E-BP1, and mTOR) (Kim et al. 2008, Yamaki and Yoshino 2012). As studies have shown that inhibition of mTORC1 with rapamycin inhibits cytokine production and antigen-specific mast cell degranulation, mTORC1 is critical in mast cell functions. In in vitro experiments performed on mast cells activated by IgE antigen, His, Lys, and Thr amino acids alone or in combination inhibit p70 S6K in the downstream pathway of mTORC1. At the same time, Leu, Ile, and Val or Leu, Ile, and Val cocktail do not affect p70 S6K phosphorylation. According to these results, various experiments were designed in vivo and with human cerebral organoids.

Researchers have drawn attention to dietary attenuation of the mTOR signaling pathway, which has promising effects on ASD-like behavioral disorders in mice (in vivo) (Wu et al. 2017). Currently, in a pioneering study conducted on human cerebral organoids, the neurodevelopmental effects of prenatal Thr, His, and Lys amino acid supplementation were analyzed using western blot, general cerebral organoid size measurement, and RNA sequencing techniques. Exposure to Thr, His, and Lys inhibited mTOR and caused a reduction in the size of cerebral organoids, supporting in vivo studies. RNA sequencing, on the other hand, revealed extensive changes in gene expression with Thr, His, and Lys administration, especially improvements in the mTOR pathway and immune functions (Berdenis van Berlekom et al. 2022).

Conclusion

In this study, current data on mitochondrial dysfunction in ASD is compiled, and treatment strategies by intestinal microbiota modulation of mitochondrial dysfunction-associated mTOR complex are presented. Current guidelines do not recommend any medical treatment for ASD, and mTOR inhibitors are promising in preclinical studies. Future research on the mTOR pathway and clinical studies of its inhibitors may radically change ASD treatments.

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