The Role of Insulin-like Growth Factor on Autism Spectrum Disorder

Bengisu Dönmez1, Kaan Erbakan1, Oytun Erbaş1

ABSTRACT

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder that is characterized by behavioral disorders including deficits in social conversations and interactions, disability in speech, and having difficulties in adapting. Insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2) are neurotrophic polypeptides, which play a significant role in survival, maturation, and developmental processes of the central nervous system (CNS), and they are believed to have potentially effective therapeutics for the treatment of autism and related disorders which are Rett Syndrome, Fragile X syndrome and Phelan-Mcdermid Syndrome whose therapeutic effects on ASD patients were analyzed, investigated in many preclinical, finished clinical and ongoing clinical studies. Recent approaches have been focused on underlying mechanisms of ASD and attempted to increase understanding and evidence for the pathogenesis of ASD. Based on animal models and clinical studies, IGF-1 administration contributes to improvements in core behaviors of ASD and restoring abnormalities. This review aimed to provide ASD with the potential role of IGFs in the treatment of ASD and place emphasis on the promising roles of IGFs.

Keywords: Autism spectrum disorder, Fragile X syndrome, insulin-like growth factors, neurotrophic factors, Phelan-McDermid syndrome, Rett syndrome

Autism spectrum disorder (ASD), a genetically heterogeneous disease, is a group name of neurodevelopmental disorders which is characterized by disabilities, social interactions, the deficit in speaking and language, and recurrent behaviors with limited interest.[1] In addition to many genetic variants involved in unknown causatives of ASD, the complex group of autism spectrum disorder includes Rett syndrome (RTT), Fragile X syndrome (FXS), and Phelan-Mcdermid syndrome (PMDS) which are caused by single-gene mutations.[2] Although there has been an increase in awareness of the disease prevalence and great effort for understanding underlying mechanisms of the disease in the last decades, still there is no exact pharmacological treatment for ASD.[3,4]

According to a Center for Disease Control report, the incidence of ASD diagnosed in eight-year-old children was one in 54 in 2020, which was an increased prevalence when compared with 2018 when the prevalence rate was found one in 58.[5]

Synaptic genes which are associated with immune action and synapse formation are impaired in cases of ASD.[2,6] Various factors and signaling pathways are involved in the development of the central nervous system (CNS) in a bid to functioning properly of neuron cells by enabling correct differentiation, interaction maturation of neurons so that any deficits within the process of development of CNS leads to disorders associated with impairments in motor, language, cognitive and behavioral patterns.[7] Moreover, proper development of the CNS is achieved through neurotrophic factors, which play a crucial role in the process of maturation and growth of neural development.[8] One of the neurotrophic factors is insulin-like growth factor 1 (IGF-1) and because of its significant contribution and effect on the central nervous development process, makes IGF-1 is one of the most promising and important targets for the treatment of ASD.[9]
INSULIN-LIKE GROWTH FACTOR-1

Insulin-like growth factor 1 is a neurotrophic growth factor, a polypeptide composed of 70 amino acids, and with IGF-2 and insulin, they are members of a superfamily of related insulin-like hormones. Production of IGF-1 is mainly occurring in the liver in adults and as a response to growth hormone (GH), which is involved in many processes including having effects on CNS development and plasticity of neurons, it is suggested that IGF-1 have a role and act as an endocrine, paracrine, and autocrine hormone. The members of the superfamily of Insulin-like peptides are found to be bound to many binding proteins which may be involved in IGF function controlling and helping IGF-1 to be targeted to some tissues.\[^9\] Their action and effects are exerted through binding to, a tyrosine kinase IGF-1 receptor, where activation of canonical signaling pathways which are the phosphatidylinositol-3 kinase/mammalian target of rapamycin-serine-threonine-specific protein kinase AKT-PKB (PI3K/mTOR/AKT1), and mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK).\[^2,10\] Expression of IGF-1 and IGF-2 occur in the CNS widely, however, IGF-1 messenger RNA (mRNA) expression is mainly in fetal brain tissue, while IGF-2’s main expression occurs in the course of human brains’ fetal and early postnatal development.\[^2\] The IGF receptor’s expression in the brain is much more than the formation of IGF-1 in CNS of adults, which may show that IGF-1 has an ability to cross the blood-brain barrier according to previous studies in which IGF-1 is injected externally.\[^7,11\]

The action mechanism of IGF-1 depends on starts with binding of IGF-1 to its receptor (IGF-1R) and β subunits of IGF-1R allow the activation of downstream signaling pathways which are P13K/mTOR/AKT1 and MAPK/ERK. In the pathway of P13K/mTOR, which involves in cell cycle regulation, expression of genes, and remodeling of cytoskeleton, firstly AKT1 is recruited which activates mTOR and activated mTOR leads to activation of P70-S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E (eIF4E) is phosphorylated, which enable ultimately increased gene expression.\[^7,12\] Also, the forkhead box O (FOXO) apoptotic pathway is prevented through activation of the AKT1 pathway. The second pathway, which is MAPK/ERK, is also significant for the cell survival, gene expression, and proliferation of neurons with the activation of ERK which promotes ETS-domain protein Elk-1 (ELK1) activation and ultimately, gene expression and transcription.\[^7,23\]

N-terminal glycine-proline-glutamate (GPE) tripeptide and des-(1-3)-IGF-1, which is an IGF-1 form lack of amino-terminal GPE tripeptide can be obtained through the cleavage of IGF-1 when in the serum and their affinities for insulin-like growth factor binding proteins (IGFBP) can be different based on the forms of IGF-1, and it was found that des-(1-3)-IGF-1 have great potential when compared to IGF-1 and des-(1-3)-IGF-1 has a great effect on plasticity and maturation of synapses along with the increasing the levels of excitatory synaptic markers which are synapsin 1 and postsynaptic density-95 (PSD-95).\[^10\]

Myelinogenesis, which is supported by IGF-1, allows progenitor cells to be differentiated into oligodendrocytes, which are involved in the production of myelin. During neurogenesis, cells that are derived from pluripotent cells are oligodendrocyte precursor cells (OPCs) and their functional production of oligodendrocytes is associated with the level of IGF-1, and decreased level of IGF-1 is linked to impaired differentiation of OPCs to oligodendrocytes and cause a decrease in the functional and rapid death of oligodendrocyte which ultimately causes demyelination and impairing of neurologic functions observed widely in patients with ASD.\[^8\]

According to observations in mice models, IGF-1 role in the CNS development is crucial in terms of structural brain functionalities and showed that mice with null mutations in IGF-1 showed a delay of the brain development, decreased number of oligodendrocytes and myelin in white matter with the impaired generation of the spine.\[^7,14\]

In the brains of people that are diagnosed with ASDs, there is neuroinflammation that derives from the over-expression of cytokines of the brain which includes interleukin-6 (IL-6) microglia are activated through IL-6.\[^15,16\] Microglia, which are the glial cells that are involved in physical and physiologic support, regulation of immunity, and promotes maintenance of homeostasis in CNS, promotes inflammation because of its action mechanism as an immune system of the CNS and microglia are found in the brains of autism as increased.\[^57\] According to previous studies, it was shown that in autism IGF-1 levels are changed.\[^18\] In young children, autism potential is increased simultaneously when a lack of IGF-1 is observed.\[^8\]

Autistic phenotypic features have been linked to
IGF-1 on a molecular level in studies. The 22q13 region is a region where the significant the SH3 and multiple ankyrin repeat domains 3 (SHANK3) protein, which acts as a scaffold for the organization of proteins at the synapse, and it is involved in connecting neurotransmitter receptors, ion channels, and some membrane-bound proteins to signaling pathways, is coded from and de novo mutations in this region may be associated with autism.\cite{3,19}

In the models of humans and animals, there have been severe phenotypic changes in response to IGF-1 impairment which indicates a significant role of IGF-1 in CNS development. The therapeutic option of IGF-1 has been studied in also other neurodevelopmental disorders which are RTT, FXS, PMDS, in which physiological and psychosocial characteristics are similar to autism.\cite{10,20}

**INSULIN-LIKE GROWTH FACTOR-1 IN PHELAN-MCDERMID SYNDROME**

The loss of a functional copy of the SHANK3 gene through the deletion of a gene or mutation in a gene leads to 22q13 deletion syndrome, a complex clinical condition known as PMDS. Haploinsufficiency of SHANK3 accounts for about 0.5% of cases of ASD and/or developmental delay mental impairments.\cite{21}

Moreover, the deletion of the SHANK3 gene comprises approximately 0.5% of the ASDs.\cite{22}

Once the hippocampal neurons from five-seven days after the birth of rat, whose neurons inhibited expression of SHANK3 in this way, in a bid to investigate the effects of SHANK3 gene in vitro studies it was observed that there is a reduction in the lengths and number of dendritic spines, however, once they were treated with SHANK3 protein, it was reversed the results, in which number and lengths of dendritic spines were increased, and as a consequence, it was found that this study leads the way of the usage of the model mouse in studies of PMDS in vitro.\cite{23}

According to a previous study, SHANK3 deficient mice has shown reduced basal neurotransmission which occurred as a result of a reduction in the expression of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA receptors) with a decrease in the mature synapses and impairment in long term potentiation, which is a measurement of learning and memory capacity.\cite{24}

Moreover, it was examined and administered the IGF-1 daily for two weeks and results were reversed in AMPA receptors.\cite{25}

In another study, SHANK3 deficient induced pluripotent stem cells (iPSCs), which were derived from the PMDS patients were used and examined and treatment SHANK3-deficiency iPSCs with IGF-1 caused a reduction in the defects once PSD-95 positive excitatory synapses formed in an increased level, as a result of treatment and an increase were observed in the frequency and number of iPSCs with restoration in the NMDA and AMPA receptors.\cite{26}

Also, in one clinical trial in which the effect of IGF-1 in patients, it was observed that IGF-1 treatment improved substantially the social impairments and restrictive behaviors.\cite{27}

**INSULIN-LIKE GROWTH FACTOR-1 IN RETT SYNDROME**

Rett Syndrome which is a widespread neurodevelopmental ASD appearing in females is caused by a mutation in the methyl-CpG-binding protein 2 (MeCP2), which encodes a protein called MECP2.\cite{28}

In people with RTT, initially normal developmental processes turn into a decline in motor, social and cognitive abilities with deficits in social relationships and intentional hand motor movements.\cite{7,29}

MeCP2 mutant mice have shown reduced levels of IGF-1 and once IGF-1 was administered daily, plasticity which depends on activity, the density of spines, and synapse frequencies abnormalities were improved with an increased number of excitatory synaptic markers.\cite{30}

Insulin-like growth factor 1 mechanism of action on RTT syndrome can be done through the effect on the mTOR pathway, whose expression is reduced in patients with RTT.\cite{31}

However, interestingly, it was shown that IGF-1 levels can be affected by MeCP2 through changing and controlling IGFBPs in models of humans and animals.\cite{32}

In one study, it was demonstrated that the degree of the disease's progression was improved and cognitive ability in patients with RTT has been increased as a response to treatment with IGF-1 in comparison to patients who were not treated.\cite{33} In another study, full-length recombinant human IGF-1 (rhIGF-1) was used and injected to analyze the effects in the MeCP2 knockout mice models, and it was found that spine dynamics were impaired was enhanced and repaired in response to a single dose of rhIGF-1.\cite{34}

**INSULIN-LIKE GROWTH FACTOR-1 IN FRAGILE X SYNDROME**

Fragile X Syndrome is an X-linked disorder result from a mutation in the Fmr1 gene, encoding a
The role of IGF on ASD

protein called ASD associated protein, fragile X mental retardation protein (FMRP) and patients with a mutation in Fmr1 cause impairment in cognitive abilities, social interaction disabilities, deficits in anxiety and attention, seizures and phenotypic abnormalities such as facial dysmorphism and macroorchidism. In one preclinical study, an analog of (1-3) IGF-1 which is NNZ-2566 was used in Fmr1 knockout mice, and it was demonstrated that phenotypic characteristics of FXS that are deficiency in learning and memory, social disability, hyperactivity were restored and deactivated ERK and AKT signaling and reduction in spine density was observed.

**INSULIN-LIKE GROWTH FACTOR-1 IN AUTISM SPECTRUM DISORDER**

Many genetic and environmental factors, which are involved in intracellular signaling pathways in a limited manner, can be causatives of autism and if suitable biomarkers are found, deficits in neurodevelopmental mechanisms may be reversed and restored. In patients with ASD, some common behavioral disorders are seen which are having problems in responding to social-emotional responses, showing stereotypic or repetitive motor movements, disabilities in maintaining, improvements and understanding relationships, having a constant interest which could be limited or repetitive, overreacting to some sounds or touches with excessive intensity, having high adherence to habitual characteristics, not showing facial expressions and having a deficiency in body languages. Moreover, gastrointestinal disorders and deficits in behavioral patterns have been associated with each other and this connection, which is disrupted in ASD patients, is explained by the microbiota-gut-brain axis, in which motility and functions of secretions are controlled by the brain and cognitive function is affected by intestines. Exerting its potential effects of IGF-1 on functions of synapses, maintenance and neuromodulatory dysfunction suggest IGF-1 is one of the effective treatment targets for ASDs. The action mechanism of polypeptide hormone IGF-1 on mitogen-activated protein kinase and PI3K/Akt signaling, which is disrupted and dysregulated in ASDs and idiopathic autism by binding to IGF-1R in neurons and activates and restores the signaling pathway. Therefore, IGF-1 shows critical benefits in the treatment of some neurodevelopmental disorders such as RTT, PMDS, and FXS.

According to a study, in a group of children with autism, it was found that IGF-1 levels which were measured from the daily urinary excretion, were substantially lower than an age-matched control group. However, a larger study demonstrated contrast results, in which a group of children with autism has shown increased levels of IGF-1 levels. There is no convergence on the idea of whether the IGF-1 levels are found at abnormal levels in autistic children based on several studies that measured levels of IGF-1 levels in the blood, urine, cortex, etc. because of usage of different measurement techniques and an inadequate number of patients in study groups. According to one study which was conducted in 2020, the level of IGF-1 or IGF-1R in the fusiform gyrus tissue from the patients of idiopathic autism were measured and evaluated the mRNA and protein levels of IGF-1 and IGF-1R. The fusiform gyrus that mediates the face perception and faces recognition, which is disrupted in ASDs, is hyperactivated in patients with ASDs. The result of the study demonstrated that IGF-1 or IGF-1R mRNA and protein levels have not been changed in the fusiform gyrus of patients with idiopathic autism and there has been not a significant difference between the study and control groups, suggesting that IGF-1 may be a potentially promising target treatment in ASDs but IGF-1 may not be used for the pathogenesis of ASDs.

In another study, iPSC-derived neurons from idiopathic ASD patients and neurotypical individuals were analyzed, and it was found that neurons that are derived from neurotypical individuals showed an alteration in the gene expression profile and the transcription showed a swift change with an acute IGF-1 administration. In contrast, the response of IGF-1 administration was heterogeneous when the neurons derived from idiopathic ASD patients were analyzed, which they assumed that the response may be associated with IGF1R expression. It was also found that the administration of IGF-1 recovered some ASD-associated transcriptional profiles, which were involved in the synaptic activity.

Insulin-like growth factor 2 polypeptide has been known as an enhancer of cognitive function in response to injection of IGF-2 to the hippocampus of rats or mice, and it exerts its effect through the IGF-2 receptor. According to a recent report, in which male BTBR T+ Itrpr3tf/J mice were used because of the resemblance of core behavior phenotypes of ASD in that mice model, it investigated potential effects of systemic injection of IGF-2. As a result of the study, it was found that through administration...
of systemic IGF-2, social interaction deficits of BTBR mice was rescued, novelty memory functions were enhanced, memory deficits were reversed through IGF-2R, stereotypic repetitive behaviors of BTBR mice was reversed and abnormalities in the regulation of mTOR pathway, which was seen in BTBR mice, was reversed substantially via systemic administration of IGF-2 treatment, which suggests IGF-2 as a promising and potential treatment option.

In conclusion, ASDs are complex and heterogeneous disorders that are characterized by deficits in many core features Today, there are no exact approved treatment options present for the treatment of autism and related disorders. However, IGF-1 is still being investigated and studied because of its advantage in terms of the ability to cross the blood-brain barrier and preclinical studies demonstrated substantially promising results with ameliorating the core symptoms of autism and related disorders. Proper CNS development has been a key for many biological processes, which are ensured by neurotrophic factors involving IGF-1 and IGF-2, such as proper maturation, motility, and survival of neurons. Insulin-like growth factor 1 and insulin-like growth factor 2 may be effective treatments for the treatment of autism. However, the levels of IGF-1 in children with autism are not consistent in the literature and additional concepts should be clarified whether abnormal IGF-1 levels lead to autism or not. So, in a bid to understand and shed light on valuable evidence about IGF treatment, deep and comprehensive studies are required, in which different parts of the brain will be investigated in terms of IGF-1 levels, and it should be valuable to identify potential patients that can benefit from the treatment at maximum efficiency with an increased number of individuals in study groups in terms of autistic children being tested. In addition to IGF-1, IGF-2 may also represent potential therapeutics for autism and related disorders based on studies that were conducted on animal models. Thus, results of ongoing clinical studies and more comprehensive studies will be valuable and essential for the future of therapy of autism and related disorders.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES