The role of IGF-1 in neurodegenerative diseases

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DOI: http://dx.doi.org/10.17486/gyr.3.1035

SUMMARY: IGF-1 is the main effector of growth hormone, exerting a great number of anabolic responses in the human body. Our review is centered around the observation that IGF-1 depletion in the brain leads to the development od neurodegenerative diseases and cognitive decline seen in elderly people. A large number of studies have unveiled various mechanisms by which levels of IGF-1 can be decreased, which in turn causes brain deterioration. In this review, we discussed in detail potential role of IGF-1 in neurodegeneration through five critical etiopathogentic aspects: neurotrophic properties, oxidative stress, cardiovascular system pathology, infammation and thesaurismoses. IGF-1 participates in survival of the neurons, it enhances synaptic transmission, brain plasticity, reduces oxidative stress and proinflammatory effects of prostangladins and cytokines, as well as amyloid β (A) formation and amyloid precursor protein (APP) overexpression. Considering its wide spectrum of physiological functions and potential pathophysiological role in neurodegenerative disorders, further insights into its mechanism of action might lead to development of new preventiive methods, diagnostic methods and pharmacological therapies.

KEYWORDS: IGF-1, neurodegenerative diseases, oxidative stress, cell survival, atherosclerosis, cognitive function

Insulin-like growth factor 1 (IGF-1), also known as somatomedin C, is a peptide hormone composed of a single chain of 70 aminoacids. It owes its name to the structural similarity to insulin. IGF-1 is part of the somatotropic axis, as it is to date considered the primary target of growth hormone (GH) action[1]. According to the original somatomedin hypothesis by Daughaday et al., GH stimulates production of IGF-1 in the liver. IGF-1 subsequently mediates its physiological role in longitudinal bone growth. IGF has a number of other roles, including that in cortical bone mass, intrauterine growth, brain development and function, insulin sensitivity, kidney and liver size, blood pressure, prostate size, etc.[2]. At present, there is a growing body of evidence on the possible role of IGF-1 in the pathology of neurodegenerative disease. The role of IGF-1 will be further considered in the text, with emphasis on its function in the brain as well as the implications concerning neurodegeneration.

IGF-1 regulation and synthesis

Although the majority of serum IGF-1 is liver-derived, IGF-1 is produced in virtually every organ and tissue. Liver-derived IGF-1 secretion is mainly regulated via GH, as opposed to locally-derived IGF-1, which is under the influence of GH and other factors that are secreted locally. Factors involved in bone IGF-1 regulation include PTH and sex hormones. Sex hormones predominantly regulate local IGF-1 production in the reproductive system[3].

The receptor for GH (GHR) belongs to a class I cytokine superfamily. GHR contains a single transmembrane domain and forms a homodimer. Upon the binding of GH to GHR, the receptor associated tyrosine kinase JAK2 transphosphorylates, becoming active. The activated JAK2, in turn, phosporylates a number of proteins, including Stat5b transcription factor. Stat5b was identified as the key intermediary between GH and IGF-1 transcription.

The IGF-1 gene, including 2 promoters and 6 exons, comprises 70-80 kb of genomic DNA. More than 100 different mRNAs have been identified in various tissues and developmental periods. This is the result of multiple transcriptional initiation sites, alternative splicing and differential polyadenilation. Out of the two promoters, the major one, P1, is active in all tissues whereas P2 is primarily limited to the liver. The interesting part is that the translation results in only two precursors which are both processed into a single, identical product[1].

Six different IGF-1 binding proteins have been identified. Along with their role in IGF-1 transport, as a reservoir, in potentiation or inhibition of action, they can exhibit IGF-1 independent effects. In circulation, 70-80% of IGF-1 exists in the form of ternary complexes, consisting of IGF-1, IGF-1 binding protein 3 (IGFBP-3) and acid-labile subunit (ALS). The complex contributes to IGF-1 stability and bioavailability.

IGF-1 suppresses GH secretion in the pituitary gland, as well as in the hypothalamus (the latter more so via locally produced IGF-1). This is observed as increased GH levels in IGF-1 knockout mice[2]. The proposed physiological role of the phenomenon is during fasting, when low hepatic production of IGF-1 results in lower serum levels, stimulating GH secretion, which in turn helps adaptation with lipolysis and insulin antagonism[4].

IGF-1 and bone growth

GH is considered to be the main hormone responsible for normal postnatal growth, with IGF-1 as its effector. IGF-1 has also been identified as the predominant factor in fetal growth and development[5]. IGF-1 is necessary for both normal longitudinal bone growth and cortical bone mass accumulation[2].

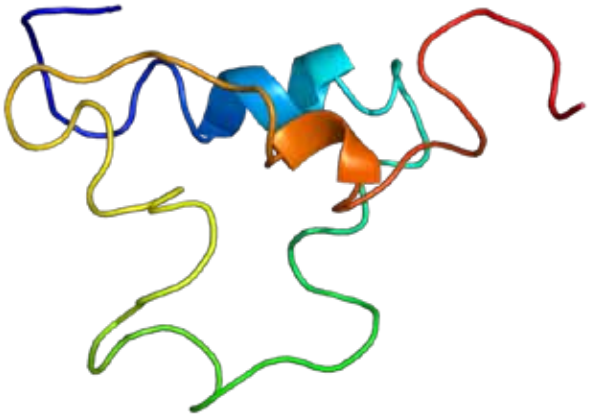

Fig. 1 IGF-1 protein

IGF-1 and metabolism

Due to the structural similarity between IGF-1 and insulin, IGF-1 can produce insulin-like effects on glucose uptake. IGF-1 also enhances insulin sensitivity, mainly by inhibiting GH secretion. It is proposed that IGF-1 has direct effects on glucose metabolism. Lack of liver-derived IGF-1 transiently increases fat mass and serum leptin levels in young mice but reduces fat mass in old mice, probably by increasing GH secretion. Although its role in lipid metabolism is uncertain, lower cholesterol serum levels were reported in humans treated with IGF-1[2].

IGF-1 and other tissues

IGF-1 exhibits antioxidant, anti-inflammatory and pro-survival effects on the blood vessels, stabilizing atherosclerotic plaques[6]. Evidence also suggests that IGF-1 is a potent vasodilator, via a mechanism mediated by NO. Furthermore, GH and IGF-1 stimulate cardiac growth and contractibility. In the kidney, IGF-1 participates in size regulation and stimulates renal sodium retention. IGF-1 increases prostate size, which can be due to the rise in the number of androgen receptors and the resulting responsiveness increase[2].

IGF-1 and the brain

IGF-1 is necessary for normal brain development. This is evident in cases of *IGF-1* gene mutations which result in microcephaly, sensorineural deafness and mental retardation[7].
Recently, it has been observed that IGF-1 has multiple functions in the adult brain as well. IGF-1 is considered to be involved in behavioral patterns - liver IGF-1 KO mice showed decreased exploratory behavior8. Circulating IGF-1 has been determined as the mediator of beneficial effects of exercise on the number of new granule cells in the adult hippocampus and as well as other exercise-induced benefits[9]. Vascular remodeling in the adult brain also requires IGF-1, while systemic injection of IGF-1 increases brain vessel density[10]. IGF-1 potentially has considerable therapeutic value, due to its ability to induce clearance of amyloid-β (Aß) through increasing the transport of Aß carrying proteins such as albumin and transthyretin[11].
IGF-1 was found to be important in spatial learning and memory, as impaired functions were found in old, liver IGF-1 knockout (KO) mice. They also exhibited increased dynorphin and enkephalin immunoreactivity, but decreased levels of their mRNA in the hippocampus. Additionally, these mice displayed astrocytosis and increased metabotropic glutamate receptor 7a-immunoreactivity, all of which suggest synaptic dysfunction and early neurodegeneration[12].
Serum IGF-1 deficient mice showed disrupted long-term potentiation (LTP) in the hippocampus but not in the cortex. This was associated with a reduction in the density of glutamatergic boutons that led to an imbalance in the glutamatergic/GABAergic synapse ratio in the hippocampus13. Both findings suggest that age-related cognitive loss may be the result of declining IGF-1 serum levels during aging.

The role of IGF-1 in neurodegenerative disease

Neurodegenerative diseases are defined as hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction. Although neurodegeneration is extensively researched, the etiology of neurodegenerative disease remains ambiguous. Available literature suggests that neurodegeneration is a result of a complex interplay between oxidative damage, defects in energy metabolism, excitotoxicity and accumulation of undegradable cellular waste products.
IGF-1 is required for normal development of human body, but its decrement in older age, ability to cross the blood-brain barrier and its critical biological role suggest it may also be an important factor in the aging and deterioration of the human brain. Neurodegenerative diseases with similar clinical manifestations show either high or low levels of circulating IGF-1 which can be explained by either low availability of IGF-1 or resistance of IGF-1 receptors[14]. A great number of studies report correlation between impaired IGF-1 signalling and decreased cognitive function in older population. Lower serum IGF-1 is associated with impaired memory, orientation skills and lower information processing speed[15].

1) IGF-1 - a potent neurotrophic factor

IGF-1 is an important neurotrophin – a protein that induces survival, development and function of neurons. Evolutionary conservation of the neurotrophic role of the IGF-1, serotonin and BDNF, along with their cooperative influence on energy metabolism, cellular stress adaptation, growth and repair, neurogenesis, learning and memory and cell survival encouraged some scientists to propose their central role in the pathogenesis of neurodegenerative disease[16].
Decreased trophic signaling may be one of the causes of the cognitive decline seen in older age and in neuroegenerative diseases. Circulating IGF-1 is hypothesised to affect learning and synaptic plasticity through its trophic effects on glutamatergic

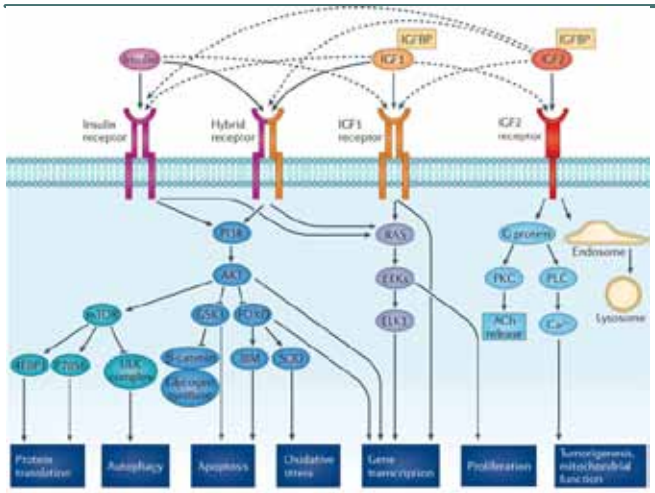

Fig. 2 Insulin, IGF-1 and IGF-2 receptors signalling cascades. 4EBP1, 4E binding protein 1 (a eukaryotic initiation factor); ACh, acetylcholine; BIM, BCL-2 interacting mediator of cell death; ELK, ETS-like transcription factor; FOXO, forkhead box protein O; GSK3, glycogen synthase kinase 3; IGFBP, IGF-binding protein; mTOR: mammalian target of rapamycin; SOD: superoxide dismutase; ULK, uncoordinated-like kinase. Dashed arrows indicate low-affinity binding of ILPs with ILP receptors. [31]

synapses[13]. Studies show that old rodents with impaired IGF-1 signalling could not sustain long-term potentiation, while old rodents with normal IGF-1 levels responded to the stimuli with LTP similar to young rats. IGF-1 seems to have both acute and chronic synaptic effects. One study demonstrated that application of des-IGF-1 increases field EPSP amplitudes by 40% in CA1 field of hippocampal slices from young rats[17].
IGF-1 seems to exert its effect on synaptic transmission and plasticity through several important mechanisms such as modulation of presynaptic neurotransmitter release, AMPA receptors and L- and N-type voltage-gated calcium channel currents. Such changes in synaptic plasticity and neuronal signalling could, in turn, lead to decreased apoptosis and therefore increased neuronal survival. One example would be potentiation of neuronal signalling through Akt or increased expression of NMDA receptors, leading to calcium signaling, activation of PI3K/Akt, and inhibition of FOXO transcription factor, all finally resulting in prevention of cell death[17].

2) Oxidative stress, IGF-1 and the brain

Oxidative stress is one of the main mechanisms proposed to explain the pathophysiology of brain aging and development of neurodegenerative disease.
Reactive radical species (ROS) produced during excessive oxidative stress, exert damage to the neurons by stimulating FOXO3, a transcription factor responsible for triggering apoptosis and upregulating genes crucial for cell death.
IGF-1 and insulin act as opponents of these processes by activating both insulin and IGF-1 receptors located in the brain tissue. Their downstream signaling cascade leads to activation of PI3K/Akt pathway, which in turn inactivates FOXO3 and many other mediators participating in cell destruction[18]. Glycogen synthase kinase 3ß (GSK-3ß), caspase-3 and p38 mitogen-activated protein kinase (p38 MAPK) are just some of the examples of enzymes involved in apoptosis, cell death and energy impairment of the cell that are inhibited via insulin and IGF-1 signaling. Not only do insulin and IGF-1 supress negative proliferation signals throughout the cell while fighting oxidative stress, but they also stimulate survival signals mediated by the expression of Bcl-2 (an antiapoptotic protein)[19] and induction of NF-ϰB. NF-ϰB is a transcription factor believed to supress the toxic effect of hydrogen peroxide on neurons, especially cerebellar and hypothalamic neurons as observed in experiments made on rats. IGF-1 does this by overexpression of the NF-ϰB subunit c-Rel, which in turn enhances its signaling[20]. Another way of fighting oxidative stress is by boosting IGF-1 bioavailability.

Exercise has been observed to reduce chronic oxidative stress and promote synthesis of many trophic factors, including IGF-1. Akt levels were also higher with exercise training[21]. That had major consequences on the brain plasticity, prevention of neuronal apoptosis and delaying neurodegeneration processes[22].
Although IGF-1(and insulin) acts neuroprotective by mitigating oxidative damage, an abrupt rise in oxidative stress reduces IGF-1 signaling through Akt blockage and leads to neuronal death, suggesting that interference with trophic input is the key in understanding neurodegeneration processes[18].

3) The protective role of IGF-1 in the cardiovascular system

A growing body of evidence proposes an association between vascular risk factors and neurodegenerative disease. In Alzheimer's disease, the most prevalent neurodegenerative disorder, more than 77% of the patients were find to have a high level of circle of Willis atherosclerosis during neuropathological examination. Several authors report that cerebrovascular atherosclerosis is more frequently find in patients suffering from neurodegenerative diseases and that cerebrovascular atherosclerosis in those patients is usually more severe. Atherosclerosis ratings are highly correlated with some of the usual signs of the neurodegenerative diseases such as neuritic plaques, paired helical filament-tau neurofibrillary tangles and cerebral amyloid angiopathy[23].
Observational studies have evalueted the association of IGF-1 with cardiovascular diseases as an independent risk factor. Recent meta-analysis suggests an association of both exceedingly low and exceedingly high IGF-1 levels with increased overall and cardiovascular mortality[6]. As we previously stated, such correlation is consistent with findings that both very high and very low concentrations of IGF-1 are associated with neurodegenerative disorders, and could imply that disruption of IGF-1 signalling can affect brain functioning through several different mechanisms. Increasing evidence points to pleiotropic effects of IGF-1 on vasculature, resulting in reduced vascular oxidant stress, apoptosis and inflammatory signaling[6].
Literature also proposes antiatherogenic effects of IGF-1 in animal models of atherosclerosis. Atiatherogenic effect are thought to be related to decreased macrophage infiltration of the atherogenic lesion, reduced aortic expression of pro-inflammatory cytokines, increased levels of endothelial progenitor cells and increased NO bioavailability (which decreases vascular superoxide levels, and therefore oxidative stress)[24]. IGF-1 signalling is also important for stabilizing already created atherosclerotic plaques, probably though its autocrine and paracrine effects on vascular smooth muscle cells and endothelial regeneration.

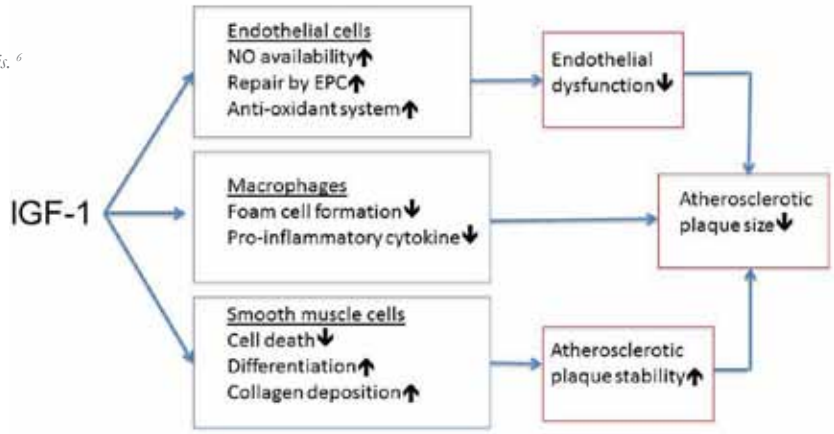

Fig. 3 Potential effects of IGF-1 on atherosclerosis. [6]

Hypertension is another important factor in vascular aging and one of the major risk factors for atherosclerosis. IGF-1 is involved in vascular tone regulation, probably via its effect on NO bioavailability, reduction in intracellular calcium levels and myosin light chain sensitivity in vascular smooth mucle cells and ability to regulate, both directly and indirectly, endothelin-1 gene expression and signalling[25].
In addition, the adult brain requires IGF-1 for reactive vessel remodeling, a process important for supporting tissue with an adequate amount of oxygen and nutrients[10].

4) IGF-1 and inflammation mediators

Prostangladins and proinflammatory cytokines are also associated with the development of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, AIDS dementia complex and cerebral ischemia. The proposed mechanism of action of these inflammation propagators is thought to be an increase in free radicals, leading to severe oxidative stress (discussed earlier in this article) and tampering with the IGF-1 signaling cascade[26].
Prostangladins are produced in large quantities during inflammation and also serve as inducers of other proinflammatory cytokines such as IL-1 and IL-6. The significance of the prostangladins' effect on brain deterioration was noted in an experiment where prostangladin A1(PGA1) and prostangladin E1 (PGE1) increased amyloid ß (Aß) levels in differentiated murine neuroblastoma cells and fetal rat hyppocampal cells. PG-induced elevation of Aß may lead to an increased binding of Aß to the 20S proteasome, resulting in a reduction of 20S proteasome-mediated degradation of ubiquitin-conjugated proteins[27]. Furthermore, PGE2 overexpression causes excessive formation of amyloid precursor protein (APP), which subsequently leads to plaque formation.
Interactions between IGF-1 and prostangladins are tissue-dependant – in the brain, they have opposing effects. IGF-1 downregulates prostaglandins expression and therefore acts neuroprotective[28]. IL-1 and IL-6, activated by prostangladins and TNFα, were found to be particulary elevated in neurodegenerative conditions, where they also contributed in APP production. The antagonistic relationship between IGF-1 and interleukins was also observed while measuring low levels of IGF-1 in the rat's brain and plasma after separate administration of IL-1 and IL-6. On the other hand, IGF-1 may act in a way that leads to a decrease in interleukin receptors expression and as a suppresor of cytokine signaling proteins[28].

TNFα is another cytokine that was thoroughly examined in the context of neurodegeneration. New studies show its ability to block the IGF-1 signaling cascade by inhibiting activation of the PI3K/Akt pathway and its downstream trophic effects. Even very low levels of TNFα were sufficient to supress IGF-1 signaling and lead to brain deterioration. Because of these findings, IGF-1 and TNFα-blockers are proposed as one of the possible methods in the treatment neurodegenerative diseases[26].

5) IGF-1 effect on amyloid β and tau

Amyloid β is 4kDa peptide derived from the larger APP. It was first isolated as the principal component of amyloid deposits in the brain and cerebrovasculature of AD and Down's Syndrome patients. The most prevalent neurodegenerative disease, AD is believed to be driven by the production and deposition of the β-amyloid peptide (Aβ).
Recent research has shown that IGF-1 has an important role in regulating Aβ peptide levels.
Animal models suggest that high brain Aβ levels are found at an early age in mutant mice with low circulating IGF-1. Moreover,Aβ burden can be reduced in aging rats by increasing serum IGF-1. Several important findings connect IGF-1 and amyloid β accumulation. IGF-1 is shown to enhance transport of Aβ carrier proteins such as albumin and transthyretin into the brain[11].
Another important finding is the direct influence of IGF-1 signalling cascade in regulation of APP metabolism, and therefore amyloid β accumulation, via its ability to increase levels of insulin degrading enzyme (IDE) and regulate phosphorylation of GSK-3α and β through phosphorylation of Akt29. IDE is a thiol metalloendopeptidase able to degrade various small peptides such as insulin and glucagon, but also amyloid β30. The GSK-3α enzyme has been demonstrated to be required for the maximal processing of β-APP, and subsequent Aβ production, while the GSK-3β isoform is involved in the phosphorylation of tau protein as well as the transcriptional factor cAMP response element-binding protein (CREB).

Conclusion

IGF-1 acts as a pleiotropic agent, having the ability to promote cell proliferation, survival, diferentiation and cell metabolism. Its effects in the context of neurodegenerative diseases are of great importance in today's reasearch circles. IGF-1 has the ability to decrease or in some cases even to revert pathophysiological mechanisms underlying neurodegeneration and brain damage.

FACTOR	ACTION	INTERACTION
PROSTAGLANDINS	1. Increase Aß levels 2. PG and PG-induced cytokines, IL-1 and IL-6, implicated in AD	1. PG decrease IGF-1 and cyclin D1 2. IGF may decrease PG production
IL-1	1. Promotes neuritic plaque formation 2. production/processing of APP 3. Increases levels of ACT 4. HPA hyperactivity	1. Decreases GH receptor mRNA 2. Decreases IGF-1 mRNA/protein 3. Inhibits GH stimulation of IGF-1 4. Alters responsiveness to IGF-1
TNF	1. Stimulates ACT production 2. Increases production of PGE2 3. Increases expression of IL 4. Accentuates Aß toxicity 5. Alters BBB permeability	1. Inhibits GH stimulation of IGF-1 2. Stimulates IGFBP-1 production 3. Alters responsiveness to IGF-1 4. Decreases IGF-1 levels
IL-6	1. Contributes to AD pathology 2. Correlated with neuropathological changes 3. HPA hyperactivity 4. Alters BBB permeability	1. Stimulates IGFBP-1 production 2. Decreases IGF-1 concentrations 3. Antagonizes IGF action

Table 1 Actions of prostaglandins and cytokines in neurodegenerative diseases and their interaction with IGF-1 system. [28]

Having in mind its promising results in reducing atherosclerotic plaque burden, oxidative stress relief, promoting brain plasticity, antiapoptotic effects, antagonistic action against proinflammatory cytokines, it is no wonder that the clinical application of IGF-1 has yet to reach its peak. Since changes in IGF-1 levels may represent one pathway through which lifestyle interventions, such as healthier lower caloric diets and increased physical activity might alter the risk of nerodegenerative diseases[15] further understanding of its mechanism of action on subcellular level could provide us with useful information in terms of prevention, but also in terms of pharmacological interference. Moreover, some some of the already available drugs such as donepezil or monoamine reuptake inhibitors fluoxetine and venlafaxine[15] have been shown to increase brain IGF-1 levels. Studies that report IGF-1 as one of only a few factors that can reverse cognitive decline with aging offer further encouragement.

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Uloga IGF-1 u neurodegenerativnim bolestima

SAŽETAK: IGF-1 kao glavni medijator hormona rasta, posreduje u brojnim anaboličkim funkcijama u ljudskom tijelu. Naš članak baziran je na činjenici da smanjena razina IGF-1 u mozgu vodi razvoju neurodegenerativnih bolesti i kognitivnom padu uočenom u starijoj životnoj dobi. Veliki broj studija navodi razne mehanizme kojima se razine IGF-1 mogu smanjiti i utjecati na propadanje moždanog tkiva. U ovom pregledu detaljno smo raspravili moguću ulogu IGF-1 u neurodegeneraciji kroz pet ključnih etiopatogenetskih aspekata: neurotrofna svojstva, oksidativni stres, patologija krvožilnog sustava, upala i bolesti nakupljanja. IGF-1 sudjeluje u preživljenju neurona, poboljšava sinaptičku transmisiju, plastičnost mozga, smanjuje oksidativni stres i upalno djelovanje prostangladina i proupalnih citokina, a također smanjuje stvaranja β amiloida i prekomjernu ekspresiju amiloidnog prekursorskog proteina. S obzirom na široki spektar fizioloških funkcija i moguću patofiziološku ulogu IGF-1u neurodegenerativnim bolestima, daljnji uvidi u mehanizam djelovanja mogli bi dovesti do razvoja novih preventivnih i dijagnostičkih metoda i farmakoloških terapija.

KLJUČNE RIJEČI: IGF-1, neurodegenerativne bolesti, oksidativni stres, preživljenje stanice, ateroskleroza, kognitivna funkcija