Neuroprotection of Insulin-like Growth Factor-1

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Insulin-like growth factor-1 (IGF-1) and its binding proteins and receptors are widely expressed in the central nervous system (CNS), proposing IGF-1-induced neurotrophic actions in normal growth, development, and maintenance. However, while there is convincing evidence that the IGF-1 system has specific endocrine roles in the CNS, the concept is emerging that IGF-I might be also important in disorders such as ischemic stroke, brain trauma, Alzheimer's disease, epilepsy, etc., by inducing neuroprotective effects towards glutamate-mediated excitotoxic signaling pathways. Research in rodent models has demonstrated rescue of pathophysiological and behavioral abnormalities when IGF-1 was administered by different routes, and several clinical studies have shown safety and promise of efficacy in neurological disorders of the CNS.

glutamate-mediated excitotoxicity signaling pathways insulin-like growth factor-1 neuroprotection animal models clinical trials

1. Introduction

Insulin-like growth factor 1 (IGF-1) is considered an attractive therapeutic alternative for diverse neurological pathologies since it plays a key trophic role in the developing nervous system and maintenance and regulation of neurological functions in the adult brain [1]. It is also recognized to date that IGF-1, together with other neurotrophic growth factors, play the first line of defense in the adult brain exposed to neurotoxic insults. Abnormalities in IGF-1 levels have been implicated in a variety of neurological and psychiatric disorders. The researchers review here selected literature suggesting that IGF-1 plays a unique role in neuroprotection towards glutamate-induced excitotoxicity in *in vitro* and *in vivo* models. Specifically, the researchers focus on the relationship between IGF-1-induced neuroprotection and glutamate-induced excitatory neurotoxicity, present the reciprocal cross-talk between IGF-1 and glutamate receptors, and briefly address preclinical and clinical studies providing pieces of evidence that IGF-I confers neuroprotection in animal models and neurological diseases [2]. Excitotoxicity is a phenomenon that describes the toxic actions of excitatory neurotransmitters, primarily glutamate, where the exacerbated or prolonged activation of glutamate receptors starts a cascade of neurotoxicity that ultimately leads to neuronal cell death and the loss of neuronal function. In this process, the shift between normal physiological function and excitotoxicity is largely controlled by astrocytes since they regulate the levels of synaptic glutamate. The molecular mechanism that triggers excitotoxicity involves alterations in glutamate and calcium metabolism and dysfunction of glutamate receptors. Excitotoxicity is the cause but also the consequence of other cellular pathophysiological processes, such as mitochondrial dysfunction, neuronal damage, and oxidative stress. It is known that the

excessive activation of glutamate receptors results in the sustained influx of calcium into neurons that leads to several deleterious consequences, including mitochondrial dysfunction, overproduction of reactive oxygen species (ROS), the impairment of calcium buffering, and the release of pro-apoptotic factors, among others, that cumulatively contribute to neuronal loss. Recent studies implicate glutamate-induced excitotoxicity as a central mechanism in the pathogenesis of many neurodegenerative diseases, including amyotrophic lateral sclerosis, Alzheimer's disease, traumatic brain injury, and epilepsy, suggesting that neurodegenerative diseases may share excitotoxicity as a common pathological mechanism [3]. Thus, IGF-1 signaling involved in neuroprotection towards glutamate-induced excitotoxicity is also of critical significance for the future clinical treatment of many neurodegenerative diseases [4]. Considering that alterations of IGF-1 levels have been implicated in human ischemic stroke [5] and brain trauma [6], and exogenous administration of IGF-1 has neuroprotective effects in animal models of ischemia [5], the investigations of the relationship between IGF-1 levels and activity and neuronal injury is of great value. They may clarify the neuroprotective role of IGF-1 [7] in glutamate-induced excitatory toxicity and allow the implementation of the findings towards novel neuroprotective therapeutic strategies, with the understanding that the targets are not specific symptoms, but the underlying molecular signaling pathways and cellular phenomena of excitotoxicity.

2. IGF-1 Modulation of Glutamate-Induced Synaptic Plasticity

Synaptic plasticity involves both short-term and long-term processes. The short-term synaptic plasticity includes facilitation, depression, and potentiation, and the long-term synaptic plasticity includes long-term potentiation (LTP) and long-term depression (LTD) [8], which can lead to synaptic dysfunction, causing learning and memory impairment once the two processes are unbalanced [9]. NMDARs and AMPARs are important excitatory receptors for synaptic transmission and plasticity. IGF-1 is one of the neurotrophic factors that is maintaining glutamatergic synaptic function by stimulating the PI3K/Akt or MAPK/Erk signaling pathway [10]. Moreover, IGF-1 is inducing phosphorylation of glycogen synthase kinase 3 beta (GSK3β) at serine-9 and thus causing its inactivation, a critical convergence event in the promotion of survival of the glutamatergic, cerebellar granule brain neurons [11]. Since GSK3β mediates the interaction between the two major forms of synaptic plasticity in the brain, NMDAR-dependent long-term potentiation (LTP) and NMDA receptor-dependent long-term depression (LTD) [12], the IGF-1 induced stimulation of the phosphorylation of GSK3β significantly affects the synaptic plasticity. Moreover, the synaptic plasticity mechanisms of IGF-1 may be accomplished by the modulation of the brain levels of the brain-derived neurotrophic factor [13], the increase in calcium influx through L-type calcium channels, and the activation of CaMKIIα [14][15], as well as by the decrease in the GABA-A receptor- alpha-1 subunit expression [16], the regulation of the astrocytes' glutamate-transporters [9], and the cooperative interactions with different neurotrophins [17].

AMPAR is expressed in a wide range of brain glial cells, besides neurons, where they regulate important cellular functions. AMPAR allows glial cells to sense the activity of neighboring neurons and synapses, rendering the glial cells sensitive to elevations of the extracellular concentration of glutamate, thus triggering neuronal pathophysiological responses and amplifying neuronal excitotoxicity [18]. The glutamate concentration and cellular

localization of AMPAR along with IGF-1, 2 expressions were upregulated in the periventricular white matter (PWM) of neonatal rats exposed to hypoxia injury [19]. In primary microglial cultures subjected to hypoxia in vitro, administration of exogenous glutamate decreased IGF-1, suggesting that increased IGF-1 expression may represent an early protective mechanism in attenuating the hypoxic damage, but a subsequent glutamate-induced decrease of IGF-1 expression may cause cell death due to excitotoxicity [18]. Intraperitoneal injections of IGF-1, over two weeks, reversed deficits in hippocampal AMPA signaling, LTP, and motor performance in Shank3-deficient mice [20].

Shank3 is part of the glutamate receptor body, which physically connects the parent-NMDA receptor to the metabolite mGlu5 receptor by interacting with the scaffold-folding protein PSD95-GKAP-Shank3-Homer [21]. These findings may suggest an important role of IGF-1 on correcting the integrity of the glutamate receptosome required for synaptic transmission and plasticity.

3. IGF-1 Modulates Calcium Pathway

IGF-1 induces within seconds a large, tyrosine-, kinase-dependent increase in calcium channel currents in cerebellar granule neurons. While P, Q, and R channels were unaffected, N and L channel activities were significantly potentiated at specific membrane voltages. Moreover, transient expression of the dominant-negative and wild-type phosphatidylinositol 3-OH kinase (PI3K) subunits, as well as the application of specific inhibitors, suggest that the role of PI3K on IGF-1 is critical, indicating that the regulation of N and L calcium channels may control calcium-dependent processes, such as neurotransmitter release and IGF-1-dependent survival [22]. In the cortex and hippocampal neurons, depolarization and IGF-1 rapidly increase phosphorylated-CREB levels, which require CaV1.3 activity and the S1486 phosphorylation site to achieve a full effect [23]. In addition, IGF-1 promotes the survival of cerebellar granule neurons by enhancing calcium influx through L-type calcium channels increased CaMK-IV activity, which acts to decrease nuclear transcription factor CCAAT enhancer-binding proteins (C/EBPβ). Conversely, NMDA receptor-mediated influx rapidly elevates nuclear C/EBPβ and induces excitotoxic death via activation of the calcium-dependent phosphatase, calcineurin (**Figure 1**). Moderate levels of AMPA receptor activity stimulated L channels to improve survival, whereas higher levels stimulated NMDA receptors and reduced neuronal survival, suggesting differential synaptic effects. Finally, N-type calcium channel activity reduced survival, potentially by increasing glutamate release [13]. The Na^+/Ca^{2+} exchanger (NCX) is an important bidirectional transporter of calcium in neurons and is involved in neuroprotection. In rat primary neuronal cultures, IGF-1 produced an increase in the NCX-mediated inward current and a decrease in the NCX-mediated outward current, indicative of its involvement in IGF-1-induced neuroprotection [24]. Therefore, the neuroprotective effects of IGF-1 on neurons can be achieved by regulation of several subtypes of calcium channels, which in turn modulate the expression and activity of CaMKs and of specific nuclear transcription factors regulating genes involved in neuronal calcium homeostasis, and maintaining the survival of neuronal cells.

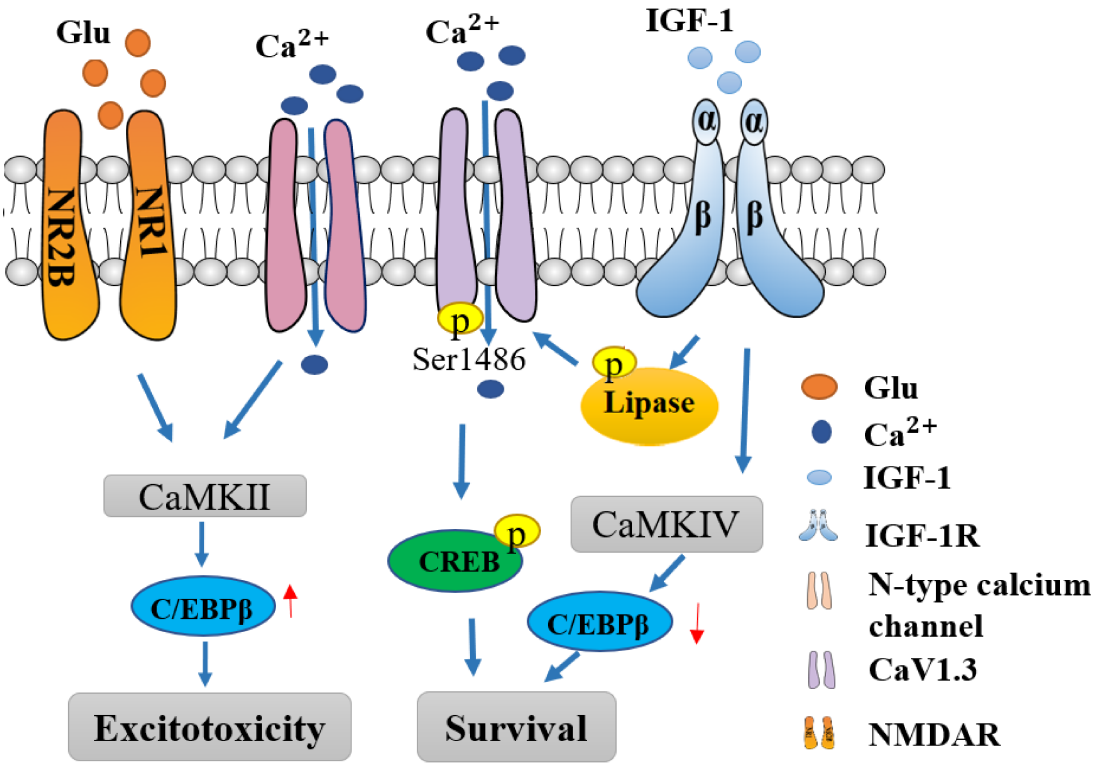

Figure 1. IGF-1 modulation of calcium signaling. Neuroprotective effects of IGF-1 on neurons are achieved by the regulation of several subtypes of calcium channels. CaV1.3 channels are modulated by IGF-1 through activation of the phospholipase C and CaMK-II-induced phosphorylation of the CaV1.3 subunit; the phosphorylation of serine residue 1486 of the CaV1.3 subunit rapidly increased CREB levels. In addition, IGF-1 promotes the survival of cerebellar granule neurons by enhancing calcium influx through L-type calcium channels, increased CaMK-IV activity that in turn acts to decrease the CCAAT enhancer nuclear binding proteins (C/EBPβ). Conversely, NMDA receptor-mediated calcium influx rapidly elevates nuclear C/EBPβ and induces excitotoxicity via activation of the calcium-dependent phosphatase, calcineurin.

4. IGF-I Confers Neuroprotection towards Neurological Diseases with Glutamate Excitotoxicity

IGF-I exerts its pleiotropic neuroprotective functions in an endocrine, autocrine, and paracrine fashion [25]. Numerous research studies indicated that the reduced IGF-1 levels in the serum followed by decreased activity of IGF-1 signaling pathways plays a significant role in the progression of many neurological disorders, including those with glutamate excitotoxicity as a common pathological pathway such as ischemic stroke and traumatic brain injury [26]. Clinically, several studies have shown that reduced levels of IGF-1 in human patients correlated with increased mortality rate, poorer functional outcomes, and increased morbidities following an ischemic stroke [5]. In animal models of ischemia, administering exogenous IGF-1 using various routes of administration (intranasal, intravenous, subcutaneous, or topical) at various time points before and/or following the insult, attenuated the neurological damage and accompanying behavioral changes (**Table 1**) [20][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43]. Therefore, since dysregulation of IGF-1 signaling was a common observation in neurodegenerative manifestations

of excitotoxicity, the clinical rationale proposed that restoration of abnormal IGF-1signaling by exogenous supplementation could result in neuroprotection and neurotrophic effects for many clinical-pathological presentations. For this purpose, different delivery routes and therapeutic protocols were used in clinical trials on human patients treated with human recombinant IGF-1 or its analog Trofinetide [glycyl-L-methylprolyl-L-glutamic acid (NNZ-2566)] [44][45]. Multiple studies show mixed pieces of evidence with regards to serum IGF-1 concentration and the long-term neuroprotective effects, tolerability, safety, and efficacy of IGF-1 in many CNS disorders, most notably stroke, traumatic brain injury, amyotrophic lateral sclerosis, Alzheimer's disease, autism spectrum disorder, and others. **Table 1** presents preclinical and human clinical studies and trials providing strong evidence that IGF-I confers neuroprotection in preclinical experimental animal models and clinical trials in human patients with different neurological diseases. However, there are many reservations about these clinical evaluations. Serum IGF-1 may not adequately reflect the concentration of IGF-1 within the brain and there are methodological variations between studies measuring IGF-1 itself, with some measuring total level and others just the free amount [46]. Interestingly, one prospective population-based study found no direct association between IGF-1 and cognition over 20 years in 746 men [47]. Much larger, prospective longitudinal clinical studies are required to establish not just correlation, but determine any direction of causation, if it exists, between IGF-1 treatment and a clinical neuroprotective, therapeutic effect.

Table 1. Preclinical and clinical studies provide evidence that IGF-I confers neuroprotection in animal models and neurological diseases.

Disease	Animal Models	Human Patients	Reference
Ischemic Stroke	Attenuated infarct size with IGF-1 treatment in MCAO and improved post-stroke neurological behaviors.	Inverse correlation between circulating IGF-1 levels and stroke incidence; The levels of IGF-1in the serum is also inversely associated with the neurological deficits following stroke.	[5][27]
Traumatic brain injury (TBI)	IGF-1 is neuroprotective. Functional neurological improvement of motor and cognitive functions in different TBI models.	IGF-1 clinical trials in TBI demonstrate that IGF-1 administration either alone or in combination with GH was safe to humans and successful in improving metabolic parameters in moderate-to-severe TBI patients.	[48]
Amyotrophic Lateral Sclerosis (ALS)	In mouse models of ALS rhIGF-1 delayed disease onset, reduced muscle atrophy, promoted peripheral motor nerve regeneration, and extended life.	Randomized, double-blind, placebo-controlled, phase two and three clinical trials reaffirmed that rhIGF-1 administration was safe and well tolerated in most subjects but efficacy was not statistically significant.	[26]
Alzheimer's Disease (AD)	In mice with increased cerebral beta-amyloid plaques serum IGF-1 modulated brain levels of beta-amyloid and prevented premature death	Multicenter, cross-sectional study to assess the relationship between IGF-1 and cognitive decline indicated that serum IGF-IGFBP-3 levels were implicated in men with AD. However, a	[25][28][29][30]

Disease	Animal Models	Human Patients	Reference
		double-blind, multicenter study using growth hormone secretagogue MK-677 which stimulates upregulation and circulation of IGF-1, failed to show efficacy in slowing disease progression.	
Autism spectrum disorder (ASD)-Phelan-McDermid Syndrome (PMS)	I.p. injection of rhIGF-1 in Shank3-deficient mice at clinically approved doses of 0.24 mg/kg/day for 2 weeks reversed the electro-physiological deficits and demonstrated reduced AMPAR-mediated transmission and showed normal LTP comparable to the wild type control mice	A clinical trial using 0.24 mg/kg/day of rhIGF-1 in divided doses, in nine children with PMS (Shank3 deficient) demonstrated safety, tolerability, and efficacy.	[20][31][33]
ASD- Fragile X Syndrome (FXS)	In Fmr1 knockout mice characterized by reduced excitatory synaptic currents, enhanced glutamate receptor dependent-LTD, 100 mg/kg i.p. injection of IGF-1 analog Trofinetide (NNZ-2566) resulted with reduced hyperactivity, improved LSTM and LTP, and normalized social recognition and behaviors.	Phase II randomized, double-blind, placebo-controlled, parallel-group, confirmed the safety, tolerability and efficacy at the high dose of treatment with oral administration of Trofinetide at 35 or 70 mg/kg twice daily, in 72 adolescent or adult males with FXS.	[35][36]
Friedreich's ataxia (FRDA)	IGF-I in FRDA-like transgenic mice (YG8R mice) conferred neuroprotection and normalized motor coordination.	In a clinical proof of concept pilot study, patients were treated s.c. with IGF-1 therapy with 50 µg/kg twice a day for 12 months and tolerability and decrease in the progression of neurological symptoms was measured, together with long-term stability of cardiac function.	[37][38][39]
Huntington's disease (HD)	IGF-1 intranasal delivery rescues HD phenotype in YAC128 mice.	In 219 patients with genetically documented HD and in 71 sex- and age-matched controls, IGF-1 serum levels were significantly higher in patients than in controls, indicating somatotropic axis is overactive to confer neuroprotection.	[40][41]
Epilepsy	IGF-I ameliorated hippocampal neurodegeneration and protected against cognitive deficits in an animal model of temporal lobe epilepsy.	57 patients with focal epilepsy and 35 healthy controls were evaluated for IGF-1 level; reduced serum levels of IGF-1were found to correlate with age and cardiovagal function, a parameter of cerebral autoregulation (the breath-	[42][43]

Disease	Animal Models	Human Patients	Reference
		hold index). Patients with a longer history of epilepsy, presented higher seizure frequency, and temporal lobe epilepsy and had lower serum levels of IGF-1.	

Abbreviations: MCAO, middle cerebral artery occlusion; rhIGF-1, human recombinant IGF-1; GH, growth hormone; i.p., intraperitoneal; s.c., subcutaneous. Fmr1, fragile X mental-retardation protein 1; Shnk3, SH3 and multiple ankyrin repeat domains-3 protein; LTD, long-term depression; LTP, long-term potentiation; LSTM, long short-term memory.

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