Review Article

Cognitive Rehabilitation Improves Ischemic Stroke-Induced Cognitive Impairment: Role of Growth Factors

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Cognitive dysfunction is the most common nonphysical impairment in the stroke survivors. This impairment has a negative impact on patients' quality of life affects their daily living activities. Both pharmacological and nonpharmacological interventions are employed to improve cognitive impairment. Recently, nonpharmacological interventions have attracted great attention. Cognitive rehabilitation is considered as a therapeutic strategy to improve and maintain cognitive skills in patients with stroke. Enriched environment (EE), as a cognitive rehabilitation strategy, has been shown to facilitate physical, cognitive, as well as social abilities. Moreover, EE has been shown to increase endogenous growth factors. Growth factors have pivotal role in neurogenesis, synaptogenesis, as well as brain remodeling through neuron development, differentiation, and survival. In addition, administration of exogenous growth factors prevents cognitive dysfunction. Here, we review preclinical and clinical evidence of cognitive rehabilitation and role of growth factors in treating poststroke cognitive impairment.

Key Words: Ischemic stroke—cognitive rehabilitation—growth factors—cognition

Introduction

Stroke is the second leading cause of death and long-term disability in older people that each year influences over 15 million people worldwide.[1] In addition to physical disability, stroke is responsible for the significant cognitive decline in one-third of patients.[2,3] The risk of proceeding cognitive impairment after stroke increases at least 5-8 times.[4] Although the exact mechanism of poststroke cognitive impairment (PSCI) are not fully understood, lesions in important areas such as hippocampus, white matter, and cerebral cortex contribute to its pathogenesis.[1] The prevalence of PSCI varies from 20% to 80% depending on the countries, the races, and the diagnostic criteria.[1] PSCI can affect patients' ability to live independently even after recovery from physical disability. PSCI also leads to an enhanced risk of recurrent strokes, further cognitive deficiency, and higher mortality.[5] Therefore, it is necessary to find effective treatments for cognitive deficits in people who have had a stroke.

A number of pharmacological and nonpharmacological methods are available to help people with cognitive impairment.[6,7] Nonpharmacological treatments are effective for persons with cognitive impairment ranging from mild cognitive impairment (MCI) to moderate dementia and are cheap and readily available in developing countries.[7,8] Cognitive rehabilitation is considered as one of the nonpharmacological treatments, which improves

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cognitive impairments via different routes such as increase in growth factors.[9-11]

In addition, administration of growth factors such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), insulin-like growth factor (IGF-1), fibroblast growth factor (FGF), and erythropoietin (EPO) has been shown to improve cognitive function in both physiological and pathological conditions.[12-17] Here, we review preclinical and clinical evidence of nonpharmacological and growth factor therapies in treatment of PSCI.

Stroke and Cognitive Impairment

Brain is a highly organized structure made up of complex networks, which are correlated to sensory, motor, and cognitive performances. Therefore, the loss of neuronal circuits and connections could lead to impairment in these domains.[18]

Cognition refers to the mechanisms in which animal obtain, process, store, and operate on information from the environment.[19] Cognition is considered of several domains including memory, attention, visuospatial functioning, executive function, and language.[20] Cognitive impairments are usually the significant outcome of neurodegenerative diseases such as Alzheimer's disease (AD) and vascular dementia.[21]

Cognitive impairment is defined as a range of mental decrease with mild to severe cognitive functional decline.[22] The terms MCI and dementia have been used to express cognitive impairment.[23,24] MCI is a transitional phase between normal aging and dementia that includes impairments in memory domains but other cognitive domains typically stay intact and individuals have the ability to perform activities of daily living. In contrast to MCI, dementia causes impairment in all cognitive domains.[23-25] Cognitive impairments can reduce the ability of a person to realize task guidelines, to plan, and initiate selfdirected activities, and to solve problems.[20]

PSCI occurs commonly among stroke survivors and is strongly associated with the poor functional outcome.[1,26] Patients with a stroke have higher rates of cognitive impairment than people who have not had a stroke.[27] Memory problems, the deficit of attention, and impaired executive function are the most common cognitive impairments observed in patients with stroke.[28] The incidence of the cognitive decline after stroke increases with age and many of stroke survivors experience the cognitive impairment within 3 months after stroke.[1,29] Some cognitive impairment after stroke may get better over time, although the recovery rates differ due to different basal features of the people.[30]

Cognitive Rehabilitation

Cognitive rehabilitation is a treatment method to improve and increase function for specific mental processes.[31] The cognitive rehabilitation goal is to improve individual's ability to perceive, explain, and answer properly to information.[32] It has been indicated that memory deficits related with aged rat model can be attenuated by cognitive activity.[33] The decline in cognitive impairment has also been seen with cognitive training in AD and traumatic brain injury models.[34,35] Findings of animal studies have shown that repeated cognitive training increases cognitive function at later age. Repeated cognitive activity produces protective effects, which can delay the cognitive decline in transgenic AD mice.[33,36] Cognitive rehabilitation in laboratory animals can be intervened by manipulation of the animal's environment by methods such as housing them in enriched environment (EE).[37,38] In addition, it has been shown that cognition in laboratory animals improves by training them on different kinds of mazes such as Hebb-Williams maze or Morris water maze.[34,39]

EE has been defined as the use of housing conditions that causes increased sensory, motor, and cognitive stimulation of the brain in comparison with standard caging.[40] EE has been shown to have positive effects on cognitive performance both in normal and pathological conditions.[41,42] Animals, which kept in EE, had increased cerebral cortex volume, thickness, and wet weight, number of the synapse, and glial cells.[43] EE or training on particular skills after stroke in injured animals was very efficient to stimulate functional recovery.[44] EE intervention in mice with cognitive impairment improved water maze performance, induced hippocampal long-term potentiation (LTP), and enhanced function of the basal forebrain-hippocampus cholinergic circuits of contralateral side of stroke compared to PSCI mice kept in standard environment.[45]

HWM has been used for evaluating the memory of rodents and it has been shown that it is sensitive to hippocampal dysfunction.[46,47] A study used HWM as a cognitive rehabilitation and showed that it improved working memory in the radial arm maze in rats.[39]

Cognitive Rehabilitation and Neural Plasticity

The common element of the rehabilitation approaches is neural plasticity.[48] Neural plasticity is considered as the brain's ability to adjust its response to alterations in the environment or lesions.[49] Brain is able to reorganize and relearn those functions that were lost after a lesion, by promoting the correction of maladaptive plasticity, and leading to more functional neural growth state.[48] Neuronal plasticity is increased during sensitive periods of postnatal development but is limited after the closure of critical periods.[50] Neuronal plasticity includes atrophic processes such as the deletion of inactive neurons and neuronal contacts and trophic processes such as neurogenesis and synaptogenesis.[50] Indeed, brain is remodeled by behavioral experience through wide variety of events and stimuli.[51] Structural mechanisms underlying experience-dependent plasticity in the adult cortex include axonal remodeling,

the growth of new dendritic spines, and synapse turnover.[52] Physiological changes involve a dynamic modification of facilitation and inhibition at selected synapses, modulating conductance, or resistance to impulse transmission without causing overt tissue alterations.[53]

Neural plasticity has been postulated as a mechanism for recovery of function after injury.[54] Brain injury makes a significant change of the neural network in the affected region.[55] Animal studies have revealed that brain damage can trigger neural plasticity.[56]

Regarding the positive effects of cognitive training, researchers have concentrated on identifying the basic mechanisms underlying the effects of cognitive activities in animal models. The training positively changes the brain's intrinsic activity at rest and its structural connectivity.[57] Neuroplasticity alterations such as increased synaptic density, enhanced cerebral gray matter, and increased volume of the hippocampus have been found by new learning in animal models.[58] Cognitive training also enhanced the total cellular activity and metabolic rate in specific brain areas.[57] Functional imaging and electroencephalography studies also indicate neuroplastic changes and neuroplasticity following cognitive training in humans.[59] Understanding of the molecular mechanism and the critical period windows of plasticity in adult-born neurons will play an important role in successful rehabilitation from ischemic stroke. Endogenous response mechanisms following exposure to hypoxia-ischemia include increased neuronal transcription factors hypoxia-inducible factors 1 and 2 expression correlated with increased expression of a number of cytokines and growth factors.[60,61]

Impact of Growth Factors on Neural Plasticity

Growth factors are driving agents in plasticity events.[62] Growth factors play important roles in the normal central nervous system (CNS) development and function.[63] Increased growth factors expression after ischemia or injury activates a series of signaling pathways that regulates various cellular processes including apoptosis, inflammation, angiogenesis, cell differentiation, and proliferation.[61,64,65] In addition, growth factors such as BDNF, VEGF, NGF, IGF-1, FGFs, and EPO promote neuronal plasticity and functional recovery following stroke.[13,66-71] Moreover, Cerebrolysin which is a mixture of different neurotrophic factors has been shown to have recovery-promoting effects after brain damage.[72]

It has been shown that the benefits of cognitive activity is mediated by increased growth factor signaling.[73] Cognitive activity results in the activation of neurons, release of glutamate from presynaptic terminals, and production of growth factors.[74] For instance, cognitive rehabilitation has demonstrated beneficial effects on cognitive deficits of Parkinson's patients in association with an increase in BDNF levels.[75] In a study on stroke patients, increased IGF-1 level after cognitive rehabilitation was observed.[76] It has also been demonstrated that combination of growth factor and rehabilitation after injury could have positive effects on the functional outcome, for instance Cerebrolysin has been shown positive effects on motor function when was applied with motor rehabilitation.[77]

Growth factors are classified into different families that act through specific receptors[78] (Table 1). Here we explain shortly the most important ones:

Brain Derived Neurotrophic Factor

BDNF, as a member of the neurotrophin family, belongs to the group of structurally related polypeptide growth factors.[79] In multiple brain regions, BDNF levels increase during the first month of postnatal development, which is possibly followed by a slight decline into adulthood.[80] BDNF is the major growth factor known to have some effects on cognitive activity in the brain.[81] BDNF involves in the formation of LTP process.[79] Moreover, BDNF serves an essential function in the neuronal survival and growth, modulates neurotransmitter release, and contributes in neuronal plasticity.[82,83]

Evidence obtained from animal studies indicates that exogenous BDNF has protective effects against cerebral ischemia. Intravenous administration of BDNF reduced the infarct size following brain ischemia in rats.[84] In addition, in a middle cerebral artery occlusion model study in adult rats, BDNF treatment reduced infarct volume; improved neurological outcome, up-regulated B-cell lymphoma 2 (Bcl2) protein, and decreased expression of the BCL2-associated X protein (Bax) protein.[85] Moreover, BDNF treatment promoted remyelination, oligodendrocyte proliferation; and improve functional postischemic recovery in the rat.[67] Another study showed that BDNF treatment caused an increase in the number of both activated and phagocytotic microglia, up-regulated IL-10 and its mRNA expression, down-regulated tumor necrosis factor α and its mRNA expression, and enhanced DNA-binding activity of nuclear factor-kappa B in middle cerebral artery occlusion model of stroke (Table 2).[86] It has also been shown that blocking of endogenous BDNF by antisense oligonucleotide negates improving effects of a rehabilitation program after focal ischemia in rats, suggesting a critical role for BDNF in rehabilitation-induced recovery.[81]

In addition, a number of neurodevelopmental, neurodegenerative, and neuropsychiatric disorders, which are characterized by abnormalities in synaptic plasticity, have been associated with deficits in BDNF function.[87] Lower serum BDNF level has been established to be related to a higher risk of incident stroke/transient ischemic attack.[88] Acute low concentrations of BDNF are associated with poor long-term functional outcome after ischemic stroke.[89] Clinical studies have shown that serum BDNF levels and hippocampal volume reductions in elderly individuals are closely correlated with memory loss.[90]

Table 1. *Classification of the known growth factors playing role in neuroplasticity*

Growth factors	Growth factor members	Growth factor receptors
Neurotrophins	Nerve growth factor (NGF)	TrkA
	Brain-derived NTF (BDNF)	TrkB
	Neurotrophin 3 (NT3)	TrkC
	Neurotrophin 4/5 (NT4/5)	TrkB
Glial cell line-derived NTF (GDNF) family ligands (GFLs)	Glial cell line-derived neurotrophic factor (GDNF)	GFRα1
	Neurturin (NRTN)	GFRα2
	Artemin (ARTN)	GFRα3
	Persephin (PSPN)	GFRα4
Bone morphogenetic proteins (BMPs)	BMP1-10, BMP15	BMPRI(A, B), BMPRII
Transforming growth factors-β (TGF-β)	TGFβ1-3	TβR1-3
Insulin-like growth factors (IGFs)	IGF-I, IGF-II	IGF1R, IGF2R
Fibroblast growth factors (FGFs)	Acidic FGF, Basic FGF	FGFR1-4
Epidermal growth factors (EGFs)	EGF, TGF-α, Neuregulins, Amphiregulin, Betacellulin	EGFR/ErbB
Interleukins	IL1-37	ILR
Platelet-derived growth factors (PDGFs)	PDGF-AA, PDGF-BB, PDGF-CC, PDGF-DD, PDGF-AB	PDGFRα, PDGFRβ
Vascular endothelial growth factors (VEGF)	VEGF-A	VEGFR-1,VEGFR-2
	VEGF-B	VEGFR-1
	VEGF-C	VEGFR-3
	VEGF-D	VEGFR-3
	VEGF-E	VEGFR-2
	PLGF	VEGFR-1
Other growth factors	Erythropoietin (EPO)	Epo-R
	Leptin	OB-Rb
	Leukemia inhibitory factor (LIF)	LIF-R
	Ciliaryneurotrophic factor (CNTF)	

VEGF

VEGF, which is primarily expressed by astrocytes and microglia, has some pleiotropic effects in the CNS.[91] VEGF is highly expressed in the ventricular neuroectoderm of embryonic and postnatal periods and its expression decreases in the adulthood.[92] VEGF demonstrates diverse biological functions including modulation of angiogenesis, vasculogenesis, vascular permeability, vascular remodeling, vascular survival, arterial differentiation, hematopoiesis, inflammatory responses, and neurotrophic activity.[93] VEGF has been identified as a neurotrophic factor in the peripheral nervous system, which increases cell survival and promotes the proliferation of Schwann cell and axonal outgrowth in cultured adult mice superior cervical ganglia and dorsal root ganglia.[94-96] VEGF induces neurogenesis not only in the subependymal zone but also in the hippocampus, thus enhances learning and memory apart from increasing angiogenesis in the hippocampus.[97] Moreover, it has been shown that LTP is significantly enhanced in the dentate gyrus by VEGF expression, and VEGF blockade abolished LTP, indicating that VEGF is required to maintain plasticity.[98]

VEGF has been shown to contribute in angiogenesis, arteriogenesis, cerebral edema, postischemic brain, and vessel repair, neuroprotection, neurogenesis, and survival of transplanted stem cells in experimental stroke.[99] Expression of VEGF and its receptors rapidly occurs in neurons and glial cells after hypoxia and ischemia.[100] Exogenous VEGF has been recognized as a possible treatment for improving cognitive function impaired by acute or chronic local cerebral ischemia.[101] VEGF treatment after ischemic stroke reduces infarct volume, induces angiogenesis in ischemic area, and improves neurogenesis and behavioral recovery.[102,103] In a focal stroke model, injection of VEGF after infarction reduced apoptosis.[104] Intranasal administration of recombinant human VEGF 3 days after 2-vessel occlusion (2-VO) surgery improved damaged hippocampal neurons and synaptic plasticity, retained the membrane potential, neuronal excitability, and spontaneous excitatory postsynaptic currents; and cognitive function in the early stage of ischemia (Fig. 1, Table 2).[13]

NGF

NGF had originally been known as a key player in the regulation of peripheral innervations. During development, NGF is present at very high levels in the septo- hippocampal system.[105] In the adult brain, the highest amount of NGF has been discovered in hippocampus, cortex, and olfactory regions.[106,107] Moreover, NGF availability can

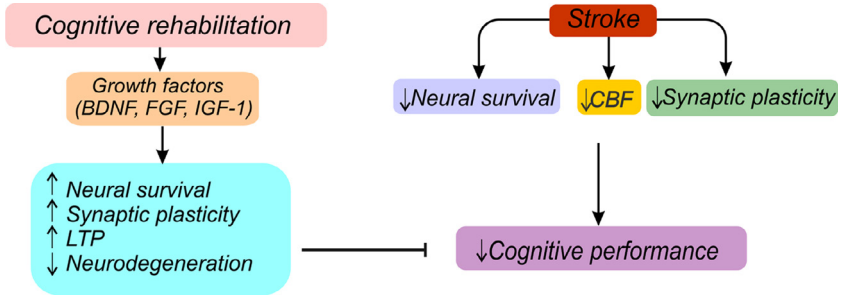

Figure 1. *Effects of stroke, cognitive rehabilitation, and growth factors on cognitive function. (Color version of figure is available online.)*

affect hippocampal physiology and behavior in the intact adult rat brain.[108] NGF facilitates the hippocampal-dependent memory and increases the synaptic plasticity in the hippocampus. Enhanced synaptic plasticity is possibly due to the augmentation of synaptogenesis since NGF treatment has been shown to elevate the density of dendritic spines in the CA3 area.[109] The blockage of endogenous NGF by anti-NGF infusion decreased the hippocampal LTP and disturbed the memory retention.[108,110] In addition, recognition memory deficits could be rescued by intranasal delivery of NGF.[68] Numerous cell signaling pathways, which are crucial for neuronal development, axonal growth, synaptogenesis, and neurotransmission, are activated by NGF.[111-113]

NGF is critical to the survival and maintenance of neurons after cerebral hypoxia-ischemia.[114] NGF mRNA increases in the hippocampal neurons after cerebral ischemia.[115] Moreover, intracerebroventricular administration of NGF before focal cerebral ischemia in mice reduces apoptotic cell death

Table 2. *Growth factors used for the treatment of stroke*

Growth factors	Model	Effects
BDNF	MCAO, rat	Reduced infarct size[84]
	Endothelin-1, rat	Increased oligodendrocyte differentiation and myelin formation; Improved functional[67]
	MCAO, rat	Reduced infarct volume; Reduced expression of the proapoptotic Bax protein in cortical neurons in the penumbra; Increased up-regulation of the antiapoptotic protein Bcl-2[85]
	MCAO, rat	Increased the number of both activated and phagocytotic microglia; Up-regulated interleukin10 and its mRNA expression; Down-regulated tumor necrosis factor α and its mRNA expression; Increased DNA-binding activity of nuclear factor-kappa B[86]
VEGF	MCAO, rat	Reduced infarct volume; Induced angiogenesis in ischemic area; Improved behavioral recovery; Enhanced neurogenesis[102]
	MCAO, rat	Reduced apoptosis[104]
	2-VO, rat	Improved the cognitive function, synaptic plasticity, and damaged hippocampal neurons; Retained the membrane potential, neuronal excitability, and spontaneous excitatory postsynaptic currents[13]
NGF	MCAO, mice	Reduced apoptotic cell death following stroke[116]
	MCAO, rat	Improved neurological function; Reduced infarct volume; Increased survival and proliferation of progenitor cells[117]
IGF-1	MCAO, rat	Increased focal ischemia-induced progenitor cell proliferation in the DG[123]
	MCAO, rat	Reduced infarct size[124]
	Hypoxia−ischemia, rat	Decreased hypoxia−ischemia-induced brain damage; Improved long-term memory and cognitive performance[15]
bFGF	MCAO, rat	Enhanced the proliferation of neural stem cells and their differentiation into neurons, astrocytes, and oligodendrocyte[70]
	MCAO, rat	Increased blood flow; Reduced infarct size; Improved behavioral function[130-132]
	2-VO, rat	Suppressed excessive autophagy; Inhibited apoptosis[133]
EPO	Embolic, rat	Improved functional outcome; Increased oligodendrogenesis and neurogenesis[142]
	Endothelin-1, rat	Increased motor and cognitive performance[17]
	2-VO, rat	Increased recovery of lost memory performance[143]

BDNF, Brain-derived neurotrophic factor; MCAO, -Middle cerebral artery occlusion; VEGF, Vascular endothelial growth factor; 2-VO, Two vessel occlusion; NGF, Nerve growth factor; IGF-1, Insulin-like growth factor; bFGF, Basic fibroblast growth factor; EPO, Erythropoietin.

following stroke.[116] NGF treatment reduces infarct volume, increases survival and proliferation of progenitor cells, and improves neurological function (Table 2).[117]

IGF-1

IGF-1, a member of the family of Insulin-Like Peptides, is a potent growth factor in the CNS with pleiotropic functions on all major cell types.[118] The early post-natal IGF-1 expression is recognized in brain areas where neurogenesis is continued after birth, including the cerebellum, olfactory bulb, and hippocampus. It has been shown that IGF-1 level falls after this period of neuronal proliferation.[119,120] IGF1 expression persists in these areas in adult brains but at much lower levels than that of early neonatal period.[121] Experimental studies have indicated a relation between IGF-I and cognition.[122] IGF1 has been implicated in the control of hippocampal LTP and learning, and synaptic plasticity through its trophic effects on central glutamatergic synapses.[69]

IGF-1 injection following stroke elevated progenitor cell proliferation in the dentate gyrus region.[123] Furthermore, infarct size reduced in IGF-1 treated animals compared to vehicle treated controls.[124] It has also been indicated that IGF-I administration improves cognition in aging animals.[125] In addition, IGF-1 significantly decreases hypoxia−ischemia-induced brain damage and improves long-term memory and cognitive performance in rats (Table 2).[15]

FGF

FGF makes up a large family of cytokines, which are expressed by and target neurons and glial cells.[126] FGF-2 is considered as the most abundant members of the FGF family in the CNS.[127] FGF2 has angiogenic effects in various tissues and organs and play a key role in the differentiation and function of the nervous system.[128] It signals through receptor tyrosine kinases encoding FGFR1-4.[128] In early brain development, FGF2 is expressed by the neural tube and later is expressed in the ventricular region of the developing cortex and the cortical plate. In the adult brain, the highest FGF2 expression has been shown in the cortical regions and hippocampus.[129]

FGF2 is effective in preventing the ischemic stroke possibly through increasing the proliferation of neural stem cells and their differentiation into neurons, astrocytes, and oligodendrocytes.[70] Exogenous FGF2 increases blood flow, reduces infarct size, and improves behavioral function.[130-132] It has also been reported that FGF2 exerts neuroprotective effects in the hippocampal CA1 region by suppressing extreme autophagy and inhibiting apoptosis after cerebral ischemia in rats (Table 2).[133]

EPO

EPO is a hemopoietic hormone, which is synthesized in the fetal liver and the adult kidney.[134,135] The pleiotropic functions of this glycoprotein consist of erythropoietic effects, modulation of the inflammatory and immune process, anti-apoptotic activity, and vasoactive action.[136-138] The multifunctional role of EPO is presented through EPO receptor (EPOR).[139,140] Expression of both EPO and EPOR is reported in cortical and hippocampal neurons, which is associated with high synaptic plasticity and cognitive function.[139-141]

Treatment with EPO increased angiogenesis and neurogenesis, and improved neurological outcome in a rat model of embolic stroke.[142] Single EPO administration has increased both motor and cognitive performance following focal cerebral ischemia in rats.[17] It has also been shown that intravenous administration of EPO increases recovery of lost memory performance in 2-VO model of stroke .[143]

Conclusion

The prevalence of PSCI in stroke survivors is high. Rehabilitation strategies hold promise for improving functional outcomes poststroke. Cognitive rehabilitation of stroke patients can lead to improved function and abilities, possibly through increasing endogenous growth factors. Exogenous administration of growth factors has also shown a promising avenue for improving cognitive performance. A combination of cognitive rehabilitation and growth factor therapy can presumably be more effective in PSCI treatment.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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