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The Use of Neurotrophic Factors as a Promising Strategy for the Treatment of Neurodegenerative Diseases (Review)

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The review considers the use of exogenous neurotrophic factors in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and others. This group of diseases is associated with the death of neurons and dysfunction of the nervous tissue. Currently, there is no effective therapy for neurodegenerative diseases, and their treatment remains a serious problem of modern medicine. A promising strategy is the use of exogenous neurotrophic factors. Targeted delivery of these factors to the nervous tissue can improve survival of neurons during the development of neurodegenerative processes and ensure neuroplasticity. There are methods of direct injection of neurotrophic factors into the nervous tissue, delivery using viral vectors, as well as the use of gene cell products. The effectiveness of these approaches has been studied in numerous experimental works and in a number of clinical trials. Further research in this area could provide the basis for the creation of an alternative treatment for neurodegenerative diseases.

Key Words: *neurodegenerative diseases; neurotrophic factors; cell therapy; gene cell therapy*

Neurodegenerative diseases are a group of diseases of the nervous system caused by the loss of neurons and glial cells, as well as violation of the myelin sheath, which leads to a violation of tissue structure and the loss of certain functions [1-4]. This group of diseases

includes Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, and others [5,6]. According to the WHO, 50 million people in the world suffer from neurodegenerative diseases, and by 2050 this number may increase to 140 million [7].

Modern therapy for neurodegenerative diseases includes pharmacotherapy, psychotherapeutic approaches, and physiotherapy. However, these strategies only relieve the symptoms and improve general condition of patients, but do not contribute to the recovery of damaged nervous tissue [8-10]. Therefore, therapeutic methods capable of restoring lost neurons and neural connections and initiating neuroregeneration processes are required [11,12].

One of the treatment options is the use of neurotrophic factors that can regulate the development

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and homeostasis of neurons and glial cells through interaction with membrane receptors. The role of neurotrophic factors in the neuronal survival *in vitro* has been demonstrated [13-16]. They also play an important role in the development of the embryonic nervous system [17-19] and in the maintenance of the adult nervous tissue via regulation of neuroplasticity and formation of long-term memory [20-23]. These features make these factors promising elements in the therapy of neurodegenerative diseases. Under pathological conditions, the levels of these factors decrease. The development of strategies and methods for delivering exogenous factors directly to the foci of pathology in CNS can be the way to solve this problem.

This review presents a brief description of neurotrophic factors and their role in the therapy of neurodegenerative diseases and considers various options for their delivery: direct injection into the brain, the use of viral constructs, or therapy with gene cell products.

Neurotrophic factors and their functions

Neurotrophic factors are a family of biomolecules that support neuronal growth, survival, and differentiation *in vitro* and *in vivo* [13-16].

These factors play a key role in the processes of embryonic development from the earliest stages. For example, it has been shown in animal experiments that brain-derived neurotrophic factor (BDNF) is involved not only at the stage of implantation, but also after it, contributing to the survival and development of the embryo [24]. At later terms, the level of neurotrophins in the fetal tissues plays an important role in the development of the embryo and its CNS. Nerve growth factor (NGF) has been shown to play a key role in early development of the nervous system in chicken embryos, but is also important for somite development through the regulation of gene expression [25]. The level of expression of neurotrophins is not the same at different stages of embryogenesis. At the early stages of development, increased levels of neurotrophin-3 (NT-3) expression are observed, but with the development of the brain, there is a change in the gradient in favor of BDNF [26]. This peptide plays an important role in brain development [27]. In turn, studies on *Danio rerio* showed that, starting from the early stages of brain formation, many sites of active BDNF expression are distinguished, which grow over time [17]. The importance of the level of neurotrophic factors in the embryonic period was also shown in the analysis of clinical data. The expression of factors is changed in pregnancy complications, e.g. in preeclampsia [28].

During the postnatal period, neurotrophic factors are involved in neuroplasticity, neuronal remyelination

processes, and long-term memory formation. They act as modulators of synaptic plasticity regulating the work of excitatory and inhibitory synapses [29]. Neurotrophic factors provide neuroprotection of dopaminergic neurons and are necessary for their differentiation and maturation under normal conditions [30]. They can also be involved in physiological processes such as energy metabolism, modulation of pain sensitivity, and apoptosis [20-23,31]. Neurotrophic factors affect embryogenesis and postnatal development of the cerebellum in mammals, stimulating the formation and contributing to an increase in the number of Purkinje cells [32]. The role of these factors in the formation of drug and alcohol addiction, as well as in the development of aggression and adaptation to stress is also known [33].

Neurotrophic factors are divided into 3 families: neurotrophins, the GDNF (glial cell line-derived neurotrophic factor) family, and neuropoietic cytokines (Table 1). Neurotrophins can interact with the p75 protein or with tyrosine kinase receptors. Although there are 3 types of tyrosine kinase receptors, they all activate related molecular pathways: Ras/MAPK, PLC γ 1, and PI3K/Akt-mTOR, and are also involved in neuronal plasticity and cell survival [34-36]. The p75 protein has 2 main molecular pathways: NF- κ B and JNK. Activation of the NF- κ B signaling pathway triggers the anti-apoptotic response that promotes cell survival. Moreover, p75 may also be involved in amplifying the signal from tyrosine kinase receptors [37]. When the JNK pathway is triggered, p53 is activated, which can lead to the development of programmed cell death [38]. Since multiple receptors can be expressed on the cell membrane, the decision to survive or trigger programmed cell death is made based on a gradient of apoptotic (alarmins and immature neurotrophins) and anti-apoptotic (mature neurotrophins) neurotrophic factors [39].

Members of the GDNF family can bind to the GFR α /RET complex, the molecular response of which is associated with the survival of nerve cells and changes in their physiology [40,41].

Since neurodegenerative diseases are characterized by mass death of neurons, the ability of neurotrophic factors to promote neuronal survival and Schwann cell migration in pathological processes makes them an important element in the therapy of neurodegenerative diseases.

Neurotrophic factors and their participation in the development of neurodegenerative diseases

The main causes of neuronal death in neurodegenerative diseases are considered to be impaired

TABLE 1. Neurotrophic Factors, Their Receptors, and Functions

Family of neurotrophic factors	Neurotrophic factor	Neurotrophic factor receptor	Main functions	
Neurotrophins	NGF	p75 (nerve growth factor receptor) [92-94]	<ul style="list-style-type: none"> Participates in the development of pro-apoptotic (JNK pathway) and anti-apoptotic (NF-κB pathway) effect 	
		TrkA (tyrosine kinase receptor A) [16,95-97]	<ul style="list-style-type: none"> Participates in the regulation of pain syndrome Participates in the differentiation of sympathetic neurons 	
	BDNF	p75 (nerve growth factor receptor) [94]	<ul style="list-style-type: none"> Amplifies the signal from tyrosine kinase receptor B (NF-κB pathway) Participates in the development of pro-apoptotic effect (JNK pathway) 	
		TrkB (tyrosine kinase receptor B) [98,99]	<ul style="list-style-type: none"> Promotes neuronal survival Participates in memory development Blocks the signal along the p75 path 	
	NT-3	p75 (nerve growth factor receptor) [39,100]	<ul style="list-style-type: none"> Participates in the development of pro-apoptotic effect (NF-κB) 	
		TrkC (tyrosine kinase receptor C) [101,102]	<ul style="list-style-type: none"> Has an anti-apoptotic effect Stimulates Schwann cell migration 	
		TrkB (tyrosine kinase receptor B) [103]	<ul style="list-style-type: none"> Regulates neuronal survival 	
		TrkA (tyrosine kinase receptor A) [104]	<ul style="list-style-type: none"> Promotes axonal growth 	
	GDNF family	GDNF	GFR α 1 (GDNF family receptor)/RET [105]	<ul style="list-style-type: none"> Activates Schwann cell migration Has an anti-apoptotic effect Stimulates axon growth
		NRTN (neurturin)	GFR α 2 (GDNF family receptor)/RET [106-107]	<ul style="list-style-type: none"> Promotes survival and functional activity of developing and mature midbrain dopaminergic neurons Promotes the survival of sensory neurons in the spinal ganglia
Neurotrophic cytokines	CNTF (ciliary neurotrophic factor)	CNTRF (CNTF receptor) [108]	Participates: <ul style="list-style-type: none"> in neuroprotection in case of injury in the development of motor neurons 	
	IL-1	IL-1R (IL-1 receptor) [109,110]	Participates: <ul style="list-style-type: none"> in the regulation of microglia in the development of pain syndrome in response to stress 	
	IL-2	IL-2R (IL-2 receptor) [111,112]	Participates: <ul style="list-style-type: none"> in the regulation of sleep patterns in the development of memory in neuroprotection in the survival and differentiation of nerve cells and glial cells 	

conformation of some cerebral proteins (α -synuclein, β -amyloid, τ , TDP-43, FUS, etc.) associated with their pathological aggregation in cells, as well as microglial inflammation, disruption of autophagy mechanisms, and other processes, which ultimately leads to the development of programmed cell death [1,3,4,42-44]. The general characteristics of neurodegenerative diseases are presented in Table 2.

In the course of a detailed study of the brain in various neurodegenerative diseases, a decrease in the

level of certain neurotrophins and their receptors was revealed (Table 2). For example, in Alzheimer's disease, the level of NGF in the nervous tissue decreases [45-47]. In Parkinson's disease, a decrease in the level of BDNF in the blood serum is observed [48], which is associated with a decrease in the size of neurons and a decrease in their activity. Patients with multiple sclerosis also have reduced levels of BDNF and NGF in the brain, which correlated with low results in neuropsychological tests [49,50].

TABLE 2. General Characteristics of Neurodegenerative Diseases

Disease	Typical neuropathology	Changes in neurotrophin concentrations	Main clinical manifestations
Alzheimer's disease [113-115]	<ul style="list-style-type: none"> • Accumulation of τ-protein and β-amyloid aggregates • Amyloid plaques in brain tissue • Primary hippocampal involvement and cholinergic denervation of the cerebral cortex 	<ul style="list-style-type: none"> • \downarrow NGF, BDNF levels in brain tissue 	<ul style="list-style-type: none"> • Cognitive decline functions (up to dementia) cortical type (amnestic syndrome, disorientation, various variants of primary progressive aphasia, acalculia, apraxia, etc.) • Psychoses
Parkinson's disease [1,116-119]	<ul style="list-style-type: none"> • Accumulation of pathological α-synuclein aggregates with degeneration of dopaminergic neurons in the substantia nigra 	<ul style="list-style-type: none"> • \downarrow serum BDNF level • \downarrow the level of expression of GDNF in brain tissue 	<ul style="list-style-type: none"> • Impaired motor functions (resting tremor, hypokinesia, muscle rigidity, and postural instability) • Non-motor manifestations (impaired vegetative, cognitive functions, depression, apathy, behavioral disorders in the REM sleep phase, psychoses, and hyposmia)
Huntington's disease [120]	<ul style="list-style-type: none"> • Accumulation of mutant polyglutamine-containing huntingtin protein in medium spike neurons of the striatum and neurons of other CNS structures • Death of neurons of the basal ganglia and associated parts of the cerebral cortex, decrease in the volume of the basal ganglia 	<ul style="list-style-type: none"> • \downarrow serum BDNF level 	<ul style="list-style-type: none"> • Motor disorders (choreic hyperkinesia, dystonia, etc.) • Cognitive decline of the subcortical type (up to dementia) • Mental disorders (depression, psychosis, dysphoria, etc.)
Multiple sclerosis [49,121,122]	<ul style="list-style-type: none"> • Foci of demyelination in CNS • Secondary axonal degeneration 	<ul style="list-style-type: none"> • \downarrow serum BDNF, NGF levels 	<ul style="list-style-type: none"> • Conduction disorders of motor and sensory functions (pyramidal paresis, spasticity, and disorders of sensitivity) • Impaired coordination of movements • Pelvic disorders • Optic nerve atrophy with visual impairment • Remitting current (in most cases)
Amyotrophic lateral sclerosis [65,123-125]	<ul style="list-style-type: none"> • Degeneration of central and peripheral motor neurons 	<ul style="list-style-type: none"> • \uparrow GDNF levels in cerebrospinal fluid 	<ul style="list-style-type: none"> • Bulbar and pseudobulbar disorders (dysphagia, dysphonia, and dysarthria) • Neurogenic muscle weakness and skeletal muscle atrophy • Spasticity • Respiratory failure • Cognitive disorders in some patients

In addition to changes in the concentration of neurotrophic factors, some neurodegenerative diseases are associated with changes in the expression of their receptors. For example, in Huntington's disease, the regulation of intracellular processes through NGF is disrupted due to impaired production of the huntingtin protein. Mutant huntingtin inhibits the receptor-associated complex and disrupts NGF signaling, which leads to pathologies in both CNS and peripheral nerve tissues [51]. Thus, neurotrophic factors play a crucial role in the development and progression of neurodegenerative diseases.

Application of neurotrophic factors in the therapy of neurodegenerative diseases and methods of their delivery

Conservative methods are currently the basis of therapy for neurodegenerative diseases. In Alzheimer's

disease, cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are used, which increase the content of acetylcholine in synapses, thus improving neuronal function. Memantine that prevents hyperactivation of the glutamergic system and reduces neurotoxicity is also used in the treatment of Alzheimer's disease [52,53]. In the treatment of Parkinson's disease, dopaminergic drugs are used to increase the level of dopamine in CNS. In addition to drug treatment and non-pharmacological therapy, deep brain stimulation using an implanted device that affects certain areas of the brain with an electric current is also used [43,54,55]. Psychotherapeutic approaches, in particular cognitive interventions and behavior management techniques, are also used to maintain the condition of patients with neurodegenerative diseases [56-58]. However, as already noted, these methods mainly have a symptomatic effect and do not contribute to the restoration of the nervous tissue [8-10].

Thus, the use of neurotrophic factors in the treatment of neurodegenerative diseases can be a promising treatment strategy with a long-term result.

Direct introduction of neurotrophic factors into CNS. The simplest method of delivery is to inject neurotrophic factors directly into the damaged area of the brain. For example, in rats with experimental Parkinson's disease, behavioral tests showed that injection of BDNF into the striatum improved survival of dopamine neurons in groups of young and old animals [59]. Transplantation of recombinant human GDNF into the brain of rhesus macaques with a model of Parkinson's disease was more conducive to the survival of dopamine neurons compared to conservative pharmacotherapy, which was shown in behavioral tests and immunocytochemical studies [60].

The effect of injection of neurotrophic factors into the brain in Alzheimer's disease is also of great interest. Immunohistochemical studies have shown that injection of recombinant human BDNF using a motor pump into the rat brain parenchyma protects serotonergic neurons from degradation [61]. Administration of exogenous NGF into the brain of rats with an experimental model of Alzheimer's disease prevented the processes associated with memory loss, according to the results of behavioral tests [62,63]. In further clinical trials involving 3 patients with Alzheimer's disease, exogenous NGF was injected for 3 months using a pump installed in the lateral ventricle of the brain. Increased brain activity and improved results in object recognition tests have been shown compared to pre-therapy results [64].

Despite the positive results, injection of neurotrophic factors directly into the nervous tissue has a number of limitations. Some researchers note the short lifetime of neurotrophic factors in the body, their low diffusion in the brain tissue, as well as complications associated with the development of pain syndrome [64,65]. Therefore, this method of delivery is not optimal. Viral vectors are being studied to develop more reliable methods of neurotrophic factors delivery.

Introduction of viral vectors encoding neurotrophic factors into the CNS. Over the past few years, active development of viral vectors encoding neurotrophic factors has continued. These vectors penetrate the cell and contribute to the long-term secretion of the transgene. Adeno-associated viruses, lentiviruses, and recombinant adenoviruses are the main groups of vectors used to deliver the transgene [66]. Adeno-associated viruses have single-stranded DNA and their size is about 4.7 kb, lentiviruses carry single-stranded RNA (usually 9 kb), adenoviruses have double-stranded DNA, and their size varies from 7.5 to 30 kb [67,68]. The use of recombinant adenoviruses and adeno-associated viruses is safe, because they do not integrate

into the genome. Lentiviruses are able to integrate into the cell genome, which limits the use of this type of vectors for the treatment of patients with neurodegenerative diseases [69]. Another important factor is the duration of transgene secretion. Lentiviruses and adeno-associated viruses cause constant secretion of the transgene, whereas cell transduction by recombinant adenoviruses leads to temporary secretion [70]. Studies of viral vectors encoding neurotrophic factors and ways to enhance the effectiveness of transduction open up new opportunities for the treatment of neurodegenerative diseases.

Great strides have been made in the treatment of experimental Alzheimer's disease using lentiviral vectors encoding NGF. For example, in preclinical trials simulating Alzheimer's disease in primates, administration of this vector maintains increased levels of NGF in the brain for at least 1 year and has a positive effect on the results of behavioral tests [71]. In clinical trials of NGF delivery using adeno-associated viruses, no improvement was observed in patients. Postmortem studies have shown that the injected vectors did not reach the target cholinergic neurons [72].

Viral vectors encoding GDNF and NRTN have been developed to maintain dopaminergic neurons in Parkinson's disease. Injection of a lentiviral vector with the GDNF gene into the striatum and substantia nigra contributed to the protection of dopaminergic neurons from damage in rats with modeled Parkinson's disease [73]. In primate models of Parkinson's disease, introduction adeno-associated viral vector with the *NRTN* gene in the same areas had a pronounced neuroprotective effect and contributed to the replacement of lost neurons. According to the histological examination of brain samples, injection of this vector prevented mass neuronal death [74]. However, experiments on rats showed that the expression of receptors for these factors decreases in Parkinson's disease, which may reduce the effectiveness of the administration of these vectors [75].

In a rat model of Huntington's disease, transgenic BDNF was investigated. The administration of the adeno-associated vector contributed to the protection of neurons from death and the maintenance of the cytoarchitectonics of the striatum, which, according to the researchers, may be of great importance in the future for the restoration of motor functions [76].

Despite the success achieved in the treatment of neurodegenerative diseases using viral vectors, the problems of developing the immune response and limited genetic capacity of vectors remain unsolved [77]. An alternative may be the development of gene-cell products based on transduced cells.

The use of gene-cell constructs in the therapy of neurodegenerative diseases. In recent years, the

delivery of neurotrophic factors using gene-cell constructs capable of expressing these factors for a long time was actively studied. This technology provides more sustained therapeutic effect due to the combined action of transplanted cells and factors.

Different cell lines are used for viral transduction: mesenchymal stem cells (MSCs), neural stem/progenitor cells (NSPC), and ensheathing cells (ECs) from the olfactory mucosa.

Transduced MSCs expressing neurotrophic factors. Transduced MSCs are extensively studied for the treatment of neurodegenerative diseases. Introduction of lentivirus-transduced NT-3-expressing MSCs into the hippocampus of rats with modeled Alzheimer's disease contributed to improved memory and learning performance in the Morris test [78]. A study in a similar model of BDNF-expressing MSCs also showed memory improvement in the Morris test and reduction in the area of damage in the hippocampus, which was confirmed by histological studies [79]. In rats with modeled Parkinson's disease, behavioral tests showed that transplantation of lentivirus-transduced MSCs expressing GDNF contributed to the normalization of dopaminergic neuronal activity [80,81]. In a model of Huntington's disease, MSCs expressing BDNF and transplanted into the affected area contributed to a decrease in striatum atrophy and increased the lifespan of rats [82].

In experiments in mice [83], the possibility of using transduced MSCs expressing BDNF in the treatment of multiple sclerosis was studied. These cells secreted this neurotrophic factor in CNS, which had a therapeutic effect expressed in reducing the severity of the disease during the acute, relapsing, and chronic phases. This result was achieved due to suppression of inflammation and demyelination.

Transduced NSPCs expressing neurotrophic factors. Neural stem cells (NSCs) transduced with adeno-associated viral vector with a human NGF transgene and injected to rats with a model of Alzheimer's disease replaced damaged neurons and contributed to the recovery of the nervous tissue functions. The role of both the cells and secreted factor in the survival of cholinergic neurons, induction of a regenerative response, and neuroprotection has been noted [84]. Transduced neural progenitor cells (NPCs) expressing GDNF were studied in a rat model of Parkinson's disease. Lentiviral transduction led to prolonged secretion of the transgene and restoration of the normal level of neurotrophic factor [85].

Transduced ECs of the olfactory mucosa expressing neurotrophic factors. EC from the olfactory mucosa is a unique type of glial cells of the peripheral nervous system. They are involved in axonal remyelination and promote neuroregeneration, as well

as secrete neurotrophic factors such as BDNF, NGF, and GDNF. At the same time, they have receptors for neurotrophic factors, which makes autocrine regulation possible [86,87] (Fig. 1). Isolation of ECs from the olfactory mucosa does not pose a risk to the patient, which makes them convenient for personalized cell therapy [88]. Transduced ECs of the olfactory mucosa have not been used for the treatment of neurodegenerative diseases, but their therapeutic effect in the treatment of spinal cord injuries is actively studied. In experiments on rats, ECs transplanted into posttraumatic spinal cord cysts have been shown to survive and contribute to cyst size reduction and recovery of axons of the damaged neurons [89]. Transplantation of these cells promoted recovery of the hindlimb motor functions in rats and reduction of the damage zone [90]. On the basis of human EC and recombinant adenovirus, a gene-cell construct expressing BDNF was obtained, however, cell transduction did not lead to improvement in their therapeutic effect [91].

The use of autologous ECs from the olfactory mucosa has great prospects in personalized therapy of neurodegenerative diseases, because olfactory mucosa sampling is a non-traumatic procedure for the patient, and the cells have a demonstrated neuroregenerative potential. The use of gene-cell constructs based on ECs expressing neurotrophic factors may become an optimal strategy for the treatment of neurodegenerative diseases due to the complex effect of the cellular component and the long-term secretion of factors.

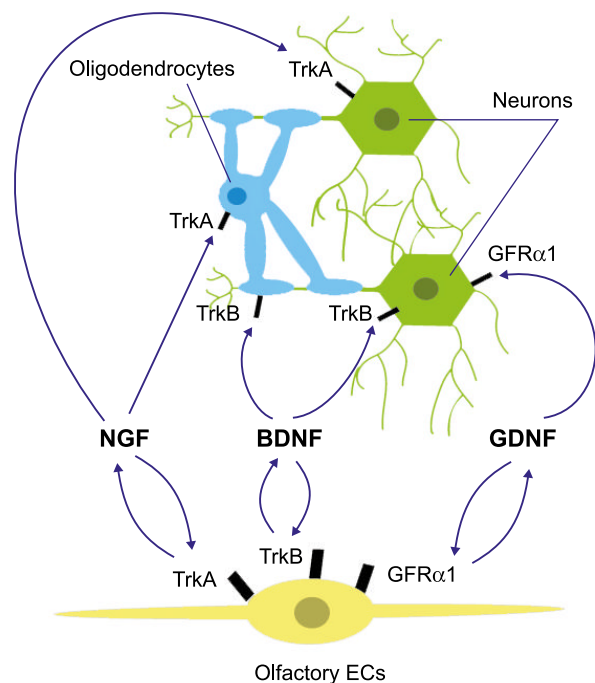


Fig. 1. Expression of BDNF, NGF, and GDNF by ECs and their binding to receptors on cells in the CNS and on the EC.

CONCLUSION

The ability of neurotrophic factors to have a neuroprotective effect and stimulate the growth and repair of axons in the area of injury makes them an important element in the treatment of neurodegenerative diseases. The most promising way to deliver them is gene-cell constructs. Recombinant adenoviruses are the optimal viruses for creating such constructs, since they do not integrate into the genome of cells and provide temporary secretion of the transgene.

The optimal cellular component of gene-cell constructs is autologous olfactory ensheathing cells from the olfactory mucosa due to their non-traumatic obtaining and neuroregenerative activity. The study of gene-cell constructs expressing neurotrophic factors in the therapy of neurodegenerative diseases will make it possible to develop an optimal treatment strategy that contributes to the restoration of damaged nervous tissue.

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Conflict of interest. The authors have no conflicts of interest to declare.

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