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The Relationship between Cognitive Impairment and Neurotrophic Factors in Patients with Parkinson's Disease Dementia

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Abstract

In addition to describing neurotrophic factors and how they affect brain neurodegeneration and the differentiation and proliferation of nerve tissues, this review article offers the findings of recent research on these topics. Data on the causes and diagnostic indicators of cognitive impairments and their relationship in Parkinson's disease patients are offered.

Key words: Parkinson's disease, dementia, neurotrophic factors.

Neyrotrofik omillarni va ularning miya neyrodejeneratsiyasiga, asab to'qimalarining differentsiatsiyasiga va proliferatsiyasiga qanday ta'sir qilishini ushbu maqola mavzular bo'yicha so'nggi tadqiqotlar natijalarini taqdim etadi. Parkinson kasalligi bilan og'rigan bemorlarda kognitiv buzilishning sabablari va diagnostik ko'rsatkichlari va ularning munosabatlari haqida ma'lumotlar keltirilgan.

Kalit so'zlar: Parkinson kasalligi, demensiya, neyrotrofik omillar.

One of the most prevalent neurodegenerative disorders of the nervous system is Parkinson's disease that lower patients' quality of life continue to be a social problem in the healthcare system. Fundamental science has long been based on conditions like Parkinsonism, Huntington's disease, and Alzheimer's disease, and research into these conditions is expensive in many parts of the world [2,3,39,40].

The World Health Organization came to the conclusion that Parkinsonism is common back in 2017. «There are 100 to 250 cases of this degenerative illness for every 100,000 people. In parallel, an increase in Parkinsonism incidence is brought on by the population's longer life expectancy. Evidence suggests that the recurrence rate may rise to 1700 instances per 100,000 people.

The disease's primary symptoms include postural instability, tremors, and slowness of movement. The severity of these illnesses and the patient's condition are highly correlated [12,21,38].

More research is being done now than ever before on cognitive impairment in Parkinson's disease. Studies, for instance, detail the prevalence of dementia, which can account for up to 80% of cases. Between 5% and 8% of people in the general population 60 years of age and older are thought to have dementia at any given moment. [16].

According to the World Health Organization (WHO), dementia is one of the most "cost" diseases for society, along with oncological and cardiological conditions. Dementia is a severe form of cognitive impairment. Typically, cerebrovascular Disorders are frequently found in the elderly, but a recent trend has shown that this condition is becoming more common in young and middle-aged adults [4,11,37]. Since therapy intervention is most effective at this stage, early detection of mild to moderate cognitive impairment is given priority.

The impact of additional variables is explored, including the length of the illness, its forms, the existence of emotional and psychotic diseases, education level, and gender [1,5,17,24,34].

Clinical practice shows that the hippocampus is a particularly vulnerable area of the brain to diseases associated with obesity, diabetes, hypertension,

ischemic disorders, brain injury, and depressive and bipolar disorders. Patients with these diseases often have a pronounced decrease in cognitive functions that are combined with hippocampal atrophy. Volume reduction hippocampus, detected by magnetic resonance imaging, is a recognized indicator of the transition from the normal aging process to moderate cognitive disorders and dementia. On the other hand, the hippocampus is a key area of neurogenesis: cause-induced atrophy of the hippocampus is associated with leveling neurogenesis. Thus, in a healthy, age-related, and “sick” brain, out to be a structural-functional triad: hippocampus - neurogenesis – cognitive function [6,7,15].

It is important to note that neurotrophic factors play an important role in both the development and maintenance of the central nervous system and the peripheral nervous system. They take part in the regulation of growth, development, differentiation, and survival of cell populations, the processes of their adaptation to external influences [27,36].

In addition, it is important to note that neurotrophins have functional diversity due to the interaction of a small number of polypeptides with the receptor apparatus of neurons, not due to a large set of factors. This allows nerve tissue to retain its plasticity and forms mechanisms for restoring neurological function has been damaged. Neuronal degeneration is prevented by these proteins [4,8]. They also stimulate the survival of different types of nerve cells, which is a prerequisite for considering them as possible drugs for the treatment of neurodegenerative diseases.[19,26]. The family of neurotrophins includes nerve growth factor (NGF), neurotrophic brain factor (BDNF), NT3, and NT4/5 neurotrophins. They support different populations of neurons to individual cells, signals for survival, differentiation, or act to prevent initiation of apoptosis in a neuron. They also induce the differentiation of progenitor cells and the formation of neurons. Neurotrophic factors play an important role in the functioning of the nervous system, and the regeneration of damaged neuronal structures.[17,20,33].

Neurogenesis - the process of creating new neurons from neuronal stem cells - is partially retained in the adult mammalian brain, despite the vast majority of neurons being formed during embryonic development. Neurotrophic factors control and stimulate this process. Neurotrophic factors are known to possess both trophic (ensuring survival) and tropic (directing axonal growth) properties. These properties may help them be used to treat neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, as well as peripheral neuropathies. NT3 is a growth factor with mm. 13.6 kDa. NT3 plays a role in the development of the sympathetic nervous system. In mice elevated levels of NT3 were found in sympathetic ganglia and organs during hyperinnervation and spontaneous hypertension. [9,13,41].

Brain-derived neurotrophic factor (BDNF), which acts through LNGFR and TrkB receptors, is one of the factors that can control the metabolism of brain cells in oxygen deficiency [4,10]. The binding of BDNF to Trk-B leads to an increase in trophic influence, which is associated with the main effects of this neurotrophin.

The influence mediated through p75 NTR receptors is more complex and ambiguous. Thus, these receptors are capable of both potentiating and inhibiting the neurotrophic action of Trk-B receptors or independently of them, triggering the apoptotic signaling cascade [11,23,31]. Normally, in most areas of the adult brain, mediated through p75 NTR receptors, activity is inhibited due to their downregulation. However, in pathological conditions, for example, with brain damage,p75 NTR receptor activity is rapidly expressed, which can cause neuronal death [29]. Trk-B receptors consist of extra- and intracellular domains. The Trk-B receptor is represented by five subunits, of which the first and third are cysteine -rich fragments, the second is leucine-rich, and the last two, the fourth and fifth, are immunoglobulin-like fragments. The activation of an intracellular domain connected to the extracellular part of the receptor initiates three cascade reactions, which are mediated by the stimulation of the Trk-B receptor. Neuronal differentiation, functional maturation, and synaptogenesis are all influenced by BDNF. Its neuroprotective activity increases in an adult organism for motor neurons during axotomy and brain neurons during ischemic episodes [10].

The substantia nigra of the brain's dopaminergic neurons degenerate, which results in Parkinson's disease. The pars compacta of this structure saw a noticeable drop in BDNF concentration at the same period. It can be believed that this factor accounts for the drop in BDNF content because the most significant loss of neurons happens in this region of the black matter. [12,32]. The amount of BDNF in the remaining substantia nigra neurons, however, was likewise decreased, according to research [8,35]. Howells et al. discovered that while BP BDNF was only present in 9.6% of pigment-containing neurons.

Lewy bodies were also shown to contain a protein that was immunoreactive to BDNF. This shows that PD-specific pathogenic alterations may manifest even when BDNF is present in the cell [14,21].

It turns out that astrocytes, the cells that produce the majority of these cells, are the main source of the glial neurotrophic factor (GDNF), which was initially identified in glioma cell cultures. The presence of degenerative processes in the human central nervous system has recently attracted major attention to the pathophysiology of astrocytes [6, 18]. It's crucial to stress this. It was quickly shown that GDNF has a trophic impact on the culture of dopaminergic neurons [7

GDNF is now acknowledged as a factor essential for the development, maintenance, and protection of nigrostriatal dopaminergic neurons, including as a potential factor preserving and restoring dopaminergic neurons affected by Parkinson's disease [9,12]. GDNF constitutes a family of structurally similar proteins with neuroturin, artemin, and which assist the migration, differentiation, proliferation, and survival

of the neuronal population.

Extracellular receptors (GFR 1-4), each of which is specific for the associated family member, are used by members of GDNF families to signal. The strongest affinity for GFR 1 is shown by GDNF. The extracellular domain of the receptor tyrosine kinase is where the GDNF-GFR-1 receptor complex attaches, influencing a number of intracellular signaling cascades [22]. In addition, Src-like kinases and MAP kinases can be activated by GDNF's direct binding to neuronal cell adhesion molecules (NCAM).

The proform of GDNF, known as proGDNF, is physiologically active and is expressed in the majority of brain regions as well as in astrocytes and and dopaminergic neurons [15].

In addition to GDNF, proGDNF is broken down to yield biologically active peptides called DNSP 11 in humans and BEP in rats. In the hippocampus, BEP increases synaptic excitation in pyramidal neurons [16], while DNSP 11 protects dopaminergic neurons just as well as the mature version of GDNF [15]. The dopaminergic area of midbrain neurons is not the only location where GDNF and its receptors are found. Numerous different brain areas include GDNF receptors, as well as their transcripts and proteins, demonstrating the versatility of GDNF [16]. Participation in synaptogenesis in the hippocampus is one of them. Ectopic presynaptic sites are induced by GDNF and GFR1, which play an instructive role in synapse development [17,22]. Interestingly, in ASC mice prone to depressive behavior, GDNF enhances spatial learning. [18].

This was discovered two weeks after a single GDNF injection into the brain's lateral ventricle and could be linked to GDNF-controlled synapse remodeling. According to several studies, GDNF/GFR 1 signaling may be crucial for the growth and operation of different types of GABAergic neurons in the human brain [20]. The blood-brain barrier's cellular components are maintained by GDNF [7,8]. When there is inflammation, astrocytes and microglial cells produce more GDNF, which suggests that GDNF is an activator of microglia and an inhibitor of neural inflammation [24]. GDNF expression also increases following the introduction of bacterial lipopolysaccharide [23] and during inflammation.

Due to its high concentration, ciliary neurotrophic factor accelerates the process of apoptosis and participates in the growth of glial cells. There are 220 amino acid residues, and its molecular weight is 22.7 kDa. In 1979, R. Adler and colleagues discovered it for the first time as a trophic factor in parasympathetic neurons of an 8-day-old chicken embryo. generated by glial cells in the central and peripheral nervous systems. The marker ciliary neurotrophic factor determines how much nerve tissue is destroyed. Additionally, this chemical has the capacity to damage retinal neurons, hippocampus, and spinal nodes. [Levi-Montalchini first identified nerve growth factor (NGF) [25] The neurotrophin family of factors, which is unique and very particular in its biological action, has its roots in NGF. Due to their extremely similar amino acid sequences, neurotrophins frequently form homodimers. For neurotrophins to perform their biological roles, dimerization is a necessary prerequisite [2,28]. These findings imply that monitoring such NGF during PD may allow for the early detection of dopaminergic system abnormalities. Such knowledge might improve treatments as well as ways to better safeguard remaining neurons [26,30].

To further demonstrate links between NGF and the level of dopaminergic degeneration, serum NGF levels in PD patients at various stages of the condition as well as in experimental models can be measured. Further study of cerebrospinal fluid is required to determine the processes governing changes in NGF in systems undergoing dopaminergic degradation, such as emotional stress, which is accompanied by increases and decreases in neurotrophic factor [27,29].

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