

Can brain-derived neurotrophic factor (BDNF) be an indicator of effective rehabilitation interventions in schizophrenia?

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Summary

The increasing body of evidence implies that brain-derived neurotrophic factor (BDNF) is the most common neurotrophin in the nervous system, playing an important role as an effectiveness indicator for rehabilitation interventions in schizophrenia patients. Currently, with the modern laboratory and instrumental diagnostic methods it is possible to diagnose deficits influencing the level of patient's functioning and use them as a basis for establishing individual re-adaptation programs for schizophrenia patients considering various forms of the therapy in different environments. Based on the PubMed and Scopus search tools a review of the available literature was performed and the paper presents current results of studies analyzing a relationship between selected rehabilitation interventions used in schizophrenia patients and changes in BDNF levels (a correlation between BDNF levels and physical activity and EEG Biofeedback therapy). Out of 240 records identified in total, the ones concerning the subject matter of the paper were taken into account. Studies concerning use of the presented method appear to indicate usefulness of BDNF factor in evaluation of effectiveness of implemented rehabilitation interventions in this group of patients. Changes in neurotrophin levels may indicate a synergy of the central and the peripheral nervous system, and high BDNF levels depending on physical activity and a neuromodulating effect of the EEG Biofeedback therapy may indicate their effectiveness. Use of various neurorehabilitation methods may improve the social functioning in schizophrenia patients. Treating BDNF as a biological indicator of those processes may represent an interesting hypothesis.

Key words: BDNF, physical activity, EEG Biofeedback, psychiatric rehabilitation

Introduction

Schizophrenia is a mental disorder of a multifactor pathogenesis affecting about 1% of the population [1]. This disorder is characterized by pronounced positive symptoms in the acute phase and pronounced negative symptoms in the post-psychotic phase. The listed symptoms are a consequence of dysfunctions in activity of various areas of the brain, mainly the frontal and temporal regions, limbic and central structures, and basal ganglia [1–4]. Dysfunctions in the prefrontal region most strongly affect processes associated with short-term memory, attention, emotions and executive functions [1, 5–8]. These anomalies have a strong influence on patients' quality of life and social functioning [1, 5, 6, 9–11].

Schizophrenia, as an illness with a varying course, requires multidirectional rehabilitation interventions, however, the basic form of therapy is pharmacological treatment [12]. When the acute psychosis is reversed, multidirectional, non-pharmacological activities are initiated [12, 13]. They are characterized by an extensive therapeutic range and focus on family, professional and social aspects. Both treatment stages are important, because they divide the whole rehabilitation process into early and delayed, accordingly [12, 14]. The early process aims at eliminating acute symptoms of the illness, restoring disrupted social relations, and reducing effects of chronization, the so-called defect and hospitalism [12–14]. The delayed period aims at compensation of diagnosed dysfunctions and establishing the scope of provided assistance. It includes: improvement in dysfunctions, increasing patient's social activity and facilitating their professional and family adaptation. Both stages are important and their integration and appropriate selection of influences facilitates compensation of deficits [14].

When establishing an individual therapeutic program for a patient, a scope of revalidation must be planned, considering not only influences such as: neurorehabilitation, psychoeducation, psychotherapy, and physical and artistic activities, but also personality predispositions of patients, their hobbies, illness duration, number of hospitalizations or their social and professional status. Only when the developed plan considers all those aspects, it is possible to achieve positive results in the whole treatment and rehabilitation process [15]. They will be visible not only in patient's daily life, but also confirmed by results of modern diagnostic tests, such as: f-MRI, PET, spectroscopy, the brain-derived neurotrophic factor (BDNF).

This paper is an attempt to demonstrate in a group of schizophrenia patients a relationship between selected rehabilitation interventions and the levels of the brain-derived neurotrophic factor (BDNF) on a basis of available publications and previous study results. The verified issues considered the effects of physical activity and the EEG Bio-feedback therapy on the neurotrophic factor (BDNF) levels in schizophrenia patients.

BDNF – brain-derived neurotrophic factor

The brain-derived neurotrophic factor (BDNF) belongs to a group of secretory polypeptides, so-called neurotrophins. Together with other proteins, including the nerve growth factor (NGF), neurotrophin NT/3 and NT/4/5 (proteins supporting

synapse development), it participates in neuron function and influences the function of the central and the peripheral nervous system [16–21]. BDNF, synthesized as glycosylated propeptide (pro-BDNF), is generated as non-glycosylated mature protein following its processing into a proteolytic factor [22–24]. The studies indicate that its highest level is present in the hippocampus, the amygdala, the neocortex and the cerebellum [23–27], and its main source are T and B cells, cells of the connective tissue and granulocytes [21].

BDNF binds to the tyrosine receptor kinase B, Trk-B, and the p75 receptor [28–29]. After activation and phosphorylation of tyrosine residues, the tyrosine receptor kinase B activates the process of intracellular cascade [30, 31] and initiates transcription factors influencing cell life, its growth and differentiation [32, 33]. The p75 receptor is not very well characterized and possibly is a common receptor for all neurotrophins. In its processing, it does not involve the kinase path, therefore, its activation at a certain level induces apoptosis and retrograde transport [30, 33–35]. It may appear that the p75 receptor is obsolete due to its negative effects; however, numerous reports suggest that at a certain stage its participation and mechanism promote axon growth and correct modulation of the Trk-B [36–38].

The BDNF factor is located (apart from the nervous system) also in the heart, skeletal muscles, smooth muscle cells, lungs, platelets and fibroblasts [39–42]. It contributes to stem cells development and differentiation, synapse development, regulation of neural circuits [27] and formation of memory pathways [20, 23, 24, 26, 27]. Its synergistic effect on the central and the peripheral nervous system is very important, because, according to the studies, BDNF contributes to neuron regeneration following various disorders, including ischemic stroke, posttraumatic disorder or toxic poisoning [43, 44]. Apart from the above-mentioned Trk-B receptor, the neuron growth and differentiation factor – NGF – also participates in those processes. Numerous studies emphasize a negative correlation between abnormal BDNF levels, Trk-B dysfunction and no BDNF–Trk-B signaling, and disorders – depression, schizophrenia, epilepsy, and Alzheimer’s and Huntington’s diseases [24, 45–49].

Mechanisms and effects of neurotrophins action in the human body are shown in Figure 1 at the end of the article.

BDNF and pathophysiology of schizophrenia

Lack of a clear standard in approach to rehabilitation and monitoring of the schizophrenia course in patients prompted researchers to focus on laboratory parameters. The increasing body of evidence implies that the brain-derived neurotrophic factor (BDNF), as the most commonly known neurotrophin in the nervous system, plays an important role in pathophysiology of mental disorders, mainly depression and schizophrenia; however, its precise role is still not known in full [50]. It is known to cause changes in synapses in various regions of the brain [23–27], and influences the neuron function, their differentiation, and synaptic plasticity. Differences in activity of this factor result in disorders in cortical and synaptic circuits in the brain, and cause anomalies in synthesis of protein polypeptide chains (translation) and neuronal dysfunction [1, 51–54].

Researchers emphasize high significance of GABA, glutamate and dopamine in schizophrenia pathogenesis [1, 54]. They consider as important the effect of dopamine produced in dopaminergic neurons. Eight dopaminergic pathways are known, transmitting stimulation through neurotransmission. The four major pathways are: mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular pathways [55].

Dopamine binds to receptors of different action profiles: receptor- D_1 , having a post-synaptic effect, and receptor- D_2 , having a pre-synaptic and post-synaptic effect. In normal conditions, dopamine levels are low [56], because the high dopamine level inhibits the respiratory chain, formation of free radicals, and induction of self-oxidation process [57]. This is confirmed by the dopamine hypothesis [58] assuming that to find the causes of schizophrenia, the following should be verified: 1) excessive activity of dopaminergic neurons, causing a psychotic state (positive symptoms) due to an increased dopamine production and excessive stimulation of D_2 receptors; 2) reduced activity of dopaminergic neurons, causing decreased stimulation of D_1 receptors resulting in development of negative (deficit) symptoms [58].

Excessive dopamine secretion observed in schizophrenia triggers biochemical processes adversely influencing normal cell functions. Those processes are associated with blocking synthesis of BDNF m-RNA that plays a protective role [1, 59–61]. Lack of a protecting factor with simultaneous inhibition of its expression results in loss of tyrosine hydroxylase, and in consequence, abnormal neuron function [60]. This conclusion is based on studies of Baquet et al. [62], who proved that mice in which BDNF expression in mid-brain and hind-brain does not occur, have lower levels of hydroxylase and clearly reduced expression of dopaminergic neurons in the substantia nigra. Tan et al. [63], verifying results obtained by Baquet et al., studied a group of schizophrenia patients, and additionally considered in the experiment dyskinesia or its lack. Their data indicate that patients with dyskinesia have lower BDNF levels versus those patients in whom dyskinesia was not observed [63]. The results of their studies probably confirm the decreased expression of dopaminergic neurons in patients with dyskinesia. Other researchers, Takahasi et al. and Durany et al., studied BDNF levels in the hippocampus and in the frontal part of the cingulate gyrus. However, their results differed. Takahasi showed higher BDNF levels in the analyzed structures, while in studies of Durany they were lower [1, 64, 65], compared to the control group. Hashimoto et al. [66] analyzed BDNF levels in the prefrontal region and found their significant reduction in schizophrenia patients versus subjects in a control group. The review of the above-mentioned studies indicates some problems with an unambiguous interpretation. They may result from many reasons – a post-mortem analysis of samples [1, 65], type of rehabilitation interventions, or a treatment process [67, 68].

An issue associated with the treatment process should be emphasized in particular. Erikson et al. [67] noticed that the chronic nature of the treatment process itself has a strong influence on the hippocampus volume. According to those authors, its reduction is frequently observed in patients treated for a long time, or completely untreated. Therefore, it should be reflected in changes in levels of parameters such as BDNF. Results obtained by Erikson et al. prove that clearly there is a relationship between lower brain volume, dendritic density and defective morphological and structural remodeling.

Influence of physical activity on the BDNF levels in schizophrenia patients

Physical activity is one of the aspects in the normally functioning body. Regular exercising influences metabolism and causes numerous changes in various systems. Those changes depend on a number of biochemical changes resulting from gasome-diators (NO, CO, H₂S) distribution and processes initiated by them [69]. Processes associated with neurogenesis, angiogenesis and activation of brain regions associated with blood flow through the brain form a basis for functional and anatomical changes. Physical activity initiates secretion of many trophic growth factors – neurotrophins: the nerve growth factor (NGF), neurotrophins 3 and 4/5 (NT3, NT 4/5), and the brain-derived neurotrophic factor – BDNF. Those neurotrophins cooperate with cell receptors p75NTR and Trk-B, and facilitate cell proliferation, migration and differentiation [19,30].

Brain-derived neurotrophic factor is expressed when neurons are active, when energy processes and associated changes in potential occur. Those processes result in production of neurotransmitters facilitating remodeling of the synaptic network and formation of new branches. This process is only possible when a change in the action potential occurs, depending on an effective stimulation. Neural cells in which those changes do not occur, cannot remodel or modify, and their function becomes limited [22, 25, 27, 32]. This is confirmed in numerous reports, including studies of Mattson and Mennerick et al., implying that lack of energy processes results in reduction in cascade biochemical processes, inhibition of neurotransmitter production and a reduced synthesis of BDNF. Following an analysis of those findings it can be concluded that lack of transmission in the signaling pathways has a negative effect on formation of the neuron circuits [70–71]. Similar data is presented in reports of Mabuchi et al. [72] and Powers et al. [73]. They indicate that by inducing an inflow of sodium and calcium ions, activity of muscle and neural cells results in an increased transport of electrons, activation of metabolic processes in cells, intensified production of proteins and enzymes, stimulation of transcription, and an increase in number of vesicles containing neurotransmitters. The researchers are of the opinion that all those processes ensure cell viability, and the increased signaling causes production of glutamate, anti-apoptosis protein Bcl-2, antioxidant enzymes, and DNA enzymes [72, 73].

A cycle of biochemical transformations induced by physical exercises limits neural degeneration and increases BDNF production. Larsson et al. [74] emphasize that a type of exercises, duration and age of a person subjected to those influences are of importance in limiting changes. Physical activity also stimulates production of cytokines (signaling glycoproteins), produced in response to an energy crisis and micro-damages in the muscle fibres [75, 76]. Their production is a beginning of muscle cells repair and regeneration, and inversion associated with reduction in levels of glycogen stored in muscles. The cells of the immune systems (neutrophils, macrophages, and pro-inflammatory cytokines TNF- α and IL- β) participate in this mechanism, as they rebuild the muscle tissue by involving transforming growth factor (TGF- β), platelet-derived growth factor (PDGF) and IL-6. IL-6 additionally stimulates expenditure of energy stored in the liver and in the adipose tissue [75].

Determining the type of physical activity appears to be questionable. Numerous reports emphasize a positive effect of long-term exercises of moderate intensity [75]. The authors explain this by a stable level of stimulation and a constant rate of regeneration allowing development of long-term potentiation memory pathways (LTP) consolidated by regular enhancement [76].

The recent progress allows stating that the levels of BDNF are also influenced by angiogenesis associated with physical activity. A process of blood vessel development with a contribution of the vascular endothelial growth factor (VEGF) is very important and depends on influences of numerous pro – and anti-angiogenic factors [77, 78]. In normal conditions, a balance between those factors is maintained [75].

It is clear that normal brain function, which is subjected to constant reorganization, influences cooperation between central and peripheral trophic factors. This relationship results from a two-directional synergism and is associated with functioning of various levels of nervous system. The first level initiates all biochemical processes in responses to stimuli from the environment. In consequence, the signaling pathway is activated, resulting in acquisition and remembering in a situation of consolidation and enhancement (LTP theory). The second level enables peripheral production of VEGF, which, after passing through the blood-brain barrier, stimulates neuron growth under the influence of irisin. This, in turn, induces proliferation and neurogenesis in the hippocampus. The whole process involves immune cells, muscles and the liver. They have an important influence on the brain, which initiates production of VEGF through biochemical processes [76]. Recent studies report that stress also influences BDNF levels. Results obtained by Nelson imply that stress initiates the HPA (hypothalamic-pituitary-adrenal) pathway and causes release of glucocorticoids, mainly cortisol. Its intensification inhibits signaling associated with BDNF production thus limiting its expression. Other factors having an adverse effect on BDNF expression include an ageing process, various diseases, excessive psychosocial burden, sleep deprivation, or incorrect dietary habits [79].

Currently, reports on a relationship between the BDNF levels and physical activity in schizophrenia patients are scarce. Majority of publications focus on an analysis of that effect in groups of patients diagnosed with Alzheimer's disease, elderly persons, after stroke, or brain damage. Interesting results were obtained by Kim et al. [80], who attempted such analysis in a group of schizophrenia patients. They exposed the studied group to a cycle of exercises for 12 weeks, three times a week, with the activating program consisting of 25 minutes of physical exercise and 25 minutes of moderate exercise (walking). An analysis of their studies confirmed the effect of physical exercise on the increase in the BDNF levels, and additionally found a positive correlation between its increase and a condition of the cardiovascular system of the subjects.

A conclusion drawn by Kim et al. indicates that providing activating interventions is of importance in comprehensive treatment of schizophrenia patients, and may be an important component of non-pharmacological therapeutic influences [80].

Brain wave modulation with EEG Biofeedback and BDNF

EEG Biofeedback is a therapy associated with modulation of brain waves, based on a feedback concerning physiological condition of the body. Effectiveness of this method is confirmed by numerous reports justifying use of this form of therapy in the psychiatric rehabilitation model [81–84]. Previous analyses indicate that regular trainings influence activity of specific brain regions [8, 49, 83, 88]. Modulation of brain waves, mainly beta-1, alpha and SMR wave, reduces cognitive deficits associated with memory, attention and executive functions [85]. Restoring of a normal activity in dysfunctional regions is the essence of the EEG Biofeedback therapy. Numerous publications, including studies of Trousselard et al. [86] and Scheinost et al. [87] confirm this relationship. The authors are of the opinion that regulation of the increased frequency of beta-1 wave has a positive effect on anxiety and stress levels, symptoms frequently accompanying schizophrenia [86, 87]. Similar conclusions are presented by Larsen who states that use of EEG Biofeedback is a desired direction in therapy of patients reacting negatively to pharmacotherapy and psychotherapy. It represents an alternative with a positive prognosis for rehabilitation [88].

Other authors, Birbaumer et al. and Mathiak et al., compare self-regulation of EEG Biofeedback to the process of learning and instrumental conditioning based on enhancing specific behaviors and rewarding. The authors state that those processes are a basis for an increase in the involvement of the dopaminergic system, and thus, for an increase in encoding the reward pathway [89–90].

Rota et al. reports interesting conclusions based on research, as they are of the opinion that EEG Biofeedback-based training to activate the frontal region of the right inferior gyrus has a positive effect on verbal functions. He observes that as a result of the training sessions there is a marked improvement in the functioning of Brodmann area 45, as confirmed by the fMRI study [91]. Similar positive effect was also observed by Ruiz et al., who emphasize a significant influence of therapy on perception of emotions in schizophrenia patients, and Naimijo et al. suggest their positive influence on executive function [92–93].

Using the description of Stoeckel et al. it can be said that “correctly selected neurotherapeutic methods are a precondition for improvement in cognitive functions and inducing a process for transformation of the brain function” [94]. Koush et al. [95] emphasize that “brain training” can be understood as a positively acquired behavioral feedback, which improves psychological function and develops brain functional network. Numerous reports emphasize an effect of NF on treatment. Research by Yuan et al. [96] implies that NF interventions improve the amygdala function in terms of receiving information from the hippocampus, hypothalamus, midbrain and temporal lobe. Restructuring of connections between the temporal regions of the cortex and the hippocampus and the amygdala results in transformation in form of enhancement in emotional regulation and reduction in schizophrenia symptoms. Similar results are presented by Gruzeliier, who also emphasizes its effect on levels of fear [97].

Although numerous reports verify a positive effect of the EEG Biofeedback therapy on activity of specific regions of the brain in patients with mental disorders, only a few

reports analyze a relationship between those effects and the level of BDNF. Assuming that the nervous system is plastic and has an ability for neuromodulation [98], and its normal function depends on two systems generating brain waves (the thalamocortical system where stimuli are processed and selected; and the septo-hippocampal system with the frontal lobes and the thalamus, where attention, concentration and memory are controlled), then a relationship between the NF therapy and the BDNF levels seems probable. This is implied by feedback loops (stimulating, inhibiting) connecting those two systems, activating the brain cortex through their cooperation. Their normal function depends on a stable neurophysiological regulation. The internal homeostasis is disrupted by adverse stimuli. Stress may be an example here, as it influences structures and functions of those two connections. It “destabilizes loops”, and in consequence, changes generation of brain waves. Therefore, when dysregulation represents the main problem, then an alternate corrective measure is to restore regulation. Using autoregulatory training techniques, Neurofeedback increases this stability, restores internal cohesiveness of neuroanatomic structures and stimulates formation of new neural circuits [98–100].

As reported by Angelakis et al. [101] and Becerra et al. [102], use of NF in elderly persons indicates a relationship between instrumental conditioning and brain activity. An increase in the alpha rhythm influences cognitive functions in the subjects, and in the future this may represent an interesting technique for their modulation and improvement. Also Wang et al. [103] obtained similar results, and confirmed improvement in working memory in those people.

Although reports clearly indicating that the EEG Biofeedback therapy influences changes in the BDNF levels are not available, previous research forms a basis for an assumption that they are correlated. The research in this direction in schizophrenia patients may be a useful tool for verification of usefulness of determination of this parameter as a biomarker in laboratory diagnostics during the EEG Biofeedback therapeutic process.

Recapitulation

Schizophrenia constitutes a complex health issue, since its etiopathogenesis is multifactorial. A complex therapy facilitates social functioning and the quality of patients' lives. Its basic feature is pharmacological treatment, neurorehabilitation and psychotherapy. The effectiveness of rehabilitation is proven by scientific research, currently mainly focusing on gene analysis [104–106]. Chiefly, the MAO, COMT and BDNF genes polymorphism is subject to verification, as they have an impact on the course of the illness. The results of research papers in the field vary. Norton et al. [107] confirm that the MAO and COMT genes may be subject to epistasis, which may predispose one to the development of schizophrenia, Tybura et al. [108] do not confirm such a relationship.

The discrepancy also applies to the impact of gene polymorphism of BDNF and COMT gene. BDNF, being a protein in dopaminergic neurotransmission influences the neurocognitive functions. Its low level is mainly regulated by antipsychotics. In the case of deficit in catechol-O-methyltransferase (COMT), which participates in dopamine degradation, cognitive disorders occur, consequently leading to negative symptoms in

schizophrenia [109]. A conclusion may be drawn that low level of BDNF and decreased COMT level results in a deficit syndrome in this illness [110].

Such a conclusion is supported by the biogenic amine hypothesis claiming that disorders in the physiology and metabolism of biogenic amines, especially catecholamines (dopamine, norepinephrine) and indolamines (serotonin) may account for the cause and course of many mental disorders [111].

Regardless of the result of research in the field of psychiatric genetics, confirming in various aspects the multifactorial etiopathogenesis of schizophrenia, one is currently looking for neurorehabilitation methods, which following the inclusion in the intervention program could increase the level of social functioning among the patients and reduce the present deficits.

There are many interesting therapeutic interventions, including a positive neuro-modulation physical activity effect and the EEG Biofeedback therapy. While seeking for laboratory biomarkers with a view of their effectiveness assessment, the BDNF seems crucial. The previous research has shown that its concentration constitutes the central and peripheral nervous system synergism index [76]. Many papers describe the relationship between BDNF and schizophrenia [60, 64–66], however, information clearly showing the direct correlation between the type of the EEG Biofeedback therapy and the increase in the factor concentration is rare. Research in this field is undoubtedly broadening knowledge. It seems justified to search for an answer to the question whether the selected rehabilitation interventions in schizophrenia influences the level of BDNF. In accordance with the Weber's law, stating that the reaction depends on the multiple changes in the stimulus, it may be possible [112].

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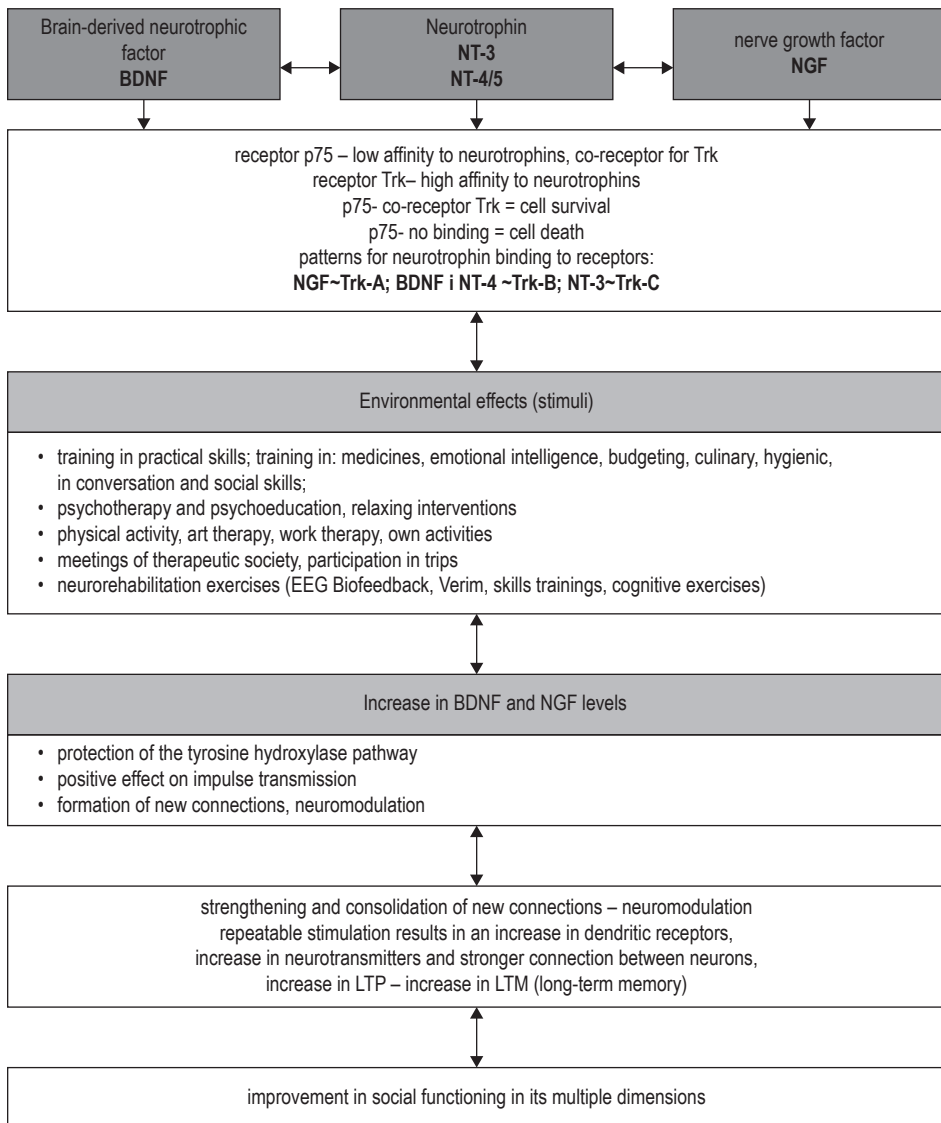
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Source: developed on a basis of [30, 100, 103, 104].

Figure 1. Mechanism underlying the effect of neurotrophins in the human body