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Brain-derived neurotrophic factor as a target for the search of anti-addiction drugs

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The relationship between the influence of the brain-derived neurotrophic factor (BDNF) on the development of alcoholism and possible ways of using this molecule or related compounds (mimetics) as targets of anti-addictive action are discusses in the article.

The aim of the work was to carry out a literature review to identify potential applications of the BDNF signaling pathways to assess the feasibility of developing new drugs.

Materials and Methods. The following abstract databases were used to search for the information materials: PubMed, EMBASE, ResearchGate, elibrary.ru. The key queries for the search included the following ones: 'BDNF', "BDNF TrkB", "BDNF LNGFR", "alcoholism therapy", "anti-addiction drugs", "signaling pathways", "alcoholism", "ethanol", "poisoning". The depth of the search was 40 years (1985–2025). The total number of the sources included in the review is 116.

Results. This study analyzed the molecular mechanisms of the action of BDNF, including its biosynthesis, structural forms (BDNF and pro-BDNF), and functions and features of TrkB and LNGFR receptors. These receptors play a key role in the regulation of the neuronal plasticity, a neuronal survival and apoptotic processes. The performed review of the scientific literature made it possible to establish that at least 9 chemical compounds with a potential anti-addictive activity that affect the receptors and signaling cascades associated with BDNF, have been identified as of 2025. Based on the data obtained, a hypothesis about the prospective use of BDNF and its signaling pathways as potential targets for developing new pharmacological agents aimed at the treatment of alcohol dependence, have been formulated. The established facts can significantly expand the therapeutic opportunities in the fight against the alcoholic dependence and associated neurotoxic conditions.

Conclusion. At least 9 compounds with a potential anti-addictive activity associated with a mimetic effect on the receptors and signaling pathways of the BDNF molecule have been analyzed and found to exist as of 2025.

Keywords: brain-derived neurotrophic factor; BDNF; anti-addiction drugs; addiction syndrome; TrkB receptors; LNGFR receptor

Abbreviations: BDNF — brain-derived neurotrophic factor; LNGFR (p75NTR, NGF) — low-affinity nerve growth factor receptor; TrkB — tropomyosin-related kinase receptor B; NTRK2 — neurotrophic receptor tyrosine kinase 2; PCs (1/2/3) — proprotein convertase (1/2/3); MMPs — matrix metalloproteinases; SHC — Src homology 2 domain-containing)-transforming protein 2; MAPK / ERK — mitogen-activated protein kinase / extracellular signal-regulated kinase; PI3K / AKT — phosphoinositide 3-kinases / serine-threonine-protein kinase; DAG / PKC — diacylglycerol / protein kinase C; IP3 — inositol-trisphosphate 3-kinase; PLC γ — phospholipase C (gamma); SP — signal peptide; LRRNT — leucine-rich N-terminal repeats; LRR — leucine-rich repeats; LRRCT — leucine-rich C-terminal repeats; IGC2-1 and IGC2-2 — immunoglobulin-like domains; CREB — cAMP response element-binding protein; TTIP — truncated TrkB-interacting protein; TACE/ADAM17 — tumor necrosis factor-α converting enzyme; CRD — carbohydrate recognition domain; NT — neurotrophin; NRAGE — neurotrophin-receptor-interacting melanoma antigen-encoding gene homolog; NRIF — neurotrophin receptor interacting factor; aPC — activated Protein C; NFκB — nuclear factor kappa-light-chain-enhancer of activated B cells; TRAF — TNF receptor-associated factor; RIPK2 — receptor-interacting serine / threonine-protein kinase 2; RhoA — Ras Homolog Family Member A; FAP-1 — Fas-Associated Phosphatase-1; GABA — γ-aminobutyric acid; PTSD — posttraumatic stress disorder; ADH — antidiuretic hormone.

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Мозговой нейротрофический фактор как мишень для поиска препаратов, проявляющих антиаддиктивные эффекты

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В данной статье рассматриваются вопросы влияния мозгового нейротрофического фактора (BDNF) на развитие алкоголизма. Рассматриваются возможные пути использования этой молекулы или родственных с ней соединений (миметиков) в качестве мишеней для антиаддиктивного действия.

Цель. Провести анализ литературных источников с целью выявления потенциальных возможностей применения сигнальных путей BDNF в сфере разработки новых лекарственных препаратов.

Материалы и методы. Для поиска информационных материалов использовали реферативные базы данных: PubMed, EMBASE, ResearchGate, elibrary.ru. Ключевые запросы для поиска включали в себя следующие слова и словосочетания: «BDNF», «BDNF TrkB», «BDNF LNGFR», «терапия алкоголизма», «антиаддиктивные препараты», «сигнальные пути», «алкоголизм», «этанол», «отравление». Глубина поиска — 40 лет (1985–2025 гг.). Общее число источников, которые вошли в обзор — 116.

Результаты. В данном исследовании проведён анализ молекулярных механизмов действия BDNF, включая его биосинтез, структурные формы (BDNF и про-BDNF), а также функции и особенности рецепторов TrkB и LNGFR. Эти рецепторы играют ключевую роль в регуляции нейрональной пластичности, выживаемости нейронов и апоптотических процессов. Выполненный обзор научной литературы позволил установить, что по состоянию на 2025 год идентифицировано не менее 9 химических соединений с потенциальной антиаддиктивной активностью, которые воздействуют на рецепторы и сигнальные каскады, связанные с BDNF. На основании полученных данных сформулирована гипотеза о перспективах использования BDNF и его сигнальных путей в качестве потенциальных мишеней для разработки новых фармакологических агентов, направленных на лечение алкогольной зависимости. Установленные факты могут существенно расширить терапевтические возможности в борьбе с алкоголизмом и ассоциированными нейротоксическими состояниями.

Заключение. Было проанализировано и выявлено, что на 2025 год существует не менее 9 веществ с потенциальной антиаддиктивной активностью, связанной с миметическим действием на рецепторы и сигнальные пути молекулы BDNF.

Ключевые слова: мозговой нейротрофический фактор; BDNF; антиаддиктивные лекарственные средства; синдром зависимости; TrkB рецепторы; LNGFR рецептор

Список сокращений: BDNF — нейротрофический фактор мозга; LNGFR (p75NTR, NGF) — рецептор фактора роста нервов; TrkB — рецептор семейства тропомиозин-киназ B; NTRK2 — нейротрофический рецептор тирозинкиназы 2; PCs (1/2/3) — пропротеиновая конвертаза (1/2/3); MMPs — матриксные металлопротеиназы; SHC — домен, гомологичный второму домену белка Src; MAPK / ERK — митоген-активируемая протеинкиназа / киназа, регулируемая внеклеточными сигналами; PI3K / AKT — фосфоинозитид-3-киназа / серин-треониновая киназа; DAG / PKC — диацилглицерин / протеинкиназа C; IP3 — инозитол-трисфосфат-3-киназа; PLC γ — фосфолипаза C (гамма); SP — сигнальный пептид; LRRNT — N-концевые повторы, богатые лейцином; LRRR — богатые лейцином повторы; LRRCT — C-концевые повторы, богатые лейцином; IGC2-1 и IGC2-2 — иммуноглобулиноподобные домены; CREB — белок, связывающий цАМФ-чувствительные элементы; TTIP — укороченный белок, взаимодействующий с TrkB; TACE / ADAM17 — фактор некроза опухоли-конвертирующий фермент; CRD — домен распознавания углеводов; NT — нейротрофин; NRAGE — гомолог гена, кодирующего антиген меланомы, взаимодействующий с нейротрофиновым рецептором; NRIF — фактор, взаимодействующий с рецептором нейротрофина; aPC — активированный протеин C; NFκB — ядерный фактор каппа-легкой цепи-усилитель активированных B-клеток; TRAF — фактор, ассоциированный с рецептором TNF; RIPK2 — рецептор серин / треонин-протеинкиназы 2; RhoA — член семейства гомологов Ras A; FAP-1 — Fas-ассоциированная фосфатаза-1; ГАМК — γ-аминомасляная кислота; ПТСР — посттравматическое стрессовое расстройство; АДГ — антидиуретический гормон.

INTRODUCTION

According to the WHO Global Report 2019[1], the global trend in the total per capita alcohol consumption has decreased by 4.5% from 2010 to 2019. At the same time, the highest consumption rates were observed in the WHO European Region (9.2 L/yr).

The problem of chronic alcoholism therapy is extremely important in the modern world. Against the background of alcoholism, exacerbations of diseases

[1] WHO. Global status report on alcohol and health and treatment of substance use disorders. Available from: https://iris.who.int/bitstream/handle/10665/377960/9789240096745-eng.pdf?sequence=1

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associated with the toxic effect of ethanol on the heart, liver, kidneys, lungs, and circulatory nervous system often occur. The nervous system is most susceptible to the toxic effects of ethanol [1].

Ethanol and its metabolites have toxic effects on the brain through several major pathways straight away: a dysregulation of the GABAergic system of the brain [1–3]; a disruption of calcium signaling [4]; a general toxic effect of acetaldehyde, the main metabolite of ethanol [5]; a disruption of the glutamatergic system of the brain [6]; and a formation of neurotoxic conjugates with monoamine neurotransmitters [7–9].

The latter toxic pathway is poorly understood; however, according to some data, these conjugates contribute to the formation of reactive oxygen species and an oxidative stress [10]. In addition, ethanol disrupts neurotropic factors (in particular BNDF). Since this protein is essential not only for the nerve cell proliferation and nerve tissue regeneration, but also for the protection of neurons from adverse effects and maintenance of their viability under normal conditions [11]. This signaling system and its alterations in alcoholism are of great interest for the study of new neuroprotective therapeutic strategies and the development of neuroprotective drugs that may be useful not only in alcoholism, but also in other toxic lesions of the nervous system that affect neurotrophin signaling.

THE AIM of the work was to carry out a literature review to identify functions of the BDNF and its relationship to the course of alcoholism; it was also the search for potential new targets for an anti-addictive action related to the TrkB receptors affected by BDNF.

MATERIALS AND METHODS

Materials for this literature review were searched and systematized in the following abstract Russian and foreign databases: PubMed, Google Academic, EMBASE, ResearchGate scientific information network and a scientific electronic library (elibrary.ru). The key queries for the search included the following ones: “BDNF”, “BDNF TrkB”, “BDNF LNGFR”, “alcohol therapy”, “anti-addiction drugs”, “signaling pathways”, “alcoholism”, “ethanol”, and “poisoning”. The depth of the search was 40 years, as it was from 1985 that the brain-derived neurotrophic factor was first described in publications as a separate protein molecule (publications in most abstract databases from 1985 to 2025). Conducting the publication search, analyzing the sources and correlating with the given target requirements took about 8 months (from January to August 2024).

About 29 899 publications were found by the main keywords: “BDNF” and its receptors. In this process, some articles were excluded due to the nosology mismatch (after specifying the query for “alcoholism”, most studies were on different types of depression (*n*=2 700), effect on the pain response (*n*=1900)), predominance of the description of physiological effects of the neurotrophic factor (*n*=5900), as well as closed access articles. In this literature review, the total number of papers containing the studies of new substances potentially influencing the reduction of the alcohol consumption by the effect on BDNF, was 31. The remaining 85 sources were used to discuss the action of BDNF on its specific receptors and the relationship to the alcohol dependence.

RESULTS AND DISCUSSION

Structure and functions of endogenous BDNF molecule and realization of its effects

The brain-derived neurotropic factor (BNDF) is a hormone of the protein nature discovered in 1982 [12].

It is mainly involved in the development of the nervous system and the process of synaptogenesis. At the molecular level, its functions are to block the triggering of apoptosis through the JAK2-dependent pathway. The BDNF gene is located on a small arm of chromosome 11 (11p14.1). The production of this protein occurs in several stages [13–15].

The initial product of the gene is pre-proBDNF, from which the signal peptide is cleaved by proteases. The product of this reaction is pro-BDNF, which further undergoes hydrolysis from the N-terminus, decomposing into the final product — BDNF proper and pro-BDNF-peptide [12, 16–19]. The studies have shown that each of the products of the BDNF gene has its own functions and the role in the regulation of the neuronal activity and its vital activity. For example, pro-BDNF-peptide has been found in presynaptic terminals and it has been suggested that it may be released by the mechanisms similar to those of classical low molecular weight neurotransmitters [14, 20] and can bind to the receptors for both neurotrophins [15, 21–24] and low molecular weight neurotransmitters [16, 25, 26]. As for the difference between the function and biosynthesis of BDNF and pro-BDNF, the studies have shown a relationship between the neuron activity and the ratio of these two forms – in the active neurons generating more frequent action potentials, proteolysis of pro-BDNF proceeds more rapidly [17, 27–29] due to the increased activity of intracellular convertases PC1, PC5, PACE4, PC7. The extracellular convertases responsible for the conversion of pro-BDNF into BDNF — MMP3, MMP7, MMP9, have also been described. This

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multifactorial regulation of the pro-BDNF / BDNF ratio has been found out to be essential for the synaptic plasticity in the hippocampus and the formation of a long-term potentiation [18] and the development of neuromuscular junctions [19, 30–32].

The main targets of the BDNF molecular action are TrkB (Fig. 1) and LNGFR receptors (Fig. 2).

TkrB (tropomyosin-related kinase receptor B) is a brain factor receptor with an autophosphorylation ability. It is encoded by the NTRK2 gene located on the long arm of chromosome 9 (9q21.33). Five different mRNAs have been found to be the product of this gene (NCBI database numbers are: NM_006180.3; NM_001007097.1; NM_001018064.1; NM_001018065.1; NM_001018066.1 — variants A, B, C, D, E, respectively [32]).

Transcripts A and C give a full version of the protein upon translation (the so-called TK+ isoform), all others give a shortened version (TK-). These forms differ both in their domain composition and in their functions [33, 34].

Mechanism of BDNF action on TrkB

The receptor dimerization is necessary to activate the mechanism of action of BDNF on TrkB. After binding to BDNF, the following mechanisms are triggered: mediated by the adaptor protein SHC — the activation of Erk / MAPK and PI3K / Akt signaling pathways triggering the transcription factor CREB; mediated by a PLC γ increase of the DAG level and a subsequent activation of PKC, an increase of the IP3 level resulting in a subsequent increase of the calcium ion level and, as in the case of other signaling pathways, the activation of CREB.

The extracellular part of both TK+ and TK- isoforms (Fig. 3) is BDNF-binding and consists of the following domains: SP, LRRNT, LRR, LRRCT, IGC2-1 and IGC2-2. TK+ forms have also got specific intracellular parts: the SHC1 binding domain, TyrKc, a tyrosine protein kinase domain involved in the phosphorylation process, and the PLCγ binding domain. In TK- forms, the TTIP (truncated TrkB-interacting protein) and Rho GDI1 binding domains are located on the intracellular part (combined into a separate (TK-)-specific exon). In both isoforms, the region between LRRCT and immunogloblin-like domains is responsible for the actual interaction with BDNF.

Other TrkB isoforms resulting from alternative splicing and gene rearrangements have also been described in the scientific literature, but their functions and clinical significance are poorly understood [35, 36].

To bind to BDNF, TrkB must switch to a dimerizated state. At present, the functions of TK+ / TK+ and TK- / TK- homodimers have been described and elucidated [37]; the functions of TK+ / TK- heterodimers are not yet fully clear, but their presence has already been confirmed, as well as the possibility for TK+ and TK- to form heterodimers with other receptors (transactivation), e.g., with the angiotensin receptor AGTR2 [38], TrkC [39] and TrkA [40] (see Fig. 3).

The TK+ homodimer is mainly involved in the processes of synaptic plasticity (the intracellular PLC-binding domain is responsible for this), the differentiation (a Ras-dependent pathway) and a cell survival (a Akt-dependent pathway). Some publications have mentioned the possibility that both homodimers are mutually regulating at the level of intracellular processes [41].

The functions of the TK- homodimer are less studied, but its influence on the regulation of the calcium ion entry into the cell is assumed. In addition, the studies suggest a role of this receptor in the phenomenon of an excitotoxicity — death or a severe damage to neurons from the calcium homeostasis disruption [42]. The influence of this receptor form on the synapto- and morphogenesis of nerve cells has also been found [43]: abnormalities of the hippocampal and amygdala development were detected in TK-deficient mice, and this was reflected in the behavioural phenotype in the form of the increased excitability and anxiety.

Several clinically relevant mutations have been described for this receptor gene, such as a number of single nucleotide polymorphisms (rs1867283, rs10868235, rs1147198, rs11140800, rs1187286, rs2289656, rs1624327, rs1443445, rs3780645, and rs2378672) associated with temporal lobe epilepsy [44] and depressive disorders [45], the rs2289656 polymorphism was also found to be associated with suicidal behavior [46]. Mutant variants of the TrkB receptor were also found in genotyping of lung [47], breast and intestinal tumors [48].

LNGFR

This nerve growth factor receptor has its specific functions, which are to restrict the nerve cell growth and migration [49] by interacting with the signaling proteins NRAGE [50], SC-1 (Schwann cell factor 1) [51], NADE [52] and NRIF [53] (see Fig. 2).

The extracellular part of both TK+ and TK- isoforms is BDNF-binding and consists of the following domains: SP, LRRNT, LRR, LRRCT, IGC2-1 and IGC2-2. TK+ forms also have specific intracellular parts: the SHC1 binding domain, TyrKc, and the PLCγ binding domain. In TK forms, the TTIP and Rho GDI1 binding domains are located on

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the intracellular part (combined into a separate (TK-)-specific exon). In both isoforms, the region between LRRCT and immunogloblin-like domains is responsible for the interaction with BDNF.

It consists of an extracellular part, which contains 4 cysteine-rich domains (CRDs) and a TACE / ADAM17 protease binding site, and an intracellular part, which contains a γ-secretase binding site, and death and Chopper domains (binds to proteins responsible for triggering apoptosis (NADE and NRIF) [54, 55].

However, when dimerized with TrkA [56], caused by the activation of the ephrin-B receptor and a subsequent phosphorylation of the adaptor proteins Kidins220 / ARMS [57], it, on the contrary, stimulates the migration of progenitor cells at the stage of a nervous system development [58]. P75NTR is also able to dimerize with TrkB. This process also occurs with the help of Kidins220, and leads to the formation of a dimeric receptor with an increased sensitivity to BDNF [59]. It is also possible to form a sortilin / TrkB / p75NTR complex, which has increased its sensitivity to pro-BDNF [60].

This receptor gene is located on the large arm of chromosome 17 (17q21.33) and several mutations have been described for it. In animal models with non-functional p75, an impaired axon formation was found, expressed in their excessive growth and reduced branching [61]. It is interesting, that this effect was most strongly expressed in the gustatory cortex of mice: the loss of taste papillae was observed in the experimental animals. In the studies on mice, the role of p75NTR mutations in the development of deafness was also established [62]. The sortilin mutations because of which it could not dimerize with p75NTR, were also described, resulting in an increase in the main, pro-apoptotic function of the latter - clinically it is expressed in the presence of the essential tremor [63].

Alcoholism and BDNF

The relationship of the of BDNF influence on the development of the alcohol dependence will be considered.

The study conducted by D. Silva-Peña et al. [64] showed a direct link between an alcohol consumption, cognitive deficits and reduced BDNF levels. In this experiment, the alcohol dependence was modeled in experimental animals for several weeks - periods of an uncontrolled access to alcohol were interspersed with taking away and returning alcohol drinks, i.e. the withdrawal component of dependence was also modeled. In addition, as part of their publication, Daniel Silva-Peña et al. also performed both a serum analysis and a statistical data collection from the alcoholic patients. Using ELISA, the levels of BDNF, NT-3, IGF-1 and IGF-2 in the serum of mice and humans were measured and their correlation with the level of cognitive and mnestic deficits (measured by FAB and MFE tests) was calculated. In the control group of patients, BDNF was at the level of 0.75–0.83 ng/mL, in patients with alcoholism (without a pronounced cognitive or mnestic deficit) —0.45–0.55 ng/mL, in patients with alcoholism aggravated by at least one of the forms of cognitive or mnestic deficit — 0.3–0.4 ng/mL. In the humans, the difference in NT-3 and IGF-2 levels was present but less pronounced. In the mice, however, the difference between the levels of BDNF and NT-3 in the blood of the control and experimental groups was much more pronounced — 650-700 mg/mL in the control group and 250–300 mg/mL in the experimental group for BDNF; 0.22–0.27 ng/mL in the control group and 0.05–0.07 ng/mL in the experimental group for NT-3. In addition, the relative mRNA levels of BDNF, NT-3, TrkB, TrkC and p75NTR in the hippocampus were measured in the mice; a decrease in the expression of BDNF and NT-3 was found in the experimental group compared to the control group, the levels of TrkB and TrkC remained almost unchanged, and the mRNA level of p75NTR increased more than one and a half times in the experimental group compared to the control. All the above data give a picture of the inhibition of neurogenesis and the work of natural neuroregenerative mechanisms [65] during the alcohol consumption (a decrease in BDNF and NT-3), and an increase in the number of apoptosis events (an increase in p75NTR [66]).

Another work contains data on the study of changes in the relative mRNA levels of individual exons of the BDNF gene, and a group of researchers studied not only the effect of ethanol *per se*, but that of the promising phytoestrogen resveratrol on the expression of this gene [67]. As a result, it was found out that the amount of mRNA belonging to the 9th exon of the BDNF gene decreased most of all (starting from the minimum dose of 0.25 g/kg of the animal body weight). Exon 9 of the BDNF gene is important from the point of view of molecular pathology and modeling of various pathological conditions, since in rodents it is the exon that encodes the protein structure directly [68], while the other exons are regulatory.

Another very important study conducted on mice, which is worthy of highlighting, found an association between an uncontrolled alcohol consumption at an early age (25-day-old rats were used) and an increased

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likelihood of developing a depression [69]. This study used the BrdU tagging method to assess the nerve cell proliferation, which resulted in a quantitative measurement of the neuronal proliferation inhibition in the dentate gyrus in the mice compared to the control. It was reduced by 30–50% in alcohol-drinking mice.

The study of the neurotropic factors' dynamics in connection with a withdrawal syndrome in alcoholism is also of great interest. It has been found that during the alcohol withdrawal, the level of GDNF (glial cell line-derived neurotrophic factor) in blood decreases [70], while the level of BDNF is inversely related to the severity of the withdrawal syndrome. This may be due to the hyperactivity of compensatory mechanisms at the early stages of the withdrawal syndrome, when the BDNF level increases too sharply [71]. The evidence that elevated BDNF is a by-product of the compensatory mechanisms' activation is also supported by the fact that levels of IL-10, an anti-inflammatory cytokine, are simultaneously increased [72]. It is also of interest that the above-mentioned increase in BDNF levels is also observed in the addiction induced by other pharmacological agents, for example, is morphine [73], cocaine [74] and nicotine [75].

It was found out that the BDNF level also vary in different brain regions, both in norm and pathology. The authors distinguish: a) cell-dependent and b) activity-dependent types of BDNF expression [76]. In the first case, a constitutive expression determined by the cell type and differentiation per se is being discussed, while in the other case any other factors influencing the expression of this protein — learning, physical activity, pathological conditions and intake of various chemicals, should be understood. Besides, if this protein localization is being discussed, the levels of anatomical and cellular structures can be also conditionally distinguished. On the cellular scale, BDNF is usually found in large amounts in glutamatergic neurons, closer to the synaptic terminal [77]. If anatomical structures of the CNS are considered, the studies on rats have shown that the largest amount of BDNF (by the mRNA level and immunohistochemical staining) is in the hippocampus [78] (detected both in the neuron body and in axons with dendrites, with a peak intensity in the CA4 region). Their large amounts are also in the cortex, with a peak intensity in layer VI and the areas adjacent to the corpus callosum. It is of interest that layer I (a molecular) of the cortex had the lowest intensity of immunohistochemical staining and mRNA levels. When considered by sections, in the cortex, the highest relative intensity was observed in temporal and parietal ones. In the amygdala, the BDNF levels are extremely low except in the central nucleus, where it is found mainly in neuronal processes.

In pathological conditions, the level of BDNF can also change. For example, in a major depressive disorder, it has been shown that its relative amount in dendrites can increase sevenfold compared to the neuron body [79]. This is thought to be due to the length of the non-coding fragment that is the substrate of the DNA / RNA-binding protein translin. It has also been shown that the increased amounts of pro-BDNF decrease the length of hippocampal dendritic spines [80]. In depressive spectrum disorders, a decrease in the relative amount of BDNF in the perirhinal and entorhinal cortex is also observed. It is assumed that this is associated with an impaired long-term potentiation [81].

The studies have also shown the effects of alcohol on the gene expression in different parts of the brain. For example, the study by Finnish scientists [82], conducted on two lines of the mice alcohol-avoiding (ANA) and alcohol-preferring (AA) — showed that a chronic ethanol consumption decreases the BDNF expression. Moreover, a dose-dependent decrease in mRNA was found in the hippocampus and nucleus accumbens (NA), and conversely, an increase was found in the ventral tegmentum area (VTA). In the frontal lobes, an interesting effect was found out: in low doses, alcohol decreased the expression compared to the intact initial state, while high doses, conversely, increased the expression. In contrast, in the amygdala, a dose-dependent increase in mRNA was found with increasing doses of alcohol. Other studies have shown an increase in BDNF mRNA in pVTA during a direct administration of nicotine and ethanol [83].

Prospective approaches to the treatment of alcoholism aimed at correcting the effectiveness of BDNF

It is difficult to underestimate an important role of the brain-derived neurotrophic factor in the development of alcoholism (especially in the presence of withdrawal) and its severity. This signaling system is currently an object of interest for research and development of anti-addiction pharmacological agents.

Resveratrol is one of such agents, which in studies has shown a clear ability to restore the mRNA level of exon 9 of the BDNF gene. Although the effect is partial and, at the same time, this agent increases mRNA levels of regulatory exons 1 (4-fold), 3 (3-fold) and 4 (6-fold) in the control animals, the research is currently ongoing, as the exact consequences of such dysregulation of the expression are currently unknown.

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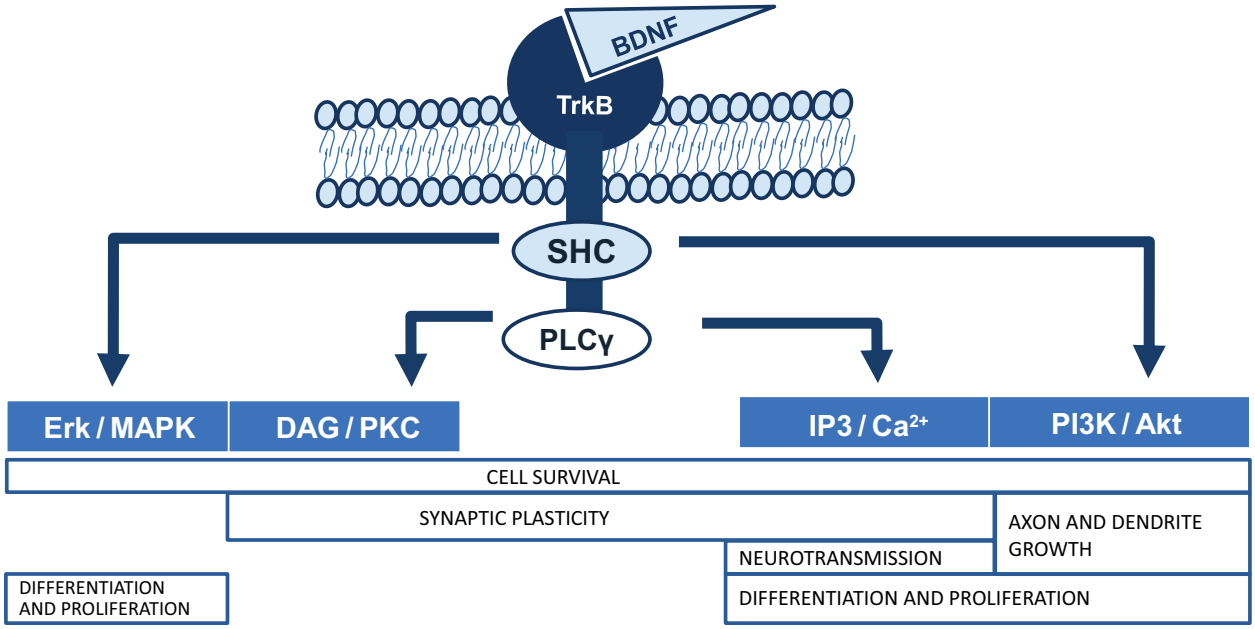

Figure 1 – Effects of BDNF when stimulated by TrkB.

Note: SHC — Src homology 2 domain containing; Erk / MAPK — mitogen-activated protein kinase / extracellular signal-regulated kinase; DAG / PKC — diacylglycerol / protein kinase C; IP3 — inositol-trisphosphate 3-kinase; PI3K/Akt — phosphoinositide 3-kinases / serine-threonine-protein kinase.

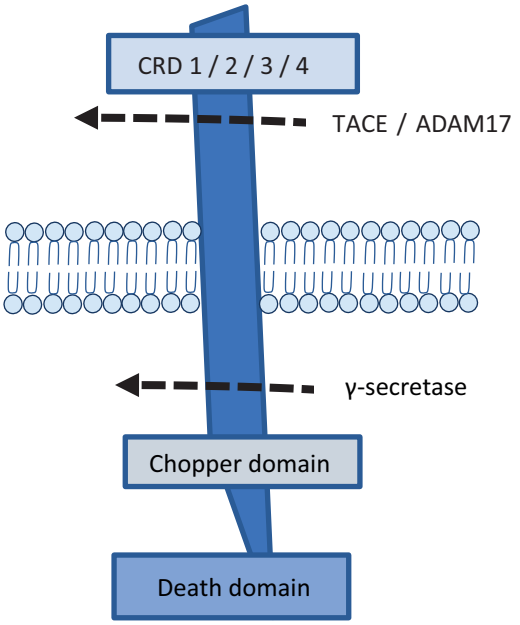

Figure 2 – Structure of LNGFR receptor.

Notes: TACE / ADAM17 — tumor necrosis factor-α converting enzyme; CRD — carbohydrate recognition domain.

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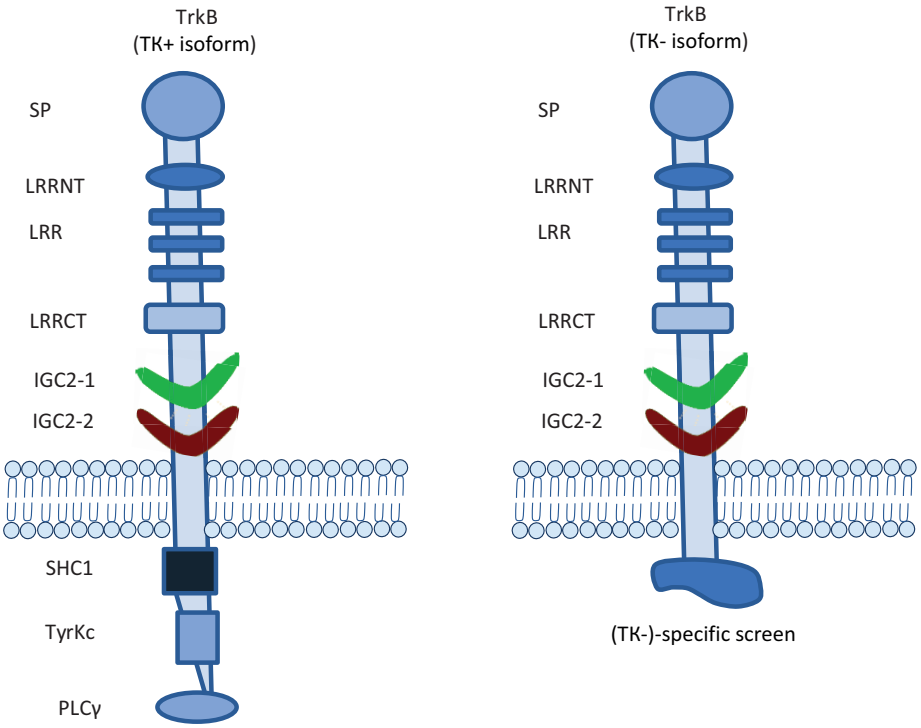

Figure 3 – Structure of TK+ and TK- isoforms of TrkB.

Notes. SP — signal peptide; PLC γ — phospholipase C (gamma); SHC1 — Src homology 2 domain containing; LRRNT — leucine-rich N-terminal repeats; LRR — leucine-rich repeats; LRRCT — leucine-rich C-terminal repeats; IGC2-1 and IGC2-2 — immunoglobulin-like domains.

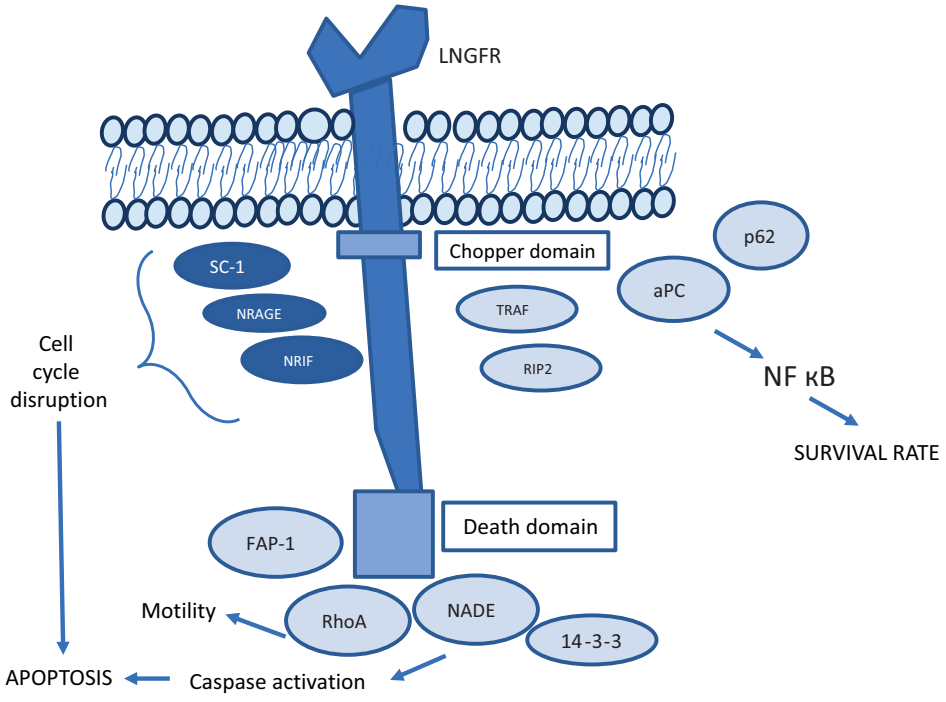

Figure 4 – Biochemical signaling pathways of LNGFR receptor.

Note: LNGFR (NGFR) — low-affinity nerve growth factor receptor; NGF — nerve growth factor; NT — neurotrophin; NRAGE — Neurotrophin-receptor-interacting melanoma antigen-encoding gene homolog; NRIF — NGF receptor-interacting factor; aPC — activated protein C; NFκB — nuclear factor kappa-light-chain-enhancer of activated B cells; TRAF — TNF receptor-associated factor; RIPK2 — receptor-interacting serine / threonine-protein kinase 2; RhoA — Ras homolog family member A; FAP-1 — Fas-associated phosphatase-1. When LNGFR interacts with neurotrophin molecules (NGF, NT-3, BDNF, and NT-4/5), mechanisms of the apoptosis initiation are triggered by the activation of NRAGE, SC-1, NADE, and NRIF signaling proteins by the receptor. In some cases, receptor-ligand interactions trigger mechanisms that support a nerve cell survival by the activation of NFkB. The interaction of the receptor with the signaling protein RhoA leads to an increase in the cell motility, as one of the main functions of this protein is the regulation of actin protein functions.

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The next promising agent is 7,8-DHF (7,8-dihydroxyflavone) — a TrkB agonist or "BDNF-mimetic" [84], which has been found to have neuroprotective effects [85], like the basic molecule BDNF [86–88] plus antidepressant effects [89, 90]. In other animal studies [69] this effect was also shown, only already in relation to alcoholism — in rodents treated with 7,8-DHF, when further counting proliferating cells of dentate gyrus (by the BrdU inclusion level), the proliferation level was almost equal to the control group. Similar results were obtained in behavioural tests such as "Sucrose preference test" and "Open field test". The experimental group of animals that received both 7,8-DHF and the alcohol-containing solution showed similar results to the control group of mice that did not receive alcohol. 7,8-DHF also showed the ability to return to the normal levels of circulating BDNF in the blood and the levels of phosphorylated TrkB (pTrkB) on cell membranes. At the moment, not only 7,8-DHF itself is being investigated, but also the compounds close to it, such as the prodrug R13, which has shown a therapeutic effect in models of neurodegenerative diseases [91], and another compound R7, which is an independent TrkB agonist and has better pharmacokinetic parameters than 7,8-DHF [92]. Although the pharmacodynamics of 7,8-DHF on humans is under-researched, the molecule is still considered a highly promising compound [93].

LM22A-4 is a BDNF-mimetic different in structure, but similar in essence. In in vitro experiments, it showed neuroprotective effects [94], and in animal models, it reduced an alcohol consumption [95, 96].

A well-known compound that has an affinity for the same receptor as BDNF is amitriptyline, an antidepressant and adjuvant analgesic [97]. The studies that included the use of this drug in alcoholism were aimed at treating comorbid depressive disorders, not the addictive effects of alcohol itself since its use in the alcohol dependence syndrome is limited due to severe side effects and a low tolerability in patients with this disease [98].

An important substance, which, by its characteristics, can be used as a neuroprotective agent in patients with alcoholism, is a synthetic steroidal drug BNN-20 (an affinity to several receptors at once: TrkA, TrkB, and p75NTR). There are published results of its testing on various animal models of neurodegenerative diseases [99, 100], but not on the model of the alcohol dependence, although, based on its mechanism of action, this substance could potentially be a promising candidate for a further testing.

Deoxygedunin (deoxygedunin) can be promising in the light of the alcohol dependence treatment and the reduction of alcohol neurotoxic effects. Its neuroprotective effect has been proved in relation to nigral neurons, in model lesions by a selective MPTP toxin [101] and a mechanical damage of the nerve fibres [102].

Currently, one of the most common means of treating alcoholism is disulfiram, an outdated ADH blocker. It stops the ethyl alcohol metabolism at the stage of the toxic acetaldehyde formation, which is manifested by hyperaemia, tachycardia, vomiting and anxiety in the patient [103].

Therefore, alcoholism, as a socially significant disease, should be studied as deeply as possible. It is necessary to pay attention not only to the behavioural abnormalities [104] caused by its use [105–107], but also to know the molecular basis of this disease [108] — its preconditions (including genetic ones [109–111]), biochemical changes occurring in cells [112], their consequences and correction potential.

Low molecular weight BDNF mimetics are being developed in the Russian Federation. Currently, there is evidence of studies of the anxiolytic activity on rodents in the "elevated cruciform maze" test of the GTS-201 molecule [113, 114], which is important because the development of alcoholism is often associated with anxiety disorders. Separate studies have been conducted on an ethanol consumption, they have also shown a potential reduction in an alcohol-motivated behaviour [115]. Pharmacokinetic and metabolomic studies have shown that the mimetic GTS-201 has both an effect on increasing serotonin, dopamine concentrations in the CNS and lowering serum cortisol [116].

CONCLUSION

The study of the brain neurotrophin system holds promise for the development of innovative and safe therapeutic strategies in the treatment of the alcohol dependence. A review of the sources from the last 40 years helped to establish that at least 9 chemical compounds with potential anti-addictive activity that target BDNF-related receptors and signaling cascades, have been identified as of 2025.

Based on these findings, it can be concluded that BDNF and its signaling pathways may become promising targets for the development of new drugs for the alcohol dependence treatment. This may significantly improve the methods of alcoholism therapy and related neurotoxic conditions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Mikhail S. Khalimanov — search and analysis of literature sources; Ekaterina M. Grigorevskikh — search and analysis of literature sources, systematization of information, manuscript writing; Sergey I. Sologov — search and analysis of literature sources, systematization of information, manuscript writing; Ksenia A. Zavadich — search and analysis of literature sources; Daria A. Trashchenkova — search and analysis of literature sources, systematization of information, manuscript writing; Kristina A. Tatzhikova — search and analysis of literature sources, systematization of information, manuscript writing; Evgeny V. Polikarpov — search and analysis of literature sources, systematization of information, manuscript writing; Susanna S. Sologova — systematization of information, manuscript editing, Dmitry A. Kudlai — systematization of information, manuscript editing; Elena A. Smolyarchuk — systematisation of information, manuscript editing.

All the authors confirm that their authorship meets the ICMJE international criteria (all the authors contributed substantially to the conceptualization, research and preparation of the article, read and approved the final version before the publication).

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