===================== REVIEW =====================

Role of BDNF in Neuroplasticity Associated with Alcohol Dependence

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Abstract—Chronic alcohol consumption is characterized by disturbances of neuroplasticity. Brain-derived neurotrophic factor (BDNF) is believed to be critically involved in this process. Here we aimed to review actual experimental and clinical data related to BDNF participation in neuroplasticity in the context of alcohol dependence. As has been shown in experiments with rodents, alcohol consumption is accompanied by the brain region-specific changes of BDNF expression and by structural and behavioral impairments. BDNF reverses aberrant neuroplasticity observed during alcohol intoxication. According to the clinical data parameters associated with BDNF demonstrate close correlation with neuroplastic changes accompanying alcohol dependence. In particular, the rs6265 polymorphism within the *BDNF* gene is associated with macrostructural changes in the brain, while peripheral BDNF concentration may be associated with anxiety, depression, and cognitive impairment. Thus, BDNF is involved in the mechanisms of alcohol-induced changes of neuroplasticity, and polymorphisms within the *BDNF* gene and peripheral BDNF concentration may serve as biomarkers, diagnostic or prognostic factors in treatment of alcohol abuse.

INTRODUCTION

Alcohol abuse causes enormous social and economic burden. According to the official report prevalence of the substance use disorders in the Russian Federation in 2020 was 1203.5 cases per 100,000 population, of these, alcohol use disorder accounted for 934.1 cases [1]. Estimates of total economic losses from the alcohol use disorder in the Russian Federation in 2017 are in the range from 302.8 billion to 2.5 trillion rubles, which corresponds to the loss of 3.9 million disability-adjusted life years [2]. Comprehensive investigations of the mechanisms of alcohol dependence represent an important research area.

Effects of alcohol on the brain are genetically determined; they are mediated by the alcohol-induced changes in epigenetic mechanisms, transcriptional activity, alternative splicing, translation activity and post-translational modifications, which eventually control CNS activity under conditions of pathological processes [3]. Ethanol affects key properties of CNS: intrinsic excitability, synaptic transmission, and plasticity in the specific neural circuits [4]. Chronic ethanol consumption results in the changes of functional activity of brain regions responsible for reinforcement and motivation (striatum and ventral tegmental area), decision making (frontal cortex), stress sensitivity (amygdaloid complex), memory and emotion (hippocampus) [4, 5]. Ethanol effects on the brain are region-specific depending on the molecular targets expressed in the specific populations of neurons and their sensitivity to ethanol [4, 5].

In vivo neuroimaging and postmortem examination of patients as well as experiments with rodents demonstrate that atrophy and degeneration accompany chronic excessive alcohol intake on the cellular and macrostructural levels [6]. Complex neuroadaptation is responsible

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for the alcohol-related phenomena such as sensitization, tolerance, and withdrawal [5]. Chronic alcohol intoxication often induces affective and cognitive impairment [5, 7], which is considered a result of aberrant neuroplasticity [8-10].

Variety of neurochemical systems underlie complex effects of ethanol on CNS, including ligand- and voltage-gated ion channels, dopamine, serotonin, GABA, glutamate, opioid peptides, endocannabinoids, substance P, orexin, adenosine, etc. [5, 6]. Among others, neurotrophins are important molecules involved in the mechanisms of alcohol dependence [11, 12]. Brain-Derived Neurotrophic Factor (BDNF) is a key neurotrophin in the context of alcohol effects [13, 14]. BDNF possesses neuroregulatory properties; it modulates strength of existing synaptic connections and is involved in formation of new synaptic contacts [15]. In particular, changes in the BDNF functioning through the changes in its expression or release are associated with pathological changes in CNS followed by development of behavioral impairment [15]. Experimental data obtained in the rodent models demonstrate that BDNF plays a crucial role in the changes of neuroplasticity associated with alcohol consumption and could determine alcohol dependence *per se* and could be also involved in the mechanisms of development of morphological changes and of affective and cognitive impairment [7]. Alcohol intoxication and development of dependence are accompanied by the change in BDNF expression in the brain regions, which most likely is the basis of BDNF functioning in the context of alcohol dependence and related aberrant neuroplasticity [12].

Animal studies demonstrate that BDNF influences voluntary alcohol intake and abstinence-related impairment of behavior. The heterozygous $Bdnf^{+/-}$ mice displayed increased voluntary ethanol intake in the two-bottle choice procedure as compared to the wild-type [16, 17]. Downregulation of endogenous BDNF in the dorsolateral striatum using siRNA increased ethanol self-administration, while infusion of exogenous BDNF attenuated self-administration [18]. Chronic intermittent ethanol vapor exposure decreased the amount of BDNF protein in the mouse medial prefrontal cortex during early abstinence, while infusion of BDNF into the medial prefrontal cortex decreased voluntary ethanol intake [19]. Hence, it can be suggested that corticostriatal BDNF controls transition from the moderate to excessive alcohol intake thus inducing dependence. It has been concluded that the BDNF level is increased in the case of moderate alcohol consumption counteracting motivation, while excessive alcohol intake results in the decrease of BDNF expression [11, 14].

The aim of the review was to analyze available experimental and clinical data related to BDNF involvement in the aberrant neuroplasticity in the context of alcohol dependence.

EXPERIMENTAL DATA

BDNF-induced signaling cascades. Interaction of mature BDNF with the tyrosine kinase receptor TrkB induces its homodimerization, autophosphorylation, and activation of intracellular signaling pathways [20-23]. The phosphorylated TrkB then binds and phosphorylates adapter protein Shc. Shc activates phosphoinositide 3-kinase (PI3K)/protein kinase AKT cascade, and stimulates activity of small GTPases of the RAS protein family, which subsequently trigger mitogen activated protein kinase (MAPK) cascade.

Each element of the TrkB-induced signaling cascade corresponds to physiological function [22]. PI3K/AKT cascade exerts anti-apoptotic activity thereby enhancing survival of neurons. Moreover, it modulates the NMDA-mediated synaptic plasticity. PI3K/AKT-mediated activation of protein kinase mTOR (mechanistic target of rapamycin kinase) is believed to be connected with protein synthesis and cytoskeleton changes underlying dendritic growth and arborization. MAPK cascade activates downstream transcription factors, e.g., CREB (cAMP-response element-binding protein), inducing expression of the genes coding for cytoskeleton proteins involved in synaptogenesis. Activation of small GTPases of the Rho family, such as Rac1 and Cdc42, stimulates actin and microtubule synthesis thereby inducing growth of neuronal fibers and maintenance of long-term potentiation.

In vitro experiments with neuronal cultures demonstrated that ethanol affected functional activity of the BDNF-mediated intracellular signaling cascades. Exposure of the striatal neurons to ethanol resulted in activation of TrkB, leading to activation of MAPK signaling pathway and subsequent increase in the expression of preprodynorphin [24]. In the cerebellar granule neurons, on the other hand, exposure to ethanol reduced basal and BDNF-induced levels of active phosphorylated protein kinase ERK (extracellular signal-regulated kinase), indicating downregulation of the MAPK pathway [25]. Ethanol treatment inhibited the BDNF-mediated activation of PI3K/AKT and JNK (Jun N-terminal kinase), and blocked the BDNF-stimulated activation of the transcription factor AP-1 (activating protein-1) in the cerebellar granule neurons [26]. Ethanol exposure increased the surface area of axonal growth cones in the fetal rat hippocampal pyramidal neurons, while it inhibited the BDNF-induced activation of small GTPases Rac1 and Cdc42 involved in axon growth [27].

Neuromorphological impairment, development of anxiety-like phenotype, and BDNF. Knock-out of the *BDNF* gene does not cause neuronal loss, but reduces density of dendritic spines and arborization of dendrites [28, 29]. BDNF activity underlies growth of dendritic spines [30], thereby regulating synaptogenesis and functioning of mature neural circuits. Association of morphological changes in the CNS emerging after subchronic

intoxication with alcohol with the development of anxiety-like behavior and activity of the BDNF-induced signaling cascades has been reported in a number of studies [31-35].

Consumption of ethanol, as a sole source of fluid, for 21 days resulted in the development of ethanol dependence and anxiety-like behaviors in rats in the open-field and elevated plus maze tests during early abstinence [31], which was accompanied with the decreased expression of BDNF mRNA and protein as well as reduced number of the BDNF-positive cells in hippocampus and nucleus accumbens after ethanol withdrawal and with the synaptic ultrastructure changes including increased synaptic cleft width and reduction in postsynaptic density thickness or synaptic curvature [31].

Acute ethanol administration to rats caused anxiolytic effects in the elevated plus maze test together with the increase of BDNF and Arc (Activity Regulated Cytoskeleton Associated Protein) levels and dendritic spine density in both central and medial amygdala [32]. Conversely, 24 h after withdrawal of the ethanol-containing complete Lieber–DeCarli liquid diet maintained for 15 days decrease of amygdalar BDNF, Arc, decreased phosphorylation of ERK and transcription factors Elk and CREB as well as decreased dendritic spine density was observed as well as development of the anxiety-like phenotype according to the results of elevated plus maze test [32]. Infusion of BDNF into central amygdala in early abstinence normalizes content of Arc, activated phosphorylated forms of protein kinase ERK, transcription factors Elk and CREB, as well as exhibits an anxiolytic effect [32]. Activation of histone deacetylases is the cause of decreased expression of BDNF and Arc, and, as a consequence, decreased dendritic spine density in both the central and medial amygdala, and development of the anxiety-like phenotype in the early abstinence 24 h after withdrawal of consumption of alcohol in the composition of complete Lieber–DeCarli liquid diet maintained for 15 days [33]. Moreover, the line of alcohol-preferring rats is characterized by the innate anxiety-like phenotype and decreased expression of BDNF and Arc, and decreased dendritic spine density in the central and medial amygdala, as compared with the alcohol-nonpreferring rats [34]. Acute exposure to ethanol had an anxiolytic effect in the alcohol-preferring but not in the alcohol-nonpreferring rats according to the elevated plus maze and light/dark chamber tests, and was associated with the increase in the mRNA and protein levels of BDNF and Arc, as well as in dendritic spine density in the central and medial amygdala [34]. Increased activity of histone deacetylase HDAC2 and corresponding decrease in acetylation of histone H3 at K9 and K19 within the promoter regions of *Bdnf* and *Arc* genes are responsible for downregulation of the BDNF and Arc expression in the central amygdala of the alcohol-preferring rats [35]. Thus, according to the hypothetical model relying on the studies by the research group of S. C. Pandey [32-35], the BDNF-dependent expression of Arc via ERK-CREB/Elk cascade plays a role in amygdalar dendritogenesis, a process underlying alcohol withdrawal-related anxiety-like phenotype, while BDNF expression in the amygdala is under epigenetic control mediated by histone deacetylases.

Cognitive impairment and BDNF. Chronic alcohol consumption is often linked with the BDNF-associated cognitive deficit. Voluntary ethanol consumption for three weeks by the mice lead to the decrease in DNA methylation of the *Bdnf* gene in the hippocampus, and upregulated TrkB-mediated activation (phosphorylation) of ERK, AKT, and CREB [36]. Upregulation of the BDNF-related cascades in the hippocampus after ethanol intake was accompanied by the impaired learning and memory analyzed in the contextual fear conditioning test and the novel object recognition task [36]. Thus, BDNF expression in the hippocampus as well as in the amygdala is under epigenetic control, and hippocampal BDNF content is linked to the alcohol-related cognitive impairment. E. Stragier and co-authors [36] have suggested that upregulation of the *BDNF* gene expression and signaling pathway is probably a reactive process to counteract the ethanol-induced behavioral deficits. On the other hand, plasma levels of BDNF and hippocampal BDNF mRNA content are decreased in the ethanol-exposed rats, and correlation between the BDNF level and cognitive impairment in the novel object recognition test has been established. In particular, the plasma BDNF concentration positively correlated with the familiar recognition memory and the hippocampal BDNF mRNA level negatively correlated with the discrimination index [37]. BDNF may mediate effects of some compounds on cognitive functions. Administration of selank, a peptide analogue of tuftsin exerting anxiolytic and nootropic activities, during abstinence after alcohol intake increased discrimination index in the novel object recognition test and prevented the ethanol-induced elevation of BDNF protein levels in the prefrontal cortex and hippocampus [38].

Synaptic activity and BDNF. BDNF plays a critical role in transmission of nerve impulses via modulating functional activity of synapses. BDNF protein is actively transported to the axonal terminals and secreted into the synaptic cleft after membrane depolarization [39, 40]. Modulation of the impulse transmission is under presynaptic control via regulation of neurotransmitter release [41]. Postsynaptic mechanisms of impulse transmission include enhancement of neurotransmitter functionality with consequent change of the related receptors activity [42]. Mechanisms of the BDNF-mediated regulation of impulse transmission rely on its binding to the cognate receptor TrkB expressed both at the pre- and postsynaptic membranes.

The L-type voltage-gated calcium channel-dependent dendritic BDNF release in the hippocampal CA3 pyramidal neurons causes long-term potentiation of the frequency of GABAA receptor-mediated spontaneous postsynaptic currents. Ethanol exposure of the neonatal rats using vapor chambers or treatment of hippocampal CA3 slices with ethanol cancelled the long-term potentiation by inhibiting the L-type voltage-gated calcium channels [43]. BDNF enhanced magnitude of the NMDA-mediated, but not of the AMPA receptor-mediated, postsynaptic currents in the pyramidal neurons as has been shown with the slices of the murine hippocampus and neocortex, while ethanol pretreatment completely blocked the effect of BDNF [44].

According to the open field and elevated plus-maze tests intermittent access to 20% ethanol two-bottle choice (IA2BC) paradigm for three weeks elevates the anxiety-like behavior in mice during early abstinence. The IA2BC procedure also enhances glutamate transmission in the pyramidal neurons of the basal and lateral amygdala, as demonstrated by the increased frequency of spontaneous excitatory postsynaptic currents in the corresponding slices [45]. Single injection of BDNF mimetic 7,8-dihydroxyflavone (7,8-DHF) shortly after withdrawal alleviated the anxiety-like behavior and attenuated the alcohol-induced enhancement of the activities in pyramidal neurons, while K252a, a tyrosine protein kinase inhibitor, blocked the effects of 7,8-DHF [45]. These results have demonstrated that the BDNF-mediated TrkB stimulation may mitigate alcohol abstinence by normalizing activity of amygdalar neurons. Meanwhile administration of 7,8-DHF for the whole period of IA2BC has minor effects on the anxiety-like behavior of rats in the open field and elevated plus-maze tests during early abstinence [46]. It seems that the effects of TrkB activation by 7,8-DHF on the anxiety-like behavior in the context of alcohol abstinence depend on the rodent species used, duration of alcohol consumption, and 7,8-DHF administration regimen.

Neurogenesis and BDNF. Alcohol intake may affect adult neurogenesis by either inducing [47], or blocking [48, 49] proliferation of neural progenitor cells. It seems that the effect depends on the alcohol intake mode used, and time point studied. Since BDNF is involved in the mechanisms of neurogenesis [50], ethanol and BDNF may interact in this context.

The BDNF contents and the number of BDNF-expressing cells in the murine hippocampus increased after three weeks of voluntary ethanol intake. Post-translational modifications of the histones within the regulatory regions of *Bdnf* gene underlie increase of the BDNF content [51]. Moreover, hippocampal cell survival and differentiation in the subgranular zone of the dentate gyrus are increased in the ethanol-drinking mice [51]. Administration of the TrkB receptor antagonist, ANA-12, during the whole stabilization period of the

free-choice ethanol paradigm, did not affect ethanol consumption but suppressed the ethanol-induced neurogenesis, suggesting a compensatory role of BDNF [51]. Withdrawal from the chronic intermittent ethanol vapor exposure for seven weeks increased the levels of BDNF and phosphorylated TrkB as well as the number of proliferating cells in the hippocampus [52]. However, the prolonged abstinence for 21 days from the chronic intermittent ethanol vapor exposure reduced BDNF expression and neurogenesis in the hippocampus to control levels [52].

Impairment of neurogenesis in response to alcohol may be sex-specific. Female rats, but not male rats, demonstrated decrease in the number of dentate gyrus granule neurons associated with both impairments of spatial navigation in the Morris water maze and decreased BDNF expression in the dorsal hippocampus as assessed after 24 h of intragastral ethanol administration at a dose of 8 g/kg per day for 4 days [53]. Significant increase in the depression-like behavior in mice during protracted abstinence from the voluntary alcohol drinking for 28 days was associated with the reduction in the number of proliferating neural progenitor cells in the dentate gyrus of the hippocampus [49]. Briones and Woods demonstrated, that the deficit of BDNF in the hippocampus may explain this issue [54]. Binge-like two-bottle choice alcohol consumption for 12 days resulted in manifestation of depressive phenotype (i.e., anhedonia and despair), decrease in survival and differentiation of proliferating neural progenitor cells in the dentate gyrus of hippocampus, as well as downregulation of the BDNF and phosphorylated TrkB levels during abstinence [54]. Administration of the BDNF mimetic 7,8-DHF for the period of ethanol consumption alleviated impairments of behavior and neurogenesis as well as alterations of the BDNF level in the hippocampus [54].

Thus, experiments *in vitro* and *in vivo* demonstrate impairments of neuroplasticity in the context of alcohol consumption. Activation of the BDNF-mediated signaling cascades alleviates impairment of neuroplasticity independent on the direction of the effects of ethanol on BDNF expression in the brain region. This is also true for the indirect experimental observations, which demonstrated positive correlation between the BDNF levels and time course of neuroplasticity impairment and *vice versa*. Table 1 summarizes available data regarding relationship between BDNF and neuroplasticity changes accompanying alcohol consumption obtained in the rodent models (Table 1).

CLINICAL DATA

Clinical data demonstrate that polymorphisms within the *BDNF* gene and peripheral BDNF concentration may serve as biomarkers of drinking behavior in alcohol

Table 1. Association of BDNF with alcohol-related neuroplasticity in rodent models

Species, strain, sex	Mode of alcohol intake	Time point	Brain region	Parameters	Association with BDNF	References
Rats, Sprague–Dawley, male	3→9% ethanol solution, 21 days, sole source of fluid	early abstinence (48 h)	hippocampus, nucleus accumbens	BDNF expression ↓; synaptic cleft width ↑; postsynaptic density thickness ↓; synaptic curvature ↓	indirect association with BDNF	[31]
Rats, Sprague–Dawley, male	9% ethanol solution, 15 days, Lieber-DeCarli liquid diet	early abstinence (24 h)	central and medial amygdala	BDNF expression ↓; Arc expression ↓; phosphorylation level of ERK, Elk and CREB ↓; dendritic spine density ↓; anxiety-like behavior ↑	direct association of BDNF with expression and behavior; BDNF infusion into the central amygdala normalizes Arc expression and phosphorylation level of ERK, Elk, and CREB, and alleviates ethanol withdrawal-related anxiety-like behavior	[32]
Mice, C57BL/6J, male	3→10% ethanol solution, 21 days, continuous access – 2-bottle choice	acute withdrawal	hippocampus	BDNF expression ↑; phosphorylation level of ERK, AKT and CREB ↑; learning and memory ↓	direct association of BDNF with expression; TrkB antagonist ANA-12 normalizes phosphorylation level of ERK, AKT and CREB	[36]
Rats, Wistar, male	5, 10, and 20% ethanol solution, 28 days, continuous access – 4-bottle choice	protracted abstinence (7 d)	hippocampus	BDNF expression ↓; phosphorylation level of ERK2 ↓; memory ↓	indirect association with BDNF	[37]
Rats, outbred, male	10% ethanol solution, 30 weeks, sole source of fluid	protracted abstinence (7 d)	prefrontal cortex, hippocampus	BDNF expression ↑; memory ↓	indirect association with BDNF; Selank increases discrimination index in the novel object recognition test and prevents ethanol-induced elevation of BDNF	[38]
Mice, C57BL/6J, male	20% ethanol solution, 21 days, intermittent access 2-bottle choice	early abstinence (48 h)	basal and lateral amygdala	frequency of spontaneous excitatory postsynaptic currents ↑; anxiety-like behavior ↑	direct association with BDNF; administration of BDNF mimetic 7,8-dihydroflavone (7,8-DHF) alleviated anxiety-like behavior and attenuated enhancement of excitability of pyramidal neurons	[45]
Mice, C57BL/6J, male	3→10% ethanol solution, 21 days, continuous access – 2-bottle choice	acute withdrawal	hippocampus	BDNF expression ↑; neurogenesis ↑	direct association with BDNF; TrkB antagonist ANA-12 suppresses neurogenesis	[51]

Table 1. (*contd.*)

Species, strain, sex	Mode of alcohol intake	Time point	Brain region	Parameters	Association with BDNF	References
Rats, Wistar, male	ethanol vapors, 7 weeks, intermittent access	acute withdrawal (3 h)	hippocampus	BDNF expression ↑; phosphorylation level of TrkB ↑; neurogenesis ↑	indirect association with BDNF; protracted abstinence (3 weeks) is accompanied by reduction of BDNF expression and neurogenesis to control levels	[52]
Rats, Long–Evans, female	8 g/kg per day, 4 days, intragastric infusion	early abstinence (8 h)	hippocampus	BDNF expression ↓; neurogenesis ↓	indirect association with BDNF	[53]
Rats, Sprague–Dawley, male	10% ethanol solution, 12 days, 30 min access (dark period) – 2-bottle choice	protracted abstinence (7 d)	hippocampus	BDNF expression ↓; phosphorylated TrkB ↓; neurogenesis ↓; depression-like behavior ↑	direct association with BDNF; administration of BDNF mimetic 7,8-dihydroflavone (7,8-DHF) prevents decrease of BDNF expression, number of proliferating cells and depression-like phenotype	[54]

Notes. Direction of changes: ↑, increase; ↓, decrease; increase of ethanol concentration in solution from → to.

dependence and recovery during the abstinence period [7, 55, 56]. Further we focus on clinical investigations of the relationship between BDNF and macrostructural changes in the brain and affective and cognitive impairments in the context of alcohol use disorder.

BDNF association with morphological impairment. Locus polymorphism rs6265 is the most studied within the *BDNF* gene. It is a single nucleotide variation G>A within the coding sequence of the *BDNF* gene, resulting in substitution of valine with methionine (*Val66Met*) in the pro-domain of BDNF protein. Presence of the *Met* allele is associated with the depolarization-induced BDNF secretion and failure of its localization to secretory granules or synapses [57]. According to the MRI studies, the healthy *Met* allele carriers demonstrate lower volume and functional activity of the hippocampus and prefrontal cortex and poorer memory formation [58, 59].

Experiments on the transgenic mice have demonstrated that the rs6265 polymorphism plays a role in alcohol intake and alcohol-related impairment. The homozygous transgenic mice carrying *Met68Met* genotype (*Val68Met* variation in the mouse *Bdnf* gene is homologous to *Val66Met* in the human *BDNF* gene) consumed excessive amounts of alcohol in the IA2BC paradigm as compared with the wild-type mice with the *Val68Val* genotype [60]. Alcohol intake by the *Met68Met* mice was reversed by overexpression of the wild-type *Val68 Bdnf* allele in the prefrontal cortex or by systemic administration of TrkB agonist LM22A-4 [60]. On the other hand, the effect of *Val66Met* on alcohol consumption may be sex-specific. The homozygous transgenic female mice carrying the human *Val66Val BDNF* gene exhibit both greater impulsivity compared to the *Met66Met* mice of the same sex, and greater propensity toward stable ethanol self-administration relative to the male mice of the same genotype in the operant paradigm [61]. Moreover, ethanol exposure in vapor chambers during the gestational and early postnatal periods reduced the cell layer volume in the dentate gyrus and in the CA1 hippocampal regions in the transgenic *Met68Met* mice but not in the transgenic *Val68Val* mice [62]; while ethanol exposure increased hippocampal volume in the hippocampal subregion CA1 *stratum radiatum* independent on the genotype [63].

MRI investigations demonstrated that polymorphisms within the *BDNF* gene, and peripheral BDNF level are associated with structural and functional impairment in the CNS of individuals with alcohol use disorders. Hippocampal volume in the individuals with alcohol dependence is lower as compared with the healthy controls [64]. Carriers of the homozygous genotype *Val66Val* rs6265 show a tendency for recovery of the hippocampal volume after seven months of abstinence [64]. Moreover, the hippocampal volume recovery positively correlates with the improvements of visuospatial memory in the carriers of homozygous genotype *Val66Val* but not *Met* allele [64]. As shown by the MRI data the rs6265 polymorphism is associated with the regional specificity of neocortical volume recovery after five weeks of abstinence period. Carriers of the Val66Val homozygotes show

significant increase in the gray matter volumes of all the cortical lobes except of occipital during the month-long abstinence period, while carriers of the Val66Met heterozygotes demonstrate significant increase of the frontal white matter and tendencies for the increased white matter in the parietal and temporal lobes [65]. For the subcortical volumes, thalamic gray matter increases only in the carriers of the Val66Val homozygotes, whereas total volumes of the cerebellum and brainstem increase only in the carriers of the Val66Met heterozygotes [65]. Moreover, in the combined group (Val66Val homozygotes and Val66Met heterozygotes), longitudinal changes in the regional cortical and subcortical gray matter volumes during abstinence are positively associated with the improvement in neurocognition as assessed by the battery of neurocognitive scales [65]. On the other hand, the BDNF-related SNPs are not necessarily associated with the brain macrostructural impairment. As shown in adolescents with alcohol abuse, rs6265 is not associated with the brain volume [66]. Moreover, as demonstrated by the functional MRI, BDNF-related parameters in the individuals with alcohol use disorder may be associated with the activity of brain regions. Component analysis of multiple genetic references have revealed that the set of SNPs within *BDNF* (including rs6265) and *CREB* genes is significantly associated with the imaging component reflecting hyperactivation in precuneus, superior parietal lobule, and posterior cingulate in the drinkers with more severe alcohol dependence symptoms [67]. Lower levels of plasma BDNF in the individuals with alcohol use disorder are associated with the decreased functional connectivity between the amygdala and regulatory regions of the prefrontal cortex [68]. In addition, lower levels of BDNF and amygdala-medial prefrontal cortex functional connectivity during the anticipated anxiety caused by unpredictable threat of shock are associated with more binge episodes and lower age of alcohol use disorder onset [68].

BDNF association with affective and cognitive impairment. Morphological changes in CNS induced by excessive ethanol intake are often associated with the presence of anxiety symptoms and impairment of mood and cognition, moreover, these disorders may be associated with the BDNF-related parameters.

BDNF concentrations in the serum of individuals with alcohol-dependence positively correlate with state anxiety level as assessed by the corresponding version of the State-Trait Anxiety Inventory (STAI) [69]. It is worth noting that interaction between the BDNF-related parameters, affective impairments, and alcohol consumption has been reported even in the absence of alcohol dependence. Healthy individuals carrying the *Met* allele of the rs6265 polymorphism are more anxious according to the Liebowitz Social Anxiety Scale (LSAS) during the physical-stress procedure (cold pressure test) and drink more alcohol per week as compared with the *Val66Val* genotype carriers [70].

During the abstinence period (2-4 days after withdrawal) the BDNF serum concentrations are lower in the individuals with alcohol use disorder independent on the comorbid depression as compared to the healthy control [71]. Moreover, the BDNF levels correlate negatively with the anhedonia score assessed by the Snaith—Hamilton Pleasure Scale (SHAPS), and, according to multiple regression, BDNF concentrations, age, and gender together explain 21% of variability in the anhedonia levels [71]. Association of the decreased level of serum BDNF with the BDNF gene polymorphisms, mood and alcohol abuse has been demonstrated. According to the linear regression analyses four factors including presence of the rs6265 Met allele, level of γ-glutamyl transferase, number of the past treatments in detoxification programs, and presence of a depressive episode (but not the clinically diagnosed depression) are significantly associated with the serum levels of BDNF at the time of admission and after six months of abstinence [55]. Nonetheless, changes of the circulatory BDNF levels are not necessarily associated with the alcohol-related depression or anxiety levels. The decreased plasma BDNF concentrations do not correlate significantly with the depression or anxiety levels as assessed by the Beck's Depression Inventory (BDI) or the STAI, respectively [72].

Concentration of BDNF in the blood plasma of Korean patients with alcohol use disorder correlates positively with the cognitive functioning as assessed by the Trail Making Test B, a part of Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [73]. Subjects with alcohol use disorder abstinent for at least four weeks have lower levels of BDNF in the plasma as compared with the healthy controls, moreover BDNF concentration positively correlates with the Frontal Assessment Battery (FAB) scores [37]. Plasma BDNF concentrations in the patients with alcohol use disorder abstinent for at least four months are significantly affected by the presence of cognitive impairment assessed using FAB and Memory Failures of Everyday Questionnaire (MFE); plasma BDNF is significantly lower in the patients with cognitive impairment than in the patients without cognitive impairment [74]. Patients with and without cognitive impairment could be distinguished based on the plasma concentration of BDNF as was shown by the logistic regression analysis [74]. Expression of the BDNF mRNA in peripheral blood lymphocytes is elevated in the patients with crack-cocaine use disorder and alcohol use disorder after detoxification treatment, and these levels in the combined population could predict the degree of cognitive impairments assessed with FAB scores [75]. After three weeks of abstinence, the serum BDNF concentrations are associated with the MoCA (Montreal Cognitive Assessment) scores [76]. Nevertheless, BDNF is not necessarily related to cognition in the context of alcohol consumption. Drinking status or serum BDNF

levels in the Chinese Han population do not correlate with cognitive performance estimated with Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [77].

Thus, clinical data demonstrate that the BDNF-related parameters are associated with the neuroplastic changes accompanying alcohol dependence. The rs6265 polymorphism within the *BDNF* gene is associated with the macrostructural changes in the brain, while the peripheral BDNF concentration may be associated with anxiety, depression, and cognitive impairment. Moreover, presence of the rs6265 polymorphism and peripheral BDNF concentration may predict time course of these disturbances. However, heterogeneity of the available clinical results prevents the use of BDNF-related parameters as biomarkers, diagnostic or prognostic factors in treatment of alcoholism. Respective clinical data are presented in Table 2.

CONCLUSION

The currently available data demonstrate that the BDNF expression changes depending on the brain region and alcohol intake mode. This could be accompanied by the specific structural rearrangement in neurons and behavioral impairment; at the same time, direct or indirect increase of local BDNF concentration reverses aberrant neuroplasticity. Increase of the peripheral BDNF concentration in the alcohol use disorder is also associated

Table 2. Relationship between BDNF and neuroplasticity in the context of alcohol dependence

Alcohol consumption	BDNF-related parameters	Morphological/clinical parameters	Association with BDNF	References
Abstinence, 7 months	rs6265 *Val66Val* genotype	hippocampal volume; visuospatial memory	hippocampal volume recovery; positive correlation between hippocampal volume recovery and improvements of visuospatial memory	[64]
Abstinence, 5 weeks	rs6265 *Val66Val* genotype	gray matter volumes of all the cortical lobes except occipital, gray matter volumes of the thalamus	increases in gray matter volumes of all cortical lobes except occipital, thalamic gray matter increase	[65]
	rs6265 *Val66Met* genotype	frontal lobe white matter volume, total volumes of cerebellum and brainstem	increase of frontal lobe white matter, increase of total volumes of cerebellum and brainstem	–
Alcohol dependence, abstinence ⩾24 h	plasma BDNF concentration	functional connectivity amygdala-medial prefrontal cortex	as shown by functional MRI lower levels of plasma BDNF are associated with the decreased functional connectivity between amygdala and medial prefrontal cortex during anticipatory anxiety elicited by unpredictable threat of shock; lower levels of BDNF and impaired amygdala-medial prefrontal cortex functional connectivity are associated with more binge episodes in the past 60 days and lower age of alcohol use disorder onset	[68]
Alcohol dependence	serum BDNF concentration	anxiety level according to the State-Trait Anxiety Inventory (STAI)	positive correlation between the serum BDNF concentrations and state anxiety level	[69]
Abstinence, 2-4 days	serum BDNF concentration	anhedonia level according to the Snaith−Hamilton Pleasure Scale	negative correlation between the BDNF and anhedonia levels; according to the results of multiple regression, BDNF concentrations, age, and gender together explain 21% of variability in anhedonia levels	[71]

Table 2. (*contd.*)

Alcohol consumption	BDNF-related parameters	Morphological/clinical parameters	Association with BDNF	References
Abstinence, 6 months	serum BDNF concentration; rs6265 *Met* allele	serum γ-glutamyl transferase; number of past treatments in detoxification programs, and presence of a depressive episode	regression analysis, presence of the rs6265 Met allele, level of γ-glutamyl transferase, number of past treatments in detoxification programs, and presence of a depressive episode are significantly associated with the serum levels of BDNF at admission time and after 6 months of abstinence	[55]
Abstinence, ≥7 days	plasma BDNF concentration	cognitive functions, Consortium to Establish a Registry for Alzheimer's Disease (CERAD)	concentration of BDNF in plasma correlates positively with cognitive functioning as assessed by Trail Making Test B, part of CERAD	[73]
Abstinence, ≥4 weeks	plasma BDNF concentration	cognitive functions, frontal assessment battery questionnaire (FAB)	positive correlation between BDNF concentration and FAB scores	[37]
Abstinence, 4 months	plasma BDNF concentration	cognitive functions, FAB and memory failures of everyday (MFE)	according to the results of regression analysis, plasma concentration of BDNF is able to distinguish patients with and without cognitive impairment	[74]
Abstinence, 3 weeks	serum BDNF concentration	cognitive functions, Montreal Cognitive Assessment (MoCA)	according to the results of regression analysis, serum BDNF concentration predicts MoCA scores	[76]

with favorable prognosis with regards to impairment of neuroplasticity occurring as a consequence of chronic intoxication. However, it is not clear whether the adaptive BDNF-mediated structural and functional changes of CNS plasticity initiates development of alcohol dependence and associated disorders or they are the results of compensatory responses to chronic excessive alcohol consumption [7]. It seems that the BDNF-mediated neuroplasticity may be pathological or adaptive depending on experimental conditions (brain region studied, alcohol intake pattern, duration of alcohol intoxication). According to the results reported by S. C. Pandey and co-authors [32-35], decrease of the BDNF content may provoke the alcohol-related impairment of phenotype, while E. Stragier and co-authors [36, 51] suggest that the increased BDNF content may be a compensatory mechanism counteracting the ethanol-induced behavioral deficit.

Despite the obvious progress in understanding of the role of BDNF in aberrant neuroplasticity accompanying alcohol intake, investigations in this area are far from being complete. There are some critical "issues" that need to be resolved in future research.

- What neurochemical systems act in coordination with BDNF? BDNF is not a direct molecular target of alcohol [4], so molecular mechanisms of the BDNF expression changes and its functional role in alcohol dependence need to be clarified. Moreover, further studies should reveal molecular targets of BDNF itself.
- Does BDNF control sensitivity to alcohol? Susceptibility to the development of alcohol dependence and alcohol-related adaptations in the brain are heterogeneous in a population. Future investigations should establish biological factors directly or indirectly associated with BDNF, which determine neuroplasticity impairment. Once this issue is clarified, it would be possible to personalize strategies for prophylaxis and therapy of alcohol abuse.

Answers to these questions would facilitate development of pharmacological and non-pharmacological agents capable of regulating activity of the BDNF system, thereby normalizing aberrant plasticity in the sensitive brain regions in the context of alcohol dependence.

Contributions. Danil I. Peregud — conceptualization of the study, writing of original draft; Danil I. Peregud, Valeria Yu. Baronets, Natalia N. Terebilina — search and analysis of the literature data; Natalia V. Gulyaeva — conceptualization of the study, editing of the final manuscript.

Ethics declarations. The authors declare no conflict of interest in financial or any other sphere. This article does not contain any studies with human participants or animals performed by any of the authors.

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