Neuroscience Letters 764 (2021) 136194

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Trophic factors as potential therapies for treatment of major mental disorders

Eliyahu Dremencov [a,*], Daniela Jezova [b], Segev Barak [c], Jana Gaburjakova [a], Marta Gaburjakova [a], Viera Kutna [d], Saak V. Ovsepian [d]

[a] Institute of Molecular Physiology and Genetics, Center of Biosciences, Slovak Academy of Sciences, Bratislava, Slovakia
[b] Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
[c] School of Psychological Sciences and the Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
[d] Department of Experimental Neurobiology, National Institute of Mental Health, Topolová 748, 250 67 Klecany, Czech Republic

ARTICLE INFO

Keywords:
Growth factor
Neuropsychiatry
Antidepressants
Antipsychotics
Targeted delivery
Polyplex nanoparticles

ABSTRACT

Notwithstanding major advances in psychotherapeutics, their efficacy and specificity remain limited. The slow onset of beneficial outcomes and numerous adverse effects of widely used medications remain of chief concern, warranting in-depth studies. The majority of frontline therapies are thought to enhance the endogenous monoaminergic drive, to initiate a cascade of molecular events leading to lasting functional and structural plasticity. They also involve alterations in trophic factor signalling, including brain-derived neurotrophic factor (BDNF), VGF (non-acronymic), vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), glial cell-derived neurotrophic factor (GDNF), and others. In several major mental disorders, emerging data suggest protective and restorative effects of trophic factors in preclinical models, when applied on their own. Antidepressant outcomes of VGF and FGF2, for instance, were shown in experimental animals, while BDNF and GDNF prove useful in the treatment of addiction, schizophrenia, and autism spectrum disorders. The main challenge with the effective translation of these and other findings in the clinic is the knowledge gap in action mechanisms with potential risks, as well as the lack of effective platforms for validation under clinical settings. Herein, we review the state-of-the-art and advances in the therapeutic use of trophic factors in several major neuropsychiatric disorders.

1. Introduction

Neuroplasticity is an umbrella term used to cover the ability of the nervous system to change and to adapt to environmental challenges, *via* structural, functional, and molecular reorganizations. Neuroplasticity is essential for both, normal and pathological activities of the brain. Accordingly, the pathobiology of multiple brain disorders, including autism [81], unipolar [20] and bipolar depression [152], post-traumatic stress disorder (PTSD) [18], and schizophrenia [73], are related to plastic changes. Neurogenesis [55], formation and pruning of dendrites and spines, synaptogenesis [108], and activity-dependent changes in synaptic strength are amongst the basic processes underlying brain plasticity [151], governed by an array of mechanisms involving trophic factors.

Brain-derived neurotrophic factor (BDNF) is one of the most ubiquitous and extensively studied neurotrophins [86]. BDNF is a short peptide acting *via* tyrosine kinase B (TrkB) receptor. The highest density of BDNF, as well as its transcripts, is detected in the hippocampus, especially in the mossy fiber axons of dentate granule cells [19]. In the context of psychiatric diseases, the autoregulation of BDNF leading to enhancement of its expression is of particular interest (Fig. 1). BDNF expression auto-regulation is viewed in conjunction with two main mechanisms. The first involves activation of the TrkB receptor, leading to VGF (non-acronymic) expression. VGF transcripts, in turn, serve as a precursor of several peptides, with one of them, C-terminal peptide TLQP-62, stimulating rapid BDNF expression [94]. The second pathway, upon activation, relates with monoamine (serotonin or 5-HT, norepinephrine, and dopamine) signalling. Direct infusion of BDNF in the brain enhances 5-HT concentration in the hippocampus, cortex, striatum, substantia nigra, and hypothalamus, while the level of dopamine

* Corresponding author at: Institute of Molecular Physiology and Genetics, Center of Biosciences, Slovak Academy of Sciences, Dúbravská cesta 9, 840 05 Bratislava, Slovakia.
E-mail address: Eliyahu.Dremencov@savba.sk (E. Dremencov).

https://doi.org/10.1016/j.neulet.2021.136194
Received 4 April 2021; Received in revised form 2 August 2021; Accepted 20 August 2021
Available online 22 August 2021

increases in the striatum and cortex [143]. Since TrkB receptors are enriched in 5-HT neurons of the dorsal raphe nucleus (DRN) [104], it is likely that increased serotonergic drive results from the activation of 5-HT neurons by BDNF. Enhancement of BDNF expression by monoamines, in turn, is mediated *via* activation of respective G-protein-coupled receptors (GPCRs; primarily, α_S-coupled GPCR, such as 5-$HT_{4/6/7}$ serotonergic and D_1 dopaminergic receptors), with the production of cyclic adenosine monophosphate (cAMP), and stimulation of cAMP response element-binding proteins (CREBs) [92].

The role of TrkB induced signalling in governing neuronal plasticity response has been well described [4,28,70]. In psychiatric diseases, the action of BDNF is viewed primarily in connection with *N*-methyl-*D*-aspartate (NMDA)-receptor-mediated signalling and glutamatergic transmission [149]. NMDA-receptor response is closely linked to the calcium/calmodulin-dependent protein kinase II (CaMKII), voltage-dependent calcium channels (VDCC), and ryanodine receptor (RYR)-mediated Ca^{2+} signalling (Fig. 2), which plays a key role in functional plasticity and remodelling of glutamatergic connections [15,61], implicated in schizophrenia and other psychiatric disorders [80]. VGF/BDNF/TrkB pathway is involved in neuronal development, differentiation, and formation of synaptic contacts, with emerging data supporting facilitator effects [54,70,110]. Accordingly, murine models over-expressing BDNF show hyper-excitability [30], while the intra-hippocampal infusion of antisense BDNF oligonucleotides lowered its expression and inhibited long-term synaptic potentiation (LTP) [103]. Of note, VGF-BDNF-TrkB activation is also linked with other neurotransmitter systems, including GABAergic, cholinergic, serotonergic, noradrenergic, dopaminergic, and histaminergic, with BDNF modulating their activity and plasticity [36,77,123]. Unlike BDNF, GDNF is enriched throughout the brain in glial cells [93], with its levels highest during development. In the adult brain, GDNF is enriched in the striatum, thalamus, cortex, and hippocampus [119,129]. GDNF signalling is mediated *via* the receptor tyrosine kinase (RET) [38], with activation of RET requiring the co-receptor GDNF-Family Receptor α1 (GFRα1) [2,79].

The primary function of VEGF and FGF2 in the brain is control of microcirculation, *via* regulation of the proliferation of vascular endothelial and connective tissue cells, respectively. Of note, the expression of VEGF depends on FGF2 [141], rendering the latter a pro-angiogenic factor [31]. VEGF also boosts the expression of endothelial nitric oxide synthase (eNOS) [50]. Taken together, FGF2/VEGF/eNOS pathway emerges as an important component of neuroplasticity, with pro-neurogenic effects of FGF2 also reported [165,166]. The neurogenic

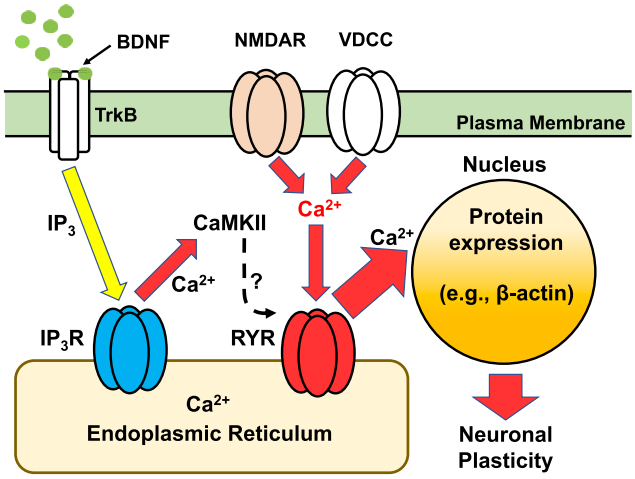

Fig. 2. Principal mechanism and putative pathways of BDNF-induced neuroplasticity: this signaling may operate in stand-alone mode as well as in conjunction with activation of N-methyl-D-aspartate-receptor(NMDAR) and voltage-dependent calcium channel (VDCC)-dependent mechanisms. BDNF, brain-derived neurotrophic factor; TrkB, tyrosine receptor kinase B; IP_3 inositol trisphosphate; IP_3R, IP_3 receptor; Ca^{2+}, calcium; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; RYR, ryanodine receptor.

and neuroplasticity effects of trophic factors are known to involve eNOS [87,130], causing also enhancement of hippocampal LTP - a cellular correlate of memory [68]. Similar to BDNF and VEGF, FGF2 has been implicated in brain development [132,160], adult neurogenesis [159], and neuronal plasticity [74]. FGF2 seems to play a key role in the maintenance of midbrain dopaminergic circuits [62,132], where it is enriched in both, neurons and astrocytes [56,132]. Mechanistically, FGF2 binds to FGF receptor 1 (FGFR1), a receptor tyrosine kinase [48], stimulating PLCγ, ERK1/2, and PI3K pathway [41,132]. In the mature brain, FGF2 plays a key role in learning and memory processes [57], with its dysregulations implicated in a variety of psychiatric diseases.

With the immense versatility of trophic factors and complexity of action mechanisms, there is a pressing need for systematic appraisal of the state-of-the-art, to highlight key trends and advancements, as well as of outstanding questions. Such inquiry should not only delineate the current state of knowledge but enable further progress with clinical translation for better disease management.

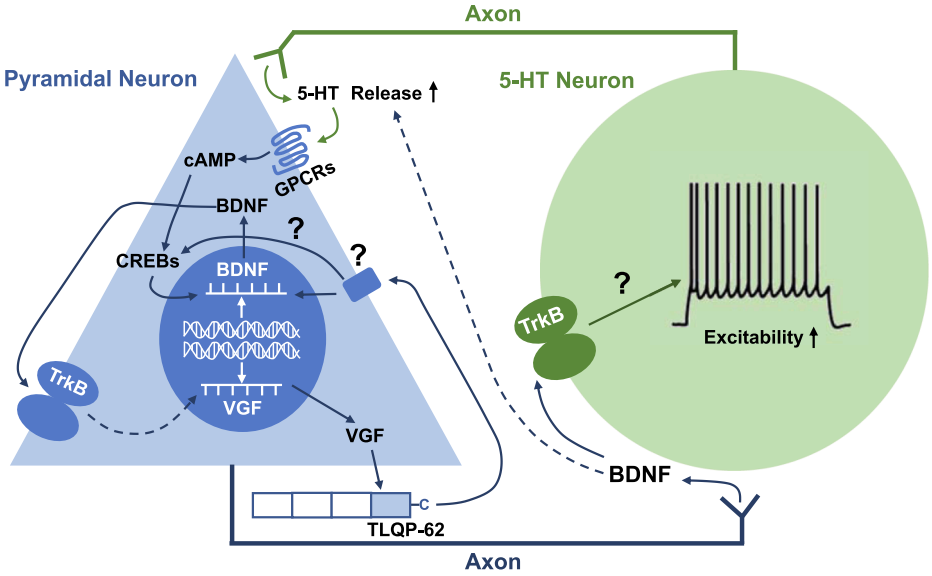

Fig. 1. Brain-derived neurotrophic factor (BDNF) upregulates the expression and release of BDNF from pyramidal neurons *via* monoaminergic mechanisms. BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CREB, cyclic AMP responsible element-binding protein; TrkB, tyrosine receptor kinase B; 5-HT, 5-hydroxytryptamine (serotonin); GPCRs, G-protein coupled receptors; VGF – VGF non-acronymic; TLQP-62 – C-terminal domain of VGF peptide. Question marks indicate yet unknown mediators implicated in signaling pathways.

2. Trophic factors as potential therapies for depression

It is well known that dysregulation of monoamine signalling (i.e., 5-HT, noradrenaline, dopamine, and histamine) might contribute to the biology of depression and related disorders. Almost all currently used antidepressants target the homeostatic mechanisms and receptors of 5-HTergic, noradrenergic, and/or dopaminergic systems. These effects are classified as (1) inhibition of the reuptake of monoamines (tricyclic drugs, selective 5-HT reuptake inhibitors or SSRIs, dual 5-HT and noradrenaline reuptake inhibitors or SNRIs, and triple 5-HT, noradrenaline, and dopamine reuptake inhibitors), (2) agonism and/or antagonism of receptors, such as 5-$HT_{2A/2C}$, 5-$HT_{2A/2C}$, 5-HT_3, and α_2-adrenergic, or 5-$HT_{1A/1B/1D}$, 5-HT_3, and 5-HT_7 receptors, or (3) inhibition of monoamine metabolism (monoamine oxidase inhibitors).

One of the principal shortfalls of current antidepressants is their protracted effects. Even though SSRIs and SNRIs rapidly elevate the levels of monoamines in the brain, symptomatic improvements are evident only after a few weeks of sustained treatment. It emerges, that the blockade or activation of monoaminergic receptors or transporters is only the first step in the cascade of events leading to therapeutic outcome [123]. The latter seems to involve a range of gradual changes resulting from the sustained effects of antidepressants, such as desensitization of specific monoaminergic receptors and remodelling of synaptic connections. Indeed, continued SSRIs treatment leads over several weeks to desensitization of presynaptic 5-$HT_{1A/1B}$ autoreceptors [113], which in turn cause a net increase in 5-HT transmission with a rise in the level of BDNF [37], FGF2 [106], and other growth factors. BDNF, in turn, stimulates neuroplasticity in selected brain areas, such as the hippocampus and prefrontal cortex (PFC), which contribute to clinical recovery [34]. This mechanistic model agrees with effects caused by the direct infusion of BDNF or TLQP-62 into the brain of experimental rats, enabling rapid symptomatic improvements (Fig. 3) [77,78,102]. Thakker-Varia and colleagues have shown that similar to BDNF, recombinant VGF produced a potent antidepressant-like effect, as measured in the forced swim test (FST) of rats [150]. Another report showed rapid onset pro-neurogenic and antidepressant action of recombinant VGF, with behavioural improvements in VGF knock-out mice [71]. This effect of VGF could be mimicked by its C-terminal peptide TLQP-62. Interestingly, Chenli and colleagues showed that TLQP-62 alleviates lipopolysaccharide (LPS)-induced memory deficit and anxiety/depression-like behaviors in mice [89]. Whether in preclinical models, BDNF, VGF, and/or TLQP-62 exhibit faster antidepressant action than frontline antidepressants remain to be shown. Research in rat models of depression (i.e., Flinder sensitive line or FSL rats) with a faster behavioural response to the rapidly acting antidepressants might provide important mechanistic insights with translational benefits [35].

With regards to the FGF2/VEGF/eNOS signalling pathway, Turner and colleagues [155] showed that infusion of FGF2 in rat brain induced a rapid onset antidepressant-like effect, as measured by the FST. In a more recent study in rats [147], administration of synthetic FGF2 in the brain reversed the LPS-induced depressiion-like behaviour and reversed the activation of microglia. This fast antidepressant-like effect of FGF2 was mediated, at least in part, by reduction of the concentration of inflammatory cytokines (interleukin-1β: IL-1β, interleukin-6: IL-6, and tumour necrosis factor-alpha: TNF-α) and reversing cytokine-induced microglia response. In the same study, selective VEGF receptor 2 (VEGFR2) inhibitor SU5402 reversed the antidepressant-like effect of FGF2 and induced depression-like behavioral phenotypes [147].

Taken together, although the antidepressant-like effects of VGF/BDNF/TrkB and FGF2/VEGF/eNOS are supported by experimental studies in animal models, it is unclear if these outcomes are related to changes in monoaminergic activity (i.e., 5-HT drive) or they are independent of monoaminergic effects. The increase in 5-HT and dopamine levels in the brain in response to BDNF and VEGF suggests possible role of monoamines in antidepressant-like effects of described trophic factors [104].

3. Trophic factors as potential therapies for schizophrenia

Similar to antidepressants, the ameliorative effects of antipsychotic drugs are largely mediated *via* changes in monoaminergic activity. While typical antipsychotics such as haloperidol act almost exclusively *via* inhibition of D_2 receptors, the effects of atypical antipsychotics involve modulation of $D_{1/5}$, $D_{2/3/4}$, 5-$HT_{1A/1B}$, 5-$HT_{2A/2C}$, and $\alpha_{1/2}$-adrenoceptor mechanisms [168]. Another similarity between antidepressants and antipsychotics is that they both require sustained administration over a long time, to achieve a beneficial outcome. It is widely assumed, therefore, that the beneficial outcome of antipsychotics, similar to antidepressants, involves plasticity changes in the brain. The latter is likely to involve trophic mechanisms, mediated *via* VGF/BDNF/TrkB and/or FGF2/VEGF/eNOS signalling.

Einoch and colleagues [40] examined the effects of typical

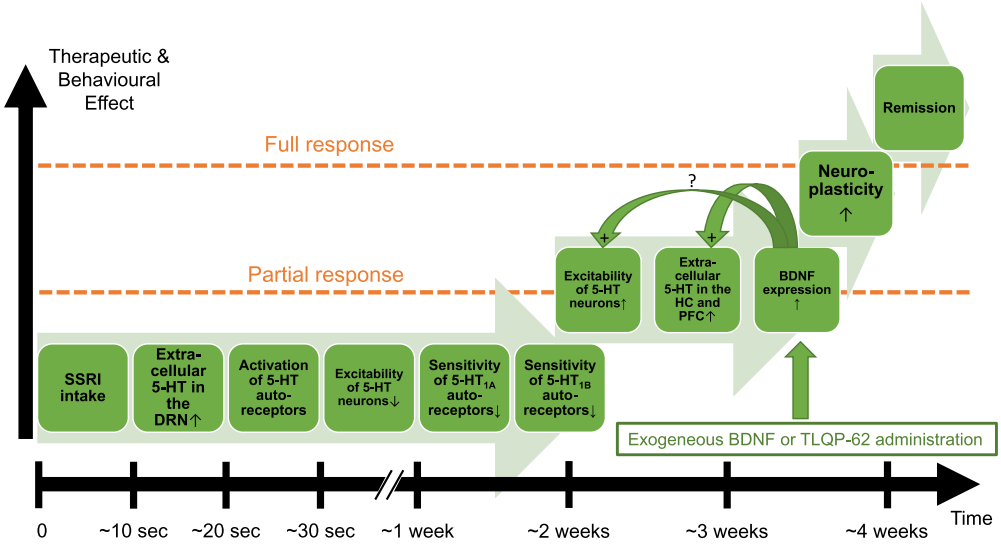

Fig. 3. Timeline and major stages of the development of therapeutic effect of classical antidepressants and putative antidepressant effects of exogenous neurotrophins. BDNF, brain-derived neurotrophic factor; DRN, dorsal raphe nucleus; HC, hippocampus; PFC, prefrontal cortex; SSRI, selective serotonin reuptake inhibitor; 5-HT, 5-hydroxytryptamine (serotonin).

(haloperidol), atypical (clozapine) antipsychotics, as well as combined effects of haloperidol with SSRI fluvoxamine on the VGF/BDNF/TrkB pathway in patients with schizophrenia. Summarizing their findings, administration of clozapine, and haloperidol, when applied together with fluvoxamine, induce stronger stimulatory effects on VGF/BDNF/TrkB pathway than antipsychotic drugs applied on their own. Interestingly, typical and atypical antipsychotics may have distinct effects on the FGF2/VEGF/eNOS pathway. Earlier work by Pillai and colleagues [128] showed that both, haloperidol and olanzapine increased hippocampal VEGF level after 14 days of treatment. Remarkably, after 45 days of sustained haloperidol treatment, the activity of VEGF returned to pre-treatment values. Interestingly, olanzapine-induced increase in the hippocampal VEGF had persisted 45 days after the last day of treatment. Another atypical antipsychotic drug quetiapine, when administered over a long time, caused an increase in FGF2 and BDNF mRNA in the rat hippocampus, but only under conditions of reduced NMDA receptor activity [51]. Potent activation of FGF2 expression was also reported under the joint administration of atypical antipsychotic olanzapine and fluvoxamine [106]. Overall, both, typical and atypical antipsychotics seem to stimulate VGF/BDNF/TrkB and FGF2/VEGF/eNOS pathways. The facilitatory effects of atypical antipsychotics on trophic factor signalling seem to be more potent than those induced by typical antipsychotics, which might explain, at least in part, the higher clinical efficacy of atypical antipsychotics, especially in ameliorating negative and cognitive symptoms of schizophrenia.

Like in humans, the pre-pulse inhibition (PPI) is considered as one of the most reliable readouts of impaired sensory-motor gating in animal models [10,146]. Accordingly, in drug-induced models of schizophrenia (e.g. apomorphine, amphetamine, and phencyclidine) PPI is altered, an effect that is antagonized by antipsychotic therapy [146]. Even though genetic deficiency of BDNF does not alter apomorphine- or MK-801-induced PPI impairments [157], it is thought that BDNF contributes to impairments of sensorimotor processing in schizophrenia. Remarkably, when BDNF deficient mice were exposed to environmental enrichment, they showed a deficit in attentional set-shifting tasks, implying impairments of executive functions characteristic to schizophrenia. In the same vein, authors report increased startle magnitude and deficit of PPI [64]. The neonatal lesion of the ventral hippocampus is another widely accepted animal model of schizophrenia-like phenotypes [95], which also demonstrates reduce BDNF mRNA in the cingulate cortex in young adults, but not prepubertal rats [8,112]. The authors show no changes in FGF2 expression. It is noteworthy that in a schizophrenia mouse model with disrupted PPI, administration of BDNF, but not GDNF, restored that PPI response [114]. These findings are in general agreement with the alleged mechanistic link between the ameliorative effects of antipsychotic drugs and the levels and activity of BDNF [5–7]. This model received support from a recent study which demonstrated that atypical antipsychotic clozapine increases BDNF expression and reverses PPI deficits induced by social isolation [90]. It also agrees with the data from human studies showing a strong link between BDNF Val66Met polymorphism with the reduced activity-dependent secretion of BDNF and schizophrenia [117]. Accordingly, an animal model of BDNF polymorphism and BDNF deficiency show a reduction in PPI [117].

Taken as a whole, the results of clinical and preclinical studies of schizophrenia suggest a potential mechanistic link between the changes in trophic signalling and ameliorative effects of both, typical and atypical antipsychotics, in schizophrenia. Further research is required to elucidate the mechanistic details of the complex crosstalk of antipsychotic therapy, trophic signalling, and clinical manifestations of schizophrenia.

4. Trophic factors as potential therapies for substance addiction

Substance use disorders are widely viewed as manifestations of maladaptive neuroplasticity [45,101] with impairments of trophic factor signalling implicated in long-lasting effects of both, drug abuse and addiction [12,26,43,53,86,96,98,134]. The specific role of BDNF and TrkB mechanisms has been demonstrated in several drug abuse studies [53,85,98]. Activation of BDNF in the mesolimbic system, for instance, was shown to enhance drug sensitization and promote self-administration, particularly for cocaine [58,69,99] and opiates [158,161]. In contrast, elevated BDNF activity in the medial prefrontal cortex (mPFC) seems to reverse molecular adaptations underlying drug-seeking behaviour [16,17,66,137,163] and reduce alcohol intake [65]. Transgenic mice with loss of BDNF functions showed elevated alcohol intake [67,109], while targeted knockdown of BDNF in the amygdala [122] or the dorsolateral striatum [75,98] were shown to promote the intake of alcohol. Importantly, repetitive administration of BDNF into the dorsolateral striatum was shown to suppress alcohol self-administration in rats [75], an effect that is mediated *via* the TrkB/ERK1/2 signalling pathway [76,98]. Such effects of BDNF administered into the striatum were not observed in rats exposed to chronic intake of alcohol [33], which was likely to result from reduced activity of TrkB receptors.

A loss-of-function mutation in BDNF in humans (G196A; also known as polymorphism rs6265) due to a single amino acid substitution (Val66Met), leads to the reduction of the activity-dependent release of BDNF [27,39]. This resulted in increased susceptibility to alcohol use disorder. Specifically, carriers of the mutation display earlier onset of alcoholism [107] with a significantly higher risk of relapse [164]. A similar mutation in mice (Val68/Met polymorphism) has led to compulsive-like alcohol consumption [162]. Thus, increased BDNF activity emerges as a promising strategy for restraining the use of alcohol, but its effects on addiction to other addictive substances are less clear. The results of similar studies of the effects of GDNF on cocaine-related behaviours are rather conflicting and conditional. Infusion of GDNF into the VTA or its over-expression in rats, for instance, was reported to increase cocaine-seeking behaviour [100] while increased GDNF levels in the NAc were associated with reduced cocaine self-administration [59,60]. Of note, general loss-of-function of GDNF in knockout mice showed increased reward response to cocaine [111,116], morphine [116], methamphetamine [116], and alcohol [23] with a higher propensity for addiction. In alcohol addiction studies, GDNF also showed therapeutic-like effects. Specifically, infusion of GDNF into the rat VTA reduces alcohol self-administration [25] and binge-like alcohol intake, an effect that lasted 48 h after a single dose [11,24]. Overexpression of GDNF in the VTA or NAc of rats prevented drinking escalation, whereas its downregulation in the mesolimbic system enhanced alcohol carving [1,14]. These and other reports suggest that GDNF might reduce alcohol intake by reversing plasticity changes in the mesolimbic dopamine system associated with withdrawal from long-term alcohol use [12,13]. Interestingly, alcohol use at early stages was reported to increase the expression of GDNF, a response that attenuates with the escalation of drinking [1], and effect that seems to involve epigenetic changes (DNA methylation) [105]. Of note, the FDA-approved drug cabergoline, an ergotamine derivative that increases GDNF expression, was found to attenuate alcohol seeking and drinking of rats [22]. Together, these findings suggest that GDNF is a negative regulator of alcohol and drug consumption, and that increase in the activity of this growth factor in the mesolimbic system can supress alcohol seeking and consuming behaviours.

Similar to GDNF, there is considerable evidence supporting the role of FGF2 and its receptor, FGFR1, in the pathophysiology of drug addiction, including cocaine, amphetamine, nicotine, and alcohol [43]. Cocaine and amphetamine were reported to increase FGF2 expression in the mesocorticolimbic and nigrostriatal regions [47,52], an effect that correlates with the extent of psychostimulant-induced psychomotor sensitization [47]. FGF2 was also shown to increase, while its deficit attenuates addiction-like behaviour in rats [43]. Indeed, a decrease in FGF2 activity in the VTA was shown to reduce amphetamine-induced sensitization [46] and fasten the extinction of cocaine self-administration [63]. Lowered FGF2 activity or FGFR1 inhibition was

also shown to reduce alcohol intake, an effect attributed to modulation of neurons in the dorsomedial striatum [42,44]. Interestingly, amphetamine treatments of neonates also increased psychomotor activity and sensitization [29], as well as the acquisition of operant cocaine self-administration [154], whereas FGF2 infusion increased alcohol intake [42,44].

Overall, these findings make a strong case for the important role of trophic factors in development of drug addiction and related behavioural changes. While BDNF and GDNF appear to reduce both, drug and alcohol craving and intake, results of FGF2 studies show opposite effects. Future research with the careful tuning of these mechanisms may therefore enable new therapeutic opportunities with potential health benefits.

5. Trophic factors in autism spectrum disorders

Autism spectrum disorder (ASD) is a developmental disability that affects communication, social interactions, and emotional bonding behaviour, with the role of neurotrophic factors implicated in many reports. Histopathological, imaging, and connectomes studies suggest significant differences in brain wiring and the length of the neuronal connections between people with autism and without, which are believed to result from neuro-developmental impairments. With essential roles played by trophic factors in brain development and synaptogenesis, there has been considerable interest in their preventive and therapeutic potentials [115,133]. A recent meta-analysis of neurotrophic factor levels changes in the blood of children with ASD and healthy controls showed significantly higher levels of BDNF, NGF, and VGF in the ASD group. The level of NT3 and NT4 in the serum, in the meantime, remained unchanged [97]. A systematic review of reports assessing peripheral BDNF levels indicated that its variation is higher in ASD, as compared with controls [167]. A Danish study showed that newborns later diagnosed with ASD had significantly lower blood levels of BDNF, with other neurodevelopmental factors also showing trends toward lower values [144]. Interestingly, the NT3 and NT4 mRNA in the blood was also lower in ASD patients compared to healthy controls [142].

In a report by Fuentealba and colleagues, a rat model autism was exposed prenatally to the anticonvulsant drug Valproate (VPA) to elucidate the role of BDNF in neurodevelopment and ASD. It was found that levels of BDNF mRNA were reduced in the dentate gyrus (DG) and CA3 areas in the VPA-treated juvenile rats. In addition, immunoreactivity of BDNF showed a significant reduction of its expression in supra-pyramidal and lucidum layers of the CA3 region [49]. Interestingly, in the VPA autism mouse model, BDNF levels were transiently increased in the foetal brains [3] but decreased in the cortex of adult animals [135]. Prenatal exposure of animal models to VPA altered dendritic morphology and spine plasticity, causing autism-like behaviour related to a reduced number of dendritic spines in the prefrontal cortex, dorsal hippocampus, and basolateral amygdala. In contrast, dendritic spine density in the nucleus accumbens and ventral hippocampus was enhanced. In the same vein, neuronal arborisation was retracted in the ventral and dorsal hippocampus but increased in the nucleus accumbens and prefrontal cortex [21]. A report by Kirsten and colleagues examined the effects of anti-diabetic drug pioglitazone in a rat model of autism induced by lipopolysaccharide (LPS) during gestation. It was found that prenatal LPS exposure led to elevated BDNF levels in plasma, whereas pioglitazone decreased the level of BDNF in plasma of juvenile rats prenatally exposed to LPS [83]. Likewise, prenatal zinc treatment decreased blood BDNF level in the LPS rat model of autism [84].

Another well-characterized rodent model of autism is Fragile X syndrome *Fmr1* knockout (KO) mouse, which lacks FMRP protein due to a disruption in its Fmr1 gene [131]. The neurochemical analysis demonstrated significant age-dependent changes in hippocampal BDNF expression. At an early age, the level of BDNF in these mice is increased, which declines after the age of 4 months [156]. Dysregulation in BDNF/TrkB signalling in the *Fmr1* KO mice is likely to contribute to altered dendritic arborisation in this model [82]. Interestingly, reports have shown also that Rett syndrome can be induced by loss-of-function mutations in the X-linked gene methyl-CpG-binding protein 2 (MECP2), which leads to developmental neuro-metabolic impairments, associated with a strong reduction in BDNF level and activity throughout the brain [91,131]. Of note, *mecp2* KO mice showed reduced dendritic arborisation and abnormal spine morphology [131]. Finally, due to autism-like behavioural phenotypes, the inbred mouse strain BTBR T + tf/j has been used as a model for studies of ASD and trophic changes. Several reports have found reduced BDNF and TrkB activity in the forebrain of these mice [32,139,145]. Described phenomenon has been suggested to be age-dependent, as the level of BDNF in the foetal BTBR mouse brain was elevated [72]. In this context, it is important to note that some evidence points that the administration of BDNF and insulin growth factor (IGF-1) can induce beneficial effects with the improved behavioural outcome. Reassuringly, human IGF-1 has already been tested and well-tolerated in clinical trials with either Rett syndrome, and has shown beneficial outcomes. Whether the restoration BDNF level or pharmacological manipulations of TrkB activity can provide effective therapeutic means for ASD treatment remains to be found.

6. Targeted strategies for delivery of therapeutic trophic factors to the brain

Growing evidence for the potential therapeutic significance of trophic factors in the treatment of several major mental disorders incited much interest in their delivery to the brain for treatment purposes. The large size and proteinaceous nature of trophic factors make their blood–brain barriers crossing highly inefficient, and render their use a as neurotherapeutics major challenge. As discussed throughout this review, under experimental settings, both natural and recombinant VGF, BDNF, FGF2, VEGF, and/or mRNA can have some beneficial effects, presumably *via* modulation of plasticity mechanisms, with nootropic, antidepressant, and anxiolytic outcomes.

The mRNA-based therapeutic approaches, in addition to complexities related to poor penetration across the blood–brain barriers, are hampered further by the low inherent stability of the cargo, with rapid degradation. Importantly, due to functional versatility and high potency, the efficient delivery of trophic factors and mRNA may come with risks of adverse side effects, owing to off-target actions as well as stimulation of uncontrolled proliferation of fibroblasts of connective tissue as well as impaired homeostasis of endothelial cells. In most experimental studies in animals, therefore, trophic factors were administrated directly into the structures of interest in the brain. While providing useful insights for preclinical research, such delivery routes are incompatible for clinical applications in patients, due to their invasive character and health risks. Recent advances in nanotechnologies for targeted delivery of therapeutic cargo and vectors to central neurons, nevertheless, enabled effective routes and methods for transfer of trophic factors, for neuronal protection and restoration of impaired functions. Using the retro-nasal delivery route for mRNA transfer to the brain with polyplex nanoparticles, Baba and colleagues [9] reported the successful delivery of BDNF-coding mRNA in rats. The delivery efficiency was confirmed by the detection of enhanced BDNF expression in the olfactory bulbs after intranasal administration of mRNA-loaded nanoparticles. Importantly, with the same approach, the authors report restoration of olfactory deficit in experimental animals [9]. Given anatomical proximity of olfactory bulbs with the piriform and entorhinal cortex, as well as dense connections with the amygdala, hippocampus, and ventral tegmental area (VTA), the retro-nasal delivery could be expended for transfer of therapeutics also to these brain areas, with implications for the management of an array of neurodevelopmental and neuropsychiatric disorders (Fig. 4). Of note, reports have demonstrated also that polyplex nanoparticles can be designed to enable effective interactions and loading onto anterograde [140,148] or retrograde [126] axonal

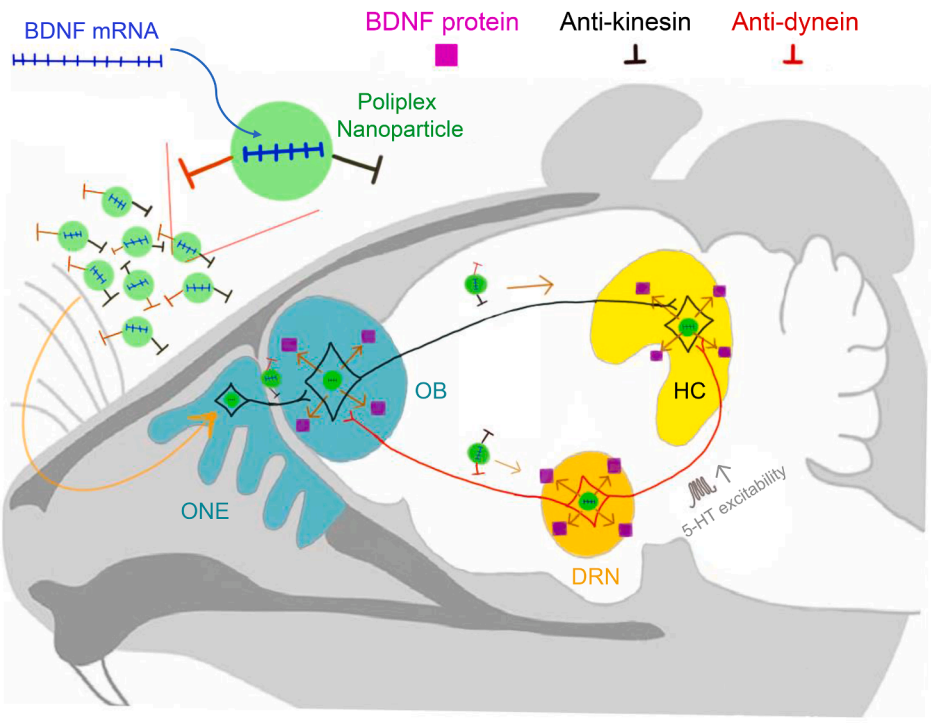

Fig. 4. Targeted retro-nasal delivery of exogenous trophic factors (e.g. BDNF mRNA) into the mammalian brain. BDNF, brain-derived neurotrophic factor; DRN, dorsal raphe nucleus; HC, hippocampus; OB, olfactory bulb; ONE, olfactory neuroepithelium; 5-HT, 5-hydroxytryptamine (serotonin). Arrows indicate the direction of the therapeutic delivery.

transport carriers, with delivery improvements. Likewise, the utility of magnetic nano-carriers for non-invasive transfer of trophic factors to central neurons has been shown [127]. Finally, the viability of the use of detoxified neurotoxins such as tetanus toxin or its atoxic fragments for retro-axonal delivery of trophic factor and other therapeutic cargo, in the bypass of blood–brain barriers, has been shown [118,120,121,153]. With this approach, delivery of insulin growth factor (IGF-1) [124,125], BDNF [136,153], and GDNF [88] with beneficial effects have been proven under preclinical settings, proving an overall promising method for effective transfer of trophic factor to the diseased brain [138].

7. Conclusion

Abnormal development and plasticity of neurons have been implicated in the pathophysiology of major mental disorders such as autism, depression, schizophrenia, addiction, and others. Since growth factors in general and neurotrophins particularly are fundamental in neuroplasticity, they contain major potential as putative therapeutic leads for medical interventions. As clear from examples and discussions throughout this study, research in both experimental animals and humans supports the therapeutic utility of trophic factors, with manipulation of their activity showing potential therapeutic benefits. FGF2 and VGF C-terminal peptide TLQP-62, for instance, when applied directly into the rodent brain, induce antidepressant-like effects, which could be reversed by the VEGF receptor inhibitor. BDNF and GDNF, on the other hand, seem to attenuate the drug-seeking and alcohol abuse behaviours, while FGF2 showing the opposite effects. In ASD models, delivery of BDNF induced lasting symptomatic improvements. Currently, there is a pressing need not only in in-depth mechanistic studies but also in elucidating the pharmacokinetic and dynamic properties of trophic factors when delivered to the brain, as well as their safety margins and potential side effects, to advance the use of these 'wonder' molecules from animal models onto the next, clinical level of translation. The letter requires methods for effective targeting and delivery, with better stability and blood–brain permeability. Rapid advances of nanotechnologies might therefore assist to resolve the major limitation of current methods, and hopefully enable more effective access to brain structures of interest for better management and therapy of major mental disorders.

Acknowledgements

The work of the authors was supported by the Slovak Research and Development Agency grant APVV-20-0202 (ED), Research Grant Agency of the Ministry of Education, Science, Research and Sport and Slovak Academy of Sciences grants VEGA-2/0046/18 (ED) and VEGA-2/0022/19 (DJ), Israel Science Foundation (ISF) grant 508/20 (SB), and German Science Foundation (DFG) grant 857/29-1 (SB). Authors thank Ms. Reyhaneh Nejati for the assistance with the figures' preparation.

References

[1] S. Ahmadiantehrani, S. Barak, D. Ron, GDNF is a novel ethanol-responsive gene in the VTA: implications for the development and persistence of excessive drinking, Addict. Biol. 19 (2014) 623–633.
[2] M.S. Airaksinen, M. Saarma, The GDNF family: signalling, biological functions and therapeutic value, Nat. Rev. Neurosci. 3 (2002) 383–394.
[3] L.E.F. Almeida, C.D. Roby, B.K. Krueger, Increased BDNF expression in fetal brain in the valproic acid model of autism, Mol. Cell. Neurosci. 59 (2014) 57–62.
[4] C.A. Altar, M.P. Vawter, S.D. Ginsberg, Target identification for CNS diseases by transcriptional profiling, Neuropsychopharmacology 34 (1) (2009) 18–54.
[5] F. Angelucci, L. Aloe, S.H.M. Gruber, M. Fiore, A.A. Mathé, Chronic antipsychotic treatment selectively alters nerve growth factor and neuropeptide Y immunoreactivity and the distribution of choline acetyl transferase in rat brain regions, Int. J. Neuropsychopharmacol. 3 (1) (2000) 13–25.
[6] F. Angelucci, S. Brenè, A.A. Mathé, BDNF in schizophrenia, depression and corresponding animal models, Mol. Psychiatry 10 (4) (2005) 345–352.
[7] F. Angelucci, A.A. Mathe, L. Aloe, Brain-derived neurotrophic factor and tyrosine kinase receptor TrkB in rat brain are significantly altered after haloperidol and risperidone administration, J. Neurosci. Res. 60 (6) (2000) 783–794.
[8] P.C. Ashe, J. Chlan-Fourney, A.V. Juorio, X.-M. Li, Brain-derived neurotrophic factor (BDNF) mRNA in rats with neonatal ibotenic acid lesions of the ventral hippocampus, Brain Res. 956 (1) (2002) 126–135.
[9] M. Baba, K. Itaka, K. Kondo, T. Yamasoba, K. Kataoka, Treatment of neurological disorders by introducing mRNA in vivo using polyplex nanomicelles, J. Control. Release 201 (2015) 41–48.

[10] S. Barak, Modeling cholinergic aspects of schizophrenia: focus on the antimuscarinic syndrome, Behav. Brain Res. 204 (2) (2009) 335–351.
[11] S. Barak, S. Ahmadiantehrani, V. Kharazia, D. Ron, Positive autoregulation of GDNF levels in the ventral tegmental area mediates long-lasting inhibition of excessive alcohol consumption, Transl. Psychiatry 1 (12) (2011) e60–e60.
[12] S. Barak, S. Ahmadiantehrani, M.L. Logrip, D. Ron, GDNF and alcohol use disorder, Addict. Biol. 24 (3) (2019) 335–343.
[13] S. Barak, S. Carnicella, Q.V. Yowell, D. Ron, Glial cell line-derived neurotrophic factor reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: implications for alcohol reward and seeking, J. Neurosci. 31 (2011) 9885–9894.
[14] S. Barak, J. Wang, S. Ahmadiantehrani, S. Ben Hamida, A.P. Kells, J. Forsayeth, K. S. Bankiewicz, D. Ron, Glial cell line-derived neurotrophic factor (GDNF) is an endogenous protector in the mesolimbic system against excessive alcohol consumption and relapse, Addict. Biol. 20 (4) (2015) 629–642.
[15] N. Benhassine, T. Berger, Large-conductance calcium-dependent potassium channels prevent dendritic excitability in neocortical pyramidal neurons, Pflugers Arch. 457 (5) (2009) 1133–1145.
[16] W.J. Berglind, R.E. See, R.A. Fuchs, S.M. Ghee, T.W. Whitfield Jr., S.W. Miller, J. F. McGinty, A BDNF infusion into the medial prefrontal cortex suppresses cocaine seeking in rats, Eur. J. Neurosci. 26 (2007) 757–766.
[17] W.J. Berglind, T.W. Whitfield, R.T. LaLumiere, P.W. Kalivas, J.F. McGinty, A single intra-PFC infusion of BDNF prevents cocaine-induced alterations in extracellular glutamate within the nucleus accumbens, J. Neurosci. 29 (12) (2009) 3715–3719.
[18] A. Besnard, A. Sahay, Adult hippocampal neurogenesis, fear generalization, and stress, Neuropsychopharmacology 41 (1) (2016) 24–44.
[19] D.K. Binder, H.E. Scharfman, Brain-derived neurotrophic factor, Growth Factors 22 (2004) 123–131.
[20] A. Borsini, P.A. Zunszain, Advances in Stem Cells Biology: New Approaches to Understand Depression. In: D. Pfaff, Y. Christen (Eds.), Stem Cells in Neuroendocrinology, Springer Copyright 2016, The Author(s). Cham (CH), 2016.
[21] M.E. Bringas, F.N. Carvajal-Flores, T.A. López-Ramírez, M. Atzori, G. Flores, Rearrangement of the dendritic morphology in limbic regions and altered exploratory behavior in a rat model of autism spectrum disorder, Neuroscience 241 (2013) 170–187.
[22] S. Carnicella, S. Ahmadiantehrani, D.-Y. He, C.K. Nielsen, S.E. Bartlett, P. H. Janak, D. Ron, Cabergoline decreases alcohol drinking and seeking behaviors via glial cell line-derived neurotrophic factor, Biol. Psychiatry 66 (2) (2009) 146–153.
[23] S. Carnicella, S. Ahmadiantehrani, P.H. Janak, D. Ron, GDNF is an endogenous negative regulator of ethanol-mediated reward and of ethanol consumption after a period of abstinence, Alcoholism, Clin. Exp. Res. 33 (2009) 1012–1024.
[24] S. Carnicella, R. Amamoto, D. Ron, Excessive alcohol consumption is blocked by glial cell line-derived neurotrophic factor, Alcohol 43 (1) (2009) 35–43.
[25] S. Carnicella, V. Kharazia, J. Jeanblanc, P.H. Janak, D. Ron, GDNF is a fast-acting potent inhibitor of alcohol consumption and relapse, PNAS 105 (23) (2008) 8114–8119.
[26] S. Carnicella, D. Ron, GDNF–a potential target to treat addiction, Pharmacol. Ther. 122 (1) (2009) 9–18.
[27] Z.Y. Chen, P.D. Patel, G. Sant, C.X. Meng, K.K. Teng, B.L. Hempstead, F.S. Lee, Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons, J. Neurosci. 24 (2004) 4401–4411.
[28] M. Chmelova, L. Balagova, M. Marko, S. Vrankova, M. Cebova, D. Jezova, I. Riecansky, N. Hlavacova, Behavioral alterations induced by post-weaning isolation rearing of rats are accompanied by reduced VGF/BDNF/TrkB signaling in the hippocampus, Neurochem. Int. 129 (2019), 104473.
[29] S.M. Clinton, C.A. Turner, S.B. Flagel, D.N. Simpson, S.J. Watson, H. Akil, Neonatal fibroblast growth factor treatment enhances cocaine sensitization, Pharmacol. Biochem. Behav. 103 (1) (2012) 6–17.
[30] S.D. Croll, C. Suri, D.L. Compton, M.V. Simmons, G.D. Yancopoulos, R. M. Lindsay, S.J. Wiegand, J.S. Rudge, H.E. Scharfman, Brain-derived neurotrophic factor transgenic mice exhibit passive avoidance deficits, increased seizure severity and in vitro hyperexcitability in the hippocampus and entorhinal cortex, Neuroscience 93 (4) (1999) 1491–1506.
[31] M.J. Cross, L. Claesson-Welsh, FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition, Trends Pharmacol. Sci. 22 (2001) 201–207.
[32] C.M. Daimon, J.M. Jasien, W.H. Wood 3rd, Y. Zhang, K.G. Becker, J.L. Silverman, J.N. Crawley, B. Martin, S. Maudsley, Hippocampal transcriptomic and proteomic alterations in the BTBR mouse model of autism spectrum disorder, Front. Physiol. 6 (2015) 324.
[33] E. Darcq, N. Morisot, K. Phamluong, V. Warnault, J. Jeanblanc, F.M. Longo, S. M. Massa, D. Ron, The neurotrophic factor receptor p75 in the rat dorsolateral striatum drives excessive alcohol drinking, J. Neurosci. 36 (39) (2016) 10116–10127.
[34] S. Deyama, R.S. Duman, Neurotrophic mechanisms underlying the rapid and sustained antidepressant actions of ketamine, Pharmacol. Biochem. Behav. 188 (2020), 172837.
[35] E. Dremencov, I. Gispan-Herman, M. Rosenstein, A. Mendelman, D.H. Overstreet, J. Zohar, G. Yadid, The serotonin-dopamine interaction is critical for fast-onset action of antidepressant treatment: in vivo studies in an animal model of depression, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 28 (1) (2004) 141–147.
[36] E. Dremencov, E. Gur, B. Lerer, M.E. Newman, Effects of chronic antidepressants and electroconvulsive shock on serotonergic neurotransmission in the rat hippocampus, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 27 (5) (2003) 729–739.
[37] R.S. Duman, S. Deyama, M.V. Fogaça, Role of BDNF in the pathophysiology and treatment of depression: activity-dependent effects distinguish rapid-acting antidepressants, Eur. J. Neurosci. 53 (2021) 126–139.
[38] P. Durbec, C.V. Marcos-Gutierrez, C. Kilkenny, M. Grigoriou, K. Wartiowaara, P. Suvanto, D. Smith, B. Ponder, F. Costantini, M. Saarma, H. Sariola, V. Pachnis, GDNF signalling through the Ret receptor tyrosine kinase, Nature 381 (6585) (1996) 789–793.
[39] M.F. Egan, M. Kojima, J.H. Callicott, T.E. Goldberg, B.S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, D.R. Weinberger, The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, Cell 112 (2) (2003) 257–269.
[40] R. Einoch, O. Weinreb, N. Mandiuk, M.B.H. Youdim, W. Bilker, H. Silver, The involvement of BDNF-CREB signaling pathways in the pharmacological mechanism of combined SSRI- antipsychotic treatment in schizophrenia, Eur. Neuropsychopharmacol. 27 (5) (2017) 470–483.
[41] V.P. Eswarakumar, I. Lax, J. Schlessinger, Cellular signaling by fibroblast growth factor receptors, Cytokine Growth Factor Rev. 16 (2) (2005) 139–149.
[42] O. Even-Chen, S. Barak, Inhibition of FGF receptor-1 suppresses alcohol consumption: role of pi3 kinase signaling in dorsomedial striatum, J. Neurosci. 39 (2019) 7947–7957.
[43] O. Even-Chen, S. Barak, The role of fibroblast growth factor 2 in drug addiction, Eur. J. Neurosci. 50 (3) (2019) 2552–2561.
[44] O. Even-Chen, Y. Sadot-Sogrin, O. Shaham, S. Barak, Fibroblast growth factor 2 in the dorsomedial striatum is a novel positive regulator of alcohol consumption, J. Neurosci. 37 (36) (2017) 8742–8754.
[45] M.W. Feltenstein, R.E. See, Systems level neuroplasticity in drug addiction, Cold Spring Harbor Perspect. Med. 3 (5) (2013) a011916–a011916.
[46] T. Flores, A.-N. Samaha, J. Stewart, Requirement of endogenous basic fibroblast growth factor for sensitization to amphetamine, J. Neurosci. 20 (2) (2000). RC55–RC55.
[47] C. Flores, J. Stewart, Basic fibroblast growth factor as a mediator of the effects of glutamate in the development of long-lasting sensitization to stimulant drugs: studies in the rat, Psychopharmacology 151 (2-3) (2000) 152–165.
[48] M. Ford-Perriss, H. Abud, M. Murphy, Fibroblast growth factors in the developing central nervous system, Clin. Exp. Pharmacol. Physiol. 28 (7) (2001) 493–503.
[49] C.R. Fuentealba, J.L. Fiedler, F.A. Peralta, A.M. Avalos, F.I. Aguayo, K. P. Morgado-Gallardo, E.E. Aliaga, Region-specific reduction of BDNF protein and transcripts in the hippocampus of juvenile rats prenatally treated with sodium valproate, Front. Mol. Neurosci. 12 (2019).
[50] D. Fukumura, T. Gohongi, A. Kadambi, Y. Izumi, J. Ang, C.-O. Yun, D.G. Buerk, P. L. Huang, R.K. Jain, Predominant role of endothelial nitric oxide synthase in vascular endothelial growth factor-induced angiogenesis and vascular permeability, PNAS 98 (5) (2001) 2604–2609.
[51] F. Fumagalli, R. Molteni, F. Bedogni, M. Gennarelli, J. Perez, G. Racagni, M. A. Riva, Quetiapine regulates FGF-2 and BDNF expression in the hippocampus of animals treated with MK-801, NeuroReport 15 (13) (2004) 2109–2112.
[52] F. Fumagalli, L. Pasquale, G. Racagni, M.A. Riva, Dynamic regulation of fibroblast growth factor 2 (FGF-2) gene expression in the rat brain following single and repeated cocaine administration, J. Neurochem. 96 (4) (2006) 996–1004.
[53] U.E. Ghitza, H. Zhai, P. Wu, M. Airavaara, Y. Shaham, L. Lu, Role of BDNF and GDNF in drug reward and relapse: a review, Neurosci. Biobehav. Rev. 35 (2) (2010) 157–171.
[54] J. Gibon, P.A. Barker, P. Séguéla, Opposing presynaptic roles of BDNF and ProBDNF in the regulation of persistent activity in the entorhinal cortex, Mol. Brain 9 (2016) 23.
[55] J.T. Goncalves, S.T. Schafer, F.H. Gage, Adult neurogenesis in the hippocampus: from stem cells to behavior, Cell 167 (2016) 897–914.
[56] A.M. Gonzalez, M. Berry, P.A. Maher, A. Logan, A. Baird, A comprehensive analysis of the distribution of FGF-2 and FGFR1 in the rat brain, Brain Res. 701 (1-2) (1995) 201–226.
[57] B.M. Graham, R. Richardson, Memory of fearful events: the role of fibroblast growth factor-2 in fear acquisition and extinction, Neuroscience 189 (2011) 156–169.
[58] D.L. Graham, S. Edwards, R.K. Bachtell, R.J. DiLeone, M. Rios, D.W. Self, Dynamic BDNF activity in nucleus accumbens with cocaine use increases self-administration and relapse, Nat. Neurosci. 10 (8) (2007) 1029–1037.
[59] T. Green-Sadan, N. Kinor, I. Roth-Deri, R. Geffen-Aricha, C.J. Schindler, G. Yadid, Transplantation of glial cell line-derived neurotrophic factor-expressing cells into the striatum and nucleus accumbens attenuates acquisition of cocaine self-administration in rats, Eur. J. Neurosci. 18 (7) (2003) 2093–2098.
[60] T. Green-Sadan, Y. Kuttner, T. Lublin-Tennenbaum, N. Kinor, Y. Boguslavsky, S. Margel, G. Yadid, Glial cell line-derived neurotrophic factor-conjugated nanoparticles suppress acquisition of cocaine self-administration in rats, Exp. Neurol. 194 (1) (2005) 97–105.
[61] P.L. Greer, M.E. Greenberg, From synapse to nucleus: calcium-dependent gene transcription in the control of synapse development and function, Neuron 59 (2008) 846–860.
[62] C. Grothe, M. Timmer, The physiological and pharmacological role of basic fibroblast growth factor in the dopaminergic nigrostriatal system, Brain Res. Rev. 54 (1) (2007) 80–91.
[63] M. Hafenbreidel, R.C. Twining, C. Rafa Todd, D. Mueller, Blocking Infralimbic Basic Fibroblast Growth Factor (bFGF or FGF2) Facilitates Extinction of Drug Seeking After Cocaine Self-Administration, Neuropsychopharmacology (2015).

[64] M. Harb, J. Jagusch, A. Durairaja, T. Endres, V. Lessmann, M. Fendt, BDNF haploinsufficiency induces behavioral endophenotypes of schizophrenia in male mice that are rescued by enriched environment, Transl. Psychiatry 11 (2021) 233.

[65] H.L. Haun, W.C. Griffin, M.F. Lopez, M.G. Solomon, P.J. Mulholland, J. J. Woodward, J.F. McGinty, D. Ron, H.C. Becker, Increasing Brain-Derived Neurotrophic Factor (BDNF) in medial prefrontal cortex selectively reduces excessive drinking in ethanol dependent mice, Neuropharmacology 140 (2018) 35–42.

[66] M.C. Hearing, S.W. Miller, R.E. See, J.F. McGinty, Relapse to cocaine seeking increases activity-regulated gene expression differentially in the prefrontal cortex of abstinent rats, Psychopharmacology 198 (1) (2008) 77–91.

[67] J.G. Hensler, E.E. Ladenheim, W.E. Lyons, Ethanol consumption and serotonin-1A (5-HT1A) receptor function in heterozygous BDNF (+/-) mice, J. Neurochem. 85 (2003) 1139–1147.

[68] R.A. Hopper, J. Garthwaite, Tonic and phasic nitric oxide signals in hippocampal long-term potentiation, J. Neurosci. 26 (2006) 11513.

[69] B.A. Horger, C.A. Iyasere, M.T. Berhow, C.J. Messer, E.J. Nestler, J.R. Taylor, Enhancement of locomotor activity and conditioned reward to cocaine by brain-derived neurotrophic factor, J. Neurosci. 19 (10) (1999) 4110–4122.

[70] L. Hromadkova, D. Bezdekova, J. Pala, S. Schedin-Weiss, L.O. Tjernberg, C. Hoschl, S.V. Ovsepian, Brain-derived neurotrophic factor (BDNF) promotes molecular polarization and differentiation of immature neuroblastoma cells into definitive neurons, Biochim. Biophys. Acta 1867 (2020), 118737.

[71] J.G. Hunsberger, S.S. Newton, A.H. Bennett, C.H. Duman, D.S. Russell, S. R. Salton, R.S. Duman, Antidepressant actions of the exercise-regulated gene VGF, Nat. Med. 13 (12) (2007) 1476–1482.

[72] S.-R. Hwang, C.-Y. Kim, K.-M. Shin, J.-H. Jo, H.-A. Kim, Y. Heo, Altered expression levels of neurodevelopmental proteins in fetal brains of BTBR T+tf/J mice with autism-like behavioral characteristics, J. Toxicol. Environ. Health A 78 (8) (2015) 516–523.

[73] A. Iannitelli, A. Quartini, P. Tirassa, G. Bersani, Schizophrenia and neurogenesis: A stem cell approach, Neurosci. Biobehav. Rev. 80 (2017) 414–442.

[74] J. Ishiyama, H. Saito, K. Abe, Epidermal growth factor and basic fibroblast growth factor promote the generation of long-term potentiation in the dentate gyrus of anaesthetized rats, Neurosci. Res. 12 (3) (1991) 403–411.

[75] J. Jeanblanc, D.-Y. He, S. Carnicella, V. Kharazia, P.H. Janak, D. Ron, Endogenous BDNF in the dorsolateral striatum gates alcohol drinking, J. Neurosci. 29 (43) (2009) 13494–13502.

[76] J. Jeanblanc, M.L. Logrip, P.H. Janak, D. Ron, BDNF-mediated regulation of ethanol consumption requires the activation of the MAP kinase pathway and protein synthesis, Eur. J. Neurosci. 37 (4) (2013) 607–612.

[77] C. Jiang, W.-J. Lin, M. Sadahiro, B. Labonté, C. Menard, M.L. Pfau, C. A. Tamminga, G. Turecki, E.J. Nestler, S.J. Russo, S.R. Salton, VGF function in depression and antidepressant efficacy, Mol. Psychiatry 23 (7) (2018) 1632–1642.

[78] C. Jiang, W.-J. Lin, S.R. Salton, Role of a VGF/BDNF/TrkB autoregulatory feedback loop in rapid-acting antidepressant efficacy, J. Mol. Neurosci. 68 (3) (2019) 504–509.

[79] S. Jing, D. Wen, Y. Yu, P.L. Holst, Y. Luo, M. Fang, R. Tamir, L. Antonio, Z. Hu, R. Cupples, J.C. Louis, S. Hu, B.W. Altrock, G.M. Fox, GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-alpha, a novel receptor for GDNF, Cell 85 (1996) 1113–1124.

[80] P. Jorratt, C. Hoschl, S.V. Ovsepian, Endogenous antagonists of N-methyl-d-aspartate receptor in schizophrenia, Alzheimers Dement. (2020).

[81] R. Khan, D. Kulasiri, S. Samarasinghe, Functional repertoire of protein kinases and phosphatases in synaptic plasticity and associated neurological disorders, Neural Regen. Res. 16 (2021) 1150–1157.

[82] S.W. Kim, K.J. Cho, Activity-dependent alterations in the sensitivity to BDNF-TrkB signaling may promote excessive dendritic arborization and spinogenesis in fragile X syndrome in order to compensate for compromised postsynaptic activity, Med. Hypotheses 83 (4) (2014) 429–435.

[83] T.B. Kirsten, R.C. Casarin, M.M. Bernardi, L.F. Felicio, Pioglitazone abolishes cognition impairments as well as BDNF and neurotensin disturbances in a rat model of autism, Biology Open 8 (2019) bio041327.

[84] T.B. Kirsten, N. Queiroz-Hazarbassanov, M.M. Bernardi, L.F. Felicio, Prenatal zinc prevents communication impairments and BDNF disturbance in a rat model of autism induced by prenatal lipopolysaccharide exposure, Life Sci. 130 (2015) 12–17.

[85] M. Koskela, S. Bäck, V. Võikar, C.T. Richie, A. Domanskyi, B.K. Harvey, M. Airavaara, Update of neurotrophic factors in neurobiology of addiction and future directions, Neurobiol. Dis. 97 (2017) 189–200.

[86] P. Kowiański, G. Lietzau, E. Czuba, M. Waśkow, A. Steliga, J. Moryś, BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity, Cell. Mol. Neurobiol. 38 (2018) 579–593.

[87] Z. Kristofikova, J. Sirova, J. Klaschka, S.V. Ovsepian, Acute and chronic sleep deprivation-related changes in N-methyl-D-aspartate receptor-nitric oxide signalling in the rat cerebral cortex with reference to aging and brain lateralization, Int. J. Mol. Sci. 20 (13) (2019) 3273, https://doi.org/10.3390/ijms20133273.

[88] K.E. Larsen, S.C. Benn, I. Ay, R.J. Chian, S.A. Celia, M.P. Remington, M. Bejarano, M. Liu, J. Ross, P. Carmillo, D. Sah, K.A. Phillips, D. Sulzer, R.B. Pepinsky, P. S. Fishman, R.H. Brown Jr., J.W. Francis, A glial cell line-derived neurotrophic factor (GDNF):tetanus toxin fragment C protein conjugate improves delivery of GDNF to spinal cord motor neurons in mice, Brain Res. 1120 (2006) 1–12.

[89] C. Li, M. Li, H. Yu, X. Shen, J. Wang, X. Sun, Q. Wang, C. Wang, Neuropeptide VGF C-terminal peptide TLQP-62 alleviates lipopolysaccharide-induced memory deficits and anxiety-like and depression-like behaviors in mice: the role of BDNF/TrkB signaling, ACS Chem. Neurosci. 8 (9) (2017) 2005–2018.

[90] M. Li, W. Wang, L. Sun, W. Du, H. Zhou, F. Shao, Chronic clozapine treatment improves the alterations of prepulse inhibition and BDNF mRNA expression in the medial prefrontal cortex that are induced by adolescent social isolation, Behav. Pharmacol. 30 (2019) 311–319.

[91] W. Li, L. Pozzo-Miller, BDNF deregulation in Rett syndrome, Neuropharmacology 76 (2014) 737–746.

[92] P. Licznerski, R.S. Duman, Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression, Neuroscience 251 (2013) 33–50.

[93] L.F. Lin, D.H. Doherty, J.D. Lile, S. Bektesh, F. Collins, GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons, Science 260 (1993) 1130–1132.

[94] W.-J. Lin, C. Jiang, M. Sadahiro, O. Bozdagi, L. Vulchanova, C.M. Alberini, S. R. Salton, VGF and its C-terminal peptide TLQP-62 regulate memory formation in hippocampus via a BDNF-TrkB-dependent mechanism, J. Neurosci. 35 (2015) 10343.

[95] B.K. Lipska, G.E. Jaskiw, D.R. Weinberger, Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia, Neuropsychopharmacology 9 (1993) 67–75.

[96] M. Liran, N. Rahamim, D. Ron, S. Barak, Growth factors and alcohol use disorder, Cold Spring Harbor Perspect. Med. 10 (12) (2020) a039271, https://doi.org/10.1101/cshperspect.a039271.

[97] S.-H. Liu, X.-J. Shi, F.-C. Fan, Y. Cheng, Peripheral blood neurotrophic factor levels in children with autism spectrum disorder: a meta-analysis, Sci. Rep. 11 (2021) 15.

[98] M.L. Logrip, S. Barak, V. Warnault, D. Ron, Corticostriatal BDNF and alcohol addiction, Brain Res. 1628 (2015) 60–67.

[99] L. Lu, J. Dempsey, S.Y. Liu, J.M. Bossert, Y. Shaham, A single infusion of brain-derived neurotrophic factor into the ventral tegmental area induces long-lasting potentiation of cocaine seeking after withdrawal, J. Neurosci. 24 (2004) 1604–1611.

[100] L. Lu, X. Wang, P. Wu, C. Xu, M. Zhao, M. Morales, B.K. Harvey, B.J. Hoffer, Y. Shaham, Role of ventral tegmental area glial cell line-derived neurotrophic factor in incubation of cocaine craving, Biol. Psychiatry 66 (2) (2009) 137–145.

[101] C. Luscher, R.C. Malenka, Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling, Neuron 69 (2011) 650–663.

[102] D. Lv, Y. Chen, M. Shen, X. Liu, Y. Zhang, J. Xu, C. Wang, Mechanisms underlying the rapid-acting antidepressant-like effects of neuropeptide VGF (non-acronymic) C-terminal peptide TLQP-62, Neuropharmacology 143 (2018) 317–326.

[103] Y.L. Ma, H.L. Wang, H.C. Wu, C.L. Wei, E.H.Y. Lee, Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats, Neuroscience 82 (4) (1997) 957–967.

[104] T.R. Madhav, Q. Pei, T.S. Zetterström, Serotonergic cells of the rat raphe nuclei express mRNA of tyrosine kinase B (trkB), the high-affinity receptor for brain derived neurotrophic factor (BDNF), Brain Res. Mol. Brain Res. 93 (2001) 56–63.

[105] H.B. Maier, M. Neyazi, A. Neyazi, T. Hillemacher, H. Pathak, M. Rhein, S. Bleich, K. Goltseker, Y. Sadot-Sogrin, O. Even-Chen, H. Frieling, S. Barak, Alcohol consumption alters Gdnf promoter methylation and expression in rats, J. Psychiatr. Res. 121 (2020) 1–9.

[106] M.E. Maragnoli, F. Fumagalli, M. Gennarelli, G. Racagni, M.A. Riva, Fluoxetine and olanzapine have synergistic effects in the modulation of fibroblast growth factor 2 expression within the rat brain, Biol. Psychiatry 55 (11) (2004) 1095–1102.

[107] S. Matsushita, M. Kimura, T. Miyakawa, A. Yoshino, M. Murayama, T. Masaki, S. Higuchi, Association study of brain-derived neurotrophic factor gene polymorphism and alcoholism, Alcohol. Clin. Exp. Res. 28 (11) (2004) 1609–1612.

[108] B.S. McEwen, C. Nasca, J.D. Gray, Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex, Neuropsychopharmacology 41 (2016) 3–23.

[109] N.N. McGough, D.-Y. He, M.L. Logrip, J. Jeanblanc, K. Phamluong, K. Luong, V. Kharazia, P.H. Janak, D. Ron, RACK1 and brain-derived neurotrophic factor: a homeostatic pathway that regulates alcohol addiction, J. Neurosci. 24 (2004) 10542–10552.

[110] W. McIsaac, A.V. Ferguson, Glucose concentrations modulate brain-derived neurotrophic factor responsiveness of neurones in the paraventricular nucleus of the hypothalamus, J. Neuroendocrinol. 29 (4) (2017), https://doi.org/10.1111/jne.12464.

[111] C.J. Messer, A.J. Eisch, W.A. Carlezon, K. Whisler, L. Shen, D.H. Wolf, H. Westphal, F. Collins, D.S. Russell, E.J. Nestler, Role for GDNF in biochemical and behavioral adaptations to drugs of abuse, Neuron 26 (1) (2000) 247–257.

[112] R. Molteni, B.K. Lipska, D.R. Weinberger, G. Racagni, M.A. Riva, Developmental and stress-related changes of neurotrophic factor gene expression in an animal model of schizophrenia, Mol. Psychiatry 6 (3) (2001) 285–292.

[113] R. Mongeau, P. Blier, C. de Montigny, The serotonergic and noradrenergic systems of the hippocampus: their interactions and the effects of antidepressant treatments, Brain Res. Brain Res. Rev. 23 (3) (1997) 145–195.

[114] V.S. Naumenko, D.V. Bazovkina, M.V. Morozova, N.K. Popova, Effects of brain-derived and glial cell line-derived neurotrophic factors on startle response and disrupted prepulse inhibition in mice of DBA/2J inbred strain, Neurosci. Lett. 550 (2013) 115–118.

[115] T. Nickl-Jockschat, T.M. Michel, The role of neurotrophic factors in autism, Mol. Psychiatry 16 (5) (2011) 478–490.

[116] M. Niwa, A. Nitta, K. Yamada, T. Nabeshima, The roles of glial cell line-derived neurotrophic factor, tumor necrosis factor-alpha, and an inducer of these factors in drug dependence, J. Pharmacol. Sci. (2007).
[117] M.J. Notaras, R.A. Hill, J.A. Gogos, M. van den Buuse, BDNF Val66Met genotype interacts with a history of simulated stress exposure to regulate sensorimotor gating and startle reactivity, Schizophr. Bull. 43 (2017) 665–672.
[118] V.B. O'Leary, S.V. Ovsepian, M. Bodeker, J.O. Dolly, Improved lentiviral transduction of ALS motoneurons in vivo via dual targeting, Mol. Pharm. 10 (11) (2013) 4195–4206.
[119] C. Ortega-de San Luis, A. Pascual, Simultaneous detection of both GDNF and GFRalpha1 expression patterns in the mouse central nervous system, Front. Neuroanat. 10 (2016) 73.
[120] S.V. Ovespian, M. Bodeker, V.B. O'Leary, G.W. Lawrence, J. Oliver Dolly, Internalization and retrograde axonal trafficking of tetanus toxin in motor neurons and trans-synaptic propagation at central synapses exceed those of its C-terminal-binding fragments, Brain Struct. Funct. 220 (3) (2015) 1825–1838.
[121] S.V. Ovsepian, V.B. O'Leary, V. Ntziachristos, J.O. Dolly, Circumventing brain barriers: nanovehicles for retroaxonal therapeutic delivery, Trends Mol. Med. 22 (2016) 983–993.
[122] S.C. Pandey, H. Zhang, A. Roy, K. Misra, Central and medial amygdaloid brain-derived neurotrophic factor signaling plays a critical role in alcohol-drinking and anxiety-like behaviors, J. Neurosci. 26 (32) (2006) 8320–8331.
[123] M. Pavlovicova, L. Lacinova, E. Dremencov, Cellular and molecular mechanisms underlying the treatment of depression: focusing on hippocampal G-protein-coupled receptors and voltage-dependent calcium channels, Gen. Physiol. Biophys. 34 (2015) 353–366.
[124] A.M. Payne, M.L. Messi, Z. Zheng, O. Delbono, Motor neuron targeting of IGF-1 attenuates age-related external Ca2+-dependent skeletal muscle contraction in senescent mice, Exp. Gerontol. 42 (4) (2007) 309–319.
[125] A.M. Payne, Z. Zheng, M.L. Messi, C.E. Milligan, E. Gonzalez, O. Delbono, Motor neurone targeting of IGF-1 prevents specific force decline in ageing mouse muscle, J. Physiol. 570 (2006) 283–294.
[126] L. Pigeon, C. Gonçalves, D. Gosset, C. Pichon, P. Midoux, An E3–14.7K peptide that promotes microtubules-mediated transport of plasmid DNA increases polyplexes transfection efficiency, Small 9 (22) (2013) 3845–3851.
[127] S. Pilakka-Kanthikeel, V.S.R. Atluri, V. Sagar, S.K. Saxena, M. Nair, S.J. Buch, Targeted brain derived neurotropic factors (BDNF) delivery across the blood-brain barrier for neuro-protection using magnetic nano carriers: an in-vitro study, PLoS ONE 8 (4) (2013) e62241.
[128] A. Pillai, S.P. Mahadik, Differential effects of haloperidol and olanzapine on levels of vascular endothelial growth factor and angiogenesis in rat hippocampus, Schizophr. Res. 87 (1-3) (2006) 48–59.
[129] N.-A.-M. Pochon, A. Menoud, J.L. Tseng, A.D. Zurn, P. Aebischer, Neuronal GDNF expression in the adult rat nervous system identified by in situ hybridization, Eur. J. Neurosci. 9 (3) (1997) 463–471.
[130] A. Reif, A. Schmitt, S. Fritzen, S. Chourbaji, C. Bartsch, A. Urani, M. Wycislo, R. Mossner, C. Sommer, P. Gass, K.-P. Lesch, Differential effect of endothelial nitric oxide synthase (NOS-III) on the regulation of adult neurogenesis and behaviour, Eur. J. Neurosci. 20 (4) (2004) 885–895.
[131] D. Reim, M.J. Schmeisser, Neurotrophic factors in mouse models of autism spectrum disorder: focus on BDNF and IGF-1, Adv. Anat. Embryol. Cell Biol. 224 (2017) 121–134.
[132] B. Reuss, O. von Bohlen Halbach, Fibroblast growth factors and their receptors in the central nervous system, Cell Tissue Res. 313 (2003) 139–157.
[133] U. Roine, T. Roine, J. Salmi, T. Nieminen-von Wendt, P. Tani, S. Leppamaki, P. Rintahaka, K. Caeyenberghs, A. Leemans, M. Sams, Abnormal wiring of the connectome in adults with high-functioning autism spectrum disorder, Mol Autism 6 (2015) 65.
[134] D. Ron, S. Barak, Molecular mechanisms underlying alcohol-drinking behaviours, Nat. Rev. Neurosci. 17 (9) (2016) 576–591.
[135] F.I. Roullet, L. Wollaston, D. deCatanzaro, J.A. Foster, Behavioral and molecular changes in the mouse in response to prenatal exposure to the anti-epileptic drug valproic acid, Neuroscience 170 (2) (2010) 514–522.
[136] S. Roux, C. Saint Cloment, T. Curie, E. Girard, F.J. Miana Mena, J. Barbier, R. Osta, J. Molgo, P. Brulet, Brain-derived neurotrophic factor facilitates in vivo internalization of tetanus neurotoxin C-terminal fragment fusion proteins in mature mouse motor nerve terminals, Eur. J. Neurosci. 24 (2006) 1546–1554.
[137] G. Sadri-Vakili, V. Kumaresan, H.D. Schmidt, K.R. Famous, P. Chawla, F. M. Vassoler, R.P. Overland, E. Xia, C.E. Bass, E.F. Terwilliger, R.C. Pierce, J.-H.-J. Cha, Cocaine-induced chromatin remodeling increases brain-derived neurotrophic factor transcription in the rat medial prefrontal cortex, which alters the reinforcing efficacy of cocaine, J. Neurosci. 30 (35) (2010) 11735–11744.
[138] M. Savolainen, D. Emerich, J.H. Kordower, Disease modification through trophic factor delivery, Methods Mol. Biol. 1780 (2018) 525–547.
[139] M.L. Scattoni, A. Martire, G. Cartocci, A. Ferrante, L. Ricceri, Reduced social interaction, behavioural flexibility and BDNF signalling in the BTBR T+ tf/J strain, a mouse model of autism, Behav. Brain Res. 251 (2013) 35–40.
[140] P.E. Seamster, M. Loewenberg, J. Pascal, A. Chauviere, A. Gonzales, V. Cristini, E. L. Bearer, Quantitative measurements and modeling of cargo-motor interactions during fast transport in the living axon, Phys. Biol. 9 (2012), 055005.
[141] G. Seghezzi, S. Patel, C.J. Ren, A. Gualandris, G. Pintucci, E.S. Robbins, R. L. Shapiro, A.C. Galloway, D.B. Rifkin, P. Mignatti, Fibroblast growth factor-2 (FGF-2) induces vascular endothelial growth factor (VEGF) expression in the endothelial cells of forming capillaries: an autocrine mechanism contributing to angiogenesis, J. Cell Biol. 141 (1998) 1659–1673.
[142] M. Segura, C. Pedreño, J. Obiols, R. Taurines, M. Pàmias, E. Grünblatt, A. Gella, Neurotrophin blood-based gene expression and social cognition analysis in patients with autism spectrum disorder, Neurogenetics 16 (2) (2015) 123–131.
[143] J.A. Siuciak, C. Boylan, M. Fritsche, C.A. Altar, R.M. Lindsay, BDNF increases monoaminergic activity in rat brain following intracerebroventricular or intraparenchymal administration, Brain Res. 710 (1-2) (1996) 11–20.
[144] K. Skogstrand, C.M. Hagen, N. Borbye-Lorenzen, M. Christiansen, J. Bybjerg-Grauholm, M. Bækvad-Hansen, T. Werge, A. Børglum, O. Mors, M. Nordentoft, P. B. Mortensen, D.M. Hougaard, Reduced neonatal brain-derived neurotrophic factor is associated with autism spectrum disorders, Transl. Psychiatry 9 (2019) 252.
[145] D.T. Stephenson, S.M. O'Neill, S. Narayan, A. Tiwari, E. Arnold, H.D. Samaroo, F. Du, R.H. Ring, B. Campbell, M. Pletcher, V.A. Vaidya, D. Morton, Histopathologic characterization of the BTBR mouse model of autistic-like behavior reveals selective changes in neurodevelopmental proteins and adult hippocampal neurogenesis, Mol. Autism. 2 (2011) 7.
[146] N.R. Swerdlow, G.A. Light, Animal models of deficient sensorimotor gating in schizophrenia: are they still relevant? Curr. Top Behav. Neurosci. 28 (2016) 305–325.
[147] M.M. Tang, W.J. Lin, Y.Q. Pan, Y.C. Li, Fibroblast growth factor 2 modulates hippocampal microglia activation in a neuroinflammation induced model of depression, Front. Cell. Neurosci. 12 (2018) 255.
[148] M. Terasaki, A. Schmidek, J.A. Galbraith, P.E. Gallant, T.S. Reese, Transport of cytoskeletal elements in the squid giant axon, PNAS 92 (25) (1995) 11500–11503.
[149] S. Thakker-Varia, J. Behnke, D. Doobin, V. Dalal, K. Thakkar, F. Khadim, E. Wilson, A. Palmieri, H. Antila, T. Rantamaki, J. Alder, VGF (TLQP-62)-induced neurogenesis targets early phase neural progenitor cells in the adult hippocampus and requires glutamate and BDNF signaling, Stem Cell Res. 12 (3) (2014) 762–777.
[150] S. Thakker-Varia, J.J. Krol, J. Nettleton, P.M. Bilimoria, D.A. Bangasser, T. J. Shors, I.B. Black, J. Alder, The neuropeptide VGF produces antidepressant-like behavioral effects and enhances proliferation in the hippocampus, J. Neurosci. 27 (45) (2007) 12156–12167.
[151] N.N. Tirko, K.W. Eyring, I. Carcea, M. Mitre, M.V. Chao, R.C. Froemke, R. W. Tsien, Oxytocin transforms firing mode of CA2 hippocampal neurons, Neuron 100 (3) (2018) 593–608.e3.
[152] B.T.D. Tobe, A.M. Crain, A.M. Winquist, B. Calabrese, H. Makihara, W.-ning. Zhao, J. Lalonde, H. Nakamura, G. Konopaske, M. Sidor, C.D. Pernia, N. Yamashita, M. Wada, Y. Inoue, F. Nakamura, S.D. Sheridan, R.W. Logan, M. Brandel, D. Wu, J. Hunsberger, L. Dorsett, C. Duerr, R.C.B. Basa, M. J. McCarthy, N.D. Udeshi, P. Mertins, S.A. Carr, G.A. Rouleau, L. Mastrangelo, J. Li, G.J. Gutierrez, L.M. Brill, N. Venizelos, G. Chen, J.S. Nye, H. Manji, J. H. Price, C.A. McClung, H.S. Akiskal, M. Alda, D.-M. Chuang, J.T. Coyle, Y. Liu, Y. D. Teng, T. Ohshima, K. Mikoshiba, R.L. Sidman, S. Halpain, S.J. Haggarty, Y. Goshima, E.Y. Snyder, Probing the lithium-response pathway in hiPSCs implicates the phosphoregulatory set-point for a cytoskeletal modulator in bipolar pathogenesis, PNAS 114 (22) (2017) E4462–E4471.
[153] J.M. Toivonen, S. Oliván, R. Osta, Tetanus toxin C-fragment: the courier and the cure? Toxins (Basel) 2 (11) (2010) 2622–2644.
[154] C.A. Turner, N. Capriles, S.B. Flagel, J.A. Perez, S.M. Clinton, S.J. Watson, H. Akil, Neonatal FGF2 alters cocaine self-administration in the adult rat, Pharmacol. Biochem. Behav. 92 (1) (2009) 100–104.
[155] C.A. Turner, E.L. Gula, L.P. Taylor, S.J. Watson, H. Akil, Antidepressant-like effects of intracerebroventricular FGF2 in rats, Brain Res. 1224 (2008) 63–68.
[156] M. Uutela, J. Lindholm, V. Louhivuori, H. Wei, L.M. Louhivuori, A. Pertovaara, K. Åkerman, E. Castrén, M.L. Castrén, Reduction of BDNF expression in Fmr1 knockout mice worsens cognitive deficits but improves hyperactivity and sensorimotor deficits, Genes, Brain Behav. 11 (2012) 513–523.
[157] M. van den Buuse, D. Biel, K. Radscheit, Does genetic BDNF deficiency in rats interact with neurotransmitter control of prepulse inhibition? Implications for schizophrenia, Prog. Neuropsychopharmacol. Biol. Psychiatry 75 (2017) 192–198.
[158] H. Vargas-Perez, R. Ting-A-Kee, C.H. Walton, D.M. Hansen, R. Razavi, L. Clarke, M.R. Bufalino, D.W. Allison, S.C. Steffensen, D. van der Kooy, Ventral tegmental area BDNF induces an opiate-dependent-like reward state in naive rats, Science 324 (5935) (2009) 1732–1734.
[159] J.P. Wagner, I.B. Black, E. DiCicco-Bloom, Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor, J. Neurosci. 19 (14) (1999) 6006–6016.
[160] P. Walicke, W.M. Cowan, N. Ueno, A. Baird, R. Guillemin, Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension, PNAS 83 (9) (1986) 3012–3016.
[161] L. Wan, Y. Xie, L. Su, Y. Liu, Y. Wang, Z. Wang, RACK1 affects morphine reward via BDNF, Brain Res. 1416 (2011) 26–34.
[162] V. Warnault, E. Darcq, N. Morisot, K. Phamluong, L. Wilbrecht, S.M. Massa, F. M. Longo, D. Ron, The BDNF valine 68 to methionine polymorphism increases compulsive alcohol drinking in mice that is reversed by tropomyosin receptor kinase B activation, Biol. Psychiat. 79 (6) (2016) 463–473.
[163] T.W. Whitfield, X. Shi, W.-L. Sun, J.F. McGinty, The suppressive effect of an intra-prefrontal cortical infusion of BDNF on cocaine-seeking is Trk receptor and extracellular signal-regulated protein kinase mitogen-activated protein kinase dependent, J. Neurosci. 31 (3) (2011) 834–842.
[164] M. Wojnar, K.J. Brower, S. Strobbe, M. Ilgen, H. Matsumoto, I. Nowosad, E. Sliwerska, M. Burmeister, Association between Val66Met brain-derived

neurotrophic factor (BDNF) gene polymorphism and post-treatment relapse in alcohol dependence, Alcohol. Clin. Exp. Res. 33 (2009) 693-702.
[165] S. Yoshimura, Y. Takagi, J. Harada, T. Teramoto, S.S. Thomas, C. Waeber, J. C. Bakowska, X.O. Breakefield, M.A. Moskowitz, FGF-2 regulation of neurogenesis in adult hippocampus after brain injury, PNAS 98 (10) (2001) 5874–5879.
[166] S. Yoshimura, T. Teramoto, M.J. Whalen, M.C. Irizarry, Y. Takagi, J. Qiu, J. Harada, C. Waeber, X.O. Breakefield, M.A. Moskowitz, FGF-2 regulates neurogenesis and degeneration in the dentate gyrus after traumatic brain injury in mice, J. Clin. Invest. 112 (8) (2003) 1202–1210.
[167] Z. Zheng, L. Zhang, T. Zhu, J. Huang, Y. Qu, D. Mu, Peripheral brain-derived neurotrophic factor in autism spectrum disorder: a systematic review and meta-analysis, Sci. Rep. 6 (2016) 31241.
[168] J. Zohar, P. Blier, J.S. Stahl, H.J. Moller, D.J. Kupfer, C. Correll, H. Uchida, F. Drago, B.J. Goodwin, D. Nutt, Neurosci. Nomenclul. (2019).