Review Article • DOI: 10.2478/s13380-013-0103-8 • Translational Neuroscience • 4(1) • 2013 • 46-58

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Translational Neuroscience

THE ROLE OF NEUROTROPHINS IN MAJOR DEPRESSIVE DISORDER

Cheng Jiang[1,4],
Stephen R. Salton[1,2,3]*

[1]Fishberg Department of Neuroscience,

[2]Brookdale Department of Geriatrics and Palliative Medicine,

[3]Friedman Brain Institute, and

[4]Graduate School of Biomedical Sciences, Mount Sinai School of Medicine, New York, NY 10029 USA

Received 28 November 2012
accepted 04 January 2013

Abstract

Neurotrophins and other growth factors have been advanced as critical modulators of depressive behavior. Support for this model is based on analyses of knockout and transgenic mouse models, human genetic studies, and screens for gene products that are regulated by depressive behavior and/or antidepressants. Even subtle alteration in the regulated secretion of brain-derived neurotrophic factor (BDNF), for example, due to a single nucleotide polymorphism (SNP)-encoded Val-Met substitution in proBDNF that affects processing and sorting, impacts behavior and cognition. Alterations in growth factor expression result in changes in neurogenesis as well as structural changes in neuronal cytoarchitecture, including effects on dendritic length and spine density, in the hippocampus, nucleus accumbens, and prefrontal cortex. These changes have the potential to impact the plasticity and stability of synapses in the CNS, and the complex brain circuitry that regulates behavior. Here we review the role that neurotrophins play in the modulation of depressive behavior, and the downstream signaling targets they regulate that potentially mediate these behavioral pro-depressant and antidepressant effects.

Keywords

• Antidepressant • Arc • Brain-Derived Neurotrophic Factor (BDNF) • Depression • Ketamine • Nerve Growth Factor (NGF) • Neuritin • Neurtrophin-3 (NT-3) • Trk • VGF

Overview of neurotrophins

Neurotrophins are a family of secreted growth factors that regulate survival, growth, differentiation and maintenance of neurons in both CNS and PNS [1-3]. Four neurotrophins, nerve growth factors (NGF) [4], brain-derived neurotrophic factor (BDNF) [5], neurotrophin-3 (NT-3) [6] and neurotrophin-4/5 (NT-4/5) [7] have been identified and their function in the nervous system has been widely explored. The various effects of different neurotrophins on neurons can be attributed to their selective binding to two classes of receptors, the Trk family of receptor tyrosine kinases and the p75 neurotrophin receptor (p75NTR). Specifically, NGF binds to TrkA, BDNF and NT-4/5 bind to TrkB, NT-3 to TrkC and all four neurotrophins interact with p75NTR [8]. Recent studies have further revealed that immature pro-neurotrophins, which have not been proteolytically processed, and mature neurotrophins bind to different receptors. For example, pro-BDNF selectively binds p75NTR with the aid of sortilin to induce apoptosis [9], long-term depression (LTD) [10], and reduce dendritic complexity and spine density [11] in the hippocampus. The binding of neurotrophins to their cognate receptors activates different intracellular signaling cascades, including the Ras/ERK (MAPK) pathway, the PLCγ pathway and the PI3K/Akt pathway [12], which mediate both unique and overlapping functions of neurotrophins in the CNS and PNS [13]. Thus there are multiple levels by which neurotrophin actions can be modulated to impact depression and the response to antidepressants, including regulation of their synthesis, secretion, and signaling, all of which are discussed below.

Is BDNF a biomarker of human depression?

Recognition by Duman and colleagues [14] that antidepressant treatment was associated with increased BDNF expression in the hippocampus led to further investigation of the role that neurotrophins play in depression and in the response to antidepressant treatment, both in human subjects and animal models of depression. Analysis of postmortem human brain tissues has revealed reduced BDNF mRNA and protein levels in hippocampus, prefrontal cortex and amygdala of depressed patients and suicide subjects [15-17]. Moreover, antidepressant treatments were found to increase BDNF protein levels in different areas of hippocampus [18].

Given the limitations of human postmortem studies, BDNF levels in blood samples have been widely studied. Reduced levels of mature BDNF, but not its precursor proBDNF, were reported in sera and plasma from depressed patients [19-22], and this reduction of BDNF was normalized by antidepressant treatment [23-25]. In addition, reduced BDNF content in platelets and decreased BDNF mRNA expression in peripheral blood lymphocytes and mononuclear cells were also reported in depressed patients [26-28]. Reduced BDNF levels in both serum and plasma have also been found in depressed patients who have attempted suicide, compared to non-suicidal depressed patients or healthy controls, and in subjects with depressive episodes of longer

* E-mail: stephen.salton@mssm.edu

duration or recurrent episodes of depression [29,30]. The association of lower serum BDNF levels with depressive personality traits in healthy human subjects suggests a possible link between BDNF levels and the susceptibility of healthy humans to depression [31]. Circulating BDNF may therefore be a potential biomarker for major depression, and although this could reinforce the relevance of identifying therapeutic targets in the peripheral circulation, recent studies demonstrate a positive correlation between BDNF levels in blood and hippocampus [32]. Further investigation of the mechanistic importance of CNS BDNF in depression and antidepressant efficacy, and the determination of its site of action within the brain, have relied on the animal studies that are discussed below.

Does depressive behavior regulate BDNF expression in animal models of depression?

Previous studies have shown that many stressors including immobilization, electrical foot shock, restraint, forced swimming, social deprivation and chronic social defeat down-regulate BDNF mRNA and protein levels in different brain regions, in particular hippocampus [33-39]. This reduction in BDNF expression is associated with the development of depressive-like behavior. What are the underlying mechanisms that control BDNF levels in depressed and antidepressant-treated animals? Stress-induced down-regulation of BDNF splice variant mRNAs in hippocampus was found to be associated with increased histone methylation of the respective BDNF promoters [40]. Antidepressant treatment reversed this down-regulation by promoting histone acetylation at these promoters, indicating that stress and antidepressants exert their effects on BDNF expression at least in part via chromatin modification.

However, a number of reports demonstrate opposing changes or no change in BDNF expression in animal models of depression and antidepressant efficacy [41,42]. Moreover, many studies have shown that both acute and chronic stress increase BDNF mRNA and protein levels in hippocampus [43-47], evoking speculation that increased BDNF levels after stress might serve as a protective mechanism to offset the destructive effects of stress on the hippocampus. Alternatively, these discrepant findings could have resulted from the use of different stressors to induce behavior, or the different procedures used to quantify BDNF levels [48]. Age might also influence BDNF levels following stress, as social defeat up-regulates hippocampal BDNF mRNA expression in adolescent but not adult rats [49].

In other brain regions, increased BDNF mRNA levels were detected in medial prefrontal cortex and amygdala within 2 hours of the last social defeat episode [50], in agreement with previous studies showing that BDNF mRNA levels were initially induced in these regions but were reduced 24 hours later [37]. Berton et al. [51] reported increased BDNF expression in nucleus accumbens (NAc) following social defeat, correlating this increase of BDNF mRNA and protein in NAc to the development of susceptibility to depression. Taken together, these human and animal studies demonstrate depression-associated and region-specific changes in BDNF protein and mRNA levels. Manipulation of BDNF expression in animal models with regional specificity should therefore provide insight into potential mechanisms that underlie major depressive disorder in humans, and these studies are described below.

What role does BDNF play in antidepressant treatment?

Altered levels of BDNF are correlated with depression, and antidepressant treatments exert their effects by reversing this alteration [52-54]. Many studies have demonstrated that almost all antidepressant treatments or activities, including electroconvulsive therapy, antidepressant drugs, exercise and environmental enrichment up-regulate BDNF mRNA and protein expression in specific brain regions and blood, and reverse depressive-like behavior [14,55-60]. The necessity of having normal BDNF function to permit antidepressants to act was demonstrated by the observed attenuated actions of antidepressant in the forced swim test (FST) after deletion of BDNF in the forebrain [61]. Consistent with these results, $BDNF^{+/-}$ germline knockout mice showed an impaired response to fluoxetine treatment [62], further supporting the role that BDNF plays in antidepressant actions. Other than their inductive effects on BDNF expression, antidepressant drugs are also able to initiate BDNF signaling by promoting the activation of TrkB receptors and the phosphorylation of cyclic AMP response element binding (CREB) protein in rodent brain [63,64]. However, and of considerable interest, BDNF is not necessarily involved in antidepressant drug-induced activation of TrkB receptors [65], suggesting that antidepressants can regulate alternative signaling pathways that increase TrkB phosphorylation.

Antidepressant and pro-depressant effects of BDNF: location, location, location.

Altered BDNF expression impacts behavior and antidepressant responses, but the region within the brain and the neurons and circuits involved define whether BDNF acts in a prodepressant or antidepressant manner. For example, localized ablation of BDNF in the ventrotegmental area (VTA), the brain region believed to be the source of NAc BDNF protein, mimicked the effects of antidepressant treatment, resulting in attenuated depressive-like behavior [51], while intra-VTA infusion of BDNF produced depressive-like behavior [66]. On the other hand, bilateral infusion of BDNF into the hippocampal dentate gyrus of rats reversed the depressive-like behaviors shown in the learned helplessness (LH) and FST paradigms with a similar efficacy to antidepressant drugs [67], and intracerebroventricular BDNF infusion induced sustained antidepressant-like effects [68]. Similarly, transgenic overexpression of BDNF in the hippocampus, which also protected dendrites in the CA3 region from atrophy [69], decreased immobility in the FST, and virally-mediated BDNF overexpression in adult rat hippocampus reversed anhedonia and reduced immobility in the FST [70]. Thus

the antidepressant or pro-depressant effects of modulating BDNF expression are very much dependent on CNS location. Antidepressant-like effects of peripherally-administered BDNF have also been observed, including dose-dependent reduction in immobility in the FST and latency to drink in novelty-induced hypophagia (NIH) [71]. Peripheral BDNF administration further rescued the anhedonia induced by chronic unpredictable stress, facilitated the survival of immature neurons in the dentate gyrus and prefrontal cortex, and induced BDNF protein and mRNA expression in hippocampus, suggesting a possible function of peripheral BDNF in the pathogenesis of depression, in addition to its role as a potential biomarker.

Behavioral effects of BDNF downregulation

Because of the severely impaired coordination and short life span of BDNF germline homozygous knockout mice [72], $BDNF^{+/-}$ heterozygous mice have been studied, and these did not show any depressive-like behaviors in the FST, learned helplessness (LH), tail suspension test (TST) or sucrose preference test (SPT) [63,73-75]. Interpretation of these early efforts was complicated by subsequent discoveries of additional functional roles for BDNF in pain pathways, including reduced pain sensitivity in $BDNF^{+/-}$ mice [73], which could have impacted the LH paradigm. However, recent studies indicate that $BDNF^{+/-}$ mice have a pro-depressive phenotype: male $BDNF^{+/-}$ mice showed increased immobility in the FST after exposure to mild stress, suggesting higher vulnerability of BDNF deficient mice to stress [76]. Moreover, Magarinos et al. observed retracted dendritic arborization in the CA3 region and reduced hippocampal volume in unstressed $BDNF^{+/-}$ mice, similar to the phenotypes of stressed wild type mice [77]. Behavioral sequelae of global BDNF reduction may therefore reflect the summation of antidepressant-like effects of BDNF in the hippocampus and prefrontal cortex, and pro-depressive effects of BDNF in the VTA [51,78], consistent with the region- and circuit-specific role of this neurotrophin.

In order to circumvent the embryonic lethality and developmental abnormalities caused by targeted deletion of *Bdnf* in the germline, and to study gene function in specific tissues or regions, BDNF conditional knockout mice have been generated. Forebrain deletion of BDNF resulted in decreased sucrose preference and longer immobility time in FST in female mice compared to wild type littermates, while male conditional knockout mice are indistinguishable from wild types, suggesting a gender difference in vulnerability to depressive-like behavior that was not applicable to antidepressant responses, as both male and female conditional knockout mice failed to attenuate their depressive-like behavior following desipramine treatment [79]. However, BDNF conditional knockout in the dentate gyrus did attenuate antidepressant efficacy [80]. Lastly, mice with conditional knockout of BDNF in the VTA have been reported to show reduced social avoidance in the social interaction test following social defeat [51], reinforcing region-specific effects of BDNF on depressive behavior.

BDNF knockdown by RNA interference in dorsal dentate gyrus resulted in depressive-like behaviors in the SPT, FST, and home-cage locomotion as well as impaired neuronal differentiation [81]. Interestingly, the same group reported that BDNF knockdown in VTA leads to decreased immobility time in the FST and increased sucrose preference [78], consistent with previous reports demonstrating that conditional deletion of BDNF in VTA induced antidepressant-like effects [51].

Defects in regulated BDNF secretion and depression: the BDNF Val66Met polymorphism

The Val66Met BDNF polymorphism is the most widely studied variation in the *BDNF* gene and has been correlated with BDNF function, hippocampal activity, and depression. This single nucleotide polymorphism (SNP) at nucleotide 196, leading to substitution of methionine (Met) for valine (Val) at codon 66, interferes with BDNF protein sorting and secretion, and BDNF mRNA trafficking to dendrites [82-84]. Abnormal memory and hippocampal function have been observed in human subjects carrying the Met-allele [82,85]. Many studies also suggest a pro-depressive role of the BDNF Met-allele, which has been correlated with smaller volumes of the hippocampus [86], parahippocampus, amygdala, and frontal gyrus [87], but higher BDNF levels in serum [88]. However, reduced hippocampal volume was not only observed in depressed patients, but also in healthy subjects [89], and no effect on hippocampal volume and BDNF levels in both plasma and serum by the Val66Met SNP have also been reported [90-92], suggesting a complex phenotype.

In addition, depressed patients carrying the Met-allele ($BDNF^{Val/Met}$ and $BDNF^{Met/Met}$) are more likely to suffer from suicidal ideation and to attempt suicide [93]. Met-allele carriers exposed to greater early life stress had smaller hippocampal volume and higher syndromal depression, while the experience of early life stress in $BDNF^{Val/Val}$ homozygotes had no effect on depression [94]. $BDNF^{Val/Met}$ and $BDNF^{Met/Met}$ subjects also respond better to antidepressant treatment compared to $BDNF^{Val/Val}$ homozygotes [95,96].

Study of the BDNF Val66Met polymorphism in rodent models has facilitated mechanistic understanding of this sorting and secretory defect. $BDNF^{Met/Met}$ mice were more resilient to chronic social defeat stress than $BDNF^{Val/Val}$ [97], which may be attributed to reduced BDNF levels in NAc. $BDNF^{Met/Met}$ rodents fail to respond to ketamine administration, having impaired synaptogenesis and longer immobility time in the FST [98]. Compared to $BDNF^{Val/Val}$ mice, $BDNF^{Met/Met}$ mice also had lower basal BDNF protein levels as well as impaired NMDA-receptor dependent LTP and LTD, and decreased survival of newly generated neurons in hippocampus, which could not be reversed by fluoxetine administration [99,100]. Recent studies further demonstrate that $BDNF^{Val/Met}$ mice have increased depressive- and anxiety-like behaviors and impaired working memory following restraint stress, and show antidepressant responses to acute administration of desipramine but not fluoxetine, perhaps suggesting more effective treatment options for depressed patients with this genetic variant [101]. Thus a relatively

subtle deficit in BDNF sorting and secretion can lead to profound behavioral modification and altered responses to antidepressants, alcohol and drugs of abuse [102,103], perhaps reflecting in part altered neural plasticity in response to both adverse and rewarding life events [104].

Modulation of depressive behavior and antidepressant efficacy by BDNF/TrkB signaling

Mice with reduced BDNF/TrkB activation are resistant to antidepressant treatment [63]. Moreover, conditional forebrain TrkB knockout mice manifest decreased spine densities and increased spine length on apical and basal dendrites in the CA1 region [105], as well as decreased neurogenesis in hippocampus and impaired behavioral improvements induced by chronic antidepressant administration or by exercise [106]. Conversely, transgenic mice with over-expressed catalytic TrkB receptors in brain showed decreased immobility in the FST [107]. These findings are consistent with the important role of BDNF/TrkB signaling in depression and antidepressant efficacy.

Binding of BDNF to TrkB activates different intracellular signaling cascades, including the Ras/ERK (MAPK), PLCγ and PI3K/Akt pathways [12] (see Figure 1), each of which have been linked to depression. Reduced levels of different effectors of the Ras/ERK (MAPK) pathway were reported in postmortem hippocampus and frontal cortex of depressed and suicide subjects [108,109]. Consistent with postmortem studies, animal studies showed that inhibition of ERK signaling in hippocampus and prefrontal cortex was sufficient to induce depressive-like behaviors [110], and activation of ERK signaling in hippocampus was necessary for the antidepressant-like effects of intrahippocampal BDNF infusion [67]. Moreover, chronic mild stress-induced reduction of ERK signaling in hippocampus and prefrontal cortex could be rescued by fluoxetine administration [111,112]. Consistent with the importance of

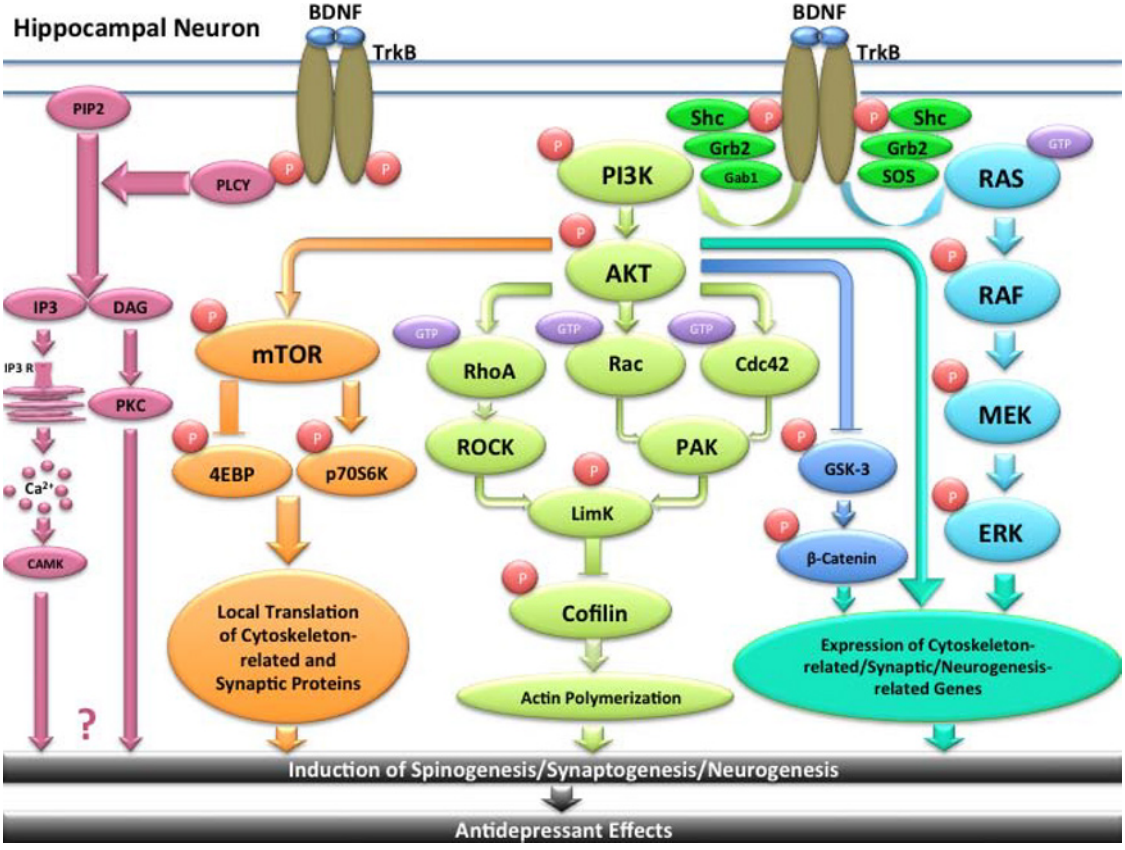

Figure 1. Hippocampal BDNF/TrkB signaling pathways that modulate depressive behavior and antidepressant responses. Binding of BDNF to TrkB activates different intracellular signaling cascades, including the PI3K/Akt, Ras/ERK (MAPK) and PLCY pathways [12]. Phosphorylation of Y490 of TrkB leads to recruitment of adaptor proteins such as Shc, Grb2 and Gab1 and subsequent activation of the PI3K/Akt pathway [192] and Rho family of GTPases (RhoA, Rac, Cdc42), which positively regulate actin polymerization through downstream signaling including ROCK/PAK, LimK and Cofilin [151-153]. Another downstream effector of the PI3K/Akt pathway is GSK-3, whose activity is negatively regulated by Akt-mediated phosphorylation [193]. One of the downstream targets of GSK-3 is β-catenin, which can be translocated into the nucleus to promote gene expression. The mTOR pathway, which facilitates local translation and the rapid antidepressant effects of ketamine, is also regulated by PI3K/Akt signaling [122]. Activation of PI3K/Akt signaling is believed to positively modulate spinogenesis, synaptogenesis and neurogenesis, thus inducing antidepressant effects. In addition to inductive effects on gene expression, the Ras/ERK (MAPK) pathway also acts through Rho family of GTPases, mTOR signaling, and synapsin to induce spinogenesis, synaptogenesis and neurogenesis (not shown) [122,153,154]. Phosphorylation of Y816 of TrkB recruits PLCY [194], inducing the hydrolysis of PIP2 to IP3 and DAG. IP3 regulates calcium release and CAMK activation, while DAG activates PKC. Both IP3/CAMK and DAG/PKC signaling regulate synaptic plasticity [195], however their roles in depression remain largely unknown.

ERK signaling in depression and antidepressant efficacy, hippocampal overexpression of MAPK Phosphatase-1 (MKP-1), a negative regulator of the MAPK pathway, induced depressive behavior, while local deletion of MKP-1 in hippocampus led to a resilient response to stress [113]. And as noted previously, the effects of BDNF signaling pathways on depression and antidepressant efficacy are location-dependent: chronic unpredictable stress promoted ERK signaling in VTA [114], while viral-mediated overexpression of ERK2 in VTA increased susceptibility to stress and ERK2 blockade in VTA produced resilience [114].

Studies of PI3K/Akt signaling in the brain provide further evidence for its modulation of depressive behavior, but a simple, region-specific pattern of signaling pathway contributions to depression does not emerge. Reduced Akt signaling has been found in hippocampus and prefrontal cortex of depressed and suicide subjects [115,116], and in animals, chronic social defeat stress and chronic unpredictable stress reduced Akt phosphorylation in the VTA [117,118], while viral-mediated blockade of Akt signaling in VTA increased susceptibility to social defeat-induced depressive behavior [118]. Recently, decreased Akt phosphorylation was also observed in basolateral amygdala following FST [119], suggesting that a generalized decrease in Akt signaling is associated with depression, distinct from region-specific ERK2 signaling described above. Lastly, blockade of the PI3K/Akt pathway was sufficient to offset increased hippocampal neurogenesis following exercise [120], and to prevent the antidepressant-like effects of folic acid [121] and ketamine [122]. Since BDNF acts through the PI3K/Akt pathway (see Figure 1), this finding suggests the involvement of BDNF in the antidepressant actions of ketamine. Interestingly, ketamine treatment failed to induce synaptogenesis in prefrontal cortex of $BDNF^{Met/Met}$ mice, and its antidepressant actions were also impaired in these mice [123]. Similarly, ketamine administration did not produce antidepressant-like effects in BDNF conditional knockout mice, but in wild type mice, ketamine induced BDNF translation by deactivating eukaryotic elongation factor 2 (eEF-2) kinase, which in turn resulted in fast-acting antidepressant-like effects [124].

One of the downstream targets of PI3K/Akt pathway, GSK-3, has drawn much attention due to its involvement in depression. Akt can phosphorylate both GSK-3α and GSK-3β isoforms in their N-terminal domains, thus inhibiting their activities. In clinical studies, increased GSK-3β activity and decreased phosphorylated GSK-3β protein levels were observed in ventral prefrontal cortex of depressed subjects [115,125], and a GSK-3β polymorphism has been correlated with altered hippocampal structure in depressed patients [126]. In rodent studies, intraperitoneal and intracerebroventricular administration of GSK-3 inhibitors induces antidepressant-like behaviors [127,128]. Similar antidepressant-like effects were also observed in both GSK-3α and GSK-3β deficient mice [129,130]. Moreover, GSK-3 knock-in mice that lack inhibitory phosphorylation of GSK-3 (GSK-3 α/β $^{21A/21A/9A/9A}$) were found to be more vulnerable to stress-induced depressive-like behaviors [131]. Does GSK also play a role in antidepressant efficacy? Recent studies demonstrate that ketamine administration enhances phosphorylation of both GSK-3α and GSK-3β in hippocampus and prefrontal cortex, and this inhibition of GSK-3 is required for the antidepressant effects induced by ketamine [132]. The effects of GSK-3 on depressive- and antidepressant-like behaviors are mediated by phosphorylation of β-catenin, resulting in its degradation. Consistent with the GSK-3 studies described above, reduced β-catenin protein levels were reported in ventral prefrontal cortex of depressed patients [125], mice with a conditional knockout of β-catenin in the forebrain displayed depressive-like behavior in the TST [133], and mice with β-catenin overexpression in brain showed antidepressant-like effects in the FST [134].

How do neurotrophins and their signaling pathways modulate depressive behavior?

Regulation of neuronal plasticity

Disruption of neuronal plasticity has been linked to impaired learning and memory, as well as mood disorders such as major depression and bipolar disorder [135]. Clinical evidence has supported reduced hippocampal volumes in depressed patients [136-141], while animal studies provide related data demonstrating that stress induces retraction of pyramidal cell dendrites in hippocampus [77,142], and the loss of pyramidal neuron dendritic spines in medial prefrontal cortex [143,144]. Working in an opposing manner, antidepressant treatments, including ECT and drugs, increase plasticity by inducing hippocampal dendritic sprouting [145], increasing dendritic spine density [146], and promoting synaptogenesis [147].

Many studies have explored the role of BDNF in the regulation of neuronal plasticity. Study of $BDNF^{+/-}$ heterozygous knockout mice revealed dendritic retraction in the hippocampus and reduced hippocampal volume [62,77]. Similarly, $BDNF^{Val/Met}$ mice were found to have impaired spine formation and synaptic function, and decreased spine density and dendritic length [62,98,101], in different brain regions, including hippocampus, prefrontal cortex and amygdala. These changes in neuronal plasticity of Met-allele carriers have been attributed to a deficiency in BDNF mRNA dendritic trafficking [84], which in turn resulted in impaired local protein translation that is required for normal synaptogenesis and spine maintenance [148]. Moreover, BDNF overexpression was shown to be sufficient to enhance dendritic complexity of dentate granule cells [149] and dendritic density in basolateral amygdala, and to prevent dendritic atrophy in CA3 induced by chronic stress [69].

The important roles that the Ras/ERK (MAPK) and PI3K/Akt pathways play downstream of BDNF/TrkB to modulate depressive behavior and antidepressant responses are likely realized in part by modulation of spinogenesis and synaptogenesis. Overexpression of PI3K or Akt is sufficient to increase dendritic complexity and soma size as well as to induce production of filopodia-like protrusions, whereas mTOR inhibition has the opposite effects [150]. In addition, Ras/ERK (MAPK) and PI3K/Akt pathways are believed to be upstream of Rho family GTPases, including RhoA, Rac and Cdc42, which are involved in the regulation of actin polymerization, thus mediating dendritic spine plasticity [151-153]. Ras/ERK (MAPK) and PI3K/

Akt pathways were also demonstrated to be necessary for ketamine-induced activation of mTOR signaling, which is functionally correlated with synapse formation [122]. Lastly, Ras/ERK (MAPK) pathway-dependent phosphorylation of synapsin regulates synaptogenesis [154]. Many of the pro-depressant and antidepressant effects of BDNF are therefore mediated by signaling pathways downstream of the TrkB receptor that impact the plasticity of neural circuits in a regionally-specific manner.

Regulation of neurogenesis

Malberg and Duman first reported that fluoxetine could reverse the stress-induced reduction in hippocampal neurogenesis [155], establishing a correlation between neurogenesis and depression. Impaired neurogenesis in hippocampus, caused by irradiation, prevented the antidepressant effects of fluoxetine and imipramine, which were observed in non-irradiated controls [156]. These findings were supported by several subsequent studies [157,158], although neurogenesis-independent effects of antidepressant treatment were also suggested [159]. *In vivo* studies have revealed that BDNF is required for antidepressant-induced hippocampal neurogenesis. Heterozygous $BDNF^{+/-}$ knockout mice showed reduced proliferation and survival of hippocampal neuronal progenitor cells [160], and reduced hippocampal neurogenesis induced by dietary restriction or environmental enrichment [160,161]. Also studying $BDNF^{+/-}$ knockout mice, Sairanen et al. did not find a major role for BDNF in promoting hippocampal progenitor cell proliferation induced by antidepressant treatment, although BDNF was required for long-term survival of newborn neurons [162]. On the other hand, viral-mediated BDNF overexpression was sufficient to enhance hippocampal neurogenesis [163], and intraventricular and intrahippocampal BDNF infusions increased neurogenesis in rat olfactory bulb [164] and hippocampus [165], respectively, while intravenous BDNF administration in a rat stroke model increased neurogenesis in the dentate gyrus and improved recovery [166].

In addition to BDNF, NT-3 deletion in dentate gyrus reduced the number of differentiated hippocampal progenitor cells [167], while intracerebroventricular NGF infusion promoted survival of newborn neurons in adult dentate gyrus [168]. Downstream of Trk receptors, PI3K/Akt and Ras/ERK (MAPK) signaling pathways have been suggested to converge on nuclear transcription factor CREB [169], which is responsible for regulating expression of genes involved in neurogenesis, such as CCNA (cyclin A) and CCND2 (cyclin D2) [170]. In addition, and relevant to the role of Akt signaling in depression, impaired neurogenesis was also observed in GSK-3 α/β 21A/21A/9A/9A knock-in mice [171] and in GSK-3β overexpressing mice [172].

Secretory and cytoskeletal targets of BDNF: potential roles in depression and antidepressant responses

BDNF modulates depressive behavior and the response to antidepressant treatment. Many of these effects are likely mediated by gene products that are transcriptionally regulated by this growth factor. VGF (non-acronymic) is a secreted protein and neuropeptide precursor that is robustly regulated by BDNF and NT-3 in CNS neurons [173]. Hippocampal VGF expression is decreased by depressive behavior and in pro-depressive SERT knockout rats, is increased by exercise and antidepressant treatment, and intrahippocampal or intracerebroventricular infusion of C-terminal VGF-derived peptides AQEE30 or TLQP62 attenuates depressive-like behavior [174-176]. Consistent with these antidepressant effects, TLQP62 regulates hippocampal neuronal progenitor proliferation and synaptic plasticity, and heterozygous VGF knockout mice have increased immobility in the TST and FST [174,175,177]. The mechanism of action of VGF in regulating depressive behavior and antidepressant responses could depend on autocrine or paracrine effects of VGF peptides on regulated BDNF secretion [177], or the role that this chromogranin/secretogranin-like protein plays in dense core secretory vesicle biogenesis, both potentially impacting regulated BDNF secretion, much as does the Val66Met BDNF polymorphism.

Arc (activity-regulated cytoskeleton-associated protein), is an immediate early gene that is regulated by BDNF and synaptic activity, and is localized to neuronal dendrites [178,179]. Chronic, but not acute, antidepressant administration [180-182] and electroconvulsive stimulation (ECS) [183] induce Arc mRNA expression in hippocampus and parietal cortex. Arc mRNA expression in the hippocampus and frontal cortex was transiently down-regulated by chronic mild stress [184], and significantly reduced Arc mRNA expression was also observed in the medial prefrontal cortex of mice that were susceptible to chronic social defeat [185], and also in three rodent models that manifest depressive-like behavior [184,186,187]. Although other studies demonstrate increased Arc mRNA levels following acute stress and social defeat stress [49,181,188,189], findings generally support a correlation between increased Arc expression and antidepressant effects, and decreased Arc levels and depressive behavior, suggesting that its role in depression is a result of its function in regulating synaptic plasticity. Consistent with the importance of dysregulated synaptic plasticity in depression, knockdown of neuritin (CPG15), an activity- and BDNF-regulated gene product that is involved in synaptic plasticity, maturation, and stabilization [190] in the hippocampus, was sufficient to block the antidepressant-like effects in the FST caused by BDNF infusion into dentate gyrus [191], indicating that the antidepressant-like effects of BDNF may also depend on other regulators of synaptic plasticity including neuritin.

Conclusions

Neurotrophins in general and BDNF in particular modulate depressive behavior and the response to antidepressant treatment, in part through the regulation of synaptic plasticity, synaptogenesis, spinogenesis, and neurogenesis. BDNF levels are affected by depression, stress and antidepressant treatment, in both CNS and blood. Region-specific modulation of BDNF levels in brain can lead to depressive behavior or antidepressant-like responses—location

and synaptic circuit are critical. Neurotrophin actions are transduced primarily via PI3K/Akt and Ras/ERK (MAPK) signaling pathways, and importantly the genes they transcriptionally regulate. A better understanding of the proteins that control synaptic plasticity and the regulated secretion of neurotrophins, and their role in the pathogenesis of depression and the control of antidepressant efficacy, in different areas of the brain including hippocampus and NAc/VTA, should improve the design of more effective treatments for this prevalent, extremely debilitating disease.

Acknowledgements

We thank members of the Salton lab for helpful discussions during the preparation of this review. Research in the authors' laboratory is supported by grants from the NIH, Diabetes Action and Education Foundation, and the Hope for Depression Foundation

References

[1] Lewin G.R.,Barde Y.A., Physiology of the neurotrophins, Annu. Rev. Neurosci., 1996, 19, 289-317

[2] Huang E.J.,Reichardt L.F., Neurotrophins: roles in neuronal development and function, Annu. Rev. Neurosci., 2001, 24, 677-736

[3] Bibel M.,Barde Y.A., Neurotrophins: key regulators of cell fate and cell shape in the vertebrate nervous system, Genes Dev., 2000, 14, 2919-2937

[4] Levi-Montalcini R., The nerve growth factor: thirty-five years later, Biosci. Rep., 1987, 7, 681-699

[5] Barde Y.A., Edgar D.,Thoenen H., Purification of a new neurotrophic factor from mammalian brain, EMBO J., 1982, 1, 549-553

[6] Maisonpierre P.C., Belluscio L., Squinto S., Ip N.Y., Furth M.E., Lindsay R.M., et al., Neurotrophin-3: a neurotrophic factor related to NGF and BDNF, Science, 1990, 247, 1446-1451

[7] Ip N.Y., Ibanez C.F., Nye S.H., McClain J., Jones P.F., Gies D.R., et al., Mammalian neurotrophin-4: structure, chromosomal localization, tissue distribution, and receptor specificity, Proc. Natl. Acad. Sci. USA, 1992, 89, 3060-3064

[8] Barbacid M., Neurotrophic factors and their receptors, Curr. Opin. Cell Biol., 1995, 7, 148-155

[9] Teng H.K., Teng K.K., Lee R., Wright S., Tevar S., Almeida R.D., et al., ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin, J. Neurosci., 2005, 25, 5455-5463

[10] Woo N.H., Teng H.K., Siao C.J., Chiaruttini C., Pang P.T., Milner T.A., et al., Activation of p75NTR by proBDNF facilitates hippocampal long-term depression, Nat. Neurosci., 2005, 8, 1069-1077

[11] Zagrebelsky M., Holz A., Dechant G., Barde Y.A., Bonhoeffer T.,Korte M., The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons, J. Neurosci., 2005, 25, 9989-9999

[12] Reichardt L.F., Neurotrophin-regulated signalling pathways, Philos. T. Roy. Soc. B, 2006, 361, 1545-1564

[13] Autry A.E., Monteggia L.M., Brain-derived neurotrophic factor and neuropsychiatric disorders, Pharmacol. Rev., 2012, 64, 238-258

[14] Nibuya M., Morinobu S., Duman R.S., Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments, J. Neurosci., 1995, 15, 7539-7547

[15] Dwivedi Y., Rizavi H.S., Conley R.R., Roberts R.C., Tamminga C.A., Pandey G.N., Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects, Arch. Gen. Psychiat., 2003, 60, 804-815

[16] Karege F., Vaudan G., Schwald M., Perroud N.,La Harpe R., Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs, Mol. Brain Res., 2005, 136, 29-37

[17] Guilloux J.P., Douillard-Guilloux G., Kota R., Wang X., Gardier A.M., Martinowich K., et al., Molecular evidence for BDNF- and GABA-related dysfunctions in the amygdala of female subjects with major depression, Mol. Psychiatr., 2012, 17, 1130-1142

[18] Chen B., Dowlatshahi D., MacQueen G.M., Wang J.F.,Young L.T., Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication, Biol. Psychiat., 2001, 50, 260-265

[19] Karege F., Perret G., Bondolfi G., Schwald M., Bertschy G.,Aubry J.M., Decreased serum brain-derived neurotrophic factor levels in major depressed patients, Psychiat. Res., 2002, 109, 143-148

[20] Yoshida T., Ishikawa M., Niitsu T., Nakazato M., Watanabe H., Shiraishi T., et al., Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder, PLoS One, 2012, 7, e42676

[21] Lee B.H., Kim H., Park S.H.,Kim Y.K., Decreased plasma BDNF level in depressive patients, J. Affect. Disord., 2007, 101, 239-244

[22] Karege F., Bondolfi G., Gervasoni N., Schwald M., Aubry J.M.,Bertschy G., Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity, Biol. Psychiat., 2005, 57, 1068-1072

[23] Shimizu E., Hashimoto K., Okamura N., Koike K., Komatsu N., Kumakiri C., et al., Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants, Biol. Psychiat., 2003, 54, 70-75

[24] Deuschle M., Gilles M., Scharnholz B., Lederbogen F., Lang U.E., Hellweg R., Changes of serum concentrations of brain-derived neurotrophic factor (BDNF) during treatment with venlafaxine and mirtazapine: role of medication and response to treatment, Pharmacopsychiatry, 2012, Epub ahead of print, doi: 10.1055/s-0032-1321908

[25] Lee H.Y.,Kim Y.K., Plasma brain-derived neurotrophic factor as a peripheral marker for the action mechanism of antidepressants, Neuropsychobiology, 2008, 57, 194-199

[26] Lee B.H.,Kim Y.K., Reduced platelet BDNF level in patients with major depression, Prog. Neuropsychopharmacol. Biol. Psychiat., 2009, 33, 849-853

[27] Lee B.H.,Kim Y.K., BDNF mRNA expression of peripheral blood mononuclear cells was decreased in depressive patients who had or had not recently attempted suicide, J. Affect. Disord., 2010, 125, 369-373

[28] Pandey G.N., Dwivedi Y., Rizavi H.S., Ren X., Zhang H.,Pavuluri M.N., Brain-derived neurotrophic factor gene and protein expression in pediatric and adult depressed subjects, Prog. Neuropsychopharmacol. Biol. Psychiatry, 2010, 34, 645-651

[29] Kim Y.K., Lee H.P., Won S.D., Park E.Y., Lee H.Y., Lee B.H., et al., Low plasma BDNF is associated with suicidal behavior in major depression, Prog. Neuropsychopharmacol. Biol. Psychiat., 2007, 31, 78-85

[30] Birkenhager T.K., Geldermans S., Van den Broek W.W., van Beveren N.,Fekkes D., Serum brain-derived neurotrophic factor level in relation to illness severity and episode duration in patients with major depression, J. Psychiat. Res., 2012, 46, 285-289

[31] Lang U.E., Hellweg R.,Gallinat J., BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits, Neuropsychopharmacology, 2004, 29, 795-798

[32] Klein A.B., Williamson R., Santini M.A., Clemmensen C., Ettrup A., Rios M., et al., Blood BDNF concentrations reflect brain-tissue BDNF levels across species, Int. J. Neuropsychopharmacol., 2011, 14, 347-353

[33] Smith M.A., Makino S., Kvetnansky R.,Post R.M., Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus, J. Neurosci., 1995, 15, 1768-1777

[34] Ueyama T., Kawai Y., Nemoto K., Sekimoto M., Tone S.,Senba E., Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain, Neurosci. Res., 1997, 28, 103-110

[35] Rasmusson A.M., Shi L.,Duman R., Downregulation of BDNF mRNA in the hippocampal dentate gyrus after re-exposure to cues previously associated with footshock, Neuropsychopharmacology, 2002, 27, 133-142

[36] Luo C., Xu H.,Li X.M., Post-stress changes in BDNF and Bcl-2 immunoreactivities in hippocampal neurons: effect of chronic administration of olanzapine, Brain Res., 2004, 1025, 194-202

[37] Pizarro J.M., Lumley L.A., Medina W., Robison C.L., Chang W.E., Alagappan A., et al., Acute social defeat reduces neurotrophin expression in brain cortical and subcortical areas in mice, Brain Res., 2004, 1025, 10-20

[38] Berry A., Bellisario V., Capoccia S., Tirassa P., Calza A., Alleva E., et al., Social deprivation stress is a triggering factor for the emergence of anxiety- and depression-like behaviours and leads to reduced brain BDNF levels in C57BL/6J mice, Psychoneuroendocrinology, 2012, 37, 762-772

[39] Gronli J., Bramham C., Murison R., Kanhema T., Fiske E., Bjorvatn B., et al., Chronic mild stress inhibits BDNF protein expression and CREB activation in the dentate gyrus but not in the hippocampus proper, Pharmacol. Biochem. Behav., 2006, 85, 842-849

[40] Tsankova N.M., Berton O., Renthal W., Kumar A., Neve R.L.,Nestler E.J., Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action, Nat. Neurosci., 2006, 9, 519-525

[41] Allaman I., Papp M., Kraftsik R., Fiumelli H., Magistretti P.J.,Martin J.L., Expression of brain-derived neurotrophic factor is not modulated by chronic mild stress in the rat hippocampus and amygdala, Pharmacol. Rep., 2008, 60, 1001-1007

[42] Lucca G., Comim C.M., Valvassori S.S., Pereira J.G., Stertz L., Gavioli E.C., et al., Chronic mild stress paradigm reduces sweet food intake in rats without affecting brain derived neurotrophic factor protein levels, Curr. Neurovasc. Res., 2008, 5, 207-213

[43] Marmigere F., Givalois L., Rage F., Arancibia S.,Tapia-Arancibia L., Rapid induction of BDNF expression in the hippocampus during immobilization stress challenge in adult rats, Hippocampus, 2003, 13, 646-655

[44] Larsen M.H., Mikkelsen J.D., Hay-Schmidt A.,Sandi C., Regulation of brain-derived neurotrophic factor (BDNF) in the chronic unpredictable stress rat model and the effects of chronic antidepressant treatment, J. Psychiat. Res., 2010, 44, 808-816

[45] Bulygina V.V., Shishkina G.T., Berezova I.V.,Dygalo N.N., BDNF protein expression in the hippocampus following exposure of rats to forced swimming stress, Dokl. Biol. Sci., 2011, 437, 82-84

[46] Shi S.S., Shao S.H., Yuan B.P., Pan F.,Li Z.L., Acute stress and chronic stress change brain-derived neurotrophic factor (BDNF) and tyrosine kinase-coupled receptor (TrkB) expression in both young and aged rat hippocampus, Yonsei Med. J., 2010, 51, 661-671

[47] Uysal N., Sisman A.R., Dayi A., Ozbal S., Cetin F., Baykara B., et al., Acute footshock-stress increases spatial learning-memory and correlates to increased hippocampal BDNF and VEGF and cell numbers in adolescent male and female rats, Neurosci. Lett., 2012, 514, 141-146

[48] Neto F.L., Borges G., Torres-Sanchez S., Mico J.A.,Berrocoso E., Neurotrophins role in depression neurobiology: a review of basic and clinical evidence, Curr. Neuropharmacol., 2011, 9, 530-552

[49] Coppens C.M., Siripornmongcolchai T., Wibrand K., Alme M.N., Buwalda B., de Boer S.F., et al., Social defeat during adolescence and adulthood differentially induce BDNF-regulated immediate early genes, Front. Behav. Neurosci., 2011, 5, 72

[50] Fanous S., Hammer R.P., Jr.,Nikulina E.M., Short- and long-term effects of intermittent social defeat stress on brain-derived neurotrophic factor expression in mesocorticolimbic brain regions, Neuroscience, 2010, 167, 598-607

[51] Berton O., McClung C.A., Dileone R.J., Krishnan V., Renthal W., Russo S.J., et al., Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress, Science, 2006, 311, 864-868

[52] Duman R.S., Heninger G.R.,Nestler E.J., A molecular and cellular theory of depression, Arch. Gen. Psychiat., 1997, 54, 597-606

[53] Duman R.S., Monteggia L.M., A neurotrophic model for stress-related mood disorders, Biol. Psychiat., 2006, 59, 1116-1127

[54] Krishnan V.,Nestler E.J., The molecular neurobiology of depression, Nature, 2008, 455, 894-902

[55] Coppell A.L., Pei Q.,Zetterstrom T.S., Bi-phasic change in BDNF gene expression following antidepressant drug treatment, Neuropharmacology, 2003, 44, 903-910

[56] Molteni R., Calabrese F., Bedogni F., Tongiorgi E., Fumagalli F., Racagni G., et al., Chronic treatment with fluoxetine up-regulates cellular BDNF mRNA expression in rat dopaminergic regions, Int. J. Neuropsychopharmacol., 2006, 9, 307-317

[57] Ferris L.T., Williams J.S., Shen C.L., The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function, Med. Sci. Sports Exerc., 2007, 39, 728-734

[58] Marais L., Stein D.J.,Daniels W.M., Exercise increases BDNF levels in the striatum and decreases depressive-like behavior in chronically stressed rats, Metab. Brain Dis., 2009, 24, 587-597

[59] Kazlauckas V., Pagnussat N., Mioranzza S., Kalinine E., Nunes F., Pettenuzzo L., et al., Enriched environment effects on behavior, memory and BDNF in low and high exploratory mice, Physiol. Behav., 2011, 102, 475-480

[60] Yang C., Hu Y.M., Zhou Z.Q., Zhang G.F.,Yang J.J., Acute administration of ketamine in rats increases hippocampal BDNF and mTOR levels during forced swimming test, Ups. J. Med. Sci., 2012, Epub ahead of print, doi: 10.3109/03009734.2012.724118

[61] Monteggia L.M., Barrot M., Powell C.M., Berton O., Galanis V., Gemelli T., et al., Essential role of brain-derived neurotrophic factor in adult hippocampal function, Proc. Natl. Acad. Sci. USA, 2004, 101, 10827-10832

[62] Chen Z.Y., Jing D., Bath K.G., Ieraci A., Khan T., Siao C.J., et al., Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior, Science, 2006, 314, 140-143

[63] Saarelainen T., Hendolin P., Lucas G., Koponen E., Sairanen M., MacDonald E., et al., Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects, J. Neurosci., 2003, 23, 349-357

[64] Rantamaki T., Hendolin P., Kankaanpaa A., Mijatovic J., Piepponen P., Domenici E., et al., Pharmacologically diverse antidepressants rapidly activate brain-derived neurotrophic factor receptor TrkB and induce phospholipase-Cgamma signaling pathways in mouse brain, Neuropsychopharmacology, 2007, 32, 2152-2162

[65] Rantamaki T., Vesa L., Antila H., Di Lieto A., Tammela P., Schmitt A., et al., Antidepressant drugs transactivate TrkB neurotrophin receptors in the adult rodent brain independently of BDNF and monoamine transporter blockade, PLoS One, 2011, 6, e20567

[66] Eisch A.J., Bolanos C.A., de Wit J., Simonak R.D., Pudiak C.M., Barrot M., et al., Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: a role in depression, Biol. Psychiat., 2003, 54, 994-1005

[67] Shirayama Y., Chen A.C., Nakagawa S., Russell D.S., Duman R.S., Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression, J. Neurosci., 2002, 22, 3251-3261

[68] Hoshaw B.A., Malberg J.E., Lucki I., Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects, Brain. Res., 2005, 1037, 204-208

[69] Govindarajan A., Rao B.S., Nair D., Trinh M., Mawjee N., Tonegawa S., et al., Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects, Proc. Natl. Acad. Sci. USA, 2006, 103, 13208-13213

[70] Taliaz D., Loya A., Gersner R., Haramati S., Chen A.,Zangen A., Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor, J. Neurosci., 2011, 31, 4475-4483

[71] Schmidt H.D., Duman R.S., Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models, Neuropsychopharmacology, 2010, 35, 2378-2391

[72] Ernfors P., Lee K.F., Jaenisch R., Mice lacking brain-derived neurotrophic factor develop with sensory deficits, Nature, 1994, 368, 147-150

[73] MacQueen G.M., Ramakrishnan K., Croll S.D., Siuciak J.A., Yu G., Young L.T., et al., Performance of heterozygous brain-derived neurotrophic factor knockout mice on behavioral analogues of anxiety, nociception, and depression, Behav. Neurosci., 2001, 115, 1145-1153

[74] Chourbaji S., Hellweg R., Brandis D., Zorner B., Zacher C., Lang U.E., et al., Mice with reduced brain-derived neurotrophic factor expression show decreased choline acetyltransferase activity, but regular brain monoamine levels and unaltered emotional behavior, Mol. Brain Res., 2004, 121, 28-36

[75] Ibarguen-Vargas Y., Surget A., Vourc'h P., Leman S., Andres C.R., Gardier A.M., et al., Deficit in BDNF does not increase vulnerability to stress but dampens antidepressant-like effects in the unpredictable chronic mild stress, Behav. Brain Res., 2009, 202, 245-251

[76] Advani T., Koek W.,Hensler J.G., Gender differences in the enhanced vulnerability of BDNF+/- mice to mild stress, Int. J. Neuropsychopharmacol., 2009, 12, 583-588

[77] Magarinos A.M., Li C.J., Gal Toth J., Bath K.G., Jing D., Lee F.S., et al., Effect of brain-derived neurotrophic factor haploinsufficiency on stress-induced remodeling of hippocampal neurons, Hippocampus, 2011, 21, 253-264

[78] Taliaz D., Nagaraj V., Haramati S., Chen A.,Zangen A., Altered brain-derived neurotrophic factor expression in the ventral tegmental area, but not in the hippocampus, is essential for antidepressant-like effects of electroconvulsive therapy, Biol. Psychiat., 2012, Epub ahead of print, doi: 10.1016/j.biopsych.2012.07.025

[79] Monteggia L.M., Luikart B., Barrot M., Theobold D., Malkovska I., Nef S., et al., Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors, Biol. Psychiat., 2007, 61, 187-197

[80] Adachi M., Barrot M., Autry A.E., Theobald D.,Monteggia L.M., Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy, Biol. Psychiat., 2008, 63, 642-649

[81] Taliaz D., Stall N., Dar D.E., Zangen A., Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis, Mol. Psychiatr., 2010, 15, 80-92

[82] Egan M.F., Kojima M., Callicott J.H., Goldberg T.E., Kolachana B.S., Bertolino A., et al., The BDNF val66met polymorphism affects activity-

dependent secretion of BDNF and human memory and hippocampal function, Cell, 2003, 112, 257-269

[83] Chen Z.Y., Bath K., McEwen B., Hempstead B.,Lee F., Impact of genetic variant BDNF (Val66Met) on brain structure and function, Novartis Found. Symp., 2008, 289, 180-188, discussion 188-195

[84] Chiaruttini C., Vicario A., Li Z., Baj G., Braiuca P., Wu Y., et al., Dendritic trafficking of BDNF mRNA is mediated by translin and blocked by the G196A (Val66Met) mutation, Proc. Natl. Acad. Sci. USA, 2009, 106, 16481-16486

[85] Hariri A.R., Goldberg T.E., Mattay V.S., Kolachana B.S., Callicott J.H., Egan M.F., et al., Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance, J. Neurosci., 2003, 23, 6690-6694

[86] Frodl T., Schule C., Schmitt G., Born C., Baghai T., Zill P., et al., Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression, Arch. Gen. Psychiat., 2007, 64, 410-416

[87] Montag C., Weber B., Fliessbach K., Elger C.,Reuter M., The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression, Psychol. Med., 2009, 39, 1831-1839

[88] Lang U.E., Hellweg R., Sander T.,Gallinat J., The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentrations, Mol. Psychiatr., 2009, 14, 120-122

[89] Hajek T., Kopecek M.,Hoschl C., Reduced hippocampal volumes in healthy carriers of brain-derived neurotrophic factor Val66Met polymorphism: meta-analysis, World J. Biol. Psychiatry, 2012, 13, 178-187

[90] Jessen F., Schuhmacher A., von Widdern O., Guttenthaler V., Hofels S., Suliman H., et al., No association of the Val66Met polymorphism of the brain-derived neurotrophic factor with hippocampal volume in major depression, Psychiatr. Genet., 2009, 19, 99-101

[91] Terracciano A., Martin B., Ansari D., Tanaka T., Ferrucci L., Maudsley S., et al., Plasma BDNF concentration, Val66Met genetic variant and depression-related personality traits, Genes Brain Behav., 2010, 9, 512-518

[92] Yoshimura R., Kishi T., Suzuki A., Umene-Nakano W., Ikenouchi-Sugita A., Hori H., et al., The brain-derived neurotrophic factor (BDNF) polymorphism Val66Met is associated with neither serum BDNF level nor response to selective serotonin reuptake inhibitors in depressed Japanese patients, Prog. Neuropsychopharmacol. Biol. Psychiatry, 2011, 35, 1022-1025

[93] Sarchiapone M., Carli V., Roy A., Iacoviello L., Cuomo C., Latella M.C., et al., Association of polymorphism (Val66Met) of brain-derived neurotrophic factor with suicide attempts in depressed patients, Neuropsychobiology, 2008, 57, 139-145

[94] Gatt J.M., Nemeroff C.B., Dobson-Stone C., Paul R.H., Bryant R.A., Schofield P.R., et al., Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety, Mol. Psychiatr., 2009, 14, 681-695

[95] Choi M.J., Kang R.H., Lim S.W., Oh K.S.,Lee M.S., Brain-derived neurotrophic factor gene polymorphism (Val66Met) and citalopram response in major depressive disorder, Brain Res., 2006, 1118, 176-182

[96] Tsai S.J., Hong C.J.,Liou Y.J., Effects of BDNF polymorphisms on antidepressant action, Psychiatry Investig., 2010, 7, 236-242

[97] Krishnan V., Han M.H., Graham D.L., Berton O., Renthal W., Russo S.J., et al., Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions, Cell, 2007, 131, 391-404

[98] Liu R.J., Lee F.S., Li X.Y., Bambico F., Duman R.S., Aghajanian G.K., Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex, Biol. Psychiatry, 2012, 71, 996-1005

[99] Bath K.G., Jing D.Q., Dincheva I., Neeb C.C., Pattwell S.S., Chao M.V., et al., BDNF Val66Met impairs fluoxetine-induced enhancement of adult hippocampus plasticity, Neuropsychopharmacology, 2012, 37, 1297-1304

[100] Ninan I., Bath K.G., Dagar K., Perez-Castro R., Plummer M.R., Lee F.S., et al., The BDNF Val66Met polymorphism impairs NMDA receptor-dependent synaptic plasticity in the hippocampus, J. Neurosci., 2010, 30, 8866-8870

[101] Yu H., Wang D.D., Wang Y., Liu T., Lee F.S.,Chen Z.Y., Variant brain-derived neurotrophic factor Val66Met polymorphism alters vulnerability to stress and response to antidepressants, J. Neurosci., 2012, 32, 4092-4101

[102] Wojnar M., Brower K.J., Strobbe S., Ilgen M., Matsumoto H., Nowosad I., et al., Association between Val66Met brain-derived neurotrophic factor (BDNF) gene polymorphism and post-treatment relapse in alcohol dependence, Alcohol. Clin. Exp. Res., 2009, 33, 693-702

[103] Jia W., Shi J.G., Wu B., Ao L., Zhang R., Zhu Y.S., Polymorphisms of brain-derived neurotrophic factor associated with heroin dependence, Neurosci. Lett., 2011, 495, 221-224

[104] Chen J., Li X.,McGue M., Interacting effect of BDNF Val66Met polymorphism and stressful life events on adolescent depression, Genes Brain Behav., 2012, Epub ahead of print, doi: 10.1111/j.1601-183X.2012.00843.x

[105] von Bohlen und Halbach O., Krause S., Medina D., Sciarretta C., Minichiello L., Unsicker K., Regional- and age-dependent reduction in trkB receptor expression in the hippocampus is associated with altered spine morphologies, Biol. Psychiatry, 2006, 59, 793-800

[106] Bergami M., Berninger B., Canossa M., Conditional deletion of TrkB alters adult hippocampal neurogenesis and anxiety-related behavior, Commun. Integr. Biol., 2009, 2, 14-16

[107] Koponen E., Lakso M., Castren E., Overexpression of the full-length neurotrophin receptor trkB regulates the expression of plasticity-related genes in mouse brain, Mol. Brain Res., 2004, 130, 81-94

[108] Dwivedi Y., Rizavi H.S., Roberts R.C., Conley R.C., Tamminga C.A., Pandey G.N., Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects, J. Neurochem., 2001, 77, 916-928

[109] Yuan P., Zhou R., Wang Y., Li X., Li J., Chen G., et al., Altered levels of extracellular signal-regulated kinase signaling proteins in postmortem frontal cortex of individuals with mood disorders and schizophrenia, J. Affect. Disord., 2010, 124, 164-169

[110] Qi X., Lin W., Wang D., Pan Y., Wang W., Sun M., A role for the extracellular signal-regulated kinase signal pathway in depressive-like behavior, Behav. Brain Res., 2009, 199, 203-209

[111] First M., Gil-Ad I., Taler M., Tarasenko I., Novak N.,Weizman A., The effects of fluoxetine treatment in a chronic mild stress rat model on depression-related behavior, brain neurotrophins and ERK expression, J. Mol. Neurosci., 2011, 45, 246-255

[112] Qi X., Lin W., Li J., Li H., Wang W., Wang D., et al., Fluoxetine increases the activity of the ERK-CREB signal system and alleviates the depressive-like behavior in rats exposed to chronic forced swim stress, Neurobiol. Dis., 2008, 31, 278-285

[113] Duric V., Banasr M., Licznerski P., Schmidt H.D., Stockmeier C.A., Simen A.A., et al., A negative regulator of MAP kinase causes depressive behavior, Nat. Med., 2010, 16, 1328-1332

[114] Iniguez S.D., Vialou V., Warren B.L., Cao J.L., Alcantara L.F., Davis L.C., et al., Extracellular signal-regulated kinase-2 within the ventral tegmental area regulates responses to stress, J. Neurosci., 2010, 30, 7652-7663

[115] Karege F., Perroud N., Burkhardt S., Schwald M., Ballmann E., La Harpe R., et al., Alteration in kinase activity but not in protein levels of protein kinase B and glycogen synthase kinase-3beta in ventral prefrontal cortex of depressed suicide victims, Biol. Psychiatry, 2007, 61, 240-245

[116] Dwivedi Y., Rizavi H.S., Zhang H., Roberts R.C., Conley R.R.,Pandey G.N., Modulation in activation and expression of phosphatase and tensin homolog on chromosome ten, Akt1, and 3-phosphoinositide-dependent kinase 1: further evidence demonstrating altered phosphoinositide 3-kinase signaling in postmortem brain of suicide subjects, Biol. Psychiatry, 2010, 67, 1017-1025

[117] Chandran A., Iyo A.H., Jernigan C.S., Legutko B., Austin M.C., Karolewicz B., Reduced phosphorylation of the mTOR signaling pathway components in the amygdala of rats exposed to chronic stress, Prog. Neuropsychopharmacol. Biol. Psychiatry, 2012, 40C, 240-245

[118] Krishnan V., Han M.H., Mazei-Robison M., Iniguez S.D., Ables J.L., Vialou V., et al., AKT signaling within the ventral tegmental area regulates cellular and behavioral responses to stressful stimuli, Biol. Psychiatry, 2008, 64, 691-700

[119] Shi H.S., Zhu W.L., Liu J.F., Luo Y.X., Si J.J., Wang S.J., et al., PI3K/Akt signaling pathway in the basolateral amygdala mediates the rapid antidepressant-like effects of trefoil factor 3, Neuropsychopharmacology, 2012, 37, 2671-2683

[120] Bruel-Jungerman E., Veyrac A., Dufour F., Horwood J., Laroche S., Davis S., Inhibition of PI3K-Akt signaling blocks exercise-mediated enhancement of adult neurogenesis and synaptic plasticity in the dentate gyrus, PLoS One, 2009, 4, e7901

[121] Budni J., Lobato K.R., Binfare R.W., Freitas A.E., Costa A.P., Martin-de-Saavedra M.D., et al., Involvement of PI3K, GSK-3beta and PPARgamma in the antidepressant-like effect of folic acid in the forced swimming test in mice, J. Psychopharmacol., 2012, 26, 714-723

[122] Li N., Lee B., Liu R.J., Banasr M., Dwyer J.M., Iwata M., et al., mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists, Science, 2010, 329, 959-964

[123] Li N., Liu R.J., Dwyer J.M., Banasr M., Lee B., Son H., et al., Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure, Biol. Psychiatry, 2011, 69, 754-761

[124] Autry A.E., Adachi M., Nosyreva E., Na E.S., Los M.F., Cheng P.F., et al., NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses, Nature, 2011, 475, 91-95

[125] Karege F., Perroud N., Burkhardt S., Fernandez R., Ballmann E., La Harpe R., et al., Protein levels of beta-catenin and activation state of glycogen synthase kinase-3beta in major depression. A study with postmortem prefrontal cortex, J. Affect. Disord., 2012, 136, 185-188

[126] Inkster B., Nichols T.E., Saemann P.G., Auer D.P., Holsboer F., Muglia P., et al., Association of GSK3beta polymorphisms with brain structural changes in major depressive disorder, Arch. Gen. Psychiat., 2009, 66, 721-728

[127] Gould T.D., Einat H., Bhat R.,Manji H.K., AR-A014418, a selective GSK-3 inhibitor, produces antidepressant-like effects in the forced swim test, Int. J. Neuropsychopharmacol., 2004, 7, 387-390

[128] Kaidanovich-Beilin O., Milman A., Weizman A., Pick C.G.,Eldar-Finkelman H., Rapid antidepressive-like activity of specific glycogen synthase kinase-3 inhibitor and its effect on beta-catenin in mouse hippocampus, Biol. Psychiatry, 2004, 55, 781-784

[129] Kaidanovich-Beilin O., Lipina T.V., Takao K., van Eede M., Hattori S., Laliberte C., et al., Abnormalities in brain structure and behavior in GSK-3alpha mutant mice, Mol. Brain, 2009, 2, 35

[130] O'Brien W.T., Harper A.D., Jove F., Woodgett J.R., Maretto S., Piccolo S., et al., Glycogen synthase kinase-3beta haploinsufficiency mimics the behavioral and molecular effects of lithium, J. Neurosci., 2004, 24, 6791-6798

[131] Polter A., Beurel E., Yang S., Garner R., Song L., Miller C.A., et al., Deficiency in the inhibitory serine-phosphorylation of glycogen synthase kinase-3 increases sensitivity to mood disturbances, Neuropsychopharmacology, 2010, 35, 1761-1774

[132] Beurel E., Song L., Jope R.S., Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice, Mol. Psychiatr., 2011, 16, 1068-1070

[133] Gould T.D., O'Donnell K.C., Picchini A.M., Dow E.R., Chen G.,Manji H.K., Generation and behavioral characterization of beta-catenin forebrain-specific conditional knock-out mice, Behav. Brain Res., 2008, 189, 117-125

[134] Gould T.D., Einat H., O'Donnell K.C., Picchini A.M., Schloesser R.J.,Manji H.K., Beta-catenin overexpression in the mouse brain phenocopies lithium-sensitive behaviors, Neuropsychopharmacology, 2007, 32, 2173-2183

[135] Duman R.S., Pathophysiology of depression: the concept of synaptic plasticity, Eur. Psychiatry, 2002, 17, Suppl. 3, 306-310
[136] Sheline Y.I., Wang P.W., Gado M.H., Csernansky J.G.,Vannier M.W., Hippocampal atrophy in recurrent major depression, Proc. Natl. Acad. Sci. USA, 1996, 93, 3908-3913
[137] Bremner J.D., Narayan M., Anderson E.R., Staib L.H., Miller H.L.,Charney D.S., Hippocampal volume reduction in major depression, Am. J. Psychiatry, 2000, 157, 115-118
[138] Frodl T., Meisenzahl E.M., Zetzsche T., Born C., Groll C., Jager M., et al., Hippocampal changes in patients with a first episode of major depression, Am. J. Psychiatry, 2002, 159, 1112-1118
[139] MacQueen G.M., Campbell S., McEwen B.S., Macdonald K., Amano S., Joffe R.T., et al., Course of illness, hippocampal function, and hippocampal volume in major depression, Proc. Natl. Acad. Sci. USA, 2003, 100, 1387-1392
[140] Campbell S.,Macqueen G., The role of the hippocampus in the pathophysiology of major depression, J. Psychiatry Neurosci., 2004, 29, 417-426
[141] Videbech P., Ravnkilde B., Hippocampal volume and depression: a meta-analysis of MRI studies, Am. J. Psychiatry, 2004, 161, 1957-1966
[142] Fuchs E., Flugge G.,Czeh B., Remodeling of neuronal networks by stress, Front. Biosci., 2006, 11, 2746-2758
[143] Radley J.J., Rocher A.B., Miller M., Janssen W.G., Liston C., Hof P.R., et al., Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex, Cereb. Cortex, 2006, 16, 313-320
[144] Izquierdo A., Wellman C.L., Holmes A., Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice, J. Neurosci., 2006, 26, 5733-5738
[145] Lamont S.R., Paulls A.,Stewart C.A., Repeated electroconvulsive stimulation, but not antidepressant drugs, induces mossy fibre sprouting in the rat hippocampus, Brain Res., 2001, 893, 53-58
[146] Norrholm S.D., Ouimet C.C., Altered dendritic spine density in animal models of depression and in response to antidepressant treatment, Synapse, 2001, 42, 151-163
[147] Hajszan T., MacLusky N.J., Leranth C., Short-term treatment with the antidepressant fluoxetine triggers pyramidal dendritic spine synapse formation in rat hippocampus, Eur. J. Neurosci., 2005, 21, 1299-1303
[148] Duman R.S., Aghajanian G.K., Synaptic dysfunction in depression: potential therapeutic targets, Science, 2012, 338, 68-72
[149] Tolwani R.J., Buckmaster P.S., Varma S., Cosgaya J.M., Wu Y., Suri C., et al., BDNF overexpression increases dendrite complexity in hippocampal dentate gyrus, Neuroscience, 2002, 114, 795-805
[150] Kumar V., Zhang M.X., Swank M.W., Kunz J.,Wu G.Y., Regulation of dendritic morphogenesis by Ras-PI3K-Akt-mTOR and Ras-MAPK signaling pathways, J. Neurosci., 2005, 25, 11288-11299
[151] Rodgers E.E., Theibert A.B., Functions of PI 3-kinase in development of the nervous system, Int. J. Dev. Neurosci., 2002, 20, 187-197
[152] Golden S.A., Russo S.J., Mechanisms of psychostimulant-induced structural plasticity, Cold Spring Harb. Perspect. Med., 2012, 2, pii: a011957
[153] Dietz D.M., Dietz K.C., Nestler E.J., Russo S.J., Molecular mechanisms of psychostimulant-induced structural plasticity, Pharmacopsychiatry, 2009, 42 Suppl. 1, S69-78
[154] Giachello C.N., Fiumara F., Giacomini C., Corradi A., Milanese C., Ghirardi M., et al., MAPK/Erk-dependent phosphorylation of synapsin mediates formation of functional synapses and short-term homosynaptic plasticity, J. Cell Sci., 2010, 123, 881-893
[155] Malberg J.E., Duman R.S., Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment, Neuropsychopharmacology, 2003, 28, 1562-1571
[156] Santarelli L., Saxe M., Gross C., Surget A., Battaglia F., Dulawa S., et al., Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants, Science, 2003, 301, 805-809
[157] Surget A., Saxe M., Leman S., Ibarguen-Vargas Y., Chalon S., Griebel G., et al., Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal, Biol. Psychiatry, 2008, 64, 293-301
[158] Overstreet D.H., Fredericks K., Knapp D., Breese G.,McMichael J., Nerve growth factor (NGF) has novel antidepressant-like properties in rats, Pharmacol. Biochem. Behav., 2010, 94, 553-560
[159] David D.J., Samuels B.A., Rainer Q., Wang J.W., Marsteller D., Mendez I., et al., Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression, Neuron, 2009, 62, 479-493
[160] Lee J., Duan W., Mattson M.P., Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice, J. Neurochem., 2002, 82, 1367-1375
[161] Rossi C., Angelucci A., Costantin L., Braschi C., Mazzantini M., Babbini F., et al., Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment, Eur. J. Neurosci., 2006, 24, 1850-1856
[162] Sairanen M., Lucas G., Ernfors P., Castren M.,Castren E., Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus, J. Neurosci., 2005, 25, 1089-1094
[163] Henry R.A., Hughes S.M.,Connor B., AAV-mediated delivery of BDNF augments neurogenesis in the normal and quinolinic acid-lesioned adult rat brain, Eur. J. Neurosci., 2007, 25, 3513-3525
[164] Zigova T., Pencea V., Wiegand S.J.,Luskin M.B., Intraventricular administration of BDNF increases the number of newly generated neurons in the adult olfactory bulb, Mol. Cell. Neurosci., 1998, 11, 234-245
[165] Scharfman H., Goodman J., Macleod A., Phani S., Antonelli C.,Croll S., Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats, Exp. Neurol., 2005, 192, 348-356
[166] Schabitz W.R., Steigleder T., Cooper-Kuhn C.M., Schwab S., Sommer C., Schneider A., et al., Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis, Stroke, 2007, 38, 2165-2172
[167] Shimazu K., Zhao M., Sakata K., Akbarian S., Bates B., Jaenisch R., et al., NT-3 facilitates hippocampal plasticity and learning and memory

by regulating neurogenesis, Learn. Mem., 2006, 13, 307-315
[168] Frielingsdorf H., Simpson D.R., Thal L.J., Pizzo D.P., Nerve growth factor promotes survival of new neurons in the adult hippocampus, Neurobiol. Dis., 2007, 26, 47-55
[169] Fournier N.M., Lee B., Banasr M., Elsayed M.,Duman R.S., Vascular endothelial growth factor regulates adult hippocampal cell proliferation through MEK/ERK- and PI3K/Akt-dependent signaling, Neuropharmacology, 2012, 63, 642-652
[170] Peltier J., O'Neill A.,Schaffer D.V., PI3K/Akt and CREB regulate adult neural hippocampal progenitor proliferation and differentiation, Dev. Neurobiol., 2007, 67, 1348-1361
[171] Eom T.Y., Jope R.S., Blocked inhibitory serine-phosphorylation of glycogen synthase kinase-3alpha/beta impairs in vivo neural precursor cell proliferation, Biol. Psychiatry, 2009, 66, 494-502
[172] Sirerol-Piquer M., Gomez-Ramos P., Hernandez F., Perez M., Moran M.A., Fuster-Matanzo A., et al., GSK3beta overexpression induces neuronal death and a depletion of the neurogenic niches in the dentate gyrus, Hippocampus, 2011, 21, 910-922
[173] Salton S.R., Ferri G.L., Hahm S., Snyder S.E., Wilson A.J., Possenti R., et al., VGF: a novel role for this neuronal and neuroendocrine polypeptide in the regulation of energy balance, Front. Neuroendocrinol., 2000, 21, 199-219
[174] Hunsberger J.G., Newton S.S., Bennett A.H., Duman C.H., Russell D.S., Salton S.R., et al., Antidepressant actions of the exercise-regulated gene VGF, Nat. Med., 2007, 13, 1476-1482
[175] Thakker-Varia S., Krol J.J., Nettleton J., Bilimoria P.M., Bangasser D.A., Shors T.J., et al., The neuropeptide VGF produces antidepressant-like behavioral effects and enhances proliferation in the hippocampus, J. Neurosci., 2007, 27, 12156-12167
[176] Calabrese F., Molteni R., Cattaneo A., Macchi F., Racagni G., Gennarelli M., et al., Long-Term duloxetine treatment normalizes altered brain-derived neurotrophic factor expression in serotonin transporter knockout rats through the modulation of specific neurotrophin isoforms, Mol. Pharmacol., 2010, 77, 846-853
[177] Bozdagi O., Rich E., Tronel S., Sadahiro M., Patterson K., Shapiro M.L., et al., The neurotrophin-inducible gene VGF regulates hippocampal function and behavior through a brain-derived neurotrophic factor-dependent mechanism, J. Neurosci., 2008, 28, 9857-9869
[178] Lyford G.L., Yamagata K., Kaufmann W.E., Barnes C.A., Sanders L.K., Copeland N.G., et al., Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites, Neuron, 1995, 14, 433-445
[179] Link W., Konietzko U., Kauselmann G., Krug M., Schwanke B., Frey U., et al., Somatodendritic expression of an immediate early gene is regulated by synaptic activity, Proc. Natl. Acad. Sci. USA, 1995, 92, 5734-5738
[180] Pei Q., Zetterstrom T.S., Sprakes M., Tordera R., Sharp T., Antidepressant drug treatment induces Arc gene expression in the rat brain, Neuroscience, 2003, 121, 975-982
[181] Molteni R., Calabrese F., Mancini M., Racagni G.,Riva M.A., Basal and stress-induced modulation of activity-regulated cytoskeletal associated protein (Arc) in the rat brain following duloxetine treatment, Psychopharmacology (Berl.), 2008, 201, 285-292
[182] Alme M.N., Wibrand K., Dagestad G., Bramham C.R., Chronic fluoxetine treatment induces brain region-specific upregulation of genes associated with BDNF-induced long-term potentiation, Neural Plast., 2007, 2007, 26496
[183] Larsen M.H., Olesen M., Woldbye D.P., Hay-Schmidt A., Hansen H.H., Ronn L.C., et al., Regulation of activity-regulated cytoskeleton protein (Arc) mRNA after acute and chronic electroconvulsive stimulation in the rat, Brain Res., 2005, 1064, 161-165
[184] Elizalde N., Pastor P.M., Garcia-Garcia A.L., Serres F., Venzala E., Huarte J., et al., Regulation of markers of synaptic function in mouse models of depression: chronic mild stress and decreased expression of VGLUT1, J. Neurochem., 2010, 114, 1302-1314
[185] Covington H.E. 3rd, Lobo M.K., Maze I., Vialou V., Hyman J.M., Zaman S., et al., Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex, J. Neurosci., 2010, 30, 16082-16090
[186] Molteni R., Calabrese F., Maj P.F., Olivier J.D., Racagni G., Ellenbroek B.A., et al., Altered expression and modulation of activity-regulated cytoskeletal associated protein (Arc) in serotonin transporter knockout rats, Eur. Neuropsychopharmacol., 2009, 19, 898-904
[187] Eriksson T.M., Delagrange P., Spedding M., Popoli M., Mathe A.A., Ogren S.O., et al., Emotional memory impairments in a genetic rat model of depression: involvement of 5-HT/MEK/Arc signaling in restoration, Mol. Psychiatr., 2012, 17, 173-184
[188] Ons S., Marti O., Armario A., Stress-induced activation of the immediate early gene Arc (activity-regulated cytoskeleton-associated protein) is restricted to telencephalic areas in the rat brain: relationship to c-fos mRNA, J. Neurochem., 2004, 89, 1111-1118
[189] Mikkelsen J.D., Larsen M.H., Effects of stress and adrenalectomy on activity-regulated cytoskeleton protein (Arc) gene expression, Neurosci. Lett., 2006, 403, 239-243
[190] Fujino T., Leslie J.H., Eavri R., Chen J.L., Lin W.C., Flanders G.H., et al., CPG15 regulates synapse stability in the developing and adult brain, Genes Dev., 2011, 25, 2674-2685
[191] Son H., Banasr M., Choi M., Chae S.Y., Licznerski P., Lee B., et al., Neuritin produces antidepressant actions and blocks the neuronal and behavioral deficits caused by chronic stress, Proc. Natl. Acad. Sci. USA, 2012, 109, 11378-11383
[192] Cunha C., Brambilla R.,Thomas K.L., A simple role for BDNF in learning and memory?, Front. Mol. Neurosci., 2010, 3, 1
[193] Li Z., Tan F., Thiele C.J., Inactivation of glycogen synthase kinase-3beta contributes to brain-derived neutrophic factor/TrkB-induced resistance to chemotherapy in neuroblastoma cells, Mol. Cancer Ther., 2007, 6, 3113-3121
[194] Blum R.,Konnerth A., Neurotrophin-mediated rapid signaling in the central nervous system: mechanisms and functions, Physiology (Bethesda), 2005, 20, 70-78
[195] Yoshii A., Constantine-Paton M., Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease, Dev. Neurobiol., 2010, 70, 304-322