ELSEVIER

Role of neurotrophic factors in depression

Eero Castrén, Vootele Võikar and Tomi Rantamäki

Major depression is associated with reduced volumes in the hippocampus and prefrontal cortex, whereas antidepressant treatments promote several forms of neuronal plasticity, including neurogenesis, synaptogenesis and neuronal maturation, in the hippocampus. Several neurotrophic factors are associated with depression or antidepressant action. Stress suppresses brain-derived neurotrophic factor (BDNF) synthesis in the hippocampus, at least partially through a sustained modification of chromatin structure. Essentially all antidepressant treatments increase BDNF synthesis and signaling in the hippocampus and prefrontal cortex. This signaling is required for the behavioral effects of antidepressant drugs in rodents, and increased BDNF levels in the hippocampus mimic the behavioral effects of antidepressants. However, injection of BDNF into the mesolimbic dopamine pathway produces an opposing depression-like response. One hypothesis emerging from these data proposes that mood disorders reflect failed function of critical neuronal networks, whereas a gradual network recovery through activity-dependent neuronal plasticity induces the antidepressant effect. Neurotrophic factors themselves do not control mood, but they act as necessary tools in the activity-dependent modulation of networks, the physiological function of which determines how a plastic change influences mood.

Addresses
Sigrid Jusélius Laboratory of Molecular Neuroscience, Neuroscience Center, University of Helsinki, PO Box 56, 00014 Helsinki, Finland

Corresponding author: Castrén, Eero (eero.castren@helsinki.fi)

Current Opinion in Pharmacology 2007, **7**:18–21

This review comes from a themed issue on
Neurosciences
Edited by Karima Chergui, Bertil Fredholm and Per Svenningsson

Available online 17th October 2006

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2006.08.009

Introduction

Neurotrophic factors are critical regulators of the formation and plasticity of neuronal networks [1]. Of these neurotrophic factors, the neurotrophin family — comprising nerve growth factor, brain-derived neurotrophic factor (BDNF), neurotrophin-3 and neurotrophin-4 — is the best characterized. However, other factors such as members of the insulin-like growth factor (IGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) families also regulate neuronal plasticity. Recently, the involvement of neurotrophic factors, particularly BDNF and its tyrosine kinase receptor TrkB, in the regulation of mood disorders and antidepressant effects has been under intense investigation. These studies, which are briefly reviewed below (for more comprehensive recent reviews, please see [2–4]), have led to the formulation of the neurotrophic hypothesis of depression, which proposes that reduced brain BDNF levels predispose to depression, whereas increases in brain BDNF levels produce an antidepressant action. However, several recent observations, together with information gained on the basic role of neurotrophins in the developing and adult brain, suggest a modified neurotrophic hypothesis which emphasises the role of BDNF as a tool of experience-dependent modifications in neural networks that regulate different aspects of mood.

BDNF in depression and stress

In humans, brain BDNF levels have been found to be reduced in postmortem samples from depressed patients, and antidepressant therapy restores brain BDNF levels to the normal range [2,5]. BDNF is found in the blood, where it mostly accumulates in platelets. Interestingly, several studies have found decreased blood levels of BDNF in depressed patients and, again, antidepressant therapy appears to normalize this change [6,7]; however, the relevance of these findings to the action of BDNF in the brain remains to be established. Furthermore, a polymorphism in the *BDNF* coding region, which produces pro-BDNF with either valine or methionine in position 66, has been associated with mood disorders in several (albeit not in all) depressed populations [2]. Interestingly, this polymorphism is also associated with other disorders, including anxiety, obsessive-compulsive disorder and eating disorders, which are successfully treated with antidepressant drugs [2].

Chronic stress is widely used as a model for mood disorders in experimental animals [8]. Stress reduces BDNF expression in the hippocampus and this reduction can be prevented by antidepressant drug treatment [9••,10]. Stressed animals and depressed patients show reduced volume of the hippocampus, and at least part of this effect can be counteracted by antidepressant drugs [8,10]. Whether neurotrophic factors are directly involved in this volume reduction is currently unclear.

BDNF and antidepressant drug action

Several studies have suggested that normal BDNF signaling is both necessary and sufficient for antidepressant drug action. We have recently found that antidepressants acting through different mechanisms rapidly increase

TrkB activation and signaling within an hour of drug administration [11,12] (Rantamäki and Castrén, unpublished). Antidepressant-induced tyrosine phosphorylation of TrkB does not induce activity of the extracellular signal-regulated kinase pathway, but does activate phospholipase-Cγ signaling and lead to the phosphorylation of cAMP-related element binding protein (Rantamäki and Castrén, unpublished), a major transcription factor directing gene expression of plasticity-related molecules. After several days of treatment, essentially all antidepressant treatments, including electroconvulsive shock treatment (ECT), antidepressant drugs and lithium, increase expression of BDNF mRNA in the hippocampus and cortex (reviewed in [4]). Thus, all antidepressants, regardless of their primary mechanism of action, share the ability to rapidly activate TrkB signaling and induce a long-lasting increase in BDNF production.

An extremely illuminating study revealed the role of chromatin remodeling in stress and antidepressant treatment, and suggested molecular explanations for several puzzling observations related to depression and antidepressant treatment [9••]. Chromatin remodeling, such as methylation or acetylation of histone subunits which wrap around chromosomal DNA, regulate the activity of gene transcription. The study reported that social defeat stress in mice produces long-lasting methylation of histone-3 subunits around the *BDNF* gene promoter region and that increased methylation correlates with suppression of *BDNF* gene transcription. This suggests that chronic stress can mark a long-lasting repressive state, which lasts for at least a month after the cessation of the stressor. Chronic anti-depressant treatment counteracted the reduction in BDNF mRNA; however, it did not reverse the methylation of histone 3, but instead induced another modification — acetylation — at the same histone subunit. This effect was mediated by anti-depressant-induced downregulation of histone deacetylase-5. Thus, although imipramine restored the level of BDNF mRNA expression suppressed by social stress, this was a compensatory effect at the chromatin level and did not 'cure' the underlying sustained histone methylation. Interestingly, imipramine induced histone acetylation in mice previously exposed to social stress but not in non-stressed controls. This might explain why antidepressant treatment helps depressed patients but does not affect the mood of healthy controls. *BDNF* is not the only gene epigenetically modified at the chromatin level by traumatic experiences and drug treatments, and therefore this landmark study should open up several new avenues for fruitful research.

We recently found that the behavioral responses produced by antidepressants in the forced swim test are lost in mice with either reduced brain BDNF levels or inhibited TrkB signaling [12], and these observations have subsequently been confirmed [13,14]. These data suggest that increased BDNF signaling is required for the normal behavioral response to antidepressant drugs, at least in experimental animals. Furthermore, BDNF signaling appears to be sufficient for antidepressant effects, as direct infusion of BDNF into midbrain areas or hippocampus induces behavioral responses that are similar to those produced by antidepressants [4]. Increased TrkB signaling produced by overexpression of TrkB in neurons also mimics the effects of antidepressants; moreover, the effects of antidepressants and TrkB overexpression are not additive [15], suggesting that their effects may be mediated through a common mechanism.

Chronic antidepressant treatment induces several plastic changes in the rodent forebrain [2–4]. ECT and antidepressant drugs both increase neurogenesis and the turnover of dentate granule neurons [10,16•]. When neurogenesis is prevented, the behavioral responses to antidepressants are lost [17]. BDNF signaling does not appear to play a role in antidepressant-induced neurogenesis, but is required for the long-term survival of newborn hippocampal granule neurons [16•]. In addition to neurogenesis, ECT increases dendritic sprouting in the hippocampus, and this response is attenuated in mice with reduced BDNF levels in the brain [18]. Furthermore, antidepressant treatment promotes morphological maturity of newly born neurons [19] and enhances synaptogenesis in many regions of the hippocampus, including the CA1 area where neurogenesis does not occur [20•]. We have recently observed that chronic antidepressant treatment induces the expression of plasticity-related proteins, such as phosphorylated CREB and polysialylated neural cell adhesion molecule, specifically in the hippocampus and prefrontal cortex [21]. Together, these data suggest that antidepressant treatment induces a relatively broad increase in neuronal plasticity, at least in the hippocampus. To what extent this increase is dependent upon BDNF signaling remains to be investigated.

Does BDNF control mood?

A straightforward interpretation of the data reviewed above is that mood is dependent upon and directly proportional to the levels of BDNF expression in the brain. However, several recent observations suggest that the relationship between neurotrophins and depression is more complex than originally thought. Although BDNF signaling is clearly involved in the antidepressant response, reduction of BDNF levels or BDNF signaling does not produce depression-like symptoms [4,12]. We have found that inhibition of BDNF signaling by overexpression of the dominant-negative TrkB receptor fails to induce depression-like effects in the forced swim test [12], but these mice do show an anxiety-type behavioral phenotype (Voikar and Castrén, unpublished). Conversely, increased TrkB signaling produced by overexpression of TrkB reduces anxiety and depressive-like behavior [15,22]. Interestingly, behavioral effects in

BDNF conditional mutant mice might be gender dependent: female mice with forebrain-specific BDNF deletion showed increased immobility in a forced swim test, consistent with depression-related behavior, whereas male mice with the same genotype did not show this behaviour [14].

Whereas infusion of BDNF into the hippocampus and raphe-nucleus region mimics behavioral effects of antidepressants, infusion of BDNF into the ventral tegmental area (VTA) produces an opposing depression-like phenotype [23]. This response appears to involve activity of the mesolimbic dopamine pathways that extend from the VTA to the nucleus accumbens, as inhibition of BDNF signaling in the nucleus accumbens by virus-mediated expression of the dominant-negative TrkB isoform increases the latency to immobility in the forced swim test (an antidepressant-like response) [23]. Furthermore, the depression-like behavioral effects produced by social defeat stress are dependent upon intact BDNF signaling in the mesolimbic dopamine pathway; these behavioral effects were blocked by local elimination of BDNF within the VTA or by chronic antidepressant treatment [24•]. Microarray analysis revealed that both inhibition of BDNF and chronic antidepressant treatment largely prevented changes in gene expression produced by social defeat stress [24•]. These important studies strongly suggest that depression and antidepressant effects are not related to levels of BDNF expression in the brain through any simple correlation. Rather, the studies are consistent with the interpretation that BDNF is a critical tool required for activity-dependent modifications in the structure of neuronal networks, and it is the function of these networks that determines whether activity-dependent plasticity produces a depression-like or antidepressant behavioral response. The functional consequences of plasticity in hippocampal–prefrontal network and mesolimbic pathways produce opposite effects, as far as depression-related behavior is concerned [25] and, therefore, it is not surprising that increased BDNF levels and inhibition of TrkB signaling produce different effects in these two networks.

Other neurotrophic factors and depression

In addition to the above-mentioned neurotrophins, members of other neurotrophic factor families also play a role in mood disorders and antidepressant drug action [4]. Dysregulation of several members of the FGF family and their receptors has been found to occur in brains of patients with major depressive disorder [26], and FGFs are regulated by antidepressant drugs [27]. IGF-I is also increased in the hippocampus by antidepressants [28], and IGF-I infusion into the brain produces behavioral responses similar to those of antidepressants and BDNF [29•]. VEGF is a key regulator of endothelial proliferation and neovascularization, but also stimulates neurogenesis in the hippocampus. ECT and fluoxetine increase cell proliferation not only in the hippocampus but also in the prefrontal cortex; however, in this brain area, cells do not differentiate into neurons, but rather into endothelial cells [30,31]. Chronic antidepressant drug treatment increases VEGF expression in the hippocampus [32]. Together, these data clearly demonstrate that many different factors with neurotrophic properties are able to produce antidepressant-like behavioral responses in experimental animals, and more factors with this potential are likely to be identified. It is probable that these behavioral responses correlate with plastic changes in neuronal pathways important in mood regulation.

Conclusions

A new view of the pathophysiology of mood disorders and antidepressant drug action is emerging from research performed during the past decade [3]. This view emphasizes defects in information processing within critical neural networks as the mechanisms underlying mood disorders, as well as the role of plasticity-induced network recovery in antidepressant treatment. Recent findings suggest that early childhood events and adult stress produce neurodegenerative changes in the brain that can eventually lead to breakdown of information processing in the neuronal networks regulating mood. Successful antidepressant treatments promote activity-dependent neuronal plasticity by activating neurotrophic factor systems, thereby gradually restoring network function and mood. The next challenge is to translate this improved understanding into better clinical strategies for the treatment and prevention of mood disorders.

Acknowledgements

We would like to thank Olivia O'Leary for her comments on the manuscript, as well as Sigrid Jusélius Foundation, Academy of Finland and Päivikki and Sakari Sohlberg Foundation for financial support.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Huang EJ, Reichardt LF: **Neurotrophins: roles in neuronal development and function**. *Annu Rev Neurosci* 2001, **24**:677-736.

2. Castrén E: **Neurotrophic effects of antidepressant drugs**. *Curr Opin Pharmacol* 2004, **4**:58-64.

3. Castrén E: **Is mood chemistry?** *Nat Rev Neurosci* 2005, **6**:241-246.

4. Duman RS, Monteggia LM: **A neurotrophic model for stress-related mood disorders**. *Biol Psychiatry* 2006, **59**:1116-1127.

5. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT: **Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication**. *Biol Psychiatry* 2001, **50**:260-265.

6. Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, 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 Psychiatry* 2005, **57**:1068-1072.

7. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato M, Watanabe H, Shinoda N, Okada S, Iyo M: **Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants**. *Biol Psychiatry* 2003, **54**:70-75.

8. Fuchs E, Czeh B, Kole MHP, Michaelis T, Lucassen PJ: **Alterations of neuroplasticity in depression: the hippocampus and beyond**. *Eur Neuropsychopharmacol* 2004, **14**:S481-S490.

9. •• Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ: **Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action**. *Nat Neurosci* 2006, **9**:519-525.
This study shows that social defeat stress produces a sustained suppression of *BDNF* transcription through histone methylation, whereas antidepressants restore BDNF synthesis through histone acetylation. Antidepressants reduce histone deacetylase-5, and overexpression of this enzyme in the hippocampus prevents the effects of antidepressants on *BDNF* mRNA.

10. Warner-Schmidt JL, Duman RS: **Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment**. *Hippocampus* 2006, **16**:239-249.

11. Rantamaki T, Knuuttila JE, Hokkanen ME, Castren E: **The effects of acute and long-term lithium treatments on trkB neurotrophin receptor activation in the mouse hippocampus and anterior cingulate cortex**. *Neuropharmacology* 2006, **50**:421-427.

12. Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, Agerman K, Haapasalo A, Nawa H, Aloyz R *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.

13. Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, Meuth S, Nagy A, Greene RW, Nestler EJ: **Essential role of brain-derived neurotrophic factor in adult hippocampal function**. *Proc Natl Acad Sci USA* 2004, **101**:10827-10832.

14. Monteggia LM, Luikart B, Barrot M, Theobold D, Malkovska I, Nef S, Parada LF, Nestler EJ: **Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors**. *Biol Psychiatry* 2006, in press.

15. Koponen E, Rantamaki T, Voikar V, Saarelainen T, MacDonald E, Castren E: **Enhanced BDNF signaling is associated with an antidepressant-like behavioral response and changes in brain monoamines**. *Cell Mol Neurobiol* 2005, **25**:973-980.

16. • 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.
This paper shows that inhibition of BDNF signaling does not influence antidepressant-induced neurogenesis, but that BDNF is required for the long-term survival of the newborn dentate granule neurons.

17. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O *et al.*: **Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants**. *Science* 2003, **301**:805-809.

18. Vaidya VA, Siuciak JA, Du F, Duman RS: **Hippocampal mossy fiber sprouting induced by chronic electroconvulsive seizures**. *Neuroscience* 1999, **89**:157-166.

19. Fujioka T, Fujioka A, Duman RS: **Activation of cAMP signaling facilitates the morphological maturation of newborn neurons in adult hippocampus**. *J Neurosci* 2004, **24**:319-328.

20. • Hajszan T, MacLusky NJ, 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.
This paper shows that antidepressants increase synaptogenesis in the hippocampus, both in the CA1 region where neurogenesis does not occur, and subsequently in the CA3 region, which is the target of newborn dentate granule neurons.

21. Sairanen M, O'Leary OF, Knuuttila JE, Castrén E: **Chronic antidepressant treatment selectively increases expression of plasticity-related proteins in the hippocampus and medial prefrontal cortex of the rat**. *Neuroscience* 2006, in press.

22. Koponen E, Võikar V, Riekki R, Saarelainen T, Rauramaa T, Rauvala H, Taira T, Castrén E: **Transgenic mice overexpressing the full-length neurotrophin receptor trkB exhibit increased activation of trkB/PLCγ pathway, reduced anxiety, and facilitated learning**. *Mol Cell Neurosci* 2004, **26**:166-181.

23. Eisch AJ, Bolanos CA, De Wit J, Simonak RD, Pudiak CM, Barrot M, Verhaagen J, Nestler EJ: **Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: a role in depression**. *Biol Psychiatry* 2003, **54**:994-1005.

24. • Berton O, McClung CA, DiLeone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M *et al.*: **Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress**. *Science* 2006, **311**:864-868.
Deletion of BDNF from the mesolimbic dopamine pathway blocks the depression-like behavior produced by repeated social defeat. BDNF deletion mimics both the behavioral and gene expression effects of antidepressant drugs.

25. Nestler EJ, Carlezon WA Jr: **The mesolimbic dopamine reward circuit in depression**. *Biol Psychiatry* 2006, **59**:1151-1159.

26. Evans SJ, Choudary PV, Neal CR, Li JZ, Vawter MP, Tomita H, Lopez JF, Thompson RC, Meng F, Stead JD *et al.*: **Dysregulation of the fibroblast growth factor system in major depression**. *Proc Natl Acad Sci USA* 2004, **101**:15506-15511.

27. Riva MA, Molteni R, Bedogni F, Racagni G, Fumagalli F: **Emerging role of the FGF system in psychiatric disorders**. *Trends Pharmacol Sci* 2005, **26**:228-231.

28. Khawaja X, Xu J, Liang JJ, Barrett JE: **Proteomic analysis of protein changes developing in rat hippocampus after chronic antidepressant treatment: Implications for depressive disorders and future therapies**. *J Neurosci Res* 2004, **75**:451-460.

29. • Hoshaw BA, Malberg JE, Lucki I: **Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects**. *Brain Res* 2005, **1037**:204-208.
Brain injection of either IGF-1 or BDNF mimics the behavioral response of antidepressants in the forced swim test, and the effects are long-lasting.

30. Kodama M, Fujioka T, Duman RS: **Chronic olanzapine or fluoxetine administration increases cell proliferation in hippocampus and prefrontal cortex of adult rat**. *Biol Psychiatry* 2004, **56**:570-580.

31. Madsen TM, Yeh DD, Valentine GW, Duman RS: **Electroconvulsive seizure treatment increases cell proliferation in rat frontal cortex**. *Neuropsychopharmacology* 2005, **30**:27-34.

32. Newton SS, Collier EF, Hunsberger J, Adams D, Terwilliger R, Selvanayagam E, Duman RS: **Gene profile of electroconvulsive seizures: induction of neurotrophic and angiogenic factors**. *J Neurosci* 2003, **23**:10841-10851.