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New insights into BDNF function in depression and anxiety

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The 'neurotrophin hypothesis of depression' is based largely on correlations between stress or antidepressant treatment and down- or upregulation, respectively, of brain-derived neurotrophic factor (BDNF). Genetic disruption of the signaling pathways involving BDNF and its receptor, the tyrosine kinase TrkB, does not seem to cause depressive behaviors, but does hamper the effect of antidepressant drugs. Thus, BDNF may be a target of antidepressants, but not the sole mediator of depression or anxiety. Advances in BDNF cell biology, including its transcription through multiple promoters, trafficking and secretion, may provide new insights into its role in mood disorders. Moreover, as the precursor proBDNF and the mature protein mBDNF can elicit opposite effects on cellular functions, the impact of proBDNF and its cleavage on mood should be considered. Opposing influences of mBDNF and proBDNF on long-term potentiation and long-term depression might contribute to the dichotomy of BDNF actions on behaviors mediated by the brain stress and reward systems.

Mood and anxiety disorders are among the most disabling of all medical disorders. They frequently appear early in life, run a chronic course and adversely affect the prognosis of other medical illnesses[1]. Understanding the cellular and molecular bases of these disorders is crucial in the effort to effect new treatments. BDNF, a secretory protein in the neurotrophin family, has been implicated in both depression and anxiety. The 'neurotrophin hypothesis of depression' is based largely on observations that decreases in hippocampal BDNF levels are correlated with stress-induced depressive behaviors and that antidepressant treatment enhances the expression of *Bdnf*[2]. Despite extensive studies over the past decade, a number of key questions remain to be fully addressed. Does BDNF dysfunction lead to depression? Are antidepressant effects mediated by BDNF, and, if so, which facets of the overall antidepressant response (for example, mood, motivation, cognition) are affected? Recent progress in understanding the cell biology of BDNF may provide new avenues examining its role in mood disorders. For example, multiple promoters drive *Bdnf* transcription, and antidepressants seem to act selectively at some promoters, but not others[3–5]. Such findings encourage a more mechanistic delineation of potential causal relationships between BDNF and discrete aspects of these complex illnesses. Future studies will benefit from separating BDNF's role in mediating depressive and anxiety behaviors from those involved in antidepressant drug action. Moreover, emerging evidence indicates that BDNF may have different and perhaps opposing roles in the brain stress system, including the hippocampus and hypothalamus-pituitary-adrenocortical (HPA) axis, and in the brain reward system, including the nucleus accumbens (NAc) and the ventral tegmental area (VTA)[6,7]. Finally, BDNF is first synthesized as a precursor proBDNF, which is proteolytically cleaved to generate mature BDNF (mBDNF). Recent studies have demonstrated that proBDNF and mBDNF facilitate long-term depression (LTD) and long-term potentiation (LTP), respectively, implying opposing cellular functions[8–10]. Thus, it is important to determine whether depressive and anxiety-like behaviors or antidepressant effects are mediated by signaling through proBDNF or through mBDNF. We discuss how these new findings affect our understanding of BDNF in mood disorders.

Stress, antidepressants and BDNF

As stressful life events have a substantial causal association with depression and anxiety[1,11], stress paradigms have long been used to model these diseases. Notably, it has been shown that stress can lead to neuronal atrophy and loss in several brain regions, including the hippocampus[2,11]. Numerous studies have also documented that stress decreases the expression of *Bdnf* mRNA in the hippocampus[2,12]. Conversely, many classes of chemical antidepressants, as well as electroconvulsive shock treatment, can significantly increase *Bdnf* mRNA expression in the hippocampus, prefrontal cortex or both[2,4,13]. This increase depends on chronic antidepressant treatment[13], which is consistent with the slow onset of therapeutic effects of antidepressants in a clinical setting. Furthermore, limited studies have shown that direct hippocampal infusions of BDNF protein can produce antidepressant effects in rodents[14,15]. These studies support the 'neurotrophin hypothesis of depression', which postulates that reduced brain levels of BDNF could contribute to atrophy and cell loss in the hippocampus and prefrontal cortex, as observed in depressed subjects, whereas antidepressants may exert their therapeutic effects by increasing BDNF expression, thereby leading to the reversal of neuronal atrophy and cell loss[2]. Although undoubtedly heuristic, the hypothesis has yet to provide mechanistic insights into how increases or decreases in BDNF could cause an antidepressant or depressive effect.

Few human studies have attempted to address this hypothesis, but the extant data do provide some correlative support. Thus, compared with normal human subjects, levels of BDNF are lower in postmortem brain tissue from depressed patients but higher in those who were

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taking antidepressants at the time of death[16]. Furthermore, brain imaging studies have documented a reduction in hippocampal volume in depressed subjects[17], which can be attenuated by antidepressant treatment[17]. In light of these and other clinical findings, studies have attempted to identify single-nucleotide polymorphisms (SNPs) in *Bdnf* that may underlie its dysfunction in mood disorders. A SNP was identified in the region encoding BDNF's pro-domain leading to a valine at amino acid 66 being substituted with a methionine (Val66-Met). Association studies with this polymorphism have been variable, but most analyses have suggested that the Met allele is protective for bipolar disorder[18,19]. Although existing studies suggested that stress and antidepressants have opposite effects on hippocampal *Bdnf* expression, they have only correlated changes in total levels of *Bdnf* mRNA or BDNF protein. Therefore, it remains unclear which *Bdnf* transcript(s), or whether proBDNF or mBDNF, is functioning to mediate a depressive or antidepressant response.

Because stress decreases other neurotrophic factors and because electroconvulsive shock treatment and antidepressants induce the expression of other growth factors[2], attempts to validate BDNF as having a central role in the pathophysiology and treatment of depression have been complicated. As we move forward, it is imperative to recognize that in the adult brain, BDNF is primarily involved in synaptic plasticity, as opposed to cell survival or dendritic growth. In this context, it is noteworthy that recent clinical studies suggest that NMDA antagonists may produce robust antidepressant effects within two hours[20], which are likely to be mediated by changes in synaptic plasticity rather than in dendritic growth.

BDNF cell biology and mood disorders

Considerable progress has been made in our understanding of the mechanisms underlying the transcription, trafficking and secretion and processing of BDNF. These new findings may have a significant impact on our understanding of BDNF's role in the pathophysiology and treatment of mood disorders. Readers may find more detailed discussions of current advances in BDNF cell biology elsewhere[8,21].

Transcription. *Bdnf* has an extremely complex genomic structure. There are at least four promoters, each of which drives a short 5′ untranslated 'exon' that is alternatively spliced to a common 3′ coding exon encoding the BDNF protein[22]. Recent studies have revealed as many as seven promoters in the *Bdnf* gene[23], but here we use a relatively old nomenclature based on the initial characterization of four promoters in the rat[22,24]. Cumulative evidence indicates that these transcripts are differentially distributed across different brain regions, in different cell types and even within different parts of the neuron. For example, exon III transcripts are detected only in cell bodies, whereas exon IV transcripts are present in cell bodies and dendritic processes of visual cortex neurons[25]. These promoters are differentially activated in response to diverse and varied signaling events. Interestingly, different antidepressants enhance *Bdnf* expression using different combinations of promoters[3–5]. Transcription through promoter III has been well studied because it is highly responsive to neuronal activity and is therefore implicated in synapse development as well as learning and memory[24].

Remarkably, promoter III is a target of epigenetic regulation[26,27]. Promoter III transcription is suppressed by MeCP2, a transcriptional repressor that binds methylated DNA. Neuronal depolarization leads to the release of MeCP2 along with its repression complex partners, HDAC1 and Sin3a[26,27]. Furthermore, chronic social defeat stress in mice (used as a model to induce depressive-like behaviors) produces long-lasting suppression of *Bdnf* transcripts III and IV in the hippocampus by means of an increase in dimethylation of histone 3 (H3) on the chromatin of the respective promoters. H3 dimethylation is associated with chromatin compaction and can lead to an enduring repressive state, which is associated with lower levels of *Bdnf* transcription[5]. Interestingly, chronic treatment with the antidepressant imipramine counteracts the reduction in exon III transcription by inducing acetylation of H3, which is associated with a more euchromatic state[5]. These results draw attention to the possible role of chromatin remodeling and epigenetic regulation in the pathophysiology of mood disorders, an area largely unexplored until recently. As social defeat behaviors have also been correlated with changes in *Bdnf* gene expression in the VTA[6], it will be interesting to determine whether epigenetic alterations at the *Bdnf* promoter III underlie these changes as well. A key unresolved question is whether upregulation of *Bdnf* through promoter III is a main target for the therapeutic actions of antidepressants. Mouse models with promoter-specific mutations may help to address this question.

Trafficking, secretion and cleavage. All *Bdnf* transcripts are translated in the endoplasmic reticulum into proBDNF, which is then folded in the trans-Golgi and packaged into secretory vesicles where it can be sorted into either the constitutive (spontaneous release) or, more frequently, the regulated (release in response to stimuli) secretory pathway[28]. BDNF-containing vesicles are trafficked to neuronal dendrites and spines, as well as to axons and terminals. Dendritic trafficking and synaptic localization are controlled by BDNF's pro-domain, particularly in the region encompassing the Val66Met SNP ('box2/3')[29,30]. Notably, this region has a key role in activity-dependent BDNF secretion[29,30]. Biochemical and imaging experiments have demonstrated that box2/3 interacts with sortilin, a newly identified neurotrophin receptor. The BDNF-sortilin interaction is markedly reduced by the presence of the Val66Met allele. Inhibition of this interaction by expressing either a truncated sortilin lacking its transmembrane domain, box2/3 peptide or Val66Met BDNF attenuates dendritic trafficking as well as depolarization-induced secretion of BDNF[30]. In a mouse knock-in model carrying the Val66Met polymorphism, activity-dependent secretion of BDNF is significantly reduced, whereas total levels of BDNF as well as its constitutive secretion are not changed[31]. Remarkably, these mice show increased anxiety-related behaviors that cannot be normalized by antidepressants. These results demonstrate the importance of dendritic trafficking, regulated BDNF secretion or both and indicate that BDNF may be a mediator of the anxiolytic effect of antidepressants[31]. Notably, hippocampal volume in the $Bdnf^{Met/Met}$ mice is reduced; whether these animals also show depressive behaviors remains to be investigated. In a larger context, activity-dependent secretion, a feature unique to BDNF and not seen with other neurotrophins or growth factors, may be one of the key elements in mood regulation. This may explain why BDNF is more likely than other neurotrophins to be involved in mood disorders.

A large proportion of neuronal BDNF is secreted in the pro-form, which is subsequently converted to mBDNF by extracellular proteases such as plasmin or matrix metalloproteinases[32] (G. Nagappan and B.L., unpublished data). Of particular interest is tissue plasminogen activator (tPA), an extracellular protease that converts the inactive zymogen plasminogen to plasmin. It has been shown that tPA, through activation of plasmin, converts proBDNF to mBDNF in the hippocampus and that this conversion is required for late phase LTP[9]. Thus, the tPA-plasmin system is critical in controlling the availability of mBDNF at hippocampal synapses. Recent studies have also implicated p11 (annexin II light chain), a membrane-associated protein known

to dramatically enhance tPA activity[33], in the pathogenesis of depression[34]. Antidepressant treatment leads to p11 upregulation, whereas transgenics overexpressing p11 behave similarly to antidepressant-treated animals[34]. Conversely, mice lacking p11 show depressive-like behaviors. Svenningsson *et al.* attributed the antidepressant function of p11 to its ability to interact with and facilitate the cell surface expression of the serotonin 5-HT_{1B} receptor. However, in light of p11's ability to enhance tPA function, it may be possible that the effect of p11 dysfunction on depressive behaviors is a result of a reduction in proBDNF cleavage.

ProBDNF, $p75^{NTR}$ and the yin-yang hypothesis. All neurotrophins arise from precursors, proneurotrophins, which are proteolytically cleaved to produce mature proteins. Proneurotrophins were previously considered predominantly inactive and their existence *in vivo* has been debated. Using antibodies specific for proBDNF, recent studies have clearly shown that proBDNF is widely and abundantly expressed throughout the adult brain[35] (G. Nagappan, K.M. and B.L., unpublished data). The idea that proneurotrophins were functionally inactive was challenged by the demonstration that they bind preferentially to the pan-neurotrophin receptor $p75^{NTR}$, as opposed to the Trk receptor tyrosine kinases, and elicit apoptosis rather than cell survival in some peripheral neurons. Recent studies have extended the reciprocal effects of pro- versus mature neurotrophins in survival versus apoptosis to the CNS by showing that cholinergic neurons in the basal forebrain are susceptible to detrimental effects of proneurotrophins, whereas their survival is promoted by mature neurotrophins[36]. Cleaved, mature neurotrophins bind their cognate Trk receptors, leading to a cascade of intracellular signaling promoting cell survival. These findings have led to the 'yin-yang hypothesis': pro- and mature neurotrophins elicit opposite biological actions through binding to $p75^{NTR}$ and Trk receptors, respectively[8]. This hypothesis can be extended beyond cell survival to synaptic plasticity in the hippocampus[8]. There, activation of TrkB has a critical role in early phase LTP[37]. In addition, conversion of proBDNF to mBDNF by the tPA-plasmin system is required for TrkB-mediated late-phase LTP[9]. In contrast, proBDNF facilitates LTD via activation of $p75^{NTR}$ (ref. 10). Activation of TrkB and $p75^{NTR}$ promotes and suppresses dendritic spine growth, respectively[38]. Cleavage of proBDNF may therefore represent a new mechanism that controls the direction of BDNF regulation: synaptic potentiation or synaptic depression.

The yin-yang hypothesis provides a new perspective on the neurotrophin hypothesis of depression and could, in theory, help to interpret some of the conflicting results obtained in relation to BDNF signaling in mood disorders. For example, most animal models with reduced BDNF signaling or a deleted *Bdnf* gene do not show a clear depressive-like phenotype[39,40]. If proBDNF and mBDNF act in opposite directions in 'depressive behaviors', deletion of the *Bdnf* gene would remove both positive and negative signals, counteracting any observable behavior. Notably, transgenic mice overexpressing the *Bdnf* gene in the forebrain show both anxiogenic and antidepressant effects[41]. Elevated levels of both proBDNF and mBDNF could offer an explanation for these two seemingly opposing behavioral phenotypes. Even more puzzling is the behavior of tPA and plasminogen mutant mice. Both lines show higher levels of proBDNF (and lower levels of mBDNF), particularly in the hippocampus[9]. Notably, acute stress does not activate MAP kinase, a key signaling event downstream of mBDNF-TrkB, in mice lacking tPA. Moreover, these mice show no anxiogenic behaviors after repeated restraint stress[42]. However, if impairment in proBDNF cleavage underlies these behaviors, it remains unclear whether these effects result from a reduction in mBDNF levels or an accumulation of proBDNF. Transgenic mice overexpressing a cleavage-resistant form of proBDNF may help to separate the distinct roles of proBDNF and mBDNF in mood behaviors. In addition, methods that can effectively detect proBDNF and mBDNF with high sensitivity and specificity are crucial in discerning the yin and yang actions of BDNF in its potential depressive and antidepressant effects. Finally, studying the function of $p75^{NTR}$ in adult animals under various stress or depression conditions may provide new insight. Whereas $p75^{NTR}$ is expressed highly and widely during development, its expression in the adult brain is restricted mainly to the cholinergic neurons of the basal forebrain. These neurons innervate many brain areas, including the hippocampus, prefrontal cortex, amygdala and nucleus accumbens, all of which have been implicated in mood and stress-related behaviors. Moreover, it has been shown that whereas hippocampal expression of $p75^{NTR}$ is very low in basal states, it is dramatically upregulated after seizure or injury[43]. Thus, it is possible that $p75^{NTR}$ expression could be elevated after behavioral stress or during depression. Interestingly, stress also enhances the expression of sortilin, a coreceptor for proBDNF[44]. While the yin-yang hypothesis does not mean that the two signaling systems carry the same weight, the emerging concept of proBDNF-$p75^{NTR}$ signaling opens up an exciting new avenue in the study of mood disorders.

New insights into puzzling experimental data

BDNF's role in depression and anxiety versus in antidepressant action. As compelling as the correlation between BDNF expression and depression seems, a key gap in the neurotrophin hypothesis is the paucity of direct evidence that inhibition of BDNF signaling leads to depressive-like behaviors[39,40]. One report showed that *Bdnf* $^{+/-}$ mice show slower escape latencies in the learned helplessness paradigm, but this result could be attributed to an impaired shock response[39]. Although two recent studies found some evidence for depressive-like behaviors in mice lacking BDNF in the forebrain, the effects were small and inconsistent (deficits in tail suspension but not forced swim test or in females but not in males)[45]. Moreover, mice lacking TrkB in the forebrain as well as transgenics overexpressing the dominant-negative T1 form of TrkB show no impairment in depressive-like behaviors[40,46]. Overall, these results question whether impairment in BDNF-TrkB signaling is a principal cause of depression. In contrast, in both BDNF knockouts and TrkB-T1 transgenic mice, antidepressant treatment is no longer effective in reducing immobility in the forced swim test (FST), indicating that BDNF-TrkB signaling is somehow necessary for the positive effect on behavioral despair[40]. Interestingly, acute treatment is sufficient to exert effects on the FST, whereas chronic (21 days) administration is required to induce the expression of *Bdnf* and *Ntrk2* mRNAs in wild-type mice[13]. Thus, the effect of antidepressants on FST is likely to be mediated by an acute increase in BDNF secretion, TrkB signaling or both[40], rather than by an enhancement of expression of either gene. It will be critical to determine the behavioral effects of chronic treatment with antidepressants in BDNF and TrkB mutant mice. Regardless of their time courses, these data raise the interesting possibility that antidepressants elicit their effects by activating the BDNF-TrkB pathway.

The incongruent findings regarding the role of BDNF in depression and that in antidepressant effects indicate the need to separate these two seemingly related phenomena. Clinical depression may not be triggered by deficits in BDNF signaling alone but, rather, may require impairments in multiple pathways. Alternatively, downregulation of BDNF-TrkB could be compensated by upregulation of other neurotrophic or growth factors. It is also possible that both genetic factors and stressors may contribute to the development of depression

through mechanisms completely independent of BDNF and that antidepressants, through activation of BDNF-TrkB signaling, may interfere with these mechanisms to attenuate depressive behaviors.

Antidepressants are also used to treat a variety of anxiety disorders. Both *Bdnf*$^{Met/Met}$ and *Bdnf*$^{+/-}$ mice show increased anxiety-related behaviors[31]. Treatment with the antidepressant fluoxetine was unable to reverse behavioral anxiety in either *Bdnf*$^{+/-}$ or *Bdnf*$^{Met/Met}$ mice, indicating that BDNF may be a downstream target of selective serotonin reuptake inhibitors[31], a class of antidepressants. Consistent with this, the *Bdnf*$^{+/-}$ and serotonin transporter *Slc6a4*$^{+/-}$ (also known as *SERT*$^{+/-}$) double mutant shows a more pronounced anxiogenic phenotype as compared with singly heterozygous mice[47]. These results imply that the antidepressant effect of selective serotonin reuptake inhibitors on anxiety is mediated by the BDNF-TrkB signaling.

Although depression and anxiety are often comorbid, they do retain separate etiologies. It is therefore important to examine the specific role of BDNF in depression and anxiety. However, behavioral assays available at present often cannot effectively separate depressive from anxiety-like behaviors and are at best a partial reflection of certain aspects of the human disease etiology. Thus, we must exercise caution in interpreting behavior data and their relevance to these behaviors in humans. Nevertheless, converging evidence indicates that the BDNF-TrkB signaling may be a main target of antidepressants but that inhibition of this pathway may not be a main cause of depression.

Differential effects on the brain stress and reward systems. Depression is characterized by 'behavioral despair' as well as by the inability to experience pleasure (anhedonia). These two sets of behaviors are likely to be controlled by two distinct, albeit interacting, brain systems: the brain stress system (hippocampus-HPA pathway) and the brain reward system (VTA-NAc and VTA–prefrontal cortex pathways). The hippocampal circuitry includes functional components for learning and memory as well as negative regulation of the HPA-mediated stress pathway, both of which are altered in depression. The dopaminergic VTA→NAc pathway has a crucial role in reward and motivation. It seems that BDNF elicits opposite effects on these two systems. Intrahippocampal infusion of BDNF produces antidepressant effects[14,15], whereas, in marked contrast, it seems to have a pro-depressive role in the VTA→NAc reward system[7]. Conversely, inhibition of BDNF-TrkB signaling by viral infection of dominant-negative TrkB-T1 in NAc, the target of VTA dopaminergic neurons, elicits a strong antidepressive effect[7]. Using a social defeat paradigm, Berton *et al.* recently showed that repeated exposure to aggression results in long-lasting social withdrawal in mice[6]. Selective deletion of the *Bdnf* gene in the NAc through injection of a Cre-recombinase virus in mice carrying a *loxP*-flanked ('floxed') *Bdnf* allele prevents social defeat, mirroring the effect obtained with chronic antidepressant treatment[6].

The clear dichotomy of BDNF actions in the hippocampus and VTA-NAc demands separate investigation of the effects of BDNF manipulations on behaviors related to (i) anhedonia and motivation and (ii) despair and stress. Inducible and region-specific genetic approaches, which are more precise and cell-type specific, will be advantageous. As the NAc is largely composed of GABAergic interneurons, which presumably do not express BDNF, local BDNF may be primarily derived from glia. Differences in the kinetics of *Bdnf* transcription or BDNF secretion in neurons and glia may lead to contrasting effects in the hippocampus and NAc. It will also be interesting to determine how efficiently proBDNF in the NAc is processed to mBDNF. Infusion of high doses of BDNF, as was the case in the study by Eisch and colleagues[7], could activate p75^{NTR}, whereas deletion of the *Bdnf* gene in the NAc, as was the case in the study by Berton and colleagues[6], deletes both proBDNF and mBDNF. Thus, we could hypothesize a pro-depressive role by proBDNF in the VTA-NAc system. Whereas the antidepressant effects on behavior despair are mediated by mBDNF-TrkB signaling in the hippocampus, it is tempting to speculate that proBDNF-p75^{NTR} mechanisms are involved in the VTA-NAc–mediated anhedonic phenotype. Selective deletion of genes encoding receptors (p75^{NTR} or TrkB) in the hippocampus or NAc may prove helpful in delineating the specific role of proBDNF and mBDNF in depressive behaviors.

Does proBDNF-p75 regulation of LTD contribute to depression? Initially, the neurotrophin hypothesis focused on the growth and survival effect of neurotrophins[2]. However, it has become increasingly clear that the main function of BDNF in the adult brain is to regulate synaptic plasticity, rather than to mediate neuronal morphology or viability. Mature BDNF is now widely recognized as a key regulator of LTP in the hippocampus[8]. In general, various forms of stress impair LTP, and antidepressants reverse that effect. It is conceivable that antidepressants promote mBDNF-TrkB signaling and expression, leading to an enhancement of hippocampal LTP. The role of proBDNF-p75^{NTR} in depression and antidepressant effects has not yet been examined.

However, emerging evidence supports the idea that LTD may have a role in depressive-like behaviors. Acute stress can induce LTD in the adult hippocampus, which normally does not show LTD[48]. Recent studies reported a correlation between behavioral stress and the induction of LTD in adult rats[49]. Moreover, chronic mild stress–induced LTD could be reversed by chronic treatment with an antidepressant[49]. However, it is unclear whether LTD is the cause or the consequence of depression in this scenario. Interestingly, activation of p75^{NTR} by proBDNF also selectively facilitates, whereas inhibition of p75^{NTR} by gene knockout selectively impairs, NMDA receptor–dependent LTD, but not LTP, in the juvenile hippocampus[10,50]. It is tempting to speculate that the LTD observed after the behavioral stress paradigms are proBDNF-p75^{NTR}–dependent, such that behavioral stress might induce secretion of proBDNF, enhanced expression of p75^{NTR} in the hippocampus or both. The proBDNF-p75^{NTR} interaction leads to LTD and spine atrophy and, therefore, attenuates hippocampus-HPA control, leading to depressive-like behaviors. Critical tests of this model include examining whether selective blockade of proBDNF-p75^{NTR} signaling or LTD can prevent stress-induced depression and whether selective elevation of proBDNF levels or enhancement of LTD can lead to depressive-like behaviors. Regardless of experimental outcomes, critically examining the role of synaptic plasticity in depression and anxiety may represent an exciting new direction in research for mood disorders.

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COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

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1. Charney, D.S. & Manji, H.K. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. *Sci. STKE [online]* **2004**, re5 (2004).
2. Duman, R.S. & Monteggia, L.M. A neurotrophic model for stress-related mood disorders. *Biol. Psychiatry* **59**, 1116–1127 (2006).

3. Dias, B.G., Banerjee, S.B., Duman, R.S. & Vaidya, V.A. Differential regulation of brain derived neurotrophic factor transcripts by antidepressant treatments in the adult rat brain. *Neuropharmacology* **45**, 553–563 (2003).
4. Russo-Neustadt, A.A., Beard, R.C., Huang, Y.M. & Cotman, C.W. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. *Neuroscience* **101**, 305–312 (2000).
5. Tsankova, N.M. *et al.* Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat. Neurosci.* **9**, 519–525 (2006).
6. Berton, O. *et al.* Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* **311**, 864–868 (2006).
7. Eisch, A.J. *et al.* Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: a role in depression. *Biol. Psychiatry* **54**, 994–1005 (2003).
8. Lu, B., Pang, P.T. & Woo, N.H. The yin and yang of neurotrophin action. *Nat. Rev. Neurosci.* **6**, 603–614 (2005).
9. Pang, P.T. *et al.* Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science* **306**, 487–491 (2004).
10. Woo, N.H. *et al.* Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. *Nat. Neurosci.* **8**, 1069–1077 (2005).
11. McEwen, B.S. Protective and damaging effects of stress mediators: central role of the brain. *Prog. Brain Res.* **122**, 25–34 (2000).
12. 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.* **15**, 1768–1777 (1995).
13. 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.* **15**, 7539–7547 (1995).
14. Siuciak, J.A., Lewis, D.R., Wiegand, S.J. & Lindsay, R.M. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol. Biochem. Behav.* **56**, 131–137 (1997).
15. 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.* **22**, 3251–3261 (2002).
16. Chen, B., Dowlatshahi, D., MacQueen, G.M., Wang, J.F. & Young, L.T. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol. Psychiatry* **50**, 260–265 (2001).
17. Sheline, Y.I., Gado, M.H. & Kraemer, H.C. Untreated depression and hippocampal volume loss. *Am. J. Psychiatry* **160**, 1516–1518 (2003).
18. Neves-Pereira, M. *et al.* The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *Am. J. Hum. Genet.* **71**, 651–655 (2002).
19. Sklar, P. *et al.* Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. *Mol. Psychiatry* **7**, 579–593 (2002).
20. Zarate, C.A., Jr. *et al.* A randomized trial of an *N*-methyl-d-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry* **63**, 856–864 (2006).
21. Chao, M.V. Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat. Rev. Neurosci.* **4**, 299–309 (2003).
22. Timmusk, T. *et al.* Multiple promoters direct tissue-specific expression of the rat BDNF gene. *Neuron* **10**, 475–489 (1993).
23. Liu, Q.R. *et al.* Rodent BDNF genes, novel promoters, novel splice variants, and regulation by cocaine. *Brain Res.* **1067**, 1–12 (2006).
24. West, A.E. *et al.* Calcium regulation of neuronal gene expression. *Proc. Natl. Acad. Sci. USA* **98**, 11024–11031 (2001).
25. Pattabiraman, P.P. *et al.* Neuronal activity regulates the developmental expression and subcellular localization of cortical BDNF mRNA isoforms in vivo. *Mol. Cell. Neurosci.* **28**, 556–570 (2005).
26. Chen, W.G. *et al.* Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science* **302**, 885–889 (2003).
27. Martinowich, K. *et al.* DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. *Science* **302**, 890–893 (2003).
28. Mowla, S.J. *et al.* Differential sorting of nerve growth factor and brain-derived neurotrophic factor in hippocampal neurons. *J. Neurosci.* **19**, 2069–2080 (1999).
29. Egan, M.F. *et al.* The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* **112**, 257–269 (2003).
30. Chen, Z.Y. *et al.* Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. *J. Neurosci.* **25**, 6156–6166 (2005).
31. Chen, Z.Y. *et al.* Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science* **314**, 140–143 (2006).
32. Teng, H.K. *et al.* ProBDNF induces neuronal apoptosis via activation of a receptor complex of $p75^{NTR}$ and sortilin. *J. Neurosci.* **25**, 5455–5463 (2005).
33. Kim, J. & Hajjar, K.A. Annexin II: a plasminogen-plasminogen activator co-receptor. *Front. Biosci.* **7**, d341–d348 (2002).
34. Svenningsson, P. *et al.* Alterations in 5–HT1B receptor function by p11 in depression-like states. *Science* **311**, 77–80 (2006).
35. Zhou, X.F. *et al.* Distribution and localization of pro-brain-derived neurotrophic factor-like immunoreactivity in the peripheral and central nervous system of the adult rat. *J. Neurochem.* **91**, 704–715 (2004).
36. Volosin, M. *et al.* Interaction of survival and death signaling in basal forebrain neurons: roles of neurotrophins and proneurotrophins. *J. Neurosci.* **26**, 7756–7766 (2006).
37. Figurov, A., Pozzo-Miller, L.D., Olafsson, P., Wang, T. & Lu, B. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature* **381**, 706–709 (1996).
38. Zagrebelsky, M. *et al.* The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons. *J. Neurosci.* **25**, 9989–9999 (2005).
39. MacQueen, G.M. *et al.* Performance of heterozygous brain-derived neurotrophic factor knockout mice on behavioral analogues of anxiety, nociception, and depression. *Behav. Neurosci.* **115**, 1145–1153 (2001).
40. Saarelainen, T. *et al.* Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J. Neurosci.* **23**, 349–357 (2003).
41. Govindarajan, A. *et al.* Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects. *Proc. Natl. Acad. Sci. USA* **103**, 13208–13213 (2006).
42. Pawlak, R. *et al.* Tissue plasminogen activator and plasminogen mediate stress-induced decline of neuronal and cognitive functions in the mouse hippocampus. *Proc. Natl. Acad. Sci. USA* **102**, 18201–18206 (2005).
43. Roux, P.P., Colicos, M.A., Barker, P.A. & Kennedy, T.E. p75 neurotrophin receptor expression is induced in apoptotic neurons after seizure. *J. Neurosci.* **19**, 6887–6896 (1999).
44. Kohen, R. *et al.* Gene expression profiling in the hippocampus of learned helpless and nonhelpless rats. *Pharmacogenomics J.* **5**, 278–291 (2005).
45. Monteggia, L.M. *et al.* Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. *Biol. Psychiatry* **61**, 187–197 (2007).
46. Zorner, B. *et al.* Forebrain-specific trkB-receptor knockout mice: behaviorally more hyperactive than "depressive". *Biol. Psychiatry* **54**, 972–982 (2003).
47. Ren-Patterson, R.F. *et al.* Loss of brain-derived neurotrophic factor gene allele exacerbates brain monoamine deficiencies and increases stress abnormalities of serotonin transporter knockout mice. *J. Neurosci. Res.* **79**, 756–771 (2005).
48. Xu, L., Anwyl, R. & Rowan, M.J. Behavioural stress facilitates the induction of long-term depression in the hippocampus. *Nature* **387**, 497–500 (1997).
49. Holderbach, R., Clark, K., Moreau, J.L., Bischofberger, J. & Normann, C. Enhanced long-term synaptic depression in an animal model of depression. *Biol. Psychiatry* **62**, 92–100 (2006).
50. Rösch, H., Schweigreiter, R., Bonhoeffer, T., Barde, Y.A. & Korte, M. The neurotrophin receptor $p75^{NTR}$ modulates long-term depression and regulates the expression of AMPA receptor subunits in the hippocampus. *Proc. Natl. Acad. Sci. USA* **102**, 7362–7367 (2005).