A Neurotrophic Model for Stress-Related Mood Disorders

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There is a growing body of evidence demonstrating that stress decreases the expression of brain-derived neurotrophic factor (BDNF) in limbic structures that control mood and that antidepressant treatment reverses or blocks the effects of stress. Decreased levels of BDNF, as well as other neruotrophic factors, could contribute to the atrophy of certain limbic structures, including the hippocampus and prefrontal cortex that has been observed in depressed subjects. Conversely, the neurotrophic actions of antidepressants could reverse neuronal atrophy and cell loss and thereby contribute to the therapeutic actions of these treatments. This review provides a critical examination of the neurotrophic hypothesis of depression that has evolved from this work, including analysis of preclinical cellular (adult neurogenesis) and behavioral models of depression and antidepressant actions, as well as clinical neuroimaging and postmortem studies. Although there are some limitations, the results of these studies are consistent with the hypothesis that decreased expression of BDNF and possibly other growth factors contributes to depression and that upregulation of BDNF plays a role in the actions of antidepressant treatment.

Key Words: Antidepressant, depression, neurogenesis, behavior, BDNF, VEGF

Over the past 10 years, molecular and cellular studies of stress, depression, and antidepressants have moved the field of mood disorder research beyond the monoamine hypothesis of depression. These studies demonstrate that stress and antidepressant treatment exert opposing actions on the expression of specific neurotrophic factors in limbic brain regions involved in the regulation of mood and cognition. Most notable are studies of brain-derived neurotrophic factor (BDNF). Moreover, the functional significance of altered neurotrophic factor expression is highlighted by studies demonstrating that stress and depression can lead to neuronal atrophy and cell loss in key limbic brain regions implicated in depression, including the amygdala, prefrontal cortex, and hippocampus, and that antidepressant treatment can block or reverse these effects. The mechanisms underlying the actions of antidepressant treatment are still under investigation, but upregulation of BDNF and other neurotrophic factors could contribute to the long-term adaptations that are required for the therapeutic actions of these treatments.

The focus of this review is to critically examine the literature on the role of BDNF and other trophic factors in depression and in the actions of antidepressant treatment. This will include a review of the studies on the regulation of BDNF by different types of stress and antidepressant treatment in animal models, as well as altered levels of BDNF in postmortem brain and blood of depressed patients. Then, we will examine the functional consequences of altered BDNF in established cellular (adult neurogenesis) and behavioral models of depression. Although there are some limitations and inconsistencies, the results of these studies are consistent with the hypothesis that decreased expression of BDNF, and possibly other growth factors, contribute to depression and that upregulation of BDNF plays a role in the actions of antidepressant treatment.

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Opposing Actions of Stress and Antidepressant Treatment on BDNF

The time delay for the therapeutic action of antidepressant treatment suggests that adaptations of receptor-coupled signal transduction proteins and their corresponding genes could contribute to the actions of antidepressants. In contrast, alterations in the expression of signaling proteins could also contribute to the effects of stress-related mood disorders. A role for BDNF in the effects of stress and the response to antidepressant treatment is supported by studies demonstrating opposing regulation of this neurotrophic factor.

Stress Decreases BDNF Expression

Stress is used as a model to study alterations of brain structure and function because mood disorders are often precipitated or exacerbated by acute or chronic stressful life events (Gold and Chrousos 2002; Brown et al 2003). Prior to studies of neurotrophic factors, there were reports that stress can cause damage and atrophy of neurons in certain brain structures, most notably the hippocampus, which expresses high levels of receptors for glucocorticoids, the major stress reactive adrenal steroid (Sapolsky 1996; McEwen 1999, 2000; Sapolsky 2001; Duman 2004b). The hippocampus is one of several limbic structures that have been implicated in mood disorders. Included in the functions of hippocampal circuitry are control of learning and memory and regulation of the hypothalamic-pituitary-adrenal (HPA) axis, both of which are altered in depression. In addition, the hippocampus has connections with the amygdala and prefrontal cortex, regions that are more directly involved in emotion and cognition and thereby contribute to other major symptoms of depression (Figure 1).

Alterations of hippocampal structure and function in response to stress provided the rationale for analysis of neurotrophic factors. A summary of these studies, which demonstrate that many different types of acute (single stress) and chronic (7 to 21 days) stress paradigms decrease the expression of BDNF in the hippocampus, is provided in Table 1. Initial studies examined the influence of acute immobilization stress and reported significant reductions of BDNF messenger RNA (mRNA) expression in the major subfields of the hippocampus, with the greatest effects observed in the dentate gyrus granule cell layer but also decreases in the CA3 and CA1 pyramidal cell layers. Subsequent work found that other types of stress, including unpredictable,

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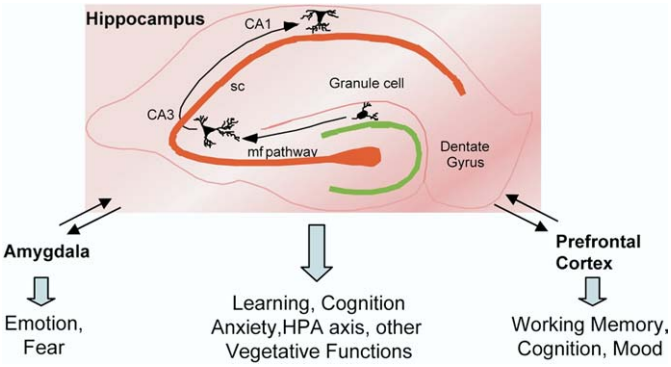

Figure 1. The putative involvement of the hippocampus in mediating depression-like behavior. The hippocampus is involved in learning, cognition, anxiety, regulation of the HPA axis, and other vegetative functions, which are altered in mood disorders. The hippocampus also has important connections to the amygdala and prefrontal cortex that may further underlie the emotional and cognitive deficits observed in some depressed patients. Stress, a factor that can precipitate mood disorders, produces neuronal atrophy as well as reduced levels of neurogenesis in specific subregions of the hippocampus whereas antidepressant treatment can reverse these cellular changes, as well as improve the emotional, cognitive and vegetative aspects of depression potentially through effects mediated, in part, by the hippocampus.

footshock, social isolation, social defeat, swim stress, and maternal deprivation, also decreased the expression of BDNF in the hippocampus (see Table 1 for references). Expression of BDNF is also decreased by a conditioned cue associated with footshock, demonstrating that prior experiences can lead to long-term alterations in the expression of BDNF (Rasmussen et al 2002). There is one study that did not find an effect of chronic (21d) restraint stress on BDNF (Kuroda and McEwen 1998). The reason for this discrepancy is unclear but could be related to the period of time (21 hours) after stress at which BDNF was assessed. Alternatively, there could be desensitization to the effects of repeated stress for 21 days.

The mechanisms underlying the downregulation of BDNF expression have been investigated. Administration of corticosterone, like stress, decreases BDNF expression and removal of the adrenal glands increases the expression of BDNF (see Table 1 for references). However, adrenalectomy does not completely block the effects of stress on BDNF (Smith et al 1995). Blockade of serotonin (5-HT) 2A receptors (5-HT_{2A}) partially blocks the effects of stress on BDNF expression, possibly via regulation of inhibitory gamma-aminobutyric acid (GABA)ergic interneurons in the hippocampus (Vaidya et al 1997). There is also evidence that interleukin-1β contributes to the downregulation of BDNF expression in the hippocampus (Barrientos et al 2003).

Stress Decreases Other Neurotrophic/Growth Factors

There is also evidence that the damaging effects of stress could be mediated by decreased expression of other types of neurotrophic and growth factors. The levels of the related neurotrophic factors, nerve growth factor (NGF) and neurotrophin-3 (NT-3), are also reported to be decreased in the hippocampus by exposure to long-term immobilization stress (Ueyama et al 1997). Nerve growth factor and NT-3 couple to the same signal transduction pathways as BDNF through their respective receptors, and decreased expression of these factors could lead to alterations in the structure and function of subpopulations of hippocampal neurons, depending on the complements of receptors that are expressed in each cell type.

Stress is also reported to decrease the expression of another class of growth factor, vascular endothelial growth factor (VEGF). This factor was originally identified as a vascular permeability factor, and it also influences the proliferation of endothelial cells (Ferrara et al 2003). However, more recent studies demonstrate that VEGF increases the proliferation of neurons in the adult hippocampus and has been implicated in a vascular niche hypothesis of adult neurogenesis (Palmer et al 2000). Exposure to unpredictable stress decreases the expression of VEGF, as well as the type 2 VEGF receptor, in the hippocampus, including the granule cell layer and hilus (Heine et al 2005). Decreased expression of VEGF and its receptor could contribute to the downregulation of adult neurogenesis by stress (see below).

Antidepressant Treatment Increases BDNF Expression

The requirement for long-term, chronic antidepressant treatment has lead to the hypothesis that alterations in functional and structural plasticity are necessary for a therapeutic response (Duman et al 1997; Nestler et al 2002). Because of the known actions of neurotrophic factors during development, as well as regulation of neuronal survival and function in the adult brain, members of the nerve growth factor family were considered potential targets for antidepressants. Initial studies conducted by our laboratory confirmed this hypothesis. In contrast to the actions of stress, we found that different classes of antidepressants significantly increased the expression of BDNF in the major subfields of the hippocampus, including the granule cell layer and the CA1 and CA3 pyramidal cell layers (Nibuya et al 1995, 1996; also see Table 1 for other references). The upregulation of BDNF is observed with different classes of antidepressants, including selective serotonin reuptake inhibitors (SSRI) and norepineprhine selective reuptake inhibitors (NESRI), monoamine oxidase inhibitors (MAOIs), atypical antidepressants, and electroconvulsive seizures (ECS). It is worth noting that the most clinically effective antidepressants, ECS and MAOIs, have the greatest effect on the induction of BDNF (Nibuya et al 1995). The induction of BDNF is also dependent on chronic chemical antidepressant treatment, consistent with the time course for the therapeutic action of antidepressants. Administration of other classes of psychotropic drugs, including opiates, antipsychotics, and psychostimulants, does not increase BDNF expression in the hippocampus, demonstrating the pharmacological specificity of antidepressants. It is also interesting and notable that other treatments that are known to have antidepressant efficacy also increase the expression of BDNF in the hippocampus. This includes administration of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)kines, *N*-methyl-D-aspartate (NMDA) receptor antagonists, transcranial magnetic stimulation, and exercise (see Table 1 for references).

As shown in Table 1, the upregulation of BDNF by antidepressant treatment has been confirmed by a number of studies from many different laboratories. However, there have been some inconsistent reports with certain classes of antidepressants. Electroconvulsive seizures and monoamine oxidase inhibitor antidepressants are consistently reported to increase levels of BDNF expression in the hippocampus (Table 1). In most studies, SSRI and NESRI antidepressants are also reported to increase the expression of BDNF, although there are some studies that have not observed this effect. This could be due to the treatment paradigm used, including the dose of drug or time of treatment (Coppell et al 2003; De Foubert et al 2004; Russo-Neustadt et al 2004). Brain-derived neurotrophic factor expression is activity-dependent and regulated by a variety of endocrine and environ-

Table 1. Regulation of BDNF by Stress, Depression, and Antidepressant Treatment

Treatment	Effect	Reference
Stress, Hippocampus		
Immobilization (45 minutes/day, 1, 7 days)	Decrease	Smith et al 1995
Immobilization (45 minutes)	Decrease	Nibuya et al 1995; Vaidya et al 1997
Immobilization (8 hours)	Decrease	Ueyama et al 1997
Unpredictable (10 days)	Decrease	Nibuya et al 1999
Footshock (.4 mA × 4, 60 minutes)	Decrease	Rasmussen et al 2002
Social Isolation (6 hours)	Decrease	Barrientos et al 2003
Social Defeat (10 minutes)	Decrease	Pizarro et al 2004
Maternal Deprivation (24 hours, P9)	Decrease (adult)	Roceri et al 2002
Swim Stress (10 minutes/day, 14 days)	Decrease	Roceri et al 2004
Restraint (6 hours/day, 21 days)	No effect	Kuroda and McEwen 1998
Restraint (4 hours/day, 3 days)	Decrease	Xu et al 2004
Corticosterone	Decrease	Barbany and Persson 1992 Smith et al 1995; Schaaf et al 1998
Adrenalectomy	Increase	Barbany and Persson 1992; Chao et al 1998
Depression, Postmortem Hippocampus		
Suicide Depressed	Decrease	Chen et al 2001
Suicide Depressed	Decrease	Dwivedi et al 2003
Suicide Depressed	Decrease	Karege et al 2005
Depression, Serum		
Depressed	Decrease	Karege et al 2002
Depressed	Decrease	Shimizu et al 2003
Depressed	Decrease	Karege et al 2005
Depressed + Antidepressant	Increase	Shimizu et al 2003
Depressed + Antidepressant	Increase	Gervasoni et al 2005
Depressed + Antidepressant	Increase	Aydemir et al 2004
Antidepressant (Chronic, Hippocampus)		
ECS	Increase	Nibuya et al 1995; Smith et al 1997 Newton et al 2003; Altar et al 2003, 2004
MAOI (tranylcypromine)	Increase	Nibuya et al 1995, 1996; Russo-Neustadt et al 1999 Coppell et al 2003; Dias et al 2003; Garza et al 2004
MAOI (tranylcypromine)	No effect	Altar et al 2003
SSRI (paroxetine, fluoxetine)	Increase	Nibuya et al 1996; Coppell et al 2003 De Foubert et al 2004; Vinet et al 2004
SSRI (sertraline)	Increase	Nibuya et al 1995; Coppell et al 2003
SSRI (citalopram)	Increase	Holoubek et al 2004
SSRI (fluoxetine)	No effect	Dias et al 2003; Conti et al 2002; Altar et al 2003; Miro et al 2002
NESRI (desipramine)	Increase	Nibuya et al 1995; Dias et al 2003; Vinet et al 2004 Russo-Neustadt et al 1999
NESRI (reboxetine)	Increase	Russo-Neustadt et al 2004
NESRI (desipramine, maprotiline)	No effect	Coppell et al 2003; Altar et al 2003
NE/SSRI (ventafaxine)	Increase	Xu et al 2003
Tricyclic (imipramine, amitriptyline)	Increase	Van Hoomissen et al 2003; Xu et al 2003
Atypical (mianserin)	Increase	Nibuya et al 1995
Atypical (mianserin, tianeptine)	No effect	Coppell et al 2003; Kuroda and McEwen 1998
AMP Akines	Increase	Lauterborn et al 2003
NMDA Antagonist (memantine)	Increase	Marvanova et al 2001
Transcranial Magenetic Stim	Increase	Muller et al 2000
Exercise	Increase	Neeper et al 1996; Adlard et al 2004 Russo-Neustadt et al 1999, 2000, 2004

BDNF, brain-derived neurotrophic factor; ECS, electroconvulsive seizures; MAOI, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors; NESRI, norepinephrine selective reuptake inhibitors; NE, norepinephrine; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl-D-aspartate.

mental stimuli, and it is imperative that housing conditions are closely monitored when conducting in vivo drug studies on the expression of this interesting neurotrophic factor.

Antidepressants Increase the Expression of Other Neurotrophic/Growth Factors

The survival and function of neurons in the central nervous system are dependent on an ever-growing list of neurotrophic/growth factors, and the influence of antidepressants on some of these has been investigated. Administration of ECS increases the expression of VEGF and thereby opposes the actions of stress (Newton et al 2003; Altar et al 2004). Preliminary studies demonstrate that chemical antidepressants also increase the expression of VEGF in the hippocampus (Warner and Duman, unpublished observations, 2006).

In addition, antidepressant treatment increases the expression

of fibroblast growth factor 2 (FGF2) in the hippocampus (Mallei et al 2002). Postmortem gene profiling studies also report altered expression of FGF2 and FGF receptors in depressed subjects and that depressed patients receiving medication (i.e., SSRI) had FGF transcript levels more similar to control subjects than unmedicated patients (Evans et al 2004). A recent study has also demonstrated that hippocampal expression of activin is increased by antidepressant treatment and is sufficient to produce an antidepressant response in the forced swim test (FST) (Dow et al 2005). A proteomics study has also reported that levels of insulin-like growth factor I (IGF-I) are increased by chronic antidepressant treatment, including fluoxetine and venlafaxine (Khawaja et al 2004).

BDNF Expression is Decreased in Depressed Patients: Reversal by Antidepressants

Although basic research studies demonstrate that stress decreases the expression of BDNF, it is difficult to extrapolate these findings to mood disorders in humans. The most direct approach to address this question is to measure levels of BDNF in depressed subjects, although these studies have limitations, including availability of tissue and heterogeneity of the patient population. However, there has been progress in studies of postmortem tissue and serum. Analysis of postmortem hippocampus demonstrates that the expression of BDNF is decreased in depressed suicide patients and increased in patients receiving antidepressant medication at the time of death (Chen et al 2001; Dwivedi et al 2003; Karege et al 2005). Another study also reports that a primary signaling cascade for BDNF, the extracellular regulated kinase (ERK) pathway, is also decreased in depressed patients (Dwivedi et al 2001).

A major limitation of studies of serum is that it is difficult to determine the significance of BDNF that is outside the blood brain barrier. However, there is evidence that other peripheral growth factors, including IGF-I and VEGF, gain access to the brain (Pan et al 1998; Trejo et al 2001; Fabel et al 2003), raising the possibility that peripheral BDNF may also influence central nervous system function. There are now several reports demonstrating that serum levels of BDNF are significantly decreased in depressed patients (Karege et al 2002; Shimizu et al 2003). In addition, there are several studies demonstrating that antidepressant treatment can reverse this effect (Aydemir et al 2004; Gervasoni et al 2005; Gonul et al 2005). Additional studies will be needed to determine if decreased BDNF reflects a state or trait marker and to determine the functional significance of altered serum BDNF.

Taken together, these reports on postmortem tissue and serum demonstrate altered BDNF levels that are consistent with the basic research models of stress and depression and with a neurotrophic hypothesis of depression. Further studies will be needed to confirm these findings in additional patient populations and to determine the specificity of these effects to depression.

Evidence of Neuronal Atrophy in Depressed Patients

Neuronal atrophy and reduced neurotrophic factor expression that are observed in preclinical models, as well as decreased expression of BDNF in depressed subjects, suggest that there could be structural alterations in mood disorder patients. Brain imaging studies have addressed this question and demonstrate a reduction in the volume of the hippocampus of depressed subjects (Sheline et al 2003; Duman 2004a, 2004b). In addition, the reduction of hippocampal volume is reversed by antidepressant treatment (Sheline et al 2003; Vermetten et al 2003). A reduction in hippocampal volume is also observed in posttraumatic stress disorder (PTSD) patients (Bremner et al 1995; Gurvits et al 1996). Additional studies are necessary to determine if there are factors that differentiate these stress-related disorders.

The majority of postmortem studies that have examined cellular/morphological changes have focused on cortical brain structures and report a reduction in the size of neuronal cell bodies and reduction in the number of glia (Ongur et al 1998; Rajkowska et al 1999; Cotter et al 2001). These studies are also consistent with reduced neurotrophic support in depression. There are fewer studies of the hippocampus. Two semi-quantitatve studies report no change in gross cellular morphology (Lucassen et al 2001; Muller et al 2001). A third study reports an increase in neuronal and glial density but a decrease in the size of neuronal cell bodies, suggesting a decrease in neuropil (Stockmeier et al 2004). Further studies are necessary to determine the cellular determinants underlying the reduction in hippocampal volume observed in brain imaging studies.

BDNF Polymorphisms in Mood Disorders

Based on basic and clinical work on BDNF, recent studies have been undertaken to identify and evaluate BDNF polymorphisms in mood disorders. A functional variant of BDNF at codon 66 (val66met) has been identified with the met allele that results in abnormal intracellular packaging and secretion of BDNF (Egan et al 2003). Carriers of the met allele are reported to have poorer episodic memory and reduced hippocampal N-acetyl aspartate (Egan et al 2003). Studies of the val66met alleles in psychiatric illness have been variable. The BDNF val allele is reported to be a possible risk locus for bipolar disorder (Geller et al 2004; Neves-Pereira et al 2002; Sklar et al 2002), but studies in Asian populations have not observed this association (Hong et al 2003; Nakata et al 2003). In addition, decreased hippocampal volume has been observed in bipolar patients that carry the substitution (H. Blumberg, personal communication, 2006). One study of childhood-onset mood disorder was negative for the BDNF val66met alleles (Strauss et al 2004). However, this study did find an association with a dinucleotide repeat. Jiang et al (2005) have reported a single nucleotide polymorphism in the BDNF exon I promoter that decreases promoter activity. This allele is associated with reduced anxious temperament, suggesting that it could be protective against anxiety. The BDNF met66 allele was also associated with increased risk for anxiety in this study (Jiang et al 2005).

These studies represent just the beginning of genetic characterization of BDNF, which is a very complex gene with multiple exon-specific promoters. Additional studies will be needed to further characterize the polymorphisms and mutations of this interesting gene and to study the presence of these variants in mood disorder patients.

Influence of BDNF in Cellular Models of Depression

The regulation of BDNF and other neurotrophic factors by stress and antidepressant treatment could result in alterations at the cellular and behavioral levels. At a cellular level, one of the most interesting areas of research is neurogenesis in the adult hippocampus and the opposing actions of stress and antidepressant treatment. The potential use of neurogenesis as a cellular model for studies of depression and antidepressant response is covered in more detail in another review in this issue. This section will provide a brief review of the literature and will focus more on the role of neurotrophic factors in the actions of stress and antidepressants (Figure 2). In addition to the regulation of

neurogenesis, stress also causes atrophy or remodeling of hippocampal neurons (McEwen 1999). Although some atypical antidepressants are reported to reverse this atrophy, other classes are ineffective, suggesting that this may not be a common target for all classes of antidepressants.

Stress Decreases Adult Neurogenesis

The hippocampus is one of two neurogenic zones in the adult central nervous system; the other is the subgranular zone which gives rise to neurons in the olfactory bulb. In the hippocampus, neural progenitor cells are localized to the subgranular zone and continue to divide and give rise to new cells that differentiate and migrate into the granule cell layer (Gage 2000; Gould et al 2000). These new neurons extend dendrites to the molecular layer and axons to the CA3 pyramidal layer and have morphological and physiological characteristics of adult granule cells.

The rate of proliferation and survival of newborn neurons in the hippocampus is also dynamically regulated up or down by a variety of stimuli (Duman 2004a). Stress is one of the most robust negative regulators of adult neurogenesis. Exposure to acute or repeated stressors, including intruder stress, predator odor, maternal separation, or footshock, decrease neurogenesis in the adult hippocampus (see Duman 2004a for review). In some cases, the downregulation of neurogenesis has been correlated with behavioral despair in the learned helplessness paradigm (Malberg and Duman 2003), although other studies do not observe a similar correlation (Vollmayr et al 2003).

Most of the stress models that decrease adult neurogenesis also decrease the expression of BDNF. However, the role of BDNF in the regulation of neurogenesis is complex. Infusion of BDNF into the lateral ventricles increases neurogenesis in several brain regions but not in the hippocampus, possibly due to low levels of diffusion to hippocampus (Benraiss et al 2001; Pencea et al 2001). Chronic infusion of BDNF directly into the hippocampus does increase neurogenesis, but this paradigm causes seizure activity and greater induction of neurogenesis on the contralateral side, as well as the ipsilateral infusion side. This makes it difficult to distinguish the direct effects of BDNF on neurogenesis from the effects of seizure activity, and previous studies demonstrate that a single seizure is sufficient to increase neurogenesis (Madsen et al 2000). Studies of BDNF+/− mice are also conflicting, with reports of decreased basal proliferation (Lee et al 2002) or no effect (Sairanen et al 2005). The latter study does provide evidence that BDNF-TrkB signaling influences the survival of new neurons. This represents an important mechanism for regulation of total number of neurons, because approximately half of the new neurons are lost within 3 to 4 weeks of proliferation.

Stress also decreases the expression of VEGF (Heine et al 2005). Given the significant role of this factor in the regulation of proliferation (Jin et al 2002; Cao et al 2004; Schanzer et al 2004) and the vascular niche hypothesis (Palmer et al 2000), it is possible that downregulation of VEGF contributes to decreased neurogenesis. Taken together, the results suggest that decreased expression of VEGF and BDNF could contribute to decreased proliferation and survival, respectively, of newborn neurons in the adult hippocampus.

Antidepressant Treatment Increases Adult Neurogenesis: Role of BDNF

The finding that antidepressants increase neurotrophic factor expression in the adult hippocampus provides the background and rationale for studies of adult neurogenesis. This led to the surprising discovery that antidepressant treatment significantly increases neurogenesis in the adult hippocampus (Malberg et al 2000; Duman 2004a). The upregulation of neurogenesis is observed with chronic, but not acute, administration of different classes of antidepressants, including SSRI, NESRI, MAOI, and ECS, indicating that neurogenesis is a common target of antidepressant medications. It is also notable that other treatments that produce an antidepressant response, including AMPAkines and exercise, also increase neurogenesis (Duman 2004a). Antidepressant treatment blocks or reverses the downregulation of neurogenesis that occurs in response to stress (Duman 2004a). In addition, blockade of neurogenesis blocks the behavioral effects of antidepressants, demonstrating a direct link between neurogenesis and behavioral responses (Santarelli et al 2003; Dranovsky and Hen 2006).

Recent studies have begun to investigate the role of neurotrophic/growth factors in antidepressant regulation of neurogenesis. The induction of cell proliferation is not significantly decreased in BDNF+/− mice or TrkB dominant negative transgenic mice (Sairanen et al 2005). However, this study did find that the survival of newborn neurons was decreased in BDNF+/− or TrkB dominant negative mice and that the increased survival induced by administration of a tricyclic antidepressant was blocked in these mutant mouse models. Studies of VEGF have also been interesting and demonstrate that infusion of an inhibitor of VEGF/Flk-1 receptor signaling completely blocks the induction of cell proliferation in response to different classes of antidepressants, including SSRI, NESRI, and ECS (Warner and Duman, unpublished data, 2006). Taken together, these studies demonstrate a role for both VEGF and BDNF in the proliferation and survival, respectively, of newborn neurons in

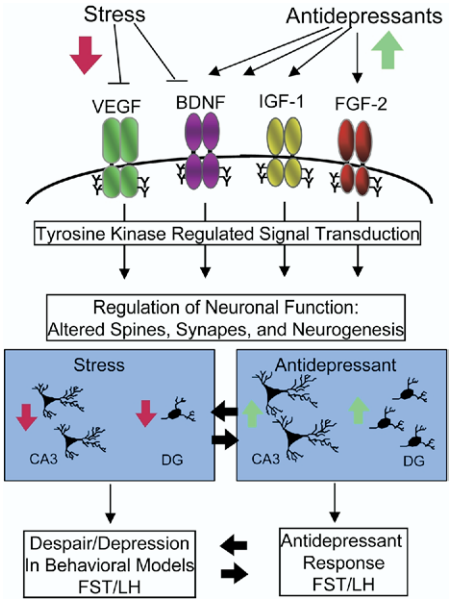

Figure 2. Involvement of neurotrophic/growth factors in the pathophysiology and/or treatment of depression. Stress has been shown to decrease levels of VEGF and BDNF in the hippocampus, a well as produce neuronal atrophy and decrease neurogenesis, which may contribute to a depression-like state. In contrast, antidepressants have been shown to increase levels of VEGF, BDNF, IFG-1 and FGF-2 which can then bind and activate tyrosine kinase receptors coupled to similar signal transduction pathways. The restoration of neuronal atrophy, the increased neurogenesis, and ultimately the antidepressant response may potentially be regulated by increases in these growth factors.

the adult hippocampus. It is possible that IGF-I, which is also upregulated by antidepressant treatment (Khawaja et al 2004), contributes to antidepressant regulation of neurogenesis. Additional studies will be required to delineate the specific cellular signaling pathways by which these different factors regulate adult neurogenesis.

Influence of BDNF in Behavioral Models of Depression

Studies of adult neurogenesis are useful for identifying cellular actions of antidepressants, but ultimately, it is essential that the behavioral actions of neurotrophic factors are also determined. In this context, the role of BDNF in several established models of depression has been determined. In addition to providing a review of these behavioral data, this section will provide a brief review of the current models of depression/antidepressant response, including the strengths and weaknesses of these models.

Behavioral Models of Depression

Three of the most common stress-based models of depression-like behavior that are responsive to antidepressants are the forced swim test (FST), the tail suspension test (TST), and the learned helplessness (LH) models (Porsolt et al 1977; Sherman et al 1979). These models have been validated primarily because the effects of stress are reversed by different classes of antidepressants, including SSRI, NESRI, MAOI, and tricyclic antidepressants (Porsolt et al 1977; Shanks and Anisman 1989). These tests have also been used to demonstrate abnormalities in mutant mouse models where genes potentially involved in antidepressant action are disrupted (Cryan et al 2001; Mayorga et al 2001; Schramm et al 2001; Conti et al 2002; Holmes et al 2002; Svenningsson et al 2002; Monteggia et al 2004). In addition, a fourth test, novelty suppressed feeding, has recently been used. Each of these models is briefly described.

Forced Swim Test. Of the three tests, the FST is probably the most widely used model that is responsive to antidepressant treatment. In the FST, rodents alternate between active responses and immobility after placement in a beaker of water. In this paradigm, the more time an animal spends in an inactive or immobile state versus active state is interpreted as a measure of depression-like behavior (Porsolt et al 1977). Most importantly, this model also reliably predicts antidepressant efficacy as antidepressant treatment decreases immobility time compared with a vehicle-treated animal (Dalvi and Lucki 1999). As such, the FST has been interpreted as model of "behavioral despair" and has been used to examine depression-like and antidepressant-like behavioral responses in numerous genetic and pharmacological models in rodents (Cryan et al 2002).

Tail Suspension Test. In the TST, mice spend periods of activity and immobility after being suspended by their tails (Thierry et al 1986). This paradigm is similar to the FST in that the time an animal spends immobile is interpreted as a measure of depression-like behavior. The TST is also able to predict antidepressant compounds, as animals administered antidepressants prior to the test display more active escape responses than those administered vehicle. While the FST and TST are similar in that they assess depression-like behavior by increased immobility or "giving up," these tests are not necessarily interchangeable. For example, a recent study demonstrates that $GABA_B$ knockout mice display less immobility in the FST but not in the TST (Mombereau et al 2004). In addition, there are also differences in the antidepressant responses in the FST and the TST, as not all antidepressants work equally well in both paradigms. In particular, the SSRI antidepressants produce a reliable response in the TST, which is generally not observed in the FST (Cryan et al 2002).

Learned Helplessness. The LH paradigm has also been interpreted as a model of behavioral despair and is responsive to antidepressant treatment in both rats and mice (Cryan et al 2002). In LH, animals that are exposed to inescapable shock subsequently fail to escape from a situation in which escape is possible (Sherman et al 1979). In the LH paradigm, animals are rated as helpless if they exhibit a decreased number of escapes or increased escape latencies following inescapable shock relative to control animals. This test also reliably predicts antidepressant efficacy, measured as increased escapes as well as shorter latencies to escape following antidepressant treatment. In addition to the escape deficits, helpless animals exhibit a variety of other behavioral and physiological changes that have been compared with depressive symptoms in humans, including decreased motor activity, loss of appetite and weight, reduced performance in self-stimulation paradigms, and immunosuppression (Willner 1990; Thiébot et al 1992). Although this paradigm is responsive to all classes of antidepressants, some antidepressants have not yet been validated in this model.

Novelty Suppressed Feeding. While the FST, TST, and LH tests can predict compounds with antidepressant efficacy, they all respond to acute or subchronic antidepressant administration. To understand the therapeutic response of antidepressants, it is necessary to develop models that respond to chronic, but not acute, antidepressant treatment. The novelty suppressed feeding (NSF) test measures anxiety-like behavior but is also responsive to chronic, and not acute, antidepressant treatment (Bodnoff et al 1988; Santarelli et al 2003). This paradigm measures the time, or latency, for a food-deprived animal to move into a brightly lit open field to consume food. The latency to eat is considered a measure of anxiety-related behavior, and chronic, but not acute, antidepressant administration decreases the latency. Although this test provides an important prerequisite (chronic treatment) for understanding the therapeutic action of antidepressants, it is also responsive to acute anxiolytics and thereby lacks pharmacological specificity. While it is true that depression and anxiety can co-segregate in some families, in others it does not, thus emphasizing the need for further research toward the development of animal models of depression.

Limitations of Behavioral Models of Depression

A major limitation of the FST, TST, and LH models is that these paradigms are responsive to acute (FST and TST) or subchronic (LH) antidepressant treatment, while the therapeutic efficacy of antidepressants in humans requires chronic treatment (3 weeks or more). While it is possible that the rapid response to antidepressants is related to the long-term therapeutic response, this discrepancy in time courses is a limitation of these models. This highlights the need for behavioral tests that are responsive to chronic antidepressant treatment. The NSF paradigm addresses this issue but is a better model of anxiety and is responsive to acute anxiolytics.

Another major limitation of the FST, TST, and LH paradigms is that it is difficult, if not impossible, to determine the state of mood/depression in a rodent based on immobility and escape behavior. Because depression in humans is usually determined by verbal responding to a battery of questions, there may never be an animal paradigm that models all aspects of depression. In addition, depression is a complex disease and affected individuals display a plethora of behavioral phenotypes and symptoms.

Table 2. Antidepressant Effects of Neurotrophic Factors

Factor	Brain Region	LH	FST	Reference
BDNF	Midbrain	AD response	AD response	Siuciak et al 1997
BDNF	HP-DG or CA3	AD response	AD response	Shirayama et al 2002
BDNF	HP-CA1	No Effect	No Effect	Shirayama et al 2002
BDNF	ICV	NA	AD response	Hoshaw et al 2005
BDNF+/−	Whole brain	Depressive[a]	No Effect	MacQueen et al 2001
BDNF+/−	Whole brain	NA	Blocks ADT	Saarelainen et al 2003
BDNF+/−	Whole brain	NA	No Effect	Chourbaji et al 2004
BDNF−/− ind	Forebrain	NA	Blocks ADT	Monteggia et al 2004
Trk dom neg	Forebrain	NA	Blocks ADT	Saarelainen et al 2003
TrkB−/− cond	Forebrain	NA	No Effect	Zorner et al 2003
NT3	HP-DG	AD response	AD response	Shirayama et al 2002
NT3+/−	Whole brain	NA	No Effect	Saarelainen et al 2003
NGF	HP-DG	No Effect	No Effect	Shirayama et al 2002
IGF-I	ICV	NA	AD response	Hoshaw et al 2005
VEGF	ICV	AD response	NA	Warner and Duman 2005
Activin A or B	HP-DG	NA	AD response	Dow et al 2005
Inhibin A	HP-DG	NA	No Effect	Dow et al 2005

Factors are infused into the indicated regions or are manipulated in mutant mice as indicated.

LH, learned helplessness; FST, forced swim test; BDNF, brain-derived neurotrophic factor; NA, not analyzed; Blocks ADT, mutation blocks the behavioral response to antidepressant treatment; BDNF+/−, BDNF heterozygous null mutant mice; BDNF−/− ind, BDNF null mutant, conditional and inducible; Trk dom neg, Trk dominant negative transgenic mice; TrkB−/−cond, conditional null mutant mice; NGF, nerve growth factor; IGF-I, insulin-like growth factor I; VEGF, vascular endothelial growth factor; HP-DG: hippocampus-dentate gyrus; ICV, intracerebroventricular; AD response, antidepressant behavioral response; No Effect, no behavioral effects; NA, not analyzed.

[a]In this study, the BDNF+/− mice had decreased pain response which could influence responding in LH.

No single behavioral paradigm will sufficiently mimic all aspects of the disease in rodents. So, another approach is to model selected core symptoms of depression, such as anhedonia, or some of the endocrine (e.g., hyperactive hypothalamic-pituitary-adrenal axis) and vegetative (e.g., abnormal sleeping, eating, and sexual activity) abnormalities.

Finally, another concern arises when using these models to study the effects of gene mutations. Although a specific gene mutation may not influence immobility or escape behavior, it does not rule out the possibility that the genetic perturbation may be important for the manifestation of the disease state in humans.

BDNF Produces Antidepressant Effects in Models of Depression

Local infusions of BDNF into specific brain regions have been shown to mimic antidepressant effects in behavioral models of depression (Table 2). In the FST, BDNF infusions into the midbrain, hippocampus, or into the lateral ventricles have been shown to decrease immobility time in the FST similar to the effects observed following administration of antidepressants (Siuciak et al 1997; Shirayama et al 2002; Hoshaw et al 2005). In the LH test, BDNF infusions after inescapable shock reduce escape latencies and failure rates relative to levels seen in vehicle control animals (Siuciak et al 1997; Shirayama et al 2002). The antidepressant effects of BDNF are observed after infusions into the dentate gyrus granule cell layer and the CA3 pyramidal cell layer but not the CA1, demonstrating regional specificity (Shirayama et al 2002). Infusion of the related factor NT-3, but not NGF, into the dentate gyrus also produced an antidepressant response in the FST and LH paradigms demonstrating neurotrophic factor specificity (Shirayama et al 2002). The efficacy of NT-3 could result from the ability of this factor to act on TrkB, as well as TrkC, receptors (Soppet et al 1991; Squinto et al 1991). Finally, drugs that block BDNF-TrkB signaling via the mitogen-activated protein (MAP) kinase cascade also block the behavioral effects of BDNF (Shirayama et al 2002). Together, these findings demonstrate that increased BDNF in the midbrain, and more specifically in the hippocampus, is sufficient to produce an antidepressant response.

Influence of Other Neurotrophic/Growth Factors in Models of Depression

In addition to the members of the nerve growth factor family, the role of other growth factors in behavioral models of depression has been examined. Based on the studies demonstrating that IGF-I is upregulated by antidepressant treatment (Khawaja et al 2004) and that IGF-I increases adult neurogenesis (Aberg et al 2000; Anderson et al 2002), studies of this growth factor have been conducted. Insulin-like growth factor infusions into the lateral ventricle produce an antidepressant response in the FST in rats (Hoshaw et al 2005). Insulin-like growth factor-I, like BDNF, binds to and activates a tyrosine kinase receptor, and it is possible that the antidepressant effect produced by these factors may be due to activation of similar signaling pathways.

Vascular endothelial growth factor is another factor that is regulated by antidepressant treatment (Newton et al 2003) and regulates the rate of neurogenesis in the adult hippocampus (Fabel et al 2003). Preliminary studies demonstrate that infusion of VEGF into the lateral ventricles produces an antidepressantlike effect in the FST and LH models (Warner and Duman, unpublished observations, 2006). Additional studies will be needed to confirm this finding.

Mechanisms for Neurotrophic/Growth Factor Regulation of Behavior

What determines whether a particular neurotrophic factor may be involved in producing an antidepressant response? While there is no definitive answer to this question, it is interesting that exogenous administration of BDNF, FGF, VEGF, and IGF-I all stimulate neurogenesis (Wagner et al

1999; Aberg et al 2000; Jin et al 2002) and that blockade of neurogenesis blocks the effects of chronic antidepressant treatment in models of depression (Santarelli et al 2003). Are FGF, VEGF, and IGF-I involved in mediating cell proliferation produced by antidepressants or are they only involved in cell survival similar to BDNF? Perhaps the antidepressant effects of these neurotrophic factors are independent of neurogenesis and instead are mediated by activation of similar signaling pathways that mediate the long-term neuroadaptive changes that are necessary for antidepressant efficacy? All of these factors couple to tyrosine kinase receptors that are capable of activitating similar signal transduction pathways, including the MAP kinase cascade. Further studies to address these questions may contribute to the future development of drug treatments for depression.

BDNF Mutant Mouse Models and Depression

A major gap in the neurotophic hypothesis of depression is the lack of direct evidence that loss of endogenous BDNF, or reduced BDNF signaling, can itself lead to depressionlike behavior or to an attenuated response to antidepressants. This question has been addressed by testing BDNF and other neurotrophic factor mutant mice in models of depression.

BDNF Constitutive (Heterozygous) Null Mutant Mice. Attempts to directly assess the role of BDNF in the hippocampus in animal models of depression-like behavior using transgenic mice have been hampered by the fact that BDNF homozygous (−/−) knockouts do not survive past postnatal days 10 to 14 (Ernfors et al 1994). Studies with BDNF heterozygous (−/+) mice have produced conflicting results regarding the role of BDNF in depression (see Table 2). There is one report that BDNF+/− mice have a depressive phenotype in the LH paradigm (MacQueen et al 2001), although this effect could be due, in part, to decreased pain sensitivity. This and other studies report no effect on basal immobility in the FST in the BDNF+/− mice (MacQueen et al 2001; Saarelainen et al 2003; Chourbaji et al 2004). One of these studies also reports that the effects of antidepressant treatment are blocked in BDNF+/− mice (Saarelainen et al 2003). The latter study also finds a normal antidepressant response in NT-3+/− mice, even though NT-3 infusions are sufficient to produce an antidepressant response in the FST and LH models (Shirayama et al 2002).

These discrepancies may be due to the fact that BDNF heterozygous mice have approximately half the normal gene product throughout their body and may still exhibit developmental abnormalities that further complicate their utility in studies of the role of BDNF in the adult brain. Alternatively, it is possible that half the normal amount of BDNF is sufficient to sustain certain physiological actions that are critical to responding in the models of depression. Finally, in studies of heterozygous constitutive null mutant mice where the gene is deleted throughout the brain as well as body, it is impossible to determine the specific brain region that controls selected behavioral responses.

BDNF Conditional Mutant Mice. To circumvent the potential problems encountered with constitutive mutant mice, conditional BDNF knockout mice have been developed. Conditional knockouts are mice where a gene is deleted in a subpopulation of cells at later stages of development compared with conventional "null" knockouts. Two independent lines of BDNF conditional knockout mice, in which BDNF is deleted in the forebrain, have been developed. Characterization of these lines has revealed behavioral phenotypes of the conditional knockouts, such as hyperactivity and learning deficits; however, to date, neither has been analyzed in behavioral models of depression (Rios et al 2001; Gorski et al 2003). Instead, a recent study has shown that an inducible BDNF knockout line of mice, in which BDNF has been deleted in broad forebrain regions of adult animals, were indistinguishable in depressive-like behavior from littermate control mice but displayed an attenuated response to antidepressants in the FST (Monteggia et al 2004). The results of this study and those discussed above on BDNF heterozygous mutants are consistent with the hypothesis that BDNF is necessary for a response to antidepressant treatment but that conditional or partial deletion is not sufficient to produce a depressive phenotype in the forced swim test. However, it is possible that more region and cell specific deletion of BDNF will be required to further examine the role of this neurotrophic factor in models of depression.

TrkB Mutant Mice. Studies have also examined whether the loss of BDNF signaling, by impairing the function of the TrkB receptor, influences depression-like behavior. TrkB conditional knockout mice, in which TrkB was deleted in the forebrain, had an indistinguishable level of immobility compared with littermate control mice in the FST, suggesting that the loss of TrkB was insufficient to increase depression-related behavior (Zorner et al 2003). Another study examined mice overexpressing a dominant negative form of TrkB expressed selectively in the forebrain found that these mutants have similar levels of immobility to control mice in the FST but displayed an attenuated response to antidepressants in this paradigm (Saarelainen et al 2003).

Interpretation of Mutant Mouse Data

Taken together, these data suggest that the loss of BDNF and signaling through the TrkB receptor in broad forebrain regions per se is not sufficient to mediate depression-like behavior. However, it is also important to remember that the behavioral paradigms used for these studies are probably not true models of depression and therefore may not reveal the effects of certain gene mutations on mood. The results do indicate that BDNF may be essential for mediating aspects of antidepressant efficacy. This suggests that the neuronal dysfunction that mediates depressionlike behavior may not be due to disruption of BDNF signaling. However, augmentation of BDNF signaling may overcome this deficiency and alleviate symptoms of depression. Further studies are necessary to assess whether the loss of BDNF and TrkB in forebrain make the mice more vulnerable to chronic perturbations. It is possible that certain mutations lead to a genetic vulnerability and that expression of a depressive-like phenotype is only observed when combined with another factor, such as stress, or even a second or third gene mutatation.

Gene Interactions. The interaction of two different gene mutations is demonstrated in a recent study of BDNF+/− and 5-HT transporter (SERT)−/− double mutants (Ren-Patterson et al 2005). Levels of 5-HT are significantly reduced in both the SERT−/− and BDNF+/− single mutants, but this effect is greater in the double mutant mice. In addition, there is a significant increase in measures of the HPA axis in the double mutant mice. Behavioral analysis also demonstrates that there is an increase in measures of anxiety in the double mutants but not the SERT−/− or BDNF+/− single mutant mice. The results of this study provide further evidence of an interaction between 5-HT and BDNF and demonstrate a gene × gene

interaction that could increase the vulnerability for anxiety and possibly mood-related behavior. Further studies are needed to test this hypothesis.

Limitations of the Neurotrophic Hypothesis

Although there is strong evidence from basic and clinical studies to support a neurotrophic hypothesis of depression, there are also several limitations. Some of the limitations or inconsistencies have been discussed. These include: 1) not all studies report an upregulation of BDNF by antidepressant treatments (Table 1); and 2) not all studies of mutant mice demonstrate a role for BDNF in models of depression. Some of these concerns can be explained by the experimental paradigm used (e.g., dose and time regimens for antidepressant regulation of BDNF expression) or by complications of BDNF mutant mouse models. Additional studies will be required to address these concerns and to further test this hypothesis.

Another caveat relates to the actions of BDNF in different brain regions. Although administration of BDNF into the midbrain, hippocampus, or lateral ventricles produces an antidepressant effect in models of depression, overexpression of BDNF in other regions has a different effect. This has been studied most extensively in the mesolimbic dopamine system or the reward circuit. Antidepressant treatment has been shown to increase BDNF levels in the ventral tegmental area (VTA) and the substantia nigra (SN) (Van Hoomissen et al 2003). However, overexpression of BDNF in the VTA produces an increase in depressive-like behaviors, and overexpression of a dominant-negative form of TrkB in the nucleus accumbens produces an antidepressant response (Eisch et al 2003). It is interesting that BDNF infusions into the mesolimbic dopamine (DA) system produces a prodepressive effect since this brain region may be involved in mediating some of the anhedonic responses observed in depressed patients. In any event, these data suggest that BDNF, and the TrkB receptor, may produce different effects on depression-like behavior depending on the brain region and could ultimately account for different aspects of the disease phenotype.

Summary

The results of this review support the hypothesis that a reduction of BDNF could contribute to depression and that antidepressants mediate their therapeutic benefit, in part, by increasing levels of this factor in the hippocampus. In addition, the regulation of other neurotrophic/growth factors, including VEGF, IGF-I, and FGF2, may also play a role in the pathophysiology and/or treatment of depression. Two common actions of these different classes of factors are the activation of tyrosine kinase receptors that couple to similar signal transduction cascades and the regulation of neurogenesis in the adult hippocampus. The regulation of intracellular signaling, such as the MAP kinase cascade, and adult neurogenesis could contribute to the actions of these factors in models of depression.

It is interesting to speculate that alterations in levels of BDNF and/or other factors could underlie or contribute to abnormal information processing, a recently proposed theory of depression (Castren 2005). Since the expression of BDNF is regulated by neuronal activity, conditions that lead to overactivation or underactivation of neural circuits could alter neurotrophic factor expression. While this may seem to suggest that neuronal activity, and not BDNF, is important for the functional alterations in neuronal circuitry, BDNF may be the crucial factor for mediating changes in neuronal plasticity (e.g., neurogenesis, stabilizing synaptic contacts) that are necessary for antidepressants to exert their therapeutic effect. These issues will require more insight into the pathophysiology of depression, future development of better animal models, and an improved understanding of the mechanism of action of antidepressants.

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Aberg M, Aberg ND, Hedbacker H, Oscarsson J, Eriksson PS (2000): Peripheral infusion of IGF-1 selectively induces neurogenesis in the adult rat hippocampus. *J Neurosci* 20:2896–2903.

Adlard P, Perreau VM, Engesser-Cesar C, Cotman CW (2004): The timecourse of induction of brain-derived neurotrophic factor nRNA and protein in the rat hippocampus following voluntary exercise. *Neurosci Lett* 363:43–48.

Altar C, Laeng P, Jurata LW, Brockman JA, Lemire A, Bullard J, et al (2004): Electroconvulsive seizures regulate gene expression of distinct neurotrophic signaling pathways. *J Neurosci* 24:2667–2677.

Altar C, Whitehead RE, Chen R, Wortwein G, Madsen TM (2003): Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. *Biol Psychiatry* 54:703–709.

Anderson M, Aberg MA, Nilsson M, Eriksson PS (2002): Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. *Brain Res Dev Brain Res* 134:115–122.

Aydemir O, Deveci A, Taneli F (2004): The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: A preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry* 29:261–265.

Barbany G, Persson H (1992): Regulation of neurotrophin mRNA expression in the rat brain by glucocorticoids. *Eur J Neurosci* 4:396–403.

Barrientos R, Sprunger DB, Campeau S, Higgins EA, Watkins LR, Rudy JW, et al (2003): Brain-derived neurotrophic factor mRNA downregulation induced by social isolation is blocked by intrahippocampal interleukin-1 receptor anatagonist. *Neuroscience* 121:847–853.

Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA (2001): Adenoviral brain-derived neurotropohic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. *J Neurosci* 21:6718–6731.

Bodnoff S, Suranyi-Cadotte B, Aitken DH, Quirion R, Meaney MJ (1988): The effects of chronic antidepressant treatment in an animal model of anxiety. *Psychopharmacology (Berl)* 95:298–302.

Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, et al (1995): MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 152: 973–981.

Brown J, Cooper-Kuhn CM, Kempermann G, Van Praag H, Winkler J, Gage FH, et al (2003): Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. *Eur J Neurosci* 17:2042–2046.

Cao L, Jiao X, Zuzga DS, Liu Y, Fong DM, Young D, et al (2004): VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat Genet* 36:827–835.

Castren E (2005): Is mood chemistry? *Nat Rev Neurosci* 6:241–246.

Chao H, Sakai RR, Ma LY, McEwen BS (1998): Adrenal steroid regulation of neurotrophic factor expression in the rat hippocampus. *Endocrinology* 139:3112–3118.

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

Chourbaji S, Hellweg R, Brandis D, Zorner B, Zacher C, Lang UE, et al (2004): Mice with reduced bran-derived neurotrophic factor expression show decreased choline acetyltransferade activity, but regular brain monoamine levels and unaltered emotional behavior. *Brain Res Mol Brain Res* 121:28–36.

Conti A, Cryan JF, Dalvi A, Lucki L, Blendy JA (2002): CREB is essential for the upregulation of BDNF transcription, but not the behavioral or endocrine responses to antidepressant drugs. *J Neurosci* 22:3262–3268.

Coppell A, Pei Q, Zetterstron TSC (2003): Bi-phasic change in BDNF gene expression following antidepressant drug treatment. *Neuropharmacology* 44:903–910.

Cotter D, Mackay D, Landau S, Kerwin R, Everall I (2001): Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry* 58:545–553.

Cryan J, Markou A, Lucki I (2002): Assessing antidepressant activity in rodents: Recent developments and future needs. *Trends Pharmacol Sci* 23:238–245.

Cryan JF, Dalvi A, Jin SH, Hirsch BR, Lucki I, Thomas SA (2001): Use of dopamine-beta-hydroxylase-deficient mice to determine the role of norepinephrine in the mechanism of action of antidepressant drugs. *J Pharmacol Exp Ther* 298:651–657.

Dalvi A, Lucki I (1999): Murine models of depression. *Psychopharmacology (Berl)* 147:14–16.

De Foubert G, Carney SL, Robinson CS, Destexhe EJ, Tomlinson R, Hicks CA, et al (2004): Fluoxetiine-induced change in rat brain expression of brain-derived neurotrophic factor varies depending on length of treatment. *Neuroscience* 128:597–604.

Dias B, Banerjee SB, Duman RS, Vaidya VA (2003): Differentiation regulation of brain derived neurotrophic factor transcripts by antidepressant treatments in the adult rat brain. *Neuropharmacology* 45:553–563.

Dow A, Russell DS, Duman RS (2005): Regulation of activin mRNA and smad2 phosphorylation by antdepressant treatment in the rat brain: Effects in behavioral models. *J Neurosci* 25:4908–4916.

Dranovsky A, Hen R (2006): Hippocampal neurogenesis: Regulation by stress and antidepressants. *Biol Psych* 59:1136–1143.

Duman R (2004a): Depression: A case of neuronal life and death? *Biol Psychiatry* 56:140–145.

Duman R (2004b): Role of neurotrophic factors in the etiology and treatment of mood disorders. *Neuromolecular Med* 5:11–25.

Duman R, Heninger GR, Nestler EJ (1997): A molecular and cellular theory of depression. *Arch Gen Psychiatry* 54:597–606.

Dwivedi Y, Rao JS, Hooriyah SR, Kotowski J, Conley RR, Roberts RC, et al (2003): Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. *Arch Gen Psychiatry* 60:273–282.

Dwivedi Y, Rizavi HS, Roberts RC, Conley RC, Tamminga CA, Pandey GN (2001): Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. *J Neurochem* 77:916–928.

Egan M, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al (2003): The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112:257–269.

Eisch A, Bolanos CA, de Wit J, Simonak RD, Pudiak CM, Barrot M, et al (2003): Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: A role in depression. *Biol Psychiatry* 54:995–1005.

Ernfors P, Lee K-F, Jaenisch R (1994): Mice lacking brain-derived neurotrophic factor develop with sensory deficits. *Nature* 368:147–150.

Evans S, Choudary PV, Neal CR, Li JZ, Vawter MP, Tomita H, et al (2004): Dysregulation of the fibroblast growth factor system in major depression. *Proc Natl Acad Sci U S A* 101:15506–15511.

Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, et al (2003): VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci* 18:2803–2812.

Ferrara N, Gerber HP, LeCouter J (2003): The biology of VEGF and its receptors. *Nat Med* 9:669–676.

Gage F (2000): Mammalian neural stem cells. *Science* 287:1433–1438.

Garza A, Ha TG, Chen MJ, Russo-Neustadt AA (2004): Exercise, antidepressant treatment, and BDNF mRNA expression in the aging brain. *Pharmacol Biochem Behav* 77:209–220.

Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH (2004): Linkage disequilibrium in the brain-derived neurotrophic fctor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry* 161:1698–1700.

Gervasoni N, Aubrey JM, Bondolfi G, Osiek G, Schwald M, Bertschv G, et al (2005): Partial normalization of serum brain-derived neurotrophic factor in remitted patients after a major depressive episode. *Neuropsychobiology* 51:234–238.

Gold P, Chrousos GP (2002): Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. *Mol Psychiatry* 7:254–275.

Gonul A, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S (2005): Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. *Eur Arch Psychiatry Clin Neurosci* 255(6):381–386.

Gorski J, Zeiler SR, Tamowski S, Jones KR (2003): Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. *J Neurosci* 23:6856–6865.

Gould E, Panapat P, Rydel T, Hastings N (2000): Regulation of hippocampal neurogenesis in adulthood. *Biol Psychiatry* 48:715–720.

Gurvits T, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, et al (1996): Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry* 40:1091–1099.

Heine V, Zareno J, Maslam S, Joels M, Lucassen PJ (2005): Chronic stress in the adult dentate gyrus reduces cell proliferation near the vasculature and VEGF and Flk-1 protein expression. *Eur J Neurosci* 21:1304–1314.

Holmes A, Murphy DL, Crawley JN (2002): Reduced aggression in mice lacking the serotonin transporter. *Psychopharmacology (Berl)* 161:160–167.

Holoubek G, Noldner M, Treiber K, Muller WE (2004): Effect of chronic antidepressant treatment in beta-receptor coupled signal transduction cascade. Which effect matters most? *Pharmacopsychiatry* 37(suppl 2):S113–S119.

Hong C, Huo SJ, Yen FC, Tung CL, Pan GM, Tsai SJ (2003): Association study of a brain-derived neurotrophic factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology* 48:186–189.

Hoshaw B, Malberg JE, Lucki I (2005): Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. *Brain Res* 1037:204–208.

Jiang X, Xu K, Hoberman J, Tian F, Marko AJ, Waheed JF, et al (2005): BDNF variation and mood disorders: A novel functional promoter polymorphism and Val66Met are associated with anxiety but have opposing effects. *Neuropsychopharmacology* 30(7):1353–1361.

Jin K, Zhu Y, Yunjuan S, Mao XO, Xie L, Greenberg DA (2002): Vascular endothelial growth factor (VEGF) stimulates neurogenisis in vitro and in vivo. *Proc Natl Acad Sci U S A* 99:11946–11950.

Karege F, Perret H, Bondolfi G, Schwald M, Bertschv G, Aubrey JM (2002): Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychol Res* 109:143–148.

Karege F, Vaudan G, Schwald M, Perroud N, La Harpe R (2005): Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. *Brain Res Mol Brain Res* 136:29–37.

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

Kuroda Y, McEwen BS (1998): Effect of chronic restraint stress and tianeptine on growth factors, growth-associated protein-43 and microtubule-associated protein 2 mRNA expression in the rat hippocampus. *Brain Res Mol Brain Res* 59:35–39.

Lauterborn J, Truong GS, Baudry M, Bi X, Lynch G, Gall CM (2003): Chronic elevation of brain-derived neurotrophic factor by ampakines. *J Pharmacol Exp Ther* 307:297–305.

Lee J, Duan W, Mattson MP (2002): 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* 82:1367–1375.

Lucassen P, Muller MB, Holsboerr F, Bauer J, Holtrop A, Wouda J, et al (2001): Hippocampal apoptosis in major depression is a minor event and absent from sub-areas at risk for glucocorticoid overexposure. *Am J Pathol* 158:453–468.

MacQueen G, Ramakrishnan K, Croll SD, Siuciak JA, Yu G, Young LT, et al (2001): Performance of heterozygous brain-derived neurotrophic factor knockout mice on behavioral analogues of anxiety, nociception, and depression. *Behav Neurosci* 5:1145–1153.

Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindrall O, Tingstrom A (2000): Increased neurogenesis in a model of electro convulsive therapy. *Biol Psychiatry* 47:1043–1049.

Malberg J, Duman RS (2003): Cell proliferation in adult hippocmpus is decreased by inescapable stress: Reversal by fluoxetine treatment. *Neuropsychopharmacology* 28:1562–1571.

Malberg J, Eisch AJ, Nestler EJ, Duman RS (2000): Chronic antidepressant treatment increases neurogenesis in adult hippocampus. *J Neurosci* 20: 9104–9110.

Mallei A, Shi B, Mocchetti I (2002): Antidepressant treatments induce the expression of basic fibroblast growth factor in cortical and hippocampal neurons. *Mol Pharmacol* 61:1017–1024.

Marvanova M, Lakso M, Pirhonen J, Nawa H, Wong G, Castren E (2001): The neuroprotective agent memantine induces brain-derived neurotrophic factor and trkB receptor expression in rat brain. *Mol Cell Neurosci* 18: 247–258.

Mayorga AJ, Dalvi A, Page ME, Zimov-Levinson S, Hen R, Lucki I (2001): Antidepressant-like behavioral effects in 5-hydroxytryptamine(1A) and 5-hydroxytryptamine(1B) receptor mutant mice. *J Pharmacol Exp Ther* 298:1101–1107.

McEwen B (1999): Stress and hippocampal plasticity. *Curr Opin Neurobiol* 5:205–216.

McEwen B (2000): Effects of adverse experiences for brain structure and function. *Biol Psychiatry* 48:721–731.

Miro X, Perez-Torres S, Puigdomenech P, Palacios JM, Mengod G (2002): Differential distribution of PDE4D splice variant mRNAs in rat brain suggests association with specific pathways and presynaptical localization. *Synapse* 45:259–269.

Mombereau C, Kaupmann K, Froestl W, Sansig G, van der Putten H, Cryan JF (2004): Genetic and pharmacological evidence of a role for GABA(B) receptors in the modulation of anxiety- and antidepressant-like behavior. *Neuropsychopharmacology* 29:1050–1062.

Monteggia L, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, et al (2004): Essential role of brain-derived neuroprophic factor in adult hippocampal function. *Proc Natl Acad Sci U S A* 101:10827–10832.

Muller M, Lucassen PJ, Yassouridis A, Hoogendijk JG, Holsboer F, Swabb DF (2001): Neither major depression nor glucocorticoid treatment affects the cellular integrity of the human hippocampus. *Eur J Neurosci* 14:1603–1612.

Muller M, Tosci N, Kresse AE, Poat A, Keck ME (2000): Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. *Neuropsychopharmacology* 23:205–215.

Nakata K, Ujike H, Sakai A, Uchida N, Nomura A, Imamura T (2003): Association study of the brain-derived neurotrophic factor (BDNF) gene with bipolar disorder. *Neurosci Lett* 337:17–20.

Neeper S, Gomez-Pinilla F, Choi J, Cotman CW (1996): Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res* 726:49–56.

Nestler E, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002): Neurobiology of depression. *Neuron* 34:13–25.

Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL (2002): 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.

Newton S, Collier E, Hunsberger J, Adams D, Salvanayagam E, Duman RS (2003): Gene profile of electroconvulsive seizures: Induction of neurogenic and angiogenic factors. *J Neurosci* 23:10841–10851.

Nibuya M, Morinobu S, Duman RS (1995): Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci* 15:7539–7547.

Nibuya M, Nestler EJ, Duman RS (1996): Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J Neurosci* 16:2365–2372.

Nibuya M, Takahashi M, Russel DS, Duman RS (1999): Repeated stress increases catalytic TrkB mRNA in rat hippocampus. *Neurosci Lett* 267:81–84.

Ongur D, Drevets WC, Price JL (1998): Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci U S A* 95:13290–13295.

Palmer T, Willhoite AR, Gage FH (2000): Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol* 425:479–494.

Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ (1998): Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology* 37:1553–1561.

Pencea V, Bingaman, KD, Wiegand SJ, Luskin MB (2001): Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, sseptum, thalamus, and hypothalamus. *J Neurosci* 21:6706–6717.

Pizarro J, Lumley LA, Medina W, Robinson CL, Shah JD, Mark B, et al (2004): Acute social defeat reduces neurotrophin expression in brain cortical and susbcortical areas in mice. *Brain Res* 1025:10–20.

Porsolt R, Le Pichon M, Jalfre M (1977): Depression: A new animal model sensitive to antidepressant treatments. *Nature* 266:730–732.

Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, et al (1999): Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol Psychiatry* 45:1085–1098.

Rasmussen A, Shi L, Duman RS (2002): Down-regulation of BDNF mRNA in the hippocampal dentate gyrus after re-axposure to cues previously associated with footshock. *Neuropsychopharmacology* 27:133–142.

Ren-Patterson RF, Cochran LW, Holmes A, Sherrill S, Huang SJ, Tolliver T, et al (2005): 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.

Rios M, Fan G, Fekete C, Kelly J, Bates B, Kuehn R, et al (2001): Conditioned deletion of brain-derived neurotrophic factor in the post-natal brain leads to obesity and hyperactivity. *Mol Endocrinol* 15:1748–1757.

Roceri M, Cirulli F, Pessina C, Peretto P, Racagni G, Riva MA (2004): Postnatal repeated maternal deprivation produces age-dependent changes of brain-derived neurotrophic factor expression in selected rat brain regions. *Biol Psychiatry* 55:708–714.

Roceri M, Hendriks W, Racagni G, Elenbroek BA, Riva MA (2002): Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. *Mol Psychiatry* 7:609–616.

Russo-Neustadt A, Alejandre H, Garcia C, Ivy AS, Chen MJ (2004): Hippocampal brain-derived neurotrophic factor expression following treatment with reboxetine, citalopram, and physical exercise. *Neuropsychopharmacology* 29:2189–2199.

Russo-Neustadt A, Beard RC, Cotman CW (1999): Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. *Neuropsychopharmacology* 21:679–682.

Russo-Neustadt A, Beard RC, Huang YM, Cotman CW (2000): Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. *Neuroscience* 101:305–312.

Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, et al (2003): Activation of the trkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J Neurosci* 23:349–357.

Sairanen M, Lucas G, Ernfors P, Castren M, Casren E (2005): 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* 25:1089–1094.

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al (2003): Requirement of hippocampal neurogenisis for the behavioral effects of antidepressants. *Science* 301:805–809.

Sapolsky R (1996): Glucocorticoids and atrophy of the human hippocampus. *Science* 273:749–750.

Sapolsky R (2001): Depression, antidepressants, and the shrinking hippocampus. *Proc Natl Acad Sci U S A* 98:12320–12322.

Schaaf M, de Jong J, de Kloet ER, Vreugdenhil E (1998): Downregulation of BDNF mRNA and protein in the rat hippocamppus by corticosterone. *Brain Res* 813:112–120.

Schanzer A, Wachs FP, Wilhelm D, Acker T Copoer-Kuhn C, Beck H, et al (2004): Direct stimulation of adult neural stem cells in vitro and neurogenesis in vivo by vascular endothelial growth factor. *Brain Pathol* 14:237–248.

Schramm NL, McDonald MP, Limbird LE (2001): The alpha(2a)-adrenergic receptor plays a protective role in mouse behavioral models of depression and anxiety. *J Neurosci* 21:4875–4882.

Shanks N, Anisman H (1989): Strain-specific effects of antidepressants on escape deficits induced by inescapable shock. *Psychopharmacology (Berl)* 99:122–128.

Sheline Y, Gado MH, Kraemer HC (2003): Untreated depression and hippocampal volume loss. *Am J Psychiatry* 160:1–3.

Sherman A, Allers GL, Petty J, Henn FA (1979): A neuropharmacologically-relevant animal model of depression. *Neuropharmacology* 18:891–893.

Shimizu E, Hashimoto K, Olamura N, Koike K, Komatsu N, Kumakiri C, et al (2003): Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry* 54:70–75.

Shirayama Y, Chen AC-H, Nakagawa S, Russell RS, Duman RS (2002): Brain derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J Neurosci* 22:3251–3261.

Siuciak JA, Lewis DR, Wiegand SJ, Lindsay R (1997): Antidepressant-like effect of brain derived neurotrophic factor (BDNF). *Pharmacol Biochem Behav* 56:131–137.

Sklar P, Gabriel SB, McInnis MG, Bennett P, Lin Y-M, Tsan G, et al (2002): Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. *Mol Psychiatry* 7:579–593.

Smith M, Zhang L-X, Lyons WE, Mamounas LA (1997): Anterograde transport of endogenous brain-derived neurotrophic factor in hippocampal mossy fibers. *Neuroreport* 8:1829–1834.

Smith MA, Makino S, Kvetnansky R, Post RM (1995): Stress alters the express of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J Neurosci* 15:1768–1777.

Soppet D, Escandon E, Maragos J, Middlemas DS, Reid SW, Blair J, et al (1991): The neurotrophic factors brain-derived neurotrophic factor and neurotrophin-3 are ligands for the trkB tyrosine kinase receptor. *Cell* 65:895–903.

Squinto SP, Stitt TN, Aldrich TH, Davis S, Bianco SM, Radziejewski C, et al (1991): TrkB encodes a functional receptor for brain-derived neurotrophic factor and neurotrophin-3 but not nerve growth factor. *Cell* 65:885–893.

Stockmeier C, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, Meltzer HY, et al (2004): Cellular changes in the postmortem hippocampus in major depression. *Biol Psychiatry* 56:640–650.

Strauss J, Barr CL, George CJ, King N, Shaikh S, Devlin B, et al (2004): Association study of brain-derived neurotrophic factor in adults with a history of childhood onset mood disorder. *Am J Med Genet B Neuropsychiatr Genet* 131:16–19.

Svenningsson P, Tzavara ET, Liu F, Fienberg AA, Nomikos GG, Greengard P (2002): DARPP-32 mediates serotonergic neurotransmission in the forebrain. *Proc Natl Acad Sci U S A* 99:3188–3193.

Thiébot M-H, Martin P, Puech AJ (1992): Animal behavioural studies in the evaluation of antidepressant drugs. *Br J Psychiatry* 160:44–50.

Thierry B, Steru L, Simon P, Porsolt RD (1986): The tail suspension test: Ethical considerations. *Psychopharmacology (Berl)* 90:284–285.

Trejo J, Carro E, Torres-Aleman I (2001): Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci* 21:1628–1634.

Ueyama T, Kawai Y, Nemoto K, Sekimoto M, Tone S, Senba E (1997): Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. *Neurosci Res* 28:103–110.

Vaidya V, Marek GJ, Aghajanian GA, Duman RS (1997): 5-HT2A receptor-mediated regulation of BDNF mRNA in the hippocampus and the neocortex. *J Neurosci* 17:2785–2795.

Van Hoomissen JD, Chambliss HO, Holmes PV, Dishman RK (2003): Effects of chronic exercise and imipramine on mRNA for BDNF after olfactory bulbectomy in rat. *Brain Res* 974:228–235.

Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD (2003): Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biol Psychiatry* 54:693–702.

Vinet J, Cara S, Blom JM, Brunello N, Barden N, Tascedda F (2004): Chronic treatment with desipramine and fluoxetine modulate BDNF, CaMKKalpha and CaMKKbeta mRNA levels in the hippocampus of transgenic mice expressing antisense RNA against the glucocorticoid receptor. *Neuropharmacology* 47:1062–1069.

Vollmayr B, Simonis C, Weber S, Gass P, HennF (2003): Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. *Biol Psychiatry* 54:1035–1040.

Wagner J, Black IB, DiCicco-Bloom E (1999): Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. *J Neurosci* 19:6006–6016.

Willner P (1990): Animal models of depression: An overview. *Pharmacol Ther* 45:425–455.

Xu B, Goulding EH, Zang K, Cepoi D, Cone RD, Jones KR, et al (2003): Brain-derived neurotropohic factor regulates energy balance downstream of melanocortin-4 receptor. *Nat Neurosci* 6:736–742.

Xu Y-L, Reinscheid RK, Hitron-Resendiz S, Clark SD, Wang Z, Lin SH, et al (2004): Neuropeptide S: A neuropeptide promoting arousal and anxiolytic-like effects. *Neuron* 43:487–497.

Zorner B, Wolfer DP, Brandis D, Kretz O, Zacher C, Madani R, et al (2003): Forebrain-specific trkB-receptor knockout mice: Behaviorally more hyperactive than "depressive." *Biol Psychiatry* 54:972–982.