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Interaction between BDNF and Serotonin: Role in Mood Disorders

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Brain-derived neurotrophic factor (BDNF) and serotonin (5-hydroxytryptamine, 5-HT) are two seemingly distinct signaling systems that play regulatory roles in many neuronal functions including survival, neurogenesis, and synaptic plasticity. A common feature of the two systems is their ability to regulate the development and plasticity of neural circuits involved in mood disorders such as depression and anxiety. BDNF promotes the survival and differentiation of 5-HT neurons. Conversely, administration of antidepressant selective serotonin reuptake inhibitors (SSRIs) enhances BDNF gene expression. There is also evidence for synergism between the two systems in affective behaviors and genetic epitasis between BDNF and the serotonin transporter genes.
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INTRODUCTION

BDNF

Brain-derived neurotrophic factor (BDNF) is the most abundant and widely distributed neurotrophin in the central nervous system (CNS). Initially isolated as a secretory protein capable of promoting the survival of peripheral neurons, BDNF is now recognized as a plethoric factor able to regulate a wide repertoire of functions, including neuronal survival, migration, phenotypic differentiation, axonal and dendritic growth, and synapse formation (Huang and Reichardt, 2001; Lewin and Barde, 1996). In addition to its prominent role in neuronal survival and differentiation during development, BDNF has emerged as a key regulator of synaptic plasticity and behavior (McAllister *et al*, 1999; Poo, 2001; Lu, 2003). Recent evidence strongly implicates a role for BDNF in cognitive functions, notably in memory acquisition and consolidation. (Tyler *et al*, 2002; Pang *et al*, 2004; Lu and Woo, 2006). It is now believed that the main function of BDNF in the adult is to regulate synaptic plasticity rather than to mediate cell survival and growth.

Functions of BDNF are mediated by two receptor systems: TrkB and $p75^{NTR}$. Binding of mature BDNF (mBDNF) to TrkB triggers tyrosine phosphorylation in its cytoplasmic domain, leading to activation of at least three signaling pathways: MEK–MAPK, phosphatidylinositol-3-kinase (PI-3-K) and phospholipase C-γ (PLC-γ) (Kaplan and Miller, 2000; Chao, 2003; Huang and Reichardt, 2003). The majority of BDNF-induced functions have been attributed to signaling through TrkB. Pro-BDNF, which preferentially binds $p75^{NTR}$, activates a different set of intracellular signaling cascades including nuclear factor-kappa B (NF-κB), c-jun kinase and sphingomyelin hydrolysis (Gentry *et al*, 2004; Teng *et al*, 2005). Activation of $p75^{NTR}$ by pro-neurotrophins has been linked to the activation of apoptotic signaling and initiation of *N*-methyl-D-aspartic acid (NMDA) receptor-dependent synaptic depression in the hippocampus (Ibanez, 2002; Lu and Je, 2003; Barker, 2004; Lu *et al*, 2005).

BDNF has a complex genomic structure rendering it an ideal target for multiple and complex transcriptional regulation (West *et al*, 2001; Lu, 2003). Multiple upstream promoters, each individually regulated, drive a short 5′ exon that is alternatively spliced onto a common 3′ exon, which encodes the pre-proBDNF protein. Evidence now indicates that the promoters of individual transcripts are regulated by diverse and varied physiological stimuli, and that these transcripts are distributed in different brain regions, different cell types and even different parts of the cell (eg soma *vs* dendrites) (Pattabiraman *et al*, 2005). Compared with other promoters, the rat promoter III is by far the most effectively regulated by neuronal activity in the amygdala, hippocampus, and cortex. Thus, alterations in transcription of *BDNF* via promoter III have been heavily studied as a

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mediator of activity-dependent processes including synapse development, plasticity, learning, and memory.

BDNF mRNA is translated in the ER into a precursor protein, which is folded in the trans-Golgi and then packaged into secretory vesicles (Lu, 2003). Upon correct folding, BDNF can be sorted into the constitutive (spontaneous release) or more frequently, into the regulatory (release in response to stimuli) secretory pathway. The trafficking and localization of BDNF appears to be controlled by its pro-domain. A single-nucleotide polymorphism (SNP) in the pro-domain of BDNF, which converts the 66th amino acid valine into methionine (Val66Met), has been identified. The Val66Met polymorphism affects dendritic trafficking and synaptic localization of BDNF as well as impairs its secretion. Human subjects carrying the Val66Met SNP exhibit deficits in short-term episodic memory and show abnormal hippocampal activation (Egan *et al*, 2003). BDNF is the only neurotrophin that is indisputably secreted in response to neuronal activity. The majority of BDNF is secreted via the regulated pathway and is derived from both pre- and postsynaptic sites.

In addition to its prominent role in hippocampal synaptic plasticity and related learning and memory mechanisms, BDNF signaling has been implicated in the regulation of adult neurogenesis (Lu and Chang, 2005). In BDNF heterozygous (+/−) mice as well as in mice with impaired TrkB activation (trkB.T1-overexpressing mice) the basal proliferation rate of new neurons in the dentate gyrus of the hippocampus is increased, but the 3-week survival of these newborn neuroblasts is significantly decreased. These results suggest that normal BDNF–TrkB signaling is requisite for the long-term survival of newborn neurons in the dentate gyrus (Sairanen *et al*, 2005). Importantly, antidepressants and the mood stabilizer lithium have been shown to elicit an increase in hippocampal neurogenesis (Chen *et al*, 2000; Malberg *et al*, 2000). This antidepressant-induced survival is lost in mice with impaired BDNF signaling (Sairanen *et al*, 2005). An additional study found evidence for the dependence of BDNF on the enhancement of hippocampal neurogenesis that is observed following environmental enrichment (Rossi *et al*, 2006).

Further implicating a role for BDNF signaling in depression and anxiety, it has been shown that decreases in hippocampal BDNF levels are correlated with stress-induced depressive behaviors (Nibuya *et al*, 1995; Smith *et al*, 1995; Vaidya *et al*, 1997; Duman, 2004; Duman and Monteggia, 2006), and that antidepressant treatment enhances the expression of BDNF (Nibuya *et al*, 1995; Russo-Neustadt *et al*, 1999; Duman and Monteggia, 2006). Moreover, the *BDNF* gene as well as the Val66Met polymorphism have been associated with increased risk for a number of neuropsychiatric disorders (Neves-Pereira *et al*, 2002; Sklar *et al*, 2002; Schumacher *et al*, 2005; Strauss *et al*, 2005; Okada *et al*, 2006).

Depression is characterized by 'behavioral despair' as well as the inability to experience pleasure, ie anhedonia. These sets of behaviors are likely controlled by two interacting brain systems: the brain stress system (hippocampus-HPA pathway), and the brain reward system (VTA-NAc, and VTA-prefrontal cortex). 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 plays a crucial role in reward and motivation. It appears that BDNF elicits opposite effects on these two systems. Intra-hippocampal infusion of BDNF produces antidepressant effects (Siuciak *et al*, 1997; Shirayama *et al*, 2002), while in striking contrast, it appears to play a pro-depressive role in the VTA→NAc reward system (Eisch *et al*, 2003). Conversely, inhibiting BDNF–TrkB signaling via viral infection of dominant-negative TrkB-T1 in NAc elicits a dramatic anti-depressive effect (Eisch *et al*, 2003). Using a social defeat paradigm, Berton *et al* (2006) recently showed that repeated exposure to aggression results in long-lasting social withdrawal in mice. BDNF gene deletion in the NAc via injection of a Cre-recombinase virus to mice carrying a floxed BDNF allele prevents social defeat, mirroring the effect obtained with chronic antidepressant treatment (Berton *et al*, 2006).

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 (1) anhedonia and motivation and (2) despair and stress. Inducible and region-specific genetic approaches, which are more precise and cell-type specific will be advantageous. Since 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 and/or secretion in neurons and glia may lead to contrasting effects in the hippocampus and NAc.

Serotonin

5-Hydroxytryptamine (5-HT) is produced by neurons located in the brainstem raphe nuclei and is released from the terminals of serotonergic neurons that project from the raphe nucleus. The serotonergic projections innervate multiple cortical brain regions to regulate a wide repertoire of behaviors, as well as cognition and mood. In addition to its prominent role as a neurotransmitter, 5-HT plays an important role in brain development via regulation of neurite outgrowth, synaptogenesis, and cell survival (Gaspar *et al*, 2003). In the adult, serotonergic neurotransmission modulates many brain functions including emotion, cognition, motor function, and pain sensitivity. Serotonin signaling also influences neuroendocrine functions including food intake, sleep and circadian rhythms, and reproductive activity.

Serotonin has the highest number of receptors of any of the neurotransmitters and the system is one of the phylogeneticaly oldest. Fifteen genes encoding 5-HT receptors have been identified in the mammalian brain (Bockaert *et al*, 2006). All of the 5-HT receptors are G-protein-coupled receptors except for the 5-HT_3 receptor, which uses an ionotropic mechanism (Bockaert *et al*, 2006). The 5-HT_1 receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}) are coupled to $G\alpha_i/G\alpha_o$ signaling proteins; the 5-HT_2 receptors (5-HT_{2A}, $5\text{-HT}_{2B,}$ 5-HT_{2C}) are coupled to $G\alpha_q$ signaling proteins; the 5-HT_4, 5-HT_6, and 5-HT_7 receptors are coupled to Gs proteins. The coupling mechanism for the 5-HT_5 receptors (5-HT_{5A} and 5HT_{5B}) remains unknown (Raymond *et al*, 2001). High densities of 5-HT_{1A} receptors

have been reported in the limbic areas and these receptors are negatively coupled to adenylyl cyclase (AC) via pertussis-toxin-sensitive $G\alpha_i$ and/ or $G\alpha_o$ proteins (De Vivo and Maayani, 1986; Weiss *et al*, 1986).

While multiple pre- and post-synaptic 5-HT receptors have been identified, removal of 5-HT from the synaptic cleft is mediated by a single protein, the 5-HT transporter (5-HTT). 5-HTT is able to take up serotonin from the synaptic cleft to the presynaptic terminals, effectively terminating the synaptic action of 5-HT. The 5-HTT determines the size and duration of the serotonergic responses and thus plays a key role in serotonergic neurotransmission (Lesch and Mossner, 1998). Of particular interest, stress is associated with reduced *5-HTT* mRNA levels in the raphe nucleus (Vollmayr *et al*, 2000). Analysis of the promoter region of *5-HTT* has revealed a polymorphism that results in allelic variation in functional 5-HTT expression (Lesch *et al*, 1996). The region containing the polymorphism is located about 1 kb upstream of the transcription initiation site and contains either 14 or 16 repetitive elements. The long (l) allele contains 16 of the elements while the short (s) allele contains 14 of the repetitive elements. Transcription from the l allele results in production of more *5-HTT* transcript and hence more functional 5-HT uptake than the s allele (Lesch *et al*, 1996).

Like BDNF, alterations in 5-HT signaling have demonstrable effects on synaptic plasticity and adult neurogenesis in the hippocampus (Brezun and Daszuta, 1999; Gould, 1999; Santarelli *et al*, 2003; Djavadian, 2004). In particular, 5-HT_{1A} activation stimulates neurogenesis in the hippocampus and this effect appears to be required for the effects of antidepressants (Brezun and Daszuta, 1999, 2000; Santarelli *et al*, 2003). Furthermore, one of the most recognized functions of 5-HT in the adult brain is its purported role in depression and anxiety. The 5-HTT polymorphism has been associated with anxiety, depression and aggression-related personality traits (Lesch *et al*, 1996; Lesch and Mossner, 1998). Disturbances in 5-HT signaling have been implicated in a plethora of psychiatric disorders including obsessive–compulsive disorder, bulimia, chronic impulsivity, aggression, and suicide (Baumgarten and Grozdanovic, 1995; Hen, 1996; Berman *et al*, 1997; Mann, 1998). Most importantly, administration of selective serotonin reuptake inhibitors (SSRIs), which serve to effectively increase 5-HT concentrations in the synaptic cleft, is one of the most widely used therapies for depression and anxiety. In line with this thinking, it has been shown that 5-HT receptor agonists also have antidepressant effects (Fuller, 1996).

Although 5-HT is mainly secreted from serotonergic neurons in the raphe, transient expression of SERT in thalamocortical fibers has been observed during development, leading to the uptake and regulated release of serotonin from these fibers (Lebrand *et al*, 1996). While interference with this process may alter the development of sensory circuits, the functional role of 5-HT release from thalamocortical fibers in depression and anxiety has not been investigated. In this context, it is important to note that anxiety-related behavioral deficits in 5HT-1_A knockout mice are due to the lack of serotonin action during development, and not in the adult (Gross *et al*, 2002).

BDNF REGULATION OF 5-HT NEURON DEVELOPMENT AND FUNCTIONS

Substantial evidence suggests that BDNF promotes the development and function of serotonergic neurons. BDNF and its receptor TrkB are co-expressed in serotonergic neurons within the dorsal raphe and median raphe (Merlio *et al*, 1992; Madhav *et al*, 2001), and BDNF is retrogradely transported from 5-HT terminals in the striatum and hippocampus to cell bodies in the raphe nuclei (Anderson *et al*, 1995). BDNF has been shown to promote the survival and morphological differentiation of 5-HT neurons both in culture and *in vivo*. Treatment of cultured neurons derived from embryonic raphe with BDNF dramatically increases the number of cells that express 5-HT markers and stimulates their morphological complexity (Eaton and Whittemore, 1996; Zhou *et al*, 2000; Rumajogee *et al*, 2002; Djalali *et al*, 2005). Intracerebroventricular infusion of BDNF stimulates sprouting of 5-HT axons, leading to hyperinnervation at the site of injection (Mamounas *et al*, 1995, 2000).

BDNF also promotes expression of serotonergic markers in raphe neurons. Infusion of BDNF into the brain enhances the expression of tryptophan hydroxylase (TpOH) (the rate-limiting enzyme in 5HT synthesis), upregulates 5-HT uptake and its activity-dependent release, and even modifies the firing patterns of serotonergic neurons in the raphe (Siuciak *et al*, 1996, 1998; Celada *et al*, 1996; Zhou *et al*, 2000; Goggi *et al*, 2002). In BDNF heterozygous mutant (+/−) mice, levels of forebrain 5-HT, fiber densities of forebrain 5-HT neurons, as well as the 5-HT clearance rate, were significantly impaired (Lyons *et al*, 1999; Szapacs *et al*, 2004; Daws *et al*, 2007). The functions of the 5-HT1_A and 5-HT2_A receptors also appear to be impaired in a mutant line in which the BDNF gene is deleted later in development (Rios *et al*, 2006; Hensler *et al*, 2007).

Mechanistic studies have suggested the existence of an auto/paracrine feedback loop in regulation of the serotonergic phenotype whereby 5-HT upregulates BDNF mRNA, and subsequent BDNF–TrkB signaling is crucial in the phenotypic development of serotonergic properties (Galter and Unsicker, 2000a, b). The BDNF–TrkB mediated induction of the serotonin phenotype appears to be coupled to 5-HT_{1A}-mediated downregulation, which results in increased cAMP production. In this model, BDNF activates TrkB on 5-HT neurons, which results in an upregulation of TpOH and 5-HT uptake. It is conceivable that an increase in cAMP concentration results in activation of protein kinase A (PKA) and the transcription factor CREB, leading to BDNF synthesis. The cycle is completed as synthesized BDNF in turn activates TrkB (Galter and Unsicker, 2000a, b).

5-HT REGULATION OF BDNF GENE EXPRESSION AND SIGNALING

Consistent studies suggest that serotonergic transmission exerts powerful control over BDNF expression, and this may be a key mechanism underlying the therapeutic effects of antidepressants.

5-HT and BDNF Expression

A prevailing hypothesis is that increases in extracellular 5-HT, as would occur upon administration of SSRIs, may increase BDNF levels because inhibition of 5-HTT enhances serotonergic transmission through 5-$HT_{4,6,7}$ receptor subtypes, which are positively coupled to adenylate cyclase and PKA. Resultant increases in CREB phosphorylation are known to positively regulate transcription of *BDNF*. Not all results are consistent with this idea. For example, in SERT knockout mice which lack the 5-HTT, and thus have elevated levels of extracellular 5-HT, upregulation of BDNF could not be observed (Szapacs *et al*, 2004).

Stress

Severe, prolonged stress is believed to initiate and exacerbate several psychiatric illnesses particularly depression and post-traumatic stress disorder (PTSD). Exposure to stressful stimuli leads to activation of several neurotransmitter and endocrine systems of which the hypothalamic–pituitary–adrenocortical (HPA) axis is the key hormonal component (Chaouloff, 1993). Acute stress has been shown to reduce the expression of *BDNF* mRNA in the hippocampus (Smith *et al*, 1995), while numerous studies have documented that both chronic and acute stress paradigms decrease the expression of hippocampal *BDNF* mRNA in animals (Smith *et al*, 1995; Vaidya *et al*, 1997; Nibuya *et al*, 1999; Duman, 2004; Duman and Monteggia, 2006). Decreased serum BDNF levels have been found in patients with mood disorder and those under inordinate amounts of stress or in depressed states (Licinio and Wong, 2002; Shimizu *et al*, 2003; Karege *et al*, 2005). Moreover, postmortem studies have shown that patients who were depressed at the time of death have decreased levels of BDNF as well as TrkB (Chen *et al*, 2001b; Dwivedi *et al*, 2003). Acute behavioral stress has been associated with a decrease in the levels of *5-HTT* mRNA in the raphe (Vollmayr *et al*, 2000). Other studies have shown disturbances in the serotonergic system at the level of their receptors in the hippocampus with different chronic stress paradigms in tree shrews and rodents (Flugge, 1995; Flugge *et al*, 1998). Since the influence of stress in the downregulation of BDNF is not significantly altered in adrenalectomized rats, it is unlikely that glucocorticoid misregulation alone can fully explain the decrease in BDNF expression by stress (Smith *et al*, 1995).

Several monoamine systems including serotonin are profoundly influenced by stress. Thus, it has been hypothesized that the stress-induced downregulation of BDNF could be mediated, at least in part, by alterations in the serotonergic system. For example, one study reported that the stress-induced reduction in *BDNF* mRNA can, at least in part, be prevented by pre-treatment with a 5-HT_{2A} receptor antagonist (Vaidya *et al*, 1997, 1999). While this may seem counterintuitive since 5-HT_{2A} receptors downregulate cAMP production, which should lead to a decrease in BDNF transcription, the authors propose that the 5-HT_{2A} receptors are located on GABAergic interneurons and that their activation increases inhibitory postsynaptic potentials (IPSPs). The resultant decrease in activity in excitatory neurons could underlie the observed downregulation of BDNF. Moreover, several studies have shown that SSRI treatment, which increases synaptic serotonin levels, can reverse the stress-induced downregulation of *BDNF* gene expression (Aydemir *et al*, 2005; Gervasoni *et al*, 2005; Gonul *et al*, 2005). In summary, stress generally inhibits BDNF gene expression, and some evidence suggests that this effect is, at least in part, mediated by a reduction in serotonin signaling.

Antidepressants

Almost all clinically used antidepressants increase the extracellular concentrations of the monoamines serotonin or norepinephrine either by inhibiting their re-uptake from the synapse of by blocking their degradation by inhibiting the monoamine oxidase (Duman *et al*, 1997; Nestler *et al*, 2002; Castren, 2005). Serotonin reuptake inhibiting drugs (SRIs) are commonly used for the treatment of both depression and anxiety. While SRIs immediately prevent the uptake of 5-HT from the extracellular space, it takes several weeks of continuous administration to observe therapeutic effects for these drugs in relieving depression and anxiety (Kreiss and Lucki, 1995; Duman *et al*, 1997; Hervas and Artigas, 1998; Trillat *et al*, 1998; Malagie *et al*, 2001; Nestler *et al*, 2002). Such observations have helped to generate a hypothesis positing that the therapeutic actions of SRIs necessitate evoking adaptive structural and functional changes at the synapse. In particular, it has been suggested that underlying these changes in plasticity may be changes in the expression, secretion, or downstream functioning of BDNF (Duman *et al*, 1997; Castren, 2004a, b).

The first clues linking expression of BDNF to the therapeutic actions of SRIs came from studies showing chronic antidepressant treatment leads to elevations in *BDNF* transcript levels in the rodent in both the hippocampus and the cortex (Nibuya *et al*, 1995, 1996). In studies extended to humans, it has been shown that expression of BDNF is increased in patients receiving antidepressant mediation at the time of suicidal death (Chen *et al*, 2001b; Dwivedi *et al*, 2003; Karege *et al*, 2005). It has been shown that direct infusions of BDNF protein into the rodent hippocampus mimic some of the antidepressant effects (Siuciak *et al*, 1997; Shirayama *et al*, 2002). Recent studies have further supported the idea that BDNF is a mediator of the antidepressant response. For example, mice engineered with a forebrain-specific knockout of BDNF do not show differences in depressive-like behaviors *per se*, but fail to respond to antidepressants (Monteggia *et al*, 2004). This effect is phenocopied in mice that are deficient in BDNF or TrkB signaling, further suggesting that BDNF signaling via TrkB is important for mediating a response to antidepressants (Saarelainen *et al*, 2003). A major unanswered question is to what degree the effects of antidepressants are mediated via BDNF signaling. In order to examine whether the extent with which BDNF mediates antidepressant responses, several key experiments are warranted: (1) can treatment with BDNF mimic any or all antidepressant effects; and (2) can blocking BDNF expression or TrkB signaling completely or partially prevent antidepressant effects. Testing these ideas, however, is not simple. Although the regulation of *BDNF* mRNA by stress and antidepressants appears to be fairly robust, the quantification of BDNF protein in the brain after these manipulations

has lagged (Duman and Monteggia, 2006). Furthermore, proBDNF and mBDNF can elicit different and often opposing effects and currently there is no easy way to distinguish between the two. However, future experiments using mutant mice blocking the downstream signaling of mBDNF (TrkB mutants) and proBDNF ($p75^{NTR}$ mutants) or newly designed more specific mouse models (ie uncleavable proBDNF transgenics) may help to discern the effects of pro- *vs* mature BDNF in the mediation of depression and the antidepressant response.

Mechanisms

While nearly all effective antidepressant therapies have been shown to lead to increases in levels of *BDNF* mRNA, specific mechanisms underlying regulation of BDNF expression/functions by stress, 5-HT or antidepressants remain largely unknown. One idea postulates that stress and/or antidepressants can alter the expression or activation (phosphorylation) of CREB, a key transcription factor involved in activity-dependent promoter III-mediated *BDNF* transcription (Nibuya *et al*, 1996; Conti *et al*, 2002). Extensive studies have shown that CREB can be activated via phosphorylation at serine 133 by three signaling pathways: cAMP-PKA, Ca^{2+}-CaMKIV, and MAPK pathways (Shaywitz and Greenberg, 1999). It is plausible that antidepressants could enhance BDNF gene expression by activating CREB through one of these pathways. In support of this idea, it has been shown that acute viral vector-mediated overexpression of CREB in the hippocampus resulted in decreased depressive-like behaviors in rats in a number of different behavioral tasks (Chen *et al*, 2001a). However, not all of the *BDNF* promoters contain consensus sites for CREB binding, and it has been shown that the increases in *BDNF* mRNA resulting from antidepressant treatment come from a wide variety of different combinations of individual *BDNF* transcripts (Dias *et al*, 2003). Moreover, CREB-deficient mice actually show an antidepressant phenotype, which is counterintuitive if CREB works to upregulate BDNF (Conti *et al*, 2002). Clearly, further work is necessary to identify additional pathways through which antidepressants work to activate *BDNF* gene expression and to better understand the relationship between CREB signaling and upregulation of BDNF in relation to antidepressant treatment and depressive-like behaviors.

The mechanisms underlying promoter III-mediated *BDNF* transcription have been extensively studied (West *et al*, 2001). Three calcium-responsive DNA elements (CaREs) have been identified within the *BDNF* III promoter that are requisite for *BDNF* transcription: the upstream stimulatory factor sequence which binds USF1/2, the Ca^{2+}-responsive sequence 1 (CaRE 1) which binds a novel calcium response factor (CaRF) (Tao *et al*, 2002), and the cAMP responsive element (CRE) which binds CREB (Shieh *et al*, 1998; Tao *et al*, 1998). Mutation of any of the three elements nearly abolishes calcium induction from promoter III. The necessity for cooperation between these three sites may serve to restrict activation until a number of varied signaling events can be integrated in the activation of these three independent sites.

Recent studies have begun to address how epigenetic mechanisms, which modify gene expression without altering the DNA code may have long-lasting effects in mature neurons that could be relevant to complex neurological and neuropsychiatric disorders (Tsankova *et al*, 2007). Chromatin remodeling mechanisms including DNA methylation, histone acetylation/deacetylation, and histone methylation work to reflect states that are either repressive or permissive for gene transcription. It was recently shown that epigenetic modifications may influence antidepressant upregulation and stress-induced downregulation of *BDNF* transcription from specific exons (Tsankova *et al*, 2006). Specifically, it was shown that social defeat stress induced long-lasting downregulation of *BDNF* transcripts III and IV by increasing repressive histone methylation on the chromatin surrounding their individual promoters. Chronic imipramine treatment was able to reverse this downregulation by inducing permissive histone acetylation at these same promoters. Further, imipramine treatment was associated with downregulation of the histone deacetylase 5 (HDAC5), which helped to promote acetylation at these promoters (Tsankova *et al*, 2006). Thus, inhibition of HDAC5 may be at least one mechanism underlying the upregulation of *BDNF* gene expression by antidepressants while a mechanism leading to enrichment of histone dimethylation at histone 3-lysine 27 (H3-K27) could be an important function in the downregulation of BDNF in response to stress.

Interestingly, acute antidepressant treatment is sufficient to exert effects on FST/TST, whereas chronic (21 days) administration is required to elicit many of the clinical benefits of antidepressants, which correlates with the time course of expression of *BDNF* and *TrkB* mRNAs in wild-type mice (Nibuya *et al*, 1995). There is clearly a discrepancy between the time course of increase in 5-HT (min) and that of increase in *BDNF* gene expression (days), induced by antidepressants. Thus, the rapid effects of antidepressants on FST/TST are likely mediated by an acute increase in BDNF secretion and/or TrkB signaling (Saarelainen *et al*, 2003), rather than by an enhancement of *BDNF/TrkB* gene expression. Future experiments should determine the behavioral effects of chronic treatment with antidepressants in BDNF and TrkB mutant mice. Regardless of their time courses or the underlying mechanisms, these data raise the interesting possibility that antidepressants elicit their effects by activating the BDNF–TrkB pathway.

GENETIC INTERACTION BETWEEN BDNF AND 5-HT IN PSYCHIATRIC DISORDERS

BDNF Mutant Mice

BDNF+/− mice develop several behavioral abnormalities, two of which, aggression and hyperphagia, are strikingly similar to those seen in 5-HT_{1B} and 5-HT_{2C} receptor knockout mice, respectively (Hen, 1996). Both phenotypes have been partially attributed to dysfunction of the 5-HT system for several reasons (Lyons *et al*, 1999). First, levels of postsynaptic 5-HT receptors (1A, 1B, 2A, and 2C) mRNA, as well as serotonergic neurotransmission, are significantly reduced in various brain region of young adult BDNF+/− mice (Lyons *et al*, 1999). Secondly, c-fos induction in response to increased synaptic serotonin is also reduced

(Lyons *et al*, 1999). Finally, the rate of 5-HT clearance is retarded in BDNF + /− mice, and this effect can be mediated by decreased 5-HTT function (Daws *et al*, 2007). Thus, endogenous BDNF regulation of aggression and appetite may be mediated by the 5-HT signaling system.

Given that levels of *BDNF* mRNA in the hippocampus of postmortem brains from depressed patients are reduced, one might predict that BDNF mutant mice would exhibit depressive-like behaviors. However, the bulk of studies addressing this issue have not borne out such a conclusion. BDNF + /− mice do not appear to behave abnormally in a number of depression-related behavioral tests (MacQueen *et al*, 2001; Saarelainen *et al*, 2003; Chourbaji *et al*, 2004). One report claims that BDNF + /− mice are impaired in the learned helplessness paradigm, which is considered a measure of behavioral despair (MacQueen *et al*, 2001), but this effect could be interpreted as resulting from their decreased pain sensitivity (Duman and Monteggia, 2006). No difference was observed between wild type and BDNF + /− mice in basal immobility in the forced swim test, an additional test of depressive-like behavior (MacQueen *et al*, 2001; Saarelainen *et al*, 2003; Chourbaji *et al*, 2004). In forebrain-specific BDNF knockouts, 5-HT1_A receptor function, but not density, was attenuated (Hensler *et al*, 2007). This functional deficit in 5-HT1_A receptor is restricted to the hippocampus and appears to be related to the loss of response to chronic corticosterone treatment. Taken together, while BDNF may be a target of antidepressants, it seems less likely that impairment in BDNF signaling is the major cause of depression. However, it is important to note that behavioral tests to model depression and anxiety are far from perfect and may only be modeling specific facets of these diseases. The lack of better behavioral assays could also be contributing to confounding the ability to determine whether and to what extent BDNF is involved in depression, the antidepressant response and/or in anxiety. It should be noted, however, that two recent studies have shown 'depressive like' behaviors in two separate sets of BDNF conditional mouse lines, using the FTS and the TST (Chan *et al*, 2006; Monteggia *et al*, 2007). Thus, further studies are necessary to sort out the conflicting results, and establish that BDNF signaling (or lack of) does not contribute directly 'depressive-like' behaviors *per se*.

Further supporting the main role of BDNF as mediating an antidepressant response, enhanced BDNF signaling resulting from overexpression of the full-length TrkB receptor (trkB.TK +), results in an antidepressant-like behavioral response (Koponen *et al*, 2005). TrkB.TK + mice display increased latency to immobility in the forced swim test, suggesting an increase in resistance to 'behavioral despair,' which is an excellent predictor of antidepressant efficacy. Fluoxetine was able to increase the latency to immobility in wild-type mice to similar levels as the TrkB.TK + mice. Despite the differences in resistance to behavioral despair observed between the TrkB.TK + and the wild-type mice, only minor differences in levels of brain monoamines were observed (Koponen *et al*, 2005).

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. Another possibility is that genetic or environmental factors may contribute to the development of depression through mechanisms completely independent of BDNF, and that antidepressants, via activation of BDNF–TrkB signaling, may interfere with these mechanisms to attenuate depressive behaviors. Moreover, it is important to note that antidepressants are used to treat many different psychiatric conditions, including a variety of anxiety disorders. Indeed, another more specific BDNF mutant mouse where the 66th amino acid, valine, is converted into methionine (Val66Met knock-in mice) exhibit increased anxiety-related behaviors (Chen *et al*, 2006). Treatment with the antidepressant fluoxetine was unable to reverse behavioral anxiety in the Val66Met knock-in mice, suggesting BDNF as a downstream target for the anxiolytic effects of selective serotonin reuptake inhibitors (SSRI) (Chen *et al*, 2006).

Genetic Epistasis

Since the BDNF and serotonergic signaling systems have significant interaction with overlapping functional targets, it might be expected that they would have synergistic effects. This idea was addressed using a double-mutant mouse model (termed sb mice) with one functional allele of BDNF (BDNF + /−) and no functional copies of the 5-HTT (5HTT−/−). Loss of BDNF appears to exacerbate brain monoamine deficiencies and increases stress abnormalities observed in 5-HTT−/− mice (Ren-Patterson *et al*, 2005). Compared with either wild-type, BDNF + /− or 5HTT−/− mice, the sb mice exhibit lower levels of 5-HT in the hippocampus and hypothalamus, impaired dendritic morphology, and increased anxiogenic behavior. Furthermore, sb mice exhibit much higher levels of the stress hormone ACTH and increased corticosterone in response to stressful stimuli. Interestingly, male mice have more pronounced deficits than females, and the gender difference could be explained, at least in part, by lower levels of TrkB expression in males (Ren-Patterson *et al*, 2006). These data support the hypothesis that loss of BDNF expression interacts with serotonin and related circuitry that are involved in modulating anxiogenic behaviors as well as the stress-response machinery.

Genetic epistasis between these two systems has also been observed in humans. Two common functional alleles of the 5-HTT gene have been identified in the human genome. The short ('s') allele encodes an attenuated promoter segment associated with reduced transcription and function of the serotonin transporter, as compared to the long ('l') allele (Lesch *et al*, 1994). In a recent study, Kaufman *et al* found that children carrying the met allele of the *BDNF* gene val66met polymorphism and two short alleles (s/s) of 5-HTTLPR had the highest depression scores, but that this vulnerability was only evident in children with maltreatment history (Kaufman *et al*, 2006). This result is somewhat surprising, because most reports studying the val66met polymorphism have suggested that the met allele is protective for anxiety (Lang *et al*, 2005; Hunnerkopf *et al*, 2007) depression (Schumacher *et al*, 2005; Strauss *et al*, 2005; Frodl *et al*, 2007), but see Jiang *et al* (2005), and bipolar disorder (Neves-Pereira *et al*, 2002; Sklar *et al*, 2002). Indeed, in a separate study, the prevalence of depression due to multiple life events was found to be

dramatically increased in s/s elders with one met allele (Kim *et al*, 2007). Moreover, structural neuroimaging reveals that the met allele of *BDNF* gene has a protective effect on the impact of 5HTTLPR s allele on amygdale-anterior cingulate cortex circuitry, a neuronal loop that has been implicated in both depression and anxiety (Weinberger DR, personal communication). Interestingly, the met allele also appears to confer better response of patients with s/s or s/l genotype to lithium, a frontline treatment for the treatment of mania and the prevention of recurrent episodes in bipolar mood disorders (Rybakowski *et al*, 2007). In addition to the protective effects of the met allele, these findings may help to develop effective treatment plans based on the personalized genetic variations of individuals. In sum, genetic interaction between 5-HTT and BDNF represents a fascinating area of research that requires further investigation.

FUTURE RESEARCH DIRECTIONS

In summary, it is clear that the BDNF and serotonin systems interact with each other to regulate the development and plasticity of neural circuits involved in mood disorders such as antidepressant responses. While much research continues on both of the individual systems regarding their effects and roles in neuropsychiatric diseases, it may be helpful to begin to think about the serial and/or parallel relationship between the two systems, the cause and effect scenarios, and how they interact to regulate major circuits involved in affective behaviors. We believe that understanding the interactions between the two systems as well as how they regulate, enhance, and affect each other, will help us to gain deeper insight into the way that depression, anxiety, and the response to antidepressant drugs may be working at a systems level. This approach, rather than looking at their effects on individual cell populations and molecular pathways may yield a more holistic and clearer picture of how the systems work to regulate mood and anxiety. This type of systems approach to mechanisms by which the brain circuits work in concert will hold the key to understanding how these systems are truly affecting the outcome of these illnesses.

Looking forward to future research on the role and relationships of BDNF and 5-HT pathways in mood regulation and affective disorders, we believe there are a number of important issues. First, how does 5-HT signaling enhance *BDNF* gene expression and through which downstream pathways does it use to upregulate *BDNF* gene expression? Specifically, does 5-HT act directly on BDNF-expressing neurons? Simple experiments in culture may help us to determine whether application of 5-HT to hippocampal neurons expressing specific 5-HT receptors leads to increases in *BDNF* mRNA, and if so which specific transcript(s) of *BDNF* is elevated. We need to understand which receptors involved in mediating the 5-HT response, and what signals downstream of the receptors (eg calcium) lead to upregulation of specific *BDNF* transcripts. Second, can antidepressants directly control *BDNF* gene expression? Given the recent findings that antidepressants regulate BDNF gene expression through epigenetic mechanisms, there exists the possibility that antidepressants interact with nuclear transcription regulators directly. For example, antidepressants may directly bind to HDAC5 or other repressors or activators, leading to an increase in BDNF transcription. Should this be the case, our view that SSRIs work by controlling synaptic 5-HT concentrations needs to be drastically changed. Third, why is chronic antidepressant treatment necessary to mount a therapeutic response? This is puzzling because most current behavioral models (eg forced swim test, tail suspension test, and other models of behavioral despair) do not require chronic treatment, and animals exhibit behavioral responses shortly after administration of antidepressants. Antidepressants may modulate BDNF signaling through two different modes: acute regulation of BDNF secretion and/or TrkB signaling, and chronic regulation of *BDNF* gene expression. A fast-acting serotonin modulation of BDNF signaling may lead to changes in synaptic plasticity. In contrast, the therapeutic effects of antidepressants require chronic administration to enhance *BDNF* gene expression, to stimulate neurogenesis in the hippocampal dentate gyrus, and to modify the structure or stability of the synapses. Fourth, an interesting idea is that antidepressants do not affect baseline 5-HT function, but serve to boost 5-HT in the presence of a stressor. Similarly, antidepressants may not affect baseline BDNF expression, but stimulate activity-dependent expression of BDNF, possibly through a de-repression mechanism. It has been shown that promoter III is repressed by an epigenetic mechanism. Thus, antidepressants may affect the phosphorylation of MeCP2, a mechanism which serves to control promoter III-mediated, activity-dependent BDNF transcription. Finally, it is interesting that antidepressants can mediate therapeutic responses to both depressive and anxiety symptoms. One may wonder whether they are working through the same or different mechanisms. It will be interesting to separate these two distinct, but often co-morbid illnesses and to examine the role of antidepressants and BDNF in these behaviors.

DISCLOSURE/CONFLICT OF INTEREST

The author(s) declare that, except for income received from my primary employer, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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