Review

Cyclic AMP response element binding protein and brain-derived neurotrophic factor: Molecules that modulate our mood?

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Depression is the major psychiatric ailment of our times, afflicting ~20% of the population. Despite its prevalence, the pathophysiology of this complex disorder is not well understood. In addition, although antidepressants have been in existence for the past several decades, the mechanisms that underlie their therapeutic effects remain elusive. Building evidence implicates a role for the plasticity of specific neuro-circuitry in both the pathophysiology and treatment of depression. Damage to limbic regions is thought to contribute to the etiology of depression and antidepressants have been reported to reverse such damage and promote adaptive plasticity. The molecular pathways that contribute to the damage associated with depression and antidepressant-mediated plasticity are a major focus of scientific enquiry. The transcription factor cyclic AMP response element binding protein (CREB) and the neurotrophin brain-derived neurotrophic factor (BDNF) are targets of diverse classes of antidepressants and are known to be regulated in animal models and in patients suffering from depression. Given their role in neuronal plasticity, CREB and BDNF have emerged as molecules that may play an important role in modulating mood. The purpose of this review is to discuss the role of CREB and BDNF in depression and as targets/mediators of antidepressant action.

1. Introduction

Depression is a widespread, incapacitating psychiatric ailment, with 10–30% of women and 7–15% of men in a population being afflicted with this disorder at any given time (Briley 2000). Despite its prevalence and social impact, its prognosis and management are often poor, due not only to the heterogeneity of this ailment, but also our lack of knowledge of the pathophysiology underlying this disorder. It is this lack of understanding of the underpinnings of depression that has resulted in no substantial improvement to antidepressant treatments, which were discovered serendipitously more than 50 years ago. Although second generation antidepressant drugs have eliminated some of the side effects associated with their predecessors, there have been few novel therapeutic targets identified that could significantly improve our management of mood disorders. The purpose of this review is to discuss emerging evidence that implicates the transcription factor, cyclic AMP response element binding protein (CREB) and the neurotrophin, brain-derived neurotrophic factor (BDNF) as potential key players in both the etiology and the treatment of depression.

While the neurobiological correlates of this disorder are still poorly understood, building evidence suggests that it is a dysfunction of specific neuro-anatomical foci, notably the hippocampus and the prefrontal cortex (PFC), which may

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Abbreviations used: ATF, Activating transcription factor; BDNF brain-derived neurotrophic factor; CRE, cAMP response element; CREB, cyclic AMP response element binding protein; CREM, cAMP response element modulator; ECS, electroconvulsive seizure therapy; HPA, hypothalmo-pituitary-adrenocortical; NPY, neuropeptide Y; PFC, prefrontal cortex; PKA, protein kinase A; VTA, ventral tegmental area.

underlie the pathogenesis of depression (Bremner 1995; Sheline *et al* 1996; Drevets *et al* 1997). There is considerable evidence demonstrating alterations in brain structure in patients suffering from depression, including volumetric loss, neuronal atrophy and cell death. Hippocampal volumetric loss has been reported in patients suffering from recurrent major depression (Sheline *et al* 1997), and alterations in PFC volume have also been documented in cases of filial depression (Drevets *et al* 1997). Additionally, reduced numbers of neurons and glia have been observed in the temporal cortex of patients suffering from unipolar depression (Rajkowska *et al* 2000). Dramatic changes in mammalian brain structure have also been documented following sustained stress exposure, which serves as an experimental animal model simulating the psychobiology of depression. Among the pathological effects that have been documented following prolonged stress exposure, is damage to limbic structures like the hippocampus and cortex. Several types of adult-onset stressors, including physical and psychosocial stressors, affect hippocampal structure: causing dendritic atrophy in the CA subfields (Watanabe *et al* 1992a; Vyas *et al* 2002) and suppressing granule cell neurogenesis within the dentate gyrus (Gould and Tanapat 1999; Pham *et al* 2003). Lending further credence to the hypothesis that it is alterations in brain structure that underlie depressive disorders, studies clearly demonstrate the reversal of the stress-induced atrophy with antidepressant therapy in animal models (Watanabe *et al* 1992b; Czeh *et al* 2001), as well as the reversal of hippocampal volumetric loss in depressed patients administered antidepressant treatment (Sheline *et al* 2003). Interestingly, antidepressant treatment can also prevent the stress-mediated reduction in hippocampal neurogenesis (Czeh *et al* 2001), while inhibiting neurogenesis, using irradiation, can hinder antidepressant action in behavioural animal models (Santarelli *et al* 2003). Taken together, these studies raise the possibility that the pathogenesis and treatment of depression may involve structural plasticity. Depression could, thus, be a consequence of the failure of specific neuronal circuits to show adaptive plasticity when exposed to external stimuli such as stress. The beneficial effects of antidepressant treatments could then arise from the reversal or amelioration of this dysfunction, or through the direct stimulation of adaptive neuronal plasticity. Although current antidepressant treatments exert their acute actions rapidly, the therapeutic benefits exhibit a lag of about 2–3 weeks. An emerging hypothesis suggests that this lag may be a consequence of the requirement to exhibit structural plasticity, which would develop gradually as a cumulative response to sustained treatment with antidepressants (Vaidya and Duman 2001).

The molecular and cellular mechanisms that (i) contribute to the damage which is implicated in the pathogenesis of depression and (ii) the repair that has been hypothesized to contribute to the therapeutic effects of antidepressant treatment remain unclear. While previous research efforts studied alterations in monoamine neurotransmitter levels, receptors or receptor-coupled second messenger systems, more recent efforts have focused on intracellular cascades and the regulation of gene expression. Exploring the role of signalling cascades and transcription factors dysregulated in depression and recruited by antidepressant therapies will most likely yield valuable data, since these molecules can affect the expression of diverse downstream target molecules. One such candidate transcriptional regulator is CREB, a transcription activator that is implicated in both stress- (Hatalski and Baram 1997) and antidepressant-induced transcriptional regulation (Conti *et al* 2002). The cAMP-CREB signalling cascade is critical to the generation of new neurons in the rodent hippocampus (Nakagawa *et al* 2002), and also facilitates their subsequent morphological maturation (Fujioka *et al* 2004). Thus, given its neuro-protective and survival-enhancing properties, it is an attractive candidate molecule that may be targeted by antidepressant therapy.

2. Cyclic AMP response element binding preotein

CREB is a nuclear protein, belonging to the family of leucine zipper transcription factors that are expressed in a variety of tissues and serve diverse functions. This family consists not only of transcriptional activators, including CREB and activating transcription factor (ATF), but also repressor molecules like cAMP response element modulator (CREM) and inducible cAMP early repressor (ICER). CREB contains a basic leucine zipper motif with which it can homodimerize or heterodimerize (to CREM or ATF) to form the functional dimer, and a DNA-binding domain with which it recognizes and binds to promoter cAMP response element (CRE) sequences. Phosphorylation of a serine residue (S133) in its kinase-inducible domain is critical to mediate its effects, as this permits recruitment of co-activator proteins and allows initiation of transcription. Phosphorylation, and hence activation, of CREB can be accomplished by a number of upstream signalling cascades. The canonical pathway that leads to CREB phosphorylation is the cAMP-protein kinase A (PKA) pathway (see reviews Montminy *et al* 1997; Casare *et al* 1999). The PKA cascade is known to be perturbed in animal models of depression and also serves as a target for antidepressant treatments and has been reviewed elsewhere (Shelton *et al* 2000; Tardito *et al* 2006). Besides the cAMP-PKA pathway, several other signalling cascades are also known to affect CREB activity through phosphorylation of the S133 and other serine residues, notably the MAP kinase signalling pathway (MEK/ERK), the calcium-CaMKII/IV cascade, as well as phospholipase C (PLC) signalling

(Johannessen *et al* 2004). Studies indicate that these pathways are perturbed in patients suffering from depression (Dwivedi *et al* 2006) and are also known to be influenced by antidepressant treatment (Tiraboschi *et al* 2004; Fumagalli *et al* 2005).

2.1 *CREB, animal models of depression and antidepressants*

While the hippocampal expression of CREB is reduced in response to stress exposure (Alfonso *et al* 2006), CREB expression in the brain is increased following chronic, though not acute, administration of a variety of antidepressants (Nibuya *et al* 1996). A diverse body of antidepressants, including serotonin-selective reuptake inhibitors (SSRIs), norepinephrine-selective reuptake inhibitors (NRIs), monoamine oxidase inhibitors (MAOIs) and electroconvulsive seizure therapy (ECS), all upregulate CREB expression in distinct brain regions that include the hippocampus and cerebral cortex. While these antidepressants have distinct acute targets, their chronic administration results in CREB upregulation. It will be interesting to know whether antidepressants can influence the translation of CREB, given recent reports that antidepressant treatment can influence translational machinery (Dagestad *et al* 2006). CREB may then serve as a common post-receptor target and thus be a central integrator for diverse upstream signalling cascades recruited by antidepressant treatment. CREB thus emerges as an exciting common target for distinct classes of antidepressants (figure 1).

Chronic administration of antidepressants not only affects CREB expression, but also CREB activity and CREB-mediated transcription. Chronic antidepressant therapy upregulates cellular PKA activity and increases the translocation of PKA to the nucleus (Nestler *et al* 1989). Enhanced CRE binding (Itoh *et al* 2004) and, studies using CRE-LacZ reporter mice (Thome *et al* 2000), indicate a region-specific increased rate of CRE-mediated transcription observed following antidepressant treatment. It has been suggested that antidepressants recruit CREB to upregulate the transcription of target genes that then lead to the trophic effects, including neurogenesis and neuronal plasticity, which underlie antidepressant action (figure 1).

2.2 *Pro- and anti-depressant activity of CREB*

CREB can, itself, act in a manner analogous to that of antidepressants. Viral-mediated over-expression of CREB in the hippocampus has an antidepressant-like effect in behavioural models of depression (Chen *et al* 2001a), notably the learned helplessness and forced swim test. Furthermore, chronic administration of rolipram, an inhibitor
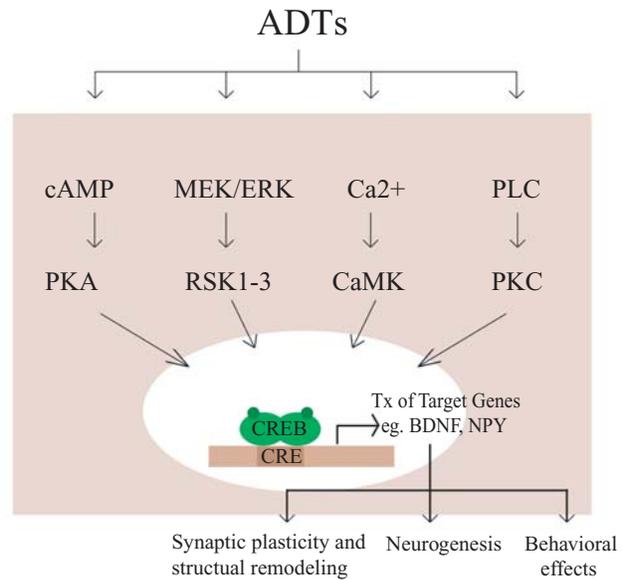

Figure 1. The CREB cascade. CREB is regulated by diverse signalling pathways, and can thus serve as a central integrator for the actions of numerous external stimuli, including antidepressants (ADT). Antidepressants which have distinct acute targets are known to recruit several signal transduction pathways, including cyclic AMP – protein kinase A (cAMP-PKA) cascade, the MAP kinase signalling pathway (MEK/ERK) as well as calcium and phospholipase C (PLC) signalling. A downstream consequence of enhanced CREB function is thought to be the increased expression of target genes like the neurotrophin, brain-derived neurotrophic factor (BDNF), and neuropeptide Y (NPY), which may contribute to the ADT-mediated changes in structural plasticity and behaviour.

of phosphodiesterases that downregulate cAMP-CREB signalling, has antidepressant actions in several behavioural tests (Itoh *et al* 2004). However, it is interesting to note that the role of CREB is highly dependent on its temporal and spatial regulation. CREB over-expression in the basolateral amygdala has pro- or anti-depressive responses depending on whether the over-expression of CREB precedes or follows training in the learned helplessness model of depression (Wallace *et al* 2004). Expression of CREB before training increases both escape failures and immobility in the forced swim test, which are pro-depressive effects. However, induction of CREB in the basolateral amygdala after training decreases the number of escape failures, an antidepressant-like response. This suggests that the timing of CREB regulation within the basolateral amygdala may be key for the various associative changes that culminate in behavioural responses. CREB expression before training may cause a strong association thus promoting a fear-conditioned state and enhancing the learned helplessness phenotype. In striking contrast, the expression of CREB in this region after the learned helplessness paradigm results in

an antidepressant-like response. This temporal consequence to CREB expression in the amygdala could be a result of different target genes being regulated by CREB. Given that CREB works in conjunction with other key transcription factors (CREM, ICER, ATF) (Masquilier and Sassone-Corsi 1992), future studies are required to address whether the composition of the transcription factors that bind to the CRE sites prior and post-training for learned helplessness are different, thus resulting in distinct functional outcomes. Interestingly, while CREB expression in the hippocampus elicits antidepressant-like responses (Chen *et al* 2001a), it has pro-depressive effects when expressed in the nucleus accumbens (Pliakas *et al* 2001). Viral mediated over-expression of CREB in the accumbens causes pro-depressive reactions in animal models of depression (Pliakas *et al* 2001), while over-expression of the dominant negative form of CREB (mCREB) results in antidepressant-like action (Pliakas *et al* 2001; Newton *et al* 2002). Thus, CREB exhibits a region-specificity in its actions, and this is a theme that will be further discussed later.

2.3 *CREB and downstream target genes*

While it seems clear that CREB has a role to play in pathogenesis of depression and in antidepressant action, the mechanistic details of the same remain obscure, in part due to the complexity of the CREB gene itself. The CREB gene can generate multiple transcripts and protein products that can serve as both transcriptional activators and as repressors. However, identifying downstream target genes, those with the necessary CRE binding sites, is crucial in revealing the action of CREB. Of the several molecules that are regulated by CREB, studying brain-derived neurotrophic factor (BDNF) seems a promising avenue given that this neurotrophin could stimulate structural plasticity and repair stress- or depression-induced damage. The BDNF gene, which consists of five individual exons in the rat, has a promoter that contains a cAMP response element and a calcium response element, both of which can bind the transcriptional-activator CREB (Tabuchi *et al* 2002). Additionally, the antidepressant-induced upregulation of BDNF expression is lost in CREB deficient mice (Conti *et al* 2002). Besides BDNF, several other molecules that are strongly implicated in depression are also known to be regulated by CREB, such as tyrosine hydroxylase (TH) (Gueorguiev *et al* 2006), corticotrophin releasing factor (CRF) (Itoi *et al* 1996), dynorphin (Carlezon *et al* 1998) and neuropeptide Y (NPY) (Pandey 2003). The effects of CREB on mood will not only depend upon the specific target gene that is altered, but also the region of the brain in which this regulation takes place and the consequent changes on structure and function of the specific neuro-circuitry. For example, the increased expression of CREB in the hippocampus is likely

to contribute to trophic changes through the recruitment of BDNF and NPY, resulting in enhanced neurogenesis (Hansel *et al* 2001; Pencea *et al* 2001) and reversal of damage. A possible consequence of these changes may be to enhance the ability of the hippocampus to exert an adaptive influence on stress reactivity by terminating the stress responses mediated via the hypothalamo-pituitary-adrenocortical (HPA) axis, incidentally, known to be dysfunctional in depression (Carroll *et al* 1976). In contrast, enhanced CREB in the hypothalamus would increase CRF thus leading to the maladaptive hyper-activation of the HPA axis. This means that a simplistic upregulation of CREB in the entire brain may not have any therapeutic relevance, and that attempts to use this molecule as a target for drug development requires identifying mechanisms that allow for a region-specific recruitment of CREB.

3. Brain-derived neurotrophic factor

BDNF is the most widely expressed member of the nerve growth factor family of growth regulators, collectively termed the neurotrophins. The neurotrophins play a critical role in the development of the brain and continue to have a seminal role in shaping plasticity in the mature nervous system (Thoenen 1995). They mediate their effects through the stimulation of a family of the tyrosine kinase-coupled receptors, known as trks (tropomyosin receptor kinase), which signal through the MAP kinase signalling cascade. The specific trk that mediates BDNF signalling is known as the trkB receptor. The BDNF gene has a complex structure, with 4 distinct non-coding 5` exons with their unique promoters, and one common 3` coding exon that generates the mature BDNF protein (Timmusk *et al* 1993). BDNF has a well-established role in the development, survival and differentiation of select populations of neurons (Hoefer and Barde 1988; Alderson *et al* 1990) and is capable of augmenting ongoing neurogenesis in the adult brain (Pencea *et al* 2001). BDNF has also been shown to elicit rapid action potentials thus influencing neuronal excitability (Kafitz *et al* 1999) and it has a demonstrable role in activity-dependent synaptic plasticity events like long-term potentiation, learning tasks and memory (Bramham and Messaoudi 2005). Thus, BDNF is involved in structural remodeling, neuronal plasticity and synaptic restructuring, and is promising as a candidate molecule underlying the structural changes associated with depression and animal models of depression, and as a potential target for antidepressants.

3.1 *BDNF in animal models of depression*

A large body of literature already documents the role of BDNF in the developing brain, and there is growing

support for the continued role of BDNF in shaping adult brain structure and function. Existing data from animal models supports a role for BDNF in the pathophysiology of depression. Prolonged exposure to several stressors, including immobilization stress, forced swim stress as well as conditioned footshock, results in a down-regulation of BDNF expression in the hippocampus (Smith *et al* 1995; Rasmusson *et al* 2002). Animal models like learned helplessness also result in a decline in hippocampal BDNF expression (Song *et al* 2006). A recent study indicates that BDNF regulation by social stress is mediated through epigenetic mechanisms of methylation, and hence transcriptional repression, of the BDNF III and IV promoters (Tsankova *et al* 2006). Our unpublished studies reveal that the same promoters (III and IV) may also be targets for another stress model, immobilization, raising the possibility that it is these specific promoters that are recruited by stress to alter BDNF expression. It is likely that environmental perturbations result in sustained chromatin remodeling and epigenetic programming thus influencing the transcriptional expression of the BDNF gene. Perturbed BDNF expression could have strong functional correlates on both the structure and activity of stress neuro-circuitry. Indeed, it is hypothesized that the down-regulation of BDNF levels may contribute to the stress-induced damage observed in the hippocampus.

3.2 *BDNF as a target of antidepressant action*

Antidepressant therapies, including physical activity – a natural antidepressant, electroconvulsive seizures, and pharmacological antidepressants robustly increase the expression of this neurotrophin in the hippocampus and cortex (Nibuya *et al* 1995; Dias *et al* 2003; Farmer *et al* 2004). Additionally, the stress-mediated reduction in BDNF expression can be prevented with pre-administration of antidepressant therapy (Nibuya *et al* 1995). Distinct classes of antidepressants appear to regulate the BDNF gene through differential recruitment of individual BDNF promoters (Dias *et al* 2003). In addition, they appear to be capable of reversing the epigenetic shut down of the BDNF III and IV promoters caused by stress (Tsankova *et al* 2006). Indeed, overexpression of histone deacetylases, which would de-repress the epigenetic control of the BDNF promoters, is shown to upregulate hippocampal BDNF expression and exert antidepressant-like effects in animal models (Tsankova *et al* 2006). Furthermore, truncated trkB over-expressing mice (Saarelainen *et al* 2003), which show reduced BDNF signalling, are resistant to the effects of antidepressants in the forced swim model of depression. In addition, some of the structural changes in the hippocampus that ensue from sustained antidepressant treatment are mediated, at least in part, by BDNF. The mossy fiber

sprouting seen in the hippocampus following chronic ECS is partially lost in BDNF heterozygote mice (Vaidya *et al* 1999). BDNF also appears to have a role in the increased survival, but not the enhancement of proliferation, of adult hippocampal progenitors observed following chronic antidepressant treatment (Sairanen *et al* 2005). Finally, the effects of the antidepressant desipramine in the forced swim test are lost in adult-onset forebrain knockouts of BDNF, thus indicating that BDNF plays a role in the behavioural actions of antidepressants (Monteggia *et al* 2004). Taken together, these reports clearly implicate BDNF in both the pathogenesis of depression and as a target/mediator of antidepressant action.

3.3 *Pro- and anti-depressant activity of BDNF*

BDNF is not only a potential target for antidepressant action, but it can, itself, act as an antidepressant. Infusion of exogenous BDNF into the ventricles, midbrain or the hippocampus of rodents has an antidepressant-like effect in several models of depression (Siuciak *et al* 1997; Shirayama *et al* 2002; Eisch *et al* 2003). In addition, BDNF receptor 'trkB' overexpressing mice exhibit antidepressant-like responses in the forced swim test (Koponen *et al* 2005). However, in a manner reminiscent of CREB, the spatial expression of BDNF is critical in its antidepressant-like activity. Whereas increased BDNF expression in the hippocampus appears to be antidepressant in nature (Shirayama *et al* 2004), increased BDNF activity in the ventral tegmental area (VTA) or nucleus accumbens (NAc) results in a pro-depressive state (Eisch *et al* 2003). Further confirming a region-specificity in the effects of BDNF on depression-associated behaviours, the blunting of BDNF action in the nucleus accumbens by over-expression of truncated BDNF TrkB receptors has an antidepressant-like activity (Eisch *et al* 2003). Thus, similar to the actions of CREB, BDNF shows a distinct region-specificity in its activity as a pro- or anti- depressant.

4. Region specificity in the action of CREB and BDNF

Depressive disorders and sustained stress exposure do involve a dysregulation of the CREB-BDNF cascade, while antidepressant therapies potentially recruit these molecules to mediate their effects. Interestingly, both CREB and BDNF have the capacity to exert both pro- or antidepressant-like effects, depending on their spatio-temporal regulation. For the purposes of this review we have focused upon two key neuro-anatomical foci that are strongly implicated in depression, namely the hippocampus and the ventral tegmental area – nucleus accumbens (VTA-NAc) reward circuitry (figure 2).
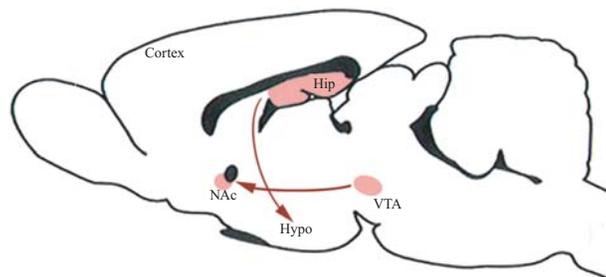
Figure 2. Sagittal schematic of the adult rat brain. Shown are the two major circuits, regulated by the CREB-BDNF cascade that, have a relevance to depression. The hippocampus (Hip) projects to the hypothalamus (Hypo) via a multi-synaptic pathway. This circuit is thought have a critical inhibitory control over the hypothalamo-pituitary-adrenocortical stress response pathway. The other circuit where CREB and BDNF have been shown to perturb depression-related behaviours is the meso-limbic dopaminergic pathway. This pathway consists of dopaminergic neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc) and modulate reward perception.

4.1 *CREB and BDNF in the hippocampus*

The hippocampus, as previously described, is a key limbic region whose structure and function is compromised in mood disorders. The hippocampus is also of particular relevance given it plays a critical role in inhibiting the HPA axis, which is the major mediator of systemic stress responses (Jacobson and Sapolsky 1991) (figure 2). In the hippocampus, increased activity of the CREB-BDNF cascade results in anti- depressive responses. Hippocampal overexpression of BDNF and CREB is capable of mimicking both the structural consequences of sustained antidepressant treatment as well as exerting antidepressant-like behavioural effects (Chen *et al* 2001a; Vaidya and Duman 2001; Shirayama *et al* 2004; Malberg and Blendy 2005). Indeed, activation of the cAMP-CREB cascade results in increased neurogenesis of dentate granule cell progenitors (Nakagawa *et al* 2002), and increased dendritic length and branching (Fujioka *et al* 2004). Additionally, transgenic mice that over-express the dominant negative form of CREB show reduced levels of hippocampal neurogenesis (Giachino *et al* 2005), mimicking the effects observed in animal models of depression. It is possible that CREB, a transcriptional activator of BDNF, recruits this neurotrophin to mediate its effects on structural plasticity (figure 3). BDNF, in addition to being a target of CREB, can itself recruit this particular transcription factor by activating the MAP kinase cascade (Arthur *et al* 2004) (figure 1), thus setting up a potential positive feed-back loop. Taken together, elevated CREB-BDNF, through their protective influences on vulnerable hippocampal neurons and their ability to directly promote structural
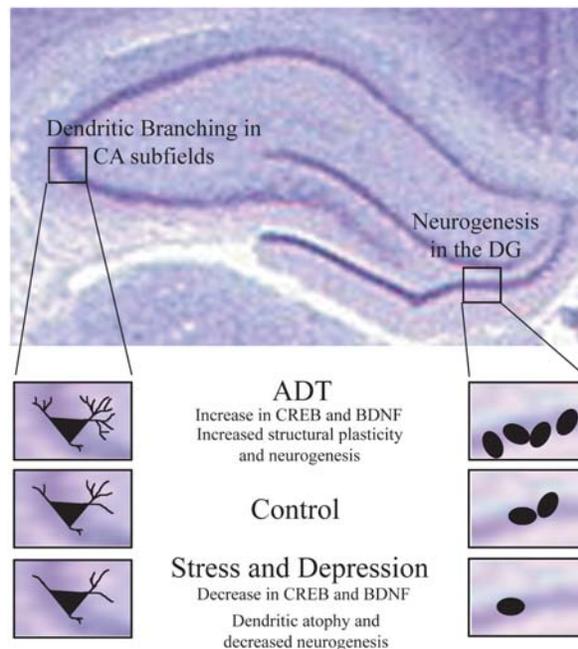

Figure 3. Role of CREB and BDNF in hippocampal structural plasticity in response to antidepressants and in animal models of depression. Shown are the hippocampal subfields, where dentate gyrus (DG) neurogenesis and CA subfield dendritic branching is regulated by both antidepressants and in depression models. While antidepressants enhance CREB-BDNF and promote neurogenesis and dendritic sprouting, animal models of depression are associated with a decline in CREB-BDNF, dendritic atrophy and decreased neurogenesis.

reorganization, could result in repair of this region known to be damaged in depression. In addition, BDNF can alter neurotransmitter release (Tyler *et al* 2002) and itself elicit an activation of postsynaptic neurons (Kafitz *et al* 1999), and may thus have potential protective functional consequences on hippocampal circuitry known to be dysfunctional in depression. A direct consequence of enhanced hippocampal function would be a restoration of the inhibitory control exerted on the stress response pathway of the HPA axis. In addition, the well-established role of BDNF and CREB in hippocampal-dependent learning and memory (Tyler *et al* 2002; Mizuno and Giese 2005) may play a critical role in ameliorating the cognitive symptoms associated with depression.

4.2 *CREB and BDNF in the VTA-NAc pathway*

The VTA-NAc dopaminergic pathway is the primary reward circuitry of the mammalian brain. Lack of pleasure seeking, anhedonia, is a characteristic symptom observed in all depressed patients, thus strongly implicating this
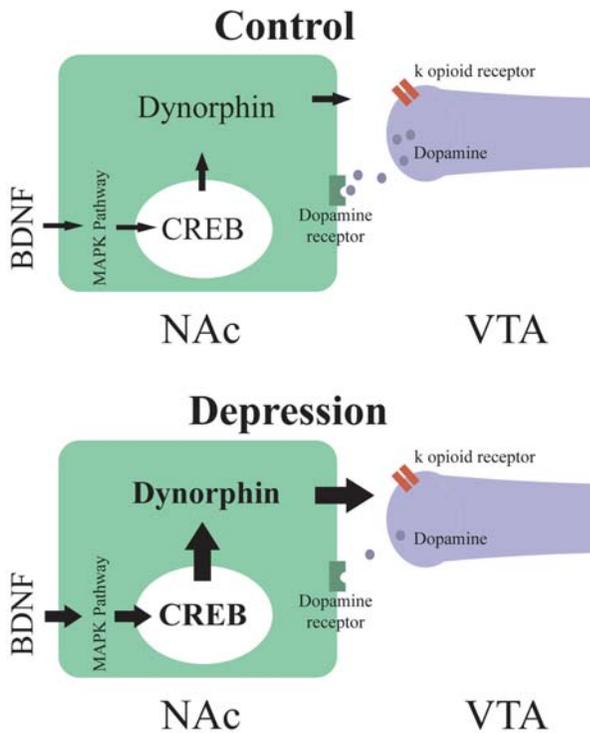
Figure 4. The role of the BDNF-CREB cascade in the ventral tegmental area (VTA) – nucleus accumbens (NAc) pathway. Enhanced BDNF-CREB signalling in the NAc in animal models of stress and depression is associated with increased dynorphin expression. Dynorphin, through a feedback inhibitory loop, activates κ opioid receptors on VTA neurons and results in an inhibitory effect on the dopaminergic neurons projecting from the VTA to the NAc. Decreased activation of the VTA-NAc pathway is associated with the pro-depressive effects induced by overexpression of CREB-BDNF in this circuit.

circuitry in the pathophysiology of this disease (Nestler and Carlezon 2006). While dysfunction of the VTA-NAc circuit is thought to underlie the anhedonia associated with depression, antidepressants have been postulated to reverse this dysfunction. In stark contrast to the effects of CREB-BDNF in the hippocampus, activation of the CREB-BDNF cascade in the VTA-NAc pathway results in pro-depressive like behaviour (Malberg and Blendy 2005). Increased CREB activity in the NAc results in a phenotype characteristic of depression, including reduced reward experience or 'anhedonia' and increased immobility in the forced swim test, symbolizing behavioural 'despair' (Pliakas *et al* 2001). Additionally, increased BDNF activity in this pathway also results in a similar pro-depressive state (Eisch *et al* 2003). The effects of BDNF are thought to be mediated via up-regulating CREB expression, through activation of the MAPK/ERK pathway (Arthur *et al* 2004). Thus BDNF, upstream of CREB, would recruit specific target genes – with

promoter CRE elements – that then affect the functioning of the VTA-NAc circuitry, resulting in a depression-like phenotype. CREB is known to positively modulate levels of dynorphin within the NAc (Carlezon *et al* 1998), and this upregulation of the endogenous opioid dynorphin could mediate the pro-depressive effects of CREB. Dynorphin is a natural ligand at the κ opioid receptors, these being present on the terminals of the meso-limbic dopaminergic neurons that originate from the VTA and innervate the NAc. Increased dynorphin, through the κ opioid receptor, negatively modulates dopaminergic transmission. Although at present it is unknown if CREB induction in the accumbens actually results in enhanced dynorphin release within the VTA, it has been hypothesized that such a change in the context of the VTA-nucleus accumbens pathway could result in dysphoria and lack of pleasure seeking (figure 4) (Nestler and Carlezon 2006). This raises the possibility that enhanced BDNF-CREB in the accumbens may, through a regulation of opioid signalling, result in an anhedonic state thus contributing to the pro-depressive effects, whereas an abrogation of BDNF-CREB signalling in this region could have beneficial consequences on behaviour and exert an antidepressant-like effect.

5. CREB and BDNF mutant mice: Animal models for depression?

Although converging lines of evidence clearly point to a role for CREB and BDNF in depression-related behaviour, CREB/BDNF loss of function mutants do not exhibit classical symptoms observed in animal models of depression. The major caveat is that most of the studies done in mutant mice do not allow for either a spatial or temporal control over the silencing of CREB and BDNF expression, hence making it difficult to dissect out both the developmental effects as well as the region-specific consequences of CREB/BDNF loss upon the depression related neuro-circuitry. However, there do appear to be specific behavioural changes in CREB deficient mice and BDNF heterozygote mice, and careful analysis of these animals may provide insights into the mood modulatory effects of these molecules.

5.1 *CREB mutant mice*

CREB-deficient mice have been reported to exhibit an antidepressant response in the footshock and tail suspension tests (Valverde *et al* 2004). Given that antidepressants are believed to recruit CREB to mediate their effects, it is contrary to expectations for CREB deficient mice to display an antidepressant-like phenotype. However, this behaviour of CREB-deficient mice mimics that seen with an abrogation of CREB function, using dominant negative

CREB (mCREB) overexpression, in the nucleus accumbens of rats (Newton *et al* 2002). The CREB-deficient mice show reduced CREB throughout the brain, and it appears that lowered CREB in the NAc is able to exert an antidepressant-like phenotype overriding any pro-depressive consequences of lowered CREB expression. Future studies clearly require a controlled spatio-temporal targeted disruption of CREB to reveal the role of this molecule in distinct neuronal circuits relevant to mood modulation.

5.2 *BDNF mutant mice*

Studies using mice with perturbations in BDNF signalling indicate a complex behavioural phenotype. While neither trkB-mutant mice (Saarelainen *et al* 2000) nor BDNF heterozygotes (+/–) (Lyons *et al* 1999) display classical depression-like behaviours, trkB overexpressing mice clearly exhibit antidepressant-like behaviour in the forced swim test (Koponen *et al* 2005). A recent study taking advantage of conditional BDNF knockouts, in which the BDNF loss of function is restricted to the adult forebrain, reveals that there is a gender-specific propensity to develop depressive behaviours, with the female mice showing an enhanced incidence of depression-like behaviours (Monteggia *et al* 2006). This is particularly interesting given the fact that the occurrence of depression is higher in women (Noble 2005), and use of this model can be made to understand the sexual dimorphism displayed with respect to the consequences of reduced BDNF signalling. What is clear is that a critical future direction for studies employing genetic perturbations of BDNF is the requirement to target the perturbation of BDNF to specific neuronal regions and at particular ages. This line of scientific enquiry is likely to provide important insights into the role of BDNF in depression models.

6. Clinical studies

While a robust body of literature exists suggesting a role for CREB and BDNF in depression as well as in antidepressant action, a majority of the work is restricted to animal models. However, building evidence from clinical studies also supports the idea that CREB and BDNF are involved in the pathogenesis of depression and in the mechanism of antidepressant action.

Postmortem studies show a decrease in CREB expression in the cerebral cortex of patients not undergoing antidepressant therapy, while CREB immunoreactivity increases in response to antidepressant treatment (Dowlatshahi *et al* 1998). Similarly, BDNF immunoreactivity is considerably decreased in the brains of treatment-naive patients, while antidepressant therapy increases BDNF expression to levels resembling that of healthy control individuals (Chen *et al*

2001b). Serum BDNF, which is believed to be reflective of BDNF levels in the brain, also shows a similar trend, with decreased levels of serum BDNF seen in patients suffering from depression. This decline in serum BDNF levels is negatively correlated with the MADRS (Montgomery-Ashberg Depression Rating Scale), i.e. with the severity of the depressive symptoms (Karege *et al* 2002).

Insights from genetic linkage studies provide further support for a role of CREB and BDNF in depressive disorders. The CREB1 locus is thought to have an epistatic influence in defining susceptibility to recurrent, early-onset, major depression (Zubenko *et al* 2003). The BDNF locus has been implicated in altered vulnerability for bipolar disorder (Neves-Pereira *et al* 2002) and childhood depression (Kaufman *et al* 2006). In addition, a single nucleotide polymorphism, val66met, in the BDNF coding region has a strong association with childhood-onset mood disorder (Strauss *et al* 2005) and geriatric depression (Hwang *et al* 2005). The val66met polymorphism is correlated with a decreased hippocampal volume and abnormal hippocampal activation, which may underlie an enhanced vulnerability to the development of depression (Bueller *et al* 2005). Furthermore, cell biological studies have revealed that the met-BDNF variant shows disruption of activity-dependent release (Egan *et al* 2003), raising the possibility that the met allele may result in deficits in the ability to mount BDNF-induced remodeling of neuronal circuits. In support of such a hypothesis, a recent study indicates that healthy individuals with the met allele exhibit reduced experience-dependent structural plasticity in the cortex (Kleim *et al* 2006). Taken together, these studies suggest that BDNF may be critical in mediating adaptive-responses to environmental changes such as stress and the inability to exhibit such an adaptive response could substantially enhance the susceptibility to stress-related disorders like depression.

7. Conclusions

The pathways and signalling cascades dysregulated in depression are undoubtedly far more complex than previously suspected. While it would be simplistic to consider the BDNF-CREB cascade as the only intracellular pathway involved, what emerges is that CREB and BDNF are likely to be key molecules involved in mood regulation. The current state of knowledge on the role of the CREB-BDNF cascade in depression provides strong impetus to further understand the regulation and action of CREB and BDNF in depression and following antidepressant therapy. In addition, CREB and BDNF may serve as potential therapeutic targets for the development of new drugs that modulate mood. However, given the region specificity of the effects of the BDNF-CREB cascade on behaviour, a critical requirement would be to identify upstream signalling cascades that recruit

these molecules in a region specific fashion. A combination of both preclinical and clinical studies are required to further explore the role of the CREB-BDNF cascade in depression, as this could shed new light on the pathogenesis and effective management of depressive disorders.

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