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Regulation of Antidepressant Activity by cAMP Response Element Binding Proteins

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Abstract

Depression is a clinically and biologically heterogeneous disease that is one of the most prevalent and costly psychiatric disorders. It is the leading cause of disability regarding job performance and burden on family members in the United States and worldwide *(1).* Although the therapeutic efficacy of antidepressant drugs has been recognized for years, the exact molecular mechanisms of action remain elusive, making the systematic approach to the development of new drugs difficult. The acute increases in levels of monoamines brought about by various classes of antidepressants cannot account for the requirement of repeated, chronic administration for up to 2–6 wk before treatment benefits become evident. Furthermore, despite their efficacy, current antidepressant drugs improve symptoms in only 60% of patients treated *(2).* The development of new and better therapies depends on a thorough understanding of the neurobiology of depression and the molecular mechanisms underlying antidepressant drug action. Early studies focusing on alterations in the levels of receptors and second messengers helped define the important signaling pathways initiated by these drugs, whereas recent molecular studies suggested that long-term adaptations in cellular signaling mechanisms may be required for the onset and/or maintenance of antidepressant effects. Attention has now focused on downstream targets of Ca^{++} and cyclic adenosine monophosphate (cAMP) in the cell, such as the activation of transcription factors. This article discusses the transcription factor cAMP response element binding protein and a related protein, cyclic AMP response element modulator, and their roles as molecular mediators of antidepressant action.

Index Entries: CREB; CREM; antidepressant; gene expression; forced swim test; tail suspension test; neurogenesis.

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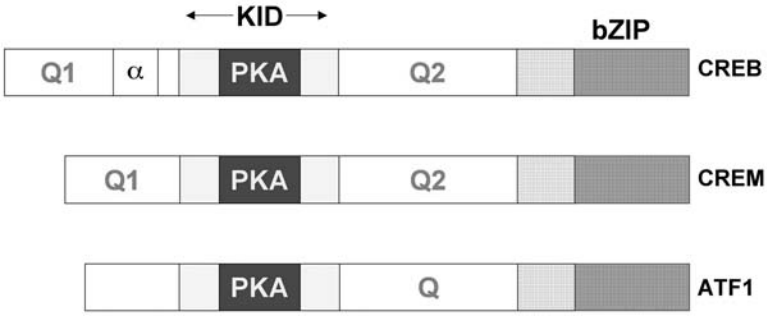

Fig. 1. Comparison of CREB, CREM, and ATF-1. The known functional regions of the CREB/ATF subgroup are shown. The bZIP regions comprise the carboxy-terminal bZIP domain that is necessary and sufficient for dimerization and DNA binding. In the case of CREM, differential splicing can give rise to either of two splice sites within the bZIP exon, generating two alternative DNA-binding domains. Several distinct elements make up the KID. PKA represents a single PKA phosphoacceptor site (serine 133 in CREB). Two Q domains surround the KID. These are glutamine-rich activation domains that contribute to transcriptional activity. The α-peptide, which is also involved in transcriptional activation, is only present in CREB. ATF-1 is also lacking an N-terminal glutamine-rich domain and instead has a small region in the amino-terminal that is not related to CREB or CREM.

cAMP Response Element Binding Protein

cAMP response element binding protein (CREB) was one of the first members of the basic domain/leucine zipper (bZIP) superfamily of transcription factors to be identified *(3).* These proteins all contain a region of C-terminal basic residues necessary for DNA recognition and a flanking leucine zipper region that mediates homo- or heterodimerization of family members *(4).* Members of the bZIP family of transcription factors can all bind the same *cis*-regulatory cAMP response element (CRE) *(5,6).* The formation of specific heterodimers has led to a subclassification of the bZIP superfamily to include CREB/activating transcription factor (ATF) family proteins. For example, CREB can form functional dimers with CRE modulator (CREM) and ATF-1 *(7–9),* partly because of the high degree of similarity in the bZIP domain of these three proteins (Fig. 1). In contrast, although ATF-2, -3, or -4 can readily bind CRE regions, none can form heterodimers with CREB, CREM, or ATF-1 *(5,6).* The ability of the CREB family transcription factors to heterodimerize greatly expands the repertoire of binding sites that are available to, and contacted by, these factors in the nucleus *(10).*

CREB was first identified as the major factor mediating a transcriptional response to elevated levels of cAMP *(11).* Activation of cAMP-dependent protein kinase A (PKA) leads to phosphorylation of a serine residue (S133) that is critical for the transactivational properties of CREB *(3,9,12–17).* Phosphorylation of CREB by PKA has been reported to stimulate binding of CREB to asymmetric CREs (i.e., tyrosine aminotransferase, 5′-CTGCGTCA-3′) but not to symmetric CREs (i.e., somatostatin, 5′-TGACGTCA-3′) *(18).* In addition, kinases that are activated by intracellular calcium, including the calcium-calmodulin-dependent kinases (CaM kinase II and CaM kinase IV), have been reported to activate or inhibit CREB transactivation depending on the serine residues that are

phosphorylated *(15,19–22).* Furthermore, a member of the ribosomal S6 kinase family, RSK2 (which is part of the Ras-dependent signaling pathway activated by mitogenic signaling), can phosphorylate CREB *(16,17,23,24).*

More recently, a family of coactivators was identified that enhances CREB-mediated transcription in a phosphorylation-independent manner. A high-throughput expression screen was used to identify proteins that enhance CREB target gene expression *(25).* A family of novel coactivator homologs was identified as complementary DNAs (cDNAs) that induced CREB activity in the absence of cAMP stimulus. These proteins, referred to as transducers of regulated CREB activity (TORCs), are specific for inducing cAMP-responsive promoters in the absence of cAMP or PKA activity and have minimal effects on promoters containing activating protein-1 (AP-1), serum response, heat shock, or glucocorticoid receptor response elements. TORCs interact with the bZIP/DNA-binding domain of CREB and enhance interactions with the basic transcriptional machinery, such as the $TAF_{II}130$ component of TFIID following its recruitment to the promoter target *(25).* Multiple pathways leading to the phosphorylation of CREB, the variability of CREB binding to CRE sequences, and the ability of nonphosphorylated CREB to affect gene expression all contribute to a complex balance of transcriptional control, which varies depending on cell type and physiological status.

Both the mouse and human genes encoding CREB are composed of 11 exons. Alternative splicing of exon 5 yields the two activator isoforms CREB-α and CREB-Δ *(26–29).* All 11 exons are used for the transcription of CREB-α, whereas CREB-Δ lacks exon 5. For translation of the CREB-α and -Δ isoforms, an initiation site in exon 2 is used. CREB-Δ exhibits threefold higher expression than CREB-α *(30,31),* although both are ubiquitously expressed. A third CREB activator isoform, CREB-β, is generated by alternative splicing of exons 2–6 *(32).* For translation, an initiation site in exon 4 is used. Although the role of CREB-β is not clearly defined, this isoform likely functions in development. Mice lacking all three CREB isoforms (α, β, and Δ; $Creb^{null}$) are not viable as a result of failure of the lungs to inflate properly and are growth-retarded *(33),* whereas mice lacking only the α and Δ isoforms *($Creb^{\alpha\Delta}$)* mature into adulthood *(32).*

Following the cloning and characterization of CREB, additional CRE-binding proteins were identified. Among the most homologous is CREM, which shares similar structural domains to CREB, including the bZIP domain and the kinase-inducible domain (KID), which contains a serine target for PKA at residue 117 and two flanking glutamine-rich transactivation domains (Fig. 1). The *Crem* gene is expressed in a tissue- and developmental-specific pattern, in contrast to the other ubiquitous, noninducible members of the CRE-binding transcription factor family *(8).* In contrast to the CREB protein, in which all alternative splice variants are transcriptional activators, there are distinct functional differences among the CREM isoforms. These isoforms arise from alternative splicing and promoter activity and result in repressor and activator proteins that can regulate CRE-mediated gene transcription.

Use of the P1 promoter yields the primary activator isoform CREM-τ. Because of the presence of the KID, CREM-τ is regulated by phosphorylation. CREM-τ is expressed in the testes at levels that are hundreds of times greater than those found elsewhere *(34).* Male CREM-deficient mice lack mature germ cells as a result of impairment of spermatogenesis *(35,36).* Activity at the P2 promoter yields the potent repressor isoform inducible cAMP early repressor (ICER) *(37).* The ICER protein consists only of the DNA-binding domain (bZIP) and has no phosphorylation domain. In addition, the ICER promoter contains four tandem CRE regions. These distinctions make ICER cAMP-inducible as well as a negative autoregulatory protein, dependent only on its cellular concentration. ICER is the most abundantly expressed CREM transcript in neuroendocrine tissues *(34,38).*

The Role of cAMP-PKA-CREB Pathway in Mechanisms of Action of Antidepressants

Alterations in the cAMP signaling pathway have been implicated in depression as well as the mechanism of chronic antidepressant treatment *(39,40).* Regulation of G proteins by antidepressants was shown at both the level of enhanced coupling of Gs-α to adenylyl cyclase *(41)* as well as an increased cyclase activity *(42).* Downstream components of the cAMP cascade, such as PKA, also were regulated by antidepressant treatment. When intracellular concentrations of cAMP increased, the regulatory and catalytic subunits of this protein dissociated, enabling the catalytic subunits to phosphorylate numerous cellular substrates. Chronic treatment with a tricyclic antidepressant (imipramine), a monoamine oxidase inhibitor (tranylcypromine), or electroconvulsive shock increased PKA activity in the cell nucleus *(43).* Antidepressants appeared to specifically affect the regulatory subunit of this enzyme complex, because chronic administration of desipramine resulted in an increase in the amount of the RII regulatory subunit *(44).* In contrast, expression of PKA C-α catalytic α-subunit messenger RNA (mRNA) did not change with chronic administration of antidepressant drugs *(45).*

CREB, a well-characterized target of PKA phosphorylation, was demonstrated to be regulated by chronic, but not acute, antidepressant treatment. Chronic administration of the selective serotonin reuptake inhibitor fluoxetine increased phosphorylated CREB levels in the mouse in several brain regions, including the amygdala, cortex, dentate gyrus, and hypothalamus, whereas desipramine increased CREB phosphorylation only in the dentate gyrus *(46).* In contrast, a recent study in rats showed that phosphorylated CREB protein levels were significantly decreased in the frontal cortex following chronic administration of desipramine or reboxetine (a selective norepinephrine reuptake inhibitor) *(47).* These differences could be species-specific; however, because of the use of different prototype drugs, these findings could reflect a differential CREB response to serotonin or noradrenergic signal activation. In addition to altering the phosphorylation state of the protein, antidepressants were also shown to regulate CREB at the level of gene transcription. CREB mRNA is increased in the hippocampus after chronic administration of fluoxetine, desipramine, and tranylcypromine and after electroconvulsive seizure *(45).* However, although these treatments increased CREB expression, only fluoxetine significantly increased CREB protein levels in the hippocampus *(45).*

The functional significance of induction of CREB mRNA and subsequent translation into protein can be evaluated in vivo with electrophoretic mobility shift assays (EMSAs). In these experiments, consensus CRE oligonucleotides are radiolabeled and incubated with cell extracts obtained from discrete brain regions. The types of proteins that make up CRE binding complexes can be identified using specific antibodies. Chronic administration of fluoxetine increased CREB binding in the rat hippocampus *(45,48)* and frontal cortex *(48),* whereas desipramine increased CREB binding only in the frontal cortex *(48).*

In vitro, a number of antidepressant drugs—including fluoxetine, desipramine, and trazodone—inhibited depolarization-induced CRE-mediated transcription of a reporter gene in neuronal cell culture *(49).* In the case of desipramine, this was attributed to the inhibition of CREB phosphorylation. However, using a transgenic mouse line expressing a gene containing tandem CRE units driving lacZ reporter expression, CRE activity was shown to increase following antidepressant treatment in a drug- and region-specific manner *(46).* For example, CRE activity increased following chronic tranylcypromine treatment in the cortex, CA3 hippocampal region, hypothalamus, and amygdala, whereas fluoxetine increased CRE activity in the cortex, amygdala, and hypothalamus *(46).* On the other hand, chronic desipramine increased CRE activity in the

Table 1
Animal Models for Examining CRE-Binding Transcription Factor Function

Type	Mutation	Effected phenotype	Reference
Transgenic	mCREB	Growth and development	Struthers et al., 1991 *(88)*
Gene ablation	$CREB^{\alpha\Delta}$	Learning	Hummler et al., 1994 *(58)*
			Bourtchuladze et al., 1994 *(89)*
		Addiction	Walters and Blendy, 2001 *(59)*
		Depression	Conti et al., 2002 *(90)*
Gene ablation	$CREB^{null}$	Development and viability	Rudolph et al., 1998 *(33)*
Conditional gene ablation	$CREB^{loxPCamKII\text{-}Cre}$	Neurodegeneration	Mantamadiotis et al., 2002 *(91)*
	$CREB^{loxPNes\text{-}Cre}$	Learning	Balschun et al., 2003 *(92)*
Viral overexpression	HSV-CREB-α; HSV-mCREB	Addiction	Carlezon et al., 1998 *(74)*
		Depression	Chen et al., 2001 *(55)*
			Pliakas et al., 2001 *(56)*
			Newton et al., 2002 *(57)*
Inducible transgenic/ bitransgenic	NSE-tTA/TetOp-CREB-α	Addiction	Sakai et al., 2002 *(75)*
	$tTA^{+}/mCREB^{+}$	Depression	Nakagawa et al., 2002 *(85)*
	$tTA^{+}/CREB^{+}$		Newton et al., 2002 *(57)*

Abbreviations: mCREB, point mutation of serine 133 to alanine: loxP, locus of crossover; CamKII, Ca^{++} calmodulin kinase II; Cre, cyclization recombination; New, nestin; HSV, herpes simplex virus; NSE, neuron-specific enolase; tTA, tetracycline transactivator; TetOp, tetracycline operator.

amygdala only. One caveat of CRE-mediated transcription of a reporter gene is the lack of specificity, because numerous transcription factors are capable of binding to CRE elements and activating these reporter genes *(50)*. Therefore, because both CREM and CREB can drive CRE-mediated gene expression, it is necessary to examine the role of each transcription factor independently in the mechanism(s) of antidepressant drugs.

Animal Models for Examining CRE-Binding Transcription Factor Function in Depression

Several rodent models have been developed to study CREB function in vivo. However, only a subset of these models has evaluated the specific role of CREB in antidepressant action (Table 1). Manipulating CREB in animal models allows for the analysis of behavior and drug–behavior interactions, which are critical components for evaluating current and novel antidepressant therapies. The forced swim test (FST) is the most widely employed paradigm for evaluating the antidepressant-like potential for both pharmacological and nonpharmacological treatments. In this paradigm, animals are placed in a circular tank of water and evaluated for total immobility time or latency to immobility. The development of immobility in the FST has been interpreted as "behavioral despair" associated with the inability of the animal to escape from water *(51)*. Antidepressant treatments have been shown to decrease immobility duration and increase latency to immobility. One emerging interpretation of

this result is that antidepressants evoke active coping behaviors and decrease the passive immobility induced by stress. In a related behavioral model, the tail suspension test (TST), animals that are suspended by the tail rapidly become immobile as a passive response to inescapable aversive stimulation *(52).* Similarly to the FST, immobility behavior in the TST may reflect the development of passive behavior that disengages the animal from active forms of coping with stressful stimuli *(53).* A third behavioral model, the learned helplessness paradigm, is based on the finding that administration of repeated uncontrollable footshock results in escape deficits that can be reversed by a broad spectrum of antidepressant treatments *(54).* This paradigm is believed to incorporate the motivational and emotional aspects of stress-induced depression.

To study how CREB is related to the biological mechanisms underlying behaviors associated with the FST, TST, or learned helplessness paradigms, several laboratories generated animal models in which CREB levels were altered. For example, acute viral vector-mediated overexpression of CREB in the dentate gyrus of the rat hippocampus significantly decreased the number of escape failures in the learned helplessness paradigm *(55),* a response similar to that of chemical antidepressants. In addition, these behavioral effects of CREB exposure were maintained for days after the dissipation of viral-mediated CREB expression, indicating longlasting effects of CREB expression on antidepressant-like behaviors. Similarly, overexpression of CREB in the dentate gyrus reduced immobility times in the FST, a response characteristic of antidepressant treatment *(55).*

In contrast to the findings that described a role for CREB in the hippocampus, Pliakas and colleagues *(56)* demonstrated that viral overexpression of CREB in the nucleus accumbens reduced the latency to immobility in the FST, suggesting that increased CREB levels in this brain region contribute to depressive-like behaviors. Similarly, Newton and colleagues *(57)* demonstrated that transgenic mice that overexpressed CREB showed an increased latency to escape uncontrollable shock in the learned helplessness paradigm, a behavior reflective of a depressive-like state. However, because CREB overexpression was not localized to a specific brain structure in these mice, it was difficult to identify the anatomical region underlying this effect.

Attempts to evaluate CREB function by blocking activity or reducing levels in vivo yielded complimentary evidence for a role of this protein in antidepressant-like behaviors. A mutation in the kinase-inducible region of the *Creb* gene (mCREB) substituted an alanine for a serine at position 133, which destroyed the PKA phosphorylation site *(13)* and effectively reduced endogenous CREB activity. Viral administration of mCREB into the nucleus accumbens increased latency to immobility in the FST, an effect associated with antidepressant efficacy *(56).* Furthermore, these studies reported that levels of phosphorylated CREB increased in the nucleus accumbens following FST *(56),* suggesting a novel role for the CREB in the nucleus accumbens regarding antidepressant-like behaviors. In additional studies, transgenic mice expressing a dominant-negative mutation of CREB as well as viral overexpression of mCREB in the nucleus accumbens experienced antidepressant-like behaviors in the learned helplessness paradigm *(57).* Although the levels of mCREB expression in the transgenic mice used in these studies were highest in the striatum (including the nucleus accumbens), expression also was observed in certain areas in the cerebral cortex and hippocampus, making it difficult to exclude these areas as contributors of the behavioral phenotype.

A global CREB-deficient mouse model was generated by targeted deletion of the CREB-α and -Δ isoforms by homologous recombination ($CREB^{\alpha\Delta}$ mutant mice; ref. *58*). This deletion reduced functional CREB binding in the brain by approx 90% as measured by EMSA *(59).* Previous phenotypes associated with this model are impaired short- and long-term contextual and cued fear conditioning *(60)* and altered somatic and reinforcing effects of drugs of abuse *(59).* $CREB^{\alpha\Delta}$ mutant mice demonstrated

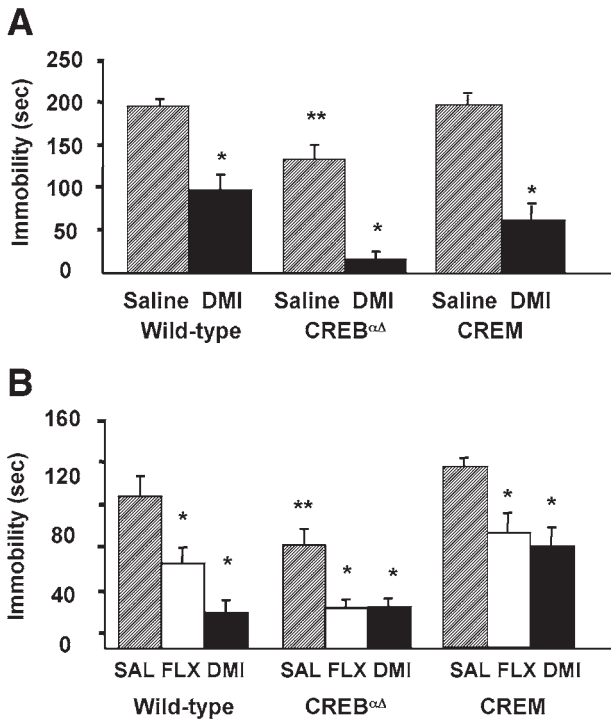

Fig. 2. Behavioral response of wild-type, CREB-deficient (CREB$^{\alpha\Delta}$ and CREM-deficient mice in the FST **(A)** and TST **(B)** after antidepressant treatment. Animals were administered saline, DMI, or FLX and evaluated for immobility in the FST or TST. DMI and FLX treatment significantly reduced immobility times in all groups compared to respective saline controls in both paradigms. Saline-treated CREB$^{\alpha\Delta}$ mutant mice had significantly lower immobility times than saline-treated wild-type mice in both paradigms. Results are presented as mean immobility ± SEM (in seconds). Repeated measures ANOVA and posthoc Newman-Keuls pairwise comparisons revealed the following differences: *, $p < 0.05$ compared to corresponding saline control; **, $p < 0.05$ compared to wild-type saline control.

significantly less immobility in their baseline response in both the FST and TST, reminiscent of an antidepressant-like effect (Fig. 2) *(90).* These results parallel those in which expression of mCREB in the nucleus accumbens resulted in antidepressant-like behaviors in the rat FST and in the mouse learned helplessness paradigm *(56,57).* Despite the altered baseline mobility score, desipramine and fluoxetine were able to further reduce immobility in the FST and TST, respectively, in CREB$^{\alpha\Delta}$ mutant mice *(90),* indicating that behavioral responses to antidepressants are intact in the absence of CREB function (Fig. 2). Collectively, these data indicate that although CREB is not critical for the behavioral effects of antidepressant drugs, global or specific CREB deficiency (e.g., in the nucleus accumbens) may confer an antidepressant-like phenotype. However, it must also be considered that the existing behavioral models are limited in their sensitivity to the multiple measures of depressive-like symptoms. For example, depression can often be accompanied or even precipitated by stress, and there is close clinical and biochemical resemblance between depressive symptoms and the response to stressful experiences. Therefore, alterations in behavioral and endocrine responses to stressful stimuli may need to be examined in these various CREB animal models.

Although CREB is involved in antidepressant action, the role of related CRE-binding transcription factors in behavioral responses to antidepressants is unclear. Deletion of the *Crem* gene results in the loss of all CREM isoforms and causes sterility in male mice *(35,36).* This phenotype most likely results from deletion of the CREM activator isoform CREM-τ, which is highly expressed in testes *(34).* Through alternative splicing, the *Crem* gene encodes various isoforms that function as either activators or repressors of cAMP-responsive transcription *(61–64).* However, little is known regarding the behavioral consequences of CREM deficiency. Previously, the only behavioral evaluation of CREM mutant mice revealed lowered anxiety-like behaviors in the open field and elevated zero maze paradigms, but conditioned reactivity to stress was normal *(65).* However, these mice did not demonstrate oscillations in locomotor activity over the light–dark cycle but displayed heightened locomotor activity during the light cycle, which makes interpretation of these data difficult *(65).* Unlike the CREB-deficient mice, CREM-deficient mice exhibit levels

of immobility in the FST and TST comparable to those of wild-type mice (Fig. 2; ref. *66*). Furthermore, desipramine and fluoxetine are able to further reduce immobility in the FST and TST, respectively, in CREM mutant mice (Fig. 2; ref. *66*).

CREB Target Genes

CREB is hypothesized to regulate downstream expression of brain-derived neurotrophic factor (BDNF), a protein involved in neuronal plasticity and differentiation *(39, 67,68).* BDNF was recently implicated as a mediator of antidepressant action. BDNF mRNA and the BDNF receptor trkB are both upregulated following chronic antidepressant treatment with the same time course and regional specificity as CREB *(45,69).* Furthermore, BDNF infusion into the midbrain *(70)* or hippocampus *(71)* of rats induced antidepressant-like behaviors in both the learned helplessness paradigm and the FST. Finally, increased BDNF expression was demonstrated in dentate gyrus, hilus, and supragranular regions in patients treated with antidepressant medications at the time of death, compared to untreated subjects *(72).*

CRE elements in the promoter region of the BDNF gene identify it as a putative downstream target of CREB *(67,73).* Similarly, activation of trkB receptors results in increased kinase activity, which can phosphorylate CREB, thus placing it downstream of BDNF signal transduction. Although CREB has been hypothesized to upregulate BDNF mRNA expression following antidepressant treatment *(39,45),* studies have only recently confirmed this hypothesis by examining BDNF in CREB$^{\alpha\Delta}$ mutant mice following chronic antidepressant administration. In these studies, chronic DMI administration upregulated BDNF mRNA in wild-type mice, but this effect was blocked in CREB$^{\alpha\Delta}$ mutant mice *(90).* Therefore, antidepressant-mediated upregulation of BDNF may not be related to behavioral responses associated with these drugs, because the latter are intact in CREB$^{\alpha\Delta}$ mutant mice *(90).* Preliminary findings in the CREM mutant mice demonstrated that DMI upregulated BDNF similarly to the levels seen in wild-type mice (unpublished observations, Conti and Blendy).

Additional putative target genes of CREB include dynorphin, which is highly expressed in the nucleus accumbens and dorsal striatum *(74).* In mCREB transgenic mice, mCREB was expressed in dynorphin-positive neurons in the nucleus accumbens *(57).* This colocalization suggests the possibility of a direct interaction between CREB and the preprodynorphin promoter, which is further evidenced by downregulation of dynorphin in mCREB-expressing cells. In contrast, induction of prodynorphin expression was observed in transgenic mice overexpressing CREB *(57,75).* These data suggest that downregulation of prodynorphin in the nucleus accumbens may underlie the antidepressant-like behavioral effects observed in mCREB transgenic mice.

CREB, Antidepressants, and Cellular Effects

As discussed earlier, antidepressant treatment upregulates BDNF expression in limbic structures such as the hippocampus *(69,76).* BDNF promotes neuronal differentiation and survival throughout development and into adulthood *(77–79).* Stress can downregulate BDNF expression in the hippocampus *(80);* however, this effect is reversed by chronic antidepressant administration *(69).* Thus, the regulation of BDNF is hypothesized to mediate alterations in hippocampal neurogenesis *(81).* Recent studies indicated that chronic antidepressant treatment increased neurogenesis in the hippocampus *(82,83).* Furthermore, treatment with the modified tricyclic antidepressant tianeptine was shown to reverse stress-induced alterations in hippocampal cell proliferation *(84).* Together, these data suggest that antidepressants can oppose the dystrophic effects of stress through a BDNF-dependent mechanism.

Nakagawa and colleagues *(85)* used an inducible transgenic mouse that overexpressed a dominant-negative CREB mutation (CaMKII-tTA × TetOP-mCREB) in which the transgene was under control of a tetracycline-responsive promoter and expressed in a region-specific manner *(86,87).* mCREB expression in the transgenic mouse was localized to forebrain regions, including olfactory bulb, cortical layers, caudate putamen, nucleus accumbens, amygdala, and hippocampus/dentate gyrus. Although newly born granule cells were not colocalized with mCREB expression, inducible expression of mCREB decreased cell proliferation in the dentate gyrus *(85).* Because mCREB is capable of heterodimerizing with CREB or CREM, these data indicate a role for one or both of these proteins in neuronal proliferation.

Conclusion

Although much work has been devoted to elucidating the mechanisms underlying the effectiveness of antidepressant drugs, the heterogeneity and complexity of depressive symptoms have limited progress in antidepressant research. Recent advances in genetic techniques have allowed the development of numerous rodent models, which permit evaluation of antidepressant drug effects at genetic, behavioral, and molecular levels. The conclusions of these studies indicate that antidepressants may alter behavioral, and molecular changes through distinct pathways, some of which are dependent on CRE-binding proteins (alterations in trophic factor expression) and some of which are not (behavioral responses to antidepressant drugs). In the case of CREB deficiency ($CREB^{\alpha\Delta}$ mouse model), rather than modeling the disease, we have modeled treatment phenotypes in that the constitutive deletion of CREB leads to a state reminiscent of antidepressant treatment. Therefore, identification of compensatory changes in these animals at a molecular and biochemical level may provide insight into the development of novel therapeutics for clinical depression.

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