

## **Cyclic AMP response element binding protein (CREB) in depression: A new role of an old molecule**

Sanjukta Misra

Department of Biochemistry, Kalinga Institute of Medical Science, KIIT University, Bhubaneswar, Odisha, India

### **Abstract**

**Depression is one of the most common and most devastating psychiatric disorders. Despite its high prevalence and socio-economic impact, little is known about its etiology. Preclinical and clinical studies have demonstrated that depression can lead to cell loss and atrophy in limbic brain structures including hippocampus. An emerging hypothesis suggests that the treatment of depression is likely to involve a plasticity of neuronal pathway. Although a variety of treatment strategies is available. A major problem in its therapy consists of unpredictability of its drug response. Antidepressant treatments may exert their therapeutic effects by stimulating appropriate adaptive changes in neuronal systems. A novel therapeutic approach consists of targeting signal transduction and gene expression pathways. One of the best investigated pathways is cyclic AMP messenger system which ultimately influences gene expression by activating the transcription factor cyclic AMP response element binding protein (CREB) via phosphorylation. Recent studies have demonstrated that cyclic AMP-CREB system is disturbed in depression. This review focuses on the molecular mechanism underlying the effects of antidepressant treatment including adaptations in the cyclic AMP transduction cascade and also suggests that increased CREB activity may result in an improved neuronal plasticity, which in turn could contribute to amelioration of the clinical symptoms of depression.**

**Key words:** Depression, Cyclic AMP transduction cascade, Cyclic AMP response element binding protein, antidepressant treatment

*Accepted January 27 2012*

### **Introduction**

Depression is one of the most common and most devastating psychiatric disorders, afflicting 20% of the population [1]. Despite its high prevalence and socioeconomic impact, the etiology and pathophysiology of this complex disorder is not well understood. It is the lack of understanding of the underpinning of depression that has resulted in no substantial improvement to antidepressant treatment. Although a variety of treatment strategies is available, a major problem in the therapy consists of the unpredictability of the drug response. Furthermore, most antidepressant drugs which usually increase serotonin and nor-epinephrine levels in the synaptic cleft, are likely to produce side effects. Therefore the quest for new options in antidepressant treatment is urgent. Although second generation antidepressant drugs have eliminated some of the side effects associated with their predecessors, there have been new therapeutic targets identified, that could significantly improve the management of depression. A novel therapeutic approach beyond manipulating the neu-

rotransmitter-receptor interaction consists of targeting signal transduction and gene expression pathways. One of the most investigated pathways is the cyclic AMP (cAMP) second messenger system which ultimately influence gene expression by activating the transcription factor cAMP response element binding protein (CREB) via phosphorylation [2]. Recent studies have demonstrated that chronic antidepressant administration up-regulates the cAMP signal transduction cascade resulting in an increased expression and function of CREB. Further enhanced CREB expression leads to an up-regulation of specific target genes, including neurotrophin brain-derived neurotrophic factor (BDNF) [3]. Purpose of this review is to discuss emerging evidence that implicates the CREB and BDNF as potential key players in both the etiology and treatment of depression

### **Pathophysiology of depression**

According to recent evidences, depression is a dysfunction of specific neuro-anatomical foci, notably hippocampus and the prefrontal cortex (PFC) [4,5]. There are con-

siderable evidences demonstrating alterations in brain structure, including hippocampal volumetric loss, alteration in PFC volume and reduced number of neurons in temporal cortex, in patients suffering from unipolar depression [6]. Moreover prolonged stress exposure has been documented to stimulate the psychobiology of depression, causing dendritic atrophy and suppressing granule cell neurogenesis within the dentate gyrus [7]. Interestingly, antidepressant treatment can prevent the stress-mediated reduction in hippocampal neurogenesis [5]. While previous research efforts studied alterations in monoamine neurotransmitter levels, receptors or receptor-coupled second messenger systems, more recent efforts have focussed on intracellular cascades and the regulation of gene expression. One such candidate transcriptional regulator is CREB, a transcription activator that is implicated in both stress and antidepressant induced transcriptional regulation [2].

### ***Intracellular messenger cascade and depression***

Regulation of intracellular messenger cascades exerts a powerful control on almost all aspects of neuronal function, inclusive of neuronal morphology, gene expression, activity and survival. Broadly the intracellular signal transduction pathways can be classified into 2 categories: 1) G-protein receptor coupled second messenger (e.g. cAMP,  $Ca^{+2}$ ), which is primarily regulated by monoamine neurotransmitters 2) Receptor coupled directly to protein kinase which is controlled by cytokines and growth factors including neurotrophin family.

Signal transduction cascade represents a common target for several classes of antidepressants that differentially influence the neurotransmitters acutely. Receptor activation leads to generation of cAMP via the stimulation of adenylyl cyclase by G-protein subtypes  $G_{sa}$ . In addition intracellular  $Ca^{+2}$  levels can also regulate certain subtypes of adenylyl cyclase. The generation of cyclic AMP then results in activation of cAMP protein kinase (PKA). The catalytic subunits of PKA are responsible for mediating effects on cellular function through the phosphorylation of specific target proteins. Amongst the subtype of PKA is the transcription factor cAMP response element binding protein (CREB), which in the dephosphorylated form constitutively regulates gene transcription and following phosphorylation, exhibits a dramatic increase in its ability to regulate transcriptional activity [8].

### ***Altered gene expression and depression***

Changes in gene expression profoundly influence the metabolism of neurotransmitters, expression of receptors, synaptic strength, neuronal activity and morphology of neurons. This eventually contributes to an adaptive response being mounted by brain in response to stimuli which perturb homeostatic balance. It is likely that aberrant programmes of gene expression, which lead to a dysfunction in neuronal plasticity, contribute to the patho-

genesis of depression [9]. Antidepressant treatments through their influence on intracellular signal transduction cascades serve to regulate specific transcription factors [10]. A major goal of current research efforts is to identify the target genes which are regulated by several classes of antidepressants treatment and to examine their role in the therapeutic effects of antidepressant action.

Antidepressant may broadly influence the expression of several genes; it is likely that several additional factors would determine the target genes eventually regulated by antidepressant treatment. The control of gene expression depends upon a complex interplay between different transcription factors in the promoter region, eventually determining the influence of antidepressant treatment on a particular gene. The regulation of transcription factors by antidepressant treatment is of great interest since these factors may serve as common intracellular target for different second messenger system cascade [10,11].

### ***Cyclic AMP response element binding protein [CREB]***

CREB is a nuclear protein. It belongs to the family of leucine zipper transcription factors that are expressed in a variety of tissues and serve diverse functions. CREB contains a basic leucine zipper motif with which it can homodimerize or heterodimerize to cAMP response element modulator (CREM) to form the functional dimer, and a DNA binding domain with which it recognizes and bind to promoter cAMP response element sequence. Phosphorylation of a serine residue (S133) in its kinase inducible domain is critical to mediate its effect, as this permits recruitment of co-activator proteins and initiation of transcription [12]. Activation of CREB can be accomplished by phosphorylation via cAMP-protein kinase A (PKA) pathway. PKA cascade also serves as a target for antidepressant treatment [13]. CREB is regulated by diverse signalling pathways and can serve as a control integrator for the action of numerous external stimuli, including antidepressant. CREB can itself act in a manner analogous to that of antidepressants. Chronic administration of antidepressants not only affects CREB expression, but also CREB activity and CREB mediated transcription. Chronic antidepressant therapy up regulates cellular PKA activity and increases the translocation of PKA [10,14]. Antidepressants which have distinct acute targets are known to recruit several signal transduction pathways including cAMP-protein kinase A cascade (cAMP-PKA), the MAP kinase signalling pathway (MEK) as well as calcium & phospholipase C (PLC) signalling [2,12]. While it seems clear that CREB has a role to play in the pathogenesis of depression and in antidepressant action, the exact mechanism remains obscure, in part due to complexity of CREB gene itself. The CREB gene can generate multiple transcript and protein products that can serve as both transcriptional activators and repressors.

However identifying downstream target genes (with necessary cyclic AMP response element binding sites) is crucial in revealing the action of CREB. 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 antidepressant treatment mediated changes in structural plasticity and behaviour [3,15].

BDNF is the most widely expressed member of nerve growth factor family called neurotrophins, which has a well established role in the development, survival and differentiation of a selected population of neurons. Further neurotrophins are capable of augmenting neurogenesis in the adult brain [16]. They mediate their effects through the stimulation of a family of tyrosine kinase coupled receptors which signal through the MAP kinase signalling cascade. Studies have clearly indicated that BDNF is promising as a candidate molecule underlying the structural changes associated with depression and as a potential target for antidepressants [17].

### ***Role of CREB and BDNF in hippocampus***

(In response to antidepressant)

According to recent evidences, depression is a dysfunction of specific neuro-anatomical foci, notably hippocampus and prefrontal cortex. So hippocampus is a key limbic region whose structure and function is compromised in mood disorders. Hippocampal over-expression of CREB and BDNF can mimic both the structural consequences of sustained antidepressant treatment as well as exerting antidepressant like behaviour [18]. Activation of cAMP-CREB cascade results in increased neurogenesis of dentate granule cell progenitors and increased dendritic length and branching. Elevated CREB-BDNF, through their protective influences on vulnerable hippocampal neurons and their ability to directly promote structural recognition, could result in repair of damaged region due to depression. In addition, BDNF can alter neurotransmitter release and itself elicit an activation of post-synaptic neurons and may thus have potential protective functional consequences on hippocampal circuit known to be dysfunctional in depression.

Furthermore, the well-established role of BDNF and CREB in hippocampal dependent learning, memory may play a critical role ameliorating the cognitive symptoms associated with depression [19].

### ***Antidepressant regulation of CREB and BDNF expression***

Different antidepressants used in depression, belong to diverse classes including selective norepinephrine, sero-

tonin re-uptake inhibitors, monoamine oxidase inhibitors and electro-convulsive seizure administration. Recent studies clearly indicate that chronic administration of several distinct classes of antidepressants up-regulate CREB mRNA expression within hippocampus [14]. In addition to an up-regulation of CREB mRNA, corresponding increase in CREB protein is observed following antidepressant treatment. The mechanism which underlies the enhanced expression of CREB mRNA is not clearly understood in vivo. However, evidence from in vitro systems implicates activation of cAMP system in this regulation. Studies demonstrating an antidepressant induced increase in cAMP cascade and nuclear translocation of PKA, suggests that antidepressant treatment may regulate cAMP responsive transcription factor CREB. This suggests that CREB may serve as a common target for antidepressant drugs [20]. In addition to this, a recent study reports that the phosphorylation and transcriptional activity of CREB is also increased by antidepressant treatment [12]. Up-regulation of CREB by chronic antidepressant treatment suggests that specific target genes are likely to be regulated in response to drug administration [3]. Amongst these target genes is BDNF, which is known to play an important role in neuronal plasticity, survival and function.

Studies have clearly indicated that BDNF serves as a target for antidepressant treatment [21]. Chronic administration of various classes of antidepressant drugs increase expression of BDNF and its receptor within hippocampus. Regions exhibiting an up-regulation of BDNF in response to antidepressant administration overlap closely with the regions that show an up-regulation of CREB. This spatial correlation suggests that CREB may contribute to the antidepressant induced increase in hippocampal BDNF expression. There are several lines of evidences that suggest a role for BDNF in the action of antidepressant treatment and in the pathogenesis of depression. It is hypothesized that enhanced BDNF expression resulting from chronic antidepressant administration may play an important role in preventing neuronal damage. Taken together it can be concluded that antidepressants up-regulate BDNF expression and BDNF exerts an antidepressant effect [22].

### **Conclusion**

Emerging insights from neurobiology suggest that chronic antidepressant treatment leads to an augmentation of cAMP signal transduction cascade. One of the functional consequences of enhanced cAMP signalling is an increase in the expression & activity of transcription factor CREB. Studies indicate that enhanced CREB function regulates diverse target genes, one of which is the trophic factor BDNF. Current state of knowledge on the role of CREB-BDNF cascade in depression provides strong impetus to further understand the regulation & action of CREB, BDNF in depression and following antidepressant ther-

apy. Further studies are required to characterize the role of CREB and BDNF in the influence of antidepressant treatments on neuronal plasticity including changes neuronal structure and function. In addition CREB and BDNF may serve as potential therapeutic targets for the development of new drugs that regulate mood. These studies will make it possible to design novel therapeutic agents for the development of depression rationally. Pre-clinical and clinical studies are required to elucidate the role of other intracellular cascade and to explore the role of CREB-BDNF cascade in depression, which could throw new light for effective management of depression

## References

1. Hamet P, Tremblay J. Genetics and genomics of depression. *Metabolism* 2005;54:10-15.
2. Johannessen M, Delghandi MP, Moens U. What turns CREB on? *Cellular signalling* 2004; 16:1211-27.
3. Conti AC, Cryan JF, Dalvi A, Lucki I, Blendy JA. cAMP response element binding protein is essential for the upregulation of brain-derived neurotrophic factor transcription, but not the behavioural or endocrine response to antidepressant drugs. *J. Neurosci* 2002; 22:3236-3268.
4. Shelton YA, Gado MH, Kraemer HC. Unwanted depression and hippocampal volume loss. *Am J Psychiatry* 2003; 160:1516-1518.
5. Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus* 2006; 16:239-249.
6. Rajkoska G. Post mortem studies in mood disorders indicate altered number of neurons and glial cells. *Bio Psychiatry* 2000;48:766-777.
7. Pham K, Nocher J, Hof PR and McEwan BS. Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in adult rat dentate gyrus. *Eur J. Neurosci* 2003; 17:879-886.
8. Conti AC, Blendy JA. Regulation of antidepressant activity by cAMP response element binding protein. *Mol Neurobiol* 2004; 30(2):143-155.
9. Angelucci F, Brene S, Mathe AA. BDNF in schizophrenia, depression and corresponding animal models. *Mol Psychiatry* 2005; 10:345-352.
10. Thome J, Impey S, Storm D, Duman RS. cAMP response element mediated gene transcription is upregulated by chronic antidepressant treatment. *J Neurosci* 2000; 20:4030-4036.
11. Shelton RC. Cellular mechanism in the vulnerability to depression and response to antidepressants. *Psychiatr. Clin. North Am* 2000; 23:713-729.
12. Nair A, Vaidya VA. Cyclic AMP response element binding protein and brain-derived neurotrophic factor: AMolecules that modulate our mood? *J.Biosci* 2006; 31(3):423-434.
13. Tardito D, Perez J, Tiraboschi E, Musazzo L, Racagni G, Popoli M. Signalling pathways regulating gene expression, neuroplasticity and neurotrophic mechanisms in the action of antidepressant: a critical overview. *Pharmacol. Rev* 2006; 58:115-134.
14. Gur TL, Conti AC, Holden J, Bechtholt AJ, Hill TE, Lucki I et al. cAMP response element binding protein allows for a rapid onset of antidepressant response. *J. Neurosci* 2007; 27:7860-68.
15. Pandey SC. Anxiety and alcohol abuse disorder: a common role of CREB and its target, the neuropeptide Y gene. *Trends Pharmacol. Sci* 2003; 24:456-460.
16. Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricles of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus and hypothalamus. *J. Neurosci* 2001; 21:6706-6717.
17. Koponen E, Rantamaki T, Voikar V, Saarelainen T, Mac Donald E and Castren E. Enhanced BDNF signaling is associated with an antidepressant like behavioural response and changes in brain monoamines. *Cell. Mol. Neurobiol* 2005;25:973-980.
18. Chen AC, Shirayama Y, Shin KH, Neve RL, Duman RS. Expression of cAMP response element binding protein (CREB) in hippocampus produces an antidepressant effect. *Biol. Psychiatry* 2001; 49:735-762.
19. Mizuno K and Giese KP. Hippocampus-dependent memory function: do memory type-specific mechanisms exist? *J. Pharmacol. Sci* 2005;98:191-197.
20. Abdol-Razaq W, Bates IE, Kendall DA. The effect of antidepressants on cyclic AMP response-element-driven gene transcription in a model cell system. *Biochemical Pharmacol* 2007; 73:1993-2003.
21. Sairanen M, Lucas G, Ernfors P, Castren M and Castren E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. *J.neurosci* 2005; 25:1089-1094.
22. Tsankova NM, Berton O, Renthal W, Kumar A, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat. Neurosci* 2006; 9:519-525.

## Correspondence to:

Sanjukta Misra  
C/o- D.P. Mishra  
N-5/354, IRC Village, Nayapally, Bhubaneswar,  
ODISHA Pin-751015  
India