

Adenylyl cyclase-cyclicAMP signaling in mood disorders: Role of the crucial phosphorylating enzyme protein kinase A

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Abstract: Mood disorders are among the most prevalent and recurrent forms of psychiatric illnesses. In the last decade, there has been increased understanding of the biological basis of mood disorders. In fact, novel mechanistic concepts of the neurobiology of unipolar and bipolar disorders are evolving based on recent pre-clinical and clinical studies, most of which now focus on the role of signal transduction mechanisms in these psychiatric illnesses. Particular investigative emphasis has been given to the role of phosphorylating enzymes, which are crucial in regulating gene expression and neuronal and synaptic plasticity. Among the most important phosphorylating enzyme is protein kinase A (PKA), a component of adenylyl cyclase-cyclic adenosine monophosphate (AC-cAMP) signaling system. In this review, we critically and comprehensively discuss the role of various components of AC-cAMP signaling in mood disorders, with a special focus on PKA, because of the interesting observation that have been made about its involvement in unipolar and bipolar disorders. We also discuss the functional significance of the findings regarding PKA by discussing the role of important PKA substrates, namely, Rap-1, cyclicAMP-response element binding protein, and brain-derived neurotrophic factor. These studies suggest the interesting possibility that PKA and related signaling molecules may serve as important neurobiological factors in mood disorders and may be relevant in target-specific therapeutic interventions for these disorders.

Keywords: protein kinase A, bipolar disorder, unipolar depression, CREB, BDNF, Rap-1

Introduction

Mood disorders are among the most prevalent and recurrent forms of psychiatric illnesses. Unipolar depression affects about 17% of the population at some point in life (Kessler et al 1994; Hirschfeld 2002). Of these, about 4% of men and 8% of women are at a lifetime risk for a severe form of depression, and an additional 20% are at risk for milder forms. Major depression is often a chronic and lifelong illness, and about 80% of the depressed population experience multiple episodes. Each depressive episode greatly increases the risk of future episodes and also lessens responsiveness to treatments. About 10% of patients who experience a single or multiple episodes of depression can have a manic episode. About 1%–2% of the total population is at risk for bipolar disorder (recurrent depressive and manic episodes), and another 2%–3% may have milder forms (Spearing 2001; Hirschfeld et al 2002). Both depression and bipolar disorders are associated with a high risk of suicide. Among teenagers, bipolar patients are at twice the risk to commit suicide as unipolar depressed patients; however, the risk of suicide is higher in elderly patients over the age of 60 who are suffering from unipolar depression. Therefore, researchers are striving for greater understanding of the neurobiology of these disorders that will lead to better treatment and prevention.

Both unipolar and bipolar disorders are complex, and no unified theory can currently satisfactorily explain this complexity. Besides the clinical manifestation,

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there are subtypes of unipolar and bipolar disorders, and patients with these subtypes respond differently to various treatment approaches. Although depression is a part of bipolar disorder, it still is unclear whether the neurobiology of unipolar depression is similar to that of the depressive state in bipolar disorder.

Earlier studies focused on the role of monoamines in the pathophysiology of mood disorders, hypothesizing decreased availability of monoamines in the synaptic cleft and probably a compensatory increase in monoamine receptors (Jans et al 2007). This was substantiated by observations of an increased availability of monoamines after treatment with antidepressants. These studies provided useful information of the involvement of monoamines and monoamine receptors in the pathophysiology of mood disorders, but they also raised several important questions. For example, monoamine depletion does not produce depressive symptoms in normal individuals. Also, not every patient responds to the antidepressants that modulate monoamines. In addition, there is a lag time between starting an antidepressant or mood stabilizing drug treatment and responsiveness. It takes about 2–4 weeks for these drugs to become fully effective and thus the immediate effects on monoamines or receptors cannot explain their mechanisms of action. In addition, a number of neurotransmitter receptors have been implicated in the pathophysiology of mood disorders, and they interact with each other in a complex fashion, mostly at the level of intracellular signal transduction mechanisms. Most neurotransmitter receptors regulate intracellular reactions by an indirect mechanism involving an intermediate transducing molecule known as guanosine 5'-triphosphate (GTP) binding protein, or G protein. Activated G proteins alter the functions of many signaling pathway downstream effectors. Most of these effectors are enzymes that produce intracellular second messengers. The second messengers trigger the signaling cascade further downstream and cause a cellular response. It is the downstream intracellular signaling mediated by these neurotransmitter receptors that co-ordinates the behavior of individual cells within the brain in various physiological processes.

Emerging evidence indicates that mood disorders are associated with altered neuronal plasticity (Duman 2000; Duman et al 2000). A number of studies using magnetic resonance spectroscopy, anatomical, and morphometric techniques have repeatedly shown that there are structural abnormalities in the brains of depressed or bipolar patients (Soares and Mann 1997; Rajkowska 2000, 2002). Adaptive responses in intracellular molecules, together with the modulation of

functional responses mediated by the phosphorylation of critical proteins, and ultimately gene expression, controlled by intracellular signaling cascades, all participate in a major way in synaptic and structural plasticity. Given the critical importance of intracellular signaling in amplifying, integrating, and regulating physiological processes and in mediating gene expression, over the last decade numerous studies have examined the role of signaling molecules in the pathophysiology of mood disorders.

One of the major intracellular signaling pathways that has been implicated in synaptic and structural plasticity is adenylyl cyclase–cyclic adenosine monophosphate (AC–cAMP) signaling. Phosphorylation mediated by the cAMP signaling pathway can be elicited by various physiological ligands in cells and is critically involved in cell growth, differentiation, apoptosis, and gene expression (Skahegg and Tasken 2000). In this review, we will discuss the role of the adenylyl cyclase–cAMP signaling pathway in mood disorders in general, including the results of investigations of cAMP and adenylyl cyclase, but major emphasis will be given for the role of the enzyme protein kinase A (PKA), which mediates phosphorylation and, therefore, physiological functions in the brain.

Adenylyl cyclase–cAMP signaling pathway

A schematic representation of the adenylyl cyclase–cAMP signaling pathway is provided in Figure 1. A number of neurotransmitter receptors, including serotonergic and adrenergic, utilize this pathway to mediate their physiological functions. In this signaling pathway, an agonist binding to receptors causes the activation of heterotrimeric guanine nucleotide binding protein (G proteins), which consist of α , β , and γ subunits. The receptor-mediated activation of G proteins causes the release of guanine nucleotide diphosphate (GDP) from α subunit, allowing GTP to bind to and dissociate the α subunit from the $\beta\gamma$ subunits. Both α and $\beta\gamma$ subunits can then modulate activity of effectors, including adenylyl cyclase. Activation of adenylyl cyclase causes the conversion of ATP to cAMP, which serves as a second messenger. cAMP then activates the phosphorylation enzyme PKA. Once activated, PKA phosphorylates various intracellular proteins and thereby modifies hormonal and neurotransmitter responses, including receptor downregulation or desensitization, alteration of neurotransmitter release, and activation or repression of gene expression (Borrelli et al 1992; Spaulding 1993; Nestler and Greengard 1994). The negative regulation of cAMP signaling occurs through

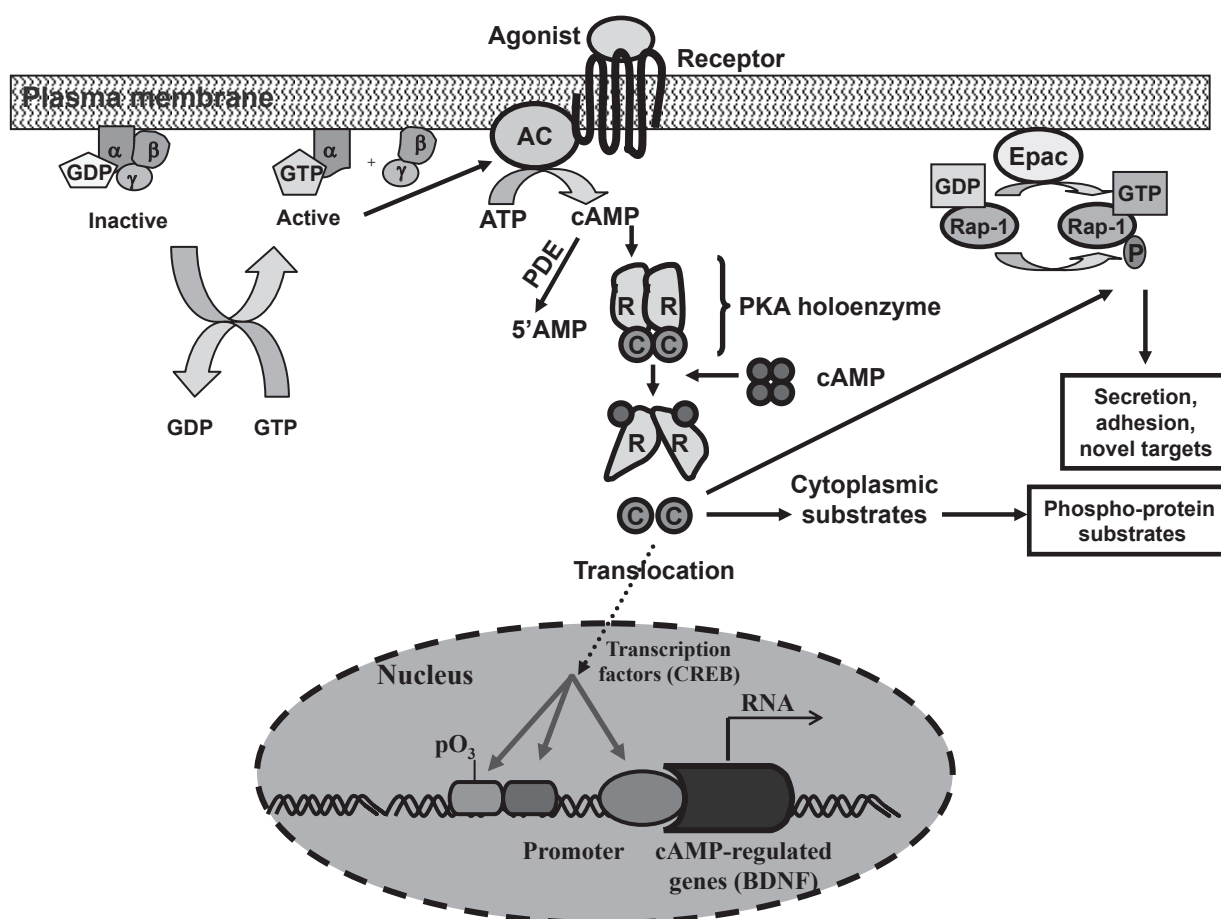


Figure 1 Overview of the adenylyl cyclase–cyclicAMP signaling system. In this signaling pathway, the binding of agonists to receptors leads to the activation of G proteins, which in turn activate adenylyl cyclase. In the inactive state the α subunit of G protein is bound to GDP and to $\beta\gamma$ subunits. The binding of agonists to receptors causes an interaction of receptors with G proteins, which, in turn, releases GDP in exchange with GTP. This leads to generation of α -GTP and a $\beta\gamma$ subunits dimer. Both α and $\beta\gamma$ subunits can interact with effectors. Activation of adenylyl cyclase causes generation of cAMP from ATP. cAMP binds to the regulatory (R) subunits of tetrameric PKA holoenzymes. The binding of cAMP to an R subunit lowers its affinity for the C subunit. This causes the release of free catalytic (C) subunits. The C subunit can catalyze reversible protein phosphorylation and irreversible phosphorylation of newly synthesized peptides. Phosphorylation of substrates can occur in the cytoplasm or, after translocation of the C subunits, in the nucleus. One of the substrates of PKA is transcription factor cyclicAMP response element binding protein CREB, which regulates transcription of many neuronally expressed genes, including brain-derived neurotrophic factor (BDNF). The exchange protein activated by cAMP (Epac) is stimulated by cAMP to exchange GDP with GTP on Rap-1. Rap can also be regulated by phosphorylation by a C subunit of PKA. Deactivation of PKA is achieved through degradation of cAMP to 5'AMP by cAMP-specific phosphodiesterases.

the activation of cAMP-specific phosphodiesterases, which convert cAMP to 5'AMP.

Adenylyl cyclase and cAMP formation in mood disorders

Since regulation of the intracellular level of a second messenger is critical for the transduction of a cellular response, many studies have examined cAMP generation in mood disorders. The intracellular level of cAMP is determined by the rate of its synthesis from ATP by adenylyl cyclase. Most earlier studies utilized peripheral tissues to examine levels of cAMP or receptor-mediated cAMP formation. For example, it was shown that the baseline level of cAMP in plasma, cerebrospinal fluid (Belmaker et al 1980; Post et al 1982; Maj et al 1984), or in leukocytes or

lymphoblast cell lines (Klysner et al 1987; Kay et al 1993), is not altered in various mood states. On the other hand, changes in receptor-mediated cAMP formation were found in these patients. The inhibition of cAMP formation by prostaglandins (PG) has commonly been used as an index of imidazoline (I_2)-adrenergic receptor responsiveness. Using this approach, Wang et al (1974) reported that PGE_1 -stimulated cAMP accumulation and norepinephrine (NE) inhibition of PGE_1 -stimulated cAMP accumulation were not changed in platelets of depressed patients. Similar results were reported by Murphy et al (1974). On the other hand, Siever et al (1984) observed decreased PGE_1 -stimulated cAMP accumulation and the inhibition of this response by NE in platelets of depressed patients; and Kanof et al (1986) observed that whereas PGE_1 -stimulated cAMP response was

significantly decreased, NE inhibition of PGE_1 -stimulated cAMP formation was not changed in platelets of depressed patients (Kanof et al 1988). Thus, studies of the responsiveness of α_2 -adrenergic receptors (ARs) in platelets of depressive patients do not consistently show decreased PGE_1 -stimulated cAMP response in depressed patients.

Besides α -AR-mediated responsiveness, the functional significance of β -ARs in depression was out by determining agonist-stimulated cAMP formation in leukocytes or lymphocytes of depressed patients and normal controls by our group (Pandey et al 1979) and other investigators (Healy et al 1983; Mann et al 1985; Klysner et al 1987; Ebstein et al 1988). Pandey et al (1979) reported for the first time that NE-stimulated [^3H]cAMP accumulation was significantly lower in leukocytes of depressed or bipolar patients; significantly lower isoproterenol-stimulated cAMP accumulation was also observed in these patients. In the same year, Extein et al (1979) reported similar findings in the lymphocytes of a mixed group of depressed or manic patients. Mann et al (1985) also observed lower isoproterenol-stimulated cAMP levels in lymphocytes of patients with endogenous depression. Ebstein et al (1988) determined isoproterenol-, forskolin-, as well as PGE_1 -stimulated cAMP accumulation in lymphocytes of depressed patients and observed that the isoproterenol-stimulated cAMP level was significantly decreased in these patients. These investigators also observed significantly lower isoproterenol-stimulated cAMP accumulation in depressed nonresponders compared with responders. Kanof et al (1989) also observed lower isoproterenol-stimulated cAMP accumulation in depressed patients. On the other hand, a number of studies suggest the opposite changes in cAMP formation in bipolar patients. For example, Young et al (1993) reported that forskolin-stimulated adenylyl cyclase activity is significantly increased in temporal and occipital cortices of bipolar patients compared with normal control subjects. Also Kay et al (1993) reported that PGE_1 -stimulated adenylyl cyclase activity was significantly increased in lymphoblast cell lines of bipolar patients. Klysner et al (1987) observed increased β_2 -AR responsiveness in manic-depressive patients compared with euthymic patients treated with antidepressants.

Adenylyl cyclase exists in multiple forms, each a unique gene product (Tang and Gilman 1991), and can be grouped into three main classes: 1) Types II, IV, and VII are activated synergistically by $\text{G}_s\alpha$ and $\text{G}\beta\gamma$ subunits; 2) Types V and VI are inhibited by $\text{G}_i\alpha$ and Ca^{2+} ; and 3) Types VIII, I, and III are activated synergistically by $\text{G}_s\alpha$ together with Ca^{2+} -calmodulin. Reiaich et al (1999) reported that

immunolabeling of specific types (Type IV) and activity of adenylyl cyclase are significantly decreased in postmortem brain of depressed suicide victims compared with normal control subjects. Although the significance of the decrease in this specific type of adenylyl cyclase is not clear, nonetheless this supports the findings of decreased cAMP signaling in depressed patients. The status of expression of adenylyl cyclase subunits in bipolar disorder has not been studied.

Overall these studies show a differential response of agonist-induced cAMP formation in response to β_2 -ARs activation. On the one hand, depressed patients show decreases in responsiveness of β_2 -ARs, adenylyl cyclase activity, and expression of a specific subtype of adenylyl cyclase; bipolar patients, on the other hand, show increased forskolin-, PGE_1 - or β -adrenergic-stimulated adenylyl cyclase response. Interestingly, a number of studies show that the changes in adenylyl cyclase responsivity are not accompanied by consistent changes in β -AR density or affinity (Mann et al 1985; Berrettini et al 1987; Jeannin-gros et al 1991), which suggests that post-receptor signal transduction mechanisms may be playing an important role in mood disorders, albeit in a different manner in unipolar versus bipolar disorders.

Protein kinase A (PKA) in mood disorders

Since most of the effects of cAMP are mediated by its receptor PKA, and since a number of studies suggest that PKA is regulated by sustained activation of cAMP (Spaulding 1993; Francis and Corbin 1999), studying the status of PKA can thus provide a direct evidence of altered cAMP signaling. In addition, PKA participates directly in many physiological functions in the central nervous system, and by phosphorylating the components of other signaling cascades, it provides the means for cross-talk between the AC-cAMP and other signaling systems (Beebe 1994; Bornfeldt and Krebs 1999; Jordan et al 2000). Therefore, a number of recent studies have focused on the role of PKA in mood disorders.

Characteristics of PKA

As shown in Figure 1, PKA is a holoenzyme composed of two genetically distinct regulatory (R) and two catalytic (C) subunits that form a tetrameric holoenzyme (R_2C_2). In the absence of cAMP, PKA exists as a stable inactive tetramer; the catalytic activity of cAMP is suppressed when the C subunits form a complex with the R subunits. After an increase in intracellular cAMP, the regulatory PKA subunits bind to cAMP in a co-operative manner,

which results in the disassociation of the holoenzyme into an $R2(cAMP)_4$ dimer and two monomers of catalytically active C kinase. The R subunits remain in the cytoplasm, and the free catalytic subunits either translocate into the nucleus (Wolf et al 1999) or remain in the cytosol. In both locations, PKA C subunits phosphorylate serine and threonine residues of specific substrates (Scott et al 1990). In the nucleus, regulation of transcription by PKA is mediated by cAMP-responsive nuclear factors, which bind to and regulate the expression of genes containing a cAMP-response element binding element (CRE) consensus in their promoter region. Phosphorylation of the CRE binding protein (CREB) modulates its activity. One of the important genes whose transcription is regulated by PKA/CREB is brain derived neurotrophic factor (BDNF), described later in this review. Besides its role in gene transcription, PKA is capable of phosphorylating a large number of substrates involved in neurotransmitter release; receptor desensitization; cell growth, differentiation, survival; and synaptic plasticity (Borrelli et al 1992; Nestler and Greengard 1994; Riccio et al 1999; Lara et al 2003).

On the basis of the elution profile on DEAE exchange chromatography, two major forms of PKA have been identified, ie, Type I and Type II. These two types differ in their structure in the regulatory subunits incorporated, termed RI or RII, whereas their catalytic subunits are either identical or very similar. Cloning studies have revealed multiple isoforms for each regulatory and catalytic subunit. Two RI subunits, termed $RI\alpha$ and $RI\beta$, and two RII subunits, termed $RII\alpha$ and $RII\beta$, have been identified. Furthermore, three distinct catalytic subunits have been identified, termed $C\alpha$, $C\beta$, and $C\gamma$. These isozymes may form either homo- or heterodimers of the R subunits yielding holoenzyme complexes of PKA composed of a number of different combinations, including $RI\alpha_2C_2$, $RI\beta_2C_2$, $RII\alpha_2C_2$, $RII\beta_2C_2$, and $RI\alpha RI\beta C_2$. The presence of multiple C subunits adds substantial diversity to the action of PKA. Each regulatory and catalytic subunit is a separate gene product and has a distinct expression pattern in different tissues (Scott et al 1987; Clegg and McKnight 1988; Skalhogg and Tasken 2000). For example, tissue distribution studies suggest that $RII\beta$ is predominantly expressed in brain, adrenal, and adipose tissues and is the principal mediator of cAMP activity in the mammalian CNS (Sarkar et al 1984), whereas $C\beta$ is expressed primarily in the brain (Uhler et al 1986). On the other hand, whereas $C\alpha$ is ubiquitously expressed, $C\gamma$ is present only in testis. We will discuss all those C and R subunits which are present in brain.

PKA in bipolar disorder

The Warsh group provided the first evidence that PKA may be altered in bipolar disorder. They found significantly decreased [3H]cAMP binding to regulatory subunits in the cytosolic but not in the membrane fractions of frontal, temporal, and occipital cortices, cerebellum, and thalamus of bipolar patients (Rahman et al 1997). They further observed greater basal and cAMP-stimulated PKA activity, and lower EC_{50} values for cAMP stimulation of PKA activity, in the temporal cortex of bipolar patients (Fields et al 1999).

Clinical studies performed in blood cells also provide evidence of abnormalities in PKA in bipolar patients. For example, Karege et al (2002a; 2004) reported that PKA activity is significantly greater in the cytosolic fraction of cultured lymphoblasts from euthymic bipolar patients compared with normal controls. In addition, they found that [3H]cAMP binding is decreased in the cytosolic fraction of lymphoblasts of bipolar patients. The results of these studies are similar to the findings in postmortem brain of bipolar patients.

In postmortem brain of bipolar patients, Chang et al (2003a) found that the levels of cytosolic $C\alpha$ and $RII\beta$ in temporal cortex were significantly higher in bipolar patients. This indicates that the increased PKA activity in postmortem brain and in platelets of bipolar patients could be due to increased levels of $C\alpha$. The authors argued that an increase in $RII\beta$ level may be associated with an increase in PKA II and a decrease in PKA I holoenzyme levels. PKA RII has a much lower affinity for cAMP than the type I PKA holoenzyme. Such a putative shift in PKA I and PKA II holoenzyme levels could have accounted for the decreased [3H]cAMP binding found in bipolar patients (Chang et al 2003a). Perez et al (1999) also reported increased PKA catalytic subunits in bipolar patients, although they did not examine whether this increase was in α or β subunits of PKA. Using the same brain tissues, Chang et al (2003b) did not find any significant differences in mRNA levels of these C and R subunits of PKA in bipolar patients, suggesting that a post-translational mechanism is responsible for the changes in protein levels of $RII\beta$ and $C\alpha$ subunits.

PKA in unipolar disorder

A number of studies in peripheral tissues of depressed patients suggest abnormalities in the cAMP signaling pathway at the level of PKA. For example, Shelton et al (1996) and Manier et al (1996) reported significantly decreased β -adrenergic receptor-stimulated PKA activity in the presence of cAMP in fibroblasts of depressed patients. Shelton et al (1999) later confirmed that β -adrenergic receptor-stimulated

PKA activity was decreased only in melancholic depressed patients but not in other depressive subtypes. More recently, Akin et al (2005) reported reduced PKA activity along with reduced expression of PKA RII α , C α , and C β subunits in fibroblasts of melancholic depressed subjects as compared with nonmelancholic and normal control subjects. Overall these studies in peripheral tissues demonstrate decreased activation of PKA in depressed patients, which could be associated specifically with melancholic subtype.

In a comprehensive study, we examined whether PKA is altered in postmortem brain of suicide subjects by comparing suicide subjects with and without major depression (Dwivedi et al 2002a). We observed that [3 H]cAMP binding and basal and cAMP-stimulated PKA activity were significantly decreased in prefrontal cortex of suicide victims. The extent of the decrease in cAMP-stimulated PKA activity was greater than that of the endogenous PKA activity. Interestingly, we found significant changes only in those suicide victims who had major depression but not in those who had other mental disorders. We recently confirmed this finding in a large population of depressed suicide victims obtained from another cohort (Dwivedi et al 2004a). We further examined whether the decreases in PKA regulatory and catalytic activities are related to altered expression of specific C and/or R subunits. Interestingly, we observed that protein levels of only PKA RII β and C β were significantly lower in prefrontal cortex of depressed suicide subjects, without any changes in protein levels of the other regulatory or catalytic subunits. These decreases were associated with decreases in their respective mRNA levels. Our results thus suggest that the decreases in [3 H]cAMP binding and PKA activity could be due to decreases in the expression of RII β and C β , respectively. Odagaki et al (2001) found similar results in prefrontal cortex of depressed patients. In a clinical population, Perez et al (2001) studied the expression of PKA R and C subunits and found that the level of regulatory subunits of type II PKA was significantly lower in platelets of untreated depressed patients compared with euthymic patients or normal controls.

Overall, studies of PKA in unipolar and bipolar patients suggest that whereas cAMP binding is decreased in both bipolar and depressed patients, PKA activity is increased in bipolar patients and decreased in depressed patients. In addition, the expression of RII β is increased in bipolar patients and decreased in depressed patients. On the other hand, whereas the C β subunit is decreased in depressed patients, the level of C α is increased in bipolar patients. Thus, it appears that PKA is differentially regulated in depressed

versus bipolar patients. The postmortem brain studies did not differentiate between melancholic and nonmelancholic subtypes, therefore, it is difficult to state that the changes in PKA in depressed subjects are specific to one subtypes as suggested in studies of peripheral tissues of depressed subjects. Further studies are required to confirm these findings.

Hypothalamic-pituitary-adrenal axis (HPA) and PKA

Effect of Stress on PKA

Stress is known to cause changes in the hypothalamic-pituitary-adrenal (HPA) axis in both humans as well as in nonhuman models. Stress or a hyperactive HPA axis is a well-known phenomenon in depression. It is, therefore, of interest to examine whether changes in PKA are related to stress. In a detailed study, we examined the effect of glucocorticoids after bilateral adrenalectomy and supplementation with exogenous glucocorticoid, as well as the effect of endogenous glucocorticoids, on various measures of PKA in rat brain (Dwivedi et al 2000). For this, rats were injected with various doses of corticosterone at different time intervals, and in a separate experiment, adrenalectomies were performed on rats who were then injected with various doses of corticosterone. We observed that 1 day of corticosterone treatment had no significant effect, but 4 days of corticosterone treatment decreased [3 H]cAMP binding to the regulatory subunit of PKA and PKA catalytic activity in the rat cortex and hippocampus. These changes were much more profound after 14 days of corticosterone. These effects were also dose dependent. The higher dose of corticosterone was much more effective in causing changes in PKA than the lower dose. Adrenalectomy produced the direct opposite results to those of corticosterone treatment, increasing [3 H]cAMP binding and PKA activity in both cortex and hippocampus in a time-dependent manner. These changes were reversed by corticosterone treatment in a dose dependent manner. The higher dose of corticosterone completely reversed the changes in PKA after adrenalectomy (Dwivedi et al 2000). A very interesting observation was noted when we examined the expression levels of PKA regulatory and catalytic subunits. We found that the mRNA and protein expressions of RI α , RII β , and C β isoforms were significantly decreased in cortex and hippocampus after corticosterone treatment. Removal of adrenal glands increased the expression of these subunits, and corticosterone treatment of adrenalectomized rats reversed the adrenalectomy-induced changes in PKA RI α , RII β , and C β subunits (Dwivedi et al 2000). These changes were very similar to those we

observed in depressed suicide subjects. Our studies thus suggest that the expression of specific isoforms of PKA regulatory and catalytic subunits is under the regulation of glucocorticoids and that stress may be playing an important role in such changes.

Effect of learned helpless behavior on PKA

Since the ability to cope with stress is critical at the human level, parallel studies of the effects of uncontrollable stress have been performed in animals, with the results of proactive interference with the acquisition of escape/avoidance responding (Seligman and Maier 1967). This phenomenon is termed learned helplessness (LH) and has been used extensively as an animal model of stress-induced behavioral depression (Petty and Sherman, 1979; Sherman et al 1982). To further examine whether there were alterations in PKA in LH behavior, we studied similar paradigms in the brain of LH rats as we studied in the brain of suicide subjects. We found very similar changes in PKA, such that [^3H]cAMP binding and PKA activity were significantly decreased along with selectively decreased expression of only RII β and C β subunits (Dwivedi et al 2004b), as we had observed in depressed suicide subjects. These changes were well correlated with the stress-induced behavioral paradigms. For example, LH behavior dissipated 4 days after the induction of LH. At the same time, in these animals, the changes in PKA also reverted to the normal level, which suggests that the changes in PKA were specific to stress-induced behavioral depression. Interestingly, very recently, Rao et al (2007a) reported that CBZ treatment significantly decreased cAMP-dependent PKA activity, but not basal PKA activity, compared with control values. On the other hand, animal model of depression show that PKA activity is increased in frontal cortex of rats (Rao et al 2007b). These studies further strengthen the hypothesis that bipolar disorder could be associated with increased PKA, which may be reversed by mood stabilizing drugs.

Mechanistic and functional aspects of PKA changes

The mechanisms responsible for the selectively altered expression of PKA subunits in bipolar or depressed patients are not clear at the present time. From Chang's study (Chang et al 2003b) it is clear that the alterations in RII β and C α protein levels in postmortem brain of bipolar patients are due to changes at the post-translational level. In depressed patients, however, we found that mRNA levels of RII β and C β were decreased (Dwivedi et al 2004a). It has been demonstrated in rat Sertoli cells, that activation of the cAMP pathway stimulates

mRNA levels of RI α , RII α , C α , and RII β , the increase in RII β being the greatest (Oyen et al 1988; Landmark et al 1993). However, prolonged stimulation with cAMP results in a decrease in RII β mRNA (Oyen et al 1988). In depressed patients, it has been shown that the expression of stimulatory G protein (G $_s\alpha$) is increased and of inhibitory G protein (G $_i\alpha$) is decreased (Pachecco et al 1996; Dwivedi 2002b), which suggests greater stimulation of the cAMP pathway. It is quite possible that this sustained stimulation may cause an adaptive change in expression of the RII β subunit. Another possible explanation of the reduced expression of the RII β subunit could be related to protein kinase C (PKC), a phosphorylating enzyme in the phosphoinositide signaling pathway. It has been shown that activation of PKC inhibits cAMP induction of RII β mRNA and that this inhibition persists even after PKC downregulation (Tasken et al 1992). The explanation of the selective decrease in the C β subunit is more complex. It has been shown that regulatory subunits associate with catalytic subunits and protect the catalytic subunits from degradation by proteolytic enzymes (Steinberg and Agard 1981). Furthermore, in brain tissues of RII β -mutant mice, there is a profound decrease in C α and C β subunit levels due to increased degradation Brandon et al (1998). However, in postmortem brain of depressed subjects, expression of only the C β subunit was decreased, and this decrease was present at both the transcriptional and the translational levels, eliminating the possibility of any degradation. It appears that additional factors or mechanisms may be involved in the regulation of the C β gene in postmortem brain of depressed suicide subjects. Irrespective of the mechanisms involved, the above-mentioned studies clearly indicate that specific catalytic and regulatory subunits of PKA are differentially regulated in unipolar and bipolar disorders.

As mentioned earlier, at the functional level, PKA is involved in myriads of physiological functions in the brain, including neurotransmitter synthesis and release, gene expression, synaptic plasticity, memory, and cell growth and differentiation. Furthermore, PKA participates in neurite outgrowth (Song and Poo 1999), neuronal differentiation (Liesi et al 1983), and cell survival (Rydel and Greene 1988; Li et al 2000). The major mechanism of PKA-mediated function is through the phosphorylation of specific substrates, which include CREB, nuclear receptors, and high mobility group-containing proteins, thus influencing their dimerization or DNA binding properties (Fimia and Sassone-Corsi 2001). Any abnormality in the expression or catalytic activation state of PKA would alter the functional capacity of the substrates that are activated in response to PKA activation. Some of

the substrates whose functions are altered in mood disorders are discussed in the next sections.

Another important aspect of PKA is its involvement in the cross-talk between different signaling mechanisms. For example, PKA interacts at various levels with other signaling pathways, including inactivation of phospholipase C (PLC) β (Liu and Simon 1996); phosphorylation of inositol 1,4,5-trisphosphate (IP₃) receptors, thereby modulating Ca²⁺ influx (Bugrim 1999); phosphorylation of G proteins, with a consequent decrease in PI hydrolysis and Ca²⁺ release (Wen et al 1992); and phosphorylation of calcium-calmodulin kinase (Matsushita and Nairn 1999). Through these actions PKA also profoundly affects physiological functions mediated by other signaling pathways.

The functions of each specific catalytic and regulatory subunit of PKA are not clear; however, Ludvig et al (1990) showed that RII β immunolabeling is associated with post-synaptic structures, suggesting that this subunit is involved in several post-synaptic neuronal functions. Also a few studies indicate that each catalytic and regulatory subunit has distinct functions in the CNS. For example, Constantinescu et al (2002) reported that in NG108-15 cells, which contain type I PKA (C α RI β) primarily in cytosol and type II PKA (C α RII β) in the particulate and nuclear fractions, forskolin- or ethanol-stimulated activation of CREB and gene activation are differentially regulated by the two different types of PKAs. Exposure of these cells to ethanol or forskolin caused translocation of only C α , but not C β , to the nucleus. They have proposed that Type II PKA is responsible for the induction of CREB. Interestingly, it has been shown that RII β can bind to and activate transcription via CRE (Srivastava et al 1998). Binding of RII β to CRE is enhanced by cAMP, and mutant mice lacking the autophosphorylation site exhibit reduced capacity to bind CRE (Srivastava et al 1998). On the other hand, Type I PKA is activated in the cytoplasm, and activates other transcription cofactors, which interact with phosphorylated CREB to induce gene transcription. Further evidence is derived from a study showing that Type I PKA controls cell growth whereas Type II PKA participates in growth arrest and induction of apoptosis (Cho-Chung 1990). Also, many studies have demonstrated that RII β and C β subunits may be specifically involved in neuronal and behavioral functions. For example, RII β -mutant mice exhibit defective motor behavior (Brandon 1998) and C β -mutant mice show impaired hippocampal plasticity (Qi et al 1996). Targeted disruption of the RI β subunit gene results in mice that exhibit defects in long-term depression and depolarization, which suggests a deficit in a learning-related form of synaptic

plasticity (Brandon et al 1998). It has also been shown that RI β deficiency produces selective defects in mossy fiber long-term potentiation (Brandon et al 1998).

Whether the observed selective abnormalities in expression of catalytic and regulatory subunits pertain to a specific disease state, such as unipolar or bipolar disorder, is not clear at the present time. However, given the significance of PKA in many biological actions in the brain, together with emerging studies demonstrating specific roles for its regulatory and catalytic subunits in physiological and behavioral manifestations, the observations of differential regulatory and catalytic activities, along with differential selective expression of selective regulatory and catalytic subunits, in mood disorder patients suggest that these abnormalities in PKA may be of critical importance in the pathophysiology of mood disorders.

Target substrates of PKA: Role in mood disorders

Rap-1 in mood disorders

Rap-1 is a member of the Ras family of small guanine nucleotide triphosphates with the highest homology to Ras and is highly expressed in the CNS (Kitayama et al 1989; Drugan et al 2000; Bos et al 2001). Rap-1 has been shown to be activated through the stimulation of various transmembrane receptors, including receptor tyrosine kinases, G protein-coupled receptors, cytokine receptors, and cell-adhesion molecules (Hattori and Minato 2003). A number of studies suggest that Rap-1 is activated directly by PKA or indirectly by cAMP through Epac (cAMP-regulated guanine nucleotide exchange factor) (de Rooij et al 1998; Bos et al 2001; Berruti 2003) and thereby modulates various pathways, including the cell survival extracellular signal-regulated kinase (ERK) and the phosphoinositide (PI) 3-kinase pathways. This leads to the modulation of physiological functions, such as cell proliferation, differentiation, adhesion, and neurite outgrowth.

To examine the functional response of altered cAMP, initially, Perez et al (1995) and Zanardi et al (1997) studied cAMP-stimulated phosphorylation of a PKA substrate in depressed or bipolar patients and found that the cAMP-stimulated phosphorylation of a 22-kDa protein (which was confirmed as Rap-1) was increased in platelets of euthymic bipolar patients. Recently, Perez et al (2000) found that cAMP-mediated endogenous phosphorylation of Rap-1 was significantly increased, along with an increase in level of Rap-1, in platelets of euthymic bipolar patients. In another study, Perez et al (1999) reported that phosphorylation of Rap-1 was significantly increased in euthymic, depressed,

or manic patients. On the other hand, they found that the level of Rap-1 was significantly lower in platelets of depressed patients (Perez et al 2001). Recently, we investigated Rap-1 in postmortem brain of depressed suicide subjects and found that Rap-1 activation was significantly reduced in prefrontal cortex and hippocampus of these subjects. This was associated with significant reductions in Rap-1 mRNA and protein levels in these brain areas (Dwivedi et al 2006). These studies indicate differences in activation and expression in Rap-1 in unipolar versus bipolar disorders. The findings of altered Rap-1 in depressed or bipolar patients not only provide the functional link to altered PKA but also indicate that abnormalities in Rap-1 may be crucial in the pathophysiology of mood disorders.

Transcription factor CREB in mood disorders

The functional significance of various signal transduction mechanisms depends upon the activation/repression of transcription factors that regulate the expression of genes involved in physiological functions. One such transcription factor is CREB, whose activity is regulated by PKA. CREB is a member of the basic leucine zipper subfamily of transcription factors (Borrelli et al 1992). Phosphorylation of CREB at serine 133 leads to its dimerization and activation by binding to the promoter region of target genes known as cAMP-response elements (CREs) at the consensus motif 5'TGACGTCA3', which is found in many neuronally expressed genes (Montminy et al 1990). It has been shown that CREB can bind to CRE even in the unphosphorylated form; however, it does not stimulate transcription unless it is phosphorylated at the serine 133 residue. CREB phosphorylation matches very well with the stimulation of transcription of CRE-containing genes. After serine 133 phosphorylation by PKA, CREB binds to the transcriptional co-activator CREB binding protein (CBP), which leads to stimulation of the transcription of many cAMP-responsive genes that are involved in several aspects of neuronal functioning, including the excitation of nerve cells (Moore et al 1996; Marshall and Dragunow 2000), central nervous system (CNS) development, long-term synaptic plasticity (Silva et al 1998), and cell survival.

A number of direct and indirect studies demonstrate that CREB could be involved in mood disorders (reviewed by Sulser et al 2002). Studies in rodents demonstrate that overexpression of CREB in hippocampus causes antidepressant-like effects in forced swim stressed or learned helpless rats (Chen et al 2001). On the other hand, in the temporal cortex of depressed patients, Dowlatsahi et al (1998)

reported decreased CREB immunoreactivity. Yamada et al (2003) examined the level of CREB and of its active form, phospho-CREB, in orbitofrontal cortex of antidepressant-free patients with major depression. They found that both CREB and phospho-CREB were significantly decreased in depressed subjects. In another study, Manier et al (2000) found that the isoproterenol-stimulated increase in phospho-CREB was significantly decreased in fibroblasts of depressed patients. Akin et al (2005) recently reported decreased phospho-CREB in fibroblasts of depressed subjects and showed that this decrease is associated with the melancholic subtype. In a postmortem brain study, we demonstrated that expression and functional characteristics of CREB were decreased in prefrontal cortex and hippocampus of a group of suicide subjects that included depressed suicide subjects (Dwivedi et al 2003a). A role for CREB in depression is further supported by a recent study demonstrating a linkage of CREB with major depression. In this study Zubenko et al (2002) performed a linkage analysis of six polymorphic markers located in a 15 cM region of chromosome 2q33-35 and unipolar depression. They found significant linkage of unipolar depression to a 451 Kb region of 2q33-34, which contains the *CREB1* gene. This suggests that the *CREB1* gene may be an attractive candidate for a susceptibility gene for unipolar depression. These described studies thus indicate decreased expression/functional response of CREB in depression.

Many different classes of antidepressants upregulate CREB expression in rat hippocampus (Nibuya et al 1996), which suggests that CREB participates in the mechanism of action of antidepressants. Recently, Koch et al (2002) investigated phosphorylation of CREB in T-lymphocytes of depressed patients before and after antidepressant treatment. They found that responders showed a significant increase in phosphorylation of CREB compared with nonresponders, suggesting that CREB may be a molecular state marker for antidepressant response. Recently, Thome et al (2000) studied the functional relevance of increased CREB by antidepressants, and observed that in transgenic mice containing the CRE-Lac Z reporter, activation of the CRE site led to increased CRE-mediated gene transcription.

In contrast to what occurs with antidepressants, Stewart et al (2001) found a lower CREB level in temporal cortex of bipolar patients treated with mood stabilizing drugs. In rat cortex and hippocampus, similar findings were noted by Chen et al (1999), who reported that lithium, but not valproate, decreased the level of phospho-CREB. An in vitro study also suggested that lithium decreases cAMP-dependent CREB phosphorylation and DNA binding activity in

neuroblastoma cells (Wang et al 1999). These studies thus suggest that mood stabilizing drugs and antidepressants behave differently in regulating CREB. Whether this means that CREB expression is increased in bipolar patients is not clear at the present time, however; these studies do point in this direction.

BDNF in mood disorders

Among the epigenetic factors that may influence the development and survival of neurons in the CNS are neurotrophins. The most important and widely distributed member of the neurotrophin family in the brain is BDNF. It has been shown that PKA/CREB activation increases BDNF transcription through a Ca^{2+} /CRE within exon III of BDNF (Finkbeiner 2000). BDNF-mediated activation of its cognate receptor, tyrosine receptor kinase (Trk) B, influences neurite outgrowth, phenotypic maturation, morphological plasticity, and synthesis of proteins for differentiated functioning of neurons and synaptic functioning (Huang and Reichardt 2001). Several studies suggest that BDNF is also involved in nerve regeneration, structural integrity, and maintenance of neuronal plasticity in the adult brain, including activity-dependent regulation of synaptic activity, and in neurotransmitter synthesis (Thoenen 1995). A pathological alteration of the neurotrophic factor system thus may not only lead to altered neural maintenance and regeneration, and therefore structural abnormalities in the brain, but also to reduced neural plasticity. The result could be an impairment of an individual's ability to adapt to crisis situations.

Emerging studies suggest that mood disorders and stress may both be associated with structural abnormalities in the brain. For example, patients with affective disorders show reductions in hippocampal volume, in density and size of cortical neurons in the dorsolateral PFC and orbitofrontal cortex, and in density of nonpyramidal neurons. There is also a layer-specific reduction in interneurons in the anterior cingulate cortex and in nonpyramidal neurons in the hippocampal formation, and a marked decrease in glial cell number and density in PFC of mood disorder patients (Rajkowska 2000; Benes et al 2001; Miguel-Hidalgo et al 2002). Similarly, several studies show that stress or glucocorticoid administration causes neuronal atrophy (Sapolsky 1996; Brown et al 1999; McEwen 1999), a decrease in the number or length of apical dendrites (Woolley et al 1990; Watanabe et al 1992), and even loss of hippocampal neurons (Sapolsky 2000). Among the epigenetic factors that may influence the development and survival of neurons in the CNS are neurotrophins. The most important and widely

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BDNF in unipolar disorder

There is a growing body of evidence that demonstrates the involvement of BDNF in unipolar disorder. For example, Siuciak et al (1996) studied the behavioral effects of midbrain infusion of BDNF in rats. They found that rats who received BDNF showed greatly reduced learned helpless behavior compared with rats who were given saline. Shirayama et al (2002) also reported that bilateral infusion of BDNF into the dentate gyrus of rats produced an antidepressant-like effect in both learned-helpless and forced-swim-test models of depression. Further evidence of the role of BDNF in depression comes from studies of BDNF expression in rat brain after different types of stresses. Immobilization stress and glucocorticoids significantly decrease BDNF expression in limbic areas (Barbany and Persson 1992; Nibuya et al 1995; Smith et al 1995a, 1995b; Duman et al 1997; Ueyama et al 1997). Chronic treatment with antidepressants prevents the stress-induced lowering of BDNF (Nibuya et al 1995; Duman 2002). More direct evidence is derived from studies showing that serum BDNF levels were significantly decreased in drug-free depressed patients and were negatively correlated with Montgomery-Asberg-Depression Rating Scale scores (Karege et al 2002b). Recently, Shimizu et al (2003) reported that the serum level of BDNF was significantly decreased in antidepressant-free depressed patients compared with those medicated with antidepressants or normal controls. They also reported that the serum BDNF level was negatively correlated with HDRS scores. More recently, we observed that expression of BDNF and of the active form of TrkB, ie, full-length TrkB, is significantly decreased in prefrontal cortex and hippocampus of depressed and nondepressed

suicide subjects (Dwivedi et al 2003b). At the genetic level, Sen et al (2003) has reported that the val allele of the BDNF val66met polymorphism is associated with neuroticism, a heritable risk factor for depression, further emphasizing the role of BDNF in depression.

Other evidence of the role of BDNF in depression comes from studies suggesting that BDNF is a target of antidepressants. For example, chronic administration of several classes of antidepressants or electroconvulsive shock upregulates the expression of BDNF in rat hippocampus (Smith et al 1995b; Nibuya et al 1995). Electroconvulsive shock also increases the expression of TrkB in rat hippocampus and blocks the downregulation of BDNF in response to restraint-induced stress (Nibuya et al 1995; Lindeforts et al 1995). A consecutive 10-day daily exposure to ECS also increases the expression of BDNF, not only in hippocampus, but also in parietal cortex, entorhinal cortex, frontal cortex, neostriatum, and septum (Altar et al 2003). Pretreatment with antidepressants blocks the stress-induced downregulation of BDNF in hippocampus (Lindeforts et al 1995). A postmortem brain study of depressed subjects who were being treated with antidepressants at the time of death also suggests an increase in the level of BDNF in hippocampal regions (Chen et al 2001).

BDNF in bipolar disorder

BDNF may also play an important role in the pathophysiology of bipolar disorder. For example, chronic lithium or valproate treatment of rats increases the expression of BDNF in hippocampus and temporal and frontal cortices (Fukumoto et al 2001). A number of genetic studies in humans indicate a linkage of BDNF to bipolar disorder. Chromosome 11p13-14 is a putative locus for the genes responsible for the development of bipolar disorder. The BDNF gene is located in this region of the chromosome. Recently, family-based association studies for the dinucleotide repeat polymorphism at position -1040 bp showed that allele A3 was preferentially transmitted to the affected individuals. The results of the val66met single-nucleotide polymorphisms (SNP) showed a significant association for allele G. Transmission/disequilibrium test haplotype analysis showed a significant result for the G-allele combination, which suggests that a DNA variant in the vicinity of the BDNF locus confers susceptibility to bipolar disorder (Neves-Pereira et al 2002). Sklar et al (2002) studied the association between 76 candidate genes and bipolar disorder by genotyping 90 SNPs in these genes and identified BDNF as a potential risk allele for bipolar disorder; although Nakata et al (2003) found no association for two polymorphisms

(-1360C > T and 196G > A) in a Japanese population with bipolar disorder. Very recently, Tsai (2004) suggested the possibility that BDNF overactivity may be associated with the manic state on the basis of studies showing: 1) there is a positive association between genetic polymorphism of BDNF and bipolar disorder, 2) agents that induce mania increase BDNF (Peet and Peters 1995; Vollenweider et al 1998; Meredith et al 2002), 3) atypical antipsychotics, often used for the treatment of mania, decrease the level of BDNF in frontal and occipital cortices, and hippocampus (Angelucci et al, 2000), and 4) there is increased mossy fiber staining in the supragranular layer in bipolar patients, which is associated with BDNF action. Further studies are required to explore such an interesting idea.

Conclusion

In this review we have critically discussed the findings pertaining to various components of adenylyl cyclase-cAMP signaling relevant to mood disorders. We have briefly included studies pertaining to cAMP formation and adenylyl cyclase, however; given the importance of PKA in mediating crucial physiological functions in the brain, especially emphasized is the role of this phosphorylating enzyme in mood disorders (Figure 2). Although not consistently, the majority of studies suggest that the changes in agonist-stimulated cAMP formation and in catalytic activation of adenylyl cyclase are direct opposites in unipolar versus bipolar states, such that cAMP formation and adenylyl cyclase activity are decreased in unipolar and increased in bipolar disorder. The most consistent findings were observed in PKA, and significant conclusions can be drawn from these findings. For example, bipolar disorder patients show increased PKA catalytic activity, which is associated with selectively increased expression of catalytic (C α) and regulatory (RII β) subunits. In contrast, unipolar depression is associated with decreased PKA activity and decrease expression of catalytic C β and regulatory RII β subunits. These observations have been further substantiated by studies in rodents which show that corticosterone administration or induction of learned helplessness behavior causes similar changes in PKA as were found in postmortem brain of depressed subjects. The opposite findings involving cAMP formation and adenylyl cyclase and PKA activities in unipolar and bipolar disorders are quite important, and the findings of the differential regulation of PKA C and R subunits in these two disorders are especially intriguing. Whether these particular PKA subunits are involved in specific behavioral and clinical manifestations, remains to be elucidated.

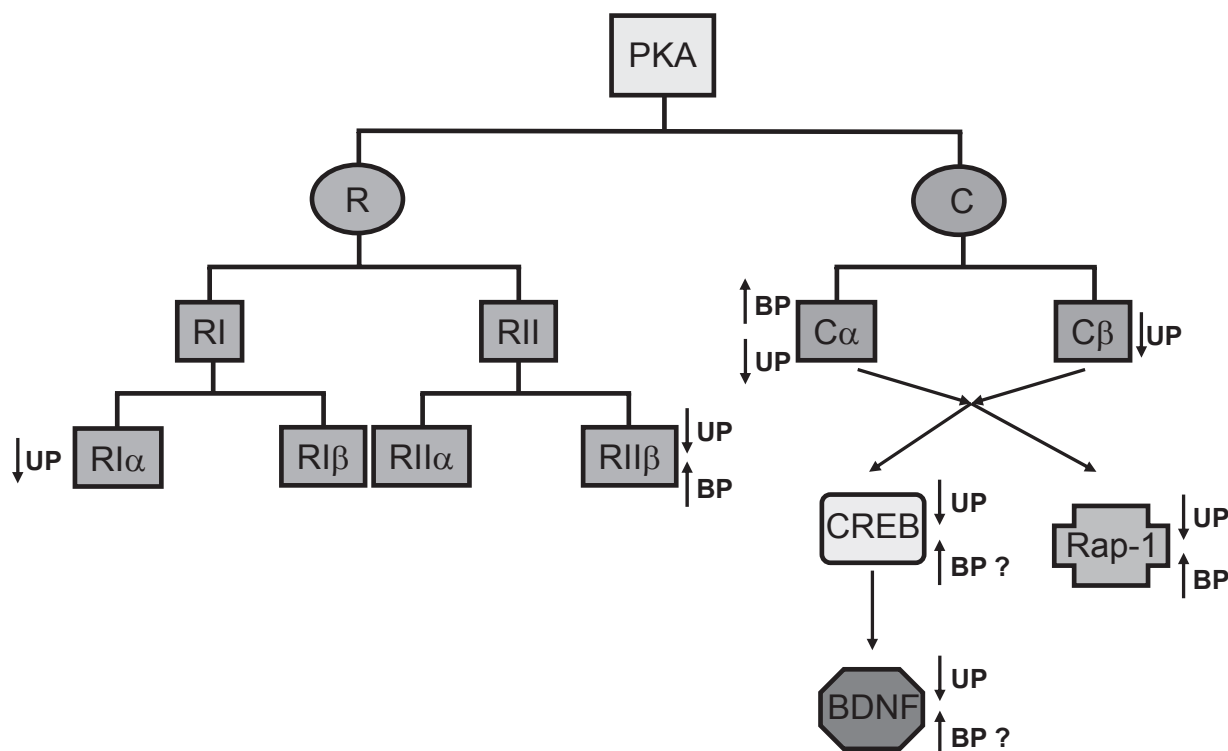


Figure 2 PKA catalytic (C) and regulatory (R) subunit isoforms expressed in brain and decrease (↓) or increase (↑) in expression of specific C and R subunits and of CREB and BDNF in unipolar (UP) and bipolar (BP) disorders. PKA R subunits are divided into two subtypes, RI and RII. RI and RII subtypes contain two isoforms each, ie, α and β . All four R subunit isoforms are expressed in brain. On the other hand, brain expresses α and β isoforms of C subunit. The indicated decreases and increases in PKA subunits are based on human postmortem and peripheral studies in unipolar and bipolar disorder patients. The question mark (?) indicates the possible upregulation of BDNF and CREB in bipolar disorder patients based on preclinical studies.

In addition, interesting findings about the substrates for PKA, namely, Rap-1, CREB, and BDNF, have emerged. For example, changes in Rap-1 also appear to be the opposite in unipolar and bipolar disorders, as has been for the changes in PKA. Similarly, an intriguing hypothesis has been put forward suggesting an induction of BDNF expression in the manic phase but reduction in its expression in the depressed phase. A systematic study in a large population of mood disorder patients is required to confirm these findings. Overall, in view of the current findings, a novel concept of the neurobiology of mood disorders is evolving in which disruptions in PKA/CREB/Rap-1/BDNF signaling could be seen as important biological risk factors that may be useful in delineating the etiology of these two disorders and eventually result in site-specific therapeutic interventions.

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