Focus on
Protein kinase A and protein kinase C, critical components of signal transduction system, in mood disorders and suicide

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Introduction
Depression is among the most prevalent forms of mental disorders, affecting 10–15% of the US population, with high rates of comorbidity and frequent suicidal behaviour. Tragically, about 30,000 lives are lost each year by suicide (Minino and Smith, 2001). Despite significant progress in research, the pathophysiology of depression and suicide is poorly understood. A number of studies suggest that abnormalities in signalling mechanisms may be crucial to various psychiatric disorders, including depression and suicide (Dwivedi et al., 2002, 2003; Jope et al., 1998; Pacheco et al., 1996; Pandey et al., 2002a). Particular attention has been paid to examining protein phosphorylation and dephosphorylation and the activation and repression of transcription factors, which are key processes in signalling mechanisms, and ultimately in modulating the expression of genes involved in various neuronal functions. Two important protein phosphorylating enzymes, protein kinase A (PKA) and protein kinase C (PKC), are components of the adenylyl cyclase-cyclic AMP (AC-cAMP) and the phosphoinositide (PI) signalling systems respectively. Activation of PKC by diacylglycerol is associated with the translocation of the enzyme from the cytoplasm to the membrane and then causes phosphorylation of important proteins and transcription factors such as cAMP response element-binding (CREB) protein, which regulates the expression of genes containing CRE consensus in their promoters. As is the case with PKC, the activation of PKA by cAMP also phosphorylates a diverse number of target proteins in both cytoplasm and the nuclear compartment. One such target in the nucleus is CREB. The activation of CREB causes the expression of genes such as brain-derived neurotrophic factor (BDNF), which has been implicated in the maintenance of neurons, cell survival, and neuronal plasticity (Huang and Reichardt, 2001). The AC-cAMP and the PI signalling systems not only converge at the level of transcription factor CREB but also interact and cross-talk at several levels. Their convergence at the transcription factor may have several important implications. Both PKA and PKC are involved in a number of physiological functions in the CNS, including neurotransmitter release, differentiation, cell survival, proliferation, gene expression and neuronal plasticity.

In the paper published in this issue by Akin et al. (2005) the authors report their studies of PKA and PKC in cultured fibroblasts obtained from patients with mood disorders. They found that the activity of PKA was decreased in fibroblast cultures of melancholic depressed patients when compared with that of non-melancholic depressive patients or normal control subjects. They also observed decreased protein expression of RIIα, Ca and Cβ subunits of PKA in fibroblasts of melancholic depressed patients when compared with that of non-melancholic depressive patients or normal control subjects. Since both PKA and PKC are critical phosphorylating enzymes, these investigators determined their functional status by examining the phosphorylation of the substrate CREB. They again found that phosphorylation mediated by PKA and PKC was significantly decreased in fibroblasts of melancholic depressed patients compared with non-melancholic depressed patients or normal...
control subjects. These findings further emphasize the role of these kinases in depression.

PKA in mood disorders and suicide

PKA, which is a tetrameric holoenzyme, is composed of a regulatory (R subunit) and a catalytic subunit. On the basis of elution patterns, two different PKA isozymes, known as PKA-I and PKA-II, have been identified. These two isozymes are comprised of two different R subunits, known as RI and RII, both of which are further comprised of subunits known as RIA, RIB, and RIIA, RIIIB respectively. In addition, three catalytic subunits, known as Ca, Cβ, and Cγ, have also been identified. Each R subunit has two cAMP-binding sites, and on activation by binding with cAMP, each disassociates into a dimeric R subunit complex and two monomeric active C subunits. Most investigators have found decreases in [3H]cAMP binding and in PKA activity and PKA subunits in patients with depression (Manier et al., 1996; Perez et al., 2001; Shelton et al., 1996) and in post-mortem brain from depressed suicide victims (Dwivedi et al., 2004a). On the other hand, increased catalytic activity of PKA and decreased [3H]cAMP binding have been reported in the post-mortem brain of bipolar patients (Fields et al., 1999; Rahman et al., 1997) and increased [3H]cAMP-mediated phosphorylation in platelets of bipolar patients (Perez et al., 1995). Of interest, however, is the change in expression of PKA subunits in these disorders. Akin et al. (2005) found a significant reduction in protein expression levels of RIIA, Ca and Cβ in cultured fibroblasts obtained from melancholic depressed patients compared with control subjects or non-melancholic subjects. In post-mortem brain studies, our group (Dwivedi et al., 2004a) reported decreased protein and mRNA expression of RIB and Cβ subunits in the prefrontal cortex (PFC) of depressed suicide victims compared to normal control subjects. A similar observation was made in the brain of behaviourally depressed rats (Dwivedi et al., 2004b) and after hypothalamic–pituitary–adrenal (HPA) axis manipulation (Dwivedi et al., 2000), suggesting that stress may regulate PKA subunits. In bipolar patients, increased protein levels of cytosolic Ca and RIIβ have been reported (Chang et al., 2003). These observations have raised the possibility that depression may be associated with lower levels of PKA RIIβ, Ca and Cβ subunits and that bipolar illness may be associated with increased Ca and RIIβ subunits.

These observations have raised the issue of the functional, mechanistic, and behavioural significance of the various PKA subunits and their relevance to mood disorders and suicide. It has been reported that one of the functions of the regulatory subunits is to protect the catalytic subunits from proteolytic degradation by binding with them and keeping them in the holoenzyme state. A decrease and/or increase in any of the R subunits may, thus, result in the proteolytic degradation of C subunits, and hence a decrease in PKA activity. The reported changes in the regulatory subunits probably lead to the changes in the catalytic subunits and PKA activity and in altered phosphorylation of their substrates such as CREB. The functional significance of R subunit genes was not fully appreciated until recently, with the advent of gene targeting and gene knockout technology. In mice, targeted disruption of the RIIβ subunit gene results in mice that exhibit defects in long-term depression and depolarization, suggesting a deficit in learning-related forms of synaptic plasticity (Brandon et al., 1998). This occurs even though there is a compensatory increase in the RIIa protein and a lack of detectable changes in total PKA activity. It was also shown that RIIβ deficiency produces selective defects in mossy fibre long-term potentiation. In RIIβ knockout mice there is an increased tendency to consume ethanol as well as decreased sensitivity to the sedative effect of ethanol (Thiele et al., 2000). Interestingly, deletion of RIIβ and Cβ do not show similar changes. The RIIβ-deficient mice also show impaired motor behaviour, loss of haloperidol-induced catalepsy, and some loss of neuronal gene expression (Adams et al., 1997; Brandon et al., 1998).

PKC in mood disorders and suicide

PKC is a key regulatory enzyme present in various tissues, including the brain, and has been subgrouped into three classes known as conventional, which includes α, βI, βII, and γ; novel, which includes δ, η, and ζ; and atypical, which includes ε and λ. Like PKA, PKC also phosphorylates transcription factors such as CREB, c-Fos, c-Jun and other substrates such as GAP-43 and myristoylated alanine-rich C kinase substrate (MARCKS). There is both direct and indirect evidence suggesting that PKC may play a crucial role in mental disorders. Friedman et al. (1993) have reported that PKC activity is increased in the platelets of bipolar patients during the manic phase. Pandey et al. (1997, 2004) reported that PKC binding and activity as well as protein and mRNA expression of PKCa, PKC βI, PKC βII, and PKCγ were significantly decreased in the PFC and hippocampus of teenage suicide victims. All these observations indicate that alterations in PKC activity and in some of its specific subunits may be
involved in the pathophysiology of mood disorders and suicide.

Akin et al. (2005) found that PKC-mediated phosphorylation of CREB was significantly decreased in the fibroblasts of those melancholic depressed subjects who also had low PKA activity. This observation implied that the decrease in PKC-mediated phosphorylation of CREB was related to the decrease in the PKC activity. However, it did not indicate if this decrease in CREB phosphorylation was associated with a decrease in any specific subunit of PKC. In a recent publication, Pandey et al. (2002b) observed a decrease in PKC activity and in the protein expression of specific subunits of PKC in the platelets of bipolar patients. They also observed that the level of MARCKS, a substrate of PKC, was increased in the platelets of these patients. They suggest that this increase in MARCKS level was related to decreased phosphorylation of MARCKS due to decreased PKC activity in these patients. The observations of Pandey et al. (2002b) and of Akin et al. (2005) indicate that a decrease in PKC activity is probably associated with decreased phosphorylation of a substrate such as CREB or MARCKS.

Conclusions

In conclusion, emerging evidence shows that both PKC and PKA are important target genes in mood disorders. Given that these phosphorylating enzymes play a central role in various physiological functions in the CNS, deficit in their activation is noteworthy, in particular, reduction in specific isozymes of PKC and PKA. Although some behavioural studies indicate phenotypic alterations as well as compromised synaptic plasticity in specific PKA subunit-deficient mice, a clear picture of the behavioural and their specific roles in mental disorders in not yet clear. Although it is intriguing that PKA subunits are differentially regulated in suicide, depression, and bipolar disorder, a comprehensive study is needed to delineate this specificity. Also, further studies are required to determine whether such defects are specific to melancholic depression, as observed by Akin et al. (2005) or are common to other types of depression and to suicidal behaviour. Our post-mortem brain studies showing altered PKA activity and subunit expression tend to indicate that a deficit in PKA may not be specific to melancholic patients. In addition, whether a decrease in PKA or PKC is the consequence of a diseased state or is secondary to changes in some other factors, such as altered HPA axis and epigenetic factors needs to be investigated. Our previous study demonstrating that stress hormones may regulate PKA and PKC genes point in this direction. Finally, research is required to further investigate the genetic linkage of these abnormalities to mental illness.

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Statement of Interest

None.

References


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