Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 831–841

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Elucidating biological risk factors in suicide: Role of protein kinase A

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ARTICLE INFO

Article history:
Received 18 June 2010
Received in revised form 17 August 2010
Accepted 26 August 2010
Available online 9 September 2010

Keywords:
Animal models
Depression
G proteins
Human postmortem brain
Protein kinase A
Suicide

ABSTRACT

Suicide is a major public health concern. Although there have been several studies of suicidal behavior that focused on the roles of psychosocial and sociocultural factors, these factors are of too little predictive value to be clinically useful. Therefore, research on the biological perspective of suicide has gained a stronghold and appears to provide a promising approach to identify biological risk factors associated with suicidal behavior. Recent studies demonstrate that an alteration in synaptic and structural plasticity is key to affective illnesses and suicide. Signal transduction molecules play an important role in such plastic events. Protein kinase A (PKA) is a crucial enzyme in the adenylyl cyclase signal transduction pathway and is involved in regulating gene transcription, cell survival, and plasticity. In this review, we critically and comprehensively discuss the role of PKA in suicidal behavior. Because stress is an important component of suicide, we also discuss whether stress affects PKA and how this may be associated with suicidal behavior. In addition, we also discuss the functional significance of the findings regarding PKA by describing the role of important PKA substrates (i.e., Rap1, cyclic adenosine monophosphate response element binding protein, and target gene brain-derived neurotrophic factor). These studies suggest the interesting possibility that PKA and related signaling molecules may serve as important neurobiological factors in suicide and may be relevant in target-specific therapeutic interventions for these disorders.

1. Introduction

Suicide is a major public health concern. Approximately one million people commit suicide worldwide each year, and 30,000 people commit suicide in the United States alone (Goldsmith et al., 2002). The lifetime suicide attempt rate among adults is approximately 10% (Minino and Smith, 2002; Bertolote, 2001); among adolescents, suicide is the third leading cause of death after motor vehicle crashes and homicide (National Center for Health Statistics, 1992). Previously, most of the studies of suicidal behavior were focused on the roles of psychosocial and sociocultural factors; however, these factors are of too little predictive value to be clinically useful. Therefore, research on the biological perspective of suicide has gained a stronghold and appears to provide a promising approach for identifying biological risk factors associated with suicidal behavior.

Recently, it has been suggested that the pathogenesis of mood disorders/suicide involves altered plasticity of neuronal pathways (Garcia, 2002). In fact, it has been proposed that mood disorders/suicide result from an inability of the brain to make appropriate adaptive responses to environmental stimuli as a result of impaired synaptic and structural plasticity (Duman et al., 2000; Dwivedi et al., 2005; Dwivedi, 2010). Support for this idea comes from studies demonstrating altered brain structure during stress and depression (major components of suicidal behavior) and from suicidal patients. The alterations include reductions in cell number, density, cell body size, and neuronal and glial density in frontal cortical or hippocampal brain areas; and decreases in the parahippocampal cortex and cortical laminar thickness (Altshuler et al., 1990; Rajkowska, 1997, 2002; Bremner et al., 2000; Rosoklija et al., 2000; Cotter et al., 2002). In addition, changes in synaptic circuitry (Aganova and Uranova, 1992), synaptic connectivity (Honer, 1999), number and shape of dendritic spines (Hajsza et al., 2005), synapse formation (McEwen, 2000), neuronal atrophy (Sheline, 2000), and spatial cognition deficits (Sackeim, 2001) have been reported in depression and/or during stress. The cellular mechanisms that underlie such compromised neural plasticity and structural impairments in mood disorders and suicide are not clearly understood; however, recent findings from our own laboratory and from others provide evidence that such changes may be a consequence of disruption in the cellular mechanisms governing structural/neural plasticity and cellular resilience (Young, 2001; Nestler et al., 2002; Dwivedi et al., 2003a,b, 2006, 2009; Joëls et al., 2004; Dwivedi, 2005, 2006; Duman and Monteggia, 2006).

A number of studies suggest the involvement of serotonergic, and to some extent, noradrenergic systems in suicide, which include

Abbreviations: BDNF, brain-derived neurotrophic factor; CREB, cyclic adenosine monophosphate response element binding protein; PFC, prefrontal cortex; PKA, Protein kinase A.

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doi:10.1016/j.pnpbp.2010.08.025

alterations in levels of serotonin and norepinephrine, their metabolites, and the receptors to which these neurotransmitters bind in the brain and peripheral tissues of subjects who have committed suicide (hereafter referred to as "suicide subjects") (Pandey and Dwivedi, 2006, 2007; Stockmeier, 1997). In addition to these neurotransmitter receptors, downstream signal transduction pathways play a critical role in regulating neural plasticity by integrating various physiological processes, which, in turn, are important for behavioral and environmental adaptations. Given the critical importance of intracellular signaling pathways in such behavioral and environmental adaptations, recent studies have focused on the role of various signaling molecules in the pathophysiology of mood disorders and suicide (Dwivedi, 2005; Pandey and Dwivedi, 2006).

Of various signaling pathways, adenylyl cyclase-cyclic adenosine monophosphate (cAMP) signaling is one of the best-characterized signal transduction mechanisms in the central nervous system (CNS). In this signaling pathway, protein kinase A (PKA) is a key phosphorylating enzyme, which, on activation by cAMP via G protein/adenylyl cyclase, triggers a wide variety of physiological responses in the brain that are important for cell survival, synaptic plasticity, and activation or repression of gene expression (Borrelli et al., 1992; Nestler and Greengard, 1994). This review focuses on the role of PKA in suicidal behavior. Because stress is an important component in suicidal behavior, we discuss whether stress regulates PKA and whether changes in PKA in suicide subjects are a consequence of the stress response. Briefly, we also discuss molecules that are substrates of PKA or whose expression is regulated by PKA. Specifically, we will discuss PKA substrate Rap1, cAMP response element binding (CREB), and target gene brain-derived neurotrophic factor (BDNF) in the context of their role in suicide.

2. Adenylyl cyclase-cAMP pathway: role of G proteins in modulating PKA and their role in suicide

Guanine nucleotide-binding proteins (G proteins) occupy a central position and play a critical role in the transduction of extracellular signals to cellular targets (Neer, 1995; Clapham and Neer, 1997; Hamm, 1998; Freissmuth et al., 1999; Neves et al., 2002). Approximately 80% of the receptors for neurotransmitters, hormones, and neuromodulators elicit their responses through G proteins, which are heterotrimers consisting of three subunits (α, β, and γ), each encoded by a specific gene. The β and γ subunits bind tightly to each other, and the β subunit also contains a common binding site for α subunit recognition. The α subunit binds to guanosine triphosphate (GTP) and confers receptor-effector specificity to G proteins. The γ subunit has been reported to have a G protein-specific recognition site. In the resting state, guanosine diphosphate (GDP) is bound to the α subunit, and the three subunits (α, β, and γ) are associated as a trimer. Receptor-mediated activation of G proteins causes the release of GDP from the α subunit, allowing GTP to bind to and induce the dissociation of the G protein α subunit from the βγ subunits. The α and βγ subunits can then activate various effectors to modulate cellular responses (Fig. 1). Based on complementary DNA sequencing and the similarity of amino acid sequences, Gα subunits have been classified into four major classes: G_s, G_i, G_q, and G_{12}. More than 16 distinct genes encode the G protein α subunits, and there is a splice variant in at least two genes (Gilman, 1987; Simon et al., 1991; Neer, 1995; Hamm, 1998). A total of 5 distinct β subunit genes and 12 γ subunit genes have also been identified (Hildebrandt, 1997). Once activated, both α and βγ subunits can activate or inhibit multiple effectors to modulate cellular responses. Of the various Gα isoforms, $G_s\alpha$ stimulates adenylyl cyclase, whereas $G_i\alpha$ mediates the inhibition of adenylyl cyclase. The activation of adenylyl cyclase catalyzes the conversion of adenosine triphosphate to cAMP. Cyclic AMP serves as a second messenger and 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; Nestler and Greengard, 1994). The response generated by cAMP can be terminated by the hydrolysis of cAMP into 5′AMP by phosphodiesterases or by removal of the phosphate group by protein phosphatases. The activity of phosphodiesterases can be enhanced through phosphorylation by PKA, thus causing an abrupt termination of the signal (Beebe, 1994).

Because G proteins play a critical role in modulating adenylyl cyclase activity and, therefore, cAMP formation, there have been some studies elucidating the role of G proteins in depression and, to some extent, suicidal behavior. These studies include examination of either expression of G protein subunits or G protein-mediated functional response in peripheral tissues and human postmortem brain. For example, Cowburn et al. (1994) reported that basal, GTPγS-stimulated, or forskolin-stimulated adenylyl cyclase activity is decreased in the cerebral cortex of depressed patients. In another study, Ozawa et al. (1993) found that AAGTP binding to $G_{i/o}$ α was decreased in the temporal and parietal cortices of depressed patients. Avissar et al. (1997) reported that levels of $G_s\alpha$ and $G_i\alpha$ were significantly decreased in mononuclear leukocytes of depressed patients. This was associated with hypofunctional $G_s\alpha$ and $G_i\alpha$, as measured by β-adrenergic and muscarinic cholinergic agonist-stimulated G protein binding capacity. On the other hand, Karege et al. (1998) measured the levels of $G_q\alpha$, $G_i\alpha$, and Gβ and found that levels of all these proteins were elevated in the platelets of depressed patients. To our knowledge, no change in the levels of $G_s\alpha$ or $G_i\alpha$ in the granulocytes (Spleiss et al., 1998) or in mononuclear leukocytes (Young et al., 1993) of depressed patients has been reported.

In a large postmortem brain study, we examined the expression levels of G proteins in suicide. We found a significant decrease in both messenger RNA (mRNA) and protein levels of $G_{i2}\alpha$ and a significant increase in levels of $G_s\alpha$ in the prefrontal cortex (PFC) of suicide subjects compared with nonpsychiatric control subjects. These changes were present in all suicide subjects regardless of psychiatric illnesses. Similar results were reported by Pacheco et al. (1996), showing a significant increase in $G_s\alpha$ in Brodmann area 10 and a decrease in $G_{i2}\alpha$ in Brodmann areas 8 and 9 of depressed suicide subjects. Although the study results in depressed subjects are somewhat inconsistent, it appears that suicide brain exhibit hyperfunctional adenylyl cyclase-cAMP activity.

Because most of the effects of cAMP are mediated by its receptor PKA, and because 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 provides direct evidence of altered cAMP signaling. In addition, PKA participates directly in many physiological functions in the CNS; by phosphorylating the components of other signaling cascades, it provides the means for cross talk between the adenylyl cyclase-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 depression and suicide.

3. PKA: a critical phosphorylating enzyme in the adenylyl cyclase-cAMP signaling pathway and its role in suicide

Protein kinase A was one of the first protein kinases to be discovered (Walsh et al., 1968). As shown in Fig. 1, PKA is a holoenzyme composed of two distinct subunits: regulatory (R) and catalytic (C). These regulatory and catalytic subunits 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. The C subunit is initially phosphorylated by phosphoinositide-dependent kinase at threonine 197 (Cauthron et al., 1998; Cheng et al., 1998) in the activation loop. This phosphorylation is necessary for the maturation and optimal biological activity of PKA (Adams et al., 1995; Steinberg et al., 1993). After an increase in intracellular cAMP, the regulatory PKA subunits bind to cAMP in a cooperative manner, which results in the conformational change in the regulatory subunits, leading to the disassociation of the