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NEUROBIOLOGY OF ADULT AND TEENAGE SUICIDE

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1. Introduction

Suicide is a major public health concern worldwide (Botsis et al 1997). About 30,000 people die of suicide in the USA and about 1 million worldwide (Botsis et al 1997; Goldsmith et al 2002). In the United States, suicide is the third leading cause of death in teenagers (Singh et al 1996). There are several risk factors for suicide, including the presence of depression (Lönqvist 2000) and other mental disorders (Caldwell and Gottesman 1992; Harris and Barraclough 1998; Lönqvist 2000; Moscicki 1997; Weissman et al 1989) and substance and alcohol abuse (Hlady and Middaugh 1988). Hopelessness (Beck et al 1993), stress (Westrin 2000), and impulsive-aggressive traits are among other risk factors (Brent et al 1999; Brent et al 1993; Linnoila and Virkkunen 1992). Recent studies also suggest that a family history of suicide and genetic and abnormal neurobiology may also be important risk factors for suicide (Ernst et al 2009; Mann 2003).

There is evidence to suggest that some factors associated with adolescent suicide may be different from adult suicide (Brent et al 1999; Zalsman et al 2008). Although impulsive-aggressive behavior is a common risk factor for both adult and teenage suicide, aggression and impulsivity are traits highly related to suicidal behavior in adolescents (Apter et al 1995). Higher levels of impulsive aggressiveness play a greater role in suicide among younger individuals with importance decreasing with age (Brent et al 1993). Brent et al. (1993) have also shown that adolescents with aggression and conduct disorders may be suicidal even in the absence of depression. Psychosocial factors associated with adolescent suicide, such as stress and contagion, bullying and peer victimization (Brunstein et al 2008; Bursztein and Apter 2009; Klomek et al 2008) may also be different from adults. Alcohol and drug abuse contribute significantly to the risk of suicide in teenagers (Apter et al 1990; Apter et al 1995). Additional potential contributors to suicidal behavior in depressed

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adolescents are early defined traits such as temperament and emotional regulation. One study suggests (Tamas et al 2007) that suicidal youth are characterized by highly maladaptive regulatory responses and low adaptive emotional regulation responses to dysphoria.

In the USA, as in many countries of the world, older adults are at greater risk for suicide; of the 35,000 people who died by suicide in the USA, more than 5,000 are among people older than 65 years (CDCPrevention 2007). Based on psychological autopsy (PA) studies it is estimated that mood disorder was the most common disorder among these cases (Conwell et al 1996). Hopelessness, stress (relationship and financial problems) are other risk factors. Biology of elderly suicide is not well studied. For suicidal behavior in elderly see review by Conwell and Thompson (2008).

Neurobiological studies in suicide have been performed either in patients with suicidal behavior or in the postmortem brain of suicide victims. In this chapter, we will primarily focus on the major neurobiological findings in suicide related to serotonin and noradrenergic mechanism, signal transduction pathways, hypothalamic adrenal pituitary axis (HPA) dysfunction, and inflammatory markers (cytokines in the postmortem brain). We will also briefly discuss the evidence from studies of suicidal patients, specifically the 5HT system leading to these studies in postmortem brain.

2. Biological Abnormalities in Suicidal Behavior: Evidence from Patient Studies

Initial studies of biological factors associated with suicide were primarily conducted in patients with suicidal behavior. Suicidal behavior in patients is defined as the presence of serious suicidal thoughts or ideation or previous suicide attempts. These studies were primarily performed in tissues such as blood cells, cerebrospinal fluid (CSF), and plasma obtained from suicidal patients.

Studies of the serotonin (5-hydroxytryptamine, 5HT) system in suicidal behavior initially focused on the determination of a metabolite of serotonin known as 5-hydroxindoleacidic acid (5HIAA) in the CSF of depressed and suicidal depressed patients (Agren 1980; Asberg et al 1984; Asberg et al 1976; Meltzer and Lowy 1987; Roy et al 1985; van Praag 1983). An important observation was made that depressed patients with suicidal behavior had a significantly lower level of 5HIAA in the CSF compared with depressed patients with non-suicidal behavior or control subjects (Agren 1980; Asberg et al 1976; Meltzer and Lowy 1987; Nordstrom et al 1994; Van Praag 1982; van Praag 1983). This observation implicated an abnormal serotonergic system in suicidal behavior. Other evidence involving serotonergic mechanisms in suicidal behavior is derived from studies of serotonin uptake and of the serotonin transporter, which mediates the uptake of 5HT, in the platelets of suicidal patients. Several investigators reported that serotonin uptake and serotonin transporter levels are decreased in the platelets of patients with suicidal behavior (Meltzer et al 1981; Perry et al 1983; Rausch et al 1986; Stanley et al 1982). Further evidence implicating serotonergic mechanisms in suicidal behavior is derived from neuroendocrine studies. Fenfluramine-induced prolactin response was found to be decreased in patients with depression compared with normal subjects (Lichtenberg et al 1992; Mann et al 1992).

Several subtypes of serotonin receptors have been identified—about 13 at this time. Of these serotonin receptor subtypes, $5HT_{2A}$ receptors have been shown to be present in the human platelets. It was shown by Pandey et al. (1990) that the B_{max} of $5HT_{2A}$ receptors was higher in depressed patients, but was also significantly higher in suicidal patients compared with non-suicidal depressed patients (Pandey et al 1990). To further examine the specificity of

increased $5HT_{2A}$ receptors in suicidal patients, Pandey et al. (1995) measured $5HT_{2A}$ receptors in the platelets of suicidal patients across diagnostic groups, including bipolar, schizophrenic, and schizoaffective patients. They reported that the platelet $5HT_{2A}$ B_{max} receptor was significantly higher in all suicidal patients irrespective of diagnosis when compared with normal controls and non-suicidal subjects. Those studies provided convincing evidence that increased $5HT_{2A}$ receptors may be associated with suicidal behavior (Pandey et al 1995).

The second line of studies was conducted by performing the dexamethasone suppression test (DST) and determining levels of cortisol in depressed and suicidal patients (Carroll 1982a). Some investigators reported that suicidal patients exhibited DST non-suppression and that DST non-suppression may be a good predictor for eventual suicide, which some patients committed (Yerevanian et al 2004).

Abnormalities of noradrenergic function have been implicated in the etiology of depressive illness; however, noradrenergic studies in suicidal behavior are fewer relative to studies of serotonin function. This may be primarily because of the involvement of serotonin in impulsive-aggressive behavior.

Although these studies provided initial evidence of abnormalities of serotonin function and the HPA axis in suicide, it was not clear if the abnormalities observed in the periphery were also present in the brain of suicidal subjects.

In this review, it is not our intention to review all biological studies in suicide; instead, we will focus on the main findings from studies of serotonin function, signal transduction mechanism, and HPA axis abnormalities in suicide. Recently, abnormalities of immune function have also been implicated in depression and to a certain extent in suicidal behavior. Accordingly, we will also include a brief discussion of studies of immune function in suicide.

3. Serotonergic Function in Suicide

Although initial studies of serotonin and the serotonin receptor subtypes in suicidal patients suggested abnormalities of $5HT_{2A}$ receptors in the platelets of suicidal patients, the major evidence suggesting abnormalities of serotonin receptor subtypes in suicide has come from studies of these receptor subtypes in the postmortem brain of suicide victims by several investigators. Several subtypes of serotonin receptors have been identified and characterized. (See Hoyer et al. (1994).) The serotonin receptor subtypes $5HT_{1A}$ and $5HT_{2A}$ receptors have been extensively studied in the postmortem brain of suicide victims, and to a certain extent the $5HT_{1B}$ receptors have been studied too. The neurotransmitter activity of serotonin is attributed to its binding to 5HT receptor subtypes. These receptors have been determined in postmortem brain samples either by binding technique or by determination of its protein and mRNA expression.

3.1 $5HT_{1A}$ Receptors in Suicide

Alterations in $5HT_{1A}$ receptors have been implicated in the pathophysiology of depression and anxiety. It was therefore not surprising that $5HT_{1A}$ receptors have also been implicated in suicide. $5HT_{1A}$ receptors in the suicide postmortem brain have been generally studied by binding techniques either using homogenate or the auto-radiographic techniques. Arango and colleagues (Arango et al 1995) determined $5HT_{1A}$ receptor sites in the Brodmann areas (BA) 8 and 9 from suicide victims and normal control subjects. Although they didn't find differences in either the B_{max} or K_D of ^{3}H-8-OH-DPAT binding between normal control subjects and suicide victims, when they divided the suicide group into violent and non-

violent subgroups they found that the non-violent suicide group had significantly higher B_{max} values compared with normal control subjects. They also made an interesting observation that ^{3}H-8-OH-DPAT binding increase was observed only in the male suicide victims but not in the female suicide victims. $5HT_{1A}$ receptors have been studied by several other investigators (Arranz et al 1994; Lowther et al 1997; Stockmeier et al 1998); however, they did not find significant changes in the $5HT_{1A}$ receptors in the prefrontal cortex (PFC) of suicide victims compared with control subjects. Matsubara et al. (Matsubara et al 1991) found an increase in $5HT_{1A}$ receptor B_{max} in the PFC of non-violent suicide victims. In another study, Stockmeier et al. (1998) found an increase in $5HT_{1A}$ receptors in the midbrain dorsal raphe nucleus of suicide victims compared with controls. More recently, Stockmeier et al. (2009) reported that while there was no difference in the antagonist binding to $5HT_{1A}$ receptors between depressed suicide subjects and control subjects, the antagonist binding was significantly decreased in outer layers of orbitofrontal cortex obtained from subjects with major depressive disorder. Joyce et al. (1993) found an increase in $5HT_{1A}$ receptor binding sites in the CA-1 area of the hippocampus of the suicide victims compared with control subjects. In summary, the results of $5HT_{1A}$ receptors studied in suicide victims appear to be inconsistent and mixed; an increase in $5HT_{1A}$ receptors in some cortical areas is reported by Joyce et al. (1993), Arango et al. (2001), and Stockmeier et al. (1998), but not by other investigators. However, it does appear that alterations in $5HT_{1A}$ receptors maybe associated with pathophysiology of suicide.

3.2 $5HT_{2A}$ Receptors in Suicide

Among the 5HT receptor subtypes, the role of $5HT_{2A}$ receptors has been studied more comprehensively by several investigators. Initial studies of $5HT_{2A}$ receptors were carried out by binding techniques, using several ligands, such as, ketanserin, spiperone, LSD, etc., and the results of the binding studies in suicide have been generally mixed. The first studies of $5HT_{2A}$ receptors was reported by Stanley and Mann (1983), who observed an increase in $5HT_{2A}$ receptor binding in the BAs 8 and 9 of suicide victims compared to normal control subjects. Subsequent to these studies, a total of about 20 studies of $5HT_{2A}$ receptor binding have been reported. Nine studies, using different ligands, report an increase in the $5HT_{2A}$ receptor binding primarily in the PFC of suicide victims compared with control subjects. Ten other studies did not find any differences in the $5HT_{2A}$ receptor binding between suicide victims and normal control subjects. Although there may be several reasons for this inconsistency in $5HT_{2A}$ receptor studies, the major reason for the inconsistency may be related to the radioligands used for these studies, as several of these ligands label receptors other than $5HT_{2A}$ receptors. It was therefore important to examine either the protein or the mRNA levels of $5HT_{2A}$ receptors in the suicide to specifically examine if $5HT_{2A}$ receptors are involved in the pathophysiology of suicide. Pandey et al. (2002a) examined $5HT_{2A}$ binding, as well as protein and mRNA expression of $5HT_{2A}$ receptors in several regions of postmortem brains obtained in suicide victims. These studies indicated a significant increase in the ^{125}I-LSD binding in the PFC of suicide victims compared with normal control subjects. They also observed that protein expression levels of $5HT_{2A}$ receptors were significantly decreased in both the PFC and hippocampus of suicide victims compared with normal control subjects. However, no significant differences in protein expression were observed in the nucleus accumbens between suicide victims and normal control subjects. Using the immunogold labeling technique, they also determined the cellular localization of $5HT_{2A}$ receptors and found that the expression of $5HT_{2A}$ receptors was most dense in pyramidal neurons (layers III, V and VI) and their apical dendrites. The mean expression levels of $5HT_{2A}$ receptors were significantly greater in the pyramidal cell of layer V of the teenage suicide victims than in control subjects. It was also found that the mean $5HT_{2A}$ mRNA levels were significantly greater in the PFC and hippocampus of teenage suicide victims compared with normal control subjects. More recently, Escriba et al. (2004) found a

significant increase in the expression of mRNA for the $5HT_{2A}$ receptors in the PFC of 12 suicide victims compared with control subjects. Shelton et al. (2009) also observed an increase in the protein expression of $5HT_{2A}$ receptors in major depressive disorder (MDD) subjects with or without suicide compared with control subjects. In summary, the studies of $5HT_{2A}$ receptors strongly indicate that increase in the binding and/or protein and mRNA expression of $5HT_{2A}$ receptors maybe associated with the pathophysiology of suicide.

3.3 $5HT_{2C}$ Receptors in Suicide

One of the serotonin receptor subtypes, known as $5HT_{2C}$ receptor, has been suggested to play a role in regulating mood, appetite, and sexual behavior. This receptor also undergoes post-transcriptional editing and is a substrate for the emanating enzyme that attacks 5 closely placed adenosine residues located within sequences encoding the putative second intracellular domain or receptors and leads to several receptor isoforms. Therefore, some investigators have studied the role of $5HT_{2C}$ receptor editing in suicide. Gurevich et al. (2002) found that in suicide victims who had a history of major depression the pre-mRNA editing for the $5HT_{2C}$ receptor at the C-site was significantly increased; whereas the editing at the D-site was significantly decreased in suicide victims compared with control subjects. In another study, Dracheva et al. (2008) found that $5HT_{2C}$ mRNA editing was different in those subjects with bipolar disorder or schizophrenia who died by suicide compared with normal control subjects. These studies suggested that altered pre-mRNA editing of $5HT_{2C}$ receptors maybe involved in the pathophysiology of suicidal behavior. Pandey et al. (2006) determined the protein and mRNA expression of $5HT_{2C}$ receptors in the PFC, hippocampus, and choroid plexus of suicide victims and normal control subjects and found higher protein expression of $5HT_{2C}$ receptors in the PFC but not hippocampus or choroid plexus of suicide victims compared with controls. In summary, these studies suggest alterations of $5HT_{2C}$ pre-mRNA editing and expression of $5HT_{2C}$ receptors in the PFC of suicide victims.

3.4 Brain Imaging Studies of Serotonin Functions

Since postmortem brain studies have generally shown abnormalities of serotonin indices, such as receptors and metabolites of 5HT, it is important to examine if such abnormalities in suicidal behavior exists *in vivo*. Thus $5HT_{1A}$ and $5HT_{2A}$ receptors have been studied using imaging techniques. Imaging studies of serotonin function have also been performed after administration of serotonergic agents, such as fenfluramine. Audenaert et al. (2001) determined $5HT_{2A}$ receptor population in patients who had recently attempted suicide, using a highly specific radio-iodinated $5HT_{2A}$ receptor antagonist using single photon emission tomography (SPET). They found a decrease in $5HT_{2A}$ binding index in deliberate self-harm patients compared with controls. They concluded that the brain SPET of the $5HT_{2A}$ receptors in attempted suicide patients shows decreased frontal binding index, which may be related to a decrease in the number or binding affinity of the receptors.

In a subsequent study this group (van Heeringen et al 2003) found a significantly lower binding potential of $5HT_{2A}$ receptors in patients who attempted suicide compared with controls. This decrease appears to be correlated with hopelessness.

Thus *in vivo* and *ex vivo* studies of $5HT_{2A}$ receptor are not consistent. The reason for this inconsistency is unclear and further *in vivo* studies are needed to clarify these discrepancies.

4. Noradrenergic Function in Suicide

While abnormalities in both serotonergic function as well as noradrenergic functions have been studied in suicide, the major focus has been on the study of serotonin function as reviewed in the previous pages. This may be primary due to the involvement of serotonin in impulsive-aggressive behavior, which has been shown to be a major risk factor in suicidal

behavior. Initial studies of norepinephrine function associated with suicidal behavior were carried out by determining the levels of norepinephrine or its metabolite 3-methoxy 4-hydroxy phenyl glycol in the CSF or urine of suicidal patients. Since the major rate limiting factor in the synthesis of norepinephrine from phenylalanine is the enzyme tyrosine hydroxylase (TH), the role of TH has also been studied in suicide. The other noradrenergic studies are the determination of receptors for norepinephrine, primary α-adrenergic receptors and β-adrenergic receptors. These studies are briefly described and reviewed in the following pages.

4.1 Norepinephrine and MHPG in Suicide

MHPG is a major metabolite of norepinephrine, and thus both norepinephrine and MHPG have been studied either in the urine, plasma, or CSF of suicidal patients. In an initial study, Ostroff et al. (1982) reported that depressed patients who made serious suicide attempts have significantly lower 24-hour NE to epinephrine ratios than depressed patients who made no suicide attempts. Secunda et al. (1986) reported that those patients with suicidal behavior have lower urinary MHPG and lower plasma level of MHPG compared with patients with no suicidal behavior. Brown et al. (1979) have also reported that suicidal patients have significantly higher CSF levels of norepinephrine and higher levels of MHPG as compared to non-suicidal patients. On the other hand, Roy et al. (1985) reported higher levels of norepinephrine in the plasma compared with control subjects but no differences in the plasma MHPG.

There are few studies of norepinephrine and MHPG in the postmortem brain. For the most part, these studies have been related to the lethality of suicide attempts. For example, Sher et al. (2006) reported that MHPG levels were negatively correlated with the maximum lethality of suicide attempts in bipolar patients. Roy et al. (1985), however, did not find any significant relationship between the levels of MHPG in the CSF for schizophrenic patients. Tripodianakis et al. (2002) found that urinary MHPG was significantly higher in all diagnostic groups who attempted suicide.

Several other investigators have studied the relationship of CSF MHPG and suicidal behavior; however it is generally negative, as reviewed by Lester (1995). Agren and Niklasson (1986) reported lower CSF MHPG in depressed suicide attempters compared to non-attempters. In a recent study, Galfalvy et al. (2009) examined the relationship of CSF MHPG with suicidal behavior. They found that lower baseline CSF MHPG was associated with increased risk of making a fatal or non-fatal suicide attempt in a year follow-up period following presentation with a major depressive episode. Lower CSF MHPG also correlated with higher medical lethality of future suicidal act. Thus, lower CSF MHPG may be used as a predictor of future suicidal attempts or completed suicide.

There are few studies of TH in suicide, and the results appear to be inconsistent both in terms of the LC neurons and LC immunoreactivity. While Arango et al. (1996) observed a decreased number of neurons, others did not. Ordway et al. (1994a) observed an increased TH immunoreactive protein levels, and Baumann et al. (1999) found no change. Biegon and Fieldust (1992) found a decrease in TH immunoreactivity in suicidal subjects.

4.2 Adrenergic Receptors in Suicide

4.2.1 Beta-Adrenergic Receptors in Suicide—The major receptors for norepinephrine have been classified as α_1-, α_2-, and β-adrenergic receptors. Each of these receptor types is further divided into at least three sub-types based on molecular and pharmacological studies. One of the earliest studies determining β-adrenergic receptors in the postmortem brain of suicide victims was reported by Meyerson et al. (1982) who found a

trend toward an increase in β-adrenergic receptor binding in the cortical tissues obtained from suicide victims compared with control subjects. Mann et al. (1986) found a significant increase in β-adrenergic receptor binding in the frontal cortex of suicide victims compared with control subjects. This was supported by another group (Arango et al 1990), which observed a significant increase in the B_{max} of β-adrenergic receptors in the outer layers of the grey matter in suicide victims compared with control subjects. A lower number of β-adrenergic receptors in the postmortem brain of suicide victims has been reported by De Paermentier et al. (1990). Thus, the results of studies of β-adrenergic receptors in the postmortem brain of suicide victims appear to be mixed. Some investigators found an increase in β-adrenergic receptors, while others did not. Future studies of β-adrenergic receptors maybe focused on determination of protein and mRNA expression of β-adrenergic receptors.

4.2.2 Alpha-Adrenergic Receptors in Suicide—Either a decrease (Gross-Isseroff et al 1990) or no change in α_1-adrenergic receptors has been reported in the postmortem brain of suicide victims. The Garcia-Sevilla group (Escriba et al 2004; Garcia-Sevilla et al 1999a; Gonzalez et al 1994; Meana and Garcia-Sevilla 1987) has extensively studied α_2-adrenergic receptors. They found a significant increase in the number of α_2-adrenergic receptors in the hippocampus and the external layers of the frontal cortex of suicide victims compared with matched control subjects. On the other hand, Ordway et al. (1994b) reported that the agonist binding (i.e., p-[^{125}I]-iodoclonidine) and not the antagonist binding (i.e., [^{3}H]-yohimbine) was significantly greater in the locus coeruleus from suicide victims compared with control subjects. Garcia-Sevilla's group also determined the protein and mRNA expression of α_2-adrenergic receptors in the postmortem brain of suicide victims and showed that the immunolabeling of α_2-adrenergic receptors in the PFC was significantly increased in suicide victims compared with control subjects (Escriba et al 2004; Garcia-Sevilla et al 1999b). Underwood et al. (2004) found that the α_2-adrenergic receptor was decreased in alcoholic suicide victims compared with control subjects in the dorsolateral prefrontal cortex and ventral-lateral B-46 and B-47 of the PFC. In summary, these studies of α_2-adrenergic receptors in suicide appear to be slightly more consistent in the sense that most investigators find α_2-adrenergic receptors to be increased in the cortex and hippocampus of suicide victims compared with normal control subjects. The studies of α_1-adrenergic receptors are few but some studies, especially the studies Underwood et al. (2004), find decreased α_1-adrenergic receptor in the postmortem brain of suicide victims. Only one study of protein and mRNA expression by the group of Garcia-Sevilla (Escriba et al 2004) found increased protein and mRNA expression of α_2-adrenergic receptors.

There are some studies of glutamate and GABA as well as cholinergic system in suicide. These studies, which are small in number, have not been reviewed in this paper.

5. Receptor-linked Signaling System in Suicide

The functional role of receptors lies in their ability to activate a signal transduction system causing not only a functional and behavioral response but also the transcription of some several important genes. The responses of the altered receptors such as $5HT_{2A}$ receptor may result in an altered functional response as well as alterations in the levels and sensitivity of individual components of the signaling cascade. It is therefore not surprising that not only the receptors but also their signaling system have been studied in the postmortem brain of suicide victims and control subjects by determination of the important components of the signaling cascade.

Receptor activation by neurotransmitters or agonists causes the transfer of signals from cell surface receptors to the nucleus along several signaling systems that have been implicated in

suicide. The phosphoinositide (PI) and adenylyl cyclase (AC) signaling systems have been widely studied and implicated in the pathophysiology of mood disorders and suicide. In the PI signaling system, activation of the G protein-coupled receptors, such as the $5HT_{2A}$ receptor, causes the hydrolysis of phosphatidylinositide-4,5 bisphosphate (PIP_2) by the PI-specific enzyme phospholipase C, resulting in the formation of two second messengers diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3). DAG activates the phospholipid- and the calcium-dependent enzyme protein kinase C (PKC) and increases its affinity for calcium. PKC subsequently activates several transcription factors, such as CREB and GSK-3β which are part of another pathway known as the Wnt signaling pathway. PKC also phosphorylates important substrates including myristoylated alanine-rich protein kinase C substrate (MARCKS), and this activation also results in transcription of several important genes, such as BDNF. Another signaling pathway implicated in mood disorders and suicide is the AC signaling system whose components are similar to those of the PI signaling system. Activation of certain receptors, such as β-adrenergic, causes the conversion of ATP to cyclic-AMP with the second messenger and activates a phosphorylating enzyme known as protein kinase A (PKA). PKA, again like PKC, activates several transcription factors, including CREB, finally resulting in the transcription of several important genes. The role of several of these components of the PI and AC signaling systems has been studied in the postmortem brain of suicide victims and is briefly discussed below.

5.1 G Proteins in Suicide

G proteins are a ubiquitous family of proteins that play a crucial role in transducing extracellular signals to cellular targets, thus transmitting messages from cell surface receptors to cellular effectors. A number of receptors are coupled to their effectors through a G protein, for example, AC, PLC phospholipase A_2 (PLA_2), and ion channels (Gilman 1984; Gilman 1987). G proteins are heterodimers, consisting of three subunits α, β, and γ, and each subunit is coded by a specific gene (Clapham and Neer 1997; Gilman 1984; Gilman 1987; Neer 1995). The α subunits of the G proteins have been divided into four major classes G_S, G_i, G_q and G_{12} and more than 16 types of Gα protein have been identified (Gilman 1984; Gilman 1987; Neer 1995; Simon et al 1991). $G_s\alpha$ stimulates AC (Birnbaumer et al 1990); whereas, $G_i\alpha$ mediates the inhibition of AC (Kurose et al 1991). $G_s\alpha$ is coupled to the PLC enzyme that is involved in PI hydrolysis (Fields and Casey 1997). $G_S\alpha$ and $G_i\alpha$ have been shown to be operative in the development of calcium and potassium channels (Birnbaumer et al 1990; Brown et al 1995). Since G proteins play an important role in signal transduction mechanisms, their roles in suicide have been studied by several investigators. Cowburn et al. (1994) found that basal and $GTP_\gamma S$-stimulated AC activity was significantly lower in suicide victims compared with control subjects, and that this effect was more profound in those suicide victims who died by violent means or had a history of depression. However, they did not find differences in the protein expression levels of $G_S\alpha$ or $G_i\alpha$ between control and suicide victims. Pacheco et al. (1996) found that GTPγS-stimulated PI hydrolysis was significantly decreased in depressed suicide victims compared with normal control subjects. They also found that the $G_S\alpha$ protein expression was significantly decreased in BA 10, but not in BA 8 or BA 9 of suicide victims compared with control subjects. Dowlatshahi et al. (1999) did not find any significant differences in the protein expression level of $G_S\alpha$ or $G_i\alpha$ or basal or forskolin-stimulated AC activity in suicide victims compared with control subjects.

Dwivedi et al. (2002b), we compared the protein expression levels of the various subunits of G proteins between total suicide victims and normal controls (including adult and teenage suicide) and found that the levels of $G_{i2}\alpha$ and $G_O\alpha$ were significantly decreased and the level of $G_S\alpha$-S was significantly increased in the PFC of suicide victims compared with normal control subjects. We did not find any significant differences in the levels of $G_S\alpha$-L,

$G_{i1}\alpha$ or $G_q\alpha$, $G\beta$, or $G\gamma$ subunits between suicide victims and normal control subjects. We then analyzed the G protein expression levels in suicide subjects by dividing them into adult (age 20 years and above) or teenage (age 13–19 years) groups. We again observed that the mRNA levels of $G_i2\alpha$ and $G_O\alpha$ were significantly decreased and $G_S\alpha$-S were significantly increased in the PFC of adult suicide victims compared with adult control subjects, without any change in mRNA levels of $G_i1\alpha$. On the other hand, there were no significant differences in the mRNA levels of any of G protein subunits between teenage controls and teenage suicide victims.

5.2 Phospholipase C in Suicide

The stimulation of G protein-coupled receptors causes the activation of the effector PLC, resulting in the hydrolysis of the substrate phosphoinositide$_2$ (PIP_2) into DAG and IP_3, and several neurotransmitter receptors use this pathway. PLC isoforms are classified into three major families and further into several subtypes based primarily on sequence homology (Anderson et al 1990; Exton 1994; Rhee and Choi 1992). These three different families include PLC β, PLC γ, and PLC δ. PLC is regulated primarily by G_q or G_O families of proteins, specifically Gq and G_{11}. Studies of the role of PLC in suicide are very limited. Pacheco et al. (Pacheco et al 1996), who determined the protein expression levels of PLC β_1 in the PFC of suicide victims with major depression and normal control subjects, did not find any significant differences between suicide victims and normal control subjects in the expression of PLC β. We have reported the only other study of PLC isozymes in the postmortem brain of suicide victims (Pandey et al 1999). We observed that the mean PI-PLC activity in BA8 and BA9 was significantly decreased in both the membrane as well as cytosol fractions of the PFC of the teenage suicide victims compared with normal controls subjects. We also found that the protein expression of PLC β_1 was significantly decreased in both the membrane and cytosol fractions of the PFC of teenage suicide victims compared with normal control subjects, whereas there were no significant differences in the protein expression levels of PLC δ_1 or PLC γ_1 between the suicide and the normal control groups. These results suggest that the PI-PLC activity and the protein expression of PLC β_1, but not the other PLC isozymes are significantly decreased in the postmortem brain of teenage suicide victims.

5.3 Protein Kinase C in Suicide

PKC, an important component of the PI signaling system, is a key regulatory enzyme that is present in various tissues and has been shown to be a family of at least structurally related isozymes. On the basis of molecular structure and enzymatic characterization, the PKC family has been sub-grouped into three classes: conventional (α, βI, βII and γ) (Hug and Sarre 1993; Kiley and Jaken 1994), novel (δ, ε, η and θ) (Nishizuka 1992), and atypical (ι, κ, λ, τ) (Akimoto et al 1994; Ono et al 1989; Tanaka and Nishizuka 1994). Marked differences occur in the distribution of PKC isozymes. Most PKC isozymes are present in the brain (Nishizuka 1995; Ono et al 1988; Shearman et al 1987); whereas in platelets, only α, β and δ isozymes have been reported (Baldassare et al 1992; Grabarek et al 1992). PKC is involved in the modulation of many neuronal and cellular functions, such as neurotransmitter synthesis and release, regulation of receptors and ion channels, neuronal excitability, gene expressions, and cell proliferation (Nishizuka 1988). PKC is activated by DAG formed in the PI signaling system and, once activated, it causes the activation of transcription factors such as CREB, which is involved in the transcription of important genes (Nichols et al 1992; Riabowol et al 1988; Xie and Rothstein 1995).

Although PKC has been implicated in the pathophysiology of mood disorders, more specifically bipolar disorders, schizophrenia and Alzheimer's disease (Cole et al 1988; Dean et al 1997; Friedman et al 1993; Manji et al 1999; Masliah et al 1990; Pandey et al 2002b;

Shimohama et al 1993; Stokes and Hawthorne 1987), the role of PKC in suicide has not been extensively studied (Pandey et al 1997; Pandey et al 2004). Besides the two studies of Pandey et al. (1997; Pandey et al 2004) in teenage suicide victims, there appears to be only one other study in suicide victims by Coull et al. (Coull et al 2000). Pandey et al. (Pandey et al 1997) found that the B_{max} of [^{3}H]PDBu binding was significantly decreased in both membrane and cytosol fractions obtained from the PFC of teenage suicide victims compared with normal control subjects. They also reported (Pandey et al 2004) that the PKC activity was significantly decreased in the membrane and the cytosol fractions of the PFC and hippocampus of teenage suicide victims compared with control subjects. They also found that the protein expression levels of PKCα, PKC βI, PKC βII and PKC γ were significantly decreased in the membrane and cytosol fractions of the PFC and hippocampus of teenage suicide victims compared with control subjects.

Although the pathophysiological significance of decreased PKC in suicide victims in not known at this time, one of the mechanisms by which PKC modulates cellular responses is the phosphorylation of numerous substrate proteins, such as MARCKS (Aderem 1992; Blackshear 1993), and growth associated protein $(GAP)_{43}$. Both these proteins have been implicated in the pathophysiology of mood disorders (Dean et al 1997; Lenox et al 1992; Manji et al 2000; Pandey et al 2002b; Wang et al 2000; Watson et al 1994). The levels of MARCKS have been studied in subjects with mood disorders, and the results suggest that the level of MARCKS may be altered in platelets of patients with bipolar disorder (Pandey et al 2002b). There have been only two studies of MARCKS in the postmortem brain of suicide victims. McNamara et al. (1999) did not observe any significant differences in the mRNA expression of MARCKS between suicide and normal control subjects, either in the hippocampus or in the PFC. Pandey et al. (2003) did not find any significant differences in the protein expression levels of MARCKS between suicide victims and control subjects, either in the membrane or in the cytosol fractions of PFC and hippocampus. However, they found that the protein expression of MARCKS was significantly increased in PFC and hippocampus of depressed suicide victims compared with normal control subjects. MARCKS protein expression was significantly decreased in the membrane fraction of suicide victims with other diagnosis. These results suggested differential regulation of MARCKS in depressed suicide and suicide victims with other mental disorders. They also found that PKC mediated phosphorylation of MARCKS was significantly decreased in the PFC of suicide victims compared with control subjects in the membrane but not in the cytosol fractions. These studies suggest specific abnormalities of PKC isozymes as well as its substrate MARCKS in the pathophysiology of suicide.

5.4 Protein Kinase A in Suicide

PKA, a key component of the AC signaling systems, is activated by camp, and the activated PKA phosphorylates several intracellular proteins and activates transcription factors such as CREB. In the absence of cAMP, the PKA holoenzyme exists as an inactive tetramer composed of two catalytic subunits bound to a regulatory subunit dimer. On the basis of elution patterns, two different PKA isozymes, known as PKA I and PKA II, have been identified. These two isozymes have been shown to be composed of two different R subunits, known as RI and RII, which are further composed of subunits known as RIα and RIβ, and RIIα and RIIβ. In addition, three catalytic subunits, known as Cα, Cβ, and Cγ, have also been identified. Each R subunit has two cAMP binding sites, and in activation and binding with cAMP each R subunit dissociates into a dimeric R subunit complex and two monomeric active C subunits (Skalhegg and Tasken 2000).

The role of PKA in mood disorders has been studied by many investigators (for review, see Dwivedi et al., (Dwivedi and Pandey 2008)). However, the studies of PKA in postmortem brain of suicide victims are limited. In a study of postmortem brain samples obtained from

suicide victims, Dwivedi et al. (2002a) reported that ^{3}H-cAMP binding and PKA activity was significantly decreased in the PFC of suicide victims. In a subsequent study, Dwivedi et al. (2004) also observed that the protein and mRNA expression of PKA subunits, PKA RIIβ, and Cβ were significantly decreased in the PFC of suicide subjects relative to normal controls.

In order to examine if abnormalities of PKA are also involved in the pathophysiology of teenage suicide, Pandey et al. (2005) determined the cAMP binding to PKA, PKA activity, and the protein and mRNA expression of different subunits of PKA in cytosol and membrane fractions obtained from PFC, hippocampus, and NA of the postmortem brain from teenage suicide victims and non-psychiatric control subjects. They found that PKA activity was significantly decreased in the PFC but not hippocampus of teenage suicide victims compared with control subjects. However, the protein and mRNA expression of only two PKA subunits, i.e., PKA RIα and PKA RIβ, but not any other subunits, such as Cα, Cβ, RIIα, or RIIβ, was observed to be decreased in the PFC of teenage suicide victims compared with control subjects. These results in the teenage suicide victims, although similar in some respects to those observed in adult suicide victims by Dwivedi et al. (Dwivedi et al 2002a; 2004), were also dissimilar in some other respects. For example, decreased cAMP binding and PKA activity was observed in both adult and teenage suicide victims. Decreased RIIα and Cβ were found in the adult suicide victims, whereas the RIα and RIβ subunits were abnormal in the teenage suicide victims. The significance and implications of these observations with regard to the pathophysiology of teenage and adult suicide are unclear at this time.

5.5 Transcription Factor CREB in Suicide

Activation of transcription factors is the final step in a signal transduction pathway, which is mediated by the binding of a cell surface receptor with an agonist. Transcription factors can alter the expression of specific genes. Activation of PKC, as well as of PKA, causes the phosphorylation of several transcription factors, such as the AP-1 family (Jun-B, Jun-D), and CREB (Holian et al 1991). CREB is one of the important transcription factors and has been recently implicated in the pathophysiology of depression and suicide. That CREB could possibly be involved in such disorders as depression and suicide is evident from studies showing increased expression of CREB in the postmortem brain of depressed patients treated with antidepressants (Dowlatshahi et al 1998) and from the observation that treatment with almost all antidepressants caused an increase in CREB in the rat brain (Nibuya et al 1996). Again, studies of CREB in suicide seem to be very limited, although Yamada et al. (2003) determined CREB protein and its phosphorylated form in the orbital frontal cortex of antidepressant-free patients with major depression and found that the immunoreactivity of both CREB and its phosphorylated form were significantly decreased in depressed subjects compared with normal control subjects.

Dwivedi et al. (2003a) found that the protein expression of CREB was significantly decreased in the nuclear fractions of both the PFC and hippocampus obtained from suicide victims compared with normal control subjects. They also observed that this decrease in protein expression levels was associated with a significant decrease in the mRNA levels of CREB in both the PFC and hippocampus of suicide victims compared with normal control subjects. The CRE-DNA binding activity was significantly decreased in the nuclear fractions of both the PFC as well as hippocampus of suicide victims compared with normal control subjects.

Pandey et al. (2007) determined CREB in the postmortem brain obtained from teenage suicide victims and normal control subjects. They found a significant decrease in the protein and mRNA expression levels of CREB in the PFC of teenage suicide victims compared with

controls and a significant decrease in the CRE-DNA binding in teenage suicide victims relative to controls. However, they did not find any significant difference in protein or mRNA expression or in CRE-DNA binding between teenage suicide victims and normal controls in the hippocampus. These observations suggest some differences in the expression of CREB between adult and teenage suicide victims. While CREB expression was found to be decreased in the PDF of both adult and teenage suicide, CREB expression was significantly decreased in the hippocampus of adult but not teenage suicide victims. These observations indicate another subtle difference in the neurobiology between teenage and adult suicides.

6. BDNF and Trk-B Receptors in Suicide

As described in the previous section, CREB, which is a transcription factor, plays an important role in the regulation of several genes, including BDNF. Activation of CREB increases BDNF transcription through the Ca^{2+} and cAMP response element within exon 3 of BDNF (Finkbeiner 2000). BDNF is a member of the neurotrophin family, which includes nerve growth factor and neurotrophins (Huang and Reichardt 2001). Neurotrophins promote the growth and development of immature neurons and enhance the survival and function of specific neuronal populations, including neuronal growth, plasticity, phenotype maturation, synthesis of proteins, and synaptic functioning (Altar et al 1997; Bartrup et al 1997; Thoenen 1995). The suggestion that BDNF may play a role in the pathophysiology of suicide is derived from studies showing that treatment with antidepressants caused an increase in BDNF in the rat brain (Nibuya et al 1995).

Dwivedi et al. (2003b) determined the protein and mRNA expression levels of BDNF in the PFC and hippocampus of suicide victims and normal control subjects and found that the protein and mRNA expression level of BDNF was significantly decreased both in the PFC and hippocampus of suicide victims compared with normal control subjects.

BDNF produces its physiological effects by binding with the TrkB receptors, which exist as truncated and full-length isoforms, both of which are functionally important in mediating the functions of BDNF (Barbacid 1994; Dechant et al 1994; Middlemas et al 1991). Therefore, the protein and mRNA expression of TrkB receptors in the PFC and hippocampus of suicide victims and normal control subjects has also been studied (Dwivedi et al 2003b). It was found that the protein and mRNA expression levels of full-length TrkB receptors, but not of the truncated isoform, were significantly decreased in the PFC and hippocampus of suicide victims compared with control subjects. Although BDNF has not been studied in the postmortem brain of suicide victims by other investigators, a recent study (Chen et al 2001) indicated that the protein expression of BDNF was increased in the postmortem brain of patients with depression who were treated with antidepressants (Chen et al 2001). Pandey et al. determined protein and mRNA expression of BDNF and TRκB receptors in victims and normal controls. They found decreased protein and mRNA expression of BDNF and full-length TRκB receptors in the PFC but not hippocampus of teenage suicide victims. The observation that both BDNF levels and TrkB receptor levels are decreased in the postmortem brain of suicide victims may have important implications. The structural abnormalities in the brain of patients with depression and during stress could be associated with a decrease in BDNF and the TrkB receptors.

7. HPA Axis Function in Suicide

Depression and stress are major risk factors for suicide. An abnormal HPA axis in depression is one of the most consistent findings in biological psychiatry (Holsboer 2000; Nemeroff 1996; Pariante and Miller 2001). Most patients with depression have been shown to have increased concentrations of cortisol in plasma and CSF, increased cortisol response

to adrenocorticotropic hormone (ACTH), and a deficient feedback mechanism, as evidenced by an abnormal DST (Carroll 1982b; Gold et al 1988; Holsboer 2000; Nemeroff 1996; Pariante and Miller 2001) and enlarged pituitary and adrenal glands (Holsboer 2000).

There is also a strong association between HPA axis dysfunction and suicide. Yerevanian et al. (Yerevanian et al 2004) found that DST non-suppressors were significantly more likely to commit and complete suicide than DST suppressors. Other investigators have also found an association between DST non-suppression and suicide (Coryell and Schlesser 1981; Lester 1992; Norman et al 1990; Yerevanian et al 2004; Yerevanian et al 1983). A meta-analysis found that suicide completions but not attempts were associated with DST non-suppression (Coryell and Schlesser 2001).

The release of corticotropin releasing factor (CRF) from the paraventricular nucleus (PVN) of the hypothalamus causes the release of ACTH from the pituitary, which stimulates the production of glucocorticoids (cortisol in humans, corticosterone in animals) from the adrenals. Glucocorticoids regulate the HPA axis through a negative feedback mechanism while binding to soluble glucocorticoid receptors in the pituitary and the hypothalamus and inhibiting the release of CRF and ACTH (Owens and Nemeroff 1991; Reul and de Kloet 1985).

In order to examine if abnormal HPA axis in suicide is related to changes in CRF and or altered corticoid receptors, some investigators have examined these components of HPA axis in the postmortem brain of suicide victims.

Nemeroff et al. (1988) have reported a significant decrease in the number of CRF receptor binding sites in the frontal cortex of suicide victims compared with controls. A shift in the ratio of CRF-R1/R2 has also been reported in the pituitary of suicide victims (Hiroi et al 2001). CRF mRNA levels have been found to be increased in the PVN of depressed patients (Raadsheer et al 1994). Although there is preliminary evidence to suggest alterations of CRF receptors in suicide, it is not clear which receptor subtypes are altered in depression or in suicide.

Meralli et al. (Merali et al 2004; Merali et al 2006) found increased levels of CRF and CRF immunoreactivity in the frontopolar cortex of suicide victims compared with control subjects. This was associated with decreased levels of CRF-R1 receptor mRNA but not CRF-R2 mRNA (Merali et al 2004). Taken together, these studies in the adult suicide brain do suggest an increase in CRF levels and a decrease in CRF-R1 but no change in CRF-R2 receptors.

The reasons for dysregulated HPA axis in depressed or suicidal patients are not clear, but it is believed that glucocorticoid-mediated feedback inhibition is impaired in major depression since administration of synthetic glucocorticoid dexamethasone (DEX) does not cause suppression of cortisol in these patients (Owens and Nemeroff 1993; Pariante and Miller 2001). The feedback regulation of the HPA axis by glucocorticoids is mediated through two different intracellular receptor subtypes, known as mineralocorticoid (MR) and glucocorticoid receptors (GR) (Reul and de Kloet 1985). It has been observed that MR have a high affinity for endogenous cortisol and that stress plays a role in the diurnal regulation of this hormone. However, GR have a high affinity for DEX and a lower affinity for endogenous cortisol. It is therefore believed that GR are more important in the regulation of the stress response when endogenous levels of glucocorticoids are high. Corticoid receptors may play an important role in depression and in dysregulation of the HPA axis.

Both GR and MR are present in high concentrations in different areas of human brain, such as the PFC, hippocampus, amygdala, locus coeruleus, and hypothalamus, as shown by *in*

situ hybridization and autoradiographic techniques. However, the studies of GR and MR in the postmortem brain are limited. Webster et al. (Webster et al 2002) and Perlman et al. (Perlman et al 2004) have observed decreased levels of GR mRNA in the PFC and hippocampus of unipolar, bipolar, or schizophrenic subjects, providing preliminary evidence for the alteration of GR in those patients; however, it has not been studied in suicidal patients.

In a preliminary study, Pandey et al. (2010) have reported decreased protein expression of GR but not MR in the PFC of teenage suicide victims as compared to controls. In order to understand the mechanism of dysregulation of the HPA axis in suicide further studies of HPA components such as CRF, GR, and MR need to be carried out in suicide brains.

8. Cytokines and Suicide

There are many interactions between neural, immune, and neuroendocrine systems, and this has led to the question of whether the immune system may also be involved in some of the brain-related disorders, such as depression (Anisman et al 2002; Hopkins and Rothwell 1995; Kronfol and Remick 2000; Muller and Ackenheil 1998). In recent years, it has been suggested that depression, which is one of the major psychiatric disorders known to be related to changes in the neuroendocrine system, may also be related to or caused by changes in the immune system.

Cytokines are a diverse group of proteins that can be considered as the hormones of the immune system. These small molecules are secreted by various cells and act as signals between the cells to regulate the immune responses to injury and infection. The responses of cytokines are mediated through cytokine receptors. As is the case with other receptors, specific cytokine receptors respond to the presence of specific cytokines and thus produce their physiological responses. Cytokine receptors are present both in soluble forms and associated with the membranes.

Although the role of cytokines and immune dysregulation has been studied in great detail in patients with mood disorders and schizophrenia, their role in suicide is less clear. Since both depression and stress are major risk factors for suicide, it is quite likely that abnormalities of pro-inflammatory cytokine may be associated with the pathophysiology of suicide. There is also some direct and indirect evidence suggesting a relationship between immune dysregulation and suicide. Steiner et al. (Steiner et al 2008) have found increased microgliosis in the postmortem brain of suicide victims with affective disorders and schizophrenia compared with normal control subjects. Goodwin and Eaton (2005) found a significant association between asthma and increased suicidal ideation and suicide attempts among adults in the community. Goodwin et al. (2005) also found that youth who are hospitalized for asthma have higher than expected levels of suicidal ideation. That an abnormality in cytokines may be associated with suicidal behavior is supported by a recent report by Tonelli et al. (2008) that found increased mRNA expression of interleukin (IL)-4 and IL-3 in the PFC of female suicide victims and IL-13 in male suicide victims compared with normal control subjects. In sum, these studies suggest that cytokines may be abnormal in suicide. Lindqvist et al. (2009) have observed increased levels of IL-6 in the CSF of suicide attempters.

Although abnormal levels of cytokines are observed in the serum of patients with depression, it is not clear if there are also abnormal levels of cytokines in the brain. The immunological aspects of the neurobiology of suicide have been reported by Steiner et al. (2008) but the cytokines in the brain of suicide victims or subjects with depression have not been systematically studied. Future studies need to examine the levels of proinflammatory cytokines and their receptors in the brain of suicide victims.

9. Summary and Conclusion

Depression is a major risk factor for suicide behavior and suicide. It is therefore often assumed that some of the neurobiological factors associated with depression may also be associated with suicide. However, schizophrenia, personality disorders, and substance abuse, whose neurobiology may be different than depression, are other risk factors for suicide. Furthermore, not all depressed patients commit suicide. The other strategy for neurobiological studies in suicide relates to the study of suicidal patients, i.e., those patients who have attempted suicide or have serious suicidal ideation. Although previous suicide attempts are one of the greatest risk factors for suicide, only a small percentage of suicide attempters complete suicide.

These observations raise a two important points: 1) the neurobiology of suicide needs to be examined as a separate entity rather than in combination with other co-morbid illnesses; and 2) studies of the brain or postmortem brain are more appropriate for studies of suicide neurobiology even though they may have many limitations.

In this review, we have summarized and critically discussed the studies related to neurobiological abnormalities in suicide using postmortem brain samples obtained from suicide victims and control subjects. Our review focuses specifically on the studies involving the monoamine receptors, such as 5HT and NE, and the components of the two signaling cascades, PI and AC, to which these receptors are linked. We also included in our review the role of some transcription factors and target genes. Another focus of our review is the discussion of possible similarities and differences in the neurobiological abnormalities between adult and teenage suicide.

These studies, primarily using postmortem brain samples obtained from suicide victims, observed increases in the serotonin receptor subtype known as the $5HT_{2A}$ receptor, as well as abnormalities of another serotonin receptor subtype known as $5HT_{1A}$. These receptors are linked to two signaling cascades, known as the PI and the AC cascades. In order to examine if the abnormalities of the receptors also have important functional consequences, and/or are causing changes downstream in the signaling cascade, the various components of these signaling cascades have recently been studied in the postmortem brain of suicide victims. The results, although not always consistent, do indicate abnormalities in the serotonin receptor subtypes, along with abnormalities of G proteins and of the effector PLC, as well as of the phosphorylating enzyme PKC. The enzyme PKC activates a transcription factor known as CREB, which in turn causes transcription of important target genes involved in CNS functions. These studies further revealed that not only the transcription factor CREB is decreased but also the target gene known as BDNF is decreased in the postmortem brain of suicide victims. BDNF produces its physiological effects primarily by interacting with tyrosine kinase receptors, and it has been reported that the TrkB receptors might also be abnormal in the postmortem brain of suicide victims.

Another neurotransmitter system implicated in suicide is the noradrenergic system. Although there have been relatively few studies of the noradrenergic system compared with studies of the serotonergic system, obviously because of its involvement with impulsive aggressive behavior, nonetheless, the studies of the AC signaling system also indicate abnormalities of the α-adrenergic receptors and of the effector AC, as well as of PKA. PKA and PKC, which activate the transcription factor CREB, converge at the level of the transcription factor. Abnormalities of this transcription factor and of its target gene receptors in suicide may be related to, and/or caused by, abnormalities in either or both signaling systems, or may be independent of the upstream events. Studies of monoamine receptors and of these two signaling cascades have been the focus of this review.

The studies of receptors and of receptor function, including the signaling cascades, do provide initial leads suggesting that there may be abnormalities of receptor subtypes and of certain specific components of the signaling systems in suicidal behavior. In this review, we have both summarized and integrated the various studies of postmortem brain samples from suicide victims and have also examined if the observed abnormalities have any functional consequences in terms of the responsiveness of the signaling cascade and their signaling molecules.

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