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# Biological basis of suicide and suicidal behavior

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## Abstract

**Objective—**Suicide is a major public health concern as each year 30,000 people die by suicide in the US alone. In the teenage population, it is the second leading cause of death. There have been extensive studies of psychosocial factors associated with suicide and suicidal behavior. However, very little is known about the neurobiology of suicide. Recent research has provided some understanding of the neurobiology of suicide, which is the topic of this review.

**Methods—**Neurobiology of suicide has been studied using peripheral tissues, such as platelets, lymphocytes, and cerebral spinal fluid obtained from suicidal patients or from the postmortem brains of suicide victims.

**Results—**These studies have provided encouraging information with regard to the neurobiology of suicide. They show an abnormality of serotonergic mechanism, such as increased serotonin receptor subtypes and decreased serotonin metabolites, such as 5-hydroxyindoleacetic acid. These studies also suggest abnormalities of receptor-linked signaling mechanisms, such as phosphoinositide and adenylyl cyclase signaling mechanisms. Other biological systems that appear to be dysregulated in suicide are the hypothalamic-pituitary-adrenal (HPA) axis, and abnormalities of neurotrophins and neurotrophin receptors. More recently, several studies also indicate abnormalities of neuroimmune functions in suicide.

**Conclusions—**These studies have been discussed in detail in the following review. Some encouraging information has emerged, primarily related to some of these neurobiological mechanisms. It is hoped that neurobiological studies may eventually result in identifying appropriate biomarkers for suicidal behavior as well as appropriate therapeutic targets for its treatment.

### Keywords

brain-derived neurotrophic factor; cAMP response element-binding protein; cytokines; hypothalamic-pituitary-adrenal axis; norepinephrine; protein kinase A; protein kinase C; serotonin; serotonin receptors; suicide

## Introduction

Suicide is a major public health concern worldwide. Each year, about 30,000 individuals die by suicide in the US and about one million die by suicide in the world (1-3). The main risk factor for suicide is the presence of mental illness, including substance abuse, as it is estimated that 90% of suicides are associated with some form of psychiatric disorder (4, 5). About 60% of all suicides associated with mental illness occur in patients with mood disorders, and the lifetime risk for suicide in major depressive disorders (MDD) and bipolar illness may be similar (6). Although the presence of mental disorders is a major risk factor,

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suicidal behavior is multifactorial, and many other risk factors, such as psychosocial factors (7), are involved in suicide. Although a large proportion of suicides occur in those subjects who suffer from mood disorders, only a small number of these subjects attempt suicide and an even smaller number commit suicide (8-10). This suggests that, while the presence of mental illness is a major risk factor for suicide, other factors also play a role in suicide.

In addition to mental illness, genetic and neurobiological risk factors may be important in predisposition to suicide. That genetic risk factors may be involved in completed suicide is based on the observation that the risk of suicide or suicidal behavior is higher in relatives of probands with mood disorders (11, 12). These genetic studies also suggest that genetic predisposition to suicide or suicidal behavior may, at least in part, be independent from the genetic risk for mood or other psychiatric disorders. This also suggests that the neurobiology of suicide needs to be studied independently of mood disorders or other mental disorders.

Neurobiological risk factors may also be important in studies of risk factors for predisposition to suicide. Besides major mental disorders, other risk factors associated with suicide are impulsive aggressive behavior, stress, and childhood abuse [see reviews by Joiner et al. (13), Mann (14), and Moscicki (15)]. Abnormalities of serotonergic mechanisms have been associated with impulsive-aggressive behavior, abnormal neuroendocrine and immune functions, and with stress (16-20). These studies therefore provide critical information not only on an association of serotonin [5-hydroxytryptamine (5HT)] in the pathophysiology of suicide, but they also provide information on specific molecular sites that may present vulnerability factors for suicide.

## Suicide and suicidal behavior

As stated earlier, not all patients with major mental disorders or mood disorders have suicidal behavior (defined as having suicidal thoughts, suicide attempts, and completed suicides). Only a small proportion of people with suicidal thoughts or suicidal attempts eventually commit suicide. Suicidal ideation and suicide attempts are major risk factors for suicidal behavior. It has been shown by several investigators that 3–13% of suicide attempters eventually died by suicide (8, 9, 21). This may suggest a difference in the neurobiology between depression and suicidal behavior and completed suicide. In general, suicidal behavior includes suicidal ideation, suicide attempts, and completed suicide. In this review, *suicidal behavior* refers to suicidal ideation and suicide attempts, and *suicide* refers to completed suicide.

Initial studies of suicide focused on patients with suicidal behavior and the follow-up of patients who eventually committed suicide. These studies have provided important initial data, and subsequent studies with postmortem brain samples suggested some common abnormalities between patients with suicidal behavior and completed suicide (22, 23). The availability of the appropriate brain collections has provided opportunities to study in detail neurobiological parameters in the brain. As a result, several studies have been carried out on the brain, providing important neurobiological data related to abnormalities in the serotonergic system, neuroendocrine system, and other neurotransmitter systems in suicide pathogenesis. It is beyond the scope of this review to discuss all the neurobiological studies either with patients or postmortem brain samples. We have therefore selected only those studies that either provide important insights into the neurobiology of suicide, present consistent results, or offer promise for future studies of the neurobiology of suicide. Accordingly, this review includes studies related to serotonergic and noradrenergic mechanisms and important findings in second messenger systems, neurotrophins, the hypothalamic-pituitary-adrenal (HPA) axis, and immune function in suicide.

The rationale for the selection of topics in this review is as follows. Abnormalities in serotonin were not only among the first to be associated with suicide but many of the studies also focused on serotonin metabolites, its receptors, and uptake systems. Brain-derived neurotrophic factor (BDNF) and its signaling mechanism have been studied in suicide both in the periphery [see reviews by Deveci et al. (24) and Lee and Kim (25)] as well as in the postmortem brain (26, 27), and the BDNF system plays an important role in neuronal function. HPA axis abnormalities are among the most consistent findings in depression and suicide, and these studies have been previously limited to the studies in peripheral sources, such as the dexamethasone suppression test (DST). Postmortem brain studies, although few on the HPA axis, provide a unique opportunity to examine the mechanism of HPA dysregulation in the suicide brain.

### Teenage versus adult suicide

Suicide is the second leading cause of death in teenagers (28, 29). The risk factors for teenage and adult suicide may be both similar and dissimilar. For example, impulsive-aggressive behavior is a common risk factor for both adult and teenage suicide; however, impulsivity and aggression are traits highly related to suicidal behavior in adolescents (30). Psychosocial factors associated with adolescent suicide, such as stress, contagion, bullying, and peer victimization, may also be different from adults. Do neurobiological studies suggest some different abnormalities associated with teenage suicide? Although it is not clear if biological abnormalities may be different in teenagers compared with adults, Zalsman and Mann (31) suggest that neurobiological studies in adolescents may add to our understanding of suicidal behavior in youth. Neurobiological studies of teenage suicide are few, but we have included these studies in our review. Suicidal behavior in teenagers is likely to have both common and different neurobiological abnormalities compared with adult suicide. Studies of these differences may have implications for an understanding of the neurobiology, prognosis, and treatment.

## Peripheral cells as neuroprobes and biomarkers

Access to the human brain for studying either the pathophysiology or clinical response in psychiatric disorders is limited. Studies of postmortem brain samples, functional neuroimaging, as well as neuroimaging techniques provide important information with regard to the cellular biochemistry, either of receptors or the signaling mechanisms. Biochemical studies have also been performed in peripheral tissues, including blood cells, cerebrospinal fluid (CSF), plasma, and urine. Although limited, they have been useful in providing information with regard to pathophysiological abnormalities. Such studies also present possible prognostic and diagnostic markers in psychiatric disorders.

Leukocytes, platelets, and to a certain degree red cells are highly useful sources for studying many cellular mechanisms. The lymphocytes (white cells) have become particularly important and interesting because of the role they play in immunological function, which has been implicated in MDD, and in their communication with the central nervous system (CNS). Their role as a central probe has been elegantly reviewed by Gladkevich et al. (32). The usefulness of lymphocytes as a neuroprobing marker in psychiatric disorders has especially become evident concerning (i) the role they play in immune response (cytokine production) altered production of different lymphocytes, and (ii) their role in HPA axis dysfunction and neuroendocrine regulation. Because of the space limitations, these two aspects cannot be discussed in detail. In brief, abnormalities of cytokines in depression have been reported by many investigators. Lymphocytes have also been suggested to be important in studying gene expression in various psychiatric disorders (33). Abnormalities in mRNA of many receptors and signal transduction molecules have been demonstrated by us and other investigators in depression and suicide. Many of these genes are also expressed in

lymphocytes, and several of these genes have similar characteristics in both the brain and lymphocytes. This presents another use of lymphocytes in studying gene expression in psychiatric disorders.

The other peripheral markers used extensively in studies of psychiatric disorders are platelets, as reviewed by Plein and Berk (34). Platelets have been used for studies of neurotransmitter function in patients, including monoamine oxidase, adrenergic receptors, $5HT_{2A}$ receptors, and BDNF. Although these studies provide important information, the significance of these studies and of the use of platelets as models of CNS function in psychiatric patients is less clear. Blood platelets exhibit various components that are similar to those in the CNS neurotransmitter system—for example, intracellular levels for biogenic amines, metabolizing enzymes, such as monoamine oxidase, and several other membrane receptors. However, the organization of the CNS 5HT system is much more complex and is modulated by other neurotransmitter systems. One of the most compelling similarities between the receptors, especially the 5HT receptors, and serotonin uptake is the observation that the proteins for the human platelet serotonin uptake site and the brain serotonin transporter are identical in structure and are encoded by the same single-copy gene assigned to chromosome-17 (35). In summary, although there may be some dissimilarity between the characteristics of the receptor systems and signaling systems between platelets and the brain, there are many similarities, and platelets have the potential to be highly useful for studying these systems in psychiatric disorders and may possibly result in diagnostic and prognostic biomarkers.

## Serotonin

### Serotonin in suicide

Abnormalities in the serotonergic system have been widely implicated in suicidal behavior and suicide. This is primarily based on the studies of 5HT and its metabolite, 5-hydroxyindoleacetic acid (5HIAA) in the CSF (36) and blood (37) of suicidal patients; studies of 5HT receptor subtypes in the platelets of suicidal patients (38), and in postmortem brains of suicide victims (39); and on serotonin neuroendocrine challenge studies (40). Although abnormalities of serotonergic mechanisms such as decreased CSF 5HIAA, and increased $5HT_{2A}$ receptors in platelets and postmortem brain, the serotonergic abnormalities may differ in different disorders such as depression, schizophrenia, and addiction. Another line of evidence linking serotonin with suicidal behavior is the observation that suicidal acts are associated with aggressive and impulsive traits, which are also associated with serotonergic dysfunction (20, 41, 42). Impulsive-aggressive behavior has also been found to be associated with suicidal behavior. However, impulsivity has also been implicated in other disorders such as cocaine addiction (43, 44)

As discussed in the following pages, these studies strongly suggest the involvement of 5HT mechanisms in suicide, although the results of these studies are not always consistent.

### Serotonin and its metabolite

The suggestion that serotonin abnormalities may be associated with suicide and suicidal behavior is derived from the involvement of the serotonergic system in depression and in impulsive-aggressive behavior, both of which are major risk factors for suicidal behavior (13, 19, 42). However, the main evidence linking serotonin with suicide was derived from studies of 5HIAA, a major metabolite of 5HT, in the CSF of suicidal patients. Åsberg et al. (45) found a bimodal distribution of CSF 5HIAA in depressed patients and noted that depressed patients with suicide attempts were found significantly more often in the group with low CSF 5-HIAA levels, suggesting a relation between low 5HIAA and suicidal behavior. Several subsequent studies found low 5HIAA in the CSF of suicidal patients (46).

Although some investigators have failed to find a correlation between suicidal behavior and low CSF 5HIAA, a meta-analysis of CSF metabolite by Lester (36) found significantly lower levels of CSF 5HIAA in subjects who made prior suicide attempts and those who subsequently committed suicide or made an attempt.

Some investigators have determined the levels of 5HT in whole blood or platelets. Rao et al. (37) and Spreux-Varoquaux et al. (47) have reported significantly lower 5HT levels in the blood or plasma of suicidal patients compared with normal control subjects. Roggenbach et al.(48) and Mann et al. (49) have reported lower levels of 5HT in platelets of suicidal patients who made suicidal attempts compared to non-attempters or non-suicidal patients. Muck-Seler et al. (50) and Tyano et al. (51) found a negative relationship between platelet or plasma 5HT levels and severity of suicidal behavior in patients.

The role of 5HT in blood or plasma of adolescent suicidal patients has not been studied in great detail. In one study, Tyano et al. (51) determined plasma 5HT levels in suicidal adolescents and controls. They found a significant negative correlation between 5HT levels and suicidal behavior severity among the suicidal patients. The plasma 5HT levels were higher in both suicidal and non-suicidal psychiatric inpatients compared to controls. This finding appears to be in the opposite direction from what was observed in adults, and the reason for this inconsistency between the two groups remains unclear. In summary, the studies of 5HT in blood and/or platelets of patients with suicidal behavior appear to be consistent, suggesting a relationship between lower blood 5HT levels and suicidal behavior. The studies of 5HT or 5HIAA in the postmortem brain are few and inconsistent.

## Receptors

**$5HT_{2A}$—**About 13 subtypes of serotonin receptors have been identified (52). Among these receptors subtypes, $5HT_{2A}$ and $5HT_{1A}$ receptors have been frequently studied in suicide and suicidal behavior. Of these two receptors, only $5HT_{2A}$ receptor is present in peripheral sources, such as the platelets. Pandey et al. (53) observed that the $B_{max}$ of $5HT_{2A}$ receptors was significantly higher in depressed patients compared with normal control subjects. When they divided the depressed patients into suicidal and non-suicidal, they observed that the $5HT_{2A}$ receptors are still more elevated in suicidal patients compared with normal controls and non-suicidal patients. Subsequently, they studied $5HT_{2A}$ receptors using $^{125}$I-LSD binding in platelets of depressed, bipolar disorder, schizophrenic, and schizoaffective patients and found that the $B_{max}$ of $5HT_{2A}$ receptor was significantly increased in all suicidal patients independent of diagnosis compared with non-suicidal patients and normal control subjects, suggesting the involvement of $5HT_{2A}$ receptor in suicidal behavior (38). Several other investigators have also reported increased $5HT_{2A}$ receptor binding in platelets of suicidal patients [for review, see Pandey and Dwivedi (54)]. At least nine investigators have found an increase in platelet $5HT_{2A}$ receptor in depressed patients (37, 53, 55-61) .

**Increased platelet $5HT_{2A}$ receptors as a risk factor for suicidal behavior:** Since increased platelet $5HT_{2A}$ receptors have been observed in suicidal patients, the effect size of one of the studies (38) was calculated to examine the level of risk associated with increased $5HT_{2A}$ receptors in the platelets of these subjects. The effect size for the suicidal patients, as well as non-suicidal patients and normal controls, along with the diagnostic group of these patient populations is shown in Table 1. As can be seen from the table, the highest effect size was observed in the suicidal patients versus normal controls, and this was again broken into diagnostic groups. It was observed that the effect size was highest in the suicidal bipolar disorder subjects and in suicidal schizoaffective subjects versus normal control subjects. On the other hand, with non-suicidal patients versus normal controls, the effect size was almost half of the suicidal patients (effect size = 0.5). Similarly, broken into diagnostic groups, the

effect size was lowest in non-suicidal bipolar disorder patients, which was almost one-third of suicidal bipolar disorder patients compared to normal control subjects. These effect size measures indicate that the risk for suicidal behavior is higher in those patients who have higher $5HT_{2A}$ receptor $B_{max}$, as compared to those patients who have lower $5HT_{2A}$ receptor $B_{max}$.

In this context it is also of interest to report that these authors also calculated the sensitivity and specificity of platelet $5HT_{2A}$ receptor with regard to its predictive value for suicidal behavior, and they found that the platelet $5HT_{2A}$ receptor has a sensitivity of 55% in predicting suicidal behavior. Thus, it identifies 55% of patients as having suicidal behavior, with a specificity of 76%, that is, 76% of patients who were below the cut-off point were correctly identified as not having suicidal behavior.

**$5HT_{2A}$ receptors in the postmortem brain of suicide victims:** There have been several studies of $5HT_{2A}$ receptors in the postmortem brain of suicide victims [for review see Pandey and Dwivedi (39)]. Half of these studies indicated no change in suicide victims compared with normal control subjects; while the other half indicated an increase in $5HT_{2A}$ receptors in the postmortem brain of suicide victims compared with normal control subjects —a finding similar to that observed in platelets (Table 2).

The discrepancy in $5HT_{2A}$ receptor studies in the postmortem brains of suicide victims has been related to the differences and non-specificity of the ligands used for labeling these receptors. However, one study by Pandey et al. (23) determined $5HT_{2A}$ receptor protein and mRNA expression as well as the $^{125}$I-LSD binding in the prefrontal cortex (PFC), hippocampus, and nucleus accumbens (NA) of suicide victims. They also found an increase in both the binding and the protein and mRNA expression of $5HT_{2A}$ receptors in the postmortem brain of teenage suicide victims compared with normal control subjects, suggesting an increase in $5HT_{2A}$ receptors in suicide. The determination of both protein and gene expression of $5HT_{2A}$ receptors, along with binding does suggest an increase in $5HT_{2A}$ receptors in suicide, and discrepancies in the $5HT_{2A}$ receptor binding studies may be due to methodological issues.

More recently, Escriba et al. (62) determined the mRNA levels of $5HT_{2A}$ receptors in the postmortem brains of suicide victims and found similar results to those of Pandey et al. (23): that there was a significant increase in the expression of mRNA for the $5HT_{2A}$ receptors in the PFC of suicide victims compared with control subjects. Shelton et al. (63) determined $5HT_{2A}$ receptor protein expression in Brodmann area 10 (BA10) and observed increased protein expression of $5HT_{2A}$ receptors compared with controls.

In summary, $5HT_{2A}$ receptor studies, especially those carried out with the radioligand binding techniques are mixed. However, studies determining the protein and/or mRNA expression have consistently found increased expression levels of $5HT_{2A}$ receptors in suicide.

**$5HT_{1A}$—**The other serotonin receptor subtype extensively studied in the postmortem brain of suicide victims is $5HT_{1A}$ receptor, which has been studied using radiolabeled ligands. Arango and colleagues (64) did not find any differences in either the $B_{max}$ or $K_d$ of $^3$H-8-OH-DPAT binding between normal control subjects and suicide victims. However, they found the non-violent suicide group had significantly higher $B_{max}$ values compared with normal control subjects; while the violent suicide subjects and the controls were not significantly different from each other in terms of the $B_{max}$.

$5HT_{1A}$ receptors have also been studied in the PFC by many investigators (65). However, none of these groups found any changes in the $5HT_{1A}$ receptors in the PFC of suicide victims compared with control subjects. Matsubara et al. (66) found an increase in $5HT_{1A}$ receptor $B_{max}$ in the PFC of non-violent suicide victims. In another study, Stockmeier et al. (67) found an increase in $5HT_{1A}$ receptors in the midbrain dorsal raphe nucleus of suicide victims compared with control subjects. However, in a recent study, Stockmeier et al. (65) reported that while there was no difference in the agonist binding to $5HT_{1A}$ receptors between depressed and control subjects, the antagonist binding was significantly decreased in outer layers of the orbital frontal cortex obtained from subjects with major depressive disorders (some of them suicidal). On the other hand, Joyce et al. (68) found an increase in $5HT_{1A}$ receptor binding sites in the CA1 area of the hippocampus of suicide victims compared with control subjects. Several other studies (Table 3) did not find any differences in the $5HT_{1A}$ receptor binding in the hippocampus of suicide victims compared with control subjects (39).

In summary, although the results of $5HT_{1A}$ receptor studies in suicide victims appear to be inconsistent, it is generally believed that suicide may be associated with an increase in $5HT_{1A}$ receptors in some cortical areas, as reported by Joyce et al. (68), Arango et al. (64), and Stockmeier et al. (65) (67).

**$5HT_{2C}$—**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 deaminating editing enzymes that attacks five closely-placed adenosine residues located within sequences encoding the putative second intracellular domain of receptors, and leads to several receptor isoforms.

Some investigators have studied the role of $5HT_{2C}$ receptor editing in suicide. Gurevich et al. (69) 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. (70) 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 may be involved in the pathophysiology of suicidal behavior. Pandey et al. (71) 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.

## Neuroendocrine

Neuroendocrine studies, often called a window to the brain, provide another useful method for studying central serotonergic function using peripheral sources. Using 5HT precursor, 5-hydrohytryptophan (5HTP), Meltzer et al. (40) measured the 5HTP-induced cortisol levels in 40 patients with MDD compared with control subjects and found that the cortisol response was significantly increased in patients who made suicide attempts or who had a history of suicidal behavior. Coccaro et al. (72) found that the prolactin response to d-fenfluramine was significantly decreased in depressed patients and patients with personality disorders who had a history of suicide attempt. Similar results were reported by Malone et al. (73) and O'Keane and Dinan (74), who observed decreased prolactin response to fenfluramine in patients with a history of suicide attempts.

## Norepinephrine (NE)

### Noradrenergic function

While abnormalities in both serotonergic function as well as noradrenergic function have been studied in suicide, the major focus has been on the study of serotonin function as reviewed in the previous pages. The studies of NE function associated with suicidal behavior are carried out by determining the levels of NE or its metabolite—3-methoxy-4-hydroxyphenylglycol (MHPG)—in the CSF or urine of suicidal patients, the enzyme tyrosine hydroxylase (TH), or the receptors for NE, primarily α-adrenergic receptors and β-adrenergic receptors in peripheral tissue or the postmortem brain.

Studies of suicidal patients suggest altered levels of NE and MHPG in suicide subjects. Whereas Secunda et al. (75) reported lower urinary and plasma MHPG levels in suicidal depressed patients compared with patients with no suicidal behavior, Brown et al. (76) reported that suicidal patients have significantly higher CSF levels of NE and MHPG compared with non-suicidal patients.

Several other investigators have studied the relationship of CSF MHPG and suicidal behavior; however, it is generally negative, as reviewed by Lester (36).

There are few studies of TH in suicide, and the results appear to be inconsistent both in terms of the locus coeruleus (LC) neurons and LC immunoreactivity. While Arango et al. (77) observed a decreased number of neurons, others did not. Ordway et al. (78) observed an increased TH immunoreactive protein levels, and Baumann et al. (79) found no change. Biegon and Fieldust (80) found a decrease in TH immunoreactivity in suicidal subjects.

### Adrenergic receptors

The major receptors for NE have been classified as $\alpha_1$-, $\alpha_2$-, and β-adrenergic receptors. Each of these receptor types is further divided into at least three subtypes based on molecular and pharmacological studies. Meyerson et al. (81) and Mann et al. (82) found an increase in β-adrenergic receptor binding in the frontal cortex of suicide victims compared with control subjects. Arango et al. (83) 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 brains of suicide victims has been reported by De Paermentier et al. (84).

Either a decrease (85) or no change in $\alpha_1$-adrenergic receptors has been reported in the postmortem brains of suicide victims. The Garcia-Sevilla group (62, 86-88) has extensively studied $\alpha_2$-adrenergic receptors. They found a significant increase in the number and immunolabeling of $\alpha_2$-adrenergic receptors in the hippocampus and the external layers of the frontal cortex of suicide victims compared with matched control subjects (62, 89). On the other hand, Ordway et al. (90) 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 LC of suicide victims compared with control subjects. Underwood et al. (91) found that the $\alpha_2$-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 $\alpha_2$-adrenergic receptors in suicide appear to be slightly more consistent in the sense that most investigators find $\alpha_2$-adrenergic receptors to be increased in the cortex and hippocampus of suicide victims compared with normal control subjects. The studies of $\alpha_1$-adrenergic receptors are few, but some studies, especially the studies in

Underwood et al. (91), find decreased $\alpha_1$-adrenergic receptor in the postmortem brains of suicide victims.

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.

## Second messengers

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 several important genes. It is therefore not surprising that not only the receptors but also their signaling systems have been studied in the suicide brain.

In the phosphoinositide (PI) signaling system, agonist-induced activation of these G protein-coupled receptors causes the hydrolysis of phosphatidylinositide-4,5 bisphosphate ($PIP_2$) by the PI-specific enzyme phospholipase C (PLC), resulting in the formation of two second messengers—diacylglycerol (DAG) and inositol 1,4,5-triphosphate ($IP_3$). DAG activates the phospholipid- and calcium-dependent enzyme protein kinase C (PKC) and increases its affinity for calcium. PKC subsequently activates several transcription factors, such as cyclic AMP (cAMP) response element-binding protein (CREB) and glycogen synthase kinase-3β (GSK-3β), which are also a part of a pathway known as the Wnt signaling pathway. Activation of transcription factors by PKC results in the transcription of several important target genes, such as BDNF. The other signaling system that has been well studied in mood disorders is the adenylyl cyclase (AC) signaling system. Several receptors, such as β-adrenergic receptors, are linked to this signaling system. The activation of β-adrenergic receptors, for example, causes the activation of the effector AC, which causes the conversion of ATP to cAMP. cAMP activates the enzyme known as protein kinase A (PKA), which activates several transcription factors, including the CREB family of transcription factors, thus resulting in the transcription of several important genes.

### Signal transduction

The role of the signaling system in the suicide brain has been examined by studying the crucial components of the signaling cascades, such as PI, AC, Wnt, and mitogen-activated protein (MAP) kinase signaling pathways. Among these components, protein kinase C (PI signaling pathway), PKA (AC signaling pathway), and GSK-3β (Wnt signaling pathway) have been more widely studied. Our review is thus limited only to these components. Although there are some studies of G protein, phospholipase C, adenylyl cyclase, MAP kinase, these studies are limited and have not been covered in this review.

**PKC—**PKC, an important component of the PI signaling system, is a key regulatory enzyme that is present in various tissues. 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) (92, 93), novel (δ, ε, η and θ) (94), and atypical (ι, κ, λ, τ) (95-97). 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 (98). 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 (99-101).

Although PKC has been implicated in the pathophysiology of mood disorders, more specifically bipolar disorders, schizophrenia, and Alzheimer's disease (102-109), the role of PKC in suicide has not been extensively studied. Pandey et al. (110) found that the $B_{max}$ of [$^3$H]PDBu binding as well as PKC activity was significantly decreased in both membrane

and cytosol fractions obtained from the PFC of teenage suicide victims compared with normal control subjects. They also found that the protein and mRNA 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.

**PKA—**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 (111).

The role of PKA in mood disorders has been studied by many investigators [for review, see Dwivedi and Pandey, (112)]. Dwivedi et al. (113) reported that $^{3}$H-cAMP binding and PKA activity was significantly decreased in the PFC of suicide victims. Dwivedi et al. (114) 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.

Pandey et al. (115) 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 the 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 the 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 from teenage suicide victims, although similar in some respects to those observed in adult suicide victims by Dwivedi et al. (113, 114), 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.

## BDNF and Trk-B receptors

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 (116). BDNF is a member of the neurotrophin family, which includes nerve growth factor and neurotrophins (117). 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 (118-120). 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 (121), and that mRNA and

protein levels of BDNF are significantly decreased in the postmortem brains of suicide victims, as discussed in the following pages.

Dwivedi et al. (26) 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 that exist as truncated and full-length isoforms, both of which are functionally important in mediating the functions of BDNF (122-124). 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 (26). 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 brains of suicide victims by other investigators, a recent study (125) indicated that the protein expression of BDNF was increased in the postmortem brain of patients with depression who were treated with antidepressants (125). Pandey et al. (27) determined protein and mRNA expression of BDNF and TrκB receptors in teenage suicide 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.

## HPA axis function

As noted earlier, 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 (126-128). Most patients with depression have been shown to have increased concentrations of cortisol in their plasma and CSF, increased cortisol response to adrenocorticotropic hormone (ACTH), and a deficient feedback mechanism, as evidenced by an abnormal DST (126-130) and enlarged pituitary and adrenal glands (126).

There is also a strong association between HPA axis dysfunction and suicide. Yerevanian et al. (131) 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 (131-135). A meta-analysis found that suicide completions but not attempts were associated with DST non-suppression (136).

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 (137, 138).

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

Nemeroff et al. (139) 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 (140). CRF mRNA levels have been found to be increased in the PVN of depressed patients (141). 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. (142, 143) 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 (142). 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 (128, 144). 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) (138). 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, LC, 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. (145) and Perlman et al. (146) have observed decreased levels of GR mRNA in the PFC and hippocampus of unipolar, bipolar disorder, 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 (147) reported decreased protein expression of GR, but not MR, in the PFC of teenage suicide victims compared with 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.

## Neuroimmune system (cytokines)

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 brain-related disorders, such as depression (148-151). 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.

There is some direct and indirect evidence suggesting a relationship between immune dysregulation and suicide. Steiner et al. (152) have found increased microgliosis in the postmortem brain of suicide victims with affective disorders and schizophrenia compared with normal control subjects. Goodwin and Eaton (153) found a significant association between asthma and increased suicidal ideation and suicide attempts among adults in the community. That an abnormality in cytokines may be associated with suicidal behavior is supported by a recent report by Tonelli et al. (154), which 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. Lindqvist et al. (155) 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. (152); however, the cytokines in the brains 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.

Pandey et al. (156) determined the protein and mRNA levels of proinflammatory cytokines, IL-1β, IL-6, and TNF-α in the PFC of teenage suicide victims and matched normal control subjects. They found that both protein and mRNA expression of IL-1β, IL-6, and TNF-α were significantly increased in the PFC of teenage suicide victims compared with controls. Since there is a strong interaction between cytokines, neuroendocrine, and serotonergic systems, this finding may suggest that abnormalities in these systems observed in suicide may be interrelated.

## State versus trait markers for suicide and suicidal behavior: role of impulsivity

Suicide is a complicated multimodal phenomenon involving several factors that include neurobiological, genetic, and psychosocial risk factors. The factors associated with suicide are both trait- and state-related. Serotonergic abnormalities may be trait-related factors, since these are known to be associated with the impulsive-aggressive behavior trait, which has been implicated in suicide and suicidal behavior. On the other hand, abnormalities of the HPA function, which may be related to stress, could be state-related phenomena in suicide. Impulsivity has been considered as a familial trait, which predisposes individuals to act on their suicidal thoughts. Impulsivity has also been considered as a trait that characterizes individuals who are at risk for suicide attempts, regardless of psychiatric diagnosis as reported by Mann et al (157). There are several risk factors which may be responsible for the development of the trait impulsivity and aggression in suicide. For example, childhood adversity or abuse may be one such factor that may lead to the development of impulsivity, aggression, and suicidal behavior, as reported by Brodsky et al. (158). Mann (20) reported that a more prolonged impulsive-aggressive trait characterizes individuals at risk for suicide attempts regardless of psychiatric diagnosis. Mann et al. (157) found that individuals with a past history of attempting suicide exhibited greater lifetime aggression and impulsivity than non-attempters with the same psychiatric illness. These studies do suggest that a familial trait known as impulsive-aggressive behavior may be a risk factor for suicide (159, 160) in combination with other markers of suicide such as serotonergic abnormalities. It has also been reported by Mann et al. (161) that impulsive-aggressive behavior and externally directed aggression and impulsivity was highly significant in distinguishing past suicide attempters from non-attempters.

Stress-related changes in HPA axis could be state markers of suicidal behavior and suicide. As reviewed in the HPA axis section, there are several studies that indicate a relationship between abnormal HPA axis function and suicide. Several investigators have postulated that DST non-suppression may be an appropriate biological marker for suicidal behavior. Coryell et al. (132) reported that of 205 patients with primary unipolar depression who have received the DST and were followed prospectively, four of whom committed suicide were among the 96 with abnormal DST results. Since stress is a major risk factor for suicidal behavior, it is possible that acute and chronic stress may lead to a long-term change in the activity of the HPA axis.

Both trait as well as state markers may be associated with suicide. The biological aspects of trait markers may be related to abnormalities in serotonergic mechanisms and the state-related changes may be reflected in changes in the HPA axis system in suicide and suicidal behavior.

## Clinical application of neurobiological studies in suicide

One of the major objectives of neurobiological studies in suicide is to examine if an understanding or the knowledge of neurobiological abnormalities observed in suicide/suicidal behavior has any clinical implications. An important factor in the prevention of suicide lies in its early identification. Biological markers for suicide may therefore serve as an important tool in early identification and prevention of suicide. Suicide is a complex multifactorial phenomenon in which several biological abnormalities in addition to genetic and environmental factors may play a role. Also, as stated before, suicidal behavior may be both state- and trait-related. Thus, no single biological marker may be sufficiently accurate for suicidal behavior prediction. Therefore, a combination of state- and trait-related markers may be more useful for such prediction.

One of the important trait-related markers in suicide may be decreased CSF 5HIAA levels and increased platelet $5HT_{2A}$ receptors. An important state-related marker may be a marker of abnormal HPA axis function, such as DST or decreased serum BDNF.

A combination of 5HT-related markers and HPA-related markers may be useful biological markers for prediction of suicidal behavior and, in combination with other clinical-behavioral markers, may be useful in early identification and prediction of suicidal behavior.

Other clinical application of this knowledge lies in the development of new and novel therapies for suicidal behavior, targeting such abnormalities. For example, the development of new serotonergic agents targeting $5HT_{2A}$ receptors or 5HTT may have some promise. Thus, 5HT agonists may be useful in the treatment and prevention of suicidal behavior. In one study, the beneficial effect of paroxetine treatment on suicidal behavior in patients with repeated suicide attempts but without depression was observed (162). Targeting CRF or GR for the development of treatment for suicidal behavior may have some promise.

## Conclusions

Biological studies in patients with suicidal behavior and postmortem brain studies on suicide victims, although still limited, have provided important insights into the neurobiology of suicidal behavior. Initial suggestions linking serotonergic abnormalities with suicide, primarily based on serotonin metabolite studies, have been substantiated and extended by studies of serotonin receptor subtypes, serotonin transporter, and neuroendocrine measures.

For example, increases in $5HT_{2A}$ receptors were observed in the platelets of suicidal patients and postmortem brains of suicide victims. Abnormal serotonin functions in suicide were

further substantiated by increased $5HT_{1A}$ receptors (although not always consistent) and an increase in the pre-mRNA editing of $5HT_{2C}$. Also, decreased prolactin response to fenfluramine administration suggested decreased 5HT activity. In terms of signaling abnormalities, decreased expression of specific PKA and PKC isoforms and decreased CREB expression suggest signaling abnormalities in suicide. A strong association between abnormal DST and suicidal behavior suggest that this may be an important biomarker for suicide.

Although several of these biological abnormalities have been observed in suicide or suicidal behavior, it is not clear which of these abnormalities may be a cause or a consequence of suicide, or are mainly associated with suicidal behavior. Since abnormalities of serotonergic markers in suicide, such as low CSF 5HIAA or increased $5HT_{2A}$ receptors, are supposedly related to specific traits, they may qualify as causal factors or vulnerability factors. However, strong animal data is needed to differentiate the cause and consequence issues. Some recent studies suggest that serotonin depletion results in increased aggression (163). These observations suggest that serotonin dysfunction may be a possible cause for suicidal behavior, but they are not conclusive.

These studies do suggest specific abnormalities of serotonergic mechanisms in suicide. Although not always consistent, serotonin-linked signaling also appears also to be altered in suicide.

Suicidal behavior is a complex disorder, and vulnerability to suicide may involve many behavioral, environmental, genetic, and neurobiological factors. Stress, besides mental disorders, is another risk factor. HPA axis abnormalities in suicide may be related to the stress phenomenon. This system offers another important biological factor for further studies of suicidal behavior. Inflammatory factors may also be important and need to be studied in greater detail in suicide. Initial studies, although few, suggest the importance of abnormal immune function in suicide. The involvement of the inflammatory markers in suicide also needs to be studied further.

In summary, significant progress has been made in understanding the biological basis of suicidal behavior. A better understanding of the neurobiology of suicide may help in developing more appropriate biomarkers and therapeutic agents that, in turn, may lead to more effective screening methods, early detection, effective management, and thus prevention of suicide.

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## Table 1

Effect size of platelet $5HT_{2A}$ receptors in suicidal behavior

| Comparison groups | $5HT_{2A}$ $B_{max}$[a] | Effect size[b] |
|---|---|---|
| Suicidal patient versus normal controls | 71.8 ± 29.2 versus 44.2 ± 19.6 | 1.12 |
| Suicidal unipolar depression versus normal controls | 69.0 ± 28.7 versus 44.2 ± 19.6 | 1.08 |
| Suicidal bipolar depression versus normal controls | 78.9 ± 23.9 versus 44.2 ± 19.6 | 1.77 |
| Suicidal schizophrenia versus normal controls | 58.8 ± 15.6 versus 44.2 ± 19.6 | 0.78 |
| Suicidal schizoaffective disorder versus normal controls | 82.2 ± 37.2 versus 44.2 ± 19.6 | 1.65 |
| Non-suicidal patients versus normal controls | 54.8 ± 21.6 versus 44.2 ± 19.6 | 0.51 |
| Non-suicidal unipolar depression versus normal controls | 56.3 ± 27.1 versus 44.2 ± 19.6 | 0.56 |
| Non-suicidal bipolar depression versus normal controls | 50.9 ± 22.4 versus 44.2 ± 19.6 | 0.33 |
| Non-suicidal schizophrenia versus normal controls | 56.2 ± 18.8 versus 44.2 ± 19.6 | 0.63 |
| Non-suicidal schizoaffective disorder versus normal controls | 56.8 ± 25.5 versus 44.2 ± 19.6 | 0.61 |
| Suicidal patient versus non-suicidal patients | 71.8 ± 29.2 versus 54.8 ± 21.6 | 0.71 |
| Suicidal unipolar depression versus non-suicidal unipolar depression | 69.0 ± 28.7 versus 56.3 ± 27.1 | 0.46 |
| Suicidal bipolar depression versus non-suicidal bipolar depression | 78.9 ± 23.9 versus 50.9 ± 22.4 | 1.28 |
| Suicidal schizophrenia versus non-suicidal schizophrenia | 58.8 ± 15.6 versus 56.2 ± 18.8 | 0.14 |
| Suicidal schizoaffective disorder versus non-suicidal schizoaffective disorder | 82.2 ± 37.2 versus 56.8 ± 25.5 | 0.86 |

[a] Mean ± standard deviation (SD) [from Pandey et al. 1995 (38)].

[b] The effect size was calculated by Cohen's *d* using pooled SD.

**Table 2**

Summary of studies of serotonin-2A receptors in postmortem brain tissue in suicide and depression

| Radioligand | Type of binding study | Brain region | Result | Reference |
|---|---|---|---|---|
| [$^3$H]spiperone | Homogenate | PFC 8, 9 | ↑ $B_{max}$ | Stanley and Mann 1983 (164) |
| [$^3$H]ketanserin | Homogenate | PFC 8, 9 | No change | Owen et al. 1983 (165) |
| [$^3$H]ketanserin | Homogenate | PFC 10 | No change | Crow et al. 1984 (166) |
| [$^3$H]ketanserin | Homogenate | Frontal cortex | No change | Owen et al. 1986 (167) |
| [$^3$H]spiperone | Homogenate | PFC 8, 9 | ↑ $B_{max}$ | Mann et al. 1986 (82) |
| [$^3$H]ketanserin | Homogenate | PFC 10 | No change | McKeith et al. 1987 (168) |
| [$^3$H]ketanserin | Homogenate | PFC 10, hippocampus | No change in PFC, ↓ in hippocampus | Cheetaham et al. 1988 (169) |
| [$^3$H]spiperone | Homogenate | PFC 8, 9 | ↑ $B_{max}$ only in violent suicides | Arora and Meltzer 1989 (170) |
| [$^{125}$I]LSD | Homogenate and sections | PFC 9 | ↑ $B_{max}$ and ↑ in sections | Arango et al. 1990 (83) |
| [$^3$H]ketanserin | Homogenate and sections | PFC, hippocampus | ↓ $B_{max}$ and ↓ in sections in PFC only | Gross-Isseroff et al. 1990 (85) |
| [$^3$H]ketanserin | Sections | PFC 9 | ↑ mid-layers | Yates et al. 1990 (171) |
| [$^3$H]ketanserin | Homogenate | PFC 10 | ↑ $B_{max}$ | Laruelle et al. 1993 (172) |
| [$^3$H]ketanserin | Homogenate | PFC 9, amygdala | ↑ $B_{max}$ | Hrdina et al. 1993 (173) |
| [$^{125}$I]LSD | Sections | Temporal and entorhinal cortex, hippocampus | No change | Joyce et al. 1993 (68) |
| [$^3$H]ketanserin | Homogenate | PFC 9, 10, 11 | No change in violent or nonviolent | Arranz et al. 1994 (174) |
| [$^3$H]spiperone | Homogenate | PFC 10, hippocampus | No change | Lowther et al. 1994 (175) |
| [$^3$H]ketanserin | Sections | PFC 10, hippocampus | No change | Stockmeier et al. 1997 (176) |
| [$^3$H]ketanserin | Homogenate | PFC 8, 9 | ↑ $B_{max}$ | Turecki et al. 1999 (177) |
| [$^3$H]ketanserin | Homogenate | PFC 9, 10, 11, hippocampus | No change in PFC, ↓ $B_{max}$ in hippocampus | Rosel et al. 2000 (178) |
| [$^3$H]LSD | Homogenate | PFC 8, 9 | ↑ $B_{max}$ | Pandey et al. 2002 (23) |

PFC = prefrontal cortex; ↑ = increase; ↓ = decrease.

## Table 3

Summary of serotonin-1A receptor studies in suicide victims

| Radioligand | Type of binding Study | Brain region | Result | Reference |
|---|---|---|---|---|
| [$^3$H]8-OH-DPAT | Homogenate | PFC 8, 9 | ↑ $B_{max}$ in nonviolent | Matsubara et al. 1991 (66) |
| [$^3$H]8-OH-DPAT | Homogenate and sections | Various PFC regions, hippocampus | No change | Dillon et al. 1991 (179) |
| [$^3$H]8-OH-DPAT | Sections | Temporal and entorhinal cortex, hippocampus | ↑ in cortical areas, ↑ in CA1 and CA3 | Joyce et al. 1993 (68) |
| [$^3$H]8-OH-DPAT | Homogenate | PFC 9, 10, 11 | No change in violent or nonviolent | Arranz et al. 1994 (174) |
| [$^3$H]8-OH-DPAT | Sections | PFC 8, 9, 11, 12, 24, 32, 45, 46, 47 | ↑ PFC area 45 and 46 | Arango et al. 1995 (180) |
| [$^3$H]8-OH-DPAT | Homogenate | Frontal cortex, hippocampus | No change | Lowther et al. 1997 (181) |
| [$^3$H]8-OH-DPAT | Sections | PFC 10, hippocampus | No change | Stockmeier et al. 1997 (176) |
| [$^3$H]8-OH-DPAT | Sections | Midbrain dorsal raphe | ↑ in dorsal and ventrolateral subnuclei | Stockmeier et al. 1998 (67) |
| [$^3$H]8-OH-DPAT | Sections | Brainstem dorsal raphe | No change, but ↓ in dorsal raphe volume | Arango et al. 2001 (64) |
| [$^3$H]8-OH-DPAT | Sections | Dorsal raphe nucleus | No change | Arango et al. 2001 (64) |
| [$^3$H]8-OH-DPAT | Sections | Dorsal raphe nucleus | Binding capacity decreased | Arango et al. 2001 (64) |
| [$^3$H]8-OH-DPAT | Sections | Rostral orbitofrontal cortex | No change | Stockmeier et al. 2009 (65) |
| [$^3$H]MPPF | Sections | Rostral orbitofrontal cortex | Decrease | Stockmeier et al. 2009 (65) |

PFC = prefrontal cortex; ↑ = increase.