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Serotonin Transporter: A Potential Substrate in the Biology of Suicide

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Suicide is a serious public health problem in the US, yet its neurobiological underpinnings are poorly understood. Suicide is highly correlated with depressive symptoms, and considerable evidence suggests that depression is associated with a relative deficiency in serotonergic neurotransmission. Serotonergic circuits also mediate impulsivity, a trait obviously relevant to suicide. These findings, taken together, suggest that alterations in the serotonergic system might contribute to suicidal behavior, serving as an impetus for researchers to scrutinize the serotonin transporter (SERT) as a potential substrate for the pathophysiology of suicide. Using post-mortem brain tissue, platelets, and DNA from suicide completers and attempters have not provided unequivocal evidence for a pre-eminent role for the SERT in the pathophysiology of suicide. This paper provides a review of several studies that have evaluated the role of the SERT in the pathophysiology of suicide.
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INTRODUCTION

Suicide is a serious public health concern in the United States and worldwide. In 1998, 30 525 individuals were reported to have died by committing suicide, ranking it as the eighth leading cause of death for all citizens and the third leading cause of death for those aged 15–24 years. The elderly (age 65 years and over) are at particular risk, having the highest rate of self-inflicted death of any age group (CDC June 2002). These statistics are believed to be underestimates, because substantial numbers of suicides go undetected as suicides *per se* and are classified as single person autoaccidents, accidental poisonings, etc. Risk factors for suicide have been characterized and include the presence of one or more psychiatric illnesses (mood and anxiety disorders, especially depression, substance use disorders, cluster B personality disorders, psychotic disorders, and panic disorder). Other long-term risk factors for suicide include single marital status, living alone, unemployment, hopelessness, a history of prepubertal child abuse, and past suicide attempt (Fawcett *et al*, 1990; McCauley, 1997). Short-term risk factors include alcohol abuse, anhedonia, psychic anxiety, diminished concentration, impulsivity, and global insomnia (Fawcett *et al*, 1990; Evans *et al*, 1996; Mann, 1998).

Investigations of biological substrates of suicide risk were initiated almost 30 years ago. The first evidence of serotonergic system alterations in the brain of suicide attempters emerged when Asberg *et al* (1976) demonstrated decreased levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin (5-HT), in the cerebrospinal fluid (CSF) of a substantial subgroup of suicide attempters. For the last quarter century, elucidation of the neurotransmitter circuits and receptors disordered in both the pathophysiology of depression and suicide has been the subject of intense study. This research has accrued substantial evidence to suggest that the serotonergic system is altered in both depressed patients and suicide victims (Malison *et al*, 1998; Owens and Nemeroff, 1998). One of the seminal, and as yet unresolved, issues in the field is whether the biology of suicide is distinct from the biology of depression. Although there may well be some overlap, there is growing evidence of a distinct biology of suicide.

The abundance of evidence suggesting that the serotonergic system is altered in suicidal behavior has prompted investigators to scrutinize the potential role of the serotonin transporter (SERT) in the pathophysiology of suicide. The SERT is believed to be primarily responsible for the termination of action of 5-HT after it is released from the nerve terminal into the synapse. It is located on the presynaptic neuron and takes up one 5-HT molecule concurrently with one Na^+ ion, decreasing extracellular fluid concentrations of 5-HT to levels where postsynaptic receptor activation ceases. Certain tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)

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enhance serotonergic neurotransmission, at least in part, by blocking the 5-HT-binding site on the SERT, thus preventing 5-HT uptake into the neuron (Backstrom *et al*, 1989; Graham and Langer, 1992). The serotonergic system is heterogenously distributed throughout the brain, with the vast majority of 5-HT neurons originating in the raphe nuclei in the brainstem. The highest densities of SERT are located in the dorsal raphe nucleus (DRN) of the rostral pons and midbrain. High densities are also found in the other areas of the raphe nucleus, substantia nigra, locus coeruleus, and some substructures of the thalamus and hypothalamus. Intermediate densities of SERT binding are located in the basal ganglia, some substructures of the amygdala and hypothalamus, and in parts of the pons and medulla oblongata that lie outside the raphe nuclei. Cortical areas, cerebellum, and most substructures of the amygdala contain lower densities of SERT (Cortes *et al*, 1988).

SERT density and function in suicide victims and attempters have been of particular interest to investigators, who have used both post-mortem brain tissue and platelets to study the alterations that potentially underlie suicidal behavior. The relatively recent identification and cloning of the SERT gene has sparked interest in understanding possible associations of polymorphisms of the SERT with suicidal behavior. Despite several attempts by investigators to elucidate a conclusive role for the SERT in the pathophysiology of suicidal behavior, the findings to date are equivocal.

SERT IN THE BRAIN

Over the last 20 years several studies have appeared in which alterations in SERT binding in post-mortem brain tissue of suicide victims were measured and compared to various control groups. The early investigations of SERT binding in suicide victims, and a few more recent ones, used [^{3}H]-imipramine as the ligand and desipramine as the displacing agent to define specific binding. In general, later studies have employed [^{3}H]-paroxetine as the radioligand. The majority of the studies using post-mortem brain tissue have measured binding of the SERT in homogenized tissue preparations from various brain regions, particularly the frontal cortex. A small number of studies have used autoradiography, allowing for a more accurate neuroanatomical resolution of potential SERT-binding alterations.

At least 26 studies of post-mortem brain SERT binding in suicide victims have been completed, yielding inconsistent

Table 1 Serotonin Transporter Binding Studies in Post-mortem Brain Tissue of Suicide Victims

	Region showing change in suicide victims	Method	Ligand
Increases in SERT binding			
Meyerson *et al* (1982)	↑ Frontal cortex	Homogenate	[^{3}H]-IMI
Gross-Isseroff *et al* (1989)	↑ Hippocampus	Autoradiography	[^{3}H]-IMI
Arato *et al* (1991)	↑ Left frontal cortex	Homogenate	[^{3}H]-IMI
Decreases in SERT binding			
Stanley *et al* (1982)	↓ Frontal cortex	Homogenate	[^{3}H]-IMI
Paul *et al* (1984)	↓ Hypothalamus	Homogenate	[^{3}H]-IMI
Crow *et al* (1984)	↓ Frontal cortex	Homogenate	[^{3}H]-IMI
Gross-Isseroff *et al* (1989)	↓ Postcental gyrus, insula, claustrum	Autoradiography	[^{3}H]-IMI
Lawrence *et al* (1990a)	↓ Putamen	Homogenate	[^{3}H]-parox
Arato *et al* (1991)	↓ Right frontal cortex	Homogenate	[^{3}H]-IMI
Laruelle *et al* (1993)	↓ Frontal cortex	Homogenate	[^{3}H]-parox
Arango *et al* (1995)	↓ Prefrontal cortex	Autoradiography	[^{3}H]CN-IMI
Dean *et al* (1996)	↓ Hippocampus	Homogenate	[^{3}H]-parox
Lawrence *et al* (1997)	↓ Putamen	Homogenate	[^{3}H]-parox
Rosel *et al* (1997)	↓ Hippocampus	Homogenate	[^{3}H]-IMI
Rosel *et al* (1998)	↓ Hippocampus	Homogenate	[^{3}H]-IMI
Lawrence *et al* (1998)	↓ Putamen	Homogenate	[^{3}H]-IMI
Mann *et al* (2000)	↓ Ventral prefrontal cortex	Autoradiography	[^{3}H]CN-IMI
No change in SERT binding			
Owen *et al* (1986)	None	Homogenate	[^{3}H]-IMI
Arora and Meltzer (1989)	None	Homogenate	[^{3}H]-IMI
Lawrence *et al* (1990b)	None	Homogenate	[^{3}H]-parox
Arora and Meltzer (1991)	None	Homogenate	[^{3}H]-IMI
Hrdina *et al* (1993)	None	Homogenate	[^{3}H]-parox
Mann *et al* (1996)	None	Homogenate	[^{33}H]-parox
Little *et al* (1997)	None	Autoradiography	[^{125}I]-RTI-55
Rosel *et al* (1997)	None	Homogenate	[^{3}H]-parox
Rosel *et al* (1998)	None	Homogenate	[^{3}H]-parox
Du *et al* (1999)	None	Homogenate	[^{3}H]-parox
Bligh-Glover *et al* (2000)	None	Autoradiography	[^{3}H]-parox
Arango *et al* (2001)	None	Autoradiography	[^{3}H]CN-IMI

IMI, imipramine; parox, paroxetine; CN-IMI, cyanoimipramine.

results (see Table 1 for a summary). The frontal cortex has been the most widely studied brain region, while numerous other brain regions have received less attention. Within the frontal cortex, researchers have found decreases (Stanley *et al*, 1982; Crow *et al*, 1984; Arato *et al*, 1991; Laruelle *et al*, 1993; Arango *et al*, 1995; Mann *et al*, 2000), increases (Meyerson *et al*, 1982), and no alterations in the SERT binding of suicides (Arora and Meltzer, 1989, 1991; Gross-Isseroff *et al*, 1989; Lawrence *et al*, 1990a, b, 1997, 1998; Hrdina *et al*, 1993; Little *et al*, 1997; Rosel *et al*, 1997, 1998; Du *et al*, 1999; Bligh-Glover *et al*, 2000). Studies in which SERT binding was measured in various other brain regions of suicide victims have produced similar discordant results (Paul *et al*, 1984; Owen *et al*, 1986; Gross-Isseroff *et al*, 1989; Hrdina *et al*, 1993; Laruelle *et al*, 1993; Dean *et al*, 1996; Mann *et al*, 1996; Lawrence *et al*, 1997; Little *et al*, 1997; Rosel *et al*, 1997, 1998).

Interestingly, relatively few studies have scrutinized the midbrain, the major site of the raphe 5-HT perikarya (Gross-Isseroff *et al*, 1989; Lawrence *et al*, 1990a, b, 1997, 1998; Little *et al*, 1997; Bligh-Glover *et al*, 2000; Arango *et al*, 2001). Of those, only two (Bligh-Glover *et al*, 2000; Arango *et al*, 2001) have specifically investigated SERT binding in the raphe nucleus, which contains the highest density of SERT in the brain. None of these latter studies has demonstrated any SERT-binding alteration in the midbrain of suicides. However, Arango *et al* (2001) noted that although the DRN SERT-binding concentration in depressed suicides did not differ from controls, had the binding capacity (region of interest volume multiplied by binding concentration) been specifically determined, it would have been decreased in the depressed suicide group. This finding would be consistent with a functional brain imaging study that revealed reduced SERT binding in the midbrain of depressed patients (Malison *et al*, 1998).

Since suicide occurs at a relatively high frequency in several psychiatric disorders, elucidation of SERT alterations in suicide completers compared to other patient groups, including normal volunteers and nonsuicidal depressed patients, has been a focus of investigation. Arato *et al* (1987) were the first to produce evidence of localized SERT binding changes in suicides compared to normal subjects, when they reported that suicides had significantly higher SERT binding in the left frontal hemisphere compared to the right, whereas normal controls had higher binding in the right compared to the left. There were, however, no hemispheric differences when suicides were compared to the control group. Others have failed to replicate this finding of reversed laterality in the frontal cortex of suicide completers (Lawrence *et al*, 1990b; Arora and Meltzer, 1991). Additional evidence has recently emerged, suggesting that SERT-binding alterations in suicide victims may be distinct from depressed patients. In an elegant study, Arango *et al* (1995) demonstrated that SERT binding in suicide completers is relatively localized to the ventrolateral aspect of the prefrontal cortex (PFC) when compared to normals. A subsequent study confirmed and extended these observations in that the localized SERT-binding pattern of suicide victims was distinct from depressed subjects, who had reduced SERT densities in most areas of the PFC (Mann *et al*, 2000).

Although many of the studies of SERT binding in post-mortem brain tissue from suicide completers have examined both violent and nonviolent suicides, several have used violent completers exclusively or have subdivided the suicide group based on the use of violent means (Meyerson *et al*, 1982; Stanley *et al*, 1982; Arato *et al*, 1987, 1991; Arora and Meltzer, 1989; Lawrence *et al*, 1990a, b, 1998; Rosel *et al*, 1997, 1998; Bligh-Glover *et al*, 2000). Other studies included only one or two suicide victims who had died by nonviolent methods, while the majority of subjects used violent means (Laruelle *et al*, 1993; Arango *et al*, 1995; Mann *et al*, 1996). Some of these studies reported a reduction in frontal cortex SERT binding (Stanley *et al*, 1982; Arato *et al*, 1991; Laruelle *et al*, 1993; Arango *et al*, 1995), one an increase (Meyerson *et al*, 1982), and the remainder no difference when compared to controls (Arato *et al*, 1987; Arora and Meltzer, 1989; Lawrence *et al*, 1990a, b, 1998; Mann *et al*, 1996; Rosel *et al*, 1997, 1998; Bligh-Glover *et al*, 2000). One group failed to find SERT density alterations in the frontal cortex of violent suicides but did find a decrease in the hippocampus using [^{3}H]-imipramine, which was not confirmed using [^{3}H]-paroxetine in the same tissue samples (Rosel *et al*, 1997, 1998).

Lawrence *et al* (1998) demonstrated a decrease in SERT binding in the putamen of nonviolent suicides with no differences in the binding of violent suicides. They speculated that the reduced SERT binding in the putamen of the nonviolent suicide completers was secondary to hypoxia associated with the overdose or poisoning antemortem, and that the putamen may be more sensitive to such hypoxic injury than other brain regions. Other investigators have not measured SERT alterations in the putamen.

The lack of congruence among post-mortem brain studies may be because of a number of methodological confounds. One of the most important is the choice of ligand for labeling the SERT and the agent used to define the specific binding. Tritiated imipramine, which was used in about half of the studies of post-mortem brain tissue, has a high affinity for the SERT, other receptor types, such as muscarinic cholinergic and α_1-adrenergic receptors (D'Amato *et al*, 1987), and a nontransporter site (Backstrom and Marcusson, 1987). More recent studies have predominately used [^{3}H]-paroxetine to label the SERT with the specific binding defined using sertraline in varying concentrations. Radiolabeled paroxetine is generally thought to bind with high affinity to a single site that is the SERT-binding site (Backstrom and Marcusson, 1987; Backstrom *et al*, 1989). However, Mann *et al* (1996) demonstrated that a proportion of high-affinity paroxetine-binding sites are nontransporter sites. In addition to the high-affinity sites, both [^{3}H]-imipramine and [^{3}H]-paroxetine bind to another site with lower affinity that is distributed throughout the brain and is not correlated with the distribution of serotonergic nerve terminals (Backstrom *et al*, 1989). The differences in SERT binding results obtained using [^{3}H]-imipramine and [^{3}H]-paroxetine were highlighted by Rosel *et al* (1998), who generated different results in the same tissue samples using the two ligands.

Other important confounds are the particular brain region that was studied and the method by which the SERT-binding concentration was measured. Most of the post-mortem studies measured binding concentrations

using homogenized tissue preparations from specific brain regions, while relatively few studies used autoradiography (Gross-Isseroff *et al*, 1989; Arango *et al*, 1995, 2001; Little *et al*, 1997; Bligh-Glover *et al*, 2000; Mann *et al*, 2000). Homogenized tissue preparation measurements have the disadvantage of being dependent on the precision used in separating white matter from gray matter in the neocortical regions. Poor separation will decrease the accuracy of the measurement. In addition, membrane preparations are distinctly inferior in resolution in terms of localizing SERT binding changes when compared with autoradiographic studies.

Antemortem treatment with antidepressants is another important confound of post-mortem tissue studies. Less than half of the completed studies excluded subjects based on the results of a toxicological screen to detect psychotropics (Gross-Isseroff *et al*, 1989; Lawrence *et al*, 1990a,b, 1998; Arora and Meltzer, 1991; Arango *et al*, 1995, 2001; Mann *et al*, 1996, 2000; Little *et al*, 1997; Bligh-Glover *et al*, 2000). In addition, some investigations included subjects who were known to be treated with psychotropic medication. Other variables that may contribute to variability in post-mortem brain tissue studies include age, gender, psychiatric disorder, post-mortem delay, storage time, season, study population, and brain region (Arango and Mann, 1992).

Although there is some evidence to suggest that the density of the SERT may be altered in the central nervous system (CNS) of suicide victims, the lack of consistency in several studies makes it less compelling than the evidence for SERT density alterations in depression. Despite the fact that the highest density of SERT is found in the raphe nucleus, only two studies have scrutinized the raphe binding of SERT in suicides (Bligh-Glover *et al*, 2000; Arango *et al*, 2001). Clearly, more work needs to be done in this area to elucidate changes in SERT that may be present in this region of the brain. Additional studies using post-mortem tissue need to be viewed in conjunction with investigations that utilize functional brain imaging measures of SERT binding, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT).

SERT IN PLATELETS

Analysis of the 5-HT circuits of patients presents a challenge for clinical investigators. Before the advent of imaging techniques, such as SPECT and PET, other means of studying the serotonergic system in patients were needed. The platelet, which contains SERT and 5-HT_{2A} receptors identical to those in the CNS, was suggested as a suitable model. Based on these and other considerations, investigators have used platelets to measure SERT alterations in patients with mood disorders and suicidal behavior. A remarkable number of studies have been published concerning SERT densities in platelets of depressed patients, and the majority has confirmed a reduction in SERT density in depressives compared to normals (Ellis and Salmond, 1994). However, such consistent findings have not been obtained from studies of platelet SERT binding in relation to suicidal behavior *per se*.

Relatively few investigations have measured SERT binding and uptake in patients with well-documented suicide attempts. Significant decreases in SERT binding in platelets of suicide attempters compared to healthy controls have been reported (Marazziti *et al*, 1995). Increases in platelet SERT binding have been reported in violent suicide attempters compared to those making nonviolent attempts (Healy *et al*, 1990). Others have been unable to demonstrate any alterations in platelet SERT density in attempters (Meltzer and Arora, 1986). Measurement of platelet 5-HT uptake and affinity of 5-HT for the SERT have also been unable to detect consistent alterations in suicidal patients (Marazziti *et al*, 1995; Roy, 1999).

In view of the small number of studies and discordant results with SERT-binding kinetics in suicide attempters, it is difficult to draw any firm conclusions about alterations of the SERT in platelets of suicidal patients. Additional studies of the SERT in platelets are difficult to justify, given the development of new imaging techniques, such as SPECT and PET, to measure SERT in the CNS *in vivo*, although expression of SERT mRNA in megakaryocytes in different patient groups, including suicidal patients, may yield novel and important information.

GENETICS OF SERT

The gene encoding the human SERT has been isolated and cloned, allowing the study of its polymorphisms and associations with various disorders and behaviors. The SERT gene, SLC6A4, has been located to chromosome 17q11.1–17q12. It spans ~31 kilobase pairs (kbp) and contains 14 exons (Lesch and Mossner, 1998). Expression of the SERT gene is regulated by a combination of positive and negative elements acting through a basal promoter unit that is defined by a variable number of tandem repeat units consisting of ~22 bp. This polymorphic repetitive element, 5-HTT gene-linked polymorphic region (5-HTTLPR), has two common alleles, designated as 'long' (or '*l*') and 'short' (or '*s*') that differ in length by 44 bp. The homozygous *ll* polymorphism has been shown to have higher transcriptional activity for the SERT *in vitro* than genotypes containing one or two *s* alleles (Heils *et al*, 1996). Additionally, the uptake of 5-HT is approximately two-fold higher in cells containing the homozygous *ll* form of the 5-HTTLPR than either the *ls* or *ss* forms (Lesch and Mossner, 1998). Other factors, such as seasonal variation, also interact with the 5-HTTLPR genotype to influence both the uptake potential and expression of the SERT (Hanna *et al*, 1998). Despite the influence of genotype on SERT expression and uptake, genotype has not been demonstrated to have any effect on 5-HT binding affinity (Greenberg, 1999).

Several research groups have demonstrated genetic contributions to suicidal behavior through both family studies and molecular genetics (Roy *et al*, 1997). Other investigators have sought to link depression and anxiety symptoms, known to be associated with suicide, to genetic variations of the SERT, although these efforts have produced inconsistent results (Lesch *et al*, 1996; Mann *et al*, 2000). Over the last few years, at least 14 studies have been conducted in which the hypothesis tested was whether polymorphisms in the SERT gene are associated with

suicide. Seven of these studies failed to demonstrate any link between suicidal behavior and SERT genotype or 5-HTTLPR allele frequency (Ohara *et al*, 1998; Chong *et al*, 2000; Geijer *et al*, 2000; Ho *et al*, 2000; Mann *et al*, 2000; Fitch *et al*, 2001; Rujescu *et al*, 2001). The remaining seven studies all found some association, albeit with differing results (Du *et al*, 1999; Bellivier *et al*, 2000; Bondy *et al*, 2000; Gorwood *et al*, 2000; Russ *et al*, 2000; Courtet *et al*, 2001; Baca-Garcia *et al*, 2002). One study demonstrated a higher frequency of the *l* allele in depressed suicide victims compared to nonsuicidal controls (Du *et al*, 1999). This finding was supported by another group who found that subjects with the *ll* genotype had significantly higher scores on Beck's Hopelessness Scale and Beck's Scale for Suicide Ideation than subjects with either the *ls* or *ss* genotype (Russ *et al*, 2000). In contrast, three other groups of researchers observed an association between the *s* allele and violent suicidal behavior, while a fourth found a link between the *s* allele and the number of lifetime suicide attempts and lethality of the suicidal behavior (Bellivier *et al*, 2000; Bondy *et al*, 2000; Gorwood *et al*, 2000; Courtet *et al*, 2001).

Although these studies have yielded conflicting results, it is impressive that the four studies that found an association between suicidal behavior or lethality of the behavior and the *s* form of the 5-HTTLPR were uniform in identifying a subset of attempters or completers that had a similar characteristic—the use of violent or highly lethal means (Bellivier *et al*, 2000; Bondy *et al*, 2000; Gorwood *et al*, 2000; Courtet *et al*, 2001). Only one study that distinguished between violent and nonviolent attempters failed to demonstrate any associations (Rujescu *et al*, 2001). The other studies that found no association or an association with the *l* allele made no such distinction in their populations. Perhaps, these latter studies were unable to find an effect of the *s* allele, because the sample was comprised of patients with suicidal behavior that was not violent or lethal. Additionally, two of the studies were conducted in Asian populations (Ohara *et al*, 1998; Chong *et al*, 2000), which have been shown to have a higher frequency of the *s* allele than Caucasian populations (Gelernter *et al*, 1999). Therefore, any effect of the *s* form of the 5-HTTLPR on suicidal behavior would require larger sample sizes than would be needed in Caucasian populations. Moreover, the two studies that found a link between the *l* allele and suicide or perceived risk of suicide both used relatively small samples, making it possible that an erroneous link was found.

An association of the 5-HTTLPR *s* allele with violent suicidal behavior supports prior studies showing lower serotonergic activity in suicidal, violent, and aggressive behaviors (Asberg *et al*, 1976; Coccaro *et al*, 1989). There is also considerable preclinical work in both rodents and nonhuman primates that support this view (Nelson and Chiavegatto, 2001). Presence of the *s* allele results in decreased expression of the SERT *in vitro* in lymphoblastoid cell lines (Heils *et al*, 1996), which could be indicative of a decrease in serotonergic activity in these violent suicide attempters and completers. Other studies have also shown an association between the 5-HTTLPR *s* allele and violent, aggressive behavior quite distinct from suicidal acts, although not universally (Frisch *et al*, 2000; Seeger *et al*, 2001). This view of the 5-HTTLPR *s* allele resulting in reduced SERT expression, thus contributing to the predisposition for violent suicidal behavior, is supported by the above evidence. However, an association between any 5-HTTLPR polymorphism and *in vivo* SERT expression in humans has not yet been demonstrated (Jacobsen *et al*, 2000; Mann *et al*, 2000; Willeit *et al*, 2001), leaving the role of 5-HTTLPR polymorphisms unclear.

The concatenation of results of studies searching for genetic associations of suicidal behavior renders it difficult to draw any firm conclusions. The effect of a genetic polymorphism of any single protein is unlikely to be the sole culprit underlying a genetic predisposition to suicide. Rather, it is much more probable that the interplay of several genetic variations will predispose a given individual to display suicidal behavior. This is an area requiring further investigations using more specific populations, such as violent suicide attempters, to help clarify the role of genetic variations in the biology of suicide.

CONCLUSION

Although it appears that the SERT plays a role in the pathophysiology of suicidal behavior, the magnitude of the contribution remains obscure. Neurochemical changes that predispose a patient to suicide are certainly not limited to one or two proteins or neurotransmitters. The alterations in SERT density and its genetic encoding observed in patients with suicidal behavior must be considered within the context of a general decrease in serotonergic functioning in these patients. Studies examining genetic associations and SERT density and function will continue, and new tools will be employed to help investigators with this task. Functional brain imaging including PET and SPECT will surely play a more prominent role in the elucidation of neurotransmitter receptor and transporter density changes in living suicidal patients. Other avenues will also be pursued to investigate variables downstream of the neurotransmitter receptors, namely scrutiny of signal transduction pathways and alterations in gene expression. In addition, further studies will be carried out to clarify whether the biology of suicide is distinct from that of other disorders such as depression. An improved understanding of these systems may lead to novel treatments for depression, suicidality, and cognate disorders.

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