

# The Neurobiology of Suicide Risk: A Review for the Clinician

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Suicidal behavior has neurobiological determinants independent of the psychiatric illnesses with which it is associated. We have found that some patients with major depression are vulnerable to acting on suicidal impulses. This vulnerability results from the interaction between triggers or precipitants and the threshold for suicidal behavior. An important factor in setting an individual's threshold for acting on suicidal impulses is brain serotonergic function. Serotonin function has been shown to be lower in suicide attempters by studies measuring serotonin metabolites in cerebrospinal fluid and studies of prolactin response to fenfluramine. Postmortem studies of suicide victims also reveal decreased serotonin activity in the ventrolateral prefrontal cortex. New neuroimaging paradigms, such as positron emission tomography (PET), offer an opportunity to visualize serotonin function in vivo in a more direct way than has previously been available. This technology may provide the possibility of timely therapeutic intervention in patients at high risk for suicide.

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**S**uicide is the cause of death for 30,000 people per year<sup>1</sup> in the United States and is a frequent outcome of major psychiatric disorders.<sup>2</sup> Between 10% to 15% of patients suffering from depression or schizophrenia commit suicide.<sup>2</sup> In the last 20 years, there has been increasing evidence that suicidal behavior has strong neurobiological determinants. Understanding the neurobiology of suicide will ultimately yield clinical tools to treat suicidal behavior and prevent deaths.

## A MODEL FOR UNDERSTANDING SUICIDAL BEHAVIOR

We studied a group of 100 depressed patients who had a mean of 3 episodes of major depression across a mean time period of 12 years.<sup>3</sup> Approximately half the patients had made a previous suicide attempt, and half the patients had never made a suicide attempt. The group with a life-

time history of suicide attempts had made a mean of 2.9 suicide attempts. Thus, this group seemed to have a predisposition toward suicide attempts. In contrast, the other group was resistant to suicidal acts despite having the same illness for the same duration.

We used survival analysis to examine the relationship of the first suicide attempt to the onset of the first episode of major depression. This analysis yielded a survival curve that is steepest at the beginning of the illness, suggesting that most of the individuals in the vulnerable group made a suicide attempt early in the course of illness. Therefore, in our findings, suicide attempts are not a result of despondency due to recurrence of depressive episodes. Rather, persons who are at risk for suicide tend to make an attempt relatively early in the course of their illness.

Thus, one may formulate a model of suicidal behavior that can be regarded as a stress diathesis or trigger-threshold model. Based on this model, risk factors are categorized in terms of belonging to one of these two domains. For example, the trigger domain comprises most of the clinical features that psychiatrists who evaluate suicidal patients focus on, such as acute psychiatric illness, substance abuse, adverse life events, or a family crisis. In the threshold domain, there are risk factors that receive less attention from psychiatrists, including genetics, personality disorders, and alcoholism. Furthermore, all these risk factors may be interrelated. We suggest that a patient must have at least one major risk factor from each domain to be at high risk for suicide. One factor is not enough to result in suicidal acts, which explains why some psychiat-

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ric patients attempt or complete suicide, and yet others with the same illness do not.

### Triggers for Suicidal Behavior

The most powerful predictor of risk for a future attempt is a past history of suicide attempt.<sup>4</sup> Many features of the risk factors in the trigger category that clinicians might expect to suggest imminent suicidal behavior do not distinguish suicide attempters from nonattempters. For example, the objective evaluation of the severity of the illness, many of the specific components of psychopathology, and life events are all poor discriminators of individuals who have a history of a suicide attempt versus those who do not.<sup>3</sup> Therefore, these features are often poor predictors of who is at risk for attempting suicide in the future.

### The Threshold for Suicidal Behavior

Traits are enduring characteristics of a patient and are related to the threshold for acting on suicidal thoughts. Attempters are distinguished from nonattempters by specific traits and by a family history of suicidal behavior.<sup>5,6</sup> These traits include more frequent comorbid borderline personality disorder,<sup>3,7,8</sup> comorbid substance abuse, comorbid alcoholism,<sup>9,10</sup> and greater lifetime aggression and lifetime impulsivity in attempters than in nonattempters.<sup>11</sup> Impulsivity—which may be defined as the rapidity and probability of acting on powerful feelings—suicidal behavior, and aggression have a well-recognized interrelationship.<sup>11</sup> Specific behaviors or disorders such as addictive and appetitive disorders, which have an association with aggression and impulsivity, also are associated with suicidal behavior.<sup>12–15</sup> High impulsivity lowers the threshold for acting on feelings and can be manifested as self-directed or externally directed aggression. Thus, triggers for suicidal acts or aggression interact with the threshold in an individual and result in aggressive or suicidal behavior.

## NEUROBIOLOGICAL FINDINGS IN SUICIDAL BEHAVIOR

The association of impulsivity with externally directed aggression, suicidal behavior, and substance abuse raises the possibility of common etiologic and predisposing factors. There is evidence for a common substrate in similar neurobiological correlates of suicidal acts and impulsive aggression.

### Clinical Studies

There have been 18 studies that have looked at serotonin function by assaying 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, in the cerebrospinal fluid (CSF) in patients with major depression (see reference 16 for a review). The biological profile that has emerged from these studies fits the model we have de-

scribed above. About two thirds of the studies that looked at suicide attempters versus nonattempters found that suicide attempters have low levels of CSF 5-HIAA. However, about one third of the published studies do not confirm this. In the studies that do find an association between suicide attempts and low CSF 5-HIAA levels, about two thirds of the attempters have low levels of CSF 5-HIAA compared with the nonattempters, of whom only one third has low levels of CSF 5-HIAA levels. Thus, there is considerable overlap in the biochemistry of serotonin in attempters and nonattempters. One of the factors that appears to determine whether or not CSF 5-HIAA is low is the lethality or severity of the attempt. The more lethal the attempt, the lower the level of CSF 5-HIAA. This negative correlation between lethality and CSF 5-HIAA also is seen in adolescents with major depression (Greenhill L, Shaffer D, Mann JJ, unpublished data, 1998). CSF 5-HIAA is low in serious suicide attempters even when the presence of a psychiatric illness such as major depression is controlled for and patients are studied in a drug-free, controlled environment.<sup>17</sup> Low CSF 5-HIAA is also found in suicide attempters with schizophrenia<sup>18,19</sup> and personality disorders<sup>20</sup> compared with patients who have the same diagnoses without a history of suicide attempts. Therefore, the relationship between low CSF 5-HIAA and suicide attempts is a general one that is found in many different psychiatric disorders. It is a biobehavioral relationship that is independent of—or in addition to—the neurobiology of specific psychiatric disorders.

A similar relationship exists between CSF 5-HIAA and severity of lifetime aggression. Goodwin, Brown et al.<sup>21–24</sup> have found that the greater the severity of the lifetime aggression, the lower the level of CSF 5-HIAA. This relationship has also been found in nonhuman primates.<sup>25,26</sup> The more aggressive and impulsive the nonhuman primates are, the lower the level of CSF 5-HIAA.<sup>27</sup> This same relationship holds true for pathologically aggressive dogs that have lower levels of CSF 5-HIAA compared with normal, nonaggressive dogs.<sup>28</sup> Thus, phylogenetically, this relationship between the behavioral trait of impulsive aggression and CSF 5-HIAA is widely found, and CSF 5-HIAA is a biological variable related to lifetime patterns of behavior.

As would be expected from a biochemical trait, CSF 5-HIAA can also predict future behavior. During the 12 months after hospital discharge, patients who had low levels of CSF 5-HIAA had a higher rate of completed suicide compared with patients who had higher levels of CSF 5-HIAA.<sup>4</sup> Low CSF 5-HIAA also predicts future impulsive aggression and has been found to predict impulsive homicide in murderers released from prison.<sup>29</sup> Hence, amongst impulsive criminals, low CSF 5-HIAA predicts future impulsive criminality, and amongst individuals who have made a suicide attempt, low CSF 5-HIAA predicts the risk of future suicide.

The prolactin response to fenfluramine is another index of serotonin responsivity. Fenfluramine causes the release of serotonin and induces serotonin reuptake inhibition. The release of prolactin by fenfluramine is via the action of serotonin on specific serotonin receptors. Although depressed patients in general have a blunted prolactin response to fenfluramine,<sup>30</sup> this blunting is mostly explained by factors other than the presence of major depression. One of those factors is a history of a highly lethal suicide attempt.<sup>31</sup> Men and women with a history (often many months or years in the past) of a very lethal suicide attempt retain a blunted prolactin response compared with individuals with major depression but no history of a very lethal suicide attempt.<sup>31</sup> Thus, using a completely different index of serotonergic function, the relationship between a reduced level of serotonergic activity and a past history of suicidal behavior holds true. That is, the more lethal the suicidal behavior, the more blunted is the serotonin function. Furthermore, this blunting of serotonergic function is also independent of how long ago the suicidal behavior was manifested.<sup>31</sup> Such a long-term relationship is characteristic of a biological trait related to a behavioral trait.

Just as was reported for CSF 5-HIAA, a similar relationship exists between the level of lifetime externally directed hostility or aggression and a blunted prolactin response to fenfluramine.<sup>32</sup> Serotonergic function, which has been shown in nonhuman primates to have trait-like qualities because it is relatively stable over time,<sup>33</sup> is associated with past and future suicidal acts. It is also associated with past and future aggression.

Factors that influence serotonergic activity may be relevant for suicidal behavior. For example, genetic factors affect the risk for suicide independently of genetic factors related to psychiatric illnesses that cause suicidal thoughts and feelings.<sup>34</sup> Genetic factors may affect suicide risk by contributing to the threshold for acting on suicidal thoughts. Genetic modulation of serotonergic activity may be one way in which the effect of genetics on suicide risk is mediated.<sup>35</sup> Sex is another factor in suicide risk that may be mediated by serotonin. Women are at lower risk for suicide than men<sup>1</sup> and have been reported to have higher levels of CSF 5-HIAA or serotonergic activity than men.<sup>36,37</sup> The relationship between cholesterol levels and suicidal behavior may be mediated through serotonergic functioning as well. In nonhuman primates, low cholesterol diets result in lower serotonergic activity and more aggression.<sup>38,39</sup> Low cholesterol levels in humans are associated with higher suicide rates, perhaps due to lower serotonergic activity, although an effect of cholesterol on serotonergic activity has yet to be shown in man.<sup>40</sup>

### Postmortem Studies

Another approach to understanding the neurobiological substrate for suicidal behavior is by the postmortem examination of the brain from suicide victims. By examining

coronal sections through the prefrontal cortex of the human brain, we can observe the anatomical distribution of serotonin receptors.<sup>41</sup> Serotonin transporter sites are densest in medial, less dense in ventral, and least dense in dorsal and dorsolateral prefrontal cortex. Serotonin transporter binding is one index of serotonin nerve terminal input into, or innervation of, cortical areas.<sup>42</sup> Comparison of suicide victims with controls who have died from other causes, regardless of the diagnosis, reveals a reduction in binding to the serotonin transporter sites in certain locations in the brain.<sup>41</sup> This reduction is most pronounced in the ventral prefrontal cortex and is not detectable in the dorsal prefrontal cortex.<sup>41,43</sup>

One of the most studied postsynaptic serotonin receptors is the 5-HT<sub>1A</sub> receptor. The 5-HT<sub>1A</sub> receptor is evenly distributed across prefrontal cortical areas,<sup>41</sup> but across cortical layers it is mainly localized to layer 2. A comparison of suicide victims and controls indicates that there is an increase in the number of these postsynaptic receptors in suicide victims.<sup>41,44-46</sup> The increase in 5-HT<sub>1A</sub> receptor binding is also mainly in ventral cortical areas. In fact, there is an inverse relationship between the number of 5-HT<sub>1A</sub> receptors and the number of serotonin transporter sites, which suggests a reciprocity in the way the two systems are regulated. A lack of neurotransmitter is often associated with a compensatory increase in postsynaptic receptor number. There may be less serotonin input to the ventral prefrontal cortical area of suicide victims, as indicated by fewer transporter sites. Therefore, the increase in 5-HT<sub>1A</sub> receptor binding may be secondary to reduced serotonergic innervation. Thus, although serotonin neurons project all over the brain, the specific projection to the ventral prefrontal cortex may be deficient. Of note, these studies demonstrate a biochemical finding that is independent of psychiatric diagnosis. It is present in suicide victims with major depression as well as in those with other psychiatric conditions.<sup>46,47</sup>

These studies of serotonin receptors raise the question of the function of the ventral prefrontal cortex. Some information is available from examining regional glucose metabolism with positron emission tomography (PET) in murderers compared with nonmurderers.<sup>48</sup> These studies found a significant reduction in the resting glucose metabolism in the prefrontal cortical areas of murderers, highlighting the potential importance of this brain region in regulating behavior. In addition, there is considerable neuropsychiatric literature on the role of the ventral prefrontal cortex in the executive function of behavioral or cognitive inhibition. A breakdown in this inhibitory role may result in a greater potential for acting on powerful feelings or impulses such as suicidal ideation or anger. In other words, the ventral prefrontal cortex may act as a restraint system underlying the ability to prevent acting on powerful feelings in a destructive way. A weaker restraint system leads to more impulsive behaviors.

### Neuroimaging Serotonergic Function in Vivo

One way of visualizing neurotransmitter systems in the living brain is by PET. We looked at regional brain glucose metabolism on a day in which placebo was used and compared it with a day when the individual received fenfluramine.<sup>49</sup> The differences in regional glucose metabolism are due to the effects of fenfluramine. For example, there are increases in metabolism that reflect increases in neuronal activity owing to the surge of serotonergic activity caused by fenfluramine.<sup>50</sup> There are also areas of decreased activity because serotonin can also activate inhibitory pathways that affect certain neurons and thereby reduce glucose utilization in parts of the brain. These differences in response by different brain regions due to serotonergic activity can be mapped statistically. We found that there is a considerable increase in metabolic activity in the ventral prefrontal cortex in response to fenfluramine. We have already described some structural and functional data from postmortem studies that suggest that there are some abnormalities in this cortical area in individuals who manifest suicidal behavior. This is a new approach that may detect defective serotonin input into prefrontal cortex. We are now using PET to examine neurotransmitters and neuroreceptors in live subjects. Guided by our findings in suicide victims, these studies will allow us to understand the neurobiology of suicide risk in patients. We propose that PET imaging in living patients of neuroreceptors that are found to be altered in the brain of suicide victims will enable us to determine whether the biochemical abnormalities detected after death in suicide victims can be detected in patients at risk for suicide while they are still alive. This approach could create the possibility for timely therapeutic intervention in patients at high risk for suicide.

### SUMMARY

We have described a model that aids in the determination of those who are at risk for suicide. Much of the clinical and biological evidence that we have found reflects a trait rather than a state. This is not only important theoretically in terms of how to evaluate suicide risk, but also offers special opportunities in terms of prevention and treatment. Detection of high-risk patients should include evaluation of the threshold for suicidal acts so that treatment interventions can potentially include ways of raising the threshold for suicidal acts as well as targeting the associated psychiatric disorders.

### REFERENCES

- Center for Disease Control and Prevention. Advance report of final mortality statistics, 1990. *Monthly Vital Statistics Report* 1993;41:1-52
- Mann JJ. The neurobiology of suicide. *Nat Med* 1998;4:25-30
- Malone KM, Haas GL, Sweeney JA, et al. Major depression and the risk of attempted suicide. *J Affect Disord* 1995;34:173-185
- Nordström P, Samuelsson M, Asberg M, et al. CSF 5-HIAA predicts suicide risk after attempted suicide. *Suicide Life Threat Behav* 1994;24:1-9
- Roy A. Family history of suicide. *Arch Gen Psychiatry* 1983;40:971-974
- Mitterauer B, Leibetseder M, Pritz WF, et al. Comparisons of psychopathological phenomena of 422 manic-depressive patients with suicide-positive and suicide-negative family history. *Acta Psychiatr Scand* 1988;77:438-442
- Corbitt EM, Malone KM, Haas GL, et al. Suicidal behavior in patients with major depression and comorbid personality disorders. *J Affect Disord* 1996;39:61-72
- Bulik CM, Carpenter LL, Kupfer DJ, et al. Features associated with suicide attempts in recurrent major depression. *J Affect Disord* 1990;18:29-37
- Cornelius JR, Thase ME, Salloum IM, et al. Cocaine use associated with increased suicidal behavior in depressed alcoholics. *Addict Behav* 1998;23:119-121
- Cornelius JR, Salloum IM, Mezzich J, et al. Disproportionate suicidality in patients with comorbid major depression and alcoholism. *Am J Psychiatry* 1995;152:358-364
- Mann JJ, Watermaux C, Haas GL, et al. Towards a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry*. In press
- Linnoila M, De Jong J, Virkkunen M. Family history of alcoholism in violent offenders and impulsive fire setters. *Arch Gen Psychiatry* 1989;46:613-616
- Branchey L, Branchey M, Shaw S, et al. Depression, suicide, and aggression in alcoholics and their relationship to plasma amino acids. *Psychiatry Res* 1984;12:219-226
- Bergman B, Brismar B. Hormone levels and personality traits in abusive and suicidal male alcoholics. *Alcohol Clin Exp Res* 1994;18:311-316
- Verkes RJ, Pijl H, Meinders AE, et al. Borderline personality, impulsiveness, and platelet monoamine measures in bulimia nervosa and recurrent suicidal behavior. *Biol Psychiatry* 1996;40:173-180
- Åsberg M, Nordström P, Träskman-Bendz L. Cerebrospinal fluid studies in suicide: an overview. *Ann N Y Acad Sci* 1986;487:243-255
- Mann JJ, Malone KM. Cerebrospinal fluid amines and higher lethality suicide attempts in depressed inpatients. *Biol Psychiatry* 1997;41:162-171
- Ninan PT, van Kammen DP, Scheinin M, et al. CSF 5-hydroxyindoleacetic acid levels in suicidal schizophrenic patients. *Am J Psychiatry* 1984;141:566-569
- van Praag HM. CSF 5-HIAA and suicide in non-depressed schizophrenics. *Lancet* 1983;2:977-978
- Gardner DL, Lucas PB, Cowdry RW. CSF metabolites in borderline personality disorder compared with normal controls. *Biol Psychiatry* 1990;28:247-254
- Goodwin FK. Suicide, aggression, and depression: a theoretical framework for future research. *Ann N Y Acad Sci* 1986;487:351-355
- Brown GL, Ebert MH, Goyer PF, et al. Aggression, suicide and serotonin: relationships to CSF amine metabolites. *Am J Psychiatry* 1982;139:741-746
- Brown GL, Goodwin FK, Bunney WE, Jr. Human aggression and suicide: their relationship to neuropsychiatric diagnoses and serotonin metabolism. *Adv Biochem Psychopharmacol* 1982;34:287-307
- Brown GL, Goodwin FK. Cerebrospinal fluid correlates of suicide attempts and aggression. *Ann N Y Acad Sci* 1986;487:175-188
- Botchin MB, Kaplan JR, Manuck SB, et al. Low versus high prolactin responders to fenfluramine challenge: marker of behavioral differences in adult male *cynomolgus* macaques. *Neuropsychopharmacology* 1993;9:93-99
- Higley JD, Mehlman PT, Taub DM, et al. Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging Rhesus monkeys. *Arch Gen Psychiatry* 1992;49:436-441
- Higley JD, Linnoila M. Low central nervous system serotonergic activity is traitlike and correlates with impulsive behavior: a nonhuman primate model investigating genetic and environmental influences on neurotransmission. *Ann N Y Acad Sci* 1997;836:39-56
- Reisner IR, Mann JJ, Stanley M, et al. Comparison of cerebrospinal fluid monoamine metabolite levels in dominant-aggressive and non-aggressive dogs. *Brain Res* 1996;714:57-64
- Virkkunen M, De Jong J, Bartko J, et al. Relationship of psychobiological variables to recidivism in violent offenders and impulsive fire setters: a follow-up study. *Arch Gen Psychiatry* 1989;46:600-603
- Mann JJ, McBride PA, Malone KM, et al. Blunted serotonergic responsivity in depressed patients. *Neuropsychopharmacology* 1995;13:

- 53–64
31. Malone KM, Corbitt EM, Li S, et al. Prolactin response to fenfluramine and suicide attempt lethality in major depression. *Br J Psychiatry* 1996;168:324–329
  32. Coccaro EF, Siever LJ, Klar HM, et al. Serotonergic studies in patients with affective and personality disorders. *Arch Gen Psychiatry* 1989;46:587–599
  33. Higley JD, King ST, Hasert MF, et al. Stability of interindividual differences in serotonin function and its relationship to severe aggression and competent social behavior in rhesus macaque females. *Neuropsychopharmacology* 1996;14:67–76
  34. Brent DA, Bridge J, Johnson BA, et al. Suicidal behavior runs in families. *Arch Gen Psychiatry* 1996;53:1145–1152
  35. Mann JJ, Malone KM, Nielsen DA, et al. Possible association of a polymorphism of the tryptophan hydroxylase gene with suicidal behavior in depressed patients. *Am J Psychiatry* 1997;154:1451–1453
  36. Bucht G, Adolfsson R, Gottfries CG, et al. Distribution of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in human brain in relation to age, drug influence, agonal status and circadian variation. *J Neural Transm* 1981;51:185–203
  37. McBride PA, Tierney H, DeMeo M, et al. Effects of age and gender on CNS serotonergic responsivity in normal adults. *Biol Psychiatry* 1990;27:1143–1155
  38. Fontenot MB, Kaplan JR, Shively CA, et al. Cholesterol, serotonin and behavior in young monkeys. *Ann N Y Acad Sci* 1996;794:352–354
  39. Kaplan JR, Shively CA, Fontenot MB, et al. Demonstration of an association among dietary cholesterol, central serotonergic activity, and social behavior in monkeys. *Psychosom Med* 1994;56:479–484
  40. Ringo DL, Lindley SE, Faull KF, et al. Cholesterol and serotonin: seeking a possible link between blood cholesterol and CSF 5-HIAA. *Biol Psychiatry* 1994;35:957–959
  41. Arango V, Underwood MD, Gubbi AV, et al. Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. *Brain Res* 1995;688:121–133
  42. Zhou FC, Lumeng L, Li T-K. Quantitative immunocytochemical evaluation of serotonergic innervation in alcoholic rat brain. *Neurochem Int* 1995;26:135–143
  43. Hrdina PD, Demeter E, Vu TB, et al. 5-HT uptake sites and 5-HT<sub>2</sub> receptors in brain of antidepressant-free suicide victims/depressives: increase in 5-HT<sub>2</sub> sites in cortex and amygdala. *Brain Res* 1993;614:37–44
  44. Matsubara S, Arora RC, Meltzer HY. Serotonergic measures in suicide brain: 5-HT<sub>1A</sub> binding sites in frontal cortex of suicide victims. *J Neural Transm* 1991;85:181–194
  45. Yates M, Ferrier IN. 5-HT<sub>1A</sub> receptors in major depression. *J Psychopharmacol* 1990;4:69–74
  46. Joyce JN, Shane A, Lexow N, et al. Serotonin uptake sites and serotonin receptors are altered in the limbic system of schizophrenics. *Neuropsychopharmacology* 1993;8:315–336
  47. Sumiyoshi T, Stockmeier CA, Overholser JC, et al. Serotonin<sub>1A</sub> receptors are increased in postmortem prefrontal cortex in schizophrenia. *Brain Res* 1996;708:209–214
  48. Raine A, Buchsbaum M, LaCasse L. Brain abnormalities in murderers indicated by positron emission tomography. *Biol Psychiatry* 1997;42:495–508
  49. Mann JJ, Malone KM, Diehl DJ, et al. Demonstration in vivo of reduced serotonin responsivity in the brain of untreated depressed patients. *Am J Psychiatry* 1996;153:174–182
  50. Mann JJ, Malone KM, Diehl JD, et al. Positron emission tomographic imaging of serotonin activation effects on prefrontal cortex in healthy volunteers. *J Cereb Blood Flow Metab* 1996;16:418–426