Karley Y. Little,[1] *M.D. and D. Larry Sparks,*[2] *Ph.D.*

Brain Markers and Suicide: Can a Relationship Be Found?

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ABSTRACT: Recent work suggests that some persons who commit suicide have altered neurochemistry in their brains. It remains unclear which of the many reported abnormalities are most reliably present and whether they reflect a specific psychiatric disorder or a disposition to violent impulsivity. A number of technical and interpretive problems must be clarified, but a postmortem test indicating that a subject was at high risk for suicide may eventually emerge. This approach would not be useful for ruling out suicide, since altered neurochemistry is not likely to be involved in every case.

KEYWORDS: psychiatry, pathology and biology, suicide, brain

Equivocal suicides present a common and often contentious certification challenge. Family and friends often deny signs of altered behavior or emotional state in the decedent; persons at the scene sometimes alter the evidence (such as laying down gun cleaning tools); the subject's sensorium may be clouded by alcohol or other drugs; and, ultimately, reconstructing any person's intent is an uncertain art. Over the last few years there has been increasing evidence of alterations in some neurotransmitters, their metabolites, and their associated receptors in the brains of suicides. Psychiatrists hope that further understanding of these abnormalities will lead to improved detection of high-risk patients and the development of more specific and efficacious therapies. These biochemical measures may also eventually have some use in forensic science. This article will review the findings reported to date, describe the technical and interpretive complexities these assays involve, and discuss sensitivity and specificity issues in the potential use of these alterations for forensic science purposes.

Suicide has generally been attributed to psychological, situational, or sociological causes. Undoubtedly, an array of possible causal and contributory factors can be cited in most suicides. Recently, however, there has been substantial exploration of the role played by physiological derangements in disordered mood and suicidal behavior. The fact that tricyclic antidepressants or lithium often produces a therapeutic response leading to normalization of mood and function in such individuals, while having no behavioral effects on well persons, strongly suggests that, in appropriately diagnosed patients, a

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[1]Assistant professor, Department of Psychiatry, School of Medicine, University of North Carolina, Chapel Hill, NC.

[2]Assistant research professor, Departments of Pathology and Neurology, University of Kentucky Medical Center, and chief biochemical consultant, Kentucky State Medical Examiner's Program, Justice Cabinet, Lexington, KY.

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biological lesion may exist. These drugs have extensively documented effects on norepinephrine- and serotonin-containing neurons [*1*]. Altered hypothalumic function leading to pituitary-adrenal [*2*] and pituitary-thyroid [*3*] disruptions is well documented in sizable subsets of depressed patients. In addition, extensive family studies have determined that serious mood disorders are familial [*4*]. Along these lines, Haberlandt reviewed the suicide literature and found mention of 146 twin pairs of which at least one had committed suicide [*5*]. Concordance was present only for monozygotic twins. In none of the 98 fraternal twin pairs did both commit suicide. In contrast, suicide occurred in both individuals in 9 of the 48 identical twin pairs. This study is methodologically limited but the findings are highly suggestive of a genetic factor in some suicides.

Three main issues have arisen in the biological approach to suicide. First, which alteration is most reliably present? To date, concentrations of neurotransmitters, their metabolic products, and their associated binding sites have been measured. The neurotransmitters studied include serotonin, norepinephrine, dopamine, acetylcholine, gamma-amino butyric acid (GABA), the peptide corticotropin-releasing factor (CRF), and the pineal hormone melatonin. Binding studies have been somewhat inconsistent but are useful because of their postmortem stability and their presumed sensitivity as indicators of recent functional activity.

The second issue involves the choice of appropriate brain areas for scrutiny. At the cellular and molecular levels, the human brain is a vast territory, with increasing evidence of regional compartmentalization and specialization. Obviously, the choice of assay may determine the brain area studied to some degree, but many neurotransmitters and receptors appear to have unique functions and drug sensitivities in different regions.

A third issue involves the clinical interpretation of these data. Studies have shown that suicides often suffer preexisting psychiatric illnesses. A major mood disorder is diagnosable in 40 to 50% of suicides, schizophrenia in 5 to 10%, and a history of chronic substance abuse problems in anywhere from 20 to 60% [*6–8*]. (Whether brain abnormalities in this last group cause excess drinking or are secondary is a further issue.) These alterations may be markers for one of these illnesses. However, it has been suggested that serotonin neurotransmitter changes may increase the propensity for self-destructive behavior (and for violence in general), independent of any psychiatric diagnosis. In this case, these changes would be specific markers of aggressive impulsivity rather than markers of preexisting psychiatric illnesses. The former condition might seem more likely, but in vivo evidence continues to accrue that serotonin metabolites in the cerebrospinal fluid (CSF) of persons who have attempted suicide [*9*] or committed homicide [*10*] or arson [*11*] are chronically altered. Also, individuals prone to excessively aggressive behavior have been found to have different neuroendocrine responses to serotonergic challenges [*12*]. At this point the question remains unsettled.

Review of Studies

Table 1 [*13–23*] lists the twelve studies that have been reported of levels of neurotransmitters and their metabolites in suicide victims. These investigators have largely focused on serotonergic factors, and their findings have displayed regional consistency. Among the seven studies of the brain stem, only one failed to find abnormalities in the levels of either serotonin or its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA). In contrast, four studies that examined cortical or hippocampal specimens were all negative. Two studies of depressed patients dying of natural causes found a similar topographic pattern. These results suggest that cortical levels do not change or that concentrations in the cortical specimens were too dilute to allow detection of changes.

The cell bodies of most neurons that use serotonin as a neurotransmitter are located

in the raphe nuclei, in the brain stem at the level of the rostral pons. These cells send large numbers of axons to many parts of the brain, especially the cortex. The cell bodies manufacture the neurotransmitter, which is transported to the axonal endings, to be released in small pulses. Receptors that receive these signals are located on other cells at the endings of these axons. The type and regional findings listed in Tables 1 and 2 reflect this anatomic distribution. The results of Lloyd et al. [*16*] were especially impressive, probably because they were the only investigators to carefully dissect out the raphe nuclei before assay. Variations in results may be related to the amount of nonspecific material included in the homogenization process. Also, since it is unlikely that all suicides have brain alterations, the relatively low number of subjects included in most studies may also explain variations in group results.

It is of note that no alterations in the level of the catecholamine norepinephrine have been found, despite considerable evidence of its involvement in depression. However, careful examination of the locus ceruleus, where these cell bodies are grouped, has not been done.

While the pineal is not brain tissue, Stanley and Brown found pineal melatonin decreased in suicides dying at night, when melatonin levels are normally substantially increased [*24*]. Melatonin is of interest because its production may be abnormal in depressed patients, it is a quantifiable and unique end product that can be manipulated in vivo by drug or environmental challenges, and its mechanism of control probably depends on interactions among noradrenergic, serotonergic, and peptidergic systems.

These assays were accomplished using gas chromatography (GC) or high-performance liquid chromatography (HPLC) techniques of mild to moderate difficulty. Standardization of measurements can be accomplished across laboratories. Consistency in dissecting samples and their pre-assay processing is critical. Also very important, several of the studies included attempts at classifying subjects as depressed, alcoholic, or other, but their findings were inconclusive. More description of premortem clinical characteristics needs to be included in this type of study. An exception is the study by Korpi et al. [*25*], who clearly identified each subject as suffering from schizophrenia, a distinct psychiatric disorder. The fact that similar neurochemical alterations occurred in this group suggests these changes are not confined to a single diagnostic class.

Table 2 lists the receptor studies that have been done at this point. Many investigators' efforts are now focused on changes in binding. As listed in Table 2, nine different types of binding have been studied, including four repeatedly: beta noradrenergic binding, serotonin Type 2 binding, imipramine binding, and muscarinic cholinergic binding. Most of these studies examined the cortex, where high numbers of receptors are, and several also examined the hippocampus. Beta noradrenergic binding appears promising; the results showed increased binding in three of five studies. In animal studies, many antidepressants have an opposite effect on beta receptors, decreasing their total number. Imipramine, a tricyclic antidepressant, is believed to bind to a presynaptic serotonin reuptake site. This location may or may not be relevant to its mechanism of action. Its status in suicides is not clear, but a recent article by Gross-Isseroff et al. provided convincingly strong evidence of its diminishment, using autoradiography [*44*].

Serotonin Type 2 binding has been reported high in the cortex, a major projection field for serotonin-producing cells in the raphe. Not every laboratory, though, has found its binding elevated (which suggests the possibility of compensatory mechanisms when serotonin is low), and this change may be more related to impulsivity/violence.

We have recently studied serotonin binding in the pineal gland, and found five of eleven suicides with values below those of any control. The significance and reliability of this finding are being pursued [*45*].

Receptor binding can be measured in two ways. Using a membrane preparation involves physically homogenizing a specimen, adding radioactive labels that bind to receptors,

TABLE 1—*Neurotransmitter/metabolite studies in suicides.*[a]

Authors	Assay	Brain Region	Subjects, *N*	Results
Shaw et al. [*13*]	5-HT	whole brain stem	17 controls (C) 11 suicides (S) (depressed)	↓ 5-HT
Bourne et al. [*14*]	5-HT, 5-HIAA, NE	whole brain stem	28 C 23 S (16 depressed)	↓ 5-HIAA, depressed suicides
Pare et al. [*15*]	5-HT 5-HIAA NE, DA	whole brain stem hypothalamus caudate	15 C 26 S	↓ 5-HT (brain stem)
Lloyd et al. [*16*]	5-HT 5-HIAA	raphe nuclei (dorsalis, cent. int.)	5 C 5 S (3 O.D.)	↓ 5-HT
Moses and Robins [*17*]	NE, DA	multiple	9 C 17 S (9 depressed) (8 alcoholic)	negative
Cochran et al. [*18*]	5-HT	multiple mesencephalic tegmentium pons tegmentium	12 C 10 S (10 depressed) (9 alcoholic)	negative

Beskow et al.	5-HT 5-HIAA, NE, DA, HVA	multiple mesencephalon	62 C 23 S	↓ 5-HIAA
Stanley et al. [*20*]	5-HIAA 5-HT	frontal cortex		negative
Korpi et al. [*21*]	5-HT 5-HIAA TRYP	multiple upper pons	29 C 14 S (schizophrenics)	↓ 5-HT ↓ 5-HIAA
Owen et al. [*22*]	5-HT 5-HIAA	cortex hippocampus	20 C 16 S	negative
Manchon et al. [*23*]	5-HT, TRYP 5-HIAA, DA NA, DOPEG GABA	hippocampus	5 C 6 S	negative
Korpi et al. [*21*]	8 amino acids, including GABA	frontal cortex	25 C 13S	negative

[a]Abbreviations: 5-HT = serotonin, 5-HIAA = 5-hydroxy-indoleacetic acid, NE = norepinephrine, DA = dopamine, HVA = homovanillic acid (dopamine metabolite), TRYP = tryptophan, GABA = gamma-butyric acid.

TABLE 2—*Receptor studies in suicides.*

Authors	Type	Brain Region	Subjects, *N*	Results
Stanley et al. [*26*]	imipramine-binding	frontal cortex	9 controls (C) 9 suicide (S)	↓ B_{max}
Meyerson et al. [*27*]	muscarinic-binding imipramine-binding, beta-noradrenergic	frontal cortex	10 C 7 S	↑ B_{max} imipramine-binding ↑ B_{max} muscarinic-binding
Stanley et al. [*28*]	serotonin-2	frontal cortex	11 11 S	↑ B_{max}
Crow et al. [*29*]	serotonin-1 serotonin-2 alpha-noradrenergic beta-noradrenergic GABA	hippocampus occipital cortex	19 C 17 S	↓ B_{max} (hippocampus) ↓ Imipramine-binding (cortex)
Stanley [*30*]	muscarinic	frontal cortex	22 C 22 S	negative
Kaufman et al. [*31*]	muscarinic	frontal cortex hippocampus pons	10 C 10 S	negative
Paul et al. [*32*]	imipramine-binding	hypothalamus	10 C 9 S	↓ B_{max}
Mann et al. [*33*]	serotonin-1 serotonin-2 beta-noradrenergic	frontal cortex	21 C 21 S	↑ B_{max} S-2 ↑ B_{max} beta
Owen et al. [*34*]	serotonin-1 serotonin-2 imipramine-binding	frontal cortex occipital cortex hippocampus	19 C 19 S	negative

Gillin et al. [*35*]	muscarinic	frontal cortex hypothalamus pons	10 C 10 S	negative
Arora and Meltzer [*36*]	serotonin-2 imipramine-binding	frontal cortex	18 C 18 S	↑ B_{max} S-2
Meana and Garcia-Sevilla [*37*]	alpha-noradrenergic	frontal cortex	10 C 5 S	↑ B_{max}
Manchon et al. [*23*]	benzodiazepine-binding	hippocampus	5C 7 S	negative
Biegon and Israeli [*38*]	beta-noradrenergic	frontal cortex	10 C 10 S	↑ B_{max}
Cheetham et al. [*39*]	serotonin-2	frontal, temporal, occipital cortex hippocampus amygdala	19 C 19 S	negative
Arango et al. [*40*]	Beta-noradrenergic	prefrontal cortex temporal cortex	19 C 9 S	↑ B_{max}
Cross et al. [*41*]	GABA-B	frontal, temporal cortex hippocampus	16 C 16 S	negative
Cheetham et al. [*42*]	benzodiasepine-binding	frontal, temporal cortex	21 C	↑ B_{max} benzodiazepine-binding
Nemeroff et al. [*43*]	CRF binding	frontal cortex	29 C 26 S	↓ CRF B_{max}
Gross-Isseroff et al. [*44*]	imipramine-binding	multiple	12 C 12 S	↓ B_{max} imipramine-binding cortex ↑ hippocampus

and then filtering out radioactivity that has become attached to tissue. In autoradiography, a very thin slice of frozen tissue is incubated with the radioactive label, and the excess is then washed off. Autoradiography is more expensive and time-consuming, but provides more sensitivity and anatomical information. Binding experiment results can be presented in raw numbers or mathematically analyzed using a Scatchard plot. By extrapolation, a Scatchard plot estimates the maximal number of binding sites possible, B_{max}, and the concentration of neurotransmitter at which 50% of the sites would be filled, K_D (a measure of the receptors' affinity). Receptor binding studies are more difficult to perform and interpret than measurements of neurotransmitters or metabolite concentrations. These procedures at present are less standardized, and careful internal quality control is necessary at each laboratory.

Overall, 13 receptor studies have been positive and 7 have been negative. No consensus has developed that any assay is "proven." Results from recent and more systematic studies are encouraging, but there is substantial overlap between the suicide and control groups in every study. This may be attributable to the complexity of the phenomenon being investigated. At this point, studies comparing a number of these markers to clarify the sensitivity of each and their dependence on or independence from each other are needed. Careful characterization of the subjects' premortem clinical states and segregation of subjects dying of overdoses or with positive toxicology are necessary. Age, sex, and postmortem intervals need to be closely matched by controls.

The studies so far have not considered the use of these assays as diagnostic tests. At this point, establishing the validity of these changes as markers of suicide and not of age, sex, postmortem interval, method of death, or exposure to ethyl alcohol or to illicit or prescribed drugs remains paramount. These assays will probably not be of use in ruling out suicide because of the substantial overlap between controls and suicides. Many types of persons kill themselves as a result of a variety of antecedent factors. However, these assays may be useful to *rule in* suicide in that subgroup with widely divergent values and might be offered as evidence that the subject was at risk.

In setting a diagnostic cutoff point (or criterion), a lower value can be chosen, which includes many abnormals and increases sensitivity, at the cost of more false positives. A criterion level can be set very high to decrease false positives (and increase specificity) at the expense of sensitivity. Generally, high specificity is required of forensic evidence. For example, two of the above articles reported beta-noradrenergic binding values for every individual included. In the study by Mann et al. (Ref *33*, p. 957), 4 of 11 suicides had values above the highest control value (16 fmol/mg protein bound, at 2.0n*M* 3H-DHA concentration), with controls averaging 8.4 ± 1.5 versus 14.5 ± 1.5. in suicides. In Biegon and Israeli's autoradiographic study (Ref *38*, p. 200), 4 of 10 suicides had values higher than the most extreme control (92 fmol/mg protein, at 150p*M* I-123-pindolol concentration), with controls averaging 58 ± 8 and suicides 86 ± 8. The positive autoradiographic study by Aranga et al. [*40*] and the earlier negative studies of Crow et al. [*29*] and Meyerson et al. [*27*] did not list individual values. If future studies find similar results, although sensitivity may be low (~40%), an extreme value might justifiably be considered specific (but obviously not definitive) evidence.

Summary

Currently, neurochemical methods for detecting suicide cannot be considered forensically useful. These assays suffer from (1) an unclear reliability, (2) a lack of standardization, and (3) an unclear clinical interpretation. However, quantifying neurotransmitters and receptor binding are widely accepted techniques, with solid neurochemical and

pathophysiological bases. There is substantial ongoing work, and interest among neurobiologists and psychiatrists is high. We believe these tests may have eventual use in forensic science but also suggest that caution is warranted against their premature introduction as legal evidence. Their usefulness will probably lie in ruling *in* suicide when levels are extreme, but this approach will never be able to rule out suicide. This will require some sophistication in ignoring negative findings. A value within the range found in controls would be *no* evidence *against* suicide.

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Address requests for reprints or additional information to
Dr. Karley Y. Little
CB-7160
Department of Psychiatry
Medical School Wing B
University of North Carolina
Chapel Hill, NC 27599