ELSEVIER

Impulsive Aggression in Personality Disorder Correlates with Platelet 5-HT_{2A} Receptor Binding

Emil F. Coccaro, M.D., Richard J. Kavoussi, M.D., Yvette I. Sheline, M.D., Mitchell E. Berman, Ph.D., and John G. Csernansky, M.D.

The purpose of this study was to examine the relationship between platelet 5-HT_{2A} receptor binding and aggressive behavior. ^{125}I-LSD B_{max} and K_d values were measured for 22 subjects meeting DMS-III-R criteria for one or more personality disorders and 12 healthy volunteer subjects. Aggression and impulsivity were assessed using the Buss–Durkee Hostility Inventory (BDHI) Assault scale, Life History of Aggression (LHA) scale, and the Barratt–11 Impulsiveness scale (BIS-11). B_{max} and K_d values did not differ between personality disordered subjects and healthy volunteers. However, both B_{max} and K_d values correlated positively with BDHI Assault scores in personality-disordered subjects but not in healthy volunteer subjects. These results suggest that assaultiveness in personality-disordered subjects may covary with increasing numbers, but decreasing affinity, of platelet 5-HT_{2A} receptor sites labeled by ^{125}I-LSD. © *1997 American College of Neuropsychopharmacology* ***[Neuropsychopharmacology 16:211–216, 1997]***

KEY WORDS: *Serotonin; Aggression; Platelet 5-HT_{2A} receptor.*

An important role for the central serotonergic (5-HT) system in suicidal and impulsive aggressive behavior has emerged for nearly 20 years of research (Coccaro et al. 1992). To date, most data suggest that reduced presynaptic 5-HT functioning is associated with suicidal and/or impulsive aggressive behavior. The role of postsynaptic 5-HT functioning in these behaviors is less clear. Many, though not all, studies using brain or platelet receptor measures reveal increased numbers of postsynaptic 5-HT receptors (particularly of the 5-HT_{2A} subtype) in suicide completers (Stanley and Mann 1983; Arora and Meltzer 1989) and attempters (Biegon et al. 1990; McBride et al. 1994; Pandey et al. 1995). Most, though not all, 5-HT pharmacochallenge studies, however, show a reduced physiological response to stimulation of post-synaptic 5-HT receptors in suicidal and/or impulsive aggressive individuals (Markowitz and Coccaro 1995).

Although a substantial body of evidence suggests an increase in 5-HT_{2A} postsynaptic receptors on central neurons of violent suicide completers and on platelets of suicide attempters, the relation between 5-HT_{2A} type receptor binding and indices of impulsive aggressive behavior has not been explored. Postmortem studies of brain 5-HT_{2A} receptor binding in impulsive aggressive individuals have not yet been performed, partly because of the difficulty and unreliability of retrospective assessment of impulsive aggressive behavior.

In this study, we examined platelet ^{125}I-LSD binding parameters as an index of 5-HT_{2A} receptor functioning in health controls and in patients with DSM-III-R per-

From the Clinical Neuroscience Research Unit (EFC, RJK, MEB), Department of Psychiatry, Medical College of Pennsylvania and Hahnemann University, Philadelphia, PA; and the Department of Psychiatry (YIS, JGC), Washington University School of Medicine, St. Louis, MO.

Address correspondence to: Emil F. Coccaro, M.D., Clinical Neuroscience Research Unit, Department of Psychiatry, Medical College of Pennsylvania, 3200 Henry Avenue, Philadelphia, PA 19129.

Received August 28, 1995; accepted December 11, 1995.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/97/$17.00
PII S0893-133X(96)00194-1

sonality disorder. Given the positive relationship between suicidal and impulsive aggressive behavior, particularly as it relates to indices of 5-HT function (Brown et al. 1979; Coccaro et al. 1989, 1992; Lopez-Ibor et al. 1990), we hypothesized that platelet ^{125}I-LSD B_{max} values would be positively associated with aggression, particularly in a personality-disordered population.

METHODS

Subjects

Subjects were 22 medically healthy outpatients (male = 14; female = 8) diagnosed with one or more DSM-III-R personality disorders, and 12 medically healthy volunteers (male = 4; female = 8) with no documented psychopathology. Personality disorder subjects were recruited by newspaper advertisements seeking individuals who (1) considered themselves to have difficulty controlling their aggressive tendencies; or (2) were willing to participate in biological studies of personality. Healthy volunteers also were recruited by newspaper advertisement. After all procedures were fully explained, written informed consent, using an IRB-approved consent document, was obtained from all subjects.

Diagnostic and Medical Evaluation

Axis I and II diagnoses were made according to DSM-III-R criteria (Spitzer 1987). Alcoholism was diagnosed using the modified Research Diagnostic Criteria as in previous reports (Coccaro et al. 1989). Research diagnoses were assigned through a best-estimate consensus process (Leckman et al. 1982; Klein et al. 1994) involving two psychiatrists (EFC, RJK) and three psychologists (MEB, JDL, LYW) based on information obtained through: (1) interviews by a trained clinician using the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer and Endicott 1978) and the Structured Interview for the Diagnosis of Personality Disorder (SIDP-R; Pfohl and Zimmerman 1989); (2) clinical interviews by a research psychiatrist; and (3) all other available clinical data. Current and past Axis I and II diagnoses are displayed in Table 1. Healthy volunteer subjects were found to be free of current or lifetime psychopathology; these subjects had no family history of psychopathology. Subjects with evidence of any current medical (including hematological) illness, whether or not medication was required, were not enrolled in this study. Medical health was confirmed by physical and laboratory examination, including a comprehensive drug screen.

Platelet Studies

Only two of the 34 subjects, both in the personality disorder group, had a history of treatment with psychotropic agents. Each had discontinued treatment at least 6 months prior to study. Subjects were instructed to remain drug-free for 2 weeks, to follow a low-monoamine diet for at least 3 days, and to fast, without smoking, from midnight prior to the study. Subjects were informed that initial and follow-up urine toxicology would be performed randomly just prior to study. Illicit drug use was not detected in any subject. Females were studied within the first 10 days of the follicular phase of their menstrual cycle. Then 20-cc blood samples were obtained between 9:00 and 9:30 A.M. through a 20-gauge

Table 1. Axis I and II Personality Disorder Diagnoses

Axis I	Axis II
Current (n = 9)	Dramatic Cluster (n = 8)
Depressive disorder-NOS (n = 3)	Borderline (n = 3)
Intermittent Exp. Disorder (n = 2)	Histrionic (n = 3)
Social phobia (n = 2)	Narcissistic (n = 2)
Dysthymia (n = 1)	Antisocial (n = 1)
Adjustment disorder (n = 1)	
Past (n = 15)	Anxious cluster (n = 6)
Alcoholism (n = 7)	Obsessive-compulsive (n = 3)
Drug abuse/dependence (n = 7)	Avoidant (n = 2)
Major depression (n = 5)	Passive-aggressive (n = 2)
Depressive disorder NOS (n = 4)	Dependent (n = 1)
Dysthymia (n = 1)	
	Eccentric cluster (n = 3)
	Paranoid (n = 2)
	Schizoid (n = 1)
	Other PD
	Personality disorder-NOS (n = 7)

indwelling intravenous catheter that was in place for other biological studies being performed in our unit. Samples were processed to determined platelet 5-HT_{2A} receptor binding parameters (receptor density; B_{max}; dissociation constant; K_d) as previously described (Sheline et al. 1995). Only samples with a correlation coefficient from the Scatchard plot analysis exceeding 0.75 were used in the data analysis. The mean for the correlation coefficients used in this study was 0.90 ± 0.06 (range, 0.78 to 0.99).

Table 2. Comparison of Patient and Control Data

	PD PATIENTS (n = 22)	CONTROLS (n = 12)	p
B_{max} (fmol/mg protein)	43.3 ± 27.09	35.7 ± 21.40	NS
K_d (nM)	0.76 ± 0.64	0.74 ± 0.31	NS
Sex (M/F)	14/8	4/8	NS
Age (years)	33.0 ± 9.7	26.5 ± 6.5	.027
GAF score	59.5 ± 9.7	88.0 ± 6.4	.001
BDHI Assault	4.6 ± 3.2	2.1 ± 1.6	.004
LHA Aggression	9.4 ± 7.3	3.3 ± 3.1	.002
BIS-11 Impulsivity	42.3 ± 17.3	32.5 ± 15.7	NS
HAM-D21 score	2.9 + 4.2	0.1 ± 0.3	.008

Behavioral Measures

The primary behavioral measures were (1) the Assault subscale of the self-report Buss–Durkee Hostility Inventory (Buss and Durkee 1957); (2) the Aggression score from the Life History Aggression (LHA) interview assessment (the LHA represents a revision of the Brown–Goodwin Life History of Aggression; Brown et al. 1979); and (3) the total score from the self-report Barratt Impulsiveness Scale (BIS-11; Barratt 1985). The 21-item Hamilton Depression Rating Scale (HAM-D) was used to assess the severity of current depressive symptoms.

Statistical Analysis

Group means are expressed as mean ± SD. Associations were tested using Pearson correlations unless otherwise specified. Group comparisons were conducted using t-tests. One-tail tests were used for the correlation between the primary aggression and impulsivity variables and ^{125}I-LSD B_{max} values; two-tailed tests, with Bonferroni correction for multiple comparisons, were used for secondary variables (e.g., other subscales) for the BDHI, LHA, BIS-11 assessments. Based on the direct relationship between suicidal behavior (a behavior closely related to aggression; Brown et al. 1979; Coccaro et al. 1989, 1992; Lopez-Ibor et al. 1990) and number of 5-HT_{2A} binding sites in brain and platelet, we hypothesized a positive correlation between ^{125}I-LSD B_{max} values and the primary aggression and impulsivity variables.

RESULTS

Males and females did not differ on ^{125}I-LSD binding parameters, age, global functioning (GAF), HAM-D21, LHA, BDHI, or BIS-11 scores, or the presence of current (or past) Axis I disorders. Accordingly, males and females were combined for further analysis. Although normal controls differed from personality-disordered subjects on a number of variables (Table 2), only the behavioral variables demonstrated any statistically significant relationship with platelet ^{125}I-LSD B_{max} and K_d values. Specifically, a statistically significant correlation between platelet ^{125}I-LSD B_{max} values and BDHI-Assault scores was noted among all subjects (r = .32, p = .032). This was due to a significant correlation in personality disordered (r = .39, p = .038; Figure 1), but not healthy volunteer (r = −.17, p > .3), subjects. A stronger positive correlation was noted between K_d values and BDHI-Assault scores among all subjects (r = .42, p = .014); again because of personality-disordered (r = .55, p = .008; Figure 1), but not healthy volunteer (r = −.35, p > .2), subjects. These primary platelet ^{125}I-LSD Binding/BDHI-Assault correlations also were statistically significant when subjected to rank-ordered statistics (Spearman Rho: B_{max}: r_s = .36, n = 22, p < .05; K_d: r_s = .61, n = 22, p = .003). The platelet ^{125}I-LSD Kd/BDHI-Assault correlation was not accounted for by the strong relationship between K_d and B_{max} values (r = .86, n = 22, p < .001); partial correlation, with B_{max} as a covariate yielded a similarly significant correlation ($r_{partial}$ = .46, df = 19, p = .036). B_{max}/K_d and BD-Assault relationships were not altered by removing the data of two subjects with life history of suicide attempt (B_{max}: r = .38, n = 20, p = .048; K_d: r = .55, n = 22, p = .01). Notably, the seven personality-disordered subjects with high (i.e., ≥7) BDHI Assault scores (i.e., mean; 8.6 ± 1.3; range, 7–10) had higher B_{max} (57.4 ± 34.4 vs. 36.8 ± 21.2; $t_{(20)}$ = 1.74, p = .049); and K_d values (1.31 ± .85 vs. 0.51 ± .28; $t_{(20)}$ = 3.38, p = .003) than the personality-disordered subjects who had low (i.e., ≤6) BDHI Assault scores (mean; 2.7 ± 1.7; range; 0–5). These differences also were significant by rank-ordered statistics (i.e., Mann–Whitney U test: B_{max}; p = .049; K_d; p = .0015). LHA-Aggression and BIS-11-Impulsivity scores were not significantly correlated with B_{max} or K_d values except for BIS-11 for all subjects (r = .34, p = .037). Analyses with the secondary BDHI, LHA, and BIS-11 variables did not reveal significant correlations with either B_{max} or K_d values. Relationships between BDHI Assault and B_{max} and K_d measures could not be accounted for by any secondary relationship with age, gender, sea-

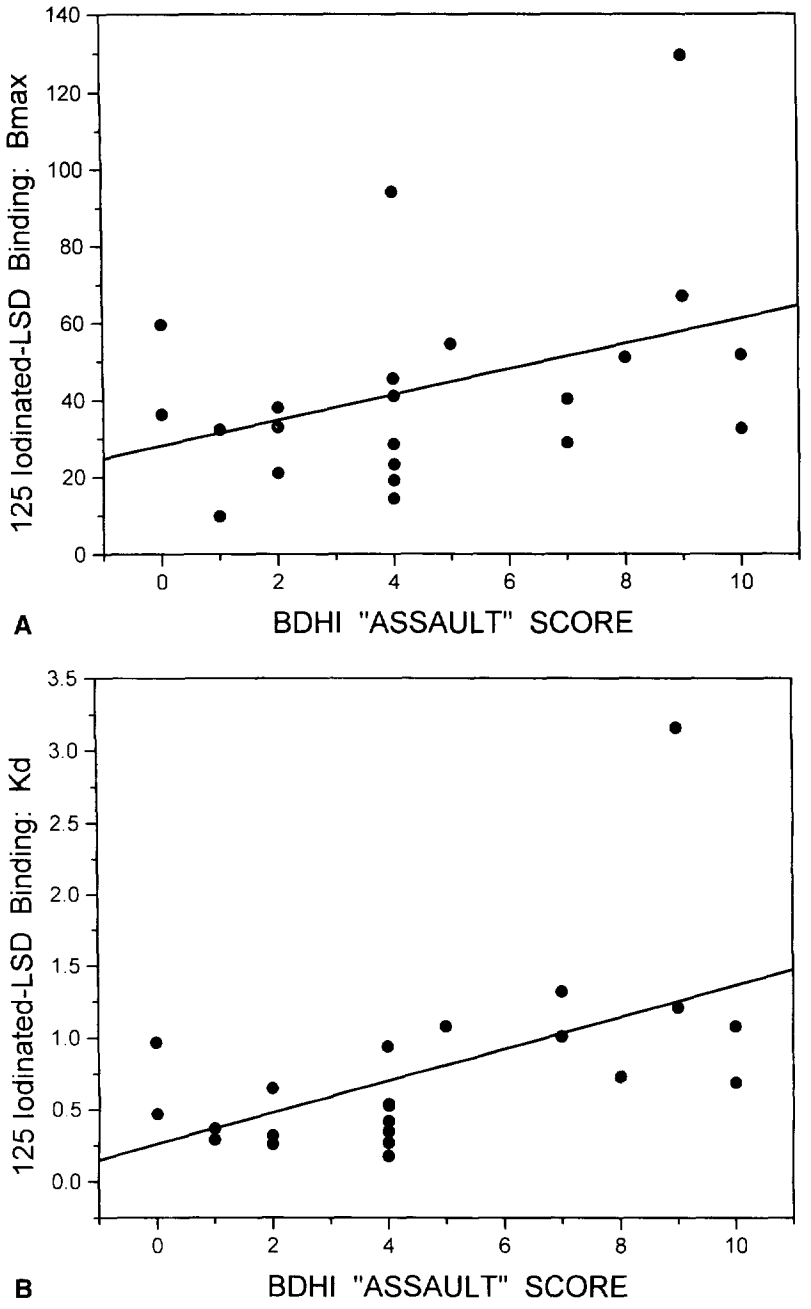

Figure 1. Correlation between Buss–Durkee Assault score and B_{max} ($r = .39$, $n = 22$, $p = .038$) **(A)** and K_d ($r = .55$; $n = 22$; $p = .008$) **(B)** values of platelet ^{125}I-LSD binding in 22 males and females with DSM-III-R personality disorder. Rank-ordered correlations of these data are also statistically significant (see text).

son of study, HAMD-21 scores, GAF scores, or life history of major depression, alcoholism, or drug abuse.

DISCUSSION

These data suggest that measures reflecting a tendency to be assaultive in personality-disordered individuals directly correlate with parameters of platelet 5-HT_{2A} receptor binding and affinity as characterized by ^{125}I-LSD binding. The relationship between the number of platelet ^{125}I-LSD binding sites (B_{max}) and self-reported assaultiveness is similar to that reported for brain ^{3}H-spiperone (Stanley and Mann 1983; Arora and Meltzer 1989) binding measures and completed suicide and between platelet ^{125}I-LSD binding and history of attempted suicide in depressed patients (Pandey et al. 1995) and between platelet ^{3}H-spiperone binding measures in nonpsychiatric subjects with history of attempted suicide (Biegon et al. 1990). The absence of correlations among healthy normal volunteer subjects may be accounted for by the limited variance in aggression scores in sample and/or the small sample size. The absence of an overall difference of B_{max} and K_d values between personality-disordered subjects and healthy volunteers indicates that there are no platelet 5-HT_{2A} receptor site abnormalities in personality-disordered

subjects as a diagnostic group. Rather, these data suggest that there is a relationship between a dimension of aggression and variables related to platelet 5-HT$_{2A}$ receptor characteristics. This is consistent with other data relevant to biological and personality variables in personality-disordered individuals (Siever and Davis 1991).

Increased 5-HT$_{2A}$ receptor binding (e.g., in the brains of suicide victims) has been interpreted as representing an upregulation of post-synaptic 5-HT$_{2A}$ receptors associated with reduced presynaptic 5-HT function. However, because platelets are not innervated by 5-HT neurons, a "denervation-type" compensatory mechanism cannot explain the increased numbers of 5-HT$_{2A}$ receptors on the platelets of suicide attempters (Biegon et al. 1990; Pandey et al. 1995), their positive correlation with lethality of suicide attempt (McBride et al. 1994), or the positive correlation with assaultiveness reported here. Moreover, animal studies suggest that experimentally reduced 5-HT function does not usually lead to changes in ligand characteristics (Seeman et al. 1980, Blackshear et al. 1981; Quik and Azmitia 1983) or in physiological responsiveness (Conn and Sanders-Bush 1986) of central 5-HT$_{2A}$ receptors. As platelet 5-HT$_{2A}$ receptors (as labeled by ^{125}I-LSD) are pharmacologically identical to brain 5-HT$_{2A}$ receptors (Elliot and Kent 1989), and are translational products of the same genes (Cook et al., 1994), it is possible that, if a compensatory mechanism is involved in such subjects, it occurs at the level of gene expression or gene structure. If so, alterations in platelet 5-HT$_{2A}$ receptor binding characteristics might reflect analogous alterations in neuronal 5-HT$_{2A}$ receptors. The existence of alteration(s) in genetic elements modulating suicidal and/or aggressive behavior is suggested by family, twin, and adoption data (Kety 1986; Plomin et al. 1990). The identities of the genetic abnormalities are unknown at this time, although a polymorphism in the intronic portion of the tryptophan hydroxylase (TPH) gene was recently reported as a correlate of suicidal behavior in a group of violent offenders (Neilson et al. 1994). A significant relationship between TPH genotype and CSF 5-HIAA concentration among impulsive violent offenders also was found. Thus, it is possible that abnormalities in genetic elements controlling both specific aspects of 5-HT function and suicidal/aggressive behavior may be identified.

The functional consequence of increased numbers (and/or decreased binding affinity) of central or peripheral 5-HT$_{2A}$ receptors in suicidal or impulsive aggressive individuals is not currently known. Some pharmacochallenge studies with 5-HT agonist probes suggest that central postsynaptic 5-HT receptors may be functionally supersensitive in suicidal/impulsive aggressive individuals (Meltzer et al. 1984). However, others suggest that these receptors are functionally subsensitive (Coccaro et al. 1989; Lopez-Ibor et al. 1990; Moss et al. 1990). Differences among the studies may be due to a variety of methodological factors, including the use of different 5-HT probes and different study populations. A more definitive answer to the functional consequence of altered 5-HT$_{2A}$ receptor numbers in suicidal/impulsive aggressive subjects must wait for the availability of a specific 5-HT$_{2A}$ receptor probe.

ACKNOWLEDGMENTS

This project was supported in part by NIHM grants RO1MH49678 and KO2MH00951 (EFC). The authors acknowledge Jennifer D. Lish, Ph.D., and Lauren Y. Weinberg, M.S.Ed., for their contributions to the best-estimate procedures involved in the final assignment of subject diagnosis. Also note are the technical contributions to Michelle Stozek, Michael Oakes, Miranda Ellis, and Jaime Jackson.

REFERENCES

Arora RC, Meltzer HY (1989): Serotonergic measures in the brains of suicide victims: 5-HT$_2$ binding sites in the frontal cortex of suicide victims and control subjects. Am J Psychiatry 146:730–736

Barrat ES (1985): Factor analysis of some psychometric measures of impulsiveness and anxiety. Psychol Reports 16:547–554

Biegon A, Grinspoon A, Blumenfeld, Bleich A, Apter A, Mester R (1990): Increased serotonin 5-HT$_2$ receptor binding on blood platelets of suicidal men. Psychopharmacology 100:165–167

Blackshear MA, Steranka LR, Sanders-Bush E (1981): Multiple serotonin receptors: Regional distribution and effects of raphe lesions. Eur J Pharmacol 76:325–334

Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF (1979): Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1:131–139

Buss AH, Durkee A (1957): An inventory for assessing different kinds of hostility. J Consult Psychol 21:343–348

Coccaro EF, Siever LJ, Klar H, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL (1989): Serotonergic studies in affective and personality disorder patients: Correlates with suicidal and impulsive aggressive behavior. Arch Gen Psychiatry 46:587–599

Coccaro EF, Kavoussi RJ, Lesser J (1992): Self- and other-directed human aggression: The role of the central serotonergic system. Int Clin Psychopharmacology 6(S6):70–83

Conn PJ, Sanders-Bush E (1986): Regulation of serotonin-stimulated phosphoinositide hydrolysis: Relations to the 5-HT-$_2$ binding site. J Neurosci 6:3669–3675

Cook EH, Fletcher KE, Wainwright M. Marks N, Yna S-Y, Leventhal BL (1994): Primary structure of the human platelet serotonin 5-HT$_{2A}$ receptor: Identity with frontal cortex serotonin 5-HT$_{2A}$ receptor. J Neurochemi 63:465–469

Elliot JM, Kent A (1989): Comparison of ^{125}I-Iodolysergic acid diethylamide binding in human frontal cortex and platelet tissue. J Neurochem 53:191–196

Kety SS (1986): Genetic factors in suicide. In A Roy (ed.), Suicide. Baltimore, MD, Williams & Wilkins, pp 41–45

Klein DN, Ouimette OC, Kelly HS, Ferro T, Riso LP (1994): Test-retest reliability of a team consensus best-estimate diagnoses of axis I and II disorders in a family study. Am J Psychiatry 151:1043–1047

Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM (1982): Best estimate of lifetime psychiatric diagnosis: A methodologic study. Arch Gen Psychiatry 39:879–883

Lopez-Ibor JJ, lana F, Saiz Ruiz J (1990): Conductas autoliticas impulsivas y serotonina. Actas Luso-Esp Neurol Psiquiatr 18:316–325

Markowitz PI, Coccaro EF (1995): Biological studies of impulsivity, aggression, and suicidal behavior. In Hollander E, Stein DJ (eds), Impulsivity and Aggression. Chichester, England, Wiley, pp. 71–90

McBride PA, Brown RP, DeMeo M, Keilp J, Mieczkowski T, Mann JJ (1994): The relationship of platelet 5-HT_2 receptor indices to major depressive disorder, personality traits and suicidal behavior. Biol Psychiatry 35:295–308

Meltzer HY, Perline R, Tricou BJ, Lowry MT, Robertson A (1984): Effect of 5-hydroxytryptophan on serum cortisol levels in major affective disorders. II. Relation to suicide, psychosis, and depressive symptoms. Arch Gen Psychiatry 41:379–387

Moss HB, Yao JK, Panzak GL (1990): Serotonergic responsivity and behavioral dimensions in antisocial personality disorder with substance abuse. Biol Psychiatry 28:325–338

Neilson DA, Goldman D, Virkkunen M, Tokola R, Rawlings R, Linnoila M (1994): Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. Arch Gen Psychiatry 51:34–38

Pandey GN, Pandey SC, Dwivedi Y, Sharma RP, Janicak PG, Davis JD (1995): Platelet 5-HT_{2A} receptors: A potential biological marker for suicidal behavior. Am J Psychiatry 152:850–855

Pfohl B, Zimmerman M (1989): Structured Interview for the Diagnosis of DSM-II-R Personality Disorders. Ames: University of Iowa College of Medicine.

Plomin R, Nitz K, Rowe DC (1990): Behavioral genetics and aggressive behavior in childhood. In Lewis M, Miller SM (eds), Handbook of Developmental Psychopathology. pp 119–113

Quik M, Azmitia E (1983): Selective destruction of the serotonergic fibers of the fornix-fimbria and cingulum bundle increases 5-HT_1 but not 5-HT_2 receptors in the rat midbrain. Eur J Pharmacol 90:377–384

Seeman P, Westman K, Coscina D (1980): Serotonin receptors in hippocampus and frontal cortex. Eur J Pharmacol 66:179–191

Sheline YI, Bardgett ME, Jackson JL, Newcomer JW, Csernansky JG (1995): Platelet serotonin markers and depressive symptomology. Biol Psychiatry 37:443–447

Siever LJ, Davis KL (1991): A psychobiological perspective on the personality disorders. Am J Psychiatry 148:1647–1658

Spitzer RL (1987): The Diagnostic and Statistical Manual, 3rd ed, revised (DSM-III-R). Washington, DC, American Psychiatric Press.

Spitzer RL, Endicott J (1978): Schedule for Affective Disorders and Schizophrenia. New York, New York State Psychiatric Institute.

Stanley M, Mann JJ (1983): Increased $serotonin_2$ binding sites in frontal cortex of suicide victims. Lancet 1:214–216