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Upregulation of the Platelet Serotonin$_{2A}$ Receptor and Low Blood Serotonin in Suicidal Psychiatric Patients

Key Words
Suicidality
Depression
Adjustment disorder
Schizophrenia
Blood serotonin
Platelet serotonin$_{2A}$ receptor

Abstract
Suicidality has been found to be associated with low pre- and postsynaptic serotonin functioning. The purpose of this study was to examine whether in *acutely* suicidal psychiatric inpatients, the blood serotonin concentration was related to the underlying psychiatric disorder and whether it was associated with changes in the affinity (dissociation constant, K_D) or in the maximal binding capacity (B_{max}) of the platelet serotonin$_{2A}$ receptor. We therefore determined the blood serotonin concentrations and the platelet serotonin$_{2A}$ receptor activities of 45 suicidal psychiatric patients and 20 healthy subjects. We found that the blood serotonin concentrations were significantly lower in suicidal patients compared to healthy subjects. In all diagnostic categories (affective disorder, schizophrenia and adjustment disorder) we noted a significantly higher maximal binding capacity of the platelet serotonin$_{2A}$ receptor. These findings support the notion that a reduction in the availability of serotonin and an upregulation of the serotonin$_{2A}$ receptors in psychiatric patients are associated with a loss of control over suicidal impulses.

Introduction

The disposition to suicidal behavior in psychiatric patients has been traced to alterations in serotonergic activity. It has been hypothesized that serotonin and its receptors function as mediators of control over irrelevant, distracting and irritating sensory stimulation, regulate impulsivity and influence auto- and heteroaggressive behavior [1, 2]. Thus reduced serotonin availability may be related to suicidal behavior [for review see 3], in that low concentrations of 5-hydroxyindoleacetic acid, a metabolite of serotonin in the cerebrospinal fluid (CSF), have been observed in acutely suicidal patients [4]. An increase [5–8], but also a decrease [9], was found in the maximal binding capacity (B_{max}) of the serotonin$_{2A}$ receptor in the postmortem brain tissue of suicide victims, while other authors observed no change [10–12].

The platelet serotonin content is regarded as an index of presynaptic serotonin function [13, 14]. Platelets contain most of the biochemical elements of serotonergic function, comparable to the serotonergic neuron; therefore, blood and platelet serotonin concentrations may serve as a paradigm to assess serotonergic activity. This agrees with what had previously been observed, namely, that there was a correlation between the blood serotonin concentrations and the platelet serotonin$_{2A}$ receptor activity, and the maximal binding capacity of the serotonin$_{2A}$ receptor in platelets and the frontal cortex in mammals and humans [15, 16].

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The aim of the present study was to investigate whether putative alterations occurred in the blood serotonin concentration and the B_{max} and dissociation constant (K_D) of the platelet serotonin$_{2A}$ receptor in acutely suicidal patients compared to healthy controls and whether these biochemical parameters were related to the patient's psychopathological findings.

Subjects and Methods

Subjects

The subjects were 45 suicidal inpatients treated at the Psychiatric Department of the University of Bonn and 20 healthy volunteers. The patients were diagnosed by the psychiatric resident and the attending psychiatrist according to a checklist derived from ICD-10 [17] criteria. All patients were seen by the same psychiatric resident. Patients recruited over a 3-year interval for crisis intervention were included in the study because of acute suicidality during the course of their illness or after a suicide attempt if they fulfilled the following criteria: (1) hospitalization due to acute suicidality or (2) presentation within 4 days after a suicide attempt (these criteria were necessary to keep the patients in a closed ward); (3) availability of psychiatric exploration and blood sampling within 4 days after the suicide attempt; (4) absence of physical illness; (5) free of antidepressants or of drugs that interfered with the serotonin parameter measurements such as clozapine, risperidone, fenfluramine, and at least 2-week use of aspirin; (6) no measurable serum concentrations of SSRI, lithium or tricyclic antidepressants, and (7) no history of alcohol or drug abuse. Data were available from routine clinical laboratory tests, drug monitoring of psychoactive drugs, drug-screening in urine and thrombocyte counts. Criteria 4–7 were applied also to healthy subjects.

Psychopathology was assessed according to the Brief Psychiatric Rating Scale (BPRS) [18], and the severity of the depressive symptoms according to the 21-item Hamilton Depression Rating Scale (HDRS) [19]; suicidal ideation and severity were rated by the Suicide Intent Scale (SIS) [20] and anxiety by the Spielberger's Anxiety Scale (STAI-G, forms 1 and 2) [21].

The study protocol was in accordance with the Declaration of Helsinki (revised form, Hong Kong 1989) and was approved by the Ethics Committee of the Medical Faculty of the University of Bonn. Patients and healthy subjects were informed on the aims and study protocols; written consent was obtained from the participants.

Patients' age ranged from 18 to 59 years, that of the healthy subjects from 18 to 66 years. Patients with affective disorder were somewhat older than patients with adjustment disorder or schizophrenia.

Methods

Blood (50 ml) was obtained from healthy subjects and patients between 8.00 and 10.00 h and at about the same time of year to avoid problems arising from circadian and circannual rhythm changes. It was withdrawn from the antecubital vein of healthy subjects and patients into vacutainers containing 0.1 ml EDTA (0.38 mol/l) for each 10 ml of blood. An aliquot of blood for platelet counting was placed in a Neubauer chamber; the results were validated by external quality control. Blood was centrifuged within 2 h for 15 min at 200 *g* (Minifuge 2, Heraeus Christ, Osterode, Germany) to obtain platelet-rich plasma. The supernatant was aspirated and centrifuged for 10 min at 2,100 *g* to obtain platelets. The plasma was carefully aspirated and the sediment, consisting of platelets, was suspended in buffer I (5 mmol/l Tris-HCl, containing 0.1% EDTA, pH 7.5) to lyse the platelets; the suspension was centrifuged for 20 min at 30,000 *g*. This procedure was repeated *twice*. The resulting sediment, which consisted of platelet membranes, was resuspended in buffer II (50 mmol/l Tris-HCl, pH 7.4, containing 120 mmol/l NaCl, 5 mmol/l KCl, 1 mmol/l $MgCl_2$ and 0.05% ascorbic acid) and stored at –80 °C. Prior to our assays, the platelet membranes were thawed on ice and homogenized in a loose-fitting Potter Elvehjem glass homogenizer (Braun, Melsungen, Germany). The final protein concentration of the platelet membrane preparations was adjusted to 1 mg protein/ml. Protein was determined according to Lowry et al. [22] using bovine serum albumin as a standard.

Serotonin$_{2A}$ receptor binding assays were carried out in triplicate in siliconized glass tubes with 150 µl buffer II and 100 µl platelet membrane suspension corresponding to 100 µg of protein. The reaction was begun by adding 50 µl ^{3}H-LSD; final concentrations ranged from 0.08 to 5.0 nmol/l corresponding to 1,700–100,000 cpm and the final volume was 300 µl. Nonspecific binding was determined by replacing 50 µl buffer II with ketanserin dissolved in buffer II at a final concentration of 1 µmol/l. Specific binding was the difference between binding in the absence and presence of ketanserin. Incubations were done at 37 °C for 3 h and terminated by rapid filtration over Whatman GF/C filters; the filters were washed twice with ice-cold buffer II and counted in 5 ml Aquasafe 300 (Zinsser Analytic, Frankfurt, Germany) in a liquid scintillation beta-counter (Packard Instruments, Downers Grove, Ill., USA). The binding data were evaluated by a modified Marquardt analysis [23, 24]. Experiments with a correlation coefficient exceeding 0.95 were included in data analysis. Quality control of the receptor determinations was carried out with platelets from the same donor (C.F.); the interassay coefficients of variation for B_{max} and K_D were 8 and 11%, respectively.

Serotonin was measured by high-performance liquid chromatography and electrochemical detection [25]. The intra- and interassay coefficients of variation were 2.9 and 4.4%, respectively. The lower limit of detection was 10 nmol/l. The serum was analyzed to check for antidepressants [26, 27]. Clinical assessment and biological measurements were carried out blindly to each other.

Statistics

Wherever appropriate, data were log-transformed to achieve normal distribution as ascertained by the Kolmogorov-Smirnov test. The mean differences in the parameters between healthy subjects and the three suicidal patient groups were assessed by an ANOVA and the interaction of age with the biological parameters by an ANCOVA. For multiple comparisons between items, the least-significance difference test was performed [28]. Statistical comparisons between two groups were carried out by the one-tailed nonparametric Mann-Whitney U test. Spearman rank-order correlations evaluated the relation between the various parameters. All data presented are mean ± one standard deviation; $p < 0.05$ was considered significantly different.

Results

The 51 suicidal patients and 22 healthy subjects eligible for the study were screened for antidepressant drugs in blood and recreational drugs in urine; 45 suicidal patients

Table 1. Demographic and nosological data of healthy subjects and suicidal patients (mean ± SD)

	Healthy subjects	Patients		
		adjustment disorder	affective disorder	schizophrenia
Subjects	20	18	16	11
Age, years	31 ± 9[b]	35 ± 13	45 ± 8[a, b]	29 ± 7[a]
BPRS		37 ± 8[d]	40 ± 8[c]	54 ± 1[c, d]
HAMD		22 ± 9	28 ± 7	27 ± 8
SIS		15 ± 9	20 ± 7	20 ± 6
STAI-G		67 ± 8	69 ± 7	66 ± 5
Time after onset (first episode) of psychiatric symptoms in months		26 ± 73[c, d]	90 ± 159[c]	83 ± 70[d]

For each group, means with common superscript are significantly different: [a, b] $p < 0.05$; [c, d] $p < 0.001$.

and 20 healthy subjects fulfilled the criteria for entering the study (table 1). All depressed patients qualified as unipolar and none of the patients had a history of heteroaggressive acts. Patients with adjustment disorder were only included when they were free of axis II pathology according to the checklist of ICD-10. None of the schizophrenic patients presented with imperative voices to commit an autoaggressive act. The depressed and schizophrenic patients were more chronically ill and had a longer hospital residence than patients with adjustment disorder. The BPRS was more pronounced in schizophrenic patients than in those with affective disorder or adjustment disorder. The level of depression was moderately severe and was highest in patients with affective disorder, followed by those with schizophrenia and adjustment disorder, although these differences were not statistically significant. The SIS were similar in patients with schizophrenia and affective disorder and somewhat lower, but not statistically significant in patients with adjustment disorder. None of the suicidal patients had committed heteroaggressive acts. Sixty-four percent of these patients were referred to us immediately after a suicide attempt; 36% were hospitalized on account of their suicidality in the context of their psychiatric ailment. Thus 22% of the patients with adjustment disorder, 38% of the depressed patients and 33% of the schizophrenic patients had never attempted suicide. Of these 45 acutely suicidal patients, 29 had previously attempted suicide, 18 patients violently and 11 patients nonviolently. There were no significant differences in the groups with violent and nonviolent suicide attempts in BPRS, HDRS, STAI-G, age or sex. Past suicidal history (no previous suicide attempt, nonviolent or violent suicide attempts) was not related to the present psychopathology rating.

We found no correlation between age and the serotonergic parameters and no difference between men and women in their serotonergic parameters in patients or controls, in agreement with what has previously been reported [29–32].

Blood serotonin concentrations were lower in the entire suicidal patient group than in healthy subjects (table 2). Patients with adjustment disorder had similar blood serotonin concentrations compared to healthy subjects, but schizophrenic patients and patients with affective disorder had lower blood serotonin concentrations, the latter of which contributed mainly to the overall decrease. The average platelet count was similar in patient groups and healthy subjects. The B_{max} of serotonin$_{2A}$ receptors was significantly higher in suicidal patients than in healthy subjects; there was no significant difference between the three different patient groups, but the B_{max} of each diagnostic category was significantly higher than that of the healthy subjects (table 2).

The blood serotonin concentration of patients with a previous suicide attempt (0.80 ± 0.29 μmol/l, n = 29) and without a previous suicide attempt (0.80 ± 0.42 μmol/l, n = 16) were not significantly different between the two groups; this applied also to the K_D of the serotonin$_{2A}$ receptor (0.70 ± 0.11 nmol/l, n = 29, vs. 0.76 ± 0.63 nmol/l, n = 16) and the B_{max} of serotonin$_{2A}$ receptors (115 ± 40 fmol/mg protein, n = 29, vs. 102 ± 34 fmol/mg protein, n = 16).

The B_{max} and K_D of serotonin$_{2A}$ receptors were well correlated in healthy subjects ($r = 0.616$, $p < 0.0027$) and somewhat less so in suicidal patients, though still significant ($r = 0.357$, $p < 0.05$). Blood serotonin correlated significantly positively with the affinity (K_D) of serotonin$_{2A}$

Table 2. Platelet counts and serotonergic parameters of healthy subjects and suicidal patients (mean ± SD)

	Healthy subjects	All patients	Patients		
			adjustment disorder	affective disorder	schizophrenia
Blood serotonin, µmol/l	0.91 ± 0.19[a, b, c]	0.80 ± 0.34[a]	0.91 ± 0.43	0.72 ± 0.25[b]	0.73 ± 0.23[c]
Platelet counts, 10^3/µl	227 ± 36	242 ± 72	258 ± 82	240 ± 42	221 ± 88
Serotonin$_{2A}$-receptor B_{max}, fmol/mg protein	85.9 ± 21.8[a, d–f]	110.3 ± 38.2[a]	113.3 ± 34.8[d]	108.4 ± 34.6[e]	107.8 ± 50.2[f]
Serotonin$_{2A}$-receptor K_D, nmol/l	0.49 ± 0.24	0.72 ± 0.55	0.80 ± 0.58	0.58 ± 0.37	0.80 ± 0.72

For each group, means with common superscript are significantly different: [a, e, f] $p < 0.05$; [b, c] $p = 0.09$; [d] $p < 0.01$.

receptors in healthy subjects ($r = 0.44$, $p < 0.05$), which were somewhat less pronounced across all suicidal patients ($r = 0.28$, $p < 0.05$). There were no significant correlations between the platelet receptor parameters and the psychopathological scores.

Discussion

Our study shows that platelet serotonergic parameters differed between acutely suicidal patients and healthy subjects, suggesting the former had an imbalance in serotonergic activity. These patients had lower blood serotonin than healthy subjects and their B_{max} of the serotonin$_{2A}$ receptor was upregulated.

When we subdivided the suicidal patients according to diagnosis, we noted a trend toward low blood serotonin in the schizophrenic patients and in patients with affective disorder. These data on blood serotonin agree with those from earlier studies that reported low blood serotonin concentrations in schizophrenic, schizoaffective and depressed patients who were acutely suicidal or had a history of previous suicide attempts [32–35].

The HDRS, STAI-G, and SIS scores were similar among patients with schizophrenia, affective disorder, and adjustment disorder. The BPRS scores of schizophrenic patients were higher than those of patients with affective disorder, but this difference did not seem to play a role with respect to the biochemical findings, as both groups had similarly low blood serotonin. Since there was a significant correlation between the scores from BPRS and HDRS, HDRS and SIS, BPRS and SIS (data not shown), we studied the graphs of this correlation analysis but found no clustering of items with respect to any diagnostic category. However, the low variance in serotonergic parameters precluded any meaningful correlation between the above psychopathological ratings. To elucidate whether any previous suicidal history influenced biological parameters, we subdivided patients into those with no previous suicide attempt(s), nonviolent suicide attempts and violent suicide attempts; again there was no significant difference between these three groups with respect to blood serotonin concentration or to B_{max} and K_D of the serotonin$_{2A}$ receptor, nor was there any association between the patients' previous suicidal history and any of the biological parameters. Previously, in a group of nonsuicidal and suicidal depressed patients, an inverse correlation had been noted between platelet serotonin and suicidal behavior [32]. However, subdividing our patients into suicide attempters and nonattempters revealed no differences, either in the biological parameters or in the psychopathological rating scores. Similar observations were reported by Meltzer and Arora [36], who neither observed differences in the platelet serotonin content of suicide attempters and nonattempters nor in the platelet serotonin content of those with a history of violent and nonviolent suicide attempts.

Psychiatric patients showed distinct fluctuations in blood serotonin concentrations that were associated with fluctuations in their psychopathology; these fluctuations were most pronounced within several days after a suicide attempt, when very low blood serotonin concentrations rose in individual patients up to 70-fold, but were still low compared to those of healthy subjects [35]. Therefore we attributed changes in serotonin turnover to suicidal impulses. For the sake of homogeneity in the patient population, only acutely suicidal patients were included in the present study; apparently we were dealing with self-directed aggressive behavior, since none of the patients committed a heteroaggressive act.

The question is whether there is an association between low blood serotonin and depression or schizophre-

nia in nonsuicidal psychiatric patients. Previous studies found no differences in the blood serotonin of nonsuicidal schizophrenic or schizoaffective patients when compared to healthy subjects [33, 34, 37], but high blood serotonin levels [30, 38, 39] were also noted; no difference in blood or platelet serotonin concentrations was reported between nonsuicidal unipolar depressed and healthy subjects [30, 36, 40–43]. The suicidal depressed and schizophrenic patients of our study were more chronically ill than patients with adjustment disorder; therefore both chronicity and suicidal behavior may be associated with the altered serotonergic function in these patients.

Across all the diagnostic groups of our acutely suicidal patients the serotonin$_{2A}$ receptor's B_{max} was higher than in healthy subjects. The B_{max} of the platelet serotonin$_{2A}$ receptor was significantly higher in depressed patients with suicidal ideation and in suicide attempters than in nonsuicidal depressed patients or in healthy subjects [36, 44–46].

In healthy subjects a positive correlation was noted earlier between the K_D and the B_{max} of the serotonin$_{2A}$ receptor [15]. In addition, in all subjects platelet serotonin regulated the affinity of the serotonin$_{2A}$ receptor, thus a higher serotonin availability was associated with a reduction in the serotonin$_{2A}$ receptor affinity, i.e., an increase in the K_D [15]. However, it may be noted that the correlation was better in healthy subjects than in suicidal patients, suggesting reactions that interfered with a putative regulatory process in these patients. The mechanism underlying the observed correlation between blood serotonin concentration and the K_D is presently unknown. Direct competition between serotonin derived from the platelet membranes and ^{3}H-LSD for the binding at the receptor site is unlikely, as shown by us previously [15], since serotonin, which is hydrophilic, is washed out during the preparation of the membranes by more than 99.5% giving rise to less than 5 n*M* endogenous serotonin in the incubation mixture. This is too low to interfere with the ^{3}H-LSD binding.

In the present study a trend toward a decrease in whole blood serotonin pertained to patients with depression and schizophrenia. The narrow range of serotonin concentrations in these subjects precluded a meaningful correlation between B_{max} and blood serotonin. Our findings, and that of others [36, 44, 46, 47], of an increase in the B_{max} of the serotonin receptor and serotonin receptor function in platelets [48] suggest a compensatory reaction elicited by low blood and platelet serotonin levels in acutely suicidal patients.

The biological markers of serotonergic function appear to be closely correlated to impulsivity, aggression and violent suicidal behavior across broad diagnostic categories; neuroendocrine challenge tests with 5-hydroxytryptophan [49] or fenfluramine [50; for review see 51] suggest a reduced central serotonergic function in these types of mood disorder which may not be specific but could be related to suicidal behavior. It is generally accepted that the blood-brain barrier singles out the way bioactive molecules are exchanged between the central nervous system (CNS) and the periphery; these findings do not rule out the possibility that receptor sites present in the CNS and periphery share similar properties. In fact the serotonin$_{2A}$ receptors in the brain and in platelets are structurally identical [52]. In adolescent schizophrenic inpatients a negative correlation between the maximal velocity of platelet serotonin uptake and aggressive behavior including suicide attempts has been reported [53], which agrees with the finding of Meltzer and Arora [36] of a diminished activity of the platelet serotonin transport in adult patients with high suicide ratings. Thus reduced transporter activity may be related to the low blood serotonin concomitant with the upregulation of the serotonin$_{2A}$ receptor activity that we noted in our suicidal patients.

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