Hyperserotonemia and Platelet Serotonin Uptake and Release in Schizophrenia and Affective Disorders

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The authors found that platelet serotonin concentrations were significantly elevated in patients with chronic schizophrenia and in patients with bipolar major depressive disorder. High-affinity serotonin uptake was significantly reduced only in patients with bipolar major depressive disorder. Thrombin-induced release of serotonin from platelets in any patient group was not different from that of normal control subjects. Platelet serotonin storage in chronic schizophrenic patients was also not different from that in normal control subjects. These platelet findings could not be explained by age, sex, or medication variables. The authors suggest that the pharmacodynamics of platelet serotonin may be different in chronic schizophrenia than in bipolar major depressive disorder. (Am J Psychiatry 140:26–30, 1983)

Increasing evidence suggests that the blood platelet can serve as a peripheral model for the study of serotonin (5-HT) uptake, storage, release, and concentration in CNS serotonergic neurons (1–3). Furthermore, platelet 5-HT pharmacodynamics are potential peripheral indicators of CNS serotonergic functioning in patients with neurologic and psychiatric disorders (1–5). Most (5–11) but not all (12, 13) investigators have reported *elevated* whole blood or platelet 5-HT concentrations in schizophrenic patients, but none of these investigators has analyzed platelet 5-HT uptake and release in the patients. On the other hand, most (14–21) but not all (22) investigators have found *decreased* platelet 5-HT uptake in depressed patients without examining whole blood or platelet 5-HT levels or release in their patients. In order to clarify the role of 5-HT in major psychiatric disorders, we simultaneously measured 5-HT concentration, high-affinity 5-HT uptake, and thrombin-induced 5-HT release from platelets of drug-free patients and normal control subjects.

METHOD

We measured platelet 5-HT levels, uptake, and release in control subjects who had no history of psychiatric illness and who were taking no medication—including aspirin (tables 1–3). We also made these measurements in hospitalized male psychiatric patients diagnosed according to Research Diagnostic Criteria (RDC) (23) (tables 1–3). The diagnostic interrater reliabilities at our clinical research center are .68 (kappa coefficient) for schizophrenia and .78 for major depressive disorder. No patient had received any medication for a minimum of 2 weeks before the study. After baseline (drug-free) studies, medications were prescribed as clinically indicated, and platelet studies were repeated, each patient serving as his own control (tables 1–3). All patients and control subjects gave informed consent to participate in the study.

We drew 30 ml of blood between 8:00 a.m. and 10:00 a.m. into EDTA-containing Vacutainer tubes using a 20-gauge needle. The platelets were immediately isolated by multiple centrifugations by a method yielding a complete population of platelets (24). The serotonin uptake and storage assays were performed within 2 hours of venipuncture by the method of Stahl and Meltzer (3). The serotonin uptake assay used intact platelets incubated with 10 nM ^{3}H-5-hydroxytryptamine at 37°C for 2 min (3). The serotonin storage assay used intact platelets incubated with .1 mM ^{3}H-5-hydroxytryptamine at 37°C for 60 min (3). The serotonin release assay was also performed within 2 hours by the method of Costa and Murphy (25). Serotonin levels were assayed by isocratic high-performance liquid chromatography using electrochemi-

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Supported by the Medical Research Service of the VA through the Schizophrenia Biologic Research Center at the Palo Alto VA Medical Center and by Specialized Research Center grant MH-30854 from NIMH to the Stanford Mental Health Clinical Research Center.

The authors thank Dr. Helena Kraemer and Ellen Bush for statistical consultation and data analysis.

TABLE 1. Platelet Serotonin Concentrations in Medicated and Unmedicated Psychiatric Patients and Unmedicated Control Subjects

Diagnosis	Age (years) Mean	Age (years) SD	Unmedicated Subjects N	Unmedicated Subjects Serotonin Concentration (ng/10^8 platelets) Mean	Unmedicated Subjects Serotonin Concentration (ng/10^8 platelets) SD	Medicated Subjects N	Medicated Subjects Serotonin Concentration (ng/10^8 platelets) Mean	Medicated Subjects Serotonin Concentration (ng/10^8 platelets) SE
None (normal control subjects)	39.5	10.6	66	69.7	3.4			
Chronic schizophrenia[a,b]	37.0	12.3	14	106.8	6.7	14	117.4	28.8
Schizoaffective disorder, depressed[c]	42.2	15.2	6	91.5	14.7	5	79.7	7.7
Bipolar major depressive disorder, depressed[a,d]	44.3	10.3	11	103.7	11.6	8	100.9	13.5
Unipolar major depressive disorder[e]	52.3	6.4	14	84.5	12.1	12	59.5	8.7
Miscellaneous psychiatric disorders	50.5	22.5	10	77.9	9.4			

[a]Concentration in unmedicated subjects significantly elevated compared with that in normal control subjects ($p<.001$, t test).
[b]Medicated with neuroleptics for at least 2 weeks; medication had no significant effect on concentration.
[c]Medicated with tricyclic antidepressants for at least 2 weeks; medication had no significant effect on concentration.
[d]Medicated with lithium carbonate for at least 2 weeks; medication had no significant effect on concentration.
[e]Medicated with tricyclic antidepressants for at least 2 weeks; medication significantly lowered concentration ($p<.01$, matched-pair t test).

TABLE 2. Platelet ^{3}H-Serotonin Uptake in Medicated and Unmedicated Psychiatric Patients and Unmedicated Control Subjects

Diagnosis	Unmedicated Subjects N	Unmedicated Subjects ^{3}H-Serotonin Uptake (pmol/10^8 platelets) Mean	Unmedicated Subjects ^{3}H-Serotonin Uptake (pmol/10^8 platelets) SE	Medicated Subjects N	Medicated Subjects ^{3}H-Serotonin Uptake (pmol/10^8 platelets) Mean	Medicated Subjects ^{3}H-Serotonin Uptake (pmol/10^8 platelets) SE
None (normal control subjects)	25	29.9	1.5			
Chronic schizophrenia[a]	14	31.9	3.7	14	24.4	2.1
Schizoaffective disorder, depressed[b]	5	28.4	5.4	3	16.2	1.8
Bipolar major depressive disorder, depressed[c,d]	11	18.9	3.0	11	19.9	4.5
Unipolar major depressive disorder[e]	14	34.4	4.8	11	13.7	5.1
Miscellaneous psychiatric disorders	9	42.2	8.6			

[a]Medicated with neuroleptics for at least 2 weeks; medication significantly lowered uptake ($p<.05$, matched-pair t test).
[b]Medicated with tricyclic antidepressants for at least 2 weeks; medication had no significant effect on uptake.
[c]Uptake significantly reduced in comparison with that of normal control subjects ($p<.05$, t test).
[d]Medicated with lithium carbonate for at least 2 weeks; medication had no significant effect on uptake.
[e]Medicated with tricyclic antidepressants for at least 2 weeks; medication significantly lowered uptake ($p<.01$, matched-pair t test).

TABLE 3. Platelet ^{3}H-Serotonin Release in Unmedicated Psychiatric Patients and Normal Control Subjects

Diagnosis	Number of Subjects	^{3}H-Serotonin Release (pmol/10^8 platelets) Mean	^{3}H-Serotonin Release (pmol/10^8 platelets) SE
None (normal control subjects)	23	44.7	6.3
Chronic schizophrenia	14	35.6	8.8
Schizoaffective disorder, depressed	5	46.6	8.8
Biopolar major depressive disorder, depressed	11	59.7	16.6
Unipolar major depressive disorder	14	45.8	8.6
Miscellaneous psychiatric disorders	9	47.2	14.1

cal detection as described by Mefford and Barchas (26).

RESULTS

Platelet 5-HT concentrations in all subjects are shown in table 1. No significant differences in platelet 5-HT concentrations were observed in age-matched male and female normal control subjects; both sexes are included in the normal control group for comparison with the all-male patient groups. Although platelet 5-HT concentrations varied across a wide range between individuals, the platelet 5-HT concentrations within individuals varied less than 10% in repetitive samplings over several months. A one-way analysis of variance (ANOVA) for 5-HT concentrations among the six diagnostic groups ($df=5, 78$, $F=4.9013$) indicated significant differences among diagnostic groups (table 1). Platelet 5-HT concentrations were significantly elevated in patients with chronic schizophrenia ($t=4.01$, $df=64$, $p<.001$) and in patients with bipolar major depressive disorder, depressed ($t=3.32$, $df=64$, $p<.001$), but not in patients with unipolar major depressive disorder compared with those in normal control subjects (table 1). Patients with schizoaffective disorder, depressed, also had a trend toward elevated platelet 5-HT concentrations (table 1), but this trend did not reach the level of significance ($t=1.62$, $df=64$, $p>.05$), perhaps because of the small number of patients in this group ($N=6$). Platelet 5-HT concentrations in hospitalized patients with several other miscellaneous psychiatric diagnoses were not significantly different from those in normal control subjects (table 1).

A regression analysis of platelet 5-HT concentration versus age in 66 normal control adult subjects revealed a slightly positive ($r=.20$) but nonsignificant ($p<.1$) correlation. In order to test whether this weak age effect influenced the findings of group differences in platelet 5-HT concentrations, we repeated the one-way ANOVA comparing age-corrected means for the five patient groups with those of normal control subjects and found that the platelet concentrations of 5-HT in patients with schizophrenic and bipolar major depressive disorders remained significantly elevated when compared with those of normal control subjects.

We also examined the effects of medications on platelet 5-HT concentrations. Neither neuroleptic medications nor lithium altered platelet 5-HT concentrations in those patients receiving them (table 1). However, tricyclic antidepressant drugs did significantly decrease platelet 5-HT concentrations (see table 1).

Platelet high-affinity 5-HT uptake values in all subjects are shown in table 2. A one-way ANOVA for 5-HT uptake values among the six diagnostic groups ($df=5, 35$, $F=3.1^{-}$) indicated significant differences among diagnostic groups (table 2). Platelet high-affinity 5-HT uptake was significantly reduced only in patients with bipolar major depressive disorder, depressed ($t=3.22$, $df=34$, $p<.05$). Platelet high-affinity 5-HT uptake was not significantly correlated with age ($r=.07$, $p<.1$). Neuroleptic medication and tricyclic antidepressant drugs significantly decreased platelet 5-HT uptake in those patients receiving them, but lithium did not significantly affect platelet 5-HT uptake (table 2).

5-HT uptake into platelet storage granules was determined in the chronic schizophrenic patients before and after neuroleptic medication was administered. The mean (±SE) platelet 5-HT granular uptake (in picomoles per 10^8 platelets) was not significantly different in the 14 unmedicated (162.1 ± 39.7) and the 14 medicated (177.4 ± 46.0) chronic schizophrenic patients compared with the 28 normal control subjects (186.7 ± 34.1) and was not significantly altered by neuroleptic medications.

Thrombin-induced release of ^{3}H-5-HT from preloaded platelets was a highly variable assay. A one-way ANOVA for ^{3}H-5-HT release values among the six diagnostic groups ($df=5, 35$, $F=1.07$) indicated no significant differences among diagnostic groups (table 3).

DISCUSSION

We determined platelet 5-HT concentrations in 55 psychiatric patients with a number of diagnoses. Although many investigators have previously determined whole blood or platelet 5-HT concentrations in patients with these same diagnoses, no single group has performed a comparative study across several diagnostic categories of drug-free psychiatric patients, nor has any group included simultaneous assays of platelet 5-HT uptake, storage, and release. The literature contains at least eight previous reports of whole blood or platelet 5-HT determinations in schizophrenic patients (6–13; see reference 5 for review). Including the patients in our present study, more than 200 chronic schizophrenic patients have now been studied. Seven groups of investigators have reported elevated mean whole blood or platelet 5-HT levels in chronic schizophrenic patients (6–11), and two groups have reported no differences between mean blood 5-HT levels in schizophrenic patients and normal control subjects (12, 13). Thus there is fairly good agreement among investigators that whole blood 5-HT levels are elevated, probably as a result of increased platelet 5-HT concentrations, in chronic schizophrenic patients as a group. Our study has shown that this finding is not an artifact of age, sex, or medication.

One of the problems in determining the importance of increased platelet 5-HT concentrations in chronic schizophrenic patients is the observation that considerable overlap exists for platelet 5-HT values among individuals in the chronic schizophrenic group with those among normal control subjects. Although we were unable to detect any clinical differences between the clinical features of the high-5-HT group and those of the normal-5-HT group, Freedman and associates (11) reported that the elevated platelet 5-HT concentrations found in chronic schizophrenic patients were more marked in chronic undifferentiated than in chronic paranoid schizophrenic patients. DeLisi and associates (10) reported that the elevated whole blood 5-HT concentrations in their chronic schizophrenic patients were even higher in those with abnormal computerized tomography (CT) brain scans than in those with normal CT brain scans.

Another problem in determining the clinical or biochemical significance of elevated platelet 5-HT concentrations in chronic schizophrenic patients is that this phenomenon is not confined to chronic schizophrenia as a diagnostic group. For example, the literature also contains at least six previous reports of whole blood or platelet 5-HT determinations in a variety of depressive disorders, with findings of increased, decreased, or normal whole blood or platelet 5-HT concentrations in unipolar, bipolar, manic, or psychotic depressed patients (6, 19, 27–30). These studies of blood 5-HT in depressive disorders are complicated by wide discrepancies in diagnostic criteria, use of whole blood in some studies and platelets in others, and a general lack of control for age, sex, medication status, and clinical symptoms (see reference 5 for review). Elevated whole blood or platelet 5-HT concentrations are associated with a number of conditions in addition to chronic schizophrenia and bipolar major depressive disorder. These include early infantile autism, a variety of mental retardation syndromes, Huntington's disease, attention deficit disorder with hyperactivity, amyotrophic lateral sclerosis, carcinoid syndrome, and celiac disease (5). Thus it is not possible for one to

relate platelet 5-HT concentrations simply to any single psychiatric disorder.

If elevated platelet 5-HT concentrations are reliably associated with some psychiatric disorders but not as a result of variables such as age, sex, or medication, is it possible that the biochemical mechanisms of the increased platelet 5-HT concentrations are different in different diagnostic groups? In order to investigate this possibility, we measured high-affinity 5-HT uptake and thrombin-induced 5-HT release from platelets in the various diagnostic groups. No significant differences in thrombin-induced release of platelet 5-HT were evident in any group, and platelet 5-HT uptake was reduced only in the bipolar depressed patients in our study. At least nine groups have published results on platelet 5-HT uptake in depression (14–22), and eight of these nine (14–21) found that platelet 5-HT uptake was decreased in groups of depressed patients, including those with unipolar, bipolar, or psychotic depression. Since platelet 5-HT uptake was normal in our study of schizophrenic patients yet reduced in most studies of depressed patients, this does suggest that platelet 5-HT pharmacodynamics may be different in schizophrenia than in depression. However, the biochemical mechanism of elevated platelet 5-HT concentrations in these two diagnostic groups remains unexplained, and possible distinctions between unipolar depression and bipolar depression are largely unexplored.

In the case of chronic schizophrenia, we have confirmed the frequently reported association of elevated platelet 5-HT concentrations in these patients and have found that this phenomenon cannot be explained by an abnormality in platelet 5-HT uptake, storage, or release. Although platelet monoamine oxidase (MAO) activity may be decreased in chronic schizophrenic patients (31), this observation does not readily explain the increased platelet 5-HT levels because platelet MAO activity apparently does not correlate with platelet 5-HT concentrations within individual chronic schizophrenic patients (9, 11). In terms of patients with bipolar major depressive disorder, we have confirmed the findings of increased platelet 5-HT concentrations reported by some investigators (29, 30) and decreased platelet 5-HT uptake reported by most investigators (14–21). It is difficult to relate decreased platelet 5-HT uptake to increased platelet 5-HT levels in bipolar depressed patients because one might predict that levels would be decreased if uptake is decreased, as is the case with Down's syndrome (32). On the other hand, we have found that platelet 5-HT uptake does not correlate with platelet 5-HT concentrations in normal control subjects (5) or in depressed patients (5); therefore, increased platelet 5-HT concentrations are not explained simply by a platelet 5-HT uptake abnormality in bipolar depressed patients. The finding of decreased platelet MAO activity reported in bipolar depressed patients (33) also fails to explain elevated platelet 5-HT concentrations in bipolar illness because of the lack of correlation between platelet 5-HT concentrations and platelet MAO activity mentioned above.

Our study suggests that the decreased platelet 5-HT uptake observed in bipolar depressed patients cannot be explained by age, sex, or medication status and may be relatively specific for bipolar major depressive illness among psychiatric disorders. Platelet 5-HT uptake may also be decreased in Duchenne-type muscular dystrophy, Down's syndrome, albinism, and Chédiak-Higashi syndrome (5). Our study also suggests that an abnormality in platelet 5-HT release is not associated with platelet 5-HT uptake or concentration abnormalities in bipolar depression. The recent reports of decreased numbers of 5-HT uptake sites in depressed patients as measured by platelet ^{3}H-imipramine binding (34–36) is consistent with the findings of decreased V_{max} for platelet 5-HT uptake reported in the studies mentioned (14–21).

In summary, chronic schizophrenic patients have elevated blood 5-HT concentrations that are exceedingly well documented in the literature, are not an artifact of age, sex, or medication, and are associated with reduced platelet MAO activity and normal platelet 5-HT uptake, storage, and release. However, the biochemical mechanism of hyperserotonemia in schizophrenia remains unexplained, and its clinical significance is obscured not only by the association of hyperserotonemia with other disorders, but also by the presence of hyperserotonemia in only a subgroup of schizophrenic patients that cannot currently be distinguished from normoserotonemic schizophrenic patients. Future studies may elucidate the significance of hyperserotonemia in schizophrenia by determining its relationship to biological and clinical variables such as diagnostic subtypes, specific symptoms, cerebral ventricular size on CT scans, and regional brain glucose utilization on positron emission tomography (PET) scans. On the other hand, patients with bipolar major depressive disorder, depressed, have decreased platelet 5-HT uptake that is very well documented in the literature, not an artifact of age, sex, or medications, and associated perhaps with elevated platelet 5-HT concentrations, normal platelet 5-HT release, and decreased platelet ^{3}H-imipramine binding sites. The significance of decreased platelet 5-HT uptake in major depressive disorders is obscured by the lack of knowledge regarding its biochemical mechanism, its relationship to other biochemical findings in platelets, and its relationship to clinical variables in depressed patients. Future studies may answer some of the questions regarding the significance of decreased platelet 5-HT uptake in depression by determining its relationship to diagnostic subtypes, CSF 5-HT metabolites, and neuroendocrine factors such as dexamethasone suppression.

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