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Time Course of Serotonin in Platelets from Patients with Affective Disorders

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Temporal variations in platelet levels of serotonin were found to be significantly decreased in patients with endogenous affective disorders, particularly those with the bipolar type of manic-depressive psychosis. The time course of serotonin content in these cells was not affected by either the sex or the age of the patients. *In vitro* incubation with lithium oxybutyrate raised mean platelet serotonin levels and stabilized their fluctuation in platelets from healthy subjects but not in those from the mental patients.

Key Words: *serotonin; platelets; lithium; depression*

It has been established beyond doubt that the serotoninergic system plays a substantial role in the pathogenesis of affective disorders. The systems of secondary messengers in neurons and platelets, the mechanisms of serotonin release, uptake, and storage by these cells, and their receptors for serotonin and imipramine have a number of similar characteristics so that platelets may be used as a convenient model for the study of serotonin transport in health and in mental disorders [9].

The purpose of this study was to examine the time course of platelet serotonin in patients with affective disorders before and during treatment and the effect of lithium oxybutyrate on the serotonin concentration in these cells *in vitro*.

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MATERIALS AND METHODS

Temporal variations in platelet serotonin were examined in 16 patients with primary endogenous affective disorders, in 11 patients with a depressive syndrome in the framework of other mental disorders (neurosis or organic brain disease), and in 20 mentally healthy donors. The patients were examined on admission to the clinic before the initiation of pharmacotherapy (or during the 2-week period before admission if pharmacotherapy was not administered) and during remission. The depression in all cases was classified as pronounced (a mean score of 26.6 on Hamilton's scale).

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TABLE 1. Coefficient of Variation of 5-HT Content (%) in Patients with Bipolar (A) and Unipolar (B) Primary Affective Disorders, in Patients with a Depressive Syndrome (C), and in Healthy Donors (D). The Values are Means±SD

Time of study	A	B	C	D
On admission	10.0±5.0	11.5±5.8	29.4±10.9	–
During remission	22.5±4.3	27.9±8.9	34.1±13.7	34.1±9.0

The serotonin content of platelets (5-HT) was measured spectrophotometrically at activation wavelength 365 nm and emission wavelength 480 nm. In each patient and healthy donor, 5-HT was measured 6-8 times at 20-sec intervals using the scheme we described previously [2]. In separate tests, platelets were incubated with lithium oxybutyrate (10 mmol/liter) for 3 min before the measurements. Changes in 5-HT levels were evaluated by the coefficient of variation (C_v) defined as the percentage ratio of the standard deviation of the 5-HT to its arithmetic mean in the individual.

RESULTS

In the healthy donors, the mean content of 5-HT was 594 ng/10^9 cells and the average C_v was 34.1%. A multivariate analysis of variance showed that the variation in 5-HT was not affected by age or sex or by the interaction between these two factors. The only factor affecting the C_v proved to be the mental health of the individual ($p<0.001$).

In the patients, the mean content of 5-HT was 515 ng/10^9 cells in those with endogenous affective disorders and 399 ng/10^9 cells in those with depression of another origin ($p<0.01$ in comparison with the healthy donors), and the mean 5-HT values did not change in the course of pharmacotherapy.

On admission, all patients with affective disorders had a significantly lower C_v than the healthy donors (21.3% vs. 34.1% using the t test; $p<0.001$), which means that the range of permissible 5-HT values was narrowed in patients with depressive manifestations. In the subgroup with primary endogenous disorders, the C_v was decreased to 10.7%, whereas in the subgroup with a nonendogenous depressive syndrome this coefficient was significantly higher (29.4%; $p<0.001$) and did not differ from the C_v obtained for healthy donors (Table 1). Moreover, the C_v values in the patients with endogenous disorders were more homogeneous than in the other patients and in the healthy donors (F test, $p<0.05$). The variation displayed by 5-HT during remission in the patients with a depressive syndrome against the background of a nonendogenous disease or with a unipolar endogenous disease was increased and did not differ from that in the healthy donors. The variation in 5-HT was also increased in the group with the bipolar type of endogenous disorders but still remained reliably low ($p<0.05$).

The use of lithium oxybutyrate as a "pharmacological loading test" was found to have very different effects in the different groups studied in the absence of antidepressive therapy (Table 2). Following the incubation of platelets from healthy donors with this drug, the mean content of 5-HT increased to 795 ng/10^9 cells and its stabilization was observed - the C_v decreased by a factor of 8.3 ($p<0.001$). The interindividual variability of the C_v also decreased, as assessed by its standard deviation in this group ($p<0.01$), which indicates that the lithium acted similarly on all donor platelets.

In contrast, no significant alterations in the mean 5-HT or C_v values were observed in the two groups of patients, i.e., the drug did not exert a stabilizing effect on the time course of platelet serotonin. The slight increase in the C_v observed for the group with endogenous disorders could be taken as evidence that this group included a subgroup in which the temporal variation in 5-HT was increased, i.e., the response of platelets to their incubation with lithium was paradoxical (as compared to healthy donors). Another indication that the responses of the serotoninergic system were not uniform within this group was the increased standard deviation of 5-HT after the incubation of platelets with lithium.

The statistical estimates of platelet serotonin presented above agree with those reported in the literature [4,6,8]. However, the dynamic approach used in this study has yielded some new results, which we will attempt to interpret within the framework of the following hypothesis.

As shown earlier, 5-HT in health is a continuously varying rather than a static parameter [2,3], and the specific value of this parameter ob-

TABLE 2. Effect of Lithium Oxybutyrate on the Coefficient of Variation of 5-HT Content. The Values are Means±SD

Group	Conventional schedule	Incubation with lithium
Donors	34.1±9.0	4.1±2.1
Endogenous affective disorders	10.7±5.4	15.3±7.5
Depressive syndrome	29.4±10.9	28.0±13.7

tained through measurement reflects, therefore, only the probability of its change within a certain range (the range of permissible values). A sign of the normal is chaotic fluctuations of the measured parameters, whose range narrows in disease or during aging [1]. A dynamic equilibrium between serotonin release and reuptake is maintained by a number of positive and negative feedbacks between the systems of intracellular secondary messengers (the adenylate cyclase and phosphatidyl inositol systems). This model presupposes a rapid and effective adaptation to changing environmental conditions through the ready adjustment of a constantly changing parameter in health and a less effective adaptation when the range of permissible values of that parameter has narrowed in disease.

The severalfold decrease in 5-HT variation observed for healthy donors' platelets after their incubation with lithium can be explained by a breakdown in the linkage between the two systems of secondary messengers. Lithium exerts its effect by competing with the magnesium ions which are required to form complexes of G proteins with GDP (G-GDP complexes), resulting in impaired signal transmission to the secondary messengers of both systems [10]. This competition has a particularly strong inhibitory effect on serotonin release [11,12] and thus leads to stabilization of serotonin in platelets and to an increase of its average content in these cells [5,7,13].

The mechanisms by which lithium is prevented from influencing the time course of platelet serotonin in mental patients require detailed investigation. The primary defect may be tentatively presumed to be located at that site of G proteins via which they bind magnesium. It has been suggested that there is a relative predominance of C phospholipase activity in the depressive phase (G_s proteins are impaired) and of adenylate cyclase activity in the maniacal phase (G_i or G_p proteins are impaired) [14]. If this is so, then the therapeutic effect of lithium may result from a decrease in the predominance of one of the two secondary messenger systems through blockage of "normal" G proteins of the other system or, to be more exact, from the restoration of the feedback links between these two systems. The alterations in serotonin uptake, in the number and affinity of serotonin receptors, and in the metabolite concentrations in biological fluids observed in patients may all be secondary to the above-mentioned defect. This hypothesis can explain why emotional disturbances of opposite types may occur within a single affective disorder and why lithium therapy is effective both in depressions and in manias. Tricyclic antidepressants appear to exert their therapeutic effects by inhibiting phospholipase C activity rather than by blocking the reuptake of biogenic amines, which is already diminished in affective disorders.

The data obtained with lithium *in vitro* cannot be extrapolated unconditionally to the *in vivo* situation in the whole organism, especially in view of the well-known differences between the action of lithium *in vitro* and *in vivo* [4,7]. Nonetheless, the present results demonstrate the usefulness of a dynamic approach to the study of the serotoninergic system on an extracerebral model.

In conclusion, the affective disorders studied here were found to differ from each other with regard to temporal variations in platelet serotonin which characterize its transport. The coefficient of serotonin variation in platelets from patients with bipolar affective disorders was significantly reduced during disease exacerbation (before treatment) and remained significantly lowered during remission. In platelets from patients with unipolar affective disorders, the coefficient of serotonin variation was reduced to a similar extent during exacerbation but returned to normal during remission. For platelets from patients with the depressive syndrome, no reduction in this coefficient occurred even during exacerbation. *In vitro* treatment with lithium failed to stabilize platelets from any of the patients, indicating that the lack of platelet stabilization under lithium action may be used as a marker of the patient's state.

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