BIOPHYSICS AND BIOCHEMISTRY

A Study of Some Components of the Serotoninergic System in Psychopathic Subjects during Depression

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It is shown that the platelet serotonin level and the maximum rate of uptake of labeled serotonin by platelets in the groups of patients with anxious-depressive and depressive-hysterical syndromes is markedly higher than in the control (patients with psychopathy without signs of depression) and in the group with the asthenodepressive syndrome. In all groups of patients with depressions the excretion of 5-hydroxyindoleacetic acid is reduced as compared to the control.

Key Words: *serotonin; serotonin uptake by platelets; 5-hydroxyindoleacetic acid; depressive disorders*

The involvement of the serotoninergic system in the pathogenesis of a number of neuropsychic diseases is now beyond question [8]. Whereas a few years ago the hypothesis of "serotonin" and "norepinephrine" types of depression was widely discussed, it is now evident that the complex of clinical manifestations of depression cannot be regarded as a pathology of a particular transmitter system [13]. The heterogeneity of the clinical manifestations of the disease with a corresponding broad spectrum of biochemical changes in the neurotransmitter and neuromodulator systems has dictated a syndromological approach to studies of the biological bases of mental disorders, particularly of depressions. The accumulated data on indolamine transmission in depressions are contradictory [9].

Simultaneous determination of the serotonin content in the plasma and platelets makes it possible to assess various aspects of its physiology and to consider the contribution of each of the independent serotonin pools (in the plasma and in the platelets) to the development of diverse pathological states, while using platelets as a model of the presynaptic endings of central serotoninergic neurons may yield information for understanding the state of serotoninergic processes in the central nervous system (CNS) [10].

The aim of the present study was to investigate the plasma and platelet level of serotonin, the ^{3}H-serotonin (^{3}H-5-OT) uptake by platelets, and the concentration of 5-hydroxyindoleacetic acid (5-OIAA) in the urine of patients with diverse types of depressive syndromes.

MATERIALS AND METHODS

Forty-seven men aged from 18 to 55 (hospitalized at the V. P. Serbskii State Center of Social and Forensic Psychiatry) were examined. Psychopathy with diverse clinical types of depressive syndromes

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(anxious-depressive, asthenodepressive, and depressive-hysterical) was diagnosed in 35 patients. Twelve patients with psychopathy without signs of depression comprised the reference group.

Stress and anxiety and periodic changes between motor and idiomotor inhibition and anxiety were typical of the anxious-depressive syndrome. Psychomotor inhibition, suppression of all psychic functions, increasing indifference and passiveness, and a marked reduction of ablebodiedness were exhibited by patients with the asthenodepressive syndrome. An unstable and superficial affect combined with irritability, discontent, and sullenness were observed in the case of the depressive-hysterical syndrome. Psychomotor inhibition was absent in the latter case.

Blood was taken from the cubital vein into plastic tubes containing anticoagulant: 1.37% citric acid, 2.5% sodium citrate, and 2% glucose. Platelet-rich plasma (PRP) was obtained after blood centrifugation at 250 g for 15 min (24°C). A portion of plasma was decanted and the platelets were precipitated from the remaining plasma at 2500 g for 15 min. The samples obtained were stored at -30°C for a maximum of 2 weeks.

The method for serotonin determination in the blood by high-performance liquid chromatography (HPLC) with electrochemical detection was developed on the basis of techniques described elsewhere [2,4]. The samples were prepared as follows: 500-μl aliquots of plasma poor in platelets or 250-μl aliquots of PRP were placed in glass vials with caps; 3 ml butanol preliminarily saturated with 1 N HCl was added to each vial; the samples were shaken for 10 min and centrifuged at 900 g for 5 min. Two-milliliter aliquots of the organic phase were transferred to clean vials, in which 4.5 ml heptane and 500 μl 0.1 N $HClO_4$ were added. Shaking and centrifugation were performed as described above. Fifty microliters of the lower inorganic phase were taken and injected into a high-pressure chromatograph.

The composition of the mobile phase was as follows: 70 mM NaH_2PO_4, 10 mM citric acid, 2 mM Na_4EDTA, 10 mM octanesulfonic acid, and 5.6% (v/v) butanol. Each series comprised the experiment with the reference plasma solution of serotonin (100 ng/ml). Serotonin-creatine sulfate (Serva, Germany) in 0.1 N HCl in a final concentration of 1 ng/μl was used as the standard.

An ODS Alltech Sherisorb column (5 μ, 150× ×4.6 mm; USA), 303 pumps (France), and a 141 Gilson detector (France) were used in the study. The potential of the test electrode (carbon, glass) was +0.7 V as against the Ag/AgCl electrode. The elution flow rate was 0.6-1 ml/min; the temperature was ambient. The effective pressure under these conditions was 150-220 atm. The retention time of serotonin was 4-6 min.

5-OIAA was assayed in the urine after Joseph et al. [7]. The main parameters of ^{3}H-5-OT uptake by platelets (K_m and V_{max}) were determined by modifications of the method of Brusov et al. [1]. The nonspecific uptake of serotonin was assessed in the samples containing 100 μM imipramine. A Dia-M multifiltration system (Moscow) was used in the study. Five milliliters of toluol scintillator were poured on dried filters, and the radioactivity was counted on an LKB Rackbeta counter. The results were statistically processed after Student.

RESULTS

Analysis of the biochemical data (Table 1) demonstrated that the platelet level of serotonin and the rate of ^{3}H-5-OT uptake were markedly higher in the case of the anxious-depressive syndrome than in the reference group. A tendency toward an increase of the plasma level of 5-OT is characteristic of patients with asthenodepressive disorders. An appreciably high level of the three above-mentioned indexes was typical of the depressive-hys-

TABLE 1. Some Parameters of the State of the Serotoninergic System in Patients with Psychogenic Depression ($M \pm m$)

Parameter	Group of examinees			
	control	anxious-depressive syndrome	asthenodepressive syndrome	depressive–hysterical syndrome
Plasma serotonin, ng/ml	2.59±1.36	2.42±0.46	5.10±1.78	9.73±1.35*
Platelet serotonin, ng/10^9 platelets	248.61±80.02	644.73±87.26**	273.52±67.48	655.24±232.48
^{3}H–5–OT uptake by platelets, V_{max}/10^9 platelets	133.50±35.60	605.86±51.94**	181.92±38.78	578.38±116.50
K_m, nM	215.00±11.00	203.33±10.03	176.92±7.71	205.00±20.20
Excretion of 5–OIAA in urine, μg/day	32.5±5.5	10.0±1.3**	12.4±3.5**	12.4±2.8**

Note. One and two asterisks denote the reliability of differences from the control for $p<0.02$ and $p<0.001$, respectively.

terical syndrome. It is worthy of note that a statistically significant reduction of the excretion of 5-OIAA, an end product of serotonin metabolism, was observed in all patients with psychopathy with depressive syndromes as compared to the patients with psychopathies without depression.

The plasma serotonin level depends on the ratio between the release of serotonin by enterochromaffin cells and its inactivation (oxidative deamination with monoaminooxidase of the A type and uptake by platelets and endothelial cells of the intestine [3]). A number of scientists regard the parameters of peripheral exchange of indolamine not only as the indicator, for example, of the activity of type A monoaminooxidase in the organism [5], but also as a model of the central neurotransmission [3]. Thus, it is evident that different types of depressions in psychopathic subjects are attended by specific disturbances of serotonin metabolism.

The platelet level of serotonin and the maximal rate of uptake of labeled serotonin by platelets in the groups of anxious-depressive and depressive-hysterical patients are markedly higher than those in the control and in the asthenodepressive group. The majority of scientists who have studied the parameters of serotonin metabolism during depressions have reported that the reuptake of serotonin and its level in platelets are reduced in the case of depressive disorders [6,11]. Nevertheless, there is a body of evidence that a functional deficiency of the postsynaptic serotoninergic mechanisms goes along with aggravation of anxiety [13]. Since the platelet is regarded by some scientists as a model of the central presynaptic terminal [12], it may be assumed that the phenomenon of increased serotonin uptake by platelets (along with a regular increase in the amount of the intracellular transmitter) reflects the increased rate of reuptake of the transmitter molecules of serotonin by the terminals of central neurons, along with a deficiency of indolamine transmission. The marked increase of the serotonin content in the plasma of patients with depressive-hysterical disorders may attest to a compensatory stimulation (in response to the serotoninergic deficiency) of serotonin synthesis and to a relatively low activity of monoaminooxidase in this group of patients.

Thus, the disturbances of the functional state of the serotoninergic system in psychopathic subjects with depressive syndromes suggest that the neurochemical disorders in patients with anxious-depressive, asthenodepressive, and depressive-hysterical disorders are different. This in turn poses the question as to what are the best tactics of psychopharmacological correction of depressive syndromes in psychopathies.

REFERENCES

1. O. S. Brusov, B. S. Belyaev, A. B. Katasonov, *et al., Zh. Nevropatol. Psikhiatr.*, **38**, 96 (1988).
2. B. M. Kogan and N. V. Nechaev, *Lab. Delo*, № 5, 301 (1979).
3. F. Artigas, M. J. Sarrias, E. Martinez, *et al., Psychopharmacology*, **99**, 328 (1989).
4. F. Artigas, M. J. Sarrias, E. Martinez, and E. Gelpi, *Ibid.*, **37**, 441 (1985).
5. P. Celada, M. J. Sarrias, and F. Artigas, *J. Neur. Trans.*, Suppl. 32, 149 (1990).
6. D. G. Grahame-Smith, *Ibid.*, p. 7.
7. M. H. Joseph, B. V. Kadam, and D. Risby, *J. Chromatogr.*, **226**, 361 (1981).
8. Y. E. Leysen, in: *Neuropharmacology of Serotonin* (Ed. by A. R. Grenn), Oxford (1985), p. 155.
9. H. Y. Meltzer, *Ann. Rev. New York Acad. Sci.*, **600**, 480 (1990).
10. J. Ortiz, F. Artigas, and E. Gelpi, *Life Sci.*, **43**, 983 (1988).
11. H. P. Schlake, H. Kuhs, L. H. Rolf, *et al., Acta Psychiat. Scand.*, **80**, Suppl. 350, 149 (1989).
12. S. M. Stahl, in: *The Platelets: Physiology and Pharmacology* (Ed. by G. Longenecker), New York (1985), p. 307.
13. H. M. Van Praag, G. M. Asnis, R. S. Kahn, *et al., Brit. J. Psychiat.*, **157**, 723 (1990).