EFFECT OF EXOGENOUS AND ENDOGENOUS SEROTONIN ON HEMOSTASIS

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Serotonin was found to have no essential role in the mechanism of blood clotting, but it participates in hemostasis as a factor stimulating aggregation of the platelets.

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Serotonin is considered by some authorities [4, 5, 10, 15] to participate in the process of blood clotting, in the mechanism of increase in the resistance of blood vessel walls, clot retraction, and in the increase in number of blood platelets; others [1, 11-13, 17] reject any role of serotonin in hemostasis. It has been shown comparatively recently [16] that serotonin causes aggregation of platelets in vitro.

Data on the effect of endogenous and exogenous serotonin on hemostasis are presented in this paper.

EXPERIMENTAL METHOD

Experiments were carried out on 117 Wistar rats of both sexes, weighing 220-400 g, anesthetized with nembutal (30 mg/kg body weight, intraperitoneally).

In the experiments of series I, aggregation of the platelets and activity of factor XIII was studied following liberation of serotonin from the tissues under the influence of reserpine. Reserpine (Rausedil, Hungary) was injected intradermally in doses of 1, 2, and 4 mg/kg. The investigations were carried out 18-20 h after injection of reserpine.

In the experiments of series II, to study the effect of serotonin on the same indices, serotonin—creatinine sulfate (Lawson, England) was injected intravenously in a dose of 0.1 mg/kg or the serotonin precursor 5-hydroxytryptophan was injected intraperitoneally (50 mg/kg body weight). Blood for the tests was taken 1-2 min after the injection of serotonin and 1 h after injection of 5-hydroxytryptophan.

All determinations were carried out on blood taken from the jugular vein of the rats into silicone-treated syringes; the blood was mixed with 3.1% sodium citrate solution (9 : 1). Aggregation of the platelets [8], activity of factor XIII [2], tolerance of the fibrin clot to plasmin [3], the plasma recalcification time [7], and the concentration of serotonin in the blood and duodenum (by a spectrofluorometric method [18]) were determined. Aggregation of the platelets was estimated from the degree of reduction in optical density of plasma containing 100,000-150,000 platelets/mm^3. Observations on aggregation continued for 20 min.

EXPERIMENTAL RESULTS

The results given in Table 1 show that after injection of reserpine in doses of 1 and 2 mg/kg a tendency was observed for the serotonin concentration to fall in the blood and duodenum (dose of 2 mg/kg). Aggregation of the platelets was increased while the activity of factor XIII showed no significant change. After injection of reserpine in a dose of 4 mg/kg, the blood serotonin concentration fell by 84% and its concentration in the duodenum by 50%. Meanwhile, aggregation of the platelets increased threefold and the activity of factor XIII rose by 35%.

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TABLE 1. Effect of Reserpine, Serotonin, and 5-Hydroxytryptophan on the Blood Clotting System

Index	Control	Reserpine (mg/kg)			Serotonin (0.1 mg/kg)	5-Hydroxytryptophan (50 mg/kg)
		1	2	4		
Aggregation of platelets (%)	100	138	163*	300*	148*	67
Activity of factor XIII (%)	100	84	101	135*	88*	97
Tolerance of fibrin clot to plasmin (sec)	119	–	–	–	105	106
Plasma recalcification time (sec)	125	–	–	–	118	132
Serotonin concentration:						
in blood (μg/ml)	0.31	0.18	0.20	0.05*	0.44	1.45*
in duodenum (μg/g)	5.13	4.13	3.52*	2.25*	–	–

*Relative to group of control animals $P < 0.05$.

It is possible that the endogenous serotonin liberated by the action of reserpine from the intestine and other tissues, being in a free state, could aggregate the platelets. If this were so, intravenous injection of exogenous serotonin ought, it would seem, also to bring about an increase in aggregation of the platelets. To test this suggestion experiments were carried out with intravenous injection of exogenous serotonin in doses close to those liberated from the tissues by the action of reserpine in a dose of 2 mg/kg.

An increase in aggregation of the platelets by 48% and a decrease in activity of factor XIII by 12% were observed 1-2 min after injection of serotonin in a dose of 0.1 mg/kg, the other indices of hemostasis remaining unchanged (Table 1).

The results given in this table also show that 1 h after intraperitoneal injection of 5-hydroxytryptophan in a dose of 50 mg/kg the concentration of bound serotonin in the blood was almost 5 times higher than in the control. However, other indices of hemostasis were not significantly different from the control.

The results of these experiments thus showed that serotonin, when in the bound form, has no effect on aggregation of the platelets.

The results of these experiments demonstrate that when serotonin is liberated from the tissues as a result of administration of reserpine, and also after intravenous injection of serotonin, an increase in platelet aggregation takes place. Serotonin had no effect on the plasma recalcification time, reflecting the over-all coagulability of the blood, on factor XIII activity and on tolerance of the fibrin clot to plasmin, i.e., on indices of the third phase of blood coagulation. It is evident that serotonin plays no essential role in the process of blood clotting. This conclusion is in agreement with much evidence in the literature [6, 13, 14].

However, the importance of serotonin in hemostasis cannot be ruled out completely. According to Correll and co-workers [9], for instance, serotonin stops bleeding by narrowing the lumen of the blood vessels. The results of the present experiments showed that another mechanism for the stopping of bleeding is possible: by conversion of serotonin into a free state, associated with increased aggregation of the platelets. Free serotonin, by increasing the ability of the platelets to aggregate, thus provides favorable conditions for microthrombus formation. Serotonin has the power to stimulate aggregation of the platelets only if in a free state. In the bound form, serotonin does not increase aggregation of the platelets, despite a marked increase in its concentration in the blood, as demonstrated by experiments with the serotonin precursor 5-hydroxytryptophan.

Serotonin thus does not play an essential role in the mechanism of blood coagulation, but it participates in hemostasis as a factor stimulating aggregation of the platelets.

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