PHARMACOLOGY AND TOXICOLOGY

Response of the Middle Cerebral Artery to Serotonin

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The effect of serotonin on blood flow in the middle cerebral and common carotid arteries was studied with the help of Doppler ultrasonography on Wistar rats under general anesthesia. Serotonin induced a constrictor-dilator reaction in the middle cerebral artery: in 50% of experiments a marked initial blood flow drop was followed by a moderate increase, and then again by a profound and long decrease of the blood flow. At the same time the blood flow augmented in the common carotid artery. The data show selective and mostly vasoconstrictor effect of serotonin of the middle cerebral artery system.

Key Words: *serotonin; ultrasonography; cerebral blood flow; middle cerebral artery*

Serotonin (5-HT) plays an important role in the cerebral vascular tone regulation and in the development of cerebrovascular disorders. Immunohistochemical studies have revealed serotoninergic fibers in the cerebral arteries, arterioles, and veins of different animals [6]. Participation of 5-HT in the pathogenesis of migraine is broadly discussed [9]. 5-HT impairs blood supply to the brain by increasing the tone of cerebral vessels [3,6,7,12]. The cerebral arterial systems have different sensitivity to 5-HT (most enhanced was the tone of the carotid basin vessels) and individual reaction to this agent of the pial microvessels of varying diameter [5,8].

We found no literature data on the influence of 5-HT on the blood flow in the middle cerebral artery.

Taking into account the role of 5-HT in the regulation of cerebrovascular tone and the importance of the middle cerebral artery in the brain blood supply as well as in genesis of migraine attack, the present study compares the effect of 5-HT on blood flow in the basin of the middle cerebral artery and common carotid artery in the rats.

MATERIALS AND METHODS

The study was carried out on 26 albino male rats under general Nembutal anesthesia (40 mg/kg intraperitoneally). Blood flow was recorded with the help of a two-channel Doppler ultrasonograph at a frequency of 27 mHz [2,10]. The blood flow was recorded simultaneously in the common carotid artery and in the basin of the middle cerebral artery. To this end a cuff-type transducer 1 mm in diameter calibrated in the units of volume flow rate was placed on the right common carotid artery. Blood flow in the middle cerebral artery basin was recorded using a 1.5×2.0 mm contact ultrasonic transducer [1,4]. For this purpose the skull orifice was perforated on the right side, a branch of the right middle cerebral artery was found, and the transducer was placed in the optimal position. The femoral artery and vein were cannulated with polyethylene catheters to record arterial pressure and to inject the test solution. The data from the blood flow and arterial pressure transducers were fed into an analog computer, which performed the on-line determination of regional

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vascular bed resistance as the mean pressure divided by the average blood flow.

5-HT (Fluka) saline solution (0.3 ml) was injected in the dose of 20 μg/kg. The results were statistically analyzed by Student's *t* test.

RESULTS

To study the effect of 5-HT on the circulation in the basin of the middle cerebral artery the dose of 20 μg/kg, which caused the most profound changes in cerebral hemodynamics [5], was chosen. In all experiments 5-HT decreased the blood flow immediately after injection. The maximum decrease in the blood flow on the 1st minute after injection being 60±3.9%. Vascular tone in the middle brain artery basin increased, vascular resistance rising to 62± 15.2% (Figs. 1, 2).

Further observations revealed the characteristic variations in cerebral hemodynamics. The complete restoration of the blood flow to the initial level on the 2nd min after injection of 5-HT was observed in 5 animals (Fig. 2, *a*, 3, *3*). In 8 animals, blood flow remained decreased by 25±6.6% (Figs. 2, *b*, 3, *2*). In 13 experiments, the increase in blood flow in the studied region (31±9.1%) was recorded on the 2nd min after injection of 5-HT (Figs. 2, *c*, 3, *1*).

It should be noted that in some experiments we observed the third phase of 5-HT effect, which usually occurred on the 3rd-5th min and manifested itself as a repeated decrease in the blood flow in the basin of the middle cerebral artery. By the 10th min, such a decrease (34±8.4%) was observed in 11 out of 26 animals.

In contrast to the middle cerebral artery, intravenous 5-HT increased blood flow in the common carotid artery by 40±5.1%. The increase was observed immediately after injection and reached the maximum on the 1st min after injection (Fig. 2). The blood flow was restored 3 min later.

On the 1st minute after injection, 5-HT decreased the vagal tone in the carotid artery basin by 55±1.7% of the initial level. After 3 min, the vascular bed resistance was restored. In all experiments, 5-HT produced a decrease in arterial pressure by 37± 2.7% on the 1st min. Restoration of initial arterial pressure was observed 5 min after injection (Figs. 1, 2).

The experiments showed that 5-HT induces profound circulatory changes in the basin of the middle cerebral artery: a decrease in the blood flow was followed by its increase in 50% experiments. In a number of cases, a repeated pronounced and long decrease of the blood flow was observed. It is noteworthy that alternation of middle cerebral artery constriction and dilation is characteristic of migraine

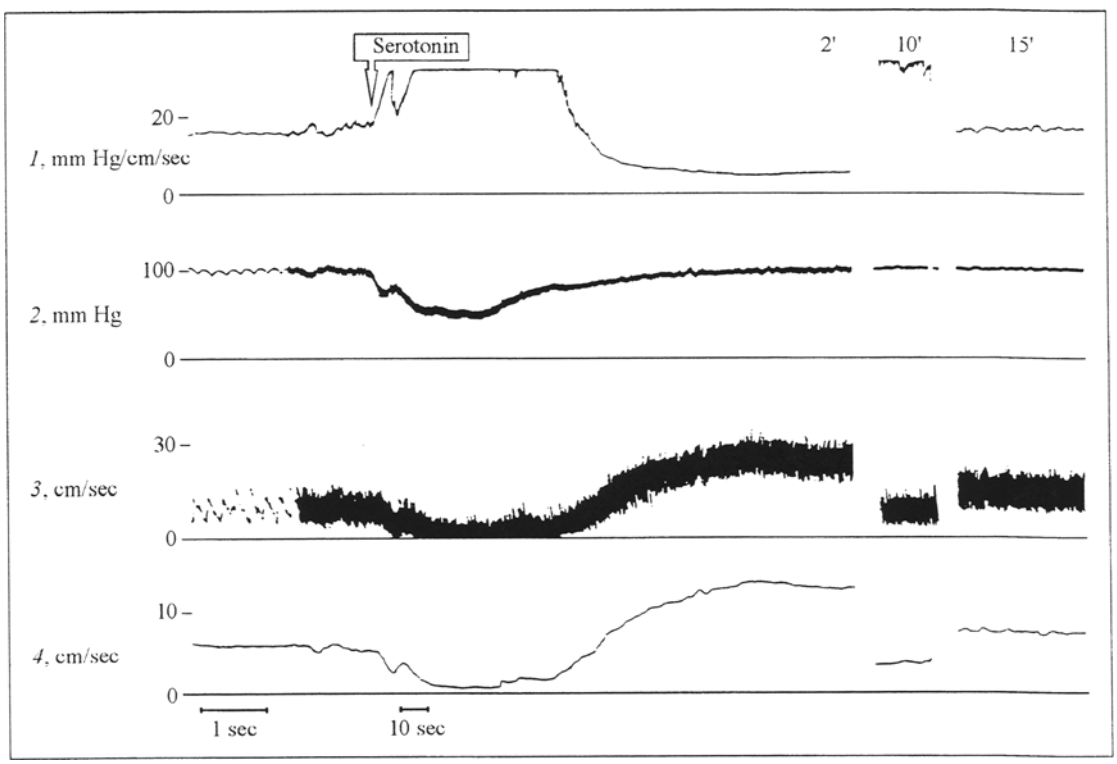

Fig. 1. Effect of serotonin (20 μg/kg intravenously) on the blood flow and the vascular bed resistance of the rat middle cerebral artery. *1*) resistance of the middle cerebral artery; 2) arterial pressure; 3) pulsatile blood flow in the middle cerebral artery; *4*) the averaged blood flow in the middle cerebral artery. Here and in Fig. 2: the upper arrow indicates serotonin administration.

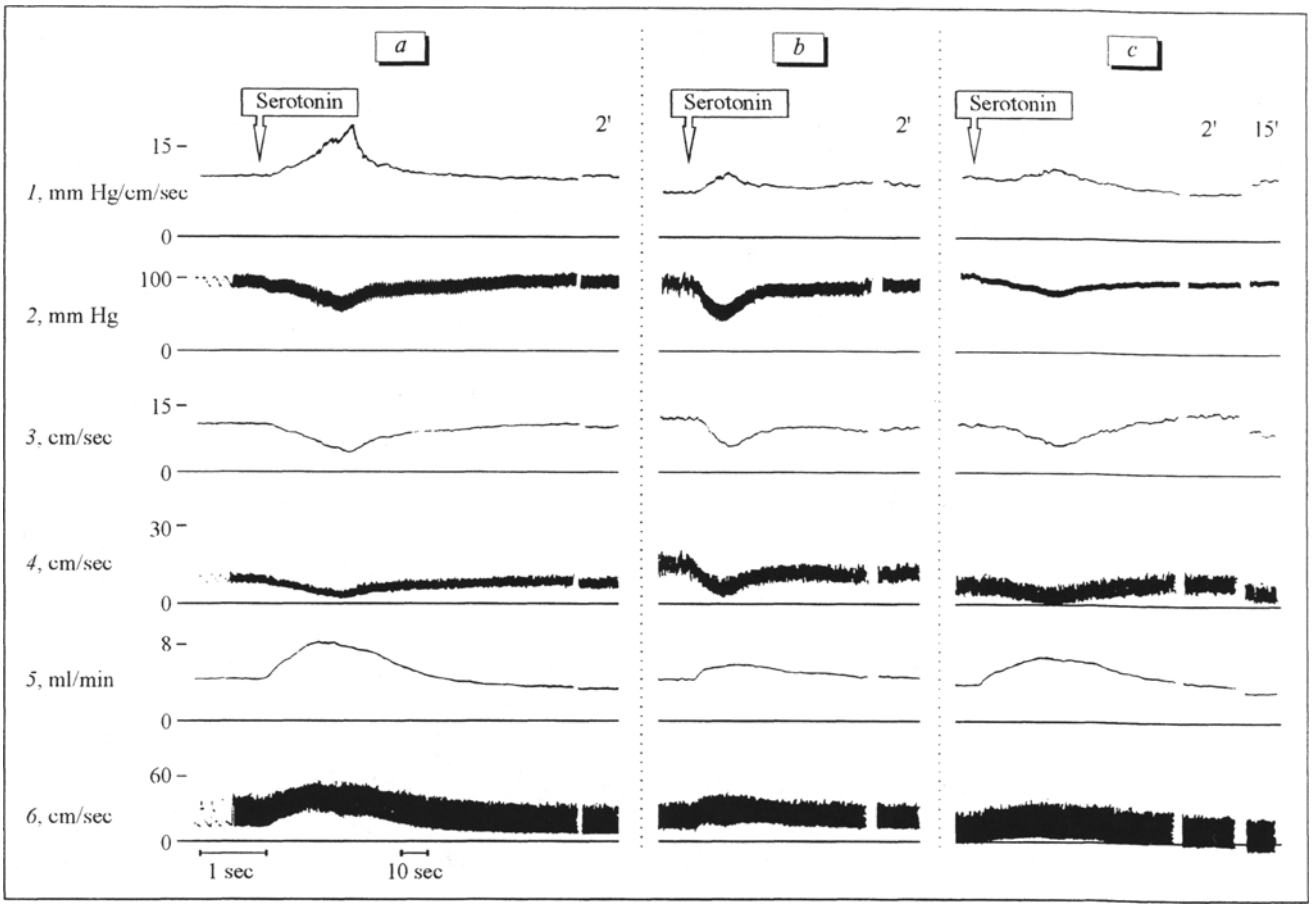

Fig. 2. Hemodynamic changes in the middle cerebral and common carotid arteries caused by serotonin (20 μg/kg intravenously). *1*) resistance of the middle cerebral artery vascular bed; 2) arterial pressure; 3) averaged blood flow in the middle cerebral artery; *4*) pulsatile blood flow in the middle cerebral artery; *5*) averaged blood flow in the common carotid artery; *6*) pulsatile blood flow in the common carotid artery; *a-c*) various experimental protocols.

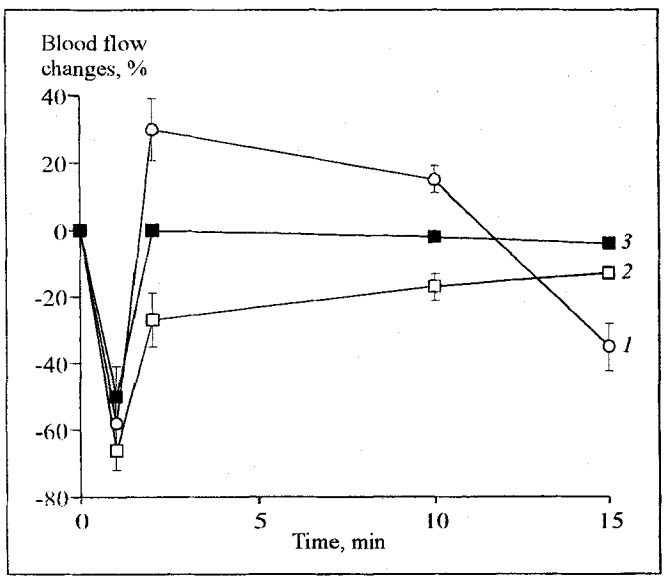

Fig. 3. Cerebrovascular effects of serotonin in different groups of experimental animals. The blood flow in three groups of animals which had increased (*1*), decreased (2) and restored (3) level of blood circulation.

attack, so our findings provide additional evidence that 5-HT is involved in the pathogenesis of migraine. At the same time, such experiments can be used as a physiological model in the screening of new antimigraine preparations.

The blood flow in the common carotid artery was changed in another way. In all experiments, 5-HT produced in this region an initial increment of blood flow to the brain with its subsequent restoration to the basal level.

Thus, 5-HT induces different vascular tone changes in the middle cerebral and common carotid arteries. While the cerebral vessels respond to 5-HT by vasoconstriction, the extracranial vessels dilate. These data indicate selective and mostly vasoconstrictor influence of 5-HT on the middle cerebral artery system. It can be supposed that the differences of 5-HT effects in the systems of middle cerebral and common carotid arteries relate to various types of serotonin receptors located in the intra- and extracranial vessels.

Comparison of the 5-HT effect on the blood flow in the rat middle cerebral artery with that on

the cerebral circulation in cats [5], shows that the vasomotor response in the middle cerebral artery is more pronounced in rats. Indeed, while the cerebral circulation in cats was decreased by 44±1.5%, the analogous decrement in the rat middle cerebral artery was 60±3.9% ($p<0.001$).

Thus, 5-HT induces the dual constrictor-dilator reaction in the rat middle cerebral artery. The component vasoconstrictor effect is characterized by marked intensity and duration. At the same time, 5-HT augments blood flow in the common carotid artery.

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