Effect of Serotonin on Respiration, Cerebral Circulation, and Blood Pressure in Rats

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The effects of intravenous serotonin on respiration, cerebral circulation, and blood pressure were examined in narcotized rats. Serotonin rapidly decreased local cerebral blood flow (by almost 30%) and blood pressure. Hemodynamic phenomena were accompanied by sharp changes in the respiration pattern: short-term apnea in all cases. The mechanism of this apnea was related to initial stages in blood pressure changes and had a neurogenic nature.

Key Words: serotonin; cerebral circulation; respiration; apnea; rat

Serotonin (5-hydroxytryptamine) is a biogenic amine with peripheral (specifically, vasomotor) and central (neurotransmitter) activity. In different animal species, intravenous injection of serotonin induces a transient decrease in cerebral circulation: in cats injection of 20 µg/kg serotonin decreases cerebral circulation by more than 40% [2]. Simulation of cerebrovascular disorders of serotoninergic origin is a necessary stage in searching for preparations to treat migraine. The effects of substances on cerebral circulation and blood pressure (BP) are usually studied on cats and rats [1]. In narcotized rats, intravenous injection of serotonin (20 μg/kg) produces a transitory (3-4 min) drop in local cerebral blood flow by 24% on average and decreases systemic BP by 20% [2]. In addition to dramatic effect on cerebral circulation, serotonin can modulate the respiratory pattern, which leads to changes in pH and blood gases and, hence, indirectly affects the reaction of cerebral vessels [5]. Our aim was to compare temporary characteristics of respiratory and cerebral circulation responses to systemic injection of serotonin and to study the mechanism of their interaction.

MATERIALS AND METHODS

Experiments were carried out on random-bred male rats (*n*=18) weighing 250-300 g under natural respira-

tion and body temperature of 37.0-38.5°C. In series 1 and 2 the rats were narcotized with intraperitoneal chloral hydrate (400 mg/kg) and sodium pentobarbital (40-50 mg/kg), respectively.

In series 1 (n=10), local cerebral blood flow in the parietal cortex was recorded. To this end, the needle sensor of an ALF-21 laser Doppler flowmeter (Transonic System) with a diameter of 0.8 mm was placed above the dura mater in the basin of the medial cerebral artery. Simultaneously, BP was recorded in the femoral artery with a BPR-01 electromanometer. Serotonin was injected intravenously in a dose of 20 μ g/kg.

In series 2 (n=8), the effect of serotonin on respiration was examined. Tracheotomy was performed in the upper $\frac{1}{3}$ part of the trachea, where the plastic tube of the corresponding diameter was inserted and fixed. Tracheal cannula was connected to the sensor to recorder the parameters of external respiration. The distal end of the sensor was connected to a valve to feed the air. The basic respiratory indices such as respiratory minute volume (RMV), respiratory rate (RR), and pneumotachogram were recorded with an instrumental respiratory module in a MX-01 polygraph under BTPS. Tidal volume was calculated as RMV/RR. Systemic BP and heart rate (HR) were measured with a catheter passed into femoral artery and connected to a MX-01 strain-gage transducer. To measure the intraesophageal pressure (IEP), a catheter with elastic balloon filled with water was passed into the esophagus and connected to another MX-01 transducer. In this sys-

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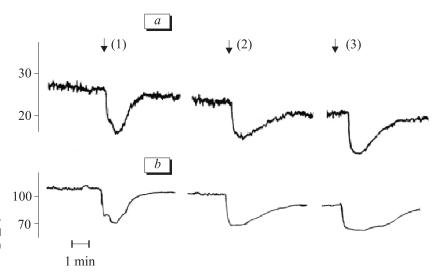


Fig. 1. Effect of the first, second, and third serotonin injections (arrows) on local cerebral blood flow (*a*, relative units) and blood pressure (*b*, mm Hn)

tem, the pressure was regulated in such a way that it was zero during passive expiration. The data were recorded in an H3031-6 ink-pen recorder. Serotonin was injected intraperitoneally in a dose of 20 μ g/kg. The results were analyzed statistically using Student's t test, the differences were significant at p<0.05.

RESULTS

In series 1, BP and local cerebral blood flow before the first injection of serotonin were 85.4±3.6 mm Hg and 23.6±1.9 arb. units, respectively. These parameters before injections virtually did not change.

After the first injection of serotonin cerebral blood flow and BP in all cases decreased by 28 and 33%, respectively. Both parameters changed in parallel: after attaining the minimum during the first minute postinjection, they returned to the initial level after 3-6 min (Fig. 1). In 40% cases, the maximal drops in cerebral blood flow and BP were preceded by biphasic oscillations of both parameters. After the second and third injections of serotonin the changes of these parameters were similar (Table 1). Serotonin produced a short-term increase in ventilation. In cases when the serotonin-induces responses of local cerebral blood

flow and BP were triphasic, activation of ventilation was followed by a short-term apnea for 3-5 sec.

In series 2, the initial ventilatory and hemodynamic parameters were RMV=24.9±2.5 (13-30) ml/min, RR=75.9±6.0 (66-90) min⁻¹, tidal volume=0.240±0.018 (0.17-0.33) ml, IEP=3.75±0.47 (3.0-6.5) mm Hg, BP=100.6±6.7, and HR=431.5±11.8 min⁻¹. These parameters did not significantly change before the second and third injections of serotonin.

In all experiments, the first injection of serotonin induced apnea lasting for 7.4±2.3 sec (Fig. 2). In 6 experiments, apnea was preceded by a short-term tachypnea lasting for 3-4 sec. After resumption of respiratory excursions, RR did not change in two experiments, while in six cases it decreased to 62.3±1.6 (by 16.5±6.0%). In all experiments, RMV increased to 22.9±4.2 ml/min (by 24.9±2.5%). The increase in RMV developed against the background bradypnea due to the rise in the amplitude of respiratory excursions resulting in an increase in tidal volume by 52.0±8.6%. IEP increased by 98.6±16.1%. RR and RMV restored in 26.9±13.5 sec (6-100 sec) and 229.0±7.5 sec (150-500 sec), respectively.

After the second injection of serotonin, apnea was 6.0±1.5 sec, while RMV, tidal volume, and IEP in-

TABLE 1. Effect of Serotonin on Local Cerebral Blood Flow (LCBF) and BP (M±m)

	1st		2nd		3rd	
Index	LCBF, arb. units	BP, mm Hg	LCBF, arb. units	BP, mm Hg	LCBF, arb. units	BP, mm Hg
Initial value	23.6±1.9	85.4±3.6	22.8±2.1	77.8±4.3	20.5±1.6	73.9±3.1
Minimal postinjection value	17.0±1.8	57.4±4.2	15.0±1.7	53.7±3.8	14.1±1.0	51.1±2.9
Percentage to initial level	-28	-33	-34	-31	-32	-31
p	<0.05	<0.001	<0.02	<0.01	<0.01	<0.001

Note. p is calculated in comparison to initial values.

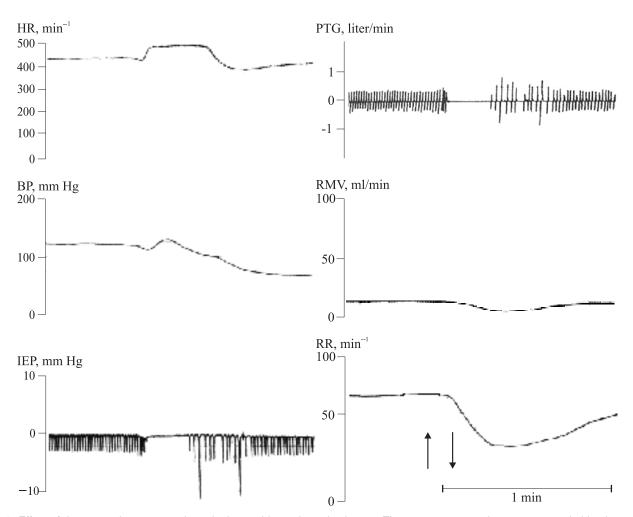


Fig. 2. Effect of the serotonin on external respiration and hemodynamics in rats. The parameters are the mean systemic blood pressure (BP), intraesophageal pressure (IEP), pneumotachogram (PTG), respiratory minute volume (RMV), and respiratory rate (RR). The arrows mark the onset and termination of injections.

creased by 47.3±19.3%, 59.0±18.7%, and 149±39%, respectively. RR and RMV restored after 59.8±9.5 sec and 165±24 sec, respectively.

After the third injection of serotonin, apnea was 6.6±1.3 sec, while RMV, tidal volume, and IEP increased by 40.0±9.3%, 45.0±12.5%, and 155±37%, respectively. RR and RMV restored in 63±39 and 165±36 sec, respectively.

Thus, intravenous injection of serotonin in a dose of 20 µg/kg induced short-term apnea followed by bradypnea and increment of respiratory excursions

resulting in total increase in RMV. IEP rose in parallel to respiratory movements.

The succession of restoration of respiratory parameters is noteworthy: the first restored parameter was RR (in two cases it even did not change), and then RMV restored to the initial value. IEP restored somewhat later. In spite of virtually constant duration of apnea during the repeated injections of serotonin, the recovery period of RR increased. There was no correlation between apnea duration and the period of subsequent recovery of RR and RMV recorded after the

TABLE 2. Respiratory Indices and Their Restoration Time to Initial Level after 1st, 2nd, and 3rd Injections of Serotonin ($M\pm m$, n=8)

Injection	Apnea duration, sec	RR, %	RR restoration time, sec	RMV, %	RMV restoration time, sec
1st	7.4±2.3	-16.5±6.0	26.9±13.5	24.9±2.5	229±8
2nd	6.0±1.5	-14.0±8.2	59.8±9.5	47.3±19.3	165±24
3rd	6.6±1.3	-11.6±8.2	63±39	40.0±9.3	165±36

first and subsequent injections of serotonin (Table 2). However, the shorter was apnea, the more pronounced was bradypnea (Table 2). Probably, both apnea and bradypnea were caused by the same process. This assumption was corroborated by the fact that in seven cases, where RR did not change after apnea, the apnea was long (7-14 sec). By contrast, the relatively shorter apnea (3 sec) was accompanied by most pronounced bradypnea (RR decreased by 17-33%).

The serotonin-induced changes in BP were phasic: in phase 1, there was a short-term (4-10 sec) decrease in the mean BP by 30%; in phase 2, BP rose for a short time of 6-12 sec up to the initial value; and in phase 3, BP again decreased by 50% on average during 150-300 sec. Similar responses were observed almost in all experiments except for cases that had no phase 2. The changes in the mean BP were accompanied by phasic variations in HR. In phase 1, HR decreased by 8%; in phase 2, it increased by 20.6%; and in phase 3, HR again decreased by 8% initial value.

Thus, in 82% cases apnea developed during phase 1 (a short-term drop of BP), and only in 18% it occurred during phase 2 (a short-term rise of BP).

The experiments revealed synchronous changes in BP and local cerebral blood flow. The cerebral blood flow decreased approximately similar irrespective to the character of respiratory reaction (presence or absence of apnea). In cases with apnea, the responses of local cerebral blood flow were triphasic: decrease—increase—decrease. In some cases apnea occurred during phase 1 of BP changes, and in other cases it developed during the second, but never during the third phases.

Evidently, apnea was determined by the same mechanisms, which underlay the first and second phases of BP changes. Similar oscillations were characteristic of cerebral blood flow, which decreased at the end of apnea, when the blood concentration of CO₂ increased. It is unlikely that metabolic component plays an important role in this moderation of cerebral circulation. No purely myogenic autoregulatory dilation was observed in response to decrease in BP. Therefore, despite parallel development of some phases, the changes in cerebral circulation and external respiration are

not directly related to each other and seem to result from different neurogenic sources.

Two possible mechanisms should be distinguished among the pneumotropic inhibitory effects of serotonin. The first one is based on the central action of amine, which is experimentally demonstrated by its injection (20-500 µg) into cerebral ventricles, including the fourth ventricle [4]. On anesthetized cats and rats, the most reliably reproducible central effects are bradypnea and decrease in tidal volume. This reaction does not depend on the integrity of IX (glossopharyngeal) and X (vagus) pairs of the craniocerebral nerves [4]. Another type of reaction (apnea) was observed only after intravenous injection of serotonin [5]. Evidently, it is caused by bronchospasm mediated by vagal nerve terminal [5]. Bilateral vagotomy or atropine eliminates this reaction [5]. Apnea of this type is an integral part of Bezold-Jarisch reflex, and it is reproduced by injections of various substances: acetylcholine, nicotine, and hellebore alkaloids [3].

Thus, during the first period of intravenous serotonin injection, when its concentration does not attain a maximum, it induces bradypnea similar to that caused by low doses of atropine. Then elevation of serotonin level in the blood provokes spasm of bronchioles leading to apnea. Probably, the increase in the resistance of respiratory airways enhances activity of the respiratory muscles, and this process underlies the first respiratory excursions after apnea.

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