EFFECT OF PRECURSORS AND SOME ANALOGS OF SEROTONIN ON THE CEREBRAL CIRCULATION

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It has been shown that 5-hydroxytryptophan and tryptamine decrease the resistance of the cerebral blood vessels and lower the velocity of the blood flow and pO_2 in the brain tissues. The systemic arterial pressure is also lowered. 5-Methoxytryptamine increases the tone of the cerebral vessels and lowers the blood flow and pO_2 in the brain tissues. The arterial pressure is lowered. Melatonin causes no essential changes in the cerebral circulation.

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5-Hydroxytryptophan and tryptamine are precursors of serotonin (5-hydroxytryptamine) [3, 6]. Mexamine (5-methoxytryptamine) and melatonin (n-actyl-5-methoxytryptamine) are close in their chemical structure to serotonin and are intermediate products of its metabolism [3]. There are data in the literature concerning the effect of these compounds on the systemic arterial pressure and peripheral vascular tone [1, 4, 8, 10]. However, their effect on the cerebral circulation has not been studied.

We have investigated the effect of 5-hydroxytryptophan, tryptamine, mexamine, and melatonin on some indices of the cerebral circulation: the volume velocity of the blood flow, the oxygen tension, and the resistogram of the cerebral vessels.

EXPERIMENTAL METHOD

Experiments were carried out on 90 cats anesthetized with urethane (1 g/kg, intraperitoneally). In the experiments of group 1 the volume velocity of the blood flow in the parietal and occipital cortex was studied by a thermoelectric method [2] and the oxygen tension (pO_2) by a polarographic method [7]. In the experiments of group 2 the tone of the cerebral vessels was investigated by perfusion of the common carotid artery (after ligation of the muscular branches) by a constant volume of blood [5]. The systemic arterial pressure (AP) was recorded in the femoral artery by means of a mercury manometer. The preparations were injected intravenously and into the carotid artery: 5-hydroxytryptophan and tryptamine in doses of 1-5 mg/kg, mexamine 25-50 μg/kg, and melatonin from 25 μg/kg to 10 mg/kg. In some experiments, to analyze the

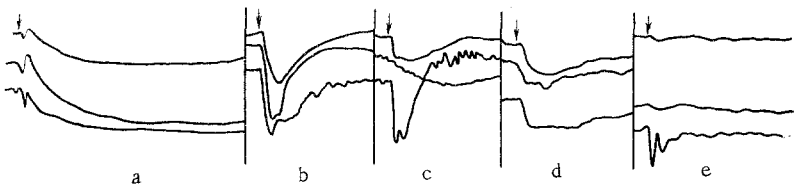

Fig. 1. Commonest variants of effect of 5-hydroxytryptophan (a), tryptamine (b, c), mexamine (d), and melatonin (e) on volume velocity of blood flow (top curve), pO_2 (middle curve), and systemic arterial pressure (bottom curve). c) Tryptamine given after preliminary administration of iproniazid.

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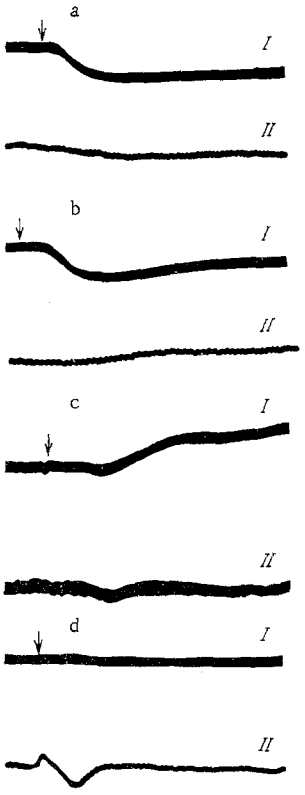

Fig. 2. Effect of 5-hydroxytryptophan (a), tryptamine (b), mexamine (c), and melatonin (d) on resistance of cerebral vessels (I) and systemic arterial pressure (II).

mechanism of action of the preparations, monoamine oxidase (MAO) inhibitors were used: pheneprazine (2 mg/kg, intravenously, 1 h before administration of serotonin precursors), or iproniazid, injected intraperitoneally in doses of 50 and 100 mg/kg 18-20 h before the experiment.

EXPERIMENTAL RESULTS

Intravenous injection of 5-hydroxytryptophan in doses of 1, 2, 3, and 5 mg/kg in most experiments lowered the volume velocity of the blood flow, pO_2 in the brain tissues, and AP (Fig. 1, a). The effect developed slowly and lasted from 2 to 26 min. Often after injection of 5-hydroxytryptophan the blood flow, pO_2, and AP did not return to their original level during the experiment.

Intravenous injection of tryptamine in doses of 1, 2, 3, and 5 mg/kg also lowered the velocity of the blood flow, pO_2, and AP in most experiments, and the decrease was more marked but less prolonged than after administration of 5-hydroxytryptophan (Fig. 1, a, b).

Administration of serotonin precursors causes the accumulation of endogenous serotonin in the tissue, inactivation of which involves the participation of MAO [3, 6]. It is natural to suggest that under conditions of lowered MAO activity following administration of iproniazid, the effects of 5-hydroxytryptophan and tryptamine would be potentiated. In the experiments carried out, preliminary administration of iproniazid as a rule did not potentiate the effects of 5-hydroxytryptophan and tryptamine (Fig. 1, c), and in some experiments their effects were actually weakened. However, it should be noted that intraperitoneal injection of iproniazid in doses of 50 and 100 mg/kg 18-20 h before the experiment caused considerable changes in the animals' condition by the beginning of the experiment (apathy, inhibition, cyanosis of the mucous membranes; the arterial blood resembled venous in color).

After intravenous injection of mexamine in a dose of 50 μg/kg the velocity of the blood flow as a rule fell immediately after administration of the drug and this effect was observed for between 2 and 17 min (Fig. 1, d). The decrease in cerebral blood flow took place against the background of arterial hypotension. However, in some experiments a decrease in cerebral blood flow was observed against the background of an increased AP. Sometimes a transient increase in blood flow took place along with a raised AP. The oxygen tension was lowered by mexamine (Fig. 1, d) even when the cerebral blood flow was increased.

Melatonin had a much less marked effect than 5-hydroxytryptophan, tryptamine, and mexamine. In most experiments it caused no essential changes in the volume velocity of the blood flow and pO_2 (Fig. 1, e). Only in a few experiments were the blood flow and the value of pO_2 in the brain tissues lowered after administration of melatonin in a dose of 10 mg/kg.

In the next group of experiments the effect of precursors and analogs of serotonin on the tone of the cerebral vessels was studied.

Intracarotid injection of 5-hydroxytryptophan and tryptamine in doses of 1 and 2 mg/kg usually lowered the perfusion pressure (by 4-20 mm Hg; Fig. 2, a, b). The lowering of the tone of the cerebral vessels was steady in character and short in duration (1-6 min). In contrast to 5-hydroxytryptophan, the effect of tryptamine on tone of the cerebral vessels was less constant. In some experiments tryptamine caused biphasic changes in tone, when slight vasodilatation was followed by slight constriction. The systemic AP was lowered by 5-hydroxytryptophan and tryptamine. However, whereas the AP as a rule was lowered by intravenous injection of tryptamine, after intracarotid injection of the drug in the same doses, the systemic AP was raised in some experiments.

The action of 5-hydroxytryptophan was also studied after preliminary administration of iproniazid and pheneprazine. In these experiments, just as in the experiments to study the volume velocity of the blood flow and pO_2, MAO inhibitors did not potentiate the effect of the serotonin precursors. Intracarotid injection of mexamine in a dose of 25 μg/kg in all cases caused an increase in perfusion pressure (by 2-80 mm Hg; Fig. 2, c). The increase in tone was steady and lasted for between 1 and 24 min. Intravenous injection of melatonin in a dose of 10 mg/kg was not accompanied by significant changes in tone of the cerebral vessels (Fig. 2, d).

These investigations thus showed that 5-hydroxytryptophan and tryptamine, which are regarded as precursors of serotonin, when injected intravenously and into the carotid artery, cause changes different from those produced by serotonin. According to our results, injection of serotonin is accompanied by an increase in tone of the cerebral vessels whereas 5-hydroxytryptophan and tryptamine produce slight dilatation of the cerebral vessels.

Dilatation of the blood vessels of an organ is known to lead to an increased blood flow in it only if the AP is increased or unchanged [2]. In our experiments, intravenous injection of 5-hydroxytryptophan and tryptamine was accompanied by lowering of the AP. It may be postulated that the decrease in velocity of the blood flow and pO_2 in the brain tissues under the influence of 5-hydroxytryptophan and tryptamine takes place, despite vasodilatation, as a result of the hypotensive effect of the drugs. However, it is difficult to explain completely the mechanism of action of these preparations.

Observations showing that MAO inhibitors do not potentiate the effect of 5-hydroxytryptophan and tryptamine are of great interest. Possibly under these experimental conditions serotonin accumulating in the nerve cells did not pass through the tissue-blood barrier into the blood stream and did not affect the extracellular serotonin-sensitive receptors [9]. However, the possibility is not ruled out that administration of MAO inhibitors sharply changes the functional state of the organism. Under these conditions the effect of serotonin precursors is not reflected in an increase in their action on the indices of the cerebral circulation which were investigated.

In the character of its action mexamine is close to serotonin. So far as melatonin is concerned, this had a weak effect on the cerebral circulation, in agreement with data in the literature [1] describing the low pharmacological activity of this n-acetyl derivative of 5-methoxytryptamine.

LITERATURE CITED

1. G. S. Arutyunyan, M. D. Mashkovskii, and L. F. Roshchina, Farmakol. i Toksikol., No. 6, 650 (1963).
2. M. E. Marshak, in: Modern Methods of Investigation of Functions of the Cardiovascular System [in Russian], Moscow (1963), p. 179.
3. M. D. Mashkovskii, in: Current Problems in Pharmacology [in Russian], Moscow (1963), p. 24.
4. M. D. Mashkovskii and G. S. Arutyunyan, Farmakol. i Toksikol., No. 1, 10 (1963).
5. V. M. Khayutin, V. M. Danchakov, and V. L. Tsaturov, Byul. Éksperim. Biol. i Med., No. 2, 117 (1958).
6. D. F. Bogdarski, H. Weissbach, and S. Udenfriend, Fed. Proc., 15, 402 (1956).
7. D. B. Cater, J. A. Silver, and G. M. Wilson, Proc. Roy. Soc. B., 151, 256 (1959).
8. K. H. Ginsel and S. R. Kottegoda, Quart. J. Exp. Physiol., 48, 225 (1953).
9. J. Offermeier and E. F. Ariens, Arch. Int. Pharmacodyn., 164, 216 (1966).
10. G. Reid, Aust. J. Exp. Biol. Med. Sci., 29, 102 (1951).