EFFECT OF SODIUM AND POTASSIUM IONS ON SEROTONIN UPTAKE BY LUNG TISSUE

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The dependence of serotonin (5-HT) uptake on the Na^+ and K^+ concentrations in the perfusion fluid was demonstrated in experiments on isolated perfused albino rat lungs. With high Na^+ concentrations in the perfusion fluid (60-150 mM), the uptake of 5-HT by lung tissue cells was high, whereas with low Na^+ concentrations (0-30 mM) 5-HT uptake was sharply reduced. The K^+ concentration in the perfusion fluid had a weak effect on 5-HT uptake. Maximal uptake was observed in the presence of K^+ in a concentration of 5 to 20 mM. A decrease or increase in K^+ concentration retarded 5-HT uptake. 5-HT uptake was sharply inhibited by strophanithin K, an inhibitor of Na,K-ATPase, in concentrations of 10^{-4}-10^{-3} M. A link is postulated between 5-HT transport through the cell membrane and Na^+ transport.

KEY WORDS: lungs; Na,K-ATPase; serotonin uptake.

Besides their generally accepted function in gas exchange, the lungs also participate in the metabolism of several biologically active substances, including serotonin (5-HT). Depending on the species of animal, the experimental method, and the dose of the substance used, from 40 to 95% of free 5-HT is broken down in the lungs during one circulation of the blood through the pulmonary vessels [3, 7]. The process takes place in two successive stages: initial active uptake of serotonin by the lung cells, followed by its enzymatic breakdown [1, 8]. Serotonin uptake by the lung cells is coupled with its transport through the cell membrane and depends on various factors, notably the concentration gradient of certain ions (Na^+, K^+, Ca^{++}) on either side of the cell membrane.

The results of a study of the role of Na^+ and K^+ in the 5-HT uptake by lung tissue cells in the process of liberation of 5-HT from the cells are described in this paper.

EXPERIMENTAL METHOD

Isolated perfused lungs of albino rats were used. Rats weighing 200-250 g were anesthetized with ether vapor, the chest was opened, and heparin injected (300 units) into the heart. The venae cavae were tied, one polyethylene cannula was introduced through the opened right ventricle into the pulmonary artery, and another through the aorta into the left ventricle. The heart–lung preparation was removed from the thorax and placed in a waterbath at 38°C. The lungs were perfused under constant pressure at the rate of about 4 ml/min with oxygenated Gaddum's solution (NaCl 150 mM, KCl 5.3 mM, $NaHCO_3$ 1.8 mM, $CaCl_2$ 0.25 mM, glucose 5.56 mM). To prevent pulmonary edema, the Gaddum's solution was made up in 20% dextran solution. In experiments in which the effect of different concentrations of Na^+ on the uptake and liberation of 5-HT was studied, some of the NaCl was replaced by an equimolar amount of sucrose. Before the beginning of perfusion, preperfusion was carried out for 5-8 min to remove blood from the lungs and to enable various substances to act on the lung tissue. Serotonin–creatinine sulfate (Reanal, Hungary) was used for perfusion in a concentration of 0.1 μg/ml, determined in the perfusion fluid by the biological method of Dalgliesh et al. [6]. Perfusion continued for 20 min and the amount of 5-HT taken up and liberated was expressed in μg/g lung tissue/min.

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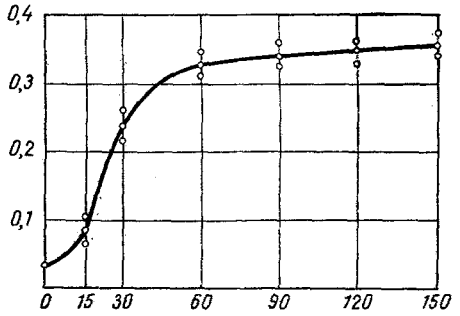

Fig. 1

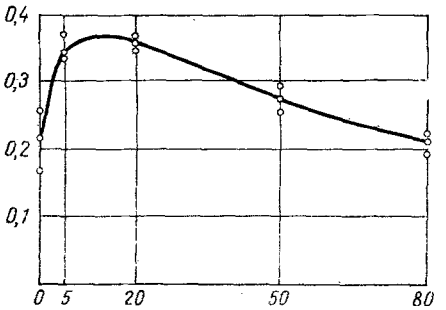

Fig. 2

Fig. 1. Effect of various concentrations of Na^+ in the perfusion fluid on serotonin uptake by lung tissue. Abscissa, Na^+ concentration (in mM); ordinate, serotonin uptake (in $\mu g/g/min$).

Fig. 2. Effect of various K^+ concentrations in perfusion fluid on serotonin uptake by lung tissue. Abscissa, K^+ concentration (in mM); ordinate, serotonin uptake (in $\mu g/g/min$).

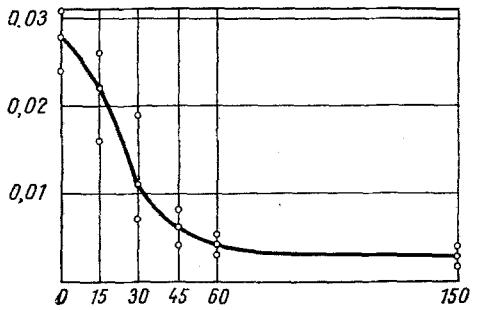

Fig. 3. Effect of various concentrations of Na^+ in perfusion fluid on removal of serotonin from lung tissue. Abscissa, Na^+ concentration (in mM); ordinate, removal of serotonin (in $\mu g/g/min$).

EXPERIMENTAL RESULTS AND DISCUSSION

To study the role of Na^+ in the uptake of 5-HT, the lungs were perfused with solutions containing decreasing concentrations of this ion. The results are shown in Fig. 1, from which it is clear that the largest amounts of 5-HT were taken up by the lung tissue when the Na^+ concentration in the perfusion fluid was between 150 and 60 mM, namely 0.352-0.328 $\mu g/g/min$. A decrease in the Na^+ concentration to 30 mM or below sharply inhibited 5-HT uptake. If Na^+ was completely absent from the perfusion fluid, the 5-HT uptake was only 0.032 ± 0.005 $\mu g/g/min$, i.e., 10 times less than with the original concentration of this ion.

The concentration of K^+ ions in the perfusion fluid also affects the binding of 5-HT by the lung tissue (Fig. 2). With K^+ concentrations in the perfusion fluid of 5 to 20 mM the 5-HT uptake reached a maximum (0.352-0.361 $\mu g/g/min$); absence of K^+ in the perfusion fluid inhibited 5-HT uptake by about one third. An increase in the K^+ concentration above 20 mM also inhibited 5-HT uptake.

Administration of the cardiac glucoside strophanthin K, an inhibitor of Na,K-ATPase [2] (the enzyme responsible for active transport of Na^+ and K^+ through the cell membrane), also inhibited 5-HT uptake. The inhibitory effect of the drug in a concentration of 10^{-4} M was small and it increased sharply with an increase in concentration to 10^{-3} M, when the 5-HT uptake was only 0.159 ± 0.010 $\mu g/g$ tissue/min ($P < 0.001$).

The $Na^+ : K^+$ ratio in the perfusion fluid also had a definite effect on the liberation of 5-HT from lung tissue (Fig. 3). In the complete absence of Na^+ from the perfusion fluid and its replacement by an equimolar concentration of sucrose maximal removal of 5-HT from the lung tissue reaching 0.028 ± 0.001 $\mu g/g/min$, was observed. An increase in the Na^+ concentration in the perfusion fluid led to a decrease in the removal of 5-HT. With an Na^+ concentration above 45 mM, removal took place at about a constant speed, namely 0.003 ± 0.0001 $\mu g/g/min$ with an Na^+ concentration of 150 mM. The effect of K^+ on removal of 5-HT from the lung tissue was much weaker: Only high concentrations of K^+ (50 mM or over) led to some increase in the rate of removal. Strophanthin K in concentrations of 10^{-4}-10^{-3} M also had a weak effect on 5-HT removal from lung tissue.

These data show that the ionic gradient on both sides of the cell membrane plays an important role in the uptake of 5-HT by the lungs and its removal from them. Na^+ ions are essential both for 5-HT uptake by lung tissue and for retention of the absorbed 5-HT. The direction in which 5-HT will be transported depends on the Na^+ concentration in the perfusion fluid: If the Na^+ concentrations are high in the extra-

cellular fluid, large quantities of 5-HT will pass into the cell; but if Na^+ concentrations are low, 5-HT transport will proceed in the opposite direction.

K^+ ions in low concentrations (5-20 mM) are essential for the normal course of both processes. The complete absence of K^+ or a sharp increase in its concentration in the perfusion fluid inhibits 5-HT uptake. Strophanthin K, which inhibits active Na^+ and K^+ transport through the cell membrane through inactivation of Na,K-ATPase sharply inhibits 5-HT uptake by lung tissue, but has only a weak effect on its removal. Similar relationships apply to a whole series of transport systems of the body with the function of transporting certain amino acids and monosaccharides through cell membranes [4, 5, 11]. The function of these systems is based on an ionic gradient on both sides of the cell membrane, supported by Na,K-ATPase. Evidence in support of the existence of such transport systems and of monoamine transport through the cell membrane has been obtained. Pletscher et al. [9], for instance, showed that 5-HT can enter platelets on account of energy systems that are inhibited by the strophanthin K analog, ouabain. Sneddon [10] found that 5-HT transport through the cell membrane is closely linked with Na^+ transport. The presence of a similar transport system for 5-HT in the lung tissue, closely linked with the function of Na,K-APTase, can therefore be postulated. It is not by accident that removal of the ionic gradient on both sides of the cell membrane (by decreasing the Na^+ concentration in the perfusion fluid and inactivating Na,K-ATPase) sharply inhibits both the uptake and removal of 5-HT.

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