EFFECT OF SEROTONIN OF RESPIRATION AND OXIDATIVE PHOSPHORYLATION IN RABBIT HEART MUSCLE TISSUE

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Serotonin depresses respiration of rabbit heart muscle homogenates. During oxidation of exogenous respiration substrates in the mitochondria, serotonin leads to a decrease in the intensity both of respiration and of oxidative phosphorylation without any marked change in the P : O.

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The property of serotonin of causing damage to the myocardium resembling an infarct [1], the lowering of monoamine oxidase (MAO) activity in myocardial infarction [7], and the possibility of serotonin accumulation in the heart tissues as a result of pathological states or low MAO activity [8] are all factors determining the need for a detailed study of the effect of serotonin on the energy metabolism of heart tissue. This problem has not yet been adequately studied. There are reports of the dissociation of respiration and phosphorylation in the liver mitochondria of the guinea pig by serotonin [6]; a decrease in intensity of oxygen consumption by brain tissue preparations has been demonstrated [9]; some noteworthy results have been obtained indicating inhibition of respiration of homogenates obtained from an area of myocardium damaged by serotonin [5].

The object of the present investigation was to study the effect of serotonin on respiration and oxidative phosphorylation in homogenates and mitochondria of the rabbit myocardium.

EXPERIMENTAL METHOD

The experimental animals were male rabbits weighing 2.5-3 kg. The test material consisted of homogenates and mitochondria isolated from the ventricles by the usual method [2, 3]. The tissue was homogenized in a glass blender with Teflon pestle.

In the experiments with homogenate the oxygen absorption was measured in the presence of endogenous respiration substrates, and in the experiments with mitochondria both the oxygen absorption and the decrease in mineral phosphate were determined [3]. The respiration substrates used were α-ketoglutarate (together with malonate), β-hydroxybutyrate, succinate, and glutamate in an amount of 10 μmole. Serotonin was added in the form of serotonin-creatinine sulfate in a dose of 10-30 μmole per sample. The volume of the incubation samples was 1 ml. Tissue preparations were incubated in buffered medium [2,3] in a Warburg apparatus in an atmosphere of air for 15 min. The mitochondria were "aged" by preincubation at 26° for 30-60 min in 0.25 M sucrose and 0.001 M EDTA solution both in the presence and in the absence of 10 μmole serotonin. For 10 mg protein, the results were calculated for 10 mg protein of homogenate and 1 mg protein of mitochondria. The protein content was determined by the biuret reaction. The results given are for 6-8 experiments.

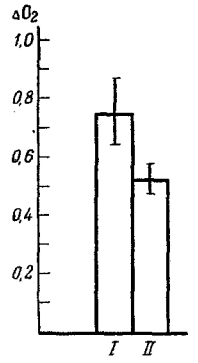

Fig. 1. Effect of serotonin on respiration of rabbit heart muscle homogenates in presence of endogenous substrates. ΔO_2 – Oxygen absorption (in μatom). I) Normal conditions (incubation without serotonin); II) incubation in presence of 10 μmole serotonin.

EXPERIMENTAL RESULTS AND DISCUSSION

The effect of serotonin on the intensity of oxygen absorption by rabbit heart homogenates is shown in Fig. 1. In the presence of 10 μmole serotonin the intensity of respiration of the homogenates fell by 28%.

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TABLE 1. Effect of Serotonin on Effectiveness and Intensity of Respiration and Oxidative Phosphorylation in Rabbit Heart Mitochondria

Respiration substrate	Serotonin (μmoles)	P : O		Changes in presence of serotonin, in %	
		normal	incubation in presence of serotonin	oxygen absorption (in μatoms)	decrease in mineral phosphate (in μatoms)
α-Ketoglutarate + malonate	10	3.7	3.8	− 34	− 34
	30	3.4	3.1	− 31	− 36
β-Hydroxybutyrate	10	2.7	3.0	− 33	− 25
	30	3.2	3.2	− 55	− 54
Succinate	10	1.3	1.3	− 15	− 15
	30	1.3	1.1	− 15	− 31
Glutamate	10	2.6	2.6	− 20	− 21

TABLE 2. Effect of Serotonin on Effectiveness and Intensity of Respiration and Oxidative Phosphorylation in Rabbit Heart Mitochondria Subjected to "Aging"

Duration of "aging" (in min)	Substrate	P : O "aging"		Changes in presence of serotonin, in %	
		without serotonin	in presence of 10 μmole serotonin	oxygen absorption (in μatoms)	decrease in mineral phosphate (in μatoms)
60	α-Ketoglutarate + malonate	2.4	2.4	− 46	− 46
30	β-Hydroxybutyrate	1.6	2.3	− 50	− 30
60	Succinate	0.87	0.72	0	− 21

The effect of serotonin on the effectiveness and intensity of respiration and phosphorylation in the rabbit heart mitochondria is illustrated in Table 1. Serotonin caused a decrease in intensity of both respiration and phosphorylation without any well-defined change in the effectiveness of the processes studied. The degree of the serotonin effect on respiration and phosphorylation during oxidation of various respiration substrates in the mitochondria varied from case to case. For instance, respiration and phosphorylation in the presence of 10 μmole serotonin during oxidation of α-ketoglutarate fell to a greater degree than during oxidation of glutamate and succinate. During oxidation of β-hydroxybutyrate in the presence of 10 μmole serotonin, a tendency was observed for the P : O ratio to rise on account of a greater decrease in the intensity of respiration than of phosphorylation.

If the dose of serotonin given was three times greater, during oxidation of α-ketoglutarate and succinate phosphorylation was inhibited more than respiration, so that the P : O ratio showed a tendency to diminish. During oxidation of β-hydroxybutyrate an increase in the dose of serotonin lowered the intensity of both processes further and to an equal degree. The results demonstrate that in freshly isolated rabbit heart mitochondria, the system of coupling of respiration with phosphorylation is highly resistant to the action of serotonin.

Under the conditions of these experiments (at pH 7.4), no oxygen was consumed by the rabbit heart mitochondria on account of oxidation of serotonin [4]. In experiments with homogenates a decrease in the intensity of oxygen consumption was always observed in the presence of serotonin (see Fig. 1).

The effect of serotonin on respiration and phosphorylation in mitochondria subjected to "aging" processes is illustrated in Table 2.

"Aging" of the mitochondria in the presence of serotonin caused equivalent inhibition of both respiration and phosphorylation during oxidation of α-ketoglutarate by comparison with these indices for mitochondrial preparations "aged" without serotonin. An equivalent reduction in the P : O ratio took place in the

"aged" mitochondria both in the presence and absence of serotonin. The enzyme system oxidizing β-hydroxybutyrate was completely inhibited during preincubation of the mitochondria for 60 min. When preincubation took place for 30 min in the presence of serotonin, respiration was inhibited more than phosphorylation and the P : O ratio increased by comparison with the corresponding values for mitochondrial preparations "aged" without serotonin. In the latter case, during oxidation of β-hydroxybutyrate in the presence of serotonin, the effectiveness of respiration and phosphorylation was close to normal.

Compared with mitochondrial preparations which "aged" without serotonin, in the mitochondria "aged" in the presence of serotonin, respirationwas not inhibited during oxidation of succinate, although inhibition of phosphorylation took place. As a result of the differential effect of serotonin on respiration and phosphorylation, the P : O ratio fell. During preincubation of the mitochondria the link between respiration and phosphorylation was weakened, and "aging" caused a decrease in the P : O ratio. The results of the experiments with "aged" mitochondria indicate that serotonin causes no significant changes in the oxidative metabolism of the mitochondria by comparison with those in preparations preincubated without serotonin.

Another factor to which attention should be drawn is the differential effect of serotonin on the system of coupling of respiration and phosphorylation during oxidation of different respiration substrates in mitochondria subjected to "aging." By comparison with mitochondrial preparations "aged" without serotonin, the effectiveness of respiration and phosphorylation in mitochondria "aged" in the presence of serotonin remained unchanged during oxidation of α-ketoglutarate, increased during oxidation of β-hydroxybutyrate, and fell slightly during oxidation of succinate.

The results described show that serotonin inhibits the basic energy-producing processes in rabbit heart tissue.

In heart homogenates the intensity of respiration fell during oxidation of endogenous respiration substrates in the presence of serotonin. In the mitochondria during oxidation of exogenous respiration substrates in the presence of serotonin, the intensity of both respiration and oxidative phosphorylation fell without any clearly defined change in the P : O ratio*.

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