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## Serotonin Regulation Of Energy Metabolism Of Mitochondria Of Various Organs Of Rats

Nuriddin Nazhmiddinovich Soliev

Lecturers Of The Department Of Physiology, Namangan State University, Uzbekistan

Odiljon Shermatovich Boymatov

Lecturers Of The Department Of Physiology, Namangan State University, Uzbekistan

### ABSTRACT

Serotonin reduces the respiratory function of the mitochondria of the brain, heart and liver of rats. Serotonin significantly reduces the transport of electrons from glutamate to the oxygen molecule along the respiratory chain relative to succinate. These changes lead to a slight increase in the oxidative efficiency of phosphorylation in the oxidation of glutamate in mitochondria.

### KEYWORDS

Serotonin, respiratory function, mitochondria, brain, heart, liver, rats, succinate, glutamate, metabolism

### INTRODUCTION

In addition to the digestive function, the gastrointestinal tract plays the role of an endocrine organ. Enterochromatidine cells of the stomach and intestines produce about 90% of the total amount of serotonin [1-3].

Serotonin plays the role of a neurotransmitter in the central nervous system. Serotonergic neurons are grouped in the brain stem: in the pons varoli and the nuclei of the suture. From the bridge there are descending projections

into the spinal cord, the neurons of the suture nuclei give ascending projections to the cerebellum, limbic system, basal ganglia, and cortex. In this case, the neurons of the dorsal and medial nuclei of the suture give axons that differ morphologically, electrophysiologically, targets of innervation and sensitivity to some neurotoxic agents, for example, methamphetamine [4, 5]. Serotonin, along with dopamine, plays an important role in the mechanisms of hypothalamic regulation of the hormonal function of the pituitary gland. Stimulation of serotonergic pathways connecting the hypothalamus with the pituitary gland causes an increase in the secretion of prolactin and some other hormones of the anterior pituitary gland - an action opposite to the effects of stimulation of dopaminergic pathways [6-8].

The exclusive role of serotonin in the hypothalamic regulation of body temperature has been proven, which involves two oppositely directed effects of norepinephrine and adrenaline, on the one hand, and serotonin, on the other [9]. Significant data have been accumulated indicating the hypothermic effect of serotonin [2, 10]. The mechanism of serotonin's hypothermic action is unclear. On the one hand, there is evidence of the central action of serotonin on hypothalamic thermoregulation, on the other hand, the introduction of serotonin into the third ventricle of the brain or anterior hypothalamus and into the preoptic zone does not affect the character of the temperature curve of the hypothalamus. Consequently, serotonin inhibits the peripheral mechanisms of thermogenesis [2, 3].

Serotonin accumulates in the body and tissues of hibernating animals [11], affects many body

functions, and suppresses mitochondrial respiration [3]. The main manifestation of hibernation or torpidity of organisms is the suppression of metabolic processes, that is, their transition to a hypobiotic state, which increases the body's resistance and economizes metabolic resources.

**Purpose:** to study the effect of serotonin on respiration and oxidative phosphorylation of the mitochondria of the liver, heart and brain of rats.

## MATERIALS AND RESEARCH METHODS

In experimental studies were used white rats weighing an average of rats - 200-230 g. The animals were kept on a mixed diet in a well-ventilated, light room, in wooden cages (50x30 cm in size), 9-10 rats each. The animals were divided into 2 groups. In the first group, serotonin was administered - 50 mg/kg of body weight. The second group of rats received saline. The animals were decapitated 15 minutes after the injection of serotonin.

Mitochondria were isolated from the tissue of the brain, liver, and heart of animals using the generally accepted method of differential centrifugation [12] with some modifications [13].

The respiration rate of mitochondria in various metabolic states ( $V_2$  - before the addition of ADP,  $V_3$  - in the presence of ADP,  $V_4$  - a state of rest, and VDNP - uncoupled respiration) were recorded polarographically using a rotating platinum electrode. The composition of the incubation medium: sucrose - 0.25M, KCl - 12mM,  $\text{KH}_2\text{PO}_4$  - 5mM, Tris - HCl buffer - 5mM (pH 7.4). Respiration and phosphorylation were analyzed with the sequential addition of 200 mkMM ADP, 2,4 - dinitrophenol (DNP) -

5.10-5M. The substrates for oxidation were 10 mM succinate (pH 7.4) and 10 mM  $\alpha$ -ketoglutarate (pH 7.4). The reaction was started by adding a suspension of mitochondria to the polarograph cell at the rate of 3-4 mg of protein [14]. The ADP/O ratio and the respiratory control coefficient (NK<sub>4</sub>) were measured according to Chance, Williams [15]. The rate of oxidation of substrates at various metabolic states was expressed in nanogrammatomes of oxygen, in min mg of protein (at 250C). The mitochondrial protein content was determined by the method of Lowry et al. [16].

## RESULTS AND DISCUSSIONS

The studies carried out have shown (Table 1) that as a result of the administration of serotonin in rats, a certain restructuring of metabolic reactions occurs at the level of the mitochondria of the brain, heart and liver.

Studies have shown that as a result of the administration of serotonin, a certain restructuring of metabolic reactions occurs in rats at the level of brain mitochondria. After the introduction of serotonin into the body of animals, the rate of glutamate oxidation in the metabolic state V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub> and VDNF decreases by 30.2; 25.6; 33.5 and 22.0%, respectively, from the control. At the same time, the values of respiratory control according to Chance and the ADP/O coefficient by glutamate increased by 11.7 and 9.7% of the control, respectively. In the presence of serotonin, the rate of oxidation of succinate in the metabolic state V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub> and VDNF decreases 24.7; 27.5; 28.0 and 15.4%, respectively, of the control level, however, the value of the respiratory control according to Chance and the ADP/O coefficient does not change. Thus, serotonin inhibits

respiration of the brain mitochondria and is consistent with the data of A.A. Aripova and others [Aripova A.A., Bogdanov E.G., Zaitsev A.A., Ignatov Yu.D., 1996].

Analyzing the results obtained, it can be concluded that serotonin inhibits the respiratory functions of the mitochondria in the brain of animals. It should be noted that serotonin to some extent increases the values of respiratory control according to Chance and the coefficient of ADP/O with glutamate.

A similar change is observed in the mitochondria of the rat heart. Thus, intraperitoneal injection of serotonin led to a decrease in the respiration rate of cardiac mitochondria in metabolic states V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub> and VDNF with glutamate by 31.8; 29.2; 34.8 and 27.3%, respectively, of the control level. At the same time, the values of respiratory control according to Chance and the ADP/O coefficient increase by 9.5 and 5.5%, respectively. The rate of oxidation of succinate in the mitochondria of the heart by serotonin in the states V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub> and VDNF decreases, respectively, 15.6 in comparison with the control; 13.5; 14.3 and 12.0%, without significant changes in the value of respiratory control according to Chance and the ADP/O coefficient.

The introduction of serotonin into the body of animals leads to a decrease in the respiratory function of the liver mitochondria. At the same time, a decrease in mitochondrial respiration is especially noticeable in comparison with glutamate of succinate. So, if the rate of oxidation of glutamate in the state V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub> and VDNF decreases by 31.7, respectively; 30.1; 35.7 and 27.2% of the control level. These changes lead to an increase in the value of respiratory control according to Chance by

8.8%, the ADP/O ratio by 6.7%. The rate of oxidation of succinate in the state V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub>, and V<sub>DNF</sub> decreases by 12.0, respectively; 15.7; 15.8 and 7.4% of the control level. In this case, the magnitude of the respiratory control according to Chance and the ADP/O coefficient does not change. Thus, serotonin inhibits the respiratory function of the liver mitochondria.

Serotonin especially significantly inhibits the transfer of electrons from glutamate to molecular oxygen along the respiratory chain of liver mitochondria. Serotonin to some extent increases the Chance respiratory control and the ADP/O ratio during glutamate oxidation.

**Table 1**  
**Effect of serotonin on respiration and oxidative phosphorylation of rat heart mitochondria (M±m; n=9-12).**

Organs	Substrates oxidation	Indicators	Respiration rate, nanogram atom oxygen / min mg protein	
			Control	Serotonin
Brain	Glutamate	V <sub>2</sub>	12,4±1,0	8,6±1,1*
		V <sub>3</sub>	36,7±2,2	27,3±1,9****
		V <sub>4</sub>	12,6±1,2	8,4±1,3
		V <sub>DNF</sub>	36,9±2,3	28,8±2,2
		ResR <sub>ch</sub>	2,91±0,14	3,25±0,12**
		ADP/O	2,76±0,11	3,03±0,10
	Succinate	V <sub>2</sub>	24,3±1,2	18,3±1,0**
		V <sub>3</sub>	63,3±1,7	45,9±2,1****
		V <sub>4</sub>	24,3±1,3	17,5±1,4****
		V <sub>DNF</sub>	68,5±2,5	57,9±2,8
Heart	Glutamate	ResR <sub>ch</sub>	2,60±0,12	2,62±0,09
		ADP/O	1,76±0,10	1,78±0,08
		V <sub>2</sub>	97±7	66±5****
		V <sub>3</sub>	226±12	160±11****
		V <sub>4</sub>	51±9	33±7****
		V <sub>DNF</sub>	125±16	91±14
	Succinate	ResR <sub>ch</sub>	4,43±0,13	4,85±0,10
		ADP/O	2,91±0,10	3,07±0,10
		V <sub>2</sub>	152±15	128±14***
		V <sub>3</sub>	325±24	281±27**
		V <sub>4</sub>	140±1	120±16***
		V <sub>DNF</sub>	332±30	292±28
		ResR <sub>ch</sub>	2,32±0,10	2,34±0,13
		ADP/O	1,80±0,18	1,87±0,09
Liver	Glutamate	V <sub>2</sub>	18,0±2,6	12,3±2,0
		V <sub>3</sub>	85,4±5,0	59,7±6,4****
		V <sub>4</sub>	15,4±2,8	9,9±2,5

		$V_{DNF}$	$87,6 \pm 5,9$	$63,8 \pm 5,0$
		$ResR_{ch}$	$5,54 \pm 0,12$	$6,03 \pm 0,13$
		ADP/O	$2,67 \pm 0,11$	$2,85 \pm 0,10$
	Succinate	$V_2$	$28,5 \pm 2,9$	$25,1 \pm 2,8$
		$V_3$	$100,7 \pm 6,2$	$84,9 \pm 5,3^{****}$
		$V_4$	$24,7 \pm 3,4$	$20,8 \pm 3,5$
		$V_{DNF}$	$128,7 \pm 8,9$	$119,2 \pm 8,4$
		$ResR_{ch}$	$4,07 \pm 0,10$	$4,08 \pm 0,14$
		ADP/O	$1,77 \pm 0,11$	$1,82 \pm 0,12$

Note: here, serotonin was injected into the body of animals intraperitoneally at a dose of 50 mg/kg of body weight, and an hour later, mitochondria were isolated and respiration and oxidative phosphorylation of mitochondria were determined. The significance of the differences: \*  $P < 0.05$ ; \*\*  $P < 0.02$ ; \*\*\*  $P < 0.01$ ; \*\*\*\*  $P < 0.001$ .

Currently, there is no single point of view regarding the regulation of mitochondrial respiration and the regulation of energy metabolism at the cell level. The most widely discussed in the literature are two hypotheses: the hypothesis of the "equilibrium" model of oxidative phosphorylation, which got its name from the assumed dynamic equilibrium between the redox state of the carriers and the phosphate potential of the cytosol [17], and the translocase hypothesis [18]. According to the first, the rate of mitochondrial respiration is controlled by four factors: 1) the concentration of carriers of the respiratory chain, 2) the concentration of molecular oxygen, 3) the intramitochondrial concentrations of substrates and the intramitochondrial ratio  $NAD^+/NADH$ , 4) the rate of ATP utilization in the cytosol and phosphate potential of the cytosol  $ATP/ADP$ .

The second, translocase hypothesis, postulates that the exchange of adenine nucleotides ( $ATP/ADP$ ) between the mitochondrial matrix and the cytosol, carried out by a special

transport system - translocase, determines the gross respiration rate.

In our opinion, according to the first "equilibrium" hypothesis, serotonin controls the supply of oxygen to the body and the respiratory function of the cell. In our opinion, serotonin stabilizes cell membranes and their organelles. Therefore, the respiratory function of the mitochondria decreases, and the parameters of oxidative phosphorylation are not disturbed, with glutamate, it even increases slightly. This means that the respiratory function of the mitochondria shifts from a high metabolic state to a lower metabolic state. Slowing down the rate of mitochondrial respiration leads to a weakening of gas-oxygen exchange, i.e. oxygen consumption of the body.

## CONCLUSION

Serotonin suppresses the respiratory function of the mitochondria of the brain, heart and liver of rats. It should be noted that serotonin, in

comparison with succinate, especially noticeably suppresses the transfer of electrons from glutamate along the mitochondrial respiratory chain to molecular oxygen. These changes occur against the background, to some extent, of an increase in the efficiency of the parameters of mitochondrial coupling during glutamate oxidation.

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