

# EFFECT OF HYDROCORTISONE ON RESPIRATION AND PHOSPHORYLATION IN THE BRAIN AND LIVER MITOCHONDRIA OF ALBINO RATS

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UDC 615.357.453.015.42: [612.82 +  
612.35].014.21:612.26

The utilization of inorganic phosphate and the P/O ratio are reduced in the mitochondria of the rat brain and liver 3 h after a single injection of hydrocortisone, and the oxygen consumption and phosphate utilization in the brain tissue are reduced 6 h after the injection. During prolonged administration of the hormone, these parameters in the brain mitochondria remain unchanged, while in the liver the oxygen absorption and phosphate utilization, the P/O ratio, and the protein content are all reduced.

Observations on the effect of an increased corticosteroid concentration in the body on oxidative processes have been made chiefly in connection with the liver mitochondria [3, 4, 6]. The results of these investigations are contradictory and they indicate that the effect of hormones may depend on their dose and the times elapsing after their administration, and also on the initial functional state of the animals.

In the investigation described below the effect of hydrocortisone on respiration and oxidative phosphorylation in the brain and liver mitochondria of rats was studied in relation to the time after administration of the hormone to the animal.

## EXPERIMENTAL METHOD

Male Wistar rats weighing 170–200 g were used. Hydrocortisone acetate was injected intraperitoneally in doses of 1 and 5 mg/100 g body weight. The mitochondria of the brain and liver were isolated and investigated 1, 3, and 6 h after injection of the hormone. In a special series of experiments the hormone was injected daily for 7 days. The mitochondria were investigated 3 h after the last injection. The technique of isolation and incubation of the mitochondria and of recording the parameters of oxidative phosphorylation was described previously [2].

## EXPERIMENTAL RESULTS AND DISCUSSION

The results are given in Table 1. No significant changes in the parameters studied were found 1 h after injection of the hormone. After 3 h the oxygen consumption of the mitochondria was unchanged but the utilization of inorganic phosphate was reduced. The P/O ratio was reduced by 14% in the brain tissue and by 11% in the liver tissue respectively. The intensity of respiration in the brain tissue 6 h after injection of the hormone (especially in the larger dose) was slightly reduced and the utilization of inorganic phosphate by the mitochondria also was reduced. These parameters in the liver were indistinguishable from normal at this time. During prolonged administration (7 days) of the hormone significant differences were found in its action on the mitochondria of the brain and liver. As Table 1 shows, no changes were found in the mitochondria of the brain, whereas in the liver with both doses of hydrocortisone respiration of the mitochondria was reduced, by 22 and 29% respectively. During prolonged administration of hydro-

Laboratory of Experimental Endocrinology, I. P. Pavlov Institute of Physiology, Academy of Sciences of the USSR, Leningrad. (Presented by Academician V. N. Chernigovskii.) Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 76, No. 7, pp. 40–43, July, 1973. Original article submitted April 29, 1972.

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TABLE 1. Effect of a Single Dose and of Prolonged Administration of Hydrocortisone on Brain and Liver Mitochondria of Albino Rats

	Time after injection of hormone	Oxygen consumption (in $\mu$ moles/mg protein)		Utilization of inorganic phosphorus (in $\mu$ moles/mg protein)	
		Ringer's solution	hydrocortisone		hydrocortisone
			1 mg /100 g	5 mg/ 100 g	
Brain	3 h	1,87 $\pm$ 0,06	1,82 $\pm$ 0,09	1,88 $\pm$ 0,07	4,07 $\pm$ 0,14
	6 h	2,00 $\pm$ 0,09	1,85 $\pm$ 0,10	1,77 $\pm$ 0,09	3,44 $\pm$ 0,19
Liver	7 days	1,99 $\pm$ 0,09	2,04 $\pm$ 0,11	0,1 > P > 0,05	3,65 $\pm$ 0,13
	3 h	1,04 $\pm$ 0,04	0,95 $\pm$ 0,05	2,04 $\pm$ 0,12	4,05 $\pm$ 0,19
	6 h	1,44 $\pm$ 0,10	1,53 $\pm$ 0,10	1,31 $\pm$ 0,08	2,59 $\pm$ 0,05
	7 days	1,53 $\pm$ 0,09	1,19 $\pm$ 0,06	1,08 $\pm$ 0,09	3,45 $\pm$ 0,18
			<0,01	<0,01	3,43 $\pm$ 0,21
					2,70 $\pm$ 0,17
					<0,05
					3,33 $\pm$ 0,22
					3,47 $\pm$ 0,21
					2,09 $\pm$ 0,20
					<0,01

TABLE 1 (continued)

	Time after injection of hormone	P/O		Content of mitochondrial protein (in mg/g tissue)	
		Ringer's solution	hydrocortisone		hydrocortisone
			1 mg/100 g	5 mg/100 g	
Brain	3 h	2,06 $\pm$ 0,06	1,76 $\pm$ 0,07	1,73 $\pm$ 0,09	—
	6 h	1,99 $\pm$ 0,05	<0,01	<0,01	—
Liver	7 days	2,09 $\pm$ 0,03	2,03 $\pm$ 0,07	2,01 $\pm$ 0,07	3,05 $\pm$ 0,09
	3 h	2,41 $\pm$ 0,06	2,14 $\pm$ 0,08	—	—
	6 h	2,34 $\pm$ 0,10	<0,01	2,46 $\pm$ 0,09	—
	7 days	2,38 $\pm$ 0,06	2,30 $\pm$ 0,04	2,02 $\pm$ 0,08	2,58 $\pm$ 0,08
				<0,02	<0,01
					2,96 $\pm$ 0,07
					<0,02
					3,20 $\pm$ 0,09
					3,56 $\pm$ 0,09

Note. Mitochondria were incubated in a Warburg's apparatus for 30 min. Substrate, pyruvate with malate.

cortisone in a dose of 5 mg/100 g body weight, inhibition of respiratory activity of the mitochondria was accompanied by lowering of the P/O ratio (by 11%). In addition, both doses of the hormone caused a decrease in the protein concentration in a suspension of mitochondria (by 17 and 27% respectively), indicating a possible disturbance of the synthesis of mitochondrial protein in the liver. These findings are in agreement with others in the literature [3, 6] concerning the inhibition of respiration and oxidative phosphorylation and a decrease in the protein concentration and in the number of cristae in the liver mitochondria after prolonged administration of corticosteroids.

Repeated injections of glucocorticoids thus caused considerable disturbances in the structure, function, and formation of the liver mitochondria. Prolonged administration of the hormone did not cause any such changes in the brain tissue. The absence of changes during prolonged administration of hydrocortisone and their presence after a single injection have also been described in respect of the content of components of the Krebs' cycle and of high-energy phosphates in rat brain tissue [1]. These facts may be evidence of rapid recovery of the energy metabolism of the brain. After a single injection the action of the hormone on the parameters studied in the mitochondria of the brain and liver was exhibited at the same times and was similar in character. The mechanism of this action remains unknown. After injection of labeled corticosteroids into animals they penetrate after a few minutes into the tissue of the brain and liver and can be found in all subcellular fractions, including the mitochondria [5]. In the case of their direct action on the respiratory chain of the mitochondria, as when large doses were given in the experiments *in vitro*, rapid changes would be expected to take place in the function of these organelles in the experiments *in vivo* also. However, since in the experiments described above the hormone gave a marked effect only 3 h after its injection, it is not safe to assume that it acts directly on the processes of oxidative phosphorylation. This problem requires further investigation.

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