MECHANISM OF LOWERING OF THE BASAL METABOLISM DURING ADAPTATION TO HYPOXIA

F. Z. Meerson and A. F. Bogomolov

UDC 612.395.2-06:612.273.2.017.2

During adaptation of rats to periodic hypoxia in a pressure chamber the oxygen consumption fell by 40%. This decrease was still found in a state of deep anesthesia and, consequently, it was independent of adaptive changes in cortical regulation of the animals' motor activity. Half of this decrease in oxygen consumption still continued during exposure of the animal to cold, noradrenalin, and 2,4-dinitrophenol (DNP), which uncouples oxidative phosphorylation. The economic utilization of oxygen during adaptation to hypoxia cannot thus be completely explained by an increase in the degree of coupling of oxidation with phosphorylation.

KEY WORDS: adaptation to hypoxia; oxygen consumption; basal metabolism.

During adaptation to hypoxia in the mountains, and also to the periodic action of hypoxia under pressure chamber conditions a fall in basal metabolism gradually develops in man and animals; this fall still continues after a return to an atmosphere containing the normal oxygen concentration and is expressed as a decrease in the oxygen consumption by 25-40% [1-3, 6, 8].

This phenomenon is not accompanied by any reduction in the activity of the organism and, according to some investigators, it is the result of increased efficiency of the utilization of energy for ATP resynthesis [1].

However, the concrete mechanism of the decrease in oxygen consumption during adaptation remains unexplained.

In the investigation described below the effects of general anesthesia, cold, noradrenalin, and uncoupling of oxidative phosphorylation by 2,4-dinitrophenol (DNP) on oxygen consumption were compared in animals adapted to hypoxia and in control animals.

EXPERIMENTAL METHOD

Male Wistar rats weighing 200-250 g were used. The animals adapted to hypoxia and control animals were divided into five groups. In group 1 the oxygen consumption of control and adapted animals not receiving general anesthetics and exposed to no other form of procedure was studied and compared. In group 2 the same comparison was carried out on animals under thiopental (50 mg/kg, intraperitoneally) anesthesia. In the remaining groups the oxygen consumption was compared in adapted and control animals, which also were anesthetized, but after determination of the initial oxygen consumption the rats of group 3 were cooled (at 10°C for 30 min). The animals of group 4 were given an injection of noradrenalin (0.8 mg/kg intramuscularly) 60 min before measurement of the oxygen consumption. In group 5, DNP was injected intraperitoneally (1 ml of a 10 mM solution/100 g body weight) 30 min before measurement of the oxygen consumption. Each of these groups included 7 or 8 control and 10-12 adapted animals.

Adaptation to hypoxia was carried out by placing the animals daily for 6 h in a pressure chamber. The adaptation program was as follows: on the first day the partial oxygen pressure in the chamber corresponded to an altitude of 2000 m, on the second day to 3000 m, the third day to 4000 m, the fourth day to 5000 m, the fifth day to 5000 m, the sixth day to 6000 m, the seventh day to 6000 m, the eighth day to 7000 m, and thereafter until the 40th day to 7000 m. The oxygen consumption was determined in the morning in the fasting state. The animals were placed in an airtight chamber for 10 min, after which a sample of air was taken from

Laboratory of Pathophysiology of the Heart, Institute of General Pathology and Pathophysiology, Academy of Medical Sciences of the USSR, Moscow. Central Research Laboratory, Ivanovo Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 9, pp. 287-289, September, 1978. Original article submitted January 20, 1978.

 0007-4888/78/8609-1152$07.50

TABLE 1. Effect of General Anesthesia, Cooling, Noradrenalin, and DNP on Oxygen Consumption in Animals during Adaptation to Hypoxia (M ± m)

Group of animals	Oxygen consumption, ml/h/100 g body weight		P
	control	adaptation to hypoxia	
1) Without anesthesia	163,00±2,1	96,8±2,1	<0,001
2) Under anesthesia	137,09±9,54	87,94±8,50	<0,001
3) Under anesthesia + cold	249,68±8,69	184,45±15,9	<0,01
4) Under anesthesia + noradrenalin	211,56±12,18	162,39±12,79	<0,02
5) Under anesthesia + DNP	348,85±16,96	275,10±7,25	<0,01

the chamber and the oxygen concentration in it was determined with a Gazokhrom-3101 gas chromatograph. The oxygen consumption of the animals was calculated from the curve of oxygen concentration, in the form of the chromatogram recorded on the KSP-4-909 recorder.

EXPERIMENTAL RESULTS AND DISCUSSION

It follows from Table 1 that the oxygen consumption in adapted unanesthetized animals was more than 40% lower than the control. If these animals were anesthetized the difference was reduced only a little, to 35%. Deep inhibition of the higher levels of the nervous system and complete abolition of the animals' motor activity thus had no significant effect on the fall of oxygen consumption during adaptation to hypoxia. This fact evidently means that the cellular mechanism responsible for the fall in oxygen consumption during adaptation to hypoxia is not directly dependent on the state of the higher levels of the brain or on the level of motor activity of the animal.

The results in Table 1 also indicate that cold, noradrenalin, and DNP regularly induced a marked increase in the oxygen consumption of both the control and the adapted animals. However, the degree of this increase relative to the initial level was rather greater in the adapted than in the control animals. Cold, for instance, caused an increase of 80% in the oxygen consumption in the control and 110% in the adapted animals, after noradrenalin the corresponding values were 50 and 80%, and after DNP they were 150 and 260%. The more marked increase in the oxygen consumption in the adapted animals had the result that at the peak of the action of cold, noradrenalin, and DNP the difference in oxygen consumption between the adapted and control animals which was present before the action of these factors was reduced, to only 21-26% compared with 35-40% previously.

Cold is known to increase heat production and oxygen consumption indirectly, through excitation of the sympathico-adrenal system and an increase in thyroxine secretion [4, 7]. An essential role in the mechanism of the rapid increase in heat production in response to cold is played by uncoupling of oxidative phosphorylation and the liberation of a large quantity of the energy of oxidative phosphorylation and the liberation of a large quantity of the energy of oxidation in the form of heat [5]. In the present experiments cold, and also noradrenalin, abolished the decrease in oxygen consumption in the adapted animals not completely, but by less than half. This suggests that the decrease in oxygen consumption in the animals during their long stay under hypoxic conditions depends partly on an adaptive increase in the degree of coupling of oxidation with phosphorylation and partly on another, more stable shift. DNP, an uncoupler of oxidative phosphorylation, like cold, in fact reduced the difference in the oxygen consumption between the adapted and control animals only by half, and did not abolish the phenomenon completely. The problem of the concrete nature of the shift which, in conjunction with an increase in the degree of coupling of oxidation with phosphorylation, may play a role in the adaptive reduction in oxygen consumption requires further study.

LITERATURE CITED

1. F. Z. Meerson, The General Mechanism of Adaptation and Prophylaxis [in Russian], Moscow (1973).
2. F. Z. Meerson and A. F. Bogomolov, in: Proceedings of the Sixth Volga Conference of Physiologists with the Participation of Biochemists, Pharmacologists, and Morphologists [in Russian], Vol. 1, Cheboksary (1973), p. 199.

3. M. M. Mirrakhimov, in: Oxygen Insufficiency [in Russian], Kiev (1963), pp. 421-429.
4. V. P. Skulachev, S. P. Maslov, V. G. Sivkova, et al., Biokhimiya, No. 1, 70 (1963).
5. R. R. Rachev and N. D. Eshchenko, Thyroid Hormones and Subcellular Structures [in Russian], Moscow (1975).
6. R. Grover, J. Appl. Physiol., 18, 567 (1963).
7. P. Hochachka and G. Somero, The Strategies of Biochemical Adaptation, Saunders, Philadelphia, 1973.
8. M. V. Strumza, C. R. Soc. Biol., 162, 1904 (1968/1969).

ROLE OF INTESTINAL HORMONES IN THE PATHOGENESIS OF EXPERIMENTAL PANCREATITIS

S. S. Elizarova and N. N. Lebedev

UDC 616.37-002-092.9-07: 616.37-008.6-092: 616.342-008.6: 577.175.73

The course of disturbances of secretory reactions of the pancreas in response to adequate stimulation by intestinal hormones was studied in acute experiments on dogs with preinduced pancreatitis. Activity of combined preparations of intestinal hormones obtained from the duodenal mucosa was found in the acute period of the disease in these dogs. In chronic experiments an increased rate of acid formation in the stomach and a change in the pH of the duodenal contents toward the acid side in pancreatitis were found in chronic experiments. It is concluded that intestinal hormones play an important pathogenetic role in the mechanism of disturbances of the external secretory activity of the pancreas in pancreatitis.

KEY WORDS: pancreas; experimental pancreatitis.

The secretin test, used in the differential diagnosis of diseases of the pancreas, is based on changes in the reactivity of the pancreas under pathological conditions to "exogenous" secretin [1, 5-7, 9-11]. To discover whether these changes reflect general changes in the reactivity of the body during pancreatitis or whether they are directly related to the pathogenesis of the disturbances of external secretory activity of the pancreas, the investigation whose results are given in this paper was undertaken.

EXPERIMENTAL METHOD

Experiments were carried out on 19 dogs. Acute pancreatitis was induced by injecting the dogs' own bile into the pancreatic duct in a volume of 0.5 ml/kg body weight. To study the responses of the pancreas to "exogenous" intestinal hormones and also for biological standardization, a combined preparation of intestinal hormones (CPIH) obtained in the laboratory by means of a standard technology [2], but without the final stages of purification, was used.

In consequence of the technology of preparation and according to the results of biological standardization tests on rabbits, the CPIH contained several intestinal hormones (secretin, pancreozymin-cholecystokinin) and a certain quantity of biologically inactive denatured protein. The preparation was obtained in sufficient quantity for all the series of experiments from the duodenal mucosa of healthy dogs. To determine changes in the activity of the intestinal hormones in pancreatitis, samples of CPIH were obtained by the same technology from the duodenal mucosa of dogs killed at different times after the beginning of the disease.

To study changes in the reactivity of the pancreas to "endogenous" secretin, responses to intraduodenal injection of 20 ml of 0.3% HCl, the physiological stimulus causing an increase in the secretin concentration in the portal blood and in the general circulation [8], were studied.

Laboratory of Pathophysiology of Digestion, Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 9, pp. 289-292, September, 1978. Original article submitted May 5, 1977.

