EFFECT OF CYCLIC NUCLEOTIDES AND OF ISOPROPYLNORADRENALIN ON THE PARTIAL PRESSURE AND CONSUMPTION OF OXYGEN

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Isopropylnoradrenalin, cyclic AMP, and dibutyryl-3',5'-AMP (DB) lower the partial pressure of oxygen (pO_2) in the liver and spleen and increase the oxygen consumption of the body. The time course of these two effects for isopropylnoradrenalin and cyclic AMP correlates closely. The increase in heat production was not accompanied by any significant change in the respiratory quotient. The effects of cyclic AMP were not abolished by pempidine or by dihydroergotamine and were only reduced to some degree by propranolol. The effect of catecholamines on pO_2 is evidently mediated through an increase in the O_2 consumption as a result of the effect of cyclic AMP; the action of cyclic AMP is basically direct, but in vivo it cannot take place through the β adrenoreceptor; the compound 2',3'-AMP reduces pO_2 and also the O_2 consumption.

KEY WORDS: *cyclic nucleotide*; *catecholamines*; *partial pressure and consumption of oxygen*; *liver and spleen tissue*.

Catecholamines lower the partial pressure of O_2 (pO_2) in the tissues [2, 3] and increase the oxygen consumption of the body [9]. The writers have shown that the fall in pO_2 is the result not of hemodynamic changes, but of an increase in O_2 consumption; this effect of catecholamines is evidently mediated through cyclic AMP [3, 4]. In fact theophylline, an inhibitor of phosphodiesterase, lowers pO_2 [3] and increases O_2 consumption [15]. However, no effect of cyclic AMP itself on O_2 consumption has been found, and this is explained by the impermeability of the cell to cyclic AMP [15]. Meanwhile, cyclic AMP in vivo stimulates the heart, lowers the vascular resistance, increases the blood concentrations of glucose, lactate, pyruvate, and potassium, and activates liver phosphorylase [12, 14, 16]. Moreover, labeled cyclic AMP passes through the membrane of hepatocytes [11]. The effect of cyclic AMP on pO_2 has not been studied.

The object of the investigation described below was to study the possible effects of cyclic AMP and its derivatives on pO_2, O_2 consumption, CO_2 liberation and heat production, to compare these effects with each other and with the effects of isopropylnoradrenalin (IPNA), and to analyze the mechanisms of the action of cyclic AMP on O_2 metabolism.

EXPERIMENTAL METHOD

Experiments were carried out on 160 CBA mice of both sexes aged 3-5 months. Usually each series consisted of 10 to 12 experiments.

All the substances were injected subcutaneously in the corresponding doses (Figs. 1 and 2; Table 1) in a volume of 10 mg/kg, the gangliolytics and adrenolytics being given 10 min before the cyclic AMP. pO_2 was determined polarographically [2] and O_2 consumption and heat production by indirect calorimetry, using a sensitive metabolimeter. The results were subjected to statistical analysis by a nonparametric method, and Spearman's correlation coefficient r_s was determined [1]. Only statistically significant changes are described in the text.

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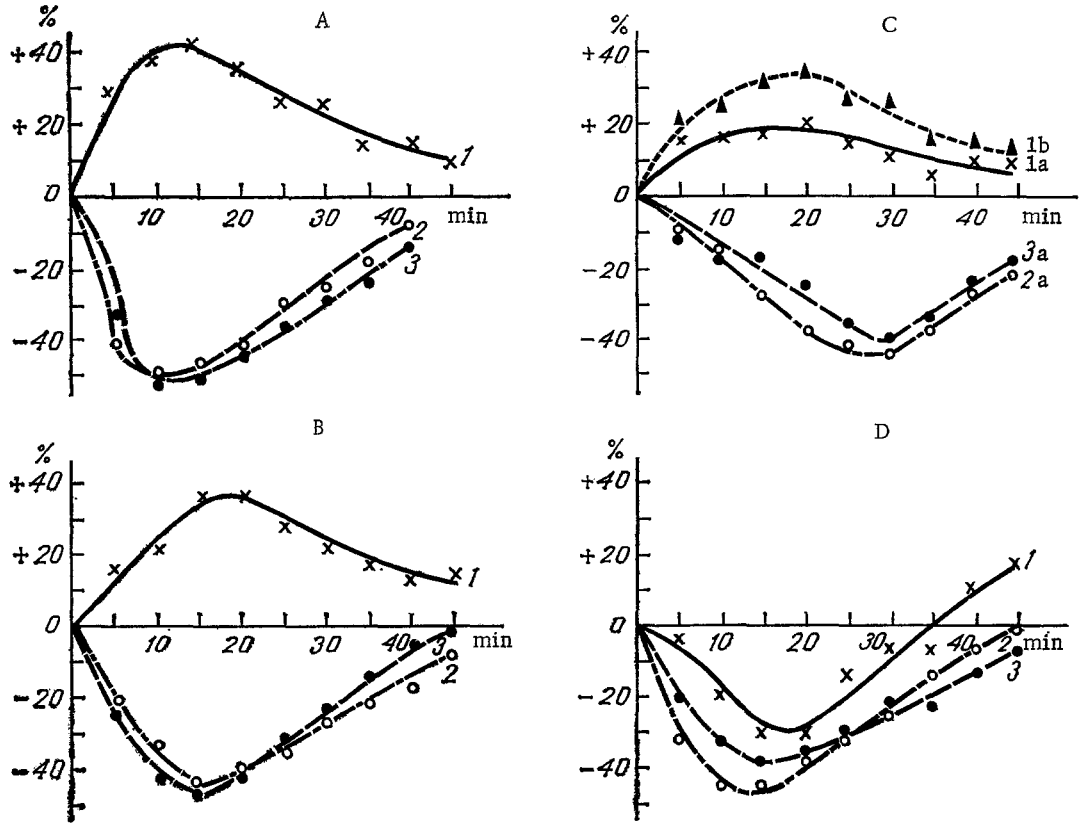

Fig. 1. Dynamics of oxygen consumption of mice (1) and pO_2 in liver (2) and spleen (3) after injection of cyclic nucleotides and IPNA: A) IPNA (11 μmoles/g); B) cyclic AMP (55 μmoles/kg); (a, 68 μmoles/kg; b, 170 μmoles/kg); D) 2',3'-AMP (55 μmoles/kg).

EXPERIMENTAL RESULTS AND DISCUSSION

DL-IPNA caused a decrease in pO_2 in the tissues and a parallel increase in O_2 consumption (Fig. 1A). Cyclic AMP gave similar effects but they were slower to develop (Fig. 1B). The increase in O_2 consumption was maximal after 15-20 min, but after 45 min it had almost completely disappeared; as a result, the increase in O_2 consumption over the whole period was only half of that at the maximum (Table 1). The absence of any effect of cyclic AMP in the experiment of Strubelt [15] could probably be due to the fact that the O_2 consumption was estimated over an excessively long period (2 h). For IPNA and cyclic AMP close correlation was found between the time course of pO_2 and O_2 consumption ($r_S = -0.94$ and -0.89, $P < 0.001$), evidence in support of the view that the decrease in pO_2 is due to activation of oxidative processes [3, 4]. The decrease in pO_2 against the background of an increase in the tissue blood flow [12, 14] shows that cyclic AMP, like catecholamines [3, 4], gives more powerful metabolic than hemodynamic effects, i.e., that stimulation of oxidative processes predominates over the increase in blood supply.

IPNA and cyclic AMP also increased CO_2 liberation and heat production but did not change the respiratory quotient or increased it only a little (Table 1). This is evidence that no change to different oxidation substrates took place.

The qualitative and quantitative agreement between all the effects of IPNA and cyclic AMP confirms that the effects of catecholamines on oxidative processes are mediated through cyclic AMP [3, 4, 6, 9]. Catecholamines evidently increase the formation of endogenous cyclic AMP through the adrenoreceptor–adenylate cyclase system, whereas the exogenous nucleotides gradually penetrate directly into the cells [11]. However, it was necessary to check whether the effect of cyclic AMP in vivo does not incorporate certain indirect components.

The powerful gangliolytic pempidine caused no change whatsoever in the effect of cyclic AMP on pO_2 in both organs (Fig. 2). The other lytic, dihydroergotamine (DHEA), delayed the development of the effect but did not change its intensity. Consequently, cyclic AMP exhibits neither reflex nor ganglion-stimulating nor α-receptor effects. The delay of the action of

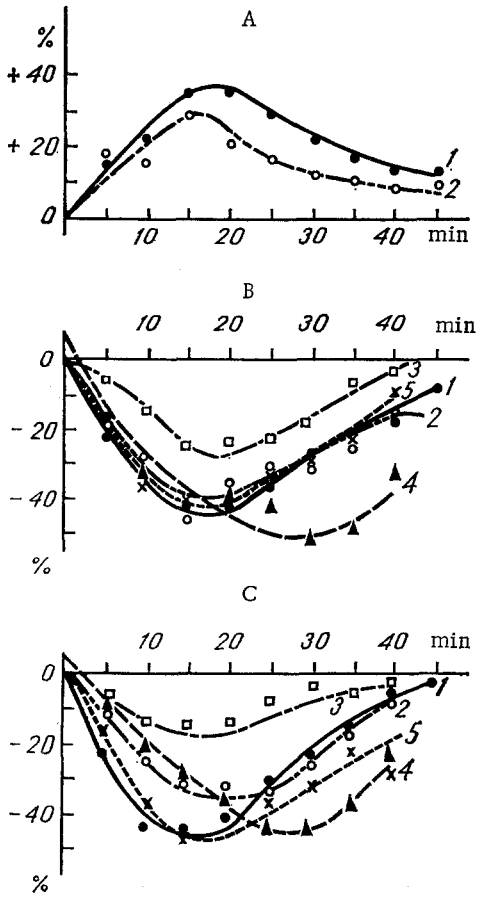

Fig. 2. Effect of gangliolytics and adrenolytics on changes caused by cyclic AMP in O_2 consumption (A) and pO_2 in liver (B) and spleen (C). 1) Cyclic AMP (55 μmoles/kg); 2) propranolol (34 μmoles/kg) + cyclic AMP; 3) propranolol (51 μmoles/kg) + cyclic AMP; 4) DHEA (1.5 μmoles/kg) + cyclic AMP; 5) pempidine (58 μmoles/kg) + cyclic AMP.

TABLE 1. Effect of Cyclic Nucleotides and IPNA on Energy Metabolism (M ± m)

Index	Control	Changes to relative control					
		IPNA	cyclic AMP	propranolol + cyclic AMP	DB		2',3'-AMP
Dose	—	11	55	34+55	68	170	55
O_2 consumption	4,53±0,085	24±3,6 c	22±2,1 c	16±3,1 a	16±2,2 c	27±3,9 c	—4,0±3,0
CO_2 liberation	3,22±0,080	21±6,2 a	27±2,2 c	40±2,7 b	52±3,5 c	41±3,9 c	0,9±4,0
Heat production	21,3±0,49	25±2,3 c	23±2,4 c	20±3,1 b	22±2,7 c	29±4,7 c	—3,0±3,1
Respiratory quotient	0,72±0,006	2,8±2,3	5,6±1,2 b	11±2,3 c	29±1,0 c	11±1,8 c	6,9±1,9 b

Note. Data for control given in absoute values; O_2 consumption and CO_2 liberation in ml/h/g weight: heat production in cal/h/g weight. Doses expressed in μmoles/kg. Significance of differences: a) $P < 0.05$, b) $P < 0.01$, c) $P < 0.001$.

cyclic AMP by DHEA could be connected with vasoconstriction [7] or could be the result of delayed absorption. The powerful and specific β-adrenolytic propranolol (Inderal), especially when the dose was increased, reduced the action of cyclic AMP on pO_2 (more so in the spleen) and O_2 consumption; under these conditions the respiratory quotient was increased. A similar partial reduction of some of the effect of cyclic AMP includes an additional β-receptor component. However, all the effects of cyclic AMP were also manifested after administration of propranolol. Consequently, cyclic AMP acts mainly directly on the cells.

DB also lowered pO_2 and increased O_2 consumption, CO_2 liberation, and heat production (Fig. 1C; Table 1). Meanwhile definite differences from the action of cyclic AMP were found: 1) a later fall in pO_2; 2) a smaller increase in O_2 consumption for the same dose; 3) an increase in the respiratory quotient. The first of these differences was probably connected with the need to remove the butyrate residues, for DB acts on the enzymes mainly after deacylation [10]. The second difference was unexpected, for it is usually considered that DB is always more active in vivo not only because of its lower vulnerability to attack by phosphodiesterase, but also because it penetrates more readily through lipid membranes [10]. However, it has recently been shown that cyclic AMP can penetrate into some cells better than DB [13]. The present results show that in experiments in vivo it is better to use not only DB, but also cyclic AMP itself. Differences between the effects of DB and cyclic AMP have been described for lipolysis [8].

The effects of 2',3'-AMP differed significantly: although pO_2 fell, heat production and CO_2 liberation were not increased, O_2 consumption actually diminished (after 10-25 min) (Fig. 1 D, Table 1). In this case the decrease in pO_2 was evidently the result not of increased expenditure of O_2 on oxidation, but a decrease in its uptake into the tissue ($r_S = +0.92$; $P < 0.001$). Presumably the hypometabolic action of 2',3'-AMP was the result of blocking the effects of endogenous cyclic AMP, as has been observed for exogenous cyclic AMP [5]. The writers suggest that 2',3'-AMP can be used in states of hypermetabolism connected with the accumulation of cyclic AMP. In this respect it would be interesting to use 2',3'-AMP for this purpose in pheochromocytoma, hyperthyroidism, and certain fevers.

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