The Role of α_1- and β-Adrenoceptors in Initiation and Development of Thermoregulatory Reactions during Fast and Slow Cooling

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Ionophoretic application of α_1- and β-adrenoceptor blockers into the skin produces no effect on the parameters of thermal homeostasis under thermoneutral conditions. α_1-Adrenoblocker verapamil inhibits cold shivering during fast and slow cold exposure; it elevates the temperature threshold and moderates the vasoconstrictor response during rapid cooling. These changes are accompanied by a compensatory decrease in the threshold and stimulation of non-shivering thermogenesis. Application of non-selective β-blocker propranolol had no effect on the temperature thresholds of the thermoregulatory reactions, but augmented the maximum amplitude of shivering during both cooling protocols, thereby compensating the decrease in non-shivering thermogenesis. In the whole organism, block of one type adrenoceptors during cold exposure is accompanied by activation of the compensatory mechanisms mediated by adrenoceptors of the other type.

Key Words: *thermoregulation; cooling; adrenoblocker; verapamil; propranolol*

Protection of the organism against cold exposure is closely related to activation of sympathetic nervous system. Ionophoretic application of exogenous norepinephrine to the skin modifies the threshold and value of thermoregulatory reactions (TRR) during cooling as well as the structure of metabolic response. The effects of catecholamines are mediated via different types of α- and β-adrenoceptors. Moderation of heat emission and constriction of cutaneous blood vessels during cooling are controlled predominantly via α_1-adrenoceptors [6], while the metabolic response to cooling is realized mostly via β-adrenoceptors in the muscles, liver, and brown fat. The triggering mechanisms of TRR and the development of its structure remain unclear. Specifically, there are no data on the effect of adrenoblockers (AB) on temperature thresholds of thermoprotective reactions, which are important parameters of the thermoregulatory system characterizing the work of thermoceptive structures of the thermal homeostasis system.

Rapid cooling accompanied by static and dynamic activity of cutaneous cold receptors leads to earlier (*i.e.*, triggered by less pronounced changes in core temperature) elevation in blood norepinephrine compared to slow cooling not accompanied by dynamic activity of cutaneous cold receptors [3].

Our aim was to study the role of α_1- and β-adrenoceptors in the formation of TRR structure at various cooling regimens (fast and slow) producing different activating effect on the sympathetic nervous system.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats (n=48) weighing 150-300 g. To exclude the emo-

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tional and stressor components, the animals were cooled under sodium etaminal narcosis (40 mg/kg). The environmental temperature was maintained at 21-24°C. Abdominal region was depilated and cooled with a thermode (contact area 25 cm^2). The rats were subdivided into two groups of 24 animals, which were subjected to thermal stimulation by individual protocols: 1) rapid cooling at a rate of 0.05°C/sec and 2) slow cooling at a rate of 0.005°C/sec. Both cooling procedures terminated when the rectal temperature dropped by 3°C.

In each group, the effects of α_1-AB verapamil (0.25% solution, n=8) or non-selective β-AB propranolol (0.1% solution, n=8) on TRR parameters were examined during cooling. AB were applied ionophoretically at 0.08 mA/cm2 for 20 min onto the abdominal skin to the region of subsequent cooling. This mode of AB application results in a high concentration of the blocker in the cutaneous layer with the greatest number of peripheral thermoreceptors. The control rats (n=8) were cooled without adrenoblockers.

During the experiments, the following parameters were continuously recorded: 1) temperature of a distant site (auricle), which lay apart from the cooling area and was thermally isolated from the environment — this temperature reported the reaction of cutaneous vessels to cooling; 2) rectal temperature to measure core temperature; 3) intracutaneous temperature of the cooled abdominal region to control the cooling rate and to determine the threshold skin temperatures of the cold-protection reactions, and 4) total O_2 consumption and electrical activity of cervical muscles to assess the total metabolic response and shivering thermogenesis in the skeletal muscles. The start of TRR during cooling was marked by the following events: drop of auricular temperature by 0.1°C, elevation of oxygen consumption by 1 ml/min/kg, or an increment of electrical activity in cervical muscles by 1 μV. The maximum parameters of TRR were recorded at the end of cooling.

The data were analyzed using original TEPM software and Student's t test.

RESULTS

Under thermoneutral conditions, the examined parameters were significantly modified by ionophoretically applied AB (Table 1).

External cooling of the abdominal region provoked the generalized cold-protection response. In all cases, a drop in auricular temperature reflecting cutaneous vasoconstriction and moderation of heat emission in response to cooling were observed before the drop in rectal temperature and before the development of metabolic reaction. Elevation of total oxygen consumption and the increment of electrical activity in cervical muscles during cooling started at the threshold drop of rectal and cutaneous temperatures.

Intracutaneous verapamil modified the cold-provoked TRR. During rapid cooling after application of verapamil, the vascular reaction developed later than in the control group. Moreover, the difference between normal and threshold temperatures increased (Fig. 1). Verapamil decreased the maximum value of the constrictor reaction (Fig. 2). However, it modified the vascular reaction only during the rapid cooling, which probably resulted from more pronounced activation of sympathetic nervous system during this type of cool exposure [3].

Verapamil decreased the latency of TRR from 80.30± 7.99 sec to 51.10±3.44 sec during rapid cooling and from 1277.0±199.4 sec to 207.0±45.3 sec during slow cooling (p<0.05). The decrements in cutaneous and rectal temperatures needed to upregulate oxygen consumption diminished both during rapid and slow cooling (Fig. 1). Verapamil produced no effect on the value of maximum increment of oxygen consumption during both modes of cooling (Fig. 2).

In both experimental groups, verapamil inhibited the thermoregulatory shivering activity of cervical muscles. In other words, cooling did not potentiate muscle activity. Unchanged consumption of O_2 in response to cold exposure despite inhibition of shivering and elimination of shivering thermogenesis suggests that under the action of

TABLE 1. Effects of Verapamil and Propranolol on Thermogenesis Parameters under Thermoneutral Conditions (M±m)

Parameter	Prior to AB application	After verapamil	After propranolol
Total consumption of O_2, ml/min/kg	17.10±0.81	16.40±0.73	16.80±0.91
Auricle temperature, °C	30.50±0.21	29.80±0.40	30.10±0.42
Intracutaneous abdominal temperature, °C	37.20±0.12	36.90±0.34	36.9±0.3
Rectal temperature, °C	36.90±0.13	36.30±0.27	36.30±0.28
Electrical activity of cervical muscles, μV	2.6±0.2	2.40±0.19	2.60±0.16

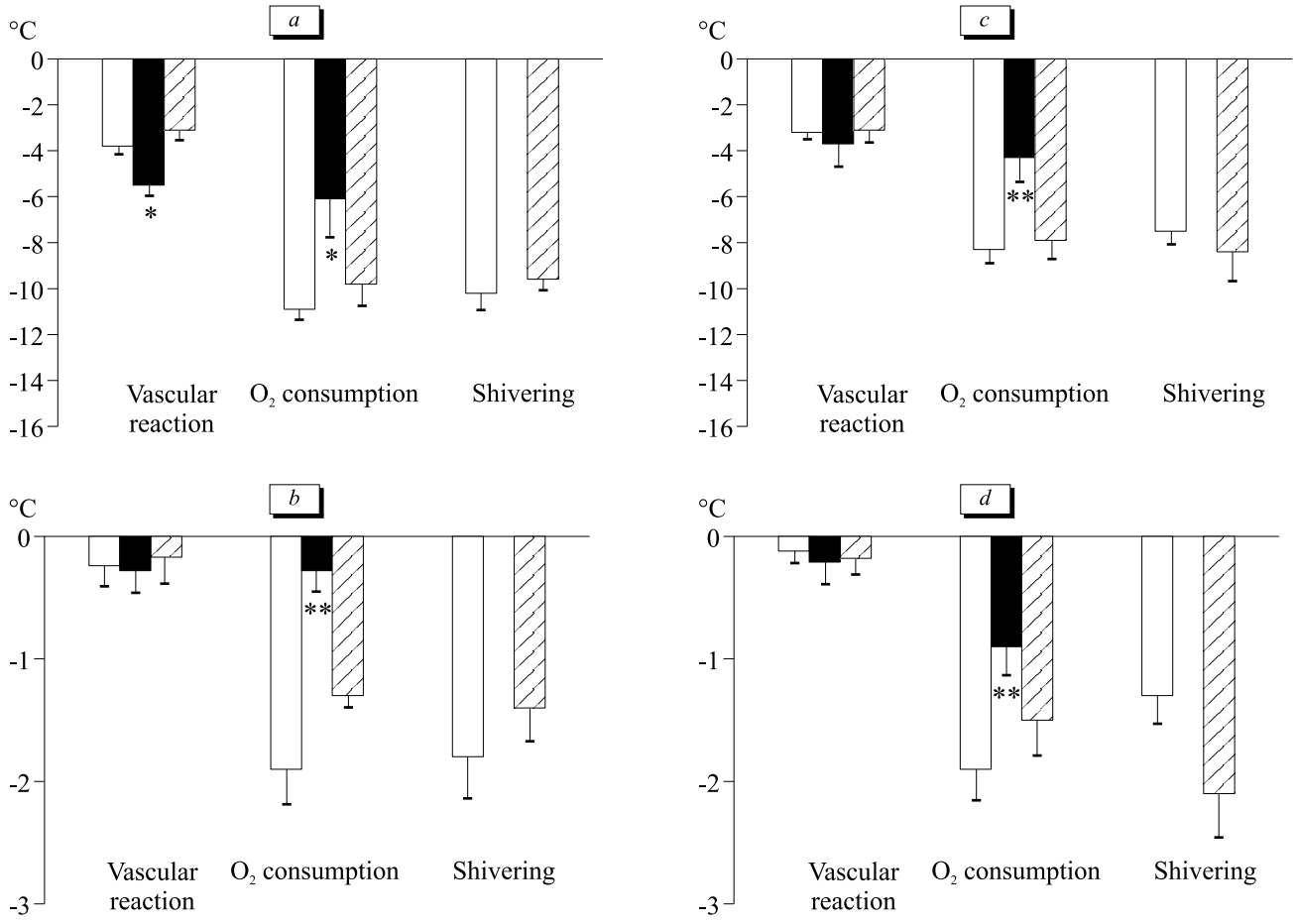

Fig. 1. Effect of ionophoretic application of α_1-AB verapamil and β-AB propranolol into the skin on the threshold of TRR evoked by rapid (*a*, *b*) and slow (*c*, *d*) cooling. The bars show the threshold drop of cutaneous (*a*, *c*) and rectal (*b*, *d*) temperatures. Here and in Fig. 2: the open bars show the control thresholds, while the closed and dashed bars represent the verapamil- and propranolol-modified thresholds, correspondingly. *p<0.05, **p<0.01 compared to initial level.

verapamil, the cold-provoked thermogenesis is effected via up-regulation of the non-shivering thermogenesis probably due to compensatory activation of β-adrenoceptors. Inhibition of the constrictor reaction of cutaneous blood vessels and suppression of shivering results from the blockade of α_1-adrenoceptors responsible for these reactions. It can be hypothesized that the effect of verapamil on TRR is also mediated via its inhibitory action on Ca^{2+} channels of the plasma membrane. The role of Ca^{2+} ions in activation of TRR was described elsewhere [1,2,5]. Specifically, we established that in comparison with verapamil, Ca^{2+} ions exerted the opposite effects on vascular reaction and shivering component of cold-induced thermogenesis.

Intracutaneous application of β-AB propranolol produced no effect on the temperature thresholds and maximum values of vascular reaction and did not change the increment of oxygen consumption during rapid and slow cooling (Figs. 1 and 2). Moreover, it did not modify the temperature thresholds of shivering in both modes of cooling (Fig. 1), but pronouncedly increased the maximum value of shivering during slow and fast cooling (Fig. 2).

These data suggest that the changes in thresholds of TRR under the action of AB and after ionophoretic application of norepinephrine [7] are mediated via α-adrenoceptors located in the thermoceptive structures.

Under normal conditions, the increment in O_2 consumption reflects total elevation of shivering and non-shivering thermogenesis. Elevation of maximum value of shivering by β-AB during both modes of cooling with unchanged increment in oxygen consumption indicates modification in the structure of thermoregulatory metabolic response.

It is established that up-regulation of non-shivering thermogenesis and increase in heat production due to muscle contractions are mediated via activation of β-adrenoceptors by norepinephrine,

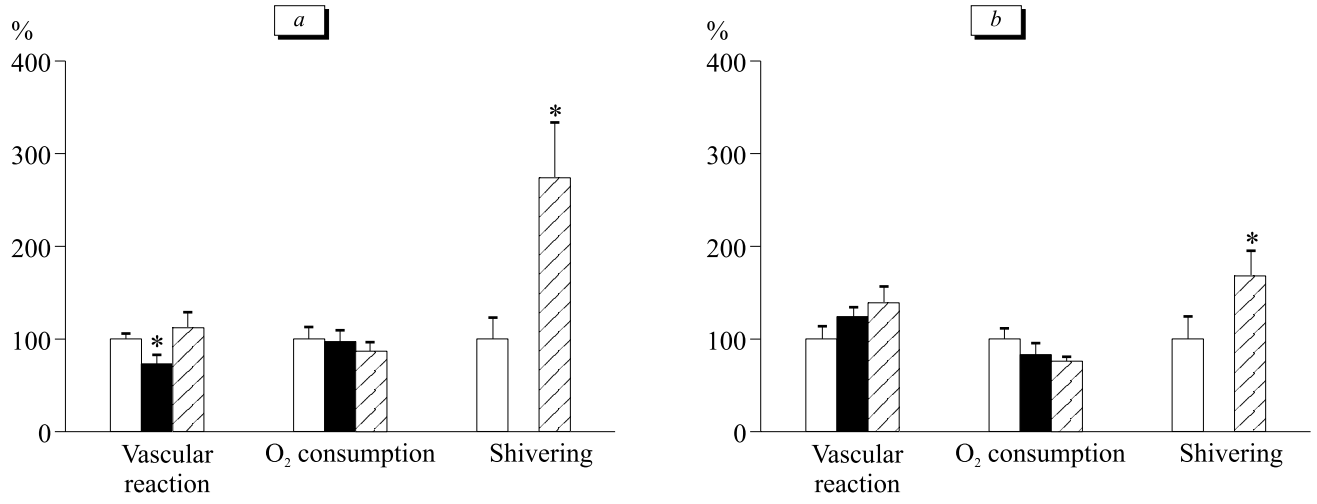

Fig. 2. Effect of ionophoretic application of α_1-AB verapamil and β-AB propranolol into the skin on maximum TRR values during rapid (*a*) and slow (*b*) cooling.

while blockade of these receptors inhibits non-shivering thermogenesis and down-regulates heat emission during muscle contraction [4]. It can be hypothesized that increment in maximum electrical activity in skeletal muscles by propranolol in our experiments compensates inhibition of non-shivering thermogenesis and decreases the thermogenic effect of muscle activity. This compensation is probably mediated via activation of α_1-adrenoceptors. Thus, cooling of the organism under conditions of blockade of one type of adrenoceptors activates the compensatory mechanisms mediated via adrenoceptors of other type.

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