Mechanisms of Modulation of Thermoregulatory Reactions during Cooling in Hypertensive Rats by the Sympathetic Nervous System

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 149, No. 1, pp. 25-29, January, 2010
Original article submitted March 18, 2009

Susceptibility of thermoregulatory responses to cold to blockage of α_1- and β-adrenoreceptors differs in health and hypertension. α_1-Adrenoceptor blockade reduces vessel reactivity during cooling and vessel reaction to cold becomes similar to that in intact normotensive rats. Changes in the structure of metabolic response to cold in favor of non-shivering thermogenesis typical of hypertensive animals becomes even more pronounced under conditions of α_1-adrenoceptor blockade due to inhibition of cold shivering. Blockage of β-adrenoceptors does not affect parameters of vascular response to cooling. In hypertensive rats, in contrast to normotensive animals, β-adrenoceptor blockade during cooling increased temperature thresholds for total metabolic reaction and shivering. The maximum shivering intensity also increased, which partially compensated inhibition of non-shivering thermogenesis. In the whole organism, blockade of one type of adrenoceptors during cooling leads to intensification of compensatory mechanisms realized through adrenoceptors of the other type. In hypertensive rats, compensatory capacities of thermogenic processes controlled by α_1- and β-adrenoceptors are impaired in comparison with normotensive animals under conditions of inhibition of both shivering and non-shivering thermogenesis.

Key Words: *thermoregulation; cold; α_1-adrenoceptor blocker; β-adrenoceptor blocker; hypertension*

Organism protection against cold is associated with activation of the sympathetic nervous system, which depends on cooling rate, *i.e.* on characteristic of the afferent signal from thermoreceptors [5]. It was previously shown that exogenous norepinephrine modulates the structure of metabolic response to cold [10]. Our previous studies of the modulating effect of norepinephrine on skin thermoceptors also revealed changes in the thresholds for thermoregulatory reactions during cooling [11].

Effects of catecholamines are mediated by various types of α- and β-adrenoceptors. The decrease in heat emission (vasoconstriction) and intensification of shivering thermogenesis during cooling are predominantly mediated by α_1-adrenoreceptors, whereas non-shivering thermogenesis (another component of the metabolic response to cooling) is realized predominantly through β-adrenoreceptors in various tissues (muscles, liver, brown adipose tissue). Our previous studies on normotensive animals showed that blockade of α_1- and β-adrenoreceptors affects temperature thresholds and magnitude of thermoregulatory reactions during cooling [7].

The sympathetic nervous system plays an important role in the development of states characterized by hypertension. Adrenoreceptor blockade is widely used in medical practice for the treatment of essential hypertension. Hypertensive rats exhibit increased sympathetic

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0007-4888/10/1491-0021

activity [13] and increased sensitivity of arterial vessels to norepinephrine [2]. Sympathetic hyperactivity typical of essential hypertension can modulate adrenorecetor activity in some organs and tissues [9,14,15]. This in turn can affect body reactions to thermal influences mediated by these structures. We revealed peculiarities of not only reaction of blood vessels, but also metabolic reactions to cooling in hypertensive rats [6].

The objective of this study was to investigate peculiarities of regulation of thermoregulatory response to cooling in arterial hypertension, a pathology characterized by altered contractile properties of blood vessels essential for heat exchange. The modulating effect of α_1- and β-adrenoreceptor blockers on the development of thermoregulatory reactions during various types of cooling differently activating sympathetic nervous system was investigated on rats with inherited stress-induced arterial hypertension.

MATERIALS AND METHODS

Experiments were performed on ISIAH rats (n=62), a biological model of inherited stress-induced arterial hypertension [12]. Mean systolic blood pressure in ISIAH rats was 172.0±2.2 mm Hg. Normotensive Wistar rats (n=62) were used as controls (mean systolic blood pressure 109.0±5.6 mm Hg). Blood pressure measurements were performed by noninvasive tail-cuff method. All manipulations were performed under Nembutal anesthesia (40 mg/kg) in order to avoid emotional stress component. Environmental temperature was maintained at 21-24°C. The abdominal area (25 cm^2) was depilated and cooled with a thermode. Two cooling regimens were used: fast (cooling rate 0.08°C/sec) and slow (cooling rate 0.008°C/sec). In both regimens, cooling was stopped, when rectal temperature decreased by 3°C.

Effects of α_1-adrenoceptor blocker verapamil and β-adrenoceptor blocker propranolol on thermoregulatory reactions during cooling were assessed after ionophoretic administration of blockers into the abdominal skin, which was further used for application of the cold stimulus. Verapamil (0.25% solution) and propranolol (0.1% solution) were used. Ionophoresis was performed at current intensity of 0.08 mA/cm^2 for 20 min.

The following parameters were continuously recorded during the experiment: ear skin temperature (remote place from cooling site and from environment) for evaluation of the reaction of skin vessels; rectal temperature for evaluation of core temperature; skin temperature at the cooling site for evaluation of cooling rate and threshold skin temperatures of protective reactions; total oxygen consumption and electric activity of neck muscles to assess metabolic reactions (nonshivering and shivering thermogenesis). The decrease in ear skin temperature by 0.1°C, increase in oxygen consumption by 1 ml/min/kg, and neck muscle electric activity by 1 μV during cooling were considered as the onset of thermoregulatory reaction. Values at the end of cooling were taken as maximum parameters.

The results were processed using Student's t test; mean values and the error of the means (M±m) were calculated.

RESULTS

Ionophoretic administration of α_1- and β-adrenoceptor blockers did not affect parameters of thermal homeostasis under thermoneutral conditions in both hypertensive and normotensive (control) rats (Table 1). Cooling against the background of adrenoceptor blocker administration allowed to reveal peculiarities of the formation of thermoregulational response to cooling in hypertensive rats.

In hypertensive animals, similar to normotensive ones, verapamil affected vascular reaction only under conditions of fast cooling. This was probably associated with earlier and more pronounced activation of the sympathetic nervous system during fast cooling, when the development of the response involves dynamic activity of cold skin receptors [5]. Under these conditions, the increase in catecholamine level was observed after smaller shifts in body temperature than during slow cooling. The clear-cut effects of verapamil under conditions of fast cooling in this case can be associated with peculiarities in activation of the sympathetic nervous system. Verapamil administration increased the temperature threshold for vascular response to fast cooling (Fig. 1), which was more pronounced in hypertensive rats (by 64%), than in normotensive ones (by 45%). Verapamil reduced the maximum value of vasoconstrictor reaction in hypertensive rats by 44% (from initial -3.40±0.34°C to -1.90±0.24°C after verapamil administration; p<0.05), but did not affect this parameter in normotensive rats. These findings attest to great contribution of α_1-adronoreceptors into the regulation of vascular response to the cold in hypertensive animals. It should be noted that parameters of vascular reaction in hypertensive animals treated with verapamil approximated those in intact animals (Fig. 1).

The initial temperature threshold for metabolic reaction in hypertensive rats was substantially lower than in normotensive animals (Fig. 2), which confirms our previous data [6]. Verapamil decreased temperature threshold for metabolic response to fast cooling, which was seen from threshold rectal temperature decrease (Fig. 2). The decrease in metabolic reaction threshold in hypertensive rats was less pronounced than in normotensive animals and was observed only during fast cooling (Fig. 2), apparently to compensate late onset

TABLE 1. Effects of α_1- and β-Adrenoceptor Blockers on Parameters Recorded under Thermoneutral Conditions in Hypertensive and Normotensive Rats

Parameter	Rat strain	Without adrenoceptor blockers	Verapamil	Propranolol
Total oxygen consumption, ml/min/kg	hypertensive	16.6±2.48	16.6±0.86	15.6±0.95
	normotensive	17.1±0.81	16.4±0.73	16.8±0.91
Ear skin temperature, °C	hypertensive	29.9±0.48	29.3±0.33	29.7±0.42
	normotensive	30.5±0.21	29.8±0.40	30.1±0.42
Intradermal abdominal temperature, °C	hypertensive	37.2±0.37	36.7±0.38	37.1±0.39
	normotensive	37.2±0.12	36.9±0.34	36.9±0.30
Rectal temperature, °C	hypertensive	36.4±0.35	36.6±0.29	36.5±0.31
	normotensive	36.9±0.13	36.3±0.27	36.3±0.28
Electric activity of neck muscles, μV	hypertensive	2.5±0.40	2.1±0.34	2.5±0.35
	normotensive	2.6±0.20	2.4±0.19	2.6±0.16

of the vascular response. Verapamil had no effect on the peak value of the metabolic response during fast cooling (oxygen consumption initially increased by 6.90±1.73 ml/min/kg and 11.40±3.35 ml/min/kg after verapamil administration; $p \geq 0.05$), but reduced it by almost 40% during slow cooling (the corresponding values were 13.30±2.28 and 8.00±1.17 ml/min/kg). The effects of verapamil in hypertensive animals were also different during fast and slow cooling: fast cooling affected only the threshold and slow cooling affected only the magnitude of the response.

Verapamil completely inhibited thermorgulatory contractile muscle activity during fast and slow cooling in both hypertensive and normotensive rats. The decrease in metabolic response to slow cooling attests to the absence of total compensation of shivering thermogenesis by non-shivering one in hypertensive animals, in contrast to full compensation in normotensive animals.

Changes in cold-protective reactions observed after verapamil administration (inhibition of constrictor reaction of skin vessels and suppression of shivering) due to α_1-adrenoreceptor blockade can be associated with changes in Ca^{2+} homeostasis (second messenger for these receptors). Calcium involvement into activation of thermoregulatory responses was shown previously [1,3], specifically our previous studies demonstrated that calcium and verapamil exhibit opposite effects on vascular reaction and shivering component of the metabolic response to cold [8]. The effects of calcium were more pronounced in hypertensive rats [4].

In hypertensive rats, similarly to normotensive animals [7], propranolol did not affect temperature thresholds of vascular response (Fig. 1) and its peak value neither during fast, nor during slow cooling.

Temperature thresholds of metabolic response and shivering initiation in hypertensive animals, in contrast to normotensive ones, increased after propranolol administrations during both fast and slow cooling (Figs. 2 and 3). Peak metabolic response was not changed after propranolol administration during fast cooling (increase in oxygen consumption before and after propranolol administration was 6.90±1.73 and 5.50±0.96 ml/min/kg, respectively; $p \geq 0.05$), but was reduced by almost 60% during slow cooling (13.30±2.28 ml/min/kg in initial state and 4.80±1.15 ml/min/kg after propranolol administration). The peak magnitude of shivering in hypertensive animals increased during both fast and slow cooling. The in-

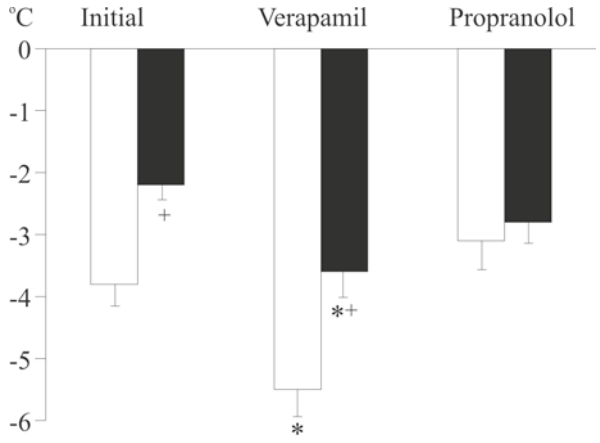

Fig. 1. Effects of ionophoretic administration of α_1-adrenoceptor blocker verapamil and β-adrenoceptor blocker propranolol on the thresholds for vascular responses to fast cooling. Here and on Figs. 2 and 3: light bars: normotensive rats, dark bars: hypertensive rats. Ordinate: threshold decrease of abdominal skin temperature. $p<0.05$ * when affected by adrenoceptor blockers in hypertensive and normotensive rats, + in comparison with normotensive rats.

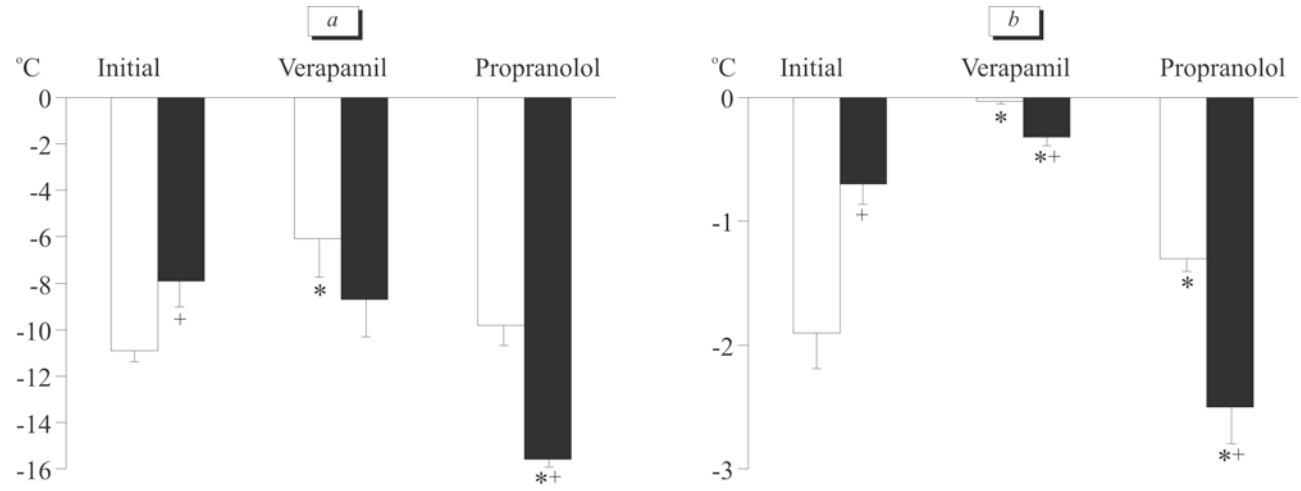

Fig. 2. Effects of ionophoretic administration of α_1-adrenoceptor blocker verapamil and β-adrenoceptor blocker propranolol on the thresholds for metabolic responses to fast cooling. *b*) Ordinate: threshold lowering of rectal temperature.

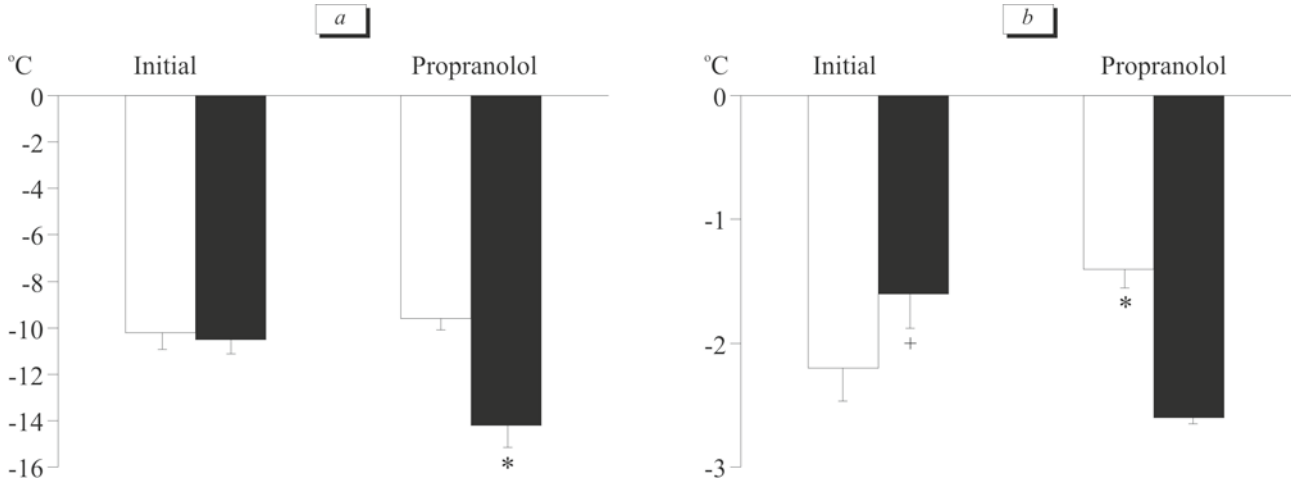

Fig. 3. Effects of ionophoretic administration of β-adrenoceptor blocker propranolol into the skin on shivering threshold during fast cooling. *b*) Ordinate: threshold lowering of rectal temperature.

crease in contractile muscle activity was 47% during fast cooling (13.90±2.40 μV initially and 20.50±0.67 μV after propranolol administration) and 80% during slow cooling (15.50±1.94 μV initially and 28.10±4.94 μV after propranolol administration).

Reduced metabolic response against the background of increased muscle contractile activity during slow cooling suggest that propranolol inhibits non-shivering thermogenesis. This inhibition is more pronounced in hypertensive animals during slow cooling. It is known that the development of non-shivering thermogenesis during cooling is associated with activation of β-adrenoreceptors through the adenylate cyclase system. Different effects of propranolol in normotensive and hypertensive animals can be explained by changes in β-adrenoreceptor density and activity of adenylate cyclase complex, which were found in hypertension [13]. The increase in cold shivering observed in our experiments can be realized through α_1-adrenoreceptors. However, this increase in muscle activity only partially compensates the decrease in non-shivering thermogenesis in hypertensive animals, in contrast to normotensive rats in whom shivering completely compensates for impaired non-shivering thermogenesis reduced by propranolol [7].

Thus, our experiments demonstrated different roles for α_1- and β-adrenoceptors in the formation of thermoregulatory effector reactions to cold in normotensive and hypertensive animals. In hypertensive animals, vascular response to cooling aimed at limiting heat emission was more sensitive to α_1-adrenoreceptor blockage (in comparison with normotensive animals). Blockade of α_1-adrenoreceptors reduced vessel reactivity during cooling and the parameters of vascular reaction to cold in hypertensive animals became closer to that in intact normotensive rats. The shift in the structure

of metabolic response towards non-shivering thermogenesis typical of hypertensive animals becomes even more pronounced after blockade of α_1-adrenoreceptors, which partially compensates for inhibition of shivering thermogenesis. Vascular response to cooling is unsensitive to blockage of β-adrenoreceptors. The increase in peak shivering magnitude during cooling after administration of β-adrenoceptor blocker partially compensates inhibition of non-shivering thermogenesis. As it was mentioned previously [6], blockade of adrenoreceptors of one type during cooling in the whole organism is associated with intensification of thermogenesis, mediated by adrenoreceptors of another type. However, it should be noted that compensatory properties of thermogenesis controlled by α_1- and β-adrenoreceptors are limited in hypertensive rats in comparison with normotensive ones under conditions of inhibition of both shivering and non-shivering thermogenesis.

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