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Skin TRPA1 ion channel participates in thermoregulatory response to cold. Comparison with the effect of TRPM8

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ABSTRACT

There was no clear evidence of the TRPA1 ion channel involvement in the formation of thermoregulatory responses. The present results convincingly show that the skin TRPA1 ion channel activation has significant influence on the formation of thermoregulatory responses of the body to cooling; it is especially strongly manifested for the metabolic component. At the TRPA1 activation by its agonist AITC (0.04%), an enhancement in thermoregulatory responses is observed: the temperature thresholds for the first phase and the second one of the metabolic response decrease, the values of all components of the metabolic response considerably increase: the increment of oxygen consumption in the first phase increases from 1.8 ± 0.24 in the control to 2.9 ± 0.35 ml/min*kg under AITC, P = 0.04; the increment of oxygen consumption in the second phase increases from 6.2 ± 2.06 to 17.4 ± 1.20 ml/min*kg, P = 0.002, as well as shivering rises from 7.8 ± 1.79 to 15.4 ± 1.87 mV, P = 0.011. In consideration of our previous results on the influence of TRPM8 ion channel activation on thermoregulatory responses (Kozyreva et al., J. Therm.Biol., 2010) it is obvious that the TRPM8 and TRPA1 ion channels have a pronounced, but unequal effects on the values of different phases of the metabolic response to cold. The TRPM8 activation manifests itself in an increase of value only the urgent first phase, this phase is associated with carbohydrate metabolism. As the recent results have shown the influence of the TRPA1 activation is realized predominantly in the clearly marked increase in the second phase of the metabolic response associated with lipid metabolism, as well as in evident shivering gain. The ability to predominantly control different parameters of thermoregulatory responses to cold may indicate the importance of both the TRPM8 and the TRPA1 ion channels in the processes of maintaining temperature homeostasis. The obtained data testify to the joint sequential operation of these thermosensitive ion channels.

1. Introduction

Vertebrates are capable of perceiving temperature stimuli due to the presence in the body of specialized sensory neurons of the peripheral and central nervous system. The sense of ambient and internal temperature is necessary to ensure temperature homeostasis and prevent temperature damage. A significant achievement in understanding the molecular basis of temperature sensitivity is the detection of temperature-sensitive ion channels, including TRP. According to modern data, it is TRP ion channels that perceive changes in temperature are sensors of temperature changes in the body of warm-blooded animals (McKemy et al., 2002; Jordt et al., 2003; Patapoutian et al., 2003; McKemy, 2005; Nilius and Flockerzi, 2014). The study of these channels contributes to the understanding and accumulation of information about the molecular basis of temperature signals perception and participation in the formation of thermoregulatory responses of the body.

Thermosensitive TRP ion channels are divided into cold and warm sensitive. Cold-sensitive TRP ion channels are TRPM8 and TRPA1 (Story et al., 2003; Brauchi et al., 2004). It has been established that TRPA1 and TRPM8 are expressed on different sensory neurons, and have different thresholds for temperature activation during cooling (Nealen et al., 2003). According to *in vitro* data, TRPM8 has the activation temperature threshold below 25–28 °C, and the TRPA1 ion channel - below 17 °C. The TRPM8 ion channel is responsible for cold sensation and TRPA1 - for the perception of strong painful cold effect (Story et al., 2003; Clapham, 2003; Dhaka et al., 2006). There are data on the influence of the TRPM8 ion channel on thermoregulatory responses (Kozyreva et al., 2010; Kozyreva and Voronova, 2015; Oliveira et al., 2014, 2015; Knowlton et al., 2010; Gavva et al., 2012; Almeida et al., 2012). The TRPA1 ion channel presence in peripheral sensory

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neurons and cold sensitivity of this channel has suggested its participation in thermoregulatory processes under the effect of cold on the body. However, there is no clear evidence of the TRPA1 ion channel involvement in the formation of thermoregulatory responses.

In the present work, we have investigated the effect of the peripheral skin ion channel TRPA1 activation by its agonist allyl isothiocyanate (AITC) on the parameters of temperature homeostasis in thermo-neutral conditions and on the formation of thermoregulatory responses at exposure to cold.

2. Methods

2.1. Animals

Male Wistar rats weighing 180–220 g were used. The experimental procedures were in compliance with the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010, its correction of 20 December 2013 (2014/63/EU) and approved by the ethic committee of the Institute of Physiology and Basic Medicine. The efforts were made to minimize the number of animals used and their suffering. All procedures including the thermocouple and muscle electrodes fixation, application of drug and cooling were done under anesthesia (Nembutal, 40 mg/kg) to exclude the emotional component and movement in the animals.

2.2. Cooling

Experiments were performed at room temperature 22–23 °C. The initial precooling temperature of the animal was maintained by a temperature controlled panel so that the rectal temperature was 37.7 ± 0.05 °C; the abdomen skin temperature was 37.4 ± 0.04 °C. A depilated skin in the abdominal area of 25 cm^2 was cooled using a special thermode and thermostat. The experimental models of rapid cooling were used; the rate of skin temperature decrease was 0,10-0,12°C/sec. Cooling was carried on until a decrease in rectal temperature by 3 °C was reached. The duration of cooling was 15–17 min. To control the depth and rate of cooling, rectal and skin temperatures were measured with a thermocouple and recorded with the «BIOPAC» (Biopac Systems Inc., Goleta, CA, USA) system.

2.3. AITC application

In thermoneutral conditions before cooling the TRPA1 agonist allyl isothiocyanate (AITC) was applied to the skin, where thermosensitive nervous ending (afferents) are concentrated. A 0.04% mixture of AITC (Sigma) in physiological saline was applied for 20 min to the area of the abdomen (25 cm^2), where the cold stimulus was further applied. For this purpose 1 ml of the mixture was evenly spread over filter paper of the corresponding size and applied to the skin. The temperature of the applied mixture was about 37 °C. In the control group the solvent (physiological saline) was applied.

2.4. Thermoregulatory response

The following thermoregulatory parameters were continuously measured throughout the experiment: (1) temperature at a site remote from the cooled spot and isolated from the environmental, the auricular floor skin and tail skin; this allowed us to judge how skin vessels respond to the AITC application and cooling; (2) rectal temperature to measure core temperature; (3) intracutaneous temperature of the cooled abdominal surface to control the cooling rate and determine the start of cooling and the threshold skin temperature and for the cold defense responses; (4) total oxygen consumption and carbon dioxide release to estimate thermogenesis and (5) electrical activity of neck muscles to estimate shivering. The following changes during cooling were accepted as threshold values: 0.1 °C for temperature, 1 ml/min kg for oxygen consumption and carbon dioxide release and 1 mV for electrical muscle activity. The latency of any response was measured as the time from the start of cooling (decrease in abdomen skin temperature by 0.1 °C) up to the start of response. For measuring oxygen consumption and dioxide release, a mask and Gas Concentration Measurement Modules (O2100C and CO2100C, Biopac) were used and the collected gas entered into the analyzer via Gas Sampling Interface Kit with NAFION's dryer. The value of respiratory coefficient (CO2/O2) was calculated to estimate the increase in utilization of either carbohydrates or lipids. All parameters were recorded by an IBM PC, using the "Biopac" system.

2.5. Design of experiment

Animals were anesthetized, and then all the sensors were fixed (for temperatures, muscle activity, oxygen consumption and carbon dioxide release). Within 5–10 min the initial parameters were recorded; then with the continuous recording of parameters during the AITC application was carried out for 20 min (in control animals it was solvent), which was followed by exposure to cold. This allowed us to identify the effect of AITC (the TRPA1 ion channel activation) in thermoneutral conditions and in cold. Every animal was cooled only once. To determine the AITC effect there were 2 experimental groups of rats: rapid cooling with and without the TRPA1 activation.

2.6. Statistical analysis

The total number of rats without the AITC application was 13 and that with the AITC application was 9. The data are presented as mean M ± SE. Statistical significance was determined using an unpaired two-tailed Student's t-test for two-group comparisons with the program "Statistica".

3. Results

In thermoneutral conditions (in the absence of temperature effect), the AITC application to skin at a concentration of 0.04% did not affect the parameters of temperature homeostasis and total metabolism, there were no significant differences between the parameters at the application of AITC and saline (control) (Table 1).

3.1. Cooling

For rapid deep cooling, a specific sequence of thermoregulatory responses (heat loss and heat production) is characteristic: first, at only skin temperature decrease, the first phase of metabolic response develops, characterized by an increase in respiratory coefficient, and i.e. increased utilization of carbohydrates; then with a greater decrease in skin temperature, but without changes in the deep body temperature the vasoconstrictor response of skin vessels is initiated. The second

Table 1
Parameters of temperature homeostasis and total metabolism at application of saline (control) and allyl isothiocyanate (AITC) in thermoneutral conditions.

Parameters	Control	AITC (0,04%)	P
Number of animals	13	9	
Weight (g)	312 ± 19,9	291 ± 7,4	P > 0.05
Temperature of auricular floor skin (^{0}C)	29,2 ± 0,49	29,6 ± 0,24	P > 0.05
Temperature of tail skin (^{0}C)	30,4 ± 0,56	29,1 ± 0,24	P > 0.05
Temperature of abdomen skin (^{0}C)	37,3 ± 0,07	37,2 ± 0,04	P > 0.05
Rectal temperature (^{0}C)	37,5 ± 0,11	37,4 ± 0,03	P > 0.05
Oxygen consumption (ml/min*kg)	17,2 ± 0,65	17,2 ± 0,70	P > 0.05
CO2 release (ml/min*kg)	14,1 ± 0,50	14,4 ± 0,54	P > 0.05
Respiratory coefficient	0,82 ± 0,024	0,84 ± 0,013	P > 0.05
Electrical muscle activity (mV)	1,2 ± 0,13	1,5 ± 0,25	P > 0.05

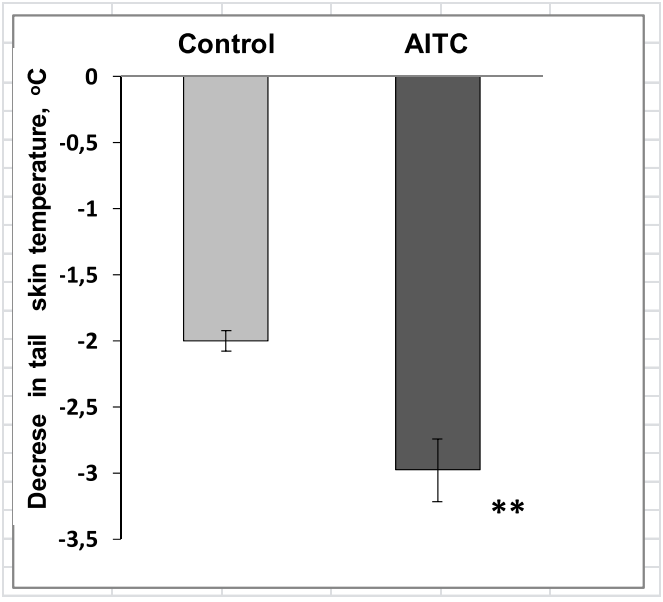

Fig. 1. Effect of AITC on the decrease in the tail skin temperature (skin blood vessel constriction) at rapid cooling. Significant differences in AITC effect in comparison with control: ** - P < 0.01.

phase of metabolic response, characterized by a decrease in the respiratory coefficient i.e. increased of lipid metabolism, occurs when not only skin but also deep body temperature drops, and is accompanied by an increase in thermoregulatory muscle activity (Kozyreva et al., 2010, 2017). This sequence of responses was observed also in these experiments.

3.2. Heat loss response to cooling

The application of the TRPA1 ion channel agonist AITC at 0.04% concentration did not affect the temperature thresholds of the constrictor response of the skin vessels in the auricular floor and tail (Fig. 1), but significantly increased the maximal value of this response for the tail skin vessels. The maximal decrease in the tail skin temperature was more pronounced by 40% (−2.1 ± 0.08 °C in control and −3.0 ± 0.25 °C at AITC application (t = 3.091, df = 16, P < 0.01).

3.3. Metabolic response to cooling

AITC caused a change in the temperature thresholds as well as latency of the body's metabolic response to cooling. The latent period has decreased from 32.0 ± 4.87 to 18.4 ± 2.58 s (t = 3.19, df = 14, P < 0.01). The skin temperature thresholds for the first phase of metabolic response (increase in oxygen consumption and CO2 release) have decreased (Fig. 2, top). Under the AITC (peripheral TRPA1 activation), temperature thresholds by rectal temperature for the second

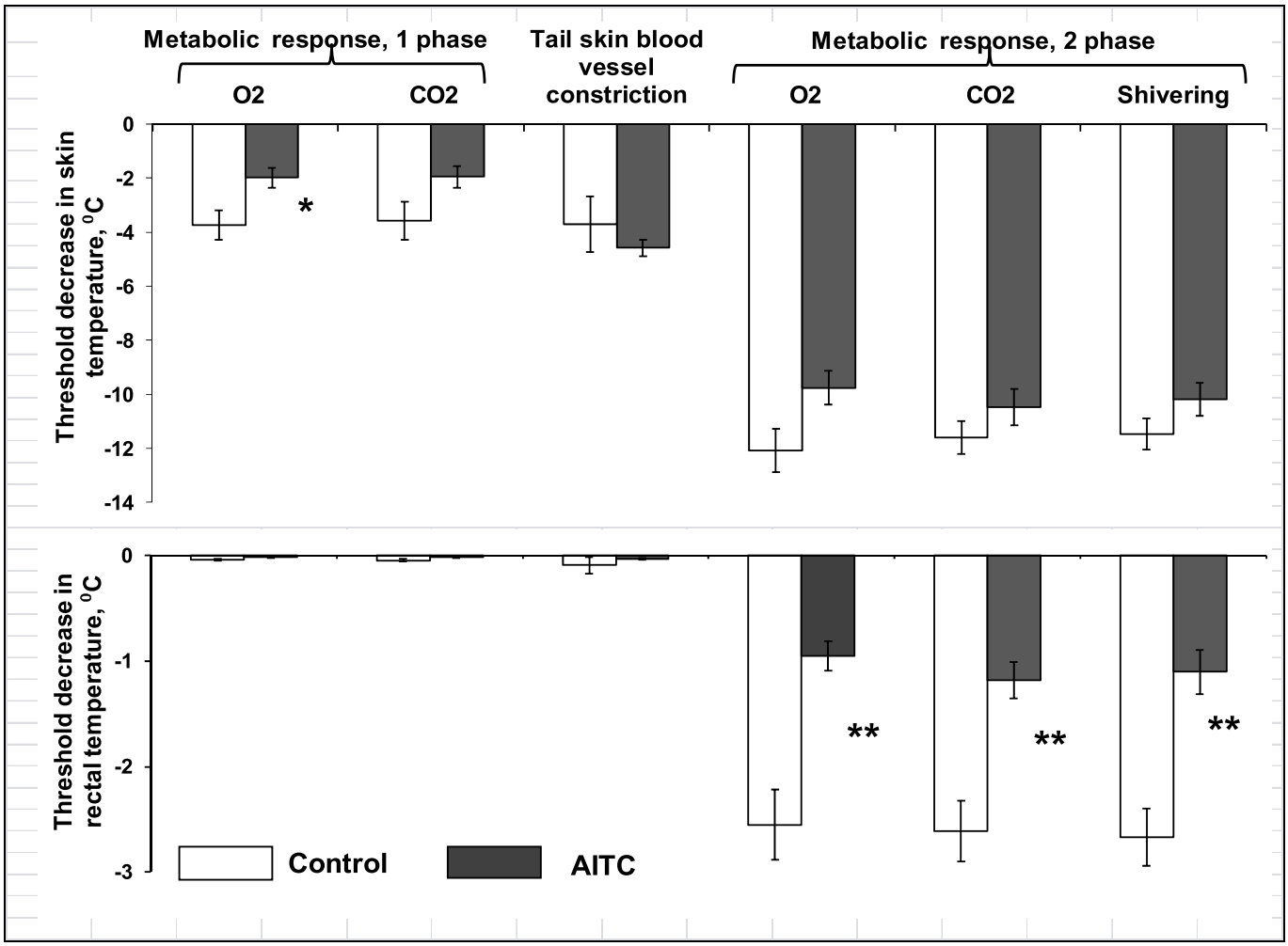

Fig. 2. Effect of AITC on temperature thresholds of thermoregulatory responses to rapid cooling. Significant differences in AITC effect in comparison with control: * - P < 0.05; ** - P < 0.03.

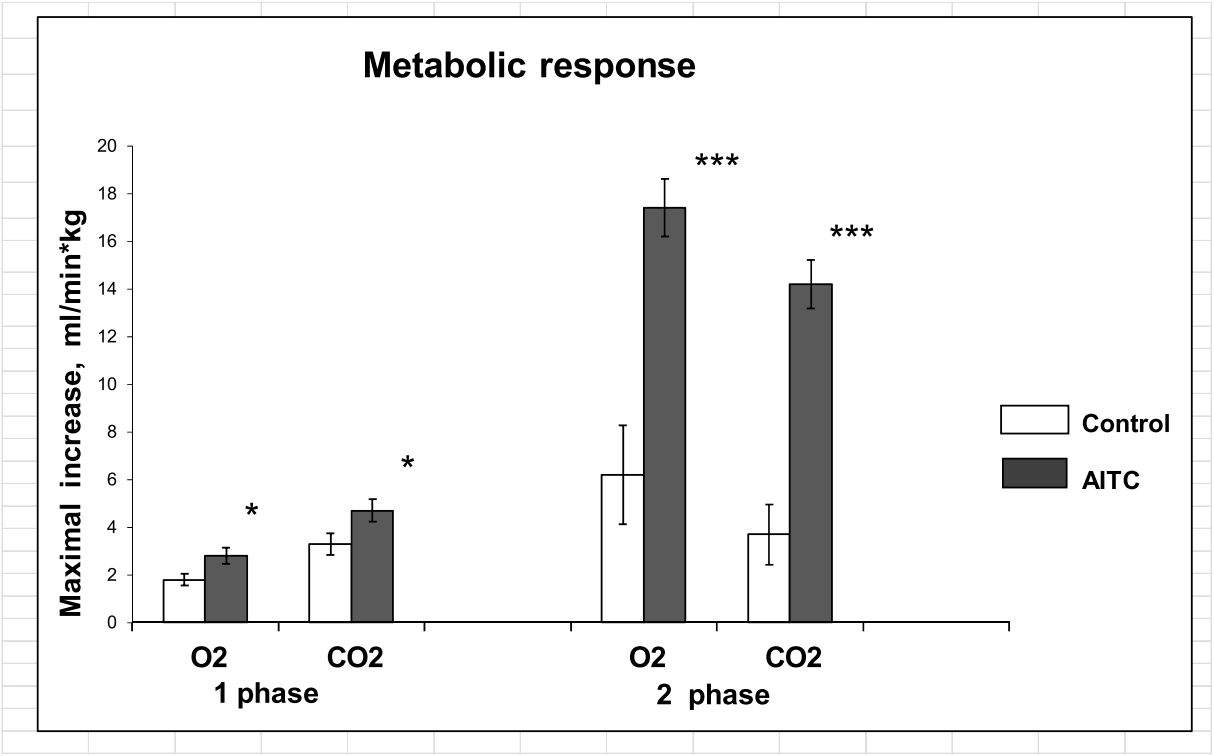

Fig. 3. Effect of AITC on the values of the first phase and the second one of metabolic response to rapid cooling. Significant differences in AITC effect in comparison with control: * - P < 0.05; *** - P < 0.01.

Table 2
Changes in respiratory coefficient in the first and second phases of metabolic response during cooling.

Groups	Respiratory coefficient			P 1-2	P 1-3
	Before cooling	1 phase of metabolic response	2 phase of metabolic response		
	1	2	3		
Control	0.826 ± 0.0223	0.959 ± 0.0262	0.760 ± 0.0057	t = 4.13,df = 12, P < 0.01	t = 2.87, df = 13, P < 0.05
AITC	0.837 ± 0.0083	0.974 ± 0.0215	0.777 ± 0.0010	t = 5.88, df = 16, P < 0.01	t = 3.42, df = 16, P < 0.01
P Control-AITC	> 0.05	> 0.05	> 0.05		

phase of the metabolic response decreased expressively (Fig. 2, bottom). The latency of the second phase of metabolic response was also shorter under AITC – 397.0 ± 52.80 in control, and 240.7 ± 20.77 s at AITC, (t = 4.05, df = 13, P < 0.01).

The maximal values of the components of the metabolic response under the AITC influence have also increased: in the first phase of the metabolic response, total oxygen consumption increased (Fig. 3) and at the second phase of metabolic response, under AITC the increase in oxygen consumption was more than twice higher. The influence of AITC on the respiratory coefficient in the first phase and the second one of metabolic response was not observed (Table 2).

3.4. Shivering

Under the AITC application thermoregulatory muscle activity (contractile thermogenesis) has also started earlier (the latency was 426 ± 25.1 in control and 254 ± 28.5 s at AITC (t = 3.96, df = 13, P < 0.01), and has decreased rectal temperature threshold (Fig. 2). The maximum value of the thermogenic muscle activity significantly increased at the AITC application (Fig. 4).

The earlier initiation of the metabolic response, as well as the increase in oxygen consumption under AITC effect, slowed down the fall in core temperature, the rate of fall in rectal temperature being 0.36 ± 0.010 °C/min in the control and 0.18 ± 0.007 °C/min after AITC application (t = 3.96, df = 13, P < 0.01).

Thus, the TRPA1 ion channel activation by its agonist AITC at a concentration of 0.04%, while reducing temperature thresholds and increasing the metabolic components, significantly enhances the body's thermal protective responses during the cooling effect. The temperature thresholds for the initiation of the constrictor response of the cutaneous blood vessels, had not been affected by AITC in used concentration, but the increased constrictor response of the tail skin blood vessels (the main heat loss organ in rats) was observed.

4. Discussion

The cold sensitivity of the TRPA1 ion channel was shown in *in vitro* experiments, but until recently its participation in the body's response to cold *in vivo* was questioned (Bautista et al., 2007; Chen et al., 2011; Oliveira et al., 2014). All these researchers worked with the deletion of the *Trpa1* gene or with blockade of TRPA1 by its antagonists. Chen and co-workers (Chen et al., 2011) investigated the blockade of TRPA1 only in thermoneutral conditions and did not get the effect. The effect of TRPA1 blocking in conditions of cooling, these authors did not study. A Bautista study (Bautista et al., 2007) showed that knockout of mice on the *Trpa1* gene did not lead to a change in their behavior at the choice

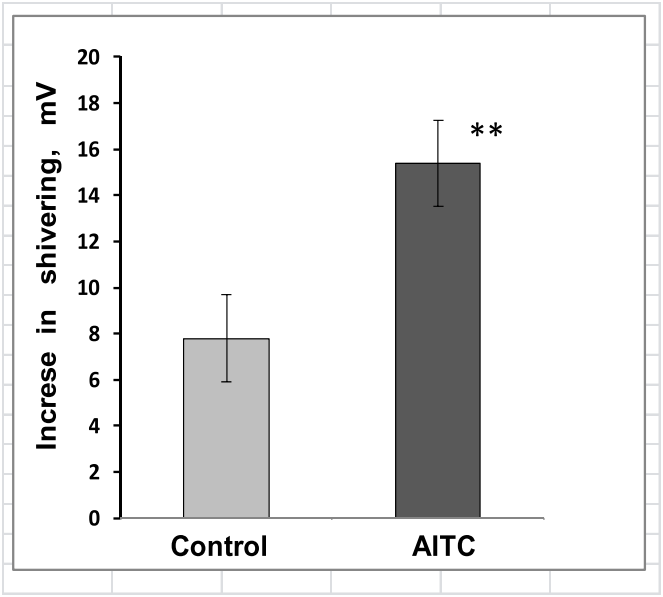

Fig. 4. Effect of AITC on the value of shivering in response to rapid cooling. Significant differences in AITC effect in comparison with control: ** - $P < 0.03$.

of preferred temperature, and it was concluded that TRPA1 does not participate in the control of the thermo-preferendum. However, in these mice the deep body temperature was not measured in order to understand whether they had decreased temperature to activate other ion channels that could compensate for afferent signal of a decrease in temperature. In addition, these mice were not exposed to cold sufficient to activate TRPA1. It should be noted that in our studies in thermoneutral conditions the effect of TRPA1 stimulation was also not observed.

In the study of Oliveira et al. (2014), with intragastric administration of TRPA1 antagonists, it was also concluded that this ion channel does not participate in the processes of thermoregulation. It should be noted that the effects of the nerve afferent stimulation in the internal organ and skin can be manifested in different ways. Moreover, it is the skin that is the organ of natural protection from the external environment including thermal exposure and it is the region of concentration of thermosensitive nerve endings that form the peripheral afferent signal for thermoregulatory responses. This is also confirmed, for example, by the data that systemic intraperitoneal administration and administration of drugs to skin have different effects (Kozyreva et al., 2017). The absence of changes in thermoregulatory responses to cold in *Trpa1* knockout mice (Oliveira et al., 2014) may be due to compensatory changes in the body and increased activity of other cold-sensitive ion channels.

The results obtained in the present work convincingly show that the skin TRPA1 ion channel activation has significant influence on the formation of thermoregulatory responses of the body to cooling, it is especially strongly manifested for the metabolic component. At the TRPA1 activation by the used concentration of its agonist AITC, an enhancement in thermoregulatory responses is observed: the latency decreases and temperature thresholds for the first phase and the second one of the metabolic response reduce; the values of all components of the metabolic response, such as oxygen consumption, carbon dioxide release, as well as shivering, increase.

As it has been noted in the introduction, two cold-sensitive TRP ion channels, TRPM8 and TRPA1, have been identified in peripheral skin nerve endings. It is interesting to compare the effects of TRPM8 and TRPA1 skin ion channels activation on thermoregulatory parameters at cooling keeping in mind that these ion channels have not co-localization. Previously our studies have shown that the TRPM8 ion channel activation by its agonist menthol (1%) reduces the thresholds for thermoregulatory responses, and increases the value but only of the first phase of the metabolic response (associated with increase in carbohydrate metabolism) without affecting the most powerful second phase of thermogenic metabolism, also not affecting muscle thermogenesis (Kozyreva et al., 2010, 2017). The TRPA1 activation by its agonist AITC at a concentration of 0.04% reduces the temperature

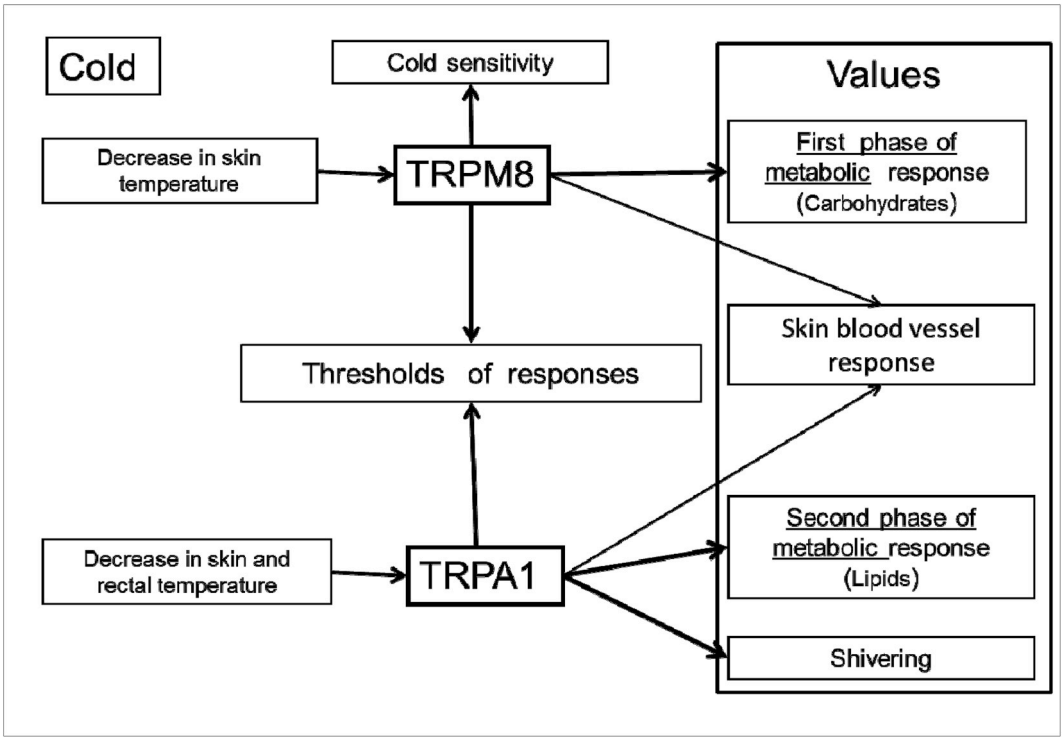

Fig. 5. The postulated scheme for thermosensitive TRPM8 and TRPA1 ion channel operation in the formation of thermoregulatory response to cold.

thresholds of the first phase and the second one of the metabolic response, but in contrast to TRPM8, it is more pronounced for the second phase by the deep rectal temperature thresholds. Regarding the maximal values of the metabolic response, the TRPA1 activation in the skin significantly enhances exactly the second phase of metabolism (associated with an increase in lipid metabolism) and shivering, the values of which are not affected by the TRPM8 activation (Fig. 5).

Thus, TRPM8 and TRPA1 influence on the thresholds of all thermoregulatory responses to cold – heat loss and heat production. However, TRPM8 and TRPA1 have an unequal effect on the temperature thresholds of metabolic components of thermo-defensive response (TRPM8 to a greater extent on the thresholds of the first phase, TRPA1 on the thresholds of the second phase of metabolic response). The divergence of the influence of these two ion channels on the values of the first phase and the second one of the metabolic response to cold is even more pronounced. According to our previous results the TRPM8 activation manifests itself in an enhancement of the first phase, only. While TRPA1 is activated, the most pronounced effect is observed for the second phase of the metabolic response to cold, and thermogenic oxygen consumption and shivering enhance significantly in the second phase. The obtained data testify to the joint sequential operation of the TRPM8 and TRPA1 thermosensitive ion channels, which ensure the formation of thermoregulatory responses to cooling: first, initiation of responses occurs due to the TRPM8 ion channel, which is more sensitive to a decrease in temperature, and then TRPA1 is involved, which, according to *in vitro* data, is activated at lower temperatures. The ability to control different parameters of thermoregulatory responses to cold may indicate the importance of the TRPM8 and TRPA1 ion channels in the processes of maintaining temperature homeostasis in the body when temperature conditions change.

It is also interesting to note that, according to our previous data (Kozyreva et al., 2015) ATP, when applied to the skin, has a predominant effect on the development of the second phase of the metabolic response and muscle thermogenesis at cooling. Moreover, PPADS antagonist of P2X receptors can suppress thermoregulatory muscle activity (Kozyreva et al., 2017). There is evidence in literature that TRPA1 is present on keratinocytes (Atoyan et al., 2009; Bíró, Kovács, 2009) and stimulation of TRPA1 by AITC leads to an increase in ATP release (Egbuniwe et al., 2014). This suggests that the effect of TRPA1 on the second phase of the metabolic response may be mediated by ATP through P2X receptors at least partially. Nevertheless, the question if there is any cross-talk between the thermo-TRP channels in the skin sensory neurons and non-neuronal cutaneous cells is still open.

Thus, the present results convincingly show that the skin TRPA1 ion channel activation has significant influence on the formation of thermoregulatory responses of the body to cooling; it is especially strongly manifested for the metabolic component including muscle thermogenesis. This data in combination with the previous results on the TRPM8 ion channel allow suggesting the pattern of the TRPM8 and TRPA1 joint participation in the formation of thermoregulatory response to cold.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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