

Neurophysiological aspects of the long-term adaptation to cold in mammals: The role of central and peripheral thermoreceptors

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Abstract

The results of many years of experimental studies of the effects of the organism's long-term adaptation to cold and noradrenaline on the impulse activity of the central hypothalamic and peripheral skin thermoreceptors are summarized. Considered are the issues pertaining to the involvement of the sympathetic nervous system in the formation of the adaptive changes in the regulatory characteristics of thermal homeostasis and also the contribution of the different components of thermoreceptors activity to the formation of effector responses. The role of various types of thermoreceptors in the formation of thermal sensation is discussed.

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1. Introduction

The problem of adaptation of humans and animals to the conditions of the external environment is currently considered as one concerned with the function of the main homeostatic systems, each sustaining the life of every facet making up the whole organism. The thermoregulatory system, which provides the thermal regime for all the chemical reactions that take place in the living organism, is one of the most important homeostatic systems.

Regulatory mechanisms, at whatever level examined, can be understood provided that the afferent signals of the receptor structures that form the input signal of the homeostatic system is taken in full account. However, the significance of the receptors, in terms of sensory structures that play an important role in the organism's adaptation, remains unclear to the present day and the mechanisms implementing the specific role of the receptors have been very scantily studied.

Studies of the thermoreceptor activity patterns have been conducted for a long time without reference to the homeostatic responses in whose regulation they are

involved. Investigation of the thermoregulatory mechanisms and of thermal adaptation was restricted to the function of the effector structures only. Explanations for the adaptive mechanisms were offered from this vantage point.

Questions remain virtually unanswered: (1) Is it feasible to modify the activity pattern and the sensitivity of the central and peripheral thermoreceptors after long-term adaptation to different thermal conditions? (2) What may be the patterns of changes in functional characteristics of the peripheral and central thermoreceptors under the effect of various biologically active substances? (3) How are these changes manifest in the effector responses? (4) What may be the role of the different parameters of the activities (static and dynamic) of the peripheral skin thermoreceptors in the formation of the effector response? (5) Is there any difference in the physiological significance of various types of cold receptors? Here, attempts will be made to fill in the gaps in our knowledge by providing some answers to these and other open questions.

The accumulated facts indicate that the organism's thermal sensitivity changes when exposed to low temperature for a long time. The changes are manifest both as an attenuation of cold sensation (Kozyreva and Yakimenko, 1978; Kozyreva, 2005) and as a shift of the thresholds of

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the cold defense responses towards the range of lower temperatures (Bruck et al., 1970; Bruck and Zeisberger, 1978, 1986; Kozyreva and Verkhogliad, 1997). This may be taken to mean that changes in the regulatory characteristics of the thermal homeostasis system have occurred. The presence of regulatory changes suggests that changes in the pattern of the function of the central and peripheral thermoreceptors might have taken place. These receptors form the afferent signal that actually determines the organism's response to change in thermal conditions.

2. Effects of the long-term adaptation to cold

Let us consider how the characteristics of impulse activity of the hypothalamic thermosensitive neurons and skin thermoreceptors, temperature thresholds for cold defense response, and temperature sensation change after long-term adaptation to cold.

Changes in the activity patterns and in the thermal sensitivity of the central and peripheral thermoreceptors were conducted in rats using Hart's method of long-term cold adaptation (Hart, 1964): the rats were exposed to an environmental temperature of $+5^{\circ}\text{C}$ for 6 weeks. Food and water were provided ad libidum. The controls were maintained under similar conditions for the same time, with the difference that the temperature was $+20^{\circ}\text{C}$. The conditions of adaptation were the same in all our studies reviewed in this paper.

The behavior of the skin temperature in the area of *n. sapheni* innervation and rectal temperature during 6 weeks adaptation to cold is shown in Fig. 1. It is obvious that at the end of cold adaptation the rats in the cold have the same skin and rectal temperatures as control rats in the warm environment. This supports the idea that there should be another regulatory pattern of the temperature homeostasis maintenance.

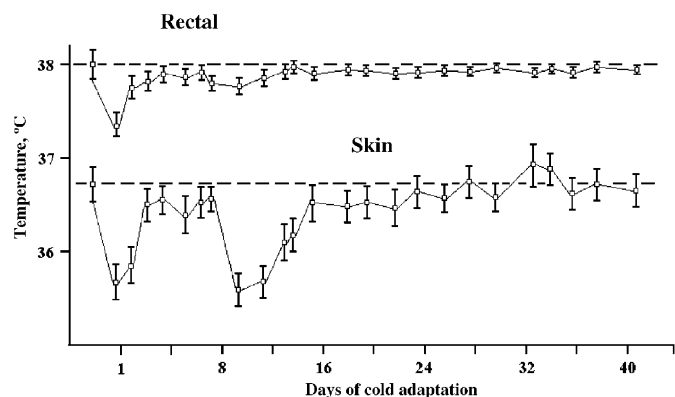


Fig. 1. The behavior of the skin temperature in the area of *n. sapheni* innervation and rectal temperature during 6 weeks adaptation to cold (23 rats). Dashed lines represent the mean skin and rectal temperatures in control rats (21 rats) in the warm environment. The recordings of temperatures were daily made. Bars are SEM (after data from Kozyreva, Yakimenko, 1979).

2.1. Central hypothalamic thermoreceptors

The central thermoreceptors of the medial preoptic area of the hypothalamus were studied in rat brain slices (Kozyreva and Pierau, 1994, 1995). The total number of thermosensitive neurons registered was 67, of these 30 were from the control and 37 from cold-adapted rats. Cells with thermal coefficients greater than 0.6 imp/s per 1°C were regarded as thermosensitive, i.e. the impulse activity of neurons changed by 0.6 or more impulses per second when temperature decreased or increased by 1°C (Boulant, 1981; Boulant and Silva, 1988; Pierau et al., 1989). Only one neuron in control animal was cold sensitive, as its activity was increased by lowering the temperature and decreased by its raising. No cold-sensitive neurons were found in the cold adapted rats. Three groups of warm sensitive neurons were distinguished both in the control and cold-adapted rats (Fig. 2A): (1) neurons sensitive to change in temperature in the $35\text{--}38^{\circ}\text{C}$ range and insensitive in the range of $38\text{--}41^{\circ}\text{C}$; (2) neurons sensitive to change in temperature in the $38\text{--}41^{\circ}\text{C}$ temperature range and not in the range of $35\text{--}38^{\circ}\text{C}$; (3) neurons sensitive to change in temperature in all the range of temperatures from 35 to 41°C .

After the organism's adaptation to cold, the portion of neurons sensitive in the low-temperature range ($35\text{--}38^{\circ}\text{C}$) decreases. On the contrary, the portion of neurons sensitive in the high-temperature range ($38\text{--}41^{\circ}\text{C}$) increases and their number is markedly prevalent (Fig. 2B). This may evidence for a decrease in the central hypothalamic sensitivity in the low-temperature range and for its increase in the high-temperature range. It is of interest that a nocturnal increase in the number of warm sensitive neurons in the preoptic hypothalamic area is observed when body temperature at this time is maintained at a lower level compared to its diurnal (Pierau et al., 1994).

2.2. Peripheral skin thermoreceptors

As for the peripheral thermal receptors, the view was long held that they do not undergo adaptive changes. At variance with this view, our studies in rats (Kozyreva and Yakimenko, 1979; Kozyreva, 1992) as well as studies in cats (Hensel and Schefer, 1982) demonstrated that the pattern for the function of the skin cold receptors substantially changed during the organism's adaptation to cold.

The impulse activity of the skin cold receptors in *n. sapheni* filaments was investigated in control (87 fibers) and long-term cold adapted (72 fibers) rats (Kozyreva and Yakimenko, 1979; Kozyreva, 1992).

In the control rats, we clearly distinguished two groups of cold receptors (Fig. 3) differing by their frequency characteristics and the temperature range of their maximum activity static (discharge rate at a constant temperature) and dynamic (transient increase in discharge rate during rapid change in temperature). In the controls, the

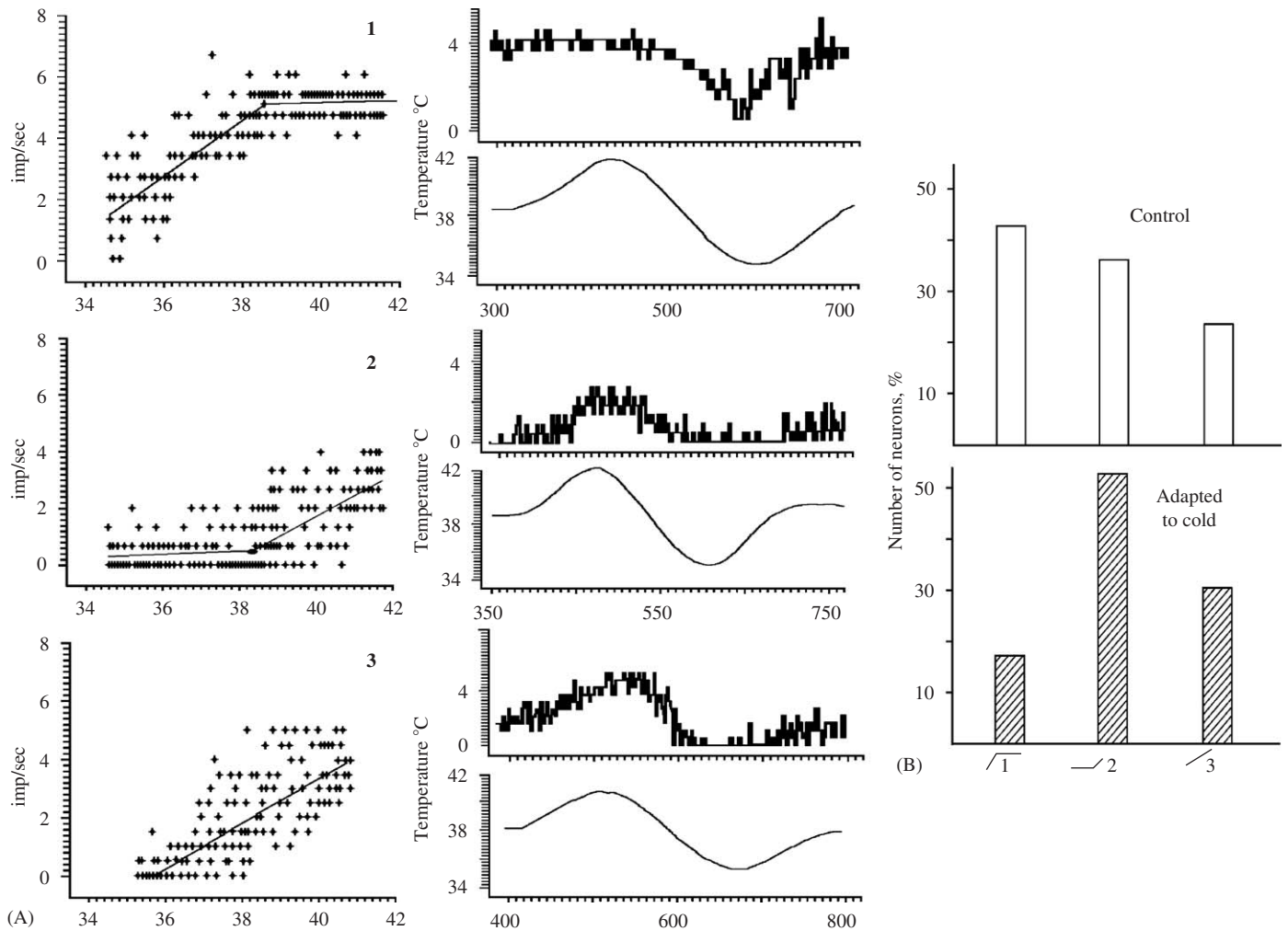


Fig. 2. Examples of thermosensitive neurons of different types in the hypothalamic preoptic area (A) and change in their relative portion (%) after long-term adaptation of organism to cold (B). The total number of thermosensitive neurons registered was 67: 30 were from the control and 37 from cold-adapted rats (figure from Kozyreva, Pierau, 1994).

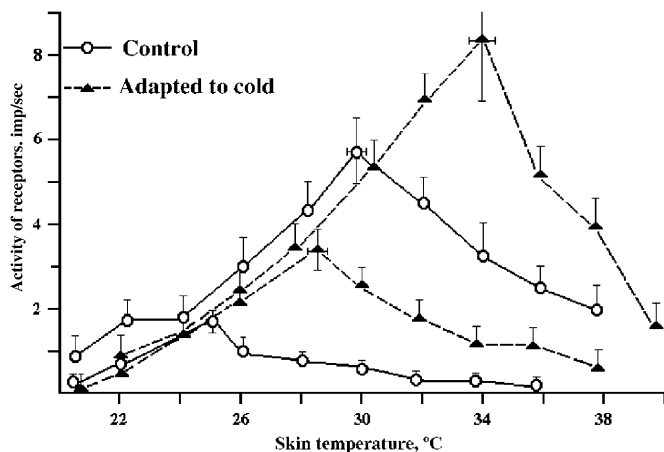


Fig. 3. The mean values of static activity of two dominant groups of skin cold receptors in control (firm lines) and two dominant groups of skin cold receptors in long-term cold adapted (dashed lines) rats. Values \pm SE. For explanation, see the text (after data from Kozyreva, Yakimenko, 1979; Kozyreva, 1992).

low-frequency receptors, whose static activity was less than 1 imp/s at skin temperature of 34–36 °C, showed maximum thermal activity in the range of lower temperatures of 24–25 °C—the first group of cold receptors, their portion was about 27% (Fig. 4). The most (about 70%) skin cold receptors in control rats had a static activity from 1 to 4 imp/s at skin temperature of 34–36 °C, and their maximum static and dynamic activity was in the 28–30 °C temperature range—the second group.

After the organism's adaptation to cold, the portion of the low-frequency cold receptors (the first group), the receptors most sensitive in the low-temperature range, decreased considerably (they virtually disappeared). The portion of the high-frequency cold receptors with a maximum at 28–30 °C (the second group) was about 70% like in control but they showed a decrease in static activity about twofold (Fig. 3). However, we clearly distinguished a group of higher frequency cold receptors with maximum activity shifted to the high-temperature range 34–35 °C

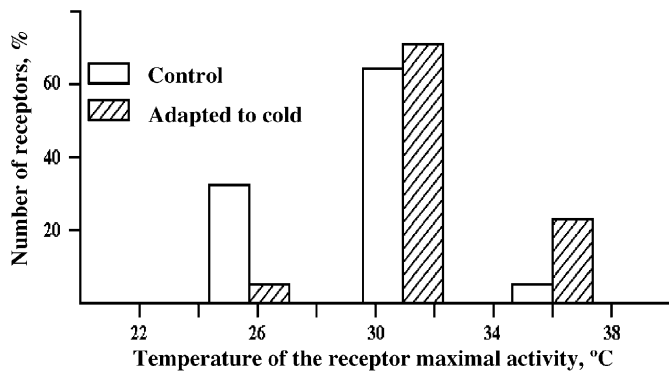


Fig. 4. Relative portion (%) of different groups of skin cold receptors in control (87 fibers) and long-term cold adapted (72 fibers) rats. For explanation, see the text (after data from Kozyreva, Yakimenko, 1979; Kozyreva, 1992).

(third group). The portion of these cold receptors was about 27% in cold adapted rats and they were practically absent in control animals (Fig. 4). The dynamic response to a rapid decrease in temperature of the cold receptors showing maximum activity at $28\text{--}30^\circ\text{C}$ decreased twofold after adaptation to cold (from 1.4 ± 0.2 to 0.7 ± 0.1 imp/s per 1°C , $P < 0.05$). There was no change in the dynamic response of other groups of the skin cold receptors. So, in cold adapted animals the most part of the skin cold receptors (70%) showed the reduced static and dynamic activity and the portion of the low-frequency cold receptors most sensitive in the low-temperature range, decreased.

Thus, under long-term adaptation to cold the sensitivity of both the central and peripheral thermoreceptors decreases in the low-temperature range and increases in the range of high temperature. This is consistent with the data indicating that, after adaptation to cold, the organism admits a greater reduction in body temperature, without triggering cold defense responses and also with the observation that it is easier to produce overheating and switch on heat loss responses in cold adapted animals (Bruck et al., 1970; Cabanac, 1975; Bruck and Zeisberger, 1978, 1986; Kozyreva and Verkhogliad, 1997).

2.3. Thermoreceptor activity and the initiation of the effector response

The rate of external cooling is of important for the skin thermoreceptor discharge rate, i.e. the formation of the afferent thermal signal. Studies concerned with the registration of the skin receptor impulse activity have demonstrated that the dynamic response of the cold receptors increases (Davies et al., 1983) and the cold sensation threshold decreases with increase in cooling rate (Kenshalo, 1984). Our studies established a dependence of the thermal thresholds for the cold defense responses on cooling rate (Kozyreva, 1996, 2000; Kozyreva and Verkhogliad, 1997). At low rates of external cooling, when skin temperature changes slower than $0.01\text{--}0.02^\circ\text{C/s}$ and the dynamic activity of the cold receptors is low, if at all

present, the contribution of both the deep body and skin temperatures are required to trigger the effector responses, that is the involvement of both the central and peripheral thermoreceptors. For example, one can see in Fig. 5 at slow cooling in control rats in the range of cooling rate from 0 to 0.013°C/s and in cold adapted rats in the range of $0\text{--}0.033^\circ\text{C/s}$ the metabolic response is initiated when both the skin and rectal temperature are lowered. In the presence of the dynamic activity of the skin cold receptors, at higher cooling rates (>0.013 in control and $>0.033^\circ\text{C/s}$ in cold adapted), the metabolic response can be observed even when the core temperature is unaltered and further increase in cooling rate result in elevation of the threshold skin temperature for the metabolic response, i.e. threshold decreases with increase in cooling rate. As indicated above, after the organism has adapted to low temperature, the dynamic response of the cold receptors decreases considerably and the patterns of slow cooling spread over to a

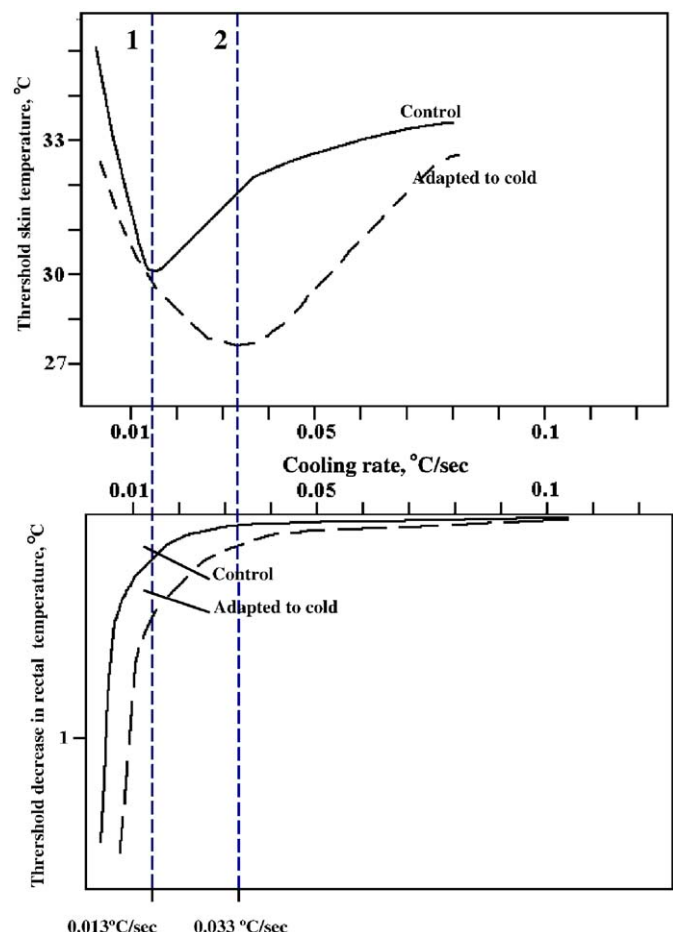


Fig. 5. Top, threshold skin temperature (absolute skin temperature at response onset); bottom, threshold decrease in rectal temperature at the metabolic response onset in control and cold adapted rats related to the skin cooling rate. Dashed vertical lines 1 and 2 show the values of cooling rate at which the order of thermoregulatory responses at slow cooling changes to those at rapid cooling in control (at 0.013°C/s) and in cold adapted (at 0.033°C/s) animals. The curves were calculated from the data obtained from 35 control and 43 cold adapted rats. $P < 0.01$ for all curves (figure from Kozyreva, 1996).

wider range of cooling rates up to $0.33\text{ }^{\circ}\text{C/s}$ (dashed vertical line 2) compared with $0.13\text{ }^{\circ}\text{C/s}$ in the control (dashed vertical line 1) and the regularities of slow cooling are spread to a greater cooling rates.

2.4. Temperature sensation

The inflow of afferent thermal information depends on the amounts of impulse activity and the number of functioning receptors. We made an attempt to estimate

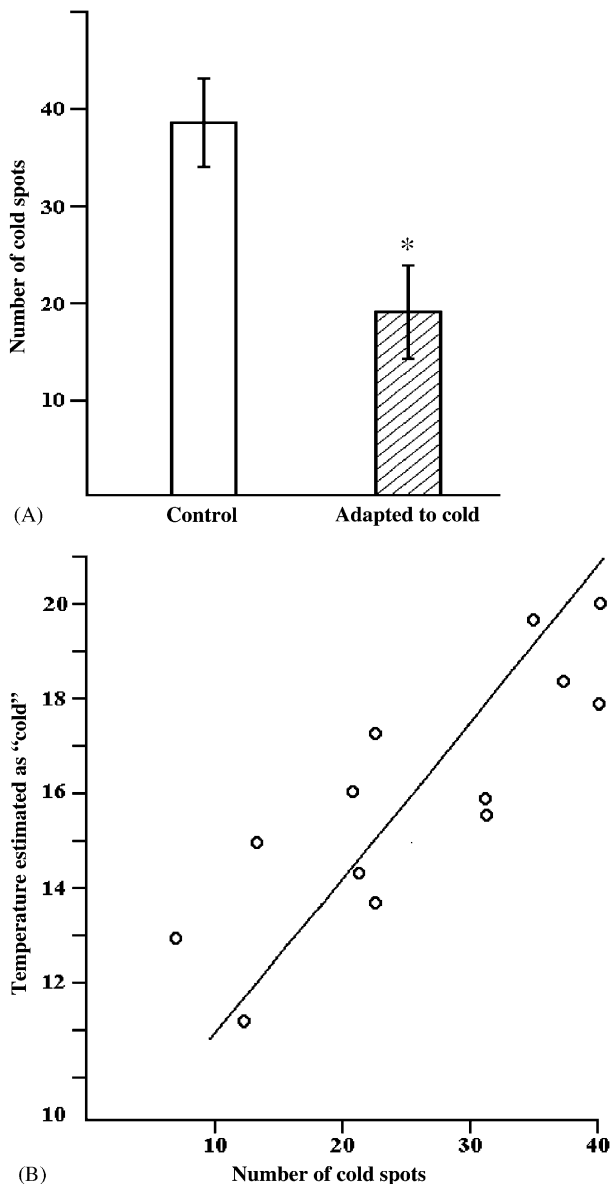


Fig. 6. (A) Change in the number of cold spots in arm after human adaptation to cold. The number of cold spots was calculated in 100 spot matrix on a 25 cm^2 surface of the internal forearm skin with the temperature of thermode as $+3$ to $4\text{ }^{\circ}\text{C}$ in a climatic chamber at $26\text{ }^{\circ}\text{C}$, 65 control and 36 cold adapted persons. Values \pm SE. $*P < 0.05$. (B) Dependence of environmental temperature value estimated as "cold" on the number of cold spots in arm. $y = 12 + 0.19x$; $r = 0.77$; $P < 0.01$ (after data from Kozyreva and Yakimenko, 1978; Kozyreva, 2005).

how the number of functioning (sensitive) skin cold receptors may change in humans long exposed to cold, because in animals this is impossible. It is known that every cold (warm) spot 1 mm in diameter is innervated by at least one cold receptor (Kenshalo and Galegos, 1967; Hensel et al., 1974). Thus, the number of functioning cold (warm) receptors may be estimated from that of the sensitive cold (warm) spots. The number of cold and warm spots was tested with the temperature of thermode as $+3$ to $4\text{ }^{\circ}\text{C}$ for cold spots and as $41\text{ }^{\circ}\text{C}$ for warm spots in 100 spot matrix on a 25 cm^2 surface of the internal forearm skin. The tests were carried out in a climatic chamber at $26\text{ }^{\circ}\text{C}$ (thermoneutral conditions for human without clothes). It proved that in builders that work out of doors in winter time in the conditions of Siberia and the Far North (cold adapted persons) the number of cold spots is decreased (Kozyreva and Yakimenko, 1978; Kozyreva, 2005). It decreased twofold in the arm, for example (Fig. 6A). The number of warm spots was unaltered. Studies we performed in climatic chamber showed that the ambient temperature is sensed as "cold" by an unclothed subject is directly related to the number of cold spots in the arm (Fig. 6B). This allows to conclude that the organism's adaptation to cold results in a decrease in the number of functioning cold receptors and in a reduction of cold sensation (perception), i.e. the elevation in the cold sensation threshold.

Based on the above observations, the changes brought about by the organism's adaptation to cold are as follows (Fig. 7): (1) a decrease in the sensitivity of the hypothalamic neurons in the low body temperature range and increase in high-temperature range; (2) a decrease in the dynamic and static activities of the high-frequency skin cold receptors; (3) a considerable decrease in the portion of the active low-frequency skin cold receptors; (4) a decrease in the number of cold spots, i.e. a decrease in functioning skin cold receptors providing sensation of low temperatures and (5) an elevation of the threshold for cold sensation and cold defense effector responses.

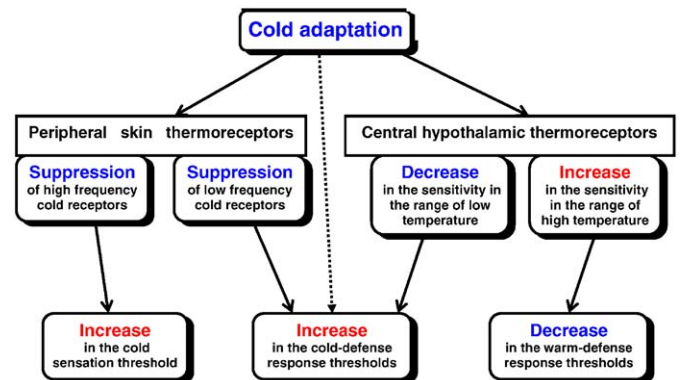


Fig. 7. A scheme of the long-term cold adaptation influence on the central and peripheral thermoreceptor activity and some parameters of effector responses according to presented data.

3. Effects of noradrenaline

The question rises what is the mechanism of these regulatory characteristic changes? The effect of biologically active substances on the central and peripheral thermoreceptors may underlie the changes in the function (sensitivity) of the thermal receptors during organism's adaptation to cold. Noradrenaline, a mediator of the sympathetic nervous system, is of special interest. Recently, it is brought out clearly that noradrenaline participates in the response of organism to cold. There are numerous reports on the activation in the sympathetic nerve activity and the increase in level of noradrenaline in blood under cold temperature exposure (Barrand et al., 1981; Depocas and Behrens, 1978; Depocas et al., 1978; Bruck and Zeisberger, 1978; Jansky, 1995; Kozyreva et al., 1999b).

Let us now examine in sequence the effect of noradrenaline on the same characteristics of the thermoregulatory system as those we studied for long-term adaptation to cold: (a) thermal characteristics of the central hypothalamic thermoreceptors and (b) of the peripheral skin cold receptors, (c) the thresholds of the cold defense responses during selective modulation of the central or peripheral thermoreceptors and also (d) thermal sensation.

3.1. Central hypothalamic thermoreceptors

Our studies on survival brain slices (Kozyreva and Pierau, 1994) have demonstrated that a stationary increase in the concentration of noradrenaline (perfusion of 10^{-6} noradrenaline) modifies the pattern of thermal sensitivity of the hypothalamic thermosensitive neurons (Fig. 8). Under the influence of noradrenaline the sensitivity of these neurons in the low-temperature range (35–38 °C) somewhat increases, the thermal coefficient increases by 30%, and, in contrast, in the high-temperature range (38–41 °C), the sensitivity considerably decreases, the thermal coefficient decreases twofold (from 1.3 ± 0.15 to 0.61 ± 0.10 imp/s per 1 °C). The latter may result in increased defense of the organism from overheating after its adaptation to low environmental temperature. It is noteworthy that changes in the thermal sensitivity of the central hypothalamic thermoreceptors during the organism's adaptation to cold are the reverse to those observed when noradrenaline concentration increases in the hypothalamic area.

3.2. Peripheral skin thermoreceptors

As for the peripheral skin thermoreceptors, our studies (Kozyreva, 1997) using intravenous noradrenaline infusion (10 ng/g min, the rate of infusion 0.03 ml/min) demonstrated the following. An increase in the concentration of noradrenaline affects both the static and dynamic activities of the skin cold receptors (Fig. 9). The effect may be different, depending on the functional characteristics of the skin cold receptors. The low-frequency cold receptors, as it

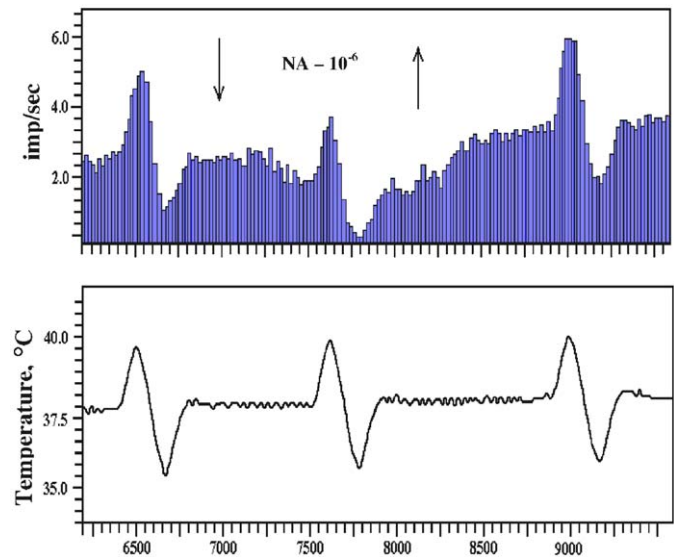


Fig. 8. An example of change in the impulse activity of a neuron of the hypothalamic medial preoptic area under the effect of temperature before, during and after noradrenaline 10^{-6} perfusion. Abscissa, time in seconds. Arrows indicate the start and end of noradrenaline perfusion. The effect of NA was studied in 19 hypothalamic neurons in control and 23 neurons in cold adapted rats. The changes in mean values of temperature coefficients calculated for all studied neurons in control and cold adapted animals, see in text (figure from Kozyreva and Pierau, 1994).

was mentioned above, showing maximum sensitivity in the low-temperature range (24–25 °C), at elevated noradrenaline concentration increased their activity and sensitivity to cooling (Fig. 9A). It will be recalled that precisely the activity of these receptors decreases during adaptation to cold. In contrast, the high-frequency cold receptors showing maximum activity and sensitivity in the higher temperature range (28–30 °C) decreased their activity and sensitivity to cooling under the effect of increased noradrenaline concentration (Fig. 9B). The latter is coincident with the observations made for the organism's long-term adaptation to cold.

3.3. Thermoreceptor activity modulation and the initiation of the effector response

This raised the question as to whether and how the modulating effect of noradrenaline on the central and peripheral skin thermoreceptors may influence characteristics, such as the thermal thresholds of the effector responses. According to Bruck and Zeisberger (1978, 1986; Zeisberger, 1978) the threshold of the metabolic response (shivering, oxygen consumption) shifts to the higher temperature range, i.e. the threshold lowers during iontophoretic application of noradrenaline to the hypothalamic area when it acts predominantly on the central thermoreceptors (Fig. 10). According to our observations (Kozyreva et al., 1997, 1999a, 2001) iontophoretic application of noradrenaline to the skin to the site of the action of the cold stimulus, i.e. when noradrenaline acts predomi-

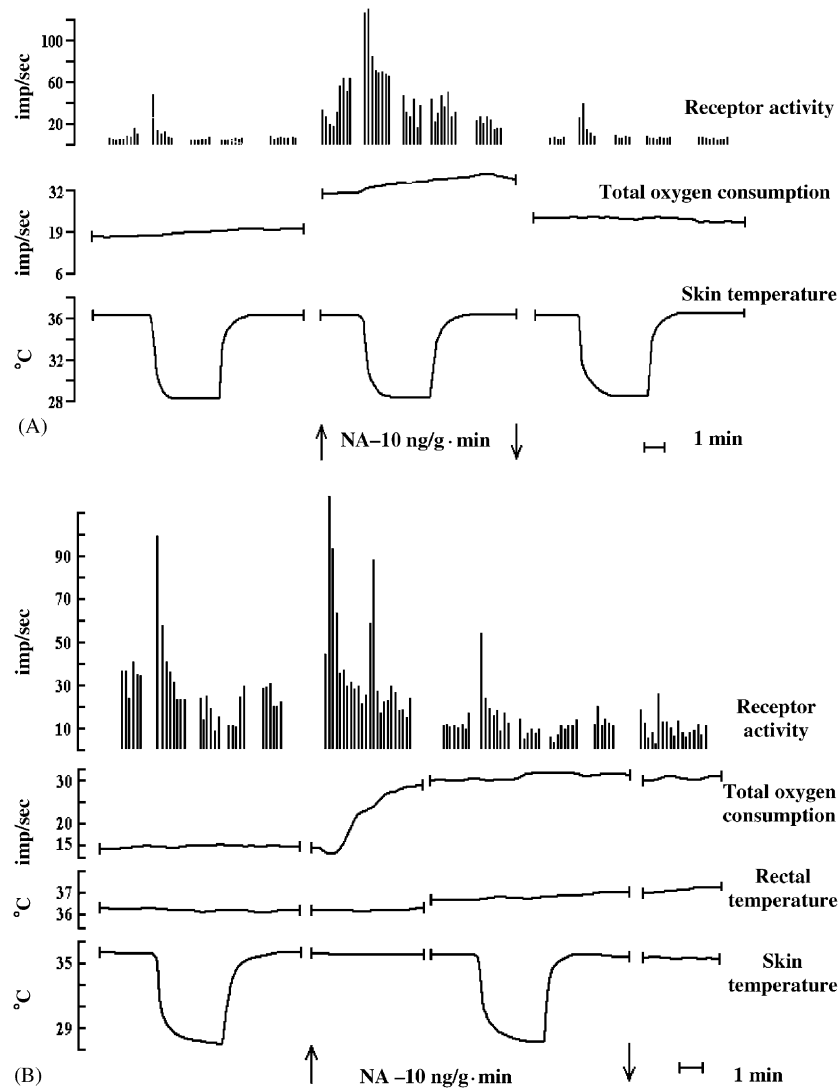


Fig. 9. An examples of change in the static and dynamic activity of low-frequency (A) and high-frequency (B) cold skin receptors in the area of *n. sapheni* innervation, total oxygen consumption and rectal temperature under the effect of intravenous noradrenaline infusion (10 ng/g min, 0.03 ml/s). Totally 28 cold receptors were studied in this series (figures from Kozyreva, 1997).

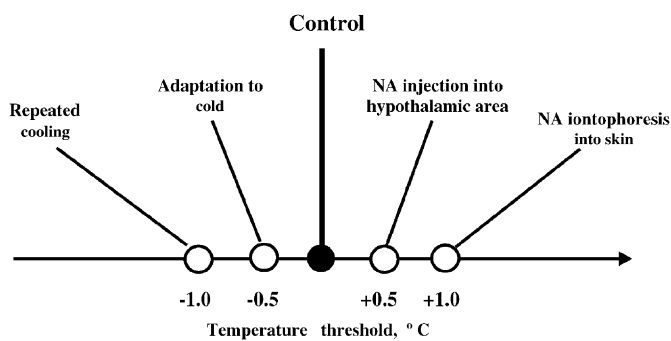


Fig. 10. Shifts of temperature threshold for metabolic response at different conditions: repeated cooling, long-term adaptation to cold, noradrenaline injection into hypothalamic area, noradrenaline iontophoresis into skin. Control—accepted as “0” means threshold for metabolic response to the first test cooling in animals living at 20–22 °C.

nantly on the peripheral thermoreceptors, the metabolic response to cooling also shifts to the higher temperature range (the threshold lowers); this is like noradrenaline

acting on the central hypothalamic thermoreceptors (Fig. 10). The reported experimental results in cold adapted animals have demonstrated quite the reverse (Bruck and Zeisberger, 1986; Kozyreva and Verkhogliad, 1997; Kozyreva et al., 1999a). Long-term adaptation of organism to cold, as well as repeated cooling, result in an elevation of the metabolic response threshold, i.e. the threshold temperature shifts to the lower temperature range, the organism allows deeper cooling without triggering the defense responses.

3.4. Temperature sensation

Judging by our results in humans (Kozyreva et al., 2001), iontophoretic noradrenaline application to the skin of the right arm (0.16 mA/cm², 20 min) produced a decrease in the number of cold spots in the iontophoretic area without associated significant change in temperature in this area (Fig. 11). In the left arm, the number of cold spots

remained unaltered. The number of warm spots did not change in both the area of iontophoresis application of the right and the left arms. Hence, an increase in noradrenaline concentration in the skin in the area where the thermoreceptors are concentrated—produces a decrease in the number of functioning cold receptors which leads to an elevation in the cold sensation threshold.

Thus, the following takes place under the effect of noradrenaline (Fig. 12): (1) the sensitivity of the hypothalamic thermosensitive neurons increases in the low-temperature range and decreases in the range of high temperatures, the reverse of what is observed for long-term adaptation to cold; (2) the static and dynamic activity of the high-frequency skin cold receptors decreases, which is similar to changes in adaptation to cold; (3) the impulse activity of the low-frequency skin cold receptors increases, the reverse of what is observed for long-term adaptation to cold; (4) the number of cold spots and cold sensation decrease, this is consistent with changes produced by adaptation to cold; (5) the thresholds of the cold defense responses decrease under the preferential effect of noradrenaline on the central and peripheral receptors, the reverse of what is observed for the organism's adaptation to cold.

Thus, the patterns for the function of the central and peripheral thermoreceptors change both during the organism's adaptation to cold and under noradrenaline effect. This is associated with shifts of a set of regulatory parameters of the thermal homeostasis system. Noteworthy is the fact that the organism's long-term adaptation to cold and noradrenaline differently modulates certain properties of the central and peripheral thermoreceptors. Thus, noradrenaline and adaptation to cold have a reverse effect on the central thermoreceptors and the low-frequency skin cold receptors that show maximum sensitivity in the low-temperature range. These reverse influences are possibly manifest as the opposite shift of the cold defense responses during the organism's adaptation to cold and the preferential action of noradrenaline on the central or

peripheral thermoreceptors. It is possible that this group of the low-frequency skin cold receptors is predominantly related to the metabolic cold defense response initiation. As to the high-frequency skin cold receptors, the effects of adaptation to cold and noradrenaline are the same in that a decrease in their static and dynamic activities occurs in both cases. It may be suggested that precisely this group of the high-frequency skin cold receptors is predominantly related to the sensation function. Evidence in favour of this possibility is also the reduction in the number of cold spots during cold adaptation and under noradrenaline effect.

Recent investigations suggest the molecular bases for these different groups of thermoreceptors. According to this new information, distinct populations of primary afferent neurons may express some thermosensitive ion channels, which are activated in different temperature ranges. The functional properties of various thermoreceptors (thermosensitive afferent fibers) can be determined by the combinations of different TRPM and TRPV channels, as well as temperature dependent K^+ and Na^+ Ca^{2+} ion channels (Viana et al., 2002; Jordt and Julius, 2002;

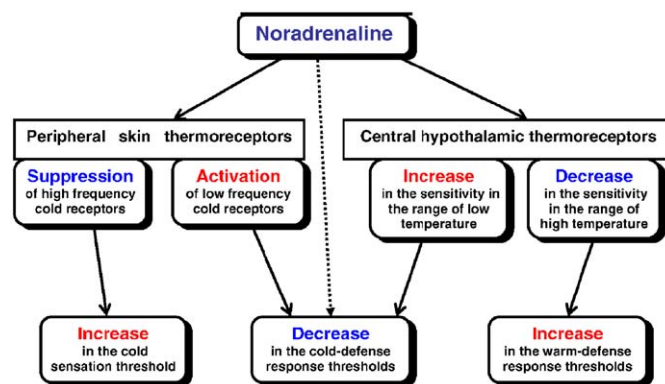


Fig. 12. A scheme of the noradrenaline influence on the central and peripheral thermoreceptor activity and some parameters of effector responses according to presented data.

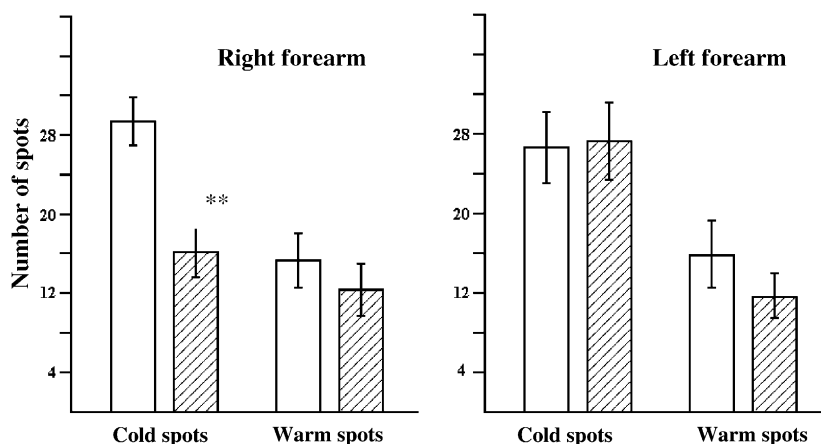


Fig. 11. Number of cold and warm spots in the forearm area (25 cm^2) in human before (open columns) and after (shaded columns) local iontophoretic application of noradrenaline (0.16 mA/cm^2 , 20 min) to the right forearm skin. Values \pm SE. ** $P < 0.01$ (figure from Kozyreva et al., 2001).

McKemy et al., 2002; Jordt et al., 2003, Naalen et al., 2003).

The obtained results also provide evidence indicating that the changes in thermoregulatory characteristics during long-term adaptation of the organism to cold are not explicable only by changes in the activity of the sympathetic nervous system; rather they are also related to the modulating action of other biologically active substances on the thermoreceptors. There are experimental data for the dependence of cold sensitivity and thermoreceptor activity on the concentration of calcium ions (Hensel and Schafer, 1974; Pierau et al., 1983; Schafer et al., 1988, 1990; Ivanov, 1996). Our data (Kozyreva et al., 1987) showed that calcium concentration in blood decreased in long-term cold adapted rats by 10% and in human by 20%. This decrease may be caused by the accumulation of calcium in mitochondria of some cells (Greenway and Himms-Hagen, 1978; Tsai et al., 2001). Moreover, in human the concentration of calcium ions in blood directly correlated with the number of cold spots in the forearm (Kozyreva et al., 1987). However, the data are as yet insufficient for validation of analysis of this kind.

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