Effects of Neokyotorphine and δ-Sleep-Inducing Peptide on Rectal Temperature of Rats in Health, Hypothermia, and during Self-Warming

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Neokyotorphine raises rectal temperature of rats in normothermia and accelerates self-warming. δ-Sleep-inducing peptide exerts an opposite effect and "masks" the effect of neokyotorphine upon combined administration of these agents.

Key Words: *rectal temperature; hypothermia; self-warming; neokyotorphine; d-sleep-inducing peptide*

Compensatory processes occuring in an organism exposed to low temperature attract the attention of scientists due to a wide use of cold narcosis and craniocerebral hypothermia in practical medicine. Studies of physiological effects of substances involved in the hibernation mechanisms, which permit the hibernating animals sustain unfavorable conditions at body temperature 3-5°C and rapidly awake after hibernation, are promising for the development of methods correcting the disorders caused by deep hypothermia.

The neuropeptide neokyotorphine (NKT) isolated from the cerebral fraction a hibernating *Citellus undulatus* is one of such substances [7,8].

Endogenous neuropeptides with regulatory effects have been used for correction of dysfunctions, for example, δ-sleep-inducing peptide (DSIP) whose antistress effect was demonstrated [2,4,5].

Our purpose was to study the effect of intraperitoneal injection of NKT, DSIP, and their combination on body temperature of rats in normothermia, hypothermia, and during self-warming.

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MATERIALS AND METHODS

Outbred albino rats weighing 120-150 g were used. Hypothermia (2.5 h) was induced in a special chamber-hole with regulated water cooling. Rectal temperature was recorded with a thermal pickup (accuracy 0.01°C). Water temperature in the chamber was 8°C. At the beginning of hypothermia rectal temperature decreased to 18°C and was maintained at this level until the rats were removed from the chambers. After hypothermia the animals were put in cages and left there at 20°C. The following protocols were used:

1) NKT intraperitoneally in a dose of 500 μg/kg 1.5 h before hypothermia;

2) DSIP intraperitoneally in a dose of 120 μg/kg 1 h before hypothermia;

3) both neuropeptides before cooling: NKT in a dose of 500 μg/kg 1.5 h before cooling and DSIP intraperitoneally in a dose of 120 μg/kg 1 h before cooling.

The doses were chosen on rats in previous experiments [1,6].

Control rats were injected with 0.5 ml/100 g 0.9% NaCl 1.5 h before hypothermia.

Rectal temperature measurements were averaged for each experimental series and used for plot-

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ting dynamic series. The rate of self-warming was estimated by the basic method. The significance of changes was evaluated by Student's *t* test.

RESULTS

A negligible (no more than 0.16°C) increase of rectal temperature was observed in the rats injected with normal saline (controls) during the entire period before hibernation, which was apparently caused by the injection procedure (Fig. 1, *4*).

NKT led to a statistically significant increase in rectal temperature in comparison with the initial value and with the temperature after injection of normal saline. Figure 1, *1* shows that the increase has three peaks: 25 ($p<0.05$), 45 ($p<0.01$), and 70 min ($p<0.05$) after injection of NKT; the second peak was the highest: the temperature increased by 1°C. After 1.5 h changes in body temperature were insignificant in comparison with the initial level.

In contrast to NKT, DSIP decreased rectal temperature, which is in line with published reports [3]. The greatest deviation (by 0.55°C, $p<0.001$) from the initial level was observed 55 min after intraperitoneal injection of DSIP (Fig. 1, *2*).

Injection of DSIP to animals whose temperature was increased by 0.84°C by NKT decreased body temperature to the initial level in 5 min and caused a further gradual decrease to the minimum level ($\Delta t=0.47$°C, $p<0.01$) by the 60th min of experiment. Then the temperature gradually normalized: 90 min after the first injection it was virtually at the initial level (Fig. 1, *3*).

Therefore, pretreatment with NKT modifies DSIP effect by reducing the prolonged decline in rectal temperature (the maximum Δt of 0.55°C decreases to 0.48°C).

In all series, rectal temperature of 18°C was attained at a rate of 0.23±0.01°C/min.

The pattern and rate of cessation of hypothermia were different in different experimental groups. Rats treated with NKT reached the initial temperature 40 min sooner than rats injected with normal saline. By contrast, animals treated with DSIP or both peptides warmed themselves 20 min later. Differences in the duration of self-warming were the greatest in the group injected with both NKT and DSIP (Fig. 2). The time course of the initial temperature recovery was different in different experimental series. In rats injected with normal saline the mean rate of self-warming increased from 0.02 to 0.2°C/min until rectal temperature of 35°C, after which it decreased again and was 0.09°C/min. The rate of self-warming of animals injected with NKT was constant starting from the moment when cold exposure ceased (0.18°C/min), decelerating to 0.07°C/min at the 335th min of experiment (34.9°C). In rats injected with both peptides and DSIP the rate of self-warming was at first slower than in the controls (0.05 and 0.04°C/min, respectively, during the first 1.5 h) and then faster (0.15 and 0.16°C/min, respectively).

Thus, NKT and DSIP affect temperature regulation in rats during normothermia and self-warming after hypothermia. Endogenous neuropeptide NKT, a hypothetical inducer of awakening of hibernating ground squirrels, accelerated self-warming of rats by enhancing the intensity of thermogenesis at the initial stages of transfer from hypothermic to normothermic state. By contrast, injection of DSIP decreased rectal temperature of animals and decelerated the rate of transfer from hypothermia at the initial stages of the process. Despite a later increase in the rate of self-warming, the animals reached the initial body temperature much later than after injection of NKT or normal saline. The effect of the universal adaptogen DSIP is probably aimed at maintaining a smooth gradual transfer from one

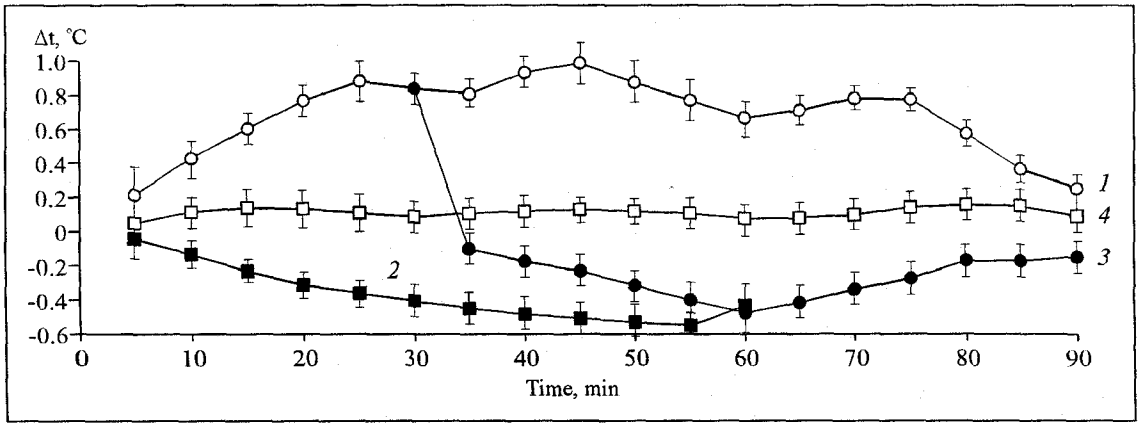

Fig. 1. Changes in rectal temperature in comparison with the initial level before hypothermia. Here and in Fig. 2: *1*) neokyotorphine; 2) δ-sleep-inducing peptide; 3) both peptides; *4*) normal saline.

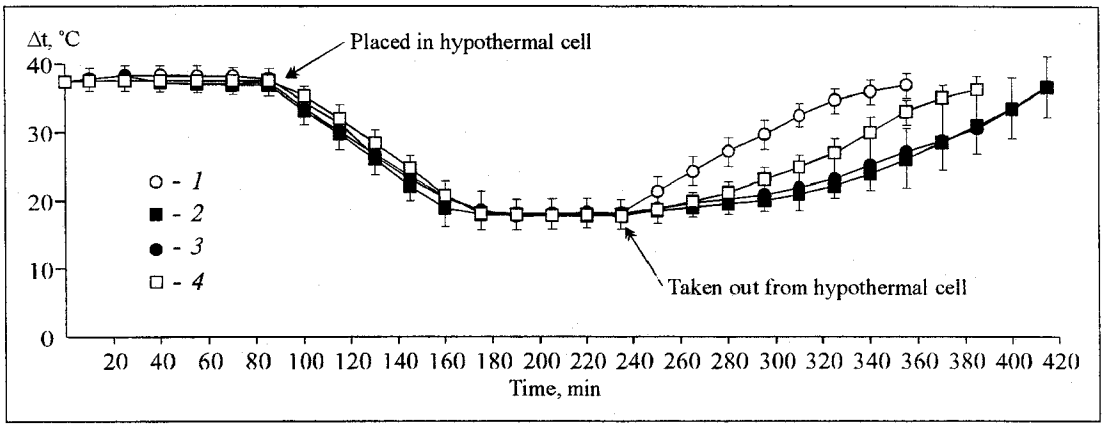

Fig. 2. Changes in rectal temperature of rats in normothermia and during cooling and self-warming.

state into another, in order to minimize the probability of damage to systems of the organism inflicted by abrupt temperature differences. It should be noted that DSIP masks the effect of NKT.

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