Effect of Dermorphin on the Development of Compensatory Thermoregulatory Vascular Reactions under Conditions of Overheating

T. G. Emel'yanova, A. B. Usenko, V. I. Deigin, and E. P. Yarova

UDC 612.1.014.46:615.212.7:547.943].08

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 118, No. 8, pp. 151-153, August, 1994
Original article submitted August 4, 1993

Dermorphin injected intraperitoneally is shown to inhibit the formation of compensatory vascular reactions. The effect of the peptide depends on the dose and on the rate of changes of ambient temperature.

Key Words: *thermoregulation; overheating; dermorphin*

There are some published data on a thermoregulatory effect of opioids [7]. Some of these compounds (morphine, β-endorphin, met-enkephalin, and dermorphin) exhibit a complex dose- and temperature-dependent effect: intracerebral administration of opioids to animals exposed to low temperatures results in hypothermia, which lessens as the ambient temperature rises and in some cases gives way to hyperthermia in a hot environment [3,6,10,11,13,14]. In this group of opioids dermorphin (H-Tyr-dAla-Phe-Gly-Tyr-Pro-Ser-NH_2) is of special interest and is characterized by a number of features: at present it is one of the most potent analgesics, a highly specific agonist of the opiate μ-receptors; due to the presence of dAla in the second position, this heptapeptide is resistant to peptidases [2,5,9,12]. Previously we showed that the nature of the thermoregulatory activity of dermorphin is preserved for peripheral (intraperitoneal) administration [8]. Moreover, peptide-induced changes in the body temperature are accompanied by a complex of peripheral vascular reactions, the dynamics of which in some cases does not agree with that of the body temperature. The data on central administration of dermorphin to animals adapted to various temperatures suggest that the peptide acts on the central mechanisms of set point regulation [4]. We believe that dermorphin may affect the sensitivity of thermoreceptors.

To elucidate this question, we studied the effect of dermorphin administered intraperitoneally on the development of peripheral compensatory vascular reactions in rats in response to a rise of the ambient temperature.

Institute of Chemical Physics, Russian Academy of Sciences, Moscow. (Presented by I. P. Ashmarin, Member of the Russian Academy of Medical Sciences)

MATERIALS AND METHODS

The study was carried out on random-bred white rats weighing 180-250 g. Dermorphin synthesized at the Peptos plant was injected intraperitoneally in doses of 50 and 500 μg/kg (1 ml/kg) in aqueous solution. Control animals were injected the same volume of distilled water.

During the experiments the rats in individual plastic boxes were placed in a thermocontrolled chamber with a programmed temperature regime, and the following temperatures were continuously recorded: rectal (6-cm depth) - Trt; tail skin - Tt; air in the chamber - Tc.

We developed an experimental model which allows for two types of dynamic temperature influences:

0007-4888/94/0008-0841$12.50

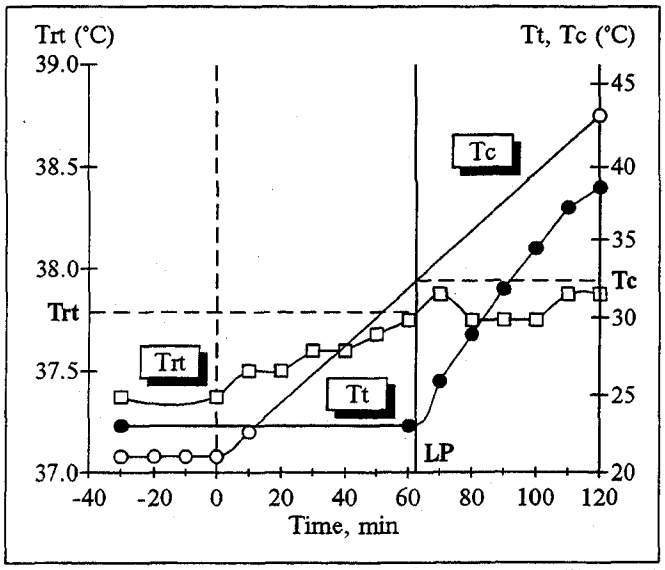

Fig. 1. Pattern of changes of body temperature (Trt) and tail skin temperature (Tt) during a monotonic rise of the ambient temperature (Tc) (regime of monotonic heating). Dotted lines: moment of injection of preparation and start of change of temperature regime; continuous line: moment of appearance of CVR.

a) monotonic heating - a gradual (0.2°C/min) rise of the air temperature (initial Tc=22.5-23°C);

b) displacement - an abrupt (10°C/sec) rise of the ambient temperature (transfer of animals from room temperature to a hot chamber, Tc=36°C).

Under these conditions a complex of compensatory reactions develops in the animals, aimed at getting rid of the excessive heat, thus preventing overheating of the organism and stabilizing the body temperature. One of the main components of this complex is dilatation of the peripheral vessels, which manifests itself in an abrupt rise of Tt, since the tail is a specific organ of heat exchange in rats.

For the prevention of a direct heat influence on the tail the rats were placed so that the tail was outside the chamber at a constant Tc.

The temperature regime was changed after a preliminary 60-min adaptation to the initial experimental conditions (when Trt and Tt of each animal remained practically unchanged during at least 30 min). The injections were performed immediately before the changes in temperature regime. The following parameters were recorded:

$$Tort=(Trt(-30)+Trt(-20)+Trt(-10)/3,$$

where Trt(-30), Trt(-20), and Trt(-10) are Trt measured 30, 20, and 10 min before the changes in the temperature regime; LP is the latent period of the compensatory vascular reaction (CVR), or the time (min) elapsing from the change of the temperature regime to the start of a sharp rise of Tt; Trt is the threshold Trt corresponding to the CVR:

$$\Delta Trt=Trt-Tort;$$

Tc is the threshold Tc corresponding to the CVR (under conditions of MH):

$$\Delta Tc=Tc-Toc.$$

Figure 1 demonstrates the dynamics of the recorded parameters in one animal under conditions of MH. Under conditions of displacement Trt and Tt change analogously, while Tc changes abruptly.

Ten animals were tested simultaneously, five of which were controls.

The results were processed statistically using the Student *t* and nonparametric Wilcoxon tests.

RESULTS

Two afferent impulses are known to cause CVR during the rise of body temperature in response to a rise of the ambient temperature: from thermosensitive peripheral receptors (body surface) carrying information about the external temperature and from receptors of internal organs carrying information about the body temperature.

Under conditions of monotonic heatinga vasodilatory reaction arises in response to significant changes of body temperature (Table 1). Tort reliably differed from the threshold value Trt, which

TABLE 1. Effect of Intraperitoneal Injection of Dermorphin on the Development of a Compensatory Vascular Reaction (Vasodilation) in Rats under Conditions of Monotonic Heating

Group	Number of animals	Tort,°C	Vasodilation reaction				
			LP, min	Tc,°C	ΔTc,°C	Trt,°C	ΔTrt,°C
Control	15	37.6	69.3	33.6	11.3	38.0°	0.35
Dermorphin, 50 μg/kg	15	37.6	72.4	34.3	11.9	37.9°	0.34
Control	20	37.6	70.6	34.1	12.0	37.8°	0.27
Dermorphin, 500 μg/kg	20	37.4	82.4*	35.9**	13.7**	37.8°°	0.51*

Note. Here and in Table 2 one and two asterisks denote reliability of differences from control by the Student *t* test for $p<0.05$ and $p<0.005$, respectively, and one and two circles denote reliability of differences from control by the Wilcoxon test for $p<0.05$ and $p<0.001$, respectively.

TABLE 2. Effect of Intraperitoneal Injection of Dermorphin on the Development of a Compensatory Vascular Reaction (Vasodilation) in Rats under Conditions of Displacement

Group	Number of animals	Tort,°C	Vasodilation reaction		
			LP, min	Trt,°C	ΔTrt,°C
Control	16	37.7	19.4	37.8	0.09
Dermorphin, 50 μg/kg	14	37.5	28.8*	37.9	0.11
Control	15	37.6	26.8	37.8	0.17
Dermorphin, 500 μg/kg	15	37.1	49.5**	37.6°	0.51*

suggests the important role of afferent impulses from thermoreceptors of internal organs in the formation of a CVR. In other words, a reflex compensatory reaction develops when the excess heat in the organism reaches a certain critical level, and a further rise of body temperature may lead to overheating of the organism.

Under these conditions intraperitoneal injection of 500 μg/kg dermorphin delayed the development of CVR (Table 1): LP, ΔTrt, ΔTc, and the threshold value of Tc in the experimental animals considerably surpassed those in controls. However, dermorphin did not affect the threshold value of Trt. Decreasing the dose of heptapeptide by an order of magnitude completely abolished this effect.

The development of CVR in the displacement regime (Table 2) did not require a considerable shift of Trt. This experiment reproduces the state which activates the so-called feed-forward system [1]. In this case the compensatory reaction is triggered primarily by afferentation from peripheral thermosensitive receptors, i.e., in response to the temperature gradient. The CVR in this case develops before the excess heat in the organism attains a critical level. Intraperitoneal injection of 500 μg/kg dermorphin considerably prolongs CVR latency (Table 2), the threshold value of Trt in the experimental group being unchanged in comparison with the control. At the same time, in rats injected a higher dose of dermorphin the development of CVR was triggered by a significant rise of the body temperature. In other words, in the experimental group CVR development required an appropriate afferent impulse from the receptors of the internal organs, indicating a critical accumulation of heat in the organism. Decreasing the dose of dermorphin by an order of magnitude diminished this effect: CVR latency was considerably shorter than in animals injected with the higher dose of dermorphin, but the differences between the control and experimental groups remained reliable (Table 2).

The obtained results suggest that the delay of CVR after injection of dermorphin may be caused by several factors. On the one hand the LP of the CVR in the experimental group may be extended due to the fact that dermorphin-induced hypothermia prevents the rise of Trt to the threshold value. This assumption is confirmed by the dose-dependent weakening of the effect and by the fact that dermorphin does not change the threshold value of Trt. On the other hand, higher values of Tc and Trt in the experimental group, which suggest that additional afferent impulses are required for the development of a CVR, are apparently due either to a reduced sensitivity of the peripheral thermoreceptors or to an elevated central threshold of CVR caused by dermorphin.

Thus, dermorphin delays the development of a vasodilatory reaction in response to a rise of ambient temperature. It increases the latency of the reaction but does not affect the threshold value of the body temperature. In animals injected with dermorphin vasodilation occurs only after a significant rise of the body temperature.

REFERENCES

1. A. D. Slonim, in: *Evolution of Thermoregulation* [in Russian], Leningrad (1986).
2. M. Amiche, S. Sagan, A. Mor, *et al., Europ. J. Biochem.*, **189**, № 3, 625-636 (1990).
3. A. S. Bloom and L. F. Tseng, *Soc. Neurosci. Abstr.*, № 5, 254 (1979).
4. M. Broccardo, *Pharmacol. Res. Commun.*, **19**, № 10, 713-721 (1987).
5. M. Broccardo, U. Erspamer, G. Improta, *et al., Brit. J. Pharmacol.*, **73**, 625-631 (1981).
6. W. G. Clark, *Neurosci. Behav. Rev.*, **3**, 179-231 (1979).
7. W. G. Clark, *Fed. Proc.*, **40**, № 13, 2754-2759 (1981).
8. T. G. Emel'yanova, A. B. Usenko, A. A. Kamenski, *et al., Biomed. Sci.*, **2**, № 6 (1991).
9. U. Erspamer, P. Melhiorri, M. Broccardo, *et al., Peptides*, **2**, Suppl. 2, 7-16 (1991).
10. J. R. Glyn-Ballinger, W. G. Clark, and J. M. Lipton, *Brain Res.*, **333**, 366-368 (1985).
11. U. J. Lotti, P. Lomax, and R. George, *J. Pharmacol. Exp. Ther.*, **150**, № 1, 135-139 (1965).
12. P. C. Montecucchi, R. Castiglione, and S. Piani, *Int. J. Peptide Prot. Res.*, **17**, 275-283 (1981).
13. G. A. Olson, R. D. Olson, and A. J. Kastin, *Peptides*, № 7, 907-933 (1986).
14. C. E. Rosow, J. M. Miller, J. Poulen-Burke, and J. Cochin, *J. Pharmacol. Exp. Ther.*, **220**, № 3, 464-467 (1982).