# EFFECT OF NEUROPEPTIDE Y ON BODY TEMPERATURE OF NORMAL AND ALCOHOL-TOLERANT RATS

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Endogenous peptides are involved in the regulation of various physiological functions under normal conditions and during the development of pathological states, including alcoholism. Individual oligopeptides (vasopressin, oxytocin, angiotensin II, bombesin, neurotensin, ACTH, cholecystokinin, endorphins, and metenkephalins) are involved in the mechanisms of development of tolerance to ethanol and alcohol dependence [1, 2, 12-14].

Meanwhile the role of those peptides that are regulators of food-related behavior in the mechanisms of formation of alcohol tolerance has received little study. Interest in these peptides is due to the fact that the formation of alcoholism is accompanied by changes in appetite and reduction of body weight, amounting in some cases to the development of alcoholic cachexia [3]. It has been shown that a pancreatic polypeptide, known as neuropeptide Y (NPY), a natural regulator of food-related behavior, can initiate food-related behavior in both hungry and satiated animals at different times of day and night [5, 10, 11].

In the investigation described below the effect of NPY on the formation of experimental alcoholism was studied, with particular reference to the development of tolerance to ethanol on a model of hypothermia induced by alcohol administration.

## METHODS

Experiments were carried out on 49 male CFY rats weighing initially 150-250 g. Steel cannulas 0.85 mm in diameter were introduced into the lateral cerebral ventricles of all the rats 5-7 days before the experiment began. All the rats were divided into four groups. The animals were kept in common cages at a temperature of 20-21°C, and allowed free access to food and water. The experiments were conducted at the same time of day, between 8 a.m. and 2 p.m. The scheme of the experiments was as follows. After measurement of body weight and rectal temperature of the experimental animals (group 4, 13 rats) NPY was injected into the lateral cerebral ventricles in a dose of 2 $\mu$g in 2 $\mu$liters of physiological saline. When this dose was chosen, we were guided by data published by other workers who noted that NPY in a dose of 1-10 $\mu$g, injected by the intraventricular route, was effective for initiating food-related behavior [6, 9]. After 30 min, a 25% solution of ethanol was injected intraperitoneally in a dose of 3 g/kg body weight. The temperature was measured 30, 60, and 120 min thereafter for 5 days. Animals of the control group (group 1 — 12 rats) received injections of the equivalent volume of physiological saline into the ventricles and intraperitoneally, and their rectal temperature was recorded at the same time intervals. As the control, the action of NPY itself and of ethanol on the time course of the rectal temperature was studied. For this purpose the rectal temperature of the rats was measured before and at the above-mentioned times after intraventricular injection of NPY combined with intraperitoneal injection of physiological saline (group 2 — 10 rats) or intraventricular injection of physiological saline followed by intraperitoneal injection of a 25% ethanol solution (group 3 — 14 rats). NPY, ethanol, and physiological

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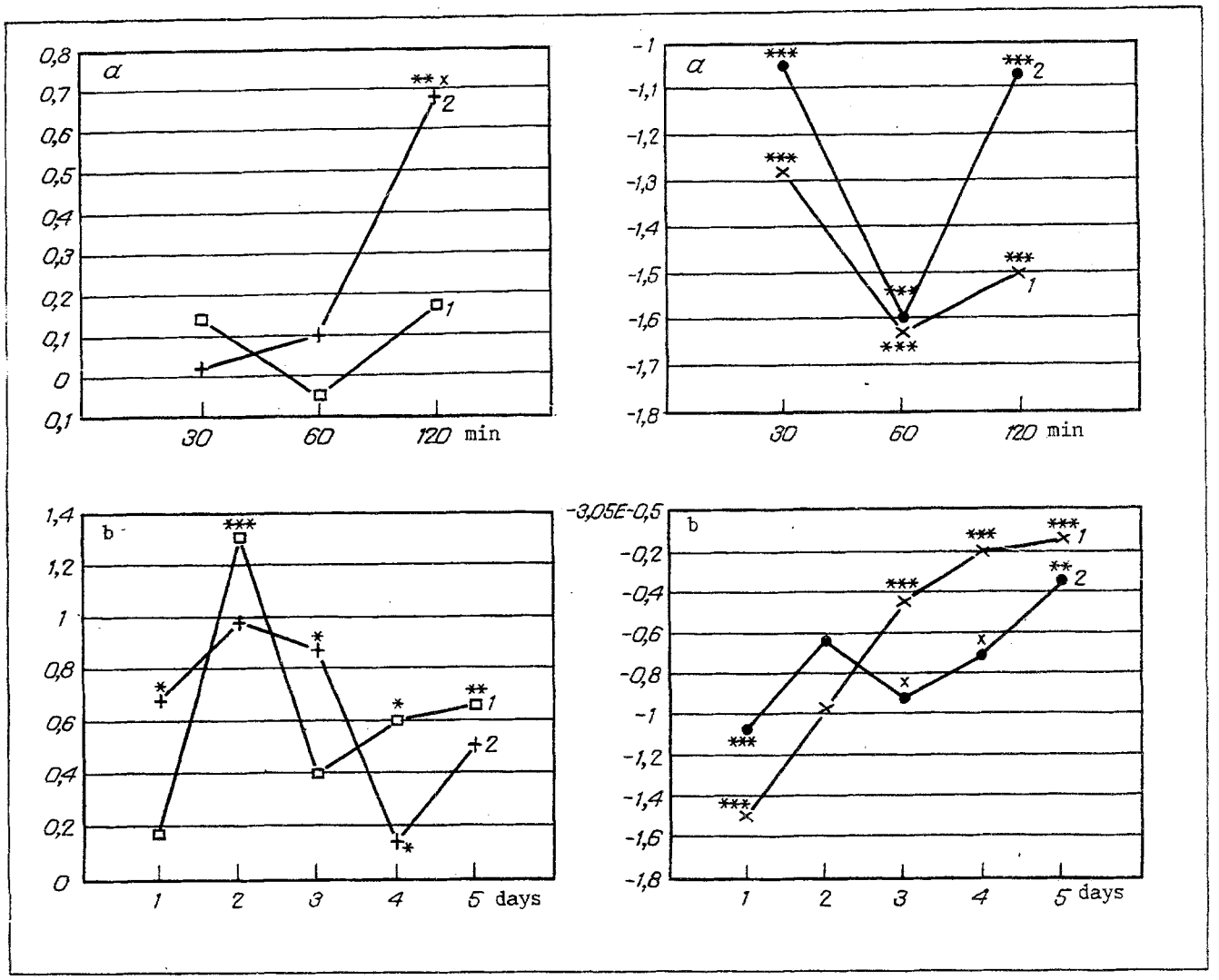


Fig. 1 Fig. 2

Fig. 1. Dynamics of changes in rectal temperature of rats of control groups receiving intraperitoneal injection of physiological saline preceded by intraventricular injection of physiological saline (1) or NPY (2) during 1st experimental day (a) and 5 days later (b). Abscissa) changes in rats' body temperature (in °C); ordinate) time (a — in min, b — in days). Here and in Fig. 2: *) $p < 0.05$, **) $p < 0.01$, ***$p < 0.001$ compared with initial data. ×) Significant differences between values for two groups compared.

Fig. 2. Time course of changes in rectal temperature in rats of control and experimental groups after intraperitoneal injection of 25% ethanol solution preceded by intraventricular injection of physiological saline (1) or NPY (2) during 1st experimental day (a) or 5 days later (b).

saline were administered in the same doses as those given to the experimental animals. The results were subjected to statistical analysis by determination of the arithmetic mean values by Student's test. The location of the tips of the cannulas in the lateral ventricles was verified against De Groet's atlas.

## RESULTS

Comparative analysis of the action of NPY and physiological saline on the rectal temperature of rats of the 2nd and 3rd control groups revealed a significant increase in body temperature on average by 0.7°C 150 min after intraventricular injection of NPY, but no significant change in body temperature under the influence of NPY on the 1st day of the investigation was observed only at the 150th minute, comparative analysis of changes in this parameter in the rats of the two groups on subsequent days of the experiments was carried out within the same time interval.

A study of the time course of fluctuations of body temperature of the rats during the 5 days after injection of NPY and physiological saline into the animals of groups 2 and 1, respectively, revealed considerable circadian fluctuations of temperature in all the rats, differing in amplitude and direction (Fig. 1b). Nevertheless, on the 1st and 3rd days of observation the rectal temperature of the animals of group 2 was 0.5 and 0.48°C higher, respectively, than in the rats of group 1 (Fig. 1b). It can accordingly be concluded that, independently of circadian fluctuations of temperatures, daily intraventricular injection of NPY led to hyperthermia on the 1st and 3rd days of observation.

Intraperitoneal injection of 25% ethanol solution into the control animals of group 3, against the background of preliminary intraventricular injection of physiological saline, led to a significant fall of rectal temperature of the rats ($p < 0.001$), which was most marked 60 min after injection of ethanol (on average by 1.6°C) (Fig. 2a). A similar time course of the fall of rectal temperature under the influence of ethanol also was found in the experimental rats (group 4) receiving NPY by intraventricular injection beforehand. On the 1st day of observation, no significant differences could be found between ethanol-induced hypothermia in the animals of the two groups. Meanwhile, 30 min and, to a greater degree, 120 min after injection of ethanol a tendency was found toward a smaller reduction of the rectal temperature of the experimental rats, possibly due to the hyperthermic effect of the peptide itself. Considering that the greatest differences in the effect of NPY and physiological saline on alcohol-induced hypothermia were noted at the 150th minute after injection of the substances, their action on the development of tolerance to ethanol was studied in the future at the same time intervals.

During repeated injection of the same dose of ethanol into animals of the control group, the intensity of hypothermia progressively diminished in the course of 5 days of observation. For instance, the average fall of body temperature of rats of the control group on the 1st day was 1.5°C, whereas on the 3rd and 4th days the fall of body temperature under the influence of ethanol was significantly lower than on the 1st day, and varied between 0.4 and 0.15°C. The results are evidence of the development of tolerance of rats of the control group to ethanol. Meanwhile, after preliminary intraventricular injection of NPY the ethanol-induced hypothermia was significantly lower (on average by 0.5°C) on the 3rd and 4th days than during the corresponding period in the control animals, receiving an injection of physiological saline into the ventricles (Fig. 2b). The formation of tolerance to ethanol in the animals receiving NPY beforehand took place more slowly than in rats of the control group. The results are evidence of an inhibitory action of NPY on the development of tolerance of the rats to ethanol.

The results of these investigations thus indicate involvement of NPY in processes of temperature regulation, in agreement with the findings of other workers [7, 8]. We discovered that NPY, if injected intraventricularly, can induce some degree of hyperthermia. We know that under physiological conditions mild hyperthermia can occur as a result of taking food [4]. Since NPY, administered centrally in the doses used, can initiate food taking, which is accompanied by behavior characteristic of the natural process of satiation [10], it can be postulated that the rise of body temperatures caused by food intake is based on activation of the endogenous NPY system.

As regards the ability of NPY to modulate ethanol-induced hypothermia, it was found that after a single injection of ethanol, NPY reduced the amount by which the rectal temperature fell. This may also be due to the hyperthermic effect of the peptide itself. However, in response to repeated injection of ethanol, NPY had an inhibitory effect on the development of tolerance to ethanol in the animals, instead of the expected acceleration of the development of tolerance (due to its hyperthermic properties). The inhibitory effect of NPY on the mechanisms of adaptation to ethanol

is evidently determined not by its hyperthermic properties, but by the ability of the peptide to participate in processes of adaptation.

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