Pestycydy, 2008, (1-2), 101-108.
ISSN 0208-8703

Effect of haloperidol (HAL) on leucopyrokinin (LPK)-induced biphasic hyper- and hypothermic effect in rats

Monika RYKACZEWSKA-CZERWIŃSKA[1], Danuta KONOPIŃSKA[2] and Andrzej PLECH[1,3*]

[1] Department of Pharmacology, Medical Faculty in Zabrze of the Medical University of Silesia, 38 H. Jordana St., 41-808 Zabrze, Poland
[*]e-mail: aplech@sum.edu.pl
[2] Faculty of Chemistry, Wroclaw University, 14 F. Joliot-Curie St., 50-383 Wrocław, Poland
[3]Cardinal August Hlond Upper Silesian College of Pedagogical Education, Faculty of Public Health, 19 Powstańców St., 41-400 Mysłowice, Poland

Abstract: The aim of present study was to evaluate mechanisms involved in thermomodulatory effect LPK in rats.Experiments were performed on adult Wistar male rats. LPK was applied either intracerebroventricularly (icv), or intraperitoneally (ip) using the similar program and technique of experiments as in our previous study. We confirmed in this paper the results of our previous reports that icv administration LPK at the dose of 20 nmol induced evident significant rectal hypothermia, while lower dose LPK of 1 nmol icv exerted significant hyperthermic effect. Peripherally applied LPK at the range of doses 10-100 nmol/100 g ip displayed slight bimodal (hyperthermic and hypothermic) effect on rectal temperature. Prior administration of haloperidol, an antagonist of central dopamine receptors blocked both effects LPK applied either icv or ip. Obtained results indicate that both hypothermic and hyperthermic effects LPK are also modulated by central dopaminergic receptors.

Keywords: leucopyrokinin, rats, rectal temperature, haloperidol

INTRODUCTION

It was demonstrated in our previous studies that either intraperitoneal (ip) or intracerebroventricular (icv) administration of insect neuropeptide

leucopyrokinin (LPK) or its active analog [2-8]-leucopyrokinin ([2-8]-LPK) exerts thermomodulatory effect in rats [8, 9]. These both peptides exert bimodal effect on rectal temperature in rats. Icv administration of LPK at the dose of 20 nmol or [2-8]-LPK at the dose of 100 nmol induced significant opioid-dependent hypothermic effect in rats as it was blocked by naloxone, an opioid antagonist [8].

On the other hand lower doses LPK (1-10 nmol icv), or peripheral administration of [2-8]-LPK (10 or 100 nmol/100 g ip) induced significant hyperthermic effect [8, 9] also blocked by naloxone, opioid antagonist [9].

As it was previously presented in several papers that different factors may modulate body temperature in humans and in animals [5, 6, 12], it seems necessary to investigate other mechanisms which may be involved in the thermomodulatory effect LPK and [2-8]-LPK.

The present study was undertaken in order to determine effect of HAL, an antagonist of central dopamine receptors on LPK-induced changes of rectal temperature in rats.

Demonstrated in our previous report [8], opioid mediation in LPK-induced hypothermia, suggests a probable interaction of central opioid and dopamine receptors in modulation activity of thermoregulatory center in rat's brain and in consequence changes of the body temperature.

MATERIALS AND METHODS

The experiments were conducted out on adult male Wistar rats of 250-300 g body weight, obtained from the Animal Farm of the Medical University of Silesia in Katowice. Animals were kept in standard conditions: on 12:12 light/dark cycle (light on from 6 a.m. to 6 p.m.), constant temperature +21 ±1°C, with free access to standard food (Murigran, Motycz, Lublin, Poland) and water. All studies were carried out during the light part of the L:D cycle between 9 a.m. and 2 p.m.. The animals were allowed 72 h adaptation for the laboratory conditions before experiments.

Intracerebroventricular (icv) cannulation

One week before experiments the polyethylene cannulas (Tomel, Tomaszów Maz., Poland) were implanted into the right lateral brain ventricle using the same technique as in our previous study [7-9]. Rats were anaesthetized with chloralhydrate 300 mg/kg ip (POCh, Gliwice, Poland), next the skin of the skull was cut and skull bones were uncovered. The polyethylene cannulas were implanted icv according to the following coordinates: a depth of 4 mm from the

surface of the skull, 2 mm to the right from the sagittal suture, and 2 mm behind the coronary suture. Cannulas were attached to the skull bones with dental cement (Duracryl, Spofa Dental, Prague, Czech Republic).

Intraperitoneal (ip) injection

Rats weighing 180-220 g were used for intraperitoneal injection LPK. They did not require any additional arrangements for experiments.

Experimental protocol

On the day of experiment animals were put into the plastic restrainers of our own construction. The rectal temperature was recorded immediately before injection and next at the constant time intervals of 20, 40, 70, 100, 130 min and 24 h after injection of LPK with an electronic thermometer TTK-3011 (Temed, Zabrze, Poland). The results of temperature measurements are expressed as Δt °C (the difference between initial temperature recorded before LPK injection and temperature recorded at time intervals presented above).

At the end of experiments rats were killed by chloral hydrate overdosing (600 mg/kg ip). The proper placement of tips of polyethylene cannulas implanted icv was checked post-mortem injecting icv 10 μl of Indian ink solution and investigations of frontal brain slices cut with freezing microtome.

LPK was synthesized at the Faculty of Chemistry, Wroclaw University [7]. This peptide was dissolved in 0.9% NaCl immediately before injection and applied icv at doses of 1 nmol in a volume of 5 μl and 20 nmol in a volume of 10 μl, or ip at doses 10, 20 and 100 nmol/100 g in a volume of 0.1 ml/100 g. Haloperidol (HAL) (Polfa, Warszawa, Poland) was injected ip at the dose of 1 mg/kg, 30 min before LPK.

Obtained results were subjected to the analysis of variance (ANOVA) and the post-ANOVA Dunnett's test [11]. The experimental protocol was approved by the local ethical committee of the Medical University of Silesia in Katowice (L.dz, 12/00).

RESULTS

Icv administration LPK at the dose of 1 nmol icv induced evident, lasting 130 min significant hyperthermic effect (Figure 1). However 20-fold higher dose LPK (20 nmol icv) induced hypothermic effect in rats, significant at 20 and 40 min after administration and insignificant at the next time intervals (70, 100 and 130 min) (Figure 2). Pretreatment rats with HAL (1 mg/kg ip) 30 min before

LPK partially inhibited effect LPK in first 70 min of experiment (Figure 1), and reversed hypothermic effect of a higher dose LPK (20 nmol icv) (Figure 2).

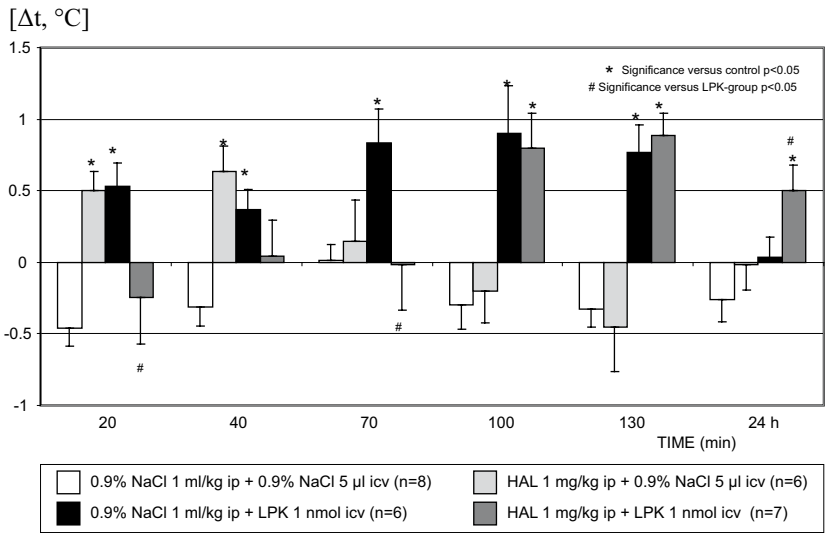

Figure 1. Effect of HAL on LPK-induced hyperthermic effect determined after icv administration LPK at the dose of 1 nmol in rats.

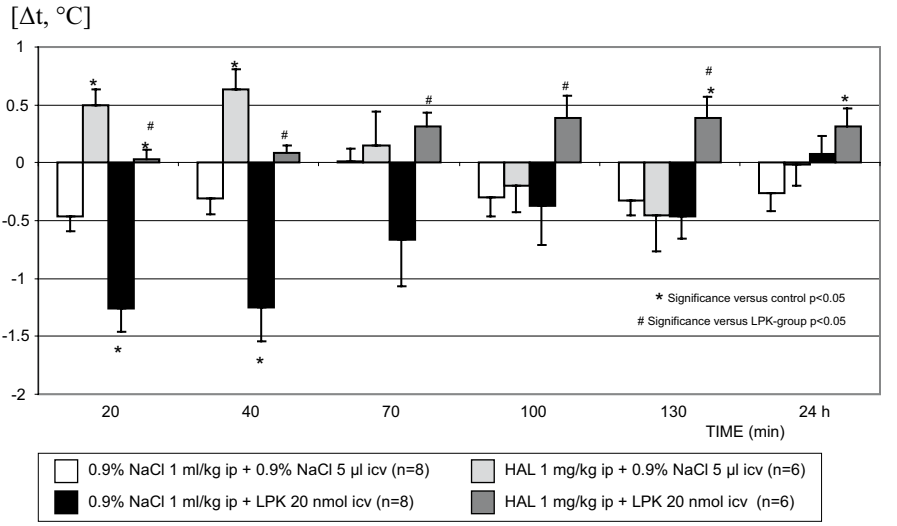

Figure 2. Effect of HAL on LPK-induced hypothermic effect determined after icv administration at the dose of 20 nmol in rats.

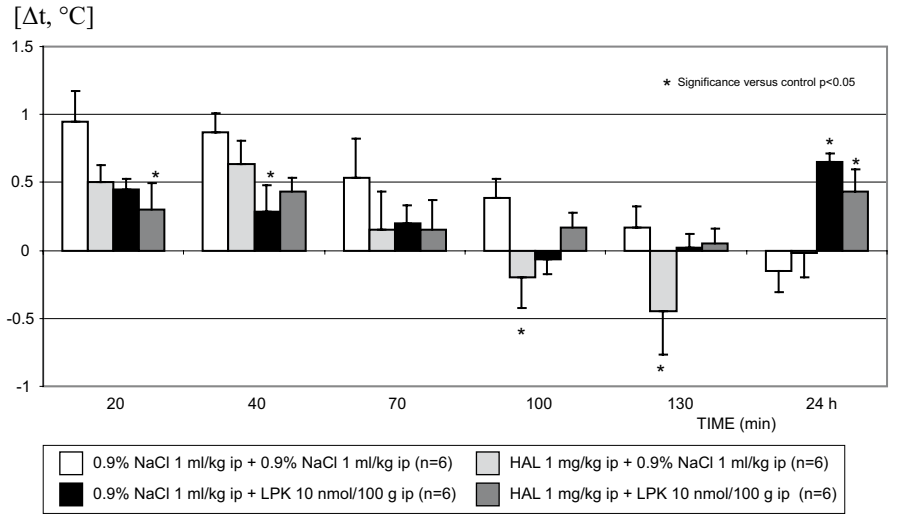

Figure 3. Effect of HAL on LPK-induced changes of rectal temperature determined after ip administration LPK at the dose of 10 nmol/100 g in rats.

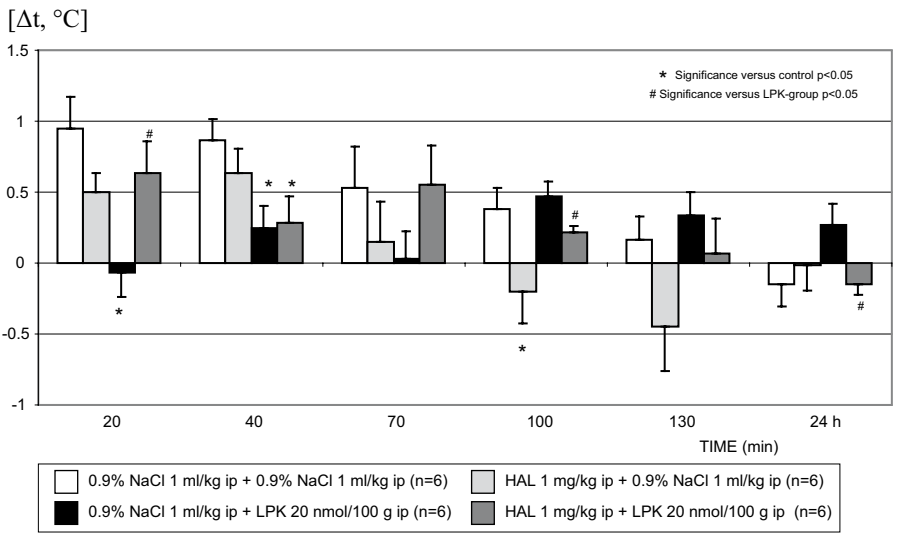

Figure 4. Effect of HAL on LPK-induced changes of rectal temperature determined after ip administration LPK at the dose of 20 nmol/100 g in rats.

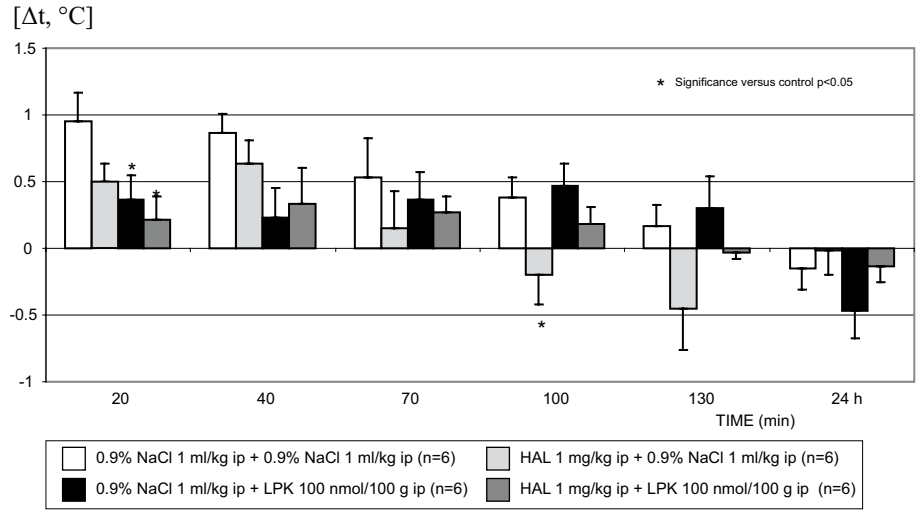

Figure 5. Effect of HAL on LPK-induced hypothermic effect determined after ip administration LPK at the dose of 100 nmol/100 g in rats.

LPK injected ip at the dose of 10 nmol/100 g induced a transient hypothermic, significant only after 40 min after administration (Figure 3) and significant hyperthermic effect after 24 h (Figure 3). The dose LPK of 20 nmol/100 g ip induced significant hypothermic effect at 20 and 40 min after administration (Figure 4.), and unsignificant hyperthermic effect after 24 h (Figure 4). These effects were blocked by prior administration of HAL (Figures 3, 4). The highest applied LPK dose of 100 nmol/100 g ip induced the only slight significant hypothermic effect at 20 min after administration (Figure 5). Pretreatment rats with HAL 30 min before LPK did not inhibit it (Figure 5).

DISCUSSION

The results of present study confirmed our previous findings that LPK exerts bimodal hyper- and hypothermic effect in rats [8, 9]. Lower doses LPK applied icv induce hyperthermia determined in rat's rectum, while administration of higher doses of this peptide results in evident hypothermia. LPK administered ip exerts hypothermic effect up to 130 min of experiment and this effect changes into hyperthermia after 24 h (Figure 3). It was previously proved that hypothermic effect LPK was strongly blocked by naloxone, an antagonist of opioid receptors [8]. However hyperthermic effect of the low dose LPK of 1 nmol icv was poorly

blocked by naloxone [9]. As it was found that both effects LPK hyperthermic effect of the dose of 1 nmol icv (Figure 1) and hypothermic effect of the dose of 20 nmol icv (Figure 2) were blocked by prior administration HAL, an antagonist of central dopamine receptors we regard that central dopamine receptors also modulate LPK effect.

The mechanism of this phenomenon is not recognized. But we speculate that stimulation of opioid receptors by LPK resulted in modulation of central dopaminergic receptors activity. Interaction between central opioid and dopaminergic system was previously described in several reports [1-3, 13].

It was previously demonstrated that icv administration of alone dopamine induced a dose-dependent hyperthermic effect in rabbits [10], blocked by prior administration HAL [10]. On the other hand intramuscular HAL injection produced significant nocturnal hypothermia in rats [4].

We conclude that obtained hypothermic and hyperthermic effects LPK are also mediated and modulated by central dopaminergic receptors.

Acknowledgements

This work was supported by grants from Medical University of Silesia, grant NN-2-083/99 and grant NN-5-076/00.

REFERENCES

[1] Boublik J.H., Funder J.W., Eur. J. Pharmacol., 1984, 107, 11-16.
[2] Broccardo M., Improta G., *ibid*., 1994, 258, 179-184.
[3] Cheido M.A., Idova G.V., Fizjologicheskij Zhurnal imieni I.M. Sechenova, 1993, 79, 18-22.
[4] Fick L.G., Fuller A., Mitchell D., Can. J. Physiol. Pharmacol., 2005, 83, 517-527.
[5] Mackowiak P.A., Arch. Intern. Med., 1998, 158, 1870-1881.
[6] Nakayama T., Japan. J. of Physiol., 1985, 35, 375-389.
[7] Plech A., Rykaczewska-Czerwińska M., Bartosz-Bechowski H., Lombarska-Śliwińska D., Małota M., Szewczyk M., Brus R., Konopińska D., Pol. J. Pharmacol., 1997, 49, 119-126.
[8] Rykaczewska-Czerwińska M., Lombarska-Śliwińska D., Konopińska D., Plech A., Pestycydy, 2004, 3-4, 133-139.
[9] Rykaczewska-Czerwińska M., Lombarska-Śliwińska D., Konopińska D., Plech A., Pestycydy/Pesticides, 2005, 4, 125-131.
[10] Srivastava A.K., Srivastava Y.P., Gupta P.P., Verma R.B., Indian J. Exp. Biol., 1991, 29, 1087-1088.

[11] Tallarida J.R., Murray R.B., Manual of Pharmacologic Calculations with Computer Programs, Springer Verlag, N. York 1987, pp. 110-121, 145-148.
[12] Tracey K., Cerami A., Ann. Rev. Med., 1994, 45, 491-503.
[13] Vezina P., Steward J., Life Sci., 1985, 36, 1095-1105.