EFFECT OF ACUTE VERAPAMIL TREATMENT ON BODY TEMPERATURE IN NUCLEUS BASALIS MAGNOCELLULARIS-LESIONED RATS

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SUMMARY

Our recent studies suggest that lesions of the nucleus basalis magnocellularis (nbm) in rats induce a significant decrease of core body temperature in standard laboratory conditions. Considering the importance of calcium homeostasis in thermoregulation, as well as in the pathogenesis of neurodegeneration, the aim of the present study was to investigate the effect of acute verapamil treatment on body temperature in nbm-lesioned rats. The body temperature was registered before and 30 min after verapamil was subcutaneously administered (1.0, 2.5, 5.0 and 10.0 mg/kg). Verapamil did not change body temperature in control animals. However, verapamil in doses of 2.5 and 5.0 mg/kg significantly increased the core body temperature in nbm-lesioned rats nearly up to the temperature of control animals. Findings that verapamil in doses of 1.0 and 10.0 mg/kg did not change body temperature in nbm-lesioned suggest the existence of an inverted U-shape curve in its effect.

Key words: Alzheimer's disease, Body temperature, Nucleus basalis magnocellularis, Rats, Verapamil.

INTRODUCTION

It is well known that the basal forebrain, which undergoes marked degeneration in patients with Alzheimer's disease (AD), plays a significant role in the control of body temperature (1). The body temperature circadian rhythm is irregularly disturbed in 59% of patients with dementia (senile dementia and multi-infarct dementia-MID) but only in 12.5% of a control group (2). Long-term body temperature monitoring in patients with AD suggests that these exhibit a well-organized body temperature rhythm (3), but with delayed temperature acrophases, when compared to healthy controls (4). There is also a significantly higher amplitude of the body temperature cycle

compared to the healthy controls and MID patients (5, 6).

Experimental data indicate that implantation of beta/A4 amyloid-positive cells into the suprachiasmatic nuclei of adult rats alters the body temperature cycle (7). Besides that, a recent study of our group suggests that lesion of nucleus basalis magnocellularis (nbm) in rats (an experimental model of AD) induces a significant decrease of core body temperature in standard laboratory conditions, as well as an increase of body temperature in cold and hot environment (8).

On the other hand, several studies indicate that calcium ions play a significant role in the thermoregulatory control system and that the application of calcium antagonists can modify the body temperature (9, 10, 11). Moreover, calcium homeostasis is disturbed in AD (12). Having in mind that acute verapamil treatment can ameliorate some cognitive and noncognitive behavioral deficits in nbm-lesioned rats (13, 14), the present study was done with the aim of analysing the effect of this drug on the core body temperature in an animal model of AD.

MATERIALS AND METHODS

Experimental animals

Experiments were carried out on adult male Wistar rats (250-280 g). The rats were housed in groups of 5 to a plastic cage in standard laboratory conditions. The rats were divided in the following groups: intact control (IC), sham operated (SO) and nbm-lesioned rats. Animals from each group were treated with saline or verapamil. Nine rats were assigned to each group.

Surgery

The rats were anesthetized with intraperitoneally (i.p.) administered sodium pentobarbital (35 mg/kg). The sham operation or bilateral electrolytic nbm lesions were made as described by Popović et al. (8). The recovery period after operation was ten days.

Core body temperature

Core body temperature was measured using a digital rectal thermometer (Ellab, Copenhagen) with an accuracy within the range of temperature recorded of ± 0.1°C. The thermistor probe was inserted 5 cm into the rectum. The animal's temperature was monitored for 3 min, before and 30 min after verapamil treatment.

Drugs

Solution of verapamil hydrochloride (Sigma, St. Louis, MO) was prepared freshly daily in light-tight bottles and diluted with physiological saline, so that all doses were administered in a constant volume of 1 ml/kg body weight. Verapamil (1.0, 2.5, 5.0 and 10.0 mg/kg) as well as physiological saline (1 ml/kg) were given subcutaneously (s.c.).

Histology

The position of nbm lesions was examined as described by Popović et al. (8) and presented on Figure 1.

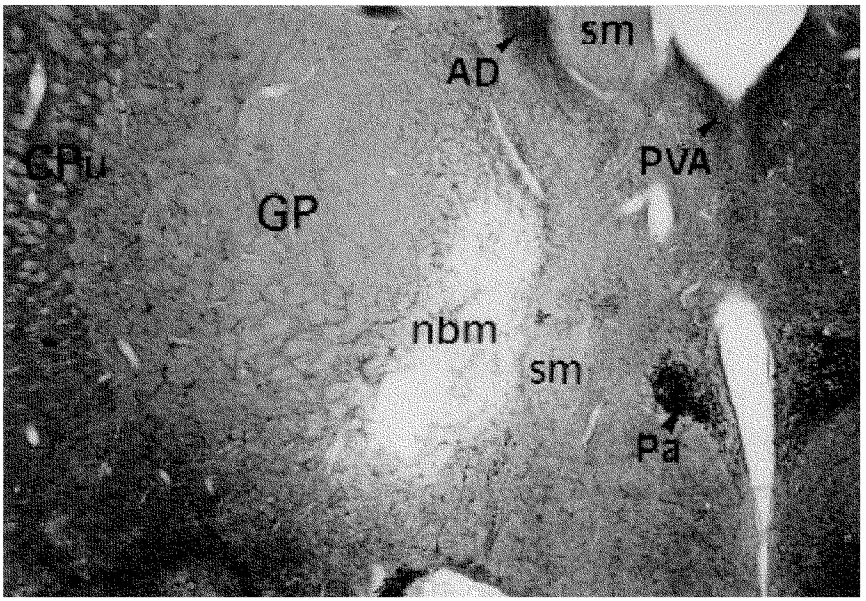

Figure 1. Photomicrograph of a histological coronal section throughout the rat basal forebrain showing a selective electrolytic lesion of the nucleus basalis magnocellularis (nbm). AD: anterior dorsal nucleus of the thalamus; CPu: caudate-putamen; GP: globus palidus; Pa: paraventricular hypothalamic nucleus; PVA: paraventricular anterior nucleus of the thalamus; sm: stria medullaris. Magnification: x 5.

Statistics

All data are presented as means ± S.E.M. Statistical comparisons were performed using the Student's t-test and Wilcoxon matched-pairs t-test. The differences were accepted as statistically significant when $p < 0.05$.

RESULTS

Since there were no statistically significant differences in core body temperature among IC and SO groups, the results of these two groups are averaged and shown as the control group. In comparison to the control group, nbm-lesioned rats shown significantly less core body temperature ($p < 0.001$).

Verapamil in the range of doses used here did not change the core body temperature in control rats (Table I). However, verapamil in doses of 2.5 and 5.0 mg/kg significantly increased core body

temperature in nbm-lesioned rats (Table II). There were no significant differences between control animals and nbm-lesioned rats treated with verapamil 2.5 and 5.0 mg/kg. Verapamil in doses of 1.0 and 10.0 mg/kg did not have any significant effect on body temperature.

Table I. Effect of verapamil (VER) on body temperature in control rats

Treatment (mg/kg)	Before treatment	30 min after treatment
SALINE	36.95 ± 0.12	36.91 ± 0.15
VER (1.0)	36.67 ± 0.12	36.73 ± 0.17
VER (2.5)	36.78 ± 0.16	36.66 ± 0.16
VER (5.0)	37.04 ± 0.12	37.03 ± 0.15
VER (10.0)	36.60 ± 0.15	36.66 ± 0.13

The data are presented as mean ± S.E.M.

Table II. Effect of verapamil (VER) on body temperature in nbm-lesioned rats

Treatment (mg/kg)	Before treatment	30 min after treatment
SALINE	35.43 ± 0.12	35.50 ± 0.18
VER (1.0)	35.63 ± 0.14	35.77 ± 0.19
VER (2.5)	35.18 ± 0.19	36.34 ± 0.15*
VER (5.0)	35.33 ± 0.16	36.62 ± 0.13*
VER (10.0)	35.21 ± 0.15	35.28 ± 0.10

The data are presented as mean ± S.E.M.

*$p < 0.001$ in comparison with temperature before verapamil treatment.

DISCUSSION

The investigation of the effect of calcium antagonists on body temperature has been of interest for many years. However, the results are variable and depend on the mode of drug administration, type of calcium antagonist, animal species and strain, as well as on the thermal state of the animal when the drugs are applied (normal temperature, hypothermia or hyperthermia).

Thus, intracerebroventricular (i.c.v.), but not i.p. administered verapamil decreases the core body temperature in control mice (15). In contrast to that, Rezvani et al. (11) did not get any significant change in body temperature in rats till 1.5 hr after i.c.v. administration of verapamil. Also there were no significant changes after i.p.- and intravenously (i.v.)-administered verapamil in rats (9, 10, 11) and mice (16). In the present study, we similarly got no significant changes of body temperature in IC and SO rats after s.c. administration of verapamil in doses of 1.0, 2.5, 5.0 and 10.0 mg/kg.

On the other hand, it was found before that peripherally administered verapamil decreases body temperature in hyperthermic, lorazepam-dependent rats (17) and morphine-treated rats (18). Besides that, i.v.-administered verapamil exerts a significant antipyretic effect on the febrile response of rats to endogenous pyrogen injected i.v. (19, 20).

However, i.c.v.-administered verapamil antagonizes hypothermia induced by agonists of delta and kappa-opioid receptors (21, 22), while s.c.-administered verapamil potentiates the hypothermic effect of kappa receptor agonists (23). On the other hand, peripherally administered verapamil antagonizes hypothermia induced by apomorphine (24) and oxotremorine (19).

Verapamil administered i.c.v. attenuates the thermolytic action of ethanol (10, 11), but its systemic administration potentiantes ethanol-induced hypothermia in rats (10) and mice (16).

In the present study, s.c. administered verapamil in doses of 2.5 and 5.0 mg/kg significantly increased the core body temperature in hypothermic nbm-lesioned rats. In these doses used verapamil bring the lesioned animal's temperature back to nearly that of the control animals. Similarly to our previous studies (13, 14), verapamil expressed an inverted U-shape curve in its effect, since the doses of 1.0 and 10.0 mg/kg did not have significant effects on body temperature in nbm-lesioned rats.

The obtained beneficial effect of verapamil may be related to the regulation of calcium homeostasis in nbm-lesioned rats (13, 14) or to an effect on the cholinergic, monoaminergic and opioid systems (9, 18, 21, 22, 23, 25), which are also disturbed in nbm-lesioned rats (26, 27). Moreover, findings that verapamil can ameliorate not only cognitive and noncognitive disturbances of AD models, but also physiological disturbances such as thermoregulation in nbm-lesioned

rats, keep us in the belief that the application of verapamil and probably some other calcium antagonists is of interest for further studies in the treatment of AD.

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