Effects of DL-propranolol on the thermoregulatory responses of rats at different ambient temperatures[1]

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Summary. Direct administration of propranolol (100–400 µg) into the lateral cerebral ventricle of rats produced a dose-dependent hypothermia at ambient temperatures (T_a) of 8 and 22 °C. The hypothermia was due to decreased metabolism and cutaneous vasodilatation. The hypothermia induced by propranolol was antagonized by pretreatment with isoproterenol (50 µg).

The effects of intracerebroventricular (i.c.v.) injections of norepinephrine and other sympathomimetic drugs on thermoregulation have been extensively studied in rats. However, there appear to be conflicts in the available data in this area of study. For example, intracranial injections of norepinephrine have produced decreases in rectal temperature[2-4], increases[5-8], or decreases followed by increases[9,10]. Recently, in our laboratories, the effects of i.c.v. administration of norepinephrine[11] and isoproterenol[12] on the thermoregulatory responses of conscious rats to different T_a have been assessed. It was found that both norepinephrine and isoproterenol both produced a dose-dependent hypothermia in rats in the cold (8 °C T_a). The hypothermia was due to a decrease in metabolic heat production (M). There was no change in either cutaneous circulation or respiratory evaporative heat loss (E_{res}). On the other hand, at both 22 and 30 °C T_a, norepinephrine and isoproterenol each produced a dose-dependent hyperthermia in rats. The hyperthermia was due to cutaneous vasoconstriction. The present investigation was an attempt to assess the effects of i.c.v. administration of a beta-adrenergic antagonist, DL-propranolol, on the thermoregulatory responses of conscious rats at different T_a. The possible interrelationship between DL-propranolol and isoproterenol (a beta-adrenergic agonist)[12] in temperature regulation were also observed.

Materials and methods. Adult male Sprague-Dawley rats weighing between 250 and 300 g were used in all experiments. Measurements were obtained from conscious animals which were trained to sit quietly under restraint in rat stocks. Between experiments the animals were housed individually in wire-mesh cages in a room of 25 ± 1.0 °C with a 12 h light/12 h dark cycle. The animals were given free access to tap water and granular chicken feed. For intraventricular injection, the ventricular cannulae were chronically implanted in the animals under anesthesia (sodium pentobarbital, 6 mg/100 g, i.p.). Implantation of ventricular cannulae were carried out according to the DeGroot coordinates: AP, 7.0; Lat., 1.0; and Hor., 0.1 mm[13]. A 27-gauge Hamilton syringe needle was connected via PE 10 tubing to a 50-µl Hamilton syringe. During the surgery the correct positioning of each guide tube was verified by the rapid flow of saline into the lateral cerebral ventricle under gravity. At least 2 weeks were allowed for the animals to recover from the operation. All drug solutions were prepared in pyrogen-free glassware which was baked at 180 °C for 5 h before use. A 5-µl aliquot containing either DL-propranolol (Sigma, 50–400 µg), isoproterenol (Sigma, 50–200 µg) or procaine hydrochloride (100 µg) was administered into the lateral cerebral ventricle through a ventricular guide tube. Metabolic rate (M), E_{res} and vasomotor activities were measured in a small-animal calorimeter[14-16]. M was calculated from the animal's oxygen consumption and expressed as W/kg b.wt. E_{res} was calculated by measuring the increase in water vapor content in the expired air. Evaporative heat loss (W) was calculated from evaporative water loss. Rectal (T_r), foot skin (T_f) and tail skin (T_t) temperatures were measured using thermocouples. All measurements were taken once per 1 min throughout the experiments, each variable being measured as a direct current potential on a Hewlett-Packard digital voltmeter (DVM 3465) interfaced to an on-line CPU 9825 computer. Each minute all temperatures, M and E_{res} were calculated instantaneously by the computer and relayed immediately back to the laboratory where they were displayed by an on-line printer HP 9871. Animals were permitted 120 min at each selected T_a to attain thermal balance before each drug injection. The maximal changes in T_r, T_f, T_t, M and E_{res} produced within a 60-min period after DL-propranolol injection were expressed as ΔT_r, ΔT_f, ΔT_t, ΔM and ΔE_{res}, respectively. The data were collected at 3 different T_a of 8, 22 and 30 °C.

Results and discussion. Although intraventricular administration of a small dose (50 µg) of DL-propranolol produced an insignificant change in rectal temperature, larger doses

Table 1. The maximal changes in thermoregulatory responses produced by an injection of DL-propranolol into the lateral cerebral ventricle (i.c.v.) or peritoneal cavity (i.p.) of conscious rats at various ambient temperatures (T_a)

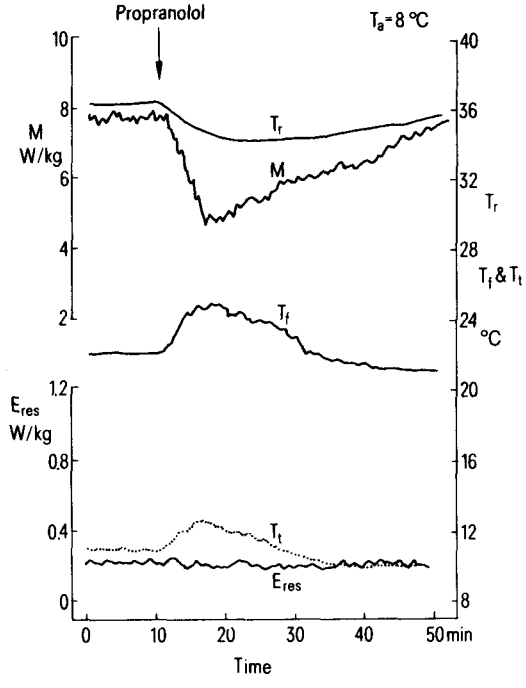
Treatment of animals	T_a, °C	ΔT_r, °C	ΔT_f, °C	ΔT_t, °C	ΔM, W/kg	ΔE_{res}, W/kg
0.9% Saline, i.c.v., n = 8	8	0.2 ± 0.09	0.5 ± 0.22	0.6 ± 0.24	0.5 ± 0.08	0.04 ± 0.02
Propranolol 100 µg, i.c.v., n = 7	8	−0.8 ± 0.13*				
Propranolol 200 µg, i.c.v., n = 8	8	−1.6 ± 0.18*	3.1 ± 0.44*	1.8 ± 0.26*	−3.0 ± 0.47*	0.04 ± 0.02
Propranolol 400 µg, i.c.v., n = 6	8	−2.6 ± 0.19*				
Propranolol 400 µg, i.p., n = 5	8	−0.2 ± 0.11				
0.9% Saline, i.c.v., n = 8	22	−0.2 ± 0.09	0.6 ± 0.27	0.5 ± 0.23	−0.6 ± 0.18	0.03 ± 0.02
Propranolol 100 µg, i.c.v., n = 7	22	−0.7 ± 0.08*				
Propranolol 200 µg, i.c.v., n = 8	22	−1.3 ± 0.11*	5.5 ± 0.57*	2.2 ± 0.39*	−1.2 ± 0.12*	0.03 ± 0.01
Propranolol 400 µg, i.c.v., n = 6	22	−2.1 ± 0.17*				
Propranolol 400 µg, i.p., n = 5	22	−0.2 ± 0.10				
0.9% Saline, i.c.v., n = 7	30	−0.2 ± 0.10	−0.6 ± 0.17	−0.5 ± 0.24	0.5 ± 0.15	0.04 ± 0.02
Propranolol 100 µg, n = 7	30	−0.1 ± 0.07				
Propranolol 200 µg, n = 8	30	0.2 ± 0.08	−0.4 ± 0.22	−0.6 ± 0.24	0.4 ± 0.12	0.05 ± 0.03
Propranolol 400 µg, n = 6	30	0.1 ± 0.06				
Propranolol 400 µg, i.p., n = 5	30	−0.1 ± 0.05				

* Significantly different from corresponding control value before the drug injection, $p < 0.05$ (1-way analysis of variance). The values are expressed as the mean ± SEM. n, numbers of rats tested.

Table 2. Effects of propranolol, isoproterenol and procain on the thermoregulatory functions of rats at different T_a

Treatment of animals	Maximal changes in rectal temperature, Δ °C		
	$T_a = 8$ °C	$T_a = 22$ °C	$T_a = 30$ °C
Propanolol 50 µg (i.c.v.)	−0.3±0.07 (7)	−0.2±0.06 (7)	0.1±0.07 (7)
Propanolol 200 µg(i.c.v.)	−1.5±0.16 (7)	−1.2±0.09 (7)	
Isoproterenol 50 µg (i.c.v.) + propranolol 200 µg (i.c.v.)	−0.4±0.06* (7)	−0.3±0.05* (7)	
Isoproterenol 50 µg (i.c.v.)	0.2±0.05 (6)	0.3±0.06 (6)	
Isoproterenol 200 µg (i.c.v.)	−2.1±0.12 (6)	1.3±0.09 (6)	1.4±0.09 (6)
Propranolol 50 µg (i.c.v.) + isoproterenol 200 µg (i.c.v.)	−0.8±0.08** (6)	0.4±0.07** (6)	0.5±0.05** (6)
Procain 100 µg (i.c.v.)	0.7±0.06 (4)	1.1±0.09 (4)	1.2±0.08 (4)

* Significantly different from corresponding control values (propranolol 200 µg), $p < 0.05$ (1-way analysis of variance). ** Significantly different from corresponding control values (isoproterenol 200 µg). $p < 0.05$ (1-way analysis of variance), The values are expressed as the mean ± SEM, followed by the numbers of rats in parentheses.



Changes in rectal temperature (ΔT_r), metabolic rate (ΔM), foot skin temperature (ΔT_f), tail skin temperature (ΔT_t) and respiratory evaporative heat loss (ΔE_{res}) produced by an injection of propranolol 200 µg into the lateral cerebral ventricle in a conscious rat at an ambient temperature (T_a) of 8 °C.

(100–400 µg) did produce a dose-dependent hypothermia in conscious rats at both 8 and 22 °C T_a (tables 1 and 2). The hypothermia induced by DL-propranolol was brought about by both decreased metabolism and cutaneous vasodilatation (as estimated by an increase in both the foot and the tail skin temperatures) (figure). However, in the heat (30 °C T_a), DL-propranolol administration produced no change in rectal or other thermoregulatory responses (table 1). The ineffectiveness of DL-propranolol in the heat was because the effectors of heat loss was already maximally activated, while the effector of heat production was already inactive[17,18]. Also, the present results show that systemic administration of propranolol (400 µg) produced an insignificant effect in thermoregulatory responses at all T_a studied (table 1). Thus, the data indicate that DL-propranolol increases heat loss and decreases heat production, which leads to hypothermia in the rat. Furthermore, the hypothermia induced by DL-propranolol was antagonized by pretreatment with isoproterenol (50 µg, lateral cerebral ventricle) (table 2).

Table 2 also showed that a larger dose (200 µg, lateral cerebral ventricle) of isoproterenol produced a hyperthermic action. The hyperthermia induced by isoproterenol was antagonized by pretreatment with a small dose (50 µg, lateral cerebral ventricle) of DL-propranolol. In the present study, antagonism by DL-propranolol of the temperature effects of isoproterenol is part of the indirect evidence that isoproterenol or DL-propranolol acts on beta-adrenoreceptors within the brain. Indeed, it was found that isoproterenol[12] decreased heat loss while DL-propranolol increased heat loss in the rat. However, it should be noted that both isoproterenol and DL-propranolol decrease heat production[12], which indicates that the simple model of a betareceptor agonist and a beta-receptor inhibitor does not apply to the central control of heat production.

Since DL-propranolol has local anesthetic action it is important to compare the effects on thermoregulation of intraventricular administration of both DL-propranolol and procaine. Table 2 shows that intraventricular administration of 100 µg of procaine produced a slight increase, rather than a decrease in the rectal temperature of conscious rats at 22 °C T_a. This suggests that the induced hypothermia is not due to the local anesthetic action of DL-propranolol.

1 This work was supported by the grants from the National Science Council (Republic of China) and the Pjing-Ling Neurological Foundation (Veterans General Hospital). The authors are grateful to Mr C.C. Wei for generous support.
2 J. Bruinvels, Neuropharmacology *9*, 277 (1970).
3 D.D. Avery, J. Physiol., Lond. *220*, 257 (1972).
4 A. Cantor and E. Satinoff, Brain Res. *108*, 125 (1976).
5 R.D. Myers and T.L. Yaksh, Physiol. Behav. *3*, 917 (1968).
6 B. Przewlocka and J. Kaluza, Pol. J. Pharmac. Pharm. *25*, 345 (1973).
7 A.L. Beckman, Am. J. Physiol. *218*, 1596 (1970).
8 P. Lomax, R.S. Foster and W.E. Kirpatrick, Brain Res. *15*, 431 (1969).
9 W. Feldberg and V.J. Lotti, Br. J. Pharmac. Chemother. *31*, 152 (1967).
10 E. Satinoff and A. Cantor, in: Temperature Regulation and Drug Action, p. 103. Ed. P. Lomax and J. Jacob. Karger, Basel 1975.
11 M.T. Lin, A. Chandra, Y.F. Chern and B.L. Tsay, Can. J. Physiol. Pharmac. *58*, 896 (1980).
12 M.T. Lin, A. Chandra, Y.C. Fan and R. Sun, Experientia *36*, 851 (1980).
13 J. DeGroot, J. Comp. Neurol. *113*, 389 (1959).
14 M.T. Lin, Y.F. Chern, Z. Wang and H.S. Wang, Can. J. Physiol. Pharmac. *57*, 469 (1979).
15 M.T. Lin, Y.F. Chern and A. Chandra, J. Pharmac. exp. Ther. *211*, 167 (1979).
16 M.T. Lin, F.F. Chen, Y.F. Chern and T.C. Fung, Can. J. Physiol. Pharmac. *57*, 1205 (1979).
17 M.T. Lin, J. Pharmac. exp. Ther. *209*, 349 (1979).
18 M.T. Lin, Y.F. Chern, G.G. Liu and T.C. Chang, Proc. nat. Sci. Counc. China *3*, 46 (1979).