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The catecholamine mechanisms of prostaglandin E_1-induced hypothermia in rats

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Intraperitoneal administration of prostaglandin E_1 (PGE_1) produced a hypothermia in rats at room temperature (22 °C). The hypothermia in response to PGE_1 was due to cutaneous vasodilatation and decreased metabolic heat production. Depletion of brain 5-hydroxytryptamine (with 5,6-dihydroxytryptamine and *p*-chlorophenylalanine) did not alter the PGE_1-induced hypothermia. However, depletion of brain catecholamines (with 6-hydroxydopamine) and blockade of central catecholaminergic receptors (with phentolamine and propranolol) both greatly reduced the PGE_1-induced hypothermia. The data indicate that PGE_1 lowers body temperature in rats by acting on the central catecholaminergic systems.

Intracerebral administration of prostaglandin E_1 (PGE_1) produces an increase in rectal temperature in animals (Milton & Wendlandt 1970, 1971; Stitt 1973). However, systemic administration of PGE_1 produces a fall, rather than a rise, in rectal temperature in rabbits (Lin 1978a) and rats (Lin 1979). Much evidence has suggested that monoaminergic systems within brain might be involved in the regulation of body temperature (Feldberg & Myers 1963, 1964; Hellon 1975). This raises a possibility that systemically administered PGE_1 produces a hypothermia via a modulation of monoaminergic transmission in the central nervous system. We have investigated the effects of monoamine depletors and receptor blockers on PGE_1-induced hypothermia in conscious rats, in order to test this possibility.

MATERIALS AND METHODS

Adult male Sprague-Dawley rats, 250–300 g, were housed individually in wire-mesh cages in a room of 25 ± 1·0 °C with natural light-dark cycles. The animals were given free access to tap water and granular feed supplied by Taiwan Sugar Corporation.

Surgical techniques. Each rat was anaesthetized with sodium pentobarbitone (6 mg/100 g, i.p.), and a craniotomy hole was drilled in the calvarium above the left lateral cerebral ventricle. The stereotaxic coordinates for the intraventricular injection were: AP, 4·8; Lat., 2·5; and Hor., 3·0 mm (DeGroot 1959). The correct positioning of the cannula was verified as 5 μl of 0·9% NaCl (saline) or the given drug solutions was permitted to flow in by gravity over about 20 s. A period of two weeks was permitted to allow the animals to recover from the operation before they were used unanaesthetized minimally restrained in rat stocks.

Drug solutions. All drugs were dissolved in pyrogen-free sterile saline and were prepared in pyrogen-free glassware which was baked at 180 °C for 5 h before use. The drugs administered intraperitoneally included prostaglandin E_1-sodium salt (PGE_1, donated by Upjohn, 0·1–2·0 mg kg^{-1}); and *p*-chlorophenylalanine methyl ester (PCPA, Sigma, 300 mg kg^{-1}, 72 h before). A 5 μl sample containing either 100 μg of 5,6-dihydroxytryptamine hydrochloride (5,6-DHT, Sigma), 100 μg 6-hydroxydopamine hydrobromide (6-OHDA, Sigma), 10 μg phentolamine (Sigma) or 30 μg propranolol (Sigma) was administered into the lateral cerebral ventricle through a ventricular guide tube. Dosage (as salts) were prepared on the day of testing.

Measurements of thermoregulatory function. Rectal (T_r) temperature was measured with a copper-constantan thermocouple enclosed in polyethylene tubing, sealed at one end, inserted 60 mm into the rectum. Tail (T_t) and foot (T_f) skin temperatures were also measured using copper-constantan thermocouples. Metabolic rate (M) was calculated from the animal's oxygen consumption assuming an RQ = 0·83 so that one litre of oxygen consumed h^{-1} was equivalent to a heat production of 5·6 W (Lin 1978a; Lin et al 1979a). Respiratory evaporative heat loss (E_{res}) was calculated by measuring the increase in water vapour content in the helmet effluent air over that of the ambient air. Evapora-

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tive heat loss expressed as watts was calculated from evaporative water loss assuming the latent heat of the vaporization of water to be 0·7 W h g^{-1} (Lin 1978a; Lin et al 1979a). These measurements were made in a small calorimeter. Measurements were taken one each minute throughout the experiments, each variable being measured as a d.c. potential. All temperatures, M and E_{res} were calculated instantaneously by computer and displayed in the laboratory.

Biochemical assays. Assay for monoamine in rats treated with 6-OHDA or 5,6-DHT were made 7 days after injection and in animals treated with PCPA 72 h after injection. The rats were decapitated, their brains rapidly removed. 5-HT, noradrenaline and dopamine assayed in each sample according to Atack & Lindqvist (1973), Boadle-Biber et al (1970), von Euler & Lishajko (1961), and Walters & Roth (1972) respectively.

The stereotaxic coordinates of ventricular cannulae were verified histologically.

Data collection and analysis. Rats were permitted 120 min to attain thermal balance before each drug injection. The maximal changes in T_x, T_f, T_t, M and E_{res} produced within a 60 min period after PGE_1 injection were expressed as ΔT_r, ΔT_f, ΔT_t, ΔM and ΔE_{res}, respectively.

RESULTS

Fig. 1 shows a typical thermal response produced by an intraperitoneal dose of 0·5 mg kg^{-1} of PGE_1 in a rat. Rectal temperature began to fall almost immediately after the injection. The hypothermia was due to decreased metabolic heat production and cutaneous vasodilatation (as estimated by an increase in both feet and tail skin temperatures). There were no changes in respiratory evaporative heat loss (Table 1). Saline i.p. or i.v.c. produced insignificant change in thermoregulatory responses.

The hypothermia induced by the systemically-administered PGE_1 was not affected by pretreatment of rats with 5,6-DHT or PCPA (Table 1). However, pretreatment with 6-hydroxydopamine (100 μg, lateral cerebral ventricle, 7 days before the

Table 1. Effects of 5,6-dihydroxytryptamine (5,6-DHT), *p*-chlorophenylalanine (PCPA), 6-hydroxydopamine (6-OHDA), phentolamine and propranolol treatment on the hypothermia induced by the systemically administered prostaglandin E_1 (PGE_1) in rats at an ambient temperature of 22 °C.

Treatment of animals	ΔT_r, °C	ΔT_f, °C	ΔT_t, °C	ΔM, W kg^{-1}	ΔE_{res}, W kg^{-1}
0·9% saline (i.c.v.) + PGE_1 0·5 mg kg^{-1} (i.p.), n = 8	37·5 ± 0·36–35·3 ± 0·26 (−2·2 ± 0·25)	4·8 ± 0·57	2·9 ± 0·35	−1·6 ± 0·36	0·04 ± 0·02
5,6-DHT 100 μg (i.c.v.) + PGE_1 0·5 mg kg^{-1} (i.p.), n = 8	37·3 ± 0·39–35·3 ± 0·23 (−2·0 ± 0·28)	5·2 ± 0·63	3·2 ± 0·57	−1·4 ± 0·44	0·05 ± 0·03
PCPA 300 mg kg^{-1} (i.p.) + PGE_1 0·5 mg kg^{-1} (i.p.), n = 8	36·6 ± 0·49–34·2 ± 0·41 (−2·4 ± 0·33)	5·7 ± 0·69	3·5 ± 0·61	−1·8 ± 0·45	0·06 ± 0·03
6-OHDA 100 μg (i.c.v.) + PGE_1 0·5 mg kg^{-1} (i.p.), n = 8	37·2 ± 0·35–36·3 ± 0·28 (−0·9 ± 0·17)*	2·0 ± 0·38	1·3 ± 0·18	−1·0 ± 0·22	0·05 ± 0·02
Phentolamine 10 μg (i.c.v.) + PGE_1 0·5 mg kg^{-1} (i.p.), n = 8	37·8 ± 0·32–36·8 ± 0·27 (−1·0 ± 0·19)*	2·4 ± 0·42	1·5 ± 0·21	−0·8 ± 0·20	0·04 ± 0·02
Propranolol 30 μg (i.c.v.) + PGE_1 0·5 mg kg^{-1} (i.p.), n = 8	37·6 ± 0·37–36·8 ± 0·26 (−0·8 ± 0·14)*	1·6 ± 0·33	1·2 ± 0·23	−0·7 ± 0·18	0·06 ± 0·03

* Significantly different from the control value (saline + PGE_1 group), *P* value less than 0·05 (one way analysis of variance). n, Number of rats tested. The values are expressed as means ± s.e.m. i.c.v. injection to lateral cerebral ventricle.

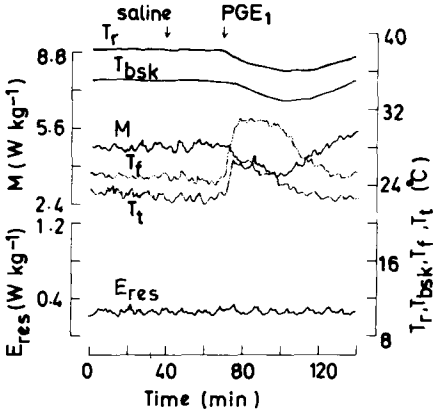

FIG. 1. Thermal responses produced by an injection of 0·5 mg kg^{-1} of PGE_1 into the peritoneal cavity in a conscious rat at an ambient temperature (T_a) of 22 °C.

PGE_1 injection), phentolamine (10 μg, lateral cerebral ventricle, 30 min before the PGE_1 injection) or propranolol (30 μg, lateral cerebral ventricle, 30 min before the PGE_1 injection) greatly reduced the PGE_1 hypothermia (Table 1, Fig. 2). This attenuation was due to the reduced metabolic and vasomotor responses to PGE_1 challenge (Table 1).

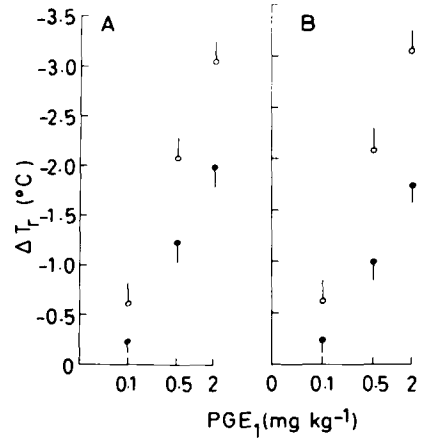

FIG. 2. A. Effects of phentolamine (10 μg lateral cerebral ventricle) treatment on the hypothermia induced by PGE_1 (i.p.). Each point contains the results from 6 animals. The points represent the mean reduction in rectal temperature (ΔT_r in degrees Celsius) and the vertical bars denote ± s.e.m. at room temperature (22 °C).
(B.) Effects of propranolol (30 μg, lateral cerebral ventricle) treatment on the hypothermia induced by PGE_1 (i.p.). Each point contains the results from 6 animals. The points represent the mean reduction in rectal temperature (ΔT_r in degrees Celsius) and the vertical bars denote ± s.e.m. at room temperature (22 °C).

The rats pretreated with 5,6-DHT, PCPA, 6-hydroxydopamine, phentolamine or propranolol maintained their rectal temperatures within a normal limit (36·6–37·8 °C) (Table 1).

Table 2 summarizes the effects of 5,6-DHT, PCPA and 6-hydroxydopamine on the monoamine contents of the rat brain during the time at which the thermal experiments were being conducted, 5,6-DHT and PCPA significantly reduced brain 5-HT concentrations but negligibly changed brain catecholamine values while, 6-hydroxydopamine significantly reduced brain catecholamine values and only negligibly changed brain 5-HT.

Table 2. Effects of 6-hydroxydopamine, 5,6-dihydroxytryptamine and *p*-chlorophenylalanine treatment on monoamine contents of the rat brain.

Treatment	Brain concentration, ng g^{-1} Noradrenaline	Dopamine	5-HT
0·9% saline, i.c.v.	597 ± 90·1 (5)	765 ± 79·3 (5)	567 ± 75·4 (5)
6-OHDA 100 μg, i.c.v.	290 ± 53·2* (5)	343 ± 56·8* (5)	520 ± 65·6 (5)
5,6-DHT 100 μg, i.c.v.	542 ± 46·7 (5)	802 ± 93·4 (5)	190 ± 43·6* (5)
PCPA 300 mg kg^{-1} i.p.	564 ± 62·3 (5)	732 ± 89·6 (5)	168 ± 33·1* (5)

* Significantly different from corresponding control value, *P* value less than 0·05 (one way analysis of variance). The values are expressed as the mean ± s.e.m., followed by the number of animals in parentheses. Injection c.v., into lateral cerebral ventricle.

DISCUSSION

The present results showed that systemic administration of PGE_1 produced a dose-dependent hypothermia in conscious rats at room temperature (22 °C). The hypothermia in response to PGE_1 was due to decreased metabolic heat production and cutaneous vasodilatation (as estimated by an increase in cutaneous temperatures). The data indicate that PGE_1 decreases heat production and increases heat loss and finally leads to hypothermia in rats.

The major interest was to explore the possible involvement of the monoaminergic pathways within brain in the elaboration or modulation of the hypothermia induced by the systemically-administered PGE_1 in rats.

Our recent findings revealed that activation of 5-HT-ergic receptors within brain with either the 5-HT precursor 5-hydroxytryptophan (Lin et al 1978b) or the specific inhibitors of uptake pump in 5-HT-ergic neurons such as fluoxetine and chlorimipramine (Lin 1978b), reduced rectal temperature in rats at 22 °C. The hypothermia induced by 5-HT-ergic receptor activation was also due to

decreased metabolic heat production and cutaneous vasodilation in rats. This is consistent with that of PGE_1 demonstrated in the present study. However, the present results did show the PGE_1-induced hypothermia was not affected by the depletion of brain 5-HT pathways (with both 5,6-DHT and PCPA), suggesting that PGE_1 may not act through the central 5-HT-ergic pathways to exert its hypothermic actions.

On the other hand, the present results showed that either depletion of central catecholamine pathways (with 6-hydroxydopamine) or blockade of central catecholamine receptors (with both phentolamine and propranolol) greatly reduced the hypothermia induced by the systemically-administered PGE_1. Inhibition of the hypothermia following intraperitoneal PGE_1 could not be due to brain tissue damage or pyrexia resulting from contaminant pyrogens, since the animals maintained their rectal temperatures within a normal limit (36·6–37·8 °C at an ambient temperature of 22 °C). Thus, the data indicate that the systemically-administered PGE_1 may act through the central catecholamine pathways to exert its hypothermic effects in rats. Indeed, intracerebral administration of noradrenaline was shown to produce a hypothermia in rats at room temperature (Avery 1972). Both systemic and central administration of dopamine (Bruinvels 1970), apomorphine (a dopaminergic agonist) (Kruk 1972; Cox & Lee 1977; Lin et al 1979b) or ephedrine (an adrenergic agonist) (Lin et al unpublished data) were also shown to produce a hypothermia in rats at room temperature. Again, the hypothermia in response to either dopamine, apomorphine or ephedrine was due to both decreased metabolic heat production and cutaneous vasodilatation. However, intraventricular administration of noradrenaline was shown to produce a hyperthermia in rats by many other investigators (Feldberg & Lotti 1967; Myers & Yaksh 1968). Thus while the results reported here are consistent with a catecholaminergic mechanism of the hypothermia induced by the systemically-administered PGE_1, other evidence indicated a need for caution in offering such an interpretation.

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