

CENTRAL CARDIOVASCULAR AND THERMAL EFFECTS OF PROSTACYCLIN IN RATS¹

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ABSTRACT

Prostacyclin (PGI₂) induced a dose-dependent decrease in blood pressure with slight increases in heart rate and body temperature, when administered at the doses of 0.1-100 µg into the lateral cerebral ventricle (i.c.v.) of the urethane-anaesthetised rat. When the same doses were administered intravenously, both the blood pressure and heart rate decreased. Central pretreatment with sodium meclofenamate (1 mg/rat i.c.v.) antagonised the central hypotensive effect of PGI₂ but i.c.v. pretreatment of the rats with indomethacin (1 mg/rat) failed to affect the PGI₂-induced hypotension. Central pretreatment with two histamine H₂-receptor antagonists, cimetidine (500 µg/rat i.c.v.) or metiamide (488 µg/rat i.c.v.), antagonised the blood pressure lowering effect of 0.1 µg dose of PGI₂ but failed to affect the hypotension induced by higher PGI₂ doses. Therefore the main central hypotensive effect of PGI₂ seems not to be associated with the stimulation of histamine H₂ -receptors in the brain.

The hypotensive effect of i.c.v. administered PGI₂ appears to be due to an action upon the central nervous system rather than to a leakage into the peripheral circulation. This assumption is supported by the fact that sodium meclofenamate i.c.v. antagonised the effect of PGI₂. In addition, the chronotropic response to i.c.v. PGI₂ was opposite to that induced by intravenous administration. The results also suggest that there may be differences in the mode of action between sodium meclofenamate and indomethacin.

INTRODUCTION

Prostacyclin (PGI₂) is formed from arachidonic acid in the rat brain (2). Intravenously (i.v.) administered PGI₂ causes a fall in blood pressure and a slowing of the heart rate in the conscious rat (3). Recently it was reported that intracerebroventricular (i.c.v.) administration of PGI₂ induces a decrease in blood pressure of conscious rats (4). However, the possible concomitant effects of centrally administered PGI₂ on heart rate and body temperature have not been reported.

In the present study increasing doses of PGI₂ were administered i.c.v. or i.v. to urethane-anaesthetised rats in order to obtain simultaneous recordings of blood pressure, heart rate and body temperature. Since sodium meclofenamate interferes with the effects of exogenous prostaglandins both in the peripheral tissues (5,6,7) and in the brain (8), it seemed worthwhile to examine the influence of this agent on the

¹ A preliminary report of this work has been presented at the Joint Meeting of the German and Scandinavian Pharmacological Societies in Travemünde, FRG (1)

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central effects of PGI₂. For comparison, the effect of indomethacin, an equally effective inhibitor of prostaglandin biosynthesis as sodium meclofenamate (9), was studied. In our previous studies indomethacin and paracetamol antagonised the central hypotensive effect of clonidine (10). The hypotensive effect of clonidine can also be blocked by histamine H₂-receptor antagonists (11). Therefore the influence of cimetidine and metiamide, two histamine H₂-receptor antagonists (11), on the central PGI₂-induced hypotension was also studied.

MATERIALS AND METHODS

Male Wistar rats (260-360 g) were used. The rats were accommodated to standard ambient conditions for at least one week before the experiments. The lights were on from 6 a.m. to 6 p.m. and the room was completely dark during the remaining 12 hours. The temperature was kept at 22 °C and the relative humidity at 40%. The rats received standard rat pellets and tap water *ad libitum*.

The rats were anaesthetised with urethane (1.5 g/kg i.p.). The trachea was cannulated with a polyethylene tube and the rats were allowed to breathe spontaneously. The mean arterial blood pressure was measured from the left femoral artery by means of a pressure transducer (Hewlett Packard 1280). The heart rate was calculated from the pulse waves by means of a rate computer (Hewlett Packard 8812A). The left femoral vein was cannulated for intravenous injections. The rats were mounted in a stereotaxic instrument and tilted caudally so that the body formed an angle of 10 degrees with the horizontal plane. Intracerebroventricular injections were performed as described in detail by Paakkari (12). Briefly, an injection needle was introduced into the right lateral ventricle of the brain. A polyethylene catheter, filled with the drug or control solution to be infused, was attached to the needle and the desired amount of the solution was allowed to flow slowly by virtue of the hydrostatic pressure. The infusion was stopped by closing the upper end of the catheter. The proper position of the needle tip was ascertained at the end of each experiment by an injection of dye (Giemsa Solution, Merck) into the cerebral ventricle. The body temperature was measured rectally with a temperature recorder (ELLAB instruments, type TE 3, Copenhagen), a probe being introduced 5 cm into the rectum. A 60 W heating lamp was placed 20 cm above the rat. Experiments on control rats showed that this distance of the heating lamp was adequate to keep the body temperature at 37.1±0.4 °C (mean±s.e.m.) in an ambient temperature of 22 °C.

Administration of drugs

Prostacyclin (PGI₂) sodium salt (kindly supplied by Dr. Pike, Upjohn Co.) was dissolved in 0.05% (w/v) NaOH, pH 12. The stock solution of PGI₂, 10 mg/ml, was stored at 0 °C for 6 days maximally and further diluted immediately before each i.c.v. or i.v. injection. The dilutions were made in 0.9% (w/v) NaCl (saline) for i.v. injections and for i.c.v. injections in a modified Krebs-Ringer bicarbonate buffer (NaCl 117 mM, KCl 2.95 mM, CaCl₂ 1.44 mM, KH₂PO₄ 0.01 mM, MgSO₄·x 7H₂O 1.12 mM and NaHCO₃ 23.6 mM, pH 7.32) to simulate the concentrations found in the cerebrospinal fluid (13). The injection volume was 0.15 ml each for i.v. injections and 10 µl each for i.c.v. injections. The control

animals received the same volume of the appropriate vehicle in each case (for the 100 μg dose of PGI_2 the vehicle was 0.05% NaOH). Increasing doses of PGI_2 were injected i.c.v. at 45 min intervals in order to obtain time-response curves for various doses of PGI_2 . The i.v. injections were performed at 20 min intervals so that the effect of the preceding dose had completely subsided.

Indomethacin (Orion Pharmaceutical Co., Helsinki) was dissolved in 0.25 N NaOH and sodium meclofenamate monohydrate (Parke, Davis & Co.) in saline. Cimetidine and metiamide (Smith, Kline and French Laboratories Ltd.) were dissolved in 1 N HCl, pH adjusted to 6 with 0.1 N NaOH and then further diluted with saline. The influence of indomethacin, sodium meclofenamate, cimetidine and metiamide on the central hypotensive effect of PGI_2 was studied after administration of these drugs i.c.v. 10-20 min before the administration of the first dose of PGI_2 i.c.v. When increasing doses of PGI_2 were administered i.c.v. at 20 min intervals, the hypotensive effect of the preceding dose had wholly subsided. The control animals received the same volume of the appropriate solvent in each case.

The fall in blood pressure by hypotensive drugs is proportional to the blood pressure level before the administration of the drug (14). To minimize the influence on the results of different blood pressure levels before the administration of the hypotensive agents, the hypotensive responses were calculated as percentages rather than absolute values.

The Student's t-test was used to calculate the statistical significance of the differences between the control and experimental groups.

RESULTS

I Effects of prostacyclin in non-pretreated rats

Effect of PGI_2 on blood pressure (Fig. 1 and 2)

Intracerebroventricular administration of PGI_2 at the doses of 0.1-100 $\mu\text{g}/\text{rat}$ decreased the blood pressure in a dose-related manner. Intravenously, PGI_2 (0.001-100 $\mu\text{g}/\text{rat}$) was even more potent as a hypotensive agent. The PGI_2 -induced hypotension was short-lasting both upon i.c.v. and i.v. administrations. The maximum effect was reached 1-2 min after each injection and the effect was completely abolished in 10-20 min, with the exception of the largest i.v. dose which lowered blood pressure for 20-25 min. A slight hypertensive effect was observed after hypotension at the PGI_2 doses of 1-100 μg i.c.v. A negligible rise of blood pressure followed the hypotension also after administrations of 1-10 μg doses of PGI_2 i.v.

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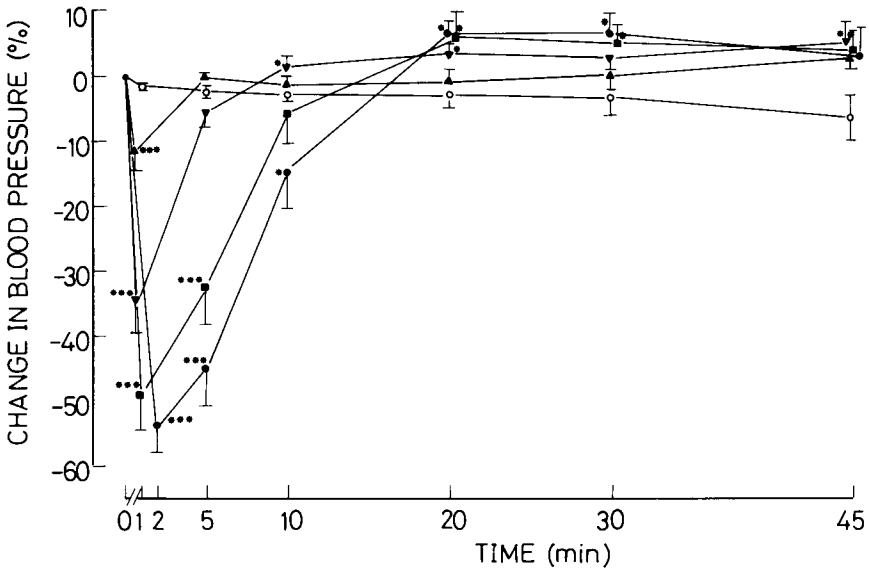


Figure 1. Time-response effect of i.c.v. administered PGI₂ on blood pressure in urethane-anaesthetised rats. Increasing doses of PGI₂ were administered i.c.v. at 45 min intervals. The blood pressure level (mean \pm s.e.m.) before each i.c.v. injection was 118 ± 6 mm Hg in the control group (○—○), 108 ± 7 mm Hg in the 0.1 μ g of PGI₂ group (▲—▲), 112 ± 9 mm Hg in the 1 μ g of PGI₂ group (▼—▼), 117 ± 9 mm Hg in the 10 μ g of PGI₂ group (■—■) and 120 ± 10 mm Hg in the 100 μ g of PGI₂ group (●—●). The differences between the baseline levels of the groups are not statistically significant. Vertical bars indicate s.e.m. Control group comprised 10 rats, other groups 6 rats. * $p < 0.05$, ** $p < 0.005$ and *** $p < 0.001$ vs. control group.

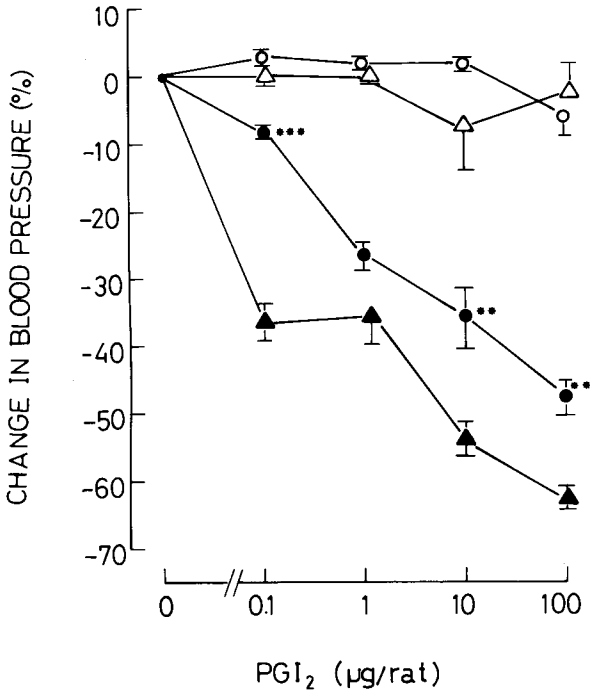


Figure 2. Dose-response effect of PGI₂ on blood pressure in urethane-anesthetised rats. Increasing doses of PGI₂ were administered i.c.v. (●—●) or i.v. (▲—▲) at 20 min intervals. Open symbols are vehicle controls. The decreases in blood pressure represent the maximum effects 1-2 min after each injection. The decreases in blood pressure induced by each PGI₂ dose are significant at the p<0.001 level as compared to the control values. The significance of the differences between the i.c.v. and i.v. groups are indicated by asterisks; **p<0.005 and ***p<0.001. Vertical bars indicate s.e.m. Each group comprised 6 rats.

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Effect of PGI_2 on heart rate (Fig. 3)

Intracerebroventricularly, PGI_2 at the doses of 0.1-100 $\mu\text{g}/\text{rat}$ induced a negligible increase in heart rate. The maximum effect was reached 1-2 min after each injection and lasted 10-20 min with the exception of the largest dose which increased heart rate for 45 min. When administered intravenously, the same doses of PGI_2 had a slight bradycardic effect which was very short-lasting. The maximum decrease in heart rate was achieved 1-2 min after each injection and the effect was completely abolished in 5 min.

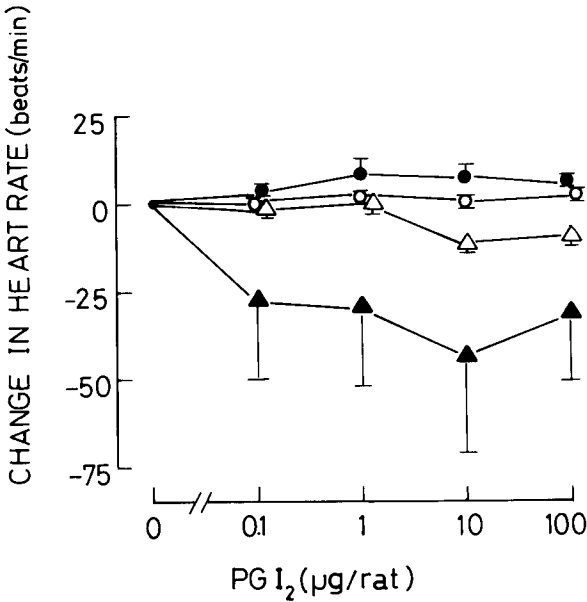


Figure 3. Dose-response effect of PGI_2 on heart rate in urethane-anesthetized rats. Increasing doses of PGI_2 were administered i.c.v. (●—●) or i.v. (▲—▲) at 20 min intervals. The changes in heart rate represent the maximum effects 1-2 min after each injection. The differences in the changes of heart rate are not statistically significant. Vertical bars indicate s.e.m. Each group comprised 6 rats.

Effect of PGI₂ on body temperature (Fig. 4)

PGI₂ at the i.c.v. doses of 0.1-100 µg/rat slightly increased the body temperature. The maximum rise, about 0.5°C, was reached with the PGI₂ dose of 1 µg/rat. Intravenously, PGI₂ (0.001-100 µg/rat) did not induce any significant changes in body temperature (results not shown).

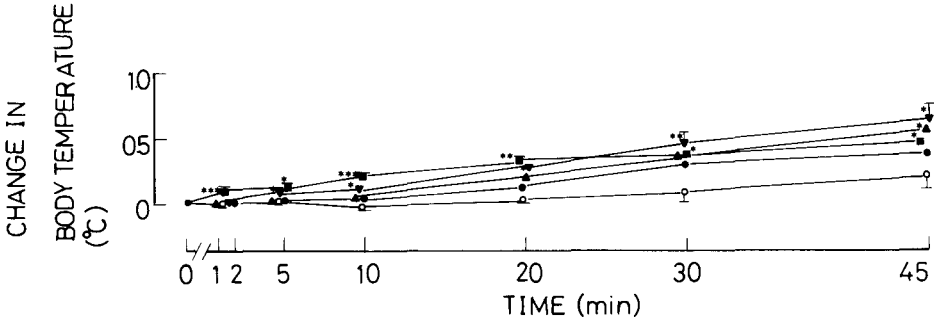


Figure 4. Time-response effect of i.c.v. administered PGI₂ on body temperature in urethane-anaesthetised rats. Increasing doses of PGI₂ were administered i.c.v. at 45 min intervals. The body temperature level (mean ± s.e.m.) before each i.c.v. injection was 36.7 ± 0.4°C in the control group (o—o), 36.0 ± 0.4°C in the 0.1 µg of PGI₂ group (▲—▲), 36.5 ± 0.5°C in the 1 µg of PGI₂ group (▼—▼), 37.1 ± 0.5°C in the 10 µg of PGI₂ group (■—■) and 37.7 ± 0.5°C in the 100 µg of PGI₂ group (●—●). Vertical bars indicate s.e.m. Control group comprised 10 rats, other groups 6 rats. *p<0.05, **p<0.005 and ***p<0.001 vs. control group.

II Effects of sodium meclofenamate and indomethacin

Centrally administered sodium meclofenamate (1 mg/rat i.c.v.) induced a slight increase in heart rate but had no significant effects on the baseline values for blood pressure or body temperature. Indomethacin (1 mg/rat i.c.v.) did not affect blood pressure, heart rate or body temperature.

III Effect of prostacyclin on blood pressure in sodium meclofenamate and indomethacin pretreated rats (Fig. 5)

Central pretreatment of the rats with sodium meclofenamate (1 mg/rat i.c.v.) antagonised the hypotensive effect of i.c.v. administered PGI₂ shifting the dose-response curve for PGI₂ significantly to the right. Pretreatment with indomethacin (1 mg/rat i.c.v.) inhibited the hypotensive response to the 0.1 µg dose of PGI₂ but failed to antagonise the blood pressure lowering effect of higher doses.

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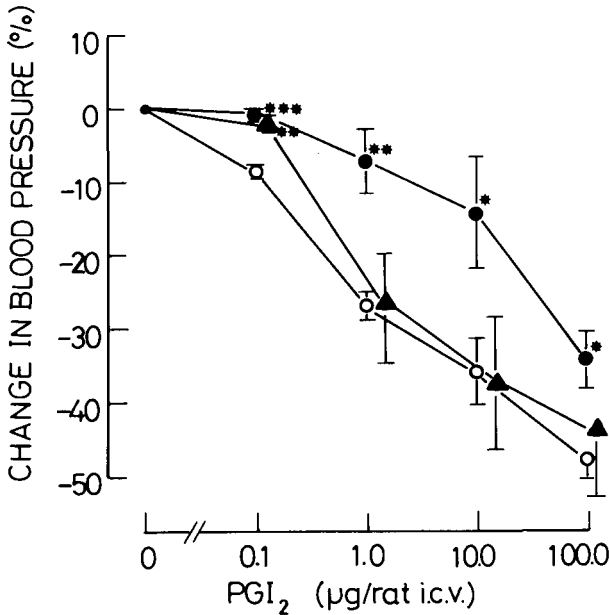


Figure 5. Effect of i.c.v. administered PGI₂ on blood pressure in sodium meclofenamate and indomethacin pretreated rats. Sodium meclofenamate, 1 mg/rat (●—●), indomethacin, 1 mg/rat (▲—▲) or vehicle (○—○) was administered i.c.v. 20 min before commencement of the administration of PGI₂. Increasing doses of PGI₂ were administered i.c.v. at 20 min intervals. The maximum changes in blood pressure at 1-2 min after each injection are shown. Vertical bars indicate s.e.m. Control group comprised 6 rats, sodium meclofenamate and indomethacin pretreated groups also 6 rats, except for the last dose (4 rats). *p<0.05

p<0.005 and *p<0.001 vs. control group.

IV Effects of cimetidine and metiamide

Centrally administered cimetidine (500 µg/rat i.c.v.) induced a significant rise of blood pressure but had no effect on heart rate or body temperature. Metiamide (488 µg/rat i.c.v.) induced short-lasting initial hypertensive and tachycardic effects. However, there was no significant difference between the baseline levels for blood pressure, heart rate or body temperature between metiamide and vehicle treated groups (see fig. 6).

V Effect of prostacyclin on blood pressure in cimetidine and metiamide pretreated rats (Fig. 6)

Central pretreatment with cimetidine (500 µg/rat i.c.v.) or metiamide

(488 $\mu\text{g}/\text{rat}$ i.c.v.) antagonised the hypotensive effect of 0.1 μg of PGI_2 i.c.v. but did not significantly influence the blood pressure lowering effect of higher PGI_2 doses.

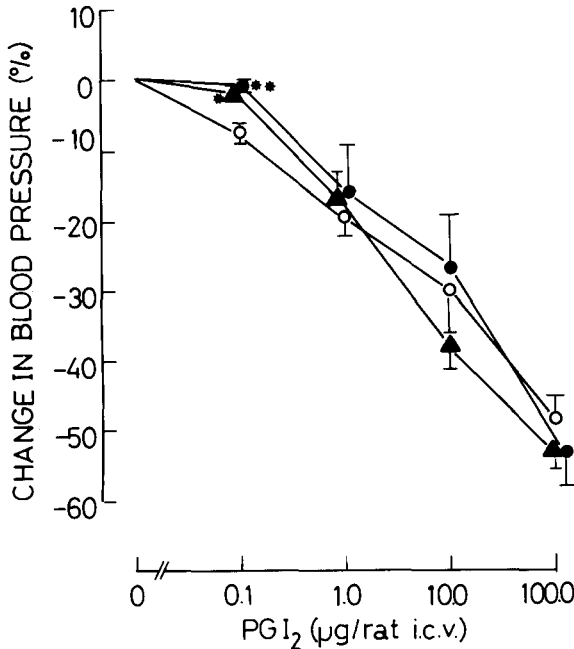


Figure 6. Effect of i.c.v. administered PGI_2 on blood pressure in cimetidine and metiamide pretreated rats. Cimetidine, 500 $\mu\text{g}/\text{rat}$ (▲—▲), metiamide, 488 $\mu\text{g}/\text{rat}$ (●—●), or vehicle (○—○) was administered i.c.v. 10 or 15 min before commencement of the administration of PGI_2 . Increasing doses of PGI_2 were administered i.c.v. at 20 min intervals. The maximum changes in blood pressure at 1-2 min after each injection are shown. Vertical bars indicate s.e.m. Each group comprised 6 rats. * $p < 0.05$ and ** $p < 0.005$ vs. control group.

DISCUSSION

PGI_2 i.c.v. decreased the blood pressure of urethane-anaesthetised rats in a dose-related manner and slightly increased the heart rate and body temperature. PGI_2 lowered the blood pressure also after intravenous administration. Since prostaglandins are known to cross the blood-brain barrier (15), the possibility cannot be excluded that the results obtained are due to a leakage of PGI_2 into the peripheral circulation. However, the rapid onset of the hypotensive response after i.c.v. adminis-

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trations suggests that this effect may have been due to an influence of PGI_2 on the blood pressure regulating centres of the brain. In addition, PGI_2 slightly decreased the heart rate upon intravenous administration. Moreover, PGI_2 elevated the body temperature upon i.c.v. but not upon i.v. administrations. This finding further suggests that the effects of centrally administered PGI_2 are due to an action on the structures of the brain. The antagonism of the hypotensive effect of PGI_2 by central pretreatment with sodium meclofenamate also lends support to the assumption of a central site of action for PGI_2 . In agreement with the present results i.c.v. applied PGI_2 at the doses of 1.25-10 $\mu\text{g}/\text{kg}$ dose-dependently decreased the blood pressure of conscious rats (4). Since PGI_2 is abundantly present in the brain (2, 16, 17, 18) and exerts a strong dose-related hypotensive effect also after central administration, this agent might be associated with the central control of blood pressure.

Centrally administered arachidonic acid and several of its metabolites, including PGE_2 and $\text{PGF}_{2\alpha}$, induce hyperthermia both in urethane-anaesthetised (8,19,20,21) and conscious rats (22). In fact, in our previous study with urethane-anaesthetised rats (8) $\text{PGF}_{2\alpha}$ i.c.v. had a strong dose-dependent hyperthermic effect with a maximum about $+2.6^\circ\text{C}$. Hyperthermia following i.c.v. administration of PGI_2 has been reported in conscious cats and rabbits but the doses of PGI_2 sufficient to induce temperature rises were over 10 times higher than those of PGE_2 (23). Furthermore, i.c.v. administration of PGI_2 at the doses of 50-500 $\mu\text{g}/\text{kg}$ caused dose-dependent hypothermic response in conscious guinea-pigs whereas smaller doses (3-30 $\mu\text{g}/\text{kg}$) had no consistent effect on body temperature (24). In the present study PGI_2 i.c.v. had only weak effect on body temperature of urethane-anaesthetised rats. The failure of PGI_2 to induce any considerable temperature change could hardly be due to the use of alkaline solvent, since NaOH at even more alkaline concentrations than used here had no effect on the hyperthermic responses to $\text{PGF}_{2\alpha}$ or PGE_2 in rats (own unpublished findings). Thus PGI_2 , unlike the other prostaglandins, seems to interfere preferentially with the central blood pressure regulation but not or only minimally with the central thermoregulation of the rat.

Central pretreatment with sodium meclofenamate antagonised the central hypotensive effect of PGI_2 , while indomethacin did not share this effect. This finding lends further support to our previous suggestion that there may be differences in the mode and/or site of action between sodium meclofenamate and indomethacin. Since indomethacin is a highly lipid-soluble agent (25), the possibility cannot be excluded that the lack of effect of indomethacin is due to its leakage into the periphery. Previous studies have shown that, in addition to the potent inhibition of prostaglandin biosynthesis (9), sodium meclofenamate and the other fenamates also antagonise the effects of exogenous prostaglandins in many peripheral tissues (5,6,7). However, the central cardiovascular and thermal effects of $\text{PGF}_{2\alpha}$ were not influenced by central pretreatment with sodium meclofenamate but, paradoxically, were enhanced by subcutaneous pretreatment with this agent (8).

The antihypertensive agent clonidine is known to stimulate the synthesis of prostaglandins in the rat brain (26). Indomethacin and paracetamol which both effectively inhibit the brain prostaglandin synthesis (27) antagonised the central hypotensive effect of clonidine in rats (10). It has been therefore suggested that PGI_2 or some other hypotensive meta-

bolite of arachidonic acid in the rat brain might be associated with the central hypotensive effect of clonidine (10). Clonidine stimulates also histamine H₂-receptors in the brain (11). Central pretreatment with the histamine H₂-receptor antagonists blocks the hypotensive effect of clonidine (11). Thus the stimulation of the histamine H₂-receptors has been implicated in the central hypotensive effect of clonidine (11). In the present study central pretreatment with cimetidine or metiamide, two antagonists of the histamine H₂-receptors (11), abolished the slight hypotensive response to 0.1 µg of PGI₂ but did not affect the blood pressure lowering effect of higher doses. The lack of antagonism at the higher doses of PGI₂ might indicate that the dose of cimetidine and metiamide was just not adequate to provide receptor blockade in the appropriate part of the brain. However, both cimetidine and metiamide blocked effectively the histamine H₂-receptors even at lower doses than those used in the present experiments (28). Furthermore, the central hypothermic effect of PGI₂ in guinea-pigs was attenuated by considerable smaller doses of metiamide than that used in this study (24). The hypotensive effect of PGI₂ i.c.v. seems therefore not to involve a stimulation of cerebral histamine H₂-receptors.

Since PGI₂ is present in the brain (2,6,17,18) and exerts strong dose-related hypotensive effect upon central administration, this agent might participate in the central regulation of blood pressure.

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