Acta Physiol Scand 1982, 116: 229–234

Central cardiovascular and thermal effects of prostaglandin E_2 in rats[1]

ANNA-LENA SIRÉN

Department of Pharmacology, University of Oulu, SF-90220 Oulu 22, Finland

SIRÉN, A.-L.: Central cardiovascular and thermal effects of prostaglandin E_2 in rats. Acta Physiol Scand 1982, 116: 229–234. Recseived 1 March 1982. ISSN 0001-6772. Department of Pharmacology, University of Oulu, Finland.

Prostaglandin E_2 (PGE_2) increased the blood pressure, heart rate and body temperature, when administered at the doses of 0.001–10 μg into the lateral cerebral ventricle (i.c.v.) of the urethane-anesthetised rat. The highest dose of 10 μg/rat induced a strong initial hypotensive effect. Intravenously (i.v.), PGE_2 at the doses of 0.01–10 μg/rat caused a biphasic blood pressure response with dose-related initial decreases followed by slight increases in blood pressure. The heart rate and body temperature were slightly increased by i.v. administrations of PGE_2. The highest i.v. dose of 10 μg/rat initially decreased also the heart rate. Central pretreatment with indomethacin (1 mg/rat i.c.v.) partly antagonised all of the recorded central effects of PGE_2, while sodium meclofenamate (1 mg/rat i.c.v.) abolished the hypertensive response to i.c.v. administered PGE_2 but failed to significantly affect the PGE_2-induced rises of heart rate and body temperature. The results support the previous suggestions that PGE_2 may participate in the central cardiovascular and thermoregulatory control. The results also suggest that indomethacin and sodium meclofenamate antagonize the effects of exogenous prostaglandins. Since sodium meclofenamate, unlike indomethacin, affected preferentially the hypertensive response to centrally administered PGE_2, there may be differences in the sites and/or modes of action between these drugs.

Prostaglandin E_2 (PGE_2) is found in the rat brain (Abdel-Halim et al. 1977), but its possible physiological functions in the central nervous system are not known. Some investigators have suggested that prostaglandins may be involved in the central control of the cardiovascular and thermoregulatory systems (Coceani 1974, Karppanen et al. 1979). PGE_2 raised the blood pressure and heart rate of conscious rats upon intracerebroventricular (i.c.v.) administration (Hoffman & Schmid 1979). Prostaglandins of the E-series are also highly active hyperthermic agents in the brain (Milton 1976, Splawiński et al. 1978). However, the possible association between the cardiovascular and thermal effects of centrally administered PGE_2 has not been studied.

In the present study increasing doses of PGE_2 were administered intravenously (i.v.) or i.c.v. to the urethaneanesthetised rat in order to obtain complete simultaneous cumulatative dose-response curves for blood pressure, heart rate and body temperature. Since sodium meclofenamate interferes with the actions of exogenous prostaglandins both in the peripheral tissues (Bennett et al. 1980*a*, *b*) and in the brain (Karppanen et al. 1979, Sirén 1981*a*, *b*), it seemed worthwhile to examine the influence of this agent on the central effects of PGE_2. For comparison, the effects of indomethacin, an equally effective inhibitor of prostaglandin synthesis as sodium meclofenamate (Flower 1974), were 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 h. The temperature was kept at 22°C and the relative humidity at 40%. The rats received standard rat pellets (Hankkija Oy, Helsinki) and tap water ad libitum.

The rats were anesthetised with urethane (1.5 g/kg intraperitoneally). The trachea was cannulated with a poly-

[1] A preliminary report of this work has been presented at the XXXII Meeting of the Scandinavian Pharmacological Society (Sirén 1981*a*).

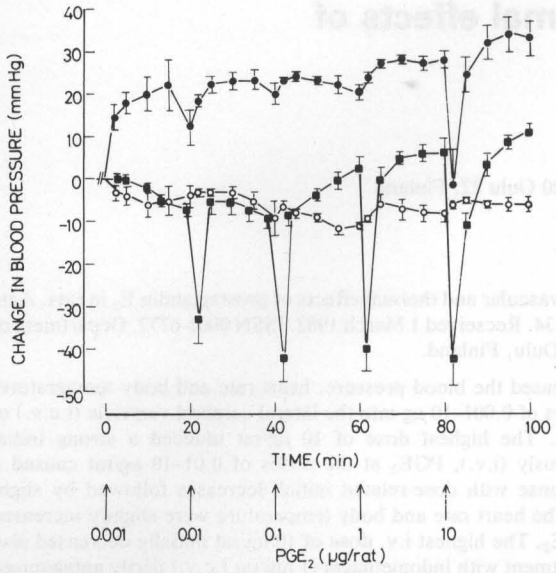

Fig. 1. Time-dose-response effect of PGE_2 on blood pressure in urethane-anesthetised rats. Increasing doses of PGE_2 were administered i.c.v. (●—●) or i.v. (■—■) at 20 min intervals. Open circles represent the vehicle i.c.v. controls. The initial blood pressure level (mean±SE) before commencement of the PGE_2 or vehicle administrations was 110±10 mmHg in the control group, 113±8 mmHg in the PGE_2 i.c.v. group and 102±6 mmHg in the PGE_2 i.v. group. The differences between the initial levels of the groups are not statistically significant. The rises of blood pressure induced by PGE_2 i.c.v. at the doses of 0.001–10 µg/rat differ significantly ($p<0.05$–0.001) from both the control group and the PGE_2 i.v. group. Vertical bars indicate SE. Each group comprised 6 rats.

ethylene 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 i.v. injections. The rats were mounted in a stereotaxic instrument and tilted caudally so that the body formed an angel of 10° with the horizontal plane. I.c.v. injections were performed as described in detail by Paakkari (1980). 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 36.9±0.3°C (mean ±SE) in an ambient temperature of 22°C.

Administration of drugs

Prostaglandin E_2 (PGE_2), kindly supplied by Dr J. Pike of the Upjohn Laboratories, was dissolved in absolute ethanol (10 mg/ml) and stored at −20°C. Further dilutions were made freshly each day in 0.9% (w/v) NaCl (saline) for i.v. injections, and in a modified Krebs-Ringer bicarbonate buffer (see Karppanen et al. 1979) for i.c.v. injections. These were given in a volume of 10 µl each and the i.v. injections in a volume of 0.15 ml each. The control animals received the same volume of the vehicle (buffer or saline solution with the corresponding concentration of ethanol as in the drug solution) in each case. Increasing doses of PGE_2 were administered i.c.v. at 20 min intervals in order to obtain cumulative dose-response curves. This interval was chosen because in the preliminary experiments (PGE_2 administered at 45 min intervals) the maximum cardiovascular effects of PGE were reached within 15–20 min after each i.c.v. injection. For comparison, the i.v. injections were also repeated at 20 min intervals to make sure that the effects induced by centrally administered PGE_2 were not due to a leakage of the drug into the peripheral circulation.

Indomethacin (Orion Pharmaceutical Co., Helsinki) was dissolved in 0.25 N NaOH and sodium meclofenamate monohydrate (Parke, Davis & Co.) in saline. The influence of central pretreatment with indomethacin or sodium meclofenamate on the central effects of PGE_2 was studied by injecting these drugs i.c.v. at a dose of 1 mg/rat 20 min before commencement of the administrations of increasing doses of PGE_2 i.c.v. The control animals received the same volume of saline or NaOH in each case.

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 prostaglandin E_2 in non-pretreated rats*

Effect of PGE_2 on blood pressure (Fig. 1). Intracerebronventricular administration of PGE_2 at the doses of 0.001–10 µg/rat raised the blood pressure. The maximum pressor effect was reached 15 to 20 min after each injection. At the highest dose of 10 µg/rat PGE_2 i.c.v. induced an initial hypotensive effet which had its maximum 1–2 min after the injection. The initial hypotension was followed by a longer lasting hypertensive phase. Intravenously, PGE_2 (0.01–10 µg/rat) induced a biphasic blood pressure response with a strong dose-related initial decrease followed by a slight increase in blood

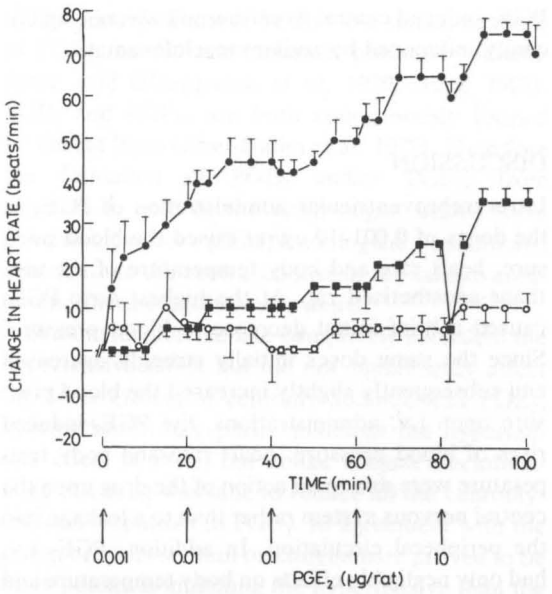

Fig. 2. Time-dose-response effect of PGE_2 on heart rate in urethaneanesthetised rats. Increasing doses of PGE_2 were administered i.c.v. (●—●) or i.v. (■—■) at 20 min intervals. Open circles represent the vehicle i.c.v. controls. The initial heart rate level (mean±SE) before commencement of the PGE_2 or vehicle administrations was 445±10 beats/min in the control group, 445±5 beats/min in the PGE_2 i.c.v. group and 425±10 beats/min in the PGE_2 i.v. group. The differences between the initial levels of the groups are not statistically significant. The tachycardic effect of PGE_2 i.c.v. at the doses of 0.001–10 µg/rat differ significantly ($p<0.05$–0.001) from both the control group and the PGE_2 i.v. group. The rises induced by PGE_2 i.v. at the doses of 0.1–10 µg/rat were significant at the $p<0.05$–0.001 level as compared to the control values. Vertical bars indicate SE. Each group comprised 6 rats.

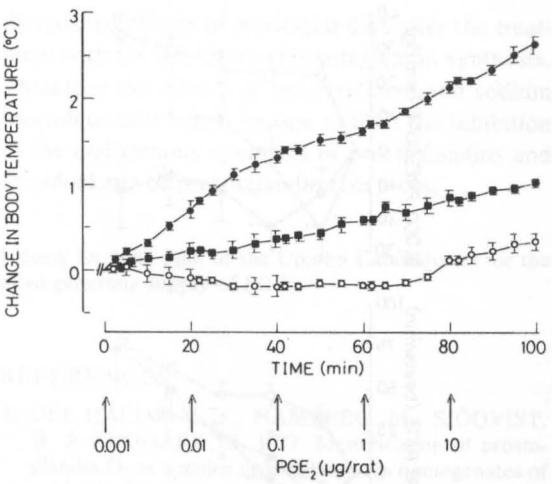

Fig. 3. Time-dose-response effect of PGE_2 on body temperature in urethane-anesthetised rats. Increasing doses of PGE_2 were administered i.c.v. (●—●) or i.v. (■—■) at 20 min intervals. Open circles represent the vehicle i.c.v. controls. The initial body temperature level (mean ±SE) before commencement of the PGE_2 or vehicle administrations was 36.3±0.2°C in the control group, 36.5±0.2°C in the PGE_2 i.c.v. group and 35.0±0.3°C in the PGE_2 i.v. group. The baseline level of the PGE_2 i.v. group differs significantly ($p<0.005$–0.001) from both the control and PGE_2 i.c.v. groups. The rises of body temperature induced by PGE_2 i.c.v. (0.001–10 µg/rat) or PGE_2 i.v. (0.01–10 µg/rat) are significant at the $p<0.05$–0.001 level as compared to the control values. The differences between the PGE_2 i.c.v. and i.v. groups are also significant at the $p<0.05$–0.001 level. Vertical bars indicate SE. Each group comprised 6 rats.

pressure. The maximum hypotensive effect was achieved 1–2 min after each i.v. injection.

Effect of PGE_2 on heart rate (Fig. 2). PGE_2 induced a substantial tachycardic effect, when administered at the doses of 0.001–10 µg/rat i.c.v. The maximum increase in heart rate was reached 10–20 min after each injection. I.v. PGE_2 at the same doses slightly increased the heart rate. In addition, at the highest i.v. dose PGE_2 caused a transient initial decrease in heart rate.

Effect of PGE_2 on body temperature (Fig. 3). PGE_2 at the i.c.v. doses of 0.001–10 µg/rat induced a strong hyperthermic effect. The maximum effect, about 2.5°C, was reached with the highest dose. I.v. the same doses of PGE_2 only slightly raised the body temperature.

II. *Effects of indomethacin and sodium meclofenamate*

Centrally administered indomethacin (1 mg/rat i.c.v.) induced a slight but statistically significant increase in heart rate (about 20 beats/min) but had no significant effect on blood pressure or body temperature. The same dose of sodium meclofenamate had no significant effect on blood pressure, heart rate or body temperature (see legend of Fig. 4).

III. *Effects of prostaglandin E_2 in indomethacin or sodium meclofenamate pretreated rats*

Effect of indomethacin pretreatment (Fig. 4). Central pretreatment with indomethacin (1 mg/rat i.c.v.) partly antagonised the central hypertensive, tachycardic and hyperthermic effects of PGE_2.

Effects of sodium meclofenamate pretreatment (Fig. 4). Central pretreatment with sodium meclo-

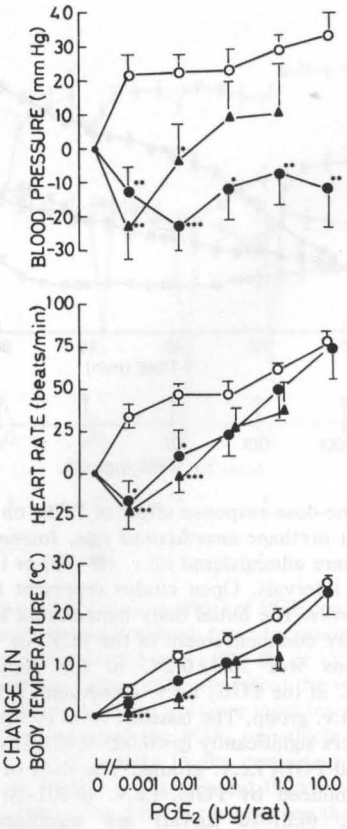

Fig. 4. Effect of i.c.v. administered PGE_2 on blood pressure, heart rate and body temperature in indomethacin or sodium meclofenamate pretreated rats. Indomethacin, 1 mg/rat (▲—▲), sodium meclofenamate, 1 mg/rat (●—●) or vechicle (○—○) was administered i.c.v. 20 min before commencement of the administration of PGE_2. Increasing doses of PGE_2 were administered i.c.v. at 20 min intervals. The maximum changes 15–20 min after each injection are shown. The initial blood pressure, heart rate and body temperature levels (means±SE) were 113±8 mmHg, 460±10 beats/min and 36.5±0.2°C in the control group, 115±8 mmHg, 480±10 beats/min and 36.9±0.3°C in the indomethacin pretreated group and 112±3 mmHg, 470±10 beats/min and 36.4±0.3°C in the sodium meclofenamate pretreated group. The difference between the initial heart rate values of the indomethacin group and control group is significant at the $p<0.05$ level. Vertical bars indicate SE. Control and indomethacin pretreated group comprised 6 rats and sodium meclofenamate pretreated group 5 rats, except for the PGE_2 doses of 1 and 10 µg/rat in experimental groups (4 rats). $*p<0.05$, $**p<0.005$ and $***p<0.001$ vs. control group.

fenamate (1 mg/rat i.c.v.) wholly abolished the hypertensive effect of i.c.v. administered PGE_2. The tachycardic response to PGE_2 i.c.v. was also partly antagonised by sodium meclofenamate, while the PGE_2-induced central hyperthermia was not significantly influenced by sodium meclofenamate.

DISCUSSION

Intracerebroventricular administration of PGE_2 at the doses of 0.001–10 µg/rat raised the blood pressure, heart rate and body temperature of the urethane-anesthetised rat. At the highest dose PGE_2 caused a brief initial decrease in blood pressure. Since the same doses initially strongly decreased and subsequently slightly increased the blood pressure upon i.v. administrations, the PGE_2-induced rises of blood pressure, heart rate and body temperature were due to an action of the drug upon the central nervous system rather than to a leakage into the peripheral circulation. In addition, PGE_2 i.v. had only negligible effects on body temperature and heart rate. Moreover, the antagonism of the central effects of PGE_2 by i.c.v. pretreatment with indomethacin or sodium meclofenamate further supports the suggestion that the effects of i.c.v. administered PGE_2 are due to an action on the cerebral structures. However, the brief initial hypotensive effect of the highest i.c.v. dose of PGE_2 was not significantly antagonised by centrally administered indomethacin or sodium meclofenamate. Since prostaglandins are known to cross the blood-brain barrier (Holmes & Horton 1968), the possibility cannot be excluded that, at least the hypotensive effect of i.c.v. administered PGE_2, might be due to a partial leakage of the drug into the periphery.

In agreement with the present results the i.c.v. administration of PGE_2 at the doses of 0.05–5000 ng/rat raised the blood pressure and heart rate of conscious rats (Hoffman & Schmid 1979). The hyperthermic effect of centrally administered PGE_2 has been previously demonstrated in many mammalians, including the rat (Milton 1976, Splawiński et al. 1978). The rises of blood pressure and heart rate after the administration of the smallest dose of PGE_2 became apparent earlier than did the increase in body temperature. It can thus be concluded that the cardiovascular changes were not a consequence of the hyperthermia. However, the dose-response curve for the hyperthermic effect of PGE_2 lies within about the same dose range as that for the cardiovascular changes so that it cannot be argued that PGE_2 is more selective in inducing cardiovascular changes than a rise of the body temperature.

The central effects of PGE_2 were similar to those of $PGF_{2\alpha}$ or the prostaglandin precursor, arachidonic acid (Karppanen et al. 1979, Sirén 1982). PGE_2 and $PGF_{2\alpha}$ are both endogenously formed by the rat brain (Abel-Halim et al. 1977). Therefore the formation of PGE_2 and/or $PGF_{2\alpha}$ from arachidonic acid in the brain might, under some physiological or pathophysiological conditions, contribute to the central control of the cardiovascular and thermoregulatory systems.

Sodium meclofenamate completely abolished the hypertensive effect but did not significantly affect the other effects of centrally administered PGE_2. Indomethacin only partly inhibited the hypertensive effect of PGE_2 but unlike sodium meclofenamate this drug was able to reduce all the centrally-induced responses to PGE_2. In agreement with the present results sodium meclofenamate proved to be more potent in inhibiting the hypertensive than the tachycardic or hyperthermic effects of arachidonic acid (Sirén 1982), while indomethacin affected equally the cardiovascular and thermal responses to i.c.v. administered arachidonic acid (Sirén & Karppanen 1981). Furthermore, the central hypotensive effect of prostacyclin was antagonised by central pretreatment with sodium meclofenamate but not with indomethacin (Sirén 1981*b*). Hence the present findings lend further support to our previous suggestion (Karppanen et al. 1979) that there might be differences in the modes and/or sites of action between sodium meclofenamate and indomethacin.

The mechanism by which indomethacin and sodium meclofenamate inhibit the responses to centrally administered prostaglandins is not known. However, in agreement with the present results an antagonism of the effects of exogenous prostaglandins by indomethacin and fenamates has also been reported in the alimentary muscle of the guinea-pig and rat (Bennett et al. 1980*a*, *b*, Lembeck & Juan 1974). The blockade of prostaglandin receptors by indomethacin and sodium meclofenamate might explain the inhibition of the effects of exogenous prostaglandins by these drugs. However, both indomethacin and fenamates effectively inhibit the synthesis of prostaglandins (Flower 1974). Due to the decreased synthesis of endogenous prostaglandins the total amount of these agents, endogenous plus exogenous, present at the receptors after the administration of exogenous prostaglandins, may be decreased. This might explain, at least partly, the diminished effects of prostaglandins after the treatment with the inhibitors of prostaglandin synthesis. Therefore the effects of indomethacin and sodium meclofenamate might be due to both the inhibition of the endogenous synthesis of prostaglandins and the blockade of prostaglandin receptors.

I thank Dr John Pike of the Upjohn Laboratories for the most generous supply of PGE_2.

REFERENCES

ABDEL-HALIM, M. S., HAMBERG, M., SJÖQVIST, B. & ÄNGGÅRD, E. 1977. Identification of prostaglandin D_2 as a major prostaglandin in homogenates of rat brain. Prostaglandins 14: 633–643.

BENNETT, A. D., PRATT, D. & SANGER, G. J. 1980*a*. Antagonism by fenamates of prostaglandin action in guinea-pig and human alimentary muscle. Br J Pharmacol 68: 357–362.

BENNETT, A. D., JAROSIK, C., SANGER, G. J. & WILSON, D. E. 1980*b*. Antagonism of prostanoid-induced contractions of rat gastric fundus muscle by SC-19220, sodium meclofenamate, indomethacin or trimethaquinol. Br J Pharmacol 71: 169–175.

COCEANI, F. 1974. Prostaglandins and the central nervous system. Arch Intern Med 133: 119–129.

FLOWER, R. J. 1974. Drugs which inhibit prostaglandin biosynthesis. Pharmacol Rev 26: 33–67.

HOFFMAN, W. E. & SCHMID, P. G. 1979. Cardiovascular and antidiuretic effect of central prostaglandin E_2. J Physiol 288: 159–169.

HOLMES, S. W. & HORTON, E. W. 1968. The distribution of tritium labelled prostaglandin E_1 injected in amounts sufficient to produce central nervous effects in cats and chicks. Br J Pharmacol 34: 32–37.

KARPPANEN, H., SIRÉN, A.-L. & ESKELI-KAIVOSOJA, A. 1979. Central cardiovascular and thermal effects of prostaglandin $F_{2\alpha}$ in rats. Prostaglandins 17: 385–394.

LEMBECK, F. & JUAN, H. 1974. Interaction of prostaglandins and indomethacin with algesic substances. Naunyn-Schmied Arch Pharmacol 285: 301–313.

MILTON, A. S. 1976. Modern views on the pathogenesis of fever and the mode of action of antipyretic drugs. J Pharm Pharmacol 28: 393–399.

PAAKKARI, I. 1980. A simple method for the verification of a successful cannulation of the rat cerebral ventricles. Experientia 36: 887–889.

SIRÉN, A.-L. 1981*a*. Central cardiovascular effects of prostaglandins D_2 and E_2 in rats. Acta Pharmacol Toxicol 49 (Suppl. I): 87.

SIRÉN, A.-L. 1981*b*. Central cardiovascular and thermal effects of prostacyclin in rats. Prostaglandins 22: 945–956.

SIRÉN, A.-L. 1982. Differences in the central actions of arachidonic acid and prostaglandin $F_{2\alpha}$ between spontaneously hypertensive and normotensive rats. Life Sci 30: 503–513.

SIRÉN, A.-L. & KARPPANEN, H. 1981. Influence of some inhibitors of prostaglandin, thromboxane and prostacyclin synthesis on the central hypertensive and thermogenic effects of arachidonic acid in rats. In: Prostaglandins and thromboxanes (ed. W. Förster), pp. 231–236. VEB Gustav Fischer Verlag, Jena.

SPLAWIŃSKI, J. A., GORKA, Z., ZACNY, E. & WOJTASZEK, B. 1978. Hyperthermic effects of arachidnic acid, prostaglandins E_2 and $F_{2\alpha}$ in rats. Pflügers Arch 374: 15–21.