Central cardiovascular and thermal effects of prostaglandin E\(_2\) in rats\(^1\)

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Prostaglandin E\(_2\) (PGE\(_2\)) increased the blood pressure, heart rate and body temperature, when administered at the doses of 0.001-10 \(\mu\)g into the lateral cerebral ventricle (i.c.v.) of the urethane-anesthetised rat. The highest dose of 10 \(\mu\)g/rat induced a strong initial hypotensive effect. Intravenously (i.v.), PGE\(_2\) at the doses of 0.01-10 \(\mu\)g/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 \(\mu\)g/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 (Cocceani 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 urethane-anesthetised rat in order to obtain complete simultaneous cumulative 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. 1980a, b) and in the brain (Karppanen et al. 1979, Siren 1981a, 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-

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1 A preliminary report of this work has been presented at the XXXII Meeting of the Scandinavian Pharmacological Society (Siren 1981a).
Fig. 1. Time-dose-response effect of PGE₂ on blood pressure in urethane-anesthetised rats. Increasing doses of PGE₂ 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 PGE₂ or vehicle administrations was 110±10 mmHg in the control group, 113±8 mmHg in the PGE₂ i.c.v. group and 102±6 mmHg in the PGE₂ i.v. group. The differences between the initial levels of the groups are not statistically significant. The rises of blood pressure induced by PGE₂ 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 PGE₂ i.v. group. Vertical bars indicate SE. Each group comprised 6 rats.

A 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 E₂ (PGE₂), 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 PGE₂ 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 (PGE₂ 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 PGE₂ 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 PGE₂ 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 PGE₂ 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

1. Effects of prostaglandin E₂ in non-pretreated rats

Effect of PGE₂ on blood pressure (Fig. 1). Intracerebroventricular administration of PGE₂ 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 PGE₂ i.c.v. induced an initial hypotensive effect which had its maximum 1–2 min after the injection. The initial hypotension was followed by a longer lasting hypertensive phase. Intravenously, PGE₂ (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
pressure. The maximum hypotensive effect was achieved 1–2 min after each i.v. injection.

**Effect of PGE2 on heart rate** (Fig. 2). PGE2 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. PGE2 at the same doses slightly increased the heart rate. In addition, at the highest i.v. dose PGE2 caused a transient initial decrease in heart rate.

**Effect of PGE2 on body temperature** (Fig. 3). PGE2 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 PGE2 only slightly raised the body temperature.
fenamate (1 mg/rat i.c.v.) wholly abolished the hypertensive effect of i.c.v. administered PGE₂. The tachycardic response to PGE₂ i.c.v. was also partly antagonised by sodium meclofenamate, while the PGE₂-induced central hyperthermia was not significantly influenced by sodium meclofenamate.

**DISCUSSION**

Intracerebroventricular administration of PGE₂ 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 PGE₂ 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 PGE₂-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, PGE₂ i.v. had only negligible effects on body temperature and heart rate. Moreover, the antagonism of the central effects of PGE₂ by i.c.v. pretreatment with indomethacin or sodium meclofenamate further supports the suggestion that the effects of i.c.v. administered PGE₂ are due to an action on the cerebral structures. However, the brief initial hypotensive effect of the highest i.c.v. dose of PGE₂ 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 PGE₂, 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 PGE₂ 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 PGE₂ has been previously demonstrated in many mammals, including the rat (Milton 1976, Splawinski et al. 1978). The rises of blood pressure and heart rate after the administration of the smallest dose of PGE₂ 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 PGE₂ lies within the same dose range as that for the cardiovascular changes so that it cannot be argued that PGE₂ is more selective in inducing cardiovascular changes than a rise of the body temperature.
The central effects of PGE\textsubscript{2} were similar to those of PGF\textsubscript{2\alpha} or the prostaglandin precursor, arachidonic acid (Karppanen et al. 1979, Sirén 1982). PGE\textsubscript{2} and PGF\textsubscript{2\alpha} are both endogenously formed by the rat brain (Abel-Halim et al. 1977). Therefore the formation of PGE\textsubscript{2} and/or PGF\textsubscript{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.

PGE\textsubscript{2} and PGF\textsubscript{2\alpha} are both endogenously formed by the rat brain (Abel-Halim et al. 1977). Therefore the formation of PGE\textsubscript{2} and/or PGF\textsubscript{2\alpha} from arachidonic acid (Siren 1982), while indomethacin affected the formation of prostaglandin D\textsubscript{2} and/or the other effects of centrally administered 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.

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REFERENCES


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