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CENTRAL CARDIOVASCULAR AND THERMAL EFFECTS OF PROSTAGLANDIN F₂α IN RATS¹

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ABSTRACT

Administration of PGF₂α (0.2–6.4 μg) into the lateral cerebral ventricle (i.c.v.) induced dose-dependent increases in blood pressure, heart rate and body temperature in urethane-anaesthetised rats, but had no effect on these parameters when the same dose range was administered intravenously. Peripheral pretreatment with sodium meclofenamate (50 mg/kg s.c.) shifted all the dose-response curves for PGF₂α (i.c.v.) to the left, but indomethacin (50 mg/kg s.c.) did not significantly affect those changes. Central pretreatment with sodium meclofenamate or indomethacin (1.25 mg per rat i.c.v.) failed to modify significantly the effects of centrally administered PGF₂α.

The results support previous suggestions that PGF₂α may participate in the central control of the cardiovascular and thermoregulatory systems, and also suggest that there may be differences in the sites and/or modes of action between sodium meclofenamate and indomethacin.

INTRODUCTION

Prostaglandin F₂α (PGF₂α) is one of the most common prostaglandin types in the central nervous system (2,3), but its possible physiological functions in the brain are not known. Some investigators have suggested that prostaglandins may be involved in the central control of thermoregulatory and cardiovascular systems (2). Prostaglandins of the E-type are highly active pyrogenic agents in the brain (4), whereas PGF₂α seems to be the most potent prostaglandin affecting the central mechanisms of cardiovascular control (5). Although it has been shown that intracerebroventricular administrations of PGF₂α increase blood pressure and heart rate in anaesthetised rats (6), no dose-response relationships have been established.

In the present study various doses of PGF₂α were administered into the lateral cerebral ventricle of urethane-anaesthetised rats in order to obtain complete simultaneous dose-response curves for blood pressure, heart rate and body temperature. Since sodium meclofenamate antagonises the effects of exogenous PGF₂α in peripheral tissues (7, 8, 9), it seemed worthwhile to examine the influence of this agent on the central effects of PGF₂α. For comparison, the effects of indomethacin, which is as effective an inhibitor of prostaglandin synthesis as sodium meclofenamate (10), were also studied.

MATERIALS AND METHODS

Sprague-Dawley rats (240–340 g) of both sexes were used, although in each type of experiment all control and experimental animals were of the same sex. The rats were accommodated to standard ambient conditions for at least one week before the experiments. The lights were on from 7 a.m. to 7 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 (Hankki ja Oy, Helsinki) and tap water ad libitum.

¹ A preliminary report of this work was presented at XXXI Meeting of the Scandinavian Pharmacological Society.
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 (Harvard apparatus 377). The heart rate was calculated from the pulse waves, 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. 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 then attached to the needle and the desired amount of the solution was allowed to flow slowly by virtue of 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 (methylene blue) into the cerebral ventricle.

The body temperature was measured rectally with a temperature recorder (ELLAB instruments, type Z8, 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 for the heating lamp was adequate to keep the body temperature at 35.3 °C - 36.7 °C in an ambient temperature of 22 °C which was kept constant automatically by air conditioning.

Administration of drugs

The stock solution of PGF$_2\alpha$, 1 mg/ml (Astra), was diluted with a modified Krebs-Ringer bicarbonate buffer (NaCl 117.0 mM, KCl 2.95 mM, CaCl$_2$ 1.44 mM, KH$_2$PO$_4$ 0.01 mM, MgSO$_4$ · 7 H$_2$O 1.12 mM, and NaHCO$_3$ 23.6 mM) to simulate the concentrations found in the cerebrospinal fluid (11). For intravenous administrations the stock solution of PGF$_2\alpha$ was diluted with 0.9 % (w/v) NaCl (saline). The intracerebroventricular injections of PGF$_2\alpha$ were given in a volume of 5 μl each, with the exception of the largest dose which was given in a volume of 10 μl. Intravenously the various doses of PGF$_2\alpha$ were injected in a volume of 0.1 ml each. The control animals received the same volume of the corresponding vehicle in each case. Increasing doses of PGF$_2\alpha$ were injected intracerebroventricularly at 15 min intervals in order to obtain a cumulative dose-response curve. This interval was chosen because the maximum pressor effect of PGF$_2\alpha$ was reached within 15 min after the i.c.v. injections. The intravenous injections were also repeated at 15 min intervals to make sure that the effects induced by centrally administered PGF$_2\alpha$ were not due to leakage of the drug into the peripheral circulation.

Indomethacin (Orion Oy, Helsinki) was dissolved in 0.05 N NaOH and sodium meclofenamate monohydrate (Parke, Davis & Co.) in saline. The influence of peripheral pretreatment with indomethacin or sodium meclofenamate on the central effects of PGF$_2\alpha$ was studied by injecting the drugs subcutaneously, 50 mg/kg, two hours before commencement of the administration of cumulative doses of PGF$_2\alpha$. The effect of central pretreatment was studied by infusing indomethacin or sodium meclofenamate i.c.v. at the dose of 1.25 mg in a volume of 5 μl 20 min before commencement of the administration of cumulative doses of PGF$_2\alpha$. In each case the control animals received the same volumes of the corresponding vehicle at the same pH as the drug solution.

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 F$_2\alpha$ in non-pretreated rats

Effect of PGF$_2\alpha$ on blood pressure (Fig. 1)

Intracerebroventricular injection of PGF$_2\alpha$ at the doses of 0.2–6.4 µg/rat increased the blood pressure in a dose-related manner, the maximum effect, about 20 mm Hg being reached with a dose of 3.2 µg/rat. Intravenously, PGF$_2\alpha$ had no significant effect on blood pressure at the doses of 0.2–6.4 µg/rat.
Fig. 1. Influence of PGF$_{2\alpha}$ on blood pressure in urethane-anaesthetised male rats. Cumulative doses of PGF$_{2\alpha}$ were administered intracerebroventricularly (---) or intravenously (---) at 15-min intervals. Each dose is indicated on the abscissa. The blood pressure level before commencement of the administration of PGF$_{2\alpha}$ or solvent i.c.v. (-----) was 100 ± 20 mm Hg in the control group, 95 ± 20 mm Hg in the PGF$_{2\alpha}$ i.c.v. group, and 80 ± 10 mm Hg in the PGF$_{2\alpha}$ i.v. group. The differences in baseline levels between the groups are not statistically significant. The rises in blood pressure as compared with the control values at doses of 0.2–0.4 µg/rat and 3.2–6.4 µg/rat i.c.v. were significant at the p < 0.05 level. The results obtained with PGF$_{2\alpha}$ i.v. did not differ significantly from the control values. Vertical bars indicate s.e. mean. Each group comprised 6 rats.

*Effect of PGF$_{2\alpha}$ on heart rate (Fig. 2)*

When administered intracerebroventricularly, PGF$_{2\alpha}$ doses of 0.2–6.4 µg/rat induced a substantial tachycardic effect, which became observable 2–5 min after the injections. The maximum change, achieved with the highest dose, was almost 200 beats/min. Intravenously administered PGF$_{2\alpha}$ had no significant effect on the heart rate at the doses used.
Fig. 2. Influence of PGF$_{2\alpha}$ on heart rate in urethane-anaesthetised male rats. Cumulative doses of PGF$_{2\alpha}$ were administered i.c.v. (●○●) or i.v. (●-●) at 15-min intervals. Each dose is indicated on the abscissa. The heart rate before commencement of the administration of PGF$_{2\alpha}$ or solvent i.c.v. (---○) was 350 ± 30 beats/min in the control group, 340 ± 20 beats/min in the PGF$_{2\alpha}$ i.c.v. group, and 360 ± 20 beats/min in the PGF$_{2\alpha}$ i.v. group. The differences in baseline levels between the groups are not statistically significant. The tachycardic effects of PGF$_{2\alpha}$ (0.2–6.4 µg/rat i.c.v.) were significant as compared with the control values at the $p < 0.05$–0.001 level. The results obtained with PGF$_{2\alpha}$ i.v. did not differ significantly from the control values. Vertical bars indicate s.e. mean. Each group comprised 6 rats.

Effect of PGF$_{2\alpha}$ on body temperature (Fig. 3)

Centrally administered PGF$_{2\alpha}$ had a dose-dependent hyperthermic effect, so that after the highest dose the average increase in body temperature was about 2.6°C. With intravenous injections PGF$_{2\alpha}$ had no statistically significant effect on body temperature.
Fig. 3. Influence of PGF$_{2\alpha}$ on body temperature in urethane-anaesthetised male rats. Cumulative doses of PGF$_{2\alpha}$ were administered i.c.v. (●—●) or i.v. (▲—▲) at 15-min intervals. Each dose is indicated on the abscissa. The hyperthermic effect of PGF$_{2\alpha}$ i.c.v. was significant as compared with the control i.c.v. values (○—○) at the p < 0.05–0.001 level at doses of 1.6–6.4 µg/rat. The results obtained with PGF$_{2\alpha}$ i.v. did not differ significantly from the control values. The differences between the i.c.v. and i.v. groups were significant at the p < 0.05–0.001 level at the doses of 0.2–6.4 µg/rat. Vertical bars indicate s.e. mean. Each group comprised 6 rats, except in the first i.c.v. dose (5 rats).

Interrelationship between PGF$_{2\alpha}$-induced changes in blood pressure, heart rate and body temperature

The time-response effects on blood pressure, heart rate and body temperature of the smallest dose of PGF$_{2\alpha}$, 0.2 µg/rat i.c.v. are demonstrated in Fig. 4. The rise in both blood pressure and heart rate was greater than that in body temperature, and preceded it in time.
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Fig. 4. Time-response effects of PGF$_{2\alpha}$ on blood pressure (---), heart rate (---) and body temperature (---) after the first administration of the dose of 0.2 µg/rat i.c.v. The number of rats was 6. Vertical bars indicate s.e. mean.

II Effects of sodium meclofenamate and indomethacin

After subcutaneous administrations neither sodium meclofenamate nor indomethacin had any significant effects of their own on the baseline values for blood pressure, heart rate or body temperature. Intracerebroventricularly administered sodium meclofenamate induced a slight increase in heart rate and a fall in body temperature (Table 1).
Table 1. Baseline values for blood pressure (B.P.), heart rate (H.R.) and body temperature (B.T.) in indomethacin and sodium meclofenamate pretreated rats and their control groups immediately before commencement of PGF$_{2\alpha}$ administrations i.c.v. The values represent means ± SD means. Each group comprised 6 rats, except for the control group for indomethacin i.c.v. (5 rats) and that for sodium meclofenamate s.c. (4 rats).

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>B.P. (mm Hg)</th>
<th>H.R. (beats/min)</th>
<th>B.T. (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Subcutaneously$^1$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saline</td>
<td>95 ± 15</td>
<td>340 ± 30</td>
<td>36.0 ± 0.0</td>
</tr>
<tr>
<td>sodium meclofenamate (50 mg/kg)</td>
<td>90 ± 10</td>
<td>320 ± 10</td>
<td>36.0 ± 0.3</td>
</tr>
<tr>
<td>vehicle</td>
<td>90 ± 20</td>
<td>390 ± 20</td>
<td>36.7 ± 0.2</td>
</tr>
<tr>
<td>indomethacin (50 mg/kg)</td>
<td>90 ± 10</td>
<td>370 ± 30</td>
<td>36.7 ± 0.2</td>
</tr>
<tr>
<td>B. Intracerebroventricularly$^2$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saline</td>
<td>85 ± 10</td>
<td>340 ± 20</td>
<td>37.0 ± 0.1</td>
</tr>
<tr>
<td>sodium meclofenamate (1.25 mg/kg)</td>
<td>85 ± 10</td>
<td>400 ± 10$^*$</td>
<td>36.0 ± 0.2$^{**}$</td>
</tr>
<tr>
<td>vehicle</td>
<td>90 ± 20</td>
<td>310 ± 30</td>
<td>36.0 ± 0.3</td>
</tr>
<tr>
<td>indomethacin (1.25 mg/rat)</td>
<td>85 ± 15</td>
<td>360 ± 20</td>
<td>36.0 ± 0.3</td>
</tr>
</tbody>
</table>

1 Male rats used. 2 Female rats used. * p < 0.05 vs. control group. ** p < 0.01 vs. control group.

III Effects of intracerebroventricular PGF$_{2\alpha}$ in sodium meclofenamate and indomethacin pretreated rats

Effects of sodium meclofenamate pretreatment

Peripheral pretreatment with sodium meclofenamate (50 mg/kg s.c.) potentiated the increase in blood pressure induced by intracerebroventricular PGF$_{2\alpha}$, shifting the dose-response curve of PGF$_{2\alpha}$ to the left (Fig. 5). A similar effect was noted upon the tachycardic and hyperthermic actions of centrally administered PGF$_{2\alpha}$ (Figs. 6 and 7).

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**Fig. 5. Effect of PGF$_{2\alpha}$ i.c.v. on blood pressure in sodium meclofenamate (---) and saline (---) pretreated male rats. Sodium meclofenamate (50 mg/kg) or saline was injected subcutaneously two hours before commencement of the administration of cumulative doses of PGF$_{2\alpha}$ i.c.v. The differences between the sodium meclofenamate and saline groups were significant at the p < 0.05 level at PGF$_{2\alpha}$ doses of 0.2–0.8 µg/rat. Vertical bars indicate s.e. Both groups comprised 6 rats.**
Fig. 6. Effect of PGF$_{2\alpha}$ i.c.v. on heart rate in sodium meclofenamate (---) and saline (-----) pretreated male rats. Sodium meclofenamate (50 mg/kg) or saline was injected subcutaneously two hours before commencement of the administration of cumulative doses of PGF$_{2\alpha}$ i.c.v. The differences between the sodium meclofenamate and saline groups were significant at the $p < 0.05 - 0.01$ level at PGF$_{2\alpha}$ doses of 0.2 - 0.8 µg/rat. Vertical bars indicate s.e. means. Both groups comprised 6 rats.

Fig. 7. Effect of PGF$_{2\alpha}$ i.c.v. on body temperature in sodium meclofenamate (---) and saline (-----) pretreated male rats. Sodium meclofenamate (50 mg/kg) or saline was injected subcutaneously two hours before commencement of the administration of cumulative doses of PGF$_{2\alpha}$ i.c.v. The differences between the sodium meclofenamate and saline groups were significant at the $p < 0.05$ level at a dose of 1.6 µg/rat, at the $p < 0.01$ level at doses of 0.8 and 6.4 µg/rat and the $p < 0.001$ level at doses of 0.2 - 0.4 and 3.2 µg/rat. The sodium meclofenamate pretreated group comprised 6 rats and the control group 4. Vertical bars indicate s.e. means.
Central pretreatment with sodium meclofenamate, 1.25 mg/rat i.c.v., 20 min before commencement of the administration of cumulative doses of PGF$_{2\alpha}$ i.c.v., did not significantly influence the hypertensive, tachycardic or hyperthermic effects of PGF$_{2\alpha}$ (results not shown).

**Effect of indomethacin pretreatment**

Indomethacin did not influence significantly any of the dose-response curves for PGF$_{2\alpha}$ when given peripherally (50 mg/kg s.c. two hours before commencement of the administration of PGF$_{2\alpha}$ i.c.v.), or centrally (1.25 mg/rat i.c.v. 20 min before commencement of the administration of PGF$_{2\alpha}$ i.c.v.). (Results not shown.)

**DISCUSSION**

PGF$_{2\alpha}$ i.c.v. raised the blood pressure, heart rate and body temperature of urethane-anaesthetised rats in a dose-related manner. These effects were not due to any leakage of the drug into the periphery, but to an action upon the central nervous systems, since the same doses of PGF$_{2\alpha}$ did not affect these parameters upon intravenous administration. This assumption is supported by the fact that PGF$_{2\alpha}$ raised the blood pressure and heart rate upon infusion into the vertebral artery in chloralose-anaesthetised dogs, but not after administration of the same doses intravenously (5). Infusion of PGF$_{2\alpha}$ into the vertebral artery of conscious dogs raised the blood pressure, but did not affect the heart rate (12). In agreement with the present results it has been reported that administration of PGF$_{2\alpha}$ at the doses of 1 or 10 $\mu$g per rat into the cerebral ventricle increases the blood pressure and heart rate of urethane-anaesthetised rats (6). The hyperthermic effect of centrally administered PGF$_{2\alpha}$ has previously been demonstrated in conscious rabbits and cats (13) and also in chickens and rats (15). Since PGF$_{2\alpha}$ is present in abundance in the brain (2,3) and exerts strong dose-dependent central effects, this agent might have a physiological role in the central control of the thermoregulatory and cardiovascular systems.

The rises in blood pressure and heart rate after administration of the smallest dose of PGF$_{2\alpha}$ became apparent earlier than did the increase in the body temperature. It can thus be concluded that the cardiovascular changes were not a consequence of the hyperthermia. The dose-response curve for the hyperthermic effect of PGF$_{2\alpha}$ lies within about the same dose range as that for the cardiovascular changes, however, so that it cannot be argued that PGF$_{2\alpha}$ is more selective in inducing cardiovascular changes than in inducing an increase in the body temperature. It is obvious that the cardiovascular and thermal effects of PGF$_{2\alpha}$ are due to an activation of the sympathetic nervous system (2, 12). The rapid onset of the effects also suggests the involvement of neuronal mechanisms.

Although indomethacin and sodium meclofenamate appear to exert their effects mainly by the inhibition of prostaglandin biosynthesis (16), sodium meclofenamate and other fenamates also antagonise the effects of exogenous PGF$_{2\alpha}$ in some peripheral tissues (8, 9, 10). The present results demonstrate that neither peripheral nor central pretreatments with indomethacin or sodium meclofenamate are able to antagonise the cardiovascular and thermal effects induced by centrally administered PGF$_{2\alpha}$. Moreover, peripheral but not central pretreatment with sodium meclofenamate augmented the effects of PGF$_{2\alpha}$. It is therefore possible that sodium meclofenamate potentiated the sympathetic activity or other mechanisms in the periphery which mediate the centrally-induced effects of PGF$_{2\alpha}$. Inhibition of prostaglandin synthesis is likely to enhance the release of noradrenaline from the sympathetic nerve endings (17). A rise in blood pressure and decreased heat loss with subsequent hyperthermia due to vasoconstriction could also be expected as the result of inhibition of the subcutaneous administration. However, sodium meclofenamate and indomethacin are both well absorbed (19) and inhibit effectively the synthesis of prostaglandins even at considerably lower doses than those used in the present experiments (20). It thus seems unlikely that the potentiation of the central effects of PGF$_{2\alpha}$ by sodium meclofenamate could be entirely due to the inhibition of
prostaglandin synthesis. At least at the high doses, sodium meclofenamate and indomethacin may also inhibit the activity of cyclic nucleotide phosphodiesterases (21). The cyclic AMP/cyclic GMP ratio in tissues may be differently affected by indomethacin and sodium meclofenamate, since these drugs have different selectivities towards cyclic AMP and cyclic GMP phosphodiesterases (21). The cyclic AMP/cyclic GMP ratio may in turn be important in the control of blood pressure (22). Further studies are needed, however, to elucidate the mechanisms by which sodium meclofenamate potentiates the central effects of PGF$\textsubscript{2\alpha}$.  

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REFERENCES

15) Podduibuk, Z.M. A comparison of the central actions of prostaglandins A$\textsubscript{1}$, E$\textsubscript{1}$, E$\textsubscript{2}$, F$\textsubscript{2\alpha}$ and F$\textsubscript{2\beta}$ in the rat. Psychopharmacology 50: 89. 1976.