CENTRAL CARDIOVASCULAR AND THERMAL EFFECTS OF PROSTAGLANDIN $F_{2\alpha}$ IN RATS[1]

H. Karppanen, Anna-Leena Sirèn and Alice Eskeli-Kaivosoja

Department of Pharmacology, University of Helsinki, SF-00170 Helsinki 17, and Department of Pharmacology, University of Oulu, SF-90220 Oulu 22, Finland

ABSTRACT

Administration of $PGF_{2\alpha}$ (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 $PGF_{2\alpha}$ (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 $PGF_{2\alpha}$.

The results support previous suggestions that $PGF_{2\alpha}$ 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 $F_{2\alpha}$ ($PGF_{2\alpha}$) 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 $PGF_{2\alpha}$ seems to be the most potent prostaglandin affecting the central mechanisms of cardiovascular control (5). Although it has been shown that intracerebroventricular administrations of $PGF_{2\alpha}$ increase blood pressure and heart rate in anaesthetised rats (6), no dose-response relationships have been established.

In the present study various doses of $PGF_{2\alpha}$ 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 $PGF_{2\alpha}$ in peripheral tissues (7, 8, 9), it seemed worthwhile to examine the influence of this agent on the central effects of $PGF_{2\alpha}$. 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 (Hankkija 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_2PO_4 0.01 mM, $MgSO_4 \cdot 7\,H_2O$ 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 admininistration 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.

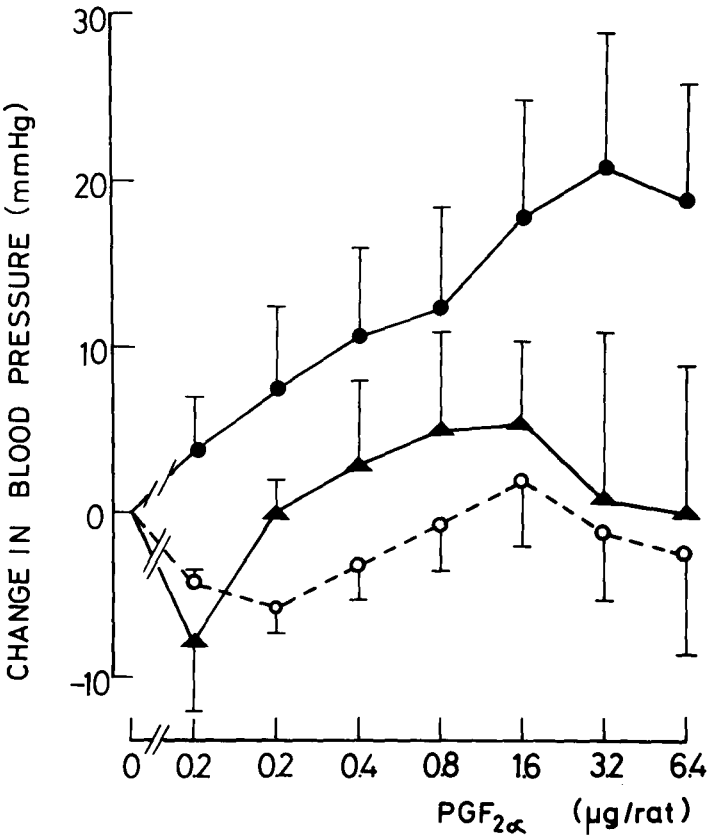

Fig. 1. Influence of $PGF_{2\alpha}$ on blood pressure in urethane-anaesthetised male rats. Cumulative doses of $PGF_{2\alpha}$ were administered intracerebroventricularly (●——●) or intravenously (▲——▲) at 15-min intervals. Each dose is indicated on the abscissa. The blood pressure level before commencement 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.

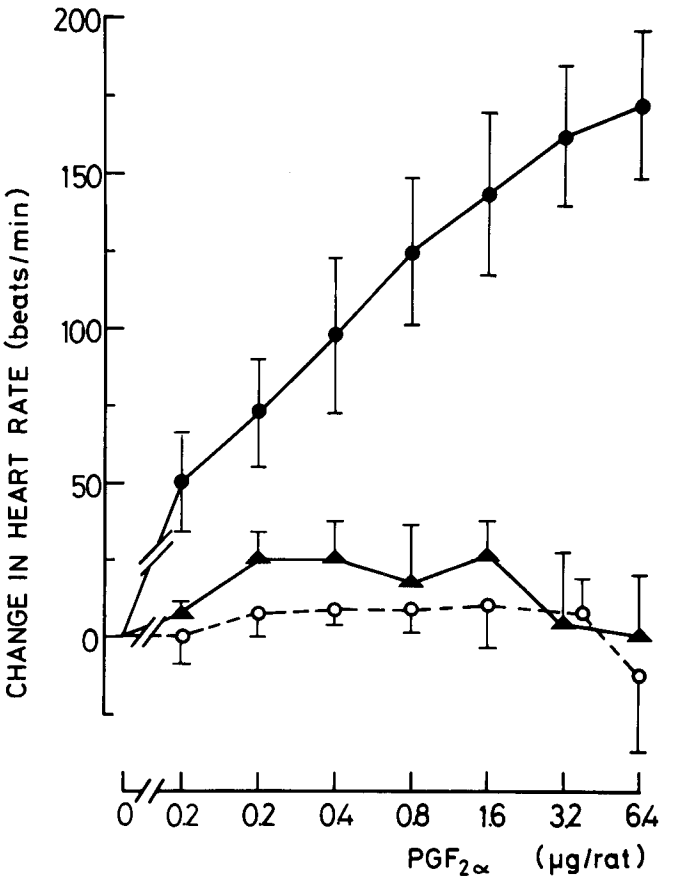

Fig. 2. Influence of $PGF_{2\alpha}$ on heart rate in urethane-anaesthetised male rats. Cumulative doses of $PGF_{2\alpha}$ were administered i.c.v. (●——●) or i.v. (▲——▲) at 15-min intervals. Each dose is indicated on the abscissa. The heart rate before commencement of the administration of $PGF_{2\alpha}$ 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.

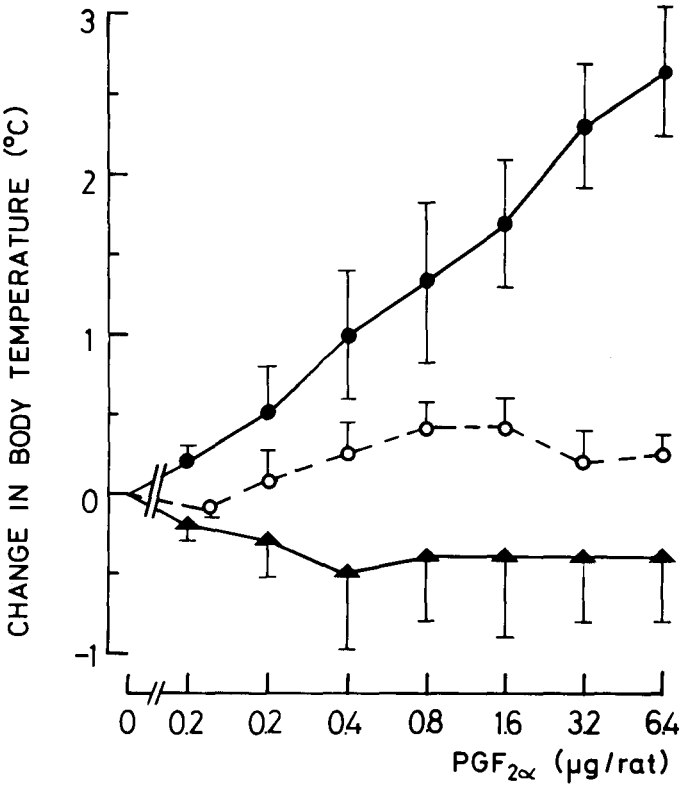

Fig. 3. Influence of $PGF_{2\alpha}$ on body temperature in urethane-anaesthetised male rats. Cumulative doses of $PGF_{2\alpha}$ were administered i.c.v. (●——●) or i.v. (▲——▲) at 15-min intervals. Each dose is indicated on the abscissa. The hyperthermic effect of $PGF_{2\alpha}$ i.c.v. was significant 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.

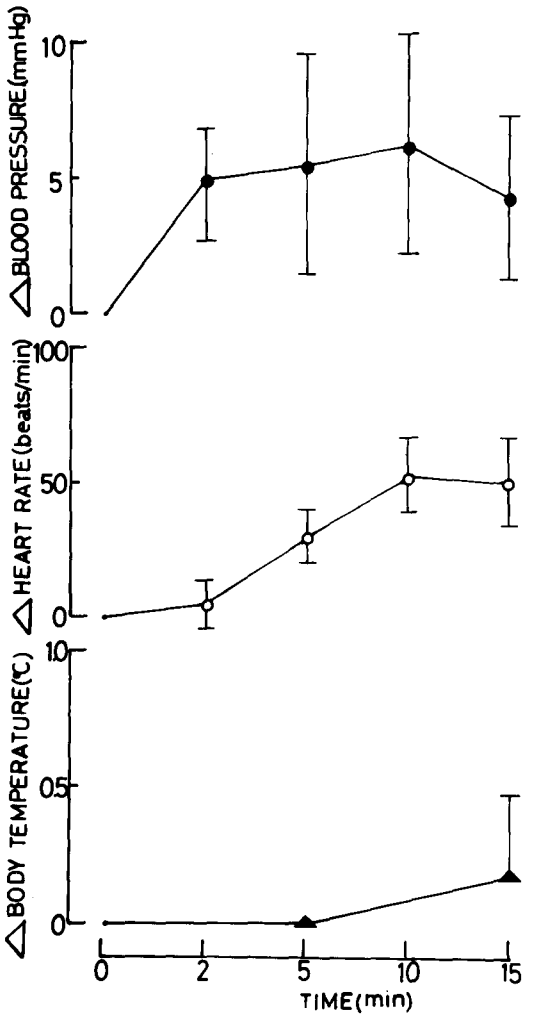

Fig. 4. Time-response effects of $PGF_{2\alpha}$ on blood pressure (●—●), heart rate (○—○) and body temperature (▲—▲) after the first administration of the dose of 0.2 μg/rat i.c.v. The number of rats was 6. Vertical bars indicate s.e. mean.

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).

Pretreatment	B.P. (mm Hg)	H.R. (beats/min)	B.T. (C)
A. *Subcutaneously*[1]			
saline	95 ± 15	340 ± 30	36.0 ± 0.0
sodium meclofenamate (50 mg/kg)	90 ± 10	320 ± 10	36.0 ± 0.3
vehicle	90 ± 20	390 ± 20	36.7 ± 0.2
indomethacin (50 mg/kg)	90 ± 10	370 ± 30	36.7 ± 0.2
B. *Intracerebroventricularly*[2]			
saline	85 ± 10	340 ± 20	37.0 ± 0.1
sodium meclofenamate (1.25 mg/kg)	85 ± 10	400 ± 10*	36.0 ± 0.2**
vehicle	90 ± 20	310 ± 30	36.0 ± 0.3
indomethacin (1.25 mg/rat)	85 ± 15	360 ± 20	36.0 ± 0.3

[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).

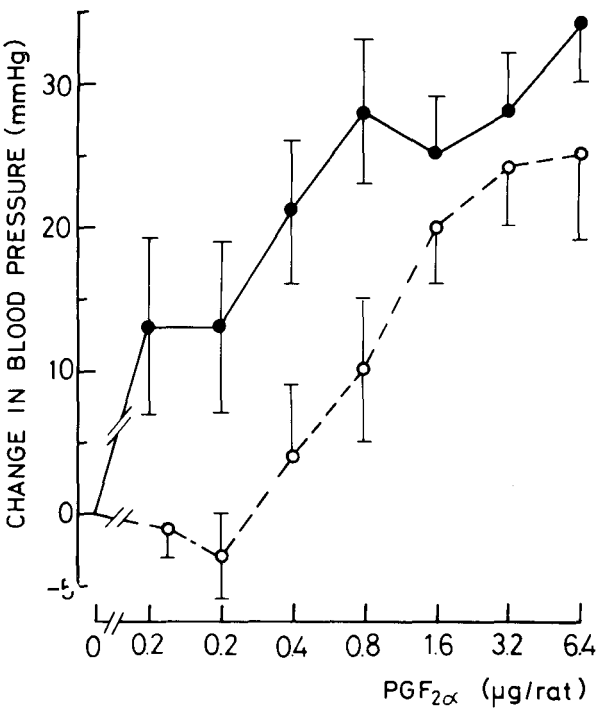

Fig. 5. Effect of $PGF_{2\alpha}$ i.c.v. on blood pressure in sodium meclofenamate (●——●) and saline (○——○) pretreated male rats. Sodium meclofenamate (50 mg/kg) or saline was injected subcutaneously two hours before commencement of the administration of cumulative doses of $PGF_{2\alpha}$ i.c.v. The 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.

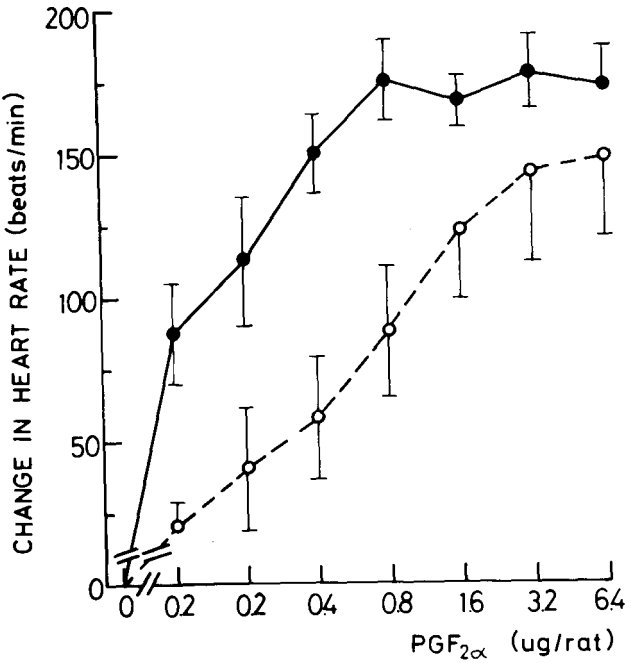

Fig. 6. Effect of $PGF_{2\alpha}$ i.c.v. on heart rate in sodium meclofenamate (●—●) and saline (○—○) pretreated male rats. Sodium meclofenamate (50 mg/kg) or saline was injected subcutaneously two hours before commencement of the administration of cumulative doses of $PGF_{2\alpha}$ i.c.v. The differences 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.

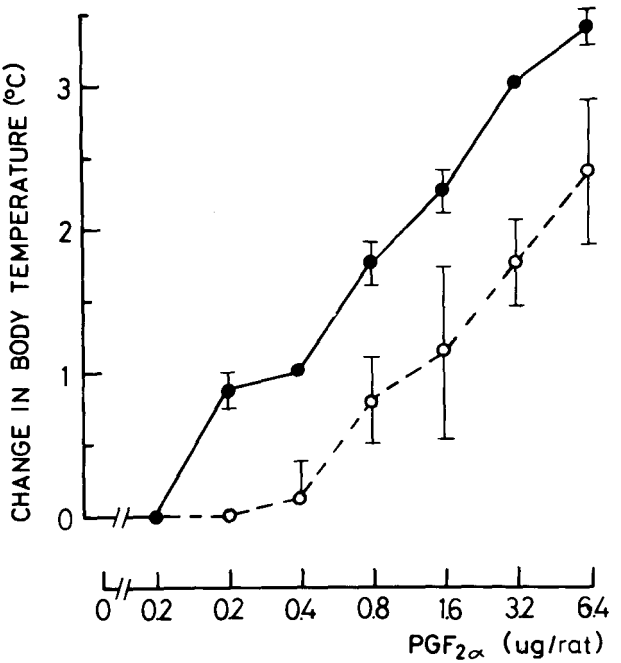

Fig. 7. Effect of $PGF_{2\alpha}$ i.c.v. on body temperature in sodium meclofenamate (●—●) and saline (○—○) pretreated male rats. Sodium meclofenamate (50 mg/kg) or saline was injected subcutaneously two hours before commencement of the administration of cumulative doses of $PGF_{2\alpha}$ i.c.v. The 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 pretreament

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 chlora lose-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 μg 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 augumented 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 vasocontriction 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 phosphodiestherases (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 $PGF_{2\alpha}$.

ACKNOWLEDGEMENT

This work was carried out under a contract with the Association of Finnish Life Insurance Companies, and it was also partly supported by the Paavo Nurmi Foundation.

REFERENCES

1) Eskeli-Kaivosoja, A., A.-L. Sirén and H. Karppanen. Central cardiovascular and thermal effects of prostaglandin F_2 in rats. Acta Pharmacol. Toxicol. **41** (Suppl. IV): 46. 1977.
2) Coceani, F. Prostaglandins and the central nervous system. Arch. Intern. Med. **133**: 119. 1974.
3) Abdel-Halim, M.S., M. Hamberg, B. Sjöquist, and E. Änggård. Identification of prostaglandin D2 as a major prostaglandin in homogenates of rat brain. Prostaglandins **14**: 633. 1977.
4) Milton A.S. Modern views on the pathogenesis of fever and the mode of action of antipyrine drugs. J. Pharm. Pharmac. **28**: 393. 1976.
5) Levery, H.A., R.D. Lowe and G.C. Scroop. Central autonomic effects of prostaglandin $F_{2\alpha}$ on the cardiovascular system of the dog. Br. J. Pharmacol. **39**: 511. 1970.
6) Brus, R., and J. Zabawska. Central action of prostaglandin $F_{2\alpha}$ on circulatory system in rats. Pol. J. Pharmacol. **28**: 455. 1976.
7) Collier, H.O.J. and W.J.F. Sweatman. Antagonism by fenamates of prostaglandin $F_{2\alpha}$ and of flow reacting substance on human bronchial muscle. Nature **219**: 864. 1968.
8) Karppanen, H. and J. Puurunen. Anatagonism of $PGF_{2\alpha}$-induced secretion of gastric acid by mefenamic acid and other fenamates. Naunyn-Schmied. Arch. Pharmacol. Suppl. **294**: 7. 1976.
9) Koss, M.C., J. Nakano and J.A. Rilger. Inhibition of prostaglandin $F_{2\alpha}$-induced reflex bradycardia and hypotension by meclofenamic acid. Prostaglandins **11**: 691. 1976.
10) Flower, R.J. Drugs which inhibit prostaglandin biosynthesis. Pharmac. Rev. **26**: 33. 1974.
11) Documenta Geigy. Scientific Tables. 7th Ed. 1970. p. 636. Basle. Switzerland.
12) Sweet, C.S., P.J. Kadowitz and M.J.L. Brody. A hypertensive response to infusion of $PGF_{2\alpha}$ into the vertebral artery of conscious dog. Eur. J. Pharmacol. **16**: 229. 1971.
13) Milton, A.S. and S. Wendlandt. Effects on body temperature of prostaglandins of the A, E, and F series on injection into the third ventricle of unanaesthetized cats and rabbits. J. Physiol. **218**: 325. 1971.
14) Whelan, J.E. The effect of intrahypothalamic infusion of prostaglandin $F_{2\alpha}$ on body temperature and behaviour in chicks. J. Pharm. Pharmac. **28**: 536. 1977.
15) Poddubiuk, Z.M. A comparison of the central actions of prostaglandins A_1, E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ in the rat. Psychopharmacology **50**: 89. 1976.
16) Vane, J.R. Inhibition of prostaglandin biosynthesis as a mechanism of action for aspirine-like drugs. Nature **231**: 232. 1971.
17) Hedqvist, P. Basic mechanism of prostaglandin action on autonomic neurotransmission. Ann. Rev. Toxicol. **17**: 259. 1977.
18) Lee, J.B. Prostaglandins and blood pressure control. Amer. J. Med. **61**: 681. 1976.
19) Levy, J.V. Changes in systolic arterial blood pressure in normal and spontaneously hypertensive rats produced by acute administration of inhibitors of prostaglandin synthesis. Prostaglandins **13**: 153. 1977.
20) Flower, R.J., R. Gryglewski, K. Herbaczynska-Cebro and J.R. Vane. The effects of anti-inflammatory drugs on prostaglandin biosynthesis. Nature **238**: 104. 1972.
21) Karppanen, H., J. Puurunen and M. Kairaluoma. Effects of non-steroidal anti-inflammatory drugs on cyclic nucleotide phosphodiesterase activities of the human gastric mucosa. Scand. J. Rheumatol. **4**: Suppl. VIII. 050. 1975.
22) Paakkari, P., A.-L. Orma and H. Karppanen. Interference of phosphodiesterase (PDE) inhibition with the hypotensive effect of imidazole acetic acid (IAA). 7th Int. Congr. Pharmacol. Volunteer Abstracts, p. 880, Paris 1978.

Received 5/1/78 - Approved 1/24/79