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DIFFERENCES IN THE CENTRAL ACTIONS OF ARACHIDONIC ACID AND PROSTAGLANDIN $F_{2\alpha}$ BETWEEN SPONTANEOUSLY HYPERTENSIVE AND NORMOTENSIVE RATS

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SUMMARY

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is one of the most common metabolites of arachidonic acid (AA) in rat brain. When administered intracerebroventricularly (i.c.v.) to rats, both AA and $PGF_{2\alpha}$ exert dose-related hypertensive, tachycardic and hyperthermic effects. Metabolic alterations in the endogenous formation of some prostaglandins in the brain-stem of spontaneously hypertensive rats (SHR) have been reported. Therefore the central effects of AA and $PGF_{2\alpha}$ on blood pressure, heart rate and body temperature were studied both in SHR and normotensive Wistar rats (NR) under urethane-anaesthesia. The hypertensive effect of AA i.c.v. (0.01-100 µg/rat) was larger in magnitude in SHR than in NR, but there was no significant difference in the AA-induced changes of heart rate and body temperature between the groups. Pretreatment of NR with sodium meclofenamate (1 mg/rat i.c.v.) antagonised the central effects of AA indicating that these effects are not due to AA itself but to its conversion to prostaglandins. Unlike the effects of AA, the central hypertensive, tachycardic and hyperthermic responses to $PGF_{2\alpha}$ (0.5-50 µg/rat i.c.v.) were significantly attenuated in SHR. The present results obtained with AA are compatible with the previous assumption that the synthesis of prostaglandins in the brain of SHR might differ from that in NR. The results also demonstrate that the central effects of $PGF_{2\alpha}$ are reduced in SHR.

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), PGD_2 and thromboxane A_2 (TxA_2) are the most common metabolites of arachidonic acid (AA) in rat brain (1,2), but PGE_2 and PGI_2 are also formed (2,3). When administered into the lateral cerebral ventricle (i.c.v.) of urethane-anaesthetised normotensive Wistar rats (NR), AA, $PGF_{2\alpha}$ and PGE_2 induce dose-related increases in blood pressure, heart rate and body temperature (4,5,6), whereas PGI_2 lowers the blood pressure also upon central administration (7,8). Though PGD_2 is the most common prostaglandin type of the rat brain (1,3), it has only slight or no central effect on the cardiovascular system of the rat (6,9). Recent studies have shown that the endogenous formation of PGE_2 and TxB_2 is increased and the PGI_2/PGE_2 ratio is decreased in the brain-stem of stroke-resistant spontaneously hypertensive rats (SHR) (10). The synthesis of PGE_2 and $PGF_{2\alpha}$ is altered also in the brain, aorta and kidney homogenates of SHR (11). Furthermore, the hypotensive effect of intra-arterially injected AA is attenuated in SHR (12). Recently it has been also reported that the central pressor response to PGE_2 is larger in magnitude in SHR than in NR (13), but the central effects of AA or its other metabolites than PGE_2 in SHR have not been reported.

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In the present study increasing doses of AA or $PGF_{2\alpha}$ were administered i.c.v. to both SHR and NR under urethane anaesthesia in order to obtain complete simultaneous dose-response curves for blood pressure, heart rate and body temperature.

MATERIALS AND METHODS

Male spontaneously hypertensive rats of Okamoto-Aoki strain, 250-330 g,12-15 weeks of age, were purchased from Møllegaards Avlslaboratorier, DK-4623, L1. Skensved, Denmark. Age-matched male normotensive Wistar rats, 290-350 g, were used as their controls. SHR had an average systolic blood pressure of 176 ± 3 mm Hg (± s.e.m.)(n=12) which was significantly greater ($p<0.001$) than the corresponding level of 140 ± 5 mm Hg in NR (n=9). Heart rate in SHR (390 ± 8 beats/min) was also significantly greater ($p<0.05$) than the corresponding level of 360 ± 10 beats/min in NR. 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 (Hankkija Oy, Helsinki) and tap water ad libitum. The rats were anaesthetised with urethane (1.5 g/kg intraperitoneally). 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) and the heart rate was calculated from the pulse waves by means of a rate computer (Hewlett Packard 8812 A). The 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 by Paakkari (14). 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 5cm 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 36.1 ± 0.3 °C (mean ± s.e.m.) in an ambient temperature of 22°C.

Administration of drugs

The stock solution of AA, grade 1, 99% (Sigma Chemical Co.), 100 mg/ml,was made in absolute ethanol and kept at-20 °C. The dilutions were made freshly each day in 0.9% (w/v) NaCl (saline) or in 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, $MgSO_4x7H_2O$ 1.12 mM, and $NaHCO_3$ 23.6 mM, pH 7.32)to simulate the concentrations found in the cerebrospinal fluid (15). Increasing doses of AA were injected i.c.v. in a volume of 10 µl or intravenously (i.v.) in a volume of 0.15 ml at 20-30 min intervals. The control animals received the same volumes of the corresponding buffer solution i.c.v. and saline solution i.v. in each case.

$PGF_{2\alpha}$, 5 mg/ml (Astra), was diluted with the modified Krebs-Ringer bicarbonate buffer and was injected i.c.v. at 30 min intervals.

Sodium meclofenamate monohydrate (Parke, Davis & Co.) was dissolved in saline and was administerered i.c.v. 20 min before the administration of AA i.c.v.

in order to study the influence of this agent on the central effects of AA.

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

RESULTS

Effects of arachidonic acid

Effects of arachidonic acid in normotensive rats

Intracerebroventricularly, AA at the doses of 0.1-100 µg/rat raised the blood pressure and heart rate, and at the doses of 1-100 µg also the body temperature of urethane-anaesthetised NR. The maximum increase in blood pressure and heart rate was achieved in 15 min. Upon intravenous administrations the same doses of AA had negligible hypotensive and bradycardic effects. Intravenously administered AA had no significant effect on body temperature either. (FIG 1)

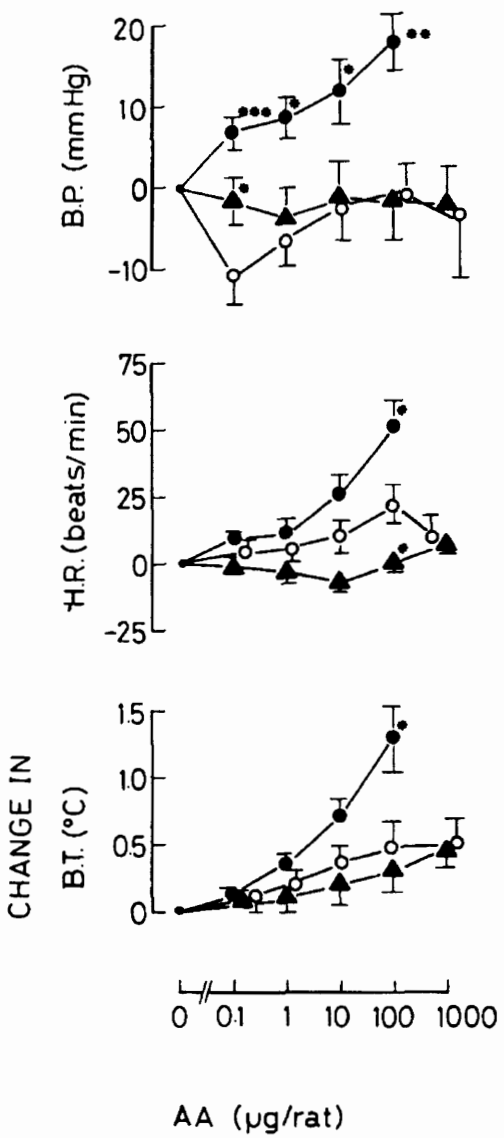


FIG 1

Influence of AA on blood pressure (B.P.), heart rate (H.R.) and body temperature (B.T.) in urethane-anaesthetised NR. Increasing doses of AA were administered i.c.v. (●—●) or i.v. (▲—▲) at 20 min intervals. The control group (○—○) received vehicles i.c.v. and i.v. The changes 15 min after each injection are shown. The initial levels for B.P., H.R. and B.T. (means ± s.e.m.) were 104 ± 4 mm Hg, 440 ± 10 beats/min and 35.6 ± 0.2 °C in the control group, 105 ± 7 mm Hg, 440 ±10 beats/min and 35.7 ± 0.2 °C in the AA i.c.v. group and 103 ± 5 mm Hg, 440 ± 5 beats/min and 35.7 ± 0.2 °C in the AA i.c.v. group. The significance of the AA-induced changes is shown by asterisks; * $p<0.05$, ** $p<0.005$ and *** $p<0.001$ vs. control group. The differences in the cardiovascular changes between AA i.c.v. and i.v. groups are significant at the $p<0.05$-0.001 level. Vertical bars indicate s.e.m. The AA groups comprised 6-7 rats, control group 11 rats, except for the last dose (4 rats).

Sodium meclofenamate (1 mg/rat i.c.v.) reversed the hypertensive and tachycardic effects of i.c.v. administered AA and almost wholly antagonised the central effect of AA on body temperature (FIG 2).

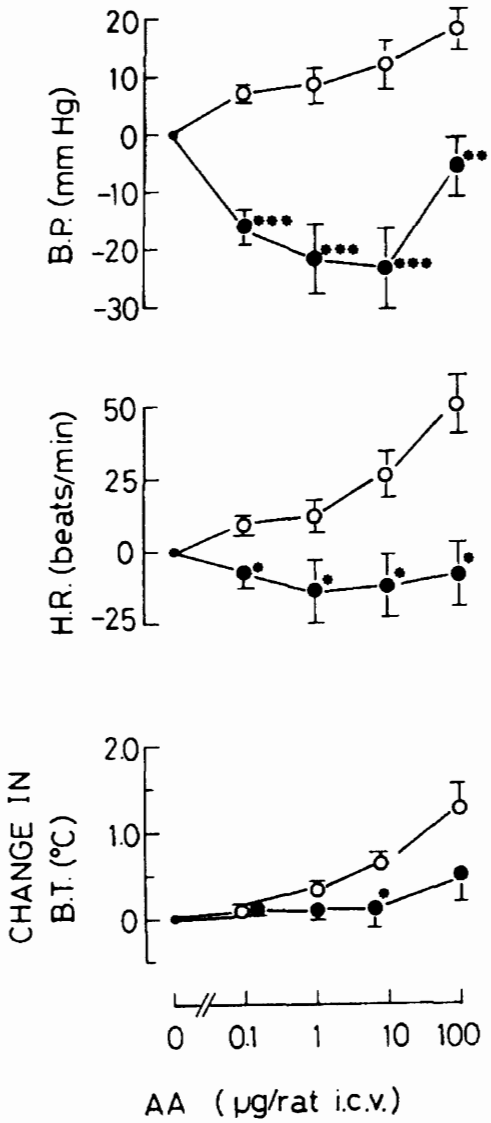


FIG 2

Influence of AA i.c.v. on blood pressure (B.P.), heart rate (H.R.) and body temperature (B.T.) in sodium meclofenamate pretreated rats and their controls. Sodium meclofenamate, 1 mg/rat (●—●) or saline (○—○) was injected i.c.v. 20 min before AA administrations. Increasing doses of AA were administered i.c.v. at 20 min intervals. The changes 15 min after each injection are shown. The initial levels for B.P., H.R. and B.T. (means ± s.e.m.) were 105 ± 7 mm Hg, 440 ± 10 beats/min and 35.7 ± 0.2°C in the control group and 104 ± 6 mm Hg, 450 ± 10 beats/min and 35.9 ± 0.2°C in the sodium meclofenamate pretreated group. The significance of the differences between the groups is shown by asterisks; * $p<0.05$, ** $p<0.005$ and *** $p<0.001$. Verticals bars indicate s.e.m. Each group comprised 6 rats.

Effects of arachidonic acid in spontaneously hypertensive rats

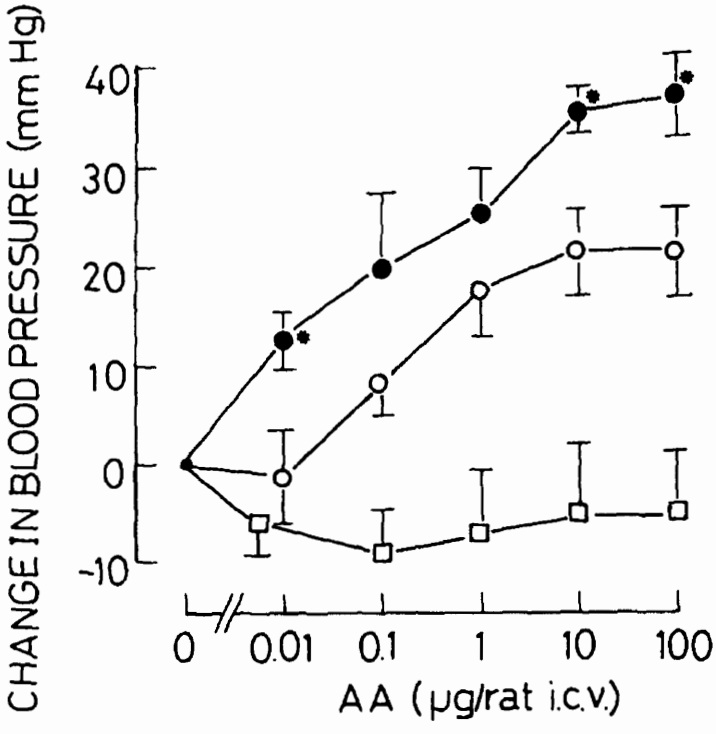
Effect of AA on blood pressure (FIG 3)

The i.c.v. administration of AA at the doses of 0.01-100 µg/rat increased the blood pressure of both SHR and NR in a dose-related manner. The maximum effect was reached 10-15 min after each injection. The AA-induced rises of blood pressure were significantly greater in magnitude in SHR than in NR.

Effect of AA on heart rate (FIG 4)

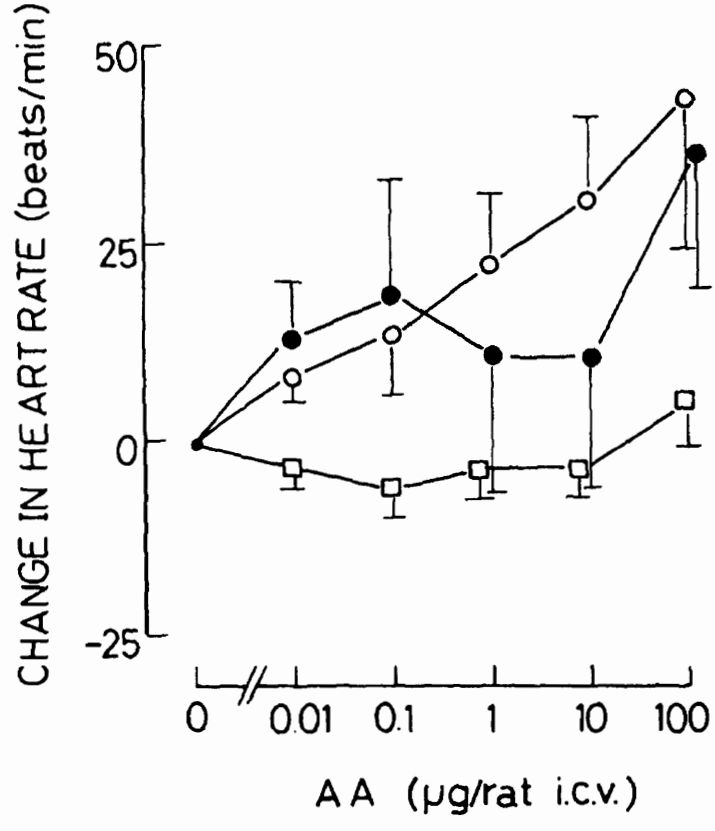
AA at the i.c.v. doses of 0.01-100 µg/rat dose-dependently increased the heart rate of NR. In SHR the AA-induced rises of heart rate were not clearly dose-related.

FIG 3



Effect of AA i.c.v. on blood pressure in urethane-anaesthetised SHR and NR. Increasing doses of AA were administered i.c.v. to SHR (●—●) or NR (○—○) at 30 min intervals. The control NR (□—□) received the same volume of vehicle i.c.v. in each case. The maximum changes 10-15 min after each injection are shown. The initial blood pressure level (mean ± s.e.m.) was 100 ± 4 mm Hg in the control NR, 100 ± 4 mm Hg in NR and 109 ± 8 mm Hg in SHR. The hypertensive effect of AA (0.1-100 µg) in NR is significant at the $p < 0.05$ level as compared to the control group. Differences in the AA-induced changes between SHR and NR are shown by asterisk; * $p<0.05$. Vertical bars indicate s.e.m. Each group comprised 6 rats, except for the control group (5 rats).

FIG 4

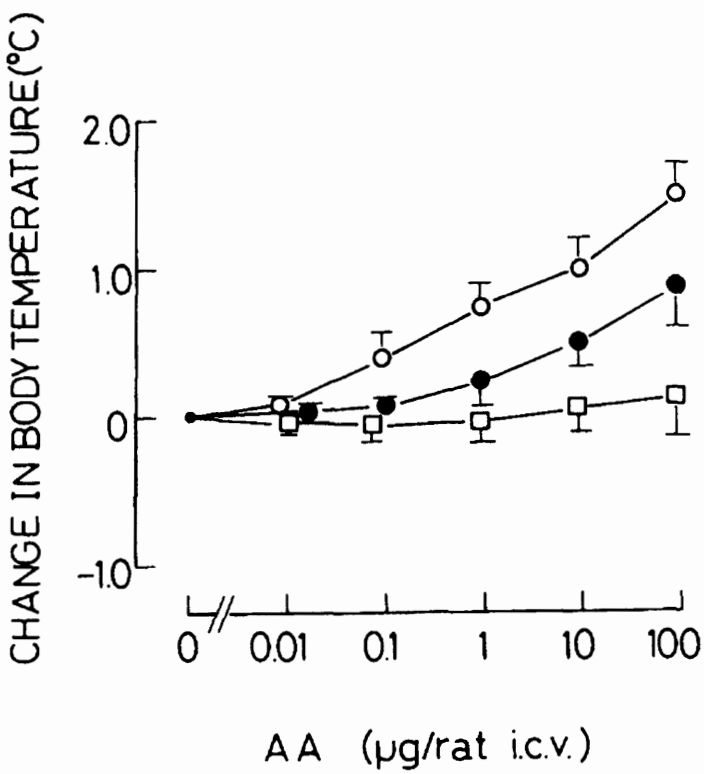


Effect of AA i.c.v. on heart rate in urethane-anaesthetised SHR and NR. Increasing doses of AA were administered i.c.v. to SHR (●—●) or NR (○—○) at 30 min intervals. The control NR (□—□) received the same volume of vehicle i.c.v. in each case. The maximum changes 10-20 min after each injection are shown. The initial heart rate level (mean ± s.e.m.) was 430 ± 10 beats/min in the control NR, 440 ±10 beats/min in NR and 380 ± 10 beats/min in SHR. The difference in the initial heart rate between SHR and NR is significant at the $p<0.005$ level. The tachycardic effect of AA (0.01-100 µg) in NR is significant at the $p<0.05$ level as compared to the control group. Vertical bars indicate s.e.m. Each group comprised 6 rats, Except for the control group (5 rats).

Effect of AA on body temperature (FIG 5)

AA induced a slight but statistically significant hyperthermic effect in NR. In SHR i.c.v. administered AA had only negligible effect on body temperature.

FIG 5



Effect of AA i.c.v. on body temperature in urethane-anaesthetised SHR and NR. Increasing doses of AA were administered i.c.v. to SHR (●—●) or NR (○—○)at 30 min intervals. The control NR (□—□) received the same volume of vehicle in each case. The changes 10-20 min after each injection are shown. The initial body temperature (mean ± s.e.m.)was 35.4 ±0.3°C in the control NR, 36.2 ± 0.2°C in NR and 35.3 ± 0.3°C in SHR. The differences in the initial body temperatures are not statistically significant. The hyperthermic effect of AA (0.1-100 μg)in NR is significant at the $p<0.05$-0.001 level as compared to the control group. Differences in the AA-induced changes between SHR and NR are not statistically significant. Vertical bars indicate s.e.m. Each group comprised 6 rats, except for the control group(5 rats).

Effects of prostaglandin $F_{2\alpha}$ in spontaneously hypertensive rats

Effect of $PGF_{2\alpha}$ on blood pressure (FIG 6)

$PGF_{2\alpha}$ at the i.c.v. doses of 0.5-50 μg/rat induced a dose-dependent rise of blood pressure in NR. The maximum effect was reached approximately 15 min after each injection. The administration of $PGF_{2\alpha}$ at the same i.c.v. doses to SHR did not alter the blood pressure. The initial blood pressure before the administrations of $PGF_{2\alpha}$ was significantly higher in SHR than in NR in spite of the urethane anaesthesia.

Effect of $PGF_{2\alpha}$ on heart rate (FIG 7)

$PGF_{2\alpha}$ dose-dependently increased the heart rate, when administered i.c.v. at the doses of 0.5-50 μg/rat to NR. In SHR the same i.c.v. doses failed to affect the heart rate.

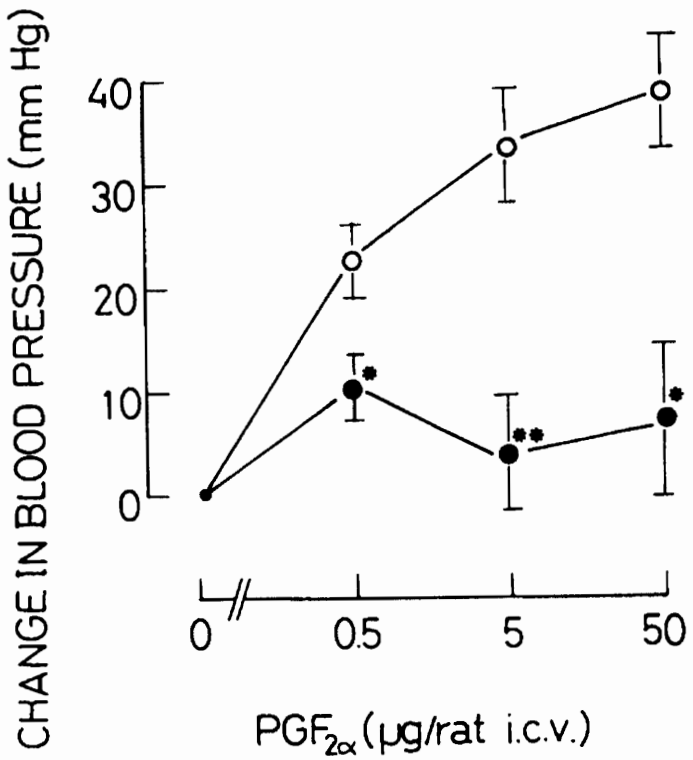


FIG 6

Effect of $PGF_{2\alpha}$ i.c.v. on blood pressure in urethane-anaesthetised SHR and NR. Increasing doses of $PGF_{2\alpha}$ were administered i.c.v. to SHR (●—●) or NR (○—○) at 30min intervals. The maximum changes about 15min after each injection are shown. The initial blood pressure (mean ± s.e.m.) was 90 ± 5 mm Hg in NR and 115 ± 9 mm Hg in SHR. The difference in the initial blood pressure between the groups is significant at the $p<0.05$ level. The differences in the $PGF_{2\alpha}$-induced changes between SHR and NR are shown by asterisks; * $p<0.05$ and ** $p<0.005$. Vertical bars indicate s.e.m. Each group comprised 6 rats.

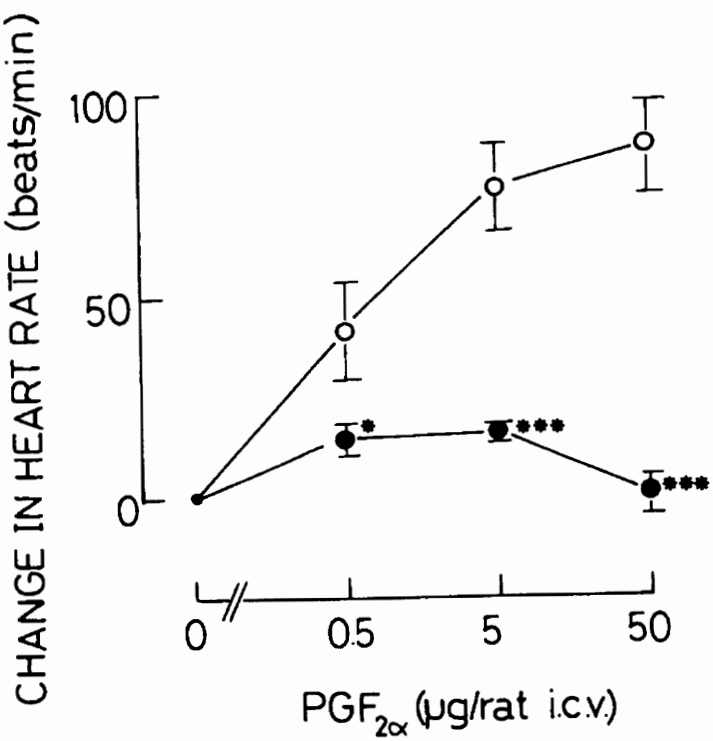


FIG 7

Effect of $PGF_{2\alpha}$ i.c.v. on heart rate in urethane-anaesthetised SHR and NR. Increasing doses of $PGF_{2\alpha}$ were administered i.c.v. to SHR (●—●) or NR (○—○) at 30 min intervals. The maximum changes about 15 min after each injection are shown. The initial heart rate (mean ± s.e.m.) was 430 ± 10 beats/min in NR and 410 ± 10 beats/min in SHR. The difference in the initial heart rate is not statistically significant. The differences in the $PGF_{2\alpha}$-induced changes between SHR and NR are shown by asterisks; * $p<0.05$ and *** $p<0.001$. Vertical bars indicate s.e.m. Each group comprised 6 rats.

Effect of $PGF_{2\alpha}$ on body temperature (FIG 8)

$PGF_{2\alpha}$, 0.5-50 µg/rat i.c.v. induced a substantial hyperthermic effect in NR. In SHR the same doses of $PGF_{2\alpha}$ had no significant effect on body temperature

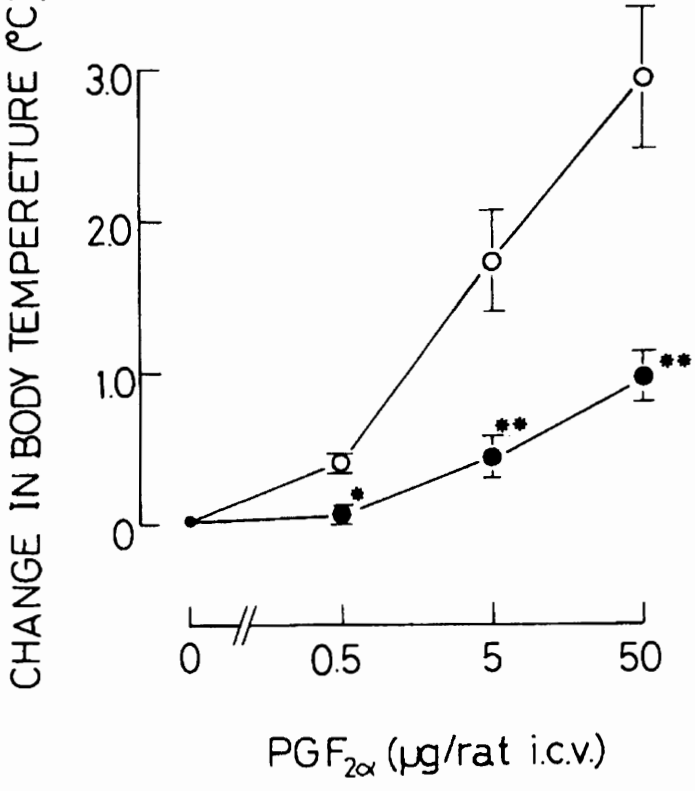


FIG 8

Effect of $PGF_{2\alpha}$ i.c.v. on body temperature in urethane-anaesthetised SHR and NR. Increasing doses of $PGF_{2\alpha}$ were administered i.c.v.to SHR(● ●) or NR (○ ○) at 30 min intervals. The changes about 15 min after each injection are shown. The initial body temperature (mean ± s.e.m.) was 36.2 ±0.3°C in NR and 35.7 ± 0.3°C in SHR. The difference in the initial body temperatures between the groups is not statistically significant. The differences in the $PGF_{2\alpha}$-induced changes between SHR and NR are shown by asterisks; * $p<0.05$ and ** $p<0.005$. Vertical bars indicate s.e.m. Each group comprised 6 rats.

DISCUSSION

Arachidonic acid (AA) raised the blood pressure, when administered i.c.v. to urethane-anaesthetised spontaneously hypertensive Okamoto-Aoki rats (SHR) or normotensive Wistar rats (NR). These results are in agreement with our previous findings that i.c.v. administered AA induced increases in blood pressure of NR (4). The AA-induced hypertensive effect was larger in magnitude in SHR than in NR. Though conscious SHR had significantly higher systolic blood pressure level than NR, there was no significant difference in the baseline mean blood pressure between SHR and NR under urethane anaesthesia. AA i.c.v. increased significantly also the heart rate and body temperature in NR, but in SHR it induced only negligible rise of body temperature and had no clear effect on heart rate. The AA-induced changes in blood pressure, heart rate and body temperature were not due to any leakage of this agent into the peripheral circulation but to an action upon the central nervous system, since the same doses of AA did not affect significantly the body temperature and even slightly decreased the blood pressure and heart rate following intravenous administrations. In the present study the normotensive control rats were of the Wistar strain and not of the Wistar-Kyoto strain (WKY) which is the antecedent colony of SHR (16). However, no significant difference in the hypotensive response to intra-arterially injected AA between WKY and NR was reported (12). Furthermore, the central pres-

sor response to PGE_2 in NR did not differ from that in WKY but was significantly greater in SHR than in WKY or NR (13). The present difference in the central hypertensive action of AA between SHR and NR seems thus to be associated with the high blood pressure in SHR rather than to some genetic differences between WKY and NR. Sodium meclofenamate, an inhibitor of prostaglandin synthesis(17), antagonised the central cardiovascular and thermal effects of AA in NR indicating that the central actions of AA were mediated by its metabolites and not by AA itself. In a previous study the hypertensive effect of AA i.c.v. was antagonised by central pretreatment with indomethacin or paracetamol (18),two inhibitors of the prostaglandin synthesis in the brain (19). PGD_2, $PGF_{2\alpha}$ and TxA_2 are the major metabolites of AA in the homogenates of the rat brain (1,3). High activity of PGD synthetase has been also detected in various regions of the rat brain (20). Since PGD_2 is a potent activator of the cyclic nucleotide adenylate cyclase system of cultured neuroblastoma cells, the role of a neuromodulator for PGD_2 in the brain has been suggested (20). However, PGD_2 at the i.c.v. doses of 1 or 10 µg/rat had no significant cardiovascular or thermal effect in conscious rats (9). In a previous study we obtained dose-related increases in heart rate and body temperature of urethane-anaesthetised NR following i.c.v. administration of 0.001-100 µg/rat doses of PGD_2, while the blood pressure response to centrally applied PGD_2 was not consistent(6,own unpublished results). The central effects of PGD_2 were also considerable smaller in magnitude than those induced by the same doses of PGE_2 (6) or $PGF_{2\alpha}$ (5). Thus PGD_2 seems to interfere preferentially with the central regulation of heart rate and body temperature but only minimally with the central blood pressure regulation of the rat. Imidazole, an inhibitor of TxA_2 synthesis (21), antagonised the central hypertensive effect of AA in NR (18), but the central effects of TxA_2 itself have not been reported. Unlike PGD_2, $PGF_{2\alpha}$ and PGE_2 i.c.v. induce strong hypertensive, tachycardic and hyperthermic effects in NR (5,6,22,23). However, $PGF_{2\alpha}$ had no significant central effects on blood pressure, heart rate or body temperature in SHR. Recent studies have shown that the synthesis of PGE_2 is increased and the ratio PGI_2/PGE_2 is decreased in the brain-stem of stroke-resistantant SHR (10). Intracerebroventricularly, PGE_2 is thus hypertensive (6, 7), while PGI_2 induce hypotension (7,8). Since AA is the precursor of prostaglandins in the rat brain (2), the potentiation of the central hypertensive effect of AA in SHR might be due to an increased formation of hypertensive prostaglandins other than $PGF_{2\alpha}$ in the brain. The recent finding by Takahashi and Buñag (13) that the central pressor response to PGE_2 was greater in SHR than in NR further suggests that an increased receptor sensibility to PGE_2 or to some other hypertensive metabolite of AA other than $PGF_{2\alpha}$ in the brain might contribute to the strong central hypertensive effect of AA in SHR.

The tachycardic response to i.c.v. administered AA was not dose-related in SHR. The central hyperthermic response to AA was also negligible in these rats However, in NR i.c.v. administered AA caused significant increases in the heart rate and body temperature. Since the hypertensive effect of AA i.c.v. was significantly greater in SHR than in NR, the pressor response to AA might be mediated by different central mechanisms than its tachycardic and hyperthermic effects. In agreement with the present findings the hypertensive effect of centrally administered PGE_2 was potentiated in SHR but not the tachycardic effect of this agent (13). The greater blood pressure effect of centrally administered AA in SHR might therefore be due to an increased formation of PGE_2 in the brain, while the actions of AA heart rate and body temperature might require the synthesis of other prostaglandins.

Recent studies have shown that intra-arterial injection of AA at the doses of 0.1-1 µmoles/kg induce significantly smaller hypotensive effect in SHR than in WKY or NR suggesting that the release of vasodepressor prostaglandins from blood vessels of SHR might be reduced (12). Similarly, the blood pressure lowering effect of intravenously administered AA, PGE_2 or PGI_2 was significantly

attenuated in unclipped renal hypertensive rats (24). However, arterial tissue from SHR releases more PGE_2(25) and PGI_2 (26) than the vascular tissue obtained from NR. Other studies have indicated that a defect in the renal prostaglandin catabolism might be an important factor in the development of high blood pressure in the New Zealand strain of genetically hypertensive rats (27). It has also been reported that the synthesis of $PGF_{2\alpha}$, a strong vasoconstrictor in rats (28), is increased in the renal papilla of SHR (29). The present results obtained with AA i.c.v. lend further support to the suggestions that the hypotensive prostaglandin/hypertensive prostaglandin ratio might be decreased even in the central nervous system of SHR. However, the failure of $PGF_{2\alpha}$ i.c.v. to induce cardiovascular and thermal effects in SHR contradicts the possibility that an increased formation of $PGF_{2\alpha}$ in the brain tissue of SHR could be associated with the high blood pressure.

In agreement with a previous study (5) $PGF_{2\alpha}$ i.c.v. induced strong dose-related hypertensive, tachycardic and hyperthermic effects in NR. When administered i.c.v. to SHR $PGF_{2\alpha}$ had no significant effect on blood pressure, heart rate or body temperature. SHR had about 25 mm Hg higher initial blood pressure level even during urethane anaesthesia than NR. However, there was no significant difference in the baseline values for heart rate or body temperature between SHR and NR. Recent studies have shown that the synthesis of $PGF_{2\alpha}$ and the ratio $PGF_{2\alpha}/PGE_2$ are decreased in the brain homogenates of SHR (11). When also the formation of PGE_2 is increased in the brain-stem of SHR (10), the possibility might exist that PGE_2 or some other metabolites of AA other than $PGF_{2\alpha}$ in the brain are involved in the central cardiovascular and thermal regulation of SHR. However, $PGF_{2\alpha}$ seems to be associated with the central cardiovascular and thermal regulation in NR. The central effects of $PGF_{2\alpha}$ in NR are likely to be due to an activation of the sympathetic nervous system (30,31). Moreover, atropine antagonised the central cardiovascular effects of $PGF_{2\alpha}$ in NR (22). Cholinomimetic drugs and $PGF_{2\alpha}$ both increased blood pressure and sympathetic activity in NR, when injected i.c.v. or into the posterior hypothalamic nuclei (30,32,33). Furthermore, cholinergic mechanisms in the posterior hypothalamus mediated also the hyperthermic effect of prostaglandins (34). Since recent studies have shown that the activity of the cholinergic system in the posterior hypothalamus is decreased in SHR (35), the lack of the central cardiovascular and thermal effects of $PGF_{2\alpha}$ in SHR might be due to a dysfunction of the central cholinergic mechanisms. However, various other central mechanisms have been also implicated in the etiology of spontaneous hypertension (33). Therefore the present finding may warrant further investigation.

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