Prostaglandins Leukotrienes and Medicine 17: 381-386, 1985

CENTRAL CARDIOVASCULAR EFFECTS OF THE ENDOPEROXIDE ANALOGUE U-46619 IN RATS [1]

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ABSTRACT

Thromboxanes are abundantly present in the rat brain but their possible physiological functions in the brain are not known. The prostaglandin endoperoxide analogue U-46619 is a selective agonist of TxA2 receptors in many peripheral tissues. In the present study the central cardiovascular and ventilatory effects of U-46619 were investigated in rats. In conscious spontaneously hypertensive rats (SHR) U-46619 (1-100 nmol/kg i.c.v.) induced a strong dose-related increase in blood pressure but had no significant effect on heart rate. In conscious normotensive rats (NR) neither blood pressure nor heart rate was significantly affected. Furthermore, U-46619 (0.1-100 nmol/kg i.c.v.) had no significant effect on blood pressure, heart rate or ventilation in urethane-anaesthetised NR .

The results demonstrate an increased sensitivity of SHR to TxA2.

INTRODUCTION

Classical prostaglandins are known to induce strong increases in blood pressure and heart rate after administration into the central nervous system (2,3). Although thromboxanes are abundantly present in the rat brain (4), the central cardiovascular effects of TxA2 or its analogues have not been reported.

U-46619 is an analogue of the endoperoxide PGH2 which stimulates selectively the receptors of TxA2 in many peripheral tissues (5,6), and has been reported to increase blood pressure after intravenous administration in dogs (7). In contrast to the classical prostaglandins, U-46619 had no thermal effects when injected into the rat anterior hypothalamus (8). Intracerebroventricular (i.c.v.) administration of U-46619 caused hypothermia associated with vomiting, increased frequency of respiration and ear skin vasodilatation in cats

1) A preliminary report of this study has been presented at the 9th International Congress of Pharmacology, London 1984 (1).
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(9). In rabbits U-46619 i.c.v. had no effect on body temperature, though an increase in the respiratory rate and sedation was observed (9).

We now wanted to study the effects of U-46619 i.c.v. on blood pressure and heart rate both in the conscious spontaneously hypertensive (SHR) and normotensive Wistar (NR) rats. In addition, the cardiovascular and ventilatory effects of U-46619 were examined in anaesthetised NR.

MATERIALS AND METHODS

Experiments on conscious rats:

Male spontaneously hypertensive rats of Okamoto-Aoki strain (Møllegaards Avlslaboratorier, Denmark), 360-410 g, 6 months of age, and weight-matched normotensive Wistar-rats were used. The rats were accommodated to standard ambient conditions for at least one week before the surgery.

One week before the experiments the rats were anaesthetised with ketamine (30-40 mg/rat i.p.) and xylazine (2 mg/rat i.m.). A polyethylene catheter was inserted into the left carotid artery. The catheter was exteriorised at the nape of the neck and sealed until use. The right lateral ventricle of the brain was cannulated with a PE-20 polyethylene cannula. The coordinates were relative to the bregma, L=1.0, AP=-3.0 and from the skull surface V=6.0 mm. After insertion of two stainless steel anchoring screws dental cement was applied to secure the cannula in place. The intracerebroventricular injections were performed by the following way: A 26 ga needle was adhered to a PE-50 polyethylene catheter and the whole system was filled with the drug or control solution to be infused. The needle was then attached to the i.c.v. cannula, and the desired amount (15 microliters) of the solution was allowed to flow slowly by the virtue of hydrostatic pressure. The blood pressure and heart rate were continuosly monitored while the rats were conscious and unrestrained in plastic boxes (26x20x13 cm). Increasing doses of U-46619 (1-100 nanomoles/kg) or vehicle were administered into the cerebral ventricles at 60 minutes intervals. The analysis and the follow-up of the experiment was carried out by a laboratory computer (PDP 11/23 Digital Equipment Corp.). The proper position of the i.c.v. cannula was ascertained at the end of each experiment by an injection of dye (methylene blue) into the cerebral ventricles.

Experiments on anaesthetised rats:

Experiments on anaesthetised rats were performed as earlier described in detail by Paakkari (10, 11). Urethane-anaesthetised male Wistar rats (200-220 g) received increasing doses of U-46619 (0.1-100 nmol/kg) or vehicle i.c.v. at 30 min intervals. Ventilation was monitored with a hot wire flow meter placed in connection with the tracheal tube, and the blood pressure and heart rate were recorded from the left femoral artery. The body temperature of the rats was kept constant with a thermostate controlled heating pad.

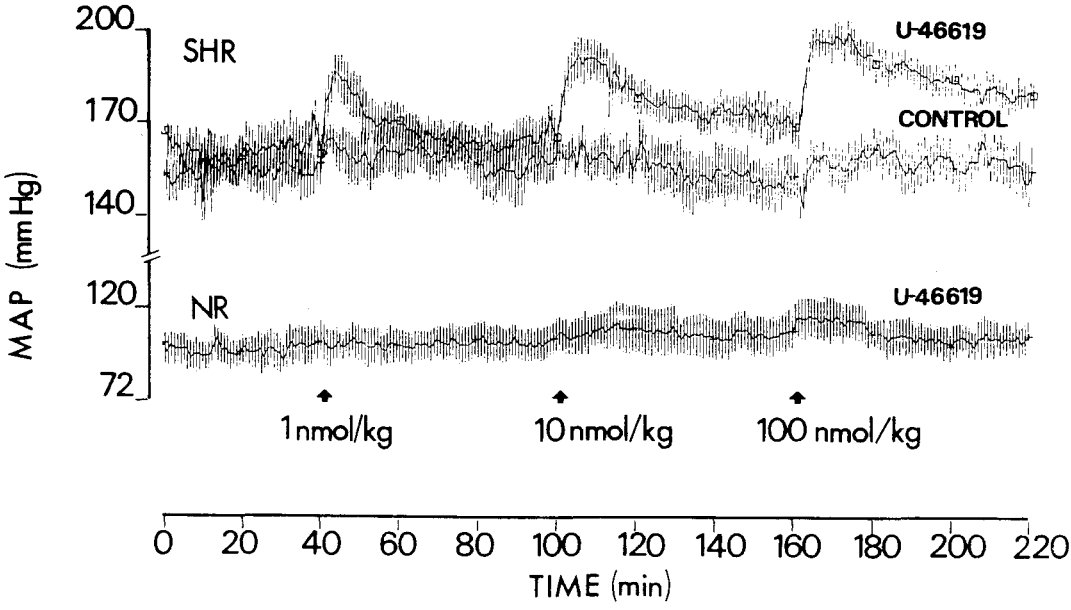

Figure 1. Effect of U-46619 i.c.v. on mean arterial pressure (MAP) in conscious rats. Increasing doses of U-46619 or vehicle were administered i.c.v. at 60 min intervals. Values represent means +S.E. N=8 in SHR treated with U-46619, n=7 in control SHR and n=5 in NR. The differences in the changes in MAP between SHR and its control group were significant at the two highest doses ($p<0.05$ and 0.001, respectively), and between SHR and NR at the highest dose ($p<0.05$). (ANOVA followed by the Bonferroni test.)

Drugs used:

The stock solution (10 mg/ml) of (15S)-hydroxy-11α, 9α-(epoxymethano) prosta-5Z, 13E-dienoic acid (U-46619) from Dr. Pike, Upjohn Company, was made in absolute ethanol and stored at +4 C. The dilutions were made freshly before each experiment in 0.9 % (w/v) NaCl (saline) and kept on ice. The control animals received the same volume of the corresponding ethanol-saline vehicle as the drug solutions in each case.

Statistical analysis of the results:

For calculations of the areas under the curves the trapezoidal method was used. The results are expressed as means $\pm$ S.E. and analysed by ANOVA for repeated measures followed by the Bonferroni test for multiple comparisons (BMDP statistical software for Burroughs large systems computers).

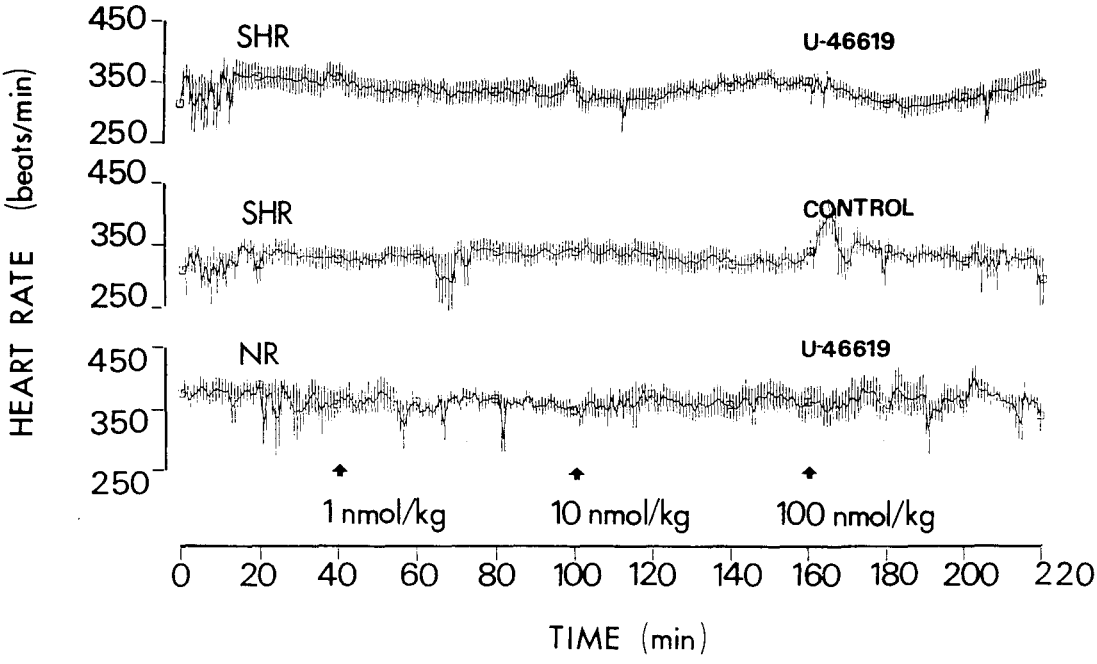

Figure 2. Effect of U-46619 i.c.v. on heart rate in conscious rats. Increasing doses of U-46619 or vehicle were administered i.c.v. at 60 min intervals. Values represent means ±S.E. N=8 in SHR treated with U-46619, n=7 in control SHR and n=5 in NR. The changes in heart rate were not statistically significant (ANOVA followed by the Bonferroni test).

RESULTS

Effects of U-46619 in conscious rats:

U-46619, 1-100 nmol/kg i.c.v., increased mean arterial pressure (MAP) dose-dependently in spontaneously hypertertensive rats (SHR) (n=8). No significant changes were seen in normotensive rats treated with U-46619 (NR, n=5) or in the SHR treated with the vehicle (SHRC, n=7). In Fig. 1 the data for SHR and NR is shown. After the dose of 1 nmol/kg i.c.v. the increase in MAP in SHR lasted about 10 min while long-lasting responses (about 55 min) were observed after the doses of 10 or 100 nmol/kg i.c.v. The maximum changes in MAP after the first dose were 22±5 mm Hg in SHR, -2±2 mm Hg in NR and 9±2 mm Hg in SHR which received vehicle. After the injection of 10 nmol/kg of U-46619 i.c.v the maximum changes in MAP during 55 min postinjection were 28±6 mm Hg, 3±3 mm Hg and 2±2 mm Hg (SHRC). The corresponding changes after 100 nmol/kg i.c.v. were 34 ±8 mm Hg (SHR), 13±4 mm Hg (NR) and 7±3 mm Hg (SHRC).

U-46619 i.c.v. had no statistically significant effect on heart rate in either SHR or NR (Fig. 2). The maximal changes in heart rate after the i.c.v. injections of either U-46619 or vehicle in both SHR and NR were smaller than ±40 beats/min.

Effects of U-46619 in urethane-anaesthetised rats:

Administration of increasing doses of U-46619 (0.1-100 nmol/kg) i.c.v. in urethane-anaesthetised NR had no significant effect on blood pressure, heart rate, ventilation rate or tidal volume. A slight increase in the ventilatory rate of about 40 vent/min was observed after the highest dose. This effect was, however, compensated by a simultaneous decrease in tidal volume. (Results not shown.)

DISCUSSION

The administration of U-46619, a selective TxA2 agonist, i.c.v. induced strong dose-related rises of blood pressure in SHR. The almost instant onset of the hypertensive effect suggests that the site of action is close to the ventricular space. However, U-46619 as a very lipid soluble agent is likely to cross the blood-brain barrier. Therefore, a peripheral site of action due to a leakage of the drug from the central nervous system cannot be totally excluded.

In contrast to the cardiovascular effects of centrally administered classical prostaglandins (2,3), the U-46619-induced pressor effect was not accompanied by tachycardia. Thus, the central pressor response of U-46619 may, at least in part, be mediated by cerebral structures different from those activated by the classical prostaglandins. Since U-46619 is a TxA2-agonist in the peripheral tissues (5), its hypertensive effect after i.c.v. administration is likely to be due to an activation of the same type of receptors also in the central nervous system.

U-46619 had no significant effect on blood pressure, heart rate or respiration in NR, anaesthetised or conscious. This finding is in agreement with the earlier reports by Hawkins and Lipton (8) that U-46619 failed to stimulate the prostaglandin-sensitive thermoregulatory areas of the rat hypothalamus or brain stem. The failure of NR to respond to the central administration of U-46619 suggests that the cerebral thromboxane system is rather inactive in the normotensive state. The strong hypertension induced by i.c.v. administration of this agent in SHR, on the other hand, suggests that cerebral structures responsive to thromboxanes have an increased sensitivity in the hypertensive state.

In conclusion, the present results showed that U-46619, a selective TxA2 agonist in many peripheral tissues, is a potent hypertensive agent in SHR but not in NR. Therefore, a modulator role for the cerebral thromboxanes in the central cardiovascular control in SHR is suggested.

ACKNOWLEDGEMENTS

We thank Dr. John E. Pike of the Upjohn Laboratories for the generous supply of U-46619. The skilful technical assistance of following persons: Mrs Helena Ekström, Mrs Anne Mäkinen and Mrs Riitta Oinonen is gratefully acknowledged.

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