Effects of Intracerebroventricular Administration of Prostaglandin D₂ and Angiotensin II on Blood Pressure in Conscious Rats

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SUMMARY

To evaluate the role of brain prostaglandins in the regulation of blood pressure, we examined the effects of intracerebroventricular injections of prostaglandin D₂, angiotensin II and indomethacin on blood pressure in conscious rats. Intraventricular administration of prostaglandin D₂, the major prostaglandin synthesized in the rat brain, did not elicit a significant change in blood pressure. On the other hand, intraventricular injection of angiotensin II resulted in an increase in blood pressure in a dose-related manner. However, this central pressor effect of angiotensin II was not affected by intraventricular pretreatment with indomethacin. Indomethacin per se did not induce any change in blood pressure. These results suggest that prostaglandin D₂ in the brain does not play an important role in the regulation of blood pressure in conscious rats. It is also suggested that the central pressor effect of angiotensin II is not mediated by prostaglandin biosynthesis in the central nervous system.

Additional Indexing Word:
Indomethacin

Since prostaglandins (PGs) were first identified in the brain,1) considerable attention has been focused on the role of PGs in the central regulation of blood pressure. Intracerebroventricular (i.c.v.) administration of PGE_{1}, PGE_{2}, and PGF_{2α} increase blood pressure and PGI_{2} administration decreases blood pressure in rats.2)–5) However, recent studies by Abdel-Halim et al6) have revealed that the main PG formed in the rat brain is

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PGD₂. In this study we examined the effect of i.c.v. administration of PGD₂ on blood pressure in conscious rats. Furthermore, since the (iso-) renin-angiotensin system appears to be present in the brain⁸ and it has been suggested that there is an interaction between PGs and angiotensin II (ANG II) in the central nervous system,⁹,¹⁰ we examined whether the central pressor effect of ANG II is modified by indomethacin, a PG synthetase inhibitor.

**Methods**

All experiments were performed in male, conscious unrestrained Wistar rats, weighing around 300 Gm. Cannulation of the lateral ventricle, carotid artery, and jugular vein was performed under pentobarbital anesthesia (pentobarbital sodium; 50 mg/Kg, intraperitoneally) according to the method of Hayden et al.¹¹ After an interval of at least 24 h, the experiments were started. Arterial blood pressure was recorded continuously with a Nihon Kohden MPU-0.5 pressure transducer coupled to a Nihon Kohden RM-25 recorder, through a catheter implanted in the carotid artery. The effects of ANG II (Protein Research Foundation, Osaka), PGD₂ (Ono Pharmaceutical Company, Osaka), and indomethacin (Nippon Merck-Banyu Company, Tokyo) were tested. They were dissolved or diluted in 10 mM phosphate buffer (pH 7.4) containing 140 mM NaCl just before injection. The pH and osmotic pressure of the final solution were adjusted to 7.4 and 300 mOsm/l, respectively. These drugs were injected i.c.v. through the cannula without anesthesia, and the change in mean blood pressure was recorded. PGD₂ was also injected intravenously (i.v.). The total injection volume was 10 μl for the i.c.v. injections and less than 0.2 ml for i.v. administration. In preliminary experiments, it was confirmed that the vehicles alone did not induce a significant change in blood pressure. Indomethacin was injected 15 min before the administration of ANG II.

Six experiments were performed in each study. The results were expressed as the mean ± SD. Comparisons were made by Student's t-test.

**Results**

The initial mean blood pressure of conscious rats tested in these experiments was between 92 and 120 mmHg. Intravenous injection of PGD₂ (3–100 μg/Kg) resulted in a decrease in blood pressure in a dose-related manner. By contrast, injection of PGD₂ (0.3–10 μg/Kg) into the cerebral ventricles slightly increased blood pressure. However, this change in blood pressure was not statistically significant (p > 0.05). Even 10 μg/Kg of PGD₂, which signi-
Fig. 1. Effects of intravenous and intracerebroventricular administration of PGD$_2$ on mean blood pressure of conscious rats; n=6 for each group. The bars indicate SD.

Significantly decreased blood pressure of conscious rats when injected i.v. ($-9 \pm 3$ mmHg, $p<0.01$), failed to produce significant changes in blood pressure when injected i.c.v. ($+3 \pm 4$ mmHg, $p>0.05$) (Fig. 1). Intraventricular injection of ANG II (10–250 ng/Kg) elicited an increase in blood pressure in a dose-related fashion. This pressor effect of ANG II was not modified by i.c.v. pretreatment with indomethacin (10 µg/Kg) (Fig. 2). This concentration of indomethacin did not induce any change in blood pressure. (The change in mean blood pressure was $-1 \pm 2$ mmHg.)

Fig. 2. Effect of intracerebroventricular injection of angiotensin II on mean blood pressure in untreated rats (open circles) and in rats pretreated with indomethacin (10 µg/Kg, i.c.v.) (closed circles); n=6 for each group. The bars indicate SD.
DISCUSSION

PGs have been identified in brains of a number of mammalian species, and their release from the brain has also been demonstrated.\(^{11,12}\) Intraventricular injections of PGE\(_1\), PGE\(_2\), PGF\(_{2\alpha}\), and arachidonic acid evoke an increase in blood pressure in rats.\(^{2)-5,13}\) Recent studies have revealed that the pressor effects of i.c.v. administration of bradykinin and carbachol are abolished by PG synthetase inhibitors,\(^{14)-16}\) suggesting that the central pressor effects of these substances are mediated by the synthesis of PGs in the brain. Furthermore, Takahashi and Bunag\(^{17}\) reported that the magnitude of the pressor response to PGE\(_2\) is greater in spontaneously hypertensive than in normotensive rats. However, these results do not necessarily indicate that PGs in the brain directly participate in the regulation of blood pressure, since the main PG formed in the rat brain is PGD\(_2\), not PGE\(_2\).\(^{6,7}\) Although PGD\(_2\) is a significant product of PG endoperoxides, its biological functions are not well understood. Armstrong et al\(^{18}\) found that injection of PGD\(_2\) into the aortic arch decreases the blood pressure of anesthetized normotensive rats. In conscious rats, we confirmed their results. In contrast to its peripheral effects, we have found that i.c.v. injection of PGD\(_2\) does not produce a significant change in the blood pressure of conscious rats. In combination with our observations that inhibition of PG synthesis by indomethacin did not change the blood pressure, these data suggest that PGD\(_2\) in the brain plays a minor role if any in direct regulation of systemic blood pressure in rats.

There is an increasing body of evidence for the existence of an endogenous (iso-) renin-angiotensin system in the brain.\(^{8}\) Recent studies have suggested that ANG II in the brain participates in the regulation of blood pressure.\(^{19,20}\) ANG II stimulates the synthesis of PGs in various tissues,\(^{21,22}\) and interaction of the brain renin-angiotensin system with PGs has been suggested.\(^{9,10}\) However, we observed that the i.c.v. pretreatment with indomethacin did not modify the central pressor effects of ANG II. Considering the doses of indomethacin used in previous studies,\(^{14,23,24}\) the dose of indomethacin administered i.c.v. seems sufficient to inhibit the synthesis of PGs in the central nervous system. Our observation is in accordance with the report of Phillips and Hoffman,\(^{19}\) who found that i.c.v. application of meclofenamate, another PG synthetase inhibitor, had no significant effect on blood pressure responses to i.c.v. administration of ANG II. Therefore, these results suggest that the central pressor effects of ANG II are not mediated by the synthesis of PGs in the brain. Recently Schölkens et al\(^{25}\) reported that the pressor effect of i.c.v. application of renin is increased by indomethacin inhibition of PG biosynthesis. In their study, though, a relatively high dose
of indomethacin was injected subcutaneously. Therefore, the augmented central pressor response to renin after indomethacin treatment may be a consequence of the removal of PG inhibition on sympathetic vasoconstrictor activity at the peripheral vascular beds.\textsuperscript{26,27}

Our present findings support our previous speculation that PGs in the brain do not play an important role in the regulation of blood pressure in conscious, normotensive rats.\textsuperscript{2} However, since we did not use hypertensive rats, our results do not necessarily rule out the possibility that brain PGs participate in the pathogenesis of hypertension. Further studies are necessary to identify the role of PGs in the central nervous system.

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