Effects of Prostaglandins E₂ and I₂, Arachidonic Acid and Indomethacin on Vascular Reactivity to Norepinephrine in the Rat

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The role of prostaglandins in the regulation of blood pressure is still controversial. In addition to their direct effects on the vascular tone, prostaglandins are thought to modulate vasoconstrictor influences and thereby participate in the overall control of the circulation. Until recently, it was considered that prostaglandin E₂ (PGE₂) was the primary prostaglandin which regulates the vascular reactivity. However, since the discovery of prostaglandin I₂ (PGI₂), this prostaglandin has been proposed as the major product of arachidonic acid metabolism in blood vessel walls.

In this study, using the conscious rats and the isolated vascular beds, we examined the effects of PGE₂ and PGI₂ on the vascular response to norepinephrine in vivo and vitro. We also tested the effects of arachidonic acid, a prostaglandin precursor, and of indomethacin, a prostaglandin synthetase inhibitor. Comparing their effects with those of PGE₂ and PGI₂, we have tried to elucidate which prostaglandin has the important role in the regulation of vascular reactivity, as a systemic hormone or a local hormone in the vascular beds.

In vivo Experiments

The experiments were performed in conscious, unrestrained male Wistar rats (300g). Arterial pressure was recorded through a catheter that had been chronically implanted in the right carotid artery.

PGE₂ (2.5–10 μg/kg), PGI₂ (1–30 μg/kg), arachidonic acid (1.5–6 mg/kg) and indomethacin (0.2–5 mg/kg) were injected into the femoral vein, and the effects of these compounds on blood pressure were examined. Then PGE₂ (0.3, 1.25 μg/kg/min), PGI₂ (50, 100 ng/kg/min), arachidonic acid (0.7, 1.4 mg/kg/min) were infused into the femoral vein. Before and 10 min after the start of infusion, 50, 100 and 200 ng of norepinephrine were injected into the jugular vein, and the pressor responses to norepinephrine were examined in the presence of prostaglandins. The norepinephrine response was also examined after the intravenous administration of indomethacin (0.2–5 mg/kg).

The results were summarized in Fig. 1. Intravenous administrations of large amounts of prostaglandins decreased the blood pressure of conscious rats in a dose-dependent manner, while intravenous administrations of large amounts of indomethacin did not have any effect on the blood pressure. In comparison with the effects of PGI₂ and arachidonic acid, the effect of PGE₂ on the blood pressure was quite transient. Infusion of small doses of prostaglandins did not change the blood pressure, but the infusion of these compounds attenuated the pressor response to norepinephrine in a dose-dependent fashion. The inhibitory effect of PGI₂ on the norepinephrine response was more than 10 times

Key Words:

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Indomethacin
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stronger than that of PGE2. On the contrary, indomethacin potentiated the pressor response to norepinephrine dose-dependently in the conscious rats.

In vitro Experiments

Male rats of the Wistar strain, weighing around 300 g were used in these experiments. The effects of prostaglandins on the norepinephrine response were tested in three different vascular beds (mesenteric artery, hind limb and splenic artery). These vascular beds were dissected out under ether anesthesia and perfused with the Krebs bicarbonate buffer at 37°C bubbled with 5% carbon dioxide in oxygen. The perfusion pressure was recorded, the flow rate being adjusted to give a steady perfusion pressure of 25–35 mmHg. At 5 min intervals 20 ng of norepinephrine was injected, which produced a transient rise in pressure of approximately 25–35 mmHg. After the constant response to injected norepinephrine had been obtained, the experiments were started.

The tested drugs were PGE2, PG12, arachidonic acid and indomethacin. These compounds were added to the perfusate and the pressor response to norepinephrine was determined in the presence of PGE2 (0.25–16 ng/ml), PG12 (20–100 ng/ml), arachidonic acid (0.1–3 μg/ml) or indomethacin (0.1–96 μg/ml). In addition, we examined the effect of PGE2 (12 ng/ml) or PG12 (10 ng/ml) on the vasoconstrictor response to norepinephrine in the vascular beds treated with 25 μg/ml of indomethacin.

The results were summarized in Fig. 2. In these three vascular beds PGE2, PG12, arachidonic acid or indomethacin in the perfusate did not change the basal pressure. In the mesenteric

<table>
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<tr>
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<th>Blood Pressure</th>
<th>Response to Norepinephrine</th>
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<tbody>
<tr>
<td>PG E₂</td>
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</tr>
<tr>
<td>PG I₂</td>
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<td>↓</td>
</tr>
<tr>
<td>Arachidonic Acid</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Indomethacin</td>
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Fig.1. The effects of PGE₂, PGI₂, A.A. and indomethacin on blood pressure and pressor response to norepinephrine.

<table>
<thead>
<tr>
<th></th>
<th>Mesenteric Artery</th>
<th>Hind Limb</th>
<th>Splenic Artery</th>
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<tbody>
<tr>
<td>PG E₂</td>
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<tr>
<td>PG I₂</td>
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<tr>
<td>Indomethacin + PGE₂</td>
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<tr>
<td>Indomethacin + PGI₂</td>
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Fig.2. The effects of PGE₂, PGI₂, A.A. and indomethacin on vascular response to norepinephrine.

artery and the hind limb, PGE2 in the perfusate potentiated the vascular response to norepinephrine, whereas PGE2 attenuated this vascular response in the splenic artery. In contrast to PGE2, PGJ2 attenuated the norepinephrine response in these three vascular beds. Arachidonic acid potentiated the vascular response to norepinephrine in the mesenteric artery and the hind limb, while it attenuated this vascular response in the splenic artery. Indomethacin in the perfusate inhibited the vascular response to norepinephrine in all these three vascular beds. In the mesenteric artery and the hind limb, PGE2 and not PGJ2 reversed the inhibitory effect of indomethacin, whereas in the splenic artery, neither PGE2 nor PGJ2 reversed the effect of indomethacin.

**DISCUSSION AND CONCLUSION**

*In vivo experiments:* Since the inhibition of prostaglandin synthesis by indomethacin did not change the blood pressure of conscious rats, the endogenous prostaglandins seem to play a minor role in direct regulation of systemic blood pressure in conscious rats. However, indomethacin potentiated the vascular reactivity to norepinephrine, suggesting that the endogenous prostaglandins act to inhibit the norepinephrine response in the systemic circulation. Dusting et al. suggested that PGJ2 and not PGE2 acts as a systemic hormone in vivo. Comparing the modulating effect of PGJ2 on the norepinephrine response with that of PGE2, our results also suggest that PGJ2 is a primary prostaglandin in the circulation which modulate the vascular reactivity as a systemic hormone.

*In vitro experiments:* Prostaglandins are also considered as local hormones producing their effects at the site of their synthesis, and it has been proved that prostaglandins are synthesized in vascular beds from arachidonic acid. Our results confirmed the previous reports that modulating effects of exogenously administered prostaglandins on the vascular response to norepinephrine vary in different vascular beds. If endogenous prostaglandins synthesized in the vascular bed contribute to the vascular reactivity to norepinephrine, indomethacin, a prostaglandin synthetase inhibitor, should modify the norepinephrine responses in a direction opposite to that produced by exogenous prostaglandins. Moreover, the exogenous prostaglandins should reverse the effect of indomethacin. In this experiment, indomethacin in the perfusate attenuated the vascular contraction induced by norepinephrine in these three vascular beds tested here. We found that PGE2 and not PGJ2 reversed the inhibitory effect of indomethacin in the mesenteric artery and the hind limb. Furthermore, exogenously administered PGE2 and not PGJ2 potentiated the norepinephrine response in the mesenteric artery and the hind limb. These results, in addition to the observations that the modulating effects of arachidonic acid are similar to those of PGE2, not PGJ2, in these two vascular beds, suggest that PGE2 and not PGJ2 is a primary endogenous prostaglandin in determining the vascular reactivity to norepinephrine as a local hormone in the vascular beds, at least in the mesenteric artery and the hind limb. However, in the splenic artery, our results presented here were not able to determine the role of endogenous prostaglandins synthesized in this vascular bed in regulating the vascular reactivity to norepinephrine.

In conclusion, our results suggest a possibility that, in the rat, PGJ2 regulates the vascular reactivity as a systemic hormone and PGE2 plays as a local hormone modulating the vascular reactivity at the site of its synthesis.

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