INHIBITORY ACTION OF PROSTAGLANDIN E ON ANGIOTENSIN II— INDUCED ENHANCEMENT OF VASOCONSTRICTOR RESPONSE TO SYMPATHETIC NERVE STIMULATION

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The inhibitory action of prostaglandin E₁ (PGE₁) on the vasoconstrictor response to an electrical stimulation of perivascular sympathetic nerve (VSNS) was examined using the perfused central artery of an isolated rabbit ear. This response to VSNS was depressed with PGE₁ (2.0 to 5.0 ng/ml in the perfusate) and was augmented with a PG synthetase inhibitor, indomethacin (1.0 µg/ml). Angiotensin II (1.0 ng/ml) enhanced the response to VSNS, whereas treatment with PGE₁ prevented the enhancing effect of angiotensin II completely. In addition, angiotensin II enhanced the response to a bolus injection of noradrenaline in an almost similar manner to that to VSNS. However, PGE₁ (2.0 to 5.0 ng/ml) did not inhibit the enhancing effect of angiotensin II on the noradrenaline response.

From these results, it is suggested that there may be remarkable antagonism between PGE and the sympathetic nervous system and/or the renin-angiotensin system in the central artery of the isolated rabbit ear, and that PGE₁ probably and more potentially acts at presynaptic sites in perivascular sympathetic nerve endings than at postsynaptic ones.

It is generally accepted that noradrenaline secretion from sympathetic nerve terminals in the vascular system is inhibited by prostaglandin E (PGE)^{1,2} while it is facilitated by angiotensin II^{3,4}. In addition, it is also accepted that the renin-angiotensin system plays an important role as a pressor system not only in the pathophysiology of renovascular hypertension, but also in that of some types of hypertension. On the other hand, the polyunsaturated fatty acids-PG system has recently been reported to modify, as a depressor system, the pathological backgrounds of hypertension⁵⁻¹⁶ particularly of human essential hypertension¹⁰⁻¹⁶. In the present study, an inhibitory action of PGE and

an enhancing action of angiotensin II on the vasoconstrictor response to VSNS were examined in order to evaluate the interactions between these 2 active substances in the vasculature.

MATERIALS AND METHODS

Male rabbits, weighing from 2.0 to 3.0 kg, were stunned by a head blow and were exsanguinated by cutting the carotid artery. Their ears were then excised at their bases, and were freshly prepared according to the procedure of DE LA Lande et al.¹⁷ The proximal portion of the central artery was cannulated with fine polyethylene tubing and superficial connective tissue was removed. Using a roller pump, these ear preparations were perfused at a constant flow rate of 3 ml/min with a modified Krebs solution consisting of the following composition (mM): Na⁺ 137.0, K⁺ 5.9, Ca⁺⁺ 1.8, Mg⁺⁺ 1.2, Cl⁻ 123.9,

Key Words:

Prostaglandin E
Perivascular sympathetic nerve
Noradrenaline
Angiotensin II

(Received July 24, 1982; accepted March 11, 1983)

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Fig.1. Effects of tetrodotoxin (A) and phentolamine (B) on the vasoconstrictor response evoked by electrical stimulation of perivascular sympathetic nerve. For further details relating to the experimental conditions, see "MATERIALS AND METHODS".

Fig.2. Effects of prostaglandin E_1 (A) and indomethacin (B) on the vasoconstrictor response evoked by electrical stimulation of perivascular sympathetic nerve. For further details relating to the experimental conditions, see "MATERIALS AND METHODS".

HCO_3^- 25.0, glucose 8.3 and sucrose 20.0. This modified Krebs solution (pH 7.4, 37°C) was equilibrated with a gas mixture of 95% O_2 + 5% CO_2 and then 0.5 $\mu\text{g/ml}$ of atropine sulfate and 25 $\mu\text{g/ml}$ of ascorbic acid were added. The proximal portion of the central artery was electrically stimulated for 15 to 30 sec through 2 Ag-AgCl electrodes, which were contacted with the artery by an interelectrode distance of 10 mm, by supramaximal rectangular pulses of 5 to 20 Hz in frequency and 1 msec in duration using an Electronic Stimulator (SEN-3101, Nihon Koden). Stimulations were repeated at 8-min intervals. These conditions of electrical stimulation were the same throughout each experiment. Zero point one ml of a noradrenaline solution, which was freshly diluted with a normal Krebs

solution containing 12.5 to 50 ng of noradrenaline per 0.1 ml, was injected intraarterially through a rubber tube connected to the central arterial cannula. The dose of noradrenaline used was determined in each experiment so as to cause almost the same change in perfusion pressure as that evoked by the preceding VSNS. Changes in perfusion pressure were recorded on a kymographion using a mercury manometer. Before each experiment, the preparation was perfused for 2 hours. Increases in perfusion pressure with VSNS and noradrenaline were measured. Then, normal Krebs solution containing appropriate doses of the various drugs studied was perfused for 30 min, and changes in the increase in perfusion pressure with VSNS and noradrenaline were studied. Tetrodotoxin was purchased from

Fig.3. Effects of prostaglandin E₁ on the angiotensin II-induced enhancement of the responses evoked by electrical stimulation of perivascular sympathetic nerve and to exogenously single bolus-injected noradrenaline.

Fig.4. Effects of prostaglandin E₁ on the angiotensin II-induced enhancement of the responses evoked by electrical stimulation of perivascular sympathetic nerve (V.S.N.S.) and to exogenously single bolus-injected noradrenaline. Five experiments were done. Vertical bar indicates standard error.

Sankyo Co., Ltd. and indomethacin was supplied by Banyu Pharmaceutical Co., Ltd.

All data were analyzed by standard statistical methods and comparisons for significance were made by Student's *t*-test. A *p* value of less than 0.05 was considered significant.

RESULTS

As shown in Fig. 1, pretreatment with 1.0 μ g/ml of tetrodotoxin or with 1.0 μ g/ml of

phentolamine prevented any increase in perfusion pressure by VSNS. The response to VSNS was reduced during the perfusion of PGE₁, 2.0 to 5.0 ng/ml (Fig. 2A). On the contrary, the response was augmented by the application of a PG synthetase inhibitor, indomethacin (1.0 μ g/ml), when compared with controls (Fig. 2B). The combined application of PGE₁ with indomethacin reduced the response to VSNS. Furthermore, the presence of 1.0 ng/ml of angiotensin II caused a significant ($p < 0.005$)

enhancement of the control response to VSNS, whereas the further application of PGE₁, 2.0 to 5.0 ng/ml, completely and significantly ($p < 0.005$) abolished the angiotensin II-induced enhancement of the response to VSNS (Figs. 3 and 4). Moreover, the angiotensin II-induced enhancement of the response to exogenously single bolus-injected noradrenaline was almost the same as that to VSNS. However, this effect of angiotensin II was not so remarkable as those to VSNS. On the other hand, the inhibitory effect of PGE₁ on angiotensin II-induced enhancement of the response to noradrenaline was neither efficient nor statistically significant within the range of the PGE₁ concentration used in this experiment (Figs. 3 and 4).

DISCUSSION

There are tissue and/or species differences regarding the action of PGE on noradrenaline secretion from adrenergic nerve terminals, i.e., a restrictive action in the vasculature of rabbits¹⁸⁻²⁰ and a facilitating one in some vasculatures of rats.^{19,21} However, it is generally accepted that such an overflow of noradrenaline induced by nerve stimulation is depressed by very low concentrations of PGE in most adrenergic nerve endings.^{1,2,18,22} It has been proposed that endogenous PGE may serve as a chemical mediator in a negative feedback control of noradrenaline release from sympathetic nerve.¹ In contrast, angiotensin II is well known to have a facilitatory effect on noradrenaline transmission at adrenergic neuroeffector junctions.^{2,3}

In the present study, the interrelation between the reducing effect of PGE₁ and the enhancing effect of angiotensin II on the response to VSNS was examined with the perfused central artery of an isolated rabbit ear. As a consequence, it was revealed that PGE₁ depressed the vasoconstrictor response to VSNS, regardless of the enhancing effect of angiotensin II. Furthermore, angiotensin II augmented the response to exogenously applied noradrenaline, while PGE₁ caused little reduction of this response. This result apparently differs from the marked effect of PGE₁ on VSNS. Since PGE₁ acts both pre-,^{1,2} and post-junctionally²³⁻²⁶ in smooth muscle preparations, these results make it tempting to consider that PGE₁ acts more potently at pre-junctional sites than at post-junctional ones of the adrenergic neuroeffector junctions in the central artery of the rabbit ear within the range

of the concentrations used in the present study. Since indomethacin augments the response to exogenous noradrenaline^{15,27} as well as to VSNS²⁰ (Fig. 2) in the central artery of the rabbit ear, as previously reported, there is a possibility that the endogenous PGE among PGs may act at both pre-junctional sites and post-junctional ones in the vascular beds of the rabbit ear. However, in the present study, whether or not the endogenous PGE acted more potently at the former than at the latter could not be ascertained.

It has been proposed that the mechanism of the inhibitory action of PGE is related to a restriction of the available Ca⁺⁺ which is indispensable for noradrenaline secretion^{28,29} or for smooth muscle contraction.^{12,30,31} Therefore, it is speculated that in the central artery of the rabbit ear, PGE₁ more potently restricts the Ca⁺⁺-dependent mechanism of releasing noradrenaline from sympathetic nerve terminals than it does the Ca⁺⁺-dependent mechanism of cell membrane excitation and/or of excitation-contraction coupling in vascular smooth muscle cells. Furthermore, the mechanism of the former is expected to relate to the inhibitory action of PGE₁ even under the angiotensin II-induced facilitation of noradrenaline secretion from adrenergic nerve endings.

In any case, these results may indicate that PGE₁ has an antagonistic action against the pressor effect of the sympathetic nervous system and/or the renin-angiotensin system. PGE depresses the sympathetic nerve activity in human vessels^{1,32} as well as in those of the rabbit. In addition, it has recently been postulated that immunoreactive PGA, PG (A + E) and PGE may participate in forming the clinical background in human essential hypertension.¹¹⁻¹⁶ Thus, the participation of PGE in the mechanism of human essential hypertension may, at least in part, be supported by a marked antagonism between PGE and the pressor systems in the vascular beds.

Acknowledgements

I wish to thank the Research Institute, Ono Pharmaceutical Co., Ltd., Japan and CIBA-GEIGY Pharmaceutical Co., Ltd., Japan for the kind gifts of authentic prostaglandin E₁ and angiotensin II, respectively. I would also like to thank Prof. O. Iimura, Second Department of Internal Medicine, Sapporo Medical College, who made many helpful suggestions in the preparation of this manuscript.

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