The role of prostaglandins in the pathogenesis of hypertension

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Summary

1. Biosynthesis of PGE₂ from [14C]arachidonic acid has been found to be lower and PGF₂α higher in the renal medulla of spontaneously hypertensive (SH) rats than in normal Wistar (NW) rats.

2. Biosynthesis of prostacyclin (PGF₁α) from [14C]arachidonic acid was decreased in lungs, aorta and heart of SH rats.

3. Metabolism of [3H]PGF₁α was decreased in renal cortex and lungs and PGE₂ increased in SH rats in comparison with NW rats. Thus the lungs of SH rats let more PGF and less PGE enter the systemic circulation.

4. Emotional stress decreased the metabolism of [3H]PGF₁α in lungs of SH and NW rats, the effect being less in SH rats.

Key words: biosynthesis and metabolism of prostaglandins, prostacyclin, emotional stress, spontaneous hypertension.

Abbreviations: PGE₂, prostaglandin E₂; PGF₂α, prostaglandin F₂α; SH, spontaneously hypertensive; NW, normal Wistar.

Introduction


In this study we have investigated the biosynthesis and metabolism of prostaglandins in the kidney and lungs of spontaneously hypertensive rats of the Okamoto–Aoki strain.

Methods

Animals

Two groups of male SH rats of the Okamoto–Aoki strain (1.5 and 3.5 months of age) were used. Their mean systolic blood pressure was 158 ± 5.5 (SEM) mmHg and 186 ± 4.5 mmHg respectively.

The normotensive control groups consisted of inbred male Wistar (NW rats) and Wistar–Kyoto (NWK) rats of the same age with mean systolic blood pressure 105 ± 4.0 mmHg and 120 ± 2.5 mmHg respectively.

Blood pressure determination

Systolic blood pressure was measured in the tail artery by an automatic plethysmographic device (Narco Biosystem, U.S.A.). Blood pressure was
determined weekly from 4 weeks and also on the day before killing.

Biosynthesis of prostaglandins

The rats were decapitated, the renal medulla was homogenized with 1 ml of KH₂PO₄ buffer (pH 7.4) containing 20 mM-EDTA, 0.57 mg of hydrocortisone and 56 mg of reduced glutathione/ml. The homogenates were incubated with 0-01 μCi of [¹⁴C]arachidonic acid (The Radiochemical Centre, Amersham, U.K.) for 1 h at 37°C in an atmosphere of 95% O₂ and 5% CO₂. After extraction by 9 vol. alcohol and thin layer chromatography in chloroform/methanol/glacial acetic acid/water (90:9:0.65:1, by vol.), the radioactivity of areas corresponding to arachidonic acid, PGF₁₀ and PGE₂ (Upjohn Company, U.S.A.) were measured in a SL-30 liquid scintillation counter (Inter-technique, France). The rate of biosynthesis was expressed as a percentage of total radioactivity.

Metabolism of prostaglandins

The rats were decapitated, 200 mg of the lungs and 300 mg of the renal cortex were homogenized with 1 ml of Bucher's solution and centrifuged for 20 min at 6000 g. Supernatants were incubated with 0-2 μCi of [³H]PGF₁₀ or [³H]PGE₂ (The Radiochemical Centre, U.K.) with the addition of 6.3 mg of NAD⁺/ml for 1 h at 37°C. After extraction by ethyl acetate and thin-layer chromatography in the chloroform/methanol/glacial acetic acid/water (90:9:0.65:1, by vol.), the radioactivity of areas corresponding to PGF₁₀ and its metabolites (15-oxo-PGF₁₀ and 13,14-dehydro-15-oxo-PGF₁₀; Upjohn Company, U.S.A.) were measured in the liquid-scintillation counter. The rate of metabolic degradation was expressed as a ratio of the non-metabolized [³H]PGF₁₀/sum of [³H]PGF₁₀ metabolites after incubation of [³H]PGF₁₀ with the renal cortex homogenate for 1 h, was found to be lower in adult SH rats than in adult NW rats (Fig. 1). With advancing age, and consequently with progression of hypertension, the metabolism of PGF₁₀ in SH rats (but not in NW rats) decreased considerably.

In lungs the metabolism of [³H]PGF₁₀ was decreased in young SH rats, suggesting that a larger amount of F-prostaglandins pass unmetabolized through the lungs of SH rats to enter the systemic circulation and to become systemic pressor factors. If one takes into account the fact that the metabolic rate of [³H]PGE₂ in lungs of SH rats has been found to be increased, a preponderance of pressor over depressor prostaglandins in the systemic circulation of SH rats becomes much more apparent.

Emotional stress (produced by full immobilization of rats on their backs for 2 h) resulted in a considerable depression of [³H]PGF₁₀ metabolism in lungs. Thus the stress enabled larger amounts of unmetabolized prostaglandins (i.e. of pressor F-prostaglandins) to pass through the pulmonary metabolic filter than is possible under conditions of physiological rest. In SH rats the stress caused similar but much smaller changes. Of special interest, however, is the fact that the metabolic rate of [³H]PGF₁₀ in SH rats at rest (i.e. before stress) was exactly the same as its metabolic rate during stress in NW rats. This may be regarded as indirect evidence for SH rats being in a state of some emotional stress even in testing conditions.

Results

Both in young (1.5 months of age) and adult (3.5 months) SH rats, in other words at early and chronic stages of hypertension, the biosynthesis of PGE₂ was lower than in NW rats of the same age. Moreover the reduction of the biosynthesis of this prostaglandin observed in NW rats with age was not found in SH rats. On the other hand the biosynthesis of PGF₁₀, although similar in young SH and NW rats, was increased in adult SH rats in comparison with adult NW rats.

The rate of metabolic degradation of [³H]PGF₁₀ in renal cortex, judged by the ratio: non-metabolized [³H]PGF₁₀/sum of [³H]PGF₁₀ metabolites after incubation of [³H]PGF₁₀ with the renal cortex homogenate for 1 h, was found to be lower in adult SH rats than in adult NW rats (Fig. 1). With advancing age, and consequently with progression of hypertension, the metabolism of PGF₁₀ in SH rats (but not in NW rats) decreased considerably.

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Finally, the data concerning prostacyclin, a new prostaglandin-like substance with strong vasodilator and platelet anti-aggregating capacity (Moncada, Griglewsky, Bunting & Vane, 1976), should be noted. With advancing age the biosynthesis of prostacyclin from $^{14}$C]arachidonic acid considerably decreases in lungs, aorta and heart of both SH rats and normotensive Wistar-Kyoto rats. At the same time the biosynthesis of prostacyclin from $^{14}$C]arachidonic acid was found to be markedly decreased in the aorta, heart and lungs of adult SH rats in comparison with normotensive Wistar-Kyoto rats of the same age. A similar trend in prostacyclin biosynthesis occurred in young SH rats at the early stage of hypertension, but these changes were insignificant. Thus the development and stabilization of hypertension in SH rats is accompanied and to some extent probably induced by a considerable reduction of prostacyclin synthetase activity.

**Discussion**

While appraising the data presented it is necessary to take into account the 'paradoxical' effects of prostaglandins on rat kidney functions. As has been shown by Malik & McGiff (1975), PGF$_{2\alpha}$ is diuretic and PGE$_{2}$ antidiuretic in rats. Therefore the increased biosynthesis of PGF and decreased biosynthesis of PGE$_{2}$ in the kidney of SH rats may be compensatory in relation to the pathogenesis of the hypertension, preventing to some extent its development.
On the other hand the aforementioned changes of metabolic degradation of PGE and PGF in the kidney and especially in lungs should promote the development of hypertension if one takes into consideration, first, the preponderance of PGF over PGE in the systemic circulation in SH rats and, second, the 'normal' pressor effect of PGF and the depressor effect of PGE.

Of special importance is the marked decrease in the biosynthesis of prostacyclin in lungs, heart and aortic wall of adult SH rats in comparison with adult normotensive Wistar–Kyoto rats. As shown earlier (Markov, Pinelis & Ismailov, 1978), the depressor effect of prostacyclin both in normotensive and hypertensive rats is much more than that even of PGE. The reduced prostacyclin biosynthesis in SH rats may also lead to the predominance of pressor mechanisms, thus promoting the development of hypertension. As a consequence the antihypertensive action of renal prostaglandins is insufficient for preventing the development of hypertension in SH rats.

As regards the prostaglandin metabolism in lungs during emotional stress two aspects should be pointed out. First, the directions of the changes observed were the same both in SH rats and in rats with DOC + NaCl-hypertension (Zadkova & Markov, 1978). This is in accordance with a role of emotional stress in the aetiology and pathogenesis of hypertension. Secondly, the full coincidence of levels of [3H]PGF

\[ \text{metabolism in lungs of SH rats before stress and [3H]PGF}_{10} \]

in lungs of NW rats during stress suggests that SH rats are in a state of some emotional stress even in resting conditions.

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References


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\[ \text{in rats with DOCA + NaCl-hypertension. In: *Prostaglandins in the Experiment and in the Clinic*, p. 137. Moscow.*} \]