Renal and vascular wall prostaglandins in spontaneously hypertensive rats

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Summary

1. Renal cortical and medullary tissue and aortic wall were removed from spontaneously hypertensive rats and from age-matched Wistar-Kyoto control animals at ages 30, 60, 90 and 120 days. The tissues were incubated and the release of prostaglandins into the incubation medium was measured.

2. Compared with Wistar-Kyoto control animals, the release of prostaglandin E from renal medullary tissue in spontaneously hypertensive rats was raised at 30 days (pre-hypertensive stage) and 90 days (early hypertensive stage), but decreased later with further establishment of hypertension. No such trend was seen with renal cortical tissue. Tissue release of prostaglandin F tended to be generally high in the spontaneously hypertensive rats compared with that in the control animals, but the difference was not significant.

3. The release of prostaglandin I\textsubscript{1}, as indicated by measurements of 6-keto prostaglandin F\textsubscript{1}\textsubscript{a}, from aortic wall tissue in the spontaneously hypertensive rat during its pre-hypertensive and early hypertensive stages was similar to values obtained in the age-matched control animal. However, aortic wall prostaglandin I\textsubscript{2} release in spontaneously hypertensive rats increased thereafter, and was significantly raised at 90 and 120 days. No similar trend was observed with thromboxan A\textsubscript{2} release. Release of prostaglandin I\textsubscript{2} and thromboxan A\textsubscript{2} from renal tissues in spontaneously hypertensive rats did not differ significantly from that in control animals.

4. It is suggested that indomethacin-induced aggravation of hypertension in the spontaneously hypertensive rat may result from suppression of aortic wall prostaglandin I\textsubscript{2} formation rather than from the suppression of renal prostaglandin E\textsubscript{2} production.

Key words: aorta, kidney, prostaglandins.

Abbreviations: PG, prostaglandin; Tx, thromboxan.

Introduction

Although the spontaneously hypertensive (SH) rat has widely been adopted for experimental studies as a model of human essential hypertension, the precise role of prostaglandins in blood pressure regulation in the rat remains controversial. Some experimental observations have suggested that, in contrast to other species, including man, the renal prostaglandin mechanism contributes to elevation of blood pressure in the rat, leading to the suggestion that the use of the rat would be unsuitable for studies in which definition of an antihypertensive role of prostaglandins is the objective [1]. However, in contrast to some investigators, we have observed a blood pressure elevating effect of indomethacin in both SH and control Wistar-Kyoto (WK) rats, suggesting the operation of an anti-hypertensive effect of prostaglandins in the rat. Release of prostaglandins \textit{in vitro} from aortic wall, renal cortex and renal medulla of SH and WK rats at different chronological ages was measured in order to define more precisely the mechanism leading to the above observations.

Methods

SH and the age-matched WK rats were given standard solid feeds and allowed free access to tap water. The animals were killed at ages 30
days (pre-hypertensive stage in SH rats), 60 days (early hypertensive stage in SH rats), 90 days and 120 days by decapitation. Experiments were performed by pairing 10 SH and WK rats of the same age for each study. After the rats had been killed, renal papilla, renal cortex and abdominal aorta were removed and weighed. The tissue was chilled after death with cold Krebs solution. Each tissue was cut into small pieces (0.5-1.0 mm) and incubated in Krebs-Henseleit medium for 2 h by the method of Sirrois & Gagnon [1]. The incubation medium was then extracted with Folch solution, and the extract chromatographed on a silicic acid column for separation of prostaglandin E (PGE) and prostaglandin F (PGF) by Jaffe's method [3] and on a Hilfosil column by Frohlich's method [4] for separation of 6-keto prostaglandin F\(_1\alpha\) (PGF\(_{1\alpha}\)) and thromboxane B\(_2\) (TxB\(_2\)) [4], which are respectively the metabolites of prostaglandin I\(_2\) (PGI\(_2\)) and thromboxane A\(_2\) (TxA\(_2\)). Prostaglandins were measured by radioimmunoassay and their release from the tissue was expressed as ng min\(^{-1}\) mg\(^{-1}\) of wet tissue.

**Results**

The release of various prostaglandins from renal and aortic tissue in SH and WK rats, measured at ages 30, 60, 90 and 120 days, is shown in Fig. 1. Compared with WK rats, the release of PGE from renal medullary tissue in SH rats was raised during the pre-hypertensive and early hypertensive stages, but decreased later with the development of hypertension. Although a similar trend was observed for PGE release from renal cortex in SH rats, the change was minimal and insignificant. No similar change in PGE release from aortic tissue in SH rats was observed. Tissue release of PGF tended to be higher in SH than in WK rats, but the difference was slight and insignificant. Release of PGI\(_2\) (measured as 6-keto PGF\(_{1\alpha}\)) from the aortic wall in SH rats during the pre-hypertensive and early hypertensive stages was comparable with the values obtained with age-matched WK control animals. However, aortic wall PGI\(_2\) release in SH rats increased thereafter and was significantly raised at ages 90 and 120 days. No similar trend was observed with TxA\(_2\) release (measured as TxB\(_2\)) from aortic wall. Although release of PGI\(_2\) and TxA\(_2\) from the kidney tended to be higher in SH than in WK rats, the difference was insignificant.

**Discussion**

Recent studies on the metabolism of renal medullary prostaglandins in SH rats have indicated that there is an increase in prostaglandin synthase activity and a decrease in the activity of
prostaglandin-degrading enzymes with age, which could lead to elevated levels of prostaglandins in the renal medulla in these animals with development of hypertension [5–8]. It has been suggested that increased renal prostaglandin levels may be important in the hypertensive mechanism in SH rats because of a prostaglandin–adrenergic interaction, whereby increased levels of a modulator, such as PGE₂, potentiate the pressor effect of the sympathetic nervous system. In contrast to the results of other investigators cited above, our present study has indicated that renal medullary PGE in SH rats during the pre-hypertensive and early hypertensive stages is increased, and that it decreases later with the establishment of hypertension. In our previous study, the relationship between renal medullary prostaglandin release and renal medullary blood flow during sodium chloride loading was investigated in SH rats [9]. The results indicated that the rise in renal medullary plasma flow in response to salt loading at age 60 days was greater in SH than in WK rats but that the relationship was inverse at ages 120 and 150 days. Furthermore, there was a positive correlation between renal medullary plasma flow and salt intake, as well as between PGE release from the renal medulla and salt intake. These results indicated that the increases in renal medullary prostaglandin production and in renal papillary plasma flow which normally occur in response to salt loading are compromised in SH rats, thereby contributing to the development of sustained hypertension [9].

Enhanced formation of PGI₂ by the aortic wall in SH rats has already been observed by several researchers [10–13], although it remains to be seen whether the arteriolar wall also participates in excessive production of PGI₂. Although the exact mechanism of the enhanced PGI₂ production in SH rats remains unsolved, it is likely that PGI₂ exerts a significant systemic anti-hypertensive action in SH rats. In our previous study, administration of indomethacin to SH rats aggravated their hypertension [9]. Meanwhile, our present experimental results indicate that vascular wall PGI₂ production increases with age and with the establishment of hypertension in SH rats, whereas renal medullary PGE production decreases. It is therefore suggested that aggravation of hypertension by indomethacin administration in SH rats probably results from suppression of aortic wall PGI₂ formation rather than from suppression of renal PGE production.

References