EFFECTS OF PROSTAGLANDIN INHIBITORS ON THE ONSET OF PROTEINURIA AND STROKE IN STROKE-PRONE SPONTANEOUSLY HYPERTENSIVE RATS

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Recent evidence suggests that prostaglandins (PGs) modulate the renal circulation and function which are implicated in the regulation of blood pressure. Stroke-prone spontaneously hypertensive rats (SHRSP) show a severe hypertension which is followed by proteinuria, mainly related with renal vascular changes, and cerebrovascular lesions (1, 2). Renal dysfunction, concomitant with afferent arteriolar changes, seems to be closely related to the onset of stroke in the SHRSP (1). The present study was designed to estimate the role of endogenous PGs in the pathogenesis of severe hypertension and its vascular complications (proteinuria and stroke) in the SHRSP, using two dissimilar PG synthetase inhibitors.

Littermates of male SHRSP at 14 weeks of age were divided into control and treated groups. Systolic blood pressure was measured weekly in conscious rats using a pulse pick-up method (3). Twenty-four hour urine sample was collected once or twice weekly, and total protein excretion was determined by a biuret method. The amount of urinary protein over 100 mg/day per 250 g body wt. was considered as “proteinuria”, since the usual level of urinary protein was 40–50 mg/day in SHRSP and normal rats (1). Indomethacin or carprofen (6-chloroalphamethyl-carbazole-2-acetic acid, Nippon Roche), suspended in 5% arabic gum solution, was subcutaneously injected in a dose of 2 mg/kg for 6 to 7 weeks. Carprofen has been shown to cause a 50% reduction in renal venous PGs, when given in a dose of 1 mg/kg i.v. (4). A solution of arabic gum was similarly administered to the respective controls. The onset of stroke was predicted by unusual behavior (stroke-signs) such as stereotyped lifting of the front leg and behavioral depression, and also by histological examination after the recognition of stroke-signs (3).

To examine the inhibitory action of indomethacin or carprofen on PG biosynthesis, depressor responses to exogenous arachidonate and PGE₂ were observed in pentobarbital anesthetized SHRSP after successive administration of the inhibitors (2 mg/kg, s.c.) for 2 weeks and 7 to 9 hours after the final administration. The femoral artery and vein were cannulated. When the blood pressure had stabilized, PGE₂ (5 μg/kg per min) or arachidonate (2.5 mg/kg per min) was infused at the rate of 0.32 ml/kg per min for 5 min through the femoral vein.

Initial systolic blood pressure was 218±2 (SE) mmHg in control and 215±2 mmHg in indomethacin-treated groups (Fig. 1A). The following increase in blood pressure was
Fig. 1. Systolic blood pressure (A) and cumulative incidences in proteinuria (B) and stroke (C) in control (n=13, □) and indomethacin-treated (n=14, ●) groups. Number of rats in both groups was reduced by the onset of stroke, and the number on day 10, 15, 20, 25, 30, 35, and 40 was 13, 11, 7, 5, 3, 3, and 1 in control group and 12, 9, 5, 2, 1, 1, and 0 in the treated group. The difference in means of blood pressure in both groups was not significant (Student’s t-test). Abscissa: time after the start of experiment, and ordinate: blood pressure (A) or cumulative incidences (B and C).

Fig. 2. Relationship of time required for the onset of proteinuria and stroke.

•; indomethacin-treated rat, ○; control rat in indomethacin experiment, ▲; carprofen-treated rat and △; control rat in carprofen experiment.

All but identical in the two groups. The rate of development of proteinuria was slightly but significantly (p<0.05 by Wilcoxon’s two sample test) faster in indomethacin-treated group than in the control group (Fig. 1B). The rate of occurrence of stroke also tended to be accelerated by the treatment (Fig. 1C). Initial blood pressure of control (n=12) and carprofen-treated (n=13) groups was 198±3 and 192±2 mmHg, respectively. The carprofen treatment did not significantly affect the development of severe hypertension (blood pressure at 4 weeks; 238±7 mmHg in control, 235±5 mmHg in the treated group), and the rate of onset of proteinuria and stroke (p>0.05).

As shown in Fig. 2, a significant correlation between the time (days) required for occurrences of proteinuria and stroke was observed in each group, indicating the close relation of proteinuria and stroke. The correlation coefficient (r) was 0.860 (n=21, p<0.001) in the two control groups of rats, 0.812 (n=14, p<0.01) in indomethacin and 0.747 (n=9, p<0.05) in carprofen treated animals.

Mean blood pressure before the infusion of arachidonate and PGE₂ did not differ between the control and the two treated groups (about 170 mmHg). Depressor response to PGE₂ in each group was comparable (20–22 mmHg reduction). However, depressor response to arachidonate was markedly inhibited in the treated groups. Decrement of blood pressure was 44±6, 2±1 and 17±3 mmHg in control, indomethacin and carprofen treated groups, respectively.

Inhibition of PG synthesis by indomethacin resulted in a slight acceleration of develop-
ment of proteinuria and stroke in SHRSP. The lack of effects of carprofen may be related with an incomplete blockade of PG synthesis. Our previous work (1) showed that, in SHRSP, an increase in protein excretion was closely associated with necrotic and proliferative changes in the renal arterioles, and that reduction of renal perfusion pressure and/or renal ischemia, which seems to be due to the arteriolar changes in the kidney, may be related to the pathogenesis of cerebrovascular lesions in SHRSP. All these findings lead to the speculation that renal PGs exert, to some extent, protective effects against the onset of hypertensive vascular lesions in the brain and kidneys by minimizing renal ischemia, in the SHRSP. This is supported by the fact (5) that in rabbits with a reduced renal blood flow, indomethacin treatment results in a production of renal failure which may be caused by the cessation of the vasodilator protective effect of PGs. However, it may be possible that different metabolites of arachidonate participate independently in the vascular lesions in the kidney and brain.

Moreover, the effects of indomethacin unrelated to PGs as well as the effects on PG metabolism in platelets, damaged tissues and the wall of cerebral blood vessels have to be considered. For these questions, there is some indirect evidence. Dexamethasone, an anti-inflammatory agent did not accelerate the onset of stroke in SHRSP (6), and indomethacin did not inhibit smooth muscle proliferation in response to arterial injury. This drug did not prevent the release, from adherent platelets, of the factor that is mitogenic for smooth muscle cells (7). Sakabe and Siesjo (8) reported that indomethacin reduced the cerebral blood flow in normocapnic rats, thereby suggesting that PGs in the cerebrovasculature may also play a role in protecting against the onset of stroke. Finally, the observation that indomethacin and carprofen did not inhibit the development of severe hypertension in SHRSP seems to parallel the findings of Quirion et al. (9) that indomethacin did not retard the development of hypertension in SHR.

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REFERENCES


