Collagen Metabolism in Blood Vessels of Hypertensive Rats

AKIRA OOSHIMA

It has been shown that collagen biosynthesis was increased in the aorta and mesenteric artery of rats either made hypertensive by deoxycorticosterone acetate (DOCA)-salt treatment or spontaneously hypertensive! Biochemical markers used in this experiment were prolyl hydroxylase activity, prolyl hydroxylase related antigen, $^3$H- or $^{14}$C-proline incorporation into collagen and the content of vascular collagen. All the markers were shown to be elevated in the blood vessels of hypertensive rats. When antihypertensive agents, reserpine and chlorothiazide were administered to DOCA-salt treated rats before the onset of hypertension, vascular collagen biosynthesis was decreased. Data with antihypertensive agents are shown in Fig. 1. When reserpine was injected after the development of hypertension, the increased prolyl hydroxylase activity was reverted to normal level concomitant with reduction in blood pressure. The same was true in blood vessels of brain (brain microvessels, pial artery, basilar artery and circle of willis) and of other tissue (testicular artery) which were successfully isolated for biochemical studies on

Fig. 1. Effects of antihypertensive agents on collagen synthesis in the aorta.
Uninephrectomized, 8-week-old, male Wistar rats were given deoxycorticosterone acetate (DOCA) (5 mg per rat) twice weekly and maintained on 1% saline as a source of drinking water. Daily intraperitoneal injection of chlorothiazide (20 mg per Kg) and reserpine (0.75 mg per Kg) was started concomitant with DOCA-salt treatment. Each bar represents the mean ± S.E. of 5 rats.

Dept. of Pathology Shimane National School of Medicine, Izumo, Shimane, Japan 693
This paper was presented at the VI Conference on the Pathogenesis of Hypertension, November 21, 1976, Tokyo.

912 Japanese Circulation Journal Vol. 41, August 1977
collagen metabolism. These results demonstrate that the vascular collagen biosynthesis was closely correlated with the level of blood pressure and could be reversible. It should be noted that the increased collagen biosynthesis can be detected before histological changes of vascular lesions appear in hypertensive rats, providing an early biochemical marker of hypertensive vascular lesions (arteriosclerosis).

Recently, it was found that blood vessels of DOCA-salt hypertensive rats showed an increase in the activity of lysyl oxidase. Lysyl oxidase is an enzyme which catalyses the formation of α-amino adipic-δ-semialdehyde (allysine) and is necessary for the initial step in the cross-linking of collagen and elastin polypeptides. This finding suggests that there might be increased cross-linkings in collagen and elastin in the vascular wall of the hypertensive rats, which will provide more vascular rigidity. Then, to examine the results of preventing the increase in vascular collagen synthesis of hypertensive rats, β-aminopropionitrile, a specific lysyl oxidase inhibitor was administered concomitant with DOCA-salt treatment. In this experiment, it was found that β-aminopropionitrile prevented the development of hypertension and reduced the amount of vascular collagen. Histological examinations revealed that arteriosclerotic changes were prevented in DOCA-salt rats treated with β-aminopropionitrile. Hypotensive effect of β-aminopropionitrile is not known, but the effect may be due to reduced vascular rigidity. Since the formation of connective tissue is an important step of vascular pathology, it is reasonable to assume that β-aminopropionitrile may prevent hypertensive vascular damage by inhibiting abnormal accumulation of fibrous tissue in the blood vessels. This concept could be therefore provide a new aspect of therapy for arteriosclerosis.

REFERENCES


Discussion

Chairman: Dr. M. Ikeda (Tokyo Univ.)

Dr. K. NISHIMURA (Ehime Univ.): Will you tell me why prolyl hydroxylase activity as a marker of collagen metabolism was remarkably decreased by reserpine compared with thiazides, although the grades of decrease in blood pressure were the same in experiments treated with reserpine and thiazides.

Dr. A. OOSHIMA: It seemed that reserpine would be a inhibitor for propyl hydroxylase, but it did not inhibit propyl hydroxylase in vitro.

The collagen metabolism seems to be controlled by sympathetic nervous system as we suggested by the experiments in which collagen metabolism were depressed by sympathetic denervation. In the present experiments, depletion of catecholamine by administration of reserpine may influence collagen metabolism. On the other hand, I suppose that reserpine may influence collagen metabolism by inhibiting the release of some hormones from pituitary gland, because hypophysectomy causes the decrease in prolyl hydroxylase activity and growth hormone increases it in hypophysectomized animals according to our other experiments.

Dr. A. EBISIHA (Jichi Med. School): I think you should measure blood pressure by canulating a tube into the aorta in unanesthetized rats. I suppose that the blood pressure you measured in rats by your method may be systolic blood pressure not diastolic one. The decrease in systolic blood pressure not diastolic one in experiments treated with BAPN could be induced by improvement of aortic rigidity where collagen deposit will be inhibited and sclerotic changes of the aorta will be prevented or improved by the administration of BAPN.

Dr. T. TAKEDA (Tokyo Univ.): How was the effect of BAPN on blood pressure and metabolism in walls when it was given in normoventive rats or young rats?

Dr. A. OOSHIMA: When BAPN has been given in normal young rats, for a long term, lathyris may occur.

The effects of BAPN to collagen metabolism are quite different by the age of rats. When BAPN was given to normal rats, the collagen content decreased somewhat but not significantly according to my experience. We used BAPN in order to inhibit excessive collagen deposition in the arterial walls in the present experiments.
Dr. A. OGAWA (Nagasaki Univ.): Firstly, will you tell me how you gave BAPN to rats, because BAPN is a strong alkaline drug. Secondly, I would like to add a comment. We have the data in which when BAPN was given in the young aged (4 weeks) of SHR, the increase in blood pressure was inhibited significantly compared with the control animals.

Dr. A. OOSHIMA: We melt a powder of BAPN fumulate into physiological saline and then gave it intravenously to rats.

As for the effect of BAPN on the blood pressure is concerned, your data and our data are almost the same as those of Udenfriend’s group which will be published in the near future.

CHAIRMAN: I have several questions and comments as the chairman of this session. Can you tell me the mechanism in which collagen metabolism in arterial walls become to increase following the elevation of blood pressure?

And I would like to know the time course of the collagen metabolism in arterial walls following development of high blood pressure. Does the increase in collagen metabolism continue for long time after the development of high blood pressure or does it decrease or recover naturally to the normal level even if high blood pressure continues?

Were there differences in the collagen metabolism of various arteries: for example, arteries of muscular and elastic types, the aorta and organ arteries; cerebral, coronary, renal arteries and so on?

I would like to know the effect of high blood pressure on collagen metabolism especially in cerebral arteries and coronary arteries, and difference of them.

Dr. A. OOSHIMA: Thank you very much your comments and questions. I would like to answer you only the one which can do among your questions. The collagen content is highest in the aorta and lower in cerebral arteries. Cerebral materials in our experiments include cerebral arteries, arterioles and venules.

But I am supposing that the effect of high blood pressure on collagen metabolism may be the same way in various organ arteries.