Effect of Sodium Intake on Hypertensive Vascular Lesions in Rabbits

Jun Fujii, M.D., Morio Kuramoto, M.D., Akira Seki, M.D., and Masao Ikeda, M.D.

SUMMARY

Effects of sodium intake on the development of hypertensive vascular lesions were studied in rabbits. Twenty-one animals (group A) were fed a low-sodium diet (7 mEq of sodium/day) and 21 animals (group B) were fed a high-sodium diet (28 mEq of sodium/day). Hypertension was produced by applying a silver clip (0.9 mm in diameter) on the left renal artery. The right kidney was left intact. Animals were killed 7 days after the surgery and hypertensive vascular lesions were examined on microscopic sections. Blood pressure was measured every day and plasma renin activity was measured on the terminal day. The average rise in blood pressure was significantly greater in group B than in group A (p<0.05). The vascular lesions were found in 6 (28.6%) of 21 animals fed on a low-sodium diet (group A) and in 13 (61.9%) of 21 animals fed on a high-sodium diet (group B). The difference in incidence between the 2 groups was statistically significant (p<0.05). However, the presence or absence of the vascular lesions did not always depend upon either the level of blood pressure or plasma renin activity.

Additional Indexing Words:
Hypertensive vascular lesions  Renal hypertension  Renin
Sodium intake

THE development of experimental renal hypertension is critically influenced by the amount of dietary sodium. Restriction of sodium intake prevents and increase in sodium intake augments the development of hypertension.7),13),16) There is also experimental evidence to show that the amount of sodium intake influences the development of hypertensive vascular lesions. Koletsky13) produced hypertension in rats by ligation of the renal arteries or by the figure of eight ligature of the kidney. Increase in sodium intake served to augment hypertension and hypertensive vascular lesions, whereas restriction of sodium intake had the opposite effect. This observation should be confirmed in other species, because the susceptibility to hypertension and hyper-
tensive vascular lesions may differ among different species. The rat is a species highly susceptible to them. Both hypertension and hypertensive vascular lesions can be produced in the rat by feeding of a high-sodium diet alone.\textsuperscript{14) In the present report, we attempted to study effects of a high- and a low-sodium diet on the development of hypertension and hypertensive vascular lesions in rabbits.}

**Method**

Male rabbits weighing 2.0 to 2.5 Kg were divided into 2 groups. Group A consisted of 21 animals which were fed a low-sodium diet containing 7 mEq of sodium and 26 mEq of potassium per 100 Gm, and group B consisted of 21 animals which were fed a high-sodium diet containing 28 mEq of sodium and 26 mEq of potassium per 100 Gm. Sodium content of the high or low sodium diet was a two-fold or a half respectively of that of the standard diet for the rabbit (CR 1, Japan Clea Ltd) which contains 14 mEq of sodium per 100 Gm. Each animal was given 100 Gm of the pellets per day and water ad libitum. All animals took the total amount of pellets offered to them during the observation period, except for the postoperative one or 2 days. After a 2-week control period hypertension was produced by applying a silver clip of 0.9 mm in internal diameter on the left renal artery. The right kidney was left intact. The operative procedure was performed through a small flank incision under sodium pentobarbital anesthesia (30 mg/Kg, iv.). Blood pressure was measured every morning on the central ear artery by an indirect method.\textsuperscript{11) All animals were killed by injecting about 150 mg of sodium pentobarbital 7 days after the surgery. Just before sacrifice about 10 ml of blood were withdrawn with a heparinized syringe for the measurement of plasma renin activity. Plasma renin activity was determined by the method of Pickens et al\textsuperscript{18) with a minor modification.\textsuperscript{7) Values for renin activity were expressed as nanogram angiotensin II amide (Hypertensin, CIBA) equivalents generated per ml of plasma after incubation for 4 hours. Normal range of plasma renin activity measured by this method was previously described.\textsuperscript{8) Plasma renin activity ranged from 1.0 to 9.7 ng/ml with an average of 3.1±2.0 (SD) ng/ml in 20 normal rabbits which were fed a standard diet containing 14 mEq of sodium and 26 mEq of potassium per 100 Gm. After sacrifice the specimen of brain, heart, lung, kidney, aorta, stomach and intestine were fixed in formol saline. Paraffin sections were stained with haematoxyline and eosin, Masson's trichrome and Weigert's elastic tissue stain.

**Results**

Clipping of the left renal artery was followed by a gradual rise in blood pressure in animals of both groups (Fig. 1). During the postoperative 7 days body weight was reduced by 40.8±31.4 (SE) Gm in group A and by 71.4±21.6 Gm in group B. The average of preoperative blood pressure was about the same in the 2 groups, but the increments were significantly greater after the
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Fig. 1. Blood pressure after clipping of renal artery. Open circles represent animals fed on a low-sodium diet (group A, N=21), and solid circles represent animals fed on a high-sodium diet (group B, N=21). Values are means ± SE.

fourth day in animals of group B which were fed a high-sodium diet than in those of group A which were fed a low-sodium diet (p<0.05).

Table I and Table II show the terminal blood pressure, average of blood pressure during the postoperative 7 days and plasma renin activity on the terminal day. The presence or absence of hypertensive vascular lesions was also indicated in the tables. At autopsy, no gross findings were found in all animals. Hypertensive vascular lesions were examined on microscopic sections. They were defined in the present study as fibrinoid necrosis of the small arteries and arterioles (Fig. 2), cellular proliferation of the intima, or lesions resembling periarteritis (Fig. 3). Necrotic lesions of the glomerular tufts were also included in the vascular lesions (Fig. 4). The most prominent was the fibrinoid necrosis of arterioles which was often found in the submucosal layer of the stomach. The vascular lesions were found in 6 (28.6%) of 21 animals fed on a low-sodium diet (group A) and in 13 (61.9%) of 21 animals fed on a high-sodium diet (group B). There was a significant difference in incidence between the two groups (p<0.05). The vascular lesions were found only in the stomach in animals of group A, whereas they were widely distributed among various organs in animals of group B.

Both the terminal blood pressure and the average of blood pressure during the postoperative 7 days tended to be greater in animals with the vascular lesions than in those without the vascular lesion, but there were a wide range of overlaps.
Table I. Blood Pressure, Plasma Renin Activity (PRA) and Hypertensive Vascular Lesions in Rabbits Fed on Low-Sodium Diet (Group A, N=21)

<table>
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<tr>
<th>No.</th>
<th>Blood Pressure</th>
<th>PRA (ng/ml)</th>
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<td>Average</td>
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Means: 122.5 (mmHg) Terminal, 105.8 (mmHg) Average, 13.9 (ng/ml)

S. E.: 2.5 (mmHg) Terminal, 1.9 (mmHg) Average, 2.3 (ng/ml)

Fig. 2. Arteriolar fibrinoid necrosis in submucosa of the stomach. Elastica-Masson's stain. ×400. (No. 633).
Table II. Blood Pressure, Plasma Renin Activity (PRA) and Hypertensive Vascular Lesions in Rabbits Fed on High-Sodium Diet (Group B, N=21)

<table>
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<td>S. E.</td>
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Fig. 3. Arterial lesions resembling periarteritis in right ventricle of the heart. Elastica-Masson’s stain. ×100. (No. 551).
Plasma renin activity was widely distributed beyond the normal upper limit both in animals of group A and in those of group B. There was no significant difference in plasma renin activity between the 2 groups despite marked difference in the amount of dietary sodium. A wide range of overlaps were also found between animals with the vascular lesions and those without the vascular lesions.

**DISCUSSION**

The present study revealed a significant role of dietary sodium in the development of renal hypertension and hypertensive vascular lesions. Both the rise of blood pressure and the incidence of hypertensive vascular lesions were significantly greater in animals fed on a high sodium diet than in those fed on a low sodium diet, although sodium content of the high or low sodium diet was not very extreme but was regarded as rather within the physiological range. The present results were essentially similar to those observed in rats by Koletsky. The mechanism responsible for the enhancement of the vascular lesions remains unsolved. The increase in blood pressure did not seem to be the chief factor in enhancing the vascular lesions. The present results indicated that the presence or absence of the vascular lesions did not always depend upon either the level of blood pressure or plasma renin activity.

The vascular lesions observed in animals with renal hypertension correspond to those in patients with malignant hypertension. They have been considered to result from an elevated intravascular pressure. This concept seems to be easy to understand, but there are evidences against it. The vascular lesions can develop regardless of the severity of hypertension in
rabbits as well as in rats. Hypertension and the vascular lesions often develop simultaneously, but either can develop independently of the other. An increasing attention has been paid to a quite different concept that the clipped kidney can release factors which produce the vascular lesions. One of the vascular permeability factors of renal origin is probably renin. Administration of crude renin can produce hypertensive vascular lesions in rats. The vascular lesions caused by renin is also influenced by the amount of dietary sodium. However, in the present study a certain relation was difficult to find between plasma renin activity and the presence of the vascular lesions. The present results suggest that unidentified factors which are different from renin can be involved in the development of hypertensive vascular lesions. We previously demonstrated that the vascular lesions can be produced by administration of nonpressor fractions of kidney extracts.

Campbell and Santos-Buch suggested that factors producing the vascular lesions remained inactive in the presence of an intact contralateral kidney. They produced hypertension in rabbits by wrapping one kidney. The vascular lesions did not develop unless an intact kidney was removed. The observation is not compatible with the results presented here. In the present study hypertension was produced in rabbits by clipping one renal artery and leaving the other kidney intact. This procedure was expected to produce a mild hypertension so that the vascular lesions might develop in a small number of animals. It should be pointed out that the vascular lesions developed as early as 7 days after the surgery even if the opposite kidney was left intact. The difference in results between Campbell and Santos-Buch and the present study may be based on the difference in method to produce hypertension. Wrapping of the kidney is not necessarily the same as the clipping of the renal artery.

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