Effect of Sodium Loading and Depletion on Vascular Reactivity and Prostacyclin Generation

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In order to estimate the modulatory activity of Prostacyclin (PGI₂) to the vascular reactivity, pressor responses to angiotensin II (A II) and noradrenaline (NA) and PGI₂ generation of aorta were measured using the rats of sodium loading or of sodium depletion. On the sodium loading, the blood pressure increased gradually and plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were decreased. The pressor responses to A II and NA were enhanced by sodium loading. The PGI₂ generation of aorta was enhanced at the initial stage of sodium loading and decreased thereafter. The increased generation of PGI₂ may represent the adaptive mechanism for the attenuation of the sustained elevation in blood pressure.

In sodium depletion, the pressor responses to A II and NA were decreased, and PRA and PAC were elevated. PGI₂ generation of aorta was also increased. These findings suggested that PGI₂ could participate in blood pressure control mechanism on sodium loading and depletion.

Increased blood pressure by sodium loading has been recognized by the expanded volume of extracellular fluid, high cardiac output and the raise of the peripheral vascular resistance. And also the pressor responses to angiotensin II (AII) and noradrenaline (NA) were also reported to be enhanced by sodium loading. Therefore salt is believed to be one of the major factors in accelerating the hypertension.

In addition, indomethacin, an inhibitor of prostaglandin (PG) synthesis, also caused to increase blood pressure after unilateral nephrectomy or salt loading. We also reported that the pressor responses to AII and NA were enhanced by the treatment of indomethacin and were suppressed by the infusion of PGE₁ solution in human subjects. These results may indicate that PG plays a physiologically important role in the mechanism regulating blood pressure.

The interaction between sodium intake and PG is also complicated at present. Intravenous infusion of saline induced the significant increase PGA and PGE in renal vein as well as increase in renal plasma flow and urinary output in human subjects. Urinary excretion of PGE was closely related to urinary sodium output at the various state of sodium intake. On the other hand, plasma PGE concentration did not change significantly during variation in sodium intake from 10 mEq to more than 100 mEq per day. In their studies, PGA levels in plasma increased on low sodium diet and decreased on

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high sodium diet. Therefore further studies are recommended to know the role of PG in the different levels of sodium intake.

Prostacyclin (PGI₂) has the most potent vasodilating activity than any of the other known vasoactive PGs. PGI₂ is generated by vascular walls from arachidonic acid or PG endoperoxides and moves into systemic circulation through pulmonary circulation; therefore PGI₂ is called as a circulating hormone. In the present study, we try to investigate the interaction between PGI₂ generating activity of vessels and sodium balance or the elevation of blood pressure by sodium loading. And we also tried to know the modulating activity of PGI₂ on the regulation of blood vessel tone and blood pressure, through the estimations of pressor responses to AII and NA.

METHODS

Male Wistar rats weighing 225 ± 4 (SE)g were divided into three groups. The control group of rats was fed a regular dry diet (Oriental Yeast Co.) containing 0.24% sodium and water ad libitum for drinking. The sodium-loading group of rats was fed a dry diet containing 0.24% sodium and a 1.3% NaCl solution as drinking fluid. The sodium-depleted group of rats was fed a low salt dry diet (Oriental Yeast Co.) containing 0.11% sodium and distilled water for drinking. The amounts of sodium intake were calculated from the weight of diet to eat and the volume of drinking fluid per day. The sodium intake of each rat was calculated as 2.0 to 3.1 mEq per day in control group, 6.4 to 9.7 mEq per day in sodium-loading group and 0.7 to 1.5 mEq per day in sodium-depleted group.

Blood pressure measurement, pressor response to angiotensin-II-amide (AII) (Hypertensin® Ciba) and noradrenaline (NA) (Nor-adrenalin® Sankyo Co.) and prostacyclin (PGI₂) activity were measured at the end of 2, 4 and 8 weeks of feeding the control and the sodium-loading diets, and at the end of 2 weeks of feeding the sodium-depleted diet. Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were measured at the end of 2 and 8 weeks of feeding the control and the sodium-loading diets and at the end of 2 weeks of feeding the sodium-depleted diet.

The rats were anesthetized by i.p. injection of pentobarbital sodium (40 mg/kg), and a polyethylene catheter was inserted into the left carotid artery and the left jugular vein. The polyethylene catheter inserted into the artery was connected to a transducer and polygraph recorder (San-Ei instrument Co.) for recording systolic, diastolic and mean blood pressure and heart rate. The venous catheter
was used for the injection of AII, NA or saline in a standard volume of 0.2 ml, and the catheter was subsequently flushed with another 0.1 ml of 0.9% saline. 20 ng per 100 g body weight of AII and NA was injected subsequently with 5 min intervals for the estimation of pressor response.

PGI$_2$ activity was assayed by bioassay system using aorta of rats. Thoracic aorta of rat was isolated under pentobarbital sodium anesthesia and put in the cold Krebs-Ringer-phosphate buffer for several minutes. The aorta was cut into small rings weighing 2 to 3 mg. The aortic ring was incubated with 0.5 ml of 0.05 M Tris-HCl buffer (pH 7.5) at room temperature for 10 min. 50 µl of supernatant of incubation medium was added to human platelet-rich plasma (PRP) prepared from the blood (one part of 3.8 percent sodium citrate was added to nine parts of blood). After mixing the PRP with the above mentioned medium for 2 min at 37°C, the aggregation of platelet induced by adenosine diphosphate (ADP) was estimated by a 3 channel-aggregometer. PGI$_2$ activity was assayed by the inhibitory percentage of platelet aggregation induced by ADP.

PRA and PAC were measured by radioimmunoassay using the blood obtained by decapitation.

RESULTS

Blood pressure of the sodium-loading rats rose gradually following the period of salt treatment. Significant elevation of blood pressure was observed systolic in 2 weeks and both systolic and diastolic blood pressure in 4 and 8 weeks of the sodium-loading rats as compared with the control rats. However no change of blood pressure was observed in sodium depletion (Fig. 1).

Effect of sodium loading and depletion on PRA and PAC was illustrated in Fig. 2. Significant elevation of PRA and PAC was observed in the sodium-depleted rats, and significant re-
DISCUSSION

The elevation of blood pressure by prolonged administration of high salt solution was reported by many investigators. The reason to increase blood pressure by sodium loading is postulated as the increase of extracellular fluid volume, which may cause the high cardiac output and increased vasoconstriction. These factors may lead to increase arterial hypertension and to raise the general peripheral resistance through the autoregulatory response. In addition, these peripheral effect may also affect the cardiovascular system by an action on central autonomic pathways. The initial period to increase blood pressure by sodium loading was reported within a week of 1% NaCl solution.

Vascular hyperreactivity to circulating pressor agents has been claimed as a cause of enhanced peripheral resistance in experimental hypertension. It is documented that an enhanced vascular contraction to AII might be due to the alteration in ion concentrations across the vascular smooth muscle, especially associated with the net movement of sodium into the cells.

One of the factors to affect the alteration in ion concentration across the cell membrane is the natriuretic factor which has an inhibitory effect on sodium-potassium-ATPase activity. It is generally recognized that vascular reactivity to AII or NA was enhanced on the suppressed state of sodium-potassium-ATPase activity by ouabain. Therefore the natriuretic factor induced the vasoconstriction, the increase of vascular resistance and the increase of blood pressure. A similar factor, sensitizing factor, was also found in the plasma of the patients with hypertension and of the patients on high sodium intake.

Therefore, the natriuretic factor or sensitizing factor may play an important role in the elevation of blood pressure on the volume-expanded state by sodium loading. In addition the existence of natriuretic or sensitizing factors may derive the role of the renin-angiotensin system for the regulation of blood pressure, even though the renin level is low on sodium loading.

Moreover Brunner et al. reported that the AII receptor affinity varied directly with sodium balance. From their concept that AII receptor affinity was enhanced in sodium loading and decreased in the state of increased AII formation in sodium depletion, therefore these changes of the receptor affinity may be involved for the
regulation of blood pressure when circulating All was normal or low.

On the other hand, the pressor response to All was impaired by sodium depletion and the inverse relationship had been demonstrated between the pressor response to All and PRA level. These results are compatible with our results in relation to All. However an acceptable relationship between catecholamine and sodium balance was not demonstrated. Recently the correlation between plasma NA and sodium intake or urinary sodium excretion was demonstrated to be similar to the negative relationship between PRA and sodium intake. Therefore the blunt response to NA at sodium depletion in the present study was reasonable from the concepts described above.

The pressor responses to All or NA and sodium balance may be influenced by the activity of PGs. As previously reported, PGE₁ decreased vasoconstrictor-responses to nerve stimulation, NA and All. The dilator effect of PGE₁ is probably the result of a direct effect on vascular smooth muscle. We have already reported that the pressor responses to All and NA were suppressed during the infusion of PGE₁, on the other hand, the pressor responses were enhanced by the treatment of indomethacin. These results indicated that PGs also modulate the vascular reactivity to vasoactive substances. PGI₂ has the more potent vasodilating activity than PGE₁, therefore, it is interesting to know the PGI₂ activity generated in the arterial wall on the various sodium balance.

It is reported that intravenous infusion of saline induced the elevation of PGE concentration in renal vein and prolonged administration of salt accelerated to excrete PGE in urine with increase of sodium excretion. These results are compatible with our results of PGI₂ generation of aorta on sodium loading, if the synthesis of PGI₂ and PGE goes on the same way. On the contrary, the elevation of PGI₂ generation on sodium depletion is not clear at present, however it may be presumed that high levels of circulating All as well as NA induced an increased release of PGI₂, when we speculate the PGI₂ generation from the review. In addition a rise in kidney kallikrein may make it possible to increase PGI₂ synthesis in sodium depletion.

From the viewpoint of hypertension, it may be presumed that PGI₂ plays an important role in the regulation of blood pressure, because of the powerful action of vasodilation. In the present study, PGI₂ activity increased following the elevation of blood pressure by sodium loading. Additional confirmation about the correlation between PGI₂ and blood pressure, was reported by Pace-Asciak and Carrara who demonstrated the exceedingly good correlation between synthesis of the vasodepressor PGI₂ and the elevation in blood pressure. These results suggest that PGI₂ synthesis may be an adaptive homeostatic response to attenuate the sustained elevation of blood pressure.

In the present study the enhanced pressor response to NA and All at 8 weeks on sodium loading may indicate that the attenuating activity of PGI₂ for the elevation of blood pressure decreased at the 8 weeks of sodium loading. The reason to decrease PGI₂ generation at 8 weeks of sodium loading is not clear, however the endothelium of vessels may happen to change by sodium loading for 8 weeks. It is also suggested that the attenuating activity of PGI₂ for elevation of blood pressure may show the biphasic pattern, as PGI₂ generation of aorta increases at the elevation of blood pressure and gradually decreases at the established state of high blood pressure. Anyway, the above results also support that PGI₂ may participate in blood pressure control mechanism.

In conclusion, sodium loading caused (1) the increase of blood pressure and (2) the decrease of PRA and of PAC. (3) Pressor response to All and NA was enhanced by sodium loading. (4) The reverse phenomenon was observed by sodium depletion. (5) PGI₂ generation in aorta was biphasically increased at 2 and 4 weeks of sodium loading and decreased at 8 weeks. The enhanced generation of PGI₂ may represent the adaptive mechanism for the attainment of the sustained elevation on blood pressure.

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