The Effect of Salt Loading on Cellular Ca^{2+} in Patients with Essential Hypertension

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INTRACELLULAR free calcium concentration ($[\text{Ca}^{2+}]_i$) is widely recognized to be important in the tension of vascular smooth muscle¹ and is supposed to be a key factor in the pathogenesis of essential hypertension. In fact, an increase in $[\text{Ca}^{2+}]_i$ has been reported in lymphocytes² and platelets³ from patients with essential hypertension. Disturbances in Ca^{2+} transport system across cell membrane and intracellular binding process, which may result in an elevation of $[\text{Ca}^{2+}]_i$, have been reported.⁴ Additionally, clinical evidence of enhanced hypotensive response to calcium entry blockade in essential hypertension suggests that calcium influx dependent vasoconstriction may be increased.^{5,6}

It is well known that dietary salt intake is linked with hypertension and that the pressor response with salt loading, i.e., salt sensitivity, is different among essential hypertensive patients.^{7,8} However, there is no convincing theory to explain the mechanism underlying the difference in salt sensitivity. In particular, there is limited information about the role of cellular calcium metabolism in salt sensitivity, although reports of the relationship of changes in hemodynamics,⁹ the renin-angiotensin-aldosterone system¹⁰ and the sympathetic nervous system¹¹ to salt sensitivity have been accumulated. The purpose of the present study was to determine 1) whether the hypotensive response to nifedipine and lymphocyte $[\text{Ca}^{2+}]_i$ is altered after salt loading and 2)

if such changes are linked with salt sensitivity.

The study included 16 inpatients (9 men and 7 women) with essential hypertension. Their mean age was 55.4 years (range, 38–64 years). All patients had sitting blood pressure readings higher than 160/95 on at least 3 occasions in outpatient clinic and were free of extensive organ damage. Secondary hypertension was ruled out on the basis of clinical and laboratory data. All subjects discontinued any medication for at least 4 weeks before admission. Informed consent was obtained from each patient.

After a control period of one week on a regular salt diet (10 g/day), all patients underwent one week of low-salt diet (3 g/day) and subsequent one week of high-salt diet (20 g/day). On the 7th morning of low- and high-salt diet periods, fasting patients were kept supine for 30 min after insertion of cannula into peripheral vein, and blood pressure was determined by mercury sphygmomanometer and venous blood was drawn for determination of lymphocyte $[\text{Ca}^{2+}]_i$. Mean blood pressure was calculated as diastolic pressure plus one third of pulse pressure. Lymphocyte $[\text{Ca}^{2+}]_i$ was measured with quin 2 as previously described.^{2,8} Thereafter, 10 mg of nifedipine was administered sublingually. Blood pressure was measured every 5 min for 60 min after administration of nifedipine. The maximal fall in mean blood pressure with nifedipine was calculated as the difference between basal and the lowest blood pressure.

After salt loading, basal mean blood pressure, lymphocyte $[\text{Ca}^{2+}]_i$ and the fall in mean blood pressure with nifedipine were increased respectively, while the lowest mean blood pressure after nifedipine was not different from that of

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low-salt period. A significant and positive correlation was observed between lymphocyte $[Ca^{2+}]_i$ and the fall in mean blood pressure with nifedipine in both low- and high-salt periods. Whereas basal mean blood pressure was not correlated with lymphocyte $[Ca^{2+}]_i$ or the fall in mean blood pressure with nifedipine in both salt diets, the increase in mean blood pressure after salt loading had a positive relation to the differences in lymphocyte $[Ca^{2+}]_i$ and in the fall of mean blood pressure with nifedipine between low- and high-salt diets.

Our data indicate that the hypotensive response to nifedipine is increased after salt loading in patients with essential hypertension. This seems to be consistent with the report of Resnick¹² that high-salt intake enhanced the hypotensive effect of calcium channel blockade. However, Waeber et al¹³ reported there was no difference in short term blood pressure response to the calcium antagonist nifedipine between sodium-depleted and sodium-replete rats with renal hypertension. An explanation for this discrepancy is that salt loading raised blood pressure in our study patients but not in their study rats. It should be stressed that the lowest blood pressure after nifedipine administration is not altered by the manipulation of dietary salt intake, while hormonal factors such as the renin-angiotensin system and the sympathetic nervous system fluctuate widely. Therefore, when basal blood pressure was not affected by salt loading, the response of blood pressure to nifedipine should be unchanged.

The finding that the ability of salt loading to raise blood pressure was closely associated with its ability to increase lymphocyte $[Ca^{2+}]_i$ and enhance the hypotensive response to nifedipine supports the responsibility of intracellular Ca^{2+} metabolism in salt sensitivity. The mechanism by which an excessive salt intake raises $[Ca^{2+}]_i$ can be explained by two hypotheses. Sodium transport hypothesis, proposed by de Wardener and MacGregor,¹⁴ and Blaustein,¹⁵ explains that a circulating Na^+ , K^+ , ATPase inhibitor, secreted in response to sodium loading, may induce an intracellular Na^+ accumulation and then raise $[Ca^{2+}]_i$ via Na^+-Ca^{2+} exchange process. We previously reported that an increase in $[Na]_i$ was positively linked with an increase in $[Ca^{2+}]_i$ in lymphocytes after salt loading.⁸ This finding may support the sodium transport hypothesis. However, it is also true that the change in $[Ca^{2+}]_i$ preceded the change in $[Na]_i$, because $[Ca^{2+}]_i$

might regulate many kinds of cell function including transmembranous Na^+ transport. Alternatively, Resnick et al¹⁶ have hypothesized that changes in calcium regulating hormones (parathyroid hormone, calcitonin and 1, 25-dihydroxy-vitamin D), after salt loading, may lead to an alteration in calcium metabolism, such as a shift of Ca^{2+} outside to inside the cells. However, it is unclear how $[Ca^{2+}]_i$ was elevated after salt loading from our data and further investigations will be needed to clarify the mechanism.

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