THE PATHOPHYSIOLOGICAL ROLE OF BLOOD IONIZED CALCIUM IN ESSENTIAL HYPERTENSION

SHINGO SHIBATA, M.D., KENJIRO KIKUCHI, M.D., IZUMI YAMAJI, M.D.
AKIHiko NOZAWA, M.D., MITSUHIRO NISHIMURA, M.D., KANAE AOKI, M.D.
TORU HASEGAWA, M.D., HIROI KOMURA, M.D., SHINICHIRO SUZUKI, M.D.
MANEO YAMAMOTO, M.D., AND OSAMU IIMURA, M.D.

Although calcium has long been linked to the molecular events of muscle contraction and hormone secretion, the role of calcium in the pathogenesis of essential hypertension has only recently received considerable attention.1-2 Some clinical studies suggest the significance of calcium deficiency in patients with essential hypertension (EHT).3-7 However, the definitive role of calcium metabolism in essential hypertension still remains to be established.

We evaluated the significance of blood ionized Ca (Ca²⁺) on blood pressure, plasma renin activity (PRA), plasma noradrenaline concentration (PNA), pressor response to infused noradrenaline (NA-R) and plasma volume in EHT.

Forty five normotensive subjects (NT) aged 20 to 61 (36 ± 2) years and 34 mild or moderate EHT aged 23 to 68 (48 ± 2) years participated in this study. They were admitted to our hospital and received a constant daily diet of 120 mEq of sodium, 75 mEq of potassium and 600 mg of calcium. The subjects had not been treated by any drug for at least 2 weeks prior to the study.

The mean values were expressed as the standard error of the mean (SEM). All statistical analysis were performed using Student's t-test.

1. Blood Ca²⁺, Blood Pressure, PRA, and PV in EHT

After overnight fasting, the subjects remained in a supine state for at least 60 minutes during the early morning. Blood pressure was measured repeatedly by the auscultatory method immediately before blood sampling for the measurements of blood Ca²⁺ (calcium ion electrode), TCa (OPCP), Alb (electrophoresis), blood pH (pH electrode), PRA (CIS's kit) and PNA (HPLC-TH). NA-R was calculated by the increments in mean arterial pressure (MAP) induced by infusion of 0.2 µg/kg/min noradrenaline. PV was measured by the 125I-RISA method and expressed as a percentage of the mean value per height of normal men or women (ml/cm² older). There was no significant difference in venous blood Ca²⁺ between NT (1.23 ± 0.01 mmol/l) and EHT (1.23 ± 0.01 mmol/l). In EHT, blood Ca²⁺ correlated positively with TCa (n = 34, r = 0.670, p < 0.001), Alb (n = 34, r = 0.501, p < 0.005) and PRA (n = 34, r = 0.387, p < 0.025), and negatively with MAP (n = 34, r = -0.432, p < 0.01) and PV (n = 14, r = -0.575, p < 0.05). No significant correlation was found between blood Ca²⁺ and age, blood pH and hematocrit (Ht) in EHT.

Recently Resnick et al8 found renin-linked heterogenous deviations of calcium metabolism among EHT, suggesting a state of calcium surfeit in high renin EHT with a higher average of serum Ca²⁺, and a calcium deficit in low renin EHT with a lower average of serum Ca²⁺. In the present study, blood Ca²⁺ levels were compared among NT, normal renin EHT (NREH; n = 26) and low renin EHT (LREH; n = 8). The mean value of blood Ca²⁺ in LREH (1.21 ± 0.01 mmol/l) was significantly lower than those in NT (1.23 ± 0.01 mmol/l, p < 0.01) and in NREH.
(1.24 ± 0.01 mmol/l, p < 0.005). There was no significant difference in blood pH, Ht, TCa and Alb between the two renin subgroups in EHT. Erne et al9 reported that platelet Ca²⁺ correlated positively with blood pressure and negatively with serum Ca²⁺ in EHT. They speculated that abnormal calcium shifting from the extracellular space to the intracellular space including vascular smooth muscle cells might occur in EHT, particularly in LREH with lower values of serum Ca²⁺.

The findings from the present study are compatible with the report by Resnick et al8 or Erne et al9 and suggest that calcium metabolism may relate not only to renin-angiotensin system or volume status but also to the hypertensive mechanisms in EHT.

2. The Relationship between Blood Ca²⁺ and PNA or NA-R in EHT

The relationship between calcium metabolism and sympathetic nerve activity or NA-R in EHT was examined. Blood Ca²⁺ correlated positively with PNA (r = 0.680, p < 0.005) and negatively with NA-R (r = −0.656, p < 0.005) in EHT. Since EHT with lower blood Ca²⁺ values also had lower PRA and higher PV, the suppression of the renin-angiotensin system and an expansion of PV might result from an attenuation of the sympathetic nerve activity in these EHT. On the other hand, our laboratory reported10 that NA-R relating inversely to PNA was significantly greater in EHT, especially in LREH than that in NT or NREH. If the hypothesis by Erne et al9 is accepted, a higher level of intracellular Ca²⁺ in vascular smooth muscle cells may cause an enhancement of NA-R in LREH with lower values of blood Ca²⁺.

3. Hypotensive Effect of Nifedipine, Blood Ca²⁺, PRA, and NA-R in EHT

To clarify the role of calcium metabolism in the hypertensive mechanisms of EHT, we examined the relationship between hypotensive effect of calcium antagonist, nifedipine tablet 60 mg daily for a period of 4 weeks and blood Ca²⁺, PRA, PNA or NA-R in 9 EHT. Following nifedipine treatment, MAP (before nifedipine: 121 ± 3, 1 week after nifedipine: 105 ± 4 4 weeks after nifedipine: 97 ± 3 mmHg), NA-R (33.8 ± 6.6, 12.8 ± 1.8, 17.0 ± 3.0 mmHg, respectively) and PV (99.5 ± 7.9, 91.3 ± 7.0, 92.2 ± 8.7 ml/cm²×normal, respectively) were all significantly decreased. On the other hand, sustained increases in PRA (0.61 ± 0.17, 1.16 ± 0.36, 1.20 ± 0.24 ng/ml/hr, respectively) and a transient elevation in PNA (162 ± 14, 215 ± 27, 161 ± 24 pg/ml, respectively) were found. No significant change, however, was observed in blood Ca²⁺ (1.22 ± 0.01, 1.20 ± 0.01, 1.23 ± 0.01 respectively). Percent changes in MAP 4 weeks after nifedipine therapy were positively correlated with blood Ca²⁺ (r = 0.678, p < 0.05), logarithm PRA (r = 0.700, p < 0.05) and PNA (r = 0.758, p < 0.05) just prior to nifedipine administration. Changes in NA-R by nifedipine therapy correlated positively with blood Ca²⁺ (r = 0.941, p < 0.001) or PNA (r = 0.759, p < 0.025) and negatively with NA-R (r = −0.930, p < 0.001) before the treatment.

These findings lead us to speculate that the volume contraction and an attenuation in sympathetic nerve activity or NA-R may contribute to the hypotensive effects of long-term nifedipine therapy.

These results from the present study suggest that the abnormal calcium metabolism relating to renin-angiotensin system, sympathetic nerve activity, NA-R or volume status may play an important role in the hypertensive mechanisms in EHT, particularly in LREH with lower values of blood Ca²⁺.

REFERENCES


Japanese Circulation Journal Vol. 51, October 1987
