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URINARY KALLIKREIN AND ELECTROLYTE CONCENTRATIONS IN HEALTHY CHILDREN: WITH SPECIAL REFERENCE TO THEIR AND THEIR PARENTS' BLOOD PRESSURES

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ABSTRACT

Urinary kallikrein and electrolyte concentrations and blood pressure were examined in 321 healthy children, aged 11 to 15 years. Urinary kallikrein and Na concentrations and Na/K ratio did not show any significant differences between normotensives and hypertensives, although urinary K concentrations were significantly lower in normotensives with a family history of essential hypertension than those without a family history of essential hypertension. In the normotensive group, there was a significant positive correlation between urinary kallikrein concentration and urinary K concentration, and a significant negative correlation between urinary kallikrein concentration and urinary Na/K ratio, but not in the hypertensive group. There was a significant positive correlation between urinary kallikrein concentration and systolic blood pressure in the systolic hypertensive group and the diastolic blood pressure in the diastolic hypertensive group, but not in the normotensive group. These results suggest that low urinary kallikrein excretion related to essential hypertension in adults may be an acquired condition.

INTRODUCTION

Several investigations conducted in recent years strongly suggest that the kallikrein -kinin system has a role in a wide range of physiopathological processes. Clinical research interest in this system was originally evoked in hypertensive conditions because

of the very potent pharmacological action of kinins on vascular smooth muscle. In addition to vasodilation, kinins regulate sodium (Na), potassium (K) and water excretions, either directly or through prostaglandin release.[8] It has, in particular, been suggested that the kinin system may regulate the control of blood pressure and circulatory homeostasis. Low urinary kallikrein excretion may be a pathogenetic factor in essential hypertension,[5,6,11] and a familial correspondence in urinary kallikrein levels has been reported.[18]

Studying urinary kallikrein excretion in children is therefore important in elucidating the mechanism of essential hypertension's development in later life. Only a few studies on urinary kallikrein have been undertaken in children, and results of excretion (concentration) in relation to blood pressure and urinary electrolyte excretion are conflicting.[2,3,18] Because a variety of factors influence the relationship between kallikrein excretion, electrolyte excretion and blood pressure when timed (that is when collected over a period of some hours) urine specimens are used, a true correlation between them may not be evident unless findings in shorter collection periods are examined. In this study, therefore, we examined the relationship between kallikrein, Na and K concentrations in spot urine specimens and blood pressure in normotensive and hypertensive children.

Materials and Methods

321 healthy children aged 11 to 15 years were studied on one occasion at a school in Niigata district in Japan. Systolic and diastolic (fifth phase) blood pressures were measured in the right arm with a mercury sphygmomanometer, using a 12 cm cuff, after the child had been lying supine for at least 30 minutes.[17] Blood pressure was measured by the authors three times at intervals of one minute and the last reading was used, as we had already confirmed this to be the most stable and reproducible reading in each individual.[13] Spot urines were collected upon waking in the morning and analyzed for Na, K and creatinine. Na and K were measured by flame photometry and creatinine by the Jaffe reaction on an autoanalyzer. Urinary kallikrein concentration was estimated in nondialyzed urine samples by the method of Morita et al.,[9] using the synthetic fluorogenic substrate, L-prolyl-L-phenylalanyl-L-arginine-4-methylcoumaryl-7-amide which was obtained from the Peptide Institute, Protein Research Foundation (Osaka, Japan). Results obtained by this method correlated well with those obtained by the bioassay method and with kinin-forming activity determined by kinin radioimmunoassay.[3] The concentrations of urinary Na, K and kallikrein were expressed as ratios in proportion to creatinine.

According to blood pressure, subjects were divided into two groups; a normotensive group and a hypertensive group. Hypertension was defined from our normal values for Japanese children.[17] These are as follows: over 135 mmHg systolic blood pressure and/or 85 mmHg diastolic blood pressure in 11-12 year-old subjects; and over 140 mmHg

systolic blood pressure and/or 90 mmHg diastolic blood pressure in 13-15 year-old subjects. Children with high blood pressure were re-examined after one month, and only the children with persistent high blood pressure were included in this study. Children with secondary hypertension or organic diseases were excluded from this study. The normotensive group was divided into two sections, namely those who had parents with essential hypertension (either one or both parents; 66 children), and those who had parents without a history of essential hypertension (232 children). Essential hypertension in adults was defined in this study as over 150 mmHg systolic blood pressure and/or 95

Table 1. Urinary kallikrein, Na and K concentrations and Na/K ratio in normotensives with or without a family history of hypertension (FH) and in hypertensives

	N	Kallikrein (nmol/min/mg Cr)	Na (mmol/mg Cr)	K (mmol/mg Cr)		Na/K ratio
Normotensives without FH	(232)	0.55±0.33	0.20±0.09	0.06±0.03	*	3.8±1.7
Normotensives with FH	(66)	0.53±0.36	0.19±0.07	0.05±0.03		3.9±1.6
Hypertensives	(23)	0.65±0.35	0.20±0.08	0.06±0.02		3.7±1.4

Statistical significance: *P<0.05

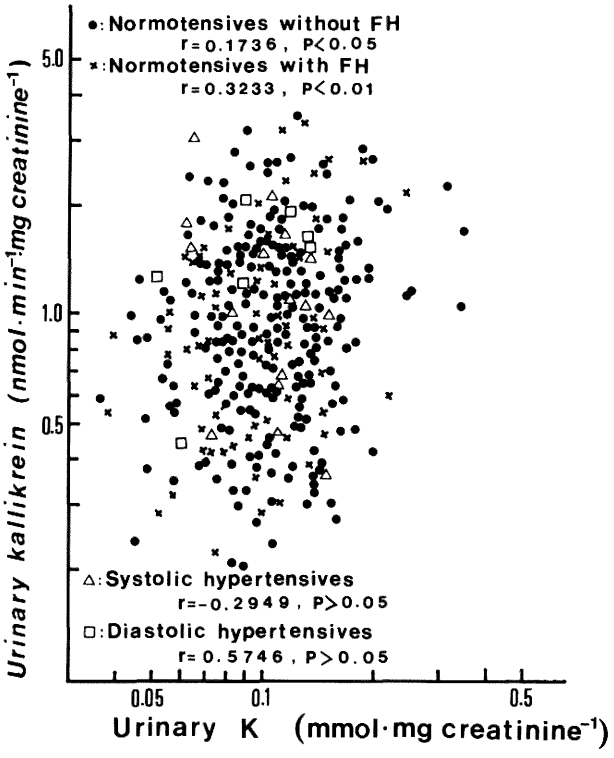

Fig. 1. Relationship between urinary kallikrein concentration and urinary K concentration in normotensives with or without a family history of hypertension (FH) and in hypertensives.

mmHg diastolic blood pressure. The hypertensive group (children with high blood pressure) was also divided into two sections, namely a systolic hypertensive group (16 children; systolic hypertension without diastolic hypertension) and a diastolic hypertensive group (7 children; diastolic hypertension with/without systolic hypertension).

Results were expressed as the mean ±SD and analyzed using unpaired t-tests. Simple correlation coefficients were calculated for blood pressure, urinary Na or K concentration, urinary Na/K ratio and urinary kallikrein concentration after logarithmic transformation.

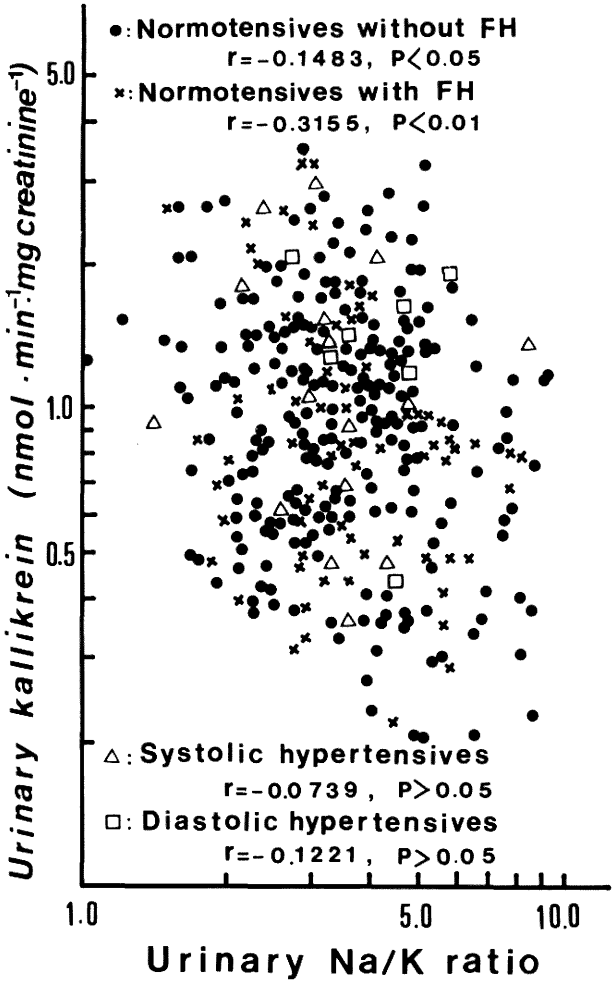

Fig. 2. Relationship between urinary kallikrein concentration and urinary Na/K ratio in normotensives with or without a family history of hypertension (FH) and in hypertensives.

RESULTS

Urinary Na and kallikrein concentrations and the Na/K ratio did not change according to a family history of hypertension in the normotensive group, although urinary K concentrations were significantly lower in children with a family history of hypertension than children without a family history of hypertension. (Table 1) The urinary Na, K and kallikrein concentrations and Na/K ratio showed similar values in both the hypertensive and the normotinsive groups. (Table 1) In the normotensive group including children with and without a family history of hypertension, there was a significant positive correlation between urinary kallikrein concentration and urinary K concentration, and a significant negative correlation between urinary kallikrein concentration and urinary Na/K ratio, but not in the hypertensive group. (Figs. 1, 2) These correlations were stronger in children with a family history of hypertension than in children without a family history of hypertension in the normotensive group.

Urinary kallikrein concentration did not correlate significantly with urinary Na concentration in either group (normotensives with a family history of hypertension; r= 0.0945, normotensives without a family history of hypertension; r=0.0740, systolic hyper-

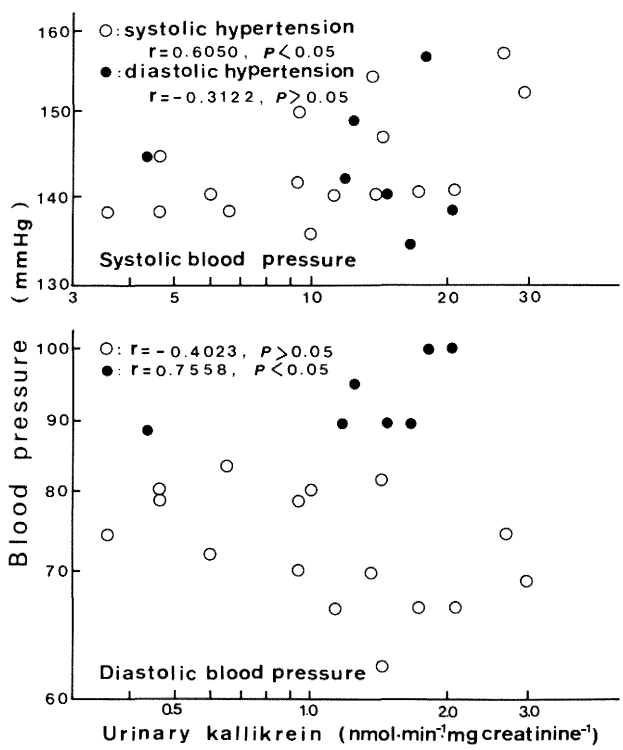

Fig. 3. Relationship between urinary kallikrein concentration and blood pressure in hypertensives.

tensives; $r=-0.3442$, diastolic hypertensives; $r=0.4150$, $P>0.05$, respectively).

There was a significant positive correlation between urinary kallikrein concentration and systolic blood pressure (SBP) in the systolic hypertensive group and the diastolic blood pressure (DBP) in the diastolic hypertensive group (Fig. 3), but there was no significant correlation between urinary kallikrein concentration (UKall) and blood pressure in the normotensive group (normotensives with a family history of hypertension; UKall vs SBP: $r=0.0503$, UKall vs DBP: $r=0.0329$, normotensives without a family history of hypertension; UKall vs SBP: $r=0.0130$, UKall vs DBP: $r=0.0441$, $P>0.05$, respectively).

Discussion

Renal kallikrein is a glandular type kallikrein situated in the distal tubular cells and is released into both the urine and the renal lymph. Other glandular kallikreins which are present in pancreas, salivary glands, sweat glands, etc. do not appear to any significant extent in the urine.[8] Renal kallikrein acts on a kininogen substrate brought in by the blood with the release of lysyl-bradykinin (kallidin) which is active in its own right but is also rapidly converted into bradykinin.[8] In the vasculature, it lowers blood pressure and increases vascular permeability.

Low excretion of urinary kallikrein has been reported in essential hypertension in adults.[5,6,11] Few studies have been undertaken in hypertensive children,[14] but zinner et al. [18] reported familial correspondence in both blood pressure and kallikrein concentration in spot urine specimens in normotensive children. They also reported that urinary kallikrein concentration was inversely related to blood pressure in normotensive children. These findings suggest that low urinary kallikrein excretion may be a pathogenetic factor in developing essential hypertension in adult life. However, we found our results conflicted with the above in that urinary kallikrein concentration increased with blood pressure, possibly reflecting increased activity of a compensating vasodilator system in children with high blood pressure, which confirmed our previous results in timed urine tests.[14]

We failed to observe significant differences in kallikrein concentration between normotensive children with or without a family history of hypertension, suggesting that low urinary kallikrein excretion related to essential hypertension in adults may be an acquired condition. An age-related decrease in urinary kallikrein excretion was reported in adults,[10] and hence the compensatory response of urinary kallikrein to blood pressure in children may reduce with age, causing fixed hypertension in later life while the hypertension in children remains labile. We have already reported that high blood pressure found in children can develop into adult hypertension,[12] but it is possible that the mechanism of hypertension may change with age. Increased renal blood flow which can stimulate urinary kallikrein excretion[4] has been reported in cases of borderline hypertension in young adults, but not in fixed hypertension cases in later life.[7]

Some investigators have reported that aldosterone stimulates urinary kallikrein

excretion in adults,[10] though this has not been confirmed in children. We[13] and Godard et al.[2] failed to demonstrate a significant correlation between urinary kallikrein excretion and urinary Na/K ratio in timed urine tests. In the present study, there was a significant positive correlation between urinary kallikrein concentration and urinary K concentration and a significant negative correlation between urinary kallikrein concentration and urinary Na/K ratio in normotensive children. However, there was no significant correlation between them in children with high blood pressure. This suggests that aldosterone may partly regulate urinary kallikrein excretion in normotensive children, as it has been reported to do in adults, since aldosterone also increases urinary K excretion and decreases urinary Na/K ratio.[16] It remains to be shown whether the absence of significant relationship between urinary kallikrein excretion, urinary K excretion and urinary Na/K ratio in children with high blood pressure is related to the pathogenesis or pathophysiology of hypertension.

High K intake appears to be a factor in reducing blood pressure in adults with essential hypertension;[1] however, its physiological basis is unclear. In the present study, normotensive children with a family history of hypertension showed significantly lower urinary K concentrations and a stronger positive correlation between urinary kallikrein concentration and urinary K concentration than normotensive children without a family history of hypertension. Hence in children with a family history of hypertension, it is possible that dietary intake of K is sufficiently low to reduce urinary K excretion and that urinary kallikrein excretion is more sensitive to K balance than it is in children without a family history of hypertension. We have already reported that children in Niigata, a district in Japan with a high incidence of adult hypertension,[17] showed significantly higher urinary Na excretion and lower urinary K excretion than American and European children.[15] A long period of low K intake from childhood into adult life may suppress urinary kallikrein excretion irreversibly as aging progresses, causing the fixed hypertension with low urinary kallikrein excretion as reported in adults. This may be more marked in children with a family history of hypertension than in children without a family history of hypertension. From this point of view, a high K intake may be recommended during and subsequent to childhood to prevent adult hypertension by the activation of urinary kallikrein excretion.

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