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Genetic Factors in Essential Hypertension, with a Special Focus on Children

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Summary. **Essential hypertension among adults is a major risk factor for cardiovascular disease. It is now generally accepted that the aberrant regulatory mechanisms which develop into essential hypertension have their onset in children. Among various factors related to the development of essential hypertension, genetic determinants play a major role in influencing blood pressure. The present study focuses on genetic factors implicated at the onset of the development of essential hypertension or during the pre-hypertensive period. At this stage, these factors are more likely to be causes of hypertension rather than a consequence of long-standing hypertension.**

Introduction

Essential hypertension among adults is a major risk factor for cardiovascular disease. Treatment of hypertension in adults reduces the risk of stroke and, to a lesser extent, coronary artery disease.[1] It is now generally accepted that the aberrant regulatory machanisms which progress to the condition of essential hypertension have their onset in children.[2,3] It follows that, we should unmask the potential contributing effects of both genetic and environmental factors in childhood, and try to prevent the development of hypertension by focusing on its childhood precursors. There is an advantage for children because there is adequate time to take measures before they mature and hypertension is established.

Among multiple factors related to the development of essential hypertension, genetic determinants play a major role in influencing blood pressure,[4] as evidenced by the stronger concordance for hypertension in identical versus fraternal twins.[5] Furthermore, repeated studies have shown that blood pressure is higher in negro children than in caucasians, suggesting a racial difference in the determinants of blood pressure,[6] although we observed no difference in blood pressure between Japanese and other countries' children after matching their heights.[7]

In the present study, the focus will be on the genetic factors implicated at the onset of the development of essential hypertension or in the pre-hypertensive period. At this stage, the abnormalities would be more likely to be causes of hypertension rather than a consequence of long-standing hypertension.

Cation transport

The etiology of essential hypertension is unknown; however, there is much evidence that abnormal sodium metabolism plays a critical role. In particular, salt intake[8] and sodium transport across cell membrane[9] have been implicated as factors causing hypertension as most actively studied in erythrocytes.

There are several pathways for active Na transport in erythrocytes.[10] Firstly, there is Na/Li countertransport, which is equivalent to Na/Na countertransport. This channel is thought to exchange a single external Na ion for a single internal one. Hence, this cannot affect the overall distribution of Na across cell membranes, and there is some doubt about its physiological role.

The second system is the Na pump, which represents the best described and most widely studied pathway for cellular sodium homeostasis. This pathway has already been demonstrated to be abnormal in normotensive children with a family history of essential hypertention[11,12] as well as in hypertensive adults.[13]

The third is furosemide-sensitive Na/K co-transport system. An increase in intracellular Na concentrations causes an increase in the Na pump activity

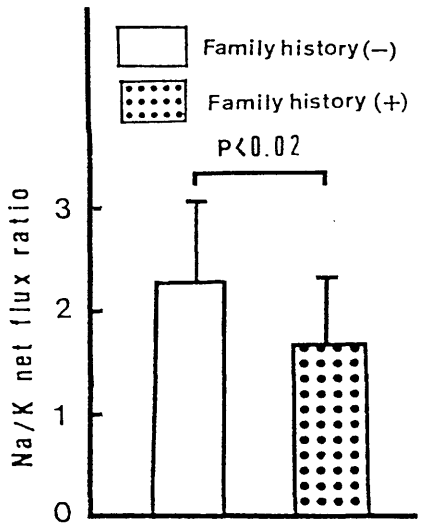

Fig. 1. Erythrocyte Na/K net flux ratio in normotensive children with or without a family history of essential hypertension.[16]

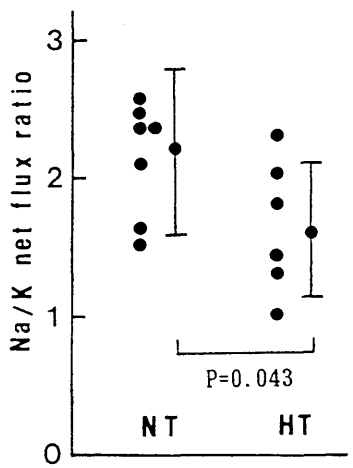

Fig. 2. Erythrocyte Na/K net flux ratio in the currently hypertensive (HT) and normoetnsive (NT) groups, all of whom were hypertensive in their junior high school days.[18]

until the Na pump is maximally stimulated.[10] When the intracellular Na concentration rises above a critical level, furosemide-sensitive Na/K cotransport system starts to support sodium extrusion, although this pathway usually lies dormant in the cell membrane. The ratio of Na/K net fluxes in Na-loaded/K-depleted erythrocytes represents the activity of this pathway.[14] An abnormally low ratio of Na/K fluxes is observed in essential hypertensive adults.[14] The absence of this abnormality in normotensive families, as in secondary hypertension, and its presence in some young normotensive adults[14,15] or children [16] in association with hypertensive parents (Fig. 1), has led us to suggest that it could be an inherited abnormality related to hypertension.

De Mendonca et al.[17] measured erythrocyte Na/K fluxes in three varieties of genetically hypertensive and normotensive control rats. They observed that abnormalities of Na or K fluxes including low Na/K flux ratio are genetically linked with hypertension, these being in several respects similar to those described in human essential hypertension.[15,16] In addition, they found a reduced erythrocyte Na extrusion in young rats at a pre-hypertensive stage,[17] which indicates that erythrocyte abnormality is not secondary to an increase in blood pressure. These findings observed in humans and rats suggest that the erythrocyte abnormality may represent biochemical markers of essential hypertension which may have a significant relevance to the development of hypertension.

Cation transport and prognosis of childhood hypertension

Abnormal sodium transport in cell membrane has been reported to be a determination of a prognosis of childhood essential hypertension. We investigated subjects aged about 35-year-old, all of whom had been hypertensive in their junior high school days.[18] We divided them into two groups according their current blood pressure, the now hypertensive group and the now normotensive group. The current hypertensive group showed significantly lower Na/K flux ratio in erythrocytes than the current normotensive group (Fig. 2). The number of sodium pumps in erythrocytes also showed nearly the same results, although urinary Na excretion did not differ between the groups. Hence, a cell membrane sodium transport defect is likely to have a significant relevance to the development of essential hypertension in adult life.[18]

Mongeau et al.[19] measured erythrocyte cation fluxes on two occasions in essential hypertensive children and adolescents to determine whether a known sodium transport abnormality can predict the severity of essential hypertension. Patients with an increased Na-Li countertransport were the most severely hypertensive in three different ways. Clinically, they presented a stable rather than a labile form of hypertension. Hemodynamically, the mean arterial pressure was higher than that of the other subgroups. Finally, in

those children followed for more than two years, this subgroup remained hypertensive with time. The patients with a decreased Na-K cotransport activity (= low Na/K flux ratio) were second in severity; however, blood pressure was often labile, mean arterial pressure was slightly lower than that of the former subgroup and all patients remained hypertensive with time, though it was mild in most cases. The patients with increased passive sodium permeability presented a mild form of hypertension. The patients with normal erythrocyte cation fluxes seemed to form a heterogeneous group. A few were severely hypertensive, but in most cases, the hypertension was borderline or transient. These findings suggest that the determination of erythrocyte cation fluxes may be a useful index of the severity of essential hypertension in children and adolescents.

A circulating Na-K ATPase inhibitor

Concerning the mechanism of abnormal Na transport, a close association between the erythrocyte total ^{22}Na efflux rate constant (the activity of the Na pump) and Na intake has been found in hypertensive adults.[20] Furthermore, De Wardner and MacGregor[21] have proposed that essential hypertension may result from renal Na retention, which in turn activates a circulating Na-K ATPase inhibitor. It has been demonstrated that this inhibitor is produced by an excessive salt intake or acute salt loading in hypertensive adults.[22,23] According to our study, however, no remarkable changes in Na-K ATPase inhibitor, blood pressure or the number of Na pump sites were observed after saline infusion in hypertensive children using the same protocol as in adults (Fig. 3).[13] Therefore, the mechanisms regulating cell membrane Na transport may differ between children and adults, i.e., congenital membrane defect in children and possibly in some hypertensive adults, and acquired defects may be induced in other hypertensive adults.

Na handling in the kidney

As mentioned above, it has been established that dietary sodium has an important role in the development of essential hypertension. However, comparisons of individual blood pressure, dietary salt intake, or urinary sodium excretion has proved inconclusive.[8] Thus, the likelihood of developing essential hypertension may be increased by certain familial abnormalities in renal sodium control mechanisms.

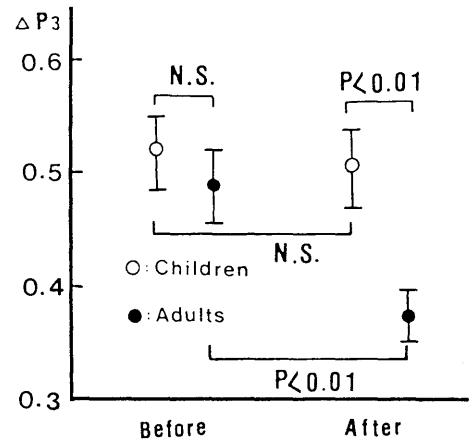

Fig. 3. Inhibition of Na-K ATPase activity ($\triangle P_3$) in hypertensive children and adults before and after saline infusion. After infusion, $\triangle P_3$ decreased (i.e. Na-K ATPase activity increased) significantly in the hypertensive adults compared with their own pre-infusion values or the post-infusion values of the hypertensive children.[13]

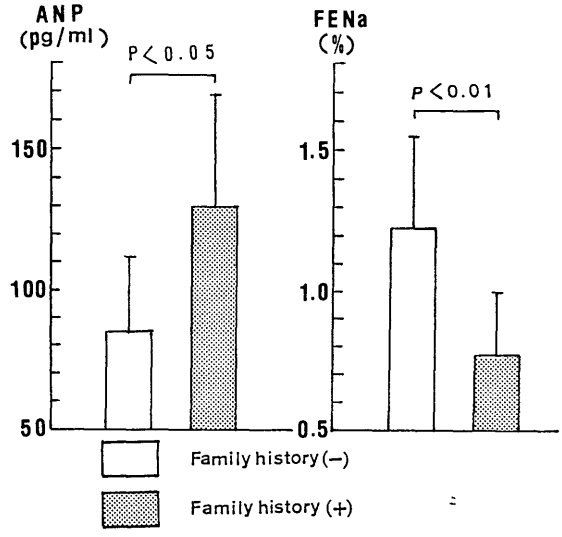

Fig. 4. Plasma atrial natriuretic peptide (ANP) and fractional excretion of filtered sodium (FENa) after saline infusion in normotenive children with or without a family history of essential hypertension.[26]

This idea is supported by the several studies which show that a familial predisposition to essential hypertension is associated with abnormalities in the renal function of Na handling.[24,25]

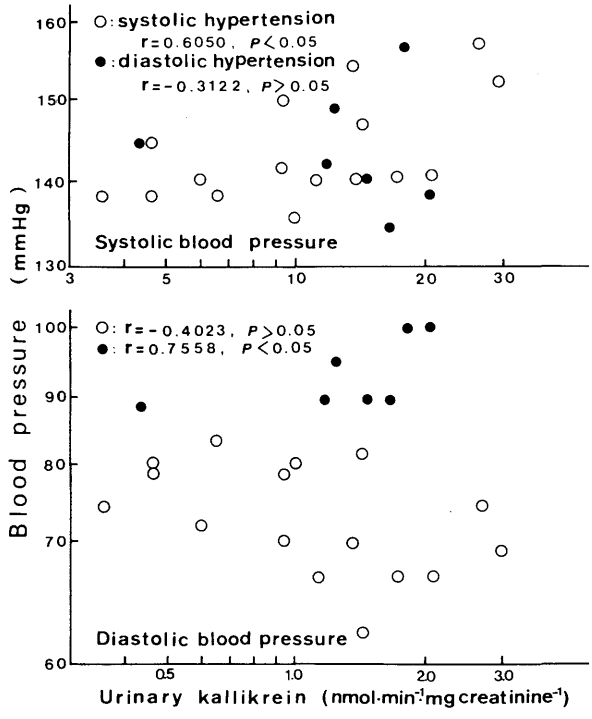

Fig. 5. Relationship between blood pressure and urinary kallikrein concentration in systolic or diastolic hypertensive children.[40]

We found a blunted natriuretic response after an infusion of physiological saline in normotensive children with hypertensive parents (Fig. 4).[26] Therefore, children predisposed to hypertension may have an inherited defect in the renal Na excretion control mechanism. Our observation of decreased natriuresis could be complementary to the findings of enhanced proximal tubular reabsorption obtained by indirect methods.[27] On the other hand, in adults with borderline[28] or established essential hypertension,[29] the kidney has been shown to handle an intravenous load of sodium chloride with an exaggerated natriuresis.

However, the presence of a blunted natriuresis and enhanced tubular function at the pre-hypertenive stage as well as exaggerated natriuresis at the hypertensive stage do not disprove the idea of a familial abnormality.[20] This has been confirmed in an animal model of hypertension using the Milan hypertenion rat, where an enhanced fluid extrusion develops concomitantly with the increase in blood pressure.[31]

Atrial natriuretic peptide (ANP) and natriuresis

The importance of ANP in volume and sodium homeostasis is well recognized.[32] Nevertheless, the part played by this peptide in the pathogenesis of essential hypertension is still subject to debate. With regard to the relationship between sodium intake and plasma ANP level, an impaired response of ANP to high sodium intake was observed in offspring of hypertensive parents, as compared with offspring of normotensive parents.[33,34] No differences were observed in plasma ANP levels between either group of offspring when their sodium intake was low. Ferrier et al.[33] did not try acute sodium loading, but considered their observation of the impaired ANP response to high sodium intake as one of the disorders related to hypertension-prone families. On the other hand, we observed an increased ANP response to saline load, which negatively correlated with fractional excretion of filtered sodium (FENa) in children with hypertensive parents.[26] Recently, similar findings have been demonstrated in salt sensitive normotensive adults.[35] As is known, atrial secretion of ANP appears to be elicited by volume expansion.[36] Therefore, our data suggest that the ability of the kidney to excrete sodium could be primarily impaired in normotensive children predisposed to essential hypertension, resulting in a greater sodium retention and corresponding compensatory increment in plasma ANP levels.[26]

Renal Kallikrein-kinin system

Renal kallikrein is a glandular kallikrein situated in the distal tubular cells, and released into both the urine and the renal lymph. Other glandular kallikreins which are present in the pancreas, salivary glands, sweat glands, etc. do not appear to any significant extent in the urine.[37] 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.[37] In the vasculature, it lowers blood pressure and increases vascular permeability.

Lower excretion of urinary kallikrein has been reported in essential hypertensive adults.[38] As for children, Zinner et al.[39] reported familial correspondence in both blood pressure and kallikrein concentration in spot urine specimens in normotensive children. They also found an inverse correlation between urinary kallikrein concentration and blood pressure. These findings suggest that lower urinary kallikrein

excretion may be a pathogenetic factor in developing hypertension in adult life. However, we observed conflicting results with the above in that urinary kallikrein excretion or spot urine concentration increased with blood pressure in essential hypertensive children (Fig. 5).[40,41] We considered it to reflect the increased activity of a compensating vasodilator system. We also failed to observe significant differences in urinary kallikrein excretion or spot urine concentration between normotensive children with or without a family history of hypertension (Fig. 6).[41,42] In both groups, urinary kallikreinexcretion or spot urine concentration showed a positive correlation with urinary sodium excretion.[41,42]

Lower urinary kallikrein excretion in hypertensive adults may result from renal damage by hypertension,[43] while the renal function is well reserved in hypertensive children.[44] This may be the reason why the renal kallikrein system works properly in terms of natriuresis and compensating high blood pressure in children. From this point of view, urinary kallikrein excretion can not be a genetic marker for essential hypertension.

Apart from the study in children, Bönner et al. have recently suggested that low urinary kallikrein excretion might be a determinant of the salt sensitivity of blood pressure in normotensive adults.[45] As they discriminated active from inactive kallikrein in human urine, these data seem very interesting. Moreover, a reduced excretion of active kallikrein is combined with the highest prevalence of familial hypertension.[46] Taken together, these data suggest that, if we measure active kallikrein, its low urinary excretion could represent an inheritable phenotype,[46] implicated in the pathogenesis of essential hypertension in subjects sensitive to salt intake. Ferri et al.[47] investigated the relationship between the urinary excretion of active kallikrein, as evaluated on a normal sodium intake, and the salt sensitivity of blood pressure in essential hypertensive patients. The urinary excretion of active kallikrein was significantly lower in salt sensitive than in salt resistant hypertensives, and a significant correlation between urinary kallikrein and plasma ANP was demonstrated in salt sensitive hypertensives. These findings indicate a strong relationship between active kallikrein excretion and blood pressure sensitivity to sodium intake in human essential hypertension, and suggest the increase in plasma ANP levels to be a compensatory mechanism to an impaired renal sodium excretory function. As already mentioned, the ability of the kidney to excrete sodium is likely to be impaired in children predisposed to essential hypertension.[26] Renal active kallikrein might be involved in this mechanism; however, there have been no reports on active kallikrein in children.

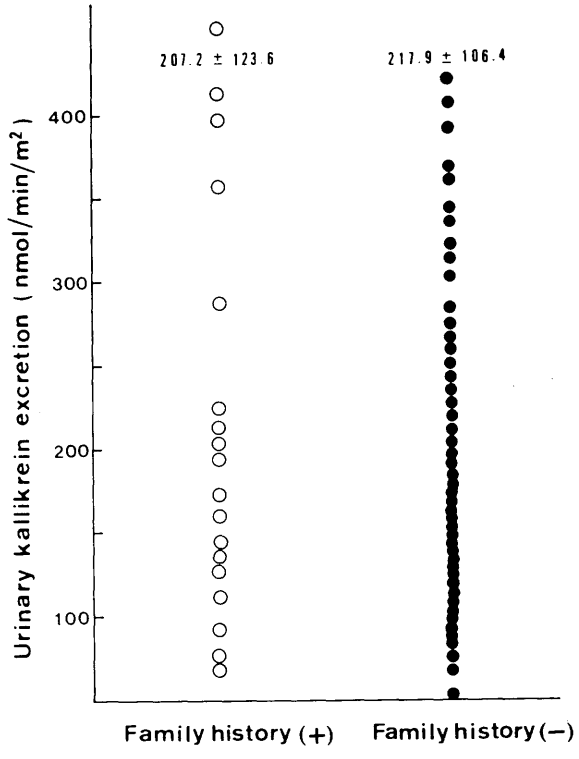

Fig. 6. Twelve-hour urinary kallikrein excretion in normotenive children with or without a family history of essential hypertension.[42]

The renin-angiotensin system

The renin-angiotensin system plays an important role in regulating blood pressure and electrolyte homeostasis.[48] Van Hooft et al.[49] reported that normotensive children with essential hypertensive parents have altered renal hemodynamics, with lower renal blood flow, plasma renin, and aldosterone concentrations than those with normotensive parents.[49] They conclude that these children are unable "to modulate normally the responsiveness of the renal vasculature and adrenal gland to angiotensin II at different levels of sodium intake". This conclusion is based on the observations in essential hypertensive adults as follows; there is a subpopulation of patients with essential hypertension that shows a delay in achieving an external sodium balance after increases in sodium intake and shows a reduced renal vascular response

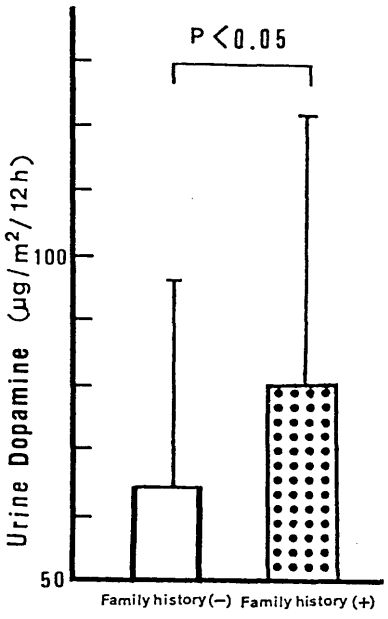

Fig. 7. Twelve-hour urinary dopamine excretion in normotenive children with or without a family history of essential hypertension.

to angiotensin II.[50]

An intriguing observation is that in many people with essential hypertension, plasma renin and angiotensin II levels that are normal or low. Experimentally, a transgenic rat in which the renin gene from the mouse submandibular gland has been inserted and expressed develops hypertension despite having low renin and angiotensin II levels in the plasma and in the kidneys.[51] Northern blot analysis showed that the concentration of renin transcripts was high in the adrenal glands of the transgenic rats. Therefore, it is speculated that the renin-angiotensin system is activated in the adrenal gland, with the consequent overproduction of steroid hormones, which causes hypertension to suppress other renin and angiotensin II production. Recently, molecular variants of the human angiotensinogen gene have been reported to be associated with essential hypertension in Caucasian populations.[52] Fifteen point mutations in the human angiotensinogen gene were identified, and an association study between these point mutations and hypertension was undertaken with a sib-pair method. The amino acid residue 174 of the angiotensinogen gene had two variant forms, threonine (T174) and methionine (M174). The allele frequencies of M174 in the hypertensive group were higher than in the normotensive control groups. The amino acid residue 235 of the angiotensinogen gene also had two variant forms, methionine (M235) and threonine (T235). The allele frequencies of T235 were higher in the hypertensive group than in control group.[52] The molecular variant of the angiotensinogen gene T235 seems to be a predisposing factor for hypertension in the Japanese population, too.[53] However, further studies are necessary to confirm whether these angiotensinogen gene variants may lead to enhanced angiotensinogen production and then to hypertension and other cardiovascular diseases.

Dopamine

Dopamine decreases blood pressure directly by vasodilatory action or indirectly by suppressing norepinephrine release. It is also natriuretic directly, or indirectly via aldosterone suppression. Kuchel[54] demonstrated that young patients with borderline essential hypertension are in a hyperdopaminergic state, and that patients with stable essential hypertension have renal dopamine deficiency.

According to our study (Fig. 7), urinary dopamine excretion was significantly increased in children with a family history of hypertension (n=30), compared with that in children without a family history of hypertension (n=71). This finding contradicts the hypothesis that essential hypertension may be caused by an inherited defect of the renal dopaminergic activity.[55]

Conclusion

Since children have been less influenced by environmental factors than adults, they are appropriate for studying genetic factors of essential hypertension. Furthermore, we have plenty of time in which to prevent the development of hypertension. Although the mechanisms involved in the establishment of essential hypertension are numerous, some genetic factors are found in normotensive children predisposed to essential hypertension as reviewed in this study. Apparently, these children are a logical group to observe and in whom possibly to institute preventive measures.

References

1) Collins R, Peto R, MacMahon S, Herbert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH: Blood pressure, stroke, and

coronary heart disease. *Lancet* **335**: 827-838, 1990.
2) Uchiyama M, Otsuka T, Shibuya Y, Sakai K: Is childhood hypertension a predictor of adult hypertension? (letter) *Lancet* i: 1247, 1984.
3) Lauer RM, Clarke WR, Mahoney LT, Witt J: Childhood predictors for high adult blood pressure. *Pediatr Clin North Am* **40**: 23-40, 1993.
4) Mongeau J-G: Pathogenesis of the essential hypertension. *Pediatr Nephrol* **5**: 404-411, 1991.
5) Ingelfinger JR: Epidemiology of hypertension. In: "Pediatric hypertension" WB Saunders Co, Philadelphia, 1982, p 79-92.
6) Berenson GS, Voors AW, Webber LS, Dalferes ER, Harsha DW: Racial differences of parameters associated with blood pressure levels in children. *Metabolism* **28**: 1218-1228, 1979.
7) Uchiyama M, Sasaki K: Studies of blood pressures in school children in Northern Japan. *Public Health* **99**: 18-22, 1985.
8) Kawasaki T, Delea CS, Bartter FC, Smith H: The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. *Am J Med* **64**: 193-198, 1978.
9) Edmomdson RPS, Thomas RD, Hilton PJ, Patrick J, Jones NF: Abnormal leukocyte composition and sodium transport in essential hypertension. *Lancet* i: 1003-1005, 1973.
10) Uchiyama M, Shah V, Willems CD, Dillon MJ: Sodium transport in erythrocytes: differences between normal children and children with primary and secondary hypertension. *Arch Dis Childh* **64**: 224-228, 1989.
11) Uchiyama M, Satokata I, Sakai K, Willems CD, Shah V, Dillon MJ: Membrane electrolyte transport in children with primary hypertension. In: Murakami K, Kitagawa T, Yabuta K, Sakai T (eds) Recent Advances in Pediatric Nephrology, *Excerpta Medica*, Amsterdam, 1987, p 133-138.
12) Deal JE, Shah V, Goodenough G, Dillon MJ: Red cell membrane sodium transport: possible genetic role and use in identifying patients at risk of essential hypertension. *Arch Dis Childh* **65**: 1154-1157, 1990.
13) Uchiyama M, Sakai K: Significant difference in the effect of acute saline loading on plasma Na-K ATPase inhibitor and blood pressure in children and adults with essential hypertension. *Jpn J Nephrol* **34**: 91-97, 1992.
14) Garay RP, Meyer P: A new test showing abnormal net Na and K fluxes in erythrocytes of essential hypertensive patients. *Lancet* i: 349-353, 1979.
15) Garay RP, Elghozi JL. Dagher G, Meyer P: Laboratory distinction between essential and secondary hypertension by measurement of erythrocyte cation fluxes. *New Engl J Med* **302**: 769-771, 1980.
16) Uchiyama M, Satokata I: Erythrocyte Na/K flux ratio in relation to sodium intake and family history of essential hypertension. *J Human Hypertens* **7**: 47-51, 1993.
17) De Mendonca M, Grichois M-L, Garay RP, Sassard J, Ben-Ishay D, Meyer P: Abnormal net Na^+ and K^+ fluxes in erythrocytes of three varieties of genetically hypertensive rats. *Proc Natl Acad Sci USA* **77**: 4283-4286, 1980.
18) Uchiyama M, Ogawa T, Sakai K: Erythrocyte sodium transport at twenty-year follow-up of childhood hypertension. *Acta Pediatr Jpn* **34**: 42-45, 1992.
19) Mongeau J-G, Mauran P, Poirot G, Davignon A: Longitudinal study of various transport abnormalities as an index of severity in children and adolescents suffering from essential hypertension. *J Hypertens* **8**: 657-662, 1990.
20) Fitzgibbon ER, Morgan TO, Myers JB: Red cell ^{22}Na efflux and urinary sodium excretion in essential hypertension. *Clin Sci* **59(Suppl. 5)**: 195s-198s, 1980.
21) MacGregor GA, De Wardner HE: Is a circulating sodium transport inhibitor involved in the pathogenesis of essential hypertension? *Clin Exp Hypertens* **3**: 815-830, 1981.
22) Myers JB, Fitzgibbon WR, Morgan TO: Effect of acute and chronic salt loading on erythrocyte ^{22}Na efflux in males with essential hypertension. *Clin Sci* **61**: 37s-39s, 1981.
23) Devynck M-A, Pernollet M-G, Deray G, Wauguier I, Delva P, Rieu M, Henning G, Cloix J-F, Crabos M, Baudouin-Legros M, Meyer P: Investigation of the endogenous Na^+-pump inhibitor in essential hypertension and blood volume expansion. *J Hypertens* **2 (Suppl 3)**: 453-455, 1984.
24) Gudmundsson O: Sodium and blood pressure. Studies in young and middle-aged men with a positive family history of hypertension. *Acta Med Scand* **(suppl 688)**; 1-65, 1984.
25) Bianchi G, Cuis D, Barlassina C, Lupi GP, Ferrari P, Picotti GB, Gatti M, Polli E: Renal dysfunction as a possible cause of essential hypertension in predisposed subjects. *Kidney Int* **23**: 870-875, 1983.
26) Uchiyama M: Renal sodium handling and plasma atrial natriuretic peptide after saline infusion in children with hypertensive parents. *Jpn J Appl Physiol* **21**: 91-95, 1991.
27) Skrabal F, Herholz H, Neumayr M, Hamberger L, Ledochowski M, Sporer H, Hörtnagl H, Schwarz S, Schönitzer D: Salt sensitivity in humans is linked to enhanced sympathetic responsiveness and to enhanced proximal tubular reabsorption. *Hypertension* **6**: 152-158, 1984.
28) Trimarco B, De Simone A, Volpe M, Ricciardelli B, Ungaro SA, Volpe M, Ricciardelli B, Ungaro B, Sacca L, Rengo F, Condorelli M: Renal function in borderline hypertensive first-degree relatives of essential hypertensives. *Cardiology* **69**: 288-296, 1982.
29) Schalekamp M, Krauss XM, Schalekamp-Kuyken MPA, Kolsters G, Birkenhäger WH: Studies on the mechanism of hypernatriuresis in essential hypertension in relation to measurements of plasma renin

concentration, body fluid compartments and renal function. *Clin Sci* **41**: 219-231, 1971.
30) Städler P, Pusterla C, Beretta-Piccoli C: Renal tubular handling of sodium and familial predisposition to essential hypertension. *J Hypertension* **5**: 727-732, 1987.
31) Bianch G, Ferrari P, Barber BR: The Milan hypertensive strain. In: de Jong W (ed) Handbook of Hypertension, Elsevier Science Publishers, Amsterdam, 1984, p 328.
32) Laragh JH: Atrial natriuretic hormone, the renin-aldosterone axis, and blood pressure-electrolyte homeostasis. *N Engl J Med* **313**: 1330-1340, 1985.
33) Ferrier C, Weidmann P, Hollmann R, Dietler R, Shaw S: Impaired response of atrial natriuretic factor to high salt intake in persons prone to hypertension (letter). *N Engl J Med* **319**: 1223-1224, 1998.
34) Van Hooft IM, Grobbee DE, Hofman A, Schiffers P, De Pont JJHHM: Atrial natriuretic factor and sodium intake in offspring of hypertensive and normotensive parents. (letter) *N Engl J Med* **320**: 867-868, 1989.
35) Overlack A, Puppert M, Kollock R, Göbel B, Kraft K, Diehl J, Scmitt W, Stumpe KO: Divergent hemodynamic and hormonal responses to varying salt intake in normotensive subjects. *Hypertension* **22**: 331-338, 1993.
36) Uchiyama M, Satokata I, Aikawa T, Sakai K: Atrial natriuretic peptide in congenital heart diseases. *Acta pediatr Scand* **76**: 669-670, 1987.
37) Mills IH: The renal kallikrein-kinin system and sodium excretion. *Q J Exp Physiol* **67**: 393-399, 1982.
38) Dessi-Fulgheri P, Espinosa E, Zingaretti O, Guazzaroti F, Sarzani R, Pupita G, Sturbini S, Catalini R, Rsppelli A: Urinary kallikrein excretion and blood pressure response to angiotensin converting enzyme inhibitors and calcium antagonists in hypertensive patients. *J Hypertens* **11**: 725-730, 1993.
39) Zinner SH, Margolius HS, Rosner B, Kass EH: Stability of blood pressure rank and urinary kallikrein concentration in childhood. An eight-year follow-up. *Circulation* **58**: 908-915, 1978.
40) Uchiyama M, Otsuka T, Shibuya Y, Sakai K: Influence of blood pressure on urinary kallikrein excretion in essential hypertension in childhood. *IRCS Med Sci* **12**: 863-864, 1984.
41) Uchiyama M, Otsuka T, Sakai K: Urinary kallikrein and electrolyte concentrations in healthy children: with special reference to their and their parents' blood pressures. *Acta Med Biol* **33**: 105-112, 1985.
42) Uchiyama M, Otsuka T, Sakai K: Urinary kallikrein excretion in children of parents with essential hypertension. *Arch Dis Childh* **60**: 974-975, 1985.
43) Holland B, Chud JM, Braunstin H: Urinary kallikrein excretion in essential and mineralocorticoid hypertension. *J Clin Invest* **65**: 347-356, 1980.
44) Uchiyama M: Clinical use of urinary N-acetyl-β-D-glucosaminidase and alanine aminopeptidase activities in children with primary and secondary hypertension. *Jpn J Appl Physiol* **20**: 301-304, 1990. (in Japanese)
45) Bönner G, Thieven B, Rutten N, Chrosch R, Krone W: Renal kallikrein is a determinant of salt sensitivity. *J Hypertens* **11(Suppl 5)**: S210-S211, 1993.
46) Berry TD, Hasstedt SJ, Hunt SC, Wu LL, Smith JB, Ash KO, Kuida H, Williams RR: A gene for high urinary kallikrein may protect against hypertension in Utah kindreds. *Hypertension* **13**: 3-8, 1989.
47) Ferri C, Bellini C, Carlomagno A, Perrone A, Santucci A: Urinary kallikrein and salt sensitivity in essential hypertensive males. *Kidney Int* **46**: 780-788, 1994.
48) Uchiyama M, Otsuka T, Shibuya Y, Sakai K: Electrolyte excretion in 12-hour urine and in spot urine. Relationship to plasma renin activity and aldosterone concentration in older children. *Acta Pediatr Scand* **74**: 394-399, 1985.
49) Van Hooft IMS, Grobbee DE, Derkx FHM, De Leeuw PW, Schalekamp MADH, Hofman A: Renal hemodynamics and the renin-angiotensin-aldosterone system in normotensive subjects with hypertensive and normotensive parents. *N Engl J Med* **324**: 1305-1311, 1991.
50) Guillery EN, Robillard JE: The renin-angiotensin system and blood pressure regulation during infancy and childhood. *Pediatr Clin North Am* **40**: 61-79, 1993.
51) Mullins JJ, Peters J, Ganten D: Fulminant hypertension in transgenic rats harbouring the mouse Ren-2 gene. *Nature* **344**: 541-544, 1990.
52) Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A, Hunt SC, Hopkins PN, Williams RR, Lalouel J-M, Corvol P: Molecular basis of human hypertension: role of angiotensinogen. *Cell* **71**: 169-180, 1992.
53) Iwai N, Ohmichi N, Nakamura Y, Mitsunami K, Kinoshita M: Molecular variants of the angiotensinogen gene and hypertension in a Japanese population. *Hypertens Res* **17**: 117-121, 1994.
54) Kuchel O: Peripheral dopamine in essential hypertension. *Am J Hypertens* **3**: 104S-107S, 1990.
55) Iimura O: Essential hypertension: its cause and epidemiology. *Jpn J Hypertens* **12**: 113-127, 1990. (in Japanese)