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OBSERVATIONS ON THE PATHOPHYSIOLOGY OF BARTTER'S SYNDROME IN CHILDHOOD

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ABSTRACT

A 20-month old boy with Bartter's syndrome was studied. Before treatment with indomethacin, he showed an abnormal response of blood pressure to Saralasin or angiotensin II infusion, elevated activity of the renin-angiotensin-aldosterone system, increased excretion of urinary kallikrein, and low distal fractional reabsorption of chloride. However, on receiving indomethacin, the boy's abnormalities returned to normal except for low distal fractional reabsorption of chloride on indomethacin. These findings suggest that a defect in chloride reabsorption in the ascending limb of Henle's loop may play a significant role in the pathogenesis of Bartter's syndrome.

INTRODUCTION

In 1962, Bartter and his colleagues described a new syndrome of hypokalemic alkalosis associated with hyperaldosteronism, juxtaglomerular cell hyperplasia, the pitressin-resistant urine concentration defect, and growth and mental delay.[1] Since that time, various etiologies on this disorder have been proposed,[2] including (a) abnormal sodium reabsorption in various portions of renal tubules[3-8]; (b) a defect in chloride reabsorption in the ascending limb of Henle's loop leading to excessive potassium secretion by the distal tubule[8,9]; and (c) overproduction of prostaglandins (PGs), prostacyclin, or bradykinin to form angiotensin-resistance.[10-13]

In an attempt to test some of these hypothese, the author has studied one child with Bartter's syndrome. The response of infusion of the angiotensin-antagoinst Saralasin

was used to assess the contribution of angiotensin to the maintenance of blood pressure. An angiotensin II infusion test was given to observe the response of blood pressure to angiotensin II. A hypotonic saline load test was attempted to assess the efficiency of urinary dilution and hence choride reabsorption. Finally endocrinological studies were made to observe the effect of indomethacin on plasma renin activity, plasma aldosterone concentration, plasma PGE, and urinary kallikrein.

PATIENT

A 20-month-old boy fulfilled the criteria for a diagnosis of Bartter's syndrome. This criteria was proposed by the Japanese Research Group on Bartter's syndrome supported by the Ministry of Welfare (Table 1).

Table 1 Criteria for Bartter's syndrome used in Japan

1) Elevated plasma renin activity
2) Increased secretion of aldosterone
3) Hypokalemia
4) Metabolic alkalosis
5) Low to normal blood pressure
6) Low response of blood pressure to exogenous angiotensin II
7) Pseudo-Bartter's syndrome should be ruled out
8) Proof of hyperplasia of juxtaglomerular apparatus not always essential

METHODS

Laboratory examination

A blood and urine chemical examination, a blood gas analysis and other laboratory examinations were undertaken with conventional methods.

Mearurement of blood volume

Circualating blood volume was measured by using ^{131}I-human serum albumin, which was calculated as follows:

Circulating blood volume (ml) = C_0V_0/C_1

C_1 = count of radioactivity in 1 ml blood

C_0 = count of radioactivity in 1 ml diluted standard solution

V_0 = dilution of ^{131}I-human serum albumin

Saralasin infusion

Blood pressure was recorded in a prone posture at 5 min intervals by using an autonomic device, the Dinamap. Once the blood pressure was stable, infusion of Saralasin was started at the rate of 50 μg/kg/min while blood pressur was monitored. The dosage of Saralasin was increased every 10 min from the rate of 50 μg/kg/min to 250 μg/kg/min.

Angiotensin II infusion

Blood pressure was recorded in a prone posture at 5 min intervals. After the blood pressure became stable, angiotensin II was started at the rate of 10 ng/kg/min while blood pressure was monitored. The dosage of angiotensin II was increased every 10 minutes from the rate of 10 ng/kg/min to 90 ng/kg/min.

Hypotonic saline infusion

Twenty ml/kg of water were given orally over 30 min. 0.45%saline was infused at the rate of 1000 ml/hour/1.73m^2 (body surface area) for 2 h. Urine samples were obtained by spontaneous voiding at 20 min intervals. In this study the subject's back was rubbed to let him void into a stool used for infants. Venous blood was collected at the midpoint of each urine collection period.

The levels of Na, K, Cl, and creatinine as well as osmorality were measured in urine and serum by using conventional methods. The distal fractional reabsorption of chloride, $C_{H_2O}/(C_{H_2O}+C_{C_l})$, was calculated.[7]

Endocrinological study

Venous blood was collected in cold tubes containing EDTA-2Na and was spun immediately at 3000 rpm at 4℃. Plasma was stored at −80℃ until the assay for plasma renin activity, aldosterone concentration and PGE_2 concentration.

Plasma renin activity and aldosterone concentration were measured by radioimmunoassay by using CIS kits.

Plasma PGE_2 was measured by radioimmunoassay by using the Jaffe's method.[14] The plasma sample was extracted with an organic solvent system at an apparent pH value of 5.8 and then chromatographed on sialic acid colunms with increasing concentrations of methanol to separate the PGA, PGE and PGF. Chromatographed sample for PGE was measured by radioimmunoassay by using Miles' antibody. Purified PGE_2 was offered by Upjohn CoLtd (USA).

Twenty-four-hour urine samples were collected for urinary kallikrein measurement, and the aliquots were stored at −80℃ until the assay. The urinary kallikrein excretion was measured in nondialysed urine samples by using the method of Morita et al.,[15] using the synthetic fluorogenic substrate L-prolyl-L-phenylalanyl-L-arginine-4-methylcoumaryl-7-amide obtained from the Peptide Institute, Protein Rerearch Foundation (Osaka, Japan).

Re-examination

The examinations mentioned above were undertaken both before and during treatment with indomethacin (2mg/kg/day).

RESULTS

Laboratory examination (Table 2)

The urine volume increased extremely before treatment, but returned to normal on using indomethacin. In connection with the change in urine volume, the decreased urine

Table 2. Changes in laboratory findings before and during treatment with indomethacin

	Off indomethacin	On indomethacin
Urine		
Volume (ml/day)	1210-2100	300-500
pH	7.5-7.7	6.0-6.5
Osmotic pressure (mOsm/l)	50-262	285-416
Na (mEq/l)	19-13	53-95
(mEq/day)	19-50	16-60
K (mEq/l)	15-18	35-60
(mEq/day)	16-36	10-35
Cl (mEq/l)	17-34	60-104
(mEq/day)	18-36	20-58
Serum		
Na (mEq/l)	132	142
K (mEq/l)	2.6	4.1
Cl (mEq/l)	88	102
total protein (g/dl)	7.7	6.7
pH	7.53	7.41
PCO_2 (mmHg)	46.8	37.5
B. E. (mEq/l)	+11.2	+2.1

osmopressure also returned to normal on using indomethacin.

Measurement of blood volume

Blood volume was 420 ml initially, but it increased to 650 ml on using indomethacin.

Saralasin infusion (Fig. 1)

Once the indomethacin was stopped, the systolic and diastolic blood pressures fell during Salarasin infusion, but returned to the original level within 30 min after stopping the infusion. This response of blood pressure to Saralasin almost disappeared after using indomethacin.

Angiotensin II infusion (Fig. 2)

Once the indomethacin was stopped, the systolic and diastolic blood pressures did not change during a low dosage of angiotensin II infusion. On using indomethacin, however, the blood pressure rose remarkably after infusion with angiotensin II.

Hypotonic saline infusion

Distal fractional reabsorption of chloride, $C_{H_2O}/(C_{H_2O}+C_{Cl})$, was 0.52 and 0.59 once indomethacin was stopped and used respectively, both of which were lower than the normal value.

Endocrinokogical study (Table 3)

The plasma renin activity and aldosterone concentration were markedly higher before treatment with indomethacin. They decreased on using indomethacin, but did not reach a normal level.

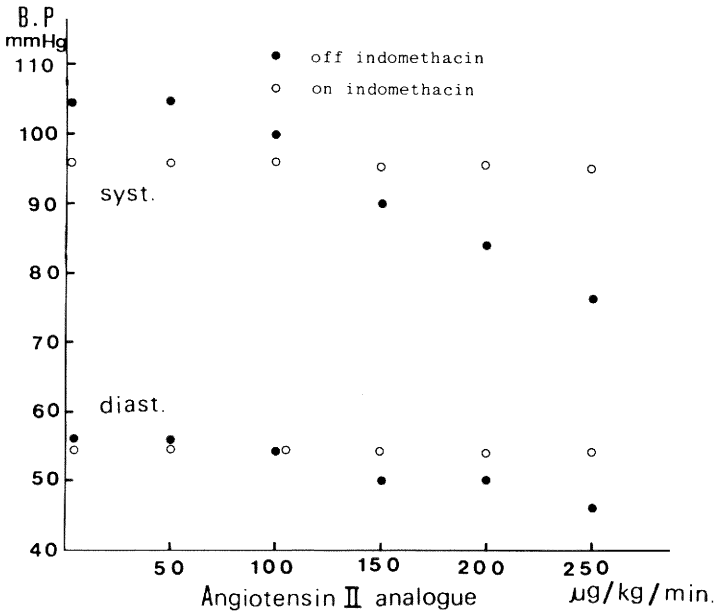

Fig. 1 Response of systolic and diastolic blood pressures to the angiotensin II-analogue (Saralasin) infusion off (●) and on (○) indomethacin

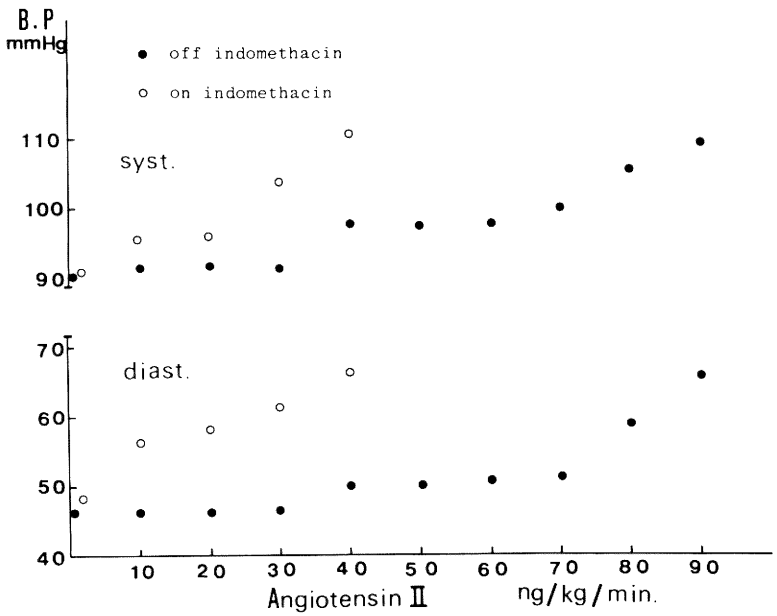

Fig. 2 Response of systolic and diastolic blood pressures to the angiotensin II infusion off (●) and on (○) indomethacin

Table 3. Changes in endocrinological findings before and during treatment with indomethacin

	Off indomethacin	On indomethacin
Urinary kallikrein (U/day)	1.55-3.06	0.02-0.5
Plasma renin activity (ng/ml/hr)	29.6-82.8	2.4-18.6
Plasma aldosterone (pg/ml)	1340-1860	140-440
Plasma PGE_2 (ng/ml)	1.5	1.3

The plasma PGE_2 was also elevated before treatment with indomethacin, but did not change remarkably on using indomethacin.

The urinary kallikrein excretion was markedly increased before treatment with indomethacin. It decreased remarkably after using indomethacin, but still did not reach a normal level.

Discussion

Since the first description by Bartter et al. (1962), the syndrome coined with his name is characterized by hypokalemic alkalosis associated with hyperaldosteronism, juxtaglomerular cell hyperplasia, a pitressin-resistant urine concentration defect, and growth and mental delay.[1] Both patients reported by Bartter were normotensive; one had increased levels of plasma angiotensin II, and both decreased vascular responsiveness to this octapeptide. Since that time, various etiologies have been proposed.[2]

The association of hyperplasia of the juxtaglomerular apparatus and the failure of angiotensin infusion to raise arterial blood pressure suggested that the syndrome resulted from a primary insensitivity to the pressor action of angiotensin II.[1] However, several findings in the present study render this hypothesis untenable. First, elevated plasma renin activity decreased either on using indomethacin or during the volume expansion study. Second, the initial response of blood pressure to Salarasin (angiotensin-antagonist) infusion disappeared on treatment with indomethacin. Third, blood pressure was raised remarkably during an angiotensin II infusion on using indomethacin, although it did not change before treatment. In addition, these findings on the abnormal functions of the renin-angiotensin-aldosterone system observed before treatment with indomethacin have been reported in the pseudo-Bartter syndrome too.[16]

Overproduction of PGs, prostacyclin, or bradykinin has been suggested to mediate the angiotensin-resistance mentioned above.[10-13] In the present study, the plasma PGE_2 level was elevated before treatment with indomethacin; however, it remained at the same level after using indomethacin. Venous PGE_2 is largely metabolized on the first passage through the pulmonary circulation; therefore, the significance of its peripheral plasma concentration is uncertain.[17] The urinary PGE-metabolite is a better indicator of total

body PGE production, and this is reported to be normal in Bartter's syndrome.[18] Therefore, overproduction of PGE seems unlikely to account for arteliolar angiotensin-resistance. On the other hand, urinary PGE_2 is principally derived from renal synthesis[18] and reported to be high in Bartter's syndrome. However, the high concentrations in Bartter's syndrome may be the consequence of a sodium and potassium deficiency since a higher urinary PGE_2 level has also been found in patients who were sodium and potassium depleted for other reasons.[7,20] The renal kallikrein-kinin system may have some role in arteliolar angiotensin-resistance since the urinary kallikrein excretion markedly increased before treatment with indomethacin. However, it decreased remarkably on using indomethacin, suggesting that the increased activity of the renal kallikrein-kinin system may be secondary to the increased activity of PGs.

A defect in chloride reabsorption in the ascending limb of Henle's loop has been reported.[8,9] In the present study, the distal tubular reabsorption of Cl was decreased, confirmation of the findings previously reported, although normal reabsorption has also been recorded in children with Bartter's syndrome.[2] This defect of active chloride reabsorption in the ascending limb of Henle's loop is known to lead to excessive potassium secretion by the distal tubule.[8,9] In the present study, this defect in chloride reabsorption in the ascending limb of Henle's loop is the unique factor that did not change when indomethacin was used and stopped while the values of other laboratory and endocrinological examinations returned to normal on using indomethacin.

In conclusion, the patient initially showed abnormal response of blood pressure to Saralasin or angiotensin II infusion, elevated activity of the renin-angiotensin-aldosterone system, increased excretion of urinary kallikrein, and low distal fractional reabsorption of chloride. However, these abnormalities returned to normal after using indomethacin except for the low distal fractional reabsorption of chloride. These findings suggest that a defect in chloride reabsorption in the ascending limb of Henle's loop may have some significant relevance to the pathogenesis of Bartter's syndrome, although many other hypothese have been proposed up to now.

Recently, the author found that erythrocyte sodium transport was abnormal in Bartter's syndrome.[21] It is, however, unknown as yet as to how this disturbance may be related to the distal tubular defect of Cl reabsorptin.

References

1) Bartter, F. C., et al.: Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. *Am. J. Med.*, **33**: 818-828, 1962.
2) Solomon, L. R., et al.: Bartter's syndrome—Observations on the pathophysiology. *Q. J. Med. New Series*, **51**: 251-270, 1982.
3) Chaimovitz, C., et al.: Studies on the site of renal salt loss in a patient with Bartter's syndrome. *Pediatr. Res.*, **7**: 89-94, 1973.
4) Chan, J. C. M., et al.: Defects in renal tubular sodium reabsorption in a patient with Bartter's syndrome. Clin. *Clin. Proc. Child. Hos. Nath. Med. Centre*, **31**: 67-71, 1975.
5) Bartter, F. C., et al.: The adrenal cortex and the kidney. *Kidney Int.*, **6**: 272-280, 1974.

6) Tomko, D. J., et al.: Bartter's syndrome. Study of a 52-year-old man with evidence for a defect in proximal tubular sodium reabsorption and comments on therapy. *Am. J. Med.*, **61**: 111-118, 1976.
7) Gill, J. R., Jr., Bartter, F. C.: Evidence for a prostaglandin-independent defect in chloride reabsorption in the loop of Henle as a proximal cause of Bartter's syndrome. *Am. J. Med.*, **65**: 766-772, 1978.
8) Kurtzman, N. A., Gutierrez, L. P.: The pathophysiology of Bartter's syndrome. *J. Am. Med. Associ.*, **234**: 758-759, 1975.
9) Verberckmoes, R., et al.: Bartter's syndrome with hyperplasia of renomedullary cells: Successful treatment with indomethacin. *Kidney Int.*, **9**: 302-307, 1976.
10) Fichman, M. P.: Role of prostaglandins in the pathogenesis of Bartter's syndrome. *Am. J. Med.*, **60**: 785-797, 1976.
11) Gill, J. R., et al.: Bartter's syndrome: A disorder characterized by high urinary prostaglandins and a dependence of hyperreninaemia on prostaglandin synthesis. *Am. J. Med.*, **61**: 43-51, 1976.
12) Gullner, H. G., et al.: Correction of increased prostacyclin synthesis in Bartter's syndrome by indomethacin treatment. *Prostaglandins Med.*, **4**: 65-72, 1982.
13) Vinci, J. A., et al.: The kallikrein-kinin system in Bartter's syndrome and its response to prostaglandin synthetase inhibitors. *J. Clin. Invest.*, **61**: 1671-1682, 1978.
14) Jaffe, B. M., et al.: Radioimmunoassay measurement of prostaglandin E. A. and F in human plasma. *J. Clin. Invest.*, **52**: 398-405, 1978.
15) Morita, T., et al.: New fluologenic substrates for α-thrombin, factor X_a, kallikreins, and urokinase. *J. Biochem.*, **82**: 1495-1498, 1977.
16) Gill, J. R., Jr.: Bartter's syndrome. *Ann. Rev. Med.*, **31**: 405-419, 1980.
17) Ferriera, S. H., Vane, J. R.: Prostaglandins: Their disappearance from and release into the circulation. *Nature*, **216**: 868-873, 1967.
18) Bartter, F. C., et al.: Prostaglandins are overproduced by the kidneys and mediate hyperreninaemia in Bartter's syndrome. *Trans. Ass. Am. Phys.*, **89**: 77, 1976.
19) Frolich, J. C., et al.: Urinary prostaglandins. Identification and origin. *J. Clin. Invest.*, **55**: 763-770, 1975.
20) Nivet, H., et al.: Raised urinary prostaglandins in patient without Bartter's Syndrome. *Lancet*, i: 333-334, 1978.
21) Uchiyama, M., et al.: Erythrocyte sodium transport in Bartter's syndrome. *Acta Paediatr. Scand.*, **77**: 873-878, 1989.