activity of any of the three enzymes during the first 4 days of life. By the eighth day, however, UDPXT and UDPGST activities increased 80 and 88% as compared with controls, respectively. UDPGT demonstrated no enhancement on *day 8* in response to phenobarbital. By the 12th day, enhancement of UDPGT became significant, reaching maximal increase on *day 16*.

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25. Requests for reprints should be addressed to: L. M. Gartner, M.D., Department of Pediatrics, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, N. Y. 10461 (USA).

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Angiotensin II
Bartter's syndrome
plasma renin activity
renin-aldosterone axis
sodium
urinary excretion

Effect of Sodium Restriction and Angiotensin II Infusion in Bartter's Syndrome

L. SANN,[30] M. DAVID, P. RICHARD, D. FLORET, J. SASSARD, C. A. BIZOLLON, AND R. FRANCOIS

Hôpital E. Herriot and Hôpital Debrousse, Lyon, France

Extract

Five patients with Bartter's syndrome were investigated. Sodium restriction (<10 mEq/day for at least 5 days) showed a renal sodium wastage in only two patients (*I* and *II*) in spite of increased aldosterone secretion rate (from 151–427 to 680–842 μg/day). The effect of angiotensin II (A II) 80 ng/kg/min for 30–180 min, on plasma renin activity (PRA), plasma aldosterone, and urinary sodium excretion was compared with the effect of a previous infusion of 5% dextrose given at the same rate, 0.5 ml/min for 1 hr. A II infusion resulted in increased plasma aldosterone levels: from 236–330 pg/ml to 800–881 pg/ml in 30 min. This increase was also observed in *patient II* (from 139 to 600 pg/ml). PRA was decreased by A II infusion (from 1,142–2,462 to 121–1,625 ng/liter/min). In *patient IV*, this decrease in PRA was also observed when he was on a salt-restricted diet (from 1,934 to 370 ng/liter/min); but the minimal PRA was still higher (370 ng/liter/min) than with a normal diet (121 ng/liter/min). In no case could normal PRA level be obtained. A II infusion induced an increase in urinary sodium excretion only in the two patients with renal sodium wastage (from 80–90 to 265–230 μEq/min in 30 min). Urinary sodium excretion decreased in the other patients from (37.5–213 to 4.30–46 μEq/min) and fractional sodium excretion was reduced in *patient V* (from 0.56% to 0.45% at 30 min and to 0.29% at 120 min). No signifi-

cant change with A II infusion was observed in *patient IV* when he was on a sodium-restricted diet (from 1 to 2.5 μEq/min in 30 min). Urinary potassium excretion was similar to sodium excretion. No change was observed in plasma potassium and sodium.

Speculation

Hypersecretion of renin is not autonomous in Bartter's syndrome. It is not explained by an insensitive feedback effect of A II on renin secretion. Hypokalemia contributes to this high level of PRA. Salt craving, which is found in 50% of the cases (28), is increased by A II. Nevertheless, the presence of renal sodium wastage cannot be explained only by the high A II levels which are constant in this syndrome. A deficient Na-K-ATPase activity is postulated in such cases.

The highest levels of PRA and A II are observed in Bartter's syndrome (1, 2). However, the mechanism of excessive secretion and their role in pathophysiology is not yet clearly understood. A II has been shown to stimulate aldosterone secretion and to suppress renin secretion in Bartter's syndrome (10, 13). Modlinger *et al.* (20) have observed an increase in renal sodium excretion under A II infusion in one patient.

Two types of Bartter's syndrome can be described in childhood according to the presence or the absence of renal sodium wastage (28). In order to elucidate the regulation of the renin-aldosterone axis and the role of A II on urinary sodium excretion in these two types of Bartter's syndrome, five patients were investigated: two had renal sodium wastage and three were without renal sodium loss. The effects of sodium restriction and of A II infusion on PRA, aldosterone secretion, and renal excretion of sodium and potassium were studied.

MATERIALS AND METHODS

CASE REPORTS

Patient I. BP, a boy born March 14, 1954, was admitted to Hôpital E. Herriot at the age of 5½ years because of polyuria, polydipsia, and growth retardation. He had a normal birth (birth weight 4,500 g) after a full term pregnancy. Physical examination was normal with normal weight (18,800 kg) but short stature (1 m; 2 SD). Blood pressure was 100/70 mm Hg.

On admission, serum potassium was 2.3 mEq/liter. Subsequent determinations revealed persistent hypokalemia (1.9–3.5 mEq/liter) with metabolic alkalosis. Serum sodium was 136 mEq/liter and urea nitrogen 30 mg/100 ml. Urine volume varied from 1,000 to 2,200 ml. Urinary excretion of potassium was found to be between 17 and 75 mEq/24 hr. Proteinuria was detected (2 g/24 hr) with a tubular electrophoretic pattern. Urine cultures were negative. Urine was negative for glucose and amino acid chromatography was normal. Creatinine clearance was 130 ml/min/1.73 m². Maximum urinary concentration after 12 hr of water restriction was 602 mOsm/kg H_2O. Impaired urinary acidification was observed. Bone marrow and slit lamp examination were normal. High basal PRA (1,142 ng/liter/min; normal for age 54 ± 10) and aldosterone secretion rate (427 μg/24 hr) were found. Renal biopsy showed enlargement of the juxtaglomerular apparatus with typical hypokalemic features. Exchangeable sodium was low: 38.24 mEq/kg body weight (normal for age 45–55 mEq/kg); exchangeable potassium was also low: 24.5 mEq/kg of lean mass (normal for age 40 mEq/kg).

The patient was treated with chloride sodium (6–20 g/24 hr) and chloride potassium (7–20 g/24 hr). Spironolactones (300 mg/24 h) were given from 8 10/12 to 18 years of age with a transient increase in serum potassium.

At the age of 10 years Cushing's syndrome was discovered; it was successfully treated with aminogluthetimide (750 mg–2.25 g/24 hr) for 8 years and the cortisol secretion rate dropped from 40 to 21 mg/m² 24 hr (normal values 11 ± 5 mg/m²/24 hr). Two episodes of rickets with hypophosphoremia (2.3–2.9 mg/100 ml) were treated with 30 mg vitamin D_2. The patient was 19½ years old when A II infusion was performed; spironolactone and aminogluthetimide were discontinued after 1½ years. A detailed description of this case has been reported (24).

Patient II. AT is a boy born November 25, 1959. He was admitted for the first time to Hôpital Debrousse for hypotrophy, polyuria, and polydipsia at the age of 13½ years.

Physical examination showed only low weight (27,400 kg; −2 SD) and short stature (134 cm; −3 SD) Blood pressure was 100/70 mm Hg.

On admission, serum potassium was 2.8 mEq/liter and subsequent hypokalemia was recorded (1.8–3.6 mEq/liter). It was associated with hyperkaluria (25–68 mEq/24 hr). Serum sodium was 135 mEq/liter, chloride 98 mEq/liter, carbon dioxide 24 mEq/liter. Urine volume was between 3.5 and 5 liters/day. Urine was negative for protein and glucose and amino acids chromatography was normal. Creatinine clearence was 81 ml/min/1.73 m². Maximum urinary osmolality after 12 hr of water restriction was 333 mOsm/kg H_2O. Urinary acidification was normal. Further investigations showed high PRA (186 ng/liter/min; normal for age 35 ± 12) and aldosterone secretion rate (151 μg/24 hr). Juxtaglomerular hyperplasia was observed on renal biopsy. Bone marrow and slit lamp examination were normal. Bone x-rays and intravenous pyelogram were normal. Treatment was carried out with potassium chloride (10 g/day) and spironolactones (200 mg/day) without any change in kalemia.

Patient III. JS was born May 13, 1969. She weighed 1,700 g at the 32nd week of an uneventful pregnancy. She was admitted to Hôpital Debrousse for the first time at the age of 3 5/12 years because of persistent vomiting. Physical examination showed only an emaciated girl with low weight (10,500 kg; −3 SD) and growth retardation (85 cm; −3 SD). Blood pressure was 85/60 mm Hg.

On admission, transient hypoglycemia (23 mg/100 ml) was observed, but all of the endocrinologic and metabolic investigations were normal. Hypokalemia (1.8–3.5 mEq/liter) was associated with hyperkaluria (15–32 mg/24 hr). Serum sodium was 140 mEq/liter, chloride 92 mEq/liter, carbon dioxide 22 mEq/liter, and urea nitrogen 33 mg/100 ml. Urine volume varied from 200 to 500 ml/day. Proteinuria (0.80 g/24 hr) showed a tubular electrophoretic pattern. Urines cultures were negative. No glycosuria was detected and amino acid chromatography was normal. Creatinine clearance was 118 ml/min/1.73 m². Maximum urinary concentration after 12 hr of water restriction was 1,500 mOsm/kg H_2O. No impaired urinary acidification was detected. Bone x-rays and intravenous pyelogram were normal. Bone marrow and slit lamp examination were normal. Further investigations showed high PRA (483 ng/liter/min; normal for age 111 ± 39); aldosterone secretion rate was at the lower limit of normal range (58.5 μg/24 hr). Renal biopsy revealed typical juxtaglomerular hyperplasia. Treatment was carried out with potassium gluconate (7 g/day) and triamterene (100 mg/day). However, no change in kalemia was observed.

Patient IV. HN was born May 19, 1960. Diabetes mellitus was discovered at the age of 10½ years and was satisfactorily treated with long acting insulin with doses between 26 and 42 U/day. Persistent hypokalemia (2.2–2.8 mEq/liter) was discovered at the age of 13 3/12 years by systematic investigations. His physical examination was normal (weight 35 kg, height 137 cm). Blood pressure was 90/50 mm Hg. Serum sodium was 142 mEq/liter, chloride 97 mEq/liter, carbon dioxide 28 mEq/liter, urea nitrogen 38 mg/100 ml, and glucose 76–118 mg/100 ml. Urinary protein (0.7 g/24 hr) showed typical tubular electrophoretic pattern. No amino acid abnormalities were detected. Urinary cultures were negative. Urinary glucose was found to be between 8.52 and 42 g/day. Hyperkaluria (35–58 mEq/24 hr) was found in spite of hypokalemia. Bone x-rays and intravenous pyelogram were normal. Further investigations showed high PRA (268 ng/liter/min; normal for age 35 ± 7) and high plasma aldosterone (288 pg/ml).

Table 1. *Effect of salt-restricted diet (Na <10 mEq/day) on urinary sodium, plasma renin activity (PRA), aldosterone secretion rate (ASR), and plasma aldosterone*

Patient and diet	K		Na		PRA, ng/liter/min		ASR, μg/24 hr[1]	Supine plasma aldosterone, pg/ml[2]
	Blood, mEq/liter	Urine, mEq/day	Blood, mEq/liter	Urine, mEq/day	Supine[3]	Erect[4]		
I (BP)								
Ad lib	2.3	(75)	135	(153)	1,142		427	
Na restricted	3.1	(62)	128	(90)			680	
II (AT)								
Ad lib	2.8	(27.7)	143	(67.7)	186.6		151	139
Na restricted	3.1	(49.6)	130	(18.7)	592		842	
III (JS)								
Ad lib	2.3	(55.5)	138	(17.4)	483	580	58.5	
Na restricted	2.6	(9.98)	131	(1.86)	953		151	
IV (HN)								
Ad lib	2.2	(58)	147	(126)	268			288
Na restricted	2.7	(37)	138	(6)	1,934			400
V (CG)								
Ad lib	2.2	(38.5)	140	(30.5)	952	2,032	59.3	330
Na restricted	2.7	(27)	140	(7.7)	1,201			500

[1] Normal value = 60–120 μg/24 hr.
[2] Normal value (in adults) = 15–40 pg/ml.
[3] Normal value (in adults) = 25 ± 3 ng/liter/min.
[4] Normal value (in adults) = 30 ± 3 ng/liter/min.

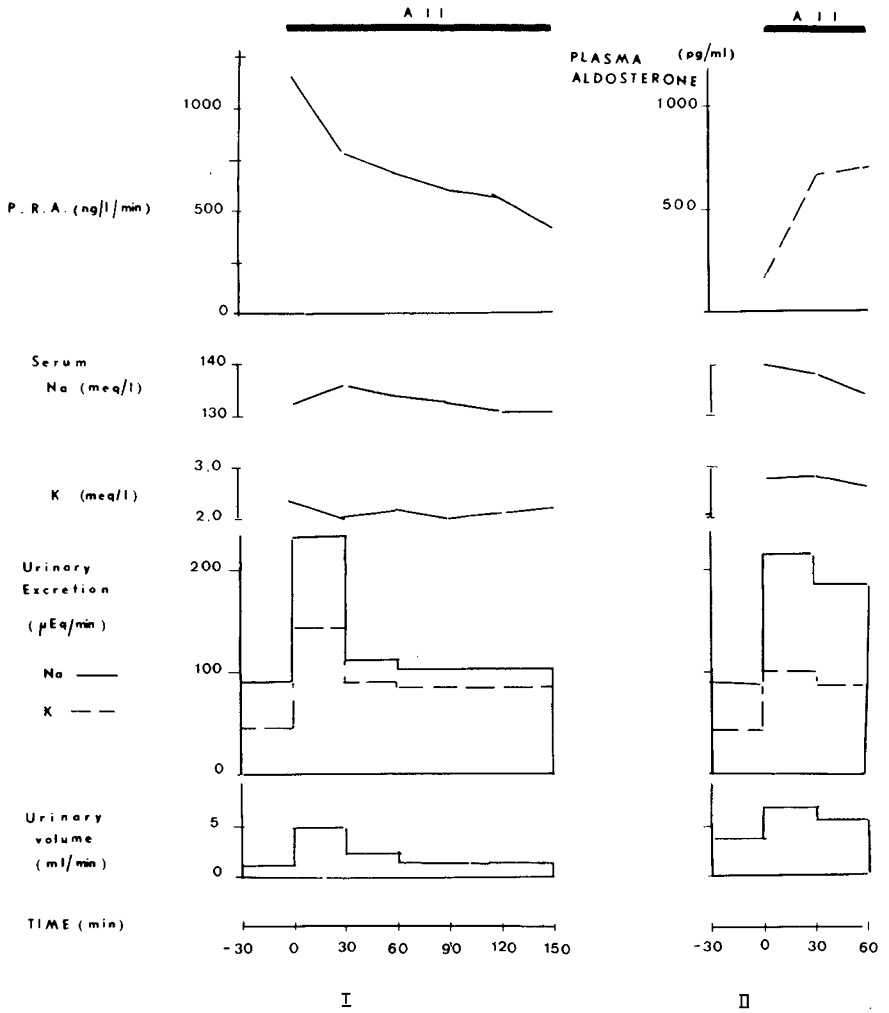

Fig. 1. Effect of angiotensin II (*A II*) infusion on plasma renin activity (*P.R.A.*) plasma aldosterone, serum and urinary sodium and potassium in the patients with renal salt loss.

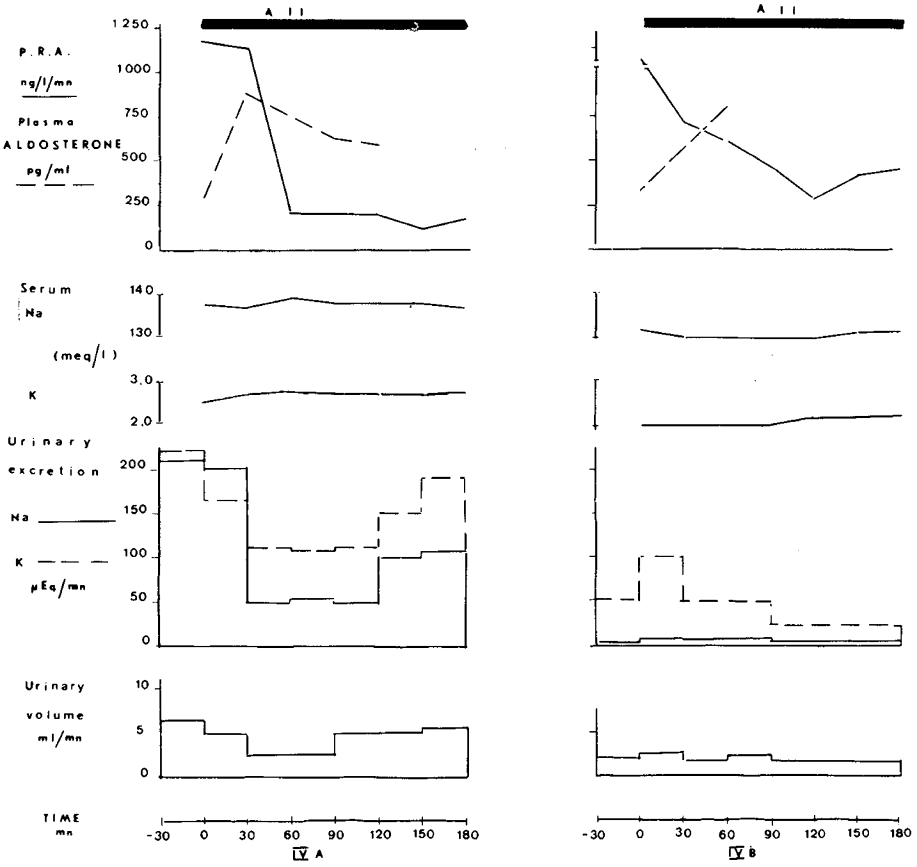

Fig. 2. Effect of angiotensin II (*A II*) infusion on plasma renin activity (*P.R.A.*) plasma aldosterone, serum and urinary sodium and potassium in one patient without renal salt loss. *IVA: patient IV* on a normal diet; *IVB: patient IV* on a salt-restricted diet (Na < 10 mEq/24 hr).

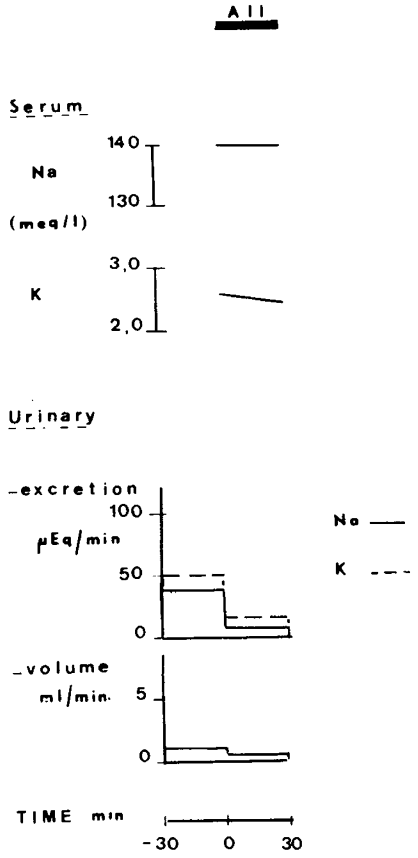

Fig. 3. Effect of angiotensin II (*A II*) infusion on plasma and urinary sodium in *patient III*.

Creatinine clearence was 132 ml/min/1.73 m^2. Bone marrow and slit lamp examination were normal. In addition to insulin, treatment included potassium gluconate (12 g/day), triamterene (300 mg/day), and NaCl (10 g/day). No change in serum potassium and PRA could be observed.

Patient V. CG was born October 22, 1968. She was first admitted to Hôpital E. Herriot at the age of 6 years because of vomiting and growth retardation. Physical examination showed only short stature (97 cm; −3.5 SD) with low weight (12 kg; −3 SD). Blood pressure was 90/50 mm Hg. Serum potassium was 1.6 mEq/liter on admission; subsequent hypokalemia (1.8–3.1 mEq/liter) and hyperkaluria (36–45 mEq/liter) were detected. Serum sodium was 140 mEq/liter, chloride 82 mEq/liter, carbon dioxide 20.5 mEq/liter, urea nitrogen, 27 mg/100 ml. Urine volume was 1,000 ml/24 hr. Urine cultures were negative and no urine glucose was detected; amino acid chromatography was normal.

Proteinuria (0.10 g/day) showed mixed glomerular and tubular pattern at immunoelectrophoresis. Creatinine clearence was 118 ml/min/1.73 m^2. Maximum urinary osmolality after 12 hr of water restriction was 768 mOsm/kg H_2O. Further investigations showed high PRA (952 ng/liter/min; normal for age 54 ± 10) and high plasma aldosterone level (330 pg/ml). Juxtaglomerular hyperplasia was observed on renal biopsy. Bone marrow and slit lamp examination were normal. Exchangeable sodium was 45 mEq/kg body weight (normal for age 45–55 mEq/kg body wt). Treatment was carried out with amiloride (5 mg/day). Serum potassium and PRA remained at abnormal levels.

MEASUREMENTS AND PROCEDURES

These were all carried out before any treatment was started or when the treatments were discontinued for at least 2 weeks. Informed consent of the parents was obtained in all cases. Aldosterone secretion rate was measured by gas chromatography

with a modified method of Flood *et al.* (11). Venous samples of PRA and plasma aldosterone assays were taken in the morning (8–9 AM), the patient resting recumbent in bed for at least a few hours. Blood was directly collected in tubes containing EDTA and kept on ice. After centrifugation at +4°, plasma was immediately separated and frozen at −20°. PRA (27) and plasma aldosterone (3) were determined by radioimmunoassay. Normal results of PRA for age have been reported previously (25). Sodium restriction was performed for at least 5 days with a controlled diet providing less than 10 mEq of sodium every day. Dietary intake of sodium was estimated by standardized tables (9). Serum and urinary electrolytes were determined by flame photometry. A II infusion was based on the procedure of Kaplan and Silah (17). The effect of a suprapressive rate of A II was tested on PRA and plasma aldosterone. At the same time, the effect of A II in 5% dextrose on serum and urinary sodium and potassium was compared with a previous infusion of only 5% dextrose. First, as in the procedure of Modlinger *et al.* (20), A II infusion was performed for 30 min (*patients II* and *III*). It was then performed for 180 min in the other patients.

Therefore, 5% dextrose in water was first infused at the rate of 0.5 ml/min for 60 min in all the patients but one (*patient II*). Then, hypertensin (Ciba) in 5% dextrose was infused at the same rate and at concentration of 80 ng/kg/min for 30–180 minutes. These infusions were all performed in early morning on recumbent patients. Blood and urinary samples were collected every 15 min in *patient II* and every 30 min in the other patients.

RESULTS

SODIUM RESTRICTION

Table 1 shows the effect of sodium restriction in the five patients. PRA and aldosterone secretion increased in all the patients. Renal sodium wastage in spite of increased aldosterone secretion was detected only in *patients I* and *II*.

ANGIOTENSIN II INFUSION (FIGS. 1–4)

No change of blood pressure was observed in any case. A II induced a sharp decrease in PRA in the patients who could be studied. When *patient IV* was on a sodium-restricted diet (Fig. 3), a similar decrease in PRA was observed but the minimal PRA was was still higher. In no case could a normal PRA be obtained. A II infusion always resulted in a marked increase in plasma aldosterone levels.

An immediate and dramatic increase in urinary sodium excretion was detected in the patients with renal sodium wastage (Fig. 1). This increase was particularly important during the first 30 min in *patient I*. In *patient II*, it occurred in spite of increased plasma aldosterone. The other patients showed no similar increase in urinary sodium excretion. Moreover, a reduction of fractional sodium excretion was observed in *patient V* (Fig. 4). No change of sodium excretion was obtained in *patient IV* when he was on a sodium-restricted diet (Fig. 2, *IVB*). Urinary potassium excretion

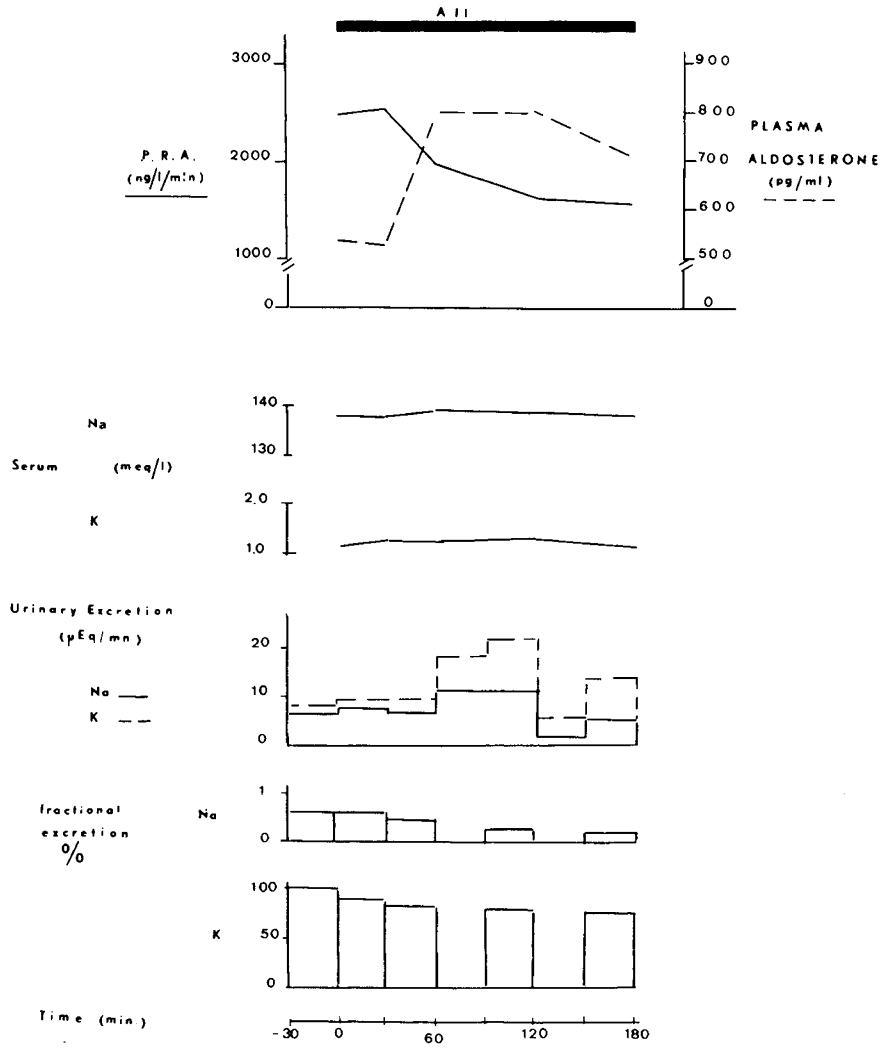

Fig. 4. Effect of angiotensin II (*A II*) infusion on plasma renin activity (*P.R.A.*) plasma aldosterone, blood and urinary sodium and potassium and on fractional excretion of sodium and potassium in *patient V*.

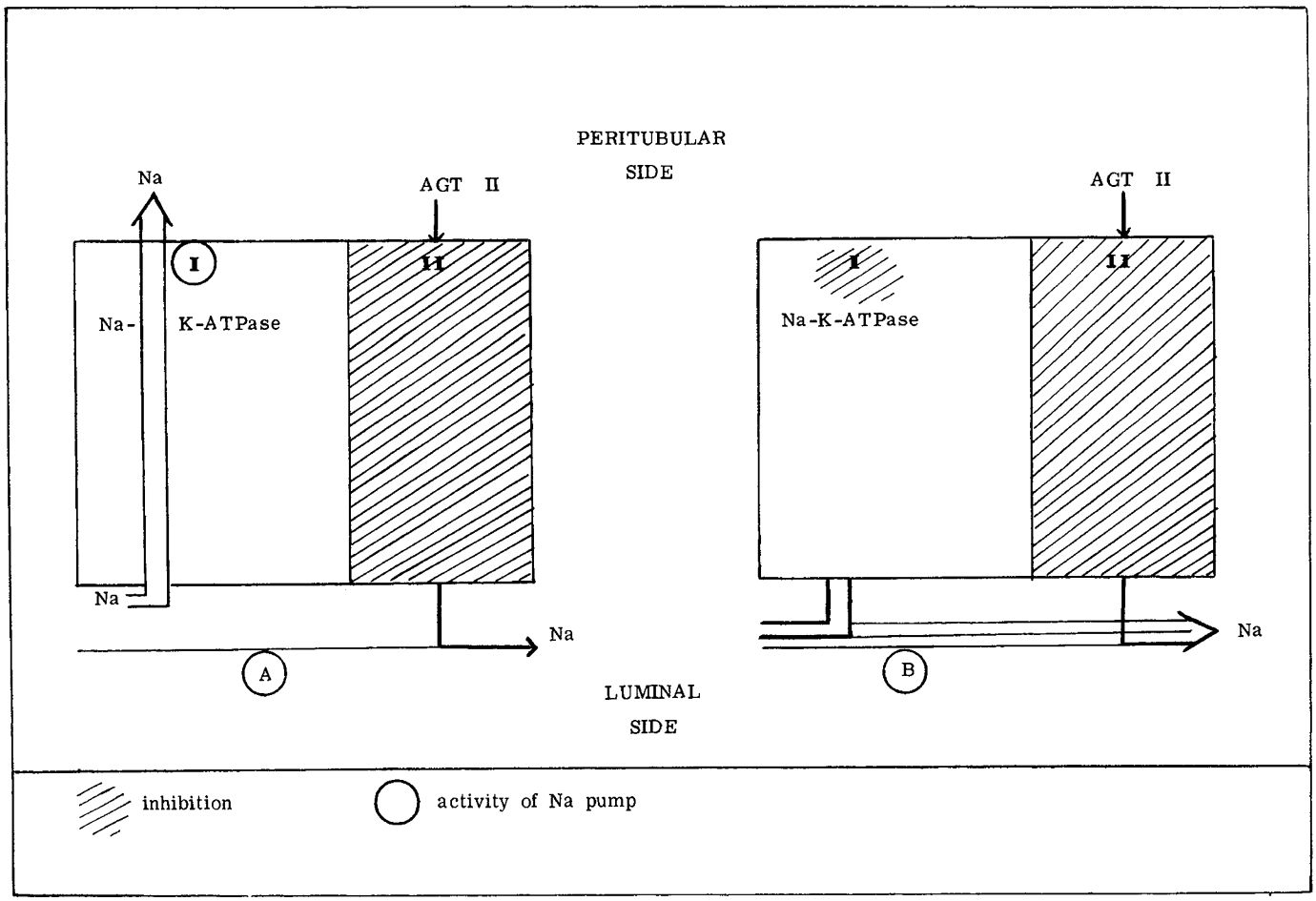

Fig. 5. Effect of angiotensin II (*AGT II*) on sodium reabsorption in the tubular cell. Angiotensin II decreases sodium pump II activity (and/or chloride-dependent reabsorption). *A:* normal Na-K-ATPase activity; *B:* decreased Na-K-ATPase activity.

was similar to the sodium excretion all patients. A dissociation was observed only when *patient IV* was on a sodium-restricted diet. The increase in urinary potassium occurred without any significant change in urinary sodium; at the same time, an increase in plasma aldosterone was observed.

Blood sodium and potassium remained unchanged during A II infusion.

DISCUSSION

The pathogenesis of renin hypersecretion in Bartter's syndrome is not known. The primary vascular insensitivity to A II proposed by Bartter (1, 2) is not yet accepted (7, 14, 29). Then Brackett *et al.* (5) suggested the existence of an autonomous secretion of renin. However, sodium restriction results in normal increase in PRA and aldosterone secretion. On the other hand, a sharp decrease of PRA and plasma aldosterone under sodium infusion has already been described in *patient I* (20). Therefore, there is a normal regulation of the renin-aldosterone axis by sodium restriction or infusion. It is known that A II has a suppressive effect on renin secretion (4). When A II was infused into our patients, this feedback effect was found. This result agrees with previous similar investigations (10, 13), but our results show that this feedback is found in patients with renal sodium wastage as well as in patients without sodium wastage. This decrease of PRA with A II infusion was observed even when *patient IV* was on a salt-restricted diet. Therefore, this study demonstrates that the secretion of renin is not autonomous in both types of Bartter's syndrome.

Despite the normal regulation of the renin-aldosterone axis, a normal PRA could not be obtained under A II infusion. The persistent high PRA value could not be explained by a disturbance of sodium balance in *patients IV* and *V* since exchangeable sodium was normal in *patient V*, since sodium restriction did not result in renal sodium wastage, and because A II infusion induced no renal sodium wastage. The only persistent abnormality which could be observed in our patients was hypokalemia, which is known to induce high PRA levels (6, 26). Therefore, we strongly support the view of Godard *et al.* (13) that potassium *per se* could play a role in the pathogenesis of renin hypersecretion independent of any change in sodium balance.

Infusions of high concentrations of A II are known to induce a natriuresis. Modlinger *et al.* (20) observed increased urinary sodium excretion when A II was infused for 30 min in one case of Bartter's syndrome with renal sodium loss. The result was confirmed only in our patients with sodium wastage. In this condition, increased urinary sodium occurred during the first 30 min. This effect was not observed in patients without sodium wastage; a marked reduction of fractional sodium excretion was observed in *patient V*.

Renal sodium loss was not explained by a defect of aldosterone secretion, since plasma aldosterone increased under A II infusion, in spite of hypokalemia. The increased urinary sodium excretion observed in spite of high plasma aldosterone in *patient II* could be possibly explained by the latent effect of aldosterone. Nevertheless, it is in keeping with sodium escape to aldosterone (24), which was observed when these patients were on a sodium-restricted diet. Therefore, renal sodium wastage in Bartter's syndrome cannot be explained by a hormonal imbalance and an intrarenal factor must be postulated.

The natriuretic effect of A II stems from an inhibition of sodium reabsorption in the ascending limb of the loop of Henle (16). According to the report of Munday *et al.* (21), A II inhibits the

glycoside-insensitive sodium pump (pump II) but not the enzyme Na-K-ATPase (19). Furthermore, chloride participates in sodium reabsorption (23) and A II can inhibit this chloride-dependent sodium reabsorption (22). In Bartter's syndrome, there is also a defect of sodium reabsorption in the ascending limb of the loop of Henle (8). A deficient activity of Na-K-ATPase was recently described (15), but the defect of sodium transport was not recognized in all patients (12). Thus, the natriuretic effect of A II in Bartter's syndrome may depend on Na-K-ATPase activity and could be explained as following (Fig. 5): when pump II is inhibited by A II, an increased compensatory activity of Na-K-ATPase would result, especially under aldosterone stimulation (18), and no renal sodium wastage would be observed. On the contrary, if the activity of Na-K-ATPase is low, pump I could not compensate the inhibition of pump II by A II and renal wastage would occur. This possibility is supported by the dissociation between sodium and potassium urinary excretion which is observed only when *patient IV* is on a sodium-restricted diet (Fig. 2). In this case, the increased urinary potassium excretion could be explained by the reactional aldosterone effect. However, our hypothesis needs further study, especially in keeping with the role of chloride in active transport of sodium (22, 23) and the effect of prostaglandins.

These results show that: (*1*) A II stimulates aldosterone secretion in these patients in spite of hypokalemia; (*2*) the feedback effect of A II on PRA exists even in patients with renal sodium wastage or when a patient is on a salt-restricted diet; (*3*) no normalization of PRA levels is observed and it is in keeping with the persistent hypokalemia; (*4*) the natriuretic effect of A II is found only in patients who show an escape to aldosterone during salt-restricted diet.

SUMMARY

Renin secretion is not autonomous in Bartter's syndrome. PRA levels were reduced by A II infusions but did not return to normal. This could be explained by the persistent hypokalemia. The natriuretic effect of A II was only observed in the salt-craving patients. Therefore, the presence of renal sodium wastage depends on an intrarenal factor.

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31. Requests for reprints should be addressed to: L. Sann, M.D., Service de Néonatalogie, Hôpital Debrousse, 29, rue Soeur Bouvier, 69002 Lyon (France).
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