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Hypokalemia, in Bartter's Syndrome and Other Disorders, Produces Resistance to Vasopressors via Prostaglandin Overproduction (40234)

NEZAN RADFAR,[1] JOHN R. GILL, JR.,[2] FREDERIC C. BARTTER, EMMANUEL BRAVO,[3] ADDISON A. TAYLOR,[4] AND ROBERT E. BOWDEN[5]

Hypertension-Endocrine Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20014

Bartter's syndrome is characterized by hypokalemia, hyperreninemia, hyperaldosteronism, normal blood pressure, hyperplasia of the juxtaglomerular apparatus of the kidneys, and a blood pressure response to intravenous angiotensin II (A II) and norepinephrine (NE) which is subnormal (1, 2). In addition, increased synthesis of prostaglandins has been observed in patients with Bartter's syndrome (3–5), and, as treatment with prostaglandin synthetase inhibitors tends to correct many of the abnormalities of the syndrome, the hypothesis that prostaglandins are a proximal cause of the disorder has been proposed (3–6). Recent experience with long-term treatment of patients with Bartter's syndrome with prostaglandin synthetase inhibitors indicates that the inhibitors may correct overproduction of prostaglandins and renin without correction of the hypokalemia (7). Also in the dog, experimentally-induced hypokalemia was associated with an increase in the renal synthesis of prostaglandins E (PGE) and a decrease in the blood pressure response to A II; treatment with a prostaglandin synthetase inhibitor then restored A II sensitivity toward control without a change in serum potassium (8). These observations suggest that hypokalemia *per se* may stimulate the synthesis of prostaglandins and thereby decrease the vascular response to A II. This possibility was studied in patients with Bartter's syndrome and in patients with hypokalemia of other causes.

Patients and methods. Three girls (9, 14, 17 years old) and five women (34–46 years old) with histologic and clinical features of Bartter's syndrome were admitted to an air-conditioned ward for the following two protocols:

The first protocol was designed to evaluate the effects of expansion of extracellular fluid and of intravascular volume on A II responsiveness in Bartter's syndrome. In one study two patients were given sodium intakes of 300–400 mEq/day for 16–20 days and the blood pressure response to A II was determined at the beginning and the end of the study. In the second study, two patients were given constant sodium intakes of 69 (Patient 1) and 109 (Patient 2) mEq/day and, when they were in sodium balance, they were infused intravenously with salt-poor human serum albumin, 50 g/day and 100 g/day, respectively, for 4 days. Plasma volume measured by an isotope dilution method with radioiodinated serum albumin (^{131}I) and the blood response to A II was determined before and after infusion of albumin.

The second protocol was designed to evaluate the role of hypokalemia in A II responsiveness in Bartter's syndrome and in patients with psychogenic vomiting. Seven patients with Bartter's syndrome and four adult women with psychogenic vomiting were given constant diets containing 109 to 115 mEq/day of sodium and 36–61 mEq/day of potassium. In addition, the patients with Bartter's syndrome were given 202 mEq/day of potassium chloride. The patients with Bartter's syndrome were studied before and during treatment with indomethacin, 100–200 mg/day (except for the 9-year-old girl who received 75 mg/day) in divided doses for 8–9 days. The patients with psychogenic vomiting were studied before and after correction of hypokalemia.

The blood pressure response to A II was determined in the patients with Bartter's syndrome before and again during treatment

[1] Present address: Department of Pediatrics, Mercy Hospital of Pittsburgh, Pittsburgh, Pennsylvania 15219.

[2] Author to whom reprint rquests should be sent.

[3] Present address: Research Division, Cleveland Clinic, Cleveland, Ohio 44106.

[4] Present address: Department of Medicine, Baylor College of Medicine, Houston, Texas 77030.

[5] Present address: Division of Cardiology, Stanford University Medical Center, Palo Alto, California 94304.

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with indomethacin and in the other hypokalemic patients before and after correction of hypokalemia, according to the following protocol. Peripheral venous blood for measurement of sodium, potassium, chloride, carbon dioxide content, creatinine and "supine" plasma renin activity (PRA) was drawn before the test after the patient had been recumbent for 1 hr. In order to establish the pressor dose of angiotensin II, an intravenous infusion of 5% dextrose in water was begun. The rate of infusion was maintained at 1 ml/min with a constant-infusion pump. After the blood pressure had been stable for 3–5 determinations, angiotensin II was added. Pulse and blood pressure were taken every 1–2 min throughout the infusion period. Ten-minute infusions of angiotensin II, alternating with 10-min infusions of 5% dextrose in water, were given at successive dosages of 2.5, 5, 7.5, 10, 15, 20, 25, 40 and 50 ng/kg/min until an amount was reached that caused a sustained elevation of diastolic blood pressure by 20 mm Hg above the averaged control values. This amount is referred to as the "pressor dose of angiotensin II". The pressor dose of norepinephrine (NE) was determined in a similar fashion by giving successive dosages of 25, 50, 100, 150 and 200 ng/kg/min in two patients with psychogenic vomiting.

Informed consent for all studies was obtained from each patient, and in the case of children, from their parents as well.

Aliquots of serum were analyzed for sodium, potassium, chloride, carbon dioxide content and creatinine by methods previously described (9). PRA, urinary aldosterone and urinary prostaglandin E-like material (iPGE) was measured by radioimmunoassay (4). Significance was determined by Student's t test and only those values for P of less than 0.05 were considered significant.

Results. A cumulative positive sodium balance of approximately 169 and 135 mEq in two patients with Bartter's syndrome had essentially no effect on PRA or the pressor dose of A II (Fig. 1). Expansion of intravascular volume with albumin which increased plasma volume from 44 to 59 ml/kg in patient 1 and from 42 to 60 ml/kg in patient 2 was associated with a trivial decrease in PRA and no change in the pressor dose of A II (Fig. 2).

The results of treatment of patients with Bartter's syndrome with indomethacin are shown in Table I. All patients were hypokalemic during the control period with a mean serum potassium of 2.3 ± 0.1 (SE) mEq/L which increased significantly to 3.1 ± 0.2 mEq/L with indomethacin. Supine PRA was high in all patients with a mean value of 29.4 ± 10 ng/ml/hr which decreased significantly to 3.1 ± 1.1 ng/ml/hr with treatment. Control urinary iPGE was elevated at 3.1 ± 0.6 μg/day (normal 0.696 ± 0.24 μg/day) and decreased significantly to 1.5 ± 0.4 μg/day with indomethacin treatment. Mean basal blood pressure was normal and did not change with indomethacin. The mean pressor dose of A II was elevated at 26 ± 5 ng/kg/min and decreased significantly to a normal value of 10 ± 2 ng/kg/min.

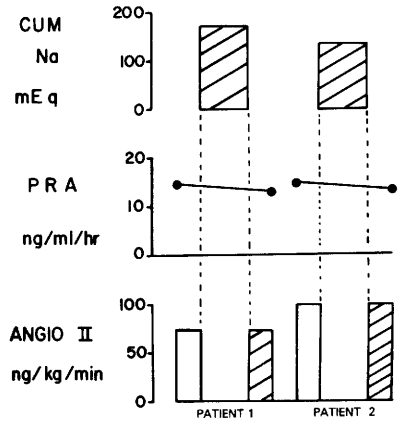

FIG. 1. Effects of expansion of extracellular fluid volume with sodium chloride (NaCl) on cumulative sodium balance (Cum Na), plasma renin activity (PRA) and the pressor dose of angiotensin II (Angio II) in two patients with Bartter's syndrome. The open bars indicate the control responses to Angio II, the hatched bars the responses after expansion of extracellular fluid volume.

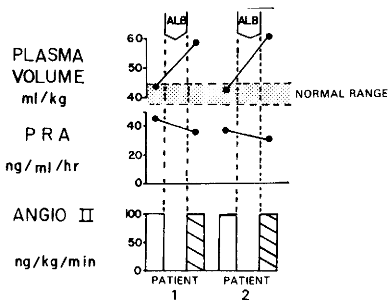

FIG. 2. Effects of expansion of intravascular volume with albumin (Alb) on plasma volume, plasma renin activity (PRA) and the pressor dose of angiotensin II (Angio II) in two patients with Bartter's syndrome. The open bars indicate the control responses to Angio II, the hatched bars the responses after expansion of intravascular volume.

TABLE I.[a]

Regimen	Serum K+ (mEq/l)	Supine PRA (ng/ml/h)	Urinary iPGE (μg/d)	Basal BP systolic/diastolic (mmHg)	Pressor Dose of A II (ng/kg/min)
Control					
Mean ± SE	2.3 ± 0.1	29.4 ± 10	3.1 ± 0.6	104/69 ± 6/3	26 ± 5
INDO					
Mean ± SE	3.1 ± 0.2	3.1 ± 1.1	1.5 ± 0.4	103/67 ± 6/5	10 ± 2
P	<0.01	<0.05	<0.05	NS	<0.02

[a] Serum potassium (K+), supine plasma renin activity (PRA), urinary immunoreactive prostaglandin E (iPGE), basal blood pressure (BP) and pressor dose of angiotensin II (A II) before and during treatment with indomethacin (INDO) in seven patients with Bartter's syndrome.

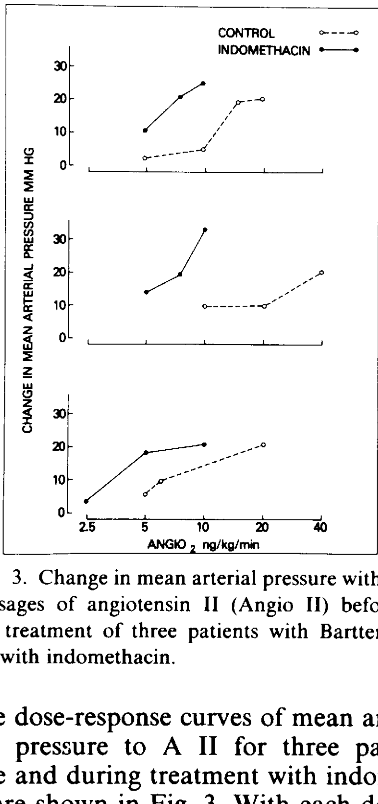

FIG. 3. Change in mean arterial pressure with different dosages of angiotensin II (Angio II) before and during treatment of three patients with Bartter's syndrome with indomethacin.

The dose-response curves of mean arterial blood pressure to A II for three patients before and during treatment with indomethacin are shown in Fig. 3. With each dose of A II there was a greater increase in mean arterial blood pressure during the period of treatment with indomethacin than during the control period, resulting in a shift of the dose-response curve to the left with indomethacin treatment.

Table II shows the findings before and after correction of hypokalemia in the four patients with psychogenic vomiting. Mean serum potassium of 2.3 ± 0.2 mEq/L increased significantly to 3.5 ± 0.2 mEq/L. Supine PRA was high in all patients with a mean value of 27.6 ± 9.8 ng/ml/hr which decreased significantly to 2.4 ± 0.4 ng/ml/hr after correction of hypokalemia. Urinary iPGE, measured in two of the four patients, was high at 1.78 and 2.03 μg/d. Mean basal blood pressure was normal before and after correction of hypokalemia. The mean pressor dose of A II, 102 ± 34 ng/kg/min decreased significantly to a mean value of 12 ± 2 ng/kg/min after correction of hypokalemia. Figure 4 shows the dose-response curves of mean arterial blood pressure to A II in two of the patients with hypokalemia secondary to vomiting before and after correction of hypokalemia. At every dosage of A II the increase in mean arterial blood pressure was greater after correction of hypokalemia than that measured while hypokalemia was present, resulting in a shift of the dose-response curves to the left. Figure 5 shows dose-response curves of mean arterial blood pressure to NE in two of the patients with hypokalemia secondary to vomiting before and after correction of hypokalemia. At every dosage of NE the increase in mean arterial blood pressure was greater after correction of hypokalemia than that measured while hypokalemia was present, resulting in a shift of the dose response curves to the left.

Discussion. In the original descriptions of Bartter's syndrome, the decreased sensitivity of blood pressure to A II observed in those patients was attributed to a defect in arterial smooth muscle and this was postulated to be a proximal cause of the syndrome (1, 2). Since these publications, hyporesponsiveness to A II has been observed in hypokalemic patients with other disorders (10). The report that experimentally-induced hypokalemia in the dog is associated with a decreased blood pressure response to A II (8) together with the present findings in patients with psychogenic vomiting provide further evidence that hypokalemia *per se* can decrease the pressor

TABLE II.[a]

Regimen	Serum K+ (mEq/l)	Supine PRA (ng/ml/h)	Basal BP systolic/diastolic (mmHg)	Pressor Dose of AII (ng/kg/min)
Hypokalemia				
Mean ± SE	2.3 ± 0.2	27.6 ± 9.8	92/59 ± 3/3	102 ± 34
Normokalemia				
Mean ± SE	3.5 ± 0.2	2.4 ± 0.4	87/54 ± 4/6	12 ± 2
P	<0.01	<0.05	NS	<0.05

[a] Serum potassium (K+), supine plasma renin activity (PRA), basal blood pressure (BP) and pressor dose of angiotensin II (AII) before and after correction of hypokalemia in four patients with psychogenic vomiting.

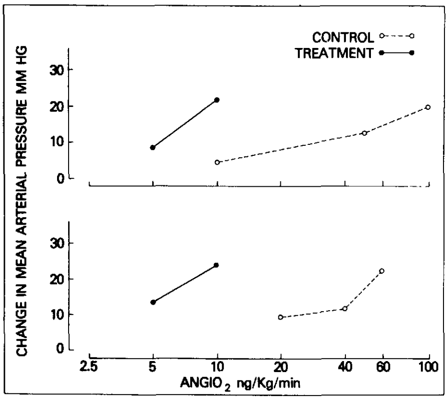

FIG. 4. Change in mean arterial pressure with different dosages of angiotensin II (Angio II) before and after correction of hypokalemia in two patients with psychogenic vomiting.

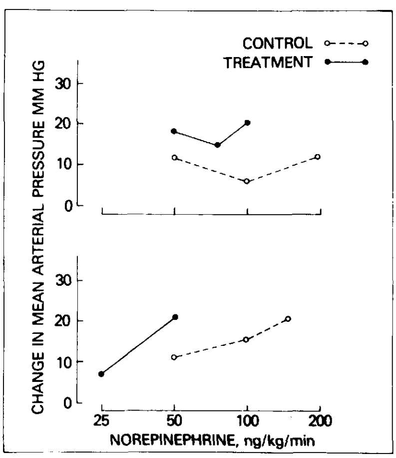

FIG. 5. Change in mean arterial pressure with different dosages of norepinephrine before and after correction of hypokalemia in two patients with psychogenic vomiting.

responsiveness to A II and probably to NE as well. The further finding that hypokalemia with potassium depletion stimulates prostaglandin E synthesis in the dog (8) and in patients with psychogenic vomiting suggests that hypokalemia may be the basis for increased production of prostaglandins found in Bartter's syndrome (3–5).

The increased release of renin which hypokalemia produces (11) may also be mediated by prostaglandins, as considerable evidence indicates that prostaglandins function as an intermediary in renin release. In the dog, infusion of PGE_1 into the aorta (12) and of PGE_1 or PGE_2 into a renal artery (13) increased PRA and ipsilateral renin secretion, respectively. In the rabbit, infusion of arachidonic acid, the natural precursor of PGE_2, into the aorta increased PRA (14). Stimulation of renin release from renal cortical slices *in vitro* by prostaglandin G_2 has also been reported (15). Conversely, a decrease in PRA in association with an inhibition of prostaglandin synthesis has been observed in normal man (16, 17) in Bartter's syndrome (3–6), and in normal (13) and hypokalemic dogs (8).

Not only does inhibition of prostaglandin synthesis decrease PRA, but it also restores vascular sensitivity to A II towards normal in sodium-depleted normal human subjects (17), in hypokalemic dogs (8) and in Bartter's syndrome as reported by others (3, 6) and confirmed by this study (Table I). These findings support the view that an increased synthesis of prostaglandins in Bartter's syndrome and in the patients with psychogenic vomiting may be the basis for their hyposensitivity to A II.

Prostaglandins could decrease the pressor response to A II by increasing PRA with a consequent increase in plasma A II concentration, through their vasodilator effects on blood vessels, or both. (Whereas direct effects of hypokalemia on arterial smooth muscle contractility cannot be excluded, an increase in pressor responsiveness to A II can occur in response to treatment with indomethacin without a change in serum potassium (8), or with only partial correction of hypokalemia as in this study.)

An inverse relationship between circulating plasma A II concentration and the pressor response to infused A II has been observed and attributed by some to a decrease in available A II receptor sites because of prior occupancy of these sites by endogenous A II (18). Others, however, have attributed this inverse relationship to an absolute decrease in the number of receptor sites as a result of an increase in concentration of endogenous A II (19), a relationship observed in the case of other peptide hormones (20).

Apart from its effects on receptor function, circulating A II may also stimulate the synthesis of prostaglandins in vascular tissue (21, 22), and prostaglandins can in themselves decrease the contractile response to A II (23). Recent studies indicate that the vasodilator bradykinin which can also stimulate the synthesis of prostaglandins (24), is increased in the plasma of patients with Bartter's syndrome (25). Thus, increased formation of prostaglandins within blood vessels stimulated by hyperreninemia (through A II) and by bradykinin may contribute to a decrease in pressor responsiveness to A II. Indeed, the observation that pressor responsiveness to NE is also decreased in patients with psychogenic vomiting (Fig. 5) as well as in patients with Bartter's syndrome (2) suggests that prostaglandins may be a more important mechanism for the vascular hyposensitivity than either prior occupancy of receptors by A II or downregulation of A II receptors, unless, of course, the receptors for NE are the same as those for A II.

Previous studies by others have led them to postulate that a renal salt-losing defect was responsible for the pathogenesis of Bartter's syndrome (26, 27). The failure of expansion of extracellular fluid volume (Fig. 1) or intravascular volume (Fig. 2) to affect plasma renin activity or blood pressure response to AII suggests that this is not the case. These results also provide additional evidence that the retention of sodium chloride and water which occurs when patients with Bartter's syndrome are treated with inhibitors of prostaglandin synthesis (3–6) contributes minimally, if at all, to the associated decrease in PRA.

Recent studies indicate that patients with Bartter's syndrome have a prostaglandin-independent defect in chloride reabsorption in the thick ascending limb of Henle's loop (28). Such a defect could explain the renal loss of potassium and the hypokalemia which occur in association with a normal ability of the kidneys to conserve sodium. The data reported and reviewed in this paper support the hypothesis that hypokalemia, by the increased synthesis of prostaglandins, can account for the hyperreninemia and the hyposensitivity of blood pressure to A II in Bartter's syndrome. The observation that prolonged treatment with inhibitors of prostaglandin synthesis corrects the hyperreninemia but not the hypokalemia (7) is consistent with this hypothesis.

Summary. The role of hypokalemia and increased synthesis of prostaglandins in the decreased response of blood pressure to intravenous angiotensin II was studied in patients with Bartter's syndrome and in patients with psychogenic vomiting. In patients with Bartter's syndrome with high urinary prostaglandin E, treatment with an inhibitor of prostaglandin synthesis corrected the hyperreninemia and restored the pressor response to angiotensin II to normal but only partially corrected the hypokalemia. In patients with psychogenic vomiting with high urinary prostaglandin E, correction of the hypokalemia corrected the hyperreninemia and restored the pressor response to angiotensin II and to norepinephrine to normal. The findings suggest that hypokalemia, by stimulation of the synthesis of prostaglandin E in the kidney, produces hyperreninemia. An increase in synthesis of prostaglandin E in vascular tissue, stimulated by hypokalemia *per se* or by angiotensin II (produced by the hyperreninemia) or by both, increases the vascular resistance to angiotensin II and to norepinephrine.

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