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Ammonium chloride metabolic acidosis and the activity of renin-angiotensin-aldosterone system in children

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Abstract. The present study was undertaken to assess the effects of acute metabolic acidosis on the activity of the renin-angiotensin-aldosterone system in 12 children with a mean age of 8.9 years who underwent NH_4Cl loading test. Ammonium chloride was given in a dose of 0.15 g/kg per day for 3 consecutive days to evaluate renal acidification. Prior to and following NH_4Cl administration blood acid-base parameters, plasma and urine electrolytes, creatinine and aldosterone concentrations as well as plasma renin activity (PRA), urine flow rate and net H^+ excretion were measured. Ammonium chloride administration significantly depressed blood pH ($P<0.05$), bicarbonate ($P<0.01$) and base excess ($P<0.01$) and resulted in a slight, but significant elevation of plasma potassium concentration ($P<0.05$). Furthermore, NH_4Cl ingestion induced a marked increase in urine flow rate ($P<0.01$) and urinary sodium, potassium and chloride excretion ($P<0.01$). In response to NH_4Cl metabolic acidosis, PRA doubled (4.72 ± 1.18 vs 8.13 ± 1.02 ng/ml per hour, $P \leq 0.05$) and there was a nearly fourfold increase in plasma aldosterone level (0.49 ± 0.12 vs 1.52 ± 0.24 ng/ml, $P<0.01$) and in urinary aldosterone excretion (19.2 ± 4.3 vs 71.8 ± 13.8 µg/day, $P<0.01$). The elevated aldosterone production observed in this study is assumed to be mediated by the combined effect of sodium and water diuresis-related increased PRA, hyperkalaemia and the direct stimulation of adrenal steroidogenesis by metabolic acidosis.

Introduction

It has been claimed that angiotensin II, extracellular sodium and potassium, as well as adrenotropic hormone are the major physiological regulators of aldosteroe production [18]. However, there have been reports indicating that disturbances in acid-base balance may also be involved in the control of activity of the renin-angiotensinaldosterone system [11, 15, 17, 21]. Metabolic acidosis has been shown either to stimulate [12, 14], to inhibit [11], or to cause no change [15–17] in renin release. Furthermore, basal and angiotensin II- or potassium-stimulated aldosterone secretion has been found to be enhanced by metabolic acidosis in glomerulosa cell preparations [5, 9], in isolated perfused adrenals [19], in conscious animals [2, 3, 16] and in healthy adult subjects [15, 17, 21]. To our knowledge, however, no data are available on the acidosis-related changes in the function of renin-angiotensinaldosterone system in the paediatric age group. The present study was undertaken to assess the effects of acute metabolic acidosis on plasma renin activity (PRA), plasma aldosterone concentration and urinary aldosterone excretion in children subjected to an NH_4Cl loading test.

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Abbreviations: GFR = glomerular filtration rate; PRA = plasma renin activity

Patients and methods

Twelve children (2 boys, 10 girls), with a median age of 12 years (range 4–16 years) were selected for the study. They were admitted for evaluation of urinary tract infection (8 patients) and/or nephrolithiasis (9 patients). Routine clincial and laboratory examinations did not reveal hypertension, impaired renal function, disturbances of fluid and electrolyte homeostasis and acid-base balance.

During the study the patients did not receive drug therapy and they were kept on standardized diet providing 1–2 mEq/kg per day sodium intake and about 0.5 mEq/kg per day potassium intake, respectively, as estimated by the daily electrolyte excretion in the urine. To assess their capacity to excrete hydrogen ion, oral NH_4Cl was given at a dose of 0.15 g/kg per day for 3 consecutive days. Prior to and following NH_4Cl administration, blood was taken at 0800 hours after an overnight fast and bed rest for measurements of acid-base parameters [1], plasma electrolytes, creatinine, aldosterone and renin activity. Simultaneously 24-h urine collections were obtained to determine urine flow rate, urinary excretion of net acids, electrolytes, creatinine and aldosterone. Creatinine clearance was used as an index of glomerular filtration rate (GFR).

Urine was collected in fractions, the specimens were refrigerated, pooled and stored at −20°C until analysed. Plasma renin activity was measured by radioimmunoassay of generated angiotensin I, according to the method of Haber et al. [8]. Plasma and uri-

Table 1. Blood acid-base parameters, plasma electrolyte concentrations, and urinary hydrogen ion and electrolyte excretion in children subjected to NH_4Cl loading test (mean ± SE)

	Blood						Urine					
	pH	tCO_2	BE	Na^+	K^+	Cl^-	GFR	Flow rate	Na^+	K^+	Cl^-	H^+
		(mEq/l)		(mEq/l)			(ml/min/1.73 m^2)		(mEq/kg/day)			
Before NH_4Cl	7.41 ± 0.02	26.16 ± 1.20	−0.14 ± 0.81	137.5 ± 1.4	4.14 ± 0.22	99.1 ± 0.9	85.7 ± 8.9	2.16 ± 0.28	1.0 ± 0.2	0.4 ± 0.1	1.7 ± 0.2	1.2 ± 0.2
After NH_4Cl	7.31 ± 0.03*	19.59 ± 1.02**	−6.82 ± 1.11**	140.4 ± 0.9	4.48 ± 0.25*	101.6 ± 1.1	99.3 ± 12.0**	2.67 ± 0.37**	2.7 ± 0.6***	1.2 ± 0.2***	4.8 ± 0.6**	3.9 ± 0.5***

* $P<0.05$; ** $P<0.01$; *** $P<0.0005$

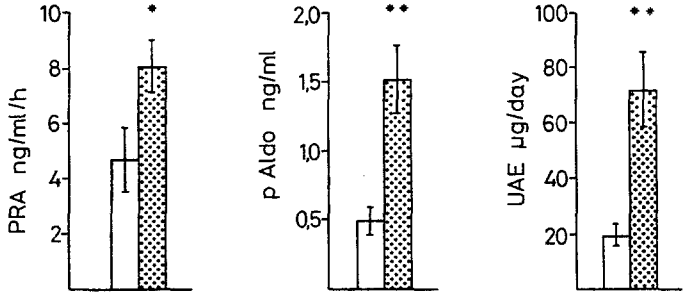

Fig. 1. Plasma renin activity (PRA), plasma aldosterone concentration (pAldo) and urinary aldosterone excretion (UAE) in children subjected to NH_4Cl loading (mean ± SE). □ before NH_4Cl; □ after NH_4Cl

nary aldosterone concentrations were also determined by radioimmunoassay as described by Vetter et al. [23] using commercial kits.

The results are presented as means ± SE and were evaluated by means of Student's paired *t*-test.

The study was approved by the Ethical Committee of the University of Pécs. Parental informed consent was obtained for the study.

Results

Table 1 shows that NH_4Cl administration induced moderately severe metabolic acidosis, as indicated by the significantly depressed blood pH, total CO_2 content and base excess. Plasma sodium and chloride concentrations remained within the normal range with a slight, but significant rise in plasma potassium levels. Endogenous creatinine clearance, urine flow rate, and urinary excretion of sodium, potassium and chloride increased significantly after NH_4Cl ingestion.

In response to NH_4Cl-induced metabolic acidosis, PRA doubled from 4.72 ± 1.18 to 8.13 ± 1.02 ng/ml/h ($P<0.05$) and there was a nearly four-fold increase in plasma aldosterone concentration from 0.49 ± 0.12 to 1.52 ± 0.25 ng/ml ($P<0.01$) and in urinary aldosterone excretion from 19.26 ± 4.38 to 71.84 ± 13.82 µg/day ($P<0.01$) as compared with the baseline values (Fig. 1).

Discussion

The present results provide evidence that NH_4Cl induced metabolic acidosis, even of moderate degree and short duration, resulted in a significant increase in creatinine clearance, renal electrolyte and water excretion, and activated the renin-angiotensin-aldosterone system in paediatric patients.

Experimental and clinical studies have demonstrated that the increased renal electrolyte and water excretion following NH_4Cl administration is associated with either unchanged or reduced GFR: it has been thought, therefore, to be due to their impaired tubular reabsorption [4, 13, 20]. Our data, showing significantly increased GFR in NH_4Cl acidosis are, however, in contrast to these observations and suggest that the acidosis-induced increase in urine flow rate and urinary electrolyte excretion may be the result of the combined effects of increased GFR and decreased tubular reabsorption. The reason for the elevated GFR is not apparent. This increase in GFR could possibly be induced by prostaglandin E_2, the production of which has been shown to be stimulated by metabolic acidosis [10, 22]. Alternatively the increase in GFR observed after NH_4Cl acidosis could be related to the activation of the renin-angiotensin system. Elevated levels of angiotensin II could indeed favour the vasoconstriction of the efferent arterioles, thereby increasing the transglomerular pressure gradient and GFR.

The influence of NH_4Cl metabolic acidosis on renin release is not clearly established. In a recent study NH_4Cl administration was demonstrated to be associated with suppression of PRA [11] while others have described that it remained unchanged or increased slightly [15–17].

The significant increase of PRA observed in our present study was possibly caused by the acidosis-induced sodium and volume depletion which may have overcome the inhibitory effect of NH_4Cl.

In agreement with previous reports we found significantly increased aldosterone production as indicated by the three- to four-fold increase in plasma concentration and urinary excretion of aldosterone. The stimulation of aldosterone production seen after acid loading appears to be mediated by the changes in intracellular hydrogen ion concentration. In support of this a marked difference has been noted in aldosterone biosynthesis by the glomerulosa cells between acidosis induced by low bicarbonate or elevated pCO_2 due to the more rapid cellular acidification in response to increased extracellular pCO_2 [19]. Moreover, amiloride and its analogues, the potent inhibitors of Na^+/H^+ antiporter system, have been demonstrated to suppress angiotensin II-induced alkaliniza-

tion and angiotensin II-stimulated aldosterone synthesis suggesting that the regulation of intracellular pH by Na^+/H^+ exchanger might be involved in the control of adrenal steroidogenesis [9].

In addition to the direct influence of metabolic acidosis to increase basal and stimulated aldosterone production, it should also be considered that moderate metabolic acidosis has been shown to enhance renal prostaglandin synthesis [10, 22], which may further contribute to the increased renin release [7] and aldosterone secretion [6] caused by NH_4Cl acidosis. Furthermore, the accentuated aldosterone response to acidosis may be regarded as a non-specific stress phenomenon implying an adrenocorticotropic hormone-mediated adrenocortical response [24].

Metabolic acidosis, as present in paediatric patients subjected to NH_4Cl loading, resulted in a significant elevation of the activity of the renin-angiotensin-aldosterone system. The increased aldosterone production observed in this study is assumed to be mediated by the combined effects of several factors including sodium and water diuresis-related increase in PRA, hyperkalaemia, and the direct stimulation of adrenal steroidogenesis by metabolic acidosis.

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