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Dietary sodium chloride intake independently predicts the degree of hyperchloremic metabolic acidosis in healthy humans consuming a net acid-producing diet

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Frassetto LA, Morris RC, Jr, Sebastian A. Dietary sodium chloride intake independently predicts the degree of hyperchloremic metabolic acidosis in healthy humans consuming a net acid-producing diet. *Am J Physiol Renal Physiol* 293: F521–F525, 2007. First published May 23, 2007; doi:10.1152/ajprenal.00048.2007.—We previously demonstrated that typical American net acid-producing diets predict a low-grade metabolic acidosis of severity proportional to the diet net acid load as indexed by the steady-state renal net acid excretion rate (NAE). We now investigate whether a sodium (Na) chloride (Cl) containing diet likewise associates with a low-grade metabolic acidosis of severity proportional to the sodium chloride content of the diet as indexed by the steady-state Na and Cl excretion rates. In the steady-state preintervention periods of our previously reported studies comprising 77 healthy subjects, we averaged in each subject three to six values of blood hydrogen ion concentration ([H]b), plasma bicarbonate concentration ($[HCO_3^-]p$), the partial pressure of carbon dioxide (P_{CO_2}), the urinary excretion rates of Na, Cl, NAE, and renal function as measured by creatinine clearance (CrCl), and performed multivariate analyses. Dietary Cl strongly correlated positively with dietary Na ($P < 0.001$) and was an independent negative predictor of $[HCO_3^-]p$ after adjustment for diet net acid load, P_{CO_2} and CrCl, and positive and negative predictors, respectively, of [H]b and $[HCO_3^-]p$ after adjustment for diet acid load and P_{CO_2}. These data provide the first evidence that, in healthy humans, the diet loads of NaCl and net acid independently predict systemic acid-base status, with increasing degrees of low-grade hyperchloremic metabolic acidosis as the loads increase. Assuming a causal relationship, over their respective ranges of variation, NaCl has ~50–100% of the acidosis-producing effect of the diet net acid load.

salt; acid-base; pathophysiology

THE SET-POINT FOR HYDROGEN ION regulation is dependent on three known factors: the partial pressure of carbon dioxide (P_{CO_2}) (15), the diet net acid load (8, 13, 16), and the age-related decline in renal function (8, 9). However, the body imperfectly responds homeostatically to perturbations of systemic acid-base equilibrium caused by variations in those factors. In fact, several studies have demonstrated that typical Western diets are net acid-producing and induce a low-grade metabolic acidosis of severity proportional to the diet net acid load as indexed by the steady-state renal net acid excretion rate (NAE) (8, 13, 16).

Several other factors have been implicated in the induction of a metabolic acidosis. Intravenous infusions of sodium chloride (NaCl) have been shown to induce a metabolic acidosis (19). Cogan et al. (5) demonstrated that the addition of oral NaCl for 7 days to a net base-producing diet resulted in an increase in the plasma chloride to bicarbonate (Cl-to-HCO_3^-) ratio and an associated increase in blood hydrogen ion concentration ([H]b; i.e., decreased pH). In the steady-state, NAE excretion [an index of net endogenous acid production (NEAP)] was virtually identical to the period in which no oral NaCl had been given, indicating that NaCl-loading reduced the set-point at which plasma bicarbonate ($[HCO_3^-]p$) was being regulated without change in NEAP. However, the sample size was small ($n = 5$).

We now investigate in a larger cohort whether a NaCl-containing diet likewise induces a low-grade metabolic acidosis of severity proportional to the NaCl content of the diet as indexed by the steady-state Na and Cl excretion rates.

METHODS

Data from 111 healthy volunteer subjects, who had previously been admitted to the University of California San Francisco (UCSF) General Clinical Research Center for a variety of different inpatient metabolic studies, were compiled. The criteria for "healthy" were based on a thorough history and physical examination, and absence of abnormalities on routine hospital admission laboratory data. We recruited the patients by advertisements (newspapers, posters in community centers), with wording approved by the Institutional Review Board. Recruitments were for a series of different metabolic intervention studies, most of which we reported on previously (1, 3, 5, 8, 10, 12, 13, 20). All studies were approved by the UCSF Institutional Review Board, and all subjects gave signed informed consent.

The participants ingested a constant nutritionally adequate diet similar to their usual diet before admission to the study. Each subject ingested one of 12 diets that yielded renal net acid excretion rates of 56 ± 39 meq/day, a wide variation within the normal range (see below). Although the 12 diets differed in composition, the recipe for each diet was identical for all subjects eating the same diet, both with respect to the specific food items (including beverages and free water) making up the diet and the quantity of each item fed to each subject per day per kilogram body weight. Before the collection of specimens was initiated for measurements of plasma and urine acid-base and electrolyte composition, the subjects ingested the diets for a period necessary for plasma and urine acid-base and electrolyte composition to reach a steady state (see, e.g., Refs. 8, 10, and 13 for how that was done). During the steady-state period, minimally three days, means of at least three blood specimens and three urine specimens were obtained from each subject.

The original purpose of the study for each of the 12 separate diet groups was not the same. The differences in study purpose are reflected in experimental maneuvers (not described) carried out subsequent to the above-described steady-state period utilized for the

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Table 1. *Patient and laboratory parameters*

Factor	Median (Range)
Sex (female:male)	39:38
Age, yr	60 (22–82)
Height, cm	167 (153–198)
Weight, kg	67 (46–116)
Test	**Values**
Arterialized blood	
pH	7.40 (0.02)
P_{CO_2}, mmHg	40.2±(2.9)
HCO_3, mmol/l	24.9±(2.1)
Urine	
Na, meq/day	102 (47)
K, meq/day	60 (22)
Cl, meq/day	100 (48)
NAE, meq/day	56 (39)
CrCl, ml/min	97 (25)

Values are expressed as means (SD).

present analysis of the effect of age on plasma acid-base composition. The present study thus constitutes a retrospective cross-sectional analysis of control data obtained for different purposes. But, except for the variable of diet, the experimental conditions were identical among subjects before and during the steady-state period selected for the present analysis.

In the steady-state preintervention periods, sufficient data were available in 77 subjects for the analyses in this paper. Data included subject's age and daily weights, nutrient-controlled dietary intake, arterialized blood gases, venous plasma, and serum samples, and 24-h urine collections for net acid excretion, electrolyte and creatinine clearance (CrCl).

We averaged in each subject three to six steady-state preintervention values of [H]b, $[HCO_3^-]$p, P_{CO_2}, the urine excretion rates of Na (UNaV), Cl (UClV), NAE, and renal function as measured by CrCl.

We performed multivariate analyses using SigmaStat (San Rafael, CA). Data are reported as means (SD).

RESULTS

Mean and median demographic and laboratory data for the subjects at steady state are reported in Table 1.

Holding NAE constant, over a range of steady-state values of UClV from 2.5 to 228 meq/day, we found that [H]b correlated positively with UClV ($P = 0.037$), and [H]b increased 0.9 meq/l per 100 meq/day increase in UClV) (Fig. 1, *top left*). $[HCO_3^-]$p and plasma chloride [Cl]p correlated inversely ($P < 0.001$). $[HCO_3^-]$p correlated negatively with UClV ($P = 0.007$), so that $[HCO_3^-]$p decreased 1.2 meq/l per 100 meq/day increase in UClV) (Fig. 1, *bottom left*).

Holding UClV constant, over a range of NAE from −48 to +158 meq/day, we found that [H]b correlated positively, and $[HCO_3^-]$p negatively, with NAE (both $P < 0.001$), and $[HCO_3^-]$p again correlated inversely with [Cl]p ($P < 0.001$). [H]b increased 2.1 meq/l per 100 meq/day increase in NAE, and $[HCO_3^-]$p decreased 2.5 meq/l per 100 meq/day increase in NAE (Fig. 1, *right*). Blood pH ranged from 7.33 to 7.44.

Table 2 demonstrates the effects on [H]b and $[HCO_3^-]$p of both UClV and NAE after adjusting for P_{CO_2}, another known determinant of the set-points [H]b and $[HCO_3^-]$p. For $[HCO_3^-]$p, the impact of NAE decreased, so that the relative impact of UClV increased (Table 2). Using the standardized regression coefficients, β, the relative effects of NAE and UClV on $[HCO_3^-]$p, namely, β-NAE/β-UClV, decreased from 1.7 to 1.0 (Table 2). For [H]b, adjusting for P_{CO_2} only minimally changed the relative impact of NAE and UClV, β-NAE/β-UClV increased from 1.8 to 2.1 (Table 2).

Table 2 also demonstrates that UClV remained a negative predictor of $[HCO_3^-]$p after adjustment for all potential predictors, NAE, P_{CO_2} and CrCl, indicating that the acidosis-predictive effect of dietary NaCl loads manifests independently of all those predictors, and, in particular, does not require age-related renal functional impairment. In this study, age was highly correlated with CrCl, $r = 0.65$, $P < 0.0001$.

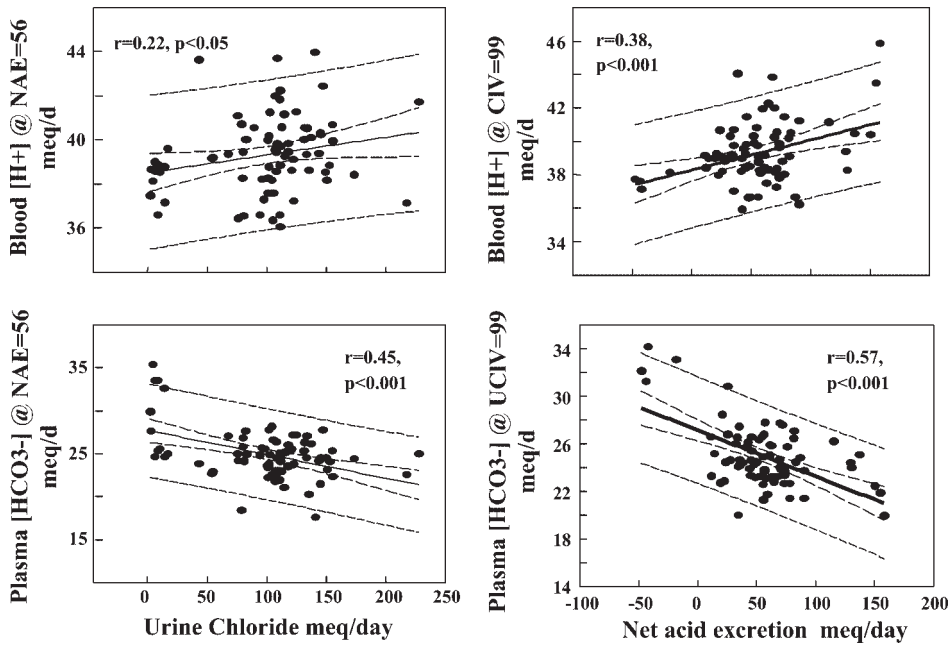

Fig. 1. *Left*: Blood hydrogen ion ([H]b) and plasma bicarbonate ($[HCO_3^-]$p) at constant net acid excretion rate (NAE): [H]b increased 0.9 meq/l per 100 meq/day increase in the urine excretion rates of chloride (UClV; $P < 0.05$) and $[HCO_3^-]$p decreased 1.2 meq/l per 100 meq/day increase in UClV ($P < 0.001$). *Right*: [H]b and $[HCO_3^-]$p at constant UClV. [H]b increased 2.1 meq/l per 100 meq/day increase in NAE ($P < 0.001$), and $[HCO_3^-]$p decreased 2.5 meq/l per 100 meq/day increase in NAE ($P < 0.001$).

Table 2. *Summary of multiple regression analyses and relative impact of dietary net acid load and chloride*

	UClV	NAE	CrCl	Blood PCO_2	β-NAE/β-UClV	Intercept	R^2	*P*
$[HCO_3]_p$								
b	−0.012	−0.025						
β	−0.272	−0.459			1.7	+27.6	0.37	<0.001
P	0.007	<0.001						
b	−0.009	−0.011		+0.460				
β	−0.202	−0.203		+0.627	1.0	+7.8	0.68	<0.001
P	0.006	0.01		<0.001				
b	−0.010	−0.007	+0.024	+0.411				
β	−0.213	−0.141	+0.405	+0.718	0.7	+7.4	0.56	<0.001
P	0.03	0.17	<0.001	<0.001				
$[H]_b$								
b	+0.009	+0.021						
β	+0.224	+0.404			1.8	+37.2	0.28	<0.001
P	0.037	<0.001						
b	+0.011	+0.028		+0.251				
β	+0.265	+0.554		+0.368	2.1	+26.5	0.38	<0.001
P	0.009	<0.001		<0.001				
b	+0.010	+0.023	−0.027	+0.312				
β	+0.195	+0.399	−0.404	+0.484	2.0	+27.1	0.41	<0.001
P	0.089	0.001	0.002	<0.001				

UClV, urine excretion rates of chloride; NAE, net acid excretion rate; CrCl, creatine clearance; β-NAE/β-UClV, dietary net acid load and chloride; b, nonstandardized regression coefficient; β, standardized regression coefficient; $[HCO_3]_p$, plasma bicarbonate; $[H]_b$, blood hydrogen ion.

We examined the mean plasma bicarbonate concentration in the lowest tertile of creatinine clearances compared with those in the highest tertile. We found no statistically significant difference (plasma bicarbonate concentration lowest tertile, 24.0 ± 1.8 meq/l; plasma bicarbonate concentration highest tertile, 24.9 ± 1.3 meq/l, $P = 0.08$), though CrCl differed (CrCl lowest tertile, 73 ± 11 ml/min; CrCl highest tertile, 125 ± 16 ml/min, $P < 0.001$). Moreover, the slope of plasma bicarbonate concentration vs. UClV for the lowest tertile did not differ significantly from that of the highest tertile, even when UClV was factored for CrCl. Those findings do not exclude the possibility that the magnitude of CrCl influences the effect of diet NaCl on plasma bicarbonate concentration, as the power of the test was low owing to insufficient sample size in this subgroup analysis.

DISCUSSION

With these data, we provide the first definite evidence that, in healthy humans, the amount of dietary sodium chloride, as indexed by urine chloride excretion, and the diet net acid load, indexed by renal net acid excretion, independently predict systemic acid-base status. We found that increasing degrees of low-grade hyperchloremic metabolic acidosis associate independently with increasing dietary NaCl loads and with increasing diet net acid loads. If the associations reflect causal effects of dietary NaCl, NaCl loads would have between 50 and 100% of the acidosis-producing effect of the diet net acid load, when compared over their respective ranges of variation. Thus the amount of sodium chloride in a net acid-producing diet independently predicts to the degree of hyperchloremic metabolic acidosis occurring in an individual.

With the present findings, we have now shown that, in otherwise healthy individuals habitually consuming the typically net acid-producing Western diet, three quantifiable factors predict the degree of hyperchloremic metabolic acidosis: *1*) the net acid load of the diet (load of metabolic acid precursors minus load of metabolic base precursors) (8, 13), *2*) the degree of age-related decline in renal acid-base regulatory function (correlated with decline in glomerular filtration rate) (8, 9), and, *3*) the amount of sodium chloride in the diet (intake from food plus discretionarily added NaCl).

Previous workers (5, 18) have presented evidence of the metabolic acidosis-producing effect of dietary sodium chloride but did not examine dose-response relations or compare their findings with the effect of the diet net acid load. In intensive care settings, large volumes of infused saline can result in hyperchloremic metabolic acidosis, often described as "dilutional acidosis" and quantified by the Stewart quantitative physicochemical approach (17), which implicates a dominant effect of a reduction in so-called strong ion difference. Although the acidosis related to dietary sodium chloride might also admit of quantitative analysis using the Stewart approach, we did not collect all of the data needed to make the calculations (see below).

As a cross-sectional study, the present study provides no definitive evidence of increasing dietary sodium chloride as causal of the associated increasing degree of hyperchloremic acidosis, though interventional studies have implicated a causal role (18). We found that the amount of dietary chloride (a positive index of dietary NaCl intake), estimated from steady-state urine chloride excretion, independently predicted plasma bicarbonate concentration (inverse relation) when we adjusted the multivariate model for renal net acid excretion, blood carbon dioxide tension, and creatinine clearance, it independently predicted blood hydrogen ion concentration (direct relation) adjusted for renal net acid excretion and blood carbon dioxide tension. Those findings would tend to rule out sodium chloride-induced changes in net endogenous acid production or renal function as contributing to the correlation of increasing

dietary sodium chloride and increasing degrees of hyperchloremic metabolic acidosis.

Assuming the causal relation, an independent effect of dietary NaCl to induce hyperchloremic metabolic acidosis in the steady-state seems reasonably interpretable as resulting in part from steady-state dilution of the extracellular fluid compartment with, in effect, a bicarbonate-free solution of NaCl, and, as mentioned above, may be interpreted in terms of the Stewart strong ion difference effect, in which hyperchloremic acidosis is the paradigmatic example of strong ion acidosis. Insufficient data were available in this cross-sectional analysis of studies carried out over many years to apply the Stewart method or to assess other measures of extracellular compartment dilution (hematocrit, albumin). Salt-loading, with its attendant extracellular volume expansion, would also be expected to reduce renal bicarbonate reabsorption and thus reduce the set-point at which plasma bicarbonate concentration is regulated (7, 11).

Are there pathophysiological consequences of a dietary NaCl-induced metabolic acidosis? Evidence suggests that dietary sodium chloride might adversely affect bone. In postmenopausal women with osteoporosis, dietary NaCl fails to lead to an increase in gut absorption of calcium sufficient to compensate for NaCl-induced urinary calcium losses, associated with a normal NaCl-induced stimulation of parathyroid hormone and calcitriol concentration and therefore may adversely affect bone by inducing or exacerbating negative calcium balance (2). Preventing the acidosis induced by NaCl with potassium citrate coadministration prevents NaCl-induced urinary calcium losses and increased bone turnover (22). In studies with the DASH diet, low sodium intake improves markers of bone turnover (14). In a longitudinal study of postmenopausal women, Devine et al. (6) observed a negative effect of sodium intake on bone mineral density in postmenopausal women. In adolescent girls, a high salt intake (168 mmol/day, mean body weight, 56 kg) significantly reduces retention of dietary calcium as measured in classic metabolic balance studies (23). To what extent NaCl-induced metabolic acidosis contributes to adverse effects on bone remains to be determined.

Evidence also suggests that dietary salt increases the risk of forming kidney stones. Sakhaee et al. (18) provided evidence in normal volunteers that salt loading reduced serum bicarbonate concentration and urinary citrate excretion and concomitantly increased urinary saturation of calcium phosphate and monosodium urate, and decreased the activity of inhibitors of calcium oxalate crystallization. They concluded that a high-salt diet increased the risk for calcium salt crystallization. In more than 3,000 men and women aged 25–74 years, Cirillo et al. (4) noted that urinary stone disease associated positively with urinary sodium-to-potassium ratio and with sodium-to-creatinine ratio.

Some might wonder whether the participants with plasma bicarbonate concentrations as high as 30 meq/l might have metabolic alkalosis, that is, an abnormal acid-base state. Our data actually do show also that participants with the lower urine chloride excretion rates had the higher plasma bicarbonate concentrations. Because the human genome was built over millions of years of human evolution when our ancestors habitually ingested a low sodium chloride diet, perhaps a plasma bicarbonate concentration of 30 meq/l is the human norm. We elaborate this concept in (21).

In summary, this cross-sectional study revealed a hyperchloremic metabolic acidosis-producing association of dietary sodium chloride independent of the association of acidosis with the diet net acid load. We argue for the biological plausibility of the diet load of sodium chloride as causal of the acidosis-producing effect and discuss the evidence suggesting participation of dietary sodium chloride in increasing the risk of osteoporosis and kidney stones in people eating a net acid-producing diet.

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GRANTS

The authors have no potential conflicts of interest or financial ties to disclose.

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