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Dietary Balance of Sodium, Potassium, and Chloride Influences Plasma Uric Acid Concentrations in Chicks (41451)

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Abstract. Studies were conducted to determine the influence of dietary electrolytes on plasma uric acid concentrations and daily uric acid excretion of chickens that had been selected genetically for uricemia (HUA strain) or low plasma levels of uric acid (LUA strain). Increasing dietary potassium from a nutritionally adequate level of 0.3% to 0.6, 1.0, and 1.5% of the diet resulted in no significant change in weight gain, food consumption, or net uric acid excretion, but significantly increased plasma uric acid concentrations in the HUA and LUA strains. Sodium was varied from a nutritionally adequate level of 0.3% to 0.6, 0.9, and 1.2% of the diet for the LUA strain only. Plasma uric acid concentrations increased with each level of dietary sodium. Dietary deficiencies of sodium and potassium caused reductions in plasma concentrations of uric acid. Excess dietary chloride (1.00, 1.25%) did not influence daily uric acid excretion in either strain of chickens, but depressed plasma uric acid levels in the LUA strain. The highest level of chloride depressed growth and food consumption of both strains. We conclude that the dietary balance of electrolytes influences the steady state concentrations of uric acid in plasma of chickens.

Humans, other higher primates, birds, and reptiles are prone to uricemia and gout. All species lack tissue uricase, and rely on renal excretion as the primary mechanism of uric acid disposal (1, 2).

Uricemia in man has been attributed to excessive biosynthesis of uric acid (3–7), and impaired excretion of uric acid (8, 9). Dietary factors such as nucleic acids (10) specific purines (11), alcohol (12), and fructose (13) have been reported to increase plasma uric acid concentrations in humans. Excess dietary protein increased the amount of uric acid excreted, but did not affect plasma uric acid levels in men (14) in one reported study.

Birds differ from humans in that uric acid is the main end product of nitrogen metabolism. Excess dietary protein increases uric acid production and plasma uric acid concentrations in chickens (15–17). The increase in plasma uric acid levels is greater in chickens that are genetically disposed to uricemia than in their normal counterpart (16, 17). Amino acid deficiencies, by virtue of their effects on protein catabolism, also increase plasma uric acid concentrations (18).

We now report that variations in dietary sodium, potassium, and chloride markedly alter plasma uric acid concentrations in young chickens.

Materials and Methods. Day-old chicks from genetic strains (19) selected for hyperuricemia (HUA strain) or low blood uric acid concentrations (LUA strain) were housed in temperature-controlled cages with raised wire floors, and were provided with 15 hr of light daily, beginning at 0700 hr. They were given a practical diet and water during the first week after hatching. Chicks were allotted to experimental groups at the beginning of the second week and provided experimental diets and water *ad libitum* for approximately 2 weeks. Weight gains and food consumption were measured throughout all experiments.

The experimental diet contained the following as percentage by weight: isolated soybean protein, 25.00; glucose monohydrate, 60.77; cellulose, 3.00; corn oil, 4.00; DL-methionine, 0.60; glycine, 0.40; vitamin premix,[1] 1.22; mineral premix,[2] 5.01; and

[1] Vitamin mix supplied the following in mg/kg diet:

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sources of sodium, potassium, and chloride. Sodium, potassium, and chloride concentrations were varied by inclusion of sodium bicarbonate, potassium bicarbonate, calcium carbonate, and HCl or $CaCl_2 \cdot 2H_2O$ in the diet at the expense of glucose to alter the elements under study and maintain constant levels of all other nutrients.

Chicks had access to feed on the day of blood sampling which was begun after 0900 hr and completed before 1200 hr in each experiment. Blood obtained by cardiac puncture, was pooled by sex and replicate, transferred to tubes containing heparin and centrifuged at 350*g* for 12 min. Plasma was retained for analysis.

Excreta were collected quantitatively in stainless steel pans, containing 0.5% lithium carbonate, that were inserted under the wire floors of the chick cages. Excreta were collected during a 24-hr period on that last day of experiment. Lithium carbonate served to dissolve the excreted uric acid and to inhibit the activity of microfloral uricases. Uric acid concentrations of plasma and excreta samples were determined colorimetrically by the reduction of phosphotungstic acid.[3] Statistical analyses were conducted by analysis of variance, and, where appropriate, by Duncan's multiple range test for comparison of individual means (20).

Results. Responses of HUA and LUA strains were measured except in the case of sodium where only the LUA strain was studied. The lowest level of sodium (0.04%) was growth limiting but none of the other sodium levels resulted in growth inferior to the growth rate permitted by 0.3% sodium. The growth response was curvilinear, with 0.6% sodium promoting better weight gains than all other levels except 0.9% sodium. The potassium requirement of both strains was satisfied by 0.3% potassium, and weight gains were unaffected by higher levels of potassium. Growth and feed consumption was not significantly affected over the range of 0.45 to 1.00% dietary chloride, but were depressed slightly by 1.25% chloride ($P < 0.05$). The HUA and LUA strains did not differ in response to potassium or chloride except for the HUA strain receiving 0.3% K in experiment 2 which consumed more feed than the LUA strain. Chicks of the HUA strain were similar in weight to those of the LUA strain, but consumed more feed in experiment 2 ($P < 0.05$). Chicks of the HUA strain were slightly larger and ate more feed than the LUA strain in experiment 4.

The amounts of uric acid excreted by HUA and LUA chicks did not differ, nor were there any significant effects of potassium or chloride on this measure of nitrogen metabolism.

Plasma uric acid concentrations were markedly affected by the nutritional variables. Figure 1 combines the data from all experiments and illustrates the effects of sodium and potassium in the LUA strain. Levels of either element below the requirement for maximum growth lowered the plasma uric levels. Levels above the requirement progressively increased uric acid concentrations. The overall response to potassium is described as a hyperbolic curve while the sodium response appeared to be exponential. Plasma uric acid concentrations were decreased as chloride increased to 1.25% of the diet. All chicks appeared normal except for those receiving 1.2% sodium. These were well fleshed and appeared healthy. Nonetheless, 48% died abruptly of acute visceral gout during the course of the experiment.

Chicks of the HUA strain had markedly higher plasma uric acid concentrations than

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Thiamine·HCl, 15.0; riboflavin, 15.0; nicotinic acid 50.0; folic acid, 6.0; pyridoxine·HCl, 6.0; biotin, 0.6; *d*-calcium pantothenate, 20.0; menadione sodium bisulfite, 1.52; vitamin B_{12}, 0.02; inositol, 250; butylated hydroxytoluene, 100. Fat-soluble vitamins were present in the following amounts (IU/kg diet): vitamin D_3, 4500; vitamin A palmitate, 4322; α-tocopherol acetate, 110.

[2] Mineral mix supplied the following in g/kg diet: $CaHPO_4$, 33.5; $CaCl_2 \cdot 2H_2O$, 9.4; $MgSO_4 \cdot 7H_2O$, 6.5; $MnSO_4 \cdot H_2O$, 0.333; $CuSO_4 \cdot 5H_2O$, 0.0167; ZnO, 0.062; $CoCl_2 \cdot 5H_2O$, 0.0017; KI, 0.0026; $NaMoO_4 \cdot 2H_2O$, 0.0083; Na_2SeO_3, 0.0003.

[3] Technicon autoanalyzer method N-13a, Technicon Instruments Corp., Tarrytown, N.Y.

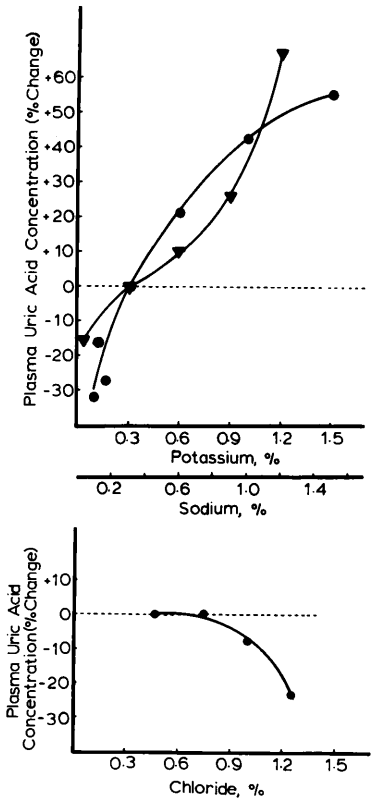

FIG. 1. Influence of dietary sodium, potassium, and chloride on plasma uric acid concentrations of the LUA strain. Variations in uric acid concentrations (*y* axis) are expressed as percentage increase or decrease relative to the plasma uric acid concentrations of chicks fed the diet common to all experiments containing 0.30% sodium, 0.3% potassium, and 0.45% chloride. Potassium, (●); sodium (▲).

those of the LUA strain, and the concentrations were not affected by chloride (Table I, Fig. 2). Although low dietary levels of potassium were without effect, high levels increased plasma uric acid concentrations (Table I, Fig. 2) ($P < 0.05$).

Discussion. Variations in the dietary levels of sodium, potassium, and chloride markedly influenced the plasma uric acid concentrations. The most striking changes occurred in chicks of the LUA strain, which were made hyperuricemic or hypouricemic by the various dietary treatments. Although the HUA strain seemed less responsive, plasma uric acid concentrations were fourfold higher in HUA chicks than in LUA chicks and generally were more variable. Excess dietary potassium increased plasma uric acid concentration in the HUA strain ($P < 0.05$), and the absolute increase was approximately equivalent to that of the LUA strain (3.6 mg% and 3.7 mg% in the LUA and HUA strains, respectively). Thus it is possible that the HUA and LUA strains of chicken responded similarly to the nutritional conditions employed, but that the responses of the HUA chicks were masked by random variability.

Dietary mineral electrolytes are important determinants of acid–base balance (24, 25). In general, acid–base balance is affected by the molar ratio of dietary cations to anions in such a way that an increased ratio tends to produce an alkalosis and a reduced ratio tends to cause an acidosis (24–28). In the present experiments those diets favoring acidosis lowered plasma uric acid concentrations whereas those favoring alkalosis increased plasma uric acid concentrations.

Acidosis leads to increased renal production and excretion of ammonia (28, 29, 31), and might be expected to reduce uric acid excretion by limiting the amount of nitrogen available for uric acid biosynthesis. This, apparently, is not necessarily the case. Okumura and Tasaki (31), varied acid–base balance in adult chickens and, although they observed large changes in net ammonia excretion, the net excretion of uric acid was unaffected. No significant changes in net uric acid excretion occurred in the present experiments in response to wide variations in dietary monovalent cations and anions. This suggests that the biosynthesis of uric acid was not affected by cation–anion balance.

Previous studies have shown that renal transport is an important determinant of blood uric acid concentrations in chickens (17, 32). Possibly the variations of blood uric acid levels in this study were due to altered transport of uric acid, occurring secondarily to altered acid–base balance. McNabb (33) has reported that a large portion of the uric acid of chicken urine is present in precipitated form or as a colloidal

TABLE I. INFLUENCE OF DIETARY Na, K, AND Cl ON GROWTH AND EXCRETION OF URIC ACID IN THE HUA AND LUA LINES

Treatment	Dietary level (%)	Weight gain[1] (g/chick)		Food consumed[1] (g/chick)		Uric acid excreted[1] (g/kg body wt/day)		Plasma uric acid[2] (mg/dl)	
		HUA	LUA	HUA	LUA	HUA	LUA	HUA	LUA
					Experiment 1[3]				
Sodium	0.04	—	126 ± 3^{a}	—	267 ± 5^{a}	—	—	—	51 ± 3^{a}
	0.30	—	149 ± 6^{b}	—	303 ± 6^{b}	—	—	—	60 ± 2^{a,b}
	0.60	—	166 ± 1^{c}	—	322 ± 5^{c}	—	—	—	66 ± 5^{a,b}
	0.90	—	159 ± 4^{b,c}	—	313 ± 2^{b,c}	—	—	—	76 ± 5^{b}
	1.20	—	151 ± 5^{b}	—	—[4]	—	—	—	105 ± 16^{c}
					Experiment 2[5]				
Potassium	0.10	56 ± 3^{a}	50 ± 2^{a}	130 ± 3^{a}	130 ± 6^{a}	2.80 ± 0.39	3.08 ± 0.10	228 ± 14^{a}	50 ± 2^{a}
	0.16	99 ± 1^{b}	100 ± 3^{b}	184 ± 4^{b,c}	176 ± 5^{b}	3.00 ± 0.15	3.04 ± 0.30	207 ± 8^{a}	54 ± 2^{a}
	0.30	112 ± 7^{c}	113 ± 2^{c}	195 ± 8^{d}	184 ± 7^{b,c}	2.62 ± 0.09	2.35 ± 0.12	214 ± 12^{a}	72 ± 4^{b}
					Experiment 3[5]				
	0.30	103 ± 2	101 ± 2	177 ± 2	168 ± 4	3.13 ± 0.11	3.02 ± 0.08	201 ± 9^{a}	64 ± 3^{a}
	0.60	105 ± 2	105 ± 2	184 ± 3	174 ± 2	3.46 ± 0.14	3.19 ± 0.07	251 ± 11^{b}	78 ± 3^{b}
	1.00	109 ± 3	107 ± 2	189 ± 5	172 ± 6	3.27 ± 0.07	3.18 ± 0.14	233 ± 11^{b}	92 ± 7^{c}
	1.50	104 ± 4	105 ± 1	188 ± 10	178 ± 2	3.01 ± 0.03	3.26 ± 0.05	248 ± 12^{b}	100 ± 3^{c}
					Experiment 4[6]				
Chloride	0.45	128 ± 2^{d}	120 ± 2^{b,c}	215 ± 3^{c}	197 ± 3^{b}	2.72 ± 0.07	2.68 ± 0.18	171 ± 8^{a}	62 ± 2^{b}
	0.75	126 ± 1^{c,d}	122 ± 2^{b,c,d}	212 ± 2^{c}	199 ± 3^{b}	2.63 ± 0.09	2.80 ± 0.17	173 ± 11^{a}	62 ± 2^{b}
	1.00	122 ± 2^{b,c,d}	117 ± 2^{b}	208 ± 2^{c}	190 ± 2^{a,b}	2.44 ± 0.12	2.67 ± 0.13	182 ± 10^{a}	57 ± 3^{b}
	1.25	118 ± 2^{b}	108 ± 3^{a}	198 ± 2^{b}	182 ± 5^{a}	2.71 ± 0.10	2.81 ± 0.06	161 ± 6^{a}	49 ± 3^{a}

[1] Each value is the mean ± SE of six replicated pens of eight chicks. In each experiment, means within and between strains having the same letter in the superscript are not significantly different ($P > 0.05$). Means that contain no superscripts also are not significantly different ($P > 0.05$).

[2] Blood was pooled by sex within each replicate for analysis. Each value is the mean of 12 pools of blood, obtained from a total of 48 chicks. Statistical comparisons are within strain only.

[3] Chicks were fed the experimental diets for 15 days beginning at 15 days of age.

[4] Food intake could not be calculated due to chick mortality.

[5] Chicks were fed the experimental diets for 14 days beginning at 7 days of age.

[6] Chicks were fed the experimental diets for 15 days beginning at 8 days of age.

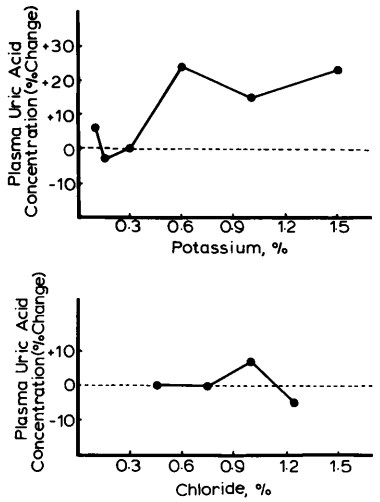

FIG. 2. Influence of dietary potassium and chloride on plasma uric acid concentrations of the HUA strain. See legend of Fig. 1.

suspension. Dantzler (34) observed significant backflux of uric acid from lumen to the peritubular bathing solution in isolated perfused snake nephrons, the backflux being dependent on soluble uric acid concentration. Since the solubility of uric acid is markedly affected by pH, it is conceivable that the concentration of dissolved uric acid, and consequently the backflux of uric acid from the lumina of nephrons, is reduced in acidosis and increased in alkalosis, resulting in improved or lowered efficiency of uric acid clearance, respectively.

The present studies reveal important impacts of dietary electrolytes on plasma uric acid concentration. The basic biological mechanisms involved and the implication of these findings in human gout are important subjects for further investigation.

Appendix. Some studies were conducted to compare the colorimetric method[3] with the more specific spectrophotometric (uricase)[4] method of uric acid analysis. Uric acid which was recrystallized from a commercial preparation of uric acid according to the method of Pudelkiewicz *et al.* (35), was used in the preparation of fresh standards for each assay of plasma and excreta.

In a comparison of seven plasma samples each from the HUA and LUA strains using the colorimetric method[3] and the uricase method[4], the relationship of the two methods was found to be $y = 0.024 + 0.912x$, where y equals the uric acid concentration obtained by the uricase method and x equals the value obtained colorimetrically. The correlation coefficient was 0.99. In a second comparison of methods, 24 chicks of an unselected strain were divided into four groups receiving the basal experimental diet or the diet supplemented to provide 0.9% Na, 1.5% K, or 1.25% Cl. Blood samples were taken from all chicks after 2 weeks. Plasma samples were extracted with hexane in an attempt to decrease the background absorbance of light at 292 nm. Extracted samples were assayed by the uricase and colorimetric methods. The relationship of the two methods was $y = 0.574 + 0.844x$; the correlation coefficient was 0.94.

In other comparisons eight samples of excreta were air-dried, ground, and extracted with 0.5% Li_2CO_3 according to the method of Pudelkiewicz *et al.* (35). Excreta were assayed in duplicate according to the colorimetric and uricase methods. Upon regression analysis, the relationship of uric acid determined by the two methods was $y = 1.08 + 0.19x$ where y = uric acid concentration by colorimetric assay and x = uric acid by uricase assay. The correlation coefficient was 0.98.

In a separate experiment, recrystallized uric acid was held at room temperature in 0.5% Li_2CO_3, and assayed by the uricase method, initially, and after 1, 2, and 5 days. The amount of uric acid detected by assay declined 6.6% per day, indicating some instability of uric acid in 0.5% Li_2CO_3. Excreta were held 2 days under refrigeration in experiments 1 and 3 and 1 day in experiment 4 prior to analysis.

These results indicate that the colorimetric method is adequate for detection of variations of uric acid in plasma and

[4] Sigma Technical Bulletin No. 292-UV. Sigma Chemical Co., Saint Louis, Mo.

excreta. Uric acid values obtained by the two methods are highly correlated: however, the uric acid values obtained by the colorimetric method are slightly higher than those obtained by the uricase method.

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