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Purine Metabolism in High- and Low-Uric Acid Lines of Chickens: Hypoxanthine/Guanine Phosphoribosyltransferase Activities[1] (41607)

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Abstract. The activity of hypoxanthine/guanine phosphoribosyltransferase (HGPRT) was examined in the livers and kidneys of two genetic lines of chickens selected for different plasma uric acid levels. Previous work demonstrated that the high-uric acid line (HUA) had significantly greater *de novo* uric acid synthesis rates in kidney tissue compared to the low-uric acid line (LUA). In addition, phosphoribosylpyrophosphate (PRPP) synthetase and xanthine dehydrogenase activities in livers and kidneys were significantly higher in the HUA compared to the LUA line. PRPP pool sizes were also significantly higher in both livers and kidneys of HUA birds. HGPRT activities in livers of HUA birds were significantly ($P < 0.05$) greater than in LUA birds. The mean value of liver HGPRT was 7.36 ± 0.25 pmole inosine-5′-monophosphate (IMP) and 6.05 ± 0.27 pmole IMP produced/μg protein/hr, respectively, for the HUA and LUA lines. There were no significant differences ($P > 0.05$) in kidney HGPRT activities between the two groups. The mean value of kidney HGPRT was 52.87 ± 1.62 pmole IMP and 50.72 ± 1.62 pmole IMP produced/μg protein/hr, respectively, for the HUA and LUA line. Elevated liver HGPRT may serve to enhance the regeneration of PRPP in the HUA liver. Elevated liver PRPP synthetase and PRPP pool size suggest an increased flux through the *de novo* purine biosynthetic pathway in HUA birds. The resulting additional pyrophosphate from the glutamine PRPP amidotransferase reaction would stimulate recovery of PRPP and spare the system from a substantial loss of energy.

Hypoxanthine/guanine phosphoribosyltransferase (HGPRT) (E.C. 2.4.2.8) catalyzes the conversion of hypoxanthine and guanine to their respective nucleotides: inosine-5′-monophosphate (IMP) and guanosine-5′-monophosphate (GMP). This purine "salvage enzyme" is especially important in tissues which contain undetectable or very low levels of *de novo* purine biosynthetic activity. Such tissues include human leucocytes (1, 2), blood platelets (3), brain tissue (4, 5), and rat lymph nodes (6). These tissues appear to rely on the liver as a major source of preformed purines (7). Purines are apparently transported between tissues either as a free plasma purine (hypoxanthine only) or by red cell carriers probably in the form of nucleosides (8).

In addition to functioning in purine salvage, HGPRT may be important in the degradation of IMP and GMP to free purine bases during uric acid formation. Provided that adequate levels of pyrophosphate and nucleotide are maintained, pyrophosphorolysis of these nucleotides wll occur (9, 10).

A variety of HGPRT deficiency diseases have been reported in man over the past two decades. The diseases generally have been due to structural changes in the HGPRT protein. A recent report has identified at least five alleles of the human HGPRT locus (11). An almost complete lack of enzymatic activity is characteristic of the Lesch–Nyhan Syndrome, a particularly devastating behavioral and neurological disorder (12, 13). Deficiency of HGPRT activity often results in hyperuricemia and, in some cases, articular gout. Purine overproduction in these individuals is considered to be due to accumulation of phosphoribosylpyrophosphate (PRPP) and to decreased feedback inhibition of PRPP amidotransferase by lowered levels of IMP and GMP (14–17).

Our investigations center on the etiology of uric acid overproduction in the high-uric acid (HUA) line of chickens (18). Previous work in our laboratory has demonstrated that in addition to significantly greater *de novo* uric acid synthesis rates in kidney tissues of the

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HUA line, xanthine dehydrogenase levels in both liver and kidney tissues are also elevated (19).

The activity of PRPP synthetase, which provides a key substrate for the rate-limiting step in *de novo* purine biosynthesis, was found to be significantly elevated in liver and kidney tissues of the HUA birds (20). PRPP pool sizes in these tissues were also increased.

This study was initiated to examine the activity of HGPRT in tissue extracts of the HUA line for a possible abnormality which might be linked to the hyperuricemia and articular gout commonly found in these birds. HGPRT activity was also examined in tissues of birds fed varying levels of dietary protein.

Materials and Methods. *Experimental chickens and husbandry.* The original stocks of HUA and low-uric acid (LUA) birds were obtained from R. E. Austic, Cornell University in 1975 and have been selected according to plasma uric acid levels. The LUA chickens served as control birds throughout the study since they were derived from a similar ancestry as the HUA line. Male broiler chickens (Hubbard × Hubbard) were obtained from Fors Farms, Puyallup, Washington.

All HUA and LUA birds were maintained in electrically heated wire brooders until approximately 4 weeks of age, then reared in floor pens for the remainder of the study. The birds were fed a chick starter ration [containing 23% crude protein (CP)] until 14 weeks of age and then fed a chicken developer diet (13% CP) until the 22nd week. After the 22nd week, the birds were maintained on a layer diet (17.5% CP).

Male broiler chicks were maintained in electrically heated wire brooders. Birds were fed a chick starter ration for the first 8 days then divided into four groups of 15 each and fed purified diets containing 29, 44, 66, or 82% crude protein (Table I) for 2 weeks.

Determination of plasma uric acid. Blood samples were taken via cardiac puncture using heparinized syringes. Plasma uric acid levels were determined by a micromethod modification (21) of the uricase spectrophotometric procedure of Feichtmeir and Wrenn (22).

Acetone powder preparation. Tissue samples were taken from HUA and LUA birds at 13 months of age and from the broiler chicks at 3 weeks of age. Immediately after collection of blood samples, livers and kidneys were removed from the birds, weighed and frozen in a dry-ice–acetone mixture. These tissues were stored at −20°C. Frozen tissues were pulverized with a mallet and suspended in a milliliter volume of acetone (−20°C) equal to 10-fold the weight in grams. The tissues were blended thoroughly in a Sorval Omnimixer. The acetone solution was filtered off through a buchner funnel and the resulting cake was resuspended in half the original volume of

TABLE I. COMPOSITION OF PURIFIED DIETS (PERCENTAGE)

Ingredient	Dietary protein level (%)			
	29	44	66	82
Isolated soybean protein[a]	28.74	45.98	68.97	86.21
Glucose monohydrate[b]	62.24	45.25	22.26	5.02
Vitamin mix[c]	0.05	0.05	0.05	0.05
Mineral mix[d]	7.44	7.44	7.44	7.44
Linoleic acid	1.00	1.00	1.00	1.00
Choline chloride	0.28	0.28	0.28	0.28
DL-methionine	0.10	—	—	—
Glycine	0.20	—	—	—

[a] Soybean protein: grade II, U.S. Biochemical Corporation, Cleveland, Ohio.

[b] Cerelose, Corn Products Co., Argo, Ill.

[c] The vitamin mixture contributed the following to the diet (mg/kg diet): thiamine HCl, 100; niacin, 100; riboflavin, 16; Ca-pantothenate, 20; Cyanocobalamin, 0.02; pyridoxine HCl, 6; biotin, 0.6; folic acid, 4; inositol, 100; menadione sodium bisulfite, 5; α-tocopherol acetate, 20; cholecalciferol, 1200 ICU; retinyl palmitate, 10,000 IU.

[d] The mineral mixture contributed the following to the diet (g/kg diet): $NaMoO_4 \cdot 2H_2O$, 0.01; $CuSO_4$, 0.02; KI, 0.05; $ZnCO_3$, 0.02; $FeC_6H_5O_7$, 0.40; $MnSO_4 \cdot 2H_2O$, 0.42; KCl 3.00; $MgSO_4 \cdot 7H_2O$, 5.00; NaCl, 6.00; Na_2HPO_4, 7.20; KH_2PO_4, 12.00; $Ca_3(PO_4)_2$, 13.95; and $CaCO_3$, 15.00.

acetone and filtered. After a second resuspension and filtering, the cakes were placed *in vacuo* for 2 days at 4°C over concentrated sulfuric acid and 2 days over Drierite (W. A. Hammond Drierite Co., Xenia, Ohio). The acetone powder preparations were stored dessicated at −20°C prior to use.

Reagents. Radioisotopes were purchased from New England Nuclear, Boston, Massachusetts. Phosphoribosyl pyrophosphate (PRPP), mercaptoethanol, and ethylene diamine tetraacetic acid (EDTA) were purchased from Sigma Chemical Company, St. Louis, Missouri. Reagents were of analytical grade.

Assay of HGPRT activity. Twelve milligrams of each acetone powder preparation were extracted gently in 4 ml of 0.05 *M* Tris–HCl (pH 8.0) buffer containing 0.01 *M* $MgCl_2$ and 0.001 *M* mercaptoethanol for 30 min at room temperature in an orbital mixer. The extract was dialyzed for 2 hr at 4°C against 50 volumes of extraction buffer with one change. The dialysate was centrifuged at 1500*g* for 15 min at 4°C and the supernatant withdrawn for protein determination and enzyme assay. Protein determination was done by the Coomassie blue dye-binding method of Bradford (23) using bovine gamma globulin as the standard. After making appropriate dilutions with dialysis buffer, 100-μl aliquots of the supernatants were added to culture tubes (12 × 75 mm). The reaction was initiated by the addition of 200 μl of 0.1 *M* Tris–HCl (pH 8.0) with 0.003 *M* $MgCl_2$, 0.0015 *M* PRPP, and either 0.1 μCi [8-^{14}C]hypoxanthine or 0.1 μCi [8-^{14}C]guanine (20 Ci/mole). The reaction proceeded at 37°C for 2 hr and was terminated by the addition of 50 μl of 0.05 *M* Tris–HCl (pH 7.8) containing 0.16 *M* EDTA. Appropriate controls were run in parallel in which the Tris–HCl–EDTA solution was added prior to incubation. Samples could then be stored frozen with undetectable loss of nucleotide. Separation of the nucleotide product from the free purine base was accomplished by anion exchange descending chromatography using Whatman DE 52 paper. Forty microliters of each reaction mixture was spotted along with 50 μg of the appropriate nonlabeled nucleotide marker (IMP or GMP). After developing with 0.02 *M* Tris–HCl (pH 8.0) the chromatograms were dried and the nucleotide spots visualized using a short-wave

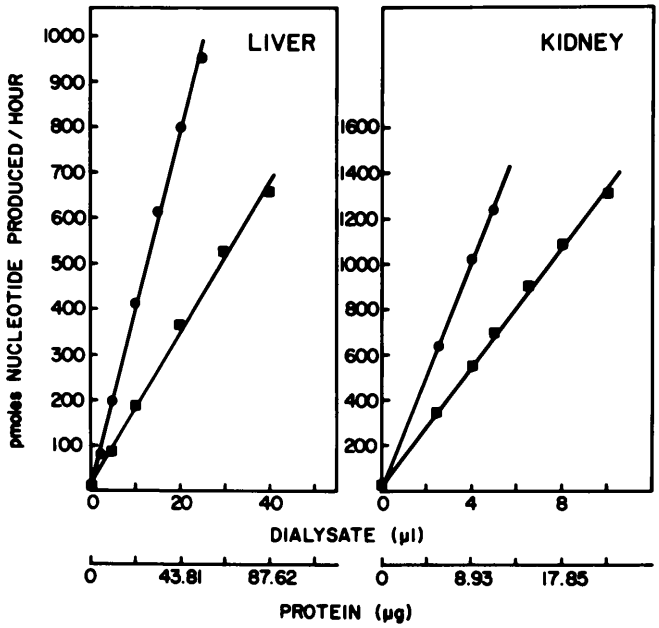

FIG. 1. Nucleotide synthesized per hour with various levels of added enzyme. Circles, picomoles guanosine-5′-monophosphate; squares, picomoles inosine-5′-monophosphate.

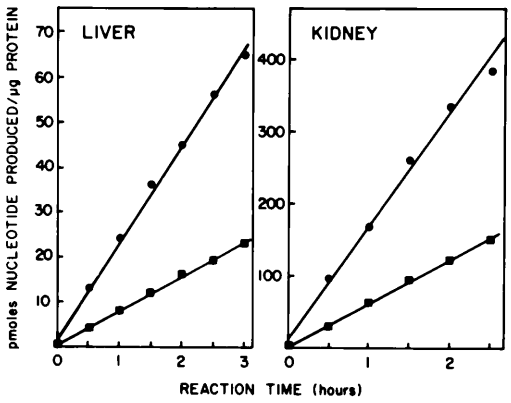

FIG. 2. Nucleotide synthesized per microgram protein vs reaction time. Circles, picomoles guanosine-5'-monophosphate; squares, picomoles inosine-5'-monophosphate.

ultraviolet-light source. The ultraviolet-light absorbing areas were cut out and extracted with 0.75 ml of 0.01*N* HCl in glass scintillation vials. Ten milliliters of Biocount (Research Products International Corp., Grove Village, Il.) was added to the mixture and the vials were counted in a Packard Tri-Carb 460 liquid scintillation counter.

Statistical analysis of the data was done with Duncan's new multiple range test (24).

Results. HGPRT activity is linear with respect to protein concentration and time when either guanine or hypoxanthine is used as a substrate (Figs. 1, 2). With guanine, values were approximately 3.3-fold and 1.5-fold greater than with hypoxanthine in liver and kidney tissues, respectively.

The plasma uric acid levels and tissue HGPRT activities in the HUA and LUA birds are shown in Table II. There are no significant differences between plasma urate levels of males and females in the LUA line. HUA males, however, have nearly twice the levels of the corresponding females. The mean plasma urate level in HUA birds is greater than that of the LUA line ($P < 0.05$). HGPRT activity is significantly elevated in HUA livers compared to controls. In addition, males of the HUA line have greater HGPRT activity than the females of this group, whereas there is no statistical difference in HGPRT activity between the sexes of the LUA line. Liver HGPRT activity of the birds correlated positively with their plasma urate levels ($r = +0.61$; $P < 0.05$).

Kidney HGPRT activities were generally seven- to eight-fold greater than that found in the corresponding livers. There was no difference between the two lines in the kidney HGPRT activities and no correlation with plasma urate levels ($r = +0.08$; $P > 0.05$). In the HUA line the females had over a 20% higher specific activity than males.

In broiler chicks daily protein consumption and plasma uric acid levels increased with increasing dietary protein except in those fed the 82% CP diet where it was equivalent to that of birds fed the 66% CP diet (Table III). The liver HGPRT activity decreased with increasing levels of dietary protein. Only in birds consuming the 82% CP diet was the difference significant, however. Kidney HGPRT levels increased when dietary protein was increased

TABLE II. HYPOXANTHINE/GUANINE PHOSPHORIBOSYLTRANSFERASE ACTIVITIES IN HUA AND LUA TISSUES

Breed-sex	Plasma UA ± SEM[1]	HGPRT activity ± SEM[2]	
		Liver	Kidney
LUA-females	5.83^{a} ± 0.56	5.64^{a} ± 0.27	$52.19^{a,b}$ ± 2.37
LUA-males	6.46^{a} ± 0.27	$6.42^{a,b}$ ± 0.44	49.25^{b} ± 2.22
LUA-mean	6.16* ± 0.38	6.05* ± 0.27	50.72 ± 1.62
HUA-females	13.65^{b} ± 1.86	6.64^{b} ± 0.23	57.28^{a} ± 1.63
HUA-males	25.48^{c} ± 2.46	8.08^{c} ± 0.27	47.96^{b} ± 1.85
HUA-mean	19.25* ± 2.03	7.36* ± 0.25	52.87 ± 1.62

Note. All values represent the mean of 10 observations.

[1] mg uric acid/dl plasma.

[2] pmole inosine-5'-monophosphate synthesized/μg protein/hr.

[a,b,c] Means within a column with the same letter in superscript are not significantly different ($P > 0.05$).

* Mean values of breeds are significantly different ($P < 0.05$).

TABLE III. BROILER CHICK DIETARY CONSUMPTION, PLASMA URIC ACID LEVELS, AND HYPOXANTHINE/GUANINE PHOSPHORIBOSYL TRANSFERASE ACTIVITIES

	Dietary protein level (%)			
	29	44	66	82
Feed consumption g/chick/day	$16.07^{a} \pm 1.13$[1]	$13.54^{b} \pm 0.86$	$11.60^{b,c} \pm 0.35$	$9.25^{c} \pm 0.32$
Energy consumption kcal M.E./chick/day	$51.33^{a} \pm 3.62$	$43.89^{a,b} \pm 2.80$	$38.15^{b,c} \pm 1.15$	$30.76^{c} \pm 1.07$
Protein consumption g/chick/day	$4.59^{a} \pm 0.32$	$5.98^{b} \pm 0.38$	$7.66^{c} \pm 0.23$	$7.56^{c} \pm 0.26$
Plasma uric acid mg/dl	$11.43^{a} \pm 0.59$	$15.74^{b} \pm 0.61$	$26.32^{c} \pm 2.30$	$25.63^{c} \pm 1.77$
Liver HGPRT activity[2]	$9.01^{a} \pm 0.41$	$8.33^{a} \pm 0.60$	$7.91^{a} \pm 0.39$	$5.69^{b} \pm 0.43$
Kidney HGPRT activity[2]	$74.04^{a,b} \pm 2.18$	$85.00^{c} \pm 2.21$	$79.64^{b,c} \pm 1.60$	$71.66^{a} \pm 2.12$

Note. Nutrient consumption values represent the mean of three groups of five chicks each. Uric acid levels and tissue HGPRT values represent the mean of 10 observations.

[1] Values are means ± SEM.

[2] pmole inosine-5'-monophosphate synthesized/μg protein/hr.

[a,b,c] Means within rows with the same letter in superscript are not significantly different ($P > 0.05$).

from 29 to 44%, but additional increase in dietary protein resulted in lowered activities.

Discussion. With excessive protein dialysate levels (more than double that used here), the apparent activities of HGPRT in both liver and kidney tissues fall markedly. This behavior is thought to be due to the activity of 5'-nucleotidase and possibly guanase (25). The activity of 5'-nucleotidase in the avian liver is quite high compared to the rat (26). The avian enzyme expresses greatest activity towards IMP and GMP and is believed to participate significantly in the degradation of these nucleotides to uric acid in the uricotelic animal (27, 28).

The results indicate that HUA birds do not have deficient HGPRT levels as is sometimes found in cases of human hyperuricemia and gout. In fact, enzymatic activity is significantly greater in livers of this line. These results are similar to that found by Hevia *et al.* (29) in genetically selected dystrophic and dystrophic gouty lines of chickens. These two breeds overproduce uric acid compared with control birds when fed an 80% protein diet (30).

When forced to convert large amounts of dietary nitrogen to uric acid, the chicken does not respond by increasing its renal or hepatic HGPRT levels. An increased flux of nitrogen through the *de novo* purine biosynthetic pathway is therefore unlikely to be responsible for elevated hepatic HGPRT activity found in HUA birds. The feed consumption and M.E. (Metabolizable Energy) intake of birds fed the high-protein diets were substantially less than

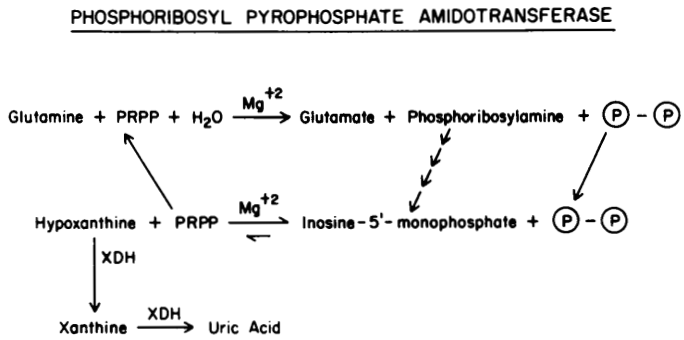

FIG. 3. Regeneration of PRPP via reversal of the HGPRT salvage pathway. Pyrophosphate (Ⓟ–Ⓟ), xanthine dehydrogenase (XDH).

optimum for broilers of this age (31) (Table III). The decrease in broiler hepatic HGPRT activity with elevated dietary protein levels may be due to increased degradation of the enzyme in response to an energy deficient diet. This type of behavior has been documented with other proteins (32).

Since PRPP is the rate limiting substrate for PRPP amidotransferase (33), increased PRPP synthetase and PRPP pool sizes found in HUA tissues favors the acceleration of phosphoribosylamine synthesis. Provided that adequate nucleotide and pyrophosphate are continuously supplied, the reversal of the HGPRT salvage pathway can occur regenerating PRPP in a cyclic fashion (Fig. 3). Additional pyrophosphate conceivably could be supplied from the synthesis of GMP via GMP synthetase. The elevated tissue xanthine dehydrogenase activities in these birds may serve to further shift the equilibrium toward PRPP production by removal of hypoxanthine. Thus, the ribose-5-phosphate moiety of PRPP acts as a carrier for the developing purine ring and the substrate pyrophosphate acts as a catalyst in the overall scheme.

It is noteworthy that the specific activity of HGPRT in the kidney is much greater than that found in the liver. The higher activity may possibly reflect a greater demand for purine salvage in this tissue or an increased recycling of PRPP.

The elevated hepatic HGPRT levels in HUA birds may function to augment the regeneration of PRPP. An expenditure of two or three high-energy phosphate bonds is necessary to produce one molecule of PRPP from ribose-5-phosphate or ribose, respectively. Regeneration of PRPP via phosphorolysis of IMP and GMP would conserve considerable metabolic energy.

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