PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 146, 931–935 (1974)

Specificity of the Renal Transport Impairment in Chickens Having Hyperuricemia and Articular Gout[1] (38222)

R. E. AUSTIC AND R. K. COLE
(Introduced by W. J. Visek)
Department of Poultry Science, Cornell University, Ithaca, New York 14850

A hereditary form of hyperuricemia and gout in chickens has recently been described in this laboratory (1, 2). Chickens which had undergone 4 generations of selection for a high incidence (HUA line) or 3 generations of selection for a low incidence (LUA line) of hyperuricemia and articular gout were found to differ in renal transport of uric acid: those of the HUA line secreted less uric acid at equivalent plasma uric acid levels, and exhibited a transport maximum for uric acid secretion of less than one half the value for chickens of the LUA line (2).

The nature of the abnormality leading to impaired uric acid secretion in the HUA line of chickens is not known. Should the defect be closely associated with uric acid transport, the 2 lines might be useful in elucidating the mechanism of renal uric acid secretion. A defect of broader specificity might be less valuable in this respect, and perhaps reflect an anatomical or morphological abnormality. In the present studies the rates of renal tubular transport of several compounds were measured in an attempt to assess the specificity of the renal impairment responsible for hyperuricemia and gout in chickens of the HUA line.

Procedures. Mature, egg-producing females were used in all experiments. Hens were maintained in environmentally controlled cages with raised wire floors, and had access to food[2] and water prior to experiment. Fifteen minutes after administration of 25–50 ml of water by intubation into the crop, each hen was secured to a restraining table and anesthetized with a commercial preparation of pentobarbital and chloral hydrate.[3] Both wing veins (l. and r. *vena cutanea ulnaris*) were cannulated: one was used for the administration of anesthetic and collection of blood samples; the other for infusion of the test substance. The ureters were prepared according to the method of Mongin (3) for the quantitative collection of urine.

The rates of tubular secretion of *p*-aminohippuric acid (PAH), creatinine, tetraethylammonium (TEA), and reabsorption of glucose and arginine by hens of the HUA and LUA lines were determined. After administration of a priming dose of inulin (1 ml of 10% solution), solutions containing 0.008 *M* inulin, 0.137 *M* mannitol, 0.078 *M* sodium chloride with the test substance were infused into one wing vein at 0.5 ml/min for as long as 2 hr in some studies. Five- or 10-min urine collections were made at various predetermined intervals during infusion, and 1–2 ml blood samples were taken at the midpoint of each urine collection period. Infusion solutions, carefully adjusted to pH 7.40 contained 0.10 *M* PAH, 0.008 *M* creatinine, 0.010 *M* tetraethylammonium chloride, 0.240 *M* D-glucose

[1] This investigation was supported in part by Public Health Research Grant R01 AM15823 of the National Institute of Arthritis and Metabolic Diseases.

[2] Cornell Breeder Diet, 1972 formula, Department of Poultry Science, Cornell University, Ithaca, New York.

[3] Equithesan, Jensen-Salsbery Laboratories, Kansas City, Mo. 64141.

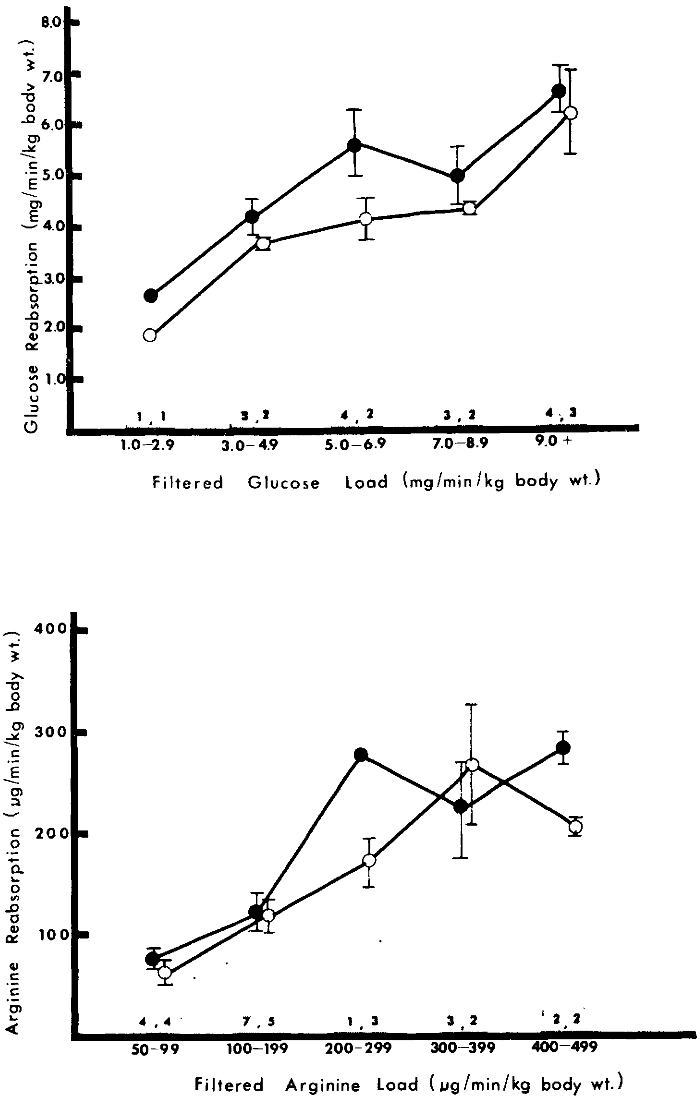

FIG. 1. Renal reabsorption of arginine and glucose. HUA line, closed circles; LUA line, open circles. Six chickens from each line were used in the arginine studies, and 6 and 5 respectively for the HUA and LUA lines in the glucose studies. Mean body wt were 1.57 ± .05 kg for the HUA line and 1.53 ± .06 kg for the LUA line. Mean inulin clearance for the 12 hens of the HUA and 11 hens of the LUA lines was 2.30 ± 0.27 and 2.26 ± 0.22 ml/min/kg of body wt (no significant differences, $P < .05$). The numbers in shaded areas indicate the numbers of observations for HUA and LUA lines respectively.

or L-arginine varying from 0.032 to 0.150 *M* in the respective tests of transport function. Individual hens were used for measurement of the transport of only one substance.

Plasma and urine were analyzed for PAH according to the method of Friedman *et al.* (4), creatinine according to the alkaline picrate method described by Taussky (5), tetraethylammonium according to the method of Mitchell and Clark (6) and

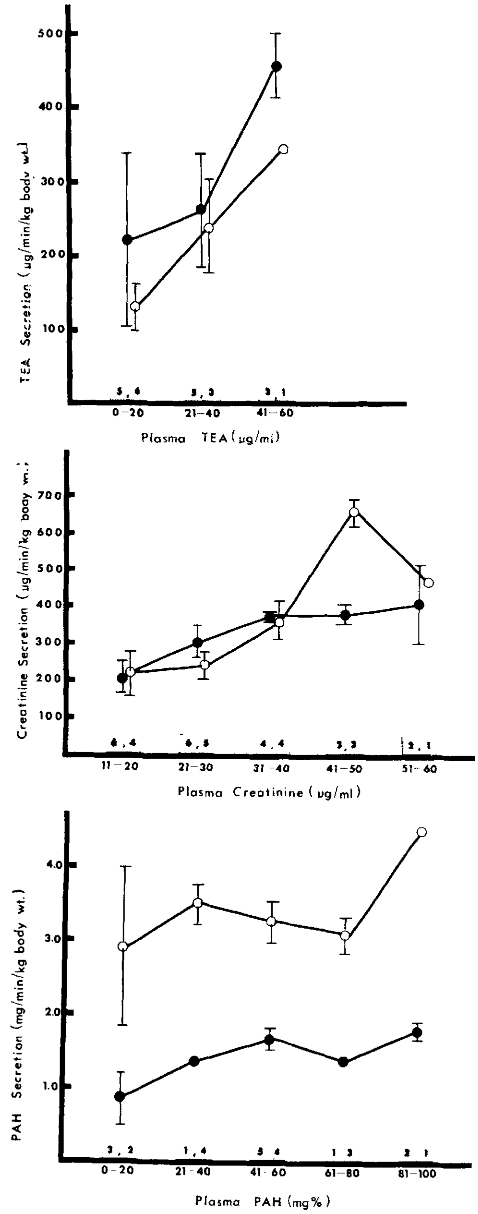

FIG. 2. Renal secretion of tetraethylammonium, creatinine, and p-aminohippuric acid. HUA line, closed circles; LUA line, open circles. Six hens of each line were used for measurement of tetraethylammonium secretion, 6 of the HUA line and 5 of the LUA line for creatinine secretion and 5 of the HUA line and 4 of the LUA line for p-aminohippuric acid secretion. Mean body wt were 1.46 ± .05 kg for the HUA line and 1.53 ± .06 kg for the LUA line. Mean inulin clearance for the 16 hens of the HUA line and 14 hens of the LUA line were 1.85 ± 0.10 and 2.03 ± .11 ml/min/kg of body wt (no significant differences, $P < .05$). The numbers in shaded areas indicate the numbers of observations for the HUA and LUA lines respectively.

glucose and arginine using automated procedures according to Technicon Methodology[4] N-2a and N-1a. Inulin was determined as described previously (2).

All data were analyzed by the t-test for determination of statistically significant differences between means (7).

Results and Discussion. The transport of only one of the 5 substances tested was found to differ in chickens of the HUA and LUA lines (Figs. 1 and 2). Over the range of plasma concentrations studied, the rates of reabsorption of arginine and glucose (Fig. 1) and the rates of secretion of creatinine and tetraethylammonium were similar for both lines (Fig. 2). The rate of secretion of PAH by hens of the HUA line, however, was only one-half the rate for hens of the LUA line (Fig. 2). The reduction of PAH transport was similar to the impairment of uric acid secretion by hens of the HUA line reported earlier (2), and seems reasonable in view of other studies which have shown that these 2 substances share a common transport system (8–10).

The clearance of inulin was similar for both lines ($P < .05$). The mean inulin clearances for the 12 hens of the HUA line and 11 hens of the LUA line used in the studies of glucose and arginine transport (Fig. 1) were 2.30 ± 0.27 and 2.26 ± 0.22 ml/min/kg of body wt, respectively. The respective inulin clearances for the 16 hens of the HUA line and the 14 hens of the LUA line used in measurement of TEA, PAH and creatinine transport (Fig. 2) were 1.85 ± 0.10 and 2.03 ± 0.11 ml/min/kg of body wt, respectively. In view of the relatively large number of hens showing no differences in inulin clearance, it appears that the small difference observed

[4] Technicon Instruments Corporation, Tarrytown, New York.

previously (2) can be disregarded as a characteristic difference between chickens of the two lines.

The substances employed in these studies were chosen for evaluation of a wide variety of transport systems. Definitive information on their site of transport in birds is lacking. However, studies with mammals suggest that they are transported by the proximal tubule (11–15). An attempt was made to infuse all substances at rates which would saturate the respective transport systems during the 2 hour infusion period. Although maximum transport rates were obtained for glucose, PAH, and arginine, transport maxima were not clearly established for TEA and creatinine. Substantial within-line variability occurred in the transport of TEA and creatinine, and insufficient data were obtained at the highest plasma levels to ascertain whether transport rates for these compounds were maximal.

Creatinine exhibits unusual properties in the avian kidney. Endogenous creatinine is reabsorbed in chickens (16), but as plasma creatinine concentration is increased by intravenous infusion of creatinine, net secretion is observed (16, 17). Creatinine has been reported to share both the organic base and organic acid systems for transport (18–20). It is significant that in the present studies creatinine appeared to be secreted equally well by hens of the HUA and LUA lines, although marked differences in rates of organic acid (PAH, uric acid) but not in organic base (TEA) transport were observed (Figs. 1 and 2) (2). It appears from these experiments that the organic acid transport system was a minor component in creatinine secretion.

It may not be possible to establish the maximum rate for tubular arginine reabsorption in the chicken. Measurement of the transport of arginine was complicated by the tendency for most hens to have an apparent net secretion of this amino acid during the latter part of the infusion period. The reabsorption of arginine increased during its infusion to a maximum which varied considerably among hens. As the filtered load of arginine was increased further, the rate of reabsorption decreased precipitously and eventually reached a negative value.[5]

The plasma concentrations of arginine at which the apparent net secretion occurred greatly exceeded normal blood concentrations. It appears that a secretory mechanism for arginine may have become prominent as blood arginine increased to excessive levels. For this reason, only the transport values for each hen which preceded and included the peak in reabsorption of arginine were used in the preparation of the data for Fig. 1. The rate of arginine reabsorption obtained in these studies approximates that obtained by Boorman (21) at comparable filtered loads of arginine. However, maximum filtered loads in the present studies were over 3-fold greater than in Boorman's experiments (16). The approximate transport maximum for arginine reabsorption derived from the present data is 250 μg arginine per min per kg body wt.

The present studies were conducted to determine whether the impaired urate secretion of chickens of the HUA line (2) represented a specific transport defect or a more general kidney malfunction. This consideration is of critical importance if these genetic lines are to be of value in studying the mechanism of uric acid transport. The similarity of rates of renal transport for glucose, arginine, creatinine and TEA, and of inulin clearance by both lines, and the marked reduction of PAH transport by the HUA line, suggest that the impaired transport of uric acid in chickens of the HUA line represents a transport defect specifically associated with the uric acid secretory system.

Summary. Studies were conducted to assess renal transport functions in chickens which had undergone genetic selection for a high (HUA line) or low (LUA line) incidence of hyperuricemia and articular gout. It was found previously that uric acid secretion was markedly reduced in chickens of the HUA line. In the present studies the rates of glomerular filtration, tubular reab-

[5] This phenomenon has been observed in other strains of chickens. Shu-heh Wang, Department of Poultry Science, Cornell University, personal communication.

sorption of arginine and glucose, and tubular secretion of tetraethylammonium and creatinine were not significantly different between chickens of the two lines. The rate of secretion of PAH in chickens of the HUA line, however, was approximately 40% of the rate for chickens of the LUA line. These results suggest that renal impairment in hyperuricemic chickens is specific for organic acid transport.

1. Cole, R. K., Austic, R. E., and Shane, S. M., Poultry Sci. **48**, 1796 (1969).

2. Austic, R. E., and Cole, R. K., Amer. J. Physiol. **223**, 525 (1972).

3. Mongin, P., Doctoral Thesis, University of Paris (1969).

4. Friedman, S. M., Polley, J. R., and Friedman, C. L., Amer. J. Physiol. **150**, 340 (1947).

5. Taussky, H. H., J. Biol. Chem. **208**, 853 (1954).

6. Mitchell, R., and Clark, B. B., Proc. Soc. Exp. Biol. Med. **81**, 105 (1952).

7. Snedecor, G. W., Statistical Methods. Iowa State College Press (1956).

8. Weiner, I. M., and Mudge, G. H., Amer. J. Med. **36**, 743 (1964).

9. Peters, L., Pharmacol. Rev. **12**, 1 (1960).

10. Berger, L., Yü, T. F., and Gutman, A. B., Amer. J. Physiol. **198**, 575 (1960).

11. Rennick, B. R., and Moe, G. K., Amer. J. Physiol. **198**, 1267 (1960).

12. Beechwood, E. C., Berndt, W. O., and Mudge, G. H., Amer. J. Physiol. **207**, 1265 (1964).

13. Davis, B. B., Field, J. B., Rodnan, G. P., and Kedes, L. H., J. Clin. Invest. **44**, 716 (1965).

14. Zins, G. R., and Weiner, I. M., Amer. J. Physiol. **215**, 411 (1968).

15. Wedeen, R. P., and Thier, S. O., Amer. J. Physiol. **220**, 507 (1971).

16. Sykes, A. H., Res. Vet. Sci. **1**, 315 (1960).

17. Shannon, J. A., J. Cell. Comp. Physiol. **11**, 135 (1938).

18. O'Connell, J. M. B., Romeo, J. A., and Mudge, G. H., Amer. J. Physiol. **203**, 985 (1962).

19. Swanson, R. E., and Hakim, A. A., Amer. J. Physiol. **203**, 980 (1962).

20. Rennick, B. R., Amer. J. Physiol. **212**, 1131 (1967).

21. Boorman, K. N., Comp. Biochem. Physiol. **39**, 29 (1971).

Received Mar. 15, 1974. P.S.E.B.M., 1974, Vol. 146.