Adaptation to Taurine Deprivation in the Phosphate-Depleted Rat

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ABSTRACT. The nonessential amino acid taurine, which is inert in renal tissue, was used to study renal adaptation in the presence of phosphate (P) depletion in the rat. Weanling rats were placed on the control diet (0.7% P, normal taurine) for 4 wk, then fed one of the experimental diets or continued on the control diet for 1 wk. The diets used were 1) P^+T^- (0.7% P, low taurine), 2) P^-T^+ (0.1% P, normal taurine); and 3) P^-T^- (0.1% P, low taurine). Taurine deficiency was associated with avid tubular reabsorption of taurine, irrespective of P status. This was associated with a 4- to 5-fold increase in the V_{max} of uptake ($p < 0.001$). On the other hand, P depletion increased the K_m of taurine uptake by 6.6- to 9.5-fold, suggesting a decrease in the affinity of the taurine symport ($p < 0.001$). This was independent of the taurine status of the animals. Although there was no effect of diet on the urinary excretion of β -alanine, P depletion, irrespective of taurine status, resulted in a 2-fold increase in the K_m of β -alanine uptake. We conclude that the taurinuria of P depletion is reversed in taurine deprivation. The adaptive response involves an increase in the V_{max} of uptake. However, the increase in K_m of taurine uptake observed in P depletion does not reverse with taurine depletion. (*Pediatr Res* 30: 146-149, 1991)

Abbreviations

P, phosphorus
BBMV, brush border membrane vesicle
HEPES, *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid
 P^+T^- , phosphate replete, taurine-depleted
 P^-T^+ , phosphate- and taurine-depleted
 P^-T^- , phosphate-depleted, taurine replete

The renal tubular epithelium is able to conserve amino acids during periods of decreased dietary intake. Rats or mice fed diets low in sulfur-containing amino acids adapt by increasing the tubular reabsorption of these amino acids, particularly taurine (1, 2). The adaptive response manifests at the luminal surface by enhanced taurine uptake by BBMV prepared from rats fed these diets (3). These changes are associated with an increase in the initial rate of uptake (V_{max}) rather than a decrease in the affinity of the symport (K_m) (3). The physiologic signal(s) for the observed changes relate, in part, to alterations in the renal cortical content of taurine (4, 5).

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On the other hand, it has been shown that vitamin D- and/or phosphate-depleted rats develop taurinuria in the absence of secondary hyperparathyroidism (6). The taurinuria manifests at the renal brush border membrane by a decrease in the affinity of the taurine symport, resulting in decreased accumulation of taurine by BBMV (7). No changes could be elicited for the V_{max} of uptake. In addition, the perturbation in uptake was not associated with alterations in plasma or renal cortex taurine concentrations, suggesting that overflow is not a regulatory signal in this model.

Although the adaptive response has been shown to exist in terms of urinary excretion at the apical surface in adult rats, little is known about the response of these animals to taurine deprivation in the presence of phosphate depletion. Herein, we describe the effect of low sulfur-containing amino acid diets on the renal handling of taurine in the P-depleted rat. In addition, we examine the effect of these diets on the accumulation of β -alanine (an amino acid that is transported by the same transporter) by BBMV prepared from these animals.

MATERIALS AND METHODS

Animals. Weanling Sprague-Dawley rats (Hilltop Laboratories, Scottsdale, PA) were used in this study. All experiments were performed on animals aged 55 to 58 d after they had been fed the specific diets for 5 wk.

Diets. The animals were fed one of the diets listed in Table 1. These specific diets were prepared by Teklad Laboratories (Madison, WI). Soy protein was used because it is nearly devoid of taurine (0.01% wt/wt) and deficient in methionine (0.2% wt/wt) and cysteine (0.24% wt/wt). Supplementation with 0.6% methionine allows normal growth (8) and promotes normal taurine homeostasis (9). All diets contained 20% protein and similar amounts of salt and vitamin mix. Dietary P was changed by varying the content of equimolar sodium phosphate to provide 0.7% P (phosphate replete, P^+) or 0.1% P (phosphate depleted, P^-). Because taurine is the focus of the study, the diets are described in terms of the potential for taurine bioavailability. Thus, diets replete in taurine are denoted by T^+ , and diets that are taurine depleted are denoted by T^- .

All weanling rats (aged 20-22 d) were fed the control diet for 4 wk, then given one of the other three diets or continued on the control diet for 7 d [a period demonstrated to be more than adequate to induce taurine and/or P depletion (1, 10) without gross evidence of hydronephrosis or renal stone formation.] One day before they were killed, the animals were placed in metabolic cages for 10 h and urine was collected. To avoid the taurinuria observed in fasted rats fed low taurine diets (11), the animals had access to food and water. No attempt was made to pair-feed the animals. When the daily intake of the rats on the various diets was compared, there were no statistically significant differences among the groups (control 15 ± 2 versus P^+T^- 14.1 ± 1.5 versus P^-T^+ 13.5 ± 1.7 versus P^-T^- 14.8 ± 1.6 g/d). This is different from the observation of Friedman *et al.* (12), who reported that

Table 1. *Composition of diets*

	Control*	P ⁺ T ⁻	P ⁻ T ⁺	P ⁻ T ⁻
Dextrose	64	64	64	64
Corn oil	5	5	5	5
Soy protein	20	20	20	20
Salt and vitamin mix	9.7	9.7	9.7	9.7
Methionine supplements	0.6	None	0.6	None
P	0.7	0.7	0.1	0.1

* Control, phosphate and taurine replete.

low taurine diets resulted in increased intake of food when compared with controls.

On the day of the experiments, the rats were lightly anesthetized with anhydrous ether, blood was obtained from the bifurcation of the aorta, and the kidneys and ureters were checked for visible hydronephrosis and stone formation. Plasma was separated by refrigerated centrifugation (4°C) at 4000 rpm and stored at -20°C. Plasma and urine Ca, P, and creatinine were determined, as previously described (6, 13). Renal cortical, plasma, and urine amino acids were separated by ion exchange chromatography as described by Moore *et al.* (14), and modified by Hamilton (15), using an amino acid analyzer (Perkin-Elmer Corp., Norwalk, CT).

Preparation of BBMVs. BBMVs were prepared by differential centrifugation and MgCl₂ precipitation, using a modification of the method of Booth and Kenny (16), as described elsewhere (3, 17). The final pellet was suspended in THM-300 (2 mM Tris-HEPES, 298 mM mannitol, 1 mM MgSO₄, pH 7.4) to yield a final protein concentration of 10 ± 1 mg/mL. The orientation of the vesicles thus prepared is right side out (18). Only fresh vesicles were used. BBMVs were assayed by using Folin reagent (19). Purity of the preparation was assessed by enrichment of brush border membrane enzymes (τ -glutamyl-transferase and 5'-nucleotidase (20, 21) with respect to the original homogenate. The activities of τ -glutamyl-transferase and 5'-nucleotidase in the final brush border fraction were 9- and 6-fold greater than in the original homogenate, respectively, signifying a pure preparation. On the other hand, ouabain-inhibitable Na⁺-K-ATPase (22), a marker for the basolateral membrane, was enriched by less than 0.5-fold, indicating a noncontaminated brush border preparation. There were no differences in these enzyme activities among the various diets. Enzyme markers of other subcellular fractions (malate dehydrogenase, succinyl cytochrome C reductase, and N-acetyl- β -D-glucosaminidase) in the final brush border suspension were reduced in activity relative to the starting homogenate.

Amino acid uptake studies. The uptakes of ³H-aurine and ³H- β -alanine were assayed by the rapid Millipore filtration technique (23) at 23°C for 0.5 to 45 min, after a preincubation period of 1 h at 23°C. Incubation was initiated by the addition of a medium containing known amounts of unlabeled and radiolabeled taurine or β -alanine (usually 8 μ Ci/mL reaction mixture are added), 1.05 mM MgSO₄, 50.54 mM mannitol, 2 mM Tris-HEPES, and 131.58 mM NaCl such as to maintain the final osmolarity at 300 mosmol and Na⁺_{out} (100 mM) > Na⁺_{in} (0 mM). After the desired interval of time, a 50- μ L aliquot was placed on a prewetted 0.45- μ m filter (Gelman Instrument Co., Ann Arbor, MI). The filtered sample was washed three times with 3 mL iced "stop solution" (containing 154 mM NaCl and 2 mM Tris-HEPES, pH 7.4). The filters were dried overnight, dissolved in Aquasol and counted in a liquid scintillation counter (Packard TriCarb 4640, Downers Grove, IL). Values for the nonspecific retention of radioactivity on the filters accounted for less than 1% of the radioactivity in the incubation mixture and were subtracted from the total counts.

Statistics. Data comparisons were made using *t*-test, analysis of variance, and linear regression analysis using SPSSPC+ statistical package (SPSS, Chicago, IL) for personal computers.

Materials. [³H]-taurine (sp act 22.4 Ci/mmol) and [³H]- β -

alanine (sp act 120 Ci/mmol) were purchased from New England Nuclear (Boston, MA). Radiochemical purity was confirmed by one-dimensional thin-layer chromatography. All chemicals used to prepare the various media were reagent grade. All media were filtered through a 0.20- μ m filter (Gelman Instrument Co., Ann Arbor, MI) on the day of the experiment.

RESULTS

In vivo. There were no changes in the creatinine clearance or the plasma Ca on the different diets (Table 2). As demonstrated previously (6, 13), P depletion resulted in hypercalciuria (urinary Ca: control 0.17 ± 0.01 versus P⁺T⁺ 14.75 versus P⁻T⁻ 12.69 ± 1.08 μ mol/100 g body wt/h). However, there was no evidence of hydronephrosis and gross renal stone formation, as assessed during nephrectomy of the animals, because P depletion was induced over 1 wk (instead of 4 wk).

The effect of dietary manipulation on plasma, renal tissue, and urine concentrations of taurine and β -alanine are shown in Tables 3 and 4. Plasma and renal cortical taurine concentrations were lower in animals fed the low-taurine diets than those assayed in the animals fed the control diet (*p* < 0.01). The diets did not affect the plasma and renal cortical concentration of β -alanine. On the other hand, low-taurine diets resulted in avid reabsorption of taurine from the urine, irrespective of P status (*p* < 0.01). P depletion caused a 2.6-fold increase in the urinary excretion of taurine in P⁺T⁺. This increase was statistically significant when compared to control (*p* < 0.001). The renal handling of β -alanine was not perturbed in any of the experimental diets.

Table 2. *Effect of dietary manipulation on creatinine clearance and plasma Ca**

Diet	Creatinine clearance (mL/min/100 g body wt)	Plasma Ca (mg/dL)
Control† (8)	1.04 ± 0.21	10.27 ± 0.17
P ⁺ T ⁻ (7)	0.98 ± 0.18	10.33 ± 0.11
P ⁻ T ⁻ (7)	0.97 ± 0.19	10.55 ± 0.12
P ⁺ T ⁺ (8)	1.01 ± 0.22	10.45 ± 0.15

* Results represent the mean ± SEM, with the number in parentheses indicating the number of samples assayed.

† Control, phosphate and taurine replete.

Table 3. *Effect of dietary manipulation on taurine homeostasis (p < 0.001)**

Diet	Taurine concentration		
	Plasma (μ mol/L)	Renal cortex (μ mol/g wet cortex)	Urine (μ mol/mg creatinine)
Control† (8)	23.76 ± 0.57 (8)	9.29 ± 0.98 (4)	4.11 ± 0.34 (14)
P ⁺ T ⁻	14.68 ± 1.30‡ (10)	3.65 ± 0.55‡ (5)	0.23 ± 0.03‡ (6)
P ⁻ T ⁻	15.76 ± 1.36‡ (5)	3.10 ± 0.47‡ (4)	0.18 ± 0.05‡ (5)
P ⁺ T ⁺	25.46 ± 1.19 (4)	8.37 ± 1.43 (4)	10.58 ± 1.44‡ (5)

* Results represent the mean ± SEM of four to 14 determinations, as indicated by the numbers in the parentheses.

† Control, phosphate and taurine replete.

‡ Significantly different from control, *p* < 0.001.

Table 4. *Effect of taurine and/or P depletion on β -alanine homeostasis*

	Renal cortex (μ mol/g wet tissue)	Plasma (μ mol/dL)	Urine (μ mol/mg creatinine)
Control*	0.49 ± 0.06	0.14 ± 0.04	0.20 ± 0.021
P ⁺ T ⁻	0.43 ± 0.05	0.13 ± 0.02	0.21 ± 0.03
P ⁻ T ⁻	0.37 ± 0.06	0.11 ± 0.01	0.19 ± 0.01
P ⁺ T ⁺	0.40 ± 0.08	0.12 ± 0.04	0.18 ± 0.03

* Control, phosphate and taurine replete.

In vitro. The uptakes of taurine (10 μ M) (Fig. 1A) and β -alanine (10 μ M) (Fig. 1B) over time were Na^+ -dependent in the presence of an inwardly directed Na^+ gradient (100 mM) and were 25 times higher than that found in the absence of an external cation gradient. The peak of the "overshoot" of uptake for both of the amino acids under consideration occurred at 6 min. The Na^+ -independent uptake of taurine and β -alanine, which represents less than 5% of the total uptake of the amino acid, was not affected by diet.

The uptake of taurine by BBMV prepared from animals fed the low-aurine, P-replete diet (P^+T^-) was more rapid than the uptake by BBMV prepared from the control diet. This was particularly significant during the "uphill" phase of the uptake, where the uptake was increased by 2-fold in the taurine-deficient diet (control 72.14 ± 6.34 versus P^+T^- 138.39 ± 16.33 pmol/mg protein/6 min, $p < 0.001$). However, the accumulation of taurine at equilibrium was not affected.

Although P depletion (P^-T^+) resulted in a 2.5 ± 0.1 -fold attenuation in the accumulation of taurine by BBMV prepared from that diet, the additive effect of taurine deprivation (P^-T^-) enhanced taurine uptake by 1.7 ± 0.1 -fold during the uphill portion of uptake when compared with P^+T^+ . The difference in taurine uptake between P^+T^+ and P^-T^- was statistically significant ($p < 0.02$). However, taurine deprivation did not normalize taurine uptake, nor did it increase uptake to levels comparable to those observed in the P^+T^- diet when P depletion coexisted in the same animal.

The kinetics of taurine accumulation over the range 10–250 μ M by BBMV prepared from animals fed the above diets is

Fig. 1. The Na^+ -dependent uptake of taurine (10 μ M) (A) and β -alanine (10 μ M) (B) by BBMV prepared from rats fed the various diets is depicted. Each point represents the mean $\pm$ SEM of four to 14 experiments done in duplicate. ○, control ($n = 14$); ●, P^+T^- ($n = 8$); △, P^-T^- ($n = 6$); ▲, P^+T^+ ($n = 4$); □, Na^+ -independent uptake ($n = 4$).

shown in Table 5. At 30 s, a time when uptake is on the linear portion of the uptake curve, so that the initial rate of uptake could be estimated (7), the accumulation of taurine was greatest in the taurine-deficient diets, irrespective of P status. The increase was due to a change in the V_{max} of uptake, and the difference from control and P^+T^+ diets was statistically significant ($p < 0.001$). Although there was no change in the K_m of uptake in P^+T^+ , P depletion effected a decrease in the affinity of the Na^+ -taurine cotransporter. The increase in K_m was statistically significant when compared with control ($p < 0.001$). However, the increase in the K_m of uptake in P^-T^- was less than that observed in P^-T^+ (198 ± 36.07 versus 285.74 ± 39.79 μ M, $p < 0.02$).

There was a 48% attenuation in the uptake of β -alanine in the P-depleted diets during the uphill phase, irrespective of taurine status (Control 56.03 ± 4.85 versus P^-T^+ 29.24 ± 4.61 versus P^-T^- 28.41 ± 4.88 pmol/mg protein/6 min). The difference when compared with control was statistically significant ($p < 0.01$). Taurine deprivation in the presence of P sufficiency did not affect the uptake of β -alanine. There was no change in the V_{max} of uptake or uptake at equilibrium. However, K_m increased 2-fold with P depletion (P^-T^- and P^-T^+ , $p < 0.01$). K_m remained unchanged in P^+T^- .

DISCUSSION

The transport of solutes at the renal brush border membrane increases during periods of deprivation. The data presented above demonstrate that the adaptive response manifests by an increase in the reabsorption of taurine in animals fed reduced amounts of sulfur-containing amino acids (taurine, methionine, and cysteine), as has been demonstrated by Chesney *et al.* (3). The adaptation is independent of the P status of these animals in that there was an 18- and 23-fold decrease in the urinary excretion of taurine in the absence and presence of P depletion, respectively. No changes were observed in the homeostasis of β -alanine.

The augmentation in the reabsorption of taurine in states of sulfur-containing amino acid depletion is associated with a 4- to 5-fold increase in V_{max} , results that confirm the findings reported by Chesney *et al.* (3, 24). When the uptake of taurine over time in P^+T^- is compared to that in P^-T^- , it becomes evident that the accumulation of taurine in the presence of P depletion is less than in P sufficiency (P^+T^- : 138.39 ± 16.33 pmol/mg protein/6 min versus P^-T^- : 45.33 ± 3.95 pmol/mg protein/6 min, $p < 0.001$). On the other hand, taurine deficiency induces a 1.45-fold increase in the uptake of taurine by vesicles prepared from animals fed the P^-T^- diet compared with those fed the P^+T^+ diet. The apparent differences in the adaptive response may be related to the effect of diet on the K_m of uptake. Although taurine deficiency alone has no effect on the affinity of the taurine symport, P depletion decreases the affinity of the transporter for taurine, as reflected in an increase in the K_m of uptake, irrespective of taurine status. This may explain the persistent attenuation in the uptake of this amino acid over time with no apparent perturbation in the observed *in vivo* adaptive response.

There was no change in taurine uptake at equilibrium, suggesting that the alterations in symport behavior are not related to the size of the vesicle formed. In addition, although the decreased renal cortex taurine content in rats fed the low sulfur amino acid diet regulates the adaptive response (4), we don't feel that it is the sole regulatory stimulus because we would expect identical changes in taurine uptake in P^+T^- and P^-T^- . The increase in the V_{max} of uptake could be related to either the synthesis of new transporters (*de novo*) or the recruitment of inactive transporters. In studies that used colchicine (a substance that blocks the incorporation of preformed symporter into the membrane) in fasting rats or animals fed a high-aurine diet, there was blocking of the rise in taurine uptake in the former, and blocking of the reduction in taurine uptake in the latter (25). The data suggested that the augmentation or attenuation in the

Table 5. *Effect of diet on kinetics of taurine uptake**

	Control† (14)	P-T ⁺ (8)	P-T ⁻ (6)	P-T ⁻ (4)
K _m (μM)	30.17 ± 2.35	285.74 ± 39.79‡§	198.64 ± 36.07‡§	36.92 ± 6.21
V _{max} (pmol/mg protein/ 30 s)	101.01 ± 6.49	157.47 ± 24.66	503.56 ± 165‡¶	420.6 ± 51.32‡¶

* Results represent the mean ± SEM, with the number in parentheses indicating the number of samples assayed.

† Control, phosphate and taurine replete.

‡ Statistically different from control, $p < 0.001$.

§ Statistically different from P-T⁺, $p < 0.001$.

|| Statistically different from P-T⁺, $p < 0.02$.

¶ Statistically different from P-T⁺, $p < 0.001$.

Na⁺-taurine symport activity is due to incorporation of already existing transporters rather than to *de novo* synthesis.

Our study, as well as other studies (3–5, 24), indicates that renal adaptive responses to dietary manipulation are membrane events. It has been shown that the change in the initial rate of Na⁺-taurine uptake and V_{max} in the taurine-deficient animal are not related to changes in the phospholipid composition and fatty acid content of the luminal membrane (26). On the other hand, we were able to demonstrate a 40% decrease in the phosphatidylcholine and phosphatidylethanolamine content of brush border membranes prepared from animals fed the P-T⁺ diet, associated with a 15% reduction in oleic, stearic, and linoleic acid, and a 15% increase in palmitic acid in the phosphatidylcholine and phosphatidylethanolamine fractions (27). Although, we have not determined the effect of P-T⁻ on phospholipid composition of the membranes, we speculate that an effect similar to that found in the P-depleted animals may occur to explain the persistence in the decreased affinity of the taurine symport, despite the increase in the initial rate of uptake or the number of Na⁺-taurine transporters. It is quite possible that these “new” transporters have a normal affinity for taurine, which could explain the lower K_m for taurine uptake in P-T⁻ (198.64 ± 36.07 μM) than in P-T⁺ (285.74 ± 39.79 μM) ($p < 0.02$).

The adaptive response illustrated in this study appears to be specific. When the uptake of β-alanine [an amino acid that shares the same transporter as taurine (28, 29)] was assayed in the same animals, we could not demonstrate a change in the V_{max}, K_m, or uptake of β-alanine over time in taurine depletion. However, P depletion (irrespective of taurine status) manifested with a decrease in the affinity of the symport for β-alanine associated with a decrease in the peak of the overshoot of uptake. These observations cannot be explained on the basis of variation in the preparation of the BBMV, inasmuch as the uptakes of taurine and β-alanine were assayed in parallel on the same day. The *in vitro* changes were not associated with perturbations in the urinary excretion of β-alanine. Thus, we speculate that factors other than affinity and/or number of active transporters may play a role in determining the final outcome of substrate conservation. The nature of these catalysts is yet to be determined.

In summary, we studied the effect of P depletion on the adaptive response to taurine deprivation in the rat. Although the rat adapts to taurine deprivation by avidly reabsorbing taurine *in vivo*, the decrease in the affinity of the Na⁺-taurine symporter persists despite the manifest increase in the V_{max} of uptake.

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