THE EFFECTS OF TAURINE IN A RODENT MODEL OF AGING

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INTRODUCTION

A number of excellent review articles have examined the various physiological roles of taurine in adult and developing organisms[19,20,39]. A conclusion that can be drawn from these various reviews is that there is a dearth of information on the role of taurine in aging and senescence. A few studies have examined the tissue content of taurine in aging animal models. In general taurine content seems to decline modestly with advanced age. What is unclear is whether the aging process may increase the demand for the protective and regulatory actions of taurine in cellular homeostasis. This article will briefly review what is known about changes in taurine content and function during senescence and describe our recent studies of taurine supplementation using a common rodent model of aging. We will also discuss the potential consequences of a diminished cytoprotective role of taurine in advanced aging due to a age-related decrement in taurine homeostasis.

The male Fischer 344 (F344) rat has served as a major model of aging for a number of years. A number of legitimate concerns have been raised about this model due to specific pathological changes that occur in this model. The major concerns with the male F344 model are the high incidence of nephropathy and testicular interstitial cell tumors[5,38]. These age-associated pathologies can confound some studies on the basic biology of aging. Human renal function also declines in a roughly linear function with age and this decline begins at about 30 years of age. Hepatic function also diminishes with age. The liver and kidney are both key organ systems in whole body taurine homeostasis. Thus, the ability to regulate the biosynthesis and the renal conservation of taurine may be compromised with advancing age. Intracellular Ca^{2+} regulation[15], protein phosphorylation[24], and antioxidant defense systems[17,22] are all compromised in aging and are also biochemical processes which involve taurine. Therefore, there is a need to have a better understanding of how whole body taurine homeostasis is maintained in advanced aging and if there is an increased functional demand for taurine in the aging organism.

R. J. Huxtable et al. (eds.), *Taurine 2*

BRIEF REVIEW OF TAURINE AND AGING

Taurine content has been measured in brain and peripheral tissues of aged rodents. Timeras *et al.*[40] measured brain regional content of taurine in Long-Evans rats that were 2, 14, 22 and 30 months of age. Taurine content was reported to decline 25-43% in the brain regions examined (spinal cord, brainstem, cerebellum and cerebral cortex) when compared to the 2 month time point. The decline in taurine content was less marked when comparing the 14 to the 30 month old group (11-37% decline)[40]. Tyce and Wong[44] found no difference in taurine content in the cerebrum and hindbrain when they compared 3 month and 22 month old female F344 rats. Banay-Schwartz *et al.*[2] examined taurine content in 53 microdissected brain regions in 3 and 29 month old male F344 rats. In general, taurine content declined about 12% when all brain areas were averaged[34]. Taurine depletion was greatest in the ventromedial nucleus of the hypothalamus where taurine content was reduced 45%. Interestingly, Donzanti and Ung[12] examined microdissected subregions of the striatum in 6 and 20 month old male F344 rats and found an average increase of 23% in taurine content in the aged rats in anterior regions of the striatum. This is in contrast to Banay-Schwartz *et al.*[2,34] who found significant reductions in taurine in the caudate, putamen and globus pallidus. Benedetti *et al.*[3] found significant reductions in taurine content in the striatum, accumbens, cerebellum and cortex of 21-22 month-old male Wistar rats when compared to 3-month-old controls. We previously examined brain taurine content in 6 month and 24 month old male F344 rats and found a consistent 6-8% depletion of taurine in cortex, striatum, and cerebellum[10,46]. Taurine was unchanged in the hippocampus and midbrain, but increased in the brainstem (18%)[46]. Subcellular fractionation of cerebral cortex from 8 month and 30 month old male F344 rats did not uncover any age-related changes in the distribution or content of taurine[9]. We have also examined taurine content in the brain regions from female Long-Evans rats that were 6 and 30 months of age[8]. Taurine was reduced in the entorhinal cortex (16%), amygdala-piriform cortex (14%), striatum (3%) and mediobasal hypothalamus (20%) and increased in the dorsal (16%) and ventral (12%) hippocampus of aged rats[8]. Massie *et al.*[25] examined whole brain taurine content in male C57BL/6J mice ranging in age from 53-932 days of age. Taurine content tended to decrease with increasing age, yielding a -0.43 correlation coefficient that did not quite reach statistical significance. Kirzinger and Fonda[21] found no difference in whole brain taurine content between 12 month and 32 month old male C57BL/6J mice.

Oja *et al.*[32] examined K^+-stimulated taurine release in brain slices from 3, 6, 12, and 18 month old mice. The stimulated release of taurine appeared to increase in the hippocampus and decline in the striatum with age. Taurine release was not substantially altered in the brainstem, cerebellum or cerebral cortex[32]. We have examined taurine efflux stimulated by the neurotoxin trimethyltin in slices of cerebral cortex from 6 month and 24 month old male F344 rats[7]. There was no age-related difference in taurine efflux stimulated by trimethyltin. Taurine content of the cortical slices was, however, significantly lower in the aged F344 slices treated with trimethyltin than the adult controls[7]. We also examined kainic acid-stimulated amino acid release in cortical slices from adult (6 month) and aged (30 month) female Long-Evans rats[8]. There was no effect of age on kainic acid-stimulated taurine release despite an age-related increase in aspartate release[8]. Ooboshi *et al.*[33] reported that ischemia-induced release of taurine was attenuated in the hippocampus of aged spontaneously hypertensive rats (SHR) (19-23 month old) when compared to adult controls (5-7 month old).

We examined the content of taurine in a number of peripheral and cardiovascular tissues[9]. Taurine content was found to be decreased in the atria, caudal artery and kidney of male 30 month old male F344 rats when compared to 8 month old controls[9]. Renal content of taurine was constant at 6, 8, and 22 months of age, but declined in 30 month old male

Table 1. Taurine concentrations in the blood of aged rodents

Animal Model (age in months)	Sample Type	Concentration (nmol/ml)	Ref.
Female Wistar Rats	Plasma (C)		
6		199 ± 31	6
18		220 ± 30	
30		220 ± 41	
Male Sprague-Dawley	Plasma (?)		
2		102 ± 10	13
6		269 ± 22	
24		275 ± 20	
Male F344 Rats	Plasma (C)		
3		36 ± 3	28
24		37 ± 6	
Male F344 Rats	Serum (DC)		
6		333 ± 22	9,46
8		322 ± 15	
24		239 ± 13	
30		255 ± 20	
Female Long-Evans	Serum (DC)		
6		315 ± 28	8
24		184 ± 23	
Female F344 Rats	Serum (CP)		
3		137 ± 7	Unpublished
24		138 ± 16	findings

C: catheter; DC: decapitation; CP: cardiac puncture.

F344 rats[9]. Corman *et al.*[6] reported that aged, female Wistar rats had a significant reduction in urinary taurine excretion. The reduction in urinary taurine excretion was present at 18 months of age and was sustained until 30 months of age[6]. Massie *et al.*[25] found that taurine content in the mouse heart increased with age, whereas liver and kidney was unchanged and leg muscle declined.

Serum and plasma levels of taurine from a number of studies of aged rodents are presented in Table 1. Our laboratory has consistently found that trunk blood collected from decapitated aged rats yields serum taurine concentrations significantly lower than adult rats. Massie *et al.*[25] found no significant age-related change in the taurine content of mouse blood. Other studies including our own that used plasma or serum collected via catheterization or cardiac puncture did not show an age-related decline in taurine concentration (Table 1). Several potential explanations are possible for these findings which include: sympathoadrenal activation may alter circulating taurine concentrations in aged rats, taurine may be released from platelets, lymphocytes, or red cells differentially in aged rats or rapid postmortem changes occur in serum from decapitated aged rats. Decapitation has previously been shown to elevate plasma taurine concentrations[27]. The aged F344 rat has a number of hematological changes that would be consistent with decreased serum taurine derived from lysed cells[5]. Nishio *et al.*[31] reported that taurine augmented mitogen-stimulated proliferative responses to a greater degree in T cells from aged mice (21-28 months old) than from adult controls (2-3 months old). Taurine was also found by Nishio *et al.*[31] to increase intracellular Ca^{2+} concentrations in T cells of aged mice in response to mitogen stimulation to levels comparable to adult mice.

It is difficult to summarize simply the effects of aging on whole body taurine homeostasis or tissue content. In general, tissue content of taurine tends to decline somewhat with advanced age. Differences in the species, strain, sex and age of the animal models used in aging research often lead to problems in the interpretation of the literature.

EFFECTS OF TAURINE IN AGING MALE F344 RATS

Animal Model and Experimental Design

Male F344 rats, 18 months of age, were obtained from Harlan Sprague-Dawley's NIA-supported colony. A group (n=12) of adult rats that were 3 months old at the start of the study were also included. The 18 month old F344 rats (n=90) were divided into 3 dietary conditions (n=30 per group). The groups included: a normal rat chow group (Purina 5012), taurine-supplemented group (5012 chow + 1.5% taurine in the drinking water) and a taurine-deficient diet group (Purina 5729C-M diet). The taurine-deficient diet was identical to the 5012 chow except plant-derived protein was substituted for animal protein to eliminate taurine. All rats were maintained in their own colony room on a 12 h light-dark cycle and food and fluids were available *ad libitum*. Food and fluid intake was monitored at weekly intervals along with body weights. The rats were maintained on these diets for 320 days or until they died. An outline of the experimental design and schedule of the parameters assessed are given in Fig. 1. Data was analyzed using analysis of variance (parametric or nonparametric) followed by appropriate post-hoc group comparisons.

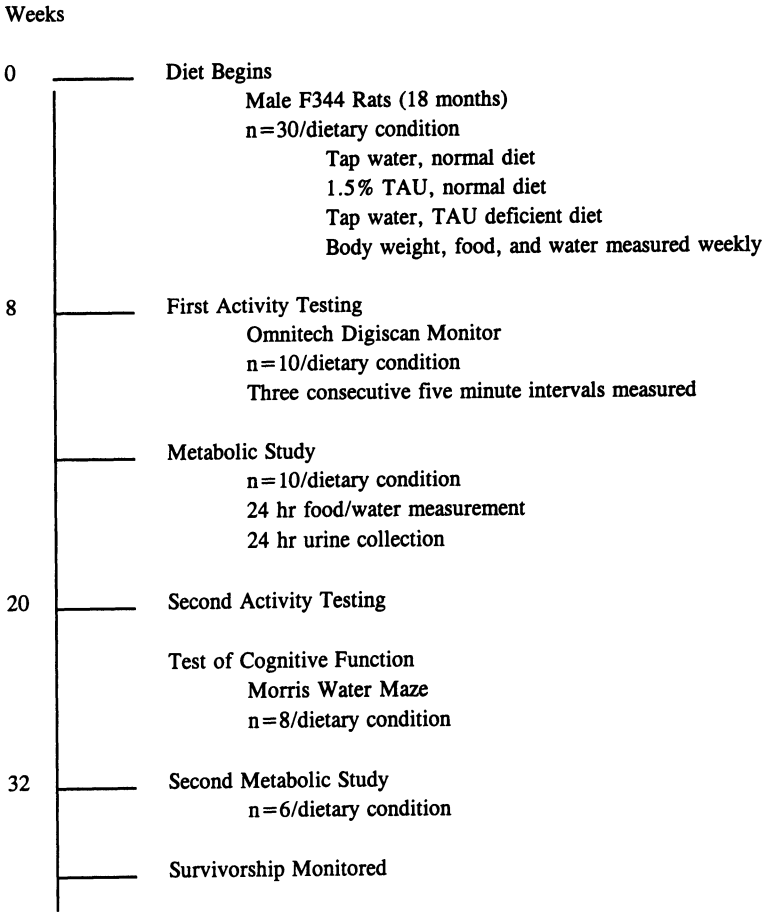

Figure 1. Experimental design.

Metabolic Studies

Metabolic studies were conducted after 12 (n=10 per group) and 32 (n=6 per group) weeks on the diets. The rats were allowed 48 h to acclimate themselves to the metabolic cages prior to collection of data. Food and fluid intake were measured for two consecutive days along with 24 h urine output. These data are presented in Table 2. The urinary excretion of Na^+, K^+, Ca^{2+}, protein, creatinine, urea nitrogen, and glucose was also measured. Urinary excretion of taurine, alanine and glycine was measured by HPLC with electrochemical detection of the o-pthalaldehyde derivatives[9].

Experimental Findings

The effects of diets supplemented with 1.5% taurine in the drinking water or devoid of taurine had no significant effect on survival when compared to a standard rodent diet (Purina 5012) (Fig. 2). The median days of survival on the diets were 241, 245 and 274 for the control, taurine-supplemented and taurine-deficient groups respectively. Taurine supplementation resulted in a greater than 5x elevation in serum taurine in the aged F344 rats

Table 2. Metabolic measures in adult and aged F344 rats

Measure	Adult Control	Aged Control	No TAU	1.5% TAU
Body Weight (g)				
I	240 ± 5	441 ± 11[a,b]	441 ± 7[a,b]	401 ± 10[a]
II	336 ± 22	430 ± 8[a]	413 ± 3[a]	430 ± 2[a]
Food Intake (g/24 h)				
I	19 ± 1	17 ± 1	16 ± 1	17 ± 1
II	25 ± 3	38 ± 2[a]	34 ± 4	39 ± 4[a]
Fluid Intake (g/24 h)				
I	23 ± 1	32 ± 3	32 ± 3	33 ± 4
II	24 ± 4	77 ± 16[a]	67 ± 13[a]	78 ± 5[a]
Urine Output (ml/24 h)				
I	10 ± 1	16 ± 2[a]	12 ± 1	17 ± 2[a]
II	11 ± 1	34 ± 4[a]	30 ± 5[a]	36 ± 5[a]
Glucose Excretion (mg/24 h)				
I	2.92 ± 0.39	5.33 ± 0.57[a]	4.74 ± 0.42	6.35 ± 0.73[a]
II	4.15 ± 1.14	8.62 ± 1.84	7.64 ± 0.95	11.85 ± 3.32
Sodium Excretion (mEq/24 h)				
I	1.63 ± 0.09	1.86 ± 0.12[c]	1.08 ± 0.09[a,b]	1.72 ± 0.16
II	1.27 ± 0.29	1.68 ± 0.20	1.57 ± 0.19	1.67 ± 0.22
Potassium Excretion (mEq/24 h)				
I	0.81 ± 0.10	1.52 ± 0.11[a,c]	0.99 ± 0.07[b]	1.54 ± 0.17[a]
II	2.97 ± 0.47	4.38 ± 0.26[a]	4.23 ± 0.24	4.15 ± 0.30
Calcium Excretion (mg/24 h)				
I	1.25 ± 0.31	1.03 ± 0.14	0.71 ± 0.10[b]	1.79 ± 0.29
II	0.38 ± 0.10	2.42 ± 0.88[a]	2.09 ± 0.41	3.69 ± 0.70[a]
Creatinine (mg/24 h)				
I	15.5 ± 0.9	18.0 ± 1.0	15.7 ± 0.8	17.2 ± 0.8
II	17.6 ± 1.6	19.0 ± 1.2	18.3 ± 1.1	17.6 ± 0.6
UUN (mg/24 h)				
I	252 ± 16	281 ± 17	246 ± 22	243 ± 25
II	228 ± 44	244 ± 57	258 ± 24	193 ± 55

I = First metabolic study: Adult = 4 month old, Aged = 20 month old; II = Second metabolic study: Adult = 10 month old, Aged = 26 month old. a = Significantly different from adult control ($p < 0.05$); b = Significantly different from 1.5% TAU ($p < 0.05$); c = Significantly different from no TAU ($p < 0.05$).

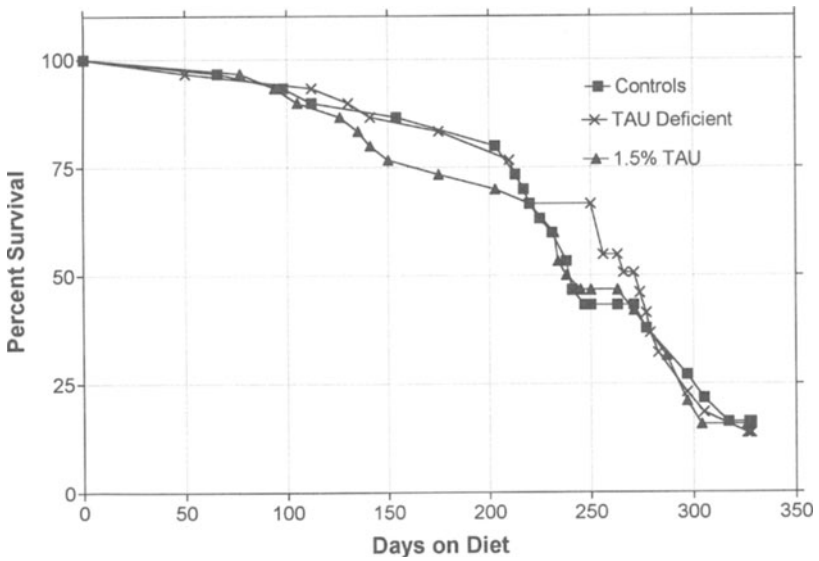

Figure 2. Effects of taurine on life span in F344 rats.

(Fig. 3). As previously reported[9,46], serum taurine was significantly ($p < 0.05$) lower in aged controls (26-29 month old) when compared to adult controls (10-11 month old) (Fig. 3). Serum taurine was also significantly ($p < 0.05$) lower in the aged rats on the taurine-deficient diet compared to the adult controls, but was not different from age matched controls (Fig. 3). Urinary taurine excretion in adult and aged rats is presented in Fig. 4. Taurine excretion was significantly ($p < 0.05$) reduced in 26 month old F344 rats on both normal and taurine-deficient diets when compared to adult (10 month old) or 20 month old F344 rats. As expected, taurine supplementation resulted in highly significant ($p<0.01$) increases in urinary taurine

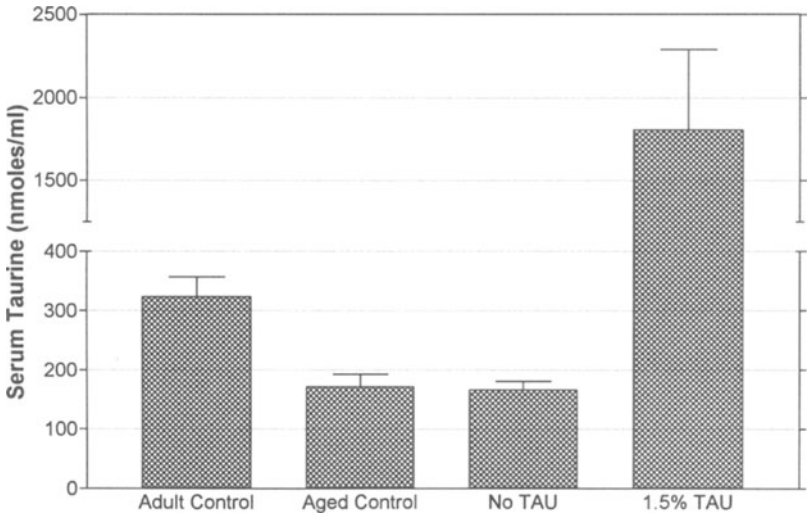

Figure 3. Effects of aging and dietary modifications on serum taurine.

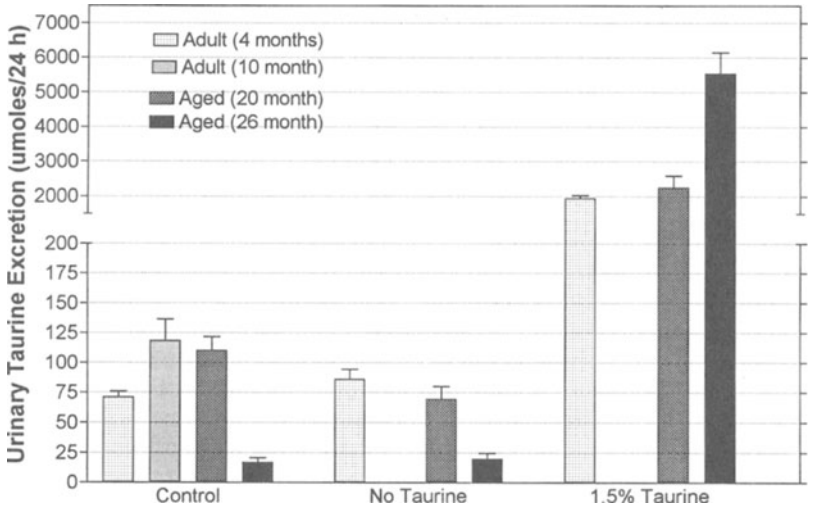

Figure 4. The effects of aging on urinary taurine excretion.

excretion in both adult and aged F344 rats. Urinary excretion of glycine and alanine was also measured in rats on the control and taurine-deficient diets. The high levels of taurine in the urine of the taurine-supplemented group necessitated diluting the urine for analysis to the point that alanine and glycine were not detectable in this group. The pattern of excretion of glycine and alanine with increasing age was distinct from that of taurine. Alanine excretion declined in a roughly linear fashion with age (data not shown). Glycine excretion exhibited a more complex change over time with excretion being stable from 4-10 months (32 μmol/24 h), falling significantly ($p < 0.05$) at 20 months (16 μmol/24 h) and increasing significantly ($p < 0.05$) at 26 months (65 μmol/24 h). Glycine excretion was not affected by the taurine-deficient diet.

There was a pronounced age-related increase in urine output and fluid intake (Table 2). Electrolyte excretion was altered by age and to a modest degree by the dietary manipulations (Table 2). We had previously found that elevated dietary intake of taurine enhanced urinary excretion of K^+ and Ca^{2+} in spontaneously hypertensive rats (SHR)[26]. Calcium excretion increased in the 26 month old rats on the control diet and the taurine-supplemented diet compared to the 10 month old rats on the control diet (Table 2). Calcium excretion was also lower in 20 month old rats on the taurine-deficient diet compared to age matched taurine-supplemented rats (Table 2). Potassium excretion was elevated in the aged rats on the control diet for both metabolic studies when compared to the adults on the control diet (Table 2). Potassium excretion in the 20 month old rats on the taurine-deficient diet was lower than the age-matched rats on the taurine-supplemented diet. However, K^+ excretion did not differ between these groups at 26 months of age (Table 2). Excretion of creatinine and urea nitrogen were not altered by age or diet (Table 2).

Taurine supplementation did not prevent or retard the age-related increase in urinary protein excretion (Fig. 5). The increase in urinary protein excretion is a good marker of the progressive nephropathy that occurs with advancing age in the F344 rat. Taurine supplementation also did not improve the heart weight to body weight ratio for the aged rats. The ratios (heart weight (mg)/100 g body weight) for the groups were: adult control (273 ± 10), aged control (366 ± 18), aged no taurine (400 ± 26) and aged taurine supplemented (369 ± 22).

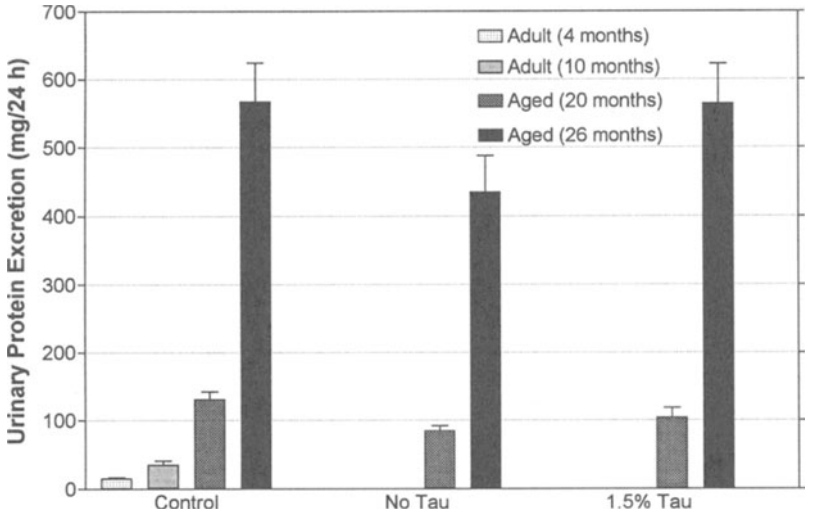

Figure 5. Urinary protein excretion in adult and aged F344 rats.

Serum creatinine and urea nitrogen were significantly ($p < 0.05$) elevated in the aged control group and the no taurine group when compared to the adult controls (Figs. 6 and 7). The aged rats on the taurine-supplemented diet had serum creatinine and urea nitrogen values that did not differ significantly from the adult controls (Figs. 6 and 7). Serum growth hormone, Ca^{2+}, glucose and Na^{+} were not affected by either age or dietary treatment (Table 3). Total serum protein levels were decreased in aged rats (Table 3).

Locomotor activity was assessed after 8 and 20 weeks on the diets. There was no significant effect of the diets on locomotor activity (data not shown). Cognitive function was assessed using the Morris Water Maze. The aged F344 rats (n=8 per dietary condition) selected for water maze training were in good general health and had no visible signs of

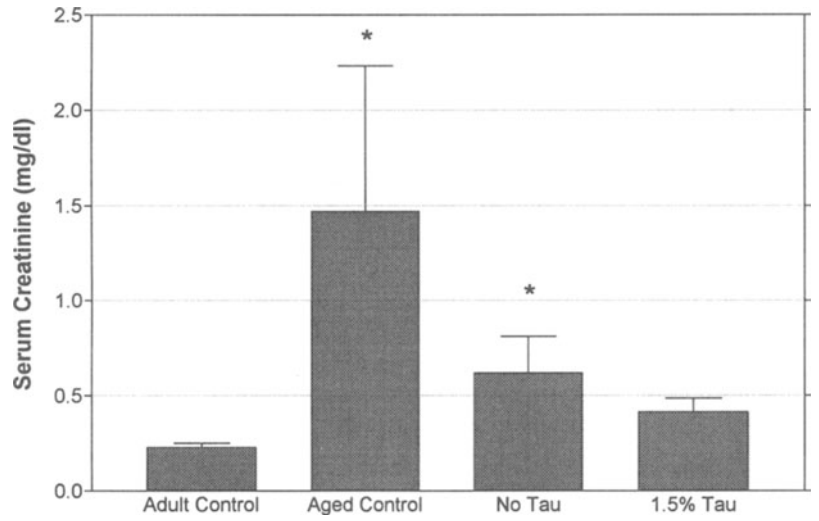

Figure 6. Serum creatinine in adult and aged F344 rats.

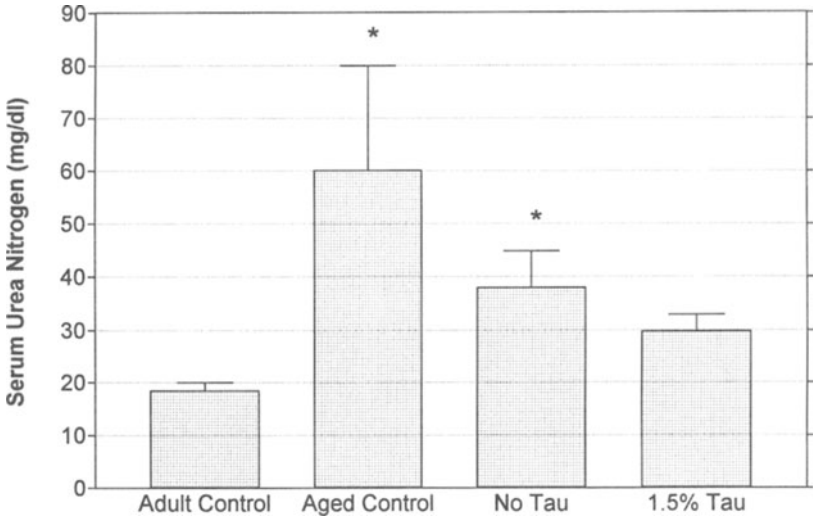

Figure 7. Serum urea nitrogen in adult and aged F344 rats.

cataracts. The aged F344 rats generally exhibited very poor maze learning performance as has previously been reported[23]. Taurine supplementation or restriction had no significant effect on acquisition or retention of the maze learning task (data not shown).

Tissue taurine content has been determined in 3 peripheral tissues (Table 4). Adrenal taurine content was not significantly altered by taurine restriction or supplementation when compared to aged rats on normal diets or adult rats on normal diets. Taurine supplementation resulted in a significant increase in liver taurine content relative to the aged rats eating the normal diet or the taurine free diet. Liver taurine content was variable within treatment groups and this resulted in the aged control group not statistically differing from the adult control group despite a 67% decrease in taurine content. Taurine content of the spleen was significantly decreased in all the aged groups when compared to the adult controls.

Table 3. Serum values for adult and aged F344 rats

Measure	Adult Control	Aged Control	No TAU	1.5% TAU
Growth Hormone (ng/ml)	13.5 ± 8.8	14.1 ± 3.4	29.0 ± 11.1	15.1 ± 4.7
Calcium (n = 3) (mg/dl)	ND	9.3 ± 0.5	10.9 ± 0.2	10.4 ± 0.5
Sodium (mEq/l)	123 ± 2	125 ± 2	129 ± 3	126 ± 3
Glucose (mg/dl)	151 ± 8	120 ± 11	120 ± 7	125 ± 7
Protein (mg/ml)	98 ± 5	70 ± 5[a,b]	61 ± 3[a]	52 ± 3[a]

ND = Not determined; a = Significantly different from adult control ($p < 0.05$);
b = Significently different from 1.5% taurine ($p < 0.05$)

Table 4. Tissue content of taurine in aged F344 rats

Group	Adrenal	Liver	Spleen
Adult Control (n = 6)	6.85 ± 0.52	9.62 ± 2.79	14.14 ± 0.38[2]
Aged Control (n = 11)	7.00 ± 0.62	3.13 ± 0.55	8.55 ± 0.70
Aged No Taurine (n = 14)	7.83 ± 0.52	6.53 ± 1.47	10.09 ± 0.79
Aged 1.5% Taurine (n = 10)	9.33 ± 1.04	20.04 ± 2.20[1]	11.66 ± 0.76

All data expressed as μmol taurine/g tissue weight ± SEM. [1]$p<0.01$ versus aged control or no taurine group; [2] $p<0.05$ versus aged control, aged no taurine or aged 1.5% taurine groups.

GENERAL DISCUSSION

This is the first comprehensive study of the long term effects of taurine supplementation in a rodent model of aging. Our previous findings of reduced serum taurine and reductions in tissue content of taurine provided the rationale for assessing the effects of taurine supplementation and restriction in the F344 model of aging. We replicated our previous findings of reduced serum taurine in the aged male F344 rat and also found that urinary excretion of taurine declines significantly with advancing age. The finding of reduced renal excretion of taurine in aged F344 rats is in agreement with Corman *et al.*[6] who reported an age-related decline in taurine excretion in aged female Wistar rats. These findings suggest that the aged F344 rat can conserve taurine via renal adaptive mechanisms[14,37] despite significant renal nephropathy. These findings also suggest that the aged F344 rat shows signs of taurine deficiency as indexed by reduced serum taurine and renal conservation of taurine. The reduction in urinary taurine could, however, reflect a decrease in liver taurine content (Table 4) as suggested by Waterfield *et al.*[47]. Restriction of the dietary intake of taurine did not greatly exacerbate the reduction in serum taurine or result in further reductions in urinary taurine excretion in the aged F344 rat. Biosynthesis of taurine from precursors (methionine and cysteine) appears normal in aged rats since elimination of a direct dietary source of taurine did not result in significant changes in serum, tissue, or urinary taurine concentrations. Studies are currently underway to complete the measurement of tissue content of taurine in these experimental groups. Thus, despite age-related impairment of renal and hepatic function, taurine biosynthesis and renal adaptive mechanisms appear to compensate for low dietary intake of taurine in the F344 rat. Detailed analysis of tissue content of taurine in specific brain regions, the kidney and cardiovascular tissues is needed to fully assess the impact of taurine restriction on whole body taurine homeostasis in this rat model. Our data on tissue content of taurine would suggest long-term dietary taurine restriction seems to blunt some of the age-related decline seen in tissue taurine content perhaps by stimulation of *de novo* synthesis of taurine. The severe renal damage in the aged rats resulted in high urinary output and excessive fluid intake suggesting a possible mild degree of dehydration (Table 2). We have previously shown in the Brattleboro rat which suffers from diabetes insipidus that brain content of taurine is increased 30-40%[11]. This increase in brain taurine content is thought to be an adaptive response to chronic dehydration[11]. If aged F344 rats do suffer mild dehydration, then the fact that taurine content in brain is not increased with advanced age may reflect an unappreciated age-related depletion of taurine. It is unclear what impact aging would have on species which do not have the high capacity that rats exhibit for taurine biosynthesis.

Table 5. Renoprotective effect of taurine

Strain or Disease State	TAU supplement	Urea	Creatinine	Urinary Protein	Ref.
SHR	1.5%	↓ 32%[1]	—	—	49
WKY	1.5%	↓ 31%[1]	—	—	
SHR	1%	—	—	↓ 58%	43
SP-SHR	1.5%	↓ 21%[3]	↓ 22%[3]	↓ 59%	unpublished findings
PAMN Nephropathy	1%	-	↓ 53%[2]	↑ 10%	41
Sprague-Dawley control	1%	—	↓ 5%[2]	NC	42
STZ Diabetes	1%	—	↓ 4%[2]	↓ 35%	
PAMN Nephropathy	1%	—	↓ 53%[2]	↓ 41%	

STZ = streptozocin; PAMN = puromycin aminonucleoside; NC = no change; 1 = plasma, 2 = serum, 3 = urine.

Taurine supplementation was expected to have a renoprotective effect in the aged F344 rat based on previous studies in a number of animal models of impaired renal function (Table 5). The elevated urinary protein excretion and other age-related changes in renal function (Table 2) were not greatly affected by taurine supplementation. Serum markers of renal nitrogenous waste removal (serum urea nitrogen and creatinine) were elevated to a greater extent in the aged control and aged rats on the taurine restricted diet when compared to the taurine supplemented group. Thus, taurine supplementation blunted the age-related increase in serum markers of nitrogenous waste. Taurine supplementation has previously been shown to reduce serum creatinine and urea nitrogen in other models of impaired renal function (Table 5). This also appears to be the case in aging since taurine supplementation did improve these measures. The age-related increase in urinary protein excretion is related to glomerular structural injury and increased glomerular basement membrane permeability[16]. The renal nephropathy and proteinuria seen in the aged F344 rat may occur by mechanisms that are unresponsive to the renoprotective effects of taurine. There is little experimental data on the influence of taurine on nitrogen balance and excretion. The biosynthesis of taurine can result in the urinary excretion of nitrogen in the form of taurine. Ammonia has been shown to stimulate the release of taurine from cultured astrocytes[1]. Aged rats exhibit deficits in ammonia metabolism[21,45]. Although renal excretion of urea nitrogen and creatinine was not increased by taurine supplementation (Table 2), serum levels were lower. This would suggest that the rate of nitrogenous waste production was diminished by taurine supplementation. The normalization of serum creatinine in taurine supplemental rats could be related to a recent report of improved skeletal muscle function in taurine treated aged rats[36]. Further studies are needed to explore the mechanism for the reduced level of serum nitrogenous waste in taurine supplemented rats.

We have recently completed a series of preliminary studies that suggest taurine may be capable of directly inhibiting iron-stimulated autoxidation of dopamine and l-dopa. Iron can act as a powerful catalysis for the autoxidation of catecholamines resulting in the generation of free radicals and cytotoxic quinones[29,30]. Quinone formation can be monitored spectrophotometrically and the rate of metal-stimulated catecholamine autoxidation can be measured[18]. The results of such an experiment in the presence and absence of taurine are presented in Fig. 8. An extensive series of control experiments has been performed suggesting that taurine and hypotaurine (HTau) can inhibit ($p < 0.05$) iron-stimulated l-dopa oxidation and taurine precursors and ß-alanine (B-Ala) either have no effect or enhance oxidation rates. While taurine can reduce iron-stimulated catecholamine autoxidation, iron-stimulated lipid peroxidation of brain homogenates was unaffected by 20 mM taurine (unpublished observations). We have also found that basal levels of lipid peroxidation in the

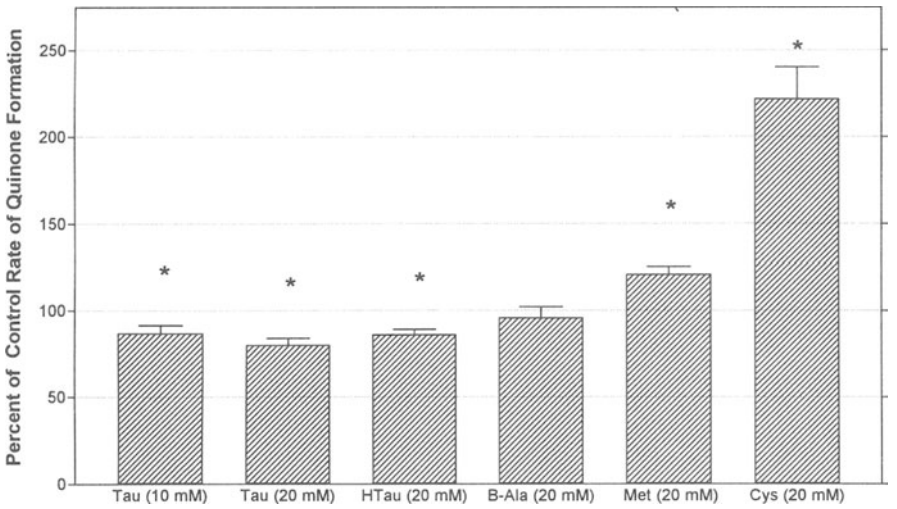

Figure 8. Effects of taurine and related amino acids on ferric chloride-stimulated l-DOPA oxidation.

adrenal glands from the rats used in this study were not altered by aging or dietary treatments. The free radical hypothesis of aging suggests that age-related cellular deterioration is related to the cumulative effects of oxidative damage and the failure to adequately repair such damage[17,22]. There is substantial evidence that oxidative stress increases with advanced age and antioxidant defense systems may not function optimally[17,22]. Taurine has been suggested to have antioxidant functions [20,48]. Specifically, taurine has been shown to protect lymphoblastoid cells from iron-induced cellular damage, but did not reduce iron-induced lipid peroxidation[35]. If taurine content declines with advanced age or whole body taurine homeostasis is altered as suggested by altered serum levels and decreased urinary excretion, then the reduced availability of taurine in advanced age may contribute to an impairment in antioxidant defense mechanisms. This may be particularly important in catecholamine rich brain regions in light of age-related increases in brain iron content[4]. Our laboratory is currently exploring the role of taurine in the aged brain and its potential antioxidant and neuroprotective functions.

Taurine has well established functions in osmoregulation, Ca^{2+} homeostasis, cardiovascular control, and the regulation of neural excitability[19,20,48]. With advancing age the ability for fine-tuned regulation of complex physiological functions diminishes and the ability to respond to metabolic and oxidative challenges also declines. An age-related decline in taurine content or a diminished ability to mobilize or regulate taurine availability could potentially contribute to compromised cellular function or lead to cell death. Clearly, the role taurine in "normal" cellular aging and age-related diseases needs further elucidation and clarification.

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