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Optimal and effective oral dose of taurine to prolong exercise performance in rat

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Summary. The aim of this study was to determine the effective and optimum dose of taurine for exercise performance and to maintain tissue taurine concentration. Rats received a respective daily dose of 0, 20, 100, and 500 mg/kg body weight of taurine (EC and ET-1, -2, -3 groups, respectively) for two weeks, and then, were subjected to treadmill until exhaustion. The running time to exhaustion was significantly prolonged by 25% and 50% in the ET-2 and -3 groups, respectively, compared to that in the EC group accompanied with maintenance of taurine tissue concentrations. Furthermore, the oxidative glutathione per total glutathione ratio in tissues was inhibited in the ET-2 and -3 groups whereas it was higher in the EC group than in both the no exercise and taurine-administered groups. Therefore the effective and optimal doses of oral taurine administration for two weeks on a transient exercise performance were between 100 and 500 mg/kg/day.

Keywords: Taurine – Exercise – Glutathione – Oxidative stress – Lipid hydroperoxide – Administration

Introduction

Taurine, 2-amino ethylsulfonic acid, is one of the most abundant amino acid-like compounds in plasma and various tissues in mammalian species. There is a body of reports both *in vivo* and *in vitro* that suggest a physiological and pharmacological role for taurine including: bile acids conjugation (Danielsson, 1963), plasma membrane stabilization (Pasantes et al., 1985), osmoregulation (Nieminen et al., 1988), neuromodulation (Kuriyama, 1980), neurotransmission (Davison et al., 1971), anti-oxidation (Nakamura et al., 1993), and detoxification (Huxtable, 1992).

We have previously reported that the rat skeletal muscle taurine concentration in the lower leg, in particular, in fast twitch-dominant fiber type muscles, was significantly decreased after a transient exercise to exhaustion on a treadmill (Matsuzaki et al., 2002a). In addition, oral taurine administration in rats was reported to prevent the loss of muscle taurine concentration during exercise and could even enhance exercise performance on a treadmill (Yatabe et al., 2003). Furthermore, several studies reported the beneficial effects of taurine administration not only in rats but also in humans (Baum et al., 2001; Dawson et al., 2002; Zhang et al., 2004). Dawson et al. have shown that 3% taurine administration in the drinking water enhanced the rat exercise performance, which was correlated with the tissue taurine concentration (Dawson et al., 2002). In humans, the exercise performance, measured as exercise time to exhaustion, VO_{2max}, and maximal workload value in a bicycle ergometer, was significantly enhanced by oral taurine administration at a dose of 6 g/day for a week (Zhang et al., 2004). Therefore, the maintenance of the tissue taurine concentration might be of importance for physical activities. However, the effective and optimal dose of taurine administration to enhance exercise performance still remains elusive.

Furthermore, taurine administration may reduce some oxidative stress markers induced by exercise (Dawson et al., 2002; Zhang et al., 2004). Indeed, taurine exhibits a protective effect against cellular-stress induced oxidation and behaves as a free radical scavenger in various cells and tissues (Timbrell et al., 1995). Therefore, there might be a relationship between the effectiveness of taurine on exercise performance and the protective function of taurine against oxidative stress. Taurine administration could affect the metabolism and/or function of glutathione

(GSH; L-γ-glutamyl-L-cysteinylglycine), which is a well-known free radical scavenger, since both taurine and GSH are biosynthesized from common precursors, i.e., the sulfur-containing amino acids methionine and cysteine (Bella et al., 1999). GSH can react with oxidative stress, and produce GSSG; glutathione disulfide, the oxidative GSH form (Sen, 1995). Therefore, the GSSG/total GSH (tGSH = GSH + GSSG) ratio would be enhanced under exercise conditions due to the increased GSSG level (Lew et al., 1985; Sen, 1995).

The aim of the present study was to determine the optimal and effective dose of oral taurine administration on the exercise performance and the tissue taurine concentration. Moreover, the relationship between taurine administration and oxidative stress parameters under exercise condition was studied.

Materials and methods

Animal, taurine administration, and exercise

Male Sprague-Dawley rats, six weeks of age, were purchased from Japan SLC (Shizuoka, Japan). The rats were randomly divided into five groups; a no taurine administered no exercise-control group (NC; $N = 6$), a no taurine administered exercise-control group (EC; $N = 7$), three exercise-taurine groups administered either a 20 mg/kg body weight (BW)/day (ET-1; $N = 7$), 100 mg/kg BW/day (ET-2; $N = 7$), or 500 mg/kg BW/day (ET-3; $N = 7$). The ET-1, -2, and -3 groups received a 0.2%, 1%, and 5% taurine solutions, respectively, as 1 mL/100 g BW by oral lavage for two weeks (Yatabe et al., 2003). The daily and total doses of taurine administered were calculated based on the respective rat's body weight. The rats in the NC and EC groups received water alone used to dissolve taurine according to the same method of administration. All rats were fed a standard diet without taurine (MF; Oriental Yeast, Tokyo, Japan) and kept at 21–25°C under 12-hour dark/light cycles, and received humane care in accordance with *The Guidelines of the University of Tsukuba for the Care of Laboratory Animals*.

After two weeks of administration, the rats in the exercise groups were placed on a treadmill (KN-73; Nazme, Tokyo, Japan) set at 25 m/min until exhaustion. The rats were considered to be completely exhausted when it was impossible for them to continue running, even after being electrically stimulated with a system attached to the treadmill, and when they were unable to upright themselves when turned on their back. This treadmill program was carried out by a blind method as previously reported (Matsuzaki et al., 2002a; Yatabe et al., 2003). The rats in the NC group did not exercise.

Sample preparation

Immediately after the end of the exercise period, the rats from the various groups were anaesthetized with ether. Blood, liver, heart, and gastrocnemius (GC) muscle were collected. Serum and plasma were isolated from the whole blood, and the collected tissues were washed with ice-cold saline, cleared of adipose, nerve and connective tissue, and weighed. The serum and tissue samples were frozen in liquid nitrogen and kept at −80°C until biochemical analyses were carried out.

Biochemical analyses

Serum levels of lactate and glucose were determined by the lactate oxidase pyruvate oxidase method (Asanuma et al., 1985) using a commercially available analysis kit (Determiner® LA; Kyowa Medex, Tokyo, Japan) and an automatic analyzer (Hitachi-7170, Hitachi, Tokyo, Japan), and by the Trinder's glucose oxidase method (Trinder, 1969) using the Glucose B-Test kit (Wako, Osaka, Japan), respectively. For the determination of taurine concentration, the serum and tissues were mixed with ten volumes of a 5% trichloroacetic acid (TCA) solution and homogenized with 20 volumes of the TCA solution, respectively. After centrifugation at 6,200 × *g* for 20 min, the supernatant was used for the determination of taurine concentration using an automatic amino acids analyzer (JLC-300V; JEOL, Tokyo, Japan) according to previously reported method (Matsuzaki et al., 2002a; Matsuzaki et al., 2002b).

Lipid hydroperoxide (LPO) assay in serum and liver

For the determination of lipid hydroperoxide (LPO) concentration, the liver was homogenized into ten volumes of PBS, centrifuged at 600 × g at 0°C for 10 min, and the supernatant was collected. The homogenized sample and serum were used for the determination of LPO concentration as hydroperoxides utilizing the redox reaction with ferrous ions (Mihaljevic et al., 1996) using a commercially available LPO assay kit (Cayman chemical company, Ann Arbor, MI, USA). The absorbance was measured at 500 nm using a plate reader (Emax® Precision microplate reader; Molecular Devices Corporation, Sunnyvale, CA, USA). The methanol and chloroform used in this assay were deoxygenated by nitrogen bubbling for at least 30 min, and all procedures for this assay were carried out at 0°C. The LPO concentration in both cardiac and skeletal muscles was undetectable.

Total glutathione (tGSH) and glutathione disulfide (GSSG) assays

The tGSH and GSSG concentrations were determined using a commercially available GSH assay kit (Cayman). The serum was mixed with an equal volume of a 5% TCA solution, and the tissue sample was homogenized in 20 volumes of the TCA solution. The supernatant was collected after centrifugation at 10,000 × g for 15 min at 4°C, and then, mixed with 4M triethanolamine. The serum sample was further concentrated by lyophilazation. The tGSH concentration in serum and tissues was determined by a GSH reductase-5,5′-dithiobis-2-nitrobenzonic acid (TNB) recycling method (Anderson, 1985). For the determination of GSSG concentration in tissues, the deproteinated sample was incubated in a one-hundredth volumes of 1M 2-vinylpyridine for 60 min at room temperature to derive the GSH. The samples were assayed for the GSSG as well as the tGSH concentration by the GSH reductase-TNB recycling method. The respective tGSH and GSSG level was measured at 405 nm. The serum GSSG level was too low to be detected by this method. The relative GSSG/tGSH ratio was also determined in the tissue sample.

Statistical analysis

All data are presented as the mean value ± SD, and all tissue concentrations expressed per wet weight. Significant differences are shown between the control (NC and EC) groups and among the four exercise groups by unpaired Student's *t*-test and one-way ANOVA post hoc Fisher's PLSD test, respectively. The statistical analyses were performed using Stat View (SAS Institute, Cary, NC, USA).

Results

Oral taurine administration, body and tissue wet weight, and serum glucose and lactate levels

The respective daily and total oral doses of taurine administered per rat in the two-week period examined were

Table 1. Body and tissue wet weight before and after taurine administration, and serum biochemical data

	NC mean ± SD	EC mean ± SD	ET-1 mean ± SD	ET-2 mean ± SD	ET-3 mean ± SD	ANOVA *P* value
BW						
PRE (g)	203.0 ± 7.1	191.0 ± 5.7	189.9 ± 4.5	189.3 ± 4.8	188.7 ± 5.1	0.8524
POST (g)	283.9 ± 13.5	278.6 ± 19.2	281.0 ± 18.7	277.6 ± 6.9	287.7 ± 18.0	0.6629
tissue wet weight						
liver (g)	10.2 ± 1.1	10.0 ± 1.3	10.8 ± 2.1	10.3 ± 0.9	10.4 ± 1.0	0.7630
heart (mg)	915.0 ± 66.3	839.3 ± 55.0	914.6 ± 82.0	902.4 ± 39.1	945.6 ± 73.5[a]	0.0358
GC (mg)	1535.3 ± 178.0	1557.0 ± 123.5	1667.1 ± 174.6	1666.3 ± 102.3	1620.9 ± 136.7	0.4063
serum biochemical data						
glucose (mg/dL)	259.5 ± 27.1	177.8 ± 39.6**	149.4 ± 47.4	142.7 ± 32.6	150.4 ± 40.6	0.4717
lactate (mg/dL)	19.0 ± 5.0	25.9 ± 9.3	21.9 ± 8.9	21.3 ± 4.1	23.6 ± 8.9	0.7798

BW, body weight; *PRE*, body weight before administration of taurine (6 weeks-old); *POST*, body weight after administration of taurine (8 weeks-old); *GC*, gastrocnemius muscle; *NC*, the no exercise no taurine group ($N=6$); *EC*, the exercise no taurine group ($N=7$); *ET-1*, the exercise and taurine administered as 20 mg/kg BW/day group ($N=7$); *ET-2*, the exercise and taurine administered as 100 mg/kg BW/day group ($N=7$); *ET-3*, the exercise and taurine administered as 500 mg/kg BW/day group ($N=7$); *ANOVA*, one-way ANOVA *P* value among the exercise groups; ** $P<0.01$, significantly different vs the NC group by unpaired Student's *t*-test; [a] $P<0.05$, significantly different vs the EC group by post hoc Fisher's PLSD test

as follows: average daily dose (ET-1; 4.9 ± 0.3, ET-2; 24.1 ± 0.5, and ET-3; 123.0 ± 6.4 mg), total dose (ET-1; 81.3 ± 7.5, ET-2; 413.4 ± 24.9, and ET-3; 2109.4 ± 170.9 mg). Table 1 shows the body weight before and after taurine administration for two weeks and the tissue wet weight after taurine administration and exercise. There was no significant difference in the body weight among all groups either before or after taurine administration. The serum glucose level in the EC group was significantly decreased compared to that in the NC group, but remained unchanged among the different exercise groups (Table 1).

Exercise time to exhaustion

The exercise time to exhaustion on a treadmill in the EC group was around 80 minutes (Fig. 1). There was a trend, although not significant, in the length of exercise to exhaustion with the amount of taurine administered. However, there were significant increases in the exercise time by over 25 and 50% for the rats in the ET-2 and ET-3 groups, respectively, versus that in the EC group.

Serum and tissue taurine concentration

The serum taurine concentration was not significantly different between the NC and EC groups and among the exercise groups (Fig. 2). In all the examined tissues, the taurine concentration was significantly decreased in the EC group compared to that in the NC group (Fig. 2). The taurine concentration was significantly higher in the liver of the ET-2 and -3 groups than in the EC group, while that in the heart was significantly lower in the ET-3 group than in the EC group. However, there

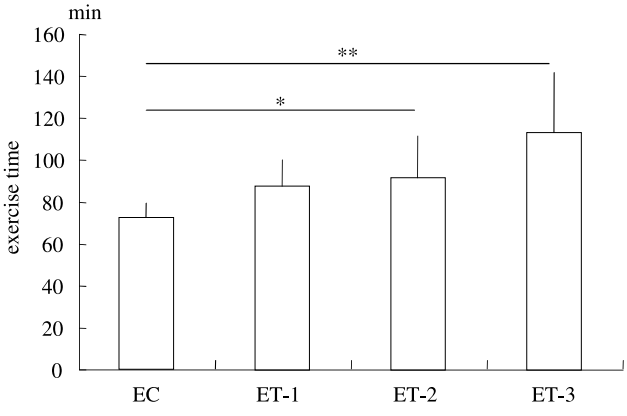

Fig. 1. Times of exercise to exhaustion on a treadmill. Each group of animals was tested on a treadmill (25 m/min) until exhaustion. The rats were considered to be completely exhausted when it was impossible for them to continue running, even after being electrically stimulated with a system attached to the treadmill, and when they were unable to upright themselves when turned on their back. Values are the mean ± SD. *EC*, the exercise no taurine group ($N=7$); *ET-1*, the exercise and taurine administered as 20 mg/kg BW/day group ($N=7$); *ET-2*, the exercise and taurine administered as 100 mg/kg BW/day group ($N=7$); *ET-3*, the exercise and taurine administered as 500 mg/kg BW/day group ($N=7$). One way ANOVA *P* value: $P=0.0146$. * $P<0.05$, ** $P<0.01$, significantly different from EC group by Fischer's PLSD post hoc test

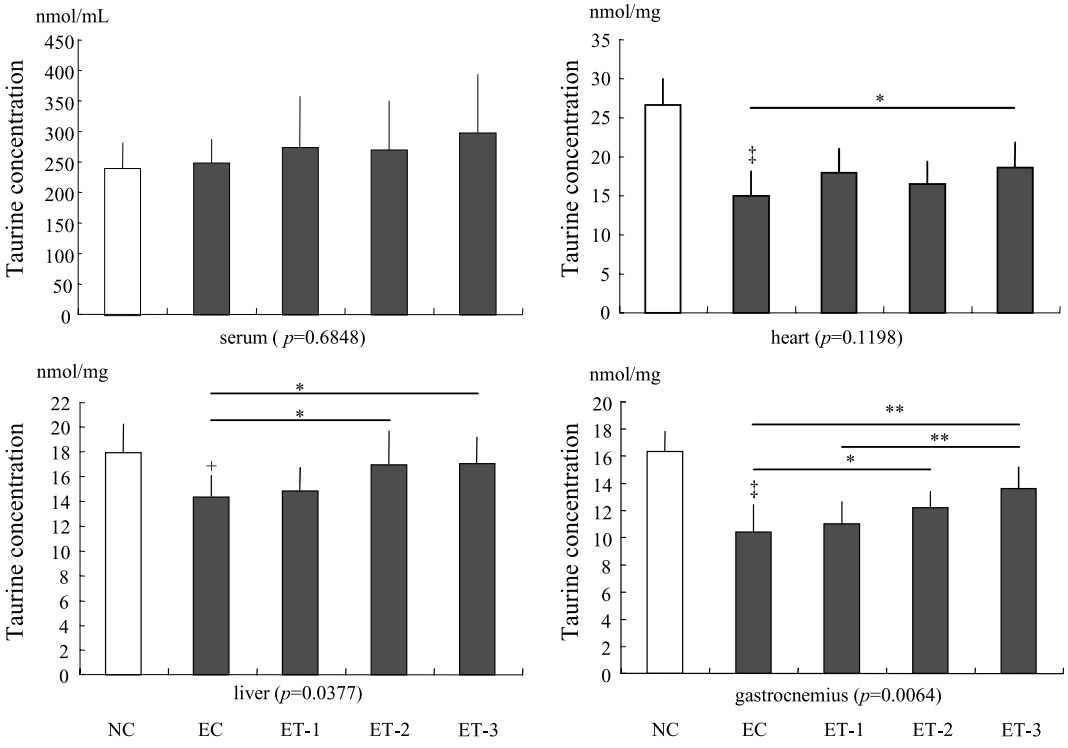

Fig. 2. Taurine concentration in serum and tissues. Values are the mean ± SD. See the legend of Fig. 1 for abbreviations and experimental details. $^{+}P<0.05$, $^{\ddagger}P<0.001$, significantly different from NC group by unpaired Student's *t*-test. $^{*}P<0.05$, $^{**}P<0.01$, significantly different by Fisher's FLSD post hoc test. The number in parenthesis shows One way ANOVA *P* value

was no significant difference in the taurine concentration in the heart and liver among the taurine-administered groups. The GC muscle taurine concentration was significantly decreased in the EC group versus the NC group. Among the taurine administered groups, the taurine concentration in the ET-3 group was significantly increased compared to that in the EC and ET-1 groups, and was significantly higher in the ET-2 group than in the EC group.

LPO concentration in serum and tissues

The LPO concentration in both the serum and liver in the EC group was significantly increased compared to

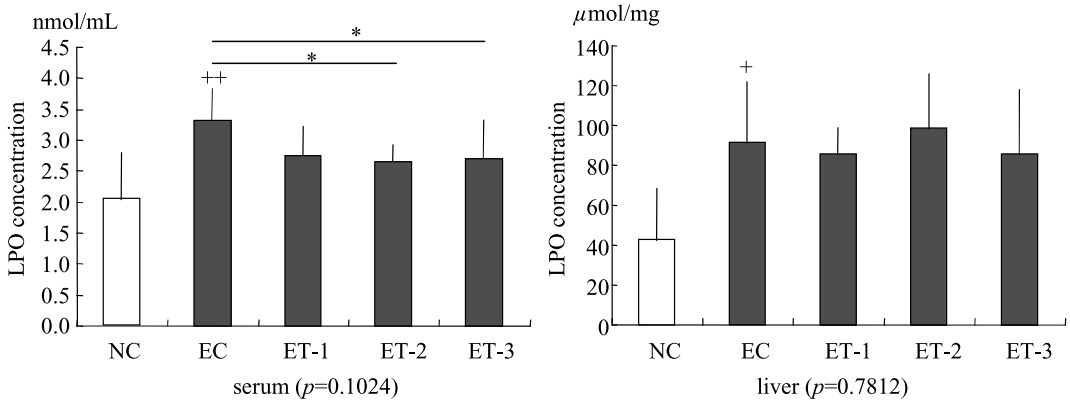

Fig. 3. Lipid hydroperoxide concentration in serum and liver. Values are the mean ± SD. See the legend of Fig. 1 for abbreviations and experimental details. $^{+}P<0.05$, $^{++}P<0.01$, significantly different from NC group by unpaired Student's *t*-test. $^{*}P<0.05$, significantly different by Fisher's FLSD post hoc test. The number in parenthesis shows One way ANOVA *P* value

that in the NC group (Fig. 3). The serum LPO concentration in the ET-2 and -3 groups was significantly lower than in the EC group while it remained unchanged in the liver among the various groups (Fig. 3).

Concentration and ratio of tGSH and GSSG in serum and tissues

The serum tGSH concentration in the EC group was significantly increased compared to that in the NC group, and remained unchanged among the exercise groups (Fig. 4). The tGSH and GSSG concentrations and the GSSG/tGSH ratio in the liver, heart and GC muscle, respectively, are shown in Fig. 5. There was no significant difference in the tGSH concentration among all the examined tissues and groups. The liver GSSG concentration and GSSG/tGSH ratio in all the ET groups were significantly decreased compared to those in the EC group, and among the ET groups, the concentration and ratio in the ET-2 and -3 groups were significantly lower than in the ET-1 group. In the heart, the GSSG/tGSH ratio was significantly decreased in the ET-2 and -3 groups compared to that in the EC group. The GC muscle GSSG concentration and GSSG/tGSH ratio were significantly increased in the EC group compared to those in the NC group. Among the exercised groups, the GC muscle GSSG/tGSH ratio in the ET-3 group was significantly decreased compared to that in the EC and ET-1 groups.

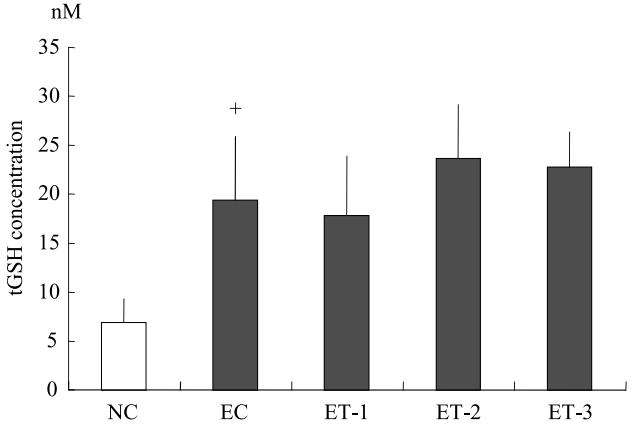

Fig. 4. Serum total glutathione (*tGSH*) concentration. Values are the mean ± SD. See the legend of Fig. 1 for abbreviations and experimental details. One-way ANOVA *P* value: $P = 0.1878$. $^{+}$ $P < 0.001$, significantly different from NC group by unpaired Student's *t*-test

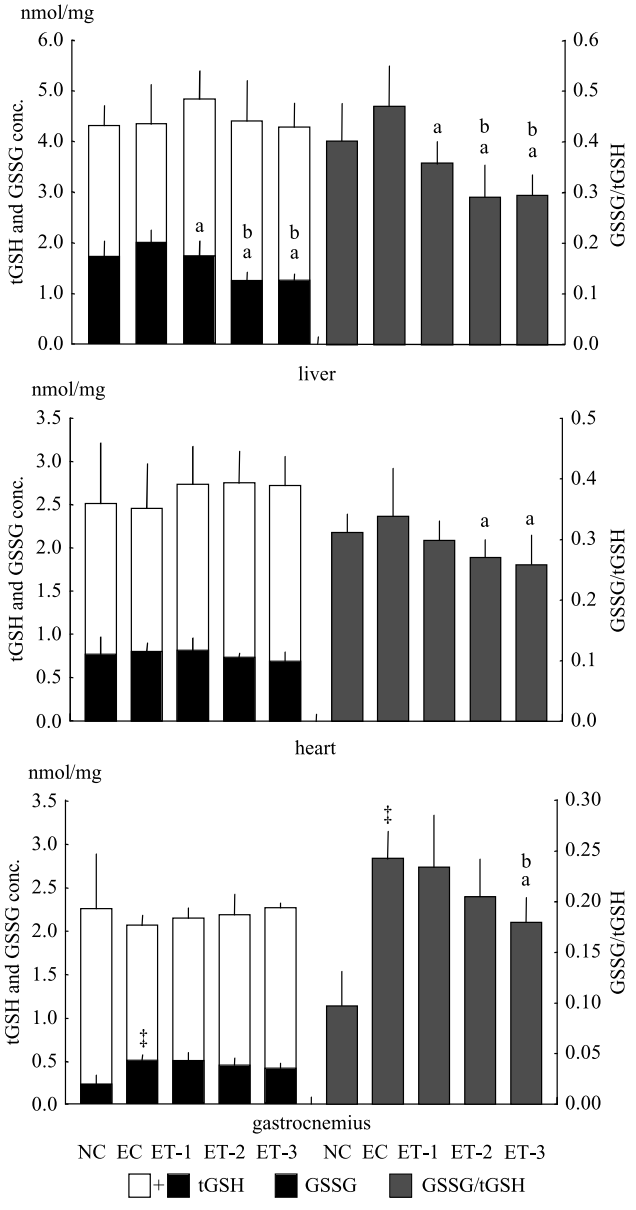

Fig. 5. Total and oxidized glutathione concentrations and the relative ratio in tissues. Values are the mean ± SD. One way ANOVA *P* value: liver; tGSH $P = 0.4024$, GSSG $P < 0.0001$, GSSG/tGSH $P < 0.0001$, heart; tGSH $P = 0.5125$, GSSG $P = 0.1275$, GSSG/tGSH $P = 0.0303$, gastrocnemius muscle; tGSH $P = 0.0949$, GSSG $P = 0.0608$, GSSG/tGSH $P = 0.0129$. *tGSH*, total glutathione; *GSSG*, oxidized glutathione; *GSSG/tGSH*, the relative ratio of tGSH per GSSG; *conc.*, concentration, and see the legend of Fig. 1 for additional abbreviations and experimental details. ‡significantly different vs the NC group, $P < 0.0001$ by unpaired Student's *t*-test [a] and [b], significantly different vs the EC and ET-1 groups, respectively, $P < 0.05$ by Fisher's PLSD post hoc test

Discussion

The present study investigated the optimal and effective dose of taurine orally administered in rats to prolong

exercise performance and to maintain the tissue taurine concentration during exercise. Oral taurine administration for two weeks had a dose-dependent beneficial effect on both the exercise performance and the maintenance of tissue taurine concentration. The most effective dose tested was 500 mg/kg BW/day, which is in the range of the dose we have previously tested (Yatabe et al., 2003). Likewise, Dawson et al. have reported that administration of 3% taurine solution (w/v) in the drinking water for a month could enhance significantly the running performance in rat (Dawson et al., 2002). The aging process leads to whole body taurine depletion mainly due to both a decreased taurine intake and a reduction in taurine biosynthesis (Dawson et al., 1999). Furthermore, increased oxidative stresses with aging could further accentuate the body's loss of taurine. Dawson et al. have also reported that the administration of 1.5% taurine in the drinking water for 10 months reduced the body's loss of taurine in aging rats (Dawson et al., 1999). From this study, the intake volumes of taurine at the intermediate and maximum doses can be calculated to be about 1,300 and 2,800 mg/kg BW/day, respectively. In addition, in the study by Son et al., oral taurine doses of up to 500 mg/kg kg BW/day were administered to rats to improve trinitrobenzene sulfonic acid-induced inflammatory bowel disease in rats (Son et al., 1998). Therefore, the concentrations of taurine administered to rats in the present study were similar if not lower than the doses used in some of these studies. However, these doses would be relatively high for humans and could not be absorbed from natural foods. The general human intake of taurine from nutrition drinks is in the range of 1,000–2,000 mg/day. Therefore, results from animal studies have to be reconciled in humans. However, a human study has shown that taurine administration at 6 g/day for a week could enhance exercise performance (Zhang et al., 2004).

There is a possibility that taurine administration at high concentrations might cause some side effects, such as diarrhea as previously suggested by Dawson et al., (2002). However, in the present study, neither diarrhea nor other visible side effects were observed in the taurine administered groups. Furthermore, there was no significant difference in rat body weight among the groups with and without taurine administration. Therefore, oral daily administration of taurine up to 500 mg/kg BW/day appears to be safe to rats.

We have previously reported that the skeletal muscle taurine concentration in rats was significantly decreased after exercise to exhaustion (Matsuzaki et al., 2002a; Yatabe et al., 2003). In the present study, not only in the skeletal muscle but also in the hepatic and cardiac tissues, taurine concentration was significantly decreased after exercise, and oral taurine administration reduced or prevented this loss. On the other hand, we have recently reported in rats that hepatic taurine concentration was significantly increased after a transient treadmill exercise (Miyazaki et al., 2004). Moreover, Dawson et al. have shown in various tissues including skeletal muscle and liver that the taurine concentration in rats was not altered after exercise while the concentration was decreased by administration of β-alanine, a specific taurine transporter antagonist (Dawson et al., 2002). One rationale to explain the discrepancy in the results from these different studies may reside in differential exercise patterns. Indeed, exercise speed to exhaustion in the present study was relatively high (25 m/min), while our previous study was a transient exercise at lower speed of 10 m/min (Miyazaki et al., 2004). The study of Dawson et al. was a repetition exercise at a speed of 16 m/min (Dawson et al., 2002). Furthermore, the age of the rats used in these studies were also difference. Therefore, the intensity of the exercise and/or the age of the rats could be important factors to be considered in the modulation of body's loss of taurine during exercise.

In the present study, there was no significant difference in tissue tGSH level with and without taurine administration, although the enhanced tissue GSSG level after exercise was reduced in the taurine administered groups. It is known that the biosynthesis of both taurine and GSH are tightly coupled by sharing the same precursor, i.e., cysteine (Bella et al., 1999). Several studies have reported that there was a tight relationship between taurine administration and GSH synthesis/metabolism (Eppler et al., 2001; Obrosova et al., 1999). However, these authors have demonstrated that 1.5% taurine administration in the drinking water to older rats affected neither the biosynthesis of GSH from cysteine nor the protein and acid-soluble thiol levels in liver and/or cerebral cortex (Eppler et al., 2001). In addition, Obrosova et al. have also reported that administration of a 5% taurine containing diet to diabetic rats could ameliorate the GSSG level and GSSG/GSH ratio in the lens without altering the tGSH level (Obrosova et al., 1999). Therefore, there is no clear collective agreement on the effectiveness of taurine administration on the GSH metabolism/synthesis.

The GSSG level was undetectable in serum because the level is two to three orders of magnitude lower than the tGSH level. However, it is possible that the serum GSSG, as well as LPO levels, could be enhanced under exercise conditions and reduced by taurine administration as

suggested in the present study. Furthermore, taurine administration can alleviate both the significant increased GSSG level and the decreased taurine concentration in the GC muscle as induced by exercise. Similarly, Dawson et al. have also shown that taurine administration could protect muscle injury caused by oxidative stress during exercise (Dawson et al., 2002). Therefore, taurine can be considered as one of the effective substances against oxidative stress induction in exercising skeletal muscle.

In the present, as well as in previous studies, taurine administration enhanced exercise performances in rats (Baum et al., 2001; Dawson et al., 2002; Yatabe et al., 2003; Zhang et al., 2004). Several studies have noted the importance of taurine for proper functioning of the excitable mammalian tissues, i.e., cardiac and skeletal muscles (Huxtable, 1992; Pierno et al., 1998; Pierno et al., 1996). In cardiac muscle, taurine modulates muscular contraction by regulating the cellular Ca^{2+} concentration (Huxtable, 1976). Moreover, taurine enhances cardiac muscle contractility after exercise as the result of increasing stroke volume and fractional shortening, observed in patients following echocardiographic examination (Baum et al., 2001). Zhang et al. have suggested an effect of taurine improvement on the regulation of Ca^{2+} homeostasis as responsible for exercise performance and enhanced cardiac and skeletal muscle contractions under exhaustive conditions (Zhang et al., 2004). Furthermore, the roles of taurine might be to increase the skeletal muscle contractile mechanism and to mitigate the oxidative damage associated with exercise (Dawson et al., 2002). Indeed, the pronounced abnormalities of muscle contraction as a reduction action potential speed and the decreased exercise capacity on a treadmill were recognized in a taurine transporter knockout mouse accompanied with depletion of skeletal muscle taurine concentration (Warskulat et al., 2004). These authors have also suggested that taurine might have beneficial effects on skeletal muscle contraction via several mechanisms, including E-C coupling and osmolyte balance. In addition, several studies have reported that taurine can effect circulation by regulating contraction and relaxation of blood vessel. Abebe and Mozaffari have reported that the aorta contraction was attenuated and aortic vasorelaxation was increased in taurine-supplemented rats while the aorta contraction was enhanced and the relaxation was decreased in taurine-deficient rats (2000, 2003a, b). Therefore, the taurine-dependent improved blood vessel contraction and blood flow could contribute significantly to the improved exercise performance.

In conclusion, the rat exercise duration to exhaustion on a treadmill was significantly prolonged by oral daily taurine administration. The effectiveness of taurine was dose dependent and 500 mg/kg BW taurine appeared to be the most effective dose without any or with limited side effects. Furthermore, taurine administration inhibited the oxidative stress markers, such as LPO and oxidation of GSH during exercise. Therefore, the results of the present study suggest that taurine affects muscle contraction and exercise performance via inhibition of oxidative stress associated with oxidation of GSH.

Acknowledgements

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