Effects of taurine administration on exercise-induced fatigue and recovery

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Received: December 12, 2016 / Accepted: December 27, 2016

Abstract Taurine (2-aminoethanesulfonic acid) is a sulfur-containing β -amino acid present in high concentrations in most tissues, including skeletal muscle, liver, blood, and brain. Taurine has been suggested to have positive effects on some of the physiologic functions considered to be a cause of fatigue during exercise: Ca^{2+} handling in excitation–contraction coupling, regulation of ion channels, oxidative stress, and the inflammatory response. However, how and where taurine affects these processes have not been elucidated fully. Some *in vitro* studies have suggested that taurine treatment improves the contractile properties of skeletal muscle. Several studies have suggested that taurine is involved in regulation of energy metabolism. In contrast, whole-body taurine transporter knockout mice exhibit severe intolerance to exercise. Based on these observations, whether taurine treatment may prevent/attenuate fatigue during exercise and then improve exercise performance in humans and experimental animals has been studied. Some recent studies have investigated the effects of taurine administration on post-exercise recovery. Our group investigated the effects of taurine treatment on fatigue induced by endurance exercise. We found that post-exercise taurine administration enhanced the recovery of skeletal muscle glycogen, which is the major determinant for exercise performance. In this review, we introduce studies investigating the effects of taurine administration on exercise-induced fatigue and post-exercise recovery.

Keywords : taurine, exercise-induced fatigue, performance, recovery

Introduction

Taurine (2-aminoethanesulfonic acid) is a sulfur-containing β -amino acid. Taurine is not used for protein synthesis and does not act as a substrate for energy metabolism. Because of its high solubility in water, taurine can act as a buffer to maintain osmolality and a homeostatic environment for the body. Taurine is thought to be involved in various physiologic processes: antioxidant processes, energy metabolism, stabilization of the plasma membrane, inflammation, osmoregulation, regulation of ion channels, and Ca^{2+} handling by the sarcoplasmic reticulum (SR)¹⁾. The mechanisms by which taurine acts on these processes have not been clarified fully.

Taurine is present in high concentrations particularly in excitable tissues such as neurons, cardiac muscle and skeletal muscle. In skeletal muscle, taurine is present at about 10–100 mmol/kg dry weight in humans²⁻⁷⁾, 10–30 mmol/kg wet weight in rats⁸⁻¹¹⁾, 40–60 mmol/kg wet weight in mice¹¹⁾. In human skeletal muscle, taurine content is higher than that of glutamine, which is the most abundant amino acid⁴⁻⁷⁾. The taurine concentration in plasma is around 10–100 μM in humans¹²⁾ and 200–350

μM in mice and rats⁸⁻¹¹⁾. Taurine is taken up by tissues through a taurine transporter (TAUT), which belongs to a family of Na^+/Cl^- -dependent neurotransmitter transporters. Rate-limiting enzymes for taurine synthesis are not present in skeletal muscle, so maintenance of taurine levels in skeletal muscle is dependent largely on uptake from the extracellular space *via* TAUT. Taurine is also found in non-excitable tissues such as blood, liver, kidney, adipose tissue, and the islets of Langerhans on the pancreas.

The taurine level in the skeletal muscle of trained humans is higher than that in humans who have not undergone physical training^{2,3)}. Furthermore, some *in vitro* studies have shown that taurine treatment improves the contractile properties of skeletal muscle¹³⁻¹⁷⁾. Conversely, whole-body TAUT knockout mice, which have a significantly lower taurine level in tissues, show severe intolerance to exercise^{18,19)}. Based on these evidences, the possibility that taurine administration may prevent or attenuate fatigue during exercise in humans and rodents has been investigated. Moreover, some recent studies have investigated the effects of taurine administration on recovery from exercise-induced fatigue. Here, we provide a brief overview of the effects of taurine administration on fatigue during exercise and post-exercise recovery focusing mainly on energy metabolism in skeletal muscle.

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Effects of taurine administration on factors related to exercise-induced fatigue and exercise performance

Fatigue can be defined as a state of deterioration in the homeostatic body condition followed by an inability to maintain power output²⁰. Taurine has been suggested to have positive effects on some of the physiologic functions considered to be a cause of fatigue during exercise: Ca^{2+} handling in excitation–contraction (E–C) coupling, oxidative stress, the inflammatory response, osmoregulation, and regulation of ion channels¹. Some studies have suggested that taurine has various benefits for the contractile properties of skeletal muscle. Acute¹⁵ and long-term¹⁶ (2 weeks) taurine administration in rats results in increases in force production in skeletal muscle during electrical stimulation *in vitro*. Interestingly, taurine treatment in *mdx* mice (the animal model of Duchenne muscular dystrophy) has been shown to rescue the reduction in grip strength and specific force, the loss of force during stimulation, and the chronic exercise-induced reduction of force production in skeletal muscle^{21–23}. Possible mechanisms by which taurine treatment influences the function of skeletal muscle are due (at least in part) to reduced oxidative stress and reduced inflammatory response during contraction according to the study using *mdx* mice²³. The positive effects of taurine administration on contractile properties may also be due to improved uptake of Ca^{2+} by SR during E–C coupling^{13,15,17}. Based on these observations, several researchers have hypothesized that taurine administration has a positive effect on fatigue during exercise in humans and experimental animals (Table 1). Several studies have shown that taurine administration attenuates the increases in oxidative stress and/or inflammatory markers by concentric^{9,24,25} and eccentric²⁶ types of endurance exercise in the same way as demonstrated in *in vitro* studies.

Taurine has been suggested to be involved in the regulation of energy metabolism in skeletal muscle. Whole-body TAUT knockout mice exhibit severe intolerance to exercise concomitant with a higher concentration of lactate in blood^{18,19}. In contrast, taurine treatment attenuates the increase in the lactate level in blood during exercise¹⁰. These results imply that taurine has some effects on the regulation of glycolysis/glycogenolysis because an increased lactate level in blood during exercise is considered to suggest activation of glycogenolysis/glycolysis in skeletal muscle. Indeed, other study showed that treatment with a TAUT inhibitor in the heart results in increases in the glycogenolytic/glycolytic flux²⁷.

Taurine could be involved in the regulation of energy metabolism not only in skeletal muscle but also in other tissues. For example, an *in vitro* study reported that taurine treatment to adipocytes increased the catalytic activity of cyclic adenosine monophosphate-activated protein kinase A²⁸. This enzyme is important for lipolysis in adipocytes, and supplies free fatty acids (FFAs) into

the blood. We previously observed a higher FFA level in serum in taurine-treated mice during post-exercise recovery²⁹. The increase in the FFA level in blood leads to an increase in fat oxidation^{30,31}. Indeed, Rutherford et al. found that administration of a single dose of taurine (1.66 g) 1 h before endurance exercise increased the reliance of fat oxidation during endurance exercise³². However, they also reported that taking 5.0 g/day of taurine (3×1.66 g) with food for 7 days elicited no changes in fat oxidation or level of energy substrate (e.g., glycogen, high-energy phosphates, lactate) in skeletal muscle during 2 h of cycling exercise⁶.

In addition, 7 days of taurine administration has been shown to attenuate the reduction in the glucose level in blood and the increase in the catecholamine level in plasma during 2 h of endurance cycling exercise³³. The same group showed that 2 weeks and 3 weeks of taurine administration altered the level of precursors of gluconeogenesis in rats³⁴. Hence, a possible explanation for the effect of taurine treatment on maintenance of the glucose level in blood during prolonged exercise may be improvement of gluconeogenesis.

Studies using rodents have shown that taurine content in skeletal muscle is reduced by endurance exercise^{8–10}. In humans, a significant change in the taurine level in skeletal muscle has not been observed in resistance⁷ or endurance^{2,4–6} exercises because (at least in part) of large individual differences in dietary intakes of taurine and precursors of taurine synthesis such as methionine and cysteine. The taurine level in blood is increased by prolonged exercise¹², so it can be assumed that taurine is released from tissues by endurance exercise. Based on the observation that the taurine concentration in blood during endurance exercise is higher in the dehydrated condition than that in the hydrated condition¹², an increased taurine level in blood due to exercise seems to be related to osmoregulation in tissues. Since the osmolality in skeletal muscle during exercise is increased by stimulation of glycolysis/glycogenolysis and phosphorylcreatine breakdown, taurine may be released from skeletal muscle for osmoregulation. However, the importance of the maintenance and release of taurine in skeletal muscle during exercise has not been clarified.

Whether taurine administration improves the performance of endurance exercise has been examined (Table 1). Some of them showed a significant improvement in exercise performance upon taurine administration, whereas others did not demonstrate significant effects. For example, improvement in a 3-km time-trial running test was observed by administration of 1 g of taurine 60 min before exercise³⁵. In contrast, the same manner of pre-exercise taurine administration did not induce a significant improvement in a 4-km time-trial cycling test³⁶. There have been many differences among studies in participant status (age, whether they have undergone physical training), exercise protocol (type of exercise, intensity,

Table 1. Effects of pre-exercise taurine administration on factors related to fatigue during exercise and performance

References	Subjects	Dose	Duration /timing	Exercise	Effects other than performance	Performance
Dawson et al. (24)	male sedentary SD rats	3% in drink	1 month	16 m/min downhill running (-16° grade) for 5 min x 18 bouts	Attenuated increase in inflammatory and oxidative stress markers	↑
Miyazaki et al. (9)	male sedentary SD rats	0.02, 0.1, 0.5 g/kg/day	2 weeks	25 m/min until exhaustion	Reduced oxidative stress markers	↑ Increased exercise duration
Yatabe et al. (10)	male sedentary SD rats	0.5 g/kg/day	2 weeks	25 m/min for 60 min or until exhaustion	Reduced urinary excretion of muscle damage marker	↑ Increased exercise duration
Zhang et al. (25)	healthy untrained men (18-20 yr)	6.0 g/day	7 days	Incremental cycling until exhaustion	Attenuated DNA damage in white blood cells	↑ Increased exercise duration and workload max
Ishikura et al. (33)	healthy untrained men (19.9 ± 1.4 yr)	6.0 g/day	7 days	2 h of cycling at 50% VO _{2peak}	Attenuated reduction of blood glucose and increase in plasma catecholamine	Not measured
Galloway et al. (6)	healthy recreationally active men (22 ± 0 yr)	5.0 g/day	7 days	2 h of cycling at ~60% VO _{2peak}	No significant effect	→
Rutherford et al. (32)	endurance-trained male cyclists (27.2 ± 1.5 yr)	A single dose of 1.66 g	1 h before exercise	90-min steady-state ride at ~65% VO _{2max} and the subsequent time trial for 5 kJ of work/kg BM.	Increased fat oxidation during 90 min of steady-state cycling	→
Balshaw et al. (35)	male trained middle-distance runners (19.9 ± 1.2 yr)	a single dose of 1.0 g	2 h before exercise	3 km time trial	No significant effect	↑ Improved 3 km time trial performance
Ward et al. (36)	male trained cyclist (34.6 ± 11.5 yr)	a single dose of 1.0 g	2 h before exercise	4 km time trial	No significant effect	→

duration), as well as the dose and duration of taurine administration. Hence, further studies are needed to ascertain if pre-exercise taurine treatment improves exercise performance.

Effects of taurine administration on post-exercise recovery

Effects of taurine administration on recovery from exercise-induced fatigue have rarely been investigated and the change in the taurine level in skeletal muscle during post-exercise has not been examined, either. However, one *in vitro* study examined the effect of 2 weeks of taurine administration on recovery of tetanic force in skeletal muscle after contraction in rats¹⁶⁾. That study showed taurine treatment enhanced recovery of force production after high-frequency stimulation, but how 2 weeks of taurine treatment improved recovery of contractile properties was not revealed. Another research group investigated the effect of 2 weeks of taurine administration (50 mg/kg/day) on recovery from eccentric exercise³⁷⁾. They showed that 2 weeks of taurine administration had no effect on the reduction in strength in skeletal muscle induced by eccentric exercise. Nevertheless, taurine treatment enhanced the recovery of isometric and concentric strength, and was accompanied by an increased level of thiols in skeletal muscle, reduced muscle soreness, a lower level of oxidative-stress markers in skeletal muscle, and a lower level of markers of skeletal muscle damage in blood.

Recently, our group investigated if taurine administration after endurance exercise enhances recovery from fatigue by focusing on energy metabolism. We provided ICR mice with a solution containing 0.5 mg/g body weight of taurine or physiologic (0.9%) saline as a control immediately after treadmill running at 25 m/min for 90 min, and then measured the voluntary wheel running distance as an indicator of recovery from exercise-induced fatigue³⁸⁾. As the voluntary wheel running distance was decreased significantly by exercise and then increased gradually to the pre-exercise level^{39,40)}, mice recovering from exercise-induced fatigue faster could run a longer distance in the voluntary wheel. In the control group, treadmill running decreased the voluntary wheel running distance significantly compared with that of mice that did not undertake treadmill running. In contrast, a significant decrease in the voluntary wheel running distance upon 90 min of exercise was not observed in the taurine-treated group. We found a main effect of taurine administration after endurance exercise on the amount of voluntary wheel running. These results suggest that taurine administration has favorable effects on recovery from fatigue caused by prolonged exercise.

The activity of voluntary wheel running is thought to be affected by several central and peripheral factors⁴¹⁾. The capacity of energy metabolism may affect the activity of voluntary wheel running. Glycogen depletion in skeletal muscle is a major cause of fatigue. There is a strong

relationship between the pre-exercise glycogen level in skeletal muscle and performance in prolonged endurance exercise and high-intensity intermittent exercise⁴²⁻⁴⁵⁾. We observed that 90 min of endurance exercise reduced the glycogen level in skeletal muscle to 40% of the pre-exercise level. Thus, glycogen repletion in skeletal muscle after exercise should be a determinant for performance in subsequent exercise. Some rodent studies have reported that taurine administration enhances glucose uptake, which is a rate-limiting step for skeletal muscle glycogen re-synthesis⁴⁶⁻⁵¹⁾. Kulakowski et al. showed that taurine administration increased incorporation of [³H] deoxyglucose into skeletal muscle at the resting state in rats compared to a control group administered glucose only⁴⁶⁾. Therefore, we investigated if post-exercise taurine administration enhances glycogen repletion in skeletal muscle²⁹⁾. At 120 min after exercise with free access to food, the glycogen concentration in skeletal muscle in the taurine-treated group was 94% higher than that in the control group. Moreover, the glycogen level in the skeletal muscle of the taurine-treated group was 136% higher than the pre-exercise level, whereas the glycogen level in the skeletal muscle of the control group was similar to the pre-exercise level, suggesting that post-exercise taurine administration induced glycogen supercompensation (Fig. 1).

We also observed a higher FFA level in serum in the taurine-treated group 60 min after endurance exercise²⁹⁾. Since an increase in the FFA level in blood leads to an increase in fat oxidation^{30,31)}, taurine administration may lead to sparing of carbohydrate towards glycogen repletion in skeletal muscle during post-exercise recovery. Therefore, we measured the levels of metabolites involved in glycogenolysis/glycolysis and the tricarboxylic acid cycle and high-energy phosphates in skeletal muscle by metabolome analyses using capillary electrophoresis-time-of-flight mass spectrometry because metabolomic profiles reflect energy metabolic states better than the maximal activities and contents of proteins⁵²⁾. We found that the level of fructose-1, 6-bisphosphate (F1, 6P), which is an intermediate of glycogenolysis/glycolysis, was significantly (56%) lower in the taurine-treated group than in the control group (Fig. 2). F1, 6P is produced by phosphofructokinase, which is a rate-limiting enzyme for glycogenolysis/glycolysis. We also found that the relative level of dihydroxyacetone phosphate and glycerol 3-phosphate (which are downstream products of F1, 6P) tended to be lower in the taurine-treated group than in the control group. These results suggest that glycogenolysis/glycolysis in skeletal muscle post-exercise was suppressed by taurine administration. This result is in accordance with the studies observing that inhibition of taurine uptake in tissues by treatment with a TAUT inhibitor²⁷⁾ or genetic disruption of TAUT^{18,19)} led to an increase in the glycolytic/glycogenolytic flux. Recent studies have implied that reducing utilization of carbohydrate as a fuel during post-exercise enhances glycogen repletion in skeletal muscle.

Fig. 1 Glycogen concentrations in the tibialis anterior muscle of mice orally administered taurine solution (taurine-treated) or saline (control) immediately after exercise. Values are the mean $\pm$ SE, $n = 5$ or 6 per group, * $p < 0.05$ vs. the control group at the same time, † $p < 0.05$ vs. baseline. Cited and modified from reference 29.

Fig. 2 Effects of taurine administration on glycolysis/glycogenolysis in the tibialis anterior muscle 120 min after exercise in mice of the taurine-treated group (white) and those of the control group (black). Values represent the relative levels of the metabolites in each group $\pm$ SE. $n = 6$ per group. G1P, glucose-1-phosphate; G6P, glucose-6-phosphate; F6P, fructose-6-phosphate; F1, 6P, fructose-1, 6-bisphosphate; DHAP, dihydroxyacetonephosphate; G3P, glycerol 3-phosphate. ** $p < 0.01$ vs. the control group. Cited and modified from reference 52.

For example, oral administration of hydroxycitrate (which increases fat oxidation) improves skeletal muscle glycogen repletion⁵³. In contrast, acceleration of carbohydrate oxidation by exposure to hot conditions attenuates post-exercise glycogen resynthesis⁵⁴. Collectively, taurine administration is beneficial for glycogen recovery in skeletal muscle by sparing carbohydrate. Further work is needed to ascertain if taurine administration also has positive effects on energy metabolism during recovery from endurance exercise-induced fatigue in humans.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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