Effect of thiamin (vitamin B₁) on carbohydrate metabolism at rest and during exercise

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Abstract Thiamin (vitamin B₁) has often been used as a reagent to prevent fatigue. There are two possibilities concerning the anti-fatigue effect of thiamin: 1) an ergogenic effect in a non-thiamin deficient state and 2) a supplementary effect under the condition of an increasing need for thiamin due to exercise. Thiamin is a coenzyme of pyruvate dehydrogenase (PDH), which is a mitochondrial enzyme for oxidation of carbohydrate-derived substrate to generate ATP. In a thiamin deficiency, oxidation of carbohydrate is decreased due to the reduced activity of PDH. Thus a supplement of thiamin improves carbohydrate metabolism in the thiamin-deficient state. Some reports have indicated that concentrations of thiamin in tissues are decreased by exercise, i.e. the need for thiamin intake is increased. However, direct evidence supporting the hypothesis of whether or not the thiamin requirement is increased by exercise is lacking. Although it is well documented that thiamin plays an important role in the normal function of PDH reactions, whether carbohydrate metabolism is activated by supplemental thiamin during and after exercise in a normal thiamin state is unclear. This review deals with the possibility of the administration of thiamin in preventing exercise-induced fatigue by focusing on two considerations: 1) whether the need for thiamin is increased with exercise and 2) the effect of thiamin not only on carbohydrate metabolism, but also on lipid metabolism at rest and during exercise under normal dietary conditions.

Keywords : thiamin (vitamin B₁), fatigue, skeletal muscle, exercise

Introduction

Thiamin (vitamin B₁) is often used as a reagent to prevent fatigue in not only muscle fatigue, but also in feelings of fatigue, particularly in Japan. As thiamin is not synthesized in the body, it is necessary to take thiamin in one's diet. The rationale for the use of thiamin as an anti-fatigue reagent has been that it can inhibit the production of lactate due to increasing activity of pyruvate dehydrogenase (PDH), because thiamin is an activator of PDH. Lactate has traditionally been regarded as an end-product of carbohydrates and as the main cause of muscle fatigue. However, muscle fatigue is not necessarily caused by the accumulation of lactate. Lactate is now known as an oxidizable fuel for muscles rather than a waste product, and as having good effects such as preventing fatigue¹⁾. Therefore, the reasons for using thiamin as a supplement for preventing fatigue have become questionable.

PDH is a mitochondrial enzyme for the oxidation of

carbohydrate-derived substrate to generate ATP. It is well documented that vitamins including thiamin play an important role in the normal function of enzyme reactions²⁾. Exercise is a condition inducing a great deal of carbohydrate oxidation. Therefore, one possibility of thiamin supplementation as an anti-fatigue reagent is that supplementation of thiamin in a thiamin-decreased state can normalize glucose metabolism particularly during and after exercise. However, it is unclear whether the need for thiamin is augmented by exercise.

Another possibility of thiamin as an anti-fatigue reagent is that thiamin has an ergogenic effect for enhancing exercise performance. Preferential carbohydrate oxidation by enhancing mitochondrial PDH activity with thiamin may further increase oxidative energy production in a non-thiamin deficient state. However, the effect of thiamin administration on carbohydrate metabolism in a non-thiamin deficient state, especially during exercise, is also unclear.

This review describes the possibility of the effect of thiamin on preventing exercise-induced fatigue by fo-

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cusing on two topics: 1) whether the need for thiamin is increased by exercise and 2) the effect of thiamin administration on substrate metabolism under normal thiamin conditions during exercise and at rest (Fig. 1).

Regulation of PDH activity

How does thiamin regulate PDH activity during exercise? PDH is inhibited by PDH kinase through phosphorylation and is activated by PDH phosphatase through dephosphorylation (Fig. 2). It has been suggested that

an allosteric regulation dominates, as substrate/product concentrations usually have minor influences on the regulation of PDH activity. An active form of thiamin, thiamin pyrophosphate (TPP) binds to the PDH complex at allosteric sites and activates PDH. Therefore, thiamin is necessary to keep normal PDH function and carbohydrate oxidation.

At rest, high ATP/ADP, NADH/NAD, and acetyl-CoA/CoA ratios and low pyruvate concentration maintain high PDH kinase activity, and a low Ca^{2+} concentration keeps PDH phosphatase activity low. Thus PDH activity is kept

Fig. 1 Administration of thiamin is generally believed to have anti-fatigue effect. One possibility is that supplement of thiamin under thiamin-decreased state rescues the deteriorated carbohydrate metabolism. The second possibility is that administration of thiamin under normal-thiamin state has ergogenic effect or promotion of behavior and/or growth.

Fig. 2 Scheme of pyruvate dehydrogenase (PDH) activation by thiamin, exercise and carbohydrate intake. PDH regulates the entry of carbohydrates into the mitochondria for oxidation to generate ATP. Thiamin is one factor for increasing PDH activity by inhibiting PDH phosphorylation. The activation of PDH during exercise is achieved by the accumulation of mitochondrial calcium and pyruvate. Calcium activates dephosphorylation of PDH and pyruvate inhibits phosphorylation of PDH. Ingestion of carbohydrate causes insulin-stimulated glucose transport. Insulin inhibits phosphorylation of PDH.

low at rest. As body storage of carbohydrate is relatively low, it is better to keep carbohydrate utilization low in order to preserve carbohydrate reserves. At the onset of exercise, increases in Ca^{2+} , pyruvate and free ADP contribute to the activation of PDH. Ca^{2+} appears to be the initial and the most powerful signal for PDH activation by the control of PDH phosphatase activity in a feed-forward manner. Glycogenolytic/glycolytic flux also increases at the onset of exercise and the concomitant increase of pyruvate inhibits PDH kinase activity and activates PDH. An increase in the free ADP concentration during exercise also decreases the ATP/ADP ratio and decreases PDH kinase activity to stimulate PDH. The control by pyruvate and ATP/ADP ratio contributes to the feedback systems maintaining the ATP level in the contracting muscle. Due to these activation mechanisms, muscle PDH activity is rapidly increased at the onset of exercise³⁾ and can be linearly increased with exercise intensity⁴⁾.

Does the need for thiamin increase with exercise?

It has been often suggested that vitamin and mineral supplements are unnecessary even in athletes if they consume well-balanced diets⁵⁾. On the other hand, the belief that the consumption of vitamins such as thiamin in addition to the normal diet is essential for both optimal health and enhancing athletic performance is widespread⁶⁾. Because exercise stresses metabolic pathways, the requirement of micronutrients including thiamin may increase in athletes and active individuals. Theoretically, increasing physical activity could increase the need for micronutrients in several ways: through decreased absorption of nutrients, by increased turnover and/or loss of nutrients, through biochemical adaptations as a result of training,

and/or through increased need for the nutrients.

We have found that a single dose (0.1 mg/g BW) of thiamin derivative, tetrahydrofurfuryl disulfide (TTFD) has no effect on muscle PDH phosphorylation and blood lactate concentrations at several intensities of exercise in mice (Fig. 3)⁷⁾. Dichloroacetate (DCA), which is another PDH activator, also failed to increase PDH activity after 5 min of exercise³⁾. Therefore, it is natural to conclude that as exercise is a very potent stimulus to increase muscle PDH activity, it is difficult to activate PDH further by some reagents with exercise induced PDH activation.

However, a recent study has shown that increased energy expenditure decreased the concentration of thiamin in rats fed with a minimum amount of daily ingestion of thiamin⁸⁾. It is known that due to genetic defects or illness, as well as growth, some individuals require a higher amount of thiamin⁹⁾. Further research is needed to elucidate the thiamin requirement with exercise.

Effect of thiamin on exercise performance under normal dietary conditions

It has been reported that thiamin ingested for several days increases the body thiamin level and changes exercise performance and some metabolic parameters. For example, higher values in vertical jump test and grip strength after ingestion of 150 mg/day of thiamin derivative, tetrahydrofurfuryl disulfide (TTFD), for two weeks were reported¹⁰⁾. Some reports also have suggested that the administration of thiamin derivative improves resistance to fatigue. Suzuki and Itokawa reported that 100 mg/day of TTFD ingestion for 3 days decreased feelings of fatigue after exercise¹¹⁾. Furthermore, in an animal study, McNeil and Mooney reported that 100x minimum

Fig. 3 Blood lactate concentration during exercise following administration of water (□) or tetrahydrofurfuryl disulfide (TTFD) (■), which is a derivative of thiamin. TTFD has no effect in blood lactate concentration in several intensities of exercise. Values are means $\pm$ SE ($n=4-7$) (7).

daily requirements of thiamin ingestion for mice with carbohydrate loading increased swim time until exhaustion (4% overload) compared to carbohydrate loading only¹². Nozaki et al. reported that rats injected with TTFD for 5 days with a normal thiamin diet had an enhanced weight-loaded forced swimming performance without an exercise-induced decrease in muscle ATP¹³. Furthermore, it has been reported that the PDH activator DCA causes higher isometric contraction at the onset of exercise¹⁴. DCA can increase acetyl-CoA, which is a product of PDH, and prevent reductions of ATP and PCr levels causing resistance to muscle fatigue¹⁵.

However, other studies have concluded that thiamin is incapable of enhancing exercise performance. Doyle et al. reported that a dose of 1 g/day for 5 days of the thiamin derivative, allithiamin, has no effect on the isokinetic parameters of muscle performance and blood lactate concentrations during isokinetic exercise¹⁶. Webster et al. have reported that administration of 1 g/day for 4 days of TTFD has no effect on $\dot{V}O_2$ peak and blood lactate concentration, and cycling performance during exercise to exhaustion¹⁷. They also investigated the time to complete a 2000 m time trial following a 50 km steady state ride on a cycle ergometer with ingestion of thiamin for 7 days with no significant effect on the performance and blood concentrations of lactate, glucose and free fatty acids and heart rate responses¹⁸. We have found that a single dose of TTFD with the amount (0.1 mg/g BW) close to the maximum dose without side effects for mice had no effect on blood lactate concentrations during exercise¹⁹. Therefore, it is unclear whether thiamin supplementation in a non-thiamin deficient state increases exercise performance. It is possible that ingestion of thiamin is effective in severe exercise conditions such as endurance exercise lasting for several hours or high supramaximal intensity exercise.

Effect of thiamin on carbohydrate and lipid metabolism at rest under normal dietary conditions

Preferential glucose oxidation can be accompanied by increased lipid metabolism. We have reported that a single dose of the thiamin derivative TTFD (0.1 mg/g BW) decreased expired $^{13}CO_2$ from exogenous ^{13}C -labeled glucose suggesting decreased glucose oxidation and concomitant increased lipid oxidation at rest (Fig. 4)¹⁹. As acetyl-CoA, which is a substrate for the biosynthesis of lipids, can be increased by the activation of PDH²⁰, thiamin can be important for lipid metabolism as well. Thiamin also works as a coenzyme of transketolase (TK), which is the constituent of the pentose phosphate shunt. The pentose phosphate shunt works mainly in the liver to generate NADPH, and shifts excess glucose towards biosynthesis of lipids. Therefore, it is possible that thiamin increases acetyl-CoA and increases lipogenesis from glucose in the liver²¹. The increased lipogenesis by thiamin might be

Fig. 4 The ratio of expired $^{13}CO_2/CO_2$ after ingestion of ^{13}C -glucose with water ($\square$) or TTFD ($\blacksquare$) at rest. The results showed that TTFD decreased glucose oxidation at rest in mice ($n=4-5$). * $P<0.05$, ** $P<0.01$. Values are means $\pm$ SE (19).

beneficial for preventing diabetes^{22, 23}.

Recently, short-chain acylcarnitines derived from mitochondrial fat oxidation have been suggested to promote metabolic flexibility²⁴. The shortest acylcarnitine, acetyl-carnitine, is synthesized from acetyl-CoA, and is responsible for buffering the mitochondrial acetyl-CoA pool and mitigating acetyl-CoA inhibition of PDH. Therefore, the effect of thiamin is not only on the activation of PDH. Thiamin can increase the acetyl-CoA pool leading to enhancing lipogenesis and metabolic flexibility. Further investigation is needed to elucidate the mechanisms of the effect of thiamin on not only carbohydrate metabolism, but also on lipid metabolism.

Conclusion

Exercise itself is a potent stimulus to activate PDH. Therefore, to increase the activity of PDH further during exercise by thiamin is considered to be difficult under a normal thiamin state. As research examining the needs of thiamin intake by exercise are still limited, it is unclear whether the thiamin requirement is increased by exercise. It is also unclear whether exercise performance is increased by thiamin during a non-thiamin deficient state. Thiamin activates transketolase and can increase the acetyl-CoA pool leading to enhancing lipogenesis and metabolic flexibility. We cannot exclude the possibility that supplemental thiamin can be beneficial for health promotion and exercise performance.

Conflict of Interests

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

References

- Allen D and Westerblad H. 2004. Lactic acid - the latest performance-enhancing drug. *Science* 305: 1112-1113.
- Carpenter KJ. 2012. The discovery of thiamin. *Ann Nutr Metab* 61: 219-223.
- Howlett RA, Heigenhauser GJ, Hultman E, Hollidge-Horvat MG and Spriet LL. 1999. Effects of dichloroacetate infusion on human skeletal muscle metabolism at the onset of exercise. *Am J Physiol* 277: E18-E25.
- Spriet LL and Heigenhauser GJ. 2002. Regulation of pyruvate dehydrogenase (PDH) activity in human skeletal muscle during exercise. *Exerc Sport Sci Rev* 30: 91-95.
- Rodriguez NR, Di Marco NM and Langley S. 2009. American College of Sports Medicine Statement. Nutrition and athletic performance. *Med Sci Sports Exerc* 41: 709-731.
- Weight LM, Noakes TD, Labadarios D, Graves J, Jacobs P and Berman PA. 1988. Vitamin and mineral status of trained athletes including the effects of supplementation. *Am J Clin Nutr* 47: 186-191.
- Masuda H, Takahashi Y, Tamura Y, Matsunaga Y, Hoshino S and Hatta H. 2014. Effects of thiamin derivative on muscular carbohydrate metabolism at rest and during exercise. *Tairyoku Kagaku (Jpn J Phys Fitness Sports Med)* 63: 60 (in Japanese).
- Shibata K and Fukuwatari T. 2013. The body vitamin B1 levels of rats fed a diet containing the minimum requirement of vitamin B1 is reduced by exercise. *J Nutr Sci Vitaminol* 59: 87-92.
- Hills JI, MS Golub, L Bettendorff and Keen CL. 2011. The effect of thiamin tetrahydrofurfuryl disulfide on behavior of juvenile DBA/2J mice. *Neurotoxicol Teratol* 34: 242-252.
- Nishiyama I, Tanaka T and Tsumura D. 1972. Effect of thiamine tetrahydrofurfuryl disulfide (TTFD) on physical fitness chiefly on muscle strength -double blind studies-. *J Phys Fitness Japan* 21: 6-15.
- Suzuki M and Itokawa Y. 1996. Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis* 11: 95-106.
- McNeill AW and Mooney TJ. 1983. Relationship among carbohydrate loading, elevated thiamine intake cardiovascular endurance of conditioned mice. *J Sports Med Phys Fitness* 23: 257-262.
- Nozaki S, Mizuma H, Tanaka M, Jin G, Tahara T, Mizuno K, Yamato M, Okuyama K, Eguchi A, Akimoto K, Kitayoshi T, Mochizuki-Oda N, Kataoka Y and Watanabe Y. 2009. Thiamine tetrahydrofurfuryl disulfide improves energy metabolism and physical performance during physical-fatigue loading in rats. *Nutr Res* 29: 867-872.
- Timmons JA, Poucher SM, Constantin-Teodosiu D, Worrall V, Macdonald IA and Greenhaff PL. 1996. Increased acetyl group availability enhances contractile function of canine skeletal muscle during ischemia. *J Clin Invest* 97: 879-883.
- Roberts PA, Loxham SJ, Poucher SM, Constantin-Teodosiu D and Greenhaff PL. 2002. The acetyl group deficit at the onset of contraction in ischemic canine skeletal muscle. *J Physiol* 544: 591-602.
- Doyle MR, Webster MJ and Erdmann LD. 1997. Allithiamine ingestion does not enhance isokinetic parameters of muscle performance. *Int J Sport Nutr* 7: 39-47.
- Webster MJ, Scheett TP, Doyle MR and Branz M. 1997. The effect of a thiamin derivative on exercise performance. *Eur J Appl Physiol Occup Physiol* 75: 520-524.
- Webster MJ. 1998. Physiological and performance responses to supplementation with thiamin and pantothenic acid derivatives. *Eur J Appl Physiol Occup Physiol* 77: 486-491.
- Masuda H, Matsumae H, Masuda T and Hatta H. 2010. A thiamin derivative inhibits oxidation of exogenous glucose at rest, but not during exercise. *J Nutr Sci Vitaminol* 56: 9-12.
- Dulloo AG, Gubler M, Montani JP, Seydoux J and Solinas G. 2004. Substrate cycling between de novo lipogenesis and lipid oxidation: a thermogenic mechanism against skeletal muscle lipotoxicity and glucolipotoxicity. *Int J Obes Relat Metab Disord* 28: S29-S37.
- Berrone E, Beltramo E, Solimine C, Ape AU and Porta M. 2006. Regulation of intracellular glucose and polyol pathway by thiamine and benfotiamine in vascular cells cultures in high glucose. *J Biol Chem* 281: 9307-9313.
- Jadidi-Babaei R, Karachalis N, Kupich C, Ahmed N and Thornalley PJ. 2004. High-dose thiamine therapy counters dyslipidemia in streptozosin-induced diabetic rats. *Diabetologia* 47: 2235-2246.
- Rabbani N, Alam SS, Riaz S, Larkin JR, Akhtar MW, Shafi T and Thornalley PJ. 2009. High-dose thiamine therapy for patients with type 2 diabetes and microalbuminuria: a randomized double-blind placebo-controlled pilot study. *Diabetologia* 52: 208-212.
- Muoio DM, Noland RC, Kovalik JP, Seiler SE, Davies MN, DeBalsi KL, Ilkayeva OR, Stevens OR, Kheterpal I, Zhang J, Covington JD, Bajpeyi S, Ravussin E, Kraus W, Koves TR and Mynatt RL. 2012. Muscle-specific deletion of carnitine acetyltransferase compromises glucose tolerance and metabolic flexibility. *Cell Metab* 15: 764-777.