Trimethylglycine (betaine)

Subjects: Nutrition & Dietetics
Contributor: Brandon Willingham

Trimethylglycine (i.e. glycine betaine or betaine)

Keywords: Betaine ; Osmolyte ; Hydration ; Thermoregulation ; Heat ; Heat Stress ; Gut Permeability

1. Introduction and Methodology

In today's global society, the demand for humans to perform work in the heat is increasing [1][2]. Whether affecting manual laborers, military personnel, or athletes, heat stress is responsible for approximately 620 deaths in the United States [3] and thousands globally [4][5][6] each year. As such, strategies to manage heat stress and prolong exercise or activity in the heat have been explored extensively [7][8][9][10]. Broadly, these strategies can be categorized into *physical* and *nutritional* strategies. Physical strategies may include pre-cooling, cold water immersion, misting fans, and/or altering clothing [11]. These strategies have become popular among sports medicine staff and have varying degrees of success. Alternatively, nutritional strategies, largely based upon defending plasma volume (i.e., consuming relatively large doses of electrolytes, carbohydrates, and cold fluids), also play a role in managing heat stress. Among these nutritional strategies of heat stress management includes the consumption of betaine.

2. Betaine

Trimethylglycine (betaine) is a derivative of the amino acid glycine. Betaine can be endogenously synthesized through the metabolism of choline, or exogenously consumed through dietary intake [12]. Although betaine concentrations in foods vary depending on cooking and preparation methods, grain products and vegetables such as wheat bran (1340 mg·100 g^{-1}), wheat germ (1240 mg·100 g^{-1}), spinach (600–645 mg·100 g^{-1}), and beets (114–297 mg·100 g^{-1}) are the best sources of dietary betaine [13]. Average dietary intake for Western culture typically ranges from 100 to 400 mg·day^{-1}, with a mean of 208 ± 90 mg·day^{-1} and results in an average resting plasma betaine concentration of 0.02–0.07 mmol·L^{-1} [14][15]. As betaine is a short-chain, neutral, amino acid derivative, absorption across the enterocyte is thought to primarily use the sodium-dependent Amino Acid Transport System A, however sodium-independent absorption is also known to occur [12][16]. A single dose of betaine (50 mg·kg^{-1}) in healthy young men (mean age: 28 years old) free of any known diseases resulted in a peak concentration of ~1 mmol·L^{-1}, in ~1 h [15]. The elimination half-life of a single dose of betaine is ~14 ± 7 h, with <5% of the original dose present in 72 h [15]. However, a loading strategy of 50 mg·kg^{-1} per 12 h for 5 days in the same population resulted in a peak concentration of ~1.5 mmol·L^{-1}, ~1 h after ingestion [15]. Likewise, the elimination half-life of the five-day loading of betaine is ~41 ± 14 h, with <5% of the original dose present in 8.6 days. Thus, a five-day loading protocol of betaine increases blood concentrations 50% more than a single dose and may function nearly three times as long.

2.1. Methyl Donation

It is universally accepted that betaine serves two primary roles in mammalian physiology [12][17]. The first is that of a methyl donor. As the name indicates, trimethylglycine (i.e., betaine) has three methyl groups, which can serve as reagents for transmethylation reactions. If this occurs, betaine is converted into dimethylglycine, or further catabolized into sarcosine, ultimately adding to the amino acid pool as glycine [12][18]. Notably, betaine metabolism supplies methyl groups for the conversion of homocysteine to methionine [19][20], and aids in the synthesis of key metabolic proteins such as creatine [21][22] and carnitine [23], especially during periods of hypertonicity [24]. These findings have led to several lines of research that examine betaine's role in health and disease prevention [12][19][25][26][27] as well as human performance [28][29][30][31][32].

2.2. Osmolyte

The second role that betaine serves is that of an osmolyte. Osmolytes are organic molecules used in the regulation of intracellular fluid concentrations and cell volume [33][34]. When presented with an external hypertonic stressor, the immediate response of mammalian cells is to decrease cell volume (i.e., fluid loss) and increase inorganic solute concentrations (i.e., electrolytes) in efforts to maintain homeostasis [33]. However, this accumulation of inorganic solutes, if severe enough, can interfere with electrical signaling and protein conformation. Therefore, in order to preserve long-term cellular function, mammalian cells seek to mitigate this problem by exchanging the potentially harmful inorganic solutes for compatible organic osmolytes, such as betaine [33][35].

Indeed, when presented with hypertonic stress, membrane-bound betaine/ -aminobutyric acid transporter 1 (BGT1) mRNA and expression are up-regulated, leading to an increase in intracellular betaine concentration [16][34]. Interestingly, once the cells are returned to an isotonic (300 mOsm) environment, BGT1 expression remains elevated for at least 24 h [16]. This may play an important role for individuals engaging in daily exercise in hot-humid environments creating hypertonic stress. Further supporting the importance of osmolyte accumulation, Alfieri et al. cultured porcine vascular endothelial cells in a hypertonic (500 mOsm) solution with and without osmolytes (0.1 mmol betaine and myo-inositol). Cultures without osmolytes present experienced a 63% mean reduction in cell number after 56 h, however cultures with betaine and inositol experienced only a 32% decrease in cell number during the same time [16]. In a separate experiment measuring morphological changes in cell cultures with and without osmolytes, the same group observed that cultures with betaine and myo-inositol grew well and maintained proper morphology, whereas those without osmolytes experienced significant apoptosis, detaching from the plates [16]. Thus, it appears that osmolytes, such as betaine, are responsible for decreasing hypertonic stress in mammalian cells, which results in preserved functionality and increased survivability.

Simultaneously, as an osmolyte, betaine acts to retain intracellular fluid and preserve the osmotic balance during hypertonic stress. As such, this has profound impacts on bolstering membrane integrity, which becomes particularly important for enterocytes undergoing heat stress.

References

1. Kark, J.A.; Burr, P.Q.; Wenger, C.B.; Gastaldo, E.; Gardner, J.W. Exertional heat illness in marine corps recruit training. Aviat. Sp. Environ. Med. 1996, 67, 354–360.
2. Wallace, R.F.; Kriebel, D.; Punnett, L.; Wegman, D.H.; Wenger, C.B.; Gardner, J.W.; Gonzalez, R.R. The effects of conti nuous hot weather training on risk of exertional heat illness. Med. Sci. Sports Exerc. 2005, 37, 84–90.
3. Berko, J.; Ingram, D.D.; Saha, S.; Parker, J.D. Deaths attributed to heat, cold, and other weather events in the United S tates, 2006–2010. Natl. Health Stat. Report. 2014, 2014, 1–15.
4. Argaud, L.; Ferry, T.; Le, Q.H.; Marfisi, A.; Ciorba, D.; Achache, P.; Ducluzeau, R.; Robert, D. Short- and long-term outc omes of heatstroke following the 2003 heat wave in Lyon, France. Arch. Intern. Med. 2007, 167, 2177–2183.
5. Azhar, G.S.; Mavalankar, D.; Nori-Sarma, A.; Rajiva, A.; Dutta, P.; Jaiswal, A.; Sheffield, P.; Knowlton, K.; Hess, J.J. He at-related mortality in India: Excess all-cause mortality associated with the 2010 Ahmedabad heat wave. PLoS ONE 20 14, 9, e91831.
6. Hoffmann, B.; Hertel, S.; Boes, T.; Weiland, D.; Jöckel, K.H. Increased cause-specific mortality associated with 2003 he at wave in Essen, Germany. J. Toxicol. Environ. Health Part A Curr. Issues 2008, 71, 759–765.
7. Garth, A.K.; Burke, L.M. What do athletes drink during competitive sporting activities? Sport. Med. 2013, 43, 539–564.
8. McCartney, D.; Desbrow, B.; Irwin, C. The Effect of Fluid Intake Following Dehydration on Subsequent Athletic and Cog nitive Performance: A Systematic Review and Meta-analysis. Sport. Med.-Open 2017, 3, 13.
9. Kenefick, R.W. Drinking Strategies: Planned Drinking Versus Drinking to Thirst. Sport. Med. 2018, 48, 31–37.
10. McDermott, B.P.; Anderson, S.A.; Armstrong, L.E.; Casa, D.J.; Cheuvront, S.N.; Cooper, L.; Larry Kenney, W.; O’Conno r, F.G.; Roberts, W.O. National athletic trainers’ association position statement: Fluid replacement for the physically acti ve. J. Athl. Train. 2017, 52, 877–895.
11. Casa, D.J.; DeMartini, J.K.; Bergeron, M.F.; Csillan, D.; Eichner, E.R.; Lopez, R.M.; Ferrara, M.S.; Miller, K.C.; O’Conno r, F.; Sawka, M.N.; et al. National athletic trainers’ association position statement: Exertional heat illnesses. J. Athl. Trai n. 2015, 50, 986–1000.
12. Craig, S.A. Betaine in human nutrition. Am. J. Clin. Nutr. 2004, 80, 539–549.

13. Zeisel, S.H.; Mar, M.H.; Howe, J.C.; Holden, J.M. Concentrations of choline-containing compounds and betaine in com mon foods. J. Nutr. 2003, 133, 1302–1307.

14. Lever, M.; Sizeland, P.C.B.; Bason, L.M.; Hayman, C.M.; Chambers, S.T. Glycine betaine and proline betaine in human blood and urine. BBA-Gen. Subj. 1994, 1200, 259–264.

15. Schwahn, B.C.; Hafner, D.; Hohlfeld, T.; Balkenhol, N.; Laryea, M.D.; Wendel, U. Pharmacokinetics of oral betaine in he althy subjects and patients with homocystinuria. Br. J. Clin. Pharmacol. 2003, 55, 6–13.

16. Alfieri, R.R.; Cavazzoni, A.; Petronini, P.G.; Bonelli, M.A.; Caccamo, A.E.; Borghetti, A.F.; Wheeler, K.P. Compatible os molytes modulate the response of porcine endothelial cells to hypertonicity and protect them from apoptosis. J. Physiol. 2002, 540, 499–508.

17. Ueland, P.M. Choline and betaine in health and disease. J. Inherit. Metab. Dis. 2011, 34, 3–15.

18. Anioła, M.; Dega-Szafran, Z.; Katrusiak, A.; Szafran, M. NH⋯O and OH⋯O interactions of glycine derivatives with squ aric acid. New J. Chem. 2014, 38, 3556–3568.

19. Finkelstein, J.D.; Harris, B.J.; Kyle, W.E. Methionine metabolism in mammals: Kinetic study of betaine-homocysteine m ethyltransferase. Arch. Biochem. Biophys. 1972, 153, 320–324.

20. Zeisel, S.H.; Blusztajn, J.K. Choline and human nutrition. Annu. Rev. Nutr. 1994, 14, 269–296.

21. Borsook, H.; Borsook, M.E. The biochemical basis of betaine-glycocyamine therapy. Ann. West. Med. Surg. 1951, 5, 82 5–829.

22. Da Silva, R.P.; Nissim, I.; Brosnan, M.E.; Brosnan, J.T. Creatine synthesis: Hepatic metabolism of guanidinoacetate an d creatine in the rat In Vitro and In Vivo. Am. J. Physiol.-Endocrinol. Metab. 2009, 296, E256–E261.

23. Pekkinen, J.; Olli, K.; Huotari, A.; Tiihonen, K.; Keski-Rahkonen, P.; Lehtonen, M.; Auriola, S.; Kolehmainen, M.; Mykkä nen, H.; Poutanen, K.; et al. Betaine supplementation causes increase in carnitine metabolites in the muscle and liver o f mice fed a high-fat diet as studied by nontargeted LC-MS metabolomics approach. Mol. Nutr. Food Res. 2013, 57, 19 59–1968.

24. Carnicelli, D.; Arfilli, V.; Onofrillo, C.; Alfieri, R.R.; Petronini, P.G.; Montanaro, L.; Brigotti, M. Cap-independent protein sy nthesis is enhanced by betaine under hypertonic conditions. Biochem. Biophys. Res. Commun. 2017, 483, 936–940.

25. Best, C.H.; Ridout, J.H.; Lucas, C.C. Alleviation of dietary cirrhosis by betaine and other lipotrophic agents. Nutr. Rev. 1 969, 27, 269–271.

26. Schwab, U.; Törrönen, A.; Toppinen, L.; Alfthan, G.; Saarinen, M.; Aro, A.; Uusitupa, M. Betaine supplementation decre ases plasma homocysteine concentrations but does not affect body weight, body composition, or resting energy expen diture in human subjects. Am. J. Clin. Nutr. 2002, 76, 961–967.

27. Abdelmalek, M.F.; Sanderson, S.O.; Angulo, P.; Soldevila-Pico, C.; Liu, C.; Peter, J.; Keach, J.; Cave, M.; Chen, T.; Mc Clain, C.J.; et al. Betaine for nonalcoholic fatty liver disease: Results of a randomized placebo-controlled trial. Hepatolo gy 2009, 50, 1818–1826.

28. Lee, E.C.; Maresh, C.M.; Kraemer, W.J.; Yamamoto, L.M.; Hatfield, D.L.; Bailey, B.L.; Armstrong, L.E.; Volek, J.S.; McD ermott, B.P.; Craig, S.A. Ergogenic effects of betaine supplementation on strength and power performance. J. Int. Soc. Sports Nutr. 2010, 7, 27.

29. Hoffman, J.R.; Ratamess, N.A.; Kang, J.; Gonzalez, A.M.; Beller, N.A.; Craig, S.A.S. Effect of 15 days of betaine ingesti on on concentric and eccentric force outputs during isokinetic exercise. J. Strength Cond. Res. 2011, 25, 2235–2241.

30. Pryor, J.L.; Craig, S.A.; Swensen, T. Effect of betaine supplementation on cycling sprint performance. J. Int. Soc. Sport s Nutr. 2012, 9, 12.

31. Cholewa, J.M.; Guimarães-Ferreira, L.; Zanchi, N.E. Effects of betaine on performance and body composition: A review of recent findings and potential mechanisms. Amino Acids 2014, 46, 1785–1793.

32. Ismaeel, A. Effects of Betaine Supplementation on Muscle Strength and Power: A Systematic Review. J. Strength Con d. Res. 2017, 31, 2338–2346.

33. Burg, M.B. Molecular basis of osmotic regulation. Am. J. Physiol.-Ren. Fluid Electrolyte Physiol. 1995, 268, F983–F99 6.

34. Sheikh-Hamad, D.; Garcia-Perez, A.; Ferraris, J.D.; Peters, E.M.; Burg, M.B. Induction of Gene Expression by Heat Sh ock Versus Osmotic Stress. Am. J. Physiol.-Ren. Fluid Electrolyte Physiol. 1994, 267, F28–F34. Available online: 10.11 52/ajprenal.1994.267.1.f28 (accessed on 21 Febuary 2019).

35. Garcia-Perez, A.; Burg, M.B. Renal medullary organic osmolytes. Physiol. Rev. 1991, 71, 1081–1115.