



A

FORMULATORS GUIDE TO Beta hydroxybutyrate - BHB

THE WORLD'S MOST POWERFUL SCIENCE BACKED INGREDIENT.

IT'S REALLY ALL ABOUT KETONES (BHB)

The rise in internet traffic for the word “keto” and “ketone” is nearly unprecedented. There has been a flurry of interest and talk regarding the benefits of adding exogenous ketones into people’s diets and lives via beta-hydroxybutyrate (as goBHB®). Although weight management is a very powerful benefit of exogenous ketones, it’s not the most powerful story behind BHB and the long-term opportunity behind the most powerful energy molecule that is called the “body’s preferred fuel.”

Beta hydroxybutyrate (as goBHB®) is a multi-patented, non-carbohydrate energy source with an ATP producing potential that is up to 2.5X that of glucose, when calculated per unit carbon consumed and per molecule of oxygen utilized in animal models. BHB has two stereoisomers: D and L (think of them as “left-handed” and “right-handed” molecules).

The D-BHB isomer is often called the “natural” isomer because it is the BHB that is synthesized in the liver from acetoacetate during normal ketogenesis (the synthesis of new ketone bodies) from triglycerides as a result of fat breakdown (lipolysis).

The L-BHB isomer is only created in small amounts in the body in the mitochondria and appears to be a powerful neuronal activator and signaling molecule. A lot more investigation is going on regarding L-BHB than ever before as to its exact metabolic pathways and distinct benefits and characteristics.

Of the many important advancements in ketogenic research, one of the most important includes discovering ketones (BHB) are the preferred energy source of the brain and heart. Additionally, researchers have discovered that D-BHB does much more than simply provide cellular energy or fuel.

This Formulator’s Guide focuses mainly on D-BHB and DL – BHB as not as much is known about L-BHB in terms of its metabolic pathways and functionality. The guide aims to provide you with our knowledge of how to take advantage of the already known benefits of our D-BHB and DL- BHB (goBHB®) in your product formulations.

USING D-BHB

D-BHB is the naturally occurring, endogenously (“inside the body”) generated isomer produced through human metabolism of acetoacetate in the ketogenic process. D-BHB can be measured by conventional ketone blood meters like the Keto Mojo and Precision-Xtra. Once D-BHB enters the blood, it does not reconver to acetoacetate, and is directly metabolized rapidly within the mitochondria for energy.

Benefits include:

- Rapid and readily available bioenergetic fuel source for body and brain via oxidation in mitochondria through the TCA cycle
- Rapid effects on satiety and insulin sensitivity/ glucose tolerance
- High aerobic capacity and energy for low to moderate intensity continuous exercise performance and muscular endurance performance
- Indirect antioxidant effects via endogenous enzyme upregulation; Direct OH-free radical scavenging and antioxidant potential
- Class I and II HDAC inhibition (increased gene expression- FOXO3a, antioxidant defense enzymes Catalase, SOD2, Metallothionein II, etc.)



8688 Ruffian Lane, Suite C
Newburgh, IN 47630

- Increased cytoplasmic NAD⁺ pool (NAD⁺:NADH ratio) over glucose metabolism
- “BHB-lation” of histone (epigenetic effects on gene expression-PPAR, mitochondrial enzymes for oxidative phosphorylation-Electron Transport Chain, proteasome, etc.)
- HCAR2 receptor activation (reduces dysregulated lipolysis from fat cells, anti-inflammatory effects, neuroprotection, gut integrity)
- FFAR3 modulation for regulating inflammation

USING DL-BHB

The racemic form of BHB appears to be the most versatile. It combines the benefits of both D-BHB and L-BHB to address a variety of issues in a much broader format than perhaps either D-BHB or L-BHB address alone.

Benefits include:

- A blend of both readily available energy/ fuel supply with the D-BHB plus a sustained reservoir of L-BHB for a prolonged ketosis effect
- Applications for individuals looking for optimal health span and human performance from exposure to increased blood concentrations of BHB
- NLRP3 inflammasome inhibition was demonstrated in a direct study using the DL-BHB form

USING L-BHB

L-BHB is the so-called “cellular” isomer of BHB that appears to reside within mitochondrial cells, as an intermediate, under normal conditions of fatty acid β -oxidation. It must be consumed exogenously (“from outside the body”). This particular isomer has not been extensively studied and is still speculative as to its functionality, but it appears to have great functional benefits. There is not a simple way to measure the amount of L-BHB within the body as it cannot be detected through current ketone blood meters like D-BHB can. We will continue to update you on our research into this exciting molecule as more knowledge unfolds.

Benefits include:

- L-BHB is metabolized slowly, creating a more sustained and prolonged elevation of ketones in the blood for up to 8 hours in humans
- Increased exposure time “may” provide an opportunity to elicit a more consistent, or robust signaling response for HDAC, NLRP3 inflammasome, HCAR2 inhibition, and ‘BHB-lation’ of histones, chaperone-mediated autophagy and direct/indirect antioxidant defense & resilience
- Better suited for “signaling” purposes due to prolonged duration and residence time in the body, many of which do not appear to be “stereospecific” to D- vs. L, but to BHB in general
- Appears to still be involved in most of the “direct” signaling responses that do not require D-BHB catabolism
- Indirect antioxidant effects via endogenous enzyme upregulation; Direct OH-free radical scavenging and antioxidant potential
- L-BHB is already contained within the cell; thus it might have an additional beneficial effect for protecting against DNA damage and cellular inflammation that contribute directly to disease
- Some studies show that L-BHB is better at synthesizing fats, thus it may be more effective in weight loss and treating obesity

THE FORMS OF BHB

BHB is not a stable molecule on its own. So it needs to either be bound to a mineral to stabilize it or dissolved in a aqueous solution of greater than 50% water. The most common minerals are sodium, calcium, magnesium and potassium, and the finished ingredient is called a “BHB electrolyte.” In the preferred embodiment of using either D-BHB or DL-BHB you should consider what form of BHB do you want to have in your end product. Is it going to be used in an RTD, a capsule, as a dissolvable powder, in a gummy, in a food product, etc.? Below is a table to suggest which form is best in what embodiment.

PRODUCT FORMS	BHB ACID	BHB SALTS
RTD	x	x
POWDER STICK OR SACHET		x
SHOT	x	
FOOD	x	x
GUMMY	x	

SUMMARY

Taking the current research in its entirety, D-BHB may be superior in energy performance, L maybe the superior signaling molecule and DL-BHB has the widest range of application. What is exciting about the ketone field of research is the number of future combinations and formulation iterations still undiscovered. We're still at the beginning stages of learning how L-BHB will work, but we are always striving to help you optimize your exogenous BHB experience by continuing future research for the answers.

[References are located on the following page]

USE CHART FOR GOBHB®

Here is the list of BHB by functionality to help you decide how best to utilize (goBHB) in products to accomplish the functionality you desire:

FUNCTIONAL AREA	D-BHB	DL BHB
ENERGY	x	
ANXIETY	x	
COGNITION	x	
MEMORY	x	
BRAIN REACTION	x	
FOCUS	x	
HYDRATION	x	x
WEIGHT LOSS		x
PERFORMANCE	x	
SLEEP		x
INFLAMMATION		x
IMMUNITY		x
DIABETES		x
ANTI-AGING	x	
CHOLESTEROL LOWERING		x
BODY BUILDING	x	
ENDURANCE	x	
GLUCOSE MANAGEMENT		x
FASTING		x
HEART HEALTH		x
VIRAL INFECTIONS	x	

REFERENCES

1. Lincoln BC, Des Rosiers C, Brunengraber H. 1987. Metabolism of S-3-hydroxybutyrate in the perfused rat liver. Arch. Biochem. Biophys. 259:149-56
2. Webber RJ, Edmond J. 1977. Utilization of L(+)-3-hydroxybutyrate, D(-)-3-hydroxybutyrate, acetoacetate, and glucose for respiration and lipid synthesis in the 18-day-old rat. J. Biol. Chem. 252:5222-26
4. Desrochers S, Dubreuil P, Brunet J, Jette M, David F, et al. 1995. Metabolism of (R,S)-1,3-butanediol acetoacetate esters, potential parenteral and enteral nutrients in conscious pigs. Am. J. Physiol. 268:E660-67
5. Gregoret IV, Lee YM, Goodson HV. 2004. Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. J. Mol. Biol. 338:17-31
6. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, et al. 2015. The ketone metabolite- hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat. Med. 21:263-69
7. Yudkoff M, Daikhin Y, Melo TM, Nissim I, Sonnewald U, Nissim I. 2007. The ketogenic diet and brain metabolism of amino acids: relationship to the anticonvulsant effect. Annu. Rev. Nutr. 27:415-30
8. Sleiman SF, Henry J, Al-Haddad R, El Hayek L, Abou Haidar E, et al. 2016. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body - hydroxybutyrate. eLife pii:e15092
9. Bhaskara S, Knutson SK, Jiang G, Chandrasekharan MB, Wilson AJ, et al. 2010. Hdac3 is essential for the maintenance of chromatin structure and genome stability. Cancer Cell 18:436-47
11. Fajas L, Egler V, Reiter R, Hansen J, Kristiansen K, et al. 2002. The retinoblastoma-histone deacetylase 3 complex inhibits PPAR and adipocyte differentiation. Dev. Cell 3:903-10
12. Knutson SK, Chyla BJ, Amann JM, Bhaskara S, Huppert SS, Hiebert SW. 2008. Liver-specific deletion of histone deacetylase 3 disrupts metabolic transcriptional networks. EMBO J. 27:1017-28
13. Gao Z, Yin J, Zhang J, Ward RE, Martin RJ, et al. 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 58:1509-17
14. Guan JS, Haggarty SJ, Giacometti E, Dannenberg JH, Joseph N, et al. 2009. HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 459:55-60
15. Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Javan S, et al. 2010. Altered histone acetylation is associated with age-dependent memory impairment in mice. Science 328:753-56
16. Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH. 2007. Recovery of learning and memory is associated with chromatin remodeling. Nature 447:178-82
17. Robinson AM, Williamson DH. 1980. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. Physiol. Rev. 60:143-87
18. Kenyon CJ. 2010. The genetics of ageing. Nature 464:504-12
19. Newman JC, Verdin E. 2014. Ketone bodies as signaling metabolites. Trends Endocrinol. Metab. 25:42-52
20. Longo VD, Panda S. 2016. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. Cell Metab. 23:1048-59
21. Mattson MP, Longo V, Harvie M. 2016. Impact of intermittent fasting on health and disease processes. Ageing Res. Rev. pii:S1568-1637(16)30251-3
22. Zhang Y, Xie Y, Berglund ED, Coate KC, He TT, et al. 2012. The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. eLife 1:e00065
23. Edwards C, Canfield J, Copes N, Rehan M, Lipps D, Bradshaw PC. 2014. D-beta-hydroxybutyrate extends lifespan in C. elegans. Aging 6:621-44
24. Sleiman SF, Henry J, Al-Haddad R, El Hayek L, Abou Haidar E, et al. 2016. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body - hydroxybutyrate. eLife pii:e15092
25. Rahman M, Muhammad S, Khan MA, Chen H, Ridder DA, et al. 2014. The-hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages. Nat. Commun. 5:3944
26. Berg JM, Tymoczko JL, Stryer L. 2012. Biochemistry. New York: Freeman Pellerin L, Bergersen LH, Halestrap AP, Pierre
27. K. 2005. Cellular and subcellular distribution of monocarboxylate transporters in cultured brain cells and in the adult brain. J. Neurosci. Res. 79:55-64
28. Dobbins RL, Shearn SP, Byerly RL, Gao FF, Mahar KM, et al. 2013. GSK256073, a selective agonist of G-protein coupled receptor 109A (GPR109A) reduces serum glucose in subjects with type 2 diabetes mellitus. Diabetes Obes. Metab. 15:1013-21
29. Graff EC, Fang H, Wanders D, Judd RL. 2016. Anti-inflammatory effects of the hydroxycarboxylic acid receptor 2. Metab. Clin. Exp. 65:102-13
30. Robinson AM, Williamson DH. 1980. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. Physiol. Rev. 60:143-87