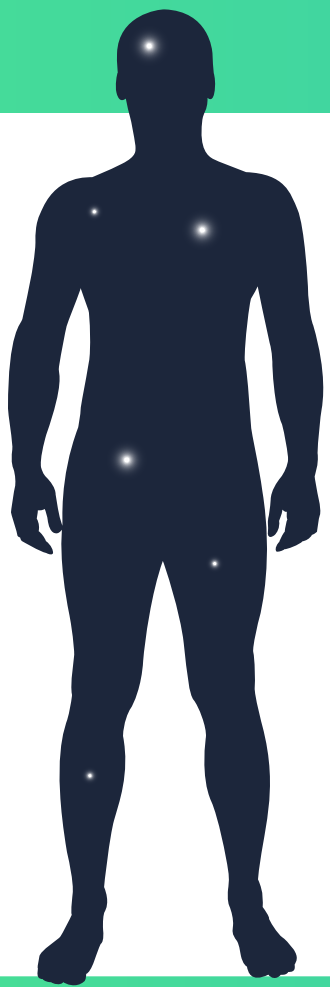
goBHB®

BHB Is 100% BHB

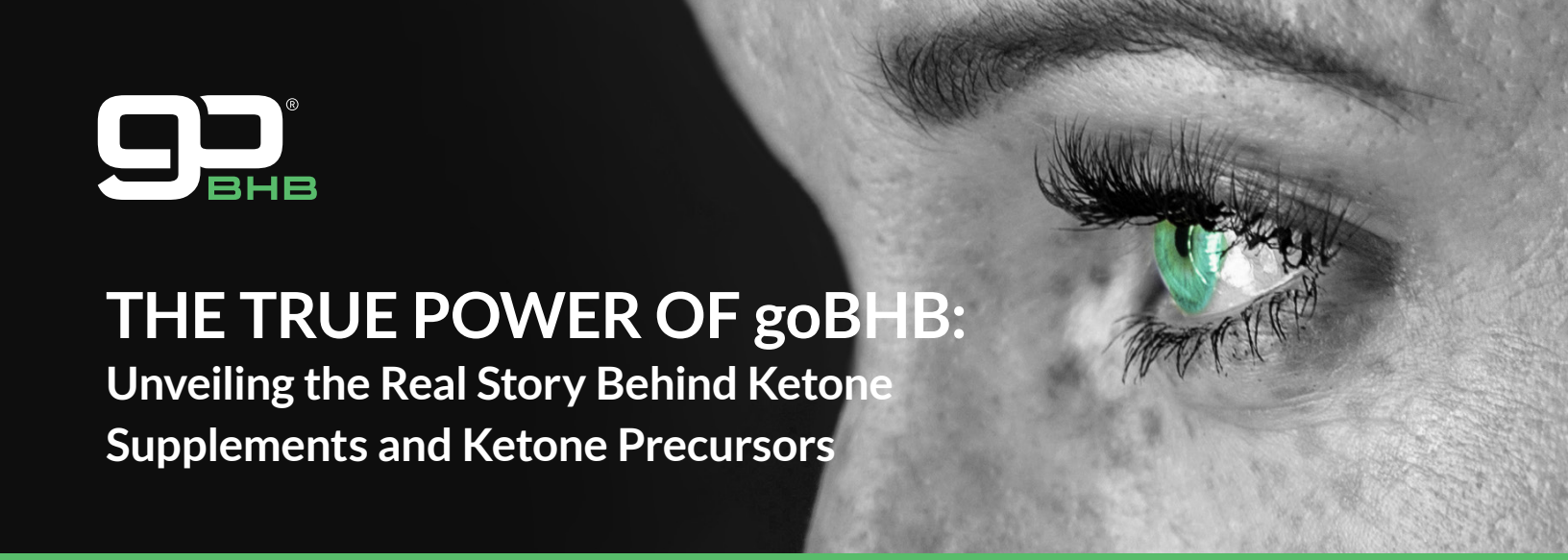
The Power of Pure BHB: No Rivals, No Substitutes, No Limits

goBHB turns back on your body's mitochondria so you go from this...

...to THIS



KETONE LABS



THE TRUE POWER OF goBHB:

Unveiling the Real Story Behind Ketone Supplements and Ketone Precursors

THE WORLD'S MOST POWERFUL SCIENCE BACKED INGREDIENT.

NNB Labs has recently released two groundbreaking studies on BHB, shedding new light on how to determine the true efficacy of BHB supplements and ketone precursors (substances that are not BHB but can convert into BHB). Traditionally, the effectiveness of BHB supplements and precursors (BHB sources) have been measured by their peak levels they reach in the blood.

However, this method is flawed as it only captures a fleeting moment, neglecting the overall impact of BHB sources efficacy. These studies challenge the traditional focus on peak BHB levels and emphasize the importance of considering the total quantity of ketones over time and the net ATP yield of each BHB source—the two key metrics that reveal the real value of different BHB sources.

The two new NNB studies dive deep into comparing the main sources of BHB in the market, in particular goBHB acid/powders (powders being acid + electrolytes), 1,3-butanediol (a ketone precursor), BHB mono esters (one BHB bonded to 1,3-butanediol), and BHB diesters (two BHBs bonded to 1,3-butanediol).

BEYOND THE PEAK: MEASURING BLOOD KETONES (BHB) WITH AREA UNDER THE CURVE (AUC)

Traditional blood ketone meters focus on peak BHB levels to determine effectiveness. This approach is limited because it only captures a fleeting glimpse of the BHB source's impact, neglecting the total quantity and duration of BHB in the blood. A more accurate measure is the Area Under the Curve (AUC), which considers the total BHB presence over time, providing a clearer picture of the source's efficacy.

Study Highlights

In the study "Beyond the Peak: Comparing the Duration and Quantity of Ketones from Three D-BHB Sources," NNB Labs demonstrated that the total quantity of ketones generated over a two-hour period was relatively equivalent among different D-BHB sources, despite differences in peak levels.

THE TRUE STORY OF BHB SOURCES: NET ATP PRODUCTION

The real value of BHB lies in its ability to yield ATP, the primary energy currency of the body. To accurately assess a BHB source's efficacy, one must examine its net ATP yield—the amount of ATP generated after accounting for the energy cost of converting the BHB source into bioavailable BHB.

Key Findings

The NNB Labs study "Impact of Different BHB Substrates and Precursors on Liver ATP" revealed significant differences in net ATP yield among various BHB sources. Both goBHB D-BHB and L-BHB enantiomers provided a substantial and continuous ATP boost to the liver. In contrast, 1,3-butanediol and all esters were found to consume excessive amounts of ATP during their conversion process. Specifically, 1,3-butanediol required over seven times the ATP to convert to BHB compared to BHB acid itself.

Furthermore, numerous studies indicate that 1,3-butanediol not only lacks efficacy, but also poses potential risks to liver and kidney health due to its alcohol nature. BHB mono esters contain 41% 1,3-butanediol, and BHB diesters contain 21% 1,3-butanediol.

For example, Karen Clarke from Oxford and Delta G Ketones writes in marketing materials, *"...ketone products that contain straight 1,3 butanediol, the alcoholic ketogenic precursor, should never be consumed in an attempt to raise blood ketones for performance, as they will carry the same deleterious effects one would see from ethanol consumption."*

Refer to our detailed paper on 1,3-butanediol for more information.

BEYOND EFFICACY: ADDITIONAL ADVANTAGES OF goBHB

1. **Taste and Flavoring:** goBHB, in both its liquid acid and electrolyte acid powder forms, offers a significantly better flavor profile compared to 1,3-butanediol and esters, which are known for their unpleasant taste. This makes goBHB a much more consumer-friendly option.
2. **Electrolyte Benefits:** goBHB can exist in an electrolyte acid powder form, and upon ingestion releases BHB acid and valuable electrolytes that aid in hydration and electrolyte balance. This is crucial for athletes and individuals with specific workout and lifestyle regimens who need a combination of energy and hydration.
3. **Formulation Flexibility:** goBHB liquid acids and electrolyte acid powders enable the creation of liquid or powdered supplements, offering versatile formulation options. In contrast, 1,3-butanediol and esters are primarily available in liquid form, limiting their use and convenience.
4. **Alcohol Concerns:** 1,3-Butanediol, being an alcohol, poses potential health risks. Its metabolism can increase the burden on the liver and kidneys, raising concerns about long-term use.
5. **Cost-Effectiveness:** goBHB is less expensive per kilogram compared to other BHB sources.

MEASURING L-BHB: THE NEW UNTAPPED POTENTIAL OF BHB TECHNOLOGY

Current ketone measurement devices only measure D-BHB, overlooking the significant presence and potential of L-BHB. This leads to an incomplete understanding of the true power of ketone sources. In one study, L-BHB was finally measured and showed a much higher peak and duration than D-BHB. goBHB is the only brand that can provide both D-BHB and L-BHB in any desired ratio and in both liquid acid and electrolyte acid powder forms.

The Hidden Power of L-BHB

Recent research has revealed that L-BHB fully metabolizes in the body and can play a crucial role in energy production, metabolic regulation, and cellular signaling. While D-BHB is widely studied and appears to be the body's primary energy source, L-BHB's unique metabolic pathways and impact might be even more profound. Emerging evidence suggests that L-BHB significantly contributes to the body's energy dynamics, metabolic signaling, and overall metabolic functionality.

For example, we are working with hospitals on rare diseases using goBHB. One of those diseases, MADD (Multiple Acyl-CoA Dehydrogenase Deficiency), a rare genetic disorder that affects the body's ability to break down certain fats and proteins for energy. It was originally believed that D-BHB could be administered to these patients as a fuel source, it was soon discovered that in order for BHB to be effective in supplying energy, it required both L-BHB and D-BHB.

goBHB: THE GOLD STANDARD OF CELLULAR ENERGY

Studies clearly show that D-BHB and L-BHB acid are superior sources of cellular energy. They deliver a direct and sustained ATP boost, aligning with our evolutionary need for stable, efficient fuel during periods of food scarcity.

Fueling Your Success: The Smart Choice for Ketone Supplements

When choosing ketone supplements, focus on the science- backed evidence pointing to ATP production rather than flashy claims about peak BHB levels. It is evident that goBHB is the gold standard. Understanding the true metabolic costs and benefits of different BHB sources empowers you to make informed choices about ingredients that will optimize cellular energy and deliver the most power in a supplement. Based on the positive results from the NNB studies Ketone Labs is moving forward to perform additional human studies on the impact of goBHB on metabolic ATP production.

Unveiling the Truth: Net ATP Production

Science-backed evidence highlights net ATP production as the true measure of a ketone supplement's efficacy. ATP, the body's primary energy currency, fuels cellular processes and drives performance. Research has unequivocally demonstrated that BHB acid reigns supreme in net ATP production, outperforming all other BHB sources, especially 1,3-butanediol.

EMPOWERING YOUR PRODUCTS WITH goBHB

By aligning your brand with the scientifically proven superiority of goBHB and leveraging our 81 patents to protect your brand's use of goBHB, you provide your customers with the most efficient and sustainable energy source. Unlike other BHB sources that deplete cellular energy and pose potential health risks, goBHB delivers the best, clean, powerful boost to cellular function without compromising safety, all at the lowest cost per kilogram.

Are You Ready to Help Fuel Your Success?

NNB Labs' studies unequivocally demonstrate the superior net ATP production and sustained energy benefits of goBHB compared to other BHB sources, particularly 1,3-butanediol. We at Ketone Labs invite you to choose goBHB, the gold standard of cellular energy for your brand.

Beyond the Peak: Comparing the Duration and Quantity of Ketones from Three BHB Supplements

STUDY BACKGROUND

Ketones are the alternative fuel source used by the body when glucose is depleted or in short supply. This generally occurs when on a low-carb, high-fat diet like the ketogenic diet or during long periods of fasting. However, exogenous ketones (bioidentical to what the body produces) can now be produced that duplicate the results of a ketogenic diet and can deliver the benefits of ketones without the rigorous compliance required for sustaining a ketogenic diet.

Multiple studies show promising evidence that using ketones for energy can improve numerous health markers including decreased inflammation[1], improved mental clarity[2], faster weight loss[3] increased performance, recovery, lowering of stress and increased satiety[4].

Research is ever-evolving and continues to confirm the optimal health and performance benefits of using ketones in dietary health and well-being, providing a new frontier of being able to take advantage of the benefits of ketones when in a either a glucose depleted or glucose fed state, thus emulating metabolic flexibility.

With the capability of administering exogenous ketones comes the debate of dosage and ketone levels. This has prompted some debate within scientific circles about whether a higher peak of blood ketones or quantity/duration directly correlates to better results when it comes to emulating ketosis and its potential benefits. Here's a breakdown of the arguments:

Arguments for Higher Peak Ketones:

- **Deeper Ketosis:** Some experts suggest that higher peak ketone levels might indicate a more intense state of ketosis, potentially leading to enhanced metabolic or treatment effects.

- **Individual variability:** Individuals may respond differently to varying ketone levels, believing higher readings might align with better outcomes. It is unknown whether high peaks pose higher risks such as ketoacidosis.

Arguments For Sustained Ketone Duration Levels:

- **Duration Matters:** More researchers argue that the total amount of time you spend in ketosis (greater than 0.5 mmol/L being the nutritional ketosis threshold) is more important and therapeutic than reaching a transient absolute peak value.

- **Adaptation:** The body adapts quickly to using ketones for fuel over time. Consistently elevated ketones suggest better metabolic adaptation and quicker entry into a state of metabolic flexibility.

Unfortunately, there are few credible studies specifically comparing the metabolic effects or benefits of varying peak ketone levels within an induced state of nutritional ketosis. Much of the current understanding is speculative and is based on theoretical models and observational findings.

However, in looking at evolutionary evidence, our hunter-gatherer ancestors wouldn't have benefited from a system prone to dramatic swings in ketone production, but rather, evolution would have favored a more stable, efficient system capable of maintaining a sustained state of ketosis during periods of low food availability. This aligns more with the concept of duration being the key factor in unlocking the true potential of mimicking ketosis with the use of exogeneous ketones.

While the anecdotal belief that a higher peak might suggest a more robust metabolic response, it's evolutionary history that points to the total time spent in ketosis, along with the total quantity of ketones delivered by the supplement, that we believe provides a much more accurate and substantiated picture of metabolic adaptation and flexibility.

STUDY PURPOSE

Currently, testing surrounding ketone supplementation often emphasizes peak blood ketone levels. This study is designed to go “beyond the peak” measurement to determine how the different forms of BHB substances or precursors perform in terms of duration and quantity (AUC, the total amount of ketones present in the blood over time) rather than just measuring peak ketone elevation in order to gain a much clearer understanding of ways to optimize ketone supplementation strategies to support health and well-being by measuring their effects of ketone quantity and duration of ketone elevation.

Our study hypothesis is that the quantity of ketones provided by these three different BHB substances and precursors generate similar amounts of blood ketones over a two-hour period of time within a defined level of ketosis, which is above 0.5mmol/liter when dosed at the same mmol dosing levels.

STUDY PROTOCOL

Since exogenous ketones can be used directly for the creation of ATP energy, we wanted to discover which exogenous BHB substances best produced ketones in the human body. In November of 2022, Axcess Global Sciences and NNB Nutrition designed and conducted a ketogenic PK study for the purpose of assessing the effects of each of three BHB substances (R-BHB liquid, R-1,3-butanediol BHB diester and R-1,3-butanediol) in their ability to produce ketones using equivalent m/mols doses.

The study was conducted on 32 ICR mice randomly divided into 4 groups. The mice were administered one of the exogenous BHB substances orally (gavage volume was 0.2 mL/10 g per mouse). The mice blood ketogenic level was measured at 0, 15, 30, 60, 90, and 120 min with the blood ketogenic meter. The ketogenic level of exogenous BHB substances was determined by measuring the body ketone concentration in the mice.

The study measured (1) the ketone levels at 0, 15, 30, 60, 90, and 120 min over the duration of two hours after administration and (2) the quantity of ketones generated above the 0.5 m/mol level (ketosis), the AUC, (Area Under the Curve). The study was constructed under the theoretical hypothesis that when all three exogenous BHB substances are dosed at an equivalent m/mol dosage, they will produce molar equivalent quantities of R-BHB ketones in the blood.

STUDY RESULTS

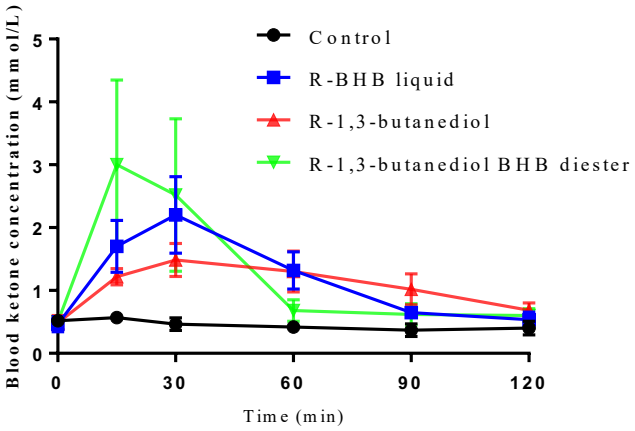


Figure 1. Conventional measurement of ketone levels of R-BHB liquid, 1,3-butanediol, and 1,3-butanediol BHB diester over 2 hours

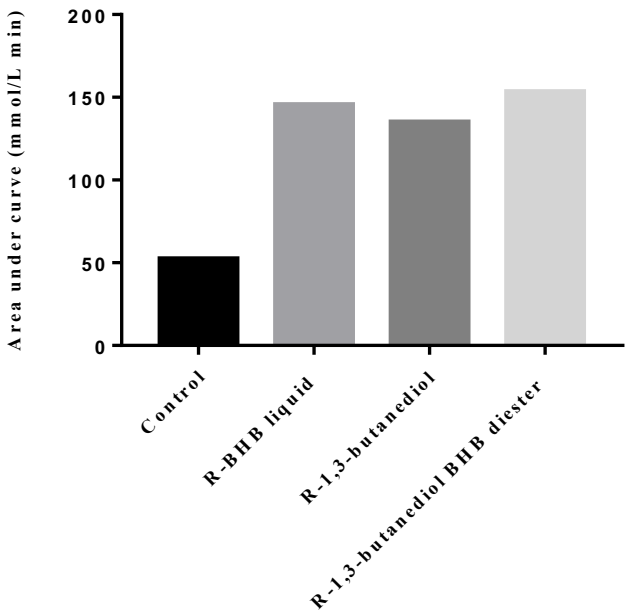


Figure 2. AUC measurement (evaluating total quantity of ketones in the blood over two hours) of R-BHB liquid, 1,3-butanediol, and 1,3-butanediol BHB diester

STUDY DISCUSSION

The study results confirmed our study hypothesis that equivalent m/mol doses of each exogenous BHB substance produces near equivalent amounts of ketones over two hours after administration, with some differences in peak levels and timing in ketone levels.

Measuring Ketone Levels at Time Intervals:

The R-1,3-butanediol BHB diester reached its ketone level peak at 15 minutes, with ketone levels quickly tailing off at the 60 minute mark. R-BHB liquid and R-1,3-butanediol reached their ketone level peak at 30 minutes with R-BHB liquid having a higher peak than 1,3 butanediol. Both R-BHB liquid and 1,3 butanediol remained elevated beyond R-1,3-butanediol BHB diester at 80 minutes. 1,3 butanediol had the lowest peak of the three BHB substances, but remained elevated the longest.

All three BHB substances remained elevated above the control at 120 minutes. Although the peak value of the R-1,3-butanediol BHB diester was higher than R-BHB liquid and R-1,3-butanediol, the R-1,3-butanediol BHB diester also saw the most rapid decline in blood ketone levels. R-1,3-butandiol had the lowest peak value, but its decline rate was slowest. R-BHB liquid had the greatest median peak and elevation of the three BHB substances.

Measuring Quantity of Ketones Over Time (Area Under the Curve):

Taking into account the different ketone level peaks and declines" (shape of the curve) of the three BHB substances, we computed the quantity of ketones generated by each BHB substance to be relatively equivalent. The R-1,3-butanediol BHB diester and R-BHB liquid were rather identical with the R-1,3-butanediol registering a slightly lower quantity. However, in comparing quantities of ketones statistically, all three BHB substances resulted in similar ketone amounts AUC (Area Under the Curve).

STUDY SUMMARY

First, that each BHB substance has its own PK curve in their ability to raise ketone levels and then maintain those ketone levels throughout a ketogenic state over 120 minutes.

The second and primary finding of the study, the final quantity of R-BHB ketones produced by each of the three exogenous BHB substances were statistically equivalent.

FUTURE RESEARCH NEEDED

While this study provided valuable insights into the peak and AUC values of D-BHB from three different sources, it did not account for the potential impact of L-BHB. Emerging research suggests L-BHB plays a crucial role in energy production, metabolic regulation, and cellular signaling. Therefore, we are initiating a Phase 2 study to directly compare peak values and AUC of L-BHB to the D-BHB sources examined here. Preliminary data and prior research on L-BHB lead us to hypothesize that L-BHB may exhibit higher peak and AUC values when measured in the blood.

However, measuring blood ketone levels alone is insufficient to fully understand the efficacy of BHB supplements. While these measurements confirm a state of ketosis, they do not reveal the efficiency with which different BHB sources generate usable energy (ATP). A comprehensive evaluation must consider the entire process, from absorption to intracellular metabolism.

Therefore, future research needs to reach beyond the measure blood BHB levels to assess the ATP values and cost associated with transporting BHB from various sources into the bloodstream. This holistic approach will provide a more accurate understanding of the net ATP yield from different BHB sources, ultimately guiding the development of more effective ketone supplements.

References:

[1] Bueno et al. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomized controlled trials. Br J Nutr. 2013 Oct;110(7):1178-87

[2] Kosinski C et al. Effects of Ketogenic Diets on Cardiovascular Risk Factors: Evidence from Animal and Human Studies. 2017 May 19

[3] Paoli A et al. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. 2013 June 26

[4] Bazzano L et al. Effects of Low-Carbohydrate and Low-Fat Diets. 2014 September 2

The Impact of Different BHB Substrates and Precursors on Liver ATP

ABSTRACT

This study investigated the impact of various beta-hydroxybutyrate (BHB) substances and BHB precursors (BHB sources) on liver ATP (adenosine triphosphate) levels. We administered L-BHB, D-BHB, BHP-Na, BKP-Na, 1,3-butanediol, C8 MCT (medium-chain triglycerides), D-BHB + C8 MCT, and related esters to a mouse model, measuring liver ATP production at 4-time intervals over 120 minutes.

Our results showed distinct differences among the BHB sources. D-BHB + C8 MCT, D-BHB, L-BHB, and C8 MCT increased liver ATP, with D-BHB + C8 MCT yielding the highest increase. Conversely, 1,3-butanediol, and 1,3-butanediol ester derivatives, significantly depleted liver ATP due to their energy-intensive metabolic conversion process into BHB.

BACKGROUND

The recent surge of interest in beta-hydroxybutyrate (BHB) and its precursors (BHB sources) as potential metabolic fuels necessitates a deeper understanding of their true ATP energy impact. While blood ketone measurements are valuable for tracking ketone blood levels and the state of ketosis (blood ketone levels over 0.5mmol/l), they offer a limited perspective on total cellular energy (ATP).

BHB substrates and precursors (BHB sources) undergo various metabolic conversions in the liver before becoming bioavailable as ketone bodies (BHB), each with a unique ATP energy cost profile. By emphasizing "net" ATP generation of BHB sources through these metabolic processes, we can paint a more comprehensive picture of their actual metabolic efficiency beyond ketosis.

Why This Distinction Matters:

- **Substrate Energetics:** Not all BHB sources are created equal. Some may require more ATP investment during their conversion process compared to others. Consequently, even if two BHB sources raise blood BHB levels comparably, the net ATP yield could differ significantly.

- **Cellular Fueling:** Cellular energy demands are not met by BHB alone. The "net" ATP generated during the conversion of BHB sources ultimately determines how efficiently a BHB source replenishes cellular energy stores. Understanding this production process helps identify which BHB sources offer the most favorable balance between BHB elevation in ketosis and the cellular energy costs of conversion.

- **Beyond Ketosis:** While measuring blood ketones is helpful for confirming ketosis, it doesn't tell the whole story about how efficiently your body uses BHB for energy (ATP). Focusing solely on blood ketone levels overlooks the complex steps involved in converting BHB into usable energy and the overall energy produced by BHB within cells (ketolysis).

- **Therapeutic Potential:** In therapeutic contexts where energy support is paramount (such as metabolic disorders or neurodegenerative conditions), deciphering the net ATP yield of various BHB sources becomes crucial. It guides us towards understanding which BHB sources most effectively fuel cellular functions under different circumstances and how BHB sources might be paired together to create even better applications, rather than simply promoting BHB sources based on ketone level elevation alone.

STUDY OBJECTIVE

This study investigates the often-overlooked metabolic costs associated with different BHB sources, focusing on liver ATP generation during their conversion into bioavailable BHB. Our goal is to provide a more comprehensive understanding of BHB source efficiency and identify metrics beyond blood ketone levels.

STUDY DESIGN

Methods:

We examined the effects of eight different BHB sources proven to increase BHB levels in the blood. ATP was measured at various time points post administration of equivalent gram dosages of each BHB substance.

Subjects:

6-8 weeks-old male ICR mice were obtained from Nanjing Wukong Biotechnology Co. LTD. Animals were fed standard laboratory chow and had access to water ad libitum. Animals were housed in pairs (4 mice per cage) in a pathogen-free animal room under controlled conditions (12-hour light/dark cycle, 25°C). Animal use protocols were approved by the Institutional Animal Care and Use Committee (IACUC), and all National Institute of Health guidelines for the care and use of animals were followed. 6-8 mice were used at each time point of 0 minutes, 15 minutes, 30 minutes, and 120 minutes (24 mice total) for each BHB substance tested.

About NNB Labs:

This study was conducted at NNB Labs. NNB is one of the world's leading companies and authorities on BHB sources and has the expertise and capabilities to manufacture any form of BHB source in this study. NNB is credentialled with NSF GMP, ISO 9001, FSSC 22000, ORGANIC NOP, ORGANIC EOS, KOSHER, HALAL, AND SMETA 4P.

STUDY METHODOLOGY

BHB Sources Investigated:

L-BHB acid, D-BHB acid, BHP-Na, BKP-Na, 1,3-butanediol, C8 MCT, D-BHB acid + C8 MCT, BHB-1,3-butanediol monoester, BHB-1,3-butanediol diester, and 1,3-butanediol C8 monoester.

ATP Measurement Technique:

- 50-100mg liver tissue sample was used to extract ATP. Added 500-1000uL of acid to extract proportionally (1:10 = tissue: acid extracting solution) the ATP in the liver tissue from different time points. Extraction was ground in homogenizer, and centrifuged at 8000 gravity at 4°C for 10 minutes into a supernatant.
- The supernatant plus an equal amount of alkaline extracting solution, used to neutralize the supernatant, was then centrifuged at 8000 gravity at 4°C for 10 minutes to create the supernatant for performing ATP measurement.
- 10uL of the supernatant was added to a 96-well plate, 40uL of creatine kinase and creatine mixture was added to the supernatant, and after incubation at 37°C for 30 minutes, 200uL of phosphomolybdate chromogenic agent was added to the

supernatant, and then the supernatant was incubated at 37℃ for 20 minutes. Light absorption values of each hole in the 96-well plate were determined at 700nm.

- The ATP detection pathway used to detect ATP was done through creatine kinase, catalyzing the reaction of creatine and ATP to produce creatine phosphate. The content of creatine phosphate was then detected by phosphomolybdate colorimetry at 700nm to determine the exact content of ATP extraction.
- Control Conditions: D-BHB acid was used as the control group, and all other groups were compared with D-BHB acid.

Experiment Design:

Mice were intragastrically gavaged for each BHB substance at a volume of 0.1 mL/10g body weight. The intragastric doses were listed in Table 1. After gavage, we took 50-100mg liver from mice in homogenate tubes with steel balls at time intervals of 0, 15, 30, 120 minutes for ATP content testing.

Table 1. Grouping methods of the test using the same mg dosage

Group	BHB Source	Molecular Weight (g/mol)	Mice Dose (mmol/kg)	Mice Dose (mg/kg)	Human Daily Dose (g)
1	1,3-butanediol	90.12	18.02	1624	12.5
2	BHP-Na	140.13	11.6	1624	12.5
3	BKP-Na	138.11	11.8	1624	12.5
4	D-BHB acid	104.11	15.6	1624	12.5
5	C8 MCT	470.68	3.5	1624	12.5
6	L-BHB acid	104.11	15.6	1624	12.5
7	80% D-BHB acid + 20% C8 MCT	177.43	13.17	1624	12.5
8	BHB-1,3-butanediol monoester	176.21	9.22	1624	12.5
9	BHB-1,3-butanediol diester	262.3	6.19	1624	12.5
10	1,3-butanediol C8 monoester	342.52	4.74	1624	12.5

STUDY RESULTS AND ANALYSIS

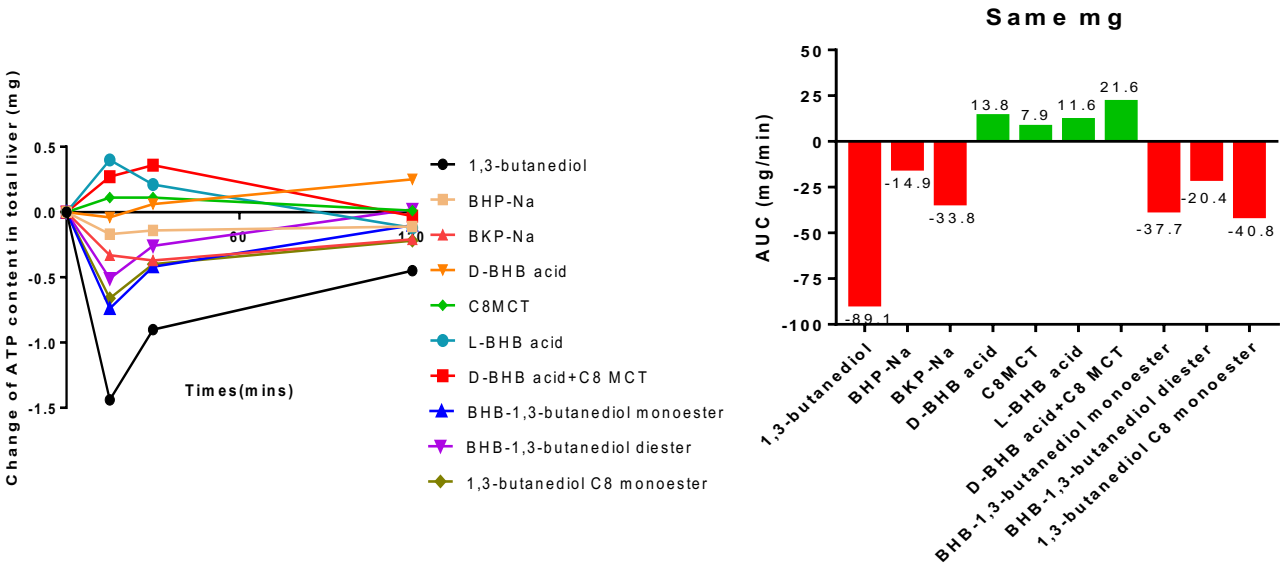


Figure 1: Changes of ATP Content in Liver and Area Under the Curve (AUC)
After Gavage with Different Ketogenic Sources in the Same mg within 2 Hours

The study data reveals two distinct groups of BHB sources:

1. **ATP Generators:** D-BHB + C8 MCT, D-BHB, L-BHB, and C8 MCT demonstrated a positive net ATP impact within the liver. Among these, D-BHB + C8 MCT showed the highest ATP yield.

2. **ATP Consumers:** Every ester and 1,3-butanediol exhibited a negative net ATP impact due to their complex, ATP-demanding metabolic conversion.

ATP Energy Trends (Generators and Consumers)

Figure 1 shows a definite trend grouping of substrates. The grouping of D-BHB + C8 MCT, D-BHB, L-BHB, and C8 all demonstrated a positive ATP Energy generative response.

The grouping of BHP-Na, BHB-1,3-butanediol diester, BKP-Na, BHB-1,3-butanediol monoester, 1,3-butanediol C8 monoester, and 1,3-butanediol demonstrated a negative ATP Energy consumption response.

D-BHB + C8 MCT demonstrates the highest level of change of ATP content in the liver, while 1,3-butanediol demonstrates the lowest.

Net ATP Energy (Area Under the Curve)

In Figure 1, this represents the ATP generated or consumed by each substance. The AUC (area data under the curve) shown in Figure 1 occurred when an equivalent human dosage of 12.5 grams per day was given for all BHB sources.

D-BHB created 13.8 mg/min of ATP as the control BHB source in our study. 1,3-butanediol consumed 89.1 mg/min of ATP (a -755% difference from D-BHB) and D-BHB + C8 MCT generated 21.6 mg/min of ATP (a 56.5% difference from D-BHB).

Net ATP Impact through Ketogenesis

From Figure 1, using the same gram dosage, we find that the order of net ATP production efficiency is:

1. D-BHB acid + C8 MCT
2. D-BHB acid
3. L-BHB acid
4. C8 MCT
5. BHP-Na
6. BHB-1,3-butanediol diester
7. BKP-Na
8. BHB-1,3-butanediol monoester
9. 1,3-butanediol C8 monoester
10. 1,3-butanediol

STUDY DISCUSSION

Our findings demonstrate two distinct metabolic profiles among the investigated BHB sources, based on their net impact on liver ATP over 120 minutes. We designate them as:

Group 1: ATP Generators

- **D-BHB + C8 MCT: Synergistic Energy** - This combination elicited the most significant ATP increase in the liver, peaking at 30 minutes followed by a gradual decline. This suggests a dual-benefit mechanism where D-BHB acid sustains energy release while C8 MCT likely fuels rapid ketone production, providing an immediate energy boost. This combination highlights the potential of strategically pairing BHB sources for optimal ATP generation.

- **D-BHB acid: Steady Direct ATP Supply** - D-BHB acid, the primary physiological ketone, exhibited a gradual ATP increase over time. As it requires no metabolic conversion, it likely provides a sustained energy source directly to liver cells.

- **L-BHB: Rapid ATP** - L-BHB showed a sharp ATP rise followed by a decline, potentially indicating rapid cellular uptake and utilization. Further research is needed to understand if this reflects specific tissue or cellular preferences for L-BHB.

- **C8 MCT: Efficient and Versatile** - C8 MCT increased liver ATP, though less dramatically than the combination of D-BHB + C8 MCT, D-BHB or L-BHB. Its conversion to acetyl-CoA drives cellular respiration (citric acid cycle) within the liver, while a portion fuels ketone generation for broader cellular energy supply.

Group 2: ATP Consumers

- **1,3-Butanediol: Energetic Burden** - 1,3-butanediol caused the most severe ATP depletion, followed by partial recovery. Its multi-step conversion to BHB is highly ATP-demanding. This highlights a critical trade-off: while 1,3-butanediol might elevate blood ketones, it severely taxes liver energy reserves in the process, potentially outweighing any benefits.

- **1,3 Butanediol Esters: Significant ATP Cost** - BHB-1,3-butanediol esters also showed negative ATP trends, though milder than 1,3-butanediol. This confirms that including 1,3-butanediol in a BHB source, even partially, compromises the net ATP yield.

- **BHP & BKP: Mitigated ATP Cost** - These sources exhibited a less pronounced ATP decline. Their conversion pathways likely require a smaller initial ATP investment compared to 1,3-butanediol and its derivatives. However, the trend emphasizes the importance of considering metabolic costs for all BHB sources.

CONCLUSION

This study reveals a critical distinction between BHB sources with potentially significant implications for energy metabolism and therapeutic applications. Our investigation highlights two contrasting metabolic profiles:

- **Group 1: ATP Generators:** D-BHB acid + C8 MCT, D-BHB acid, L-BHB acid, and C8 MCT demonstrated a positive net impact on liver ATP. The combination of D-BHB acid + C8 MCT proved most potent, offering both rapid and sustained energy support.

- **Group 2: ATP Consumers:** 1,3-butanediol and its related esters exhibited a negative net ATP impact due to their energy-intensive metabolic conversion processes. They raise blood ketones but at a significant cost to cellular energy reserves.

KEY STUDY TAKEAWAYS

- **Need to Focus Beyond Ketones:** Measuring blood ketones alone fails to capture the true ATP yield and metabolic efficiency of a BHB source. Considering the metabolic 'costs' within the liver is essential for evaluating the overall energy benefits of any BHB source.

- **Importance of Metabolic Profiling:** Understanding the metabolic pathways and ATP conversion requirements of different BHB sources provides a more comprehensive picture. This conversion knowledge can be critical for tailoring BHB source selection to achieve specific metabolic goals in health and performance contexts.

- **Using Strategic Combinations:** Synergistic pairings like D-BHB acid + C8 MCT demonstrate the potential for optimizing ATP generation by providing both immediate and sustained energy support.

- **ATP: The Cellular Fuel:** This study emphasizes the need to understand the fundamental links and pathways between BHB sources and ATP. C8 MCT's fast, direct pathway provides rapid energy, while combinations like D-BHB + C8 MCT ensure continued ATP supply for various cellular functions.

- **Therapeutic Potential:** BHB sources hold promise for treating metabolic diseases, neurodegenerative conditions, myopathies, and other energy-compromised states. Understanding how ATP-generating and conversely, ATP-depleting sources figure into these contexts is crucial.

FUTURE DIRECTIONS

- **Long-term Studies:** Research should investigate the long-term effects of BHB source combinations on cellular energy metabolism and explore their potential in managing both non-chronic and chronic conditions.

- **Human Studies:** Translating these findings to human applications of BHB sources is crucial for determining optimal dosages and protocols for specific health scenarios. We have already started this and will be publishing these results shortly.

- **Targeted Applications:** Focused research on developing synergistic ATP-generating combinations like D-BHB acid + C8 MCT for brain energy support (dementia, epilepsy) and enhancing muscle function (myopathies, exercise performance) offers exciting possibilities.

In conclusion, this study underscores the importance of going beyond simplistic blood ketone measurements in considering the net ATP yield of administering various BHB sources. This understanding paves the way for further optimizing their use in both health and performance settings.

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SERIES 1 - THE FACTS ABOUT 1,3 BUTANEDIOL

Beta Hydroxybutyrate (BHB) is considered the gold standard of clean cellular energy.

- BHB is more efficient than glucose at producing energy. It can be converted into ATP (adenosine triphosphate), the body's main energy currency, more quickly and easily than glucose.
- BHB does not require insulin to carry it into the cell.
- BHB is preferred by the brain, heart, kidney, and almost every other cell in the body over glucose.
- BHB produces far less damaging free radicals (ROS) and increases levels of BDNF (brain-derived neurotrophic factor), a protein that helps to promote the growth and repair of cells.

The utilization of BHB in promoting superior performance and health is well documented.

What is 1,3 Butanediol? Chemically 1,3 butanediol IS AN ALCOHOL that can be converted through the liver into BHB. It ISN'T a ketone body like BHB. 1.3 butanediol is what you call a "ketone precursor," a substance capable of converting into BHB in the liver to increase BHB levels in the blood. However, the ability of 1,3 butanediol to convert into BHB does not necessarily mean that supplementing with 1,3-butanediol will result in the desired increased levels of BHB in the blood or the side effects that come from the conversion.

The Process the Liver Goes Through to Convert 1,3-butanediol into BHB: Converting 1,3-butanediol into BHB must be done in the liver. Converting 1,3-butanediol to BHB is a complex enzymatic process that is subject to a variety of factors, including the individual's metabolic state and the presence of other nutrients in the body necessary to fully metabolize the 1,3-butanediol. It cannot be directly absorbed into the blood like BHB. The conversion is done through a metabolic pathway known as the 1,3-butanediol pathway. In this pathway, because 1,3-butanediol is an alcohol, it must first be converted to beta-hydroxybutyraldehyde (BHBA) by the enzyme alcohol dehydrogenase (ADH). BHBA must then be oxidized to form BHB by the enzyme beta-hydroxybutyrate dehydrogenase (BDH).

The Energy Cost of Conversion: Converting 1,3 butanediol into BHB takes time and ATP energy. In a most recent study by NNB Labs entitled "The Impact of Different BHB Substates and Precursors on Liver ATP," 1,3 butanediol consumed 89.1 mg/min of ATP to convert 12.5g of 1,3 -butanediol into BHB. This is in contrast to BHB acid which provides 13.6 mg/min of ATP to the liver in transporting it into the blood within a 2 hour period of time. This equated to a comparative loss of 755% in ATP liver energy using 1,3, butanediol as a BHB source versus BHB acid in supplying BHB into the blood with similar dosages.

The Risks of 1,3, butanediol: While 1,3-butanediol is recognized as safe for consumption and even marketed as a vodka substitute (such as in products like Ketohol), its classification as an alcohol raises potential concerns. Similar to other alcohols, it necessitates processing by the liver, which could impact liver function over time. Additionally, from a performance perspective, 1,3-butanediol may pose challenges due to its impact on ATP energy levels, potentially impairing physical and cognitive function compared to non-alcoholic BHB sources.

For further information on Ketohol, you can visit their website: https://shop.ketoneaid.com/products/hard-ketones

Here are some of the key concerns of 1,3 Butanediol:

1. **Dehydration:** Alcohol is a diuretic, which means it increases urine production which can lead to dehydration. Dehydration

can impair athletic performance, as it can lead to fatigue, muscle cramps, and decreased endurance.

2. **Impaired coordination:** Alcohol can impair coordination, reaction time, and balance. This can be dangerous for athletes who require precision and coordination.
3. **Reduced muscle growth and recovery:** Alcohol consumption can reduce protein synthesis, which is the process by which muscles grow and repair. This can lead to slower recovery times after exercise and reduced muscle growth over time.
4. **Decreased endurance:** Alcohol consumption can decrease endurance and performance during aerobic exercise, such as running or cycling.
5. **Reduced mental focus:** Alcohol consumption can impair cognitive function and reduce mental focus, making it more difficult for athletes to concentrate and perform at their best.

The Side Effects of 1,3 butanediol: The literature also identifies 1,3-butandiol can cause a range of adverse health effects, including drowsiness, dizziness, and loss of coordination. Additionally, long term consumption of 1,3-Butanediol has been linked to the development of liver and kidney damage, as well as respiratory problems such as asthma.

Here are a few studies highlighting the risks of using 1,3 butanediol:

- In a recent study presented at the 4th International Keto Live® Conference in Switzerland, conducted by Csilla Ari, Dominic D'Agostino, and Zsolt Kovacs, called "Review of exogenous ketone supplements with enantiomer and concentration dependent effects," showed the liver damage after administration of 1, 3, butanediol and ketone esters after 100 days in tissue histology. This is in contrast to administration of ketone salts (which contain BHB acid + electrolytes), and noted these are the most suitable exogenous ketones for chronic administration.
- A study published in the journal "Clinical Toxicology" in 2006 found that 1,3-butanediol can cause kidney damage in rats. The study found that rats that were given high doses of 1,3-butanediol for 12 weeks had significant damage to their kidneys. This damage was similar to the damage that is seen in people who have kidney disease.
- A study published in the journal "Neurotoxicology and Teratology" in 2008 found that 1,3-butanediol can cause neurotoxicity in rats. The study found that rats that were given high doses of 1,3-butanediol for 12 weeks had significant damage to their brains and spinal cords. This damage led to neurological problems, such as seizures, coma, and death.

The Taste is Horrible: Beyond 1,3 butanediol's reduced effectiveness and inherent risks compared to BHB acid, 1,3-butanediol has an incredibly unpleasant taste. It is often described as having a very chemical or medicinal after taste, while BHB acid is often described as having a more natural or slightly sweet fruity taste. And from a price perspective, 1,3 butanediol is more expensive per gram than BHB acid in either a liquid or electrolyte acid powder form.

The Choice is Clear: 1,3 butanediol is a "want to be BHB," and is no match for the authentic, gold standard of clean cellular energy of BHB.

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SERIES 2 – BHB, THE FOURTH MACRONUTRIENT:

Unveiling the Power of Beta-Hydroxybutyrate (BHB) in ATP Production

In the realm of nutrition and metabolism, the commonly recognized macronutrients are carbohydrates, proteins, and fats. However, emerging research highlights the significance of exogenous Beta-Hydroxybutyrate (BHB) as an already refined and potent "4th macronutrient." Unlike its more familiar counterparts, BHB offers a unique and efficient pathway for adenosine triphosphate (ATP) production (the body's energy currency), positioning BHB as a superior source of cellular energy with remarkable advantages over glucose.

This paper aims to elucidate the pivotal role of ATP in the body, the mechanisms of its production, and the exceptional efficacy of BHB in generating ATP with minimal oxidative stress.

The Energy Currency of Life: Understanding ATP

ATP, often referred to as the body's energy currency of the cell, is indispensable for virtually all biological processes. It powers muscle contraction, nerve impulse propagation, chemical synthesis, and active transport across cell membranes. Structurally, ATP consists of an adenine base, a ribose sugar, and three phosphate groups. The energy is stored in the high-energy phosphate bonds, and when ATP is hydrolyzed into adenosine diphosphate (ADP) an inorganic phosphate (Pi) releases the energy required for all cellular activities.

ATP is primarily created in the mitochondria, the powerhouse of the cell, through a process called "oxidative phosphorylation" during cellular respiration. Additionally, ATP can be produced in the cytoplasm through glycolysis, albeit much less efficiently. The generation of ATP is analogous to electricity production from power plants that provides the electricity that powers our homes, cars, and tools. ATP fuels the biochemical machinery of life in our bodies.

Mechanism of ATP Production from Beta-Hydroxybutyrate (BHB)

Beta-Hydroxybutyrate (BHB) is a ketone body. It can be produced endogenously by the liver during periods of low carbohydrate intake, fasting, or ketogenic diets. BHB can also be administered exogenously now through goBHB. BHB serves as an alternative energy source to glucose, especially for the brain and muscles. Now it can be obtained through exogenous supplementation in a glucose fed state. Here's a step-by-step explanation of how BHB is converted into ATP:

- **Transport into Cells:**
  - BHB is transported from the bloodstream into cells via monocarboxylate transporters (MCTs).
- **Conversion to Acetoacetate:**
  - Inside the cell, BHB is converted back to acetoacetate by the enzyme beta-hydroxybutyrate dehydrogenase. This reaction takes place in the mitochondria and involves the reduction of NAD+ to NADH.
- **Activation to Acetoacetyl-CoA:**
  - Acetoacetate is then activated to acetoacetyl-CoA by the enzyme succinyl-CoA:3-oxoacid CoA transferase (also known as SCOT or OXCT1). This step bypasses the need for ATP, which is a significant advantage over glycolysis.

- **Cleavage to Acetyl-CoA:**
  - Acetoacetyl-CoA is cleaved into two molecules of acetyl-CoA by the enzyme thiolase. This acetyl-CoA can then enter the Krebs cycle (citric acid cycle).
- **Krebs Cycle and Oxidative Phosphorylation:**
  - Krebs Cycle: The acetyl-CoA enters the Krebs cycle, where it undergoes a series of reactions to produce NADH and FADH2.
  - Electron Transport Chain (ETC): NADH and FADH2 donate electrons to the ETC in the inner mitochondrial membrane. The flow of electrons through the ETC drives the pumping of protons across the mitochondrial membrane, creating a proton gradient.
- **ATP Synthase:**
  - — The proton gradient powers ATP synthase, an enzyme that synthesizes ATP from ADP and inorganic phosphate (Pi).

BHB: A Superior Source of ATP

BHB, is referred to as the body's preferred fuel. It provides an alternative energy source to glucose and has very efficient pathway for ATP production. BHB, can then be utilized by various tissues, especially the brain and muscles, as a direct energy source. Here is why BHB is a superior source for producing ATP:

1. **Enhanced ATP Yield:** BHB metabolism produces more ATP per molecule compared to glucose. BHB enters the mitochondria and is converted into acetyl-CoA, which then enters the Krebs cycle. The subsequent oxidative phosphorylation of BHB-derived substrates yields more ATP molecules with fewer steps compared to glucose metabolism.
2. **Reduced Reactive Oxygen Species (ROS) Production:** One of the remarkable benefits of BHB metabolism is its lower production of ROS compared to glucose metabolism. ROS are byproducts of cellular respiration that can cause oxidative damage to cells and tissues, contributing to aging and various diseases. BHB's cleaner ATP production process minimizes oxidative stress, promoting better cellular health.
3. **Gold Standard of Cellular Energy:** Due to its efficient ATP production and reduced oxidative stress, BHB can be considered the gold standard of cellular energy. Its role in sustaining energy levels during metabolic states where glucose is scarce underscores its importance as a macronutrient.

Advantages of BHB in ATP Production

1. **Higher ATP Yield:**
   - The conversion of BHB to ATP is more efficient than glycolysis and glucose metabolism, as BHB produces more reducing equivalents (NADH and FADH2) that feed into the ETC, resulting in a higher ATP yield.
2. **Reduced Reactive Oxygen Species (ROS) Production:**
   - BHB metabolism produces fewer reactive oxygen species (ROS) compared to glucose metabolism. ROS are highly active and harmful byproducts that can damage cells and tissues. Lower ROS production means less oxidative stress and cellular damage.
3. **Alternative Energy Source:**
   - BHB provides a crucial energy source during periods of low carbohydrate availability, ensuring that critical organs like the brain continue to receive a steady supply of energy.

Summary and Conclusion

The production of ATP from BHB involves a pathway that not only yields a higher amount of ATP, but also produces less oxidative stress compared to glucose metabolism, highlighting the efficiency and advantages of BHB as an energy source.

Beta-Hydroxybutyrate (BHB) stands out as a formidable 4th macronutrient, offering a superior pathway for ATP production compared to traditional glucose metabolism. Its efficient conversion to ATP with minimal ROS generation positions BHB as an exceptional source of cellular energy, potentially redefining our understanding of macronutrients. As research continues to unveil the benefits of BHB, its role in nutrition and metabolism may become increasingly prominent, offering new avenues for optimizing human health and performance.