β-Hydroxybutyrate (BHB): An Adaptive Energy Source for Hypoglycemia Recovery

Summary

In the management of hypoglycemia, the restoration of euglycemia is often viewed as the definitive endpoint of treatment. Evidence in patients with type 1 diabetes (T1D) shows a persistent "Recovery Gap" where cognitive functions (choice, reasoning, attention) can remain impaired for hours, despite normalized plasma glucose levels.

The adaptive energy source, β-hydroxybutyrate (BHB), has metabolic advantages that make it uniquely suited to rescue neuronal energy metabolism and mitigate oxidative stress during and after hypoglycemia. This white paper examines the rationale for using BHB to bridge the Recovery Gap - mitigating short-term symptom burden for patients and addressing the potential long-term risks to cognitive health in T1D.

1. Post-Hypoglycemic Metabolic Stress in the Brain

Standard-of-care glucose-only products effectively raise blood glucose levels, but often fail to deliver a complete return to normal function in the hours following treatment. Clinical studies consistently demonstrate that cognitive dysfunction can persist after systemic euglycemia is achieved, suggesting a mismatch between blood glucose correction and neuronal energy restoration (1-4). For patients, this manifests as persistent "hangover" symptoms.

This arises because the brain enters a state of post-hypoglycemic metabolic stress (7-9). As detailed in other white papers, hypoglycemia acts as an acute stressor that triggers an ‘energy bottleneck’, impairing the brain's capacity to convert glucose into ATP (10, 11). The rapid reintroduction of glucose can then divert metabolism into pathways that drive reactive oxygen species (ROS) production, exacerbating damage (12).

Patients with T1D are exposed to repeated hypoglycemic episodes over a lifetime, subjecting the brain to recurrent stress. Evidence links frequent hypoglycemia to poorer performance on cognitive assessments (3) and an increased risk of dementia (13–15).

This has driven increasing interest in strategies that leverage non-glucose energy pathways. By sustaining ATP production when glycolysis is transiently impaired and reducing oxidative stress, these approaches have the potential to improve functional recovery following hypoglycemia and long-term outcomes.

Adaptive Energy Sources

2. An Evolutionary Perspective

Glucose is the brain's primary energy source under normal physiological conditions, but the brain has evolved adaptive mechanisms to preserve energy supply during periods of metabolic stress, like fasting, starvation, or intense exercise, when glucose availability or utilisation is limited (16, 17).

BHB is a ketone body produced by the liver under periods of metabolic stress that can be used by the brain to sustain ATP production (17). BHB can also be provided via oral supplementation to elevate plasma levels without the need for prolonged fasting. In recent years, BHB has attracted increasing attention for its benefits in supporting brain energy metabolism during states of metabolic stress, including hypoglycemia.

3. Why BHB is Metabolically Distinct

Rapid Cerebral Uptake

BHB readily crosses the blood-brain barrier via monocarboxylate transporters (MCTs) (18). In people with T1D it has been shown that MCT activity is upregulated two-fold and MCT gene expression rises, suggesting a natural adaptive response that facilitates cerebral uptake of BHB during hypoglycemia (19).

Bypassing Impaired Glycolysis

Glucose metabolism stalls at the energy bottleneck during hypoglycemia. BHB bypasses the glycolytic pathway, providing a alternative route to ATP generation (Figure 1) that relies on mitochondrial NAD^+ rather than the depleted cytosolic pool of NAD^+. BHB enters the mitochondria and is oxidised to acetyl-CoA.

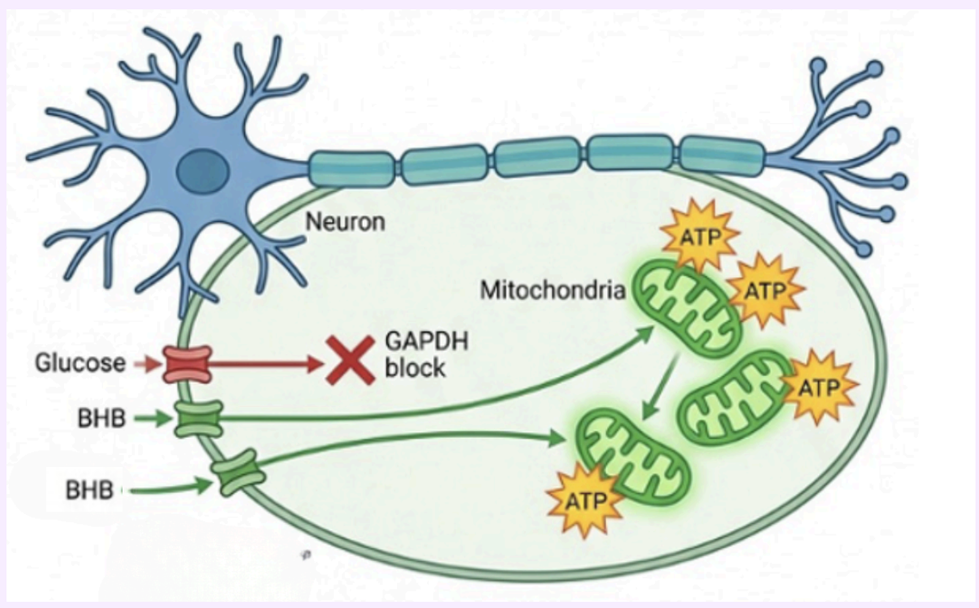

***Figure 1**. BHB is rapidly transported into the mitochondria via MCTs and bypasses the glycolytic bottleneck, sustaining mitochondrial function and ATP levels during the post-hypoglycemic recovery window.*

Efficient Energy Production

BHB is a highly efficient, energy-dense substrate. Compared to glucose, it delivers 21% more usable energy per gram (20) and improves mitochondrial efficiency, generating more ATP per unit of oxygen consumed (21). Additionally, BHB has been shown to increase cerebral blood flow by 30% in humans (22). These properties allow the brain to sustain function during metabolic stress without additional physiological strain.

4. Effects of BHB on Brain Function

Acute Cognitive Support

Elevated BHB levels are associated with improved cognitive performance in low-energy states. During hypoglycemia, BHB has been shown to reduce neuroglycopenic symptoms by 70%, preserve attention and processing speed, and protect memory (23, 24). Cognitive benefits are also seen under normal glucose conditions (25), suggesting that BHB may enhance neuronal function rather than simply compensating for glucose deficiency.

4. Effects of BHB on Brain Function

Neuroprotection

Preclinical research demonstrates that BHB confers broad neuroprotection by mitigating oxidative stress and reducing neuroinflammation. Oxidation of BHB generates fewer ROS than glucose, reducing the cellular oxidative burden (26,27). In addition, BHB acts as a direct antioxidant, scavenging free radicals and upregulating the production of endogenous antioxidant enzymes (28, 29, 30).

Mechanistic studies also identify BHB as a regulator of neuroinflammation during hypoglycemia recovery. It suppresses activation of inflammatory pathways triggered by overactivation of the NLRP3 inflammasome during hypoglycemia (31). At the same time, BHB activates protective signalling in the brain, such as the HCA2 pathway, which promotes an anti-inflammatory and neuroprotective response (32).

Support for Long-Term Brain Health

Clinical evidence links regular BHB exposure to lasting improvements in cognitive performance in low-energy or metabolically stressed states (33,34). Preclinical studies suggest this is driven by neurotrophic support: BHB stimulates the production of brain-derived neurotrophic factor (BDNF) in hippocampal neurons to support neuronal survival (35), and has also been shown to stimulate synaptic plasticity pathways (36). Together, these structural adaptations strengthen neural connections, potentially enhancing long-term learning and memory.

Clinical Briefing

Ketosis vs. Diabetic Ketoacidosis (DKA).

- DKA is a life-threatening complication driven by insulin deficiency and runaway ketone production, with blood ketone levels ≥3.0 mmol/L and severe acidification of the blood.
- Physiological ketosis - a normal process - occurs after fasting, when glucose and glycogen stores are depleted and the body shifts to using fat for fuel.
- Ketosis via exogenous BHB involves a controlled, mild and transient elevation of ketones (~0.5–1.0 mmol/L). At these levels, BHB acts as an adaptive energy substrate rather than an acid load, supporting brain metabolism without risking acidosis.

5. Clinical relevance in Type 1 diabetes

The rationale for using BHB alongside glucose to support neuronal recovery in T1D is now backed by early clinicalevidence. Data from a novel multi-energy substrate (MESH) formulation, Klario®, demonstrated significantly improved recovery outcomes (37) compared to glucose-only treatment. Klario® was associated with significantly improved time-in-range, 27% reduction in recurrent hypoglycemia and improved patient experience in the hours following hypoglycemia. The study found significant improvements in patient-reported after-effects (fatigue, brain fog), faster symptom resolution and return to normal daily activities. These findings represent the first clinical evidence that co-delivering BHB with glucose can provide superior outcomes in hypoglycemia management compared to glucose alone.

Conclusions

BHB is a natural, efficient energy substrate with well-defined metabolic and neuroprotective effects. Its ability to support ATP production, reduce oxidative stress, and preserve cognitive function are relevant for addressing the burden of hypoglycemia in T1D and closing the Recovery Gap.

Data from the MESH formulation, Klario®, support an evolution in the management of hypoglycemia - moving beyond simple glucose replacement toward comprehensive metabolic support, with the potential to improve both clinical outcomes and quality of life of individuals with diabetes worldwide.

References

1. Zammitt NN, Warren RE, Deary IJ, Frier BM. Delayed Recovery of Cognitive Function Following Hypoglycemia in Adults With Type 1 Diabetes. Diabetes. 2008 Mar 1;57(3):732–6.
2. Strachan MW, Deary IJ, Ewing FM, Frier BM. Recovery of cognitive function and mood after severe hypoglycemia in adults with insulin-treated diabetes. Diabetes Care. 2000 Mar 1;23(3):305–12.
3. Ebadi SA, Darvish P, Fard AJ, Lima BS, Ahangar OG. Hypoglycemia and cognitive function in diabetic patients. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2018 Nov;12(6):893–6.
4. Sommerfield AJ, Deary IJ, McAulay V, Frier BM. Short-Term, Delayed, and Working Memory Are Impaired During Hypoglycemia in Individuals With Type 1 Diabetes. Diabetes Care. 2003 Feb 1;26(2):390–6.
5. Frier BM, Jensen MM, Chubb BD. Hypoglycemia in adults with insulin-treated diabetes in the UK: self-reported frequency and effects. Diabetic Medicine. 2016 Aug 7;33(8):1125–32.
6. Brod M, Christensen T, Thomsen TL, Bushnell DM. The Impact of Non-Severe Hypoglycemic Events on Work Productivity and Diabetes Management. Value in Health. 2011 Jul;14(5):665–71.
7. Suh SW, Hamby AM, Gum ET, Shin BS, Won SJ, Sheline CT, et al. Sequential Release of Nitric Oxide, Zinc, and Superoxide in Hypoglycemic Neuronal Death. Journal of Cerebral Blood Flow & Metabolism. 2008 Oct 11;28(10):1697–706.
8. Sheline CT, Behrens MM, Choi DW. Zinc-Induced Cortical Neuronal Death: Contribution of Energy Failure Attributable to Loss of NAD + and Inhibition of Glycolysis. The Journal of Neuroscience. 2000 May 1;20(9):3139–46.
9. Suh SW, Aoyama K, Chen Y, Garnier P, Matsumori Y, Gum E, et al. Hypoglycemic Neuronal Death and Cognitive Impairment Are Prevented by Poly(ADP-Ribose) Polymerase Inhibitors Administered after Hypoglycemia. The Journal of Neuroscience. 2003 Nov 19;23(33):10681–90.
10. Ying W, Garnier P, Swanson RA. NAD+ repletion prevents PARP-1-induced glycolytic blockade and cell death in cultured mouse astrocytes. Biochem Biophys Res Commun. 2003 Sep;308(4):809–13.
11. Alano CC, Garnier P, Ying W, Higashi Y, Kauppinen TM, Swanson RA. NAD+ depletion is necessary and sufficient for poly(ADP-ribose) polymerase-1-mediated neuronal death. J Neurosci. 2010;30(8):2967-2978.
12. Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. Journal of Clinical Investigation. 2007 Apr 2;117(4):910–8.
13. Whitmer RA, Gilsanz P, Quesenberry CP, Karter AJ, Lacy ME. Association of Type 1 Diabetes and Hypoglycemic and Hyperglycemic Events and Risk of Dementia. Neurology. 2021 Jul 20;97(3).
14. Lacy ME, Gilsanz P, Karter AJ, Quesenberry CP, Pletcher MJ, Whitmer RA. Long-term Glycemic Control and Dementia Risk in Type 1 Diabetes. Diabetes Care. 2018 Nov 1;41(11):2339–45.
15. Lacy ME, Moran C, Gilsanz P, Beeri MS, Karter AJ, Whitmer RA. Comparison of cognitive function in older adults with type 1 diabetes, type 2 diabetes, and no diabetes: results from the Study of Longevity in Diabetes (SOLID). BMJ Open Diabetes Res Care. 2022 Mar 28;10(2):e002557.
16. Jensen NJ, Wodschow HZ, Nilsson M, Rungby J. Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. Int J Mol Sci. 2020;21(22):8767.
17. Kolb H, Kempf K, Röhling M, Lenzen-Schulte M, Schloot NC, Martin S. Ketone bodies: from enemy to friend and guardian angel. BMC Med. 2021 Dec 9;19(1):313.
18. Chasseigneaux S, Cochois-Guégan V, Lecorgne L, Lochus M, Nicolic S, Blugeon C, et al. Fasting upregulates the monocarboxylate transporter MCT1 at the rat blood-brain barrier through PPAR δ activation. Fluids Barriers CNS. 2024 Apr 8;21(1):33.
19. Mason GF, Petersen KF, Lebon V, Rothman DL, Shulman GI. Increased Brain Monocarboxylic Acid Transport and Utilization in Type 1 Diabetes. Diabetes. 2006 Apr 1;55(4):929–34.
20. Masood W, Annamaraju P, Khan Suheb MZ, Uppaluri KR. Ketogenic Diet [Internet]. StatPearls (internet) . U.S. National Library of Medicine; 2023 [cited 2025 Sep 8]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499830/
21. Sato K, Kashiwaya Y, Keon CA, Tsuchiya N, King MT, Radda GK, et al. Insulin, ketone bodies, and mitochondrial energy transduction. The FASEB Journal. 1995 May;9(8):651–8.
22. Svart M, Gormsen LC, Hansen J, Zeidler D, Gejl M, Vang K, et al. Regional cerebral effects of ketone body infusion with 3-hydroxybutyrate in humans: Reduced glucose uptake, unchanged oxygen consumption and increased blood flow by positron emission tomography. A randomized, controlled trial. PLoS One. 2018 Feb 28;13(2):e0190556.
23. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J. Effect of Hyperketonemia and Hyperlacticacidemia on Symptoms, Cognitive Dysfunction, and Counterregulatory Hormone Responses During Hypoglycemia in Normal Humans. Diabetes. 1994 Nov 1;43(11):1311–7.
24. Page KA, Williamson A, Yu N, McNay EC, Dzuira J, McCrimmon RJ, et al. Medium-Chain Fatty Acids Improve Cognitive Function in Intensively Treated Type 1 Diabetic Patients and Support In Vitro Synaptic Transmission During Acute Hypoglycemia. Diabetes. 2009 May 1;58(5):1237–44.
25. Jensen NJ, Nilsson M, Ingerslev JS, Olsen DA, Fenger M, Svart M, et al. Effects of β-hydroxybutyrate on cognition in patients with type 2 diabetes. Eur J Endocrinol. 2020 Feb;182(2):233–42.
26. Xin L, Ipek Ö, Beaumont M, Shevlyakova M, Christinat N, Masoodi M, et al. Nutritional Ketosis Increases NAD+/NADH Ratio in Healthy Human Brain: An in Vivo Study by 31P-MRS. Front Nutr. 2018 Jul 12;5.
27. Maalouf M, Sullivan PG, Davis L, Kim DY, Rho JM. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. Neuroscience. 2007 Mar;145(1):256–64.
28. Julio-Amilpas A, Montiel T, Soto-Tinoco E, Gerónimo-Olvera C, Massieu L. Protection of Hypoglycemia-Induced Neuronal Death by β-Hydroxybutyrate Involves the Preservation of Energy Levels and Decreased Production of Reactive Oxygen Species. Journal of Cerebral Blood Flow & Metabolism. 2015 May 4;35(5):851–60.
29. Greco T, Glenn TC, Hovda DA, Prins ML. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. Journal of Cerebral Blood Flow & Metabolism. 2016 Sep 22;36(9):1603–13.
30. Haces ML, Hernández-Fonseca K, Medina-Campos ON, Montiel T, Pedraza-Chaverri J, Massieu L. Antioxidant capacity contributes to protection of ketone bodies against oxidative damage induced during hypoglycemic conditions. Exp Neurol. 2008 May;211(1):85–96.
31. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease. Nat Med. 2015 Mar 16;21(3):263–9.
32. Rahman M, Muhammad S, Khan MA, Chen H, Ridder DA, Müller-Fielitz H, et al. The β-hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages. Nat Commun. 2014 May 21;5(1):3944.
33. Juby AG, Blackburn TE, Mager DR. Use of medium chain triglyceride (MCT) oil in subjects with Alzheimer's disease: A randomized, double-blind, placebo-controlled, crossover study, with an open-label extension. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2022 Jan 14;8(1).
34. Heidt C, Fobker M, Newport M, Feldmann R, Fischer T, Marquardt T. Beta-Hydroxybutyrate (BHB), Glucose, Insulin, Octanoate (C8), and Decanoate (C10) Responses to a Medium-Chain Triglyceride (MCT) Oil with and without Glucose: A Single-Center Study in Healthy Adults. Nutrients. 2023 Feb 24;15(5):1148.
35. Hu E, Du H, Zhu X, Wang L, Shang S, Wu X, et al. Beta-hydroxybutyrate Promotes the Expression of BDNF in Hippocampal Neurons under Adequate Glucose Supply. Neuroscience. 2018 Aug;386:315–25.
36. Di Lucente J, Persico G, Zhou Z, Jin LW, Ramsey JJ, Rutkowsky JM, et al. Ketogenic diet and BHB rescue the fall of long-term potentiation in an Alzheimer's mouse model and stimulates synaptic plasticity pathway enzymes. Commun Biol. 2024 Feb 16;7(1):195.
37. Russell-Jones D, Smout V, Roy S, Myers G, Littlewood R, Shojaee-Moradie F. A novel glucose beta-hydroxybutyrate combination improves hypoglycemia recovery and patient-reported outcomes in type 1 diabetes. Diabetes Obes Metab. 2025; published online ahead of print