Addressing The Post-Hypoglycemia Recovery Gap with Multi-Energy Substrate (MESH) Formulations

Summary

Patients frequently highlight a significant "Recovery Gap" following self-treatment of hypoglycemia — a period of persistent cognitive dysfunction that lingers after blood glucose levels have normalized.

Experimental evidence suggests this gap is driven by a glycolytic bottleneck within the brain, where coenzyme (NAD+) depletion inhibits efficient processing of glucose by neurons.

This white paper examines the pathophysiology of the post-hypoglycemic brain and evaluates the efficacy of Multi-Energy Substrate for Hypoglycemia (MESH) formulations - specifically the novel product Klario®. By combining fast-acting carbohydrates with β-hydroxybutyrate (BHB) and lactate, this therapeutic strategy aims to bypass the glycolytic bottleneck and accelerate recovery.

1. The Clinical Problem: The Recovery Gap

In the management of hypoglycemia, the restoration of euglycemia is often viewed as the definitive endpoint of treatment (1). 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 (2,3,4).

Understanding the **metabolic basis** for the lag in functional recovery is important to direct future research and innovative product development, in order to improve patient outcomes and quality of life.

RECAP:

Glucose metabolism & the NAD^+-dependent step

- Glucose metabolism in the brain occurs in two linked stages: glycolysis in the cytoplasm, followed by mitochondrial oxidation via the tricarboxylic acid (TCA) cycle to support ATP generation.
- Glycolysis provides the initial breakdown of glucose into downstream intermediates and reducing equivalents that feed mitochondrial metabolism (Figure 1a).
- A critical step in this pathway is catalysed by the enzyme GAPDH, which requires cytosolic NAD^+ as an essential coenzyme.
- Continuous cytosolic NAD^+ availability is necessary to sustain glycolytic flux and rapid neuronal ATP production.

2. The Pathophysiology

Evidence suggests that restoration of neuronal ATP after hypoglycemia may be limited by a **transient impairment of glucose utilization** within the brain (Figure 1b).

The acute metabolic stress of hypoglycemia triggers a **cascade of cellular events** that transiently inhibit glycolytic flux:

1. *The Trigger*

Hypoglycemia induces excitotoxicity and release of reactive oxygen species (ROS), which activates **PARP-1** – a DNA repair enzyme (5,6).

2. *The Metabolic Drain*

Once activated, PARP-1 rapidly **consumes cytosolic NAD+**, leading to a temporary shortage (7).

3. *The Bottleneck*

With cytosolic NAD+ **depleted**, the GAPDH step becomes a rate-limiting metabolic **bottleneck** that constrains glucose metabolism (8).

4. *Metabolic Mismatch*

Self-management restores glucose **delivery** to the brain, but ATP energy production is limited by NAD+ availability (9).

5. *Secondary Injury*

When stalled at the bottleneck, incoming glucose is diverted into the hexose monophosphate shunt. This can exacerbate oxidative stress (10).

3. The Strategy: Metabolic Bypass

Providing energy substrates that can sustain ATP production independently of glycolysis offers an opportunity to bypass this metabolic bottleneck (Figure 1c). Adaptive energy sources such as β-hydroxybutyrate (BHB) and lactate, which are naturally produced and utilized during exercise or starvation, enable this strategy by providing substrates for mitochondrial respiration independent of the glycolytic pathway.

3.1 β-Hydroxybutyrate (BHB)

BHB crosses the blood-brain barrier via monocarboxylate transporters. These transporters are upregulated in diabetes (11), facilitating increased cerebral uptake of BHB.

In the brain, BHB is oxidized within the mitochondria to acetoacetate and then acetyl-CoA, allowing entry into the TCA cycle while bypassing cytosolic glycolysis *(Figure 2*).

Because this pathway is **mitochondrial** and relies on mitochondrial NAD^+ rather than cytosolic NAD^+, BHB metabolism can **proceed even when the cytosolic pool is depleted**, thereby supporting continued ATP generation.

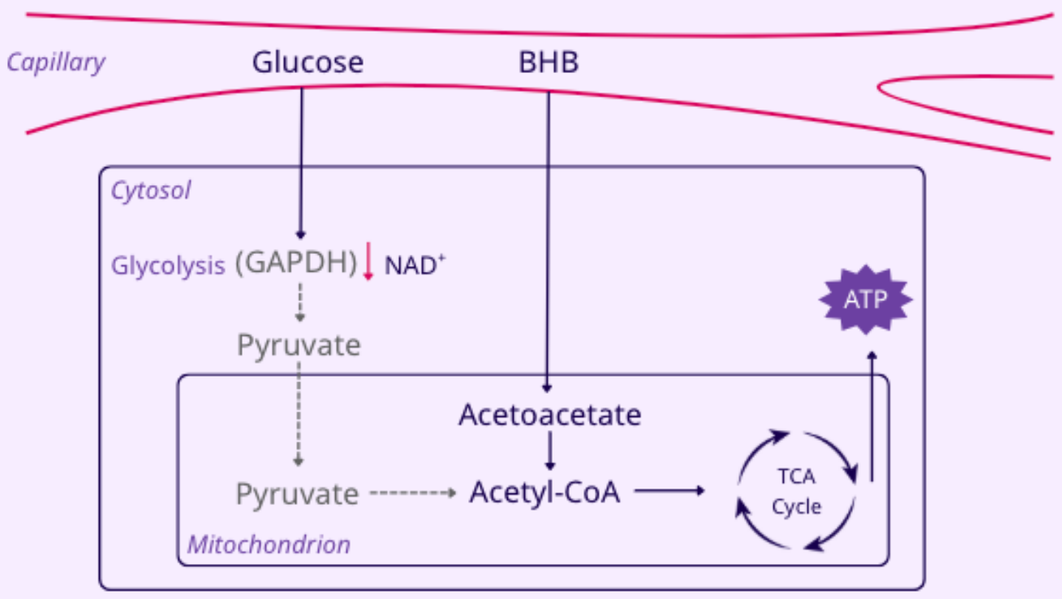

Figure 2. Neuronal metabolism of β-hydroxybutyrate (BHB). *Circulating BHB crosses from the capillary into neurons and is oxidized to acetoacetate and then converted to acetyl-CoA, bypassing the inhibited GADPH step of glycolysis to enter the mitochondrial tricarboxylic acid (TCA) cycle and support ATP production.*

3.2 Lactate

Lactate is a **reversible product of glycolysis**, formed from pyruvate when mitochondrial oxidation is limited, for example by oxygen availability. Following uptake, lactate is readily converted back to pyruvate by lactate dehydrogenase. This pyruvate can then enter the mitochondria to **support ATP production**. In this way, lactate supplies the same downstream substrate that glycolysis normally produces, allowing mitochondrial energy generation to continue when glycolytic flux is constrained.

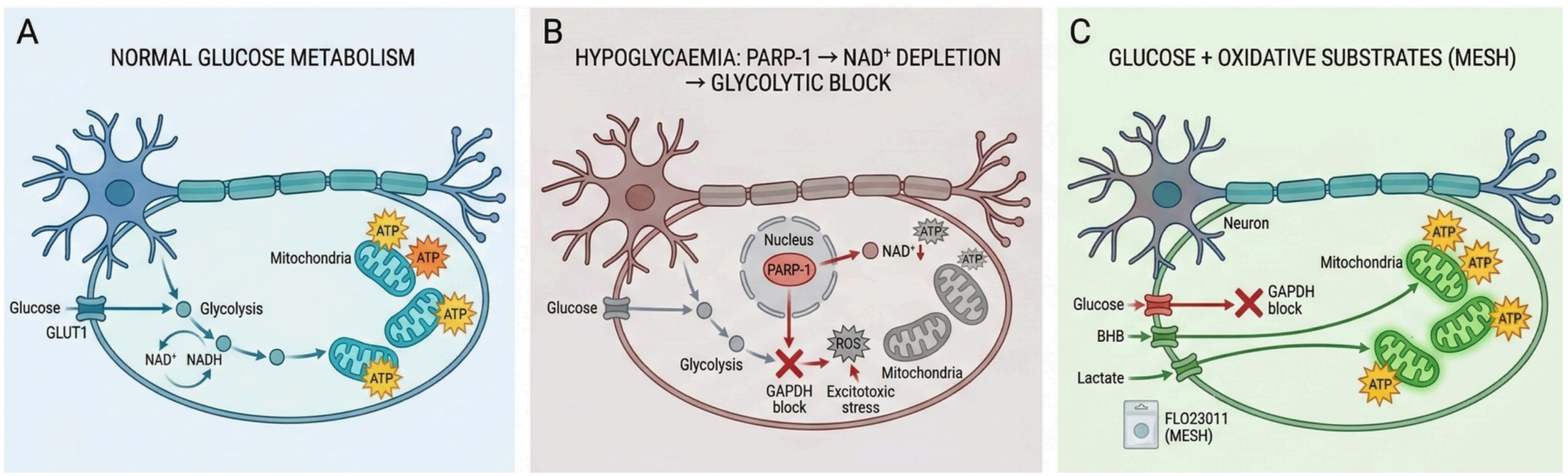

Figure 1. A. Normal metabolism. *Glucose generates ATP via glycolysis and the mitochondrial TCA cycle.* ***B. The Bottleneck****. Hypoglycemia triggers PARP-1-mediated NAD^+ depletion, inhibiting GAPDH. This renders the brain unable to metabolize glucose efficiently despite systemic correction.* ***C. Metabolic Rescue.*** *Adaptive energy substrates (BHB, lactate) bypass the glycolytic bottleneck, sustaining mitochondrial function and ATP levels during the post-hypoglycemic recovery window.*

4. MESH Formulations & Klario®

The MESH approach - inclusion of adaptive energy sources alongside glucose - may **advance hypoglycemia care**, shifting treatment from simple sugar replacement to active metabolic rescue.

Experimental and clinical evidence indicates important neuroprotective and functional benefits of MESH:

- **Preserving ATP:** In pre-clinical models, co-administering BHB/lactate with glucose preserves cerebral ATP levels and reduces neuronal cell death by 70–90% (12–15).
- **Faster Cognitive Recovery:** Clinical studies show that elevated plasma concentrations of BHB and lactate are associated with improved memory, attention, and reaction time during the post-hypoglycemia recovery window (16,17,18).
- **Reduced Oxidative Stress:** BHB reduces the production of ROS and increases antioxidant enzymes; glucose metabolism alone can increase oxidative stress (19).
- **Neuronal Growth:** BHB stimulates the production of Brain-Derived Neurotrophic Factor (BDNF), a critical protein which promotes the growth and survival of neurons (20).

Klario®

Klario® is an novel MESH formulation that combines fast-acting carbohydrates with BHB and lactate to aid post-hypoglycemic recovery.

Klario® is designed to help patients feel and function better after a hypo, by providing adaptive energy that can bypass the glycolytic bottleneck and rapidly restore neuronal energy supply.

Real-world data from more than 1,000 hypoglycemic episodes validates the **clinical advantage of MESH** approaches over standard glucose-only treatments (18). Results showed **higher time-in-range and fewer recurrent hypoglycemic episodes** in the hours after treatment, alongside significant **patient-reported improvements** in speed of symptom resolution and functional recovery.

4. Conclusions

Pairing fast-acting carbohydrates with adaptive energy sources that enter mitochondrial metabolism directly offers a way to support brain energy production while glycolysis remains transiently impaired after hypoglycemia.

Clinical study results demonstrate the effectiveness of Klario®'s novel MESH formulation. Evolving hypoglycemia management from simple sugar replacement to active metabolic rescue with MESH formulations can help to address the recovery gap and improve outcomes for people with diabetes.

Glossary

- **Hypoglycemia (Hypo)** - Low blood glucose. Clinically defined as below 3.9 mmol/L (70 mg/dL), but often experienced as both physical and cognitive symptoms.
- **Glycolysis** - The first step in the process cells use to turn glucose into energy (ATP). During and after a hypo, this pathway can temporarily slow or stall.
- **ATP (Adenosine Triphosphate)** - The cell's main energy source. Low ATP in the brain contributes to fatigue, brain fog, and slowed thinking.
- **PARP-1 (Poly(ADP-ribose) polymerase 1)** - A DNA repair enzyme. When activated during metabolic stress, it consumes NAD^+, which can reduce energy production.
- **NAD^+ (Nicotinamide Adenine Dinucleotide) -** A coenzyme required for glycolysis to work. During hypoglycemia, NAD^+ can be depleted, limiting the brain's ability to use glucose for energy.
- **GAPDH (Glyceraldehyde-3-phosphate dehydrogenase)** - A key enzyme in glycolysis that depends on NAD^+. When NAD^+ is low, this step becomes blocked, creating an energy bottleneck.
- **Mitochondria** -Subcellular organelles that house the tricarboxylic acid (TCA) cycle and oxidative phosphorylation, supporting cellular energy metabolism.
- **TCA Cycle (Tricarboxylic Acid Cycle)** - Also known as the Krebs cycle or citric acid cycle. A central metabolic pathway occurring within the mitochondria that generates energy (ATP) by oxidizing acetyl-CoA derived from carbohydrates, fats, and proteins.
- **β-Hydroxybutyrate (BHB)** - A natural adaptive energy source the brain can use when glucose metabolism is impaired.
- **Lactate** - A naturally occurring energy source that the brain can use to support energy production, especially when glucose processing is disrupted.
- **Adaptive energy** - Natural energy sources (such as BHB and lactate) that help the brain maintain energy when glucose use is limited.

References

1. Holt RIG, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2021 Dec 30;64(12):2609–52.
2. Zammitt NN, Warren RE, Deary IJ, Frier BM. Delayed recovery of cognitive function following hypoglycemia in adults with type 1 diabetes. Diabetes. 2008;57(3):732-736.
3. Evans ML, Pernet A, Lomas J, Jones J, Amiel SA. Delay in onset of awareness of acute hypoglycemia and of restoration of cognitive performance during recovery. Diabetes Care. 2000;23(7):893-897.
4. Blackman JD, Towle VL, Sturis J, Flewis G, Spire JP, Polonsky KS. Hypoglycemic thresholds for cognitive dysfunction in insulin-dependent diabetes mellitus. Diabetes. 1992;41(3):392-399.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. Suh S, Aoyama K, Matsumori Y, Liu J, Swanson RA. Pyruvate Administered After Severe Hypoglycemia Reduces Neuronal Death and Cognitive Impairment. Diabetes. 2005 May 1;54(5):1452–8.
13. 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.
14. Won SJ, Jang BG, Yoo BH, Sohn M, Lee MW, Choi BY, et al. Prevention of Acute/Severe Hypoglycemia-Induced Neuron Death by Lactate Administration. Journal of Cerebral Blood Flow & Metabolism. 2012 Jun 28;32(6):1086–96.
15. Choi BY, Kim JH, Kim HJ, Yoo JH, Song HK, Sohn M, et al. Pyruvate Administration Reduces Recurrent/Moderate Hypoglycemia-Induced Cortical Neuron Death in Diabetic Rats. PLoS One. 2013 Nov 22;8(11):e81523.
16. 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.
17. 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.
18. 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;
19. Newman JC, Verdin E. β-Hydroxybutyrate: A Signaling Metabolite. Annu Rev Nutr. 2017 Aug 21;37(1):51–76.
20. 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.