Boosting the injured brain with supplemental energy fuels.

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Background

Clinical investigation, using cerebral metabolic assessment with positron emission tomography, magnetic resonance spectroscopy and regional cerebral microdialysis, has repeatedly disclosed major alterations of neuroenergetics in the aftermath of traumatic brain injury (TBI). Impairment of neuroenergetics is characterized by elevated cerebral glucose demand, increased glycolysis and diversion of the main substrate, glucose, to be used in injury-related reparative pathways, such as the pentose-phosphate pathway (PPP) [1]. Ultimately, these secondary processes lead to cerebral metabolic glucose depression, decreased availability of cerebral extracellular glucose and energy dysfunction, which in turn exacerbates brain damage and may worsen neurological recovery [2]. Use of alternative cerebral energy substrates – including lactate (LAC) and ketone bodies (KB, including β-hydroxy-butyrate [BHB] and acetoacetate [AcAc]), to compensate for glucose shortage, may therefore be a key adaptive mechanism following TBI. Further, LAC and KB may provide improved substrate availability, as their transport to the brain via mono-carboxylate transporters (MCT) is up-regulated after TBI [3].

Alternative energetic substrates to glucose for the brain: lactate and ketones

Increased astrocyte glycolysis generates LAC, which trans-locates to the brain extracellular space. This astrocytic glycolysis is not accompanied by oxidative metabolism of substrates, even in the presence of oxygen (hence termed *aerobic glycolysis*), which recapitulates obligate glycolytic metabolism in cancer cells (*Warburg effect*). LAC can be transferred to neurons (*astrocyte-neuron lactate shuttle*), and provide a substrate for neuronal energetic needs, while also acting as a modulator of various essential neuronal functions, including excitability, plasticity and memory consolidation [4].

The main source of KB is from endogenous ketosis, through lipolysis and hepatic metabolism of free fatty acids. Astrocytes are also able to generate KB locally. Plasma and local brain derived KB bypass glycolysis to provide substrates that directly enter the tricarboxylic acid (TCA) cycle (a process known as *anaplerosis*) and can be metabolized to provide energy in mitochondria, where the TCA cycle is linked to the generation of adenosine triphosphate (ATP). Apart from their energetic function, KB have key neurotrophic and neuroprotective properties, including up-regulated expression of brain-derived neurotrophic factor, reduction of oxidative stress, promotion of mitochondrial biogenesis, and enhancing synaptic plasticity and cellular stress resistance [5].

Therapeutic energy supplementation after TBI

Lactate therapy

Exogenous supplemental LAC can be administered in the form of hyperosmolar (hypertonic) sodium lactate (Na-LAC) solutions. Experimentally, Na-LAC (given intravenously or by direct intraventricular administration) attenuates lesion extent and cognitive dysfunction, and promotes synaptic plasticity and memory consolidation [4]. In patients with TBI, sodium 3-^{13}C-labelled LAC – administered locally through a cerebral microdialysis catheter [6], or intravenously [2, 7] – can be effectively utilized by the injured brain, with favorable effects on regional neuroenergetics [6]. Systemic administration of intravenous Na-LAC (30 µmol/kg/min, to raise blood arterial lactate to 2-4 mmol/L) increases the availability of cerebral microdialysis glucose and has additional favorable effects on the cerebral circulation, by reducing intracranial pressure and improving cerebral blood flow [8]. Na-LAC has other potentially advantageous systemic effects: contrary to chloride, contained in standard hypertonic saline solutions, LAC is an active metabolic substrate, therefore Na-LAC therapy may prevent hyperchloremic acidosis [9]. Lactate may have additional benefits in terms of signaling, but these have not been explored in humans.

Ketone therapy

Exogenous ketone therapy can be delivered under the form of ketogenic diets (KD), using enteral formulas enriched with medium-chain triglycerides (MCT, comprising octanoic and decanoic acids). KD has been repeatedly tested in experimental and clinical studies as a non-pharmacological approach to the treatment of refractory epilepsy, diabetes, brain cancer and neurodegenerative disorders [10]. Regarding acute phase treatment, continuous enteral feeding using KD takes ≈ 3-5 days to reach stable therapeutic blood KB levels (2-4 mmol/L; compared 0.1-0.2 mmol/L in untreated subjects) [11], while MCT enriched enteral KD boluses may only achieve ≈ 0.5-0.6 mmol/L blood KB levels [12]. Ketone supplementation also can be achieved exogenously in a more direct form, by way of enteral administration of ketone esters (KE) or ketone salts (KS) [13] that allow rapid increase (within 30 min) of blood KB to therapeutic levels comparable to those obtained by intravenous Na-BHB solutions [14].

Ketone supplementation has various neuroprotective effects in experimental models of brain injury [15], in particular by attenuating seizures [16] and oxidative stress [17]. Also, systemic Na-BHB acts as histone deacetylase (HDAC) inhibitor [13]:

degradation of histone deacetylation is involved in memory and cognitive impairments seen in neurodegenerative diseases, therefore HDAC inhibition by KB therapy might translate into improved or restored cognitive recovery following TBI. A recent clinical investigation in subjects with TBI demonstrated that brain microdialysate KB levels were consistently increased during fasting (when compared to the fed state) and correlated well with systemic KB levels, implying effective KB transfer from the systemic circulation to the injured brain, and suggesting a potential therapeutic role for KB supplementation [18]. Enteral KB supplementation improves cerebral oxidative metabolism (increased NAD^+/NADH) in healthy volunteers [12] and provides extra energy under the form of acetyl-CoA to the TCA cycle, thereby reducing the reliance on glycolysis, in athletes [19]. Systemic Na-BHB administration has been recently shown to achieve effects comparable to Na-LAC on neuroenergetics, by reducing cerebral glucose consumption (glucose sparing effect) and increasing cerebral blood flow [20]. In these human studies, KB supplementation was shown to have additional positive systemic effects, by stabilizing blood glucose to normal levels [19]. Altogether, these data provide the rationale for future clinical investigation of ketone therapy during the acute phase of TBI. Long-term progressive neurodegeneration following TBI also may be potentially amenable to enteral KB supplementation, as in other neurodegenerative disorders [10].

Future perspectives

TBI constitutes a persistent challenge to global health care, being the leading cause of mortality in young adults and a major cause of death and disability across all ages worldwide, with a disproportionate burden of disability occurring in low-income and middle-income countries [21]. Given the current lack of targeted pharmacological therapies, boosting neuroenergetics with lactate or ketone therapy may be a valid therapeutic approach to attenuate secondary energy dysfunction, with various additional potentially favorable effects against acute phase and progressive neurodegenerative post-TBI processes (**Figure 1**). This approach appears relatively safe, inexpensive and therefore easily available worldwide, supporting the conduct of further clinical physiological studies and future large-scale multicenter outcome trials.

References

1. Carpenter KL, Jalloh I, Hutchinson PJ (2015) Glycolysis and the significance of lactate in traumatic brain injury. Front Neurosci 9:112

2. Glenn TC, Martin NA, Horning MA, McArthur DL, Hovda DA, Vespa P, Brooks GA (2015) Lactate: brain fuel in human traumatic brain injury: a comparison with normal healthy control subjects. J Neurotrauma. 2015 32:820-32

3. Magistretti PJ, Allaman I (2018) Lactate in the brain: from metabolic end-product to signalling molecule. Nat Rev Neurosci 19:235-249

4. Zhou J, Burns MP, Huynh L, Villapol S, Taub DD, Saavedra JM, Blackman MR. (2017) Temporal changes in cortical and hippocampal expression of genes important for brain glucose metabolism following controlled cortical impact injury in mice. Front Endocrinol 8:231

5. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A (2018) Intermittent metabolic switching, neuroplasticity and brain health Nat Rev Neurosci 19:63-80

6. Jalloh I, Helmy A, Howe DJ, Shannon RJ, Grice P, Mason A, Gallagher CN, Murphy MP, Pickard JD, Menon DK et al (2018) A Comparison of Oxidative Lactate Metabolism in Traumatically Injured Brain and Control Brain J Neurotrauma 35:2025-2035

7. Wolahan SM, Mao HC, Real C, Vespa PM, Glenn TC (2018) Lactate supplementation in severe traumatic brain injured adults by primed constant infusion of sodium L-lactate J Neurosci Res 96:688-695

8. Carteron L, Solari D, Patet C, Quintard H, Miroz JP, Bloch J, Daniel RT, Hirt L, Eckert P, Magistretti PJ et al (2018) Hypertonic lactate to improve cerebral perfusion and glucose availability after acute brain injury Crit Care Med 46:1649-1655

9. Ichai C, Payen JF, Orban JC, Quintard H, Roth H, Legrand R, Francony G, Leverve XM (2013) Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial Intensive Care Med 39:1413-22

10. Augustin K, Khabbush A, Williams S, Eaton S, Orford M, Cross JH, Heales SJR, Walker MC, Williams RSB (2018) Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders Lancet Neurol 17:84-93

11. Stubbs BJ, Cox PJ, Evans RD, Santer P, Miller JJ, Faull OK, Magor-Elliott S, Hiyama S, Stirling M, Clarke K (2017) On the Metabolism of Exogenous Ketones in Humans Front Physiol 8:848

12. Xin L, Ipek Ö, Beaumont M, Shevlyakova M, Christinat N, Masoodi M, Greenberg N, Gruetter R, Cuenoud B (2018) Nutritional Ketosis Increases NAD_+/NADH Ratio in Healthy Human Brain: An *in Vivo* Study by ^{31}P-MRS Front Nutr 2018 5:62
13. Hashim SA, VanItallie TB (2014) Ketone body therapy: from the ketogenic diet to the oral administration of ketone ester J Lipid Res 55:1818-26
14. White H, Venkatesh B (2011) Clinical review: ketones and brain injury Crit Care 15:219
15. Prins ML, Matsumoto JH (2014) The collective therapeutic potential of cerebral ketone metabolism in traumatic brain injury J Lipid Res 55:2450-7
16. Kim DY, Simeone KA, Simeone TA, Pandya JD, Wilke JC, Ahn Y, Geddes JW, Sullivan PG, Rho JM (2015) Ketone bodies mediate antiseizure effects through mitochondrial permeability transition Ann Neurol 78:77-87
17. Greco T, Glenn TC, Hovda DA, Prins ML (2016) Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity J Cereb Blood Flow Metab 36:1603-13
18. Bernini A, Masoodi M, Solari D, Miroz JP, Carteron L, Christinat N, Morelli P, Beaumont M, Abed-Maillard S, Hartweg M et al Modulation of cerebral ketone metabolism following traumatic brain injury in humans (2018) J Cereb Blood Flow Metab Oct 24:271678X18808947 [Epub ahead of print]
19. Cox PJ, Kirk T, Ashmore T, Willerton K, Evans R, Smith A, Murray AJ, Stubbs B, West J, McLure SW et al (2016) Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes Cell Metab 24:256-68
20. Svart M, Gormsen LC, Hansen J, Zeidler D, Gejl M, Vang K, Aanerud J, Moeller N (2018) 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. 13 e0190556
21. Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, Bragge P, Brazinova A, Büki A, Chesnut RM et al (2017) Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research Lancet Neurol 16:987-1048

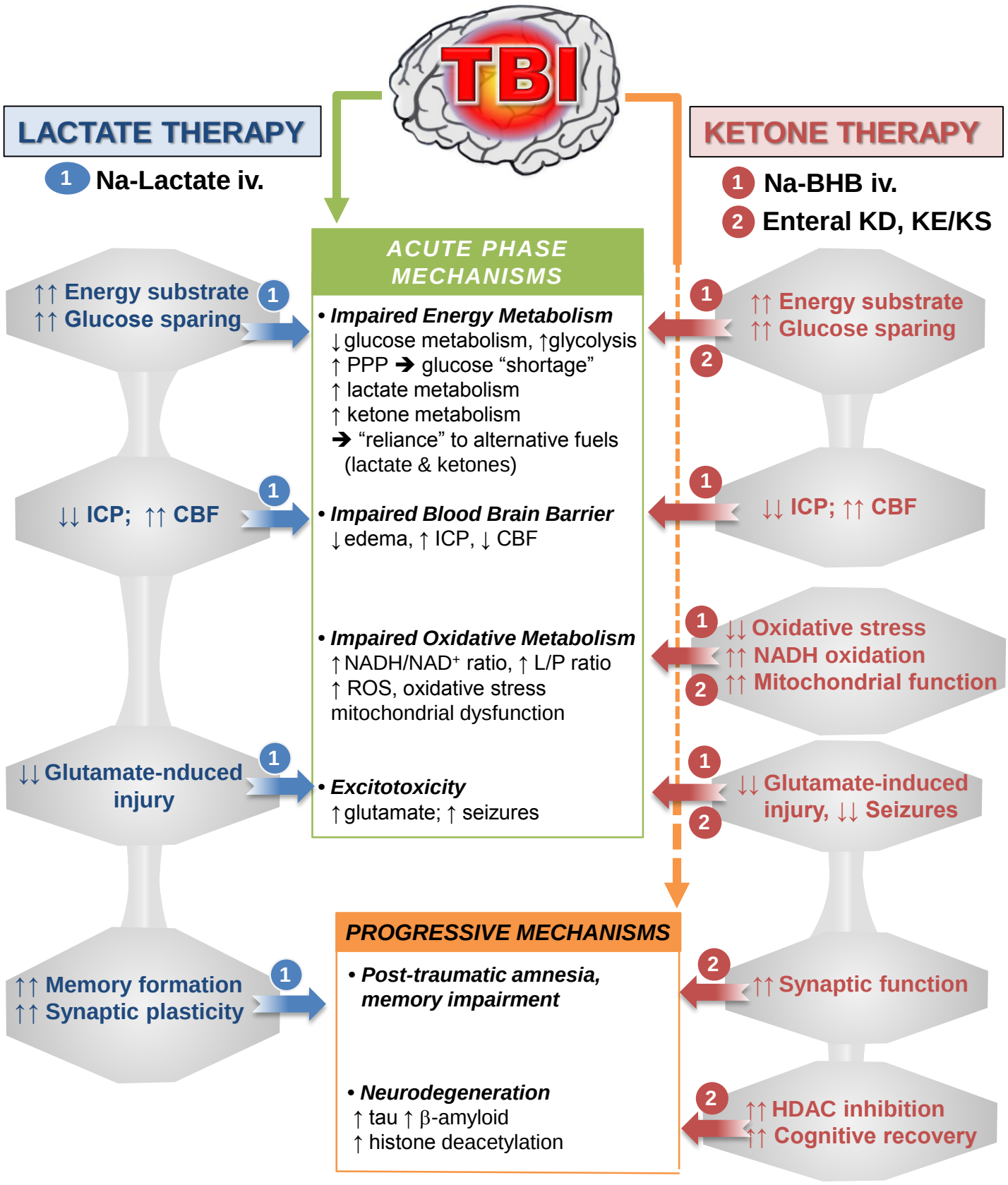
Figure legend.

Figure 1. Rationale for therapies aimed at improving neuroenergetics following traumatic brain injury.

Pathophysiologic mechanisms of secondary cerebral damage following traumatic brain injury (TBI) involve acute phase (≈0-7 days; green box) and progressive (>7 days-weeks; orange box) mechanisms that contribute to aggravate the initial injury and overall patient prognosis. Interventions targeted to improve neuroenergetics – such as lactate therapy (in blue) or ketone therapy (in red), by counteracting TBI mechanisms at various levels (arrows), have the potential to attenuate secondary cerebral damage.

Abbreviations: BHB, β-hydroxybutyrate; CBF, cerebral blood flow; HDAC, histone deacetylase; ICP, intracranial pressure; KD, ketogenic diet; KE, ketone esters; KS, ketone salts; L/P, lactate/pyruvate; NAD^+, nicotinamide adenine dinucleotide (oxidized); NADH nicotinamide adenine dinucleotide (reduced); PPP, pentose-phosphate pathway; ROS, reactive oxygen species.

Figure


TBI
LACTATE THERAPY
1 Na-Lactate iv.
KETONE THERAPY
1 Na-BHB iv.
2 Enteral KD, KE/KS
ACUTE PHASE MECHANISMS
↑↑ Energy substrate
↑↑ Glucose sparing
↓↓ ICP; ↑↑ CBF
↓↓ Glutamate-nduced injury
↑↑ Memory formation
↑↑ Synaptic plasticity
• Impaired Energy Metabolism
↓glucose metabolism, ↑glycolysis
↑ PPP ➔ glucose "shortage"
↑ lactate metabolism
↑ ketone metabolism
➔ "reliance" to alternative fuels (lactate & ketones)
• Impaired Blood Brain Barrier
↓edema, ↑ ICP, ↓ CBF
• Impaired Oxidative Metabolism
↑NADH/NAD+ ratio, ↑ L/P ratio
↑ ROS, oxidative stress
mitochondrial dysfunction
• Excitotoxicity
↑glutamate; ↑ seizures
↑↑ Energy substrate
↑↑ Glucose sparing
↓↓ ICP; ↑↑ CBF
↓↓ Oxidative stress
↑↑ NADH oxidation
↑↑ Mitochondrial function
↓↓ Glutamate-induced injury, ↓↓ Seizures
PROGRESSIVE MECHANISMS
• Post-traumatic amnesia, memory impairment
• Neurodegeneration
↑ tau ↑ β-amyloid
↑ histone deacetylation
↑↑ Synaptic function
↑↑ HDAC inhibition
↑↑ Cognitive recovery