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WHAT'S NEW IN INTENSIVE CARE

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 cerebral energy metabolism in the aftermath of traumatic brain injury (TBI). Impairment of cerebral energy metabolism 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. Ultimately, these secondary processes lead to a reduction of the cerebral metabolic rate of glucose and a decreased availability of cerebral extracellular glucose. To compensate for glucose shortage, cerebral lactate metabolism and uptake are increased in patients with TBI [1]. Use of alternative cerebral energy substrates—including lactate (LAC), but also ketone bodies (KB) such as β-hydroxybutyrate (BHB) and acetoacetate (AcAc)—may therefore be a key adaptive mechanism following TBI.

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

Increased astrocyte glycolysis generates LAC, which translocates to the brain extracellular space. This astrocytic glycolysis is not accompanied by oxidative metabolism of substrates, even in the presence of oxygen (hence it is termed aerobic glycolysis). LAC can be transferred to neurons via monocarboxylate transporters (MCT) (a process called astrocyte–neuron lactate shuttle), and provides additional energy substrate to neurons, while also acting as a modulator of various other essential functions, including excitability, plasticity, and memory consolidation [2].

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 TCA cycle and can be metabolized to provide energy in the form of ATP. Apart from their energetic function, KB have key neurotrophic and neuroprotective properties, including upregulated expression of brain-derived neurotrophic factor, reduction of oxidative stress, promotion of mitochondrial biogenesis, and enhancing cellular stress resistance [3].

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 [2]. In patients with TBI, sodium 3-^{13}C-labelled LAC—administered locally through a cerebral microdialysis catheter [4], or intravenously [1, 5]—can be effectively utilized by the injured brain, as evidenced by increased cerebral extracellular pyruvate [4]. Systemic administration of intravenous Na-LAC (30 μmol/kg/min, to raise blood arterial lactate to 2–4 mmol/L) was shown to increase the availability of cerebral microdialysis glucose and to improve cerebral blood flow [6]. In this latter study, intracranial pressure was normal and cerebral perfusion pressure was maintained stable, arguing against simply an osmotic effect of Na-LAC. Altogether, the results of these phase II clinical studies show improved cerebral energy metabolism and cerebral perfusion upon exogenous LAC

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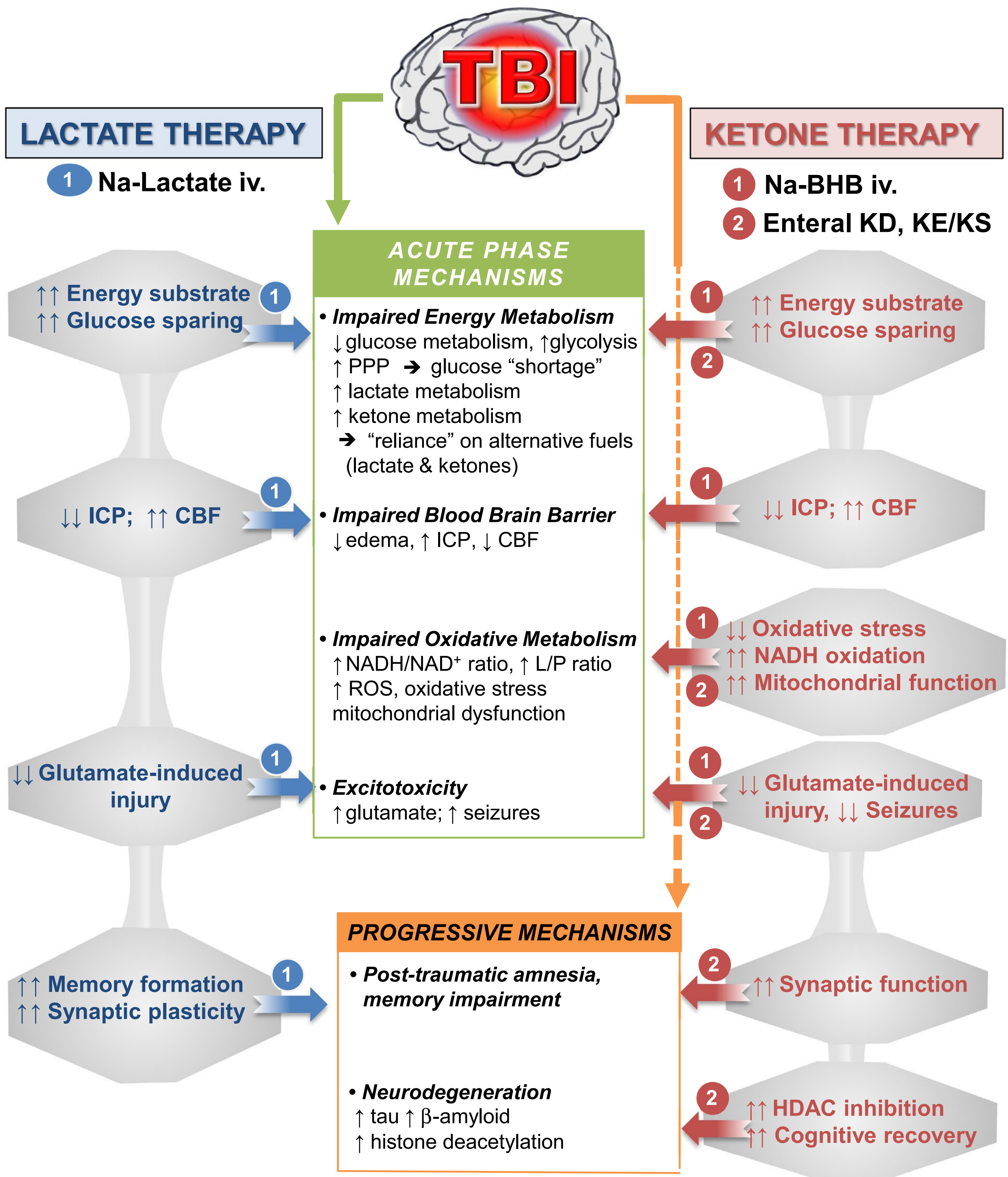

Fig. 1 Rationale for therapies aimed at improving cerebral energy metabolism following traumatic brain injury. Pathophysiologic mechanisms of secondary cerebral damage following traumatic brain injury (TBI) involve acute phase (approx. 0–7 days; green box) and progressive (> 7 days to weeks; orange box) mechanisms that contribute to aggravate the initial injury and overall patient prognosis. Interventions targeted to improve cerebral energy metabolism—such as lactate therapy (in blue) or ketone therapy (in red)—have further therapeutic potential by counteracting TBI mechanisms at various levels (arrows). *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

supplementation in humans with TBI. In addition, 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 [7].

Ketone therapy

Exogenous ketone therapy can be delivered in the form of ketogenic diets (KD), using enteral formulas enriched with medium-chain triglycerides (MCT, comprising octanoic and decanoic acids) and containing very low doses of carbohydrates. 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 [8]. Regarding acute phase treatment, continuous enteral feeding using KD takes approximately 3–5 days to reach stable therapeutic blood KB levels (2–4 mmol/L; compared to 0.1–0.2 mmol/L in untreated subjects) [9], while MCT-enriched enteral KD boluses may only achieve approximately 0.5–0.6 mmol/L blood KB levels [10]. 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) [11] that allow rapid increase (within 30 min) of blood KB to therapeutic levels comparable to those obtained by intravenous Na-BHB solutions [12].

Ketone supplementation has various neuroprotective effects in experimental models of brain injury, in particular by attenuating seizures and oxidative stress [3]. Also, systemic Na-BHB acts as a histone deacetylase (HDAC) inhibitor [11]: 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 [13]. Enteral KB supplementation improves cerebral oxidative metabolism (increased NAD^+/NADH) in healthy volunteers [10], and in athletes provides extra energy in the form of acetyl-CoA to the TCA cycle, thereby reducing the reliance on glycolysis [14]. Long-term progressive neurodegeneration following TBI also may be potentially amenable to enteral KB supplementation, as in other neurodegenerative disorders [8].

Systemic Na-BHB administration has been recently shown to achieve effects comparable to Na-LAC on cerebral energy metabolism, by reducing cerebral glucose consumption (glucose-sparing effect) and increasing cerebral blood flow [15]. Studies with intravenous infusion of Na-LAC and Na-BHB seem to suggest that exogenous LAC and KB may cross the blood–brain barrier and reach neurons: the upregulation of MCT observed after TBI may facilitate transport of exogenous LAC and KB to the brain.

Administration of hyperosmolar Na-LAC and Na-BHB infusions may cause sodium overload and metabolic alkalosis. Regarding glycemic control, exogenous LAC may be (at least in part) metabolized by the liver, thereby potentially increasing glycemia; on the contrary, exogenous KB may reduce blood glucose and contribute to maintain normoglycemia.

Future perspectives

Given the current lack of targeted pharmacological therapies in TBI patients, lactate or ketone therapy may be a valid therapeutic approach to boost cerebral energy metabolism that may exert various other potentially favorable effects against acute phase and progressive neurodegenerative post-TBI processes (Fig. 1). Such therapeutic approaches appear relatively safe, inexpensive, and may theoretically benefit moderate-to-severe TBI patients worldwide. Cerebral metabolic studies have highlighted the potential of LAC and KB supplementation in patients with TBI; however, further large-scale studies, using more robust neuroimaging and functional outcome end points, are needed.

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Compliance with ethical standards

Conflicts of interest

The authors have no conflict of interest to declare.

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