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Unstructured abstract

The goal of neurocritical care is to prevent and reverse the pathologic cascades of secondary brain injury by optimizing cerebral blood flow, oxygen supply and substrate delivery. While glucose is an essential energetic substrate for the brain, we frequently observe a strong decrease in glucose delivery and/or a glucose metabolic dysregulation following acute brain injury. In parallel, during the last decades, lactate and ketone bodies have been identified as potential alternative fuels to provide energy to the brain, both under physiological conditions and in case of glucose shortage. They are now viewed as integral parts of brain metabolism. In addition to their energetic role, experimental evidence also supports their neuroprotective properties after acute brain injury, regulating in particular intracranial pressure control, decreasing ischemic volume, and even improving cognitive functions as well as survival. In this review, we present available data supporting a future therapeutic use of lactate and ketone bodies in acute brain injury. We also review preclinical and clinical evidence exploring the mechanisms underlying their neuroprotective effects, and identify research priorities in the field of neuroenergetics.

Keywords: alternative brain fuels, brain metabolism, ketone bodies, lactate, neuroprotection, stroke, TBI, hypoxia.

Introduction

Acute brain injury refers to brain damage that occurs suddenly, such as traumatic brain injury (TBI), stroke, subarachnoid hemorrhage (SAH) or global ischemia, for example. The insult itself leads to a primary injury, which is followed by secondary brain damage, a pathologic cascade that arises hours to days after the initial injury. The main causes of this secondary brain injury are cerebral blood flow disturbances, which lead to hypoxia and a strong decrease of glucose delivery to the brain. To improve patient outcome, the goal of neurocritical care, after detection of the acute brain injury, is to avoid or reverse the underlying cascades that occur during this secondary brain injury period by optimizing cerebral blood flow, oxygen supply and substrate delivery to the brain.[2] Glucose is an essential substrate to satisfy brain energy requirements. However, its availability is frequently reduced following acute brain injury.[3,4] In the last decades, lactate and ketone bodies have been identified as alternative fuels to provide energy to the brain and preserve glucose for other critical metabolic needs. Results are also accumulating concerning their potential neuroprotective effects and clinical applications.

In this review, we present available data supporting a therapeutic use of lactate and ketone bodies in acute brain injury. We also review preclinical and clinical evidence exploring the mechanisms underlying their neuroprotective effects, and identify research priorities in the field of neuroenergetics.

Glucose for brain energy supply

While the brain represents only 2% of the total body mass, its glucose consumption is around 20% of the systemic consumption, which represents more than 10 times the predicted value relative to its mass. Glucose is an essential substrate to maintain normal brain metabolism and function. It is required for glycolysis, which in turn provides 2 ATP, and 2 pyruvates that can enter the tricarboxylic acid (TCA) cycle to ensure energy production, in majority through the generation of reducing equivalents (NADH and $FADH_2$), which are then used in the electron transport chain

to generate around 30 more ATP molecules (the exact yield of ATP from one round of the TCA cycle can vary but it has been experimentally estimated that NADH can contribute about 2.5 to 3 ATP, and each $FADH_2$ can contribute about 1.5 to 2 ATP) (**Figure 1**). In addition to provide energy to the brain, glucose is a precursor in the synthesis of neurotransmitters and participates in the pentose phosphate pathway (PPP), also known as the hexose monophosphate shunt, which is a metabolic pathway that runs parallel to glycolysis and is essential for NADPH and pentose sugar production, as well as for redox homeostasis. Indeed, the PPP plays a crucial role in maintaining reduced glutathione (GSH) levels in cells by supplying the necessary reducing equivalents in the form of NADPH. Reduced glutathione acts as a critical antioxidant and contributes to the cellular defense mechanisms against oxidative stress due to reactive oxygen species (ROS) production. The PPP is therefore a major pathway for neuronal protection after an acute brain insult during which high amount of ROS are produced.

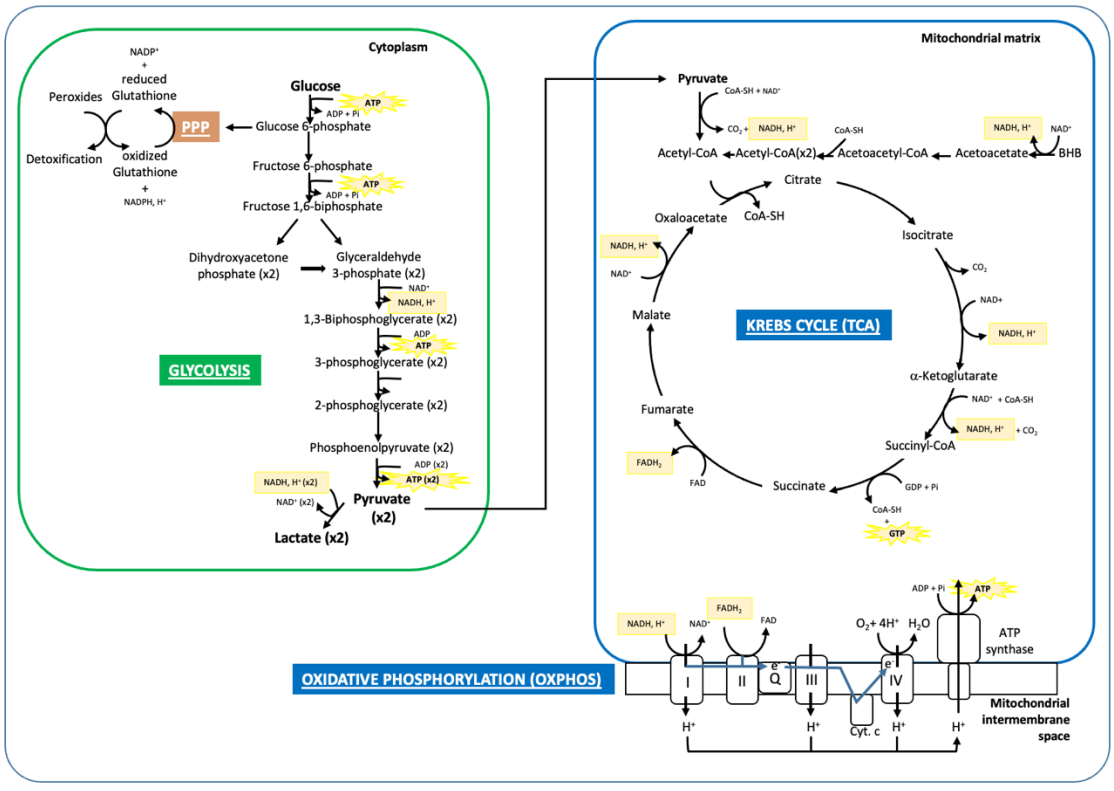

Figure 1: ***Glucose metabolism pathway.*** *In the cytoplasm, glucose is metabolized to pyruvate through glycolysis. This pyruvate can either provide lactate or be redirected to the mitochondria to provide ATP through (i) the Krebs cycle (TCA cycle) coupled to (ii) oxidative phosphorylation (OXPHOS).*

During the acute phase following brain injury, cerebral glucose availability may become insufficient to meet the metabolic demands due to cerebral blood flow failure, blood-brain barrier dysfunction or diffusion impairment. Indeed, glucose storage is very low in the brain. If glycogen can be found in astrocytes, its consumption during ischemia can sustain brain functions for only 2 min (measurements made in rats (Swanson et al. 1989)). In human, a decrease in glycemia linked with a decrease in cerebral glucose concentration was demonstrated to be deleterious in the context of acute brain injury, leading to neuroglycopenia [Vespa P, McArthur DL, Stein N, et al. Tight glycemic control increases metabolic distress in traumatic brain injury: a randomized controlled withinsubjects trial. Crit Care Med 2012; 40:1923–1929 / Magnoni S, Tedesco C, Carbonara M, et al. Relationship between systemic glucose and cerebral glucose is preserved in patients with severe traumatic brain injury, but glucose delivery to the brain may become limited when oxidative metabolism is impaired: implications for glycemic control. Crit Care Med 2012; 40:1785–1791].

Glucose infusion following brain injury has been tested decades ago on a rat model of brain ischemia, aiming to reverse this substrate-deprived state and restore brain energy metabolism. Surprisingly, it was associated with increased mortality and extension of injury.[1] Since then, these results have been consistently replicated in various experimental models of ischemic brain injury.[1–3] In patients, spontaneous high plasma glucose levels have also been associated with increased infarct size, worse clinical outcomes and increased mortality in ischemic stroke and SAH, especially when it happens before or early after ischemia.[1–3]

With the same idea in mind to control glucose level, insulin therapy was also tested, based on the early promising results of intensive insulin therapy in critically ill surgical patients[1]. Many trials have investigated whether insulin-based glycemic control could improve the outcomes of brain-injured patients. Among these, the large GIST-UK trial failed to show a benefit of intensive insulin therapy in patients with acute stroke, although it was likely underpowered due to slow enrollment

which justified its early termination.[1] Overall, this trial and other studies pooled in two recent systematic reviews suggest that tight glycemic control causes more symptomatic and asymptomatic hypoglycemic episodes, both associated with poor outcomes.[1,2]

Ketone bodies and lactate as alternative fuels

It is well established that the brain is metabolically flexible and can metabolize other substrates, such as ketone bodies (KB) and lactate.[5] KB are produced in the liver from fatty acids. They represent a major source of energy for the brain in neonates, who rely on breastfeeding for their diet which is rich in lipids. In adults, when glucose availability is limited in situations such as fasting, a very low-carbohydrate diet (ketogenic diet), or prolonged exercise, KB are produced as alternative fuels and used significantly by the brain. The three main KB synthetized by the liver are acetoacetate (AcAc), beta-hydroxybutyrate (BHB; AcAc can be converted to BHB, which is the predominant ketone body in circulation) and acetone, a minor KB that is produced as a byproduct. KB enter the brain via monocarboxylate transporters (MCTs) and provide energy to the brain in the form of acetyl-CoA entering the tricarboxylic acid cycle to be oxidized, hence reducing reliance on glycolysis for energy production. This alternative energy production turns out to be highly efficient: BHB, one of the main KB, is converted to acetyl-CoA through only three enzymatic reactions, compared to the ten reactions with several rate-limiting enzymes required to convert glucose to acetyl-CoA. It has been shown in non-fasted adult humans infused with [2,4-$^{13}C_2$]-BHB and using ^{1}H-^{13}C polarization transfer spectroscopy that KB can cross the blood-brain barrier and are metabolized by the brain [PMID : 12142574]. These observations have been confirmed in pre-clinical studies (Roy et al. 2015). In euglycemic conditions, ketone bodies are predominantly metabolized by neurons and account for 6% of total coenzyme A oxidation in normal conditions.[1] This phenomenon was found to be amplified in a model of trauma.[1] On a juvenile rat model of TBI infused with [2,4-$^{13}C_2$]-BHB, it has been shown using ^{13}C magnetic resonance spectroscopy (MRS) that KB were extensively metabolized, mainly in neurons [PMID : 36005582].

Concerning lactate, experiments in the 1990s led by Pellerin and Magistretti suggest that lactate is commonly used for basal brain metabolism under physiological conditions. They described a metabolic cooperation between astrocytes and neurons, termed the astrocyte-neuron lactate shuttle (ANLS) (Pellerin and Magistretti 1994). In this model, glutamate released as part of synaptic activity is then taken up by astrocytes, one of their major function to avoid exitotoxicity. Concomitantly with glutamate uptake, a Na^+ influx will occur and its intracellular concentration will rise. As a consequence, Na^+/K^+ ATPase activity will increase, leading to enhanced glucose utilization and lactate production by astrocytes. This astrocytic lactate is then transferred to neurons, through the MCTs (isoforms MCT1 and 4 for astrocytes, MCT2 for neurons; same transporters as the ones used for KB). Once in neurons, lactate is converted back to pyruvate and used as an energetic substrate. Since its description, the ANLS has gained popularity and has been validated in experimental models *in vitro*, *ex vivo* and *in vivo*, although remaining controversial (Bak and Walls 2018, Barros and Weber 2018). Using infusion of [3-^{13}C]lactate and ^{13}C MRS it has been shown in rats that lactate efficiently cross the blood-vrain-barrier and once in the brain, it is preferentially a neuronal substrate (Bouzier et al. 2000). These observations were confirmed in another study that showed that extracerebral lactate contributes at least two-fold more to replenish the neuronal than the glial pyruvate pools [PMID : 25522255]. Authors concluded that a primary utilization of exogenous lactate takes place in neurons rather than in astrocytes (Bouzier et al. 2000). Moreover, lactate entry into neurons through its transporter MCT2 was shown to be necessary to sustain brain function (Suzuki et al. 2011, Netzahualcoyotzi and Pellerin 2020, Roumes et al. 2021). Under supraphysiological conditions, lactate can represent up to 60% of brain energy supply. More recently, preferential lactate uptake by the brain over glucose has been described in a healthy rat model[1] and in exercising man[1–3], likely reflecting an adaptation of the cerebral metabolic ratio to transient hyperlactatemia and relative glucose shortage. A similar observation has been made in patients with acute brain injury, for who an

increase in lactate production occurred during spontaneous glucose depletion despite the absence of brain hypoxia.[1–3] Finally, blocking astrocyte lactate transport in a rat model of cerebral ischemia altered functional recovery, suggesting an obligatory role of lactate in basal neuroenergetics.[1] This obligatory role was further confirmed in another rat model of neonatal hypoxia-ischemia, in which reductions in brain lesion volume and ROS production were observed when lactate was injected, but not when it was co-administered with oxamate, a lactate dehydrogenase inhibitor therefore avoiding its conversion into pyruvate and therefore its metabolism (Roumes et al. 2021).

Thus both KB and lactate can serve as an alternative oxidative substrate for the brain and are mainly metabolized by neurons. They both enter through MCTs and deliver energy after their oxidation in the TCA cycle, entering either at the acetylCoA or at the pyruvate level, respectively (**Figure 2**). In both cases, their metabolism also lead to the conversion of cytosolic NAD^+ into NADH and thus modify the redox potential of the cell (during the conversion of BHB into AcAc or lactate into pyruvate).

Taken altogether, challenges in glucose availability after an acute brain injury, combined with the possibility of the brain to metabolize efficiently KB and lactate, offer new perspectives. A direct modulation of neuronal metabolism by these alternative energy substrates could be of major interest in the search for therapeutic avenues in the context of acute brain injury.

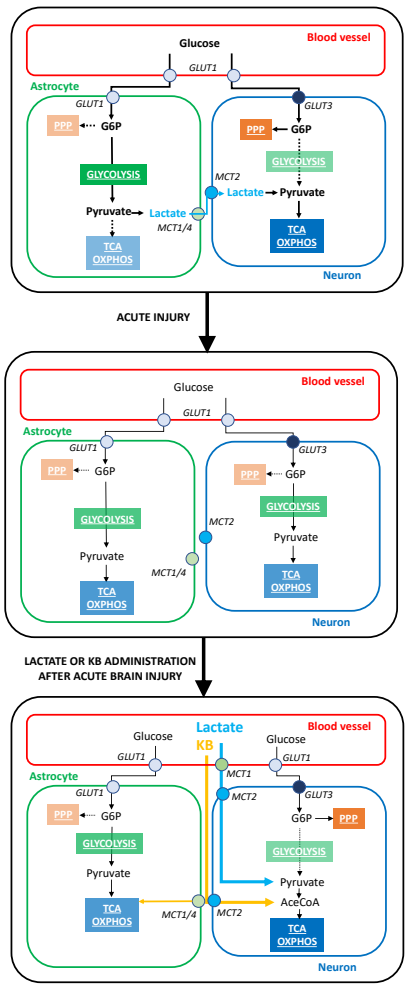

Figure 2: ***Compartmentalization of cerebral glucose metabolism and consequence in brain injury as well as for neuroprotection strategies.*** *A- In the brain, glucose from the bloodstream enters both astrocytes and neurons. It is metabolized to pyruvate in the cytoplasm (glycolysis) then supplies ATP via pyruvate oxidation into the mitochondria (TCA cycle + OXPHOS). However, astrocytes have a greater glycolytic capacity compared to neurons, which are highly oxidative cells (Herrero-Mendez et al. 2009). Astrocytes are known to produce high level of lactate, which can be further transferred to neurons where it can be used as an energy substrate through the TCA and OXPHOS. Glucose can also enter directly into the neuron. Low glycolysis in neurons allows glucose conversion into the pentose phosphate pathway PPP to sustain antioxidant protection. B- In acute brain injury condition, the low level of circulating glucose can not meet cerebral energy needs and the metabolic cooperation between astrocyte and neurons can notbe maintained. Glucose is mainly used for oxidative metabolism in both cell types to maintain ATP level. C- In order to overcome the energy deficit induced by acute brain injury, energy substitution strategies could be adopted. Lactate or exogenous ketone bodies enter directly into brain cells but predominantly in neurons (Pan et al. 2002, Duarte et al. 2015, Scafidi et al. 2022). Lactate is then converted into pyruvate, while ketone bodies are precursors of acetyl-CoA. Pyruvate and Acetyl-CoA are then oxidized through TCA cycle and OXPHOS to provide energy. Saved glucose can be redirected to the PPP pathway to reestablish the antioxidant defense.*
GLUT, glucose transporter; KB, ketone bodies; MCT, monocarboxylate transporter; OXPHOS, oxidative phosphorylation, PPP, pentose phosphate pathway; TCA, tricarboxylic acid cycles.

Alternative fuels and the pentose-phosphate pathway

Neuronal glycolysis is controlled by the enzymatic complex APC/C-Cdh1 that degrades the proglycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3). The enzyme PFKFB3 is less abundant in neurons than in astrocytes, resulting in a lower glycolytic rate and in the redirection of glucose-6-phosphate through the PPP.[30,92] Astrocytes, on the other hand, exhibit a greater PFKFB3 activity, resulting in higher glycolytic rate and lactate production. Hence, this compartmentalization suggests that neurons use glucose preferentially for regulation of their redox state rather than for energy requirements (Bolanos 2016). In stressed states, such after an oxygen-glucose deprived condition, the reperfused neurons showed elevated PFKFB3 expression (Li et al. 2019). Such changes directed neuronal glucose metabolism from PPP to

aerobic glycolysis compared to normal neurons, resulting in increased ROS production and apoptosis during reperfusion. Interestingly, both KB and lactate are oxidative substrates and provide acetylCoA or pyruvate, respectively, while contributing to the conversion of cytosolic NAD^+ into NADH. An increase in the NAD^+/NADH ratio will inhibit glycolysis and redirect glucose through the PPP, and therefore will increase the pool of reduced glutathione. Indeed, it has been shown that both alternative fuels can decrease ROS damages réf 12 + Kim, do Y., et al. Ketone bodies are protective against oxidative stress in neocortical neurons. J. Neurochem. 2007; 101:1316–1326. [PubMed: 17403035] Maalouf M, et al. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. Neuroscience. 2007; 145:256– 264. [PubMed: 17240074] Jarrett S, et al. The ketogenic diet increases mitochondrial glutathione levels. J. Neurochem. 2008; 106:1044–1051. [PubMed: 18466343] + [Joseph Lemire 1, Christopher Auger, Ryan Mailloux, Vasu D Appanna. Mitochondrial lactate metabolism is involved in antioxidative defense in human astrocytoma cells. J Neurosci Res . 2014 Apr;92(4):464-75. doi: 10.1002/jnr.23338. Epub 2014 Jan 22.] whereas the activity of G6PD, the key enzyme of the first (and irreversible) step of the PPP, was significantly increased with lactate in neuronal cultures Pötzsch A, Zocher S, Bernas SN, Leiter O, Rünker AE, Kempermann G. L-lactate exerts a pro-proliferative effect on adult hippocampal precursor cells *in vitro*. iScience. 2021 Feb 3;24(2):102126. doi: 10.1016/j.isci.2021.102126. PMID: 33659884; PMCID: PMC7895751.

Lactate and ketone bodies to control neuroinflammation

Emerging data suggest that lactate and ketone bodies have anti-inflammatory properties, but the underlying mechanisms remain unclear. Microglia are key regulators of brain homeostasis and act as Janus-faced cells regarding neuroinflammation.[93] After an ischemic event, microglia are activated and release pro-inflammatory factors, such as TNF-α, IL-1ß, IL-6 and IFN-y, exhibiting

a pro-inflammatory or “M1” microglial phenotype.[94] On the other hand, microglia can also promote tissue and vascular remodeling via expression of anti-inflammatory factors such as IL-10, VEGF, TGF-ß and BDNF, exhibiting an anti-inflammatory or “M2” phenotype. These microglial phenotypes are tightly linked to their metabolism, and lactate was shown to switch microglial profiles from a glycolytic M1 to an oxidative M2 phenotype, hence promoting microglial energy production. [95] Lactate has been shown to inhibit microglia-mediated neuroinflammation through the Akt-pathway leading to elongation of microglial processes [Hong, Hongxiang; Su, Jianbin; Zhang, Yi; Xu, Guanhua; Huang, Chao; Bao, Guofeng; Cui, Zhiming. A novel role of lactate: Promotion of Akt-dependent elongation of microglial process. International Immunopharmacology June 2023 119 DOI: 10.1016/j.intimp.2023.110136]. BHB was shown to exert similar effects through induction of microglial ramifications and of an anti-inflammatory response in a Akt-dependant manner.[96] There is also evidence that a ketogenic diet reduces ROS generation and suppresses inflammasome activation.[97] In another study, ketogenic diet and BHB post-treatment reduced infarct volume and suppressed the over-activation of microglia in a mouse model of MCA occlusion reference 85.

Together with glucose redirection through the PPP, these anti-inflammatory effects might constitute an elegant hypothesis to explain some of the clinical benefits observed with alternative fuel supplementation in acute brain injury.

Increase in cerebral blood flow

In an *in vitro* study on rat hippocampal and neocortical slices, cerebral vasomotor tone was influenced by the metabolic state of the tissue. In hypoxic conditions, astrocyte glycolysis and lactate production were increased, causing vasodilation via an attenuation of prostaglandin uptake.[6,68] In a cohort of patients with severe acute brain injury (SAH and TBI), a lactate infusion increased extracellular glucose levels and improved cerebral blood flow estimated by transcranial Doppler.[50] Explanation of this mechanism is not well understood. Lactate could act as a

transmitter of metabolic information by modulating prostaglandin action and cerebral vasodilatation causing cerebral blood flow to increase, regulates the NAD^+/NADH redox ratio by conversion to pyruvate, and/or activates a G-protein coupled receptor in neurons, astrocytes, and capillaries (Gordon 2008, Begersen 2012, Lauritzen 2014). Interstingly, KB can also increase cerebral blood flow as shown in mice by MRI[69], and in human healthy subjects by PET scan[65] and the Kety-Schmidt technique[70].

Control of brain edema

Intracranial hypertension is one of the major challenges faced by neurocritical care clinicians following TBI, massive SAH or hypoxic-ischemic brain injury. To control intracranial pressure (ICP), conventional treatment is based on a stepwise approach mostly described in TBI and involves deep sedation and analgesia, correct positioning of the patient, and hypertonic sodium chloride or mannitol infusions.[71] If the efficacy of osmotic therapy to control ICP is well established, it is also associated with side effects, among which are hyperchloremic acidosis and fluid overload.[72] Based on its favorable molecular profile, sodium lactate has been identified as a potential agent to control ICP while avoiding these deleterious effects. It was first tested in a randomized trial in humans against mannitol in the treatment of intracranial hypertension during severe TBI. In this study, lactate was associated with a greater and more prolonged decrease in ICP than mannitol.[51] This result has since been replicated, and was also shown to prevent intracranial hypertensive episodes and fluid overload.[49,73,74] Moreover, half-molar sodium lactate administered to patients with severe head trauma was associated with a mild metabolic alkalosis, counteracting the hyperchloremic acidosis associated with “traditional” osmotic therapy.[52] This control of brain edema might explain why lactate has been associated with increased tissue oxygenation. In rat models of TBI, exogenous sodium lactate increased cerebral tissue oxygen pressure, possibly via improvement of oxygen diffusion due to reduced tissue edema.[75,76] The antiedematous effect of sodium lactate might be induced by an increased expression of VRAC,

KCC2 and AQP4, channels involved in cell volume regulation and free water movements across membranes, rather than by an osmotic effect.[75] Concerning KB, their neuroprotective effects were examined in rats with transient occlusion of middle cerebral artery. The administration of BHB (30 $mg.kg^{-1}.h^{-1}$) significantly reduced cerebral infarct area and edema formation. https://doi.org/10.1254/jjp.89.36. Réf 81

Reduction of ischemic lesion volume

As described just before, KG have been associated with reductions in infarct volume after middle cerebral artery occlusion[81 85] but also after TBI.[82,83] *In vitro* experiments on cultured cortical neurons showed that a BHB-based treatment prevents neuronal death induced by glucose deprivation or hypoxia by stimulation of the autophagic flux thus preventing autophagosome accumulation abd improving neuronal survival.[84] Moreover, both lactate and ketone bodies can limit excitotoxicity, reducing neuronal death as well as lesion volume. In a glutamate excitotoxicity context, pyruvate coming from lactate is metabolized to produce ATP. This ATP in turn activates the PI3K pathway leading to KATP channels opening. This results in the hyperpolarization of the neuron, decreasing neuronal excitability and leading to a neuroprotective effect [P. Jourdain1,2, K. Rothenfusser1,2, C. Ben-Adiba2, I.Allaman 1, P. Marquet2,3,4,5 & P. J. Magistretti1,2,6. Dual action of L-Lactate on the activity of NR2B-containing NMDA receptors: from potentiation to neuroprotection Scientific ReportsOpen AccessVolume 619 February 2016 Article number 21250]. The neuroprotective effect of ketone bodies, targeting glutamate excitotoxicity, has also been shown in rat neocortical neurons [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) 145:256–64. doi: 10.1016/j.neuroscience.2006.11.065]. In this deleterious context, ketone bodies can compete with the Cl^- anion and inactivate the vesicular glutamate transporters (VGLUTs), decreasing

presynaptic glutamate release [Juge N, Gray JA, Omote H, Miyaji T, Inoue T, Hara C, et al. Metabolic control of vesicular glutamate transport and release. Neuron. (2010) 68:99–112. doi: 10.1016/j.neuron.2010.09.00]. A summary of *in vivo* studies showing a reduction of the infarct volume after KB administration can be found in Table 2 of the following review (https://doi.org/10.1038/sj.jcbfm.9600).

Lactate was also shown to decrease brain lesion volume in several rat models after acute brain injuries such as neonatal hypoxia-ischemia réf 12 et 80, TBI and stroke, [12,77–80] ajouter Castillo 2015 JCBFM.

Improvement of recovery and survival

Both substrates have been associated with improvement of cognitive function. In a rat model of neonatal hypoxia-ischemia, lactate administration was associated with short and long term improvement of motor and cognitive functions (réf 12). Improvement of long term cognitive functions was also observed after lactate injections in rat models of TBI or stroke. [87–89] Ketone bodies might as well promote cognitive recovery after TBI since they act as histone deacetylase inhibitors, an enzyme involved in memory and cognitive impairment in neurodegenerative diseases.[44] A ketogenic diet or BHB administered post-treatment improved neurological function in a mouse model of MCA occlusion.[85] Finally, in a recent meta-analysis of 49 studies on murine models of TBI, ketones were associated with an improved survival, particularly in the adult subgroup.[90] Interestingly, the plasma level of ketosis was the only predictor of the neuroprotective effect. Another meta-analysis of studies on animal models of stroke described a protective effect of ketosis on outcome [91] while a recent review summarized the different studies showing the neuroprotective effet of KB in acute brain injuries (different models, different species, different ages) https://doi.org/10.1038/sj.jcbfm.9600543.

Lactate and ketone bodies as pharmacological agents

Lactate can be administered as an intravenous solution of sodium lactate.[1] All interventional studies on TBI used solutions with an osmolality ranging from 500 mmol/L to 1000 mmol/L, the latter being approximately iso-osmolar to 20% mannitol.[48–54] In two studies, investigators injected sodium lactate directly in the brain using a microdialysis technique using 4 and 8 mmol/L microdialysis solutions.[55,56] Both methods of lactate administration aimed to improve brain function and reduce damage associated with head trauma. However, they differed since systemic injection involves administering lactate intravenously and therefore distributing the compound throughout the body. The objective of this method is to provide an additional energy substrate to the entire body including brain cells. Lactate can be used by neurons to produce energy, even when brain metabolism is disrupted by head trauma. In contrast, cerebral lactate injection involves directly administering lactate into the brain, usually by microdialysis or intracerebral injection. This method helps to deliver a high concentration of lactate directly to brain cells. Currently, there is no clear consensus on the optimal method of administration of lactate.

Ketone bodies can be administered through various formulations. Ketogenic diets are based on carbohydrate deprivation, either by fasting or by enteral formulas containing medium-chain triglycerides and low amounts of carbohydrates. An exclusive ketogenic diet such as used to treat epilepsy in children takes 3 to 5 days to reach therapeutic blood levels. These delays render the ketogenic diet of limited interest in acute neurocritical care. Moreover, ketogenic diets are difficult to prepare and compliance is a challenge.[57] Ketone bodies may also be infused as intravenous sodium BHB or sodium acetoacetate solutions. Finally, enteral ketone bodies are now available in the form of ketone esters (such as 1,3-butanediol monoester of beta-hydroxybutyrate or glyceryl-tris-3-hydroxybutyrate, two precursors of ketone bodies). The compound (R)-3-hydroxybutyl (R)-3-hydroxybutyrate is now considered a safe food supplement for humans by the U.S. Food and Drug Administration. Ketone esters induce a rapid and significant ketosis after a single oral intake and as such, represent an interesting therapeutic avenue in acute care.[57,58]

Clinical trials

Based on such preclinical evidence, the idea of providing fuel support to brain-injured patients progressively emerged and a few clinical trials started. Bouzat *et al*. were the first to infuse hypertonic lactate in patients with severe TBI undergoing CMD monitoring. They observed a significant increase in extracellular cerebral glucose.[49] Overall, these data suggest that both endogenous and exogenous lactate are associated with an increased cerebral glucose availability. This “excess” glucose may then be redirected for other metabolic purposes, such as the neuronal PPP.[56]

In human, clinical trials of lactate administration after TBI or SAH….Developer un peu plus les essais cliniques TBI, SAH et lactate et what about KB ou ester de cetones ?

Conclusion and Perspectives

After being considered as unwanted metabolic wastes, lactate and KB are now widely viewed as integral parts of brain metabolism. Data accumulating over the last thirty years support their important role in energy production during rest states, as well as alternative substrates in case of glucose shortage or unavailability. They have also been tested as therapeutics in animal models and human cohorts with acute brain injury with beneficial results concerning excitotoxicity, neuroinflammation, cerebral blood flow control, reduction of brain lesion volume, improvement of cognitive function and survival (**Figure 3**). In addition, KB and lactate share a commun mechanism: modulation of brain metabolism. Indeed, when administrered, lactate and ketone bodies exert a glucose-sparing effect leading to neuronal glycolytic regulation and redirection of glucose through the PPP which helps to fight against ROS produced during oxidative stress (**Figure 3**). Overall, data in animal models and small human cohorts call for a confirmation of their benefits in large therapeutic trials targeting acute neurocritical care populations. After decades of

preclinical research and encouraging new clinical data, we are at the dawn of a new period during which lactate and ketone bodies might become an integral part of neurocritical care therapeutics.

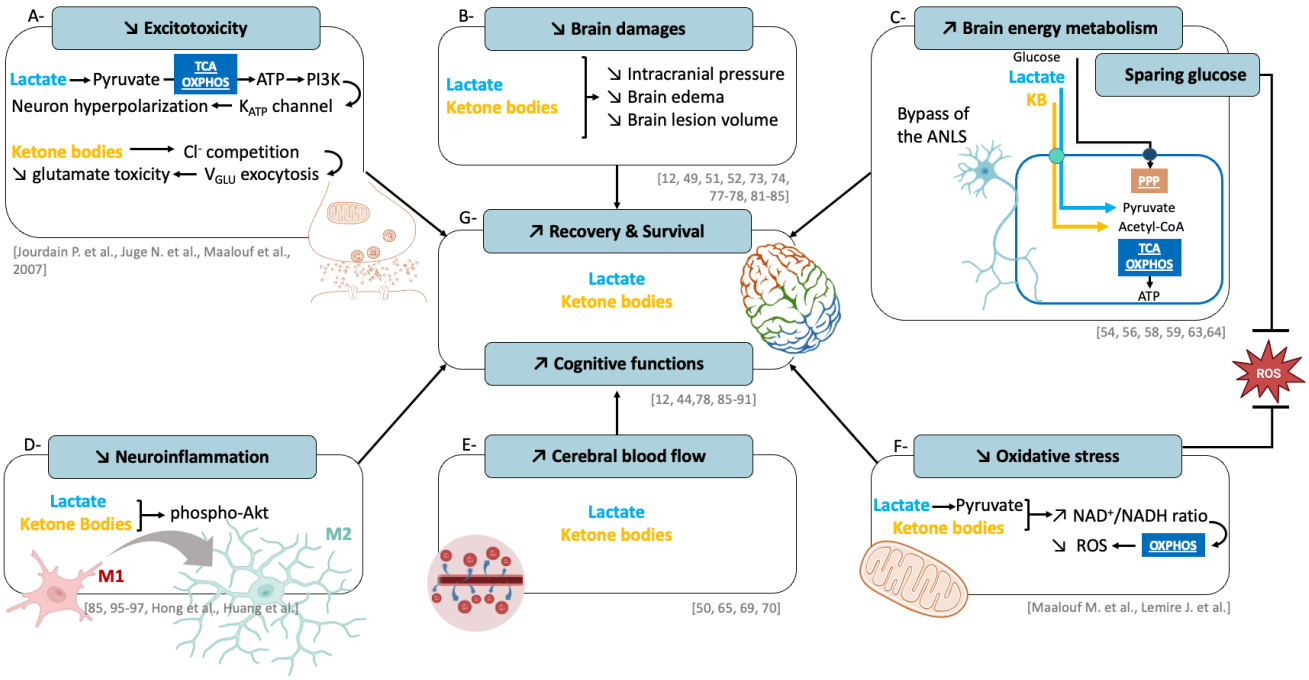

Figure 3: ***Neuroprotection by exogenous lactate and ketone bodies, as alternative energy substrates, in a context of brain injury.*** *A- Lactate conteracts glutamate excitotoxicity through the PI3K pathway leading to neuronal hyperpolarization. Ketone bodies also decrease excitotoxicity through a competition with Cl-, responsible of a decrease in vGLU exocytosis. B- Both exogenous lactate and ketone bodies limit brain damages by decreasing intracranial pressure, brain edema as well as brain lesion volume. C- Lactate and ketone bodies increase brain energy metabolism by providing respectively pyruvate and acetyl-CoA to feed the TCA cycle and OXPHOS. D- Both alternative substrates also switch microglia from an inflammatory M1 to a anti-inflammatory M2 phenotype, through a stimulation of the Akt pathway. E- Lactate and ketone bodies increase cerebral blood flow. F- Both lactate and ketone bodies regulate the oxidative stress by increasing the NAD+/NADH ratio. G- Altogether, beneficial effects of exogenous lactate and ketone bodies lead to increase recovery and survival, as well as improvement of cognitive functions.*
ANLS, astrocyte-neurone lactate shuttle; OXPHOS, oxidative phosphorylation; PPP, pentose phosphate pathway; ROS, reactive oxygen species; TCA, tricarboxylic acid; vGLU, vesicular glutamate transporters.

Disclosure/conflict of interest

All authors have no disclosures or conflict of interests.

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Figure legend

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