The Basic Science of Fluid Therapy
Lactate and the injured brain – friend or foe?

Martin Smith, MBBS, FRCA, FFICM
University College London Hospitals, UK

The pathophysiology of acute brain injury is multifactorial, but energy dysfunction is increasingly recognized as a key factor [1]. This lecture will discuss cerebral metabolism after acute brain injury, evidence that lactate can act as a preferential energy substrate for the injured brain and recent clinical studies suggesting that lactate supplementation might be beneficial.

Glucose and lactate metabolism in the injured brain
The brain is highly metabolically active and adenosine triphosphate (ATP), its most important energy source, is produced almost entirely from the oxidative metabolism of glucose in neurons [2]. This occurs in the cytoplasm and results in production of pyruvate, lactate, and ATP. The majority of pyruvate (>85%) then diffuses into the mitochondria where it enters the tricarboxylic acid (TCA) cycle to generate further ATP. If oxygen supply is limited, pyruvate no longer enters the TCA cycle but, instead, is converted into lactate in the cytosol allowing anaerobic ATP synthesis. In this circumstance the increase in brain extracellular fluid lactate to pyruvate (LP) ratio (secondary to increased lactate and decreased pyruvate concentration) identified in microdialysis studies of traumatic brain injury is a marker of brain hypoxia/ischemia and associated with poor outcome [3]. Acute brain injury is often associated with increased brain energy demand in the absence of ischemia, which may lead to a non-ischemic cerebral metabolic crisis characterized by an increase in LP ratio in the presence of normal or high pyruvate as a consequence of mitochondrial dysfunction [4]. This is also associated with poor outcomes after traumatic brain injury [5].

Lactate as a glucose-sparing fuel
The injured brain has increased energy demands. Cerebral hyperglycolysis is an important factor but other acute events such brain edema, fever and seizures are likely contributors to the acute energy imbalance. The availability of glucose – the main energy substrate of the brain – may be reduced if metabolic demand is high [6], and there is substantial evidence that the brain can use substrates other than glucose to meet its energy needs [7]. Although historically regarded as an unwanted waste product of anaerobic metabolism, it is now clear that lactate is one of several additional fuels that can be utilized by the brain.

Cerebral lactate can be elevated early after acute brain injury because of hyperglycolysis rather than hypoxia/ischemia, and hyperglycolytic-generated lactate can serve as an aerobic substrate for neurons [4]. This might explain why accumulation of cerebral lactate in the absence of hypoxia has been associated with good long-term clinical outcomes after subarachnoid haemorrhage [8]. Astrocytes, but not neurons, are able to store glycogen, giving them a key role in the provision of alternative energy substrates. In an energy-deprived (as well as normal) brain, glutamate stimulates astrocytic production of lactate which is transported into the extracellular fluid via specific lactate transporters and then ‘shuttled’ into neurons where it can be used as an additional (or preferential) substrate to sustain energy requirements [9]. This alternative metabolic pathway, whereby the brain
utilizes lactate via the TCA cycle of neurons, was proposed more than two decades ago and has become known as the astrocyte-neuron lactate shuttle hypothesis.

Lactate imported from the systemic circulation can also undergo oxidative metabolism via the TCA cycle in neurons [10]. Under normal conditions the contribution of lactate to cerebral energy metabolism is approximately 10%, but this can increase to 60% when plasma lactate concentration is increased to supra-physiological levels [11]. The finding of high serum lactate concentration in severe traumatic brain injury might therefore reflect a protective mechanism whereby higher lactate availability promotes its utilization as an alternative fuel source to maintain cerebral metabolic activity [12]. Up-regulation of lactate transport into the brain after traumatic brain injury also facilitates the injured brain’s ability to meet its greater energy substrate demands via lactate [13].

There is substantial in vitro evidence that increased lactate concentration results in a shift from glucose to lactate utilization, and that lactate supplementation is neuroprotective particularly in conditions of hypoglycemia [14]. In animal models of traumatic brain injury an increase in peripheral lactate uptake has been demonstrated at the site of impact, suggesting localized utilization of lactate by ‘at risk’ brain tissue [15]. Direct evidence of brain utilization of lactate in the clinical setting was demonstrated in a 2009 study of traumatic brain injury patients [16]. 13C labelled lactate was administered to the brain via a microdialysis catheter and subsequent nuclear magnetic resonance spectroscopy analysis of the simultaneously collected microdialysate identified 13C labelling in glutamine which is indicative of lactate utilization via the TCA cycle.

**Lactate as a therapeutic intervention**

Neuroprotection by exogenous lactate administration has been documented in various conditions including prolonged starvation and diabetes, but clinical evidence of beneficial effects of lactate on the injured brain is limited to small observational studies [17].

Half-molar lactate infusion has a more effective intracranial pressure (ICP)-lowering effect than an equi-osmolar dose of mannitol after traumatic brain injury [18] and, when used as a pre-emptive measure, effectively prevents secondary increases in ICP and reduces the overall burden of intracranial hypertension compared to intravenous 0.9% saline fluid replacement [19]. In a small prospective pilot study of 15 patients with traumatic brain injury supranormal arterial lactate concentration (5 mmol/L) induced by an intravenous bolus and short (< 3 h) maintenance infusion of hypertonic sodium lactate solution was associated with beneficial cerebral metabolic effects as well as reduced ICP [20]. The preferential use of lactate as an energy substrate appears to be particularly important in the context of cerebral hypoglycemia [21]. Whether the beneficial effects of intravenous hypertonic lactate relate to the aerobic utilization of lactate with consequent sparing of cerebral glucose, reductions in ICP, or both remain to be determined. Recent data suggest that acute glucose and lactate metabolism also plays a significant role in brain injury associated cognitive impairment, suggesting that supplementation with exogenous fuels may have therapeutic potential for cognitive recovery after traumatic brain injury [22].

The increasing evidence that exogenous administration of lactate may be beneficial seems at odds with the previously described association between high (endogenous) brain lactate and poor outcome after TBI [3]. To understand this apparent discrepancy it is crucial to appreciate the
important (patho)physiological context of the astrocyte-neuron lactate shuttle hypothesis, i.e. that functional mitochondria are required for any benefits of lactate (endogenous or exogenous) to be realized [23]. If neurons are too damaged to utilize the lactate produced by astrocytes or hyperglycolysis, the resultant poor outcomes are likely to be related to the severity of the underlying brain injury rather than the high brain lactate concentration per se [24]. On the other hand, improved outcomes associated with low brain extracellular fluid lactate levels might be the result of more efficient neuronal uptake of astrocyte-derived lactate and its utilization via the TCA cycle [16].

Although preliminary clinical data suggest that targeting neuroenergetics via exogenous oxidative fuel supplements in the form of lactate might be a promising strategy to minimize bioenergetic injury after traumatic brain injury, further research is required to confirm any benefits on clinical outcomes and clarify indications and optimal modes of treatment.

References
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