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Hypertonic lactate and the injured brain: facts and the potential for positive clinical implications

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Dear Editor,
We thank Nordström and colleagues for their interest in our study. We shall try to summarize their criticisms and to answer them point by point.

1. The statement that cerebral glucose increase following lactate infusion may be due to a shift in the cell redox state is debatable in the absence of NADH/NAD ratio measurement. Lactate can increase because of anaerobic glycolysis, due to lack of oxygen, but also—frequently—when brain oxygen is normal [1]. In such conditions, exogenous lactate can then be converted to pyruvate, which is subsequently metabolized via the TCA cycle, a process known as aerobic glycolysis [2].
2. Lactate oxidation yields 32 mol ATP vs. 34 mol ATP during glucose oxidation, a small difference. In contrast to glucose oxidation, lactate oxidation does not require ATP, which is an advantage in conditions of limited energy reserves.
3. Abundant evidence shows that exogenous supplemental lactate acts as a "glucose-sparing substrate". Semantic debate remains as to whether lactate might be described as a "preferential" or "opportunistic" substrate [3]. What is more relevant from the clinical standpoint is the potential benefit of sparing cerebral glucose: since low cerebral microdialysis (CMD) glucose is frequent after traumatic brain injury (TBI) and is associated with worse outcome [4], increasing CMD glucose during the early critical phase of TBI with lactate therapy clearly appears beneficial. Directly increasing glucose delivery to the brain with glucose infusions cannot be recommended because it might lead to hyperglycemia and hypotonicity, thereby exacerbating cerebral damage.
4. A positive correlation between CMD pyruvate and outcome has been described [4]; therefore the increase of brain pyruvate during lactate infusion seems beneficial. A pattern of elevated lactate-to-pyruvate ratio with normal to high pyruvate is not an exclusive hallmark of mitochondrial dysfunction, because it is also observed during activated cerebral glycolysis.
5. Finally, using robust mixed-effects model statistical analysis we found that all CMD markers, including CMD glutamate, did not change in the 6 h previous to the intervention [5]. During lactate therapy CMD glutamate (that should have indeed been presented in μmol/L instead of mmol/L) decreased almost significantly ($p = 0.06$). Since CMD glutamate might rise dramatically after TBI [4]—and the failure to remove this excess glutamate might lead to excitotoxic damage and cell death—providing energy in the form of lactate, by increasing glucose availability, helps sustain glutamate uptake in astrocytes and allows neurons to prevent glutamate "leak".
6. The decrease of ICP following lactate infusion might indeed primarily be due to hypertonic sodium. Therapy of intracranial hypertension with hypertonic lactate solutions might therefore exert favorable anti-edematous and pro-energetic effects and could be a valid therapeutic strategy after TBI.

In summary, we provided convincing data that exogenous supplemental lactate can be used as a preferential glucose-sparing substrate by the injured brain and that hypertonic lactate might improve neuroenergetics and reduce brain edema, thereby attenuating secondary cerebral damage after TBI. These data constitute robust arguments against all criticisms by Nordström and colleagues. More importantly, they support clinical investigation to examine the potential therapeutic advantages of hypertonic lactate solutions after brain injury.

Conflicts of interest None to declare.

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