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ORIGINAL

Cerebral metabolic effects of exogenous lactate supplementation on the injured human brain

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Take-home message: Exogenous systemic supplemental lactate can be efficiently used by the injured human brain with beneficial sparing of cerebral glucose. These clinical interventional study further suggests resuscitation with hypertonic lactate may be a valid therapeutic strategy after TBI.

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Abstract *Purpose:* Experimental evidence suggests that lactate is neuroprotective after acute brain injury; however, data in humans are lacking. We examined whether exogenous lactate supplementation improves cerebral energy metabolism in humans with traumatic brain injury (TBI). *Methods:* We prospectively studied 15 consecutive patients with severe TBI monitored with cerebral microdialysis (CMD), brain tissue PO_2 ($PbtO_2$), and intracranial pressure (ICP). Intervention consisted of a 3-h intravenous infusion of hypertonic sodium lactate (aiming to increase systemic lactate to ca. 5 mmol/L), administered in the early phase following TBI. We examined the effect of sodium lactate on neurochemistry (CMD lactate, pyruvate, glucose, and glutamate), $PbtO_2$, and ICP. *Results:* Treatment was started on average 33 ± 16 h after TBI. A mixed-effects multilevel regression model revealed that sodium lactate therapy was associated with a significant increase in CMD concentrations of lactate [coefficient 0.47 mmol/L, 95 % confidence interval (CI) 0.31–0.63 mmol/L], pyruvate [13.1 (8.78–17.4) μmol/L], and glucose [0.1 (0.04–0.16) mmol/L; all $p < 0.01$]. A concomitant reduction of CMD glutamate [−0.95 (−1.94 to 0.06) mmol/L, $p = 0.06$] and ICP [−0.86 (−1.47 to −0.24) mmHg, $p < 0.01$] was also observed. *Conclusions:* Exogenous supplemental lactate can be utilized aerobically as a preferential energy substrate by the injured human brain, with sparing of cerebral glucose. Increased availability of cerebral extracellular pyruvate and glucose, coupled with a reduction of brain glutamate and ICP, suggests that hypertonic lactate therapy has beneficial cerebral metabolic and hemodynamic effects after TBI.

Keywords Brain metabolism · Lactate · Cerebral microdialysis · Traumatic brain injury · Hypertonic

Introduction

Mechanisms of secondary cerebral damage after traumatic brain injury (TBI) rely on the complex interplay between cerebral blood flow, oxygen, and energy supply [1]. Clinical investigations using PET scans and the cerebral microdialysis (CMD) technique have shown that TBI is associated with increased cerebral glucose utilization that may eventually culminate into a state of energy dysfunction [2, 3]. In this setting, the supply to the injured brain of the main energy substrate—i.e., glucose [4]—may become limited, leading to reductions of cerebral extracellular glucose below critical thresholds, a scenario which is associated with worse outcome [5, 6].

Experimental evidence repeatedly demonstrated that the brain can use substrates other than glucose to sustain increased activity, including lactate [7–11]. Increased lactate can be the consequence of anaerobic metabolism, i.e., the formation of lactate in the presence of low oxygen. However, emerging evidence demonstrated that in patients with TBI increased lactate seems predominantly non-hypoxic/ischemic and rather the consequence of increased cerebral glycolysis [2, 12, 13]. Lactate formed under such glycolytic conditions is shuttled from one lactate-producing cell (astrocyte) to another lactate-consuming cell type (neuron) (*astrocyte–neuron lactate shuttle*) [14, 15]. Utilization of lactate as an alternative fuel may be an adaptive response to maximize energy function and limit substrate reduction. Uptake of endogenous cerebral lactate has indeed been demonstrated after TBI in animals [16] and in humans [3, 17].

Administration of supplemental lactate significantly contributes to brain metabolism: at supraphysiologic concentrations (ca. 5 mmol/L) "extra" lactate becomes the preferential energy substrate for neurons with sparing of glucose [18] and might be neuroprotective after experimental TBI [19]. The ability of the injured brain to use supplemental lactate as a glucose-sparing fuel may be important to overcome post-TBI increased energy demand. To test this hypothesis we designed a prospective interventional study to examine in patients with TBI monitored with CMD whether hypertonic lactate therapy—administered intravenously during the acute phase of injury—might have beneficial effects on cerebral energy metabolism.

Methods

Study type

This was a prospective phase II interventional study that was performed at the Department of Intensive Care Medicine, CHUV, Lausanne, Switzerland. The study was approved by the Ethical Research Committee of the University of Lausanne. Informed consent was obtained from each patient's next of kin.

Patients

Inclusion criteria

Patients with severe TBI, defined by an admission Glasgow Coma Scale (GCS) < 9, aged 18–60 years, with abnormal admission brain CT scan (defined by a Marshall score ≥ 2), who underwent intracranial monitoring with CMD, brain tissue oxygen tension ($PbtO_2$), and intracranial pressure (ICP).

Exclusion criteria

Penetrating TBI, age <18 or >60 years, history of neurological disease, brain death or expected death within 48 h, pregnancy, more than one major extracranial injury with sustained hemodynamic instability and persistent elevation of blood lactate >4 mmol/L for >6 h before intervention, time from TBI to study inclusion >72 h.

Intracranial monitoring

Cerebral microdialysis consisted of a 70 MD bolt catheter with 20-kDa cutoff (M Dialysis AB®, Stockholm, Sweden). Microdialysis samples were collected hourly and analyzed for brain extracellular concentrations of glucose, lactate, pyruvate, and glutamate. $PbtO_2$ was measured using a Licox® catheter (Integra Neurosciences, Plainsboro, NJ, USA) calibrated to the patient's temperature. Intracranial pressure was measured using a Codman® probe (Raynham, MA, USA). Probes were inserted through a triple-lumen bolt in the operating room by a neurosurgeon and placed into the brain parenchyma (subcortical white matter), in the right frontal lobe. Brain CT scan was performed at approximately 24 h to confirm the correct placement of intracranial monitors.

General management

All patients were treated according to a standard protocol for the management of severe TBI following international guidelines [20, 21]. Sedation–analgesia consisted of propofol and sufentanil. All patients were mechanically ventilated to maintain PaO_2 at 90–100 mmHg and $PaCO_2$ at 35–40 mmHg. Brain physiological targets were set to maintain ICP < 20 mmHg and cerebral perfusion pressure (CPP = mean arterial pressure, MAP–ICP) >60 mmHg. Blood glucose was targeted at 6–8 mmol/L.

Study intervention

The intervention consisted of a continuous infusion of hypertonic sodium lactate (Na^+ 1,000 mmol/L, lactate 1,000 mmol/L, prepared by the Division of Pharmacy, CHUV, Lausanne), administered over 3 h (at 40 µmol/kg/min for 60 min, followed by 30 µmol/kg/min for an additional 120 min) started within 72 h from TBI (clinicaltrials.gov identifier NCT01573507).

Study endpoints

Study efficacy

The treatment aimed to rapidly increase blood arterial lactate to supraphysiological concentrations (ca. 5 mmol/L) using a bolus dose over 30 min, followed by a maintenance dose up to 3 h. This infusion protocol was in line with previous clinical studies in healthy human subjects [22, 23] and performed according to a previous investigation at our institution in critically ill non-neurological patients [24]. The primary endpoint was to analyze the effect of sodium lactate infusion on CMD concentrations of lactate, pyruvate, and glucose. Secondary endpoints were to analyze the effect of lactate therapy on CMD glutamate, $PbtO_2$, and ICP.

Study safety

Safety parameters included blood arterial pH, bicarbonate, sodium, and osmolarity. Safety thresholds were set at pH > 7.55, sodium >155 mmol/L, and osmolarity >320 mosm/L.

Data collection and processing

Clinical and radiological variables included age, gender, admission GCS, Marshall CT scan score [25], type of injury, time from TBI to intracranial monitoring, and duration of monitoring. Neurological outcome at 6 months was assessed using the GOS. Cerebral microdialysis variables were collected hourly. Main brain physiological variables ($PbtO_2$, ICP, and CPP) were recorded every 60 s via a computerized medical chart system (Metavision®, IMD soft, Tel-Aviv, Israel) and were matched at the exact time of CMD analysis. For $PbtO_2$, data were corrected for temperature and PaO_2. Arterial blood was sampled hourly for concentration of pH, PaO_2, $PaCO_2$, bicarbonate, lactate, glucose, sodium, chloride, and osmolarity.

Statistical analysis

Each patient's individual response to intervention was graphically plotted for CMD lactate, pyruvate, and glucose. Data distribution was tested for each variable and logarithmic transformation was applied for non-normal data. Results were expressed as mean ± SD for the two main conditions, i.e., *baseline* (immediately before the start of sodium lactate infusion) and *sodium lactate* (maximum increase during intervention).

Data analyzed included CMD (lactate, pyruvate, glucose, glutamate) and main brain physiologic (ICP, $PbtO_2$, CPP) and systemic (lactate, glucose, pH, bicarbonate, sodium, chloride, osmolarity) variables. Longitudinal data analysis was used to account for repeated measures of physiological variables across different patients over time. Analysis was conducted using mixed-effects multilevel regression with time as an independent variable and allowing it to have a random intercept and a random slope according to the patient. The same model was also applied to analyze the data obtained during the 6 h preceding the intervention, to verify data stability prior to sodium lactate therapy. Correlations were tested using the Pearson's correlation coefficient. Statistical analyses were performed using STATA 12 (STATA® Corporation, College Station, TX, USA), and statistical significance was set at $p < 0.05$.

Results

Patient characteristics

From April 2012 to March 2013, a total of 24 consecutive patients were screened for the intervention, of which 9 were excluded, and 15 patients with isolated severe TBI were included (Fig. 1). Baseline characteristics of the 15 studied patients are summarized in Table 1. Mean age was 40 ± 15 years and median admission GCS was 7 (range 3–8). Intracranial monitors were placed close to each other in the right frontal subcortical white matter in all patients, in an area that corresponded to visually normal brain parenchyma on control head CT scan (i.e., not around a contusion or hematoma, Fig. 2). Median time from TBI to intracranial monitoring was 6 h (interquartile range 3–15 h) and patients were monitored for a median of 4 (3.5–7.0) days. There was no catheter-related complication. At 6 months, 9 patients had a favorable neurological recovery [Glasgow Outcome Score (GOS) 4 or 5] and 6 patients had an unfavorable outcome [including 2 with severe disability (GOS 3), 1 with vegetative state (GOS 2), and 3 non-survivors (GOS 1)].

Effect of sodium lactate therapy on cerebral variables

Sodium lactate therapy was started 33 ± 16 h from TBI. Following sodium lactate infusion, blood lactate increased from a baseline pretreatment value of 1.0 ± 0.4 mmol/L to a maximum of 6.1 ± 1.6 mmol/L. Each patient's

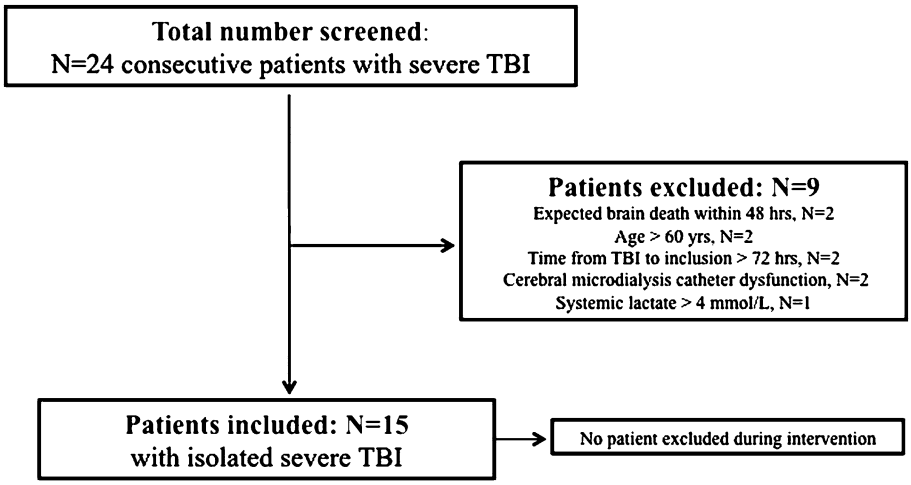

Fig. 1 Study flow chart. A total of 24 patients with isolated severe traumatic brain injury (TBI) were screened over the 1-year study period; 15 patients were included and concluded the study

Table 1 Patient characteristics

Patient no.	Age (years)	Gender	Admission GCS	Marshall score	Injury type	Time from TBI to intracranial monitoring (hours)	Time from TBI to sodium lactate therapy (hours)	Duration of intracranial monitoring (days)	GOS (at 6 months)
1	54	F	3	2	Diffuse	13	21	4	4
2	39	M	8	2	Focal	52	57	3	4
3	19	M	6	2	Diffuse	7	24	4	5
4	55	M	8	3	Diffuse	6	20	11	5
5	30	M	7	5	Diffuse	8	30	10	3
6	24	M	6	2	Diffuse	6	34	6	2
7	46	M	8	2	Diffuse	7	66	3	4
8	60	M	8	3	Focal	23	64	5	1
9	24	F	6	2	Diffuse	6	24	3	4
10	41	M	3	2	Diffuse	6	24	8	1
11	24	M	8	2	Diffuse	17	23	3	4
12	52	F	7	2	Diffuse	26	38	4	4
13	24	M	7	3	Diffuse	5	21	4	1
14	60	M	6	2	Diffuse	7	24	4	4
15	55	M	8	6	Diffuse	13	27	11	3

F female, *GCS* Glasgow Coma Scale, *GOS* Glasgow Outcome Score, *M* male, *TBI* traumatic brain injury

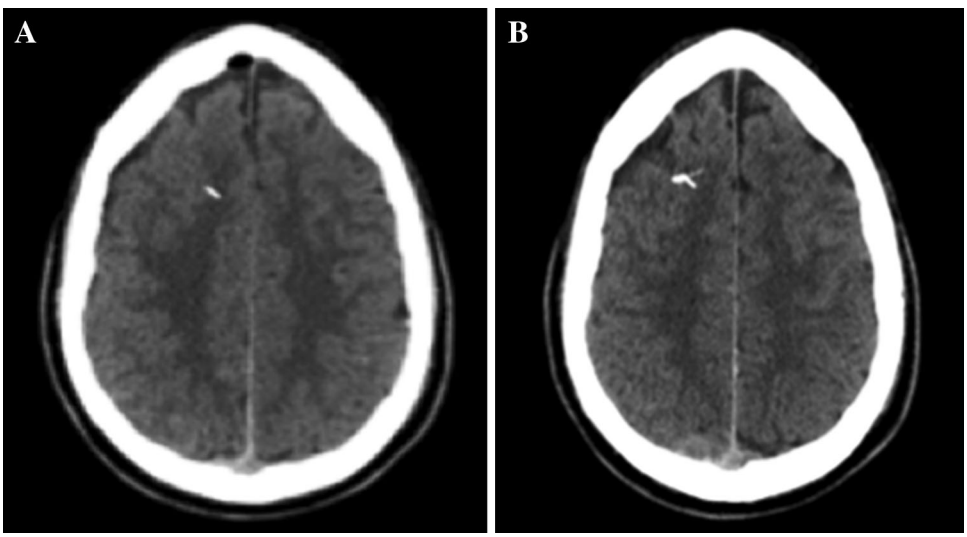

Fig. 2 Location of cerebral microdialysis and brain tissue PO_2 catheters. **a** One illustrative example of probe location in the right frontal subcortical white matter, with close positioning of CMD and brain tissue PO_2 catheters (**b**)

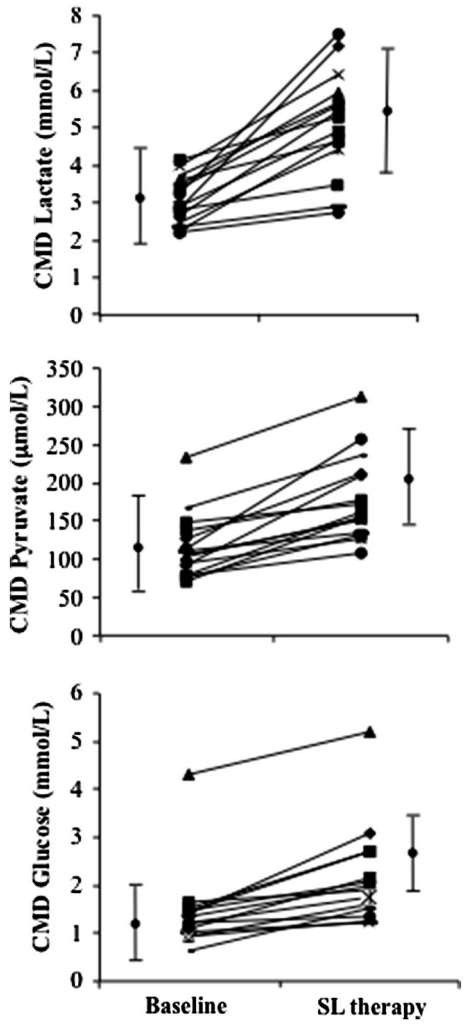

Fig. 3 Effect of sodium lactate therapy on cerebral energy metabolism across individual patients ($n = 15$). *Horizontal lines* illustrate individual baseline and maximum values during sodium lactate (SL) therapy of cerebral microdialysis (CMD) concentrations of lactate, pyruvate, and glucose. Differences in means (±SD) of extracellular brain lactate concentration between baseline (*left side* of the graphic) versus SL therapy (*right side* of the graphic) are also shown (CMD lactate, 3.1 ± 0.6 versus 5.1 ± 1.4 mmol/L; CMD pyruvate, 115.6 ± 42.9 versus 180.2 ± 55.7 µmol/L; CMD glucose, 1.4 ± 0.9–2.2 ± 1.0 mmol/L)

individual response to intervention for CMD lactate, pyruvate, and glucose is shown in Fig. 3: sodium lactate was associated with an increase in CMD concentrations of lactate (from baseline 3.1 ± 0.6 to a maximum of 5.1 ± 1.4 mmol/L during sodium lactate therapy), CMD pyruvate (115.6 ± 42.9 vs. 180.2 ± 55.7 µmol/L), and CMD glucose (1.4 ± 0.9 vs. 2.2 ± 1.0 mmol/L). All three patients with pretreatment low CMD glucose (<1 mmol/L) had normalized brain glucose values at the end of sodium lactate therapy.

Results of mixed-effects analysis for changes of cerebral variables during intervention are shown in Table 2. During sodium lactate therapy, we found a significant increase in CMD concentrations of lactate [coefficient 0.47 mmol/L, 95 % confidence interval (CI) 0.31–0.63 mmol/L], pyruvate [13.1 (8.78–17.4) µmol/L], and glucose [0.1 (0.04–0.16) mmol/L; all $p < 0.01$]. A concomitant decrease of CMD glutamate [−0.95 (−1.94 to 0.06) mmol/L, $p = 0.06$], $PbtO_2$ [−0.58 (−1.14 to −0.01) mmHg, $p = 0.04$], and ICP [−0.86 (−1.47 to −0.24) mmHg, $p < 0.01$] was also observed. The effect of sodium lactate on ICP reduction was greater in the two patients who had baseline ICP > 20 mmHg. Cerebral perfusion pressure and lactate-to-pyruvate ratio (LPR) did not change significantly during the intervention. Altogether, our data indicate aerobic utilization of systemic lactate with sparing of cerebral glucose and overall metabolic benefit for brain tissue.

Of note, blood lactate as well as CMD lactate, pyruvate, and glucose did not change significantly over the 6 h prior to sodium lactate infusion (all $p > 0.1$, mixed-effects analysis, see example of an individual patient in Fig. 4), indicating data stability before treatment start. Concentrations of CMD lactate, pyruvate, and glucose returned to baseline values at 6 h post-treatment start.

A majority of patients (10/15, 67 %) displayed baseline LPR > 25, a marker of increased energy distress: interestingly, we observed a significant correlation between LPR and the percentage of CMD pyruvate increase (Pearson's $r = 0.60$, $p = 0.02$; Fig. 5), suggesting that metabolic conversion of lactate into pyruvate during sodium lactate therapy was more pronounced in patients who had a higher degree of cerebral energy demand.

Effect of sodium lactate therapy on systemic variables

Results of mixed-effects analysis for changes of systemic variables during sodium lactate therapy are shown in Table 2. Blood arterial concentrations of pH, bicarbonate, sodium, and osmolarity all increased during sodium lactate infusion (all $p < 0.01$) and returned to pretreatment values within 6 h from the end of infusion. Systemic chloride did not change during treatment. Importantly, concentrations of systemic glucose did not change significantly during sodium lactate therapy ($p = 0.39$). Means of other relevant systemic physiological variables (including MAP, heart rate, body temperature, PaO_2, and $PaCO_2$) were within normal ranges in all patients and a mixed-effects model did not show significant changes of these variables during the treatment.

Discussion

The findings of this study can be summarized as follows: (1) we showed for the first time in humans with acute

Table 2 Changes of main cerebral and systemic variables during sodium lactate therapy

	Coefficient ± SE	95 % Confidence interval	*p* value
Cerebral variables			
CMD lactate (mmol/L)	0.47 ± 0.08	0.31 to 0.63	<0.01
CMD pyruvate (μmol/L)	13.10 ± 2.20	8.78 to 17.40	<0.01
CMD glucose (mmol/L)	0.10 ± 0.04	0.04 to 0.16	<0.01
CMD glutamate (mmol/L)	−0.95 ± 0.51	−1.94 to 0.06	0.06
$PbtO_2$ (mmHg)	−0.58 ± 0.29	−1.14 to −0.01	0.04
Intracranial pressure (mmHg)	−0.86 ± 0.32	−1.47 to −0.24	<0.01
Systemic variables			
Glucose (mmol/L)	0.08 ± 0.09	−0.11 to 0.28	0.39
Sodium (mmol/L)	1.96 ± 0.25	1.48 to 2.44	<0.01
Chloride (mmol/L)	−0.08 ± 0.25	−0.57 to 0.42	0.76
pH	0.04 ± 0.01	0.00 to 0.02	<0.01
Osmolarity (mosm/L)	3.57 ± 0.44	2.71 to 4.43	<0.01

Analysis was conducted using mixed-effects multilevel regression with time as an independent variable and allowing it to have a random intercept and a random slope according to patient
CMD cerebral microdialysis, *$PbtO_2$* brain tissue oxygen tension

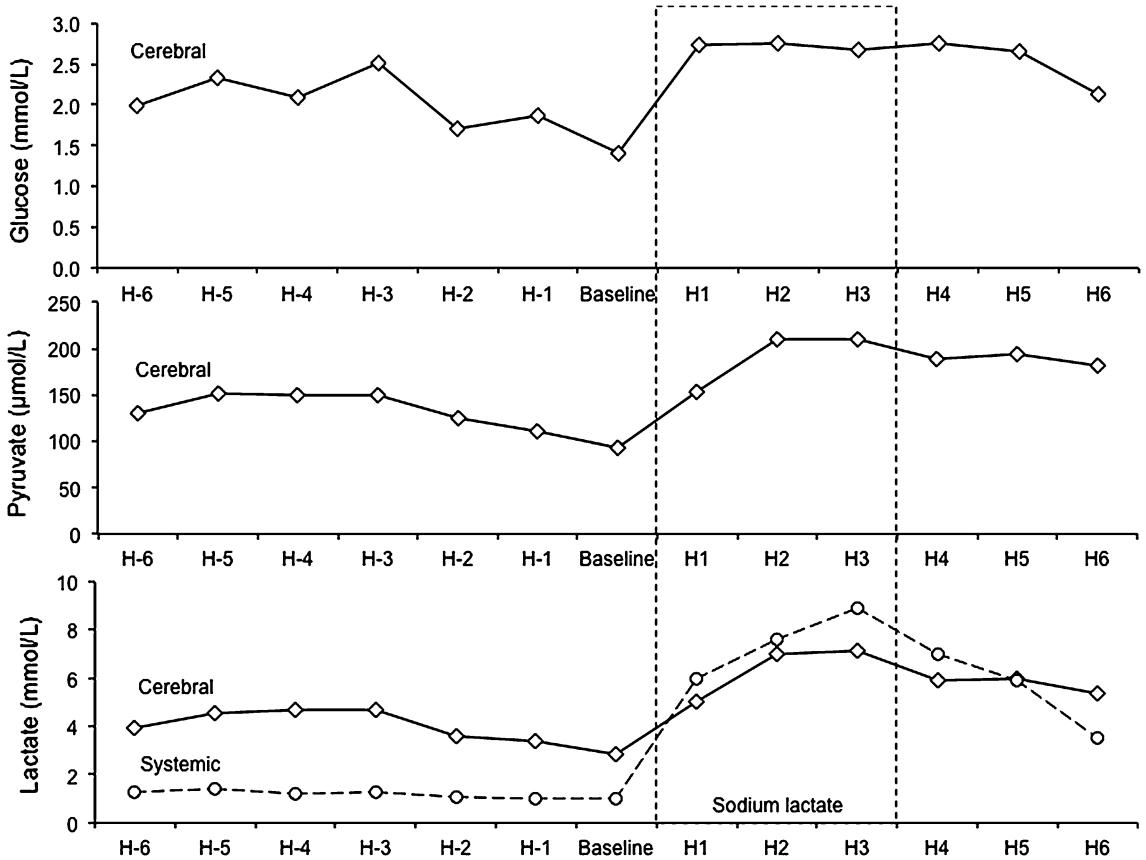

Fig. 4 Dynamic changes over time of systemic lactate and brain energy metabolites upon sodium lactate therapy in one representative patient. The line graph shows the time course in one illustrative patient of cerebral microdialysis (CMD) glucose, CMD pyruvate, and systemic and CMD lactate during the 6 h prior to the intervention, during sodium lactate supplementation (*box with dashed lines*), and over the 3 h following the treatment

brain injury that exogenous systemic lactate may be utilized aerobically as a preferential energy substrate over glucose; (2) by increasing the availability of cerebral extracellular pyruvate and glucose, exogenous lactate supplementation resulted in improved brain energetics during the early phase of TBI, (3) hypertonic lactate

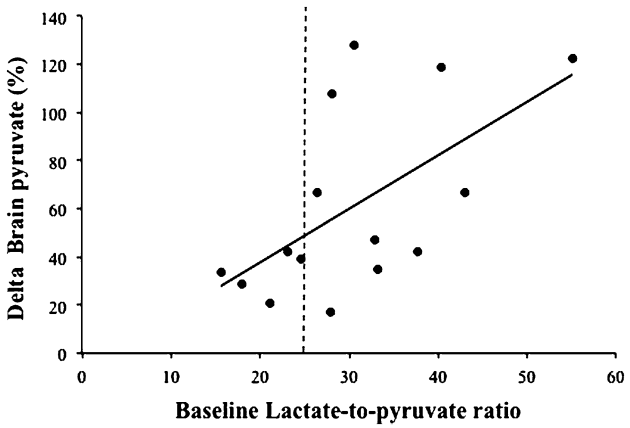

Fig. 5 Lactate conversion to pyruvate is proportional to baseline cerebral energy demand. The graph shows the positive linear correlation between baseline lactate-to-pyruvate ratio (marker of cerebral energy demand) and the extent of CMD pyruvate increase (delta brain pyruvate, expressed in % increase from baseline) observed during sodium lactate infusion ($n = 15$ patients with severe TBI; Pearson's $r = 0.60$, $p = 0.02$)

therapy was associated with a reduction of ICP and brain glutamate. Overall our findings suggest that hypertonic lactate therapy has both a positive effect on cerebral energy metabolism and on ICP reduction, suggesting that it may be a valid therapeutic option to test in the future in patients with TBI.

Evidence of lactate utilization by the injured human brain

Generally considered as a by-product of anaerobic metabolism, lactate was shown to support synaptic function [7] and to act as an alternative substrate to glucose [8–10]. Evidence of endogenous lactate utilization has been provided in humans with TBI [12] and subarachnoid hemorrhage (SAH) [26]. This may be important after TBI, where utilization of the predominant brain substrate (glucose) can be dramatically increased [2, 3, 27], leading to reduced glucose availability and worse outcome [5, 6].

We showed that supplemental lactate from the systemic circulation may be converted by the brain into pyruvate, and we found that cerebral pyruvate increase was proportionate to the extent of cerebral energy dysfunction. Importantly, pyruvate increase was coupled with a moderate but statistically significant decrease of $PbtO_2$, whereas LPR remained stable during sodium lactate therapy. $PbtO_2$ is equal to the product of CBF with the difference between PaO_2 and PvO_2 [28]. During the study, CPP, $PaCO_2$, MAP, and temperature (all major determinants of CBF) did not change. PaO_2 also was kept stable throughout the study. Actually, in a subset of patients ($n = 6$) in whom transcranial Doppler was measured during sodium lactate infusion, a significant increase in CBF velocities was found (data not shown), in line with experimental findings showing that lactate can act as local cerebral vasodilator [29]. Therefore, we can conclude that the observed reduction of $PbtO_2$ is secondary to a decrease in PvO_2, indicating increased oxygen extraction by the tissue. These findings suggest that lactate was actively converted into pyruvate to be utilized aerobically by the injured human brain. Additional issues warrant further discussion. The first pertains to the relationship between lactate and oxygen. Lactate can increase as a consequence of anaerobic glycolysis, where increased lactate production is due to insufficient oxygen availability that will hamper the Krebs cycle metabolism of pyruvate. Under such conditions, exogenously administered lactate cannot be metabolized further. However, emerging clinical data suggest that lactate increase is mainly non-hypoxic in patients with TBI [13, 30, 31]. In the present study, TBI patients did not display low $PbtO_2$, meaning that the administered lactate could indeed be converted to pyruvate, which is subsequently metabolized via the TCA cycle and the associated ATP-generating oxidative phosphorylation. This metabolic sequence occurs under normoxic conditions, and is also known as the Warburg effect [32]. In our study, lactate is provided exogenously under essentially normoxic conditions, which allows its utilization by lactate-consuming brain cells to produce ATP. The second issue relates to cerebral extracellular pyruvate increase. It should be kept in mind that the concentrations of lactate are about 10 times higher than those of pyruvate (2–3 mmol/L vs. 100 µmol/L). Thus, given the mass action effect, the normoxic conditions (which allow conversion of lactate to pyruvate) and the relative kinetic properties of lactate dehydrogenase (LDH) type A and pyruvate dehydrogenase, it is not surprising that more pyruvate is formed that can be metabolized through the TCA cycle, thereby resulting in a net increase of CMD pyruvate concentrations.

Lactate supplementation is associated with sparing of cerebral glucose

Sparing of cerebral glucose was demonstrated by the concomitant increase of CMD glucose concentration. Given that systemic glucose did not change during sodium lactate infusion, the observed increase of CMD glucose can only be attributable to preferential lactate utilization over glucose by the injured brain. Our study confirms previous experimental data and studies in healthy humans [18, 23]. Increasing the availability of cerebral glucose is important in the setting of human TBI where reductions of CMD glucose are frequent and are associated with worse prognosis [5, 6]. Restoration of cerebral glucose reserves by hypertonic lactate therapy indeed appears to be of benefit in the setting of TBI. Glucose is the essential substrate for brain metabolism,

participating in bioenergetics, reactive oxygen species regulation, neurotransmission, and biosynthesis [33]. The use of lactate as an alternative energy fuel could enable extra glucose to be available during the early phase of injury for these important rescue processes.

Additional effects of sodium lactate supplementation

Sodium lactate therapy was associated with a reduction of brain glutamate, which almost reached statistical significance ($p = 0.06$). Given that glutamate was stable prior to sodium lactate therapy, we considered the observed glutamate decrease as physiologically and clinically relevant. Glutamate accounts for 80–90 % of the synapses in the brain and is the major excitatory neurotransmitter. The concentration of glutamate into the synaptic space rises dramatically after TBI, and failure of astrocytes to remove this excess of extracellular glutamate might lead to excitotoxic damage and neuronal death [34]. Increased glutamate release is a concomitant marker of energy failure; thus, providing energy in the form of lactate would allow neurons to control glutamate release and prevent glutamate "leak". Lactate supplementation leads to increased glucose availability to sustain glutamate uptake in astrocytes.

Sodium lactate infusion also resulted in a significant reduction of ICP, which was most marked in patients with intracranial hypertension, further substantiating the view that hypertonic lactate may be a valid therapeutic option after TBI. Since the majority of patients did not have elevated ICP, additional studies are needed to confirm the effect of hypertonic lactate solutions in patients with intracranial hypertension. Lactate was administered as a hypertonic solution; therefore, we cannot completely rule out a potential anti-edematous effect: further discrimination between the metabolic and the anti-edematous effect of hypertonic lactate solutions requires future studies comparing hypertonic lactate to hypertonic saline.

Clinical implications of the study

Sodium lactate may be used for volume resuscitation, providing positive effects on brain energy metabolism, while avoiding adverse effects (hyperchloremic acidosis) of other standard resuscitative solutions, such as sodium chloride [35]. Hypertonic lactate could be an alternative for the treatment of intracranial hypertension [36, 37]. Altogether the findings of this prospective interventional study warrant further clinical investigation in a larger setting to confirm whether sodium lactate therapy is beneficial in patients with TBI and other forms of acute cerebral diseases, and to compare the effects of hypertonic lactate versus standard hypertonic saline solutions for the treatment of intracranial hypertension.

Study limitations

The main limitation of this study is the small sample size. However the cohort consisted of a homogenous group of patients with isolated severe TBI, with predominantly diffuse injury, who were all monitored in the same tissue region and were treated with a standardized algorithm. The time from TBI to sodium lactate therapy was variable among patients; however, this did not influence the results. Lactate therapy was given over a limited period of time (3 h). This was mainly to limit the potential side effects (hypernatremia, increased osmolarity, metabolic alkalosis), the relevance of which is unclear. Although the main relevant systemic physiological variables (MAP, heart rate, body temperature, PaO_2, and $PaCO_2$) did not change over time, we cannot entirely exclude potential confounders; therefore, our findings in this small cohort of patients must be considered as preliminary. Additional limitations include that brain metabolism was measured using CMD and $PbtO_2$, i.e., with focal monitoring. This approach has several advantages, e.g., it allows the monitoring of dynamic changes of different brain metabolites upon therapy and it is accessible at the bedside. However, we did not use PET scans in this study and therefore we cannot provide global measurement of cerebral lactate uptake and $CMRO_2$. Despite these technical limitations, we believe that combined monitoring of CMD, $PbtO_2$, and ICP provided us with essential tools to test the dynamic changes of cerebral energy metabolism following sodium lactate therapy.

Conclusions

We showed that exogenous systemic lactate is utilized by the injured human brain as a preferential energy substrate with subsequent sparing of cerebral glucose. The increase of pyruvate and glucose in brain interstitial tissue—together with the decrease of cerebral glutamate and intracranial pressure—suggests that hypertonic lactate therapy has positive effects on cerebral energy metabolism and on ICP reduction in the early phase following TBI. Our findings support further investigation to test the value of this therapeutic strategy in patients with acute brain injury and to evaluate whether the observed cerebral biochemical and physiological effects of hypertonic lactate might translate into a better neurological outcome.

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Conflicts of interest The authors have no conflict of interest to declare.

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