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Laboratory Investigation

LABORATORY INVESTIGATION

# Hypertonic sodium lactate reverses brain oxygenation and metabolism dysfunction after traumatic brain injury

A. Millet[1,2,3], A. Cuisinier[1,2,4], P. Bouzat[1,2,4], C. Batandier[5], B. Lemasson[1,2], V. Stupar[1,2], K. Pernet-Gallay[1,2], T. Crespy[1,2,4], E. L. Barbier[1,2] and J. F. Payen[1,2,4,*]

[1]Institut National de la Santé et de la Recherche Médicale, Grenoble, France, [2]Université Grenoble Alpes, Grenoble Institut des Neurosciences, Grenoble, France, [3]Pôle Couple Enfant, Hôpital Michallon, CHU Grenoble Alpes, Grenoble, France, [4]Pôle Anesthésie Réanimation, Hôpital Michallon, CHU Grenoble Alpes, Grenoble, France and [5]Institut National de la Santé et de la Recherche Médicale, U1055, Laboratoire de Bioénergétique Fondamentale et Appliquée, Université Grenoble Alpes, Grenoble, France

*Corresponding author. E-mail: jean-francois.payen@univ-grenoble-alpes.fr.

## Abstract

**Background:** The mechanisms by which hypertonic sodium lactate (HSL) solution act in injured brain are unclear. We investigated the effects of HSL on brain metabolism, oxygenation, and perfusion in a rodent model of diffuse traumatic brain injury (TBI).

**Methods:** Thirty minutes after trauma, anaesthetised adult rats were randomly assigned to receive a 3 h infusion of either a saline solution (TBI–saline group) or HSL (TBI–HSL group). The sham–saline and sham–HSL groups received no insult. Three series of experiments were conducted up to 4 h after TBI (or equivalent) to investigate: 1) brain oedema using diffusion-weighted magnetic resonance imaging and brain metabolism using localized $^{1}$H-magnetic resonance spectroscopy ($n = 10$ rats per group). The respiratory control ratio was then determined using oxygraphic analysis of extracted mitochondria, 2) brain oxygenation and perfusion using quantitative blood-oxygenation-level-dependent magnetic resonance approach ($n = 10$ rats per group), and 3) mitochondrial ultrastructural changes ($n = 1$ rat per group).

**Results:** Compared with the TBI–saline group, the TBI–HSL and the sham-operated groups had reduced brain oedema. Concomitantly, the TBI–HSL group had lower intracellular lactate/creatine ratio [0.049 (0.047–0.098) *vs* 0.097 (0.079–0.157); $P < 0.05$], higher mitochondrial respiratory control ratio, higher tissue oxygen saturation [77% (71–79) *vs* 66% (55–73); $P < 0.05$], and reduced mitochondrial cristae thickness in astrocytes [27.5 (22.5–38.4) nm *vs* 38.4 (31.0–47.5) nm; $P < 0.01$] compared with the TBI–saline group. Serum sodium and lactate concentrations and serum osmolality were higher in the TBI–HSL than in the TBI–saline group.

**Conclusions:** These findings indicate that the hypertonic sodium lactate solution can reverse brain oxygenation and metabolism dysfunction after traumatic brain injury through vasodilatory, mitochondrial, and anti-oedema effects.

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Keywords: brain injuries; traumatic; hypertonic solutions; mitochondria; sodium lactate

### Editor's key points

- Diffuse traumatic brain injury is associated with impaired brain metabolism and oxygenation.
- In a rat model, it was investigated whether hypertonic lactate solution has better preservative properties than normal saline with respect to brain metabolism and oxygenation after brain injury.
- Hypertonic lactate solution reversed the impairment of brain metabolism and oxygenation after brain injury through a reduction in brain oedema, increase in mitochondrial respiration, and reduced mitochondrial changes.
- Hypertonic lactate solution might be considered for the preservation of cerebral integrity in traumatic brain injury, although clinical studies are still required.

There has been a growing interest in the exogenous supplementation of lactate through the administration of hypertonic sodium lactate (HSL) solution after traumatic brain injury (TBI).[1] The rationale for using such a solution was based on accumulating evidence of endogenous lactate as a major oxidative substrate utilised by injured brain cells.[2–4] It was shown that exogenous lactate anions could also enter injured brain cells to be utilised as an energy source.[5–7] Exogenous lactate constitutes a preferential oxidative substrate over glucose for neuronal metabolism.[8,9] In patients with no evidence of brain ischaemia after TBI, HSL infusion was associated with a significant increase in extracellular concentrations of lactate, pyruvate, and glucose.[10] HSL was proposed to act as a glucose-sparing substrate through increasing pyruvate availability for the mitochondrial tricarboxylic acid cycle, and then improving oxidative metabolism after TBI. In this line, HSL may ultimately reverse the failure of mitochondrial respiration described after TBI.[11,12] Such a notion would imply a benefit of such lactate flooding on mitochondrial function in injured brain tissue, a hypothesis that remains unexplored.[13] Alternatively, the cerebral effects of HSL may be caused by lactate-related vasodilator effects,[14,15] and hyper-osmotic and anti-oedematous effects leading to a reduction in intracranial pressure.[10,16,17]

In order to clarify the exact role of HSL as a whole solution in brain injury, we compared HSL *vs* isotonic saline solution in injured and normal brain. To document the possible versatile properties of HSL, we used multiple techniques to study intracellular lactate, brain-tissue oxygenation and perfusion, and mitochondrial metabolism in a rodent model of diffuse TBI. We hypothesised that HSL solution could reverse brain metabolism and oxygenation dysfunction induced by diffuse TBI through a possible utilisation of exogenous lactate by injured brain cells.

## Methods

A series of three experiments were conducted on each of four groups of adult male Wistar rats (350–500 g). In the first series of experiments, we studied the effect of HSL on combined measurements of brain oedema and brain metabolism after diffuse TBI. We used diffusion-weighted magnetic resonance imaging (MRI) to assess brain oedema before TBI, at 2 h (H2) and 4 h (H4) after TBI or equivalent time; thus, each rat ($n = 10$ per group) acted as its own control. Simultaneously, brain metabolism was assessed using *in vivo* localised $^{1}$H-magnetic resonance spectroscopy ($^{1}$H-MRS). The rats were then killed to measure the mitochondrial respiratory control ratio (RCR) of extracted mitochondria from brain tissue using oxygraphic analysis. The rats were randomly assigned to one of four groups: the TBI–saline group received a saline treatment and the TBI–HSL group was treated with HSL; sham–saline and sham–HSL rats received no TBI insult. In the second series of experiments using a similar protocol and four groups of rats, we investigated the effect of HSL on combined measurements of brain perfusion and brain oxygenation. We used multiparametric quantitative blood-oxygenation-level-dependent (BOLD) approach to measure brain-tissue oxygen saturation ($StO_2$) ($n = 10$ per group) and vessel size index (VSI; $n = 5$ rats per group) before TBI and at H2 and H4 after TBI or equivalent time. In the third series of experiments using a similar protocol, we evaluated the morphological disruption of mitochondria using electron microscopy at H4 ($n = 1$ rat per group).

### Experimental protocol

The study design was approved by the local Internal Evaluation Committee for Animal Welfare and Rights. The experiments were performed in accordance with the guidelines of the French Government (licenses 380819 and B3851610008) and the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines. The experimental protocol was similar to the one described previously (Supplementary files).[18]

Injury was induced according to the initial description of the impact-acceleration model in anaesthetised and mechanically ventilated rats. The reference time (H0) corresponded to the impact (TBI–saline and TBI–HSL) or equivalent time (sham operated). Thirty minutes after H0, the rats were randomly allocated to intravenously receive 0.5 ml kg$^{-1}$ h$^{-1}$ of either an isotonic saline solution or a solution of HSL 11.2% ($Na^+$ 1000 mmol litre$^{-1}$ and lactate 1000 mmol litre$^{-1}$, prepared by the Assistance Publique des Hôpitaux de Paris, Paris, France) during a continuous infusion lasting 3 h. Randomisation was achieved using pieces of paper folded and placed in a receptacle, with each piece of paper recording an animal number. A piece of paper was randomly withdrawn without replacement on the day of each experiment to allocate each animal into a group. A number was then allocated to each animal for data analysis of MRI, oxygraphy, and electron-microscopy measurements. The group allocation was disclosed after completion of data analysis.

### MRI measurements

In the first series of experiments, MRI was performed before, 2 h (H2), and 4 h (H4) after TBI (or equivalent time) at 9.4*T* in a horizontal bore magnet (BioSpec AVANCE III HD; Bruker BioSpin,