Isoflurane Elevates Brain Lactate in a Dose-dependent Manner: A Localized ^{1}H MRS Study of Mouse Brain In Vivo

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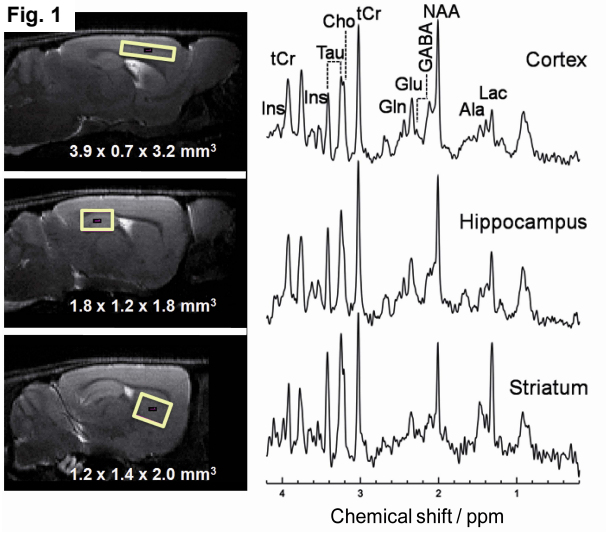
Fig. 1



Objectives: Volatile anesthetics like isoflurane are widely used in animal research and human medicine. An isoflurane-induced increase in lactate (Lac) was reported from cell culture studies [1]. On the other hand, isoflurane has been discussed as a neuro-protective agent in stroke [2]. Here, we evaluated the influence of isoflurane on brain Lac concentrations in comparison to intravenous anesthetic drugs using localized proton MRS of healthy mice.

Methods: In vivo localized proton MRS (STEAM, TR/TE/TM = 6000/10/10 ms) was performed at 9.4 T (Bruker Biospin GmbH, Germany) on healthy adult female NMRI mice in different regions of the brain (cortex: 3.9 x 0.7 x 3.2 mm^3, n = 12, NA = 64-128; hippocampus: 1.8 x 1.2 x 1.8 mm^3, n = 11, NA = 160-256; striatum: 1.2 x 1.4 x 2.0 mm^3, n = 9, NA = 256; CSF: 3.3 x 2.0 x 1.8, n=7, NA= 64-128; cerebrum: 4 x 3 x 4 mm^3, n = 45, NA = 32, **Fig. 1**) and under different anesthesia protocols (isoflurane 0-5%, ketamine/medetomidine 150/15 mg/kg, and pentobarbitone 45 mg/kg). Mice were initially anesthetized with 5% isoflurane, subsequently intubated and kept under anesthesia with 1.75% isoflurane in ambient air. To avoid movement artifacts in periods without isoflurane, pancuronium (15 mg/kg) was administrated 15 min before switching off the isoflurane supply. Intravenous anesthetic drugs were given after 35 min of isoflurane-free maintenance. Metabolite quantification involved spectral evaluation by LCModel and calibration with brain water concentration.

Fig. 2

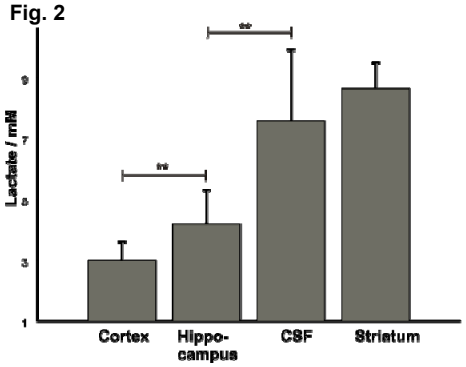


Fig. 3

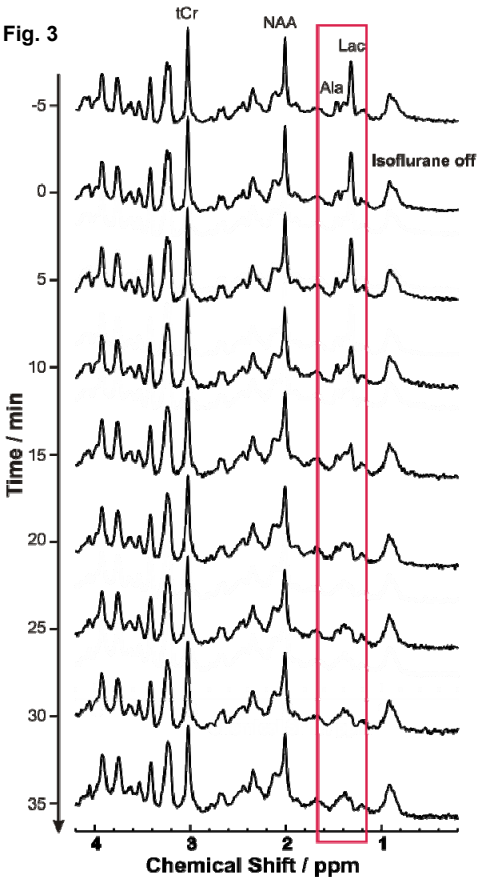
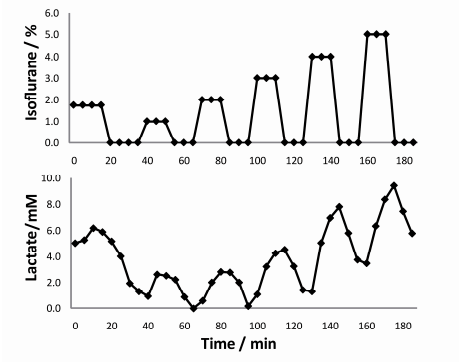


Fig. 4



Results: Under 1.75% isoflurane the highest Lac concentrations were observed in CSF and striatum, whereas the lowest concentration was found in the cortex (**Figs. 1** and **2**). Spectra of the cerebrum (obtained every 5 minutes) revealed that withdrawal of isoflurane resulted in undetectable Lac concentrations after about 20 to 30 min (**Fig. 3**). The combined administration of pancuronium and isoflurane showed similar Lac concentrations as isoflurane alone. Isoflurane increased Lac in a dose-depended manner. Lac increases were reversible even after exposure to 5% isoflurane (**Fig. 4**). The increase of Lac was accompanied by an increase in alanine (Ala) and a reduction of glucose (Glc). Moreover, isoflurane exposure resulted in a shift from phosphocreatine (PCr) towards creatine (Cr). Similar results were obtained with other volatile anesthetics such as sevoflurane, desflurane and halothane, although to a different extent (data not shown). In contrast, neither ketamine/medetomidine nor pentobarbitone administration alone resulted in detectable Lac levels.

Discussion and Conclusion: Volatile anesthetics provoke a dose-dependent and regionally different, but reversible elevation of brain Lac, which was not seen in any of the applied intravenous anesthetic drugs. These findings suggest that the Lac elevation is not primarily related to neuronal activity. In fact, the accompanying increase in Ala, the reduction in Glc and in PCr indicate a possible disturbance of mitochondrial function. The present observations may be crucially important not only for animal MRS studies of brain metabolism, but also for human anesthesiology.

References: 1: Molliex, Br J Anaesth, 1999, 82, 767; 2: Matchett et al, Neurol Res, 2009, 31, 128