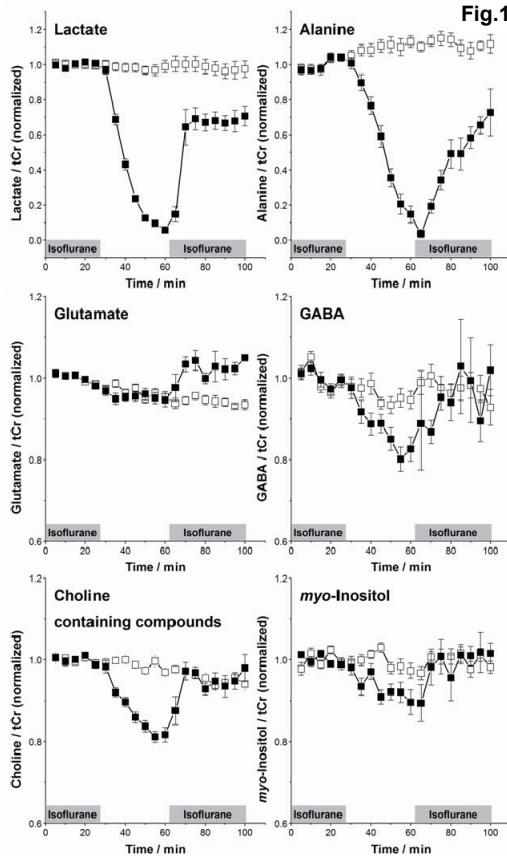


## Common isoflurane anesthesia causes multiple changes of brain metabolism in mice

Susann Boretius<sup>1,2</sup>, Roland Tammer<sup>1,3</sup>, Thomas Michaelis<sup>1</sup>, and Jens Frahm<sup>1,3</sup>

<sup>1</sup>Biomedizinische NMR Forschungs GmbH, Max-Planck-Institut für biophysikalische Chemie, Göttingen, Germany, <sup>2</sup>Klinik für Diagnostische Radiologie, Universitätsklinikum Schleswig-Holstein, Kiel, Germany, <sup>3</sup>DFG Center of Molecular Physiology of the Brain (CMPB), Göttingen, Germany

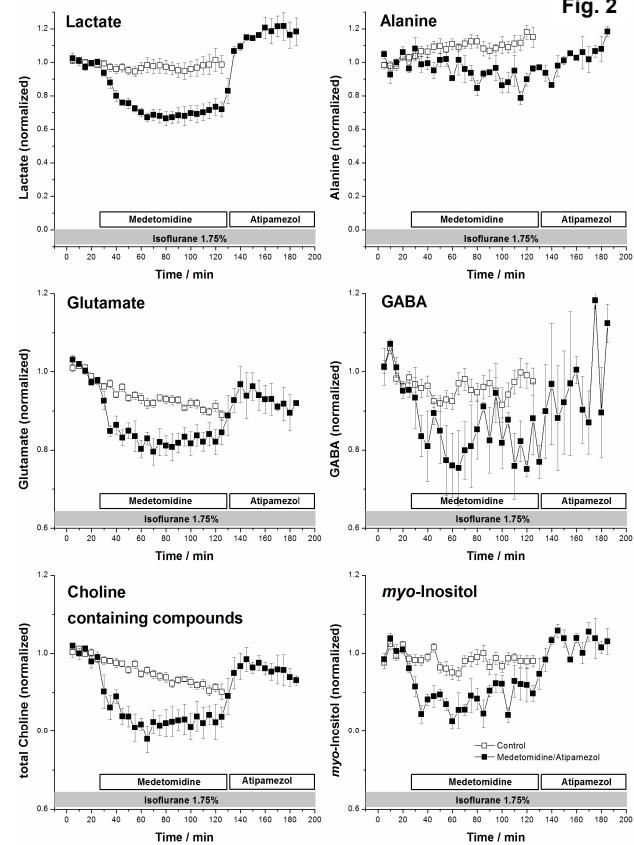
**Introduction:** General anesthesia using isoflurane is a most common procedure in medicine and research. A series of possible mechanisms of isoflurane action has been described, but it is largely unknown how brain metabolism and signaling is changed in the intact organism by exposure to isoflurane. Such knowledge may be important to reduce adverse effects and to correctly interpret results from animal experiments conducted under such anesthesia.



We performed localized proton MR spectroscopy in mice with and without exposure to isoflurane. To further understand metabolic changes observed, exposure to isoflurane was combined with known modulators of the adrenergic system.

**Methods:** In vivo localized proton MRS (STEAM, TR/TE/TM=6000/10/10 ms) of the cerebrum (VOI: 4 x 3 x 4 mm<sup>3</sup>) was performed at 9.4T (Bruker Biospin GmbH, Germany) on healthy, adult, female NMRI mice (n = 25). Metabolite quantification involved spectral evaluation by LCModel and calibration with brain water concentration. Mice were initially anesthetized with 5% isoflurane, subsequently intubated and kept under anesthesia with 1.75% isoflurane in ambient air. Spectra were obtained every 5 min. After acquiring 5 spectra under 1.75%, isoflurane was switched to 0%. To avoid movement artifacts in periods without isoflurane, pancuronium (0.15 mg/kg) was administrated 15 min before switching off isoflurane supply. After 35 min of 0%, isoflurane was again supplied at 1.75%. A second group of mice (n = 11) received isoflurane constantly at 1.75% over 120 min. In a third group (n = 3), mice received isoflurane constantly at 1.75% and in addition the alpha 2 receptor agonist medetomidine (0.5 mg/kg) was administered after 25 min followed by the alpha 2 receptor antagonist atipamezol (2.5 mg/kg) 100 min later.

**Results:** Further detailed analyses aimed at elucidating the increase of lactate and alanine during isoflurane exposure<sup>[1]</sup> also revealed an increase of GABA and choline containing compounds of about 20% and an increase of myo-inositol of about 10%. Interestingly the glutamate concentration initially increased but



then continually decreased under constant isoflurane concentration (Figure 1, white squares - isoflurane constant, black squares - isoflurane on-off-on).

The described metabolic effects of isoflurane were significantly attenuated by suppression of the adrenergic nervous system using the presynaptic alpha2 receptor agonist medetomidine. Moreover, isoflurane-induced metabolic changes were partially amplified by alpha2 receptor antagonist stimulating central adrenergic receptors (Figure 2, white squares - isoflurane constant, black squares - isoflurane constant with alpha2 receptor agonist/antagonist).

**Conclusion:** Already at common concentration isoflurane causes multiple changes of the brain metabolism in mice, most of them are partially reversible by alpha 2 agonist, indicating the adrenergic system as one possible target of isoflurane. Apparently, functional brain studies like fMRI and MRS using isoflurane anesthesia must take these major metabolic changes into consideration.

**References:** [1] Boretius et al., ISMRM, 2247, 2011