

# Propofol Increases GABA Concentration and Decreases Regional CBF in the Thalamus – an In-vivo 1H MRS/MRI Study in Normal Human Volunteers

Maolin Qiu<sup>1</sup>, Ramachandran Ramani<sup>2</sup>, Magret Rose<sup>2</sup>, and R. Todd Constable<sup>1</sup>

<sup>1</sup>Diagnostic Radiology, Yale University, New Haven, CT, United States, <sup>2</sup>Anesthesiology, Yale University, New Haven, CT, United States

**Introduction** Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. In-vitro studies have shown it plays an important role in anesthesia introduced by Propofol, an i.v. general anesthetic widely used in the operating room. The anesthesia state could be achieved by the potentiation of the GABA<sub>A</sub> receptor [1], facilitation of the GABA release [2], and regulation of the ambient GABA level [3]. To date, however, most reports investigating the actions of general anesthetics on their targets are based on in vitro data. Using a combination of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) in this work, we have measured the resting-state regional CBF for the whole brain and the GABA and glutamate/glutamine concentrations in the thalamus in healthy volunteers. These measurements were performed with and without Propofol administration, to assess the effects of general anesthetics on regional CBF and GABA, and to examine how Propofol influences the relationship between them. We test the hypothesis that, Propofol increases GABA levels while decreasing the glutamate/glutamine cycling in the thalamus, with these changes reflected indirectly through regional CBF measurements.

**Materials and Methods** Twenty six healthy subjects (19-35 years) underwent MR sessions that included pulsed arterial spin-labeling MRI, for the resting-state absolute CBF, and 1H MRS, for GABA, in the right thalamus during the anesthesia-free condition and the sub-anesthetic state induced by Propofol, with a target concentration of 2 µg/ml. Propofol i.v. infusion was administered through a target-controlled infusion pump (Stanpump, Stanford University, Palo Alto, CA) based on the age, sex, weight and height of the subject, targeting at a plasma concentration of 2 µg/ml. MRI/MRS data were acquired on a 3T whole-body scanner Trio (Siemens Medical Systems, Erlangen, Germany) with a 12-channel phased-array head coil. QUIPSS II PASL was used for measuring the resting-state CBF in the awake and anesthesia conditions. A 20-slice ASL acquisition was implemented and all slices were AC-PC angled and positioned to provide full brain coverage. The ASL acquisition parameters were: field of view FOV = 256×256 mm<sup>2</sup>; matrix = 64×64; bandwidth = 2004 Hz/pixel; slice thickness = 5 mm, and inter-slice gap = 2.5 mm. The repetition time was TR = 3000 ms; the echo time was TE = 26 ms. Two PASL runs, each of 250 volumes, were acquired for both the pre-anesthesia condition and during Propofol infusion condition. BiImageSuite was used for multi-subject data integration. GABA-edited 1H MR spectra were acquired from a 3×3×3 cm<sup>3</sup> volume positioned in the right thalamus using the MEGA-PRESS method with the following parameters: TE = 68 ms; TR = 1500 ms; vector length = 512, and total number of excitations = 340 repeats. GABA-edited 1H MRS sequence and water measurements were performed twice on each subject, once for the anesthesia-free condition and the other during the Propofol condition. The water peak was used to normalize the GABA level measured within the same ROI. JMRUI was used for MRS peak quantification.

**Results and Discussion** The subject-pooled regional CBF data demonstrate that one of the areas with the largest decrease in local CBF upon administration of Propofol is the thalamus (Fig. 1), with a mean CBF value of 58.4±16.6 ml/100g/min (mean±stdev) for the baseline condition and 46.2±13.6 ml/100g/min during Propofol infusion, resulting in a significant decrease of 21% (p<0.0001, paired t). For each subject, the peaks at 3 ppm and 3.75 ppm in spectra were used for quantification of GABA and Glx. The area under the peaks was first estimated and then normalized by the water peak measured in the same session. As shown in Fig. 2, the GABA level from group analyses for the non-Propofol condition was 0.247±0.03 (mean±stdev, a.u.) and 0.279±0.05 during Propofol administration, with a significant increase of 13% (p<0.01). The Glx level for the baseline condition was 0.2±0.05 (mean±stdev, a.u.) and 0.185±0.05 for Propofol, with a decrease of 7% (n.s.). The observation of a significant change in the thalamic GABA concentrations during Propofol anesthesia is consistent with previous in-vitro reports in animals that the reticular formation is rich in GABAergic neurons and GABA receptors [4]. The observed increases in GABA levels suggest several possible sources 1) Propofol enhanced the release of GABA transmitters, 2) Propofol inhibited the uptake of GABA transmitters, and 3) Propofol competed with GABA for postsynaptic receptors, resulting in more free GABA. Findings in the literature about effects of Propofol on Glx levels have been controversial. Our results indicate that the effects of Propofol on Glx were minimal. **Conclusion** To our knowledge, this is the first in-vivo study of investigating anesthetic effects in healthy humans using non-invasive MRI and MRS techniques, and in this study we have measured regional CBF for the whole brain and monitored GABA/Glx concentrations in the thalamus. Our results show the thalamus is a region strongly influenced by Propofol anesthesia. GABAergic neurons and GABA receptors play a major role in achieving anesthesia over the range of Propofol plasma concentrations examined. Cross sectional results also indicate that at higher concentrations Propofol may affect Glutamatergic neurons and Glutamate receptors by inhibiting Glutamate release. This study supports the hypothesis that the thalamus is the key structure in the brain whose function is altered upon administration of the anesthetic agent Propofol.

**References:** [1] Bhattacharya AA et al. The Journal of biological chemistry 2000;275(49):38731-38738. [2] Mantz J et al. Anesthesiology 1995;82(2):502-511. [3] Kubo K et al. The Journal of pharmacology and experimental therapeutics 2009;329(2):592-599. [4] Ambardekar AV et al. Neuroscience 2003;118(4):1033-1043.

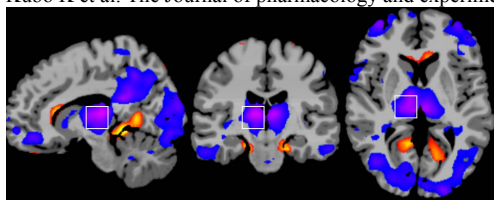


Fig 1 Regional CBF changed by Propofol (subject-pooled). Region of interest located at the right thalamus where GABA/Glx was measured by 1H MRS.

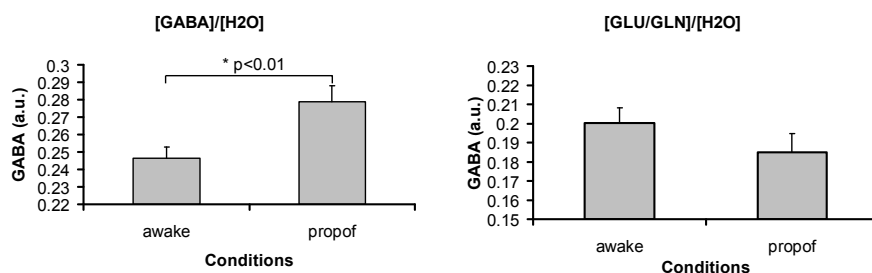


Fig. 2 Group analyses of changes in normalized GABA and Glx concentrations in the right thalamus with and without Propofol anesthesia.