Anesthetic Effects of Propofol on the Brain – Preliminary Results from MRI and MRS in Normal Human Subjects

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Introduction Despite the fact that general anesthetics produce a common set of endpoints, there is no universal pathway that explains all the actions of general anesthetics [1,2]. Preclinical studies suggest that propofol potentiates GABA activity [3], promotes GABA release [4,5], and inhibits Glutamate release [6]. We examine MRI(CBF&fMRI)&MRS measures of propofol anesthesia on the normal human brain, and show that propofol increases GABA concentration in thalamus, affects regional CBF in a drug-specific manner, but has little effect on functional connectivity.

Materials and Methods BOLD and PASL imaging was performed on a 3T Siemens (Erlangen, Germany) Trio system with a 12-channel phased-array head coil. Images in the resting state were acquired with BOLD and PASL MRI in 5 healthy human subjects during the awake and 2 μg/ml propofol anesthesia. PASL data covered 20 AC-PC aligned axial slices with slice thickness=5mm, gap=2.5mm, FOV=256mm, matrix size=64×64, TR=3s, TE=26ms, TI=1.4s, flip angle=90^o. BOLD volumes were collected using a single-shot gradient EPI sequence: 33 interleaved slices with a thickness of 4mm, no gap, FOV=256mm, matrix size=64×64, TR=2s, TE=30ms, flip angle=90^o. For each condition, awake or anesthesia, 1 PASL run of 250 volumes and 2 BOLD runs of 200 volumes each were obtained. Regional CBF was estimated from the PASL acquisitions [7] for each condition and compared between conditions. Group analyses were performed in the MNI reference space using a non-linear registration (www.bioimagesuite.org). For each BOLD run, data were temporally and spatially realigned and corrected to remove slice mean and drift after the first 10 volumes were discarded. Signal at each voxel was low-pass filtered at a cut-off frequency of 0.08 Hz with a 4th degree elliptical filter and the 6 estimated motion parameters were regressed from the data [8], as were the mean signals of white matter and CSF. Cardiac and respiratory signal were continuously recorded during the study and used to remove the physiological noise [9]. Intrinsic connectivity contrast (ICC) maps were computed for the whole brain using Bioimage Suite. GABA-edited MR spectra were acquired from a 3×3×3 cm^3 volume positioned to cover the right thalamus with TR=1.5s, TE=68ms, and a total acquisition time of 17min for each condition. In all participants, resolved MRS peaks were observed for both GABA at 3ppm and Glx (Glutamate and Glutamine) at 3.75ppm.

Results and Discussion GABA concentration was significantly increased by propofol from 22.1±3.6 (a.u.) to 26.9±2.3 ($p<0.05$, paired-t test), while the change in the Glx concentration was not significant (from 18.7±4.7 for the awake condition to 16.2±2.4 under anesthesia). These results support previous preclinical observations that propofol enhanced spontaneous GABA release, while inhibiting Glutamate release in a complex manner [3-6].

The resting-state CBF (Fig 1, top) was suppressed by propofol in most of the brain regions (Fig 1, bottom). Compared with the anesthetic effect of sevoflurane on rCBF reported in previous studies [10], in which sevoflurane increased rCBF in the ACC and insula, propofol suppressed rCBF in the same areas. Anesthetic effects on ICC remain minimal, which is consistent with results from previous human [11] and animal studies [12]. The ICC map (Fig 1, middle row) and CBF show similarity, which is further examined in this study by using spatial correlation between regional CBF and ICC and the results are shown in Fig 2. The similarity of the spatial CBF and ICC patterns during the resting state suggest that resting state CBF and ICC are associated with common components of underlying neuronal processes [12], however, CBF are more subject to change as neuronal activity increases.

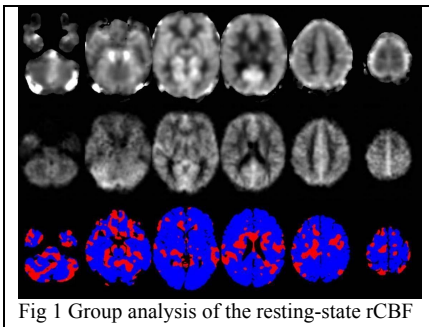

Fig 1 Group analysis of the resting-state rCBF for the awake condition (top), ICC for the awake condition (middle), and changes in rCBF induced by propofol (bottom).

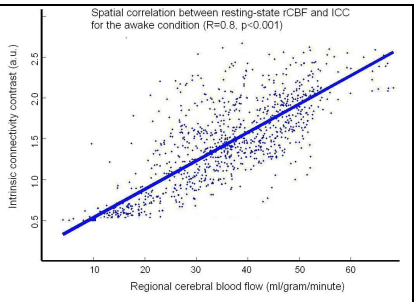

Fig 2 Spatial correlation between regional CBF and ICC shows they have similar spatial pattern.

Conclusion In this study, we employed both MRI and MRS to examine the anesthetic effects of propofol on regional CBF, intrinsic connectivity, and concentration or release of GABA, Glutamate and Glutamine in the normal human brain. Our preliminary data suggest the GABA receptor may be the most sensitive of all neurocepors and play an important role in propofol anesthesia. Propofol affects regional CBF in a drug-specific manner. Although CBF and ICC show similar spatial patterns, CBF is more responsive to changes in brain's activity than ICC. The robustness of the ICC measure to external anesthetic state suggests that ICC reflect a fundamental and intrinsic property of functional brain organization [12,13].

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