Decreased Glutamate Levels With Acute Exposure to Anesthetic Agent Propofol: A Preliminary *in vivo* ^{1}H Spectroscopy Study

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Introduction:

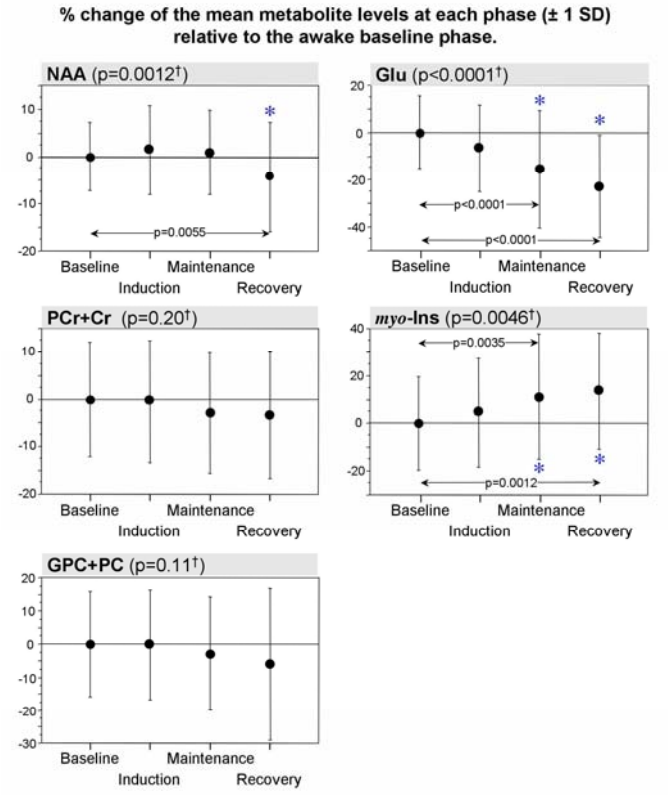
Propofol is the most commonly used intravenous anesthetic and is thought to exert its sedative-anesthetic effects via an agonist interaction with the $GABA_A$ receptor complex. This in turn may potentiate the hyperpolarization of the cell membrane, leading to inhibition of release of the major excitatory neurotransmitter glutamate. Preliminary high-resolution magic angle ^{1}H NMR (11.7T) studies measuring the neurochemical profile of *ex vivo* rat brain tissue have shown decreased glutamate in several brain regions including the anterior cingulate cortex (ACC) following acute propofol administration, consistent with the notion that enhanced $GABA_A$ receptor activity inhibits glutamate containing principle neurons. Moreover, electrophysiological studies have shown that the ACC is involved in mediating consciousness and anesthesia as well as being a generator of θ EEG activity, which may be synonymous with GABAergic action. *In vivo* ^{1}H spectroscopy also can monitor the time course of potential metabolite changes such as glutamate and it remains to be determined if these changes occur in humans treated with anesthetic doses of propofol. Therefore, the aim of this study is to use *in vivo* ^{1}H spectroscopy to monitor potential metabolite level changes in the ACC during induction, maintenance and emergence from propofol anesthesia to test the hypothesis that acute propofol would decrease ACC glutamate levels.

Subject and Methods:

Six males (mean age 27.3±4.8 yrs; age range 20.1 to 34.5 yrs old), who were American Society of Anesthesiology physical status classification Class 1 (normal and healthy), participated in the study. The subjects were instructed not to eat for 8 hours, not to drink for 4 hours, and to refrain from consuming alcohol, caffeine or using any medication 24 hours prior to the study sessions. Two anesthesia-recording sessions of approximately 105 minutes each were conducted in each subject. The first recording session was used to 1) assess subject's reaction to propofol administration, 2) ensure safety, 3) estimate the required propofol dosage and 4) habituate the subject in preparation for the second session in the MR scanner. During both sessions, physiological monitoring was conducted. During the MR scanning, ECG, blood pressure, heart rate and SaO_2 were continuously monitored and propofol was administered via an intravenous catheter located in the antecubital vein (forearm vein).

Each session started with a 15-minute awake baseline phase, followed by a slow induction of anesthesia phase (15 minutes) to achieve a slow transition from wakefulness to unconsciousness, a 30-minute maintenance phase of general anesthesia, and ended with a 15- to 30-minute recovery phase. The propofol dosage during the 30-minute maintenance phase of the propofol administration ranged between 165 and 175 micrograms/kilogram/minute.

The MR was conducted on a 4 Tesla Bruker MedSpec whole body MR imager. The MR scanning included a set of sagittal anatomical T_1-weighted images, which were used to determine the ^{1}H spectroscopy ACC voxel position (2.0x1.5x1.5cm^3), followed by continuous *in vivo* short-TE single-voxel ^{1}H spectroscopy measurements of the ACC during the four phases in blocks of 15 minutes. The acquisition parameters were as follows: SVS_SE pulse sequence (i.e., PRESS); TE= 22ms and TR= 3.7sec; data points= 2,048 and bandwidth= 2kHz; 16 averages and 14 measurements per block. The water-unsuppressed measurement parameters were the same except for the TR of 10sec, 4 averages and 1 measurement per block. The LC Model software package was used to quantify the ^{1}H metabolites [NAA, glutamate, glutamine, *myo*-inositol, GPC+PC, phosphocreatine plus creatine (PCr+Cr; high-energy phosphate metabolites), taurine, alanine, aspartate, gamma-amino-butyric acid (GABA), glucose, *scyllo*-inositol, lactate and NAAG] as well as lipid resonances and macromolecule resonances. Using the unsuppressed water signal, metabolite levels were expressed as mmol/kg wet weight. At 4 Tesla, the reliable quantified metabolites, NAA, glutamate, *myo*-inositol, GPC+PC and PCr+Cr, were used in the statistical analysis. The SAS Mixed procedure was use to statistically model the metabolite levels with phase (i.e., baseline, induction, maintenance and recovery) as the main term and the metabolite levels within subjects were treated as repeated measurement. The post-hoc test included the differences of least squares means.



Results:

The phase term was significantly different for glutamate (p<0.0001), NAA (p=0.0012), PCr+Cr (p=0.20) and *myo*-inositol (p=0.0046) (see Figure). Post-hoc analyses showed a glutamate reduction (p<0.0001) and increased *myo*-inositol (p<0.0035) during the maintenance and recovery phases (all compared to baseline values). Also, the NAA was significantly reduced at the recovery phase when compared to the baseline phase (p=0.0055).

Discussion and Conclusion:

This is the first report of the effect of the $GABA_A$ agonist propofol on real-time changes in glutamate in human subjects using *in vivo* ^{1}H spectroscopy. As predicted from our preclinical studies in rats, the anesthetic propofol reduced glutamate in the ACC of human subjects; an observation consistent with enhanced GABA mediated inhibition of glutamatergic pyramidal neurons. Relative to baseline levels, NAA levels also were reduced and *myo*-inositol levels were significantly elevated both at the maintenance and/or recovery phases. These metabolite changes were delayed relative to drug initiation and tended to show greatest changes in the recovery phase. The time course of glutamate recovery, as well as the mechanism underlying NAA and myo-inositol changes, remains to be determined. Finally, the results provide 1) novel mechanistic information on the action of general anesthetics, and 2) an opportunity to develop an MRS-based neurochemical challenge capable of assessing $GABA_A$ receptor function in various human psychiatric disorders.

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