Comparision of α-chloralose and domitor anesthesia for fMRI and electrophysiology studies

B. G. Sanganahalli[1], P. Herman[1,2], H. Blumenfeld[3], and F. Hyder[1,4]

[1]Diagnostic Radiology, Yale University, New Haven, CT, United States, [2]Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest, Hungary, [3]Neurology, Yale University, New Haven, CT, United States, [4]Biomedical Engineering, Yale University, New Haven, CT, United States

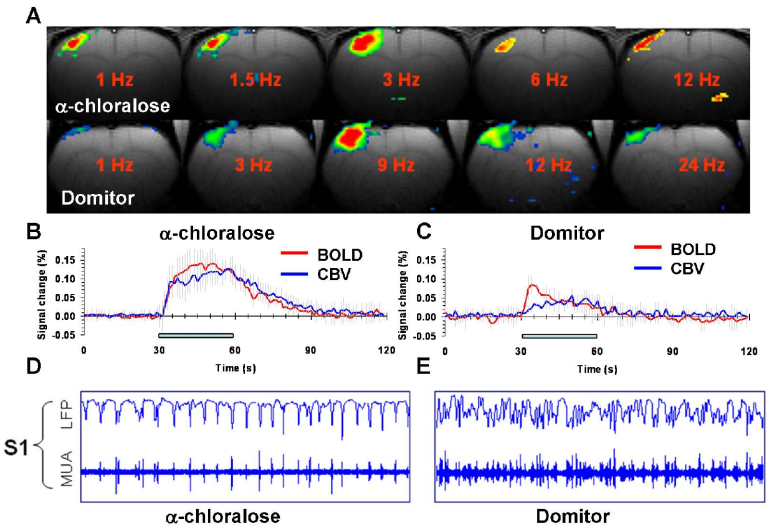
INTRODUCTION

Anesthetized animal studies are valuable for many experimental situations and settings including high resolution fMRI, electrophysiology and optical imaging. Reproducible BOLD activation patterns are observed with a wide range of anesthetics using forepaw, whisker and visual stimuli [1–6]. Different anesthetics have diverse effects on systems responsible for arousal and conscious states, and the design of such studies may be affected by the profound metabolic and electrical effects of using different anesthetics [7]. Stimulation-induced BOLD responses depend on basal blood flow and neuronal activity. Anesthetics can alter BOLD signal by suppressing neuronal activity and affecting the neurovascular coupling. α-chloralose has become the popular anesthetic of choice for functional studies in rodents. Recently, domitor (α_2-adrenergic agonist) has been studied as a potential anesthetic for longitudinal studies in rodents [5, 8-9]. α-chloralose and domitor have different powers in the γ band range of neural activity, which presumably reflect different arousal states. Therefore, we were interested in comparing the functional responses obtained under domitor and α-chloralose anesthesia during sensory stimulation in rodents.

MATERIALS and METHODS: ***Animal preparation****:* Sprague-Dawley rats were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). During the animal preparation isoflorane (2 to 3%) was used for induction. Intraperitoneal lines were inserted for administration of α-chloralose (46±4 mg/kg/hr) or domitor (0.1mg/kg/hr) and D-tubocurarine chloride (1 mg/kg/hr). An arterial line was used for monitoring physiology (blood pH, pO_2, pCO_2) throughout the experiment. ***Forepaw stimulation*****:** Stimulation was achieved by insertion of thin needle copper electrodes under the skin of the forepaw. Electrical stimulation consisted of 0.3ms square wave pulses provided with a stimulus isolation unit (World Precession Instruments, FL, and USA). Variation of functional response was achieved by varying the frequency (1 – 24 Hz) of the stimulus. The stimulus was controlled with a computer by custom written scripts with a 30s off 30s on block design. ***fMRI (n=16):*** All fMRI data were obtained on a modified 11.7T Bruker horizontal-bore spectrometer (Billerica, MA) using a ^{1}H surface coil (Ø = 1.4 cm). The images were acquired with gradient echo EPI sequence (TR/TE = 1000/15). CBV signal was measured by the same EPI parameters but in the presence of an intravenous injection of iron oxide nanocolloid particles (Combidex, 15 mg/kg, AMAG, Cambridge, MA). ***Electrophysiology measurements (n=8):*** The rat was placed in a stereotaxic holder on a vibration-free table inside a Faraday cage. Tiny burr holes were made above the contralateral and ipsilateral somatosensory regions [4.4 mm lateral and 1.0 mm anterior to bregma] and tungsten microelectrodes (FHC inc, Bowdoinham, ME) were inserted up to layer 4 (1mm depth) with stereotaxic manipulators (Kopf). All signals were then digitized (>20 kHz) with a μ-1401 interface using SPIKE-2 software.

RESULTS and DISCUSSION:

We evaluated forepaw stimulation-induced activity patterns in the rat somatosensory area. Electrical stimulation (2 mA) of the forepaw with 0.3 ms duration pulses for 30 s evoked a strong positive BOLD signal change in the contralateral primary somatosensory area of the forelimb (S1FL) under both anesthetics with stimulus frequency above 1Hz. We found frequency tuning response curves for α- chloralose and domitor where the BOLD (Fig 1.A) and CBV (data not shown) responses peaked at 3Hz for chloralose and 9 Hz for domitor. There were significant differences in the amplitude and shape of the BOLD and CBV response curves under domitor as compared to α-chloralose (Fig 1B (3Hz) and Fig 1C (9 Hz)). The reproducibility of responses from inter and intra subjects was better with α- chloralose as compared to domitor. Baseline multiunit (MUA) and local field potential (LFP) recordings from S1FL regions under α-chloralose and domitor showed different power in the γ band range of neural activity, which presumably reflects different arousal states. There is a dramatic difference in the power of the γ band range of neural activity in the cortex (Fig 1D and Fig 1E, 10s time window), where activity/energy is significantly higher in the domitor state. Cortical slow oscillations were increased under α-choralose, along with a decreased mean rate of neuronal firing, presumably reflecting a lower basal energy state. These differences in basal spontaneous neuronal activity may be responsible for differential response magnitudes in BOLD and CBV under these two anesthetics. These results will benefit the interpretation of fMRI experiments in anesthetized rodents as well as the understanding of brain function.



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