Isoflurane supplement prevents epileptic activity in fMRI studies under medetomidine anesthesia

Xiaopeng Zong¹, Mitsuhiro Fukuda¹, Alberto Vazquez², and Seong-Gi Kim³
¹Department of Radiology, University of Pittsburgh, Pittsburgh, PA, United States

Target audience: Researchers carrying out animal or pharmacological MRI studies.

Purpose: To investigate the effects of dexmedetomidine (DEX) – the active ingredient of medetomidine (MED) which is the latest popular sedative for functional magnetic resonance imaging (fMRI) in rodents – on multiple unit activity, local field potential (LFP), cerebral blood flow (CBF), pial vessel diameter (indicative of cerebral blood volume, CBV), and blood-oxygenation-level-dependent (BOLD) fMRI.

Methods: Twenty five male Sprague-Dawley rats weighting 260 – 450 g were used; 31 for optical and electrophysiological studies and 4 for fMRI. The right femoral artery and vein were catheterized for measuring arterial blood pressure (MABP) and administering drugs, respectively. A cranial window was made for recording neural activity, vessel diameter and CBF. After surgery under 2% isoflurane (ISO), a DEX bolus of 50 μg/kg was injected intravenously (IV) and the ISO was turned off or reduced to <0.5%. Fifteen minutes after the bolus injection, continuous infusion of DEX started at a rate of 50 μg/kg/h. Forepaw stimulation pulses with width of 1 ms, current of ≤1.5 mA and frequencies of 3 – 12 Hz were delivered for 10 s. No MABP change due to the stimulation was observed. The cortical surface was illuminated by yellow-green light (570 ± 10 nm) to capture images for measuring the diameters of pial vessels. A microelectrode with the tip diameter of 5 μm was placed at a depth of ~0.3 mm below the cortical surface of the forepaw area to record neural activity. Neural activity was recorded using an electrophysiological data acquisition system (Plexon, Inc.) at a 1 kHz sampling rate. Then we determined multiple unit activity (MUA) and LFP activity. A needle-type laser Doppler flow (LDF) probe with tip diameter of 450 μm (PeriFlux 4001, Perimed) measured parenchymal CBF. Functional MRI experiments were performed on Varian 9.4 T with a 2.3-cm diameter surface coil. Four coronal slices covering the primary somatosensory area (S1) was acquired with GE EPI with a matrix=64×64×4, FOV = 2.3 × 2.0 × 0.8 cm², TE/TR = 20/1000 ms.

Results and Discussion: Robust, stimulation frequency-dependent CBF responses were observed under DEX-only anesthesia, consistent with earlier fMRI studies (1,2). However, epileptic responses to the 10-s stimulation were observed in runs at >120 min after the initial DEX administration (see open arrow heads above the LFP and CBF traces in Fig. 1A right column). To attempt to avoid this epileptic effect, the DEX dose was increased from 50 to 150 μg/kg after 120 min from the initial dose. However, epileptic LFP and CBF responses were still elicited as soon as the stimulation started (Fig. 1A right column). These results suggest that evoked responses are prone to become epileptic when DEX is infused at a rate of 50 μg/kg/h for longer than 120 min. Supplementing with inspired ISO at 0.1 - 0.5% successfully mitigated the stimulation-evoked epileptic response (Fig. 1B). The use of supplementary ISO, a known vaughn-dead, did not seem to affect the baseline CBF level under DEX anesthesia (e.g., compare Figs. 1, A and B). Importantly, at a level of 0.5%, ISO did not decrease the amplitude of the evoked LFP response; however, the amplitude of the CBF response was slightly smaller than that obtained under DEX-only sedation (compare Figs. 1A and 1B).

Conclusions: We have demonstrated that forelimb stimulation under continuous administration of DEX of 50 μg/kg/h for approximately more than 2 hours elicited epileptic LFP responses with concomitant large increases in CBF (Fig. 1). The addition of supplementary isoflurane (e.g., ~0.3%) suppressed the generation of the epileptic activity. DEX constrains arterial and venous vessels similarly, and induces both arterial and venous vessel dilations during stimulation (5). The DEX+ISO combination yields robust CBF and BOLD fMRI responses, and is a suggested anesthesia for 2-3 hr fMRI studies.