Effects of Ketamine and Ketamine-Xylazine Anesthesia on Cerebral Blood Flow in Rat Observed Using Arterial Spin Tagging Perfusion Imaging

Hao LEI[1], Casmier I. Nwaigwe[1], Heather Williams[1], Jeffrey F. Dunn[1]
[1]Department of Diagnostic Radiology, Dartmouth Medical School, HB 7786, Vail 709, Hanover, NH USA;

Introduction

Ketamine with xylazine is a generally accepted anesthetic for laboratory rats[1]. Ketamine produces short-lasting unconsciousness with analgesia. Xylazine is a supplement drug used to minimize the side effects of using ketamine alone such as tremor, muscle rigidity and excitement during recovery.

Anesthetics often affect cerebral blood flow (CBF) and cerebral metabolism. Understanding these effects is not only of essential importance in managing anesthesia, but also in experiments in which the physiological conditions under general anesthesia are considered as control. Recent studies using eletron paramagnetic resonance (EPR) oximetry showed that there is a 30-50% reduction in cortical partial pressure of oxygen (P_tO_2) in ketamine-xylazine anesthetized rats compared to unanesthetized rats[2]. The underlying mechanisms which result in the differences in P_tO_2 need to be determined. However, the cause should relate to the changes in CBF and cerebral metabolic rate of oxygen ($CMRO_2$) caused by these drugs. Literature data on the effects of ketamine on CBF and $CMRO_2$ are controversial[3,4]. Little is known about the effects of xylazine on CBF. In this study, we measured regional CBF in the forebrain of rats under isoflurane anesthesia, ketamine anesthesia, and ketamine-xylazine anesthesia using MR arterial spin tagging perfusion imaging.

Materials and Methods

The experiments used 10 male Sprague-Dawley rats weighting 290-410 g. After tracheotomy, the rat was mechanically ventilated using 1.1% isoflurane in 26% oxygen with balance nitrogen to obtain normal blood gases. Baseline CBF under isoflurane anesthesia was measured. Ketamine-xylazine (87/17 mg/kg; n=5; Group 1) or ketamine (50 mg/kg; n=5; Group 2) was then injected through an i.p. catheter, followed by disconnection of isoflurane. Measurements of CBF under ketamine or ketamine-xylazine anesthesia started when the fraction of isoflurane in the inspired gases decreased below 0.2%, which often occurred 10-15 minutes after the disconnection of isoflurane.

MR experiments were carried out on a Varian INOVA console connected to a 7T/20cm Magnex magnet. A 4 cm diameter Varian quadrature volume coil was used for both transmission and reception. Perfusion imaging was done using a continuous arterial spin tagging sequence with snapshot FLASH read-out[5], a 4 × 4 cm^2 FOV, a 2 mm thick slice at striatum level, 128 × 128 matrix size, TR 5.0 ms, TE 3.0 ms, 12° flip angle, 96 averages and a 400 ms post-tagging delay[6]. Four sets of FLASH images were acquired using a four-step gradient-offset cycling protocol to eliminate the asymmetrical magnetization transfer effect[7]. $T1_o$ maps were acquired and perfusion images were calculated as previously described[5]. The degree of spin tagging (α) and the brain-blood partition coefficient for water (λ) were assumed to be 0.75 and 0.9 ml/g respectively. Regional CBF was measured from 6 regions of interest (ROIs; Fig. 1) in the forebrain. Statistical analysis was carried out using a two-tailed paired *t*-test.

Results

Figure 1 shows typical MR perfusion images from rats under isoflurane, ketamine-xylazine and ketamine anesthesia. The six boxes drawn on Fig. 1a indicate the ROIs for quantitative perfusion measurements (Fig. 2). Except in the corpus callosum which had lower CBF, CBF was relatively homogenous under isoflurane anesthesia. The overall signal intensity in Fig. 1b was lower than that in Fig. 1a, indicating a lower overall CBF under ketamine/xylazine anesthesia. After ketamine/xylazine was administered, CBF also became inhomogeneous across the brain, with the highest CBF in the caudate putamen, and the lowest in the septal/hypothalamus regions. There was little difference between the images shown in Fig. 1c and 1d.

Figure 2 shows the results of quantitative CBF measurements. CBF in the ketamine-xylazine group was significantly lower than CBF in the corresponding isoflurane group (isoflurane 1) in all 6 ROIs. However, the extent of CBF reduction varied from region to region, ranging from 30% in the caudate putamen (ROI 4) to 65% in the septal/hypothalamus regions (ROIs 5 and 6). Ketamine alone did not cause any significant changes in CBF in all ROIs compared to the corresponding isoflurane group (isoflurane 2), although there seemed to be a modest, but insignificant, CBF increase in the cingulate cortex (ROI 1).

Conclusion

Ketamine alone at a dose of 50 mg/kg does not cause significant changes in forebrain CBF in mechanically ventilated rat. The reduction of CBF in ketamine-xylazine anesthetized rats is region dependent, and most likely caused by xylazine. The reduction in CBF might be due to stimulation of central α2-adrenergic receptors by xylazine[8] and would account for the reduced P_tO_2 observed previously[2].

References

1. C. J. Green et al, *Lab. Anim.*, **15**, 163-70, (1981).
2. K. J. Liu et al, *Brain Res.*, **685**, 91-8, (1995).
3. M. Cavazzuti et al, *J. Cere. Blood Flow Metab.*, **7**, 806-11, (1987).
4. R. E. Oren et al, *Stroke*, **18**, 441-4, (1997).
5. H. Lei et al, *Magn. Reson. Med.*, **41**, 563-8, (1999).
6. D. Alsop et al, *J. Cere. Blood Flow Metab.*, **16**, 1236-49, (1996).
7. J. Pekar et al, *Magn. Reson. Med.*, **35**, 70-9, (1996).
8. J. M. McCormick et al, *Neurosurgery*, **32**, 974-79, (1993).

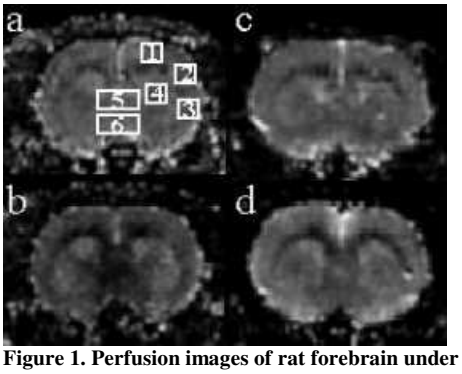

Figure 1. Perfusion images of rat forebrain under different anesthesia: Groups 1 (a) and 2 (c) isoflurane, ketamine-xylazine (b) and ketamine (d). Boxes 1-6 show regions of interest (ROIs) for quantitative CBF measurements (see Fig. 2).

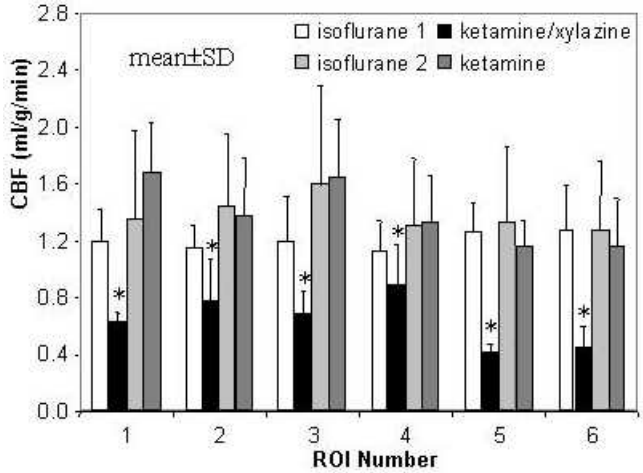

Figure 2. Quantitative CBF measurements in rat forebrain under isoflurane (two groups), ketamine-xylazine and ketamine anesthesia. (*p<0.05 compared to isoflurane 1).