Improved anesthesia protocols for fMRI studies in rats: the use of medetomidine for stable, reversible sedation

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α-Chloralose is the standard anesthetic for functional MRI experiments in rats. There are however some disadvantages related to the use of this anesthetic. The most prominent ones are the fluctuating depth of anesthesia due to the slow onset of action, the induced metabolic acidosis and the non-recovery aspect of the experiment. An alternative anesthetic was found that circumvented these problems without diminishing the BOLD response: medetomidine (Domitor®). Using a dosage regime of 50 μg/kg and a continuous infusion of 100 μg/kg/hr results in a stable longlasting deep sedation and a quick recovery at the end of the experiment.

Introduction

Although the use of α-chloralose is obsolete in most fields of laboratory animal science, it remains the drug of choice for fMRI studies in rats, because it provides a stage of deep sedation, which does not affect the function of the cerebral cortex.

The disadvantages[1] which arise using α-chloralose are:

1) the slow onset of action, which impedes the development of a steady state situation, makes it difficult to estimate the depth of anesthesia and to titrate towards the desired level.
2) α-chloralose disturbs homeostasis during anesthesia by inducing a metabolic acidosis.
3) it is unsuitable for survival studies, since it has a long recovery period, accompanied by a fierce excitation stadium of the animals.

The anesthetic medetomidine does not have the above mentioned disadvantages[2]: it has a short elimination half-life which makes it easy to control the depth of anesthesia and it is also possible to antagonize the drug with atipamezole (Antisedan®) to realise a quick recovery.

The purpose of this study is to investigate whether the intensity of the fMRI response using forepaw stimulation is similar during α-chloralose and medetomidine anesthesia.

Materials and Methods

Laboratory animals Adult, male rats (HsdCpb:WU, 250-350 g)

Anesthesia The animals were anesthetized (2% isoflurane; O_2+air mixture, FiO_2 >30%), orally intubated and artificially ventilated using IPPV ventilation. Further instrumentation included placement of an i.v. canula in the tail vein for continuous infusion, a rectal temperature probe, a pulseoximetry sensor on the hindpaw and electrodes in the forepaw. Temperature was maintained at 38.0 ± 0.5 °C, SaO_2>=95%.

After the preparation, the medetomidine loading dose of 50 μg/kg i.v., maintenance dose 100 μg/kg/hr i.v. using an continous infusion system. After placement of the animal prone in the cradle and on the heat blanket, the isoflurane was discontinued.

BOLD stimulation protcol All rats were stimulated with a Grass stimulator + constant current unit (3 Hz, duration=0.5 ms, I=1 mA)

MRI setup The experiments were performed on a S.M.I.S. 7T/200 mm horizontal-bore MR spectrometer using a 20 mm surface coil. For functional imaging, a gradient-echo sequence was used (TE= 10 ms; TR=300 ms; RF pulse angle=45°; FOV=50x50 mm; matrix size=128x128, slice thickness=1 mm). The Z-score substraction images were rendered with high resolution spin-echo images (TE=50 ms; TR=3000 ms; FOV=50x50; matrix size=256x256, slice thickness=1 mm). Data was postprocessed using MEDx 3.2.

Results and Discussion

The stimulation protocol applied in the presence of medetomidine resulted in activation of the somatosensory region of the brain as expected (see figure 1).

To make an estimation of the maximum signal difference which can be achieved using medetomidine, the pixel with the maximum difference in intensity was used to show the time course during one session of control images (n=6) and stimulation images (n=6) (see figure 2) The average signal intensity increase ± SD in this pixel is 14 ± 3 %.

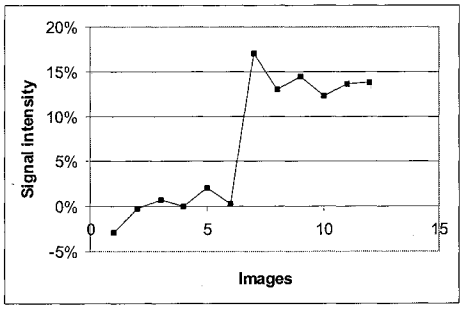

Figure 2 Relative signal intensity time course of pixel with maximum signal intensity increase

Both the activated region as well as the intensity of the BOLD signal are in line with expected results from previous publications in literature[3], making fMRI experiments during medetomidine anesthesia equivalent to α-chloralose anesthesia regarding the induced activation.

Conclusions

The use of medetomidine as an alternative anesthesia regime for fMRI experiments in rats improves the quality of anesthesia during the experiment without affecting the intensity of the fMRI response and opens new possibilities for survival studies.

References

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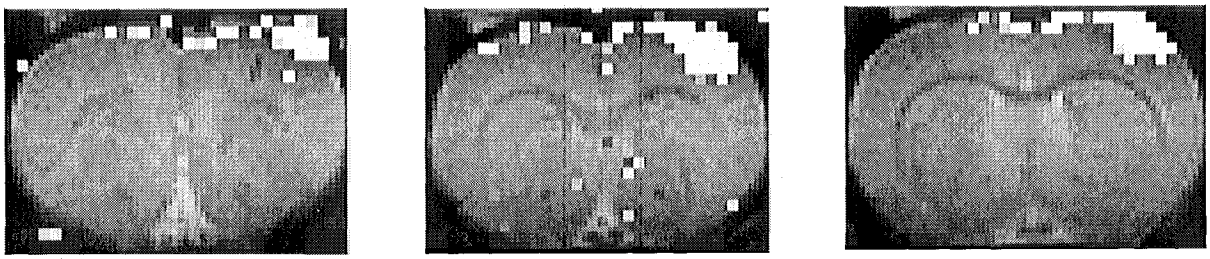

Figure 1 Three contiguous transversal slices showing the activated cortex area on the right after left forepaw stimulation. Colored overlay pixels resulted from a paired t-test (p-value ■ ≤ 0.05, ▨ ≤ 0.01)