VASCULAR RESPONSE TO DIFFERENT HYPERCAPNIC CHALLENGES IN FREE BREATHING OR VENTILATED C57BL/6 MICE.

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Target audience

This abstract is relevant to scientists with an interest in vascular response or reserve capacity in rodents and the effects of different anesthetics on mouse brain perfusion levels as determined with arterial spin labeling.

Purpose

Periods of decreased perfusion are relevant to several neurovascular diseases such as ischemic stroke. There is also strong evidence that in certain neurodegenerative diseases (e.g. Alzheimer's disease (AD)) vascular changes and the associated perfusion abnormalities may affect disease progression and even influence disease onset. Arterial spin labeling (ASL) provides a means for quantifying cerebral blood flow (CBF) in a non-invasive and longitudinal manner. It has therefore become an important tool to study regional cerebral perfusion in mouse models of human diseases and their relation to vascular disorders. Recent ASL applications in mice include models of stroke [1] and AD [2]. Besides basal flow, the increase in CBF to a hypercapnic challenge might be a more sensitive marker of vascular defects. In this study, we determined the reproducibility of a pulsed ASL protocol and the impact of different anaesthetics on the cerebral vascular response (CVR) in mice under both free breathing and ventilated conditions.

Materials & Methods

C57J/BL6 mice (9 ± 1 week old) were scanned using a 9.4T/200 Biospec (Bruker) equipped with a 7cm linearly polarized resonator and an actively-decoupled surface coil (Rapid Biomedical). Perfusion maps were recorded using a FAIR protocol (10 TI: 300-3000ms, hyperbolic secant 14ms; TR 18s, single slice over the cortex, hippocampus and thalamus) with RARE readout. A dynamic ASL protocol was also used during the challenge (as above but only TI 1500ms). Animals were scanned under free breathing conditions (two sessions 'a' and 'b' within 1 week) or ventilated [3] under isofluorane or a ketamine/xylazine anesthesia (the latter with rocuronium or pancuronium as muscle relaxant). Hypercapnia was induced by either inhalation of a 5% CO_2/95% O_2 gas mixture (carbogen) or a hypoventilation procedure [3]. CBF values were calculated using the T_1 difference method [4].

Results

CBF values were similar for both free breathing sessions (figure 1a: mean difference = 16 ± 27, 9 ± 22, 10 ± 37 ml/100g/min (n=6) or relatively 7 ± 12 , 4 ± 10, 3 ± 13 %, for cortex, hippocampus and thalamus, respectively. The inter-observer variability was similar: average (95%CI's) = 0.7 (-16.5/17.9), 6 (-20/32) and 0 (-8.8/8.8) 0.1 ± 6.0, -4.5 ± 9.6 and -0.2 ± 3.6 ml/100g/min (order as above). A 5%CO_2 challenge under free breathing isofluorane anesthesia did not elicit a reproducible increase in CBF (figure 1a), nor was there a substantial short term increase as evident from the dynamic perfusion weighted scan. This was confirmed by the very limited changes in arterial pCO_2 induced by this challenge under free breathing conditions (figure 1b). A similar limited response was seen in the ventilated group under isofluorane anesthesia (figure 2). Under ketamine-xylazine anesthesia an increase in CBF was observed during both the carbogen as during the hypoventilation challenge.

Discussion

The CBF levels measured in two sessions within one week were reproducible with only 10-13% variability. This variability could partly be explained by the limited resolution and the difficulty of accurately delineating the different regions as evident from the inter-observer variability. A reproducible vascular response was mostly absent under isoflurane, likely due to the vasodilating effect of this anesthetic but also seemed to be depended on proper ventilation control. For the ketamine/xylazine anesthesia, reproducible CBF and CVR levels were found in good agreement with a previous study using urethane and alpha-chloralose as anesthetics [3].

Conclusion

Determination of vascular reserve capacity seems dependent on the anesthetic agent and is best performed under ventilation control.

Fig.1a

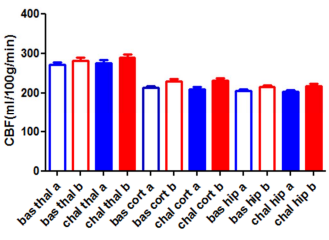


Fig.1b

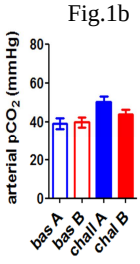
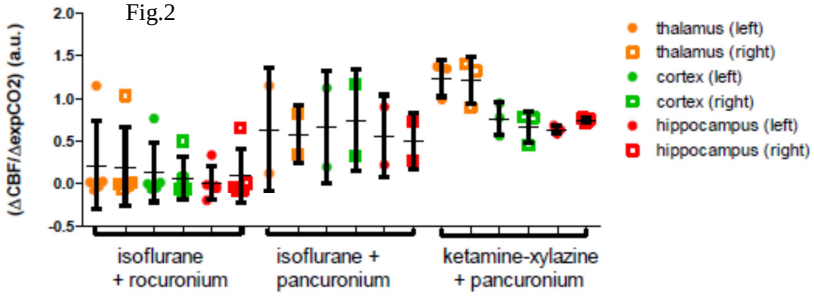


Fig.2



References

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