BOLD variations and reduced CBF increases upon hypoxia are indicative for the hippocampal vulnerability

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Introduction

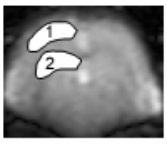
Oxygen delivery is one of the critical requirements for maintaining viability. A result of this viability threshold is the suppression of electrical activity during hypoxia to maintain the balance between oxygen consumption and supply (1). It is known that neurons within the hippocampus are more vulnerable to cell death after global cerebral ischemia, resulting in severe neuronal damage. Several factors that modulate the high susceptibility of the hippocampal formation and the relative resistance of other cortical areas have been proposed (2). While regional differences in oxygen delivery or different size of vascular response could hold a plausible explanation for the well documented hippocampal vulnerability, none of these were examined before. We aimed at investigating this issue focusing on the difference between the cortex and hippocampal formation.

Material and Methods

We used FVB/N mice (n=4, 3m) for bolus tracking (BT) and arterial spin labeling (ASL) experiments on a 7T MR Solutions (Guildford, U.K.) horizontal MR-system. 5% Isoflurane (Forene®) was used for induction and 0.4%-0.8% for maintenance anaesthesia in a mixture of O_2:N_2O (3:7) (600 ml/min). Refined monitoring systems retained mice whose physiological parameters remained within strict boundaries such as 37.0±0.2°C for body temperature (Kent, UK), 180±20 for breaths per minute and 3.5±0.5% for the end-tidal CO_2 (Capstar-100, Linton Instruments, UK). Single-slice GE-EPI was optimized and applied in both BT and ASL. BT was accomplished by a series of 200 horizontal images (TR 300ms, FOV 20 mm, slice thickness 1 mm, matrix 32*64, 0.2mmolGd/kg) for mapping absolute CBV and CBF. Continuous ASL revealed alternating control and labeled images. Labeling of the arterial spins was established using a slice selective RF inversion (gradient amplitude of 426 Hz/mm) with a duration of 4000 ms. The inversion slice was located at a 20 mm offset to the detection slice. The post-inversion time was set to 500 ms, TR 5000 ms and TE 17.4 ms. During ASL acquisitions, a period of normoxia was followed by hypoxia (8%O_2, 200s) and a subsequent normoxic recovery. Pairwise subtraction between temporally adjacent labeled and control acquisitions enables mapping of the relative perfusion contribution for normoxia (M_1) condition and for recovery upon the hypoxia challenge (M_2). A parameteric BOLD map was calculated from the control images during hypoxia, providing the change in transverse relaxation rate, a factor linearly dependent on the corresponding change in the deoxyhemoglobin fraction and the CBV.

Results

All results are summarized in table 1. The CBF is significantly different between the cortex and the hippocampus while the CBV values are the same. Next to a lower basal CBF, the hypoxia-induced CBF increase in the hippocampus is also significantly smaller (up to 50%) as compared to the cortex values. Hypoxia elicited a global BOLD signal decline in both gray and white matter and the same global pattern was present in every subject. The hippocampus presents a larger drop in BOLD contrast as compared to the cortex.



	basal values		CBF increase upon hypoxia (M2-M1)/M1	hypoxic sensitivity ΔR2*
	CBF	CBV		
Cortex (1)	82 ± 9 *	6.1 ± 0.4	29 ± 3 *	0.0042
Hippocampus (2)	65 ± 8	6.5 ± 0.6	15 ± 2	0.0085
Entire brain	84 ± 9	7.2 ± 0.7	33 ± 1	

Table 1: Summary of regional perfusion parameters (* $p<0.05$) and illustration of a GE-EPI raw image with indication of ROIs. CBF (ml/100g/min) and CBV (ml/100g) values are results from the bolus tracking and show that basal CBF in normal condition is lower in the hippocampus. From ASL, (M2-M1)/M1 gives in percent the relative contribution of the perfusion in different ROIs after hypoxia. In the hippocampus, the relative CBF increase is significantly smaller in comparison with the cortex. Hypoxic sensitivity is given by the analysis of the change in transverse relaxation rate reflected in the BOLD drop during hypoxia, $\Delta R_2^* = \ln (S_{hypoxia}/S_{normoxia})/TE$. For the hippocampus, the BOLD drop is larger.

Discussion

The hypoxia induced increase in deoxyhemoglobin levels exerts a stronger influence on the global BOLD signal than the concomitant CBF increases, resulting in a net BOLD signal decline. The BOLD signal depends in part on the vascular density. Related to the intrinsic lower blood volume of the hippocampus, a lower deoxyhemoglobin content per voxel and hence a smaller change in BOLD contrast upon hypoxia would be expected. This is in contrast with our observations suggesting that a higher oxygen extraction rate or a lower vascular reactivity might be reflected in the larger BOLD drop. First, an indication of higher oxygen extraction rate, given by the ratio of CBV/CBF, is inherent to the lower baseline hippocampal CBF together with a similar CBV as the cortex. Secondly, the hippocampus shows in addition a lower CBF response upon hypoxia. Undoubtedly this small CBF increase limits the scope of the hippocampus to cope with a reduced arterial oxygenation and helps explaining its vulnerability to hypoxia or ischemia, which is extensively documented.

References
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