The Cerebrovascular Coupling Under COX-2 Blockade

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Introduction The coupling between neuronal activity and focal hemodynamics lies at the heart of blood oxygenation level dependent (BOLD) fMRI. While a range of different molecules have been implicated in this coupling, the COX-2 derived arachidonic acid metabolites have recently received much attention [1,2]. In the current work, we investigated the role of COX-2 pathway in the coupling between BOLD, CBF and neuronal responses to functional stimulation in an anesthetized rodent model.

Methods The experiment was conducted on eighteen α-chloralose anesthetized Sprague-Dawley rats. A continuous ASL sequence (2.253 s RF pulse, 2 cm proximal to isocenter; 200 ms post labeling; TR/TE 2500/25 ms; 200x200x2000 μm^3) was used to measure CBF and BOLD responses before and during a COX-2 inhibition by Meloxicam, MEL, (4.75 mg/kg in initial bolus; 3.56 mg/kg/hr constant infusion), followed by administration of a 1-mL i.v. bolus (10 μg) of a major vasodilatory product of COX-2 pathway, prostaglandin E_2 (PGE_2). Somatosensory-evoked potentials (SEPs) were recorded via intracranial electrodes and COX enzymatic activity measured post mortem. The functional paradigm comprised 75 epochs of 45s off/30s on/45s off blocks, with the stimulation interval made up of 90 0.3-ms, 2-mA pulses, played out at 3 Hz. The bolus of MEL was administered 15 mins following the start of the experiment; MEL constant infusion started 15 mins thereafter and PGE2 administered 30 mins prior to the end. The MRI experiments were carried out on a 7 T (13.0 cm) Bruker BioSpec/AVANCE system (Ettlingen, Germany).

Results The average pre-drug CBF response was 62.4 ± 2.2%; BOLD, 5.9 ± 0.1%. MEL decreased brain COX enzymatic activity by 57 ± 14 % and had a significant effect ($p<10^{-6}$) on the stimulation-elicited CBF, and BOLD changes in each animal, without affecting the baseline perfusion. The CBF response decreased to 32±2% of its predrug value, with the largest decline in cortical layer IV, as shown in Fig. 1. Concomitantly, the BOLD response dropped to 46±1% of its value prior to MEL administration. In turn, administration of PGE_2 resulted in a partial recovery of functional hyperemia, with the CBF response recovering to 52±3% and the BOLD response to 56±2%, of their respective values prior to MEL administration. There was no concomitant decrease in either amplitudes or latencies of SEP components.

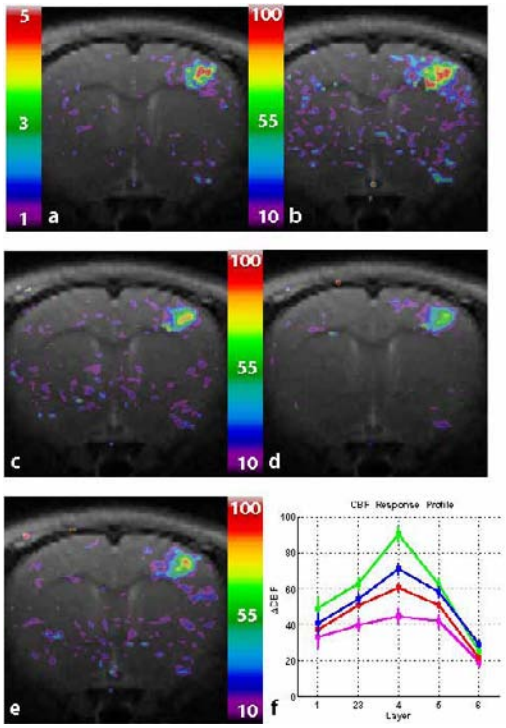

Figure 1. (a) The t-value map corresponding to the CBF data collected during the pre-drug baseline. (b-e) Percent difference maps, obtained in the same subject, corresponding to stimulation induced ΔCBF, averaged over all epochs: during the pre-drug baseline condition (b), post-MEL bolus (c), during constant infusion of MEL (d), and following administration of PGE_2 bolus (e). (f) CBF response profiles across the cortical laminae: pre-drug baseline (green), post-MEL bolus (magenta), constant infusion of MEL (red), and post-PGE_2 bolus administration (blue).

Discussion In agreement with the suggested role of prostaglandins in the elicitation of functional hyperemia [1,2], we observed a pronounced decrease of the hemodynamic response to functional stimulation following COX-2 inhibition. Moreover, PGE_2 appears to play a modulatory role in the coupling, as its administration resulted in a partial recovery of the responses. In view of the preserved neuronal responses despite a large hemodynamic response attenuation, the data describe a prolonged, pharmacologically induced disruption in the cerebrovascular coupling and are indicative of a metabolic buffer in the tissue.

[1] Niwa, J Neurosci, 20, 763-770, 2000.

[2] Bakalova, Exp Biol Med, 227, 465-473, 2002.