Cerebral blood volume imaging of spreading depression in S218L mouse model of familial hemiplegic migraine type 1

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INTRODUCTION

Spreading depression (SD), a slow propagating wave of neuronal and glial depolarization, is implicated in pathophysiology of migraine and peri-infarct depolarization. Recently, SD has been reported to occur not only in the cerebral cortex but also in the subcortical areas. S218L Mutant mouse, an animal model of familial hemiplegic migraine, exhibits such propagation of SD into subcortical regions such as striatum, hippocampus, and thalamus [1]. However, cerebrovascular response to SD in subcortical regions is not well studied so far. In this study, we investigated cerebral blood volume (CBV) changes induced by SD in both cortical and subcortical regions using T2*-weighted MRI and an intravascular contrast agent.

MATERIALS & METHODS

Nine S218L mutant mice were used in this study. Animals were kept under anesthesia with 1% isoflurane. SD was induced by applying 300 mM KCl solution (50 μl) on the dura matter of the right hemisphere through cranial window. MRI experiments were performed using a 9.4T horizontal bore (Magnex Scientific) scanner with a Bruker Advance console and a custom made surface-RF coil. A conventional spoiled gradient echo pulse sequence was used for continuous imaging for 40 minutes with following parameters: TR/TE = 180 ms/ 2.134 ms, FOV 14 mm, slice thickness = 0.500 mm, matrix = 80 x 80. 16 coronal slices were acquired with temporal resolution of 14.4 sec. In order to monitor CBV changes, we intravenously administered a blood pool T2 contrast agent (superparamagnetic ion oxide nanoparticles, SPION: 36 mg (FeO_2)/kg). After the administration, $\Delta R2^*$ maps were created to calculate CBV(t). This approach involves the measurement of shifts in the transverse relaxation rates (i.e., $1/T2^*$) caused by the intravascular SPION [2].

RESULTS & DISCUSSION

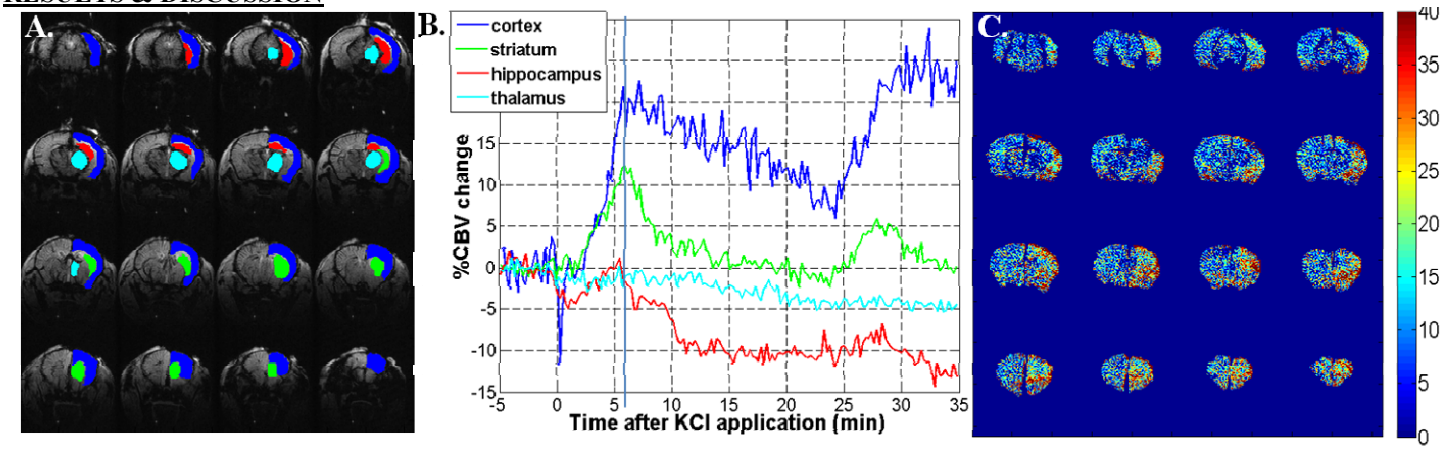

Fig. 1. Spatiotemporal profile of CBV changes in spreading depression. A. ROIs: cortex, blue; striatum, green; hippocampus, red; thalamus, cyan. B. ΔCBV response in ROIs. Vertical blue line: peak response of 1st SD. C. Spatial map of ΔCBV (% baseline) at the peak response of 1st SD (vertical blue line in Fig 1B).

Transient CBV increase induced by SD was observed in 6 of 9 animals. The CBV increase was observed in ipsilateral cortex, striatum, and hippocampus (Fig. 1), but not often in thalamus (weak response in only one animal). In general, the CBV response reached a peak long time after the SD onset observed in electrophysiology, and the SD onset latency observed with electrophysiological recordings was obscured in the CBV response (Table 1). The slope of CBV increase was highest near the KCl application site in the cortex, and tended to be lower in distant part of cortex and subcortical regions (Fig 2). This can arise from the difference in the level of SD activity across regions, and/or the difference in neurovascular coupling in each region. In future study, imaging technique with higher temporal resolution or multi-modality is required to elucidate the mechanism underlying the vascular response observed in this study.

Latency after KCl application (sec)	Cortex	Striatum	Hippocampus	Thalamus
SD onset (Electrophysiology)	31±4	80±17	97±12	148±56
CBV peak (MRI)	355±33	331±38	322±46	-

Table 1. Comparison between SD onset in electrophysiology and CBV peak response in MRI (mean±S.D.)

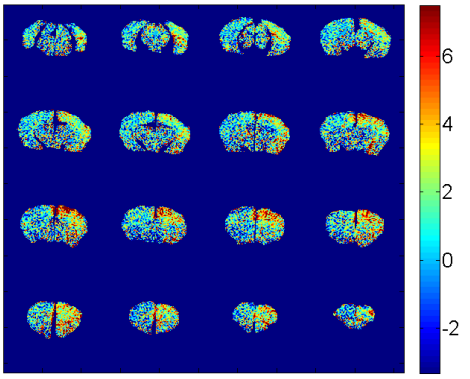

Fig. 2. Map of slope in rCBV increase (% change / min)

CONCLUSION

Cerebrovascular response of SD in this study was gradual and sustained much longer than the actual cellular depolarization, which is largely different from the normal neurovascular coupling. Such coupling between SD and cerebrovascular response requires thorough investigation in the future.

REFERENCE

[1] Eikermann-Haerter K et al. J Clin Invest 2009; 119(1):99-109. [2] Fisel CR et al. Magn Reson Med 1991; 17:336–347.