BRAIN RESEARCH 1537 (2013) 350–355

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Brain Research

Research Report

Hemodynamic changes during neural deactivation in awake mice: A measurement by laser-Doppler flowmetry in crossed cerebellar diaschisis

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ARTICLE INFO

Article history:
Accepted 18 September 2013
Available online 25 September 2013

Keywords:
Cerebellar blood flow
Red blood cell velocity
Red blood cell concentration
Neuronal deactivation
Awake animal
Crossed cerebellar diaschisis

ABSTRACT

Crossed cerebellar diaschisis (CCD) caused by contralateral supratentorial lesions can be considered a condition of neural deactivation, and hemodynamic changes in CCD were investigated with positron emission tomography (PET) in humans. In the present study, to investigate the effects of neural deactivation on hemodynamics, we developed a new mouse model of CCD, which was caused by middle cerebral artery occlusion (MCAO), and measured changes in cerebellar blood flow (CbBF), red blood cell (RBC) velocity and concentration due to CCD using laser-Doppler flowmetry (LDF) in awake mice. The ratio of the CCD side to the unaffected side in the cerebellum for CbBF 1 day after MCAO was decreased by −18% compared to baseline (before CCD). The ratio of the CCD side to the unaffected side for RBC concentration 1 day after MCAO was decreased by −23% compared to baseline. However, no significant changes in the ratio of the CCD side to the unaffected side were observed for RBC velocity. The present results indicate that the reduction of CbBF induced by neural deactivation was mainly caused by the decrease in RBC concentration. In contrast, our previous study showed that RBC velocity had a dominant role in the increase in cerebral blood flow (CBF) induced by neural activation. If RBC concentration can be considered an indicator of cerebral blood volume (CBV), hemodynamic changes due to neural activation and deactivation measured by LDF in mice might be in good agreement with human PET studies.

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http://dx.doi.org/10.1016/j.brainres.2013.09.023

1. Introduction

Positron emission tomography (PET) studies of the hemodynamics of crossed cerebellar diaschisis (CCD), which is caused by contralateral supratentorial lesions, have shown reductions in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) in human (Lenzi et al., 1982; Martin and Raichle, 1983; Pantano et al., 1986; Yamauchi et al., 1992a, 1992b, 1999a, 1999b; Ito et al., 2002). CCD can be considered as neural deactivation (Ito et al., 2002), which is a reduction of neural activity as compared to the baseline level (spontaneous neural activity). In our previous study, we reported that hemodynamic changes in CCD measured with PET in humans showed almost the same degree of decrease in cerebral blood volume (CBV) and CBF (Ito et al., 2002). Animal studies, for which invasive procedures can be applied, can also be useful for investigating the mechanism of CCD resulting from neuronal deactivation. An anesthetized rodent model study reported the reduction of cerebellar blood flow (CbBF) associated with attenuation of spontaneous neural spiking activity, which was caused by middle cerebral artery occlusion (MCAO) and common carotid artery (CCA) occlusion (Gold and Lauritzen, 2002).

Recently, many investigators reported that anesthesia significantly affects the physiological states including the regulation of cerebral circulation throughout the brain (Martin et al., 2002, 2006; Lahti et al., 1999; Peeters et al., 2001; Sicard et al., 2003; Takuwa et al., 2011, 2012). Thus, we previously developed a system for measurement of cerebral hemodynamics in awake rodent using laser-Doppler flowmetry (LDF; Takuwa et al., 2011). Moreover, using this system, we investigated hemodynamic changes during neural activation in awake mice (Takuwa et al., 2012), and showed that the increase in red blood cell (RBC) velocity was far greater than that in RBC concentration and that it had a dominant role in the increase in CBF induced by neural activation.

On the other hand, hemodynamic changes caused by neuronal deactivation in awake animals was still unknown. To the best of our knowledge, no study has investigated the dynamics of RBC velocity and concentration independently in awake animals. In the present study, in order to investigate the effects of neural deactivation on hemodynamics, we developed a CCD mouse model caused by MCAO and measured changes in CbBF, a product of RBC velocity and concentration in cerebral microvessels, using LDF before and after neural deactivation under awake conditions.

2. Results

2.1. Changes in CbBF and RBC velocity and RBC concentration during CCD

Fig. 2 shows the percentage changes in the ratio of the CCD side to the unaffected side for CbBF and RBC velocity and concentration at one day after MCAO. The percentage changes in the ratio of CCD to the unaffected sides for CbBF, RBC velocity and concentration were $-18\pm11\%$, $5\pm14\%$ and $-23\pm17\%$, respectively. The percentage changes in the ratio of CCD to the unaffected sides for CbBF ($P<0.05$) and RBC concentration ($P<0.01$) were significantly lower than the ratios before MCAO (baseline), whereas no significant difference was observed in the ratio of CCD to the unaffected sides for RBC velocity between baseline and one day after MCAO (Fig. 2).

2.2. Longitudinal measurement in hemodynamic response to CCD

Longitudinal LDF measurement was performed for 2 weeks (Fig. 1). Before this experiment, we confirmed that CbBF and RBC velocity and concentration in intact animals (without MCAO but with attached cranial window) were quite stable for 14 days (data not shown). The percentage changes in the ratio of the CCD side to the unaffected side for CbBF at 7 days and 14 days after MCAO were $-18\pm8\%$ and $-21\pm11\%$, respectively (Fig. 2). The percentage changes in the ratio of CCD to the unaffected sides for RBC velocity at 7 days and 14 days after MCAO were $3\pm11\%$ and $-2\pm3\%$, respectively. The percentage changes in the ratio of CCD to the unaffected sides for RBC concentration at 7 and 14 days after MCAO were $-21\pm12\%$ and $-19\pm7\%$, respectively. The ratios of CCD to the unaffected sides for CbBF and RBC concentration at 7 and 14 days after MCAO were significantly lower than those at baseline ($P<0.01$). No significant difference was observed in CbBF and RBC concentration between 7 and 14 days after MCAO. No significant difference was observed in the ratio of CCD to the unaffected sides for RBC velocity throughout all measurements (Fig. 2).

2.3. MRI measurement in MCAO

The high intensity area in the cerebral cortical region of the MCAO side indicates infarction in the MCA territory in the T2-weighted image two weeks after MCAO for all mice (Fig. 3).

3. Discussion

We newly developed an awake mouse model of CCD (neural deactivation) caused by MCAO. Using these CCD model mice, the hemodynamic responses to neural deactivation including

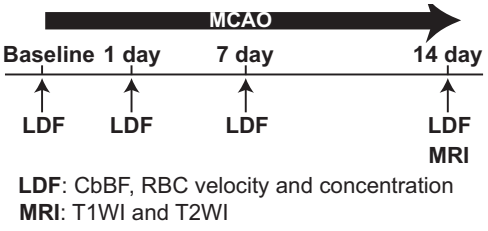

Fig. 1 – Experimental protocol for LDF measurement and MRI. LDF measurements were performed before (baseline) and 1, 7, and 14 days after MCAO. In each examination, changes in CbBF and RBC velocity and concentration were measured in both CCD side and unaffected side in awake mice. MRI experiments (T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI)) were performed 14 days after MCAO.

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