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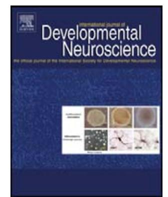

Metabolic changes in visual cortex of neonatal monocular enucleated rat: a proton magnetic resonance spectroscopy study

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ABSTRACT

Neonatal monocular enucleation (ME) is often employed to study the developmental mechanisms underlying visual perception and the cross-modal changes in the central nervous system caused by early loss of the visual input. However, underlying biochemical or metabolic mechanisms that accompany the morphological, physiological and behavioral changes after ME are not fully understood. Male Sprague-Dawley rats ($N = 14$) were prepared and divided into 2 groups. The enucleated group ($N = 8$) underwent right ME (right eye removal) at postnatal day 10, while the normal group ($N = 6$) was intact and served as a control. Three weeks after ME, single voxel proton magnetic resonance spectroscopy (^{1}H MRS) was performed over the visual cortex of each hemisphere in all animals with a point-resolved spectroscopy (PRESS) sequence at 7 T. The taurine (Tau) and N-acetylaspartate (NAA) levels were found to be significantly lower in the left visual cortex (contralateral to enucleated eye) for enucleated animals. Such metabolic changes measured *in vivo* likely reflected the cortical degeneration associated with the reduction of neurons, axon terminals and overall neuronal activity. This study also demonstrated that ^{1}H MRS approach has the potential to characterize neonatal ME and other developmental neuroplasticity models noninvasively for the biochemical and metabolic processes involved.

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1. Introduction

The neocortex has an enormous capacity to functionally adapt in response to external perturbations and compensate functional loss after injury (Feldman, 2009; Lewis and Gonzalez-Burgos, 2008). Morphological, functional, behavioral and biochemical changes following injuries have been used to understand the cellular and synaptic plasticity mechanisms that uphold adaptive behavior in brain (Bavelier and Neville, 2002; Rauschecker, 1995; Schroeder et al., 2003; Stein and Stanford, 2008). Neonatal monocular enucleation (ME) has been often utilized to study developmental mechanisms underlying visual perception and neuroplasticity of the brain because of the extensive changes and reorganization in various regions of the visual system following the complete loss of one eye (Toldi et al., 1996). Previous studies suggested that ME during early postnatal period initiates not only neurodegeneration in both dorsal lateral geniculate nucleus (DLGN) and superior colliculus (SC) in the enucleated side, but also a series of adaptive reactions in the visual and other sensory systems at a later stage (Karlen et al., 2006; Toldi et al., 1994; Yagi et al., 2001).

Upon neonatal ME, anatomical structures in projection targets of the visual system are largely affected (Toldi et al., 1996). Physiological changes including enlarged ipsilateral visual field and receptive field in the visual system were observed at 3 months after ME (Fukuda et al., 1983; Jeffery and Thompson, 1986). Plasticity resulted from recruitment of resources to the remaining left eye for adaptation and cross-modal effects were also observed at 3 months to 1 year after ME (Karlen et al., 2006; Toldi et al., 1994; Yagi et al., 2001). However, underlying biochemical or metabolic mechanisms that accompany the morphological, physiological and behavioral changes after ME are not fully understood (Steeves et al., 2008; Toldi et al., 1988, 1994; Yaka et al., 2000). Decreased local cerebral glucose utilization in both DLGN and SC was found in rats within hours to days after ME (Grunwald et al., 1993; Zilles et al.,

Abbreviations: ^{1}H MRS, proton magnetic resonance spectroscopy; 2D, two-dimensional; Ace, acetate; Ala, alanine; Asp, aspartate; Cho, choline; Cr, creatine; CRLBs, Cramer-Rao lower bounds; DLGN, dorsal lateral geniculate nucleus; FOV, field of view; FSE, fast spin-echo; Glu, glutamate; HLSVD, Hankel–Lanczos Singular Value Decomposition; Lac, lactate; m-Ins, myo-inositol; ME, monocular enucleation; NAA, N-acetylaspartate; NEX, number of excitations; OVS, outer volume suppression; PRESS, point-resolved spectroscopy; QUEST, quantitation based on quantum estimation; SC, superior colliculus; SD, standard deviation; Tau, taurine; TE, echo time; TR, repetition time; RF, radiofrequency; VAPOR, variable power RF pulses with optimized relaxation delays.

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1989), which was likely associated with the pronounced neuronal cell death in those regions (Oppenheim, 1991). Alteration of fatty acids incorporation in contralateral visual areas was observed at 1 day after ME (Wakabayashi et al., 1994). High turnover rate of dopamine, serotonin and glutamate was also observed in the SC in neonatal enucleated rats at 3 months old (Vizuete et al., 1993). Although most biochemical studies only dealt with the first-order (DLGN and SC) but not second-order visual centers (visual cortices), several studies suggested that there are significant neurophysiological changes specifically in the visual cortex as a consequence of visual deprivation (Amedi et al., 2007; Merabet et al., 2007, 2005).

Proton magnetic resonance spectroscopy (^{1}H MRS) can provide metabolite distribution in selected volume in brain *in vivo*, revealing the roles of major neurochemicals as markers for neurodegeneration and neuroprotection upon degenerative illness (Choi et al., 2007). This technique has been utilized to investigate *in vivo* information on neurochemistry of various neurodegenerative diseases noninvasively, including Huntington's disease, Parkinson's disease and Alzheimer's disease (Brownell et al., 1998; Ferrante et al., 2000; Marjanska et al., 2005). A recent study investigated the repair processes and plasticity of stem cell transplantation into rat brain with photochemical lesion (Herynek et al., 2009); suggesting that ^{1}H MRS may be capable to provide insights into metabolic activity, neurogenesis and plasticity changes. Regarding the visual system, reduction of choline (Cho) in the visual cortex of glaucomatous rat possibly due to dysfunction of the cholinergic system in the visual pathway was reported by our group with ^{1}H MRS (Chan et al., 2009b). Such MRS technique has also been recently applied on blind subjects to reveal elevation of myo-inositol (m-Ins) in the visual cortex, probably due to the participation of glial cells in the reorganization of the brain upon visual deprivation in adult human subjects (Bernabeu et al., 2009).

Measurements of metabolites in brain may provide valuable biochemical information to study neurophysiological changes. Upon neonatal ME, characteristic structural and physiological changes in the visual system are induced. We hypothesized that neonatal ME would lead to metabolite changes in visual cortex. In this study, we aimed to detect and characterize the metabolic changes in ME rat neonates *in vivo* with ^{1}H MRS at 7 T. Such information can be valuable to the future investigation of cortical reorganization and changes associated with the adaptive reactions in the visual and other sensory systems in neonatal ME and other neuroplasticity models.

2. Materials and methods

All MRI measurements were acquired on a 7 T MRI scanner with a maximum gradient of 360 mT/m (70/16 PharmaScan, Bruker Biospin GmbH, Germany). A 72-mm birdcage transmit-only radiofrequency (RF) coil with an actively decoupled receive-only quadrature surface coil was used. All animal experiments were approved by the local institutional animal ethics committee.

2.1. Animal preparation

Male Sprague-Dawley neonatal rats (20–22 g, $N = 14$) were prepared and were divided into 2 groups. The enucleated group ($N = 8$) underwent right ME at postnatal day 10 under inhaled isoflurane anaesthesia through an incision in the conjunctiva followed by sectioning of the extraocular muscles and the optic nerve. The right eyeball was removed and the empty socket was filled with oxidized regenerated cellulose Surgicel® (Johnson & Johnson) (Prusky et al., 2006; Vargas et al., 2001). The normal intact group ($N = 6$) was intact and served as a control. Three weeks later, ^{1}H MRS was performed at the visual cortex of each hemisphere in all animals after the critical period of visual development (Berardi et al., 2000).

2.2. MR spectroscopy

During MRI, the animals were anesthetized with isoflurane/air at 3% for induction and 1.5% for maintenance via a nose cone with respiratory monitoring (Wu et al., 2004; Yang and Wu, 2008). Body temperature was maintained at about 37 °C by circulating warm water in a heating pad. Scout images were first acquired in three planes with a fast spin-echo (FSE) sequence to position the subsequent voxel for ^{1}H MRS along standard anatomical orientations in a reproducible manner. High resolution anatomical images were acquired with two-dimensional (2D) FSE sequence using repetition time (TR) = 4200 ms, echo time (TE) = 38.7 ms, field of view (FOV) = 32 mm × 32 mm, acquisition matrix = 256 × 256, spatial resolution = 0.125 mm × 0.125 mm × 0.8 mm, echo train length = 8 and number of excitations (NEX) = 2. ^{1}H MRS data was acquired using a protocol previously described (Chan et al., 2009a,b, 2010b). In brief, a 0.8 mm × 2.8 mm × 2.8 mm voxel was placed over each side of the visual cortex. The volume of interest was maximized to obtain high signal-to-noise ratios and to cover the gray matter in the visual cortex, while avoiding the margins of the white matter structures, which were clearly distinguishable in the FSE images underneath the cortex (Chan et al., 2009a,b). After automatically adjustments of first- and second-order shim terms for localized voxel using the field map based shimming technique (Webb and Macovski, 1991), a full-width half-maximum linewidth of water signal of ≤20 Hz would be achieved. The water signal was suppressed by variable power RF pulses with optimized relaxation delays (VAPOR). Outer volume suppression (OVS) combined with point-resolved spectroscopy (PRESS) sequence was used for signal acquisition using TR = 2500 ms, TE = 20 ms, spectral bandwidth = 3 kHz, 2048 data points and 512 averages.

2.3. Data and statistical analysis

The *in vivo* MR spectra were processed as previously described using the jMRUI software (version 4.0, http://www.mrui.uab.es/mrui/) (Chan et al., 2009a,b, 2010b; Ratiney et al., 2005). The raw data were apodized with a 15-Hz Gaussian filter. In addition, the signal of residual water was filtered with Hankel–Lanczos Singular Value Decomposition (HLSVD) algorithm preprocessing with 25 spectral components for modeling. Spectral peaks were assigned in the references to the singlet peak of CH_3-group of N-acetylaspartate (NAA). Metabolite areas were estimated using the quantitation based on quantum estimation (QUEST) method combined with subtraction approach for background modeling (Cudalbu et al., 2008). Note that the background signal was well modeled with both lipid resonances (at 0.9 and 1.3 ppm) and the three principal resonances of macromolecules (at around 2 ppm, 3 ppm and 3.9 ppm) being well identified under this quantitation scheme (Cudalbu et al., 2008). To reduce the systematic variations among the animals studied and to extract the dominating metabolite changes, a relative quantification method using creatine (Cr) peak as the internal spectral reference was applied given that concentration of Cr was observed to be relatively constant *in vivo* (Malisza et al., 1998). The numerical time-domain modal functions of 10 metabolites, including acetate (Ace), alanine (Ala), aspartate (Asp), NAA, Cho, Cr, taurine (Tau), glutamate (Glu), lactate (Lac) and m-Ins, were used as prior knowledge in QUEST for quantitation of major resonance peaks. These metabolite model signals were quantum mechanically simulated in NMR spectra calculation using operators (NMRSCOPE) for the *in vivo* experimental protocol used. Tau:Cr, NAA:Cr, Glu:Cr, Cho:Cr and m-Ins:Cr ratios were statistically evaluated. The reliability of metabolite quantitation was assessed using the Cramer-Rao lower bounds (CRLBs) (Cudalbu et al., 2008). An estimate was considered as relevant when the corresponding bound was found below 25% of the estimate. All data were presented as mean ± standard deviation (SD). Two-tailed paired Student's *t* tests were performed between contralateral sides for enucleated and normal groups respectively, while two-tailed unpaired Student's *t* tests were performed between enucleated and normal groups in the same hemisphere.

3. Results

Fig. 1 illustrates the voxel placements to the visual cortex in the FSE images and Fig. 2 shows the typical ^{1}H MRS spectra on each side of the visual cortex for the enucleated animals and major peaks were labeled correspondingly. All enucleated animals consistently showed a marked difference in Tau signal with respect to Cr signal between the left visual cortex (contralateral to enucleated eye) and the right visual cortex. Spectra similar to that in the right visual cortex were observed for normal animals.

Table 1 shows the estimated metabolite ratios and the respective CRLBs at each side of the visual cortex for all the animals studied. Tau:Cr, NAA:Cr, Glu:Cr, Cho:Cr and m-Ins:Cr ratios were qualified with CRLBs less than 25%, indicating the reliability of metabolite quantitation. All enucleated animals showed a decreased Tau signal (with respect to Cr signal) in the left visual cortex (contralateral to enucleated eye) as compared to that in the right visual cortex of both enucleated animals (19% with $p < 0.01$) and normal controls (24% with $p < 0.05$). In addition, NAA:Cr ratio in the left visual cortex of enucleated animals was found to be significantly lower than that of normal animals by 38% ($p < 0.05$). No apparent difference was observed in other metabolites between contralateral sides of the visual cortex for enucleated animals as

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