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Author(s)	Chow, AMK; Zhou, IY; Fan, SJ; Chan, KWY; Chan, KCW; Wu, EX
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TAURINE CHANGE IN VISUAL CORTEX OF NEONATAL MONOCULAR ENUCLEATED RAT: A PROTON MRS STUDY

A. M. Chow[1,2], I. Y. Zhou[1,2], S. J. Fan[1,2], K. W. Chan[1,2], K. C. Chan[1,2], and E. X. Wu[1,2]

[1]Laboratory of Biomedical Imaging and Signal Processing, The University of Hong Kong, Pokfulam, Hong Kong SAR, China, People's Republic of,
[2]Department of Electrical and Electronic Engineering, The University of Hong Kong, Pokfulam, Hong Kong SAR, China, People's Republic of

INTRODUCTION

Animal models of neonatal monocular enucleation has been used to study developmental mechanisms underlying visual perception, due to its extensive changes and reorganization in various parts of the visual system[1]. It has also been used to investigate the cross-modal changes in the central nervous system caused by early loss of the visual input[2,3]. As a consequence of visual deprivation, experimental evidence suggests that there are neurophysiological changes in the visual cortex[4]. Proton magnetic resonance spectroscopy (^{1}H MRS) has been utilized to provide metabolic distribution in selected volume in brain *in vivo*, revealing the roles of major neurochemicals as markers for neurodegeneration and neuroprotection upon degenerative illness[5]. In this study, we aim to characterize metabolic changes and investigate cortical reorganization in monocular enucleated rat neonates with ^{1}H MRS at 7 T.

METHODS

Animal Preparation: Male Sprague-Dawley rats (N = 4) were prepared. Right monocular enucleation was performed at postnatal day (P) 10 under inhaled isoflurane anaesthesia through an incision in the conjunctiva followed by sectioning of the extraocular muscles and the optic nerve. The eyeball was removed and the empty socket was filled with oxidized regenerated cellulose Surgicel® (Johnson & Johnson). Three weeks after injury, ^{1}H MRS was performed at the visual cortex to all animals. Throughout the experiments, the left eye and the right visual cortex served as the internal control.

MRI: All MR measurements performed on a 7 T Bruker MRI scanner using a 72-mm birdcage transmit-only RF coil with an actively decoupled receive-only quadrature surface coil. Under inhaled isoflurane anaesthesia, the animal was kept warm under circulating water at 37 ºC. T_2-weighted anatomical images were acquired using 2D RARE sequence. For ^{1}H MRS, $0.8 \times 2.8 \times 2.8$ mm^3 voxel was placed over each side of the visual cortex. The volume of interest was maximized to obtain higher signal-to-noise ratios and to cover the gray matter predominantly in the visual cortex, while avoiding the margins of the white matter structures, which were clearly distinguishable in T_2-weighted images underneath the cortex. After first- and second-order localized voxel shimming with field map based shimming technique, 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.

Data Analysis: MR spectra were processed as previously described[6] using the jMRUI software[7],. The raw data were apodized with a 15-Hz Gaussian filter. In addition, the signal of residual water was filtered with Hackel–Lanczos Singular Value Decomposition (HLSVD) algorithm preprocessing with 25 spectral components for modeling. Spectral peaks were assigned in the references of the singlet peak of NAA (CH$_3$-group). Metabolite areas were estimated using the quantitation based on quantum estimation (QUEST) method combined with subtraction approach for background modeling[8]. To reduce systematic variations among studied animals and to accurately 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 remains relatively constant *in vivo*[9]. The numerical time-domain modal functions of 10 metabolites [acetate (Ace), alanine (Ala), aspartate (Asp), N-acetylaspartate (NAA), Cho, Cr, taurine (Tau), glutamate (Glu), lactate (Lac) and myo-inositol (m-Ins)] were used as prior knowledge in QUEST. These metabolite model signals were quantum mechanically simulated in NMR spectra calculation using operators (NMRSCOPE) for the *in vivo* experimental protocol. NAA:Cr, Cho:Cr, Tau:Cr, Glu:Cr, Lac:Cr, and m-Ins:Cr ratios were statistically evaluated. The reliability of metabolite quantitation was assessed using the Cramer-Rao lower bounds (CRLB)[8]. An estimate was considered as relevant when the corresponding bound was found below 25% of the estimate. Wilcoxon matched pairs test was employed between contralateral sides of all measurements with $p < 0.05$ considered as statistically significant.

RESULTS AND DISCUSSIONS

Figure 1 illustrates the voxel placements to the visual cortex, and the typical ^{1}H MRS spectra on each side of the visual cortex for the same animal. Figure 2 shows the estimated metabolite ratios for all the animals studied. It was consistently observed that all animals showed a marked change in Tau signal with respect to Cr signal between the left enucleated visual cortex and the right control visual cortex by 10% ($p < 0.05$). Tau is a sulphur β-amino acid and is elevated in many tissues including the retina, brain, skeletal and cardiac muscles when being excited[10]. Physiological roles of Tau include membrane stabilization, osmoregulation, neuromodulation, regulation of calcium homeostasis, and antioxidation[11]. Previous study also showed that Tau might also act on various cellular processes such as proliferation, differentiation and inhibition of apoptosis[12]. The significant change observed in Tau:Cr ratio may be due to the increased Tau signal in the right control visual cortex, likely caused by the plasticity resulted from recruitment of resources to the remaining left eye for adaptation[13]. Decreased Tau signal in the left enucleated visual cortex, which probably arose from degeneration of left visual cortex in response to the right eye enucleation, may also contribute to such observation. When compared to study of normal neonatal rat brain[14], Tau:Cr ratio in the left enucleated visual cortex was consistent with reported value, while that in the right control visual cortex was slightly higher than the reported value[14]. The increased Tau signal in the right control visual cortex may possibly be a dominating factor for the observation, as the left enucleated visual cortex may be used for somatosensory and auditory function, as observed in earlier studies[2,3,15], and may possess comparable Tau signal as in normal rats. Work is currently underway to further verify the governing factor of this observation through comparison of Tau:Cr ratio of normal rats of same age.

CONCLUSIONS

The experimental results of this study showed that alteration in the metabolism in visual cortex is associated with neonatal monocular enucleation. The change in Tau signal with respect to Cr signal between the left enucleated and the right control visual cortices may possibly be due to the increased Tau signal in the right control visual cortex, likely caused by the plasticity resulted from recruitment of resources to the remaining left eye for adaptation. This may provide insights into the changes in plasticity, as well as the adaptive and compensatory modifications within the brain following neonatal monocular enucleation.

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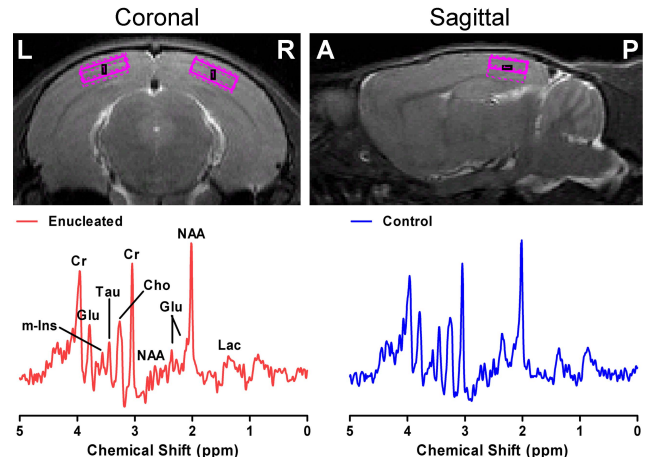
FIG. 1 (Top row) Illustration of the voxel placements (solid-line boxes) in the enucleated (L) and control (R) rat visual cortex for ^{1}H MRS. (Bottom row) Typical ^{1}H MRS spectra on each side of the visual cortex 3 weeks after right monocular enucleation at P10 for the same animal. Note the higher Tau signal in the right control visual cortex then in the left enucleated visual cortex. (L: left; R: right; A: anterior; P: posterior)
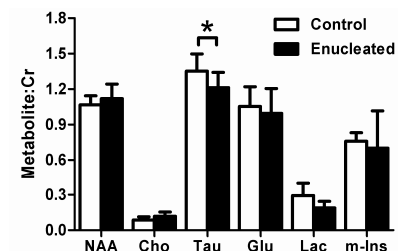

FIG. 2 Metabolite ratios at each sides of the visual cortex 3 weeks after monocular enucleation. Wilcoxon matched pairs test was performed with * for $p < 0.05$.