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METABOLIC ALTERATIONS IN THE CORTEX OF A MOUSE MODEL WITH GLUTATHIONE DEFICIT – RELEVANCE TO SCHIZOPHRENIA
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Background: Glutathione (GSH) is a major redox regulator and antioxidant and is decreased in cerebrospinal fluid and prefrontal cortex of schizophrenia patients [Do et al. (2000) Eur J Neurosci 12:3721]. The genes of the key GSH-synthesizing enzyme, glutamate-cysteine ligase catalytic (GCLC) and modifier (GCLM) subunits, are associated with schizophrenia, suggesting that the deficit in GSH synthesis is of genetic origin [Gysin et al. (2007) PNAS 104:16621]. GCLM knock-out (KO) mice, which display an 80% decrease in brain GSH levels, have abnormal brain morphology and function [Do et al. (2009) Curr Opin Neurobiol 19:220]. Developmental redox deregulation by impaired GSH synthesis and environmental risk factors generating oxidative stress may have a central role in schizophrenia. Here, we used GCLM KO mice to investigate the impact of a genetically dysregulated redox system on the neurochemical profile of the developing brain.

Methods: The neurochemical profile of the anterior and posterior cortical areas of male and female GCLM KO and wild-type mice was determined by in vivo 1H NMR spectroscopy on postnatal days 10, 20, 30, 60 and 90, under 1 to 1.5% isoflurane anesthesia. Localised 1H NMR spectroscopy was performed on a 14.1 T, 26 cm VNMRS spectrometer (Varian, Magnex) using a home-built 8 mm diameter quadrature surface coil (used both for RF excitation and signal reception). Spectra were acquired using SPECIAL with TE of 2.8 ms and TR of 4 s from VOIs placed in anterior or posterior regions of the cortex [Mlynářík et al. (2006) MRM 56:965]. LCModel analysis allowed in vivo quantification of a neurochemical profile composed of 18 metabolites.

Results: GCLM KO mice displayed nearly undetectable GSH levels as compared to WT mice, demonstrating their drastic redox deregulation. Depletion of GSH triggered alteration of metabolites related to its synthesis, namely increase of glycine and glutamate levels during development (P20 and P30). Concentrations of glutamine and aspartate that are produced from glutamate were also increased in GCLM KO animals relative to WT. In addition, GCLM KO mice also showed higher levels of N-acetylaspartate that originates from the acetylation of aspartate. These metabolites are particularly implicated in neurotransmission processes and in mitochondrial oxidative metabolism. Their increase may indicate impaired mitochondrial metabolism with concomitant accumulation of lactate in the adult mice (P60 and P90). In addition, the GSH depletion triggers reduction of GABA concentration in anterior cortex of the P60 mice, which is in accordance with known impairment of GABAergic interneurons in that area. Changes were generally more pronounced in males than in females at P60, which is consistent with earlier disease onset in male patients.

Discussion: In conclusion, the observed metabolic alterations in the cortex of a mouse model of redox deregulation suggest impaired mitochondrial metabolism and altered neurotransmission. The results also highlight the age between P20 and P30 as a sensitive period during the development for these alterations.

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THE DIFFERENCES OF 2ND TO 4TH DIGIT LENGTH RATIO BETWEEN SCHIZOPHRENIA PATIENTS AND NORMAL CONTROLS
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Background: The ratio of 2nd to 4th finger(2D:4D) is known to be an indirect measure for prenatal sex hormone exposure. Sex hormone influences the brain development through structural and epigenetic modifications of neuron. We examined 2D:4D in schizophrenia patients and normal controls to investigate the relationship between prenatal sex hormone exposure and genesis of schizophrenia.

Methods: The subjects were 187 schizophrenia patients(male:94, female:93), and 190 normal controls(male:95, female:95). Handedness was measured with Edinburgh Handedness Inventory. Age of onset was examined by clinical records or questioning directly to the patients. The length of digit was measured by vernier caliper. T-test, ANOVA and ANCOVA were performed to analyze the data.

Results: There were no significant differences of the 2D:4D between schizophrenia patients and normal controls. Also, there was no significant correlation between 2D:4D and the age of onset. Among normal controls, 2D:4D was significantly higher in females than in males (F=4.937,p=.027). But, there were no significant sex differences of 2D:4D among schizophrenia patients (F=3.429,p=.066).

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