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ORIGINAL ARTICLE

Metabolomic profiling on rat brain of prenatal malnutrition: implicated for oxidative stress and schizophrenia

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Abstract

Schizophrenia is a kind of neurodevelopmental disease. Epidemiological data associates schizophrenia with prenatal exposure to famine. Relevant prenatal protein deprivation (PPD) rodent models support this result by observing decreasing prepulse inhibition, altered hippocampal morphology and impaired memory in offspring. All these abnormalities are highly consistent with the pathophysiology of schizophrenia. We developed a prenatal famine rat model by restricting daily diet of the pregnant rat to 50% of low protein diet. A metabolomics study of prefrontal cortex was performed to integrate GC-TOFMS and UPLC-QTOFMS. Thirteen controls and thirteen famine offspring were used to differentiate in PLS-DA (partial least squares-discriminate analysis) model. Furthermore, metabolic pathways and diseases were enriched via KEGG and HMDB databases, respectively. A total of 67 important metabolites were screened out according to the multivariate analysis. Schizophrenia was the most statistical significant disease ($P = 0.0016$) in our famine model. These metabolites were enriched in key metabolic pathways related to energy metabolism and glutamate metabolism. Based on these important metabolites, further discussion speculated famine group was characterized by higher level of oxidized damage compared to control group. We proposed that oxidative stress might be the pathogenesis of prenatal undernutrition which is induced schizophrenia.

Keywords Schizophrenia · Prenatal malnutrition · Metabolic

Introduction

Schizophrenia (SCZ) is considered as a neurodevelopmental disease which may partly stem from early adverse events(Rapoport et al. 2005). Epidemiological studies of Dutch Hunger Winter and the 1959–1961 Chinese famine revealed that fetuses exposed to famine had a two-fold increase in the susceptibility of SCZ as adults (St Clair et al. 2005; Susser et al. 1996; Xu et al. 2009). Magnetic resonance brain imaging of patients with schizophrenia who suffered Dutch Hunger Winer during the first trimester of

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gestation showed decreased intracranial volume, which may induce brain abnormalities(Hulshoff Pol et al. 2000). In addition to prenatal malnutrition, other prenatal or neonatal factors, including viral infection (Brown 2006), vitamin D deficiency (McGrath et al. 2004), maternal stress (van Os and Selten 1998) and obstetric complications (Cannon et al. 2002), were also associated with an increasing risk of schizophrenia. Evidence from the postmortem brain showed schizophrenic patient with abnormal neuronal migration, bolstering the hypothesis that the development of schizophrenia could trace back to individual early life (Akbarian et al. 1996).

There is little question that nutrition is the greatest environmental influence on the development of fetal brain. All nutrients to a certain extent have influence on brain maturation, especially protein. Amino acids are essential for the growth of brain. Various of them are the precursors of neurotransmitters or themselves are neurotransmitters. Also, they form enzymes and peptide hormones, which can result in a broad distortion on central nervous system. Lesions from prenatal protein deprivation (PPD) model (6% protein diet throughout the whole gestation period) principally involved distortions of neuron ratios, altered neuron migration, disorders of lamination phase of cortical organization, neurotransmitter imbalance, axonal and dendritic pruning and synaptic elimination. Offspring of PPD dams exhibited impaired learning and memory (Tonkiss and Galler 1990; Tonkiss et al. 1990), along with alterations in hippocampal morphology (Morgane et al. 2002) and dysfunction in neurotransmitter receptor systems (Chen et al. 1997). Furthermore, these animals also displayed decreasing prepulse inhibition and increasing NMDA receptor binding in the striatum and hippocampus (Palmer et al. 2004). All these abnormalities are highly consistent with the pathophysiology of schizophrenia. Prenatal malnutrition could be proposed as a potential risk factor for the development of schizophrenia. Therefore, PPD model is often used to develop schizophrenia, which can simulate schizophrenia-like phenotypes.

Based on the PPD model, we developed a prenatal famine rat model by restricting daily diet of pregnant rat to 50% of low protein diet (6% protein), reflecting both protein and energy deficiency which were likely to prevail in famine period. Transcriptomic and epigenetic profiling data from the hippocampus and prefrontal cortex (PFC) showed reprogramming postnatal brain gene expression. In PFC, differential expressed genes were focus on neurotransmitters and olfactory function, while in hippocampus, differences were related to synaptic function and transcription regulation (Xu et al. 2014). We also observed decreasing level of tumor necrosis factor alpha (TNFA) and Interleukin 6 (IL6) in fetal brain, implicating that pro-inflammatory factors may increase the risk of schizophrenia (Shen et al. 2008).

The present study aimed to explore the metabolomic profiling of PFC in a prenatal famine rat model. Metabolomics is defined as quantitative assessment of global small molecule metabolites in living systems. Metabonomic-based diagnostics detects the changes in the level of metabolites which reflect a stress situation such as disease (Spratlin et al. 2009). A combined technique was applied in this experiment: gas chromatography-time-of flight mass spectroscopy (GC-TOFMS) and ultra-performance liquid chromatography-quadrupole time-of light mass spectrometry (UPLC-QTOFMS). We intended to gain important metabolic variation, which can be better to understand the pathogenesis of prenatal famine induced schizophrenia.

Experimental procedure

Animal model

16 female Sprague Dawley (SD) rats were obtained from Shanghai Laboratory Animal Center (Chinese Academy of sciences, Shanghai), and housed under a controlled condition of 23 ± 3 °C and 35 ± 5% humidity with a 12 h dark/12 h light cycle. After a two-week accommodation period, they were randomly divided into two groups after the presence of vaginal plug. The control group (7 dams) was given a standard rodent diet (20% protein, Research Diets, Inc. D12450B), whereas the "famine" group (RLP50 group, 9 dams) was assigned to receive the low protein diet with 50% daily intake throughout pregnancy (6% protein, Research Diets, Inc. D06022301). All rats were given water ad libitum. At birth, all dams were switched to the standard rat chow. Litter size was adjusted to ten pups per mother. After 4 weeks, pups were weaned and placed to new cages with same-sex littermates. Rats were anesthetized and killed when they were raised to be 10 weeks old. All the experimental procedures and protocols were complied with the National Institute of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee at Experimental Animal Center in Shanghai Jiao Tong University.

Sample preparation

PFC samples from offspring of both control ($n = 13$) and RLP50 (n = 13) rats were isolated and stored in liquid nitrogen. Each sample was divided into two parts (50 mg ± 2 mg per) for different experimental platforms.

UPLC-MS profiling

Each piece of tissue was placed into a 5 ml tube with 250 μL mixture solvent (chloroform: methanol: water = 1:2.5:1), ground for 2 min and vortex-mixed for 1 min. After keeping in −20 °C for 20 min, the tube was centrifuged at 12,000 rpm for 10 min at 4 °C and then the supernatant was transferred

into a 1.5 ml tube. Residue was added with 250 μL ethanol and then followed the same step, supernatant was mixed with the prior one in the 1.5 mL tube. The supernatant continued to centrifuge at 12,000 rpm for 10 min at 4 °C. Finally, 40 μL of the supernatant was transferred into a vial with 20 μL 0.3 mg/mL 2-Chloro-L-phenylalanine and 40 μL water. Quality control was prepared in this experiment by two different methods. One is to pool and mix the same volume of each sample, the other is to set internal standard (2-Chloro-L-phenylalanine). Samples were injected into a Waters ACQUITY ultra-performance liquid chromatograph coupled to a Micromass Q-Tof micro™ system (Waters Corporation, Milfold, MA, USA). A 100 nm × 2.1 mm ACQUITY UPLC BEH C18 1.7 μM analytical column was used to separate metabolites. The mobile phase consisted of 0.1% formic acid in water (A) and acetonitrile (B). Linear gradient was optimized as follows (flow rate, 0.4 ml/min): 0–1 min (1–20% B), 1–3 min (20–70% B), 3–8 min (70–85% B), 8–9 min (85–100% B), 9–10.5 min (100% B), 10.5–11.3 min (100–5% B), 11.3–11.8 min (5–1%B), 11.8–13 .3 min (1% B). Column and sample manager temperature were set at 40 °C and 4 °C, respectively.

Mass spectrometry was performed in positive and negative electrospray ionization modes based on Zevo G1 QTOFMS (Waters Corp., Manchester, UK). Optimized conditions were as follows: In negative ion (ESI−) mode, capillary voltage 2.5 kV, sample cone voltage 40 V, and source temperature 110 °C were optimized; In positive ion (ESI+) mode, capillary voltage 3.2 kV, sample cone voltage 35 V, source temperature 100 °C were optimized. Lock Mass calibrations at *m/z* 556.2771 in positive mode and *m/z* 554.2615 in negative mode were used for complete analysis.

GC-MS profiling

Preliminary procedure was the same as UPLC-MS. After ground twice, 300 μL of the supernatant which was collected in the 1.5 mL vial was added with 10 μL 1 mg/mL heptadecanoic acid and 0.3 mg/mL 2-Chloro-D-phenylalanine. Then it was transferred to a glass tube then evaporated to dryness under a stream of nitrogen gas. The dried residue was reconstituted in 80 μL of methylhydroxylamine hydrochloride(15 mg/mL, dissolved in pyridine) for 90 min at 37 °C and catalyzed for 1 h at 70 °C with 80 μL of BSTFA (containing 1% trimethylchlorosilane). After being vortexed for 1 min and being incubated at room temperature for another hour, the final mixture was subjected to GC/MS analysis based on GC-TOFMS platform (Pegasus HT, Leco Corp., St. Joseph, MI; electron ionization (EI) mode). Similar to the UPLC-QTOFMS analysis, quality control was based on mixed samples and internal standard (2-Chloro-D-phenylalanine and heptadecanoic acid). A DB-5MS (5% Diphenyl cross-linked 95% dimethylpolysiloxane) capillary column (30 m × 250 μm I.D., 0.25 μm film thickness) separated metabolites. Aliquot (1 μL) of the derivatized solution was injected. Optimized condition as follows (constant flow rate, 1 mL/min): 80 °C (2 min), 80–180 °C (10 °C/min), 180–230 °C (6 °C/min) 230–295 °C (40 °C/min), and 295 °C (8 min). Measurements were obtained using 70 eV electron impact ionization and *m/z* 40–600 full scan mode.

Statistical analysis

The UPLC-QTOFMS spectral data were obtained from MassLynx software (Waters). Parameters including retention time, mass range, mass tolerance, intensity threshold, retention time tolerance and noise elimination level, were set by MarkerLynx Applications Manager Version 4.1 (Waters). A list of the ion intensities of the detected peaks with corresponding retention time and mass data was generated. Then each peak of ion intensities was normalized, within each sample, to the sum of the peak intensities in that sample. Similar to the UPLC-QTOFMS data preprocessing, GC-TOFMS data were also extracted, peak-identified and corrected. Resulting multi-dimensional data were further removed peaks with missing value more than 60% samples and exported to multivariate statistical analysis by using SIMCA-P 12.0.1+ (Umetrics, Umea, Sweden) software for PLS-DA (Partial Least Square Discriminant Analysis).

PLS-DA is a supervised analysis model in metabolomics, which can obtain better separating effect. The quality of the model is evaluated by Q^2 and R^2Y, R^2Y represents how well the model fit the Y data, whereas Q^2 is an estimate of how well the model predicts the Y. Another important variable called VIP (Variable importance in the projection) was created to detect potential biomarkers on the basis of the threshold VIP >1.

Metabolite identification was performed on HMDB (Human Metabolome Database (http://www.hmdb.ca/) integrated with other metabonomic database, such as METLIN (http://metlin.scripps.edu). Based on these differential metabolites, related KEGG pathways and HMDB diseases were gathered on the Metabolites Biological Role (MBRole) platform. *P* value was two tailed and calculated with the cumulative hypergeometric distribution by comparing the number of compounds. $P < 0.05$ was considered statistically significant (Lopez-Ibanez et al. 2016) .

Results

PFC metabolic profiling analysis

We obtained 354 spectral features from GC-TOF-MS, 2081 spectral features from UPLC-Q-TOF-MS ES- and 5856 spectral features from UPLC-Q-TOF-MS ES+. A total of 233 metabolites could be annotated. In this work, both PCA and PLS-

DA were carried out to do multivariate analysis. However, PCA failed to discriminate between RLP50 rats and normal rats on the scores plot. While in the PLS-DA model (Fig. 1), RLP50 group revealed a distinct separation from the control group, using three principal components with satisfactory modeling and predictive abilities ($R^2Y = 0.921$, $Q^2 = 0.536$).

Disturbance of metabolic pathways

Metabolites that significantly contributed to the clustering of PLS-DA model were selected for further study according to the VIP value (VIP > 1). A total of 67 important metabolites were screened out in Supplemental Table 1. These metabolites enriched in key metabolic pathways (Supplemental Table 2) related to energy metabolism and glutamate metabolism. Furthermore, schizophrenia was the most statistical significant disease according to the HMDB database ($P = 0.0016$) (Table 1).

Table 1 Significant diseases enrichment based on HMDB database

Disease	*P* value*	Number of Metabolites
Schizophrenia	0.0016	6[#]
Anoxia	0.0027	4
Leukemia	0.0028	6
Epilepsy	0.0028	6
Tuberculous meningitis	0.0056	2
Uremia	0.0056	2
Gestational diabetes mellitus (GDM)	0.0161	2
Heart failure	0.0333	3
Meningitis	0.0436	3

**P* value from Fisher exact test

[#] HMDB00812(N-Acetyl-aspartic acid); HMDB00158 (Tyrosine); HMDB00148 (Glutamic acid); HMDB00161 (α-alanine); HMDB00251 (Taurine); HMDB00168 (Asparagine)

Discussion

Our study found a panel of important metabolites based on the PLS-DA model. In fact, univariate analysis (student's t test) was also used to evaluate these potential biomarkers, but only three metabolites (fucose, lactate and NAA) presented statistical significance. Considering the number of samples was small, following discussion is based on the result of multivariate analysis. Schematic overview of potential biomarkers involved in key metabolic pathways was showed in Fig. 2, which helped us to understand the mechanism of prenatal malnutrition induced mental disorder.

The thrifty phenotype hypothesis proposed that early nutritional experience was associated with degenerative risks, like the development of type 2 diabetes. Reduced capacity for insulin secretion could make individual adapt to adverse environment (Hales and Barker 2001). Result from our micro-PET scanning of ^{18}F-Fludeoxyglucose on this famine model supported this hypothesis, with a decreasing glucose utilization in prefrontal cortex of RLP50 group (data unpublished).

Glucose is the major fuel for brain metabolism. Astrocytes and neurons consume large proportion of brain energy. When glucose enters cells through glucose transporters, it will be phosphorylated to produce glucose-6-phosphate. Glucose-6-phosphate has three different routes, choosing glycolysis to lactate production, or choosing pentose phosphate pathway (PPP) to provide more reductants, or choosing glycogenesis to store energy (only in astrocytes). According to the astrocyte-neuron lactate shuttle (ANLS) model (Kasischke et al. 2004), astrocytes displayed lower rates of oxidative reaction compared to neurons but presented a higher glycolytic

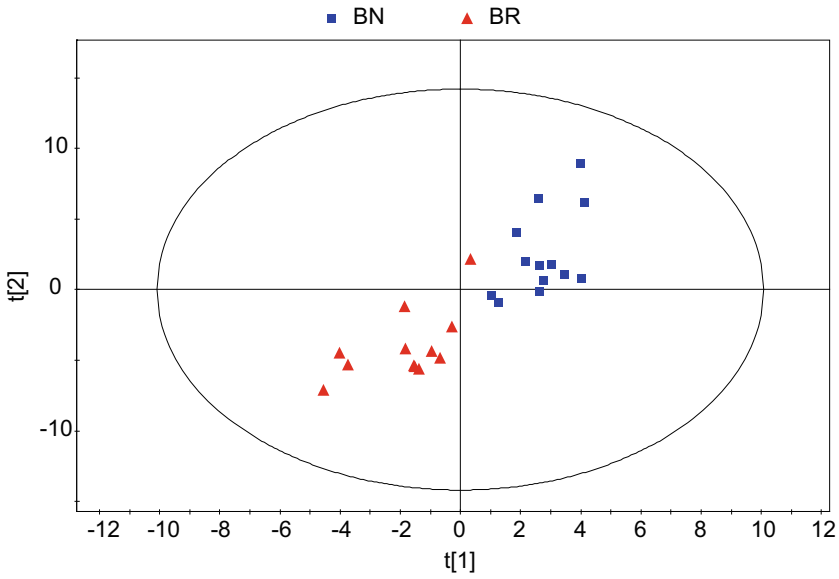

Fig. 1 PLS-DA score plot discriminates the PFC from RLP50 and control rats: X axis is component 1 labeled t[1]. Y axis is component 2 labeled t[2]. Score scatter plots (t1/t2) show all samples are plotted in the global matrix, which display an obvious distinction between two groups. *Abbreviations*: **BN**: normal sample; **BR**: RLP50 sample

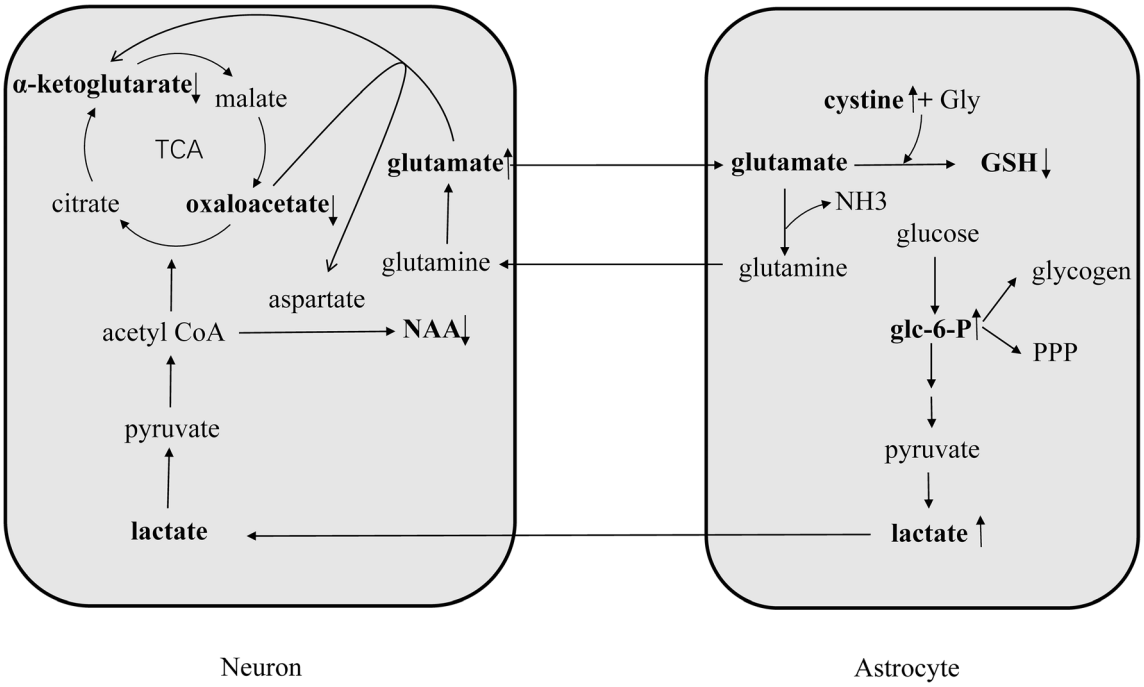

Fig. 2 Simplified pathway involved in energy metabolism and glutamate metabolism. *Down arrow indicates down-regulated in RLP50 group compare with control group, upward arrow indicates up-regulated metabolites in RLP50 group

rate, implicated for the compartmentalization of glucose metabolism between astrocytes and neurons (Itoh et al. 2003). Lactate is supposed to be released from astrocytes and function as fuel for neighboring neurons (Figley 2011). In this study, we found increasing concentration of glucose-6-phosphate (FC = 1.22) and lactate (FC = 1.41) in RLP50 rat brain, which meant glycolytic flux enhanced in astrocytes. Correspondingly, PPP and glycogenesis pathways might be weakened. PPP produces considerable NADPH, which is important for the maintenance of cellular antioxidant potential. Declined level of glutathione (GSH) (FC = 0.71) accompanied by elevated oxidized cysteine (cystine) (FC = 2.47) were observed in our result and represented an oxidized environment in brain. GSH is an important electron donor in the detoxification of reactive oxygen species (ROS). High rate of oxidative pressure generates more ROS, without more GSH to eliminate, brain is vulnerable to damage (Yao and Reddy 2011). Inhibitory amino acid taurine was also correlated with oxidative stress (Saransaari and Oja 2000). In a post-mortem brain of schizophrenia metabolomics study, taurine was detected with an elevated level (Prabakaran et al. 2004), which is consistent with our data (FC = 1.22).

Reduced oxaloacetate (FC = 0.69) and α-ketoglutarate (FC = 0.65) indicates an altered TCA cycle. The TCA cycle is implicated in ATP production. Decreased levels of intermediate metabolites may indicate the hypofunction of mitochondria. *N*-acetylaspartate (NAA) is highly concentrated in neurons. After traumatic brain injury, brain NAA was found to be reduced, paralleled by a loss of ATP (Vagnozzi et al. 2007). Acetyl CoA and aspartate synthesize NAA, because of the changes of TCA cycle, NAA was reduced (FC = 0.63). This, in turn, implied to a certain degree of brain damage for the prenatal undernutrition. Glutamate is the major excitatory transmitter in central nervous system. Glutamate-glutamine cycle begins with the release of glutamate from neurons, then glutamate is transported to astrocytes, where it is converted to glutamine. Glutamine is released back to neurons and regenerated to glutamate via phosphate-dependent glutaminase (Daikhin and Yudkoff 2000). Maintenance of glutamate pool is important for the normal neuron activity specially because glutamate also provides additional energy to the TCA cycle. Glutamatergic dysfunction has been showed in schizophrenia patients (van Elst et al. 2005). Aspartate aminotransferase converts oxaloacetate and glutamate to aspartate and α-ketoglutarate (Schousboe et al. 2014). Decreased level of oxaloacetate repressed this reaction, although the concentration of glutamate was high (FC = 1.48). Glutamate is released at the synapse and taken up by astrocytes via excitatory amino acid transporters together with 3 Na^+ ions. The extrusion of Na^+ needs the assistance of Na^+/K^+ ATPase, consuming ATP (Belanger et al. 2011). Due to the deficiency of ATP, absorption of glutamate in astrocytes was repressed, resulting in a reduced GSH synthesis.

Brain is particularly susceptible to oxidative damage. Many psychiatry disorders including schizophrenia display a common feature of oxidative injury (Ng et al. 2008). GSH as the most abundant antioxidant molecule in the brain, can be used to clean ROS. If the equilibrium is broken, excess ROS

will injure the mitochondria. With a low rate of TCA cycle for the mitochondrial dysfunction, the brain metabolomics profiling might be reprogrammed.

In conclusion, a metabolomics study in PFC samples of prenatal famine was performed integrating GC-TOFMS and UPLC-QTOFMS. PLS-DA as a multivariate method was used to differentiate RLP50 rats from normal rats and select features from all metabolites based on VIP values. Combined with KEGG and HMDB databases, we found that these potential biomarkers were involved in some key metabolic pathway, implicated for schizophrenia. Prenatal undernutrition might hamper the citric acid cycle, as a result of the elevated of oxidative stress. We speculate that oxidative stress might be the pathogenesis of prenatal undernutrition induced schizophrenia.

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Author's contribution HG and ZXZ conceptualized this experiment. LX analyzed data and provided ideas for this manuscript. XF wrote this paper. Others participated in the course of rats feeding.

Compliance with ethical standards All the experimental procedures and protocols were complied with the National Institute of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee at Experimental Animal Center in Shanghai Jiao Tong University.

Conflict of interest All authors have no conflicts of interest in this work.

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