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BRAIN RESEARCH

Research Report

Differential expression profiling of the synaptosome proteome in a rat model of antipsychotic resistance

Baohu Ji[a,b], Zhao Zhang[a,b], Ming Zhang[a,b], Hui Zhu[a,b], Kejun Zhou[a,b], Jinglei Yang[a,b], Yang Li[a,b], Liya Sun[a,b], Guoyin Feng [c], Yujiong Wang[d], Lin He[a,b,e,*], Chunling Wan[a,b,*]

[a]Bio-X Center, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Shanghai Jiao Tong University, Shanghai, China
[b]Institute for Nutritional Sciences, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Shanghai, China
[c]Shanghai Institute of Mental Health, Shanghai, China
[d]School of Life Science, Ningxia University, Yinchuan, China
[e]Institutes of Biomedical Sciences, Fudan University, Shanghai, China

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ABSTRACT

This study used a comparative proteomics approach to identify the effects of the antipsychotic drugs, Chlorpromazine (CPZ), Clozapine (CLZ), and Quetiapine (QTP) on the synaptosomal protein of the cerebral cortex of Sprague–Dawley (SD) rats. The multivariate statistical test partial least squares-discriminant analysis (PLS-DA) was applied to build the models for screening out the variable important plot (VIP). The PLS-DA models were able to distinguish each drug treatment group and the control group; more importantly, the univariate differentially expressed protein spots were capable of being verified by the VIP of the models. The interrelationships among the identified proteins were analyzed using Pearson's correlation analysis and pathway analysis. Through the synaptosome proteome experiments, we established that the energy production of the mitochondrial function and 'Glycolysis/Gluconeogenesis' were involved in the response to antipsychotic medications. Furthermore, the G protein-coupled signal transduction system was also inhibited by antipsychotic medications. The result of our study should contribute to the understanding of the effects of antipsychotic drugs on synaptic function.

1. Introduction

An increasing number of studies have suggested that synaptic function may be altered in the cerebral cortex of schizophrenic patients, which indicates that synapse might play an important role in schizophrenia (SCZ). Synapse is essential for neurotransmission, and provides the communication between neurons in the central nervous system. Several etiologic theories suggest that the neuropathology of SCZ largely lies in the cerebral cortex, involving dopaminergic, glutamatergic, neurodevelopmental and synaptic alterations (Vawter et al., 2002). These hypotheses are supported by examples of abnormalities in the morphology and distribution of certain cortical neurons (Spencer and McCarley, 2006), and of expression abnormalities of synapse-related genes in the cerebral cortex of schizophrenic patients, which suggests that synaptic pathology is present in SCZ and points to synaptic abnormality as a feature of SCZ (Eastwood et al., 1995).

* *Corresponding authors*. Bio-X Center, Shanghai Jiao Tong University, 1954 Huashan Road, Shanghai, 200030, China. Fax: +86 21 62822491.
E-mail addresses: helinhelin@gmail.com (L. He), clwan@sjtu.edu.cn (C. Wan).

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Antipsychotic drugs remain the current standard of care for the clinical treatment of SCZ (Snyder and Murphy, 2008). Understanding the mechanism of antipsychotic drugs, and identifying new targets and new drugs are the most important challenges facing the clinical treatment of SCZ. In this study, we used two dimensional electrophoresis-mass spectrometry (2DE-MS) to assess expression changes of synaptosomal proteins from the cerebral cortex of SD rats following a 34 day treatment with typical antipsychotics (CPZ) and atypical antipsychotics (CLZ and QTP) compared to one control group. Our goal was to find some differentially expressed synaptosomal proteins to elucidate variations in the response of SD rats and thereby shed light on the response of schizophrenic patients to these antipsychotics. This should give some broader insight into the potential relationship between synapse and antipsychotic drugs and provide further understanding of their curative and side effects.

2. Results

2.1. *Comparative proteomics analysis and MS*

A total of 24 2DE gels (CPZ: CLZ: QTP: control = 6:6:6:6) (Fig. 1) of synaptosomal proteins were obtained. After amendment, each gel had about 850 protein spots. 210 of these spots were analyzed and 17 protein spots showed univariate statistically significant changes in quantity (Table 1), and 12 of them were successfully identified using MS (Table 2.).

2.2. *PLS-DA and MS*

The multivariate statistical approach, PLS-DA, was applied to assess the data of synaptosomal proteome of the cerebral cortex of SD rats with antipsychotic medications. Four groups were generally separated from each other in a1 model (Fig. 2, a1) which was built using all 210 protein spots, a reflection of their different protein profiling. The b1 model (Fig. 2, b1) constructed from 17 univariate differential protein spots was not able to separate the CPZ group (1 in Fig. 2, b1) and CLZ group (2 in Fig. 2, b1). Both these models had poor predictive ability (Q^2) (Fig. 2, a2 and b2), which implied that neither the totality of protein spots nor univariate differential protein spots were appropriate for building the PLS-DA model, at least in the context of our data. We therefore built the PLS-DA model using 210 protein spots between each treatment group and the control group. With this model, the treatment group could be separate from the control group (Fig. 2, c1 for CPZ, d1 for CLZ, and e1 for QTP), although, the Q^2 of these models were still not adequate (Fig. 2, c2 for c1, d2 for d1, and e2 for e1). We then selected only the top 15 protein spots from each model to re-build the PLS-DA model, and found that the three new models (Fig. 2, c3 and c4 for CPZ, d3 and d4 for CLZ, e3 and e4

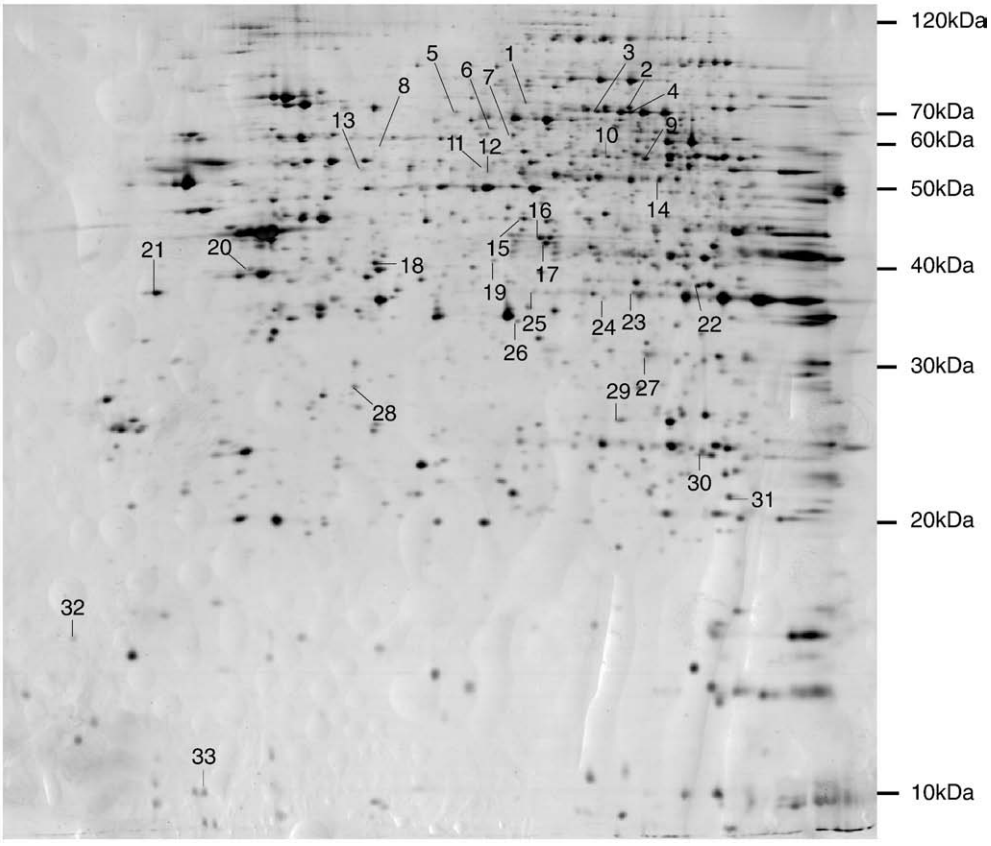

Fig. 1 – Representative 2DE gels of synaptosomal proteins. The serial numbers of the protein spots in the silver stained gel correspond to the significant proteins identified by univariate and multivariate statistical tests.