Journal of Psychiatry

Zhiguo et al., J Psychiatry 2017, 20:1
DOI: 10.4172/2378-5756.1000396

Research Article OMICS International

The GC/TOFMS based Serum Metabolomics in Rats with Depression-like Behavior after Exposure and Re-exposure to Chronic Unpredictable Mild Stress

Zhiguo Li[1,2], Shuguang Yang[1], Changqiang Zhu[1], Jianhua Chen[3], Xinghua Ding[1], Yong Liu[1], Liang Jiao[2], Fangting Dong[3]* and Shaojun Liu[1]*

[1]*State Key Laboratory of Proteomics, Department of Neurobiology, Institute of Basic Medical Sciences, Beijing, China*
[2]*Medical Experiment Center of Hebei United University, Hebei, China*
[3]*National Center of Biomedical Analysis, Beijing, China*

Abstract

The Recurrent depression leads to disability and high health care costs. Identification of biomarkers for diagnosis recurrent depression will be helpful to predict and prevent the recurrence of depression. Sprague-Dawley rats were exposed and re-exposed to chronic unpredicted mild stress to mimic onset and recurrent depression. Rat's serum was collected and analyzed by gas chromatography/time-of-flight mass spectrometry. Palmitinic acid and oleinic acid were found decreased in the onset depression and alanine, 6-Desoxy-Mannopyranose, oleinic acid, stearic acid, cholesterol was found decreased in recurrent depression. These data shows rats suffer recurrent depression have much more serious metabolic disturbance than onset depression, and they may provide valuable information for the potential biomarkers of distinguish onset and recurrent depression.

Keywords: Depression; Depressive disorder; Pathophysiology; Chromatography; Biochemical

Abbreviations: CUMS: Chronic Unpredictable Mild Stress; SD Rats: Sprague-Dawley Rats; GC/TOF-MS: Gas Chromatography/Time-of-Flight Mass Spectrometry; MDD: Major Depressive Disorder; TICs: Total Ion Chromatograms; PLS-DA: Partial Least Squares Discriminant Analysis

Introduction

Major depressive disorder (MDD) is ranked the second on a list of 15 major diseases in terms of burden in 2030 [1]. The major burden of MDD to disability and health care costs is largely due to its highly recurrent nature [2,3]. At least 50% of those who are recovered from the first episode of depression will have one or more additional episodes in their lifetime, and approximately 80% of those with a history of two episodes will have another recurrence [4]. Once the first episode occurs, recurrent episodes will usually begin within five years of the initial episode; on average, individuals with a history of depression will have five to nine separate depressive episodes in their lifetime [4]. Due to the highly recurrent nature of depression, it would be fascinated to identify biomarkers for recurrent depression, so we can predict and prevent the recurrence of depression.

Recently, a few literatures reported a recurrence model of depression [5]. The model is created based on the CUMS (chronic unpredictable mild stress) model, which is the exposure of animals to several random mild stressors. The CUMS model can mimic several human depressive symptoms, and has good face validity, construct validity, predictive validity. This makes it is one of the most commonly used depression models which is suitable to study pathophysiology of depression [6]. The recurrent depression model is developed by exposing rats to CUMS again after they are recovered from the first CUMS-induced depression, and then recurrence of depression is simulated [5].

Metabolomics can provide valuable information on biochemical perturbations, and is regarded as a complementary approach to genomics and proteomics approaches [7-9]. It can be used as a versatile tool for the discovery of molecular biomarkers in many areas, such as diagnosing or prognosticating clinical diseases, exploring the potential mechanisms for diverse diseases, and assessing the therapeutic effects of drugs as well [10,11]. Gas chromatography/time-of-flight mass spectrometry (GC/TOF-MS) is one of the most important metabolomics tools because of its high resolution, selectivity and easily accessible NIST database [12] and is used to sensitively determine and quantify the complex samples such as plasma and urine [13]. Recently, including GC/TOF-MS method, several metabolomics studies were successfully carried out on depression. Several differentially expressed metabolites were found in the plasma of elder adults with depression [14], CUMS rat brain tissues [15], plasma [10], urine [16,17] etc. To our knowledge, however, there is little evidence about metabolomics change in recurrent depression. Therefore, through investigate the dynamic changes of metabolites in the plasma of onset and recurrent depression models, will increase our knowledge about metabolic changes and identify potential biomarkers of onset and recurrent depression.

Materials and Methods

Animals

Male Sprague-Dawley (SD) rats, weighing 200 ± 20 g, were purchased from the Experimental Animal Center of Military Medical Sciences Academy, and were kept under standard conditions (24 ± 1°C, 45 ± 15% relative humidity, 12-12 h light-darkness shift, free access to water and food). All the experimental procedures were approved by the laboratory animal welfare and ethics committee of our institute, which is consistent with the guidelines from Ministry of Science and Technology of the People's Republic of China.

***Corresponding author:** Fangting Dong, National Center of Biomedical Analysis, National Center of Biomedical Analysis, 27 Taiping Road, Beijing 100850, China, Tel: +86-10-68186281; Fax: +86-10-68186281; E-mail: dft@proteomics.cn

Prof. Shaojun Liu, State Key Laboratory of Proteomics, Department of Neurobiology, Institute of Basic Medical Sciences, Institute of Basic Medical Sciences, 27 Taiping Road, Beijing 100850, China, Tel:+86-10-66931304; Fax: +86-10-68213039; E-mail: liusj@nic.bmi.ac.cn

Received December 21, 2016; **Accepted** January 16, 2017; **Published** January 23, 2017

Citation: Li Z, Yang S, Zhu C, Chen J, Ding X, et al. (2017) The GC/TOFMS based Serum Metabolomics in Rats with Depression-like Behavior after Exposure and Re-exposure to Chronic Unpredictable Mild Stress. J Psychiatry 20: 396 doi:10.4172/2378-5756.1000396

Experimental design

After one week adaptation, the body weight, sucrose preference test, open-field test and forced swimming test were measured in all rats. The unqualified rats were discarded, and the remaining rats were randomly assigned to control and depression group for further research. The control rats were housed without disturbing except for necessary procedures such as weighting or cage cleaning. The depression group rats were treated with CUMS regime. Behaviors tests (sucrose preference, locomotor activity and forced swimming test) of rats in both group were recorded and were used to monitor whether the rats show depression-like behavior. 6 rats of control and depression were randomly selected and sacrificed. Remaining control group were housed without disturbing except for give vehicle (physiological saline) for a week as control of recurrent depression group (REDEPR CONT). And remaining depression rats were recovered by fluoxetine treatment. After a week of drug washout period, behavioral tests were performed to determine whether they were recovered. The recovered rats were suffered with the second CUMS regime and their behaviors were recorded again. 6 rats of recurrent depression (REDEPR) and recurrent control groups were randomly selected and sacrificed. The details of experimental procedure are listed in Figure 1.

Procedure for CUMS generation: CUMS generation was slightly modified from the procedure described by Katz [18] and Willner [19]. Rats were subjected to various mild stressors for 4 weeks: swimming in 4°C water for 5 min, cage tilting (45°) for 24 h, electric stimulation to foot for 5 min (36 v, last for 10 s and interval 20 s), paired housing for 24 h, damp sawdust (200 ml water per individual cage) for 24 h, food deprivation for 24 h, water deprivation for 24 h, and alteration of the light/dark cycle. One stressor was applied per day and the whole stress procedure lasted for 28 days in a completely random order.

Fluoxetine treatment and drug washout period: Fluoxetine (Pantheon, France) was dissolved in normal saline freshly before use. Rats were give fluoxetine (10 mg/kg) or saline vehicle through intragastric administration for 3 weeks. Since the half-life of fluoxetine is approximately 9 to 15 h in rats [20], it is likely that tissue concentration of selective serotonin reuptake inhibitor (SSRI) falls substantially after 1 day [21], thus we set one week as the washout period in the present study.

Behavior test:

Sucrose preference test: After a 24 h period of water deprivation, rats were housed in individual cages with two bottles containing water and 1% sucrose solution. The ratio of the intake of sucrose solution to total ingested solution within 1 h represented the parameter of anhedonic behavior.

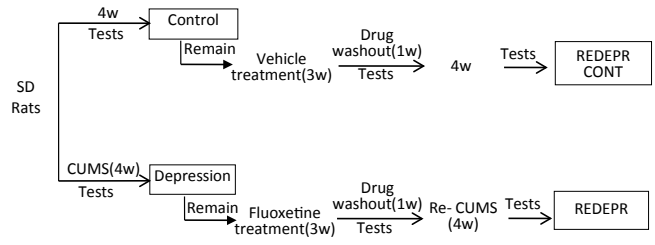

Figure 1: Details of the experimental procedure. Rats in control and depression groups were sacrificed after the depression group suffer first CUMS regime and behavior tests. Rats in REDEPR CONT and REDEPR group were sacrificed after REDEPR group the second CUMS regime and behavior tests.

***Open-field test*:** Open-field test was used to observe exploratory behavior and emotional responses, and was conducted in a soundproof box between 8:00 am and 12:00 am (≤ 60 dB). The open-field box was a 75 cm × 75 cm × 40 cm opaque box. Each animal was tested in the apparatus once. The rat was placed in the center of apparatus and recorded by camera system for 5 min. The locomotor activity was evaluated by the traveled distance using a video-computerized tracking system.

Forced swimming test: Forced swimming test was carried out in Plexiglas cylinders [22] (60 cm high, 25 cm in diameter) containing water (24-26°C, 40 ± 5 cm deep). After swimming session, the rat was dried and placed in an individual cage 15 min for rest and recovery, and then returned to their home cage. Immobility (i.e., the time that rat floated in the water and kept the head above the water without struggling) was used to measure the behavioral despair.

***Statistics analysis*:** Body weight and behavioral data, including sucrose preference test, open-field test, and forced swimming test of each group were analyzed by t test. Statistical significant of group difference was set as $p<0.05$.

Sample collection and derivatization

All rats were anesthetized and blood samples from heart were collected quickly in micro tubes. Blood samples were allowed to clot over 2 h at 20°C and centrifuged at 1,300×g for 15 min. The supernatant was collected and re-centrifuged at 3,000×g for 15 min to remove any debris. The supernatant was aliquot and stored at -80°C until use.

Before GC/TOF-MS analysis, serum was derivatized as previous report. Each sample (100 µl serum) was mixed with 500 µl methanol, 15 µl ribitol solution (0.2 mg/ml in deionized water), and 15 µl deionized water. The mixture was shaken at 70°C for 15 min and centrifuged at 15,700×g for 10 min. The supernatant was mixed with 450 µl deionized water and 270 µl chloroform, shaken (80 rpm) at 35°C for 5 min, and centrifuged at 3, 220×g for 10 min. The polar phase was separated and evaporated under a stream of nitrogen gas to dryness. The dried residue was dissolved in 40 µl methoxamine hydrochloride (20 mg/ml pyridine) and incubated at 30°C for 90 min with continuous shaking (130 rpm). Then 40 µl N-Methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA) with 1% trimethylchlorosilane (TMCS) was added at 37°C for 30 min to exchange the acidic protons. The derivatized samples were stored at room temperature for 120 min before injection.

GC/TOF-MS method

GC/TOF-MS analysis was performed on an Agilent 6890N gas chromatograph configured with a Waters Micromass GCT mass spectrometer. Chromatography was performed on a DB-5 MS capillary column (30 m×0.25 mm i.e., 0.25µm thickness). Helium carrier gas was set at a constant flow rate of 1 ml/min. The GC oven temperature was first held at 70°C for 6 s and then ramped at 5°C/min to a final temperature of 310°C with a 1-min hold time. The temperatures for injection, interface and source were set at 230, 290, and 220°C, respectively. The electron energy was set at 70 eV. After a solvent delay of 5 min, mass spectra were acquired over a mass to charge ratio (m/z) of 50-800.

Identification of the endogenous metabolites

Using Mass Lynx software (Waters, Milford, MA), total ion chromatograms (TICs) were acquired. All of detected peaks in TICs were identified by searching the NIST library with electron impact

(EI) spectra. Since the EI spectra for different sugars were very similar, incorrect results were usually obtained. Therefore, the standard sample was used to confirm the sugar identity. Ribitol was added as an internal standard to minimize any variations during sample preparation and analysis. Following acquisition, the GC/TOF-MS data were processed using Marker Lynx Application Manager Software (Waters). The intensities of peaks were normalized to the internal standard, which was arbitrarily set to 100. Marker Lynx extracted the components and generated a matrix of detected peaks, which are represented by their m/z and retention time pairs along with their associated intensities. These data were exported as text files for further multivariate analysis.

Data analysis

Multivariate pattern recognition analysis for GC/TOF-MS data was carried out by using SIMCA-P+ software (version 10.0, Umetrics, Umeå, Sweden). Partial least squares discriminant analysis (PLS-DA) was performed for data from different groups to detect the distributions and separations among those groups. Prior to PLS-DA, all data variables were mean-centered and preprocessed using orthogonal signal correction (OSC) to remove variations from noncorrelated factors such as the instability of spectrometer, inconstancy in sample preparation, and variability of some metabolites depending on the subject [23,24]. Score plots from the first two principal components (PCs) were used to visualize the separation between groups. The intensities of identified metabolites were further compared between groups by independent samples t-test with the threshold of P-value at 0.05 [17]. To minimize the influence of missing values, only identified metabolites that were consistently detected in at least 80% of samples were included in this t-test.

Results

Effect on behavior tests and body weight by first and second CUMS

The results for sucrose preference test (Figure 2A), open-field test (Figure 2B), body weight (Figure 2C), and forced swimming test (Figure 2D) of depression and recurrence depression were shown in Figure 2. The t-test indicated after first CUMS regime, depression group showed significantly decreased sucrose preference ($p<0.001$), less locomotor activity ($p<0.001$), loss of body weight ($p<0.001$) and more immobility ($p<0.001$) when they were forced to swim compared with control group. This implies, CUMS-DEPR group rats were in a state of depression-like which show anhedonic, less active, less body weight and more desperation compared to control animals. The data indicate that the CUMS model is reliable and accurate. The t-test also indicated REDEPR group showed significantly decreased sucrose preference ($p<0.001$), less locomotor activity ($p<0.01$), loss of body weight ($p<0.001$) and more immobility ($p<0.01$) when they were forced to swim compared with REDEPR CONT group. This implies, these animals suffered in depression state again that show an hedonic, less active, loss body weight and more desperation compared to REDEPR CONT group. The data indicate that the recurrence model is reliable and accurate.

GC/TOF-MS metabolites profiling of serum

GC/TOF-MS was used to analyze all serum samples. More than 250 peaks were detected in the TICs during a 50-min measurement period (Figure 3). The metabolites were identified by comparing with the corresponding standards according to their retention times and mass spectra characteristics or searching the mass spectral database library. 42 metabolites were identified in the serum profiling, including amino acids, fatty acids, sugars, and organic acids.

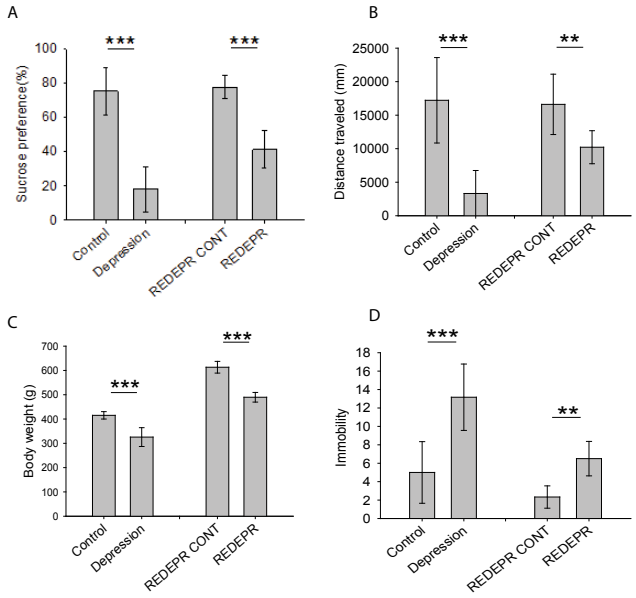

Figure 2: The data for behavior tests in all groups were expressed as mean±SD (n=6). (A) sucrose preference test; (B) open-field test; (C) body weight; (D) forced swimming test.
Note: * P<0.05, ** P<0.01, *** P<0.001

PLS-DA analysis for rats serum metabolites after the first and second CUMS

The PLS-DA score plots (Figure 4) illustrated the metabolic disturbance in rat serum after the first and second CUMS regime. As shown in Figure 4A, after first CUMS regime, the control and depression group could be separated each other completely, which indicates that the biochemical changes in the serum of depression group are obviously enough to differentiate each other. After the second CUMS regime, REDEPR group clearly separated from REDEPR CONT group (Figure 4B). This suggests that the biochemical changes between recurrent depression and normal is enough to differentiate each other.

The changes of serum metabolites after the first onset and recurrence of depression

As shown in Table 1, after the first CUMS regime, the concentrations of palmitinic acid ($p<0.05$) and oleinic acid ($p<0.05$) were decreased in the serum of CUMS-DEPR group.

While after the second CUMS regime, as shown in Table 1, compared with REDEPR CONT group, the concentrations of alanine ($p<0.01$), 6-Desoxy-Mannopyranose ($p<0.05$), oleinic acid ($p<0.05$), stearic acid ($p<0.05$) and cholesterol ($p<0.05$) were decreased in the rat serum of REDEPR group.

Discussion

In this study, we used GC/TOF-MS to analyze serum metabolomics of onset and recurrent depression rat model. 2 differentially expressed metabolites were identified in onset depression and 4 in recurrent depression.

Previous study reported 12 differentially expressed metabolites in the CUMS rats plasma [17] and the palmitinic acid was only decreased

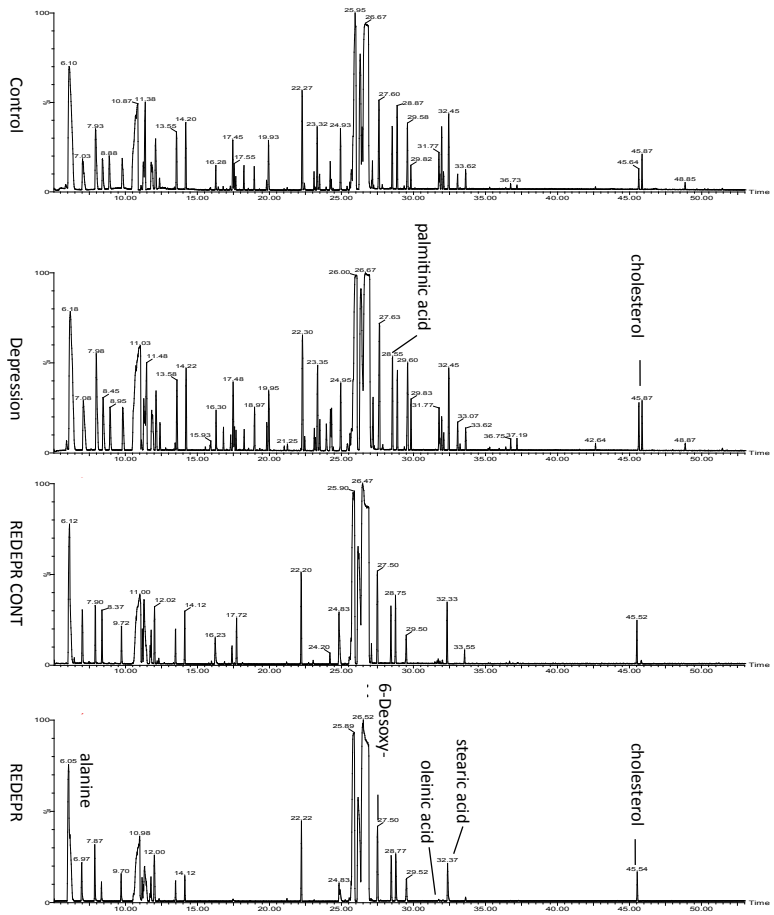

Figure 3: Comparison of GC/TOF-MS TICs of serum samples in all groups. (A) Control, (B) Depression, (C) REDEPR CONT, (D) REDEPR. Each peak represents a metabolite. The metabolites that were identified by t-test were highlighted above their peaks.

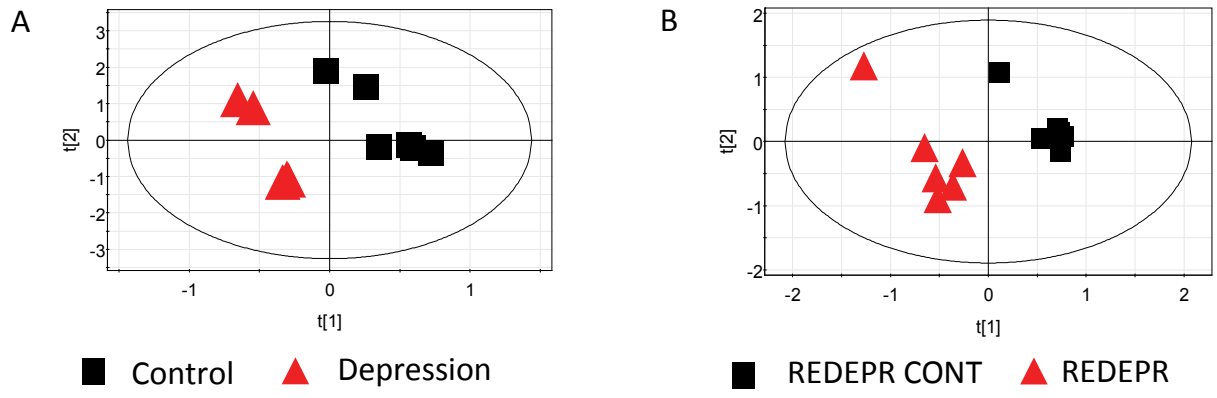

Figure 4: PLS-DA analysis for rat serum metabolites for depression and recurrent depression rat model. (A) Control vs. CUMS-DEPR; (B) REDEPR CONT vs. REDEPR.

metabolite in both studies after CUMS treatment, so probably palmitinic acid may be reliable potential metabolic biomarkers of onset depression. These big differences might be caused by different CUMS regime, methods for samples collection, sampling error or other reasons.

It can be see, there is much more metabolic changed in REDEPR group than onset depression group. This result implies the more serious metabolic perturbation occurred when recurrent depression occurs. Oleinic acid changed in both onset and recurrent depression group, so oleinic acid is changed in CUMS induced rat depression no matter onset or recurrent. And remain metabolomics changed just in depression and REDEPR group. It could be see, palmitinic acid maybe

No.	Retention time (min)	Metabolites	Control	Depression	Redepr Cont	Redepr
1	7.016	alanine	0.81 ± 0.26	0.64 ± 0.12	0.82 ± 0.08	0.61 ± 0.04 b**
2	28.468	6-Desoxy-Mannopyranose	0.52 ± 0.07	0.56 ± 0.06	0.73 ± 0.09	0.62 ± 0.07 b*
3	28.768	palmitinic acid	0.72 ± 0.16	0.55 ± 0.02 a*	0.65 ± 0.09	0.58 ± 0.09
4	31.851	oleinic acid	0.31 ± 0.10	0.14 ± 0.02 a*	0.02 ± 0.004	0.01 ± 0.006 b*
5	32.351	stearic acid	0.76 ± 0.20	0.62 ± 0.04	0.67 ± 0.18	0.45 ± 0.15 b*
6	45.519	cholesterol	0.34 ± 0.23	0.24 ± 0.08	0.42 ± 0.14	0.16 ± 0.18 b*

Note: * P<0.05, [a] Control vs. Depression; [b] REDEPR CONT vs. REDEPR

Table 1: Relative levels of serum metabolites after the first and the second CUMS regime detected by GC/TOF-MS (mean±SD, n=6).

potential biomarkers for the onset depression, and alanine, 6-Desoxy-Mannopyranose, oleinic acid, stearic acid, cholesterol is potential recurrent depression biomarkers.

We identified the concentrations of palmitinic acid and oleinic acid were decreased in the serum of onset depression group. Indicate in onset depression fatty acids metabolism was disturbed. Fatty acids can be decomposed by β-oxidation to acetyl coenzyme A to participate in tricarboxylic acid (TCA) cycle for energy supply. The decrease of fatty acid levels may reduce energy supply, and may cause fatigue. Energy deficiency or fatigue is one of the most frequently represented depressive symptoms in major depressive disorder [25]

In recurrent depression rats serum concentrations of alanine, 6-Desoxy-Mannopyranose, oleinic acid, stearic acid and cholesterol were decreased. We can see rats not only suffer much serious energy disturbance, but also suffer other metabolic disturbance. Alanine was found decreased in recurrent depression. Alanine decrease may due to either synthesis decreasing or degradation increasing [26]. It is hypothesized that alanine aminotransferase can metabolize glutamate to a-ketoglutaric acid [27]. And this process is accompanied by transfer amino to pyruvic acid the production of alanine. So, the decreased alanine may cause by glutamate decrease. Glutamate is an important excitatory neurotransmitter, and was found decreased in the depression rats [14-16]. Cholesterol was also found decreased in recurrent depression rat model serum. Cholesterol has many important functions: it is required to build and maintain membranes and can modulates membrane fluidity. It is an important precursor molecule for the synthesis of vitamin D and the steroid hormones, including the adrenal gland hormones cortisol and aldosterone, as well as the sex hormones progesterone, estrogens, testosterone, and their derivatives. Many studies have demonstrated an association between suicidal behavior and low levels of total serum cholesterol [28] considering recurrent depression are associated with suicide [29]. It seems like that recurrent depression can decrease serum cholesterol level and maybe contribute to suicidal behavior.

Conclusions

In this study, we applied GC/TOF-MS to analyze the metabolomics profiles in the serum from the rats of the first onset and recurrent depression. And this study aimed to investigate the metabolic biomarkers for the first and recurrent depression. After the first CUMS regime, the concentrations of palmitinic acid and oleinic acid were decreased in the onset depression rats, indicating they might be serum biomarkers for the onset depression. After recovery from the onset depression, the recurrent depression rat serum decrease the concentrations of alanine, 6-Desoxy-Mannopyranose, oleinic acid, stearic acid and cholesterol. Indicating they might be potentially metabolic biomarkers for recurrent depression. These data shows rats suffer recurrent depression have much more serious metabolic disturbance than onset depression, and they may provide valuable information for the potential biomarkers of diagnosis.

Acknowledgements

This work was supported by the Chinese National Key Project of Basic Research (2009CB918301), and the Chinese National Natural Science Foundation (81370051).

References

1. Mathers CD, Loncar D (2006) Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 3: e442.
2. Murray CJ, Lopez AD (1997) Regional patterns of disability-free life expectancy and disability-adjusted life expectancy: global Burden of Disease Study. Lancet 349: 1347-1352.
3. Vos T, Haby MM, Barendregt JJ, Kruijshaar M, Corry J, et al. (2004) The burden of major depression avoidable by longer-term treatment strategies. Arch Gen Psychiatry 61: 1097-1103.
4. Burcusa SL, Iacono WG (2007) Risk for recurrence in depression. Clin Psychol Rev 27: 959-985.
5. Yang C, Wang G, Wang H, Liu Z, Wang X (2009) Cytoskeletal alterations in rat hippocampus following chronic unpredictable mild stress and re-exposure to acute and chronic unpredictable mild stress. Behav Brain Res 205: 518-524.
6. Willner P (1997) Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology (Berl) 134: 319-329.
7. Craig, A, Sidaway J, Holmes E, Orton T, Jackson D, et al. (2006) Systems toxicology: integrated genomic, proteomic and metabonomic analysis of methapyrilene induced hepatotoxicity in the rat. J Proteome Res 5: 1586-1601.
8. Nicholson JK, Connelly J, Lindon JC, Holmes E (2002) Metabonomics: A platform for studying drug toxicity and gene function. Nat Rev Drug Discov 1: 153-161.
9. Nicholson JK, Holmes E, Lindon JC, Wilson ID (2004) The challenges of modelling mammalian bio complexity. Nat Biotechnol 22: 1268-1274.
10. Gao X, Zheng X, Li Z, Zhou Y, Sun H, et al. (2011) Metabolomics study on chronic unpredictable mild stress and intervention effects of Xiaoyaosan in rats using gas chromatography coupled with mass spectrometry. J Ethnopharmacol 137: 690-699.
11. Li L, Sun B, Zhang Q, Fang J, Ma K (2008) Metabonomic study on the toxicity of Hei-Shun-Pian, the processed lateral root of Aconitum carmichaelii Debx. (Ranunculaceae). J Ethnopharmacol 116: 561-568.
12. Pasikanti KK, Ho PC, Chan EC (2008) Gas chromatography/mass spectrometry in metabolic profiling of biological fluids. J Chromatogr B Analyt Technol Biomed Life Sci 871: 202-211.
13. Kaddurah-Daouk R, Kristal BS, Weinshilboum RM (2008) Metabolomics: A global biochemical approach to drug response and disease. Annu Rev Pharmacol Toxicol 48: 653-683.
14. Paige LA, Mitchell MW, Krishnan KR, Kaddurah-Daouk R, Steffens DC (2007) A preliminary metabolomic analysis of older adults with and without depression. Int J Geriatr Psychiatry 22: 418-423.
15. Ni Y, Su M, Lin J, Wang X, Qiu Y (2008) Metabolic profiling reveals disorder of amino acid metabolism in four brain regions from a rat model of chronic unpredictable mild stress. FEBS Lett 582: 2627-2636.
16. Wang X, Zhao T, Qiu Y, Su M, Jiang T, et al. (2009) Metabonomics approach to understanding acute and chronic stress in rat models. J Proteome Res 8: 2511-2518.

17. Zheng S, Yu M, Lu X, Huo T, Ge L, et al. (2010) Urinary metabonomic study on biochemical changes in chronic unpredictable mild stress model of depression. Clin Chim Acta 411: 204-209.

18. Katz RJ, Roth KA, Carroll BJ (1981) Acute and chronic stress effects on open field activity in the rat: implications for a model of depression. Neurosci Biobehav Rev 5: 247-251.

19. Willner P, Towell A, Sampson D, Sophokleous S, Muscat R (1987) Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology (Berl) 93: 358-364.

20. Caccia S, Cappi M, Fracasso C, Garattini S (1990) Influence of dose and route of administration on the kinetics of fluoxetine and its metabolite norfluoxetine in the rat. Psychopharmacology (Berl) 100: 509-514.

21. Anthony JP, Sexton TJ, Neumaier JF (2000) Antidepressant-induced regulation of 5-HT(1b) mRNA in rat dorsal raphe nucleus reverses rapidly after drug discontinuation. J Neurosci Res 61: 82-87.

22. Vitale G, Ruggieri V, Filaferro M, Frigeri C, Alboni S, et al. (2009) Chronic treatment with the selective NOP receptor antagonist [Nphe 1, Arg 14, Lys 15]N/OFQ-NH 2 (UFP-101) reverses the behavioural and biochemical effects of unpredictable chronic mild stress in rats. Psychopharmacology (Berl) 207: 173-189.

23. Beckwith-Hall BM, Brindle JT, Barton RH, Coen M, Holmes E, et al. (2002) Application of orthogonal signal correction to minimise the effects of physical and biological variation in high resolution 1H NMR spectra of biofluids. Analyst 127: 1283-1288.

24. Gavaghan CL, Wilson ID, Nicholson JK (2002) Physiological variation in metabolic phenotyping and functional genomic studies: use of orthogonal signal correction and PLS-DA. FEBS Lett 530: 191-196.

25. Serretti A, Mandelli L, Lattuada E, Smeraldi E (2004) Depressive syndrome in major psychoses: A study on 1351 subjects. Psychiatry Res 127: 85-99.

26. Murakami T, Yamane H, Tomonaga S, Furuse M (2009) Forced swimming and imipramine modify plasma and brain amino acid concentrations in mice. Eur J Pharmacol 602: 73-77.

27. Waagepetersen HS, Sonnewald U, Larsson OM, Schousboe A (2000) A possible role of alanine for ammonia transfer between astrocytes and glutamatergic neurons. J Neurochem 75: 471-479.

28. Olié E, Picot MC, Guillaume S, Abbar M, Courtet P (2011) Measurement of total serum cholesterol in the evaluation of suicidal risk. J Affect Disord 133: 234-238.

29. Hantouche E, Angst J, Azorin JM (2010). Explained factors of suicide attempts in major depression. J Affect Disord 127: 305-308.

Citation: Li Z, Yang S, Zhu C, Chen J, Ding X, et al. (2017) The GC/TOFMS based Serum Metabolomics in Rats with Depression-like Behavior after Exposure and Re-exposure to Chronic Unpredictable Mild Stress. J Psychiatry 20: 396 doi:10.4172/2378-5756.1000396