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Urinary metabolomics study on the anti-depression effect of different exercise modes on CUMS model rats

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Objective To study the effects of different exercise modes on CUMS depression model rats by ^{1}H-NMR metabolomics technique, and to explore the mechanism of exercise anti-depression and to find the best exercise mode.
Methods Forty-eight male SD rats were divided into control group (group C), model group (group M), aerobic exercise group (group A), and resistance exercise group (group R), 12 per group. The group C was routinely reared, chronic mild unpredictable stress + orphaned 8 weeks to establish a depression model of CUMS rats. In the 5th week of modeling, rats in group A and group R were trained in aerobic and resistance exercise for 4 weeks. The changes of body mass were observed during the experiment. The effects of exercise on the behavior of CUMS rats were observed by sucrose preference experiment and open field experiment. The levels of plasma BDNF, CORT and 5-HT were measured to reveal the pathological changes of the model. ^{1}H-NMR metabolomics techniques combined with multivariate statistical analysis methods were used to investigate the regulation of urinary endogenous metabolites and the regulation of metabolic pathways in CUMS depression rats.
Results 1) After four weeks of modeling, compared with the group C, the body weight, saccharide water preference rate, the crossing number and the number of erectings in the group M, group A and group R were significantly lower ($P<0.05$ or $P< 0.01$), indicating that the modeling was successful; after eight weeks of modeling, compared with the group C, the body weight, saccharide water preference rate, the crossing number and the number of erectings in the group M, was significantly lower ($P<0.01$). There was no significant difference in the group A and group R. 2)Compared with group C, the levels of BDNF and 5-HT in group M were significantly decreased ($P<0.05$ or $P<0.01$), the level of CORT was significantly increased ($P<0.01$), and the levels of BDNF, 5-HT and CORT in group A were not significantly different, the CORT levels were significantly increased in group R($P <0.01$), BDNF and 5-HT levels were not significantly different; compared with group M, BDNF, 5-HT levels in group A were significantly increased ($P <0.05$) and the level of CORT was significantly decreased ($P<0.01$), the levels of BDNF and 5-HT in group R were significantly increased ($P<0.01$), but there was no significant difference in CORT level. Compared with group A, the levels of BDNF and 5-HT in group R were not significant,but CORT levels increased significantly ($P<0.05$). 3)A total of 14 potential biomarkers in the urine of CUMS depression model rats were found . Compared with group C, the levels of leucine, valine, lactic acid, citric acid, inositol, pyruvic acid, β-hydroxybutyric acid, acetoacetic acid, trimethylamine, pantothenic acid, β-hydroxyisovaleric acid, alanine and succinic acid in the urine of group M were significantly increased, and the level of α-ketoglutaric acid was significantly decreased ($P<0.05$ or $P<0.01$). Group A can significantly callback 8 potential biomarkersof leucine, lactic acid, citric acid, pyruvic acid, β-hydroxybutyric acid, alanine, lactic acid and pantothenic acid ($P<0.05$ or $P<0.01$) , the group R can significantly callbackt the 6 potential biomarkers of lactic acid, acetoacetic acid, inositol, trimethylamine, β-hydroxy isovaleric acid and alanine. Two types of exercise can regulate urinary metabolites in depressed rats. 4) ^{1}H-NMR metabolic pathway analysis showed that aerobic exercise mainly improves the urine metabolism of depressed rats by regulating TCA cycle, pantothenic acid and COA biosynthesis, and pyruvate

metabolism. The resistance exercise mainly improved the urine metabolism characteristics of depressed rats by regulating the synthesis and degradation of ketone bodies, pyruvate metabolism and inositol phosphate metabolism.
Conclusions Aerobic exercise and resistance exercise all can effectively improve depressive symptoms, adjust the urine biomarkers of depressed rats to varying degrees, which may be related to different metabolic pathways involved in exercise modes.