ERK-BAX signaling is involved in GLP-1-mediated antidepressant effects of metformin and exercise in CUMS mice

Weina Liu, Jiatong Liu, Zhuochun Huang, Lingxia Li, Wenbin Liu, Zhiming Cui, Zhengtang Qi

1. Key Laboratory of Adolescent Health Assessment and Exercise Intervention of Ministry of Education, East China Normal University
2. School of Physical Education & Health Care, East China Normal University

Objective  Both depression itself and antidepressant medication have been reported to be significantly related to the risk of type 2 diabetes mellitus (T2DM). Glucagon-like peptide-1 (GLP-1), a treatment target for T2DM, has a neuroprotective effect. As an enhancer and sensitizer of GLP-1, metformin has been reported to be safe for the neurodevelopment. The present study aimed to determine whether and how GLP-1 mediates antidepressant effects of metformin and exercise in mice.

Methods  Male C57BL/6 mice were exposed to chronic unpredictable mild stress (CUMS) for 8 weeks. From the 4th week, CUMS mice were subjected to oral metformin treatment and/or treadmill running. A videocomputerized tracking system was used to record behaviors of mice for a 5-min session. ELISA, western blotting and immunohistochemistry were used to examine gene expression in mouse serum or hippocampus.

Results  Our results supported the validity of metformin as a useful antidepressant; moreover, treadmill running favored metformin effects on exploratory behaviors and serum corticosterone levels. CUMS reduced GLP-1 protein levels and phosphorylation levels of extracellular signal-regulated kinase 1/2 (ERK1/2), but increased protein levels of B-cell lymphoma 2-associated X-protein (BAX) in mice hippocampus. All these changes were restored by both single and combined treatment with metformin and exercise.

Conclusions  Our findings have demonstrated that ERK-BAX signaling is involved in GLP-1-mediated antidepressant effects of metformin and exercise, which may provide a novel topic for future clinical research.