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

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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 sensitiser 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.