Exercise Biochemistry Review

Proceedings of IBEC 2018, Beijing, China, October 23-25
PO-062

Acute exercise intervention combined with metformin's influences on glucose homeostasis in T2D mice

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Objective Type 2 diabetes mellitus is a common chronic diseases prevailing in the world and the amount of diabetic and pre-diabetic patients is increasing gradually. Exercise combined with hypoglycemic drug is the first recommended therapy to treat type 2 diabetes. Metformin was found from galegine in 1957 and has been used now as the first cheap and effective hypoglycemic guanidines. Our study aims to explore the effects of different ways of acute exercise intervention combined with high dose of metformin on glucose homeostasis and its relative molecular mechanisms in type 2 diabetic mice.
Methods Adopt 4-week high fat diet (HFD, 45% fat content) and one-time STZ (Streptozocin, 100mg/kg) intraperitoneal injection to build type 2 diabetic mice. There are 84 mice in total, 24 mice were divided into three groups: normal control (NC) group, normal acute resistance training (NCR) group and normal acute endurance training (NCE) group, N=8 each group, they were fed normal chow. The rest 60 mice were fed HFD as T2D modeling group. 48 mice were developing type 2 diabetes and they were divided into 6 groups: diabetic control (DC) group, diabetic acute resistance training (DCR) group, diabetic acute endurance training (DCE) group, high dose of metformin control (HMC) group, high dose of metformin combined with acute resistance training (HMR) group and high dose of metformin combined with acute endurance training (HME) group, N=8 each group. Acute resistance training is climbing 1 meter ladder from down to up, 5 times a group, 3 groups in total, monitoring the glucose change with extracting mouse tail vein blood during each group, using ACCU-CHEK monitor. Acute endurance training is running at the speed of 18 m/min on the platform for 50 minutes and blood glucose change was monitored every 10 minutes by extracting mouse tail vein blood. HMC, HMR and HME group mice were intraperitoneally injected high dose of metformin (200mg/kg) one hour before the acute exercise intervention. Comparatively, NC, NCR, NCE, DC, DCR, DCE group mice were intraperitoneally injected 0.9% saline one hour before the acute exercise intervention. ELISA, RT-PCR and Western Blot were used to evaluate relative serum indicators, mRNA and protein expression of regulating blood glucose homeostasis.
Results 1) 4-week high fat diet and one time 100mg/kg Streptozocin intraperitoneal injection induces mice to develop type 2 diabetes. The fasting blood glucose, IPGTT, ITT, glucose AUC and insulin AUC of T2D group mice are significantly higher than NC group. 2) Compared with DCR group, the blood glucose value and fluctuation of HMR group mice are both significantly decreased, but the blood glucose value of DCR and HMR group mice are significantly higher than NCR group. In the same way, the blood glucose value and fluctuation of HME group mice is lower than DCE group and the whole blood glucose level of both group are higher than NCE group. Acute resistance training and acute endurance training combined with high dose of metformin have not affected the weight of type 2 diabetic mice. Hence compared with HMC group, the eWAT (epididymal white adipose tissue) of HMR and HME group mice is significantly declined. 3) Compared with NC group, the indicators of serum glucose, GSP (glycosylated serum protein), serum TG and serum T-CHO of DC group are notably increased, further reflect that the success model of type 2 diabetic mice. Compared with HMC group, the indicators of serum glucose, GSP, serum TG and serum T-CHO of HMR group mice are notably decreased, in the mean time, the indicators of serum glucose and serum TG of HME group mice are significantly declined. Interestingly, the serum insulin of HME group mice is notably lower

than HMR group. 4) Compared with DC group, the indicators of mRNA expression about hepatic gluconeogenesis key rate-limiting enzymes PEPCK and G6pase of HMC group are significantly declined, but mRNA expression of regulating hepatic glucose homeostasis GLUT2 of HMC group is notably raised. Compared with HMC group, G6Pase mRNA expression of HMR and HME group is significantly escalated and Fbp mRNA expression of both groups are significantly declined. Compared with HMC, the indicators of mRNA expression about regulating hepatic glucose homeostasis GLUT2 and Gck of HMR and HME group mice show opposite trend, the former is down and the latter is up. Compared with HMC group, PEPCK mRNA expression of HMR group mice is notably escalated. Compared with HMR group, PEPCK and G6Pase mRNA expression of HME group mice are notably raised. 5) In the liver, there is a signaling pathway of AMPKα-PGC-1α-CREB to regulate glucose homeostasis and hepatic gluconeogenesis. Our study find that compared with HMC group, AMPKα_2, PGC-1α and CREB mRNA expression of HMR and HME group mice are notably increased and only AMPKα_1 mRNA expression of HMR group mice is significantly increased.

Conclusions 1) Acute resistance training and acute endurance training combined with high dose of metformin can effectively reduce glucose fluctuation during exercise in type 2 diabetic mice, therefore these two way can both improve glucose homeostasis during acute exercise intervention in type 2 diabetic mice. 2) Acute resistance training and acute endurance training combined with high dose of metformin can improve serum glucose and lipid metabolism in type 2 diabetic mice, but acute resistance training combined with high dose of metformin are better to improve serum lipid metabolism. 3) Acute exercise intervention combined with high dose of metformin can comparatively increase hepatic gluconeogenesis key rate-limiting enzymes PEPCK and G6Pase and regulating hepatic glucose transport Gck mRNA expression. In the opposite, these two ways inhibit the other hepatic gluconeogenesis key rate-limiting enzyme Fbp and regulating hepatic glucose transport GLUT2 mRNA expression. 4) Compared with acute endurance training combined with high dose of metformin, acute resistance training combined with high dose of metformin can better improve glucose homeostasis and hepatic gluconeogenesis in type 2 diabetic mice via the signaling pathway of AMPKα-PGC-1α-CREB.