Fulvic acid-induced mitochondrial membrane potential improves diabetic symptoms in mice

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Type 2 diabetes has reached an epidemic level globally. Most current treatments ameliorate the hyperglycemic symptom of the disease but are not effective in correcting its underlying cause. One important causal factor of type 2 diabetes is ectopic accumulation of lipids in metabolically sensitive organs such as liver and muscle. Shilajit, an adaptogen composed primarily of humic substances such as fulvic acid (FA), has a long history of use in Ayurvedic medicine, however, both the pharmacological effect and mechanism of action by FA are not clarified. In the current study, we documented on the application and the mechanism of action of FA both in vitro and in vivo analysis.

In C2C12 muscle progenitor cells, FA promoted ATP consumption activity and glucose uptake activities. Mitochondrial membrane potential in C2C12 cells was elevated by FA. In addition, we performed behavior analysis by open field test. FA increased the locomotive activities. These results indicated that FA has an action like exercise which enhances metabolism and promotes ATP consumption while protecting mitochondrial membrane potential. In attempt to examine the effect of FA on systemic metabolisms, mice were tried to high-fat diet (HFD) test for 6 weeks. HFD+FA fed group dramatically reduced body weight compared to HFD fed group. FA normalized irregular blood glucose and plasma insulin elevations. Histological analyses and lipid content quantification (TG, LDL-C, HDL-C) showed that FA treatment correlated with a lower degree of lipid accumulation in the liver, even though the mice were still on the HFD. The elevated ALT, AST, LDH, and ChE values in HFD also markedly normalized by FA. Furthermore, FA improved insulin-resistant diabetic condition by HFD in OGTT test. These combined evidences demonstrated that FA was effective in preventing and reducing HFD-induced insulin resistance, glycemic metabolisms, hepatic steatosis, by presumably stimulating mitochondrial membrane potential. Given the well-documented safety profile of FA, our study provides a potentially new and practical pharmacological approach for treating type 2 diabetes.