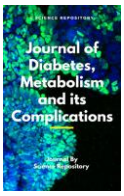

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Research Article

Exogenous Hydrogen Sulfide Alleviated Left Ventricular Fibrosis Via Enhancing Cardiac Autophagy and Decreasing Cardiomyocyte Apoptosis in Streptozotocin-Induced Diabetic Rats: From Network Pharmacology to Experimental Pharmacology

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ABSTRACT

Streptozotocin (STZ)-induced diabetes mellitus (DM) model shows the signal of cardiac dysfunction, which is manifested as myocardial fibrosis and hypertrophy. This study was designed to predict targets of sodium hydrosulfide (NaHS) for diabetic cardiomyopathy and its corresponding triggered pathways by network pharmacology analysis and test the effects of NaHS as well as its mechanism as possible modulators of left ventricular remodeling in diabetic rats. The drug-target networks were constructed via approaches of network pharmacology, and the predicted targets and pathways were validated by *in vivo* experiments. Rats were randomly divided into 3 groups (n=6/group): STZ-induced DM group (STZ-DM); STZ-induced DM treated with H_2S group (STZ-NaHS); control group. The control group was treated with daily saline (i.p.); the diabetic model was induced by intraperitoneal (i.p.) injections of 40 mg/kg/day STZ. After 12 weeks, the rat cardiac function was determined, and the pathological morphology of the heart was analysed by Masson trichrome staining in each group. The expression level of matrix metalloproteinase 9 (AGEs), CSE, CBS and several autophagy associated proteins were detected by the ELISA analysis. Results from the PPI network implied that 27 targets were key regulators. The AGE-RAGE signaling pathway in diabetic complications and the apoptotic signaling pathway was discovered to be the key to anti-diabetic cardiomyopathy of NaHS upon the GO enrichment analyses and KEGG pathway. In the *in vivo* experiment, compared with the control group, cardiac fibrosis and attenuated left ventricular function were observed. Furthermore, compared with the control group, the expression level of CSE, CBS and autophagy associated proteins Atg5 was significantly decreased, while that of AGEs, autophagy associated proteins p62 and p-ERK1/2 was significantly increased in the STZ-DM group ($P<0.05$). In the STZ-NaHS group, cardiac fibrosis and ventricular dysfunction were ameliorated, the expression level of CSE, CBS and autophagy associated proteins Atg5 was increased, and the expression level of AGEs, autophagy associated proteins p62 and p-ERK1/2 was significantly decreased ($P<0.05$). In conclusion, H_2S may alleviate cardiac fibrosis of the STZ-induced DM rat model by enhancing cardiac autophagy, inhibiting cardiomyocyte apoptosis and downregulating p-ERK1/2.

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