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Metformin and Its Combination with Sodium Hydrosulfide Influences Plasma Galectin-3 and CSE/H_2S System in Diabetic Rat's Heart

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Abstract : Background and Aims: Galectin-3 is a marker of subclinical cardiac injury and is elevated in individuals with type 2 diabetes mellitus; while hydrogen sulfide (H_2S), metabolite of sulfur-containing amino acids, is considered having antifibrogenic effects. This study was designed to investigate whether metformin and its combination with NaHS can influence plasma galectin-3 and cystathionine-γ-lyase/hydrogen sulfide (CSE/H_2S) system in diabetic rat's heart. Methods: 32 healthy male rats (180-250 g) were divided into 4 groups. To induct diabetes, rats (group 2-4) were injected with streptozotocin (STZ, 40 mg/kg/i.p., 0.1 M citrate buffer (pH 4.5). Rats from 3d (STZ+Metf) and 4th (STZ+Metf+NaHS) groups were given metformin (500 mg/kg/day) orally, and rats from 4th (STZ+Metf+NaHS) group were injected sodium hydrosulfide (NaHS, 3 mg/kg/i.p.) once per day starting from 3 to 28 day after streptozotocin injection. Rats of first group (control) were administered the equivalent volumes of 0.9% NaCl. Plasma galectin-3 was measured by ELISA. Rats' hearts were sampled for determination of H2S by reaction with N,N-Dimethyl-p-phenylenediamine. Determination of CSE gene expression was performed in real time using PCR in the presence of SYBR Green I, using DT-Light detecting amplifier ('DNA-technology', Russia). Results: Induction of streptozotocin diabetes (STZ-diabetes, group 2) was followed by low myocardial H2S concentration and CSE expression (by 35%, $p < 0.05$ and 60.5%, $p < 0.001$ respectively, than that in controls), while plasma galectin-3 in this group was significantly higher than in controls (by 3.8 times, $p < 0.05$). Administration of metformin (group 3) resulted in significantly higher H_2S concentration (by 28.5%, $p < 0.05$), whereas CSE expression was only by 6% more than that in STZ-diabetes, as well as plasma galectin-3 was only by 14.8% lower in comparison with untreated diabetic rats. The inhibition of H_2S generation and CSE activity by diabetes was greatly attenuated in STZ+Metf+NaHS group. The combination of metformin with NaHS significantly stimulated H_2S production (by 48%, $p < 0.05$ and 15%, $p < 0.05$ more than STZ-diabetes and STZ+Metf respectively) and CSE gene expression (by 64.8%, $p < 0.05$ compared to STZ-diabetes and by 55.4%,$p < 0.05$ compared to STZ+Metf). Besides, plasma galectin-3 in rats receiving metformin and NaHS was significantly lower by 42%, $p < 0.05$ and 32.5%, $p < 0.05$ compared to STZ-diabetes and STZ+Metf groups respectively. Conclusions: To summarize, dysfunction of CSE/H2S system and galectin-3 stimulation was found in streptozotocin-induced diabetic rats. Metformin and its combination with exogenous H2S effectively prevented the development of metabolic changes induced by diabetes. These findings suggest that CSE/H_2S system can be integrated into pathogenesis of diabetic complications through modulation of pro-inflammatory and pro-fibrogenic mediator galectin-3.

Keywords : cystathionine-γ-lyase, diabetic heart, galectin-3, hydrogen sulfide, metformin, sodium hydrosulfide
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