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Phosphodiesterase-5 inhibition and cardioprotection: potential role of hydrogen sulfide

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Background

Our laboratory has shown that phosphodiesterase-5 (PDE-5) inhibitors including sildenafil, vardenafil and tadalafil induce powerful protection against myocardial ischemia-reperfusion injury. We have shown that sildenafil protects through activation PKC, expression of eNOS/iNOS, protein kinase G (PKG) and opening of mitochondrial KATP (mitoKATP) channels [1]. Hydrogen sulfide (H2S) is a gaseous molecule that is produced enzymatically and exerts physiological actions in the cardiovascular system. Similar to PKG, H2S has been shown to protect the heart via opening of mitoKATP channel [2]. In the current study, we hypothesized that tadalafil, the long acting inhibitor of PDE-5 mediates cardioprotection through H2S signaling in a PKG-dependent fashion.

Methods and results

After baseline transthoracic echocardiography (TTE), adult ICR mice were injected i.p. with vehicle (10% DMSO) or tadalafil (1 mg/kg) with or without KT5823 (KT, PKG blocker, 1 mg/kg) or dl-propargylglycine [PAG, Cystathionine-γ-lyase (CSE, H2S-producing enzyme) blocker; 50 mg/kg] 1 h prior to coronary artery ligation for 30 min and reperfusion for 24 h, whereas C57BL-wild type and CSE-knockout mice were treated with either vehicle or tadalafil. After reperfusion, TTE was performed and hearts were collected for infarct size (IS) measurement using TTC staining. Survival was increased with tadalafil (95%) compared with control (65%, $P < 0.05$). Infarct size was reduced with tadalafil (13.2 ± 1.7%) compared to vehicle (40.6 ± 2.5%; $P < 0.05$). KT and PAG abolished tadalafil-induced protection (IS: 39.2 ± 1% and 51.2 ± 2.4%, respectively) similar to genetic deletion of CSE (47.2 ± 5.1%). Moreover, tadalafil preserved fractional shortening (FS: 31 ± 1.5%) compared to control (FS: 22 ± 4.8%, $P < 0.05$). Baseline FS was 44 ± 1.7%. KT and PAG abrogated the preservation of LV function with tadalafil by decline in FS to 17 ± 1% and 23 ± 3%, respectively. Compared to vehicle, myocardial H2S production was significantly increased with tadalafil and was abolished with KT.

Conclusion

PKG activation with tadalafil limits myocardial infarction and preserves LV function through H2S signaling.

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