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Poster presentation

Pharmacological activation of soluble guanylate cyclase activator protects the heart against isoproterenol-induced myocardial ischemia in rats

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Background

The role of the NO-cGMP-PKG pathway in myocardial protection and preconditioning has been object of intensive investigations. The novel NO- and haem-independent soluble guanylate cyclase (sGC)-activator cinaciguat (BAY 58-2667), has been reported to elevate intracellular cGMP concentration and activate the NO-cGMP-PKG pathway *in vivo*. We investigated the effects of cinaciguat on myocardial infarction (MI) induced by isoproterenol in rats.

Materials and methods

Rats were treated orally twice a day for 4 d with vehicle or cinaciguat (10 mg/kg). Isoproterenol (85 mg/kg) was injected subcutaneously 2 d after the first treatment at an interval of 24 h for 2 d to produce MI. After 17 h, histopathological examination of heart tissue was performed and plasma lactate dehdyrogenase (LDH) activity, thiobarbituric acid reactive substances (TBARS) were measured. We performed left ventricular pressure-volume (PV) analysis to assess cardiac function using a microtip Millar PV conductance catheter. Expression of different genes was analysed by quantitative real time PCR. Isolated canine coronary arterial rings exposed to peroxynitrite were investigated for vasomotor function and immunohistochemistry was performed for cGMP and nitrotyrosine (NT).

Results

The present results show that cinaciguat treatment improves cardiac performance (showed by increased load-independent, PV loops derived contractility indexes), improves impaired cardiac relaxation (as reflected by prolonged time constant of pressure decay), and improves histopathological lesions. Cinaciguat also reduces oxidative stress (showed by decreased level of TBARS), ameliorates intracellular enzyme release (as evidenced by decreased LDH activity), decreases COX-2, TGF-β and β-actin mRNA expression in experimental MI in rats. *In vitro* exposure of coronary arteries to peroxynitrite resulted in an impairment of endothelium-dependent vasorelaxation (showed by reduced maximal relaxation to acetylcholine), increased nitro-oxidative stress and reduced intracellular cGMP levels (as demonstrated by higher NT- and lower cGMP-immunoreactivity) which were all improved by cinaciguat incubation of coronary arterial rings.

Conclusion

Pharmacological sGC activation could be a novel approach for prevention and treatment of ischemic heart disease.