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Cardioprotective effect of MMP-2-inhibitor-NO-donor hybrid during ischemia/reperfusion injury

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BACKGROUND

Hypoxic injury of cardiovascular system is one of the most frequent complications following ischemia. Heart injury arises from increased degradation of contractile proteins, such as myosin light chains (MLCs) and increased activity of matrix metalloproteinase 2 (MMP-2). It has also been well established that an increased production of toxic peroxynitrite (ONOO-) during oxidative stress is a source of increased nitration/nitrosylation of contractile proteins, which may enhance their degradation due to an increased affinity to MMP-2.

PURPOSE

The aim of the current research was to study the effects of 5-phenyloxyphenyl-5-aminoalkyl nitrate barbiturate (MMP-2-inhibitor-NO-donor hybrid) on hearts subjected to ischemia/reperfusion (I/R) injury.

METHODS

Primary human cardiac myocytes (ScienCell Research) and Wistar rats perfused using Langendorff method have been used. Cardiomyocytes in vitro and rat hearts ex vivo were subjected to I/R in the presence or absence of tested hybrid. Hemodynamic parameters of heart function, markers of I/R injury, MMP-2 gene and protein expression as well as MMP-2 activity, levels of LDH (as a marker of tissue injury), inducible form of NOS (iNOS), asymmetric dimethylarginine (ADMA), myosin light chain 1 (MLC1) and cardiomyocytes contractility were measured.

RESULTS

Mechanical heart function, coronary flow, and heart rate were decreased in hearts subjected to I/R. Treatment of hearts with the hybrid (10 µM) resulted in recovery of mechanical function (p=0.002, Fig.1A), improved coronary flow (p<0.001) and heart rate (p=0.002). This improvement was associated with decreased tissue injury (p=0.01) and reduction of expression and activity of MMP-2. Decreased activity of intracellular MMP-2 led to reduced degradation of MLC1 (r=-0.70, p=0.022) and improved myocyte contractility in a concentration dependent manner (8.5 vs 15.5, p=0.001). An infusion of MMP-2-inhibitor-NO-donor hybrid into I/R hearts decreased an expression of iNOS and reduced level of ADMA ( r=0.72, p=0.004), due to exogenous source of NO (Fig. 1B).

CONCLUSION

In conclusion, this study confirms the potential, dual cardioprotective role of an MMP-inhibitory nitrate hybrid compound in the development of I/R injury. We showed that the hybrid compound can suppress MMP-2 expression and activity, hence limiting I/R injury. Moreover, as exogenous NO donor it leads to decreased iNOS/ADMA production, and subsequently to reduction of NO synthase uncoupling. On this basis, the current study may have important pharmacological implications for prevention/treatment of ischemia and coronary revascularization.
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**Fig. 1. (A)** Recovery of heart mechanical function due to infusion of hybrid, n=6-10. (B) Correlation between iNOS expression and NO production in I/R hearts, n=15. *p < 0.05 vs Aero; #p < 0.05 vs I/R22; Aero-aerobic control; I/R22- ischemia/reperfusion control, RPP- heart rate x left ventricular developed pressure, AU-arbitrary units.