Abstract: P4607

A specific complex I-induced ROS modulator, OP2113, is a new cardioprotective agent against acute myocardial infarction injuries during reperfusion.

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Introduction: Hospital death rates due to myocardial infarction are still a concern and heart failure occurs in nearly a quarter of older patients who present with ST elevation myocardial infarction. Novel therapies are thus desperately needed to reduce infarct size to preserve left ventricular function and to prevent the onset of heart failure.

Purpose: OP2113, trithio-p-methoxyphenylpropene (anethole trithione, 5-(4-methoxyphenyl)-3H-1,2-dithiole-3-thione, anethole dithionethiol), a potential suppressor of complex I superoxide/hydrogen peroxide (ROS) production was evaluated in a sheep model of regional ischemia in order to demonstrate cardioprotective properties against infarct size and left ventricular function remodeling.

Methods: A series of experiments was performed in vitro on isolated mitochondria and on C2C12 cells to clarify the mechanism of action and to test whether OP2113 impacts biological variables of mitochondria. In vivo, anesthetized sheep underwent 60 min ischemia and 120 min reperfusion and either received OP2113 (1-5 µg/kg, i.v at start of and for the duration of the reperfusion) or the vehicle. The animals underwent then a 3-day follow-up period until euthanasia. Ischemic biomarkers, troponin I, CPK, and ventricular function through echocardiography were quantified during reperfusion and infarct size through histological analysis.

Results: OP2113 reduced ROS production from site IQ in mitochondria isolated from rat skeletal muscle, with IC50 of 26 ± 1.4 µM (n = 3). It is specific; IC50 values for other sites are at least 15-fold higher (site IIIQo – 414 µM; site IIF – 582 µM; sites IF/DH, PF, GQ > 5 mM). Furthermore, OP2113 did not affect oxidative phosphorylation, respiration or growth of C2C12 cells. In the sheep model, OP2113 (1-10 µg/kg) dose-dependently prevented reperfusion-induced ST segment increase during the first minutes. When OP2113 plasmatic concentration was superior to 1 ng/mL (generally associated with a threshold dose of 5 µg/kg), troponin Ic levels measured over the experiment was strongly decreased and the cardiac function significantly improved (+86%), when compared to the vehicle group (left panel). Finally, the infarct size was diminished by 57% comparing to the vehicle group (10.3% vs 23.8%, respectively, right panel).

Conclusion: In a large animal model of ischemia-reperfusion, OP2113 with very low infused dose, reduced ST segment elevation, reduced troponin release, improved left ejection fraction and reduced infarct size. Collectively, these results demonstrate that OP2113, through a new mechanism of action, is a potent cardioprotective compound.