Pre-ischemic succinate dehydrogenase inhibition is protective against ischemia-reperfusion injury in rat and human myocardium with and without diabetes mellitus

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Background:
Ischemia-reperfusion (IR) injury can be attenuated through modulation of mitochondrial metabolism with succinate dehydrogenase (SDH) inhibition by dimethyl malonate (DiMAL). However, it is unknown whether SDH inhibition yields protection in aged, diabetic individuals and whether protection translate into human cardiac tissue.

Purpose:
We wished to evaluate if SDH inhibition can be protective in aged, diabetic rat hearts and could be translated to the human myocardium.

Methods:
We studied infarct size in aged non-diabetic and diabetic rat hearts subjected to isolated, retrograde perfusion and global ischemia and reperfusion. The hearts were randomized to: Sham hearts, IR injured hearts and IR injured hearts co-perfused with 0.1 mM or 0.6 mM DiMAL. Infarct size and mitochondrial respiratory capacity were evaluated post-ischemic. To translate our findings into human cardiac tissue, we tested the efficacy of DiMAL treatment in human atrial trabeculae from patients with and without diabetes mellitus undergoing cardiac surgery. We randomized atrial trabeculae to: IR injury, IR injury treated with ischemic preconditioning (IPC) and IR injury treated with 5 mM DiMAL. Contractile force recovery and mitochondrial respiratory capacity were evaluated post-ischemic.

Results:
In non-diabetic rat hearts, DiMAL 0.1 mM reduced infarct size/area-at-risk (IS/AAR) compared to IR hearts (53 ± 7% vs. 69 ± 6% of IS/AAR; p<0.05). In diabetic hearts, an increased concentration of 0.6 mM DiMAL was required to confer protection (62 ± 13% vs. 80 ± 8% of IS/AAR; p<0.05). Mitochondrial complex I linked respiratory capacity was higher in both Sham and DiMAL 0.1 mM groups than with DiMAL 0.6 mM in non-diabetic hearts (157.4 ± 26.5 and 140.0 ± 35.3 vs. 81.8 ± 42.4 pmol O2/(s*mg); p<0.01 and p<0.05). In trabeculae from humans without diabetes mellitus, IPC and DiMAL improved contractile force recovery compared to IR (43 ± 12% and 43 ± 13% vs. 23 ± 13%, p<0.05). In trabeculae from patients with diabetes, IPC but not DiMAL administration improved contractile force recovery compared to IR (48 ± 16% and 19 ± 7% vs. 25 ± 13%, p<0.01 and p>0.99). Mitochondrial complex I linked respiration capacity did not improve by IPC or DiMAL compared to IR in non-diabetic trabeculae (p>0.99).

Conclusion:
Inhibition of the SDH by DiMAL protects the aged non-diabetic and diabetic heart from IR injury but the threshold for cardioprotection is increased in diabetic rat hearts. DiMAL provides cardioprotection similar to IPC in non-diabetic trabeculae but does not protect the human diabetic myocardium when given in identical concentrations. SDH inhibition can provide protection in both animal and human tissue and may provide a new target for pharmacologic conditioning in patients.
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