Inhibition of Type 2 Sodium-Glucose Transporters and Na^+/H^+ Exchanger-1 produces similar cardioprotective effects in response to ischemia-reperfusion injury

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Background and Hypothesis: Recent studies indicate that inhibition of Type 2 Sodium-Glucose Transporters (SGLT2i) augments diastolic filling volume and mitigates myocardial ischemic injury. This study tested the hypothesis that inhibition of the Na^+/H^+ Exchanger-1 (NHE-1) mimics the cardioprotective effects of SGLT2i in response to ischemia-reperfusion injury.

Experimental Design or Project Methods: Lean swine (~50 kg) were anesthetized, a thoracotomy performed, and perivascular flow transducers placed around the left anterior descending (LAD) and circumflex coronary (LCX) arteries. A pressure-volume (PV) catheter was then inserted into the left ventricle. Swine received a 15 min infusion of vehicle (DMSO; n = 3), the SGLT2i Canagliflozin (30 μM; n = 3), or the NHE-1 inhibitor Cariporide (1μM; n = 3) prior to a 60 min total occlusion of the LCX and 2-hour reperfusion period. Following reperfusion, the LCX was re-occluded and a 2.5% Patent Blue 5 solution was administered to identify area at risk. The heart was excised, sectioned, and incubated in a 2,3,5-triphenyltetrazolium chloride (TTC) solution. Images were collected and analyzed for area at risk and infarct size.

Results: In the vehicle treated group, 2 of the 3 swine studied died prematurely before the completion of the protocol; one at baseline and one during ischemia. Our initial findings support that left ventricular end diastolic volume increases in response to regional myocardial ischemia in swine that received either Canagliflozin or Cariporide. This increase in diastolic volume was associated with an increase in stroke volume (i.e. Frank-Starling effect) and a reduction in myocardial infarct size in both treatment groups. Blood pressure tended to decrease to a similar extent in all groups.

Conclusion and Potential Impact: These pilot studies suggest that inhibition of SGLT2 and NHE-1 produces similar functional and protective effects in response to regional ischemia-reperfusion injury. Further experiments are needed to corroborate these findings and examine the extent to which SGLT2i directly modulates NHE-1 activity.