

SGLT2 inhibitors: reviving the NHE cardioprotection hypothesis?

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The sodium-glucose linked transporter-2 (SGLT2) inhibitors, designed and targeted to improve glycaemic control by attenuating renal glucose re-uptake, are emerging to be one of the most impactful cardiovascular drug classes of recent times. With clear and rapid-onset benefit upon cardiovascular outcomes, particularly in respect to heart failure rehospitalisation, SGLT2 inhibitors are rapidly becoming an essential part of the Cardiologist's pharmacopeia. Remarkably however, the mechanisms belying the cardioprotective effects of SGLT2 inhibitors remain far from clear. Understanding how these drugs manifest their benefits is not a purely academic exercise: identifying how they influence the cardiovascular system will not only improve our understanding of these drugs and the pathophysiology of cardiovascular disease, but also enable re-purposing of these drugs beyond their current indication of patients with type 2 diabetes mellitus.

There has been much speculation as to the mechanisms of SGLT2 inhibitor-mediated cardioprotection, with many hypotheses being proffered. One such mechanism is through an off-target effect of SGLT2 inhibitors upon the sodium-hydrogen exchanger (NHE). A plasma membrane-bound antiporter, NHE plays vital role in maintaining intracellular pH and ion homeostasis under physiologic conditions. Within the myocardium, NHE-1 is the predominant NHE isoform. During myocardial ischaemia, lactic acidosis leads to activation of NHE, extruding H⁺ ions to the extracellular space driven by inward Na⁺ exchange. The resultant rise in intracellular Na⁺ consequentially leads to elevation of intracellular calcium (Ca²⁺) through sodium-calcium exchanger (NCX) activity attempting to maintain Na⁺ homeostasis. With calcium-induced calcium release from the intracellular calcium stores such as sarcoplasmic reticulum, disruption of outer mitochondrial membrane integrity, mitochondrial swelling and release of apoptosis-inducing factors including cytochrome-C, the myocardial cellular population is rendered vulnerable to both necrosis and programmed cell death. This vulnerability becomes particularly acute during reperfusion; restoration of intracellular pH and the release of reactive oxygen species, in conjunction with already calcium-loaded cells, is a particularly fertile environment favouring opening of the mitochondrial transition pore and activation of lethal cell death pathways.

NHE inhibition is thus an attractive hypothesis in the prevention of ischaemia and reperfusion injury. Many pre-clinical studies in animal models of coronary artery occlusion have shown that use of NHE inhibitors during ischemia have the potential to reduce infarct size, myocardial contracture, arrhythmias, post-ischemic myocardial oedema and improve functional recovery upon reperfusion. Increased NHE activity in the heart, vasculature and kidney has also been reported in the setting of diabetes, cardiac hypertrophy and heart failure and chronic NHE inhibition has been shown to alleviate symptoms of hypertrophy and heart failure in rabbits. Despite this, clinical translation of the fundamental research findings has largely been disappointing. Crucially, NHE needs to be inhibited prior to the onset of ischaemia, whereas administration of NHE inhibitors just prior to or soon after the onset of reperfusion has been found to be largely ineffective. This limits the use of NHE inhibitors to situations where there is a predictable myocardial injury, such as coronary artery bypass surgery. But if one were to want to tackle episodes of unpredictable ischaemia (acute coronary syndromes) or cellular injury (as found in heart failure), the ideal solution would be administer the drug over the long-term, such that it was always present at the time of myocardial jeopardy.

SGLT2 inhibitors, in the management of type 2 diabetes, are drugs that are taken every day to ensure good glucose control – and if they were also to function as a NHE inhibitor, could represent the ideal “anti-ischaemic injury” drug for the management of patients at high-risk of myocardial ischaemia. Unsurprisingly, therefore, recent work from Bartscheer et al. and Uthman et al. has renewed interest in the area of NHE1 inhibition and cardioprotection. Bartscheer et al. showed that the SGLT2i Empagliflozin directly inhibits NHE1 activity in isolated rat and rabbit cardiomyocytes, independent of its effect on cardiac SGLT activity. Uthman et al. also showed that the SGLT2i Empagliflozin, Dapagliflozin and Canagliflozin directly inhibited NHE1 activity in isolated mouse cardiomyocytes potentially through direct interaction with the extracellular Na⁺-binding site of NHE1. Thus, SGLT2 inhibitors appear to have an off-target NHE inhibitory effect, and as such may be cardioprotective: an attractive hypothesis that may go some way to explain the early separation of cardiovascular events in the clinical outcome studies, EMPA-REG, CANVAS and DECLARE-TIMI58.

In a recent study published in Cardiovascular Research, Uthman et al. have undertaken to further study SGLT2/NHE hypothesis, to extend their prior in-vitro data into an ex-vivo Langendorff mouse model of ischaemia reperfusion. Comparing the effects of Empagliflozin with the NHE-1 inhibitor, Cariporide, they find equivalent alterations in the time to ischaemic-contraction, and the two drugs did not appear to interact with one another from the perspective of this end-point. However, the anticipated reduction of infarct size, clearly seen following the pre-administration of the NHE inhibitor, was absent with Empagliflozin. At first, this data appears surprising, but the absence of SGLT2-mediated protection, ex-vivo, is entirely consistent with emerging data from a number of labs. We have seen a complete absence of protection in both mouse and rat with Phlorizin, a mixed SGLT2 and SGLT1 inhibitor (unpublished data), and similarly with the SGLT2 inhibitor, Canagliflozin in rat (Lim et al). Botker’s group also fail to observe significant attenuation of infarct size, ex-vivo, following Empagliflozin administration in rat. However both we, with Canagliflozin in rat, and Andreadou et al., with Empagliflozin in mouse, show significant attenuation of infarct size when the SGLT2 inhibitor is administered over a period of weeks to the whole animal. The ex-vivo heart model may therefore have some limitations in terms of understanding the mechanisms of cardioprotection as it relates to the benefits found following SGLT2 inhibition. In this study, Uthman have attempted to make their ex-vivo perfusion system more “physiological” by the addition of insulin, which has the potential to increase myocardial glucose uptake through GLUT4 mediated mechanisms. Interestingly, insulin abrogated the previously observed changes in ischaemic contraction in both the SGLT2 inhibitor and the NHE inhibitor groups.

These data could be taken to weaken the strength of the SGLT/NHE cardioprotection hypothesis. One needs to be cautious with this interpretation however. The Langendorff model is a useful, reductionist model that has its strengths and weaknesses, and the data needs to be interpreted in this light. SGLT inhibitors do not *directly* protect the heart against necrotic cell death following injurious ischaemia/reperfusion injury ex-vivo. However they do protect in-vivo, which may implicate a remote target other than directly upon the heart to manifest this effect. Moreover, the NHE inhibitory effect of SGLT2 inhibitors remains extremely interesting. Cardioprotection can be defined in many different ways: protection against lethal cell injury, adverse myocardial remodelling, myocardial dysfunction or cardiac arrhythmia. One of the most potent effects of SGLT2 inhibition in the clinical trials has been the reduction of patient hospitalisations with decompensated heart failure. In this respect, an in-vivo model may offer the best opportunity to reveal a benefit – and protection of cellular function against the adverse remodelling and ionic milieu of the failing heart may be one of the key mechanisms of protection. As experimental data evolves, we will need to develop new models of heart failure, ischaemia reperfusion injury and arrhythmia – most likely in-

vivo – to better understand the mechanisms of SGLT2 inhibition mediated protection in order to optimise their application, both in type 2 diabetes and potentially also, to non-diabetic patients.

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