Mitochondrias’ sense of SNO: pathway to cardioprotection in ischaemic preconditioning

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This Editorial refers to ‘Ischaemic preconditioning preferentially increases protein S-nitrosylation in subsarcolemmal mitochondria’ by J. Sun et al., pp. 227–236.

Ischaemic heart disease (IHD) is the leading cause of death worldwide. The optimal therapy in an acute myocardial infarction is the timely reperfusion of the ischaemic myocardium. This leads to a reduction in infarct size (IS) and improves the prognosis of the patients. The reperfusion of the ischaemic myocardium, however, can cause injury itself and first clinical investigations revealed that up to 50% of the final IS may be caused by reperfusion (for review, see1). As the prevalence of IHD increases and becomes obvious that modulation and protection of SSM is of special interest in protecting the heart from I/R injury.

During the last years, different endogenous cardioprotective strategies such as ischaemic preconditioning (IPC), ischaemic postconditioning, and remote ischaemic preconditioning have been introduced. IPC has emerged as one of the most powerful cardioprotective strategies for reducing IS even in man, although the relevance of IPC is limited to experimental studies or elective percutaneous coronary interventions and coronary artery bypass graft surgery in patients.

The signalling pathways underlying IPC are numerous, complex, and still not fully understood (for detailed review, see6). Nitric oxide (NO), derived from NO synthases (NOS) or nitrite,5–7 seems to play an important role in mediating the cytoprotective effects of IPC. Early studies have suggested that NO activates the classical soluble guanylyl cyclase (sGC)/cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) pathway, thereby acting cardioprotective (for review, see6,9). This theory has at least been extended, suggesting that S-nitrosylation of cardiac proteins through stimulation of the endogenous NOS–NO pathway may be crucial in cardioprotection. Here, mitochondria express their own NOS and produce NO,10 and indeed mitochondria can be protected by IPC independent of cytosolic signalling.11

Mitochondria, the key regulators of cardioprotection, represent the main target in SNO formation in the heart during IPC. One reason might be that a large number of mitochondrial proteins contain cysteins and it has been suggested that the NO signal is transduced via caveolae to the mitochondria (for review, see12). Cardiac mitochondria comprises at least two distinct subpopulations: one beneath the sarcolemma (subsarcolemmal mitochondria; SSM), and another along the myofilaments (interfibrillar mitochondria; IFM) with only 10% of total mitochondria being SSM. Ultrastructure and protein content differ between these two mitochondrial subpopulations.13 Increased nitrosation of one key protein involved in initiating cardioprotection but only being present in SSM, namely connexin-43, occurs with IPC modulating the release of reactive oxygen species.14 SSM are critical in the regulation ofionic homeostasis and cell integrity and disruption of these mitochondria initiate pathways leading to cell death. It therefore becomes obvious that modulation and protection of SSM is of special interest in protecting the heart from I/R injury.

Sun et al.15 take a further step and shed light on the protein SNO formation in the different subpopulations of mitochondria during IPC. In an ex vivo perfused Langendorff mouse heart model, SNO was higher in SSM compared with IFM. Following IPC, SNO significantly increased in SSM (Figure 1), but not in IFM and the protection afforded by IPC on mitochondrial function was abolished by ascorbate (a reducing agent which decomposes SNO) only in SSM; these findings confirm previous data that only SSM are a target of IPC.11 In the latter study, IPC did not protect SSM when connexin-43 was replaced by connexin-32, and indeed endothelial NOS, caveolin-3, and connexin-43 were also only detected in SSM in Sun et al. Thus, only SSM but not IFM may play a crucial role in IPC-mediated cardioprotection. The results of the present study are indeed very important and may change our future direction in IPC-research focusing on SSM as an important target.

The study by Sun et al.15 is of great importance and the authors should be congratulated. Nevertheless, the current experimental approaches need to be extended in the future to in vivo models. Whether the results of saline perfused Langendorff ex vivo hearts can easily be transferred to the in vivo situation can only be hypothesized. It is well known that SNO chemistry may differ in the surrounding of plasma proteins and red blood cells presenting with huge amounts of free sulphydryl groups.16 Although such an approach may be tricky, it should not be neglected. This is surely a crucial step to further try and include cardioprotective strategies into clinical practice.
Figure 1  Subsarcolemmal (SSM) and interfibrillar (IFM) mitochondria contain S-nitroso(yl)ated proteins (SNO); the amount of SNO is greater in SSM compared with IFM at baseline. Nitric oxide (NO) is produced within SSM and IFM through an NO synthase (NOS). With ischemic preconditioning, endothelial NOS (eNOS), which is normally localized in caveolae at the sarcolemma, translocates towards SSM thereby selectively increasing its SNO content. One important protein which becomes S-nitroso(yl)ated is connexin-43 (Cx43), being present only in SSM and being essential for ischemic preconditioning’s cardioprotection.

References