Mitochondrial metabolism revisited: a route to cardioprotection

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This editorial refers to 'Inhibition of the malate–aspartate shuttle by pre-ischaemic aminooxyacetate loading of the heart induces cardioprotection' by N.B. Støttrup et al., pp. 257–266, this issue.

Ischaemic preconditioning confers strong protection against myocardial ischaemia–reperfusion injury. Although its therapeutic application in the case of acute coronary syndromes is not possible in general, the cellular and molecular processes leading to preconditioning protection may be of interest for the designing of cardioprotective therapies.

Many cellular processes have been shown to be involved in preconditioning, including the stimulation of adenosine, bradykinin, and opioid membrane receptors, signalling cascades including PKCe and PKG, nitric oxide, and pro-survival kinases such as Akt. Mitochondria, a platform of cell signalling and a switch for cell death and survival, are generally regarded to play a key role in transmission and amplification of preconditioning signalling.

It appears that many signalling processes involved in ischaemic preconditioning converge at the mitochondria. Støttrup et al. show that by inhibiting the malate–aspartate shuttle (MAS), they can induce cardioprotection and suggest that this inhibition can be a mechanism inherent to ischaemic preconditioning. The MAS is a biochemical system that translocates reducing power from the cytosol into the mitochondria, thus linking glycolysis with the electron transport chain. Although previous studies have shown that treatments aimed at reducing cell death also improve mitochondrial respiratory capacity at the time of reperfusion, the present work demonstrates that modifying mitochondrial function through inhibition of the MAS is able to induce cardioprotection and provides original and detailed information on the link between mitochondrial metabolism and cardioprotection. Thus, modification of mitochondrial function is not only a consequence of preserved cell viability during reperfusion but can also itself prevent cellular death.

Heart metabolism is extremely versatile and able to cope with highly variable energy demands. Its modulation for therapeutic purposes has been proposed to be useful in different conditions.

Mitochondrial metabolism is a pharmacological target in heart failure, where it has been shown that shifting mitochondrial oxidation preference from fatty acids to glucose improves clinical outcome, and it is being increasingly used in the treatment of angina. In the context of myocardial infarction, metabolic modulation has been attempted usually with glucose–insulin–potassium solutions, an unspecific approach that has provided dubious results. Although there is no evidence that a pharmacological treatment destined to alter energetic metabolism would work in the case of ischaemia–reperfusion injury, a specific modulation of heart metabolism could in theory provide important advantages. Thus, it would appear to be well worth the effort to investigate strategies such as MAS inhibition. In fact, although some studies have focused on how mitochondrial integrity (oedema, morphology) or, better, respiration (oxygen consumption) is affected by a variety of drugs and treatments and how this is related to cell survival, very little is known about the relation between energy (ATP) production and cardioprotection. One has to bear in mind that oxygen consumption is just a by-product of energy production. Taking all this into account, it makes sense to study glucose oxidation in order to know how the modulation of energy metabolism could influence cardioprotection.

A strong point of the article by Støttrup et al. is that they are able to show that by blocking the MAS, metabolic changes reach far beyond the mitochondria, from membrane glucose trafficking to glycolysis in the cytoplasm. In this case, metabolic changes could also trigger preconditioning-like cardioprotection by switching signalling cascades. Since energy metabolism is at the heart of mitochondria, the idea of cardioprotection and metabolism being linked is plausible.

The authors try to explain the link between mitochondrial metabolism and cardioprotection through reactive oxygen species (ROS) production. They measure complex I activity and ROS production prior to index ischaemia. Although MAS inhibition and ischaemic preconditioning show a similar reduction in respiratory control ratio when compared with controls, only MAS inhibition is able to reduce ROS production. Unfortunately, the authors are unable to draw conclusions about the effect of MAS inhibition on myocardial ROS formation during ischaemia and reperfusion. The authors analyse the effects of MAS inhibition on a variety of mechanisms of protection.
against reperfusion injury; however, it cannot be excluded from their data that MAS inhibition acts through other mechanisms as well, e.g. a slower restoration of ATP availability during the first few minutes of reperfusion could protect cardiomyocytes against hypercontracture during the initial minutes of reperfusion. Other interventions resulting in progressive rather than abrupt restoration of normal conditions during reperfusion, in particular, ischaemic post-conditioning, have proven protective against cell death. In fact, post-conditioning has been shown to reduce phosphocreatine overshoot during reperfusion. In conclusion, the work by Støttrup et al., by showing that metabolic modulation may affect cell survival during ischaemia–reperfusion, opens a new field of opportunities to generate preconditioning-like cardiac protection by means of pharmacological intervention. Further studies should address in detail whether this modulation has a protective effect through a direct mechanism or if it works through a metabolic signalling cascade.

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**References**