Mitochondrial metabolism revisited: a route to cardioprotection

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Online publish-ahead-of-print 5 August 2010

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 PKC ε 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.
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.15

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.

Conflict of interest: none declared.

References