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PERSPECTIVES

Cardioprotection by preconditioning: K_{ATP} channels, metabolism, or both?

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When Noma (1983) discovered ATP-sensitive K^+ (K_{ATP}) channels in the sarcolemma of cardiac muscle, he also proposed a function; shortening the cardiac action potential and so sparing energy in hypoxia or ischaemia. This idea became of particular interest soon after the description of ischaemic preconditioning (IPC), in which brief periods of ischaemia protect the heart against damage by subsequent prolonged ischaemia. Several studies showed that IPC could be mimicked by pharmacological K_{ATP} channel activators, while the K_{ATP} channel blocker glibenclamide was found to prevent IPC. Thus the sarcolemmal K_{ATP} channel became widely accepted as a mediator of the cardioprotection resulting from IPC. In the latter 1990s, however, studies showing that cardioprotection was not always associated with action potential shortening led to the suggestion that a different K_{ATP} channel, expressed in the mitochondrial inner membrane (mitoK_{ATP}), played a central role in protection (reviewed by Gross & Fryer, 1999; Grover & Garlid, 2000). The mechanism by which mitoK_{ATP} opening might be protective is uncertain; hypotheses include mitochondrial depolarisation to limit Ca^{2+} accumulation, mitochondrial uncoupling, preservation of mitochondrial intermembrane architecture, and the release of reactive oxygen species (ROS).

The molecular structure of mitoK_{ATP} remains unknown, however, and the evidence for its involvement in cardioprotection is almost entirely pharmacological, based on the selectivity for mitoK_{ATP} of the channel opener diazoxide and the inhibitor 5-hydroxydecanoate (5-HD), which have been widely shown to mimic and block IPC, respectively. However, diazoxide has been shown to also activate sarcolemmal K_{ATP} when ADP is raised (D'hahan *et al.* 1999). In this issue of *The Journal of Physiology* Hanley *et al.* (2002) show that both of these compounds also have metabolic effects in the heart that are independent of K_{ATP} channels, but could explain their effects on cardioprotection. They show that diazoxide inhibits succinate oxidation and succinate dehydrogenase activity, in agreement with the finding that diazoxide reduces succinate-dependent respiration in intact cardiac myocytes (Ovide-Bordeaux *et al.* 2000). Hanley *et al.* (2002) propose that partial inhibition of electron transport may be responsible for the preconditioning effect of diazoxide. Several studies have shown that respiratory chain inhibitors can confer preconditioning, possibly triggering protective pathways via the release of ROS. Importantly, Hanley *et al.* (2002) also suggest an alternative mechanism of action of 5-HD, showing that it forms a substrate for the mitochondrial enzyme acyl-CoA synthetase, which can convert it to 5-hydroxydecanoyl-CoA (5-HD-CoA). They propose that the inhibitory effect of 5-HD on preconditioning might result from β-oxidation of 5-HD-CoA, so partially bypassing inhibition of the respiratory chain.

The demonstration of non-channel effects of diazoxide and 5-HD in the heart makes identification of the role of the mitoK_{ATP} channel more difficult. It is no longer possible to assume that effects of either diazoxide or 5-HD necessarily indicate the involvement of mitoK_{ATP}. Another approach that has been used to indicate mitoK_{ATP} activation in cardiac muscle is an increase in flavoprotein autofluorescence, indicative of mitochondrial oxidation (Liu *et al.* 1998). However, Hanley's paper and other recent work (Lawrence *et al.* 2001) shows that diazoxide, at concentrations expected to open mitoK_{ATP} very effectively and that are cardioprotective, does not increase flavoprotein fluorescence in guinea-pig or rat myocytes. These findings raise questions about the reliability of flavoprotein oxidation as an indicator of mitoK_{ATP} activation. Perhaps the key step that is now needed is elucidation of the molecular composition of mitoK_{ATP}, opening the way for the use of molecular rather than pharmacological strategies to clarify its functional roles.

Interestingly, the sarcolemmal K_{ATP} channel, whose molecular composition is established, is undergoing a rebirth in terms of its role in cardioprotection. Recent studies suggest that it does play a protective role in ischaemia, and may be especially important in functional recovery after reperfusion (Toyoda *et al.* 2000; Sanada *et al.* 2001). Strong evidence for a major role in the mouse heart has come from knockout of Kir6.2 (the pore subunit of sarcolemmal K_{ATP}), which abolishes the protective effect of IPC (Suzuki *et al.* 2002). Protective mechanisms involving K_{ATP} channels, either sarcolemmal or mitochondrial, and metabolic effects like those described by Hanley *et al.* (2002) are not mutually exclusive. For example, metabolic effects could trigger later channel activation, while it has been proposed that mitoK_{ATP} opening, like partial respiratory chain inhibition, might lead to release of ROS (Pain *et al.* 2000). Although Hanley *et al.* (2002) show an alternative way in which diazoxide could generate ROS, their paper does not preclude such an effect. Thus the relative importance of sarcolemmal or mitochondrial K_{ATP} channels and of non-channel metabolic effects for cardioprotection, either pharmacological or induced by IPC, remains to be established. This, and the exact mechanisms by which these components cause protection, remain fascinating questions for future research.

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