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COMMENTARY

The role of mitochondrial K_{ATP} channels in the antiarrhythmic effects of ischaemic preconditioning in dogs

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Myocardial preconditioning (IPC) is a phenomenon in which brief periods of ischaemia produce a phenotype in the heart and other organs in which the tissue is protected against the deleterious consequences of a subsequent more prolonged period of ischaemia (Murry *et al*., 1986). IPC has been shown to exist in all species tested so far including man and has been shown to consistently produce a marked reduction in myocardial infarct size in all species and models tested and in some studies a reduction in myocardial stunning and the incidence of cardiac arrhythmias and ventricular fibrillation (VF), although the latter end point (arrhythmias, VF) of ischaemia/reperfusion injury has been less thoroughly studied and is more controversial. A number of triggers and mediators of IPC to reduce infarct size have been identified and one of the central triggers and mediators is thought to be the ATP-dependent potassium channel (K_{ATP} channel). Two K_{ATP} channels have been suggested to exist in the cell, the sarcolemmal (sarc K_{ATP}) and a mitochondrial (mito K_{ATP}) channel (Gross & Fryer, 1999; Grover & Garlid, 2000).

Recent studies have suggested that it is the mito K_{ATP} channel that is responsible for the marked cardioprotective effect of IPC to reduce infarct size (Garlid & Grover, 1997; O'Rourke, 2000). On the other hand, the role of either K_{ATP} channel to mediate a protective effect of IPC to attenuate the incidence of cardiac arrhythmias is less well established. In one of the first studies to address the role of K_{ATP} channels in the antiarrhythmic effect of IPC, Vegh *et al.* (1993) observed that the nonselective K_{ATP} channel blocker glibenclamide, did not block the effects of two 5 min episodes of IPC to attenuate arrhythmias or the incidence of VF in the canine heart. Based on these data the authors concluded that the mechanisms responsible for the protective effect of IPC to reduce the severity of arrhythmias and infarct size are different. Subsequently, Rioufol *et al.* (1997) presented data to suggest that the K_{ATP} channel plays no role in VF in preconditioned pig hearts. In this study, glibenclamide was used as a blocker of K_{ATP} channels and nicorandil as an opener of K_{ATP} channels.

In the current issue of the journal, Vegh and Parratt (1993) have re-examined the role of the K_{ATP} channel, in particular the mito K_{ATP} channel, in preconditioning against arrhythmias and the incidence of ventricular fibrillation (VF) in a canine heart subjected to 25 min of occlusion and 10 min of reperfusion. Their intriguing results suggest that the mito K_{ATP} channel appears to act as a trigger to prevent the incidence of VF based on the observation that the putative mito K_{ATP} selective antagonist 5-hydroxydecanoic acid (5-HD) only prevented the protective effect of IPC to reduce VF when it was administered prior to a single 5 min preconditioning stimulus but not when administered after IPC but prior to and during the 25 min ischaemic period. In further support for a key function of the mito K_{ATP} channel in IPC against VF, the authors also demonstrated that pretreatment with the putative selective mito K_{ATP} channel opener diazoxide reduced the incidence of VF similar to that of IPC and this effect was also blocked by 5-HD.

These results are in agreement with those of Kita *et al.* (1998) who also showed that 5-HD blocked the antifibrillatory and antiarrhythmic effect in preconditioned rat hearts subjected to one 2 min preconditioning stimulus. Additionally in the current study, both IPC and diazoxide reduced the number of ventricular premature beats, the number of episodes of ventricular tachycardia, the severity of ST segment elevation during ischaemia and the degree of inhomogeneity of electrical activation. These effects were abolished when 5-HD was administered before IPC or diazoxide administration but only the arrhythmias and not the incidence of VF were attenuated when 5-HD was administered after IPC. These results suggest that mito K_{ATP} channel opening is more important as a trigger of IPC than as an end effector against arrhythmias which is in agreement with recent results of Pain *et al.* (2001) when studying the role of the mito K_{ATP} channel against infarction in rabbit hearts.

However, a recent study by Wang *et al.* (2001) suggested that diazoxide produces IPC against infarction and that its effect to trigger cardioprotection was antagonized by 50 μM 5-HD, whereas 200 μM of 5-HD was required when the antagonist was administered during the prolonged ischaemic period. Based on these results, it may be possible if Vegh & Parratt (current study) had administered a higher dose of 5-HD after IPC or diazoxide treatment, they might have observed a more important role for the mito K_{ATP} channel as a mediator of protection against VF and other arrhythmias than that observed in the present study. In addition, it is somewhat surprising that 5-HD was able to block the protective effects of IPC on VF and other arrhythmias in this model and glibenclamide, which would also be expected

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to block both sarc and mito K_{ATP} channels equally, was not effective in this same model in their previous study.

One possible reason for this discrepancy may be the result of a slight difference in their protocols in the two studies. In the first study, two 5 min IPC stimuli were used to produce IPC, whereas in the current study, one only 5 min IPC stimulus was used. It is likely that it is more difficult to block the protective effect of multiple preconditioning episodes as opposed to a single IPC stimulus and there are a number of examples suggesting that this is the case in the preconditioning literature (Gross & Fryer, 1999).

Another possibility may reside in the different properties of glibenclamide on the incidence of arrhythmias independent of IPC. In several studies in canine hearts, Billman *et al*. (1993; 1998) have shown that sulphonylurea compounds such as glibenclamide (Billman *et al*., 1993) or HMR 1883 (Billman *et al*., 1998) are antifibrillatory in dogs so it is possible that this direct effect prevented glibenclamide from demonstrating an antagonistic effect against VF in the previous canine study by Vegh *et al*. (1993). In addition several studies (Kita *et al*., 1998; Wolk *et al*., 1999) have shown that 5-HD has no direct effect on the incidence of VF or ventricular tachycardia in the absence of IPC, which would suggest that this K_{ATP} antagonist is a better tool for studying the role of K_{ATP} channels in IPC when VF or ventricular arrhythmias are the endpoint of injury.

One important caveat that should be mentioned concerning the use of pharmacological agents to make firm conclusions about the triggers and mediators of IPC or ischaemia/reperfusion injury in this and other studies is that none of the drugs used have an absolute specificity for the ion channel being studied. Several recent studies (Ovide-Bordeaux, 2000; Hanley *et al*., 2002) have presented evidence that diazoxide and 5-HD may not be producing their effects directly by acting on a mitoK_{ATP} channel and may in fact be exerting their effects directly on the electron transport chain. These investigators both showed that diazoxide produces an inhibitory effect on the succinate dehydrogenase step in the electron transport chain and by producing reactive oxygen species (ROS) this compound may be activating key intracellular kinases which may be responsible for the ultimate cardioprotection observed. Concomittantly, Hanley *et al*. (2002) and Das & Halestrap (2002) also found that 5-HD can be converted to 5-HD CoA in mitochondria and this compound could have important effects on cellular energy metabolism which may be antagonistic to the effects of IPC produced by ischaemia or drugs such as diazoxide. Obviously, future studies are needed to further address the locus of action of these K_{ATP} channel active compounds in the cell and mitochondria.

In conclusion, the results of the present study are important and suggest that the mechanism responsible for the infarct limiting and antifibrillatory and antiarrhythmic effects of IPC, at least in the context of the K_{ATP} channel, may be similar in this canine model. Further studies in other species and models are necessary to confirm these findings obtained in dogs and to address the cellular mechanisms responsible for these dramatic effects on arrhythmis and VF in the ischaemic/reperfused myocardium.

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