Cardiovascular controversies

An explanation for the reported observation that ATP dependent potassium channel openers mimic preconditioning

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The ischaemic preconditioning phenomenon remains one of the enigmas of cardiology. While adenosine A1 receptors appear to play a key role in this response, at least in rabbits, dogs, and pigs, the end effector responsible for the protection remains obscure. Recently Aachempach and Gross found that the ATP sensitive potassium channel (KATP) blockers, glibenclamide and 5-hydroxydecanoate (5HD), could block the protective effect of preconditioning.1,2 They and others further found that openers of the channel could mimic preconditioning. Most recently, they showed that preconditioning with adenosine could be blocked by glibenclamide. These observations prompted them to propose that the key element of preconditioning was an early opening of KATP channels during ischaemia. Opening the channel could be protective in that it shortens the action potential which would translate to less time in contraction and both spare ATP and allow less calcium entry, a putative mediator of ischaemic injury. 5HD has been reported to block adenosine induced preconditioning in the pig as well.3 The problem arose when we found that glibenclamide would not block the protection afforded by preconditioning in our rabbit model of infarction; nor would the KATP opener, pinacidil, mimic preconditioning.4 Glibenclamide also failed to alter preconditioning in the rat heart.5,6 The rat and rabbit observations would suggest that opening of KATP channels is not an absolute requirement for protection and therefore not likely to be the end effector of protection. An interesting twist in this story is that the anaesthetic agent seems to affect this system. Switching the anaesthetic from pentobarbitone to ketamine/xylazine has no effect on the ability of preconditioning to protect the rabbit heart. Surprisingly, however, the protection is completely blocked with glibenclamide when ketamine/xylazine is used as the anaesthetic (unpublished observation of the author and 7). Furthermore, pinacidil becomes protective with the new anaesthetic. Even more confusing, however, is the fact that we find that the adenosine receptor blocking agent, 8-p-sulphophenyl theophylline (SPT), completely eliminates the protective action of pinacidil.

One possible explanation for the discrepant data might be that pentobarbitone interferes with the ability of glibenclamide to interact with the KATP channel, but that seems unlikely since Gross and Aachempach used pentobarbitone in their dog studies2 and Grover et al used isolated anaesthesia-free rat hearts.8 Furthermore, we saw a brisk hypoglycaemic response to glibenclamide in pentobarbitone anaesthetised rabbits, suggesting that KATP blockade was working, at least at the pancreas. I, of course, have no explanation for all of these observations but I am willing to speculate on one. Burnstock’s laboratory9 have found that glibenclamide blocks the KATP blocker could block preconditioning. Perhaps enough adenosine is released from the myocytes during ischaemia under pentobarbitone anaesthesia for the extracellular ATP derived adenosine not to be required. That theory would certainly explain why SPT can block protection from pinacidil. The theory would also predict that blocking ecto 5’ nucleotidease would block preconditioning in dogs. Confirmation of the extracellular ATP theory will obviously require direct measurements of interstitial adenosine.

A final shortcoming of the KATP theory is that it fails to explain the “memory” associated with preconditioning. When the heart is exposed to a 5 minute period of ischaemia and then reperfused, it somehow remembers that it has been preconditioned and stays in a preconditioned state for up to one hour.10 To explain preconditioning one must not only show that A1 receptors are linked to the effector but one must also show why the preconditioned heart is different. Kirsch et al11 found that occupancy of A1 adenosine receptors caused KATP channels to open in rat myocytes. If that is the case, then why would these channels only open in preconditioned hearts when the A1 receptors should be fully populated soon after the onset of ischaemia in both preconditioned and virgin hearts? It is also difficult for me to understand why shortening of the action potential by 10% or 20% should be so protective. Varying the heart rate should have a similar effect on calcium entry, yet infarct size is very independent of heart rate in the rabbit model, even when paced.

References:
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