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COMMENTARY

Modulation of receptor sensitivity: possible therapeutic target?

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Ischaemic preconditioning and post-conditioning are cardioprotective interventions that salvage ischaemic myocardium and reduce infarct size. Yet this cardioprotective effect is not the sole response of the heart to ischaemic preconditioning and post-conditioning. It was known that protein kinase C activation in the signalling cascade of ischaemic preconditioning increased the affinity of the adenosine A_{2b} receptor so that much lower concentrations of adenosine caused A_{2b} receptor-dependent signalling. In this issue of the *British Journal of Pharmacology*, these cardioprotective interventions are shown to block desensitization of surface receptors on the sarcolemma of the cardiomyocyte and this receptor effect is divorced from any cardioprotection. Modulating receptor function through signalling pathways is a novel idea but, currently, whether these observations have any clinical relevance is not known. Additional investigations are warranted to determine whether this effect on receptors can be generalized to other surface receptors, and whether the effect can be harnessed to improve treatment of the patient with acute myocardial infarction.
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Abbreviations: GSK-3β, glycogen synthase kinase-3β; IPC, ischaemic preconditioning; IPoC, ischaemic post-conditioning; PTHrP, parathyroid hormone-related peptide

It is well known that ischaemic heart disease is the greatest cause of mortality in the USA and many other industrialized countries. Therefore, it is not surprising that there has been an enormous investment of time and resources to uncover pharmacological agents or other interventions that might affect favourably this threat to public health. Despite many efforts, there was no way of consistently salvaging ischaemic myocardium until the landmark report by Murry *et al*. (1986) who first introduced us to ischaemic preconditioning (IPC). Simply, four cycles of 5 min coronary occlusion/5 min reperfusion prior to 40 min of occlusion of the left anterior descending coronary artery in dogs reduced infarct size by 75%, compared with those dog hearts experiencing only the 40 min coronary occlusion. Paradoxically, more myocardial ischaemia made the heart resistant to infarction.

In the two decades that have passed since the initial report of preconditioning, we have learned a lot about the intracellular signalling pathways that are involved. Signalling can be divided into a pre-ischaemic trigger phase and a mediator phase at reperfusion (Tissier *et al*., 2007). Agonists to G_i-coupled receptors are released by the ischaemic cardiomyocytes during the preconditioning cycles. Those receptors initiate complex signalling that involves, variously, activation of matrix metalloproteinase, transactivation of the epidermal growth factor receptor and activation of phosphatidylinositol 3-kinase, Akt, nitric oxide synthase and protein kinase G. Opening of mitochondrial K_{ATP} channels causes release of reactive oxygen species from mitochondria, which in turn activate protein kinase C.

The mediator pathway is thought to protect the heart from the formation of lethal mitochondrial permeability transition pores, which destroy mitochondria in the first minutes of reperfusion. In preconditioned hearts, pore formation at reperfusion seems to be inhibited by the survival kinases, Akt and extracellular signal-regulated kinase, which are thought to exert that inhibition through another kinase, glycogen synthase kinase (GSK)-3β. It is unclear why that pathway is only active in hearts that have been subjected to IPC. We have published evidence that adenosine A_{2b} receptors control those kinases. The adenosine A_{2b} receptor is a very low affinity receptor with a K_d for adenosine of 16 $\mu mol \cdot L^{-1}$. Even in deeply ischaemic myocardium, the concentrations of adenosine would never get high enough to occupy that receptor effectively. Our finding was that protein kinase C appears to increase the affinity of the adenosine A_{2b} receptor so that

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much lower concentrations of adenosine can cause A_{2b} receptor-dependent signalling. We proposed that the difference between preconditioned and non-preconditioned hearts was the affinity state of adenosine A_{2b} receptors. Indeed adenosine A_{2b} receptor antagonists prevent protection in preconditioned hearts (Solenkova *et al.*, 2006), and knocking out the adenosine A_{2b} receptor produces a phenotype that cannot be preconditioned (Eckle *et al.*, 2007). Finally, adenosine A_{2b} receptor-selective agonists administered during late ischaemia and early reperfusion will mimic the protection conferred by IPC (Kuno *et al.*, 2007).

Ironically, IPC has little potential clinical value as it must be applied before the onset of ischaemia, an impossibility in the patient presenting to the hospital with an ongoing acute myocardial infarction, following plaque rupture and occlusion of the coronary artery. However, the discovery that IPC exerts its protection at reperfusion has allowed translation of the approach so that interventions can be applied just before reperfusion, an eminently feasible approach preceding opening of the coronary artery with an intravascular balloon and/or stent. There is an ever growing list of strategies that have been demonstrated to invoke protection by IPC at reperfusion. Foremost among them is ischaemic post-conditioning (IPoC) in which several very brief reperfusion–re-occlusion cycles immediately follow a prolonged period of coronary occlusion. In dogs, IPoC results in salvage of ischaemic myocardium, to an extent similar to that seen after IPC (Zhao *et al.*, 2003). Signalling in IPoC is also very similar to the post-ischaemic signalling observed in IPC (Yang *et al.*, 2004; 2005) and is believed to protect by the same mechanism as IPC. One theory holds that the staccato reperfusion keeps the pH of the tissue low during the first minutes of re-oxygenation (Cohen *et al.*, 2007). The low pH inhibits transition pores until IPC's signalling pathways can activate the survival kinases.

The key to our adenosine A_{2b} receptor theory is the idea that receptor signalling can be modulated in a way to provide a benefit to the heart. Modulating receptor function through signalling pathways is a novel idea. In this issue of *British Journal of Pharmacology*, Schreckenberg *et al.* (2009) report that IPoC and probably also IPC initiate signalling that acts to prevent ischaemia-induced parathyroid hormone-related peptide (PTHrP) receptor desensitization. Although their observations centre on the PTHrP receptor, they have some evidence that the β-adrenoceptor may respond similarly. PTHrP is released by ischaemic myocardium and appears to contribute to the functional recovery of hearts after ischaemia (Jansen *et al.*, 2003; Grohé *et al.*, 2004). PTHrP administered 30 min following release of a coronary occlusion in rat hearts has little effect, whereas in hearts protected with IPoC and, to a lesser extent IPC, PTHrP produces a significant negative inotropic effect, suggesting preservation of PTHrP responsiveness. These results were supported by the observation that a PTHrP antagonist administered just minutes before myocardial ischaemia can also preserve PTHrP responsiveness. Thus it appears that PTHrP released by ischaemic myocardium quickly desensitizes the receptors and this desensitization can be prevented by IPoC. Whether this actually contributes to IPoC's protective mechanism was not addressed; nor did they measure receptor number or affinity to determine whether the receptor was the target or one of its coupling proteins.

The mechanism by which IPoC prevented receptor desensitization is not known, but it is clearly not linked to successful myocardial salvage. Although the protein kinase C blocker chelerythrine blocked IPoC's cardioprotective effect, it did not prevent IPoC's ability to maintain receptor responsiveness. This divorce of receptor effect from myocardial salvage is unexpected and serves to stress how much we do not know about IPC and IPoC. The clinical relevance of these observations is uncertain. Perhaps, as suggested by Schreckenberg *et al.* (2009), preservation of receptor coupling may affect the remodelling process. As is often the case, this study leads to many other questions that will undoubtedly generate further investigations. It can certainly be said that IPC and IPoC are more than interventions that merely salvage ischaemic myocardium. In 1986, Murry *et al.* could not possibly have foreseen the far reaching studies that would be prompted by their most improbable observation, made 23 years ago.

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