Oestrogen plays a permissive role in cardioprotection

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This editorial refers to 'Loss of ischaemic preconditioning in ovariectomized rat hearts: possible involvement of impaired protein kinase C ε phosphorylation' by K. Shinmura et al., pp. 387–394, this issue.

Ischaemic preconditioning (IPC) is a powerful cardioprotective intervention. It can salvage upwards of 75% of the myocardium destined to otherwise infarct. This potent cardioprotective strategy has been observed in all animal species examined to date including mammals and birds.1 We have observed IPC’s protection in non-human primates (unpublished observation) and strong evidence exists of its efficacy in man.2,3 Since the initial description of IPC in 1986 by Murry et al.,4 many investigators have toiled to uncover its mechanism in the hopes of being able to apply the strategy clinically. As a result, much is now known concerning its mechanism.5

The protection results from signal transduction pathways emanating from surface receptors. During the preconditioning ischaemia, the receptor agonists bradykinin, opioid, and adenosine are released. The first two bind to G1-coupled receptors that trigger a complex cascade that involves nitric oxide production and opening of potassium channels in the mitochondria with subsequent redox signalling, which activates an important signalling molecule called protein kinase C (PKC). Adenosine, the third receptor agonist released by ischaemic myocardium, binds to its G1-coupled receptor, but its signalling bypasses the above pathway and activates PKC directly through phospholipases.6 Once the preconditioned state has been triggered, PKC is then poised to initiate another complex signalling pathway when the ischaemic heart is reperfused. That second mediator pathway is thought to protect by blocking the formation of the mitochondrial permeability transition pore.

Although IPC is not gender-specific, a second endogenous form of cardioprotection is. It is well known that women before menopause have a lower incidence of coronary artery disease and associated mortality. Following menopause, the incidence of both increases and eventually is equivalent to that seen in males.7 For many years oestrogen has been touted as the reason for this difference between females and males. Accordingly, it was believed that oestrogen supplements after menopause would block the inevitable increase in coronary disease. Large trials were organized. Regrettably few positive effects of oestrogen were observed and unwanted side-effects such as peripheral deep vein thrombosis and pulmonary emboli resulted in the early termination of trials and subsequent proscription of the use of oestrogen in post-menopausal women to prevent heart disease.8–10

The result of the large trials notwithstanding, there has been longstanding interest in how these two cardioprotective strategies might influence each other. In a clever experimental design, Shinmura et al.11 ovariectomized young female rats and treated some by replacing with oestrogen for 4 weeks and others with placebo. Then hearts from both the groups underwent 30 min of global ischaemia and 120 min of reperfusion. Infarct size was not different in the groups despite a trend for smaller infarcts in the oestrogen-treated hearts. Hence, oestrogen itself was not cardioprotective. When the hearts were ischaemically preconditioned, however, the placebo-treated ovariectomized hearts failed to be protected but the oestrogen-treated hearts were.

Although others have made similar observations, Shinmura et al. went one step further and tried to define a mechanism. Perhaps, it is not surprising that the investigators focused on PKCε. A specific activator of this isoform rescued the ovariectomized hearts exposed only to placebo. Curiously, 1,2-dioctanoyl sn-glycerol (DOG), a drug which is a non-specific activator of all isoforms of PKC (more than 11 have been described), failed to rescue the hearts, suggesting that other PKC isoforms may counter the beneficial influence of PKCε.12–14

Numerous reports have trumpeted the ε isoform of PKC as being the one responsible for cardioprotection.15 The present study reveals that the missing step in ovariectomized rats is upstream of the activation of PKC. The defect could be at any one of the many steps that have been identified in preconditioning’s trigger pathway. Future investigations will be necessary to identify the precise site of the signalling block.

Could this mechanism of improved PKC sensitivity explain oestrogen’s protection in women? Hardly, because IPC has been found to be independent of gender, at least in laboratory animals. However, there is evidence that some
patients with acute myocardial infarction (AMI) may be in a preconditioned state, either from antecedent angina or from drugs such as opioids, and they would theoretically profit from IPC’s ability to salvage ischaemic myocardium. If that were the case, then it is possible that loss of preconditioning in some post-menopausal women could contribute to worse outcomes as suggested by Rezkalla and Kloner. Since Shinmura demonstrated that chronic oestrogen replacement in the oestrogen-deficient female rats restored IPC’s protection, one might consider this to be a beneficial and worthwhile goal of oestrogen treatment. However, in light of the recent clinical trials it is unlikely that oestrogen replacement in post-menopausal women will be a feasible treatment option. But as demonstrated by Shinmura et al. selective activation of PKCε is a possible alternative to acutely restore IPC cardioprotection. Unfortunately, preconditioning, except in certain controlled circumstances such as the operating theatre, is of little clinical use because patients presenting to the hospital with AMI do so only after the onset of ischaemia. However, those patients could conceivably be treated with post-conditioning, where several alternating cycles of reperfusion/coronary re-occlusion following the restoration of flow in the occluded infarct artery decrease infarct size and improve left ventricular function. Although Shinmura et al. did not test whether oestrogen-deficient rats could be post-conditioned, there is a high likelihood that they cannot be, since post-conditioning, like IPC, relies on redox signalling to activate PKC in the first seconds of reperfusion. In that case, there might be a real indication to treat these post-menopausal women with a direct PKCε activator at the time of reperfusion.

References