An Overlooked Mechanism for Ischaemic Preconditioning?

Eric H. Harley
Emeritus Professor, Division of Chemical Pathology, Department of Pathology, University of Cape Town, South Africa.

Corresponding author:
28 River View Way, Tokai Estate,
Tokai, 7945, South Africa.
Tel: 27 21 7123642.
E-mail address ehharley@gmail.com

Ischaemic preconditioning is a process whereby a period of partial ischaemia, short of a duration resulting in damage, can protect against a subsequent more severe ischaemic episode. The phenomenon was first reported by Murry et al. [1] who showed that short periods of coronary artery occlusion in dogs produced a degree of protection to the heart against more prolonged occlusion. Subsequently it was found that the protective initial ischaemia did not need to be produced in the tissue later exposed to the major ischaemic insult [2], but that cardioprotection, for example, could be effected by short periods of limb ischaemia using a simple blood pressure cuff around the arm. This is termed remote (or distal) ischaemic preconditioning and has become one of the most powerful interventions for reducing myocardial infarction size in ischaemic hearts [3], as, for example, in patients undergoing heart valve surgery. They noted however, as have many others, that incomplete comprehension of the mechanisms underlying the process could be impairing the design of clinical trials and the interpretation of their results.

Most investigations into mechanisms of remote ischaemic preconditioning have centred around hormonal effects and signalling pathways e.g. those involving adenosine, bradykinin and opioid receptors with the possible involvement of ATP-dependent K+ channels, G proteins and protein kinase C. However, an alternative mechanism which appears to have been overlooked and deserves further examination is provided for by studies in 1988 [4] and 1990 [5] on red blood cell purine metabolism. These showed that under conditions of low pH, high inorganic phosphate concentrations, and low PO2, all these conditions being present in anoxic ischaemic tissues, erythrocytes actively take up hypoxanthine and sequester it as inosine monophosphate (IMP). In a limb made temporarily ischaemic by application of a blood pressure cuff, the erythrocytes in that limb will accumulate phosphoribosyl pyrophosphate and become primed to metabolise hypoxanthine, which they will encounter when the cuff is released and (some of) these erythrocytes subsequently pass through ischaemic tissue.

Hypoxanthine has been implicated as a cause of postischaemic tissue injury [6]. This is a consequence of the conversion in ischaemic tissues of the enzyme xanthine dehydrogenase to xanthine oxidase; the latter catalyses the conversion of hypoxanthine to xanthine (and then xanthine to uric acid) in reactions which release highly damaging reactive oxygen species, especially when the tissues encounter plentiful oxygen again if and when reperfusion occurs. The removal of hypoxanthine from these ischaemic cells by appropriately primed erythrocytes would be expected to alleviate damage by reducing levels of the prime substrate in these reactions.

It seems surprising that this mechanism has been overlooked, especially since it provides for novel therapeutic interventions. For example, blood could be withdrawn from a patient prior to transplant surgery, or other operative procedures requiring an organ to be temporarily ischaemic; the erythrocytes in this blood could then be incubated under conditions of low pH, high inorganic phosphate concentrations, and low PO2, and used as a first pass through the organ prior to normal circulation being restored. This somewhat cumbersome procedure is in effect simulated by remote ischaemic preconditioning, when the erythrocytes are primed by the same conditions in the patient’s own limb at the time of or shortly before the surgical procedure. It might be beneficial to future research on ischaemic preconditioning if awareness of this proposed mechanism, whether acting by itself or together with other mechanisms, were taken into account more widely.

Declarations of Interest
The author declares no conflicts of interest.

Acknowledgements
The author states that he abides by the “Requirements for Ethical Publishing in Biomedical Journals” [7].
References


