British Journal of Pharmacology (2005) 145, 701–702
www.nature.com/bjp

COMMENTARY

New insights into adenosine-mediated myocardial protection

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British Journal of Pharmacology (2005) **145,** 701–702. doi:10.1038/sj.bjp.0706262; published online 16 May 2005

Keywords: Adenosine; adenosine receptors; interstitial fluid; vascular; extra-cardiac; cardioprotection; remote preconditioning

Abbreviations: NOS, nitric oxide synthase; LNNA, N^{ω}-nitro-L-arginine; ISF, interstitial fluid

The cardiovascular effects of the endogenous purine, adenosine, have been recognized since 1929 when Drury & Szent-Györgyi (1929) reported that an extract isolated from bullock heart muscle produced rapid, transient decreases in heart rate, atrioventricular conduction and arterial blood pressure in dogs and guinea pigs. Forty years later, the first pharmacological evidence of adenosine receptors in the brain was postulated based on the effects of the methylxanthine, theophylline (Sattin & Rall, 1970). Since that time there is substantial evidence that adenosine exerts its effects in numerous tissues *via* the activation of at least four adenosine receptor subtypes.

The notion that adenosine can also protect the heart (as well as other organs) during ischemia–reperfusion has similarly evolved over the years. Initial studies, nearly two decades ago, were based on the hypotheses that adenosine exerted its cardioprotective effects by stimulating the purine salvage pathway for ATP synthesis and *via* increased coronary blood flow. Although these effects are clearly beneficial, the results of numerous studies with adenosine receptor agonists and antagonists support the hypothesis that adenosine's cardioprotective effects are mediated primarily *via* the activation of cardiac adenosine receptor subtypes, expressed on ventricular cardiomyocytes and endothelial cells.

The study by Manintveld *et al*. (2005) entitled 'Intravenous adenosine protects the myocardium primarily by activation of a neurogenic pathway' raises several interesting new insights into adenosine cardioprotection. These authors observed that the infarct reducing effect of intravenous adenosine in intact rats was blocked by both the ganglionic blocker hexamethonium and the nitric oxide synthase (NOS) inhibitor N^{ω}-nitro-L-arginine (LNNA). Surprisingly, despite the fact that rats were administered adenosine at a dose of $\sim 500\,\mu g\,kg^{-1}\,min^{-1}$, the authors observed no increase in cardiac interstitial fluid (ISF) adenosine levels or its metabolites. Thus these observations support the authors' hypothesis that adenosine exerted its beneficial effect *via* vascular and/or extracardiac mechanisms.

We (Lasley & Mentzer, 1998; Lasley *et al*., 1999) have previously observed in both *in vitro* and *in vivo* preparations that adenosine must be delivered at a concentration sufficient to reach the myocardial ISF to exert its protection against postischemic myocardial dysfunction. So it is possible that, as the authors discussed, their inability to detect an increase in adenosine or its metabolites in myocardial ISF may have been due to the low recovery rate of their dialysis fibers. Alternatively, the end point in the present study was myocardial infarction, and there may be differences in the mechanisms by which adenosine reduces reversible and irreversible myocardial ischemic injury. The conclusions of Manintveld *et al*. (2005) do support an increasing body of evidence that adenosine may exert its cardioprotective effects *via* multiple mechanisms. It has previously been reported that polyadenylic acid, which is confined to the vascular space due to its large size, protected *in vivo* rabbit myocardium when administered during reperfusion presumably by an adenosine A_{2a} receptor mechanism (Todd *et al*., 1996). An intravascular-confined adenosine A_1 receptor agonist has been reported to induce a negative dromotropic effect in isolated guinea pig hearts (Rubio *et al*., 1999). Interestingly, this effect was blocked by an NOS inhibitor, consistent with the current results of Manintveld *et al*. (2005).

Additional support for intravascular and extracardiac mechanisms of adenosine cardioprotection are the results of an increasing number of remote preconditioning studies, in which arterial occlusions at various sites (infrarenal aorta, mesenteric, skeletal muscle, cerebral) induce myocardial protection (for a review, see Przyklenk *et al*., 2003). Several studies have implicated a role for adenosine receptors in this phenomenon (Liem *et al*., 2002; 2005). Given the rapid metabolism of adenosine by erythrocytes and endothelial cells, it is unlikely (although not yet reported) that these remote interventions induce an increase in cardiac ISF adenosine levels. It is also possible that there may be tissue-specific mechanisms of remote preconditioning. The present authors have reported that in intact rats, mesenteric artery occlusion remote preconditioning is blocked by hexamethonium (Liem *et al*., 2002), whereas Weinbrenner *et al*. (2002) reported that infrarenal aortic occlusion remote preconditioning in rats was not blocked by ganglionic blockade.

Several additional questions arise from this study that are pertinent to both experimental and clinical myocardial ischemia. Myocardial preconditioning protocols with adenosine receptor agonists are typically associated with both decreases in heart rate and blood pressure, which raises the possibility that reflex mechanisms associated with these responses may contribute to their protection. In addition to adenosine, opioids and bradykinin have been implicated as mediators of remote preconditioning (Schoemaker & Van

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Heijningen, 2000; Patel *et al*., 2002; Przyklenk *et al*., 2003). Thus although the heart appears to possess numerous preconditioning mechanisms, it still remains unknown why one receptor antagonist can essentially block this protection. A more complete understanding of the heart's intrinsic and extrinsic defense mechanisms may ultimately lead to the design of new therapies for the treatment of ischemic heart disease.

References

DRURY, A.N. & SZENT-GYÖRGYI, A. (1929). The physiological activity of adenine compounds with special reference to their action upon the mammalian heart. *J. Physiol. (London),* **68,** 213–237.

LASLEY, R.D. & MENTZER JR, R.M. (1998). Dose dependent effects of adenosine on interstitial fluid adenosine and postischemic function in the isolated rat heart. *J. Pharmacol. Exp. Ther.,* **286,** 806–811.

LASLEY, R.D., RANDHAWA JR, M.P.S., HEGGE, J.O. & MENTZER JR, R.M. (1999). Effects of adenosine and acadesine on interstitial nucleosides and myocardial stunning in the pig. *Can. J. Physiol. Pharmacol.,* **77,** 259–267.

LIEM, D.A., TE LINTEL HEKKERT, M., MANINTVELD, O.C., BOOMSMA, F., VERDOUW, P.D. & DUNCKER, D.J. (2005). Myocardium tolerant to an adenosine-dependent ischemic preconditioning stimulus can still be protected by stimuli that employ alternative signaling pathways. *Am. J. Physiol. (Heart Circ. Physiol.),* **288,** H1165–H1172.

LIEM, D.A., VERDOUW, P.D., PLOEG, H., KAZIM, S. & DUNCKER, D.J. (2002). Sites of action of adenosine in interorgan preconditioning of the heart. *Am. J. Physiol. (Heart Circ. Physiol.),* **283,** H29–H37.

MANINTVELD, O.C., HEKKERT, M.T.L., KEIJZER, E., VERDOUW, P.D. & DUNCKER, D.J. (2005). Intravenous adenosine protects the myocardium primarily by activation of a neurogenic pathway. *Br. J. Pharmacol.,* **145,** 703–711 (this issue).

PATEL, H.M., MOORE, J., HSU, A.K. & GROSS, G.J. (2002). Cardioprotection at a distance: mesenteric artery occlusion protects the myocardium *via* an opioid sensitive mechanism. *J. Mol. Cell. Cardiol.,* **34,** 1317–1323.

PRZYKLENK, K., DARLING, C.E., DICKSON, E.W. & WHITTAKER, P. (2003). Cardioprotection 'outside the box' – the evolving paradigm of remote preconditioning. *Basic Res. Cardiol.,* **98,** 149–157.

RUBIO, R., CEBALLOS, G. & BALCELLS, E. (1999). Intravascular adenosine: the endothelial mediators of its negative dromotropic effects. *Eur. J. Pharmacol.,* **370,** 27–37.

SATTIN, A. & RALL, T.W. (1970). The effect of adenosine and adenine nucleotides on the cyclic adenosine 3′,5′-phosphate content of guinea pig cerebral cortex slices. *Mol. Pharmacol.,* **6,** 13–23.

SCHOEMAKER, R.G. & VAN HEIJNINGEN, C.L. (2000). Bradykinin mediates cardiac preconditioning at a distance. *Am. J. Physiol. (Heart Circ. Physiol.),* **278,** H1571–H1576.

TODD, J., ZHAO, Z.Q., WILLIAMS, M.W., SATO, H., VAN WYLEN, D.G. & VINTEN-JOHANSEN, J. (1996). Intravascular adenosine at reperfusion reduces infarct size and neutrophil adherence. *Ann. Thorac. Surg.,* **62,** 1364–1372.

WEINBRENNER, C., NELLES, M., HERZOG, N., SARVARY, L. & STRASSER, R.H. (2002). Remote preconditioning by infrarenal occlusion of the aorta protects the heart from infarction: a newly identified non-neuronal but PKC-dependent pathway. *Cardiovasc. Res.,* **55,** 590–601.

(Received April 1, 2005
Accepted April 11, 2005
Published online 16 May 2005)