Role of adenosine A2B receptor stimulation in ischaemic postconditioning: dawn of a new paradigm in cardioprotection

EXPERT’S PERSPECTIVE

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This editorial refers to an article by S. Philipp et al.16 published in Cardiovascular Research in 2006. It is accompanied by a retrospective editorial by two authors of that original article, J.M. Downey and M.V. Cohen, pp. 198–201, this issue, as part of this Spotlight on Landmark Papers in Cardiovascular Research.

1. Introduction

Adenosine has a long and storied history in the field of cardioprotection. A wealth of evidence accrued over three decades has demonstrated the ability of adenosine-based pharmacological strategies (and, in some instances, adenosine per se) to attenuate multiple facets of myocardial ischaemia-reperfusion injury.1–15 It is equally well established that the favourable effects of adenosine and adenosine agonists are receptor-mediated and initiated by the stimulation of one or more of the family of four adenosine receptor subtypes (A1, A3, A2A, A2B; reviewed in 1–3). Initial attention focused on the A1 subtype, with a host of studies reporting that pre-treatment with A1 receptor agonists significantly attenuated post-ischaemic contractile dysfunction and reduced the myocardial infarct size. Subsequent studies utilized both pharmacological and genetic approaches to interrogate the A1, A2A, and A3 receptors, and, in particular, the potential role of these receptor subtypes in the endogenous cardioprotection afforded by ischaemic preconditioning, postconditioning, and remote conditioning.1–3 In 2006, Philipp et al.16 extended this line of investigation to encompass the fourth subtype—the adenosine A2B receptor—and provided the first evidence implicating A2B receptor stimulation as a requisite mediator of the infarct size reduction with postconditioning.

2. Protocol summary and pivotal results

Using a standard in vivo rabbit model of coronary artery occlusion-reperfusion, Philipp et al.16 assessed the role of the adenosine A2B receptor in postconditioning via the administration of a comprehensive battery of pharmacological agonists and antagonists in cohorts of control and postconditioned animals. A total of 21 groups were enrolled, and three pivotal observations were made:

(i) The infarct-sparing effect of postconditioning was abrogated by the administration of either the non-selective adenosine receptor antagonist 8-p-(sulfophenyl)theophylline (SPT), the selective A2B antagonist MRS1754, or the protein kinase C (PKC) inhibitor chelerythrine. In contrast, selective A1 and A2A antagonists [8-cyclopentyl-1,3-dipropylxanthine (DPCPX) and 8-(13-chlorostyryl)caffeine (CSC)] had no inhibitory effect.

(ii) 5′-([N-ethylcarboxamido]adenosine (NECA, a nonselective adenosine agonist with high affinity for the A2B receptor), given in lieu of postconditioning, mimicked the reduction in the infarct size achieved with postconditioning. Moreover, the infarct-sparing effect of NECA was blocked by co-administration of the A2B antagonist MRS1754.

(iii) Direct activation of PKC, achieved by an infusion of phorbol myristate acetate, was as protective as NECA and was inhibited by MRS1754.

Based on these data, the authors concluded that ‘salvage of ischaemic myocardium by postconditioning is dependent on activation of adenosine A2B receptors’.16 This concept is, arguably, provocative, given the low-binding affinity of the A2B receptor together with its reportedly weak expression in cardiomyocytes.1,17 However, this issue is potentially reconciled by the finding that ‘PKC must also be activated during postconditioning to elicit protection, perhaps by increasing the sensitivity of the adenosine A2B receptor’.16 Thus, in contrast to the conventional paradigm of receptor stimulation initiating kinase activation, the authors propose that ‘PKC activation is upstream of the critical binding of adenosine A2B receptors’.16
3. Contributions to the field of cardioprotection

As of 1 May 2012, this landmark study has been cited in 156 subsequent papers (Thomson Reuters Science Web of Knowledge; all databases). Approximately half (47%) of these publications acknowledge the contribution of Philipp et al. in the context of review articles; not surprisingly, most of these reviews focused on the concepts of ischemia-reperfusion injury, cardioprotection, and myocardial conditioning, while others summarized recent advances in medical chemistry and the development of novel A2B receptor agonists. The remaining papers were original studies investigating the mechanisms of ischemia-reperfusion injury, cytoprotection, and conditioning paradigms in the heart and other organs including the liver, the kidney, and skeletal muscle.

The work of Philipp et al. was, first and foremost, the cornerstone for later studies that elaborated on the molecular mechanisms by which adenosine A2B receptor stimulation evokes cardioprotection. Notable observations extending their findings have included the role of zinc (and its reportedly favourable effects on mitochondrial stability) in A2B-mediated protection, the interplay between PKC and the A2B receptor, the novel site of the A2B receptor (purportedly intracellular and in close proximity to mitochondria), and the concept that A2B receptor stimulation attenuates superoxide production from mitochondrial Complex I.

Secondly, the aforementioned results undoubtedly prompted subsequent studies aimed at investigating the cardioprotective efficacy of BAY 60–6583, the prototype adenosine A2B receptor agonist that became available after the completion of these initial experiments. Finally, a recurring theme among many of the ensuing publications is complexity, i.e. the observation that other adenosine receptor subtypes are also involved in the infarct size reduction with postconditioning, and that coordinated activation of multiple receptor subtypes may be required to achieve cardioprotection. Thus, the study by Philipp et al. has fostered the burgeoning interest in the concept of receptor–receptor interaction.

4. Unanswered questions and future directions

Despite the insights yielded by Philipp et al. and subsequent publications citing their work, several key aspects of these observations beg further study. For example, all current evidence in support of the involvement of the adenosine A2B receptor in postconditioning has been deduced from the use of agonists and antagonists. Corroboration of the role of the A2B receptor using a genetic approach would complement and augment the hypothesis but, to date, has only been pursued in the context of ischemic preconditioning. Additional questions revolve around the intriguing concept that PKC increases the affinity of cardiomyocyte A2B receptors, including: (i) the underlying mechanism by which this increase in affinity is achieved; (ii) the precise temporal profile of PKC activation and the resultant receptor modification required to elicit protection; and (iii) the identity of the PKC isofoms that interact with and activate the A2B receptor. Future investigations aimed at resolving these questions will expand on the PKC-adenosine A2B paradigm initiated by Philipp et al. and amplify the contribution of this important publication to our understanding of the mechanisms of ischemia-reperfusion injury and the infarct-sparring effect of postconditioning.

Conflict of interest: none declared.

References


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