EDITORIAL COMMENT

Adenosine at Reperfusion
A Conundrum Ready to Be Resolved*

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The purine nucleoside adenosine is the parent compound of the ubiquitous intracellular high-energy compound adenosine triphosphate (ATP). During aerobic metabolism the intracellular adenosine concentration is only 30 to 300 nM because adenosine is being used to synthesize ATP. However, during anaerobic metabolism cellular ATP stores are depleted and the adenosine concentration increases 100-fold to as much as 10 μM. Adenosine itself has vasodilatory and negative chronotropic effects and thus causes hypotension and bradycardia when injected into the circulation. The latter effect has been used to great advantage in the acute treatment of supraventricular arrhythmias. Its use as a cardioprotective agent in both experimental animals and humans, however, has had a checkered history.

The phenomenon of ischemic preconditioning (IPC), several laboratories began to assess possible mechanisms. An early observation by Liu et al. (2) suggested that IPC was dependent on adenosine, presumably released by ischemic cells, which would bind to its sarcolemmal G1 protein-coupled receptor to trigger downstream intracellular signaling and eventual activation of the hypothesized cardioprotective end-effector. Although the signaling is much more complicated than these investigators first imagined, even at the level of the very initial agonist-receptor binding, adenosine retained its great appeal as a promising trigger of cardioprotection, and several investigators imagined that exogenous adenosine might have the same result, thus leading to development of an effective strategy for clinical use.

Forman’s group (3–7) pioneered investigation of the potential of exogenous adenosine to salvage ischemic myocardium. In a series of reports in various experimental animal models, these researchers claimed that an intravenous infusion of adenosine could indeed reduce the extent of myocardial infarction. However, other investigative groups were unable to duplicate these results (8–10). The meticulous protocol of Vander Heide and Reimer (9), which carefully duplicated that used by Forman’s group, failed to produce any benefit of intravenous adenosine on infarct size in dogs. We also tested exogenous adenosine in rabbits in a comparable ischemia/reperfusion protocol (11). None of the intravenous doses of adenosine that we infused had any salutary effect. We were limited in the amount of adenosine that could be infused because of its profound hypotensive effect, and perhaps a higher intracoronary dose would have protected the heart. Despite these contradictory pre-clinical results, 2 large clinical studies have examined the effect of adenosine infusion in patients with acute myocardial infarction (12,13). The results have been mixed.

In this issue of the Journal, Takahama et al. (14) have developed a new technique for the delivery of adenosine to ischemic hearts that circumvents the problem noted above. They encapsulated adenosine in polyethylene glycol-coated (PEGylated) liposomes. These investigators infused these liposomes into rats for 10 min starting 5 min before release of a left coronary artery occlusion. The liposomes were found to be extensively taken up by the ischemic myocardium, but curiously not by nonischemic myocardium. Remarkably PEGylated liposomal adenosine at a dose of 450 μg/kg/min had no significant effects on either mean blood pressure or heart rate, whereas the same dose of free adenosine lowered mean blood pressure by 25.4%. Thus, they concluded that it is possible to intravenously administer high doses of adenosine to the ischemic heart without affecting hemodynamics.

Takahama et al. (14) then measured infarct size in rats treated with PEGylated liposomal adenosine. An infusion of 450 μg/kg/min reduced infarct size from 53.2% of the risk zone in untreated hearts to 29.5% (p < 0.05). Although it will be important for other investigators to confirm these results, it is likely that high-dose adenosine can be cardioprotective if complicating hypotension and bradycardia can be avoided.

Although up to now the ability of authentic adenosine to be cardioprotective was controversial, there is less dispute regarding whether adenosine receptor subtypes can protect the heart at the time of reperfusion. The receptor-selective adenosine analog BAY 60–6583, a highly selective adenosine A2b agonist, reduced infarction in rabbit hearts when infused minutes before reperfusion (15). Consistent with this observation was the determination that the protective effect of ischemic post-conditioning was abrogated by a specific A2b antagonist (16). Although Kin et al. (17) reported that an A2a antagonist blocked post-conditioning’s protection, the selectivity of that agent is probably not sufficient to exclude an A2b mechanism. The A2a-selective agonists have also been reported to reduce infarct size when...
given at reperfusion by an anti-inflammatory mechanism (18). Adenosine is quickly metabolized in the tissues, and it may be that authentic adenosine simply cannot achieve a sufficiently high concentration to populate the receptors on the cardiomyocyte when delivered by an intravenous route. The analogs are stable and pass intact through the capillary endothelium.

Takahama et al. (14) administered liposomal adenosine to hearts and also infused either the nonselective adenosine receptor antagonist 8-[(p-sulfophenyl) theophylline (8-SPT) or 1 of the selective adenosine A1, A2a, A2b, or A3 receptor subtype antagonists. Not surprisingly, 8-SPT blocked protection confirming involvement of an adenosine receptor. What is puzzling is that an antagonist to each of the 4 adenosine receptor subtypes also attenuated protection from liposomal adenosine. It seems unlikely that all 4 subtypes would be involved in protection. This implausible result could even reflect false-positive observations related to the very wide range of infarct sizes in some groups (3% to 48% and 16% to 65% infarction of the ischemic zone in the liposomal adenosine and liposomal adenosine plus MRS1754 groups, respectively). Such wide ranges make statistical significance difficult to determine, especially when the numbers of experiments are small and a normal distribution has not been achieved. Hence, the identity of the specific adenosine receptor subtype or subtypes involved in these studies has not yet been fully determined and additional experimental studies are probably warranted.

Thus, a novel delivery vehicle for adenosine has been described that minimizes adverse hemodynamic effects and permits delivery of large amounts of the drug to ischemic tissue. Although the exact pathways involved in the protection remain obscure, the clinical implications are obvious. The intravenous route of administration simplifies use of this drug delivery system and adenosine is clearly not toxic. This liposomal adenosine can be added to a growing list of drugs that seem to limit infarct size in animal models when administered at the time of reperfusion (19).

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