Editorial

Symbols within words: Have we neglected the AdeNOsine A2 receptor?

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See article by Xu et al. [10] (pages 803–812) in this issue.

1. Adenosine and cardioprotection in patients: a crossroads?

Although considerable experimental effort has been expended during the past two decades in identifying mechanisms of cardioprotection, little of this work has been of direct benefit to patients. Thus, Bolli et al. have expressed concern that the field of myocardial protection is at a crossroads and have emphasized that there is an urgent need for the extensive experimental work in this area to be translated into clinically effective therapy [1]. The authors of this article, who represented a Working Group convened by the National Heart, Lung and Blood Institute, concluded that a Phase III clinical trial of adenosine be undertaken in patients with acute myocardial infarction [1]. This recommendation was based on preclinical studies and on Phase I and II clinical trials of adenosine and related compounds, which showed promise, but which only studied surrogate markers or were insufficiently powered to demonstrate definitive clinical benefit [2–4]. Thus, accumulating a greater understanding of the mechanisms of action of adenosine and its cognate receptor subtypes is both relevant and timely.

2. Adenosine: a molecule skilled at multi-tasking

It is well-recognized that adenosine has multiple effects on the cardiovascular system. Among its many actions, adenosine enhances coronary blood flow, inhibits adenylyl cyclase activation, and has direct effects, both positive and negative, on myocardial inotropic state. Through its effects on conduction tissue, it modulates heart rate. During myocardial injury, it affects neutrophil accumulation, reactive oxygen intermediate generation and endothelial function. These pleiotropic actions, many of which are generally considered to be cardioprotective, are usually attributed to activation of adenosine A1 and A3 receptors [5]. Relatively but not altogether neglected has been the role of adenosine A2 receptors. For example, reports in dog models showed that adenosine A2 receptor activation reduced reperfusion injury by inhibiting neutrophil accumulation and coronary endothelial adherence of these cells [6], and attenuated reperfusion-induced apoptotic cell death by inhibiting expression of Bcl-2 and Bax proteins [7]. Other studies in the rabbit showed that adenosine A2 receptor agonists improved hemodynamics, reduced creatine kinase release, and preserved ATP content when these agonists were given at the time of reperfusion [8,9].

3. Insights into mechanisms of adenosine A2 receptor agonism: what’s new?

In this issue of Cardiovascular Research, Xu et al. have focused on the ability of adenosine, via the A2 receptor and a subsequent series of signaling events, to induce nitric oxide (NO) by downstream activation of endothelial nitric oxide synthase (eNOS) [10]. Despite its name, eNOS is constitutively expressed in the particulate subcellular fraction of cardiac myocytes and is targeted to caveoli [11]. The intermediate signaling events elucidated by the authors include a number of molecules such as PI 3-kinase and Akt that appear to constitute a pathway used...
by many G-protein-coupled agonists that promote cell survival. Their report is the first to show that adenosine is capable of directly stimulating the production of NO in cardiac myocytes. Using inhibition experiments, they also demonstrate that cGMP-dependent protein kinase (PKG) is involved in the cardioprotective effect of adenosine. Their data suggest that, by stimulating NO and thereby activating PKG, the H2O2-induced depolarization of the mitochondrial membrane potential as measured by TRME fluorescence was prevented. These observations are consistent with a prior publication by Xu et al. in which it was reported that S-nitroso-N-penicillamine (SNAP)-induced reactive oxygen species generation is mediated by activation of PKG and subsequent opening of mitochondrial K<sub>ATP</sub> channels, a sequence of events that leads to cardioprotection [12].

4. Adenosine <sub>A2</sub> receptor agonism: what we don’t know

Like all stimulating work, the paper by Xu et al. provokes a number of additional questions that can only be answered by further research. First, the authors used pharmacological concentrations of adenosine in an in vitro system to obtain their results. A threshold concentration of adenosine needs to be established and available selective adenosine <sub>A2</sub> agonists [6–9] then tested both in vivo and in vitro to determine their effects on the measures reported by Xu and colleagues. Whether the data will hold across species also needs to be studied, but the benefit afforded by adenosine <sub>A2</sub> agonists in dogs and rabbits is encouraging [6–9]. The data of Xu et al. are additionally intriguing because NO at low concentrations, such as are likely to be generated by activation of eNOS, is cytoprotective [13]. Whether segments of the MAP kinase cascade other than ERK [12], such as JNK 1/2 [13], are involved in NO-induced cytoprotection by activation of adenosine <sub>A2</sub> receptors should be ascertained. NO generated within mitochondria by a neural form of NOS may be directly involved in the function of these organelles; this possibility has not been explored using selective adenosine <sub>A2</sub> agonists.

5. Group therapy

As the authors indicate, PKC and mitochondrial K<sub>ATP</sub> channels are important in the protective effects of adenosine <sub>A1</sub> receptor activation, but their roles in adenosine <sub>A2</sub> receptor activation remain unknown. It is well recognized that PKC<sub>ε</sub> is a critical signaling component of ischemic and of several forms of pharmacologic preconditioning. In this connection, Otani et al. recently reported that adenosine, diazoxide and the NO donor SNAP each activated PKC<sub>ε</sub>, but this PKC isoform was inactivated after washout [14]. In contrast, after triple pharmacologic preconditioning with these agents in combination, PKC<sub>ε</sub> remained activated and persistent cardioprotection ensued. This cardioprotective effect was abolished by treatment prior to the index ischemia with the PKC inhibitor chelerythrine [14]. These observations suggest that a single agent is likely to be ineffective in achieving optimal myocardial salvage, and that testing one drug alone, as recommended by the NHLIBI Working Group [1], may be insufficient. Rather a “cocktail” of agents may be better suited for cardioprotection, much as is done under other circumstances by our oncology colleagues. Such an approach is underscored by recent data indicating that cardioprotection is induced by both the physical and functional coupling of a signaling module consisting of PKC<sub>ε</sub>, Akt and eNOS [15]. All three components of this module can be activated by adenosine <sub>A2</sub> receptor agonists in combination with one or more other agents as described above. Thus, not only does the word adeNOsine resemble a signaling module, but, based on the data of Xu et al. [10], the symbol NO in the word may be real.

References

[10] Xu Z, Park S-S, Mueller RA, Bagnall RC, Patterson C, Boysen PG. Adenosine produces nitric oxide and prevents mitochondrial...


