0026-895X/05/6705-1385–1387$20.00
MOLECULAR PHARMACOLOGY
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Mol Pharmacol 67:1385–1387, 2005

Vol. 67, No. 5
11783/1198163
Printed in U.S.A.

PERSPECTIVE

Adenosine in Tissue Protection and Tissue Regeneration

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Received February 3, 2005; accepted February 9, 2005

ABSTRACT

Adenosine promotes tissue protection and repair through four general modes of action: increased oxygen supply/demand ratio, preconditioning, anti-inflammatory effects, and stimulation of angiogenesis. A novel means by which adenosine stimulates angiogenesis is the topic of the article by Desai et al. in the April 2005 issue of *Molecular Pharmacology*. The report demonstrates that agonists of A_{2A} adenosine receptors inhibit the release of the anti-angiogenic factor thrombospondin 1. Multiple cell types and all four adenosine receptors participate in these responses. Exploiting these effects of adenosine has great therapeutic potential.

Adenosine produced in hypoxic, ischemic, or inflamed environments reduces tissue injury and promotes repair by several receptor-mediated mechanisms. The intracellular production of adenosine is increased during hypoxia or ischemia and transported across cell membranes by various transporters (Thorn and Jarvis, 1996). In addition, adenine nucleotides are released from nerves, platelets, and other cell types in granules or through various channels (Dutta et al., 2004; Fabbro et al., 2004) and metabolized to adenosine primarily by ecto-apyrase (CD39) and ecto-5′-nucleotidase (CD73) (Koszalka et al., 2004). Adenosine signals through four widely expressed G protein coupled receptors: A_1, A_{2A}, A_{2B}, and A_3. There are four general modes of responses by which adenosine receptor activation protects tissues and facilitates tissue repair; these are summarized in Table 1: increased oxygen supply/demand ratio, preconditioning, anti-inflammatory effects, and stimulation of angiogenesis. A novel means by which adenosine stimulates angiogenesis is the topic of the article by Desai et al. (2005) in this issue. These new findings add to accumulating evidence that all four adenosine receptor subtypes participate in various ways to protect and facilitate regeneration of injured tissues.

Increases in Oxygen Supply/Demand Ratio

Tissue protection by adenosine was first attributed to its cardiovascular effects. Vascular smooth muscle of coronary arteries was found to have a high density of A_{2A} adenosine receptors and to be very sensitive to adenosine partly because of spare receptors (Shryock et al., 1998). Adenosine produces vasodilation to increase oxygen delivery to the hypoxic heart. Blood vessels in other tissues are generally less sensitive to adenosine than coronary arteries but also dilate in response to adenosine through a combination of A_{2A} and A_{2B} receptors. Adenosine also acts to reduce oxygen demand in excitable tissues such as heart and neurons as a result of the activation of A_1 receptors that increase neuronal conductance to potassium ions or decrease conductance to calcium ions (Dolphin et al., 1986). In addition, activation of A_1 receptors on sympathetic nerve terminals reduces the release of norepinephrine, resulting in decreased cardiac output and decreased peripheral vascular resistance (Burgdorf et al., 2001, 2005). It has been shown recently that hypoxia increases the sensitivity of endothelial cells to adenosine in part by causing a rapid induction of A_{2B} receptor mRNA (Eltzschig et al., 2003).

Ischemic Preconditioning and Postconditioning

Adenosine also protects tissues through its role in ischemic preconditioning—defined as a reduction in tissue infarct size during a prolonged ischemic episode as a result of a short prior episode of ischemia. Preconditioning has been most

Article, publication date, and citation information can be found at http://molpharm.aspetjournals.org.
doi:10.1124/mol.105.011783.
Please see the related article on page 1406.

ABBREVIATIONS: ZM241385, 4-{2-[7-amino-2-(2-furyl)[1,2,4]triazolo-[2,3-*a*][1,3,5]triazin-5-ylamino]ethyl}phenol.

extensively studied in the heart but also occurs in other tissues. Adenosine produced in the ischemic heart participates in this response by activating A_1 and A_3 receptors, protein kinase C, and mitochondrial K_{ATP} channels (Miura et al., 2000; De et al., 2002). It has been demonstrated recently that "postconditioning", a brief period of ischemia after prolonged ischemia, can reduce myocardial inflammation and infarct size (Zhao et al., 2003). It is likely that adenosine released during postconditioning contributes to inhibition of inflammation, probably as a result of activation of A_{2A} receptors on inflammatory cells.

Anti-Inflammatory Responses. Many recent studies indicate that adenosine acting on A_{2A} receptors can powerfully inhibit inflammation and reperfusion injury. The A_{2A} adenosine receptor is found on most bone-marrow–derived cells and produces cellular effects that in general inhibit inflammation. The cellular responses seem to be mediated predominately by cyclic AMP and result in inhibition of oxidative burst in neutrophils (Fredholm et al., 1996), reduced TNFα release by monocytes (Link et al., 2000), reduced platelet activation (Hourani, 1996), and inhibition of lymphocyte activation (Lappas et al., 2005). In aggregate, these responses prevent the release of pro-inflammatory cytokines and oxygen radicals, prevent endothelial cell activation, and greatly reduce microvascular occlusion, which can exacerbate tissue injury during reperfusion of previously ischemic tissues.

A_{2B} Receptors are Proinflammatory. Both A_{2A} and A_{2B} receptors couple to the heterotrimeric G protein, Gs; in many cell types, however, A_{2B} receptors have been found to be dually coupled to Gs and Gq. Signaling through Gq results in calcium mobilization and activation of phospholipase C and mitogen-activated protein kinase (Gao et al., 1999). This signaling pathway seems to be responsible for pro-inflammatory actions of adenosine mediated by A_{2B} receptors that results in facilitation by adenosine of antigen-induced deregulation of canine or human but not rodent mast cells (Feoktistov and Biaggioni, 1995; Auchampach et al., 1997). In addition, activation of A_{2B} receptors has been shown to increase the release of interleukin 6 from epithelial cells, astrocytes, and fibroblasts (Schwaninger et al., 1997; Sitaraman et al., 2001; Zhong et al., 2005). Hence, the activation of adenosine receptors is not invariably protective of tissues. In fact, A_{2B} blockers may be useful as anti-inflammatory agents.

Angiogenesis

In addition to protecting tissues, adenosine has long been known to stimulate angiogenesis, which is necessary for tissue repair (Teuscher and Weidlich, 1985; Dusseau et al., 1986). As is the case for tissue protection by adenosine, multiple adenosine receptor subtypes participate in the stimulation of angiogenesis. Activation of the A_1 receptors powerfully stimulates angiogenesis in vivo by an as-yet-undefined mechanism (Linden et al., 2003). Stimulation of angiogenesis also is caused in part by activation of A_{2B} receptors on endothelial cells (Feoktistov et al., 2002) and A_{2B} or A_3 receptors on mast cells (Feoktistov et al., 2003) that induce the release of angiogenic factors including VEGF. The report by Desai et al. (2005) in this issue describes another means by which adenosine receptors on human umbilical vein endothelial cells stimulate angiogenesis. Adenosine inhibits the release of the anti-angiogenic protein thrombospondin 1, resulting in increasing vascular tube formation. Blockade of this response by the A_{2A}-selective antagonist ZM241385 is not surmountable by high doses of A_{2A} agonists, but despite this peculiarity, the pharmacological profile of the response suggests that it is mediated by the A_{2A} receptor. Desai et al. (2005) also show that in the presence of antibodies to TSP1 or CD36, the receptor for TSP1, A_{2A} agonists fail to stimulate vascular tube formation. These results indicate that vascular tube formation by adenosine A_{2A} receptor activation is largely mediated by suppression of TSP1 secretion.

Conclusion

Tissue protection and regeneration by adenosine is mediated by multiple different cells types and involves participation of all four adenosine receptor subtypes. Fully understanding and exploiting these protective and regenerative mechanisms has great clinical potential.

TABLE 1
Tissue protection and repair by adenosine receptors

Receptor	Tissue Response	Reference
Increase in oxygen supply/demand ratio		
A_{2A}, A_{2B}	Vasodilation	Belardinelli et al., 1998; Ngai et al., 2001
A_1	Decreased heart rate	Dhalla et al., 2003
	Decreased neuronal activity	Dunwiddie and Masino, 2001
	Decreased sympathetic nerve activity	Burgdorf et al., 2005a
Ischemic preconditioning and postconditioning		
A_1, A_3	Preconditioning	De et al., 2002b
A_{2A}?	Postconditioning	Zhao et al., 2003
Anti-Inflammatory Responses		
A_{2A}	Heart	Lasley et al., 2001; Glover et al., 2004
A_{2A}	Kidney	Day et al., 2003
	Liver	Ohta and Sitkovsky, 2001; Day et al., 2004
	Spinal cord	Reece et al., 2004
	Skin	Peirce et al., 2001
	Lung	Ross et al., 1999
Angiogenesis		
A_{2A}	Decreased endothelial cell thrombospondin	Desai et al., 2005
A_1	Chorioallantoic membrane	Linden et al., 2003
A_{2B}	Increase endothelial cell release of angiogenic factors	Feoktistov et al., 2002
A_{2B}, A_3	Increased mast cell release of angiogenic factors	Feoktistov et al., 2003

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