

PERSPECTIVE

Autoregulation of Cyclic AMP in Vascular Smooth Muscle: A Role for Adenosine Receptors

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The concentration of cyclic AMP within cells is regulated by the activities of adenylyl cyclases and phosphodiesterases (PDE) and the receptors and G proteins that modulate their activities. The extent to which cyclic AMP accumulates in a given cell and activates protein kinase A (PKA) is subject to tight transcriptional and post-transcriptional autoregulation (Table 1). For example, cyclic AMP accumulation in vascular smooth muscle (VSM) is limited through PKA-mediated phosphorylation and activation of PDE3A and PDE4 and through phosphorylation and inhibition of adenylyl cyclases type V/VI (Murthy et al., 2002). Activation of A_{2A} adenosine receptors, which directly couple to Gs to increase cyclic AMP, can also reduce cyclic AMP accumulation in PC12 cells due to up-regulation of PDE4 transcription (Chang et al., 1997) and inhibition of adenylyl cyclase VI (Chern et al., 1995).

Adenosine plays a physiologically important role as a dilator of VSM, largely via cyclic AMP-dependent mechanisms. Adenosine dilates VSM by activating Gs coupled A_{2A} and A_{2B} adenosine receptors. Adenosine production is increased in hypoxic tissues and transported across cell membranes to gain access to cell surface receptors on VSM cells (Kiss et al., 2000). In addition, adenine nucleotides released from nerves, platelets, mast cells, macrophages, and endothelial cells are

rapidly degraded to adenosine by ectonucleotidases (Zimmermann, 2000). Cyclic AMP represses the ecto-5'-nucleotidase promoter (Spychala et al., 1999) providing a feedback mechanism by which cyclic AMP accumulation may diminish adenosine production from 5'-AMP in the extracellular space. In addition, recent analyses of changes in A_3 adenosine receptor transcript and vascular tone in A_3 receptor knock-out mice suggest that the Gi-coupled A_3 receptors serve as a break on A_{2A} - and A_{2B} -receptor mediated cyclic AMP accumulation and vasodilation (Zhao et al., 2000).

Because adenosine receptors modulate cyclic AMP production in VSM, the density of adenosine receptors on the cell surface also serves to regulate cyclic AMP and tone in VSM exposed to adenosine (Table 1). It is notable that the inhibitory A_3 receptor undergoes unusually rapid and extensive phosphorylation and internalization (Ferguson et al., 2000) which may result in a rapid loss of A_3 -receptor mediated inhibitory actions during continuous exposure of VSM to adenosine. Activation of A_1 adenosine receptors also indirectly influences cyclic AMP in VSM through the action of an inhibitory prejunctional receptor on sympathetic nerve terminals, resulting in reduced norepinephrine release and reduced VSM β -adrenergic receptor activation. In this issue,

TABLE 1
 Roles of PKA and adenosine in autoregulation of cyclic AMP accumulation in vascular smooth muscle

Targets	Effect	Response
PKA		
cAMP phosphodiesterases	Induce; activate	Lower cAMP
Adenylyl cyclases	Inhibit	Lower cAMP
Ecto-5'-nucleotidase gene	Repress	Lower adenosine
A_3 receptor gene ^a	Induce	Lower cAMP
Adenosine		
A_1 receptor presynaptic	Inhibit NE release	Reduce β -receptor activation
A_{2A} and A_{2B} receptor activation	Activate adenylyl cyclase	Raise cAMP
A_3 receptor activation	Inhibit adenylyl cyclase	Counteract A_{2A} - and A_{2B} -mediated cAMP formation
A_3 receptor phosphorylation	Rapid down-regulation	Disinhibit A_{2A} and A_{2B} receptors

^a Yaar et al. (2002) describe enhancement of A_3 adenosine receptor transcription by a CRE-family promoter element in rat vascular smooth muscle as a newly described mechanism of PKA autoregulation.

ABBREVIATIONS: PDE, phosphodiesterase; PKA, protein kinase A; VSM, vascular smooth muscle; CRE, cAMP response element.

Yaar et al. (2002) describe factors involved in the transcriptional regulation of the A₃ adenosine receptor gene in VSM. The A₃ gene contains a cyclic AMP response element (CRE) that differs by 3 base pairs at the 3' end from a consensus CRE site. The CRE-like site in the A₃ adenosine receptor promoter seems not to be regulated by the well characterized transcriptional activator, CREB, but rather is repressed by the binding of an inhibitory CRE binding protein, CREM1, that is capable of forming heterodimers with c-JUN. Yarr et al. (2002) show that cyclic AMP accumulation in VSM reduces binding of the CREM1 repressor to the CRE element in the A₃ receptor promoter to enhance A₃ receptor transcription. The net effect is to lower cyclic AMP accumulation in response to adenosine. This newly described mode of regulation of A₃ receptor transcription by cyclic AMP provides yet another mechanism for autoregulation of cyclic AMP accumulation in VSM. The physiological function of all of these mechanisms of buffering cyclic AMP may be to maintain levels of the cyclic nucleotide in a narrow range that sensitively regulates the activity of PKA and the tone of VSM.

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