**Brief Review**

**Contrasting Excitatory and Inhibitory Effects of Adenosine in Blood Pressure Regulation**

Italo Biaggioni

Administration of adenosine results in profound hypotension without the expected activation of reflex sympathetic and renin mechanisms in most animal models. This action can be explained by the vasodilatory and neuroinhibitory effects of adenosine. It is generally considered an inhibitory neuromodulator because it inhibits the release of virtually all neurotransmitters studied and produces hyperpolarization of neurons. In contrast, adenosine produces vasoconstriction of some vascular beds, including the renal and pulmonary circulations. Renal vasoconstriction is caused by activation of \( A_2 \) receptors and involves an interaction with angiotensin II. In other vascular beds adenosine releases eicosanoids, including thromboxane, also resulting in vasoconstriction. Adenosine-induced vasoconstriction is transient and species dependent. Neither the receptor type, the molecular mechanisms of these actions, nor their significance to pathophysiologic processes have been defined. Adenosine also has an apparent excitatory effect in the nucleus tractus solitarii. Microinjections of adenosine into this brain stem nucleus lead to decreased sympathetic tone and hypotension similar to those produced by the excitatory amino acid glutamate. The mechanism that explains this action has recently been explored and involves the release of glutamate by adenosine. Adenosine also stimulates afferent fibers mediating sympathetic activity, including renal and myocardial afferent nerves, and carotid and aortic chemoreceptors. Afferent nerve activation seems to be more pronounced in humans and may explain most of the cardiovascular and respiratory actions of adenosine in this species. Finally, animal studies suggest that endogenous adenosine plays a role in the regulation of the baroreceptor reflex and restrains the full expression of renin-dependent hypertension. (Hypertension 1992;20:457-465)

**Key Words** • adenosine • vasoconstriction • neuroregulators • neurons, afferent • brain stem

Adenosine dilates most vascular beds, depresses sinus node automaticity, delays atrioventricular node conduction, and inhibits norepinephrine and renin release (Table 1). In most animal species adenosine lowers blood pressure without the reflex activation of sympathetic or renin mechanisms typical of other vasodilators. In addition to its cardiovascular actions, adenosine is generally considered an inhibitory neuromodulator. It produces hyperpolarization of neurons, decreases nerve firing, and has central depressor actions. It also prevents seizure activity and inhibits the release of practically all neurotransmitters studied, both centrally and peripherally. The actions of adenosine are mediated by distinct receptors: \( A_1 \) receptors are coupled to \( G_i \) proteins and their activation results in inhibition of adenylate cyclase and opening of potassium channels; \( A_2 \) receptors are coupled to \( G_0 \) proteins and their activation results in stimulation of adenylate cyclase. Subtypes of the \( A_2 \) receptor are a third type of receptor have been proposed.

These antihypertensive and neuroinhibitory effects of adenosine are of potential importance in the regulation of blood pressure, as will be discussed in the last section of this overview. First, I will review a growing number of studies that suggest adenosine may have excitatory actions. In particular, I will discuss situations in which adenosine produces vasoconstriction instead of the expected vasodilation, as well as times when it appears to act as an excitatory neuromodulator. The purpose of this review is to highlight the contrasting effects of adenosine and to encourage research into the mechanisms responsible for its apparent excitatory actions.

**Adenosine-Induced Vasoconstriction**

Adenosine is a vasodilator in virtually all vascular beds, and endogenous adenosine is postulated to play a role in blood flow autoregulation in many organ systems. There are excellent reviews on these subjects, so I will concentrate on the exceptions. The renal circulation is an example of a vascular bed where adenosine has a constrictor effect. This effect, however, is transient. Even if adenosine is administered as a continuous infusion, renal blood flow decreases initially but then returns to baseline, or even above baseline, values. The decrease in renal blood flow is primarily due to constriction of afferent arterioles in cortical glomeruli. This effect is mediated through \( A_2 \) adenosine receptors and involves a complex interaction with angiotensin II. Angiotensin II antagonists prevent the renal vasoconstriction produced by adenosine and, con-
versely, adenosine receptor antagonists prevent the renal vasoconstrictor effects of angiotensin II.9

Pulmonary vasoconstriction caused by adenosine is less widely recognized. Drury and Szent-Gyorgy10 first reported that adenosine increased pulmonary artery pressure in dogs. These authors interpreted this finding as secondary to an increase in blood flow rather than as pulmonary vasoconstriction. More recently, intravenous adenosine was found to increase pulmonary artery pressure in awake sheep with little change in cardiac output, thus reflecting significant pulmonary vasoconstriction (Figure 1A).11 This effect is not only blocked by the adenosine receptor antagonists theophylline and dipropylsulfophenylxanthine, but is also completely abolished by inhibition of cyclooxygenase or by antagonism of thromboxane receptors and is greatly reduced after inhibition of thromboxane synthesis. Therefore, adenosine produces pulmonary vasoconstriction in this animal model by stimulating the release of eicosanoids, which then activate thromboxane receptors. Thromboxane A2 is a probable mediator of the change because adenosine increases the transpulmonary gradient of its metabolite thromboxane B2 (Figure 2).11 The contribution of other vasoconstrictive eicosanoids is possible, inasmuch as prostaglandin D2 and prostaglandin F2α can also activate thromboxane receptors in this model.12

Pulmonary vasoconstriction is transient and, even when adenosine is infused continuously, pulmonary artery pressure returns toward baseline values. It is not clear whether this represents tachyphylaxis with desensitization of adenosine receptors or limited capacity of the target cell to release eicosanoids.

Adenosine produces pulmonary vasoconstriction in other animal species. In cats this action is blocked by meclofenamate13 and, therefore, probably involves eicosanoid release. Adenosine increases the baseline tone

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Table 1. "Antihypertensive" Actions of Adenosine

<table>
<thead>
<tr>
<th>A1-mediated effects</th>
<th>A2-mediated effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression of sinus node automaticity</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Slowing of atrioventricular node conduction</td>
<td></td>
</tr>
<tr>
<td>Inhibition of norepinephrine release</td>
<td></td>
</tr>
<tr>
<td>Inhibition of renin release</td>
<td></td>
</tr>
<tr>
<td>Depression of central nervous system activity</td>
<td></td>
</tr>
</tbody>
</table>

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Figure 1. Line graphs show pressure changes caused by vasoconstriction produced by adenosine in pulmonary circulation of sheep (panel 1a) and in portal circulation of rats (panel 1b). Panel 1a demonstrates effects of constant infusion of adenosine into superior vena cava of chronically instrumented, awake sheep. Baseline cardiac output (5.2 ± 0.3 l/min) did not change significantly during adenosine infusion. Panel 1b demonstrates effect of constant perfusion of adenosine in an in situ, buffer-perfused, nonrecirculating system. Flow rate was kept constant (3.5–4.5 ml/min/g liver). Note that rapid tachyphylaxis to effects of adenosine was observed in both cases. These effects were abolished by pretreatment with cyclooxygenase inhibitors, implying that the vasoconstrictor effects of adenosine are mediated by release of eicosanoids in these models. (Data obtained from References 11 and 15.)

Figure 2. Bar graph shows effect of adenosine on plasma concentrations of thromboxane B2 (TXB2) in awake sheep. Plasma samples were obtained from pulmonary artery (PA) and left atrium (LA) before (open bars) and after (hatched bars) bolus injection of adenosine. Adenosine was given at doses that increased PA pressure by 30 cm H2O. Adenosine produced significant increase in transpulmonary gradient of TXB2 (Grad; calculated as LA–PA, p < 0.05). Similar increase in thromboxane concentration by adenosine has been reported in perfused rat liver.15 (Data obtained from Reference 11.)

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Referenced studies:
- Drury and Szent-Gyorgy (1992)
- Meclofenamate (1992)
- Prostaglandin D2 and Prostaglandin F2α (1992)
- Cyclooxygenase (1992)
- Thromboxane A2 (1992)
- Thromboxane B2 (1992)
- Prostaglandin D2 (1992)
- Prostaglandin F2α (1992)
of guinea pig pulmonary artery spiral strips in vitro and enhances the vasoconstriction produced by transmural nerve stimulation and by exogenous norepinephrine. It has not been determined whether this effect involves eicosanoid mechanisms. Adenosine-induced pulmonary vasoconstriction has not been observed in isolated rat lungs (Edwin K. Jackson, personal communication) or humans and may, therefore, be species dependent. Because cardiac output has not been measured continuously in human studies, a transient increase in pulmonary vascular resistance, such as that produced by adenosine in sheep, may have been overlooked.

A striking similarity has been found between the effects of adenosine in the sheep pulmonary circulation and the rat hepatic circulation. Continuous perfusion of adenosine to the in situ, buffer-perfused rat hepatic circulation produces a transient increase in portal pressure (Figure 1B) and release of thromboxane B_2 and prostaglandin D_2 in the effluent. Cyclooxygenase inhibitors and thromboxane receptor antagonists attenuate this vasoconstrictive effect. Again, there may be species differences in the actions of adenosine in the liver because adenosine vasodilates the hepatic artery of cats.

Adenosine has been reported to produce paradoxical vasoconstriction of primate coronary artery strips in vitro. Vasoconstriction could be systematically reproduced in some coronary artery strips but was totally absent in others. When present, it was blocked by indomethacin and rapid tachyphylaxis was observed. These results contrast with the significant coronary vasodilation produced by adenosine in practically all other animal models, including humans.

In summary, in certain vascular beds adenosine produces vasoconstriction instead of the expected vasodilatation. This vasoconstrictive effect was initially described in the renal circulation and, more recently, has been described in the pulmonary circulation of sheep, cats, and guinea pigs as well as in the rat hepatic circulation and in the primate coronary artery. The vasoconstrictive effect of adenosine on the renal circulation is due to activation of A1 receptors and involves an interaction with angiotensin II. The vasoconstrictor effect in other vascular beds is due to release of vasoconstrictor eicosanoids including thromboxane. The effect is mediated through adenosine cell surface receptors, but neither the cell type, the receptor type (A1 versus A2), nor the molecular mechanisms involved have been fully characterized. Given the transient nature of adenosine-induced vasoconstriction, the significance of this observation to pathophysiological processes will need to be determined. It is remarkable, however, that the hemodynamic characteristics, the time course, and the mediators involved are virtually identical in these diverse models. This suggests that the interaction between adenosine and vasoconstrictor eicosanoids is not an isolated finding and may be more widespread than previously recognized.

**Neuroexcitatory Actions of Adenosine**

Adenosine has been proposed to play the role of an inhibitory neuromodulator. It inhibits neurotransmitter release through putative presynaptic inhibitory receptors in both the brain and the periphery. This is true of practically all neurotransmitters studied, including norepinephrine, acetylcholine, dopamine, glutamate, aspartame, γ-aminobutyric acid, and serotonin. In addition to its putative presynaptic effects, adenosine hyperpolarizes neurons, decreases nerve firing, and prevents seizure activity. The neuroinhibitory actions of adenosine have been reviewed recently. In contrast to these inhibitory effects, a growing number of studies describe apparent neuroexcitatory actions of adenosine. For clarity, I will describe separately the effects of adenosine in efferent pathways, on ganglionic neurotransmission, on the central nervous system, and on afferent nerves.

**Effects of Adenosine in Efferent Pathways**

Adenosine inhibits the release of neurotransmitters in efferent nerve terminals through putative presynaptic inhibitory receptors. This appears to be a universal phenomenon. Adenosine, however, reportedly enhances the vasoconstrictor effects of transmural nerve stimulation in guinea pig pulmonary arteries. It is suggested that this effect was partially due to presynaptic inhibition of norepinephrine release, but such a conclusion is confounded by a postsynaptic enhancement of the contractile effects of exogenous norepinephrine by adenosine in this model. Postjunctional potentiation of norepinephrine-induced vasoconstriction by adenosine has been reported in the rabbit kidney and in the canine subcutaneous adipose tissue; at the same time, adenosine inhibits norepinephrine release from these tissues. Postjunctional potentiation by adenosine of vagal nerve stimulation has been observed in rabbits. Therefore, even though adenosine may increase the constriction produced by nerve stimulation, this action can be attributed to postsynaptic effects in most tissues, rather than to enhancement of neurotransmitter release.

**Effects of Adenosine on Ganglionic Neurotransmission**

A limited number of studies have investigated the effect of adenosine on ganglionic neurotransmission, and most of them show an inhibitory effect. Adenosine inhibits the release of acetylcholine presynaptically and blocks calcium currents postsynaptically in the superior cervical ganglion of rats. Adenosine may also inhibit neurotransmission in the cat parasympathetic vesical ganglia. Indirect evidence suggests that intravenous adenosine inhibits ganglionic transmission in vivo in anesthetized rats. However, adenosine was found to increase the pressor effects of nicotine in rats, presumably by enhancing the effects of nicotine in sympathetic ganglia. The mechanisms that would explain this apparent contradiction have not been elucidated.

**Effects of Adenosine on Central Nervous System**

An overwhelming number of studies emphasize the inhibitory actions of adenosine on transmitter release and nerve firing in the central nervous system. However, Nishimura et al found that adenosine (10 nM to 1 μM) enhanced the postsynaptic field potential elicited by electrical stimulation in guinea pig hippocampal slices. The excitatory effect was not observed immediately upon the application of adenosine but was delayed. Higher concentrations produce the classic inhibitory effect. Furthermore, stable analogues of adenosine...
produced only inhibitory actions. The effects of specific adenosine receptor antagonists were not explored. Therefore, it is unclear if these excitatory effects are mediated through specific adenosine receptors. Brown et al. reported receptor-specific stimulation of acetylcholine release by adenosine in cholinergic nerve terminals purified from rat striatum. In this preparation, adenosine inhibits acetylcholine release through A₁ receptors. It is only after A₁ receptors are blocked with selective antagonists that an enhancement of acetylcholine release produced by preferential A₂ adenosine analogues is unmasked. A similar effect was found in the rat striatum in vivo. Adenosine analogues perfused in this region through a microdialysis catheter inhibit dopamine release through A₁ receptors. Again, when A₁ receptors were selectively antagonized, an increase in dopamine release produced by activation of A₂ receptors became apparent. The physiological relevance of these findings is unclear inasmuch as the inhibitory actions of adenosine in these regions will predominate under normal conditions given the higher affinity for the A₁ receptor. But these findings do indicate the existence of “excitatory” A₂ receptors in the brain.

The central excitatory effects of adenosine have been best characterized in the nucleus tractus solitarii (NTS). This brain stem center is particularly important for autonomic blood pressure control because it harbors the first synapse for afferent impulses arising from the carotid baroreceptors. An increase in blood pressure sensed by the baroreceptors will increase impulses in the NTS and ultimately lead to a compensatory inhibition of sympathetic outflow. Activation of the NTS by electrical stimulation, or by microinjection of excitatory amino acids such as glutamate, will decrease blood pressure, heart rate, and sympathetic outflow. Conversely, depression of the NTS with local anesthetics will result in increased sympathetic outflow. Given the inhibitory effects of adenosine elsewhere in the central nervous system, it is remarkable that injection of adenosine into the NTS has the same effects as injection of the excitatory amino acid glutamate, that is, decreases in sympathetic nerve activity and blood pressure (Figure 3). These effects are blocked by the adenosine receptor antagonist dipropylsulfophenylxanthine and appear to be mediated through A₂ adenosine receptors. The mechanism that explains this apparent excitatory action of adenosine has been recently explored and involves the release of glutamate by adenosine. Perfusion of adenosine into the NTS through a microdialysis probe increases interstitial concentrations of glutamate in rabbits (Figure 4). Furthermore, the depressor effects of adenosine in the NTS are attenuated by the glutamate receptor antagonists kynurenic acid or glutamic acid diethyl ester, implying that the effects of adenosine are mediated through glutamic acid. The increase in the release of glutamate in the NTS by adenosine contrasts with its inhibitory effect on glutamate release in slices of rat dentate gyrus and hippocampus. How adenosine selectively increases glutamate release in the NTS remains to be determined. Adenosine could release glutamate directly, suppress an inhibitory pathway that tonically restrains glutamate release, or inhibit glutamate metabolism or uptake, thus increasing its concentration in the interstitial space.

The potential relevance of the effects of adenosine in the NTS has been shown by Mosqueda-Garcia et al. They investigated the role of endogenous adenosine in the modulation of the baroreceptor reflex because of the importance of the NTS in the integrity of this reflex. Baroreceptor reflex sensitivity (measured as the magnitude of reflex bradycardia in response to the pressor effects of intravenous phenylephrine) was blunted after selective blockade of adenosine in the NTS, implying that adenosine mechanisms were operative under these conditions. Similarly, caffeine has been found to blunt reflex bradycardia in humans.

**Effects of Adenosine on Afferent Nerves**

While adenosine usually inhibits efferent nerves and the central nervous system (except as described above), it excites afferent fibers. Indeed, I am not aware of any instance in which adenosine has been shown to inhibit afferent nerves. In particular, this review will describe the excitatory effects of adenosine on afferent sensory nerves and on afferent nerves that mediate sympathetic activation. It has been proposed that adenosine activates sensory pain fibers in humans. For example, intra-arterial administration of adenosine into the forearm reportedly produces ischemic-like pain, an effect not explained by local vasodilatation. Intravenous administration of adenosine can produce chest discomfort described as resembling that of myocardial angina or peptic ulcer. It has been proposed that adenosine may be a mediator of pain in myocardial ischemia. It is not known if these putative effects on sensory afferents are species dependent.

Acute administration of adenosine into the renal artery of dogs increases blood pressure, plasma norepinephrine, and renal afferent nerve activity, implying activation of renal afferent nerves. Infusion of adenosine into the renal pelvis produces an identical but
earlier response, suggesting that adenosine-sensitive afferents are located within or near the renal pelvis. This effect may be relevant to the development of hypertension in one-kidney, one clip rats inasmuch as blood pressure was decreased in this animal model by intrarenal infusion of adenosine deaminase, used to degrade endogenous adenosine. Chronic intrarenal infusion of adenosine, however, has no sustained effect on blood pressure in awake normotensive rats, spontaneously hypertensive rats (SHR), or dogs.

Adenosine has excitatory effects on arterial chemoreceptors located in the carotid bodies and in the aortic arch that modulate respiration. Intracarotid injections of adenosine in cats and rats increase carotid sinus nerve activity, implying carotid body chemoreceptor activation. This effect is independent of the vascular effects of adenosine and is also observed in the isolated superfused cat carotid and aortic bodies. This effect is blocked by 8-phenyltheophylline and is thought to be mediated through adenosine A2 receptors.

Activation of arterial chemoreceptors appears to be particularly prominent in humans. Although intravenous adenosine lowers blood pressure in virtually all animal models, adenosine increases heart rate, systolic

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**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Saline</th>
<th>Adenosine</th>
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<tbody>
<tr>
<td>Heart Rate</td>
<td>65 ± 4</td>
<td>97 ± 6</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>128 ± 4 / 69 ± 4</td>
<td>138 ± 4 / 63 ± 5</td>
</tr>
<tr>
<td>C.V.P.</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Ventilation</td>
<td>7.8 ± 0.7</td>
<td>14.8 ± 1.2</td>
</tr>
<tr>
<td>M.S.N.A.</td>
<td>198 ± 52</td>
<td>452 ± 92</td>
</tr>
</tbody>
</table>

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**FIGURE 4.** Line graph shows increase in glutamate release by adenosine in nucleus tractus solitarii (NTS) of rabbits. Arrow indicates stereotaxic implantation of microdialysis probe in right NTS. Either artificial cerebrospinal fluid or increasing concentrations of adenosine (10⁻⁴ and 10⁻³ M) were perfused through microdialysis probe for 60-minute periods while collecting perfusate for glutamate measurements. Bar graph insert shows average data. (Data obtained from Reference 42.)

**FIGURE 5.** Tracings indicate increase in sympathetic nerve activity produced by adenosine in humans. Figure shows effect of saline (left) or adenosine (right) on heart rate, blood pressure, central venous pressure (C.V.P.), minute ventilation, and muscle sympathetic nerve activity (M.S.N.A.) in normal volunteers. Adenosine was administered intravenously as constant infusion. Sympathetic nerve activity was measured through electrode placed in peroneal nerve. (Data obtained from Reference 59.)
blood pressure, plasma catecholamines, and sympathetic efferent nerve activity in humans (Figure 5). These results are probably explained by arterial chemoreceptor activation; adenosine increases blood pressure and stimulates respiration if infused into the aortic arch at a site proximal to the origin of the carotid arteries but decreases blood pressure and has no effect on ventilation when infused into the descending aorta (Figure 6). Furthermore, the cardiovascular and sympathetic effects of adenosine are of magnitudes similar to those produced by acute hypoxia when both stimuli are matched for the degree of respiratory stimulation. Such changes are antagonized by theophylline and caffeine and are magnified by dipyridamole, implying that they are mediated by extracellular adenosine receptors.

Administration of adenosine into the human coronary circulation produces an increase in systemic blood pressure that is not observed in transplanted, and therefore denervated, hearts. This suggests that adenosine activates myocardial afferent nerves, with subsequent sympathetic activation. It is surprising that such an effect has not been described previously in animals, even though adenosine has been extensively administered in the coronary circulation to study its vasodilatory effects, suggesting that, as with arterial chemoreceptors, this effect may be seen to a greater extent in humans. Preliminary studies do suggest that epicardial application of adenosine activates cardiac sympathetic afferents in cats. Likewise, aminophylline attenuates the reflex increase in sympathetic nerve activity triggered by myocardial ischemia in dogs, which suggests that endogenous adenosine plays a role in this reflex.

Finally, intravenous adenosine increases gastric acid secretion, which can be prevented by vagotomy and atropine. This effect seems to be mediated by an A2 adenosine receptor and, because central administration of adenosine has opposite effects, it suggests that this action is explained by activation of efferent pathways.

In summary, adenosine has apparent excitatory actions on afferent nerves, including renal afferents, carotid and aortic chemoreceptors, and myocardial afferents. Activation of these afferent fibers leads to sympathetic activity. Although they are found in animals, these effects seem to be more pronounced in humans. Arterial chemoreceptor activation, for example, can explain most of the cardiovascular and respiratory effects of intravenous administration of adenosine in humans. These changes appear to be mediated

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**Figure 6.** Tracings show differential effects of bolus injections of adenosine in humans, depending on site of administration. Adenosine produces increase in blood pressure, early increase in heart rate, and respiratory stimulation (measured as increase in thoracic excursion) when infused proximal to origin of carotid arteries (aortic arch) (left panel). Adenosine lowers blood pressure, produces late (probably reflex) tachycardia, and has no effect on ventilation when infused into descending aorta (right panel). Increases in blood pressure and ventilation are, therefore, probably explained by activation of arterial chemoreceptors. (Data obtained from Reference 60.)

![Figure 6](http://hyper.ahajournals.org/)

**Figure 7.** Line graph shows caffeine exacerbates hypertension in two-kidney, one clip (2K-1C) rats, animal model for renovascular hypertension. Figure shows systolic blood pressure (SBP) in two-kidney, one clip rats during continuous administration of caffeine (0.1% in drinking water) (2K-1C, caffeine) or plain water (2K-1C, control) and in sham-operated rats receiving caffeine (sham, caffeine) or water (sham, control). Plasma renin activity (P.R.A.) at end of 6 weeks is also shown for each group. Three of eight rats died in 2K-1C, caffeine group. No deaths were observed in other groups. (Data obtained from Reference 71.) *p<0.05 different from 2K-1C, control.

![Figure 7](http://hyper.ahajournals.org/)
Potential Role of Adenosine in Hypertension

Relatively few studies have explored the role of adenosine in the development and maintenance of hypertension. The relative decrease in blood pressure produced by intravenous adenosine is greater in SHR than in Wistar-Kyoto (WKY) rats. This difference disappears after ganglionic blockade, implying that the additional hypotensive effect seen in SHR is due to a greater inhibition of sympathetic tone in this model. However, an attempt to determine if endogenous adenosine modulates sympathetic tone in vivo produced negative results. Likewise, long-term administration of the adenosine receptor antagonist caffeine does not produce a sustained increase in blood pressure in WKY rats or SHR or in normotensive or borderline hypertensive humans. On the other hand, endogenous adenosine appears to play a role in animal models of renin-dependent hypertension. The initial observation was made in two-kidney, one clip rats, an animal model for human renovascular hypertension in which stenosis of one renal artery is produced with a silver clip while the other kidney is left intact. Caffeine administration exacerbated hypertension, leading to malignant hypertension and decreased survival (Figure 7). This effect can be explained by a greater increase in plasma renin activity in caffeine-treated animals and a potentiation of the slow pressor effects of angiotensin II. This latter effect appears to be related to an interaction with the sympathetic nervous system. The increase in plasma renin activity produced by caffeine is likely due to inhibition of endogenous adenosine and is shared by other methylxanthines that are more specific adenosine receptor antagonists. It is possible, therefore, that although caffeine has no sustained pressor effect in normotensive and borderline hypertensive individuals, it may worsen renovascular hypertension. The relevance of these findings to human renovascular hypertension, however, awaits further study.

In summary, although most of the actions of adenosine on efferent pathways and end-organs relevant to blood pressure control lead to decrease in blood pressure. While it inhibits neuronal function and neurotransmitter release in most areas of brain, adenosine activates nucleus tractus solitarii, resulting in inhibition of sympathetic tone and lowering of blood pressure. Activation of afferent nerves by adenosine ultimately leads to increases in sympathetic tone and blood pressure.

### Table 2. Adenosine and Autonomic Regulation of Blood Pressure

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Receptor type</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afferent input</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal afferents</td>
<td>A2</td>
<td>↑ Sympathetic tone, ↑ blood pressure</td>
</tr>
<tr>
<td>Arterial chemoreceptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial afferents</td>
<td>A1 (activation)</td>
<td></td>
</tr>
<tr>
<td>Sensory afferents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system (brain stem)</td>
<td>A1</td>
<td>↓ Sympathetic tone, ↓ blood pressure</td>
</tr>
<tr>
<td>Nucleus tractus solitarii</td>
<td>(activation)</td>
<td></td>
</tr>
<tr>
<td>Efferent pathways</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenergic nerve terminals</td>
<td>A1 (inhibition)</td>
<td>↓ Norepinephrine release</td>
</tr>
<tr>
<td>End-organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculature</td>
<td>A2</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Heart</td>
<td>A1</td>
<td>Bradycardia, ↓ atrioventricular conduction</td>
</tr>
<tr>
<td>Kidney</td>
<td>A2</td>
<td>↓ Renin release</td>
</tr>
</tbody>
</table>

Adenosine can have excitatory or inhibitory effects, depending on site of action. Effects of adenosine on efferent pathways and end-organs relevant to blood pressure control lead to decrease in blood pressure. While it inhibits neuronal function and neurotransmitter release in most areas of brain, adenosine activates nucleus tractus solitarii, resulting in inhibition of sympathetic tone and lowering of blood pressure. Activation of afferent nerves by adenosine ultimately leads to increases in sympathetic tone and blood pressure.
In conclusion, adenosine may act on afferent, central, or efferent autonomic pathways involved in blood pressure regulation (Table 2). Although most of adenosine's actions are inhibitory in nature, this review has highlighted the apparent excitatory actions. These effects are of potential importance, but more research is needed before the role of endogenous adenosine in blood pressure control is defined. Animal studies suggest that endogenous adenosine plays a role in the regulation of the baroreceptor reflex within the NTS in normotensive rats and may restrain the full expression of hypertension in models of renin-dependent hypertension.

Acknowledgments

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