Adenosine Attenuates the Response to Sympathetic Stimuli in Humans

Paul Smits, Jacques W.M. Lenders, Jacques J. Willemsen, and Theo Thien

The effect of adenosine on the forearm vasoconstrictor response to α-adrenergic and sympathetic stimulation was studied in healthy volunteers. During a predilated state achieved by infusion of sodium nitroprusside into the brachial artery, subsequent infusion of norepinephrine induced a mean increase in forearm vascular resistance of 571%, whereas this response was only 270% when an equipotent vasodilator dose of adenosine was used instead of sodium nitroprusside (nitroprusside versus adenosine, \( p < 0.05, n=6 \)). A comparable difference was found when the endogenous release of norepinephrine was stimulated by the local infusion of tyramine, with tyramine-induced increments in forearm vascular resistance of 438% during nitroprusside versus 93% during adenosine (\( n=6, p < 0.05 \)). During these tyramine infusions a similar increase in the calculated forearm norepinephrine overflow occurred in the adenosine and the nitroprusside tests. In a third experiment, we demonstrated that adenosine also reduced the vasoconstrictor response to lower body negative pressure, an endogenous stimulus, of the sympathetic nervous system. During nitroprusside, lower body negative pressure induced an increase in forearm vascular resistance of 135%, whereas this was 39% during adenosine (\( n=6, p < 0.05 \)). We conclude that adenosine attenuates the response to sympathetic nervous system-mediated vasoconstriction in humans, and that this effect may at least partly be explained by a postsynaptic inhibition of α-adrenergic vasoconstriction. Therefore, we think that adenosine may be an important endogenous modulator of sympathetic nervous system activity in humans. (Hypertension 1991;18:216–223)

Adenosine is an endogenous nucleoside that exerts several physiological effects by stimulating the so-called P₁ subtype of purinergic cell surface receptors. With respect to the cardiovascular system, the vasodilator response to adenosine is well known and has been documented convincingly in humans. Apart from its effects on smooth muscle cells, there is a growing body of evidence that adenosine may alter vascular tone by an interaction with the autonomic nervous system. In instrumented rats, adenosine has been reported to influence the response to sympathetic stimuli by interacting with at least three sites: sympathetic ganglia, postganglionic adrenergic nerve terminals, and sympathetically innervated effector cells. At the level of the sympathetic ganglia, adenosine has been shown to potentiate the sympathomimetic effects of nicotine. Further, adenosine was found to inhibit the release of norepinephrine at the adrenergic nerve terminal and to modulate postsynaptic α-adrenergic receptor-mediated processes in experimental animals. The effects of adenosine on the latter two items have never been studied in humans. Since adenosine is a widely occurring substance in the human body, this nucleoside may be an important endogenous modulator of sympathetic nervous system activity. The evidence that adenosine 5'-triphosphate (ATP) is co-released together with norepinephrine in sympathetic nerve endings makes this item even more relevant since ATP is rapidly converted to adenosine in the synaptic cleft.

The main objective of the present in vivo study was to investigate whether adenosine alters sympathetic nervous system-mediated vasoconstriction in humans.

**Methods**

Eighteen healthy normotensive volunteers participated in this study. The protocol was approved by the local ethics committee (University Hospital Nijmegen, The Netherlands), and all subjects gave their written informed consent before participation. The characteristics of the volunteers are summarized in Table 1. The forearm volume of all subjects was...
measured because the dosages of all drugs used were calculated per 100 milliliters of forearm volume (FAV).

Each experiment started with cannulation of a deep antecubital vein and the neighboring brachial artery in the subject's left arm. The main study variables were forearm blood flow (FBF) (measured by venous occlusion mercury-in-Silastic strain gauge plethysmography), blood pressure and heart rate (recorded intra-arterially by a Hewlett-Packard monitor, type 78353B, Hewlett-Packard GmbH, Böblingen, FRG), and plasma concentration of norepinephrine (determined by a radioenzymatic assay). From these parameters, the norepinephrine overflow was calculated as the product of the FBF and the difference between the plasma norepinephrine concentrations of simultaneously sampled venous and arterial blood. All parameters were measured during occlusion of the hand circulation by a wrist cuff inflated to 100 mm Hg above the systolic blood pressure at least 1 minute before the measurements. The experiments started after an equilibration period of 45 minutes. Before each test, all subjects had to abstain from coffee and other caffeinated products for 36 hours because caffeine is a well-known adenosine receptor antagonist at the level of the forearm vasculature. In each individual, blood was sampled to determine the baseline plasma caffeine concentration by reversed-phase, high-performance liquid chromatography.

Each subject participated in only one of three different tests. 1) The FBF response to local norepinephrine infusion was studied in six subjects to determine the baseline plasma caffeine concentration by reversed-phase, high-performance liquid chromatography. Two increasing dosages of norepinephrine were used (4 and 12 ng/FAV/min, 4 minutes per dose). This procedure was performed twice, once during local intra-arterial infusion of adenosine (for dosages, see later on), and once during infusion of sodium nitroprusside (SNP) (0.12 µg/FAV/min). The vasodilator SNP was used as a control vasodilator to achieve a similar degree of forearm vasodilation before the subsequent norepinephrine administration. The infusion of adenosine and SNP was started 5 minutes before and lasted until the end of the norepinephrine infusion. Between the adenosine and the SNP experiment, an equilibration period of 45 minutes was allowed. During infusion of adenosine or SNP, FBF was recorded six times, and blood pressure and heart rate were recorded continuously during a 1-minute period. During the last 2 minutes of each norepinephrine dose, another six FBF readings were made, and blood pressure and heart rate were measured again at the highest norepinephrine dose. To prevent β-adrenergic receptor-mediated effects of norepinephrine, these infusions were given in the presence of propranolol (6 µg/FAV/min i.a.).

2) In another six subjects, the FBF response to intra-arterial tyramine infusion was studied to evaluate whether adenosine altered the response to endogenously released norepinephrine. Tyramine was administered in two increasing rates (4 and 8 µg/FAV/min, 5 minutes per dose), once in the presence of adenosine and once in the presence of SNP as in the first experiment. Norepinephrine overflow was measured before and at the end of the highest tyramine dose. Blood pressure, heart rate, and FBF were recorded as in the norepinephrine experiments.

3) In the final group of six subjects lower body negative pressure (LBNP) (−5 kPa) was applied during 5 minutes. In contrast to the first two series of tests, this experiment enabled us to evaluate eventual effects of adenosine on the release of norepinephrine during an endogenous sympathetic stimulation. Measurements of blood pressure, heart rate, FBF, and norepinephrine overflow were made as in the aforementioned experiments, during adenosine as well as during SNP, and during the subsequent application of LBNP.

In all these tests, blood pressure and heart rate readings were performed during 1-minute periods just before the interventions, at the highest infusion rates of norepinephrine and tyramine, and during the last minute of LBNP to detect possible drug-related systemic effects. Because the number of subjects is relatively small, the two possible sequences concerning the administration of adenosine and SNP were not randomized but alternated within each series of tests.

Before starting the three aforementioned experiments, pilot infusions with adenosine and SNP were performed in each individual in dosages of 4 µg/FAV/min and 0.12 µg/FAV/min, respectively, for 5 minutes. This was done to investigate whether the dosages were equipotent with respect to their vasodilator effects. If necessary, the dose of adenosine was adjusted in such a way that a similar degree of vasodilation was observed as there was during SNP (0.12 µg/FAV/min). All drugs were infused by an automatic syringe infusion pump (type STC-521, Terumo Corporation, Tokyo) at an infusion rate of 50 µl/FAV/min.
Drugs and Solutions
Sterile solutions of adenosine and tyramine (both Sigma Chemical Co., St. Louis, Mo.) were prepared with NaCl 0.9% at the pharmaceutical department of our hospital. The following commercially available solutions were used for norepinephrine and SNP: norepinephrine tartrate (Centrafarma, Etten-Leur, The Netherlands) and SNP (Hoffmann-La Roche, Mijdrecht, The Netherlands); these drugs were dissolved in NaCl 0.9% and glucose 5%, respectively.

Statistical Analysis
The FBF readings were averaged to one mean value for the following periods: baseline (for the pilot infusions), at the end of the adenosine or SNP infusion just before the subsequent intervention, at the end of each infusion rate of norepinephrine and tyramine, and from the end of the second to the third and from the fourth to the fifth minute of the LBNP test. Afterwards, these means were used to calculate the percentage changes of forearm vascular resistance (FVR) by dividing the simultaneously recorded mean arterial pressure through the FBF. Within each subgroup, differences in the parameters between the SNP and the adenosine tests were analyzed by a paired analysis. Because of a non-Gaussian distribution, we used the paired Wilcoxon test for the analysis of FBF, FVR, and norepinephrine overflow. Data on blood pressure and heart rate appeared to show a Gaussian distribution and were therefore analyzed by the paired Student's t test. All differences were considered to be statistically significant at values of \( p<0.05 \) (two-tailed). The results will be presented as mean values±SEM, unless indicated otherwise.

Results
Pilot Infusions of Adenosine and Sodium Nitroprusside
The mean FBF under baseline conditions was 1.5±0.2 ml/FAV/min. Figure 1 presents the results of the pilot infusions of adenosine and SNP in the whole group of 18 volunteers. The first adenosine infusion (4 \( \mu \)g/FAV/min) elicited an increase in mean FBF to 8.1±2.3 ml/FAV/min. A steady state in the vasodilator response to adenosine occurred after 1 minute of infusion. The subsequent infusion of SNP induced a maximal increase in mean FBF from 1.6±0.2 to 6.0±0.7 ml/FAV/min, again with a steady-state value after about 1 minute. To obtain a comparable vasodilator response to adenosine and SNP, dose reductions for adenosine were necessary in seven of the 18 subjects. After these adjustments, adenosine showed a mean increase of FBF from 1.4±0.2 to 6.3±1.1 ml/FAV/min in the whole group of 18 subjects (adenosine dose, 3.2±0.3 \( \mu \)g/FAV/min; range, 0.8–4.0 \( \mu \)g/FAV/min). These individually predetermined adenosine dosages were used in the subsequent experiments.

Table 2 presents the data on mean arterial pressure, FBF, FVR, and heart rate during the pilot infusions. As shown in this table, no consistent changes in blood pressure or heart rate occurred during the pilot infusions during either adenosine infusion or administration of SNP.

Response to \( \alpha \)-Adrenergic Receptor Stimulation
Figure 2 shows the averaged values of FBF during the three tests. In the norepinephrine experiments, the mean steady-state value of FBF during the infusion of SNP was 3.4±0.3 ml/FAV/min. Subsequent infusion of norepinephrine induced a dose-dependent reduction in FBF to a mean trough value of 0.7±0.1 ml/FAV/min at the highest infusion rate. In the presence of adenosine, infusion of norepinephrine induced a fall in FBF from 2.6±0.4 to an ultimate trough value of 1.0±0.2 ml/FAV/min. Table 3 summarizes the mean absolute data on the mean arterial pressure, FBF, FVR, and heart rate just before and during the three vasoconstrictor stimuli.

As presented in the upper panel of this table, norepinephrine infusion altered the FBF and the FVR significantly during adenosine as well as during SNP infusion. Figure 3 shows a comparison of the percent-change in blood flow before and during 5 minutes of intra-arterial infusion of the first dose of adenosine (ADO) (4 \( \mu \)g/FAV/min), the fixed dose of sodium nitroprusside (SNP) (0.12 \( \mu \)g/FAV/min), and the adjusted (final) dose of adenosine (3.2±0.3 \( \mu \)g/FAV/min) in the 18 subjects. FAV, per 100 ml of forearm volume.

Table 2. Mean Arterial Pressure, Forearm Blood Flow, Forearm Vascular Resistance, and Heart Rate Before and at the End of the Pilot Infusions of Adenosine and Sodium Nitroprusside in the Whole Group of 18 Subjects

<table>
<thead>
<tr>
<th>Parameters (n=18)</th>
<th>Before</th>
<th>During</th>
<th>Before</th>
<th>During</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>83.4±2.0</td>
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<td>83.1±1.9</td>
<td>81.8±1.6</td>
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<td>FBF (ml/FAV/min)</td>
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<td>5.9±0.8*</td>
<td>1.6±0.2</td>
<td>5.6±0.6*</td>
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<tr>
<td>FVR (AU)</td>
<td>72.4±9.0</td>
<td>19.2±2.6*</td>
<td>60.5±5.1</td>
<td>17.4±1.9*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70.3±2.4</td>
<td>71.2±2.5</td>
<td>69.7±2.2</td>
<td>70.7±2.3</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MAP, mean arterial pressure; FBF, forearm blood flow; FAV, per 100 ml of forearm volume; FVR, forearm vascular resistance; AU, arbitrary units; HR, heart rate. *p<0.01 vs. before.
forearm vascular resistance (•/•)

FOREARM WOOD flow(ml/100ml/min)

FIGURE 2. Line graphs show course of mean forearm blood flow before and during the two infusion rates of norepinephrine (NOR) (4 and 12 ng/100 ml forearm tissue/min) and tyramine (TYR) (4 and 8 µg/100 ml forearm tissue/min) and before and during the application of lower body negative pressure (LBNP) (−5 kPa), all in the presence of adenosine (ADO) or sodium nitroprusside (SNP). For statistics, see Table 3 and Figure 3.

In the tyramine experiments, the steady-state FBF during SNP administration was 7.6±1.2 ml/FAV/min, whereas equipotent dosages of adenosine resulted in a mean FBF of 7.2±1.4 ml/FAV/min in this group of subjects. The upper panel of Table 4 presents the venous and arterial plasma norepinephrine concentrations and the data on the calculated norepinephrine overflow during the predilated state achieved by the adenosine and SNP infusion and during the subsequent tyramine administration. It is obvious from this table that the “baseline” norepinephrine levels just before the tyramine infusion showed comparable values in the adenosine and the SNP tests. Further, tyramine infusion significantly increased the norepinephrine levels in the venous effluent as well as the calculated forearm norepinephrine overflow. However, the tyramine-induced increase in the norepinephrine-induced percentage increase in FVR averaged 571±167% versus 270±113% in the SNP and adenosine test, respectively (p<0.05).

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TABLE 3. Mean Arterial Pressure, Forearm Blood Flow, Forearm Vascular Resistance, and Heart Rate During the Predilated State Achieved by Intra-arterial Infusion of Adenosine or Sodium Nitroprusside and at the End of the Three Subsequent Interventions: Norepinephrine Infusion, Tyramine Infusion, and the Lower Body Negative Pressure Experiment

<table>
<thead>
<tr>
<th></th>
<th>ADO</th>
<th>ADO+NOR</th>
<th>SNP</th>
<th>SNP+NOR</th>
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<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>86.2±2.8</td>
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<td>84.8±1.9</td>
<td>88.3±0.8*</td>
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<td>FBF (ml/FAV/min)</td>
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<td>3.4±0.3</td>
<td>0.7±0.1*</td>
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<tr>
<td>FVR (AU)</td>
<td>37.7±6.2</td>
<td>115.2±19.5*</td>
<td>25.7±1.8</td>
<td>162.1±35.1*</td>
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<tr>
<td>HR (beats/min)</td>
<td>64.8±5.5</td>
<td>62.8±5.5</td>
<td>63.5±6.1</td>
<td>63.3±5.1</td>
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<tr>
<td>Tyramine (n=6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>81.7±4.4</td>
<td>86.7±5.0*</td>
<td>82.3±3.6</td>
<td>86.2±3.7*</td>
</tr>
<tr>
<td>FBF (ml/FAV/min)</td>
<td>7.2±1.4</td>
<td>6.0±2.5</td>
<td>7.6±1.2</td>
<td>1.6±0.2*</td>
</tr>
<tr>
<td>FVR (AU)</td>
<td>13.0±2.2</td>
<td>27.6±7.7†</td>
<td>11.9±1.5</td>
<td>62.5±12.3*</td>
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<td>HR (beats/min)</td>
<td>73.3±4.6</td>
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<td>Lower body negative pressure (n=6)</td>
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<td>MAP (mm Hg)</td>
<td>91.5±2.8</td>
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<tr>
<td>FBF (ml/FAV/min)</td>
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<tr>
<td>FVR (AU)</td>
<td>24.0±4.4</td>
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<td>19.6±1.7</td>
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<tr>
<td>HR (beats/min)</td>
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<td>74.0±2.7‡</td>
<td>72.1±1.5</td>
<td>74.7±2.4†</td>
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</table>

Values are mean±SEM. ADO, adenosine; NOR, norepinephrine; SNP, sodium nitroprusside; MAP, mean arterial pressure; FBF, forearm blood flow; FAV, per 100 ml of forearm volume; FVR, forearm vascular resistance; AU, arbitrary units; HR, heart rate; TYR, tyramine; LBNP, lower body negative pressure.

‡0.05<p<0.10, *p<0.05, and †p<0.01 vs. ADO or SNP alone.
nephrine overflow did not differ between the adenosine and the SNP test (respective mean increments, 5.69±0.77 versus 4.94±1.09 pmol/FAV/min, p>0.1). Despite this comparable overflow of norepinephrine in the forearm, the FBF response to tyramine was attenuated in the presence of adenosine when compared with SNP, as shown in Figure 2. In contrast to the SNP test, tyramine did not change FBF or FVR significantly in the presence of adenosine (Table 3). The increase in FVR as a result of the highest dose of tyramine was 438±83% during SNP versus 93±40% during adenosine (p<0.05) (Figure 3).

The responses of blood pressure, FBF, FVR, and heart rate to the highest infusion rate of norepinephrine and tyramine are presented in Table 3. Small though significant increments in blood pressure occurred during both norepinephrine and tyramine infusions. However, the systemic pressor response to norepinephrine did not differ between the adenosine and the SNP tests (Δmean arterial pressure, 4.5±1.1 versus 3.5±1.1 mm Hg, p>0.1), and this was not the case for the tyramine infusions either (5.0±1.6 versus 3.8±1.4 mm Hg, p>0.1). The heart rate did not change significantly as a result of the local infusion of norepinephrine or tyramine. As shown by the arterial norepinephrine levels presented in Table 4, the local tyramine infusion did induce a small but significant effect on systemic norepinephrine levels, but again these responses did not differ between the adenosine and the SNP tests.

**Response to Sympathetic Stimulation**

The right panel of Figure 2 shows the course of the averaged FBF during the application of LBNP. Just before starting LBNP, the mean FBF during SNP infusion was 4.9±0.5 ml/FAV/min. As a result of LBNP, FBF decreased to a mean value of 2.1±0.1 ml/FAV/min. In the adenosine experiments, LBNP induced a less pronounced fall of FBF from 4.5±0.8 to 3.0±0.4 ml/FAV/min. As shown in Figure 3, the mean percentage vasoconstrictor response to LBNP was significantly less during adenosine when compared with SNP (ΔFVR, 39±14% versus 135±25%, p<0.05).

Baseline plasma norepinephrine concentrations during the predilated state just before LBNP did not differ between the adenosine and the SNP test (lower panel Table 4). Application of LBNP significantly increased the venous plasma norepinephrine concentrations in both tests. However, during local adenosine infusion, LBNP failed to increase the overflow of norepinephrine in the forearm, whereas the latter variable was nonsignificantly raised by LBNP in the SNP test. In five of the six subjects, the LBNP-induced change in norepinephrine overflow was higher in the SNP test when compared with the adenosine test. The mean LBNP-induced changes in norepinephrine overflow measured 0.27±0.22 versus −0.13±0.30 pmol/FAV/min in the SNP and adenosine tests, respectively (0.05<p<0.1).

LBNP did not induce significant changes in mean arterial blood pressure (Table 3). Neither was there any difference in the blood pressure response to LBNP between the adenosine and the SNP tests (ΔMAP, 0.0±2.0 versus 0.3±1.6 mm Hg, p>0.1). However, during adenosine as well as during SNP, LBNP induced a significant but comparable increase in heart rate and arterial plasma norepinephrine levels in both the adenosine and the SNP test (lower panels of Tables 3 and 4).

In 14 of the 18 volunteers the baseline plasma caffeine concentration was below detection level (<0.1 mg/l). In the other four subjects, plasma caffeine concentration ranged from 0.3 to 0.9 mg/l, indicating an excellent overall compliance with respect to caffeine abstinence. Within this small range of plasma caffeine levels (<0.1–0.9 mg/l), there was no significant correlation between the baseline plasma caffeine concentration and the percentage forearm vasodilator responses to intra-arterial adenosine infusions.

**Discussion**

The most prominent finding of the current study is the attenuation of α-adrenergic receptor-mediated
vasoconstriction by adenosine. We demonstrated this first by showing a reduced response to exogenous norepinephrine while β-adrenergic receptors were blocked by propranolol. Moreover, an attenuated vasoconstriction to the tyramine-mediated endogenous release of norepinephrine was observed. From in vitro studies, it has been suggested that adenosine does not influence the tyramine-induced release of norepinephrine. Indeed, the increments in norepinephrine overflow in the forearm as a result of tyramine infusion were comparable in the adenosine and the SNP tests, and this at least suggests that the release of endogenous norepinephrine was similar in both experiments. Therefore, our tyramine experiments appeared to be a suitable model to study the postsynaptic effects of adenosine on α-adrenergic receptor-mediated processes. Consequently, the results of both the norepinephrine and the tyramine experiments support the premise that adenosine inhibits the response to α-adrenergic stimulation in humans.

The adenosine-induced attenuation of α-adrenergic receptor-mediated vasoconstriction cannot be explained by the vasoactive effects of adenosine itself, because a similar degree of vasodilation was obtained by SNP infusion in the control experiments. As shown clearly in Figure 1, the pilot infusions of adenosine and SNP also show that FBF showed steady-state values at the time that the infusion of norepinephrine or tyramine was started. Data from the literature further show that the vasodilator response to intra-arterial adenosine infusion remains stable even for periods up to 2 hours. Consequently, it is unlikely that the attenuated vasoconstrictor response in the adenosine tests was brought about by an increasing vasodilator effect with ongoing adenosine infusion.

Because the pilot infusions failed to bring about any change in systemic blood pressure or heart rate (Table 2) and because there were no differences in the blood pressure and heart rate responses to norepinephrine or tyramine between the adenosine and SNP experiments (Table 3), we think that cardiovascular reflex mechanisms did not account for the observed differences in the response to α-adrenergic receptor stimulation. According to the literature, intravenous infusion of adenosine (more than 40 µg/kg/min) may induce a stimulation of the sympathetic nervous system as a result of carotid body chemoreceptor stimulation. When administered intra-arterially, even lower infusion rates of adenosine have been reported to induce sympathetic stimulation in rats as well as in humans as a result of afferent nerve stimulation. In those studies, the stimulation of the sympathetic nervous system was always accompanied by increments of blood pressure. During our experiments no signs of adenosine-mediated stimulation of the sympathetic nervous system occurred since the systemic plasma norepinephrine levels just before the application of the vasoconstrictor stimuli as well as the blood pressure levels at that time were well matched in the adenosine and the SNP tests (Tables 3 and 4), suggesting a comparable baseline sympathetic tone.

Our results suggest an adenosine-induced modulation of α-adrenergic receptor-mediated processes at the postsynaptic side. Such a modulation has also been observed in experimental animals, for instance the rat, in which an attenuated vascular response to phenylephrine infusion during the administration of adenosine was found. On the other hand, in the guinea pig a potentiation of α-adrenergic receptor-mediated processes has been observed in the vas deferens as well as in the brain. However, the latter observations concern nonvascular animal structures and therefore cannot be extrapolated to the human cardiovascular system.

As shown by the LBNP tests, local adenosine infusion seems to reduce the vasoconstrictor response to an endogenous stimulation of the sympathetic nervous system. Of course, this may entirely be explained by the aforementioned postsynaptic effect of adenosine on α-adrenergic receptor-mediated vasoconstriction. Theoretically, a presynaptic mechanism of action, resulting in an adenosine-mediated reduction of norepinephrine release may be an additional explanation for the reduced vasoconstrictor response to a sympathetic stimulation. In the rabbit kidney, adenosine was able to inhibit the release of norepinephrine induced by nerve stimulation by approximately 70%, and in isolated rabbit hearts, adenosine induced a dose-dependent inhibition of stimulation-evoked outflow of norepinephrine from the hearts of more than 40%. Comparable data were obtained in several other tissues and species. However, our own data on the norepinephrine overflow do not convincingly support the view that adenosine inhibits the release of norepinephrine in the human vascular system. The difference in the LBNP-induced increase in norepinephrine overflow between the adenosine and the SNP experiments was statistically not significant. Moreover, we were only able to measure the overflow of norepinephrine in the forearm and not the release and the extraction of neurotransmitter, and therefore we can only speculate on a prejunctional mechanism of action of adenosine in humans.

Because basal FBF is an important determinant of forearm norepinephrine extraction, it is relevant to realize that baseline FBFs just before the application of LBNP were nearly equal in the adenosine and the SNP experiments (right panel Figure 2). Because the extraction of norepinephrine is inversely related to FBF, it might be expected that the attenuated fall in FBF during LBNP in the adenosine tests would be responsible for a smaller increase in forearm extraction of norepinephrine when compared with the SNP experiments. Thus, a larger LBNP-induced increase in norepinephrine overflow would be expected during the adenosine experiments when compared with the SNP controls. In contrast, the increase in norepinephrine overflow during LBNP
seemed lower in the presence of adenosine when compared with SNP, and this observation might argue for a reduced release of endogenous norepinephrine during this procedure. However, we can not exclude any specific effect of adenosine on the extraction of norepinephrine, which would provide additional explanations for the difference between the adenosine and the SNP tests. Therefore, further studies are needed to address this item. To evaluate these mechanisms, steady-state infusions with tritiated norepinephrine would be useful to calculate the norepinephrine forearm extraction under different circumstances as described by Esler et al.22

Although we were successful in attaining a comparable degree of vasodilation in the SNP versus the adenosine tests, there appeared to be a considerable interindividually random variation in the vasodilator response to local infusion of SNP and adenosine. In previous studies we also observed large ranges in the forearm vasodilator response to adenosine.4 Combined with the relatively small groups of subjects, this large range may explain the differences in the steady-state baseline FBF between the norepinephrine, the tyramine, and the LBNP tests (Figure 2). We think, however, that these differences do not complicate the interpretation of the results since the vasodilator response to SNP and adenosine were nearly equal within the three subgroups of subjects.

Based on our results, adenosine may be considered to act as a modulator of sympathetic nervous system activity in humans. Endogenous adenosine is released from tissues to the interstitium, especially when the breakdown from ATP to adenosine surpasses the production of ATP, as in states of ischemia.23 Because we previously have shown that the widely used methylxanthines like caffeine and theophylline behave like adenosine receptor antagonists in the human vascular system,3 it is tempting to speculate that both drugs will increase the vasoconstrictor response to sympathetic stimulation. Recently, Taddei et al24 found evidence for this view by showing an increased LBNP-induced forearm vasoconstriction during intra-arterial infusion of theophylline in humans.24

In conclusion, adenosine significantly reduces the vasoconstrictor response to stimulation of the sympathetic nervous system in humans. The mechanism of this action may be based on a postsynaptic inhibition of a-adrenergic receptor–mediated vasoconstriction. The present findings suggest that adenosine may be an important endogenous inhibitor of sympathetic nervous system activity in humans. Further studies are needed to elucidate the putative prejunctional inhibiting effect of adenosine on the release of norepinephrine in humans.

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