Mechanism of Hind Limb Vasoconstriction Due to Cyclosporin A in the Dog

Francois Tronc, Michel Carrier, and Conrad L. Pelletier

Cyclosporin A (CSA) causes an acute vasoconstriction of hind limb arterial vessels. To determine the mechanism of action of CSA on the peripheral arterial bed, studies were performed on the isolated femoral artery perfused at constant flow in 61 dogs. Changes in femoral perfusion pressure reflected variations in vascular resistance. Pure powder CSA was dissolved in autologous blood and injected at doses of 1, 5, 10, and 20 mg. Infusions of 1 and 5 mg CSA caused nonsignificant mean increases of 4±2 mm Hg (95% confidence interval [CI], 0–8; p>0.05) and 10±4 mm Hg (95% CI, 0–21; p>0.05) in femoral perfusion pressure, with CSA blood levels in the femoral vein averaging 40±16 and 126±50 nmol/l, respectively, at the end of the injections. Infusions of 10 and 20 mg CSA caused significant increases in femoral perfusion pressure averaging of 8±3 mm Hg (95% CI, 1–14; p<0.05) and 20±4 mm Hg (95% CI, 11–29; p<0.05) in femoral perfusion pressure. CSA blood levels at the end of injections averaged 271±99 and 431±146 nmol/l, respectively, in the femoral vein. Blockade of α-adrenergic receptors with phentolamine and surgical lumbar sympathectomy decreased significantly the CSA vasoconstrictive effect in peripheral arterial vessels, with increases in perfusion pressure averaging 29±5 mm Hg before and 14±3 mm Hg after phentolamine (p<0.05) and 30±2 mm Hg before and 8±2 mm Hg after sympathectomy (p<0.05). The response to CSA was not due to cerebral stimulation, nor was it caused by stimulation of arterial chemoreceptors or intrathoracic receptors, since bolus injections of CSA in the carotid artery and in the right atrium did not cause significant changes in hind limb perfusion pressure. After lumbar sympathectomy, injections of 1, 2, and 4 μg norepinephrine caused average increases of 16±3, 36±5, and 56±6 mm Hg (p<0.05) in femoral perfusion pressure, respectively. After injection of CSA, 1, 2, and 4 μg norepinephrine caused increases of 28±3, 48±4, and 65±5 mm Hg in perfusion pressure, respectively. During CSA infusion, tyramine (50 μg/kg) caused an increase of 23±3 mm Hg (95% CI, 17–29) in perfusion pressure compared with 38±4 mm Hg (95% CI, 30–46) before CSA injection, indicating a significant difference (p<0.05). Therefore, in the dog, CSA causes an acute vasoconstriction of peripheral arterial vessels through an increase in adrenergic activity, resulting at least partly from the inhibition of neuronal norepinephrine reuptake. No central or reflex effects appear to be involved in the response.

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**KEY WORDS** • peripheral vasoconstriction • sympathetic stimulation • neuronal norepinephrine reuptake

Cyclosporin A (CSA), a fungal cyclic polypeptide, has become the immunosuppressive drug of choice in organ transplantation. However, hypertension and renal insufficiency are frequent side effects.1–3 Most patients on CSA therapy need treatment for hypertension compared with less than 20% of patients on a conventional immunosuppressive regimen.3,4 Although renal insufficiency has been widely explored in clinical and experimental studies, data on the effects of CSA on the peripheral vascular bed are scanty.

In rats5 and dogs6 treated with CSA, previous studies using radiolabeled microspheres showed a decrease in regional blood flows, except in the skeletal muscle, the liver, and the brain. In the human, an increase in sympathetic nervous activity was found.7 It has been suggested that the vascular effect of CSA may be mediated through a central cerebral action or a stimulation of the carotid chemoreceptors, resulting in an increase in sympathetic activity, or through a potentiation of the peripheral effect of norepinephrine (NE).8

The goal of the present study was to evaluate the effect and mechanism of action of CSA on peripheral arterial vessels in the isolated hind limb, the possible role of cerebral and reflex mechanisms in the response, and the influence of CSA on neuronal reuptake of NE.

**Materials and Methods**

Sixty-one mongrel dogs weighing 20–35 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and artificially ventilated, after endotracheal intubation, at 10–12 cycles per minute using a Harvard ventilator (Harvard Apparatus, South Natick, Mass.). Polyethylene cannulas were inserted into the right femoral artery for blood pressure monitoring and into

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the femoral vein for systemic drug administration. During the experiment, isotonic saline was administered to replace fluid loss. Systemic and peripheral arterial pressures were recorded with strain-gauge transducers and a multichannel recorder (Grass Instrument Co., Quincy, Mass.).

After retrograde cannulation of the external iliac artery and antegrade cannulation of the femoral artery, the left hind limb was perfused at a constant flow with a roller pump using autologous blood from the aorta. The circuit tubing included a depulsator and a heat exchanger to maintain the blood temperature at 37°C. To eliminate other sources of arterial inflow to the limb, all branches of the terminal aorta were ligated. Adequate isolation of the hind limb from the systemic circulation was indicated by a decrease in retrograde pressure to 40 mm Hg or less when the pump was stopped. Before cannulation of the blood vessels, heparin (3 mg/kg) was given intravenously.

Perfusion pressure of the left hind limb was measured from the arterial line just proximal to the femoral inflow cannula. Perfusion flow to the femoral artery was adjusted by controlling the pump speed at the beginning of each experiment to obtain a mean hind limb perfusion pressure equal to the mean aortic pressure. Changes in hind limb perfusion pressure reflected changes in peripheral arterial resistance.

Blood samples were obtained regularly throughout the experiments to measure blood pH, PaO2, and PaCO2. Blood pH was maintained between 7.3 and 7.4 by ventilation adjustments and bicarbonate infusions as needed. For local injections, drugs were infused directly into the femoral arterial inflow to the perfused limb, proximal to the insertion of the femoral artery cannula and to the site of pressure monitoring. Drugs were injected over a period of 10 minutes, and changes in perfusion pressure were recorded throughout the infusion period.

Nitroglycerine (5 mg in 55 ml isotonic saline) was injected in the hind limb at the beginning and at the end of each experiment to test the reactivity of the peripheral vascular bed. Pure powder CSA was dissolved into autologous blood (60 ml) and injected. Autologous blood alone was also injected to test reactivity to the vehicle. At the end of each CSA infusion, left femoral vein and systemic blood samples were obtained to determine CSA serum levels by the fluorescence polarization immunnoassay technique.

In six dogs, injections of four different doses of CSA (1, 5, 10, and 20 mg) in the femoral arterial inflow of the perfused hind limb were performed. The effect of systemic injections of CSA in the contralateral femoral vein at doses of 20 mg was studied in six dogs. In another group of six dogs, the effect of blockade of α-adrenergic receptors with an infusion of 10 mg phenolamine was evaluated. NE was given at a dose of 3 μg before and after phenolamine to test for the completeness of α-adrenergic blockade. A left lumbar sympathectomy was performed in six dogs by surgical dissection of the left lumbar sympathetic trunk, which was interrupted at the level of L-2, and the rami from L-2 to L-4 were cut.

Typically, hind limb perfusion pressure reached a plateau 5–9 minutes after the beginning of CSA injection and persisted 5 minutes or more after the end of the injection. This plateau was taken as the maximal effect of the drug on hind limb vessels.

To study the central and reflex response to CSA, seven dogs were submitted to the same protocol described previously under thiopental (15 mg/kg) and chloralose (60 mg/kg) anesthesia to minimize the depressing effect. Additional doses of α-chloralose (10 mg/kg) were administered hourly. The right carotid chemoreceptors and baroreceptors were denervated by sinus nerve section achieved after ligation of the occipital artery at its origin from the external carotid artery and by careful dissection and removal of the immediate adjacent tissues. The left carotid bifurcation was left intact. To eliminate the effects of intrathoracic receptors,9 a bilateral cervical vagotomy was performed, and the animals were paralyzed with a neuromuscular blocking agent (pancuronium bromide, 0.1 mg/kg) to prevent the ventilatory response to chemoreceptor activation.

The integity of the left carotid baroreceptors and chemoreceptors and the efficacy of the right carotid sinus nerve section were assessed with carotid occlusions (30 seconds) and injections of nicotine (0.1 μg/kg), a potent carotid chemoreceptor stimulant,10,11 into the common carotid arteries. Arterial blood gases and pH in systemic and reinfused autologous blood were carefully kept within the physiological range throughout the course of the experiment to prevent chemoreceptor activation by hypoxia, hypercapnia, or acidosis.12 Bolus injections of 10 ml autologous blood through catheters in the denervated right carotid artery and in the intact left common carotid artery were followed by injections of 20 mg pure powder CSA dissolved in 20 ml autologous blood. The right carotid sinus pressure was measured through a catheter in the external carotid artery, and variations in pressure never exceeded 5 mm Hg during the experiment. Blood samples were obtained from the right and left superficial jugular veins to determine CSA serum levels.

The effect of intrathoracic receptor stimulation by CSA was studied with bolus injections of 20 mg pure powder CSA diluted in 20 ml autologous blood directly into the right atrium in six animals with vagal and sinus nerves left intact. Fluoroscopic control was used to position the infusion catheter in the right atrium before infusion. In 10 dogs, the effect of CSA on the vascular response to NE was studied after a left lumbar sympathectomy. NE was first injected at doses of 1, 2, and 4 μg in the femoral arterial perfusion inflow before CSA administration. NE injections were repeated after systemic injections of 40 mg pure powder CSA dissolved into 120 ml autologous blood infused over a 20-minute period. Between each NE injection, hind limb perfusion pressure was allowed to return to the control level.

Neuronal NE recapture was studied with injections of tyramine, a sympathomimetic drug, which acts after uptake into the adrenergic nerve terminal and displacement of NE from the nerve endings. Injections of tyramine (50 μg/kg) were performed in 10 dogs. An initial control injection was followed by a second bolus of tyramine injected during CSA infusion (40 mg pure powder CSA dissolved in 120 ml blood infused over a 20-minute period). Tyramine was not injected until several minutes had elapsed and hind limb perfusion pressure after the beginning of CSA infusion had sta-
lized. In four experiments, phenylephrine (3 μg) was also injected before and during CSA infusion. In six of those dogs, tyramine (50 μg/kg) was injected before and after the administration of desmethylimipramine, a drug causing long-lasting inhibition of the carrier responsible for the transport of NE. In four experiments, the effect of three consecutive injections of tyramine was studied. Finally, in another group of four dogs, CSA (20 mg) was injected before and after the administration of desmethylimipramine.

The data are presented as mean±SEM changes in hind limb perfusion pressure and 95% confidence interval (CI). CSA plasma levels are expressed as mean±SEM. Changes in perfusion pressure were compared using Student’s paired t test. Comparisons between multiple groups were made by analysis of variance using Fisher’s exact test for intergroup comparisons. The level of statistical significance was established at 95%. All animals were treated in accordance with the “Guide for the Care and Use of Laboratory Animals” published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Results

Effect of Nitroglycerine and Autologous Blood

In the first group of six dogs, the infusion of nitroglycerine caused an average decrease of 63±5 mm Hg (95% CI, 50–77; p<0.05) in hind limb perfusion pressure, indicating a good reactivity of peripheral arterial vessels. Basal perfusion pressure before nitroglycerine injection averaged 132±7 mm Hg and decreased to an average of 68±5 mm Hg during the injection. Infusion of 60 ml autologous blood did not cause any significant change in perfusion pressure (1±2 mm Hg; 95% CI, −3–−1; p>0.05).

Response to Cyclosporin

In the same group of six animals, after return of hind limb perfusion pressure to the control level (119±5 mm Hg), injections of 1 and 5 mg CSA directly into the femoral arterial inflow caused average increases of 4±2 mm Hg (95% CI, 0–8) and 10±4 mm Hg (95% CI, 0–21) in hind limb perfusion pressure, respectively, changes that were not statistically significant (p>0.05); the mean CSA levels obtained from ipsilateral femoral venous blood at the end of injections were 40±16 and 126±50 nmol/l, respectively, and systemic CSA levels averaged 14±3 and 24±6 nmol/l, respectively.

Direct infusion of 10 and 20 mg CSA caused increases of 8±3 mm Hg (95% CI, 1–14) and 20±4 mm Hg (95% CI, 11–29), respectively, in hind limb perfusion pressure. Ipsilateral femoral CSA levels averaged 271±99 and 431±146 nmol/l at the end of injections, with mean systemic levels averaging 53±10 and 77±21 nmol/l, respectively. The changes in peripheral vascular resistance and in CSA serum levels obtained with these doses of CSA were all significant (p<0.05, Figure 1).

Effect of α-Adrenergic Blockade

After effective blockade of α-adrenergic receptors in six dogs, as shown by the absence of significant vasoconstrictive response to 3 μg NE (mean pressure increase, 38±5 mm Hg before and 0±1 mm Hg after blockade), direct intra-arterial injection of 20 mg CSA caused an average increase of 14±3 mm Hg in hind limb perfusion pressure compared with 29±5 mm Hg before the blockade, indicating a significant difference (p<0.05).

Effect of Sympathectomy

A direct infusion of 20 mg CSA after surgical sympathectomy in six dogs caused an average increase of 8±2 mm Hg in peripheral perfusion pressure compared with 30±2 mm Hg before sympathectomy, indicating a significant difference (p<0.05).

Cerebral and Reflex Effects of CSA

There was no change in hind limb perfusion pressure during occlusion for 30 seconds of the right common carotid artery (mean increase, 2±1 mm Hg; 95% CI, −1–+6; p>0.05). Nicotine injection into the right carotid artery caused only a late increase (39 seconds after the end of injection) in hind limb perfusion pressure, averaging 46±12 mm Hg (95% CI, 18–75; p<0.05) and resulting from stimulation of the contralateral intact left carotid chemoreceptors with recirculation. The absence of increase in hind limb perfusion pressure with right carotid occlusion and the delayed response to nicotine injection indicated complete denervation of the right carotid sinus. Hind limb perfusion pressure did not change significantly when 20 mg CSA was injected directly into the right common carotid artery (average increase, 1±2 mm Hg; 95% CI, −4–+7; p>0.05). The CSA level from ipsilateral jugular vein blood at the end of injection averaged 282±54 nmol/l.

Left common carotid occlusion for 30 seconds caused a significant increase in hind limb perfusion pressure of 22±4 mm Hg (95% CI, 12–32; p<0.05). Injection of nicotine into the left common carotid artery caused an immediate (within 13 seconds after the end of injection) and marked increase in hind limb perfusion pressure, averaging 58±17 mm Hg (95% CI, 17–99; p<0.05). These vascular responses indicated the integrity of the left carotid baroreceptors and chemoreceptors. Bolus injections of 20 mg CSA into the left common carotid artery in these seven dogs did not cause any significant changes in hind limb perfusion pressure (average increase, 1±1 mm Hg; 95% CI, −1–+4; p>0.05), and the CSA levels in the left jugular venous blood averaged 673±102 nmol/l.

Systemic injections of 20 mg CSA in six dogs caused a nonsignificant increase of 5±2 mm Hg (95% CI, 0–10;
Injections of 20 mg CSA directly into the right atrium of six dogs with vagal and sinus nerves intact caused a nonsignificant increase of 1±2 mm Hg (95% CI, -4±6; p>0.05) in hind limb perfusion pressure, with systemic CSA serum levels averaging 470±166 nmol/l.

**Effect of CSA on the Response to Norepinephrine**

In 10 dogs, direct injections of 1, 2, and 4 µg NE in the perfused limb caused average increases of 16±3 (95% CI, 9-23), 36±5 (95% CI, 26-46), and 56±6 (95% CI, 41-70) mm Hg in hind limb perfusion pressure, respectively, changes that were all significant (p<0.05, Table 1). After systemic injection of 40 mg CSA, the NE injections increased the hind limb perfusion pressure by 28±3, 48±4, and 65±5 mm Hg, respectively, with a mean CSA serum level of 321±41 nmol/l. The difference in the response to NE before and after CSA infusion was significant at 1 and 2 µg (p<0.01), but it did not reach significance at 4 µg (p>0.05).

**Effect of CSA on the Response to Tyramine**

In 10 dogs, direct injections of tyramine (50 µg/kg) in the perfused limb caused an average increase of 38±4 mm Hg (95% CI, 30-46; p<0.05) in perfusion pressure compared with 23±3 mm Hg (95% CI, 17-29; p<0.05) during CSA infusion in the perfused limb, indicating a significant decrease in the response (p<0.05). CSA blood level in the femoral vein at the end of injection averaged 489±48 mmol/l. The decrease in the response to tyramine was not the result of an increase in the baseline perfusion pressure caused by CSA, since pressure increases caused by phenylephrine injections before (69±14 mm Hg) and during (63±9 mm Hg) CSA injection in four experiments were similar (p>0.05).

On the other hand, the decreased response to tyramine with CSA was not the result of a tachyphylactic effect, since three consecutive injections of tyramine in four dogs resulted in similar increases in perfusion pressure (44±12, 45±15, and 39±9 mm Hg; p>0.05). Finally, no significant increase in perfusion pressure was obtained with tyramine (0±2 mm Hg) or with CSA (5±6 mm Hg, p>0.05) injections after tyramine carrier blockade with desmethylimipramine.

**Discussion**

Clinical and experimental studies have shown a vasoconstrictive effect of CSA on renal arterial vessels. This vascular effect is probably responsible for the acute and chronic renal insufficiency and possibly for the hypertension observed after transplantation in patients treated with CSA immunosuppression. The decrease in blood flow is not confined to the renal circulation.

**Table 1. Changes in Hind Limb Perfusion Pressure With Injections of Norepinephrine at Three Different Dosages Before and During Cyclosporin A Infusion in 10 Dogs**

<table>
<thead>
<tr>
<th>Dosage (µg)</th>
<th>Control infusion</th>
<th>During CSA infusion</th>
<th>Difference between control and CSA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 µg NE</td>
<td>Control perfusion pressure (mm Hg) 96±3</td>
<td>101±5</td>
<td>5±7</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Maximal perfusion pressure (mm Hg) 111±5</td>
<td>129±6</td>
<td>18±8</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Increase in pressure (mm Hg) 16±3</td>
<td>28±3</td>
<td>12±4</td>
<td>0.01</td>
</tr>
<tr>
<td>2 µg NE</td>
<td>Control perfusion pressure (mm Hg) 96±4</td>
<td>92±4</td>
<td>4±5</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Maximal perfusion pressure (mm Hg) 132±8</td>
<td>140±8</td>
<td>9±8</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Increase in pressure (mm Hg) 36±5</td>
<td>48±4</td>
<td>12±4</td>
<td>0.01</td>
</tr>
<tr>
<td>4 µg NE</td>
<td>Control perfusion pressure (mm Hg) 96±4</td>
<td>95±6</td>
<td>1±8</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>Maximal perfusion pressure (mm Hg) 151±9</td>
<td>159±10</td>
<td>8±12</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Increase in pressure (mm Hg) 56±6</td>
<td>65±5</td>
<td>9±6</td>
<td>0.16</td>
</tr>
</tbody>
</table>

CSA, cyclosporin A. Values are mean±SEM.

**Table 2. Changes in Hind Limb Perfusion Pressure With Tyramine and Phenylephrine Injections Before and During Cyclosporin A Infusion**

<table>
<thead>
<tr>
<th>Agent (µg)</th>
<th>Control infusion</th>
<th>During CSA infusion</th>
<th>Difference between control and CSA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyramine</td>
<td>Control perfusion pressure (mm Hg) 110±5</td>
<td>129±6</td>
<td>20±6</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Maximal perfusion pressure (mm Hg) 148±5</td>
<td>152±8</td>
<td>5±6</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Increase in pressure (mm Hg) 38±4</td>
<td>23±3</td>
<td>15±4</td>
<td>0.01</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Control perfusion pressure (mm Hg) 116±15</td>
<td>139±12</td>
<td>23±5</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Maximal perfusion pressure (mm Hg) 185±11</td>
<td>201±12</td>
<td>16±9</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Increase in pressure (mm Hg) 69±14</td>
<td>63±9</td>
<td>6±12</td>
<td>0.63</td>
</tr>
</tbody>
</table>

CSA, cyclosporin A. Values are mean±SEM.

*p=10 dogs; †n=4 dogs.
since CSA has been reported to cause a generalized increase in vascular resistance. However, there is a lack of objective data on the effect of CSA on peripheral arterial vessels. In the present study, pure powder CSA was dissolved in autologous blood to eliminate the potential vascular effects of other vehicle or solvent agents. Although it may be possible that CSA does not dissolve completely in blood, the measurements obtained from venous blood in all experiments have shown serum levels to be consistent with the dosages of CSA that were administered and to reach levels usually encountered in clinical transplantation. However, the variability from one experiment to the other may have been due to incomplete dissolution of CSA in the blood used as vehicle. This fact does not affect interpretation of the data, since it is related to the CSA serum levels obtained rather than to the quantity of the drug administered. A modest but significant increase in peripheral hind limb vascular resistance has been consistently found after CSA administration in previous and present studies. These increases were observed with CSA blood levels within the therapeutic range normally used in clinical immunosuppression.

The CSA-related vasoconstriction was at least partly due to activation of adrenergic receptors through the sympathetic nervous system, since α-adrenergic blockade and sympathectomy both significantly decreased the vasoconstrictive effect of CSA on hind limb vessels. Experimental studies in the rat showed that efferent sympathetic nerve activity was increased by 60% after CSA infusion. In heart transplant recipients with chronic CSA therapy and sustained hypertension, Scherrer et al found a higher vascular resistance in the calf and a threefold increase in sympathetic nerve discharge, measured with intraneuronal electrodes in the peroneal nerve, compared with non-CSA-treated patients. Plasma and urinary levels of NE were slightly higher, although within the normal range, among patients treated with CSA. Therefore, it was suggested that CSA-induced hypertension was related to activation of the sympathetic nervous system. Our findings are consistent with this conclusion.

The effect of CSA on sympathetic adrenergic activity could result from cerebral stimulation, from reflex activation, or from increased sensitivity of the peripheral vessels to catecholamines. In the present study, direct injections of CSA in the cerebral circulation through denervated carotid arteries, at the innervated carotid glomus, and in the heart did not cause any significant change in peripheral vascular resistance. This suggests that the changes due to CSA are peripheral rather than caused by cerebral stimulation or reflex activation.

Garr and Paller showed a potentiation effect of CSA on NE vasoconstriction of arterial vessels in the rat. In the present study, potentiation of NE vasoconstriction by CSA was also observed after injections of 1 and 2 μg NE. The increase in perfusion pressure was not significant at 4 μg NE, since the maximal vasoconstriction effect was probably obtained at this high dose. In vitro studies of isolated rat tail arteries have shown an increased response to neural stimulation and to exogenous NE after exposure to CSA, suggesting that both the release and the response to the neurotransmitter may be involved in the enhanced vasoconstriction.

The ability of CSA to potentiate the response to NE could be explained either by an increase in adrenergic neurotransmission with CSA, by a direct effect of CSA on smooth muscle cells, or both. Enhanced adrenergic activation could result from such mechanisms as inhibition of recapture of NE or modulation of presynaptic receptors. CSA therapy in human does not decrease presynaptic α-adrenergic receptors, which prevents further release of NE from sympathetic nerves.

On the other hand, if NE reuptake is inhibited, increased NE concentration at the postsynaptic site could be at least partly responsible for the increase in vascular resistance. In the present study, this mechanism was studied using tyramine, which enters the nerve endings through the NE carrier and acts indirectly by stoichiometric displacement of NE from storage sites in the synaptic vesicle or from extravascular binding sites. Conversely, the effect of tyramine is abolished by drugs such as desmethylimipramine, which inhibits the NE transport system.

Our results suggest that CSA has an effect similar to that of desmethylimipramine, as shown by the marked decrease in the vascular response to tyramine with CSA infusion. Thus, a decrease in NE neuronal reuptake due to CSA could at least partly explain the increase in vascular resistance observed during CSA infusion. On the contrary, the response to phenylephrine remained unaltered after CSA infusion. Since this drug is not taken up into nerve endings, it also supports our hypothesis that CSA blocks NE uptake. The effect of CSA on NE uptake demonstrated in peripheral nerve endings of vascular smooth muscle cells may also occur centrally, since exocytosis and NE carrier-mediated processes operate in central nerve terminals as well.

Reports of increased sympathetic nerve discharges in humans and in animals under CSA therapy would support this hypothesis.

Thus, in the dog, CSA causes an increase in hind limb vascular resistance at serum levels within the therapeutic range used in clinical transplantation. This response is dependent on the sympathetic nervous system and adrenergic receptors but does not result from central or reflex stimulation. CSA causes a significant potentiation of NE vasoconstriction, which appears to be due to inhibition of NE reuptake at peripheral nerve endings, which could at least partly explain the adrenergic response to CSA.

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References


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