Effect of a Monoclonal Antibody to Angiotensin II on Hemodynamic Responses to Noradrenergic Stimulation in Pithed Rats

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A specific angiotensin II monoclonal antibody, KAA8, was used to examine the interaction between sympathetic function and angiotensin II in pithed rats. KAA8, at 5 or 50 μg/kg i.v., did not alter the mean blood pressure, cardiac output, total peripheral resistance, or heart rate responses to sympathetic neural stimulation (0.25–4.0 Hz) or to norepinephrine (0.3–3 μg/kg i.v.) and to angiotensin III (0.3–10 μg/kg i.v.). KAA8 treatment also reduced the plasma immunoreactive angiotensin II from 2,880±475 pg/ml to an undetectable level. In contrast, captopril (5 mg/kg i.v.) and saralasin (10 or 50 μg/kg/min i.v.) inhibited the mean blood pressure and total peripheral resistance responses, but not the cardiac output and heart rate responses, to sympathetic neural stimulation and to norepinephrine. These results, which confirm previous findings by Kaufman and Vollmer (Kaufman LJ, Vollmer RR: Endogenous angiotensin II facilitates sympathetically mediated hemodynamic responses in pithed rats. J Pharmacol Exp Ther 1985;235:128-134), demonstrate that angiotensin II selectively potentiates the sympathetic vascular function in the pithed rat. However, our results suggest that circulating angiotensin II does not appear to interact with the sympathetic vascular function. It is speculated that in the pithed rat the sympathetic vascular response is enhanced by vascular-formed angiotensin II. (Hypertension 1989;14:488-497)

It has been well documented that exogenous angiotensin II (Ang II) enhances noradrenergic neurotransmission in isolated preparations and in intact animals (for review, see references 1 and 2). Studies using blockers of the renin-angiotensin system (RAS), such as the peptide Ang II receptor antagonists and angiotensin converting enzyme (ACE) inhibitors, have provided evidence that endogenous Ang II facilitates sympathetic responses in certain pathophysiological conditions (for review, see references 1 and 2). However, the interpretation of these results is complicated by the partial agonistic properties of the peptide Ang II receptor antagonists and the bradykinin potentiating effect of ACE inhibitors. Consequently, the physiological importance of this pharmacological effect has been difficult to ascertain.

Recently, we have demonstrated that a monoclonal antibody to Ang II, KAA8, exerts specific functional Ang II antagonism. Unlike the peptide Ang II receptor antagonists, the Ang II antibody is devoid of agonistic effects, and in contrast to the ACE inhibitors, this antibody lacks the bradykinin potentiating action. We reasoned, therefore, that KAA8 may represent a useful tool for study of the involvement of endogenous Ang II in responses to sympathetic stimulation. Because the pithed rat has been used in several laboratories to demonstrate the importance of the interaction between the sympathetic nervous system and the RAS, we therefore selected this model for the purpose of our study. Furthermore, it has been noted that the inhibitory effect of ACE inhibitors on the vasoconstrictor response to sympathetic stimulation in the pithed rat was not fully restored by Ang II infusion. A possible explanation, as suggested by MacLean and Hiley, is that Ang II infusion may not replace the vascular sources of Ang II that are depleted by ACE inhibition. Alternatively, Ang II infusion may release prostaglandins that impair sympathetic nerve function as a combined pretreatment of indomethacin and Ang II infusion completely restored the pressor response to sympathetic stimulation. Nevertheless, a possible role for Ang II of vascular origin in the
hemodynamic effect of sympathetic stimulation cannot be excluded. It was interesting, therefore, to examine the effect of KAA8 in the pithed rat to gain possible insights on the relative contributions of circulating and vascular-generated Ang II in mediating these hemodynamic responses to sympathetic stimulation, a question not readily addressable with other inhibitors of the RAS.

Materials and Methods

General

The model of the pithed rat, described by Kaufman and Vollmer, was used in this study with some modifications. Male CD Sprague-Dawley rats (300–400 g) (Charles River Labs., Inc., Kingston, New York) were anesthetized with hexobarbital at 150 mg/kg i.p. and an adrenalectomy was performed. Atropine (4 mg/kg i.p.) was given and both vagus nerves were sectioned to prevent any parasympathetic effect. After the trachea was cannulated, each rat was pithed through the orbit with a steel rod. Artificial respiration with room air was immediately started with a Harvard rodent respirator (Harvard Apparatus Co., Inc., South Natick, Massachusetts) at a volume of 1 ml/100 g body wt and at a rate of 70 strokes/min. Rats were kept warm at 37° C by means of thermostat-controlled heating boards. The carotid artery and the jugular vein were cannulated for arterial pressure measurement and intravenous administration of drug. Tubocurarine was given at 1 mg/kg i.v. to prevent voluntary muscle activity. The thoracic cavity was opened through a ventral midline incision, and a calibrated electromagnetic flow probe (Carolina Medical Electronics, Inc., King, North Carolina) with a lumen circumference of 7 mm was placed on the thoracic ascending aorta to measure cardiac output (excluding coronary blood flow). In six of these rats, blood samples for plasma renin activity (PRA) determination were collected after decapitation.

Blood pressure was measured with a Gould Statham P23ID pressure transducer (Gould Inc., Oxnard, California) coupled to a Grass Model 7 polygraph (Grass Instrs., Co., Quincy, Massachusetts). Heart rate (HR) was measured by a Grass tachograph, triggered by the arterial pressure pulse wave. Mean blood pressure (MBP) was determined as the sum of diastolic blood pressure and one third of the pulse pressure. Both pulsatile and mean aortic blood flow were recorded by a Carolina electromagnetic flowmeter coupled to a Grass polygraph. Cardiac output (CO) was expressed as milliliters per minute per kilogram of body weight. Total peripheral resistance (TPR) was calculated by dividing MBP by CO.

Hemodynamic Responses to Electrical Spinal Cord Stimulation

After surgery, the rats were treated with saline (1 ml/kg or 0.2 ml/kg/min i.v.), captopril (5 mg/kg i.v.), or saralasin (10 or 50 mg/kg/min i.v.). Fifteen minutes later, the spinal cord was stimulated electrically at 0.25, 1, and 4 Hz for 15 seconds at 50 V with square wave pulses of 2 msec duration delivered by a Grass stimulator with the pithing rod as the cathode and a hypodermic needle inserted under the skin of the hindlimb as the anode. Sufficient time was allowed between stimulation periods to ensure that MBP and CO had completely returned to the control values.

In the second group of rats, hemodynamic responses to electrical stimulation were also determined at 15 minutes after pretreatment with phosphate buffer (vehicle for KAA8, 1 ml/kg i.v.) of the following composition (mM): CaCl2-2H2O 1, MgCl2-6H2O 5, KCl 5, KH2PO4 1, NaCl 150, Na2HPO4 5, and KAA8 at 5 mg/kg i.v., KAA8 at 50 mg/kg i.v., or a combined treatment with captopril (5 mg/kg i.v.) and KAA8 (5 mg/kg i.v.).

In the last group, rats were pretreated with the vehicle or KAA8 at 5 mg/kg i.v. for 2 hours before the hemodynamic responses to electrical stimulation were determined. One frequency-response curve was determined in each rat.

Hemodynamic Responses to Norepinephrine

A similar protocol as described above was followed except that in place of electrical stimulation norepinephrine was given at 0.3, 1, and 3 μg/kg i.v. in rats pretreated with saline (1 mg/kg i.v. or 0.2 ml/kg/min i.v.), captopril (5 mg/kg i.v.), saralasin (10 μg/kg/min i.v.), phosphate buffer (1 ml/kg i.v.), or KAA8 (5 or 50 mg/kg i.v.). One dose-response curve for norepinephrine was studied in each rat.

Hemodynamic Responses to Angiotensin II

Rats, pretreated with phosphate buffer (1 ml/kg i.v. or KAA8 (5 mg/kg i.v.), were challenged with Ang II at 0.03, 0.1, 0.3, and 1 μg/kg i.v. by use of a similar protocol as described above. One dose-response curve for Ang II was determined in each rat.

Hemodynamic Responses to Angiotensin III

In this group, a similar protocol as described above was followed except that challenges were with angiotensin III (Ang III) at 0.3, 1, 3, and 10 μg/kg i.v. in rats pretreated with phosphate buffer (1 ml/kg i.v.) or KAA8 (5 or 50 mg/kg i.v.). One dose-response curve for Ang III was determined in each rat.

Hemodynamic Responses to Vasopressin Infusion

In this group, rats were pretreated with captopril (5 mg/kg i.v.) and vasopressin (0.01–0.03 IU/kg/min i.v.) or saline (1 ml/kg+0.2 ml/kg/min). Fifteen minutes later, basal MBP, HR, CO, and TPR were determined.

Analyses and Statistics

Measurement of PRA was performed by radioimmunoassay with a Du Pont New England Nuclear radioimmunoassay kit (Boston, Massachusetts).
To study the effect of KAA8 on the circulating Ang II, 100 \mu l arterial plasma samples were collected from groups of the vehicle- and KAA8-treated rats. Radioimmunoassay of free Ang II levels was performed on unextracted plasma, at volume, of 100 \mu l with a high-affinity, rabbit Ang II antiserum (Chemicon Intl. Inc., El Segundo, California). The limit of detection was 5–10 pg Ang II in this assay.

Statistical analyses used were analysis of variance (one-way and two-factor experiments with repeated measurements on one factor) and Duncan's new multiple-range test for multiple comparison. The level of significance was taken at \( p < 0.05 \). All data were expressed as the mean±SEM.

**Drugs**

Ang II, Ang III, atropine, hexobarbital, norepinephrine, saralasin, tubocurarine, and vasopressin were obtained from Sigma Chemical Company (St. Louis, Missouri). Captopril was synthesized at E.I. du Pont de Nemours and Company (Wilmington, Delaware). KAA8 was prepared as described previously.

**Results**

No statistically significant differences between effects of saline injection at 1 ml/kg i.v. or saline infusion at 0.2 ml/kg/min on hemodynamic responses to spinal cord stimulation or norepinephrine were observed. Therefore, we pooled the data together as our vehicle group for the captopril-treated and saralasin-treated groups. PRA in the pithed rat averaged 38.1±5 ng Ang I/ml/hr (\( n = 6 \)).

**Baseline Hemodynamics**

Effects of saline, vehicle, captopril (5 mg/kg i.v.), and saralasin (10 and 50 \( \mu g/kg/min \) i.v.) on basal MBP, CO, TPR, and HR are shown in Table 1. The hypotensive effect of captopril was due to decreases in CO and TPR. In contrast, the decrease in MBP by saralasin at the low or high dose was mainly due to a reduction of CO. Neither agent changed HR. The doses of captopril and saralasin were effective in blocking the pressor responses to Ang I and Ang II, respectively (Table 1).

Effects of vehicle and KAA8 (5 and 50 mg/kg i.v.) on baseline MBP, CO, TPR, and HR are shown in
Table 2. KAA8 did not alter MBP, CO, TPR, and HR at the low dose, and slightly decreased MBP, TPR, and HR at the high dose. Both doses of KAA8 reduced the plasma immunoreactive Ang II to an undetectable level and inhibited the pressor responses to Ang II significantly.

Hemodynamic Responses to Electrical Spinal Cord Stimulation

Effects of vehicle, captopril, and saralasin on the hemodynamic responses to spinal cord stimulation are shown in Figure 1. Stimulation of the lumbar sympathetic outflow caused a frequency-dependent increase in MBP, which is contributed by increases in CO and TPR. Both captopril and saralasin reduced the pressor responses to spinal cord stimulation by a reduction of the TPR but not the CO component. HR response was not altered by captopril or saralasin. In contrast, KAA8 at low and high doses did not alter the hemodynamic responses to sympathetic stimulation (Figure 2).

A combined treatment with captopril (5 mg/kg i.v.) and KAA8 (5 mg/kg i.v.) inhibited the pressor response to Ang II and reduced the plasma immunoreactive Ang II to a nondetectable level (Table 3). KAA8 still reduced the hemodynamic responses to spinal cord stimulation in these KAA8-treated rats (Figure 3).

Pretreatment of rats with KAA8 for 2 hours did not alter the hemodynamic responses to spinal cord stimulation (Figure 4) but still inhibited the pressor response to Ang II and reduced the plasma immunoreactive Ang II to a nondetectable level (Table 3).

Hemodynamic Responses to Norepinephrine

Effects of captopril and saralasin on the hemodynamic responses to norepinephrine are shown in Figure 5. Both agents reduced the pressor responses to norepinephrine. As with the hemodynamic responses to sympathetic stimulation, captopril and saralasin inhibited the pressor responses to norepinephrine by reducing the TPR but not the CO response. Again, KAA8 at low and high doses did not alter responses to norepinephrine (Figure 6).

Hemodynamic Responses to Angiotensin II and Angiotensin III

As shown in Figure 7, KAA8 at 5 mg/kg i.v. almost totally abolished the hemodynamic responses to Ang II. Similarly, KAA8 at 5 and 50 mg/kg i.v. was very effective in blocking the hemodynamic responses to Ang III (Figure 8).

Hemodynamic Responses to Vasopressin Infusion

In the saline-treated group (n=5), MBP, HR, CO, and TPR were 47±3 mm Hg, 338±10 beats/min, 139±5 ml/min/kg, and 0.338±0.011 mm Hg/ml/min/kg, respectively. In the vasopressin-infused group receiving captopril (n=5), MBP, HR, CO, and TPR were 48±3 mm Hg, 368±30 beats/min, 115±7 ml/min/kg, and 0.422±0.025 mm Hg/ml/min/kg, respectively. Basal CO and TPR in the

FIGURE 1. Line graphs showing effects of vehicle (1 ml/kg i.v., n=15), saralasin (10 and 50 µg/kg/min, n=8 and 6, respectively), and captopril (n=6) on mean blood pressure, cardiac output, total peripheral resistance, and heart rate responses to spinal cord stimulation in pithed rats. *Indicates significant difference (p<0.05) between frequency-response curve (mean blood pressure and total peripheral resistance) in vehicle-treated group and that in captopril- or saralasin-treated groups.
vasopressin-captopril-treated group were significantly different from those in the saline-treated group, respectively \((p<0.05)\).

**Discussion**

We, and others, have demonstrated that both captopril and saralasin reduced the blood pressure and TPR responses, but not the CO and HR responses, to sympathetic neural stimulation and norepinephrine in the pithed rat. However, our results indicate that the Ang II monoclonal antibody KAA8 did not significantly change the hemodynamic responses to sympathetic neural stimulation and norepinephrine. Effective doses of KAA8 were used in this study, as KAA8 at 5 mg/kg i.v. blocked the hemodynamic response to Ang II and completely reduced the plasma immunoreactive Ang II to a nondetectable level. In addition, a higher dose of KAA8 (50 mg/kg i.v.) did not significantly alter the vasoconstrictor effect of sympathetic neural stimulation. Identical results were also observed in pithed rats pretreated with the antibody for 2 hours before measurement of hemodynamic responses.

It is possible that KAA8, which displays 32% cross-reactivity with Ang III as determined by radioimmunoassay may not completely neutralize

**Table 3. Baseline Hemodynamics in Vehicle-, Captopril and KAA8-, Vehicle-, and KAA8-Treated Pithed Rats**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vehicle* ((n=6))</th>
<th>Captopril and KAA8* ((n=6))</th>
<th>Vehicle† ((n=6))</th>
<th>KAA8† ((n=5))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>48±3</td>
<td>32±2†</td>
<td>36±3</td>
<td>36±2</td>
</tr>
<tr>
<td>Cardiac output (ml/min/kg)</td>
<td>118±7</td>
<td>89±3†</td>
<td>93±5</td>
<td>88±6</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>0.41±0.03</td>
<td>0.34±0.02‡</td>
<td>0.40±0.04</td>
<td>0.42±0.05</td>
</tr>
<tr>
<td>(mm Hg/ml/min/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>327±9</td>
<td>308±7</td>
<td>298±14</td>
<td>320±14</td>
</tr>
<tr>
<td>Plasma Ang II (pg/ml)</td>
<td>3,667±1,327</td>
<td>n.d.</td>
<td>3,092±1,298</td>
<td>n.d.</td>
</tr>
<tr>
<td>Ang II pressor response (1 µg/kg i.v.)</td>
<td>80±3</td>
<td>5±1‡</td>
<td>47±3</td>
<td>3±0‡</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Ang II, angiotensin II; n.d., not detectable.

*Animals were pretreated with vehicle or a combination of captopril (5 mg/kg i.v.) and KAA8 (5 mg/kg i.v.) for 15 minutes.

†Animals were pretreated with vehicle or KAA8 (5 mg/kg i.v.) for 2 hours.

‡\(p<0.05\) compared with vehicle control (analysis of variance).
FIGURE 3. Line graphs showing effects of vehicle (n=6) and treatment with captopril (5 mg/kg i.v.) and KAA8 (5 mg/kg i.v.) combined (n=6) on mean blood pressure, cardiac output, total peripheral resistance, and heart rate responses to spinal cord stimulation in pithed rats. *Indicates significant difference (p<0.05) between frequency-response curve (mean blood pressure and total peripheral resistance) in vehicle-treated group and that in KAA8- and captopriltreated groups.

FIGURE 4. Line graphs showing effects of vehicle (1 ml/kg i.v., n=5) and KAA8 (5 mg/kg i.v., n=6) on mean blood pressure, cardiac output, total peripheral resistance, and heart rate responses to spinal cord stimulation in pithed rats. It should be noted that rats were pretreated with vehicle or KAA8 in this group 2 hours before spinal cord stimulation.
effects of active angiotensin metabolites. For example, Ang III has been found in rat blood and, though less potent than Ang II as a vasoconstrictor, can enhance the adrenergic neurotransmission in the isolated perfused rat mesenteric vascular bed. However, our results indicate that KAA8 was very effective in blocking the hemodynamic responses to Ang III, suggesting that the doses of the antibody used in this study were sufficient to neutralize any effect of endogenous Ang III present in the circulation. The possibility that other angiotensin metabolites besides Ang II and Ang III may account for the different effects of KAA8 and captopril or saralasin cannot be totally excluded. However, these peptides are in general very weak partial agonists in comparison with Ang II or Ang III and, thus, not likely to be involved. An alternate explanation for the ineffectiveness of KAA8 in reducing the vasoconstrictor responses to sympathetic stimulation, in comparison with captopril and saralasin, is that unlike these agents, the antibody cannot, within the experimental time period, access Ang II generated at vascular sites. Thus, vascular-generated Ang II may facilitate the vasoconstrictor responses to sympathetic stimulation. The observation that captopril still inhibited the vasoconstrictor effect of sympathetic neural stimulation, even though the circulating Ang II had been neutralized by KAA8, supports this hypothesis.

The ACE inhibitor captopril was found to decrease blood pressure in this model, and the hypotension was due to decreases in both CO and TPR. In contrast, the decrease in blood pressure by the Ang II receptor antagonist saralasin was mainly caused by a reduction of CO. The different results with these inhibitors of the RAS are not related to the doses used. In our studies, these doses were effective in blocking the pressor responses to Ang I and Ang II. It is possible that the bradykinin potentiation by captopril or the partial agonistic effect of saralasin may partly account for this differential effect on TPR. However, Kaufman and Vollmer reported that the hypotensive effects of captopril and saralasin in the pithed rat were entirely attributable to a decrease in CO without alteration of the TPR. The reasons for the discrepant results between their study and ours are not obvious, but factors such as different experimental conditions cannot be excluded. However, enalapril, another ACE inhibitor, was also shown to decrease both CO and TPR in the pithed rat, as we have demonstrated with captopril. Nonetheless, taken together, these data indicate the involvement of endogenous Ang II in maintaining CO in the pithed rat. Perhaps Ang II may support CO by maintaining cardiac contractility or by inducing venous constriction. Since Ang II does not appear to have a direct positive inotropic effect in the rat cardiac muscle, it is more likely that endogenous Ang II maintains CO by decreasing venous capacitance.

Unlike captopril and saralasin, KAA8 at 5 mg/kg i.v. did not lower blood pressure in the pithed rat,
although it greatly inhibited the pressor response to Ang II and reduced the plasma immunoreactive Ang II level to a nondetectable level. Slight reductions of blood pressure, TPR, and HR were observed with the high dose of KAA8 (50 mg/kg i.v.). The biological significance of these reductions is not clear. Pretreatment of the pithed rats with KAA8 at 5 mg/kg i.v. for a longer period, 2 hours, did not alter baseline hemodynamics but abolished both the pressor response to Ang II and the plasma level of Ang II. The possibility exists that more than 2 hours may be needed for the antibody to completely penetrate the extracellular compartment and to exert its maximal Ang II neutralizing effect. However, KAA8 has previously been shown to induce its maximal antihypertensive effect within 10 minutes of administration to a high renin hypertensive rat model, an effect related to the blockade of the RAS.5 Thurston and Swales21 have previously observed that in the two-kidney Goldblatt hypertensive rat, another high renin model, a polyclonal Ang II antiserum failed to lower blood pressure even though it inhibited the pressor response to Ang II. Interestingly, saralasin still lowered blood pressure when administered after the Ang II antiserum.21 On this basis, they proposed that Ang II generated locally in the vasculature maintained the high vascular tone in the two-kidney Goldblatt hypertensive rat, and this source of Ang II was accessible to saralasin but not to the much larger antibodies.21 We have observed a similar result in this study with captopril, which lowered blood pressure in the KAA8-treated pithed rat. Thus, our results support the hypothesis that under certain experimental conditions vascular-generated Ang II may play an important role in the control of vascular tone.

De Jonge et al9 have suggested that vasodilatation per se may functionally reduce the vasoconstrictor capacity of the vasculature in the pithed rat. Thus, it is possible that nonspecific functional antagonism may contribute to the inhibitory effect of captopril on the hemodynamic responses to sympathetic stimulation. Thus, when the reduction in basal blood pressure with captopril was prevented by vasopressin, captopril did not alter the pressor responses to norepinephrine and sympathetic stimulation.21 Because this study9 only monitored blood pressure, we examined the effect of vasopressin infusion on MBP, CO, TPR, and HR in captopril-treated pithed rats. Our result indicates that vasopressin infusion restored the basal MBP in captopril-treated rats as a result of decreased CO and increased TPR. Thus, TPR was much higher in the vasopressin-captopril-treated pithed rats than in the control rats, suggesting that the vascular smooth muscle tone in these animals was in fact greater than in the control rats. Unlike vasopressin, Ang II infusion restored MBP by increasing TPR without altering CO10 or by increasing CO and TPR.11 Therefore, the results obtained with vasopressin by de Jonge et al9 as evidence for attributing the sympathoinhibitory effect of captopril to nonspecific functional antagonism is
Figure 7. Line graphs showing effects of vehicle (1 ml/kg i.v., n=6) and KAA8 (5 mg/kg i.v., n=6) on mean blood pressure, cardiac output, total peripheral resistance, and heart rate responses to angiotensin II (AII) in pithed rats. *Indicates significant difference (p<0.05) between the dose-response curve in the vehicle-treated and that in the KAA8-treated groups.

Figure 8. Line graphs showing effects of vehicle (1 ml/kg i.v., n=6) and KAA8 (5 and 50 mg/kg i.v., n=6 and 5, respectively) on mean blood pressure, cardiac output, total peripheral resistance, and heart rate responses to angiotensin III (AIII) in pithed rats. *Indicates a significant difference (p<0.05) between the dose-response curve in the vehicle-treated and those in the KAA8-treated groups.
still debatable. On the other hand, our data suggest that nonspecific functional antagonism may not totally explain the inhibitory effect of captopril on the hemodynamic response to sympathetic stimulation. For example, saralasin, which did not alter TPR significantly, still reduced the hemodynamic response to sympathetic stimulation. In addition, KAA8 at 50 mg/kg, which decreased TPR to a level below that of saralasin, did not alter the hemodynamic response to sympathetic stimulation. These results suggest that peripheral vasodilatation may not totally contribute to the inhibitory effects of captopril and saralasin on the hemodynamic responses to sympathetic stimulation.

In summary, we have demonstrated that in the pithed rat captopril and saralasin inhibited the blood pressure and TPR responses to sympathetic neural stimulation and norepinephrine but not the increases in CO and HR responses. These results confirm previous findings by Kaufman and Vollmer indicating that endogenous Ang II selectively potentiates the sympathetic vascular function in the pithed rat. The inability of the Ang II monoclonal antibody KAA8 to equal captopril and saralasin in altering the hemodynamic responses to sympathetic neural stimulation and norepinephrine, suggests that the Ang II responsible for the potentiation of the sympathetic vascular response is not accessible to the antibody. It is tempting to speculate that Ang II generated locally in the vasculature enhances the sympathetic vascular response, and that KAA8, by nature of its ability to discriminate circulating from vascular-generated Ang II, represents a powerful tool to complement existing inhibitors in the study of the vascular RAS.

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