Effects of angiotensin I and angiotensin II on hindlimb and coronary vascular resistance

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Britton, Steven, and Joseph Di Salvo. Effects of angiotensin I and II on hindlimb and coronary vascular resistance. Am. J. Physiol. 225(5): 1226-1231. 1973.—Effects of angiotensin I (A-I, 0.2-3.2 μg) and angiotensin II (A-II, 0.1-1.6 μg) on pump-perfusion pressure were examined in the hindlimb vasculature and in the vasculature supplied by the circumflex coronary artery in pentobarbitalized dogs. In both vasculatures A-I and A-II caused dose-dependent increases in perfusion pressure reflecting directionally similar changes in resistance to blood flow. Local vasoconstriction produced with A-I in the hindlimb still occurred when none of the injected agonist was permitted to reach the systemic circulation. In both the hindlimb and coronary vasculatures, A-I responses were blocked with SQ 20881 (Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro), a synthetic nonapeptide that inhibits enzymatic conversion of A-I to A-II. SQ 20881 did not alter responses to A-II in either bed. In contrast 1-Sar-8-Ala-angiotensin II (P-I 13), a specific A-II antagonist, abolished increases in perfusion pressure produced by A-I or A-II. These results suggest that resistance increases caused by local administration of A-I in the hindlimb or coronary vasculatures are largely ascribable to A-I enzymatic conversion to A-II. Such conversion may occur to the extent of 31% in the hindlimb and 26% in the vasculature supplied by the circumflex coronary artery.

Blood flow; converting enzyme; peptides

It is generally stated that the major site for enzymatic conversion of the decapeptide, angiotensin I (A-I), to the markedly vasoactive octapeptide, angiotensin II (A-II), occurs in the lungs (1, 3, 5, 22). However, recent studies from this laboratory suggest that significant conversion of A-I to A-II occurs in the renal circulation (9), in the intestinal vascular bed (7), and in the vasculature supplied by the hepatic artery (6). Evidence that local formation of A-II from A-I also occurs in the hindlimb has recently been reported (2). These findings are consistent with the hypothesis that local conversion of A-I to A-II could be involved in regulation of blood flow.

This communication reports on effects of A-I and A-II on resistance to blood flow in the canine hindlimb and in the vasculature supplied by the circumflex coronary artery. Studies were performed in the presence and absence of a newly described synthetic nonapeptide, SQ 20881 (Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro) that inhibits angiotensin converting enzyme (5, 6, 10, 11, 13, 23, 27, 28). Studies were also performed in the presence and absence of 1-Sar-8-Ala-angiotensin II, a specific A-II antagonist (26). The results suggest that local enzymatic conversion of A-I to A-II could occur in the hindlimb to the extent of 31% and that such conversion could occur in the coronary vasculature to the extent of 26%.

METHODS

Experiments were performed in 22 mongrel dogs of either sex (12-15 kg) anesthesitized with sodium pentobarbital (30 mg/kg iv). Systemic arterial blood pressure was measured through a catheter inserted in the femoral artery (Narco P-1000A).

Series I. Experiments in the hindlimb (n = 14). Animals were intubated and permitted to breathe spontaneously. The left common carotid artery was exposed and separated from the vagus nerve. A right flank incision was used to expose the right internal and external iliac arteries. The right internal iliac artery was ligated, and heparin (500 U/kg iv) was administered to prevent blood clotting.

Blood from the left common carotid artery was diverted through a Sigmamotor pump (7B) and used to perfuse the distal end of the right external iliac artery at a constant flow rate. Perfusion pressure was continuously monitored through a catheter in the outflow tubing of the pump. Initially, flow through the pump, and hence the hindlimb, was increased until perfusion was within 80-90% of aortic blood pressure. Preliminary experiments showed that pump perfusion pressure remained constant and that the preparation was stable throughout the duration of experiments (3-4 hr).

Drugs were rapidly (1-3 sec) injected (0.5 ml) into the inflow side of the perfusion pump to permit thorough mixing with blood before reaching the hindlimb vascular bed. When flow is maintained constant, changes in perfusion pressure that occur in response to drug injection reflect directionally similar changes in resistance to blood flow.

In three dogs two rubber tourniquets were tied between the femur and thigh muscles, taking care not to damage the sciatic and femoral nerves. Virtually all flow to the hindlimb was via the perfusion pump, whereas flow draining to the vasculature to the extent of 26%.

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With the clamp closed, drugs injected in the perfusion line circulated through the limb and returned to the heart. With the clamp opened and the femoral vein distal to the 'T' tube occluded, drugs injected in the perfusion line circulated through the limbs, but were diverted from the dog so that none reached the systemic circulation. Thus, the direct effects of A-I on the hindlimb vasculature could be evaluated. During the diversion maneuver (2-3 min), blood from a donor dog was infused into a jugular vein at a rate equal to the hindlimb flow rate.

The drugs used were a) A-I (Schwarz BioResearch, Inc., [Asp¹, Ileu²]-) b) A-II (Ciba, [Asp¹, Val³]) c) SQ 20881, a synthetic nonapeptide (Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro) that inhibits angiotensin converting enzyme, and d) P-113, 1-Sar-9-Ala-angiotensin II, a specific A-II antagonist. The purity of angiotensin preparations was established by amino acid and peptide analysis (0.65 nmole peptide/mg A-I, 0.78 nmole peptide/mg A-II, optical density at 280 nm using ethyl tyrosinate as standard and) Sar and pressor activity in dogs and rats. In this and previous studies with these preparations, A-I (1-2 pg/kg iv) had about 85-95% of the pressor activity of an equal weight of A-II administered to pentobarbitalized dogs (6, 7, 9). Drugs were dissolved in saline, adjusted to pH 7.3, and stored in the frozen state. In each experiment, the animal was challenged with A-I (1.3 μg/kg iv) and A-II (1.3 μg/kg iv) to insure that agonists did not deteriorate during storage. Doses of A-I tested were 0.2, 0.4, 0.8, 1.6, and 3.2 μg, whereas doses of A-II tested were 0.1, 0.2, 0.4, 0.8, and 1.6 μg. The maximal increase in perfusion pressure that occurred after drug injection was taken as the principle response and expressed as percent of control perfusion pressure (6). The ratio of equipotent doses of A-II to A-I, with respect to increasing hindlimb perfusion pressure multiplied by 1.25 (to correct for the difference in molecular weight between A-I and A-II), was used to calculate percent conversion of A-I to A-II (7-9).

Responses to A-I and A-II in the presence and absence of SQ 20881 (100 μg/kg, bolus injection iv) were studied in eight dogs. To insure that inhibition of the converting enzyme with SQ 20881 had occurred, systemic pressor responses produced with A-I (1.3 μg/kg iv) and A-II (1.3 μg/kg iv) were assessed before and 5 min after administration of SQ 20881. Systemic responses were also assessed after all challenge doses of A-I and A-II were tested. The experiments were terminated (60-90 min) after administration of SQ 20881.

In three dogs responses to A-I and A-II were examined before and during infusion of P-113 (100 μg/kg per min). Infusion of P-113 into the inflow side of the perfusion pump (0.5 ml/min) was in progress for 5 min prior to commencing agonist challenges and was maintained until challenges were completed. Studies in the hindlimb, coronary, and hepatic (6) vasculatures showed that the dose and method of administering P-113 were adequate to antagonize constrictor effects of A-II over the dose range examined (0.1-1.6 μg).

The injection schedule with respect to agonist and dose was randomized. Sufficient time (5-10 min) elapsed between injections so that tachyphylaxis did not develop. All data are expressed as the means ± 1 se. Significance of differences between responses in the presence and absence of inhibitors or antagonists was assessed with the Student 't' test for paired values (17).

Series II. Experiments in the coronary circulation (n = 8). Dogs were intubated with a cuffed endotracheal tube and artificially ventilated with room air. A left thoracotomy was performed between the fourth and fifth intercostal space. After moving the lung aside, the pericardial sac was opened and a short segment (5-8 mm) of the circumflex artery was dissected from surrounding tissue. Blood from the left common carotid artery was diverted through a Sigmanmotor pump to perfuse the circumflex coronary artery. Pressure infusion was adjusted to within 85-95% of systemic arterial pressure as described for the hindlimb.

Injections of A-I and A-II into the coronary perfusion system and evaluation of responses were performed as in series I experiments. In five animals increases in coronary artery perfusion pressure caused by A-I and A-II were examined in the presence and absence of SQ 20881. In three different dogs responses were examined before and during infusion of P-113.

Results

Hindlimb vascular bed. Mean systemic arterial blood pressure for dogs in this series was 119 ± 6 mm Hg at the start of experiments and averaged 104 ± 6 mm Hg when the experiments were terminated. Corresponding values for hindlimb perfusion pressure were 95 ± 5 and 99 ± 6 mm Hg. Blood flow through the hindlimb averaged 44 ± 2 ml/min.

Collection of hindlimb venous blood during and for 2 min after injection of A-I (0.8 μg) into the perfusion line so that none of the injected agonist reached the systemic circulation did not alter the local response to A-I. Injection of A-I (n = 3) increased perfusion pressure to 128 ± 5% of control when hindlimb venous blood was diverted from the dog, but systemic arterial pressure was not altered. When the injection was repeated while hindlimb venous blood was permitted to return to the dog (see METHODS), the same dose of A-I increased perfusion pressure to 126 ± 6% of control. A delayed increase in mean arterial pressure occurred (24 ± 5 mm Hg) when the injected agonist was permitted to reach the systemic circulation.

Injections of A-I or A-II into the perfusion system of 11 dogs caused dose-dependent increases in hindlimb perfusion pressure (Fig. 1) which were rapid in onset (10-15 sec), attained maximal levels in about 20 sec, and returned to control levels in an additional 1-3 min (Fig 2). Injections of saline into the perfusion system usually produced a transient decrease in perfusion pressure. Similar decreases were seen with either A-I or A-II prior to the marked increase resulting from drug-induced vasoconstriction. These transient decreases in perfusion pressure were interpreted as local responses produced by the injection maneuver and were not studied further. Although dose-response curves for A-I and A-II were similar in shape, the response to A-I was always smaller than the response to an equal weight of A-II. Generally, A-II was about 4 times as potent as A-I.

For each dose of A-I tested, the dose of A-II required to produce an equivalent increase in hindlimb perfusion pressure...
FIG. 1. Dose-response curves for increase in hindlimb perfusion pressure (% of control) caused by angiotensin I (open circles) and angiotensin II (closed circles). Each point represents mean response from 11 dogs. Small vertical bars represent ± se. Agonist dose is shown on a log scale (abscissa). Angiotensin II was more potent than angiotensin I in causing hindlimb vasoconstriction.

FIG. 2. Effects of angiotensin I (top panel) and angiotensin II (bottom panel) on hindlimb perfusion pressure (HLPP) and systemic arterial pressure (SAP) before and after inhibition of angiotensin converting enzyme with SQ 20881 (100 µg/kg iv). Arrows indicate time of agonist injection. SQ 20881 attenuated increase in HLPP and SAP caused by angiotensin I, but did not alter markedly responses to angiotensin II.

Increases in perfusion pressure caused by A-I were significantly attenuated after inhibition of the angiotensin converting enzyme with SQ 20881 (Figs. 2 and 3). For example, in eight animals, 0.8 µg of A-I increased hindlimb perfusion pressure to 125 ± 3% of control prior to administration of SQ 20881, whereas the same dose of A-I increased perfusion pressure to only 112 ± 4% of control (P < 0.05) after administration of SQ 20881. In contrast, hindlimb vasoconstriction (increases in perfusion pressure) caused by A-II was not altered by SQ 20881. Baseline levels of hindlimb perfusion pressure or systemic arterial pressure were not influenced by the dose of SQ 20881 used (100 µg/kg iv).

In eight dogs tested, SQ 20881 abolished systemic pressor responses normally produced with A-I (1.3 µg/kg iv), but did not alter responses produced with A-II (1.3 µg/kg iv). Thus, before SQ 20881, intravenous injection of A-I increased mean arterial blood pressure from an initial value of 115 ± 10 to 158 ± 9 mm Hg, but 5 min after SQ 20881, it increased pressure to only 120 ± 4 mm Hg (P < 0.01). In contrast, systemic responses to A-II were not significantly different before (173 ± 12 mm Hg) and after (177 ± 12 mm Hg). Inhibition of A-I responses persisted for at least 90 min after the single bolus injection of SQ 20881.

Blockade of A-II receptors with P-113 (100 µg/kg per

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**TABLE 1. Percent conversion of angiotensin I to angiotensin II in pump-perfused hindlimb vasculature**

<table>
<thead>
<tr>
<th>Angiotensin I Tested, pg</th>
<th>Estimated Equivalent Dose of Angiotensin II, µg</th>
<th>Percent Conversion of Angiotensin I to Angiotensin II</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>0.10</td>
<td>31.25</td>
</tr>
<tr>
<td>0.8</td>
<td>0.26</td>
<td>40.62</td>
</tr>
<tr>
<td>1.6</td>
<td>0.36</td>
<td>28.12</td>
</tr>
<tr>
<td>3.2</td>
<td>0.65</td>
<td>23.39</td>
</tr>
</tbody>
</table>

Calculated mean conversion = 31.35

*Estimated from dose-response curves in Fig. 1. † A-II, µg/A-I, µg X 1.25 X 100.
HINDLIMB AND CORONARY CONVERSION OF ANGIOTENSIN I

RESPONSES BEFORE P 113
RESPONSES AFTER P 113

FIG. 4. Effects of angiotensin I (left panel) and angiotensin II (right panel) on hindlimb perfusion pressure in presence (dark bars) and absence (clear bars) of angiotensin II antagonist P-113 (100 µg/kg per min ia). Mean responses (n = 3) are given by large bars; whereas small bars represent ±1 se. Responses to angiotensins I and II were abolished by P-113.

FIG. 6. Effects of angiotensin I (top panel) and angiotensin II (bottom panel) on circumflex coronary artery perfusion pressure (CAPP) and systemic arterial pressure (SAP) before and after blockade of angiotensin II receptors with P-113 (100 µg/kg per min ia). Arrows indicate time of agonist injection. P-113 abolished increase in CAPP and SAP caused by either angiotensin I or angiotensin II.

TABLE 2. Percent conversion of angiotensin I to angiotensin II in vasculature supplied by pump-perfused circumflex coronary artery

<table>
<thead>
<tr>
<th>Angiotensin I Teste, µg</th>
<th>Estimated Equivalent Dose of Angiotensin II, *µg</th>
<th>Percent Conversion of Angiotensin I to Angiotensin II</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>0.10</td>
<td>31.25</td>
</tr>
<tr>
<td>0.8</td>
<td>0.18</td>
<td>28.12</td>
</tr>
<tr>
<td>1.6</td>
<td>0.26</td>
<td>20.31</td>
</tr>
<tr>
<td>3.2</td>
<td>0.38</td>
<td>14.84</td>
</tr>
</tbody>
</table>

Calculated mean conversion = 26.23

* Estimated from dose-response curves in Fig. 5. † A-II, µg/A-I, µg × 1.25 × 100.

TABLE 3. Effects of angiotensins I and II on circumflex coronary artery perfusion pressure before and after inhibition of angiotensin converting enzyme with SQ 20881

<table>
<thead>
<tr>
<th>Agonist, µg</th>
<th>Circumflex Coronary Artery Perfusion Pressure, % of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before SQ 20881</td>
</tr>
<tr>
<td>Angiotensin I</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>112 ± 2</td>
</tr>
<tr>
<td>0.8</td>
<td>124 ± 5</td>
</tr>
<tr>
<td>3.2</td>
<td>130 ± 3</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>117 ± 5</td>
</tr>
<tr>
<td>0.4</td>
<td>140 ± 4</td>
</tr>
<tr>
<td>1.6</td>
<td>149 ± 7</td>
</tr>
</tbody>
</table>

Values represent means ±1 se in five animals. * 100 µg/kg iv. † P < 0.001 between responses obtained before and after administration of SQ 20881.

In the coronary vasculature, A-I and A-II caused dose-dependent increases in perfusion pressure which were rapid in onset (Figs. 5 and 6), but A-II was about 4 times as potent as A-I. Accordingly, if responses produced with A-I are attributable to local enzymatic conversion to A-II, such conversion could occur to the extent of 15–31% (Table 2, see METHODS, and hindlimb results).

min ia) significantly attenuated hindlimb vasoconstriction caused by either A-I or A-II (Fig. 4), but did not alter responses to norepinephrine. Prior to administration of P-113, norepinephrine (2 µg ia) increased hindlimb perfusion pressure to 130 ± 6% of control (n = 3). After administration of P-113, norepinephrine increased perfusion pressure to 132 ± 6% of control. Blockade of responses produced with either A-I or A-II persisted for 30–60 min after the infusion of P-113 was terminated.

Coronary vasculature. Blood flow through the pump-perfused circumflex coronary artery was 43 ± 3 ml/min. Starting and terminal coronary perfusion pressures were, respectively, 88 ± 9 and 94 ± 7 mm Hg. Mean systemic arterial pressure for dogs in this series was 102 ± 8 mm Hg at the beginning of experiments and averaged 110 ± 11 mm Hg when the experiments were concluded.
Inhibition of angiotensin converting enzyme with SQ 20881 significantly attenuated responses produced with A-I (Table 3). In contrast, blockade of A-II receptors with P-113 reduced coronary vasoconstriction caused by either A-I or A-II at each agonist dose tested (Table 4). Thus, results obtained with SQ 20881 and P-113 in the vasculature supplied by the circumflex coronary artery were similar to those obtained in the hindlimb.

### Discussion

The present studies, in both the hindlimb vasculature and in the vasculature supplied by the circumflex coronary artery, show that a) A-I and A-II cause dose-dependent increases in resistance to blood flow, b) A-II is more potent than A-I, c) during inhibition of angiotensin converting enzyme with SQ 20881 vasoconstriction produced by A-I is significantly attenuated, but constriction caused by A-II is unaltered, and d) constriction produced by either A-I or A-II is significantly reduced by blockade of A-II receptors with P-113. Furthermore, hindlimb vasoconstriction produced with A-I persists when none of the injected agonist is permitted to reach the systemic circulation. These findings are consonant with the hypothesis that vasoconstrictor action of A-I in either the hindlimb or coronary vasculature is attributable largely to local enzymatic conversion to A-II. Such conversion appears to occur to the extent of 31% in the hindlimb and 26% in the coronary vascular bed (Tables 1 and 2).

Levels of systemic arterial pressure and perfusion pressure through either hindlimb or circumflex coronary artery were not significantly altered from control values when experiments were terminated. Since tachyphylaxis to injected agonists did not develop, all animals probably maintained responsiveness to A-I and A-II throughout the experimental period (2-3 hr).

Our finding that A-II produced marked vasoconstriction in the hindlimb and coronary vasculatures agrees with results reported from other laboratories (13, 19, 20). Vasoconstriction caused by A-I in the hindlimb has also been reported for dogs (2, 3) and sheep (25). Similarly, Gilmore and Gerlings (16) recently showed that A-I produces coronary vasoconstriction.

Hindlimb or coronary vasoconstriction produced with A-I appears to be due to a local mechanism, since a) A-I still increased hindlimb perfusion pressure when it was excluded from the systemic circulation, and b) A-I reportedly produces coronary vasoconstriction in the isolated heart preparation (16). Furthermore, local responses to A-I in either vascular bed were initiated before changes in systemic arterial pressure occurred and attained maximal levels before the maximal systemic pressor responses occurred (Figs. 2 and 6).

Hindlimb and coronary vasoconstriction produced with A-I could result from direct interaction with vascular smooth muscle or from local enzymatic conversion to A-II or from both. Accordingly, SQ 20881 could inhibit responses to A-I by preventing interaction between A-I and vascular smooth muscle or by inhibiting angiotensin converting enzyme. Either view is consistent with the finding that SQ 20881 did not alter responses to A-II (Figs. 2 and 3, Table 3). Ample evidence exists showing that SQ 20881 inhibits angiotensin converting enzyme in vitro and in vivo (5, 6, 23, 27, 28). Data bearing on interaction between SQ 20881 and A-I receptors are lacking. Therefore, the evidence favors the view that effects of SQ 20881 observed in this study are attributable to inhibition of angiotensin converting enzyme. Constrictor responses to A-I that persist in the presence of SQ 20881 could result partly from incomplete inhibition of angiotensin converting enzyme and partly from the small degree of vasoactivity of A-I (1).

Inhibition of hindlimb and coronary constrictor responses to either A-I or A-II by blockade of A-II receptors with P-113 (Figs. 4 and 6, Table 4) supports the hypothesis that A-I constrictor responses result from formation of A-II and subsequent stimulation of A-II receptors. Since P-113 did not antagonize responses to norepinephrine, blockade of A-II receptors appears to be specific. Furthermore, P-113 does not antagonize responses produced with norepinephrine in rabbit aortic strips (26) or in the canine hepatic circulation (6). Similarly, in pithed rats, increases in arterial blood pressure produced with vasopressin, phenylephrine, or tyramine are unaltered by P-113 (26). Strictly speaking, however, the possibility that P-113 blocks A-I receptors as well as angiotensin II receptors should be borne in mind.

It is possible that formation of A-II from injected A-I occurs in blood during the time required for transit from site of injection to site of action in the responsive vasculatures. This is not likely, since the angiotensin converting activity in dog blood is simply too low to permit extensive conversion of A-I to A-II in the time elapsed between injection of A-I into the pump-perfusion system and onset of either hindlimb or coronary vasoconstriction (24, 28).

Our findings in the hindlimb are fundamentally in accord with those reported by Aiken and Vane (2). We studied hindlimb vascular responses to A-I and A-II in a constant-flow, pump-perfused preparation, employed a long-acting nonapeptide, SQ 20881, to inhibit angiotensin converting enzyme, and utilized a new blocking agent, P-113, for A-II receptors. Aiken and Vane studied responses in a natural flow preparation, employed a short-acting pentapeptide, SQ 20475 (Pyr-Lys-Try-Ala-Pro) to inhibit angiotensin converting enzyme, and did not utilize an A-II antagonist. They reported that hindlimb angio-

### Table 4. Effects of angiotensins I and II on circumflex coronary artery perfusion pressure before and after blockade of angiotensin II receptors with P-113

<table>
<thead>
<tr>
<th>Agonist, µg</th>
<th>Circumflex Coronary Artery Perfusion Pressure, % of Control Before P-113</th>
<th>After P-113*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-I</td>
<td>109 ± 4</td>
<td>98 ± 3†</td>
</tr>
<tr>
<td></td>
<td>132 ± 3</td>
<td>100 ± 4†</td>
</tr>
<tr>
<td>A-II</td>
<td>124 ± 5</td>
<td>101 ± 6†</td>
</tr>
<tr>
<td></td>
<td>141 ± 7</td>
<td>106 ± 7†</td>
</tr>
</tbody>
</table>

Values represent means ± 1 SE in three animals. * 100 µg/kg per min ia. † P < 0.001 between responses obtained before and after administration of P-113.
tensin conversion occurs to the extent of about 40%, whereas we found conversion to the extent of 32%. This small difference could be due to differences in agonist purity.

In contrast to our findings and those published by Aiken and Vane (2), Oparil, Sanders, and Huber (24) reported that conversion of A-I to A-II could not be demonstrated in the canine hindlimb. However, Oparil et al. employed a radioimmunoassay technique for detecting newly formed A-II, whereas we and Aiken and Vane calculated extent of A-II formation from quantitated vasconstrictor responses. Studies by Cain et al. (4) and Goodfriend et al. (18) show that interaction between A-II antibodies and A-II is often incomplete and variable, so that strict comparison between immunoassay and bioassay procedures may not always be appropriate.

The present studies as well as the recent demonstrations that significant local conversion of angiotensin I to angiotensin II occurs in the renal (2, 9, 10), mesenteric (7), and hepatic vasculatures (6) are consistent with the view that local formation of angiotensin II may be importantly involved in local regulation of peripheral blood flow.

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