SHORT COMMUNICATION

COMPARISON OF EFFECTS OF LOCALLY INFUSED ANGIOTENSIN I AND II ON HAND VEINS AND FOREARM ARTERIES IN MAN: EVIDENCE FOR CONVERTING ENZYME ACTIVITY IN LIMB VESSELS

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SUMMARY

1. The effects of angiotensin I (AI) and angiotensin II (AII) have been compared during local infusions into peripheral arteries and veins in man.
2. Both AI and AII produced constriction of hand veins and forearm arteries; the potency of AI was somewhat less than AII.
3. When infused into the vein, the converting enzyme inhibitor SQ 20,881 abolished or markedly attenuated the effect of AI but not that of AII.
4. The results suggest the local presence of converting enzyme in human peripheral arteries and veins.

Key words: angiotensin, converting enzyme, forearm arteries, hand veins.

It has been suggested that renin can generate angiotensin II at a local vascular level (Thurston & Swales, 1974). For this to occur, angiotensin converting enzyme must also be present. This enzyme occurs predominantly in the vascular bed of the lungs of animals (Vane, 1974), but it has also been shown to occur in the arterial bed of the hind limb of the dog (Aiken & Vane, 1972) and sheep (Osborn, Tildesley, O'Gorman & Mahler, 1971), the dog intestine (Di Salvo & Montefusco, 1971) and kidney (Aiken & Vane, 1972).

In man, conversion of angiotensin I (AI) into angiotensin II (AII) has been shown to take place in the pulmonary vascular bed (Biron, Campeau & David, 1969), but it is not known if conversion can also take place at other sites. We have studied this problem by comparing the response of superficial hand veins and the forearm arterial bed to locally infused AI and AII. We have also examined the effect on the venous response of an angiotensin converting enzyme inhibitor, the nonapeptide BPP₉₇ or SQ 20,881 (Collier, Robinson & Vane, 1973).

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METHODS

Studies were carried out on four subjects, all of whom gave their informed consent. Permission to use SQ 20,881 was obtained from the Ethical Committee of this hospital. The subjects rested supine throughout the study, at a constant laboratory temperature of 22–24°C.

Hand vein distensibility

Hand vein distensibility was measured by a modification of the technique previously described (Nachev, Collier & Robinson, 1971). The vein was distended by a cuff around the wrist, which was maintained at a constant pressure of 35 mmHg and the change in size of the vein was recorded continuously by means of a light-weight lever, the tip of which rested on the vein while the other end was connected to an electronic transducer. Measurements of vein size were made every 24 min, the vein being congested for 2 min and allowed to collapse for 30 s. Physiological saline (0-15 mol/l NaCl) or saline containing drugs was infused into the vein at 0.25 ml/min through a 26 SWG unmounted needle positioned so that the tip was approximately 1 cm upstream to the point of measurement. Saline was infused initially and vein size recorded until it was stable. AII (angiotensin II amide, Hypertensin-Ciba) was then infused at a dose within the range 15–48 pmol/min (15.6–50 ng/min) for 5–7½ min and the change in venous distensibility measured. Saline was then infused and the vein allowed to relax. 25–47 min after the infusion of AII, A1 (Ileu\(^{-2}\)-angiotensin 1, Schwartz–Mann, batch number Gen 700H/YJ3) was infused for 5–7½ min at a dose twice by weight that of the previous dose of AII in four experiments and eight times in one experiment. Both drugs were given at only one dose to avoid the development of tachyphylaxis, which occurs with cumulative dose-response curves (Collier, Nachev & Robinson, 1972). In three experiments, the converting enzyme inhibitor (SQ 20,881) was then infused at 23 nmol/min (25 μg/min) into the vein, first by itself for 5–7½ min and then with A1 and AII in turn; the two angiotensins were given in the same doses and for the same time as in the first part of the experiment.

Forearm blood flow

Forearm blood flow was measured by means of venous occlusion plethysmography using a temperature-compensated mercury-in-rubber strain gauge. Collecting cuff pressure was 40 mmHg and wrist occlusion pressure approximately 200 mmHg. Flows were recorded for 10 s in every 15 s.

Saline or angiotensin (I or II) dissolved in saline was infused at 0-25 ml/min into the brachial artery of one arm through a 26 SWG unmounted needle by means of a constant-rate infusion pump. The initial dose of angiotensin I or II was infused for 4–5 min, at the end of which time the dose was increased two- or four-fold. The doses of A1 used were within the range 12.5–100 pmol/min (16–128 ng/min), and those of AII were 7.8–31 pmol/min (8–32 ng/min). The average of the last five flow measurements at each dose rate was taken for estimation of the response; measurements of flow in the opposite arm served as a control.

RESULTS

Effect of local infusion of AI and AII on hand vein distensibility

In four studies the dose of A1 was double that of AII; in three of these the constriction in response to A1 was less than that to AII; in the fourth the response was slightly greater (Table
Angiotensin conversion in man

TABLE 1. Effect of SQ 20,881 on the venous response to AI and AII

Results are shown for five experiments in three subjects.

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Angiotensin I</th>
<th>Angiotensin II</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Dose (pmol/min)</td>
<td>Reduction in vein size (%)</td>
</tr>
<tr>
<td></td>
<td>AI alone</td>
<td>AI+SQ 20,881</td>
</tr>
<tr>
<td>1</td>
<td>98</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>78</td>
<td>63</td>
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<td>49</td>
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<td>39</td>
<td>45</td>
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<tr>
<td>3</td>
<td>39</td>
<td>32</td>
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</tbody>
</table>

In one study in which the dose of AI was eight times that of AII, the response to AI was clearly greater. The relative potency of AI compared with AII thus appeared to be within the range 1:2 to 1:8. The initial response of the vein to AI was delayed by about 30 s compared with that to AII: the responses waned at a similar rate.

Effect of SQ 20,881 on the resting venous distensibility and response to AI and AII

Infusion of SQ 20,881 (23 nmol/min; 25 µg/min) did not affect the distensibility of the resting vein (three experiments in three subjects). SQ 20,881 had no effect on the vеноconstrictor response to AII (three experiments in three subjects), but it either abolished (two studies) or markedly attenuated (one study) the response to AI.

Effect of AI and AII on forearm blood flow

Infusion of AI (12.5–100 pmol/min; 16–128 ng/min) and AII (7.8–31 pmol/min; 8–32 ng/min) into the brachial artery caused a dose-dependent fall in forearm blood flow (three experiments in three subjects), and maximum reduction varying from 39 to 50%; no significant changes in flow were seen in the control arm. In one study AI and AII appeared equipotent, whereas in the other two studies AI was approximately half as potent as AII.

DISCUSSION

The direct action of angiotensin I when conversion is prevented has been shown to be very much less than that of angiotensin II in all vascular beds in which it has been studied (Vane, 1974). In our experiments, however, local infusion of AI caused vеноconstriction similar to that produced by AII, the potency ratio lying within the range 1:2 to 1:8; the response to AI but not that to AII was abolished or much diminished by simultaneous infusion of the converting enzyme inhibitor SQ 20,881. These findings indicate that conversion of AI into AII can occur in the periphery and, since conversion in the plasma is relatively slow (Poulsen & Poulsen, 1971), the converting enzyme activity is likely to reside in the vein wall. It seems probable that conversion can also take place in the forearm arterial bed, since AI is only slightly less potent than AII when infused into the brachial artery.
The potency ratio of systemically infused AI and AII was 1:2 in a previous study in which their pressor effect was measured (Collier et al., 1973). The observation that the potency ratio is similar with local infusion suggests that at the dosage used, conversion in the vessels studied is not significantly less efficient than in the pulmonary bed. This raises the question as to whether the pulmonary vascular bed is, as has been previously suggested, the only site of angiotensin conversion which is of major physiological importance (Ng & Vane, 1968; Oparil, Sanders & Haber, 1970). Evidence obtained from the rat suggests that renin may be able to generate AI and AII at local vascular level, and this would require the local presence of converting enzyme (Swales & Thurston, 1973; Thurston & Swales, 1974). Our studies indicate that there is converting enzyme activity in human peripheral vessels, and this raises the possibility that a similar mechanism of local AII production could exist in man.

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REFERENCES


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