CENTRAL VASOMOTOR STIMULATION BY ANGIOTENSIN

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(Received 9 January 1970)

SUMMARY

1. When angiotensin was infused at low rates into the vertebral arteries of anaesthetized dogs, it raised the blood pressure. When infused at similar rates intravenously or into the internal carotid artery it either did not change blood pressure, or raised it only very slightly. The difference in response was highly significant over the range of 1–50 ng kg⁻¹ min⁻¹.

2. During intravenous infusion at higher rates, angiotensin usually produced the well-known reflex bradycardia and fall of cardiac output, but on infusion into the vertebral arteries it rapidly raised systemic arterial pressure, often increased heart rate, and usually produced a transient increase of cardiac output.

3. Angiotensin by both routes raised peripheral resistance, but noradrenaline, by contrast, produced the same response whether it was given into the vertebral arteries or into a vein.

4. These observations suggest that part of the pressor effect of intravenous angiotensin may be mediated by a direct stimulation of some part of the hind brain.

There are several means by which angiotensin may raise systemic arterial pressure. In addition to its direct arterial vasoconstrictor action, it can release catecholamines from the adrenal medulla (Braun-Menéndez, Fasciolo, Leloir & Muñoz, 1940), stimulate or facilitate transmission in sympathetic ganglia (Lewis & Reit, 1966) and enhance the peripheral vasoconstrictor response to endogenously released noradrenaline (McCubbin & Page, 1963a, b). In very large doses it was reported, 9 years ago, to cause central stimulation of the sympatho-adrenal system when infused into the dog’s cerebral circulation which was isolated and perfused from another animal (Bickerton & Buckley, 1961). The special importance of the vertebral artery territory in mediating the central stimulatory effects of angiotensin, and the extreme sensitivity to angiotensin when given into the vertebral artery, was first observed in conscious rabbits (Dickinson, 1965; Yu & Dickinson, 1965) and in anaesthetized rabbits after blood

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pressure had been lowered by bleeding. Initial attempts to demonstrate the phenomenon in anaesthetized dogs had failed (Dickinson & McCubbin: unpublished observations quoted by Dickinson, 1965) probably because the infusion rates used were too high. More recently the phenomenon has been successfully demonstrated in anaesthetized and otherwise intact dogs (Scroop & Lowe, 1968; 1969; Lowe & Scroop, 1969). In this paper we report further observations on the effects of angiotensin when infused into the vertebral arteries of anaesthetized dogs, with special reference to the relative effects on heart rate, cardiac output and peripheral resistance.

METHODS

Nine dogs (16 to 22 kg) were anaesthetized with morphine (2 mg/kg) and intravenous chloralose (100 to 130 mg/kg). In six of the dogs, in which electromagnetic flowmeters had been implanted around the ascending aorta at a previous operation, stroke volume, heart rate, cardiac output and peripheral resistance were continuously recorded by methods previously described (Ferrario, McCubbin & Page, 1969). Systemic arterial pressure was recorded in all dogs by a Statham P 23 db strain gauge transducer from a catheter in the femoral artery.

In all animals both vertebral arteries and (in three dogs) both common carotid arteries were cannulated with fine, non-obstructing, 22 gauge polyethylene catheters near their origins. The external carotid and lingual arteries were tied. In all animals another catheter was put in a femoral vein. From a common reservoir containing val-5-angiotensin II amide ('Hypertensin-Ciba'), a motor driven pump infused fluid at a constant rate, set between 0.11 and 1.21 ml/min, either into both vertebral arteries, both common carotid arteries, or into a femoral vein. The angiotensin infusions lasted for 6 min and were spaced at least 5 min apart.

RESULTS

Infusions at rates of 1–10 ng kg^{-1} min^{-1}, which were ineffective when given intravenously or into the carotid arteries, consistently raised systemic arterial pressure when given into the vertebral arteries (Fig. 1). At higher rates (20–50 ng kg^{-1} min^{-1}), although infusion at all sites raised the blood pressure, responses to vertebral artery infusion were significantly greater than those to infusion elsewhere (Table 1). The vertebral artery responses had certain characteristic features: (1) the rise of pressure was rapid, and usually began 30–45 s after starting the infusion (Fig. 2); (2) it was always accompanied by an elevation of diastolic pressure, though with high doses systolic pressure was raised by a similar amount; (3) it was usually accompanied by increased heart rate (Table 1), whereas a comparable pressor response to an intravenous infusion was associated with a small fall in heart rate; and (4) cardiac output was usually transiently elevated but after a few minutes it tended to return to control levels, while the raised blood pressure was sustained by increased peripheral resistance. Stroke volume changes were variable and not significant on average (Table 1). Occasionally most of the response was mediated by a rise in cardiac output. The record of one dog in which this response was seen is shown in Fig. 3.

By comparison, higher doses of angiotensin given into a vein or into the carotid arteries produced a fall of heart rate and cardiac output, and the rise of blood pressure was maintained entirely by an increased peripheral resistance (Table 1). Sensitivity was similar for infusion by the two routes.
Vertebral artery angiotensin infusion

**FIG. 1.** Dose-response curve obtained for infusions of angiotensin at various rates either into the vertebral arteries or intravenously. Values are means of blood pressure elevations in mmHg (± SD) obtained from at least ten measurements in nine dogs.

Similar comparisons with noradrenaline, infused at 2–6 ng kg⁻¹ min⁻¹ and at 600–800 ng kg⁻¹ min⁻¹ in three animals failed to reveal any significant differences between carotid, vertebral artery, and intravenous infusions. By any route of infusion the main cause of the rise of blood pressure at the higher rate was an increase in both cardiac output and peripheral resistance, and heart rate consistently fell.

**DISCUSSION**

These results confirm previous observations in conscious rabbits (Dickinson & Yu, 1967), and in anaesthetized dogs (Scroop & Lowe, 1968). Assuming a cardiac output of 2000 ml/min, an intravenous infusion rate of 50 ng kg⁻¹ min⁻¹ and a 70% rate of angiotensin inactivation per circulation, the concentration in arterial blood should be of the order of 75 ng/100 ml for a 20 kg dog. Assuming a total cerebral blood flow of about 55 ml 100 g⁻¹ min⁻¹, or about 70 ml/min
**Table 1. Summary of haemodynamic changes during angiotensin infusions on twelve occasions in six dogs**

<table>
<thead>
<tr>
<th>Angiotensin infusions: (ng. kg.⁻¹ min⁻¹)</th>
<th>Vertebral artery</th>
<th>Intravenous</th>
<th>PR (100 × mmHg ml⁻¹ min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SV (ml)</td>
<td>HR (b/min)</td>
<td>CO (ml/min)</td>
</tr>
<tr>
<td>AVERAGES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>37±4</td>
<td>57±5</td>
<td>2076±134</td>
</tr>
<tr>
<td>Response: first min 1</td>
<td>n.c.</td>
<td>+7±2*</td>
<td>+385±50*</td>
</tr>
<tr>
<td>Response: fifth min</td>
<td>-5±1*</td>
<td>+8±4</td>
<td>+80±100</td>
</tr>
<tr>
<td>Response: first min 20</td>
<td>+1±1</td>
<td>+12±5</td>
<td>+375±98*</td>
</tr>
<tr>
<td>Response: fifth min</td>
<td>-3±1*</td>
<td>+10±2*</td>
<td>+100±60</td>
</tr>
<tr>
<td>Response: first min 48</td>
<td>-1±1</td>
<td>+13±3*</td>
<td>+382±118*</td>
</tr>
<tr>
<td>Response: fifth min</td>
<td>-2±1</td>
<td>+9±3</td>
<td>+170±76</td>
</tr>
</tbody>
</table>

SV = stroke volume; HR = heart rate; CO = cardiac output; MAP = mean systemic arterial pressure; PR = peripheral resistance. n.c. = no measurable change; Values are means ± 1 SEM for control, and the mean difference change ± 1 SEM of 12 pressor responses averaged over the first and fifth minute of angiotensin infusion. * Probably significant difference from control (P<0.01).
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for 120 g brain, of which perhaps 1/3 is contributed by the vertebral arteries, having a blood flow of about 25 ml/min, a 1.0 ng kg\(^{-1}\) min\(^{-1}\) infusion rate of angiotensin into the vertebral arteries should give an effective vertebral artery concentration of about 80 ng/100 ml blood.

![Diagram](image)

**FIG. 2.** Pressor effect of angiotensin infused into the vertebral arteries. From above down: aortic blood flow; pulsatile aortic blood pressure; mean aortic blood pressure; heart rate; cardiac output; peripheral resistance (Aortic pressure divided by cardiac output). To obtain cardiac output the heart stroke volume was displayed as vertical steps added and re-cycled every 4 s (see expanded time traces); to obtain peripheral resistance mean aortic pressure was electronically and continuously computed at 4 s intervals. Signal mark A: infusion of 1.0 ng kg\(^{-1}\) min\(^{-1}\) angiotensin into the vertebral arteries; B: same, at 3.5 ng kg\(^{-1}\) min\(^{-1}\). Both infusion rates were without effect when angiotensin was delivered into a vein.

Thus, for a total rise of pressure of about 30 mmHg at an intravenous infusion rate of 50 ng kg\(^{-1}\) min\(^{-1}\), about 10 mmHg of the rise might be attributed to the central effect achieved by the concentration of angiotension in vertebral artery blood. Although this argument is difficult to prove, the figures are likely to be of the correct order of magnitude, and at least make it
likely that part of the pressor response to intravenous infusion of angiotensin at moderate rates is due to the central action of angiotensin.

Our results are generally similar to those of Scroop & Lowe (1968): the main difference is that in our animals the increase in cardiac output at low vertebral artery infusion rates of angiotensin was usually transient (Table 1), and except in the one animal (whose response is shown in Fig. 3) the rise of blood pressure could be almost entirely attributed to a rise of peripheral resistance. Table 1 indicates that the increase of cardiac output 5 min after starting an infusion at 20 ng kg⁻¹ min⁻¹ was negligible (about 5%) compared with the increase of peripheral resistance (about 30%). We would therefore lay less stress on the great importance of angiotensin...
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the cardiac output component and on the tachycardia (which appears to be due mainly to release of vagal tone (Scroop & Lowe, 1969)). A possible difference is that we used mongrel dogs, whereas Scroop and Lowe used greyhounds. Greyhounds are capable of enormous increases in cardiac output on demand and it is possible that a cardiac output response may be specially characteristic of this animal.

We have as yet no explanation for this central action. Cerebral ischaemia has been suggested (Dickinson, 1965) but on the other hand the response is rapid and noradrenaline responses are different from those to angiotensin. We are at present trying to measure local hind brain blood flow during angiotensin infusion.

REFERENCES


