Angiotensin activates sympathetic reflexes in the anaesthetized cat

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Summary

1. Lower-body subatmospheric pressure has been used to stimulate sympathetic reflexes in anaesthetized cats and the effects of an angiotensin converting enzyme inhibitor and [Sar\(^1\), Ala\(^8\)]angiotensin II have been investigated on this reflex.

2. At the prevailing level of renin activity (2.9–3.2 ng of angiotensin I h\(^{-1}\) ml\(^{-1}\)) the converting enzyme inhibitor had no effect on blood pressure yet it potentiated the initial fall in blood pressure caused by the reduced pressure and it impaired its recovery. After 10 min, therefore, blood pressure was still reduced after converting enzyme inhibitor treatment whereas in control experiments full recovery occurred within 30 s.

3. When converting enzyme inhibitor was given 75 s after the start of a 10 min period of reduced pressure, at a time when plasma renin activity had not been increased, it caused a greater and more sustained fall in pressure than it caused when administered alone. The angiotensin II antagonist, [Sar\(^1\), Ala\(^8\)]angiotensin II, produced similar effects.

4. These findings suggest that the renin–angiotensin system interacts with the sympathetic nervous system to maintain systemic arterial pressure.

Key words: [Sar\(^1\), Ala\(^8\)]angiotensin II, blood pressure, converting enzyme inhibitor, sympathetic reflexes.

Introduction

Antagonists of the renin–angiotensin system have antihypertensive actions in both animals and man, especially in circumstances when plasma renin activity is elevated (Conway, Hatton, Keddie & Dawes, 1979). The reflex tachycardia which should accompany the fall in blood pressure has often been reported to be absent after treatment with renin–angiotensin antagonists (Gavras, Brunner, Turini, Kershaw, Tiff, Cuttelod, Gavras, Vukovich & McKinstry, 1978; Conway et al., 1979).

Clough, Conway, Hatton & Scott (1979) investigated this aspect of the actions of angiotensin converting enzyme inhibition in conscious dogs and showed that the lack of tachycardia was due to a change in set-point of the baroreflex. Angiotensin also has previously been shown to interact with the sympathetic nervous system via a prejunctural action augmenting noradrenaline release (Zimmerman, 1978) or inhibiting noradrenaline re-uptake (Khairallah, 1972). It therefore seemed likely that at least part of the antihypertensive actions of renin–angiotensin antagonists could be due to interference with cardiovascular sympathetic reflexes.

In the present study, lower-body subatmospheric pressure has been used to stimulate the sympathetic homeostatic reflexes which are activated as blood is pooled in the hindquarters (Bennett, Fentem, Tomlinson & Yates, 1976). The actions of an angiotensin converting enzyme inhibitor and [Sar\(^1\), Ala\(^8\)]angiotensin II have been investigated on this reflex to determine whether there is a physiological role for angiotensin in the maintenance of sympathetic reflexes.

Methods

Cats weighing between 2.5 and 4.2 kg were anaesthetized with \(\alpha\) chloralose (80 mg/kg intraperitoneally). Blood pressure, heart rate, central venous pressure and plasma renin activity were measured and the cats were exposed to...
lower-body subatmospheric pressure as described previously (Adigun, Clough, Conway & Hatton, 1980).

The antagonists of the renin–angiotensin system used were the nonapeptide converting enzyme inhibitor Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro-OH (Beckman Laboratories), which is structurally identical with SQ 20881, and the ANG II antagonist [Sar¹,Ala⁸]ANG II (saralasin-Norwich).

The cats were exposed to a reduced pressure of -50 mmHg for periods of 10 min. Thirty to 40 min later they received converting enzyme inhibitor (1 mg/kg intravenously) either before a further period of reduced pressure or 75 s after the start of the reduced pressure period. Some cats also received a saralasin infusion (8–10 μg min⁻¹ kg⁻¹ intravenously) during exposure to reduced pressure.

The results are expressed as mean ± SEM and statistical comparisons were made by Student’s paired t-test.

Results

Exposure of the lower abdomen and hindquarters to reduced pressure caused transient reductions in central venous pressure (−2.2 ± 0.1 cm water) (P < 0.001) and systolic arterial pressure (−16 ± 0.9 mmHg) (P < 0.001) as circulating blood volume fell. While the reduced pressure was maintained blood pressure recovered within 30 s and there was a partial recovery in central venous pressure. There was a tachycardia of 20 ± 1.2 beats/min (P < 0.001) (Fig. 1). The resting plasma renin activity values ranged between 2.9 ± 0.3 and 3.2 ± 0.4 ng of ANG I h⁻¹ ml⁻¹ and it was unaltered after the first 75 s of reduced pressure. It rose significantly after 10 min to 6.6 ± 0.8 ng ANG I h⁻¹ ml⁻¹ (P < 0.01).

Converting enzyme inhibitor alone caused only a small and transient fall in blood pressure, which had recovered to control levels within 2–5 min. The pressor response to injected ANG I was, however, still reduced by 85% during the 10–15 min after injection.

The initial fall in blood pressure caused by lower-body reduced pressure was potentiated after administration of converting enzyme inhibitor and the recovery in blood pressure was impaired so that complete recovery did not occur during the 10 min of reduced pressure.

Converting enzyme inhibitor was also administered during suction at 75 s when blood pressure had already been restored to control levels. Converting enzyme inhibitor now caused a sustained fall in pressure of 28 ± 3.2 mmHg (Fig. 1), which was greater and longer lasting than that observed before the lower-body reduced pressure. Saralasin, which alone caused only transient and small changes in pressure, also caused a marked and sustained reduction in blood pressure when administered during the period of reduced lower-body pressure.

Discussion

Exposure of the lower body to reduced pressure is a reliable and reproducible way of eliciting cardiovascular homeostatic reflexes (Bennett et al., 1976). The reflex restoration of blood pressure has been shown to be due to activation of the sympathetic nervous system (Bennett et al., 1976), making this a useful technique for investigating the role that angiotensin may play in the control of sympathetic reflexes.

We have previously shown that both converting enzyme inhibitor and saralasin interfere with the reflex response to 75 s of reduced pressure (Adigun et al., 1980), at which time plasma renin activity had not been elevated. The present findings extend these observations to long periods of reduced pressure, during which there is an appreciable elevation of plasma renin, and confirm that this impairment of the reflex is maintained throughout the entire period of low pressure.

The effects of blocking angiotensin on the reflex adjustments to reduced pressure are more dramatically illustrated when the inhibitor is given during the reduced pressure period after the reflex restoration in blood pressure has occurred (Fig. 1). Converting enzyme inhibitor now caused a large fall in blood pressure in spite of the fact that at this time plasma renin activity had not been elevated. In the control experiment this dose of converting enzyme inhibitor did not lower blood pressure; therefore this action of angiotensin to facilitate sympathetic reflexes occurred at a level lower than that required for a direct vasoconstrictor action. Since the ANG II antagonist saralasin produced the same effects as a converting enzyme inhibitor, it is unlikely that potentiation of the actions of bradykinin played any part in the actions of converting enzyme inhibitor on this reflex.

In conclusion, these findings suggest that angiotensin interacts with the sympathetic nervous system to maintain systemic arterial pressure during central hypovolaemia and this interaction occurs at levels of angiotensin which do not have a direct vasoconstrictor action.
Angiotensin and sympathetic reflexes

Fig. 1. Effects of 10 min of lower-body subatmospheric pressure on heart rate, systolic blood pressure and central venous pressure in anaesthetized cats (left) and the effect of angiotensin converting enzyme inhibitor (CEI: 1 mg/kg intravenously) given 75 s after the onset of the reduced pressure period on these responses (right). LBNP, Lower-body reduced pressure.

References


