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CAPTOPRIL AND THE MAINTENANCE OF BLOOD PRESSURE AFTER SINOAORTIC DENERVATION IN THE RABBIT

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1 At a dose of 1 mg/kg intravenously, captopril lowered blood pressure in conscious rabbits, that had undergone denervation of sinoaortic baroreceptors, but had no effect on heart rate. In sham-operated controls, this dose caused only an increase in heart rate.

2 In the same experiments, captopril caused a substantial inhibition of plasma angiotensin converting enzyme (CE) activity of rapid onset and gradual decline over 2 to 3 h. The time course of recovery of blood pressure and plasma CE activity were similar.

3 Saralasin, by intravenous infusion, lowered blood pressure in sinoaortic rabbits but to a smaller extent than captopril.

4 The fall in blood pressure observed after captopril is not dependent on the integrity of baroreceptor afferents.

Introduction

Captopril (2-D-methyl-3-mercaptopropanoyl-L-proline) is an orally active dipeptidase inhibitor (converting enzyme inhibitor). It has been shown to lower blood pressure in essential and renovascular hypertension in man (Gavras, Brunner, Turini, Kershaw, Tifft, Cuttelod, Gavras, Vukovich & McKinstry, 1978), without significantly increasing the heart rate, in spite of significant falls in blood pressure. While it has been suggested that this is a consequence of venous, in addition to arteriolar dilation (Cody, Tarazi, Bravo & Fouad, 1978), it could reflect an effect on baroreceptor reflex function as suggested after converting enzyme (CE) inhibition by Clough, Conway, Hatton & Scott, (1979). Captopril does not readily enter the central nervous system: thus one possible site of action of the CE inhibitor may be on the peripheral afferent arterial baroreceptors in the carotid sinus and aortic arch. The effects of captopril have been examined in intact conscious rabbits after deafferentation of the carotid sinus and aortic arch to achieve sinoaortic denervation.

Methods

All experiments were performed on concious male New Zealand white rabbits, weighing 2 to 4 kg. The carotid sinus and aortic arch baroreceptors were denervated or sham operations were carried out using a technique based on that described by Chalmers & Wurtman (1971). The animals were used for experimental purposes 7 days after operation.

Blood pressure was continuously measured directly with a strain gauge transducer and displayed on a Devices M2 recorder from a polypropylene catheter introduced into the central ear artery under local anaesthesia (1% w/v lignocaine). Heart rate was derived from the arterial pressure trace. A further catheter was placed in a marginal vein of the ear for drug administration. Animals rested quietly in individual boxes for at least 1 h after these procedures before drug administration.

Captopril (1 mg/kg) was injected intravenously and the effect on mean arterial pressure (MAP) and heart rate (HR) observed at intervals during the following 180 min. This dose was selected on the basis of preliminary experiments over the range 0.1 to 10 mg/kg intravenously. The dose selected caused in normal rabbits a substantial degree of inhibition of plasma CE activity and antagonism of angiotensin I and potentiation of bradykinin (Petty, Reid & Miller, 1980). Blood samples were collected from the arterial catheter at intervals up to 180 min after administration of this dose. CE activity was measured in the plasma by a radiometric assay procedure (Ventrex Laboratories, Portland Maine). The total blood volume sampled during each experiment did not exceed 12 ml and this volume was replaced by 0.9% w/v NaCl solution (saline).

In a further group of denervated rabbits, Sar^1, Ala^8-angiotensin (Saralasin, Norwich Pharmaceutical Co., New York), the angiotensin II antagonist, was infused in doses ranging from 0.13 μg/min to 20 μg/min for 10 min periods and the effect on MAP and HR observed.

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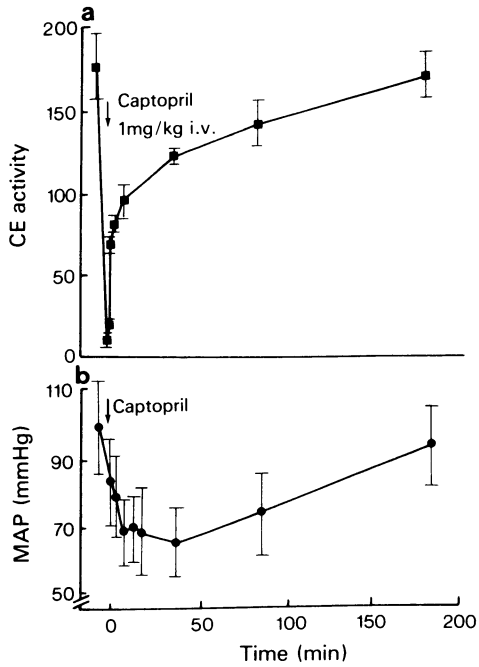

Figure 1 The effect of 1 mg/kg captopril, administered intravenously, on plasma converting enzyme activity (a) and blood pressure (b) of baroreceptor denervated rabbits. Results are expressed as mean of 6 to 10 determinations; vertical lines show s.e. mean.

All values used in analysis represent the mean ± s.e. mean of 6 to 10 determinations. The significance of differences between denervated animals as compared to sham-operated controls was calculated by Student's *t* test for paired data.

Results

Sinoaortic denervation caused an increased lability of blood pressure and a small but significant increase in MAP ($P<0.05$) to 99.2 ± 14.1 mmHg in denervated animals compared to 88.6 ± 3.3 mmHg in sham-operated controls. Captopril (1 mg/kg i.v.) administered to the denervated animals resulted in a lowering of pressure to 83.2 ± 13.3 mmHg at 2 min and 68.7 ± 10.9 mmHg ($P<0.01$) at 10 min. The pressure remained significantly reduced for the next 30 min returning to control values by 180 min (Figure 1). No consistent change in MAP was observed after captopril administration to sham-operated controls.

Denervation also increased HR to 252.5 ± 13.3 from 212.7 ± 6.4 beats/min ($P<0.05$) in sham-operated controls. After 1 mg/kg captopril no change in HR was observed in the denervated group. In sham-operated animals, 2 min after captopril administration, HR was increased to 251.3 ± 12.6, reaching a maximum of 259 ± 16.3 beats/min at 20 min ($P<0.05$) and returning to control values by 180 min.

In denervated rabbits, captopril (1 mg/kg) reduced plasma CE activity immediately from 175.1 ± 18.9 nmol min^{-1} ml^{-1} before administration to 11.2 ± 4.1 nmol min^{-1} ml^{-1} at 0.5 min. At 1.5 min there was a recovery to 18.5 ± 3.9 and by 2 min activity was 69.4 ± 5.8 nmol min^{-1} ml^{-1}. After this period there was a gradual return to control levels by 180 min (Figure 1).

Saralasin was infused into the denervated animals in doses ranging from 0.13 μg/min to 20 μg/min for 10 min periods. At the lowest dose there was a fall in MAP from 80.3 ± 1.5 mmHg to 68.7 ± 4.7 mmHg at 10 min ($P<0.01$); there was no effect on HR. At the highest doses a short lasting rise in pressure was observed. Saralasin did not lower blood pressure of normal rabbits at the doses used.

Discussion

We have investigated the effects of captopril in rabbits in which arterial baroreceptor reflexes have been interrupted by bilateral section of the aortic depressor and carotid sinus nerves in the neck. Baroreceptor deafferentation removes important inhibitory influences on sympathetic efferent outflow leading to increased peripheral sympathetic activity, tachycardia and a labile blood pressure (Chalmers & Wurtman, 1971) which tends to be increased in comparison to sham-operated controls. Captopril (1 mg/kg) lowered the blood pressure in these animals, although there was no effect on heart rate. Conversely in sham-operated controls, captopril had no effect on blood pressure but produced a slight increase in heart rate.

The antihypertensive effect of captopril probably results from the inhibition of CE activity (Rubin, Laffan, Kotler, O'Keefe, Maio & Goldberg, 1978). The time course of plasma CE inhibition differs from the hypotensive effect. The maximum fall in blood pressure was delayed and occurred between 10 and 40 min, whereas maximum inhibition of plasma enzyme occurred within 2 min of administration. Both enzyme activity and MAP had returned to control values by 180 min. This relationship with a delay in the onset of effect may have a kinetic explanation where the site of action is not directly accessible to captopril in plasma and only reaches an equilibrium with plasma after some time. Thurston & Swales (1977) suggested that the site of action of CE inhibition may be at the level of the smooth muscle cells of the vessel wall. The results we have obtained would be consistent with this hypothesis.

Sinoaortic denervation in rabbits, because of the

increased peripheral sympathetic activity and lability of blood pressure can be considered as a model of 'neurogenic hypertension'. The increased peripheral sympathetic activity may increase neurogenically mediated renin release (Peach, 1977). Thus at least part of the 'neurogenic hypertension' may result from activation of the renin-angiotensin system, a conclusion supported by the observations after saralasin infusion. Saralasin, a competitive angiotensin II antagonist, at a dose of 0.13 μg/min for 10 min caused a gradual fall in MAP. Although the fall in pressure was not so great as that observed after captopril, and higher doses did not lower pressure, this may be related to the partial agonist action of saralasin (MacGregor & Dawes, 1976). Alternatively the lower baseline pressures before saralasin, a reflection of the lability of blood pressure, may have influenced the extent of the fall as may additional effects of captopril on bradykinin.

The contribution of angiotensin II to the maintenance of hypertension may be either directly through vasoconstriction or indirectly by further amplifying the increased peripheral sympathetic activity. This latter effect could be achieved through an action on presynaptically located angiotensin II receptors on noradrenergic neurones which appear to exert a positive feedback on transmitter release (Langer, 1977).

In conclusion, hypotensive effects of the CE inhibitor, captopril, were revealed in rabbits after baroreceptor deafferentation, suggesting that intact baroreceptor mechanisms in the carotid sinus and aortic arch are not important in the generation of hypotensoin with this drug.

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