Contribution of the kidneys but not adrenal glands to the acute antihypertensive effects of captopril in spontaneously hypertensive rats

M. J. ANTONACCIO, J. P. HIGH, B. RUBIN AND T. SCHAEFFER
The Squibb Institute for Medical Research, Princeton, New Jersey, U.S.A.

Summary

1. Captopril (100 mg/kg, orally) decreased blood pressure in spontaneously hypertensive (SH) rats.
2. Bilateral adrenalectomy either before or after captopril administration did not alter the antihypertensive effect of captopril.
3. Bilateral nephrectomy reversed the established antihypertensive effect of captopril and prevented any change in blood pressure to a subsequent dose of captopril.
4. It is concluded that kidneys but not adrenal glands are essential to the antihypertensive actions of captopril in SH rats.

Key words: angiotensin, antihypertensive drug, bradykinin, captopril, converting enzyme.

Abbreviations: MAP, mean arterial blood pressure; SH, spontaneously hypertensive.

Introduction

Captopril, the orally active inhibitor of angiotensin converting enzyme, is effective in reducing blood pressure in renal hypertensive rats (Laffan, Goldberg, High, Schaeffer, Waugh & Rubin, 1978; Rubin, Antonaccio, Goldberg, Harris, Itkin, Horovitz, Panasevich & Laffan, 1978; Bengis, Coleman, Young & McCaa, 1978), dogs (Rubin, Antonaccio & Horovitz, 1978) and humans (Brunner, Gavras, Walker, Kershaw, Turini, Vukovich & McKinstry, 1979). The magnitude of reduction of blood pressure caused by captopril was related to plasma renin activity and, probably, the amount of angiotensin II maintaining high blood pressure. In addition, plasma aldosterone concentrations were concomitantly reduced by captopril, presumably a result of the reduced formation of angiotensin II, which provides the main stimulus to aldosterone synthesis and release (McCaa, McCaa, Bengis & Guyton, 1979).

Captopril is also effective in reducing blood pressure of spontaneously hypertensive (SH) rats, a moderate reduction being observed acutely (Laffan et al., 1978) followed by a cumulative effect during chronic therapy, which results in normalization of arterial pressure (Antonaccio, Rubin, Horovitz, Laffan, Goldberg, High, Harris & Zaidi, 1979). Furthermore, captopril is capable of preventing the development of hypertension when administered for 16 weeks to weanling SH rats (Ferrone, Antonaccio & High, 1979). Since SH rats do not have elevated plasma renin activities (Koletsky, Shook & Rivera-Velez, 1970; Sen, Smeby & Bumpus, 1972; Antonaccio et al., 1979), the mechanism of the antihypertensive action of captopril in this model remains unresolved.

The purpose of this study was to determine the relative contribution of the kidneys and the adrenal glands to the reductions in blood pressure caused by captopril in SH rats.

Methods

Several groups of four to eight adult male SH rats of the Okamoto–Aoki strain were used. Mean arterial blood pressures (MAP) and heart rates of conscious SH rats were obtained by direct cannulation of the abdominal aorta as described.
Fig. 1. Effects of captopril (100 mg/kg, orally) on mean blood pressure (MAP, mmHg) and heart rate of SH rats before and after either sham (a) or actual (b) bilateral nephrectomy. The space in the tracings is the result of removing the animals from the recording device, anaesthetizing them, performing the indicated surgery, allowing for recovery from anaesthesia and again placing them in the recording apparatus. Mean values bracketed by (± SEM) are shown. (c) Mean values obtained in (a), continuous line, plotted simultaneously with those obtained in (b), dashed line, for comparison purposes. Control MAP for group A was 184 ± 6 mmHg and for group B was 179 ± 3 mmHg.

Previously (Laffan et al., 1978). All surgery was performed under ether anesthesia.

Results

Oral administration of captopril (100 mg/kg) to conscious SH rats caused a moderate reduction in MAP (Fig. 1a and b). After sham nephrectomy in one group of SH rats, blood pressure remained reduced after captopril and a subsequent additional dose of captopril to these rats caused a further modest reduction in MAP (Fig. 1a). In contrast, the reduction in MAP caused by the administration of captopril to another group of SH rats
was not maintained after actual bilateral nephrectomy. MAP returned to pre-dose hypertensive values and a second dose of captopril to these rats did not have any significant effect on MAP (Fig. 1b). The MAP of the two groups are shown together in Fig. 1(c).

Heart rates after bilateral nephrectomy dropped precipitously (Fig. 1b). However, this was not the result of captopril administration since (1) it did not occur in the sham nephrectomized rats receiving captopril (Fig. 1a), (2) bilateral nephrectomy in water-vehicle-treated rats had similar reductions in heart rate, and (3) captopril administration to bilaterally adrenalectomized rats had no significant effect on heart rate.

In another group of SH rats, MAP 24 h after bilateral adrenalectomy was 134.3 ± 11.8 mmHg, a significant reduction from MAP before surgery (179.8 ± 3.7 mmHg; P < 0.001). Administration of captopril (100 mg/kg, orally) to these adrenalectomized rats resulted in a 30-7% reduction in MAP, which was very similar to the 24.5% reduction observed in control intact SH rats.

In still another group of intact SH rats, captopril (100 mg/kg, orally) reduced MAP from 177.5 ± 2.3 to 155.3 ± 11.5 mmHg 2.5 h after dosing. Bilateral adrenalectomy at this time resulted in a reduction of MAP to 126.2 ± 5.6 mmHg. Subsequent administration of a second dose of captopril to these rats decreased MAP still further to 108.2 ± 6.3 mmHg.

Discussion
The present study demonstrates that the kidneys of SH rats are essential for the acute antihypertensive effects of captopril to be manifested. In contrast, removal of the adrenal glands either before or after the administration of captopril did not alter the response to captopril. Thus reductions in aldosterone release observed after captopril administration in other forms of hypertension (see the Introduction section) cannot be responsible for the acute antihypertensive actions observed in SH rats. These results are consistent with the lack of effect of captopril both on urinary aldosterone (Antonacci et al., 1979) and on sodium and water excretion in SH rats (Muirhead, Prewitt, Brooks & Brosius, 1978; Antonaccio et al., 1979). Furthermore, these results are consistent with the low plasma concentrations of aldosterone in SH rats (Freeman, Davis, Versano-Aharon, Ulick & Weinberger, 1975; Willis & Bauer, 1978), the lack of a diuretic response to spironolactone, an aldosterone antagonist (Willis & Bauer, 1978), and the ineffectiveness of spironolactone in acutely reducing blood pressure in SH rats (our unpublished observations).

Bilateral nephrectomy before captopril administration has previously been shown to prevent its antihypertensive effect in SH rats (Laffan et al., 1978). In the present study we have demonstrated that the removal of both kidneys in SH rats after the administration of captopril causes blood pressure to return to pre-dose hypertensive values. Furthermore, a subsequent dose of captopril was without effect on blood pressure. These data suggest that (1) either captopril causes the release of a renal vasodilator substance or (2) the kidneys secrete a pressor substance which captopril effectively counteracts. With regard to the latter possibility, arterial wall renin activity in SH rats has been shown to be elevated, responsive to captopril administration and dramatically decreased by bilateral nephrectomy (Asaad & Antonaccio, 1979). Therefore it is possible that captopril may act to reduce blood pressure in SH rats by inhibiting the generation of vascular wall angiotensin II (Antonacci et al., 1979).

References


