The kallikrein–kinin system in blood pressure homeostasis


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Summary

1. The acute effects of the kallikrein inhibitor aprotinin (498 kiu./min), and the kininase II inhibitor SQ 14 225 (250 μg), given intravenously during saralasin-induced angiotensin blockade, were studied in conscious sham-operated rats and rats with benign and malignant two-kidney, one-clip Goldblatt hypertension during dietary sodium restriction.

2. The blood pressure of conscious sham-operated rats increased significantly in response to aprotinin. It remained unchanged after SQ 14 225 in contrast to the significant vasodepressor effect seen when SQ 14 225 was given to the same rats under surgical stress and pentobarbital anaesthesia.

3. Benignly hypertensive rats showed a consistent vasopressor response to aprotinin and a marked vasodepressor response to SQ 14 225. The effects of both inhibitors were markedly and significantly blunted in malignantly hypertensive rats.

4. Our demonstration that two agents with known opposite actions on the kallikrein–kinin system produced predictable and opposite effects on blood pressure may indicate that this system is involved in the homeostatic regulation of blood pressure. It may play an important antihypertensive role in benign two-kidney, one-clip Goldblatt hypertension, a role which might be impaired in malignant hypertension.

Key words: angiotensin-converting enzyme, aprotinin, hypertension, inhibitors, kallikrein, kininase II, renin.

Introduction

Among the proposed mechanisms which may subserve the antihypertensive function of the kidney, the potent vasodepressor, natriuretic and diuretic kallikrein–kinin system has been implicated (Terragno & Terragno, 1977; Levinsky, 1979). Suggestive evidence that this system might be involved in the hypertensive state is provided by the studies which demonstrated reduced kallikrein (Margolius, Horwitz, Pisano & Keiser, 1974) and kinin excretion (Shimamoto, Ando, Nakao, Tanaka, Sakuma & Miyahara, 1978) in essential hypertension, increased kallikrein excretion in primary aldosteronism (Margolius et al., 1974), reduced excretion in renovascular hypertension (Keiser, Margolius, Brown, Rhamey & Foster, 1976b) and various abnormalities in kallikrein excretion in hypertensive animal models (Keiser, Geller, Margolius & Pisano, 1976a; Carretero, Amin, Ocholik, Scicli & Koch, 1978).

To assess the possible antihypertensive role of the kallikrein–kinin system we studied the effects of the kininase II inhibitor SQ 14 225 (Ondetti, Rubin & Cushman, 1977), and the kallikrein inhibitor aprotinin (Vogel & Werle, 1970), on the blood pressure of sham-operated normotensive rats, and rats with benign and malignant two-kidney, one-clip Goldblatt hypertension.

Methods

Male Sprague–Dawley rats were subjected either to sham operation or to unilateral renal artery constriction by use of solid silver clips of 0.25 or 0.20 mm internal diameter to produce benign or malignant two-kidney, one-clip Goldblatt hypertension respectively. All rats were maintained on a low-sodium diet (Lonalac, Mead Johnson) to challenge the kallikrein–kinin system (Wong, Talamo, Williams & Colman, 1975) and studied at 28–35 days postoperatively. Malignant hypertension in the 0.20 mm-clipped rats was assessed by the sudden appearance of a rapid decrease in body weight gain accompanied by evidence of increased
fluid turnover (Gross, Dietz, Mast & Szokol, 1975).

On the day before study, one cannula in the carotid artery and two cannulae in the same jugular vein were implanted and exteriorized between the scapulae respectively, for measuring mean arterial pressure and for facilitating drug administrations with minimal disturbance of the animal. All operative procedures were performed under ether anaesthesia and the studies were conducted with the animals in the conscious, unrestrained state except for one group of sham-operated rats, in which the response to SQ 14 225 was studied soon after cannulation under pentobarbital anaesthesia (35 mg/kg, intraperitoneally) as well as in the conscious state.

To eliminate its angiotensin-dependent effects on blood pressure, SQ 14 225 (Captopril, Squibb) was injected as an intravenous bolus of 250 μg in 0.25 ml of 5% glucose solution after restabilization of blood pressure during continuous angiotensin II blockade produced by saralasin infusion (10 μg/min) (Thurston & Swales, 1978). This dose of SQ 14 225, when superimposed on an intravenous infusion of bradykinin (4 μg/min), markedly potentiated the vasodepressor effects of the infused bradykinin tested in six rats (−15 ± 5.0 vs −88 ± 15.2 mmHg), and the infusion dose of saralasin completely prevented the pressor response to 360 ng of angiotensin II. Aprotinin (Trasylol, FBA Pharmaceuticals) was administered as an infusion, first at a priming dose of 5000 ki.u./min for 1 min and then followed by a maintenance dose of 498 ki.u./min for 60 min.

Plasma renin activity (PRA) in arterial plasma collected via the carotid cannula at least 24 h after SQ 14 225 administration was determined by radioimmunoassay (Maxwell, Marks, Varady, Lupu & Kaufman, 1975).

Results

The data on resting mean arterial pressure, PRA, body weight, and changes in pressure in response to saralasin, SQ 14 225 and aprotinin are shown in Table 1. The responses to all three drugs generally attained plateaux at 20–30 min and the values reported represent the plateau responses. The 0.20 mm-clipped rats which developed malignant hypertension lost significantly more weight (P < 0.005) and attained significantly higher mean pressures (P < 0.005) than the 0.25 mm-clipped, benignly hypertensive rats. Although PRA and the magnitude of the response to saralasin infusion (P <
0.01) varied with the severity of hypertension in the two groups of hypertensive rats, only benignly hypertensive rats showed a consistent vasopressor response to aprotinin infusion, as well as a marked vasodepressor response to SQ 14 225 administration, which was not previously demonstrable in conscious sham-operated rats. In contrast, the effects of both inhibitors were markedly and significantly blunted in malignantly hypertensive rats when compared with the effects seen in benignly hypertensive rats (P < 0.005 for both).

Discussion

Our demonstration that SQ 14 225 and aprotinin produced predictable and opposite effects on the blood pressure of benign two-kidney, one-clip Goldblatt hypertensive rats indicates that alterations in the kallikrein–kinin system were most likely to have been responsible for our results. Since significant changes in external electrolyte and fluid balance are unlikely to have occurred during our acute experiments, the effects which we observed most probably reflected the direct vasodilatory activities of changing kinin concentrations in the circulation. The lack of an effect by SQ 14 225 on the resting mean arterial pressure of conscious sham-operated rats, in contrast to the response in anaesthetized rats, seems at variance with the above conclusions. However, kininase II is but one of two major enzymes which metabolize kinins and, at least in plasma, it has been shown to represent only approximately 10% of the kininase activity (Zacest, Oparil & Talamo, 1974). It appears, therefore, that the vasopressor effect of kallikrein inhibition, and presumably inhibition of kinin generation, may be indicative of participation by the kallikrein–kinin system in the homeostatic regulation of normal blood pressure.

The enhanced vasodepressor response to kininase II inhibition in the benignly hypertensive rats suggests the possibility that the kallikrein–kinin system may play an important antihypertensive role in this form of hypertension. The mechanism for the enhancement is unclear. There may have been a decrease in kininase I activity. This possibility is consistent with that suggested by Williams & Hollenberg (1977) to explain their observation that kininase II inhibition increased the plasma bradykinin concentration of patients with essential hypertension only, without any effect in normal subjects. The absence of an enhanced pressor response to kallikrein inhibition in the benignly hypertensive rats, however, does not support the suggestion that an activation of the kallikrein–kinin system might have occurred.

Renal kallikrein excretion (Keiser et al., 1976a) and kinin release into renal venous blood (Hulthén, Lecerf & Hökfelt, 1977) have been shown to vary directly with renal blood flow. It would be reasonable to speculate that an increase in renal perfusion pressure as well as an existing state of hyperangiotensinaemia in unilateral renal artery stenotic disease might result in a compensatory activation of the kallikrein–kinin system in the contralateral kidney, since there is evidence that angiotensin II stimulates the kallikrein–kinin system (Levinsky, 1979). An increase (Johnston, Matthews & Dax, 1976), as well as a decrease (Keiser et al., 1976a), in kallikrein excretion, as an index of renal kallikrein–kinin activity (Levinsky, 1979), have been reported in two-kidney, one-clip Goldblatt hypertensive rats. In view of the disparate effects of SQ 14 225 and aprotinin in the benign and malignant hypertensive rats, the reported inconsistencies in kallikrein excretion may be related to the phases of hypertension. The lack of any blood pressure response to either kininase II or kallikrein inhibition in the malignant hypertensive rats suggests an impaired kallikrein–kinin system in this condition. Renal parenchymal damage is associated with a reduced kallikrein excretion (Mitas, Levy, Holle, Frigon & Stone, 1978) and may be the cause of the non-responsiveness to SQ 14 225 and aprotinin which we observed in the malignantly hypertensive rats. Although Muirhead, Brooks & Arora (1974) reported that prolonged treatment with another kininase II inhibitor (SQ 20 881) prevented the development of malignant one-kidney, one-clip Goldblatt hypertension in the rabbit, it remains an enigma whether an impaired renal kallikrein–kinin system is primary or secondary to the development of malignant hypertension.

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References


