Angiotensin II blockade in normal subjects and essential hypertensive patients

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Summary

1. Saralasin (Sar\(^1\)-Ala\(^8\)-angiotensin II), a competitive inhibitor of angiotensin II (AII), has been infused into normal subjects and patients with essential hypertension when deprived of sodium by 5 days of a 10 mmol/day sodium diet.

2. When saralasin was given by an incremental rate of infusion starting at 0.25 μg min\(^{-1}\) kg\(^{-1}\), sodium-deprived normal subjects showed a fall in standing blood pressure with no change in lying blood pressure, sodium-deprived normal-renin hypertensive patients showed no change in lying or standing blood pressure and sodium-deprived low-renin patients showed a significant sustained rise in lying and standing blood pressure.

3. These findings suggest that: (a) standing blood pressure in sodium-deprived normal subjects is angiotensin II dependent; (b) normal-renin hypertensive patients when sodium deprived by diet alone do not appear to be angiotensin II dependent (angiotensin II is unlikely therefore to be directly maintaining their blood pressure on their normal sodium intake); (c) the rise in blood pressure seen in low-renin hypertensive patients with saralasin may be a further way of distinguishing this group of patients.

Key words: angiotensin II, hypertension, saralasin, sodium.

Introduction

The importance of the renin-angiotensin system in essential hypertension is controversial. A competitive inhibitor of angiotensin II, Sar\(^1\)-Ala\(^8\)-angiotensin II (saralasin, P113), has been shown to lower the blood pressure in hypertensive patients in whom angiotensin II was causing the raised blood pressure (Brunner, Gavras, Laragh & Keenan, 1973; Streeten, Anderson, Freiberg & Dalakos, 1975). When the endogenous level of angiotensin II is low, however, saralasin has agonist effects (Mimran, Hinrichs & Hollenberg, 1974; Anderson, Freiberg, Dalakos & Streeten, 1975). In this study we have looked at the effect of saralasin infusion in normotensive volunteer subjects and patients with essential hypertension first when sodium loaded and then when sodium deprived.

Methods

Three normotensive males and twenty-five patients with essential hypertension agreed to take part in the study, the purpose of which was fully explained to them. The patients were referred from the local area of the hospital, and were shown to have, on routine investigation, no underlying cause for their high blood pressure. They had normal renal function and the patients all had a sitting diastolic pressure of greater than 95 mmHg over a 3 weeks’ observation period. Angiotensin II (sitting upright), plasma renin activity (sitting upright), 24 h urinary sodium excretion and blood pressure were measured in all subjects on their normal diet, on the fifth day of a high sodium intake (200 mmol/day + normal diet) and on the fifth day of a low sodium diet (10 mmol/day). In the first eight patients and three normal subjects, saralasin was infused on the fifth day of the high sodium intake and on the fifth day of the low sodium diet, at an infusion rate of 5 μg min\(^{-1}\) kg\(^{-1}\) for 30 min, and 10 μg min\(^{-1}\) kg\(^{-1}\) for 60 min. These three
normal subjects and eight patients had a water diuresis induced with 5% glucose solution (MacGregor & Dawes, 1976) so that measurements of urine flow and sodium excretion could be made. Subsequently the same three normal subjects and a further seventeen patients were infused with saralasin on the fifth day of the low sodium diet only, an incremental rate of infusion being used: normal, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0 \( \mu g \) min\(^{-1} \) kg\(^{-1} \); hypertensive, 0.25, 1.25, 5.0, 10 \( \mu g \) min\(^{-1} \) kg\(^{-1} \). Each infusion rate was given for 15 min. The infusion pump (Harvard) speed was kept constant at 0.76 ml/min throughout the infusion and different dilutions of saralasin with 5% glucose solution were used for the different infusion rates. The three normal subjects, but not the seventeen hypertensive patients, had a water diuresis induced with 5% glucose solution. Blood pressure was measured with an Arteriosonde every 30 s to 2 min for 1 h before infusion, during infusion and for 1 h after infusion. Standing blood pressure was measured every 15 min after standing upright for 1 min and repeated four or five times at 1 min intervals. PRA\(^{(1)}\) (sitting upright) was measured again just before the infusion of saralasin was stopped. Plasma angiotensin II was measured by the method of D"usterdieck & McElwee (1971) and PRA was measured by radio-immunoassay of angiotensin I generated during plasma incubation for 60 min at 37°C and pH 6.0.

Results

Effect of infusion of saralasin (5-10 \( \mu g \) min\(^{-1} \) kg\(^{-1} \))

On the fifth day of the high sodium intake, mean AII and PRA were suppressed, in the three normal subjects 15.5 pmol/l and 0.30 ng h\(^{-1} \) ml\(^{-1} \) respectively, and in the eight hypertensive patients 12.7 pmol/ml and 0.34 ng h\(^{-1} \) ml\(^{-1} \) respectively. Saralasin infusion (5-10 \( \mu g \) min\(^{-1} \) kg\(^{-1} \)) caused a transient rise in blood pressure lasting 3-5 min in both the normal and hypertensive subjects. The hypertensive but not the normal subjects showed a significant sustained rise in blood pressure during the infusion (average rise in mean lying pressure = 6 mmHg SEM 1.2, \( P < 0.01 \)). Urine flow and sodium excretion fell in the normal subjects during saralasin infusion from a mean of 11.4 ml/min and 390 \( \mu g \) mol/min before to a mean of 6.6 ml/min and 108 \( \mu g \) mol/min during saralasin. All eight hypertensive patients showed decreases in urine flow and sodium excretion similar to the normal subjects.

On the fifth day of the low sodium diet mean PRA had risen in the three normal subjects to 3.96 ng h\(^{-1} \) ml\(^{-1} \) and in the eight hypertensive patients mean AII and PRA had risen to 31.0 pmol/l and 3.35 ng h\(^{-1} \) ml\(^{-1} \) respectively. Saralasin infusion (5-10 \( \mu g \) min\(^{-1} \) kg\(^{-1} \)) at this time caused no fall in lying or standing blood pressure in either the three normal or the eight hypertensive subjects. In all eight hypertensive patients, but not the normal subjects, there was a transient rise in blood pressure lasting 3-5 min on starting the saralasin, and a sustained rise in the four patients who had values of PRA and angiotensin II below our normal sodium-deprived range (established in twenty-five normotensive control subjects). The four other patients all had values of PRA and angiotensin II within the normal sodium-deprived range.

Effect of incremental infusion of saralasin (0.25-10 \( \mu g \) min\(^{-1} \) kg\(^{-1} \))

When the same three normal subjects were sodium deprived on a separate occasion mean angiotensin II and PRA values rose to 44.3 pmol/l and 2.80 ng h\(^{-1} \) ml\(^{-1} \) respectively. Saralasin infused incrementally (0.25-10 \( \mu g \) min\(^{-1} \) kg\(^{-1} \)) caused a fall in standing blood pressure but no change in the lying pressure (Fig. 1). Mean PRA increased during infusion to 5.33 ng h\(^{-1} \) ml\(^{-1} \).

Eighteen hypertensive patients have been infused with the incremental infusion of saralasin on the fifth day of the low sodium diet. In none of the patients studied was there a fall in either lying or standing blood pressure. The hypertensive patients were divided into two groups: seven 'normal-renin', who had values of AII and PRA with sodium deprivation below our normal sodium-deprived range, and eleven 'low-renin', who had values of AII and PRA with sodium deprivation below the normal range. The eleven 'low-renin' patients had a significant sustained increase in blood pressure with the incremental infusion and a significant fall in PRA during infusion (Fig. 1). The seven 'normal-renin' patients individually showed no change in blood pressure and there was no significant change in the group as a whole (Fig. 1). Mean PRA rose in these seven 'normal-renin' patients during saralasin in spite of the fact that blood pressure had not changed.

\(^{(1)}\) Abbreviations: PRA, plasma renin activity; AII, angiotensin II.
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(Fig. 1), but the change was not significant. The weight loss with sodium deprivation, urinary sodium excretion on the fifth day of low sodium diet, and age were not significantly different in the two groups of hypertensive patients. There were six negroes in the low-renin group and none in the normal group. None of the patients studied had values of PRA or AII above our normal range on the high sodium intake, normal diet or low sodium diet.

Discussion

Saralasin infused incrementally into sodium-deprived normal subjects caused a reduction in standing blood pressure with no effect on lying blood pressure. These results are in agreement with Haber, Sancho, Re, Burton & Barger (1975), who used a converting enzyme inhibitor. Angiotensin II is therefore directly maintaining upright but not lying blood pressure in young sodium-deprived normal subjects. The fall in standing blood pressure occurred with saralasin only when it was infused incrementally. This may be related to the agonist effect that saralasin can have (Mimran et al., 1974; Anderson et al., 1975).

The agonist action of saralasin was most clearly seen in the reduction of urine flow and sodium excretion that occurred in the normal and hyper-
tensive subjects when endogenous levels of angio-
tensin II had been suppressed by sodium loading. In the sodium-loaded hypertensive group there was also a sustained rise in blood pressure. This presumed agonist effect on the blood pressure was also present in low-renin hypertensive patients even when sodium deprived and infused incrementally. This might be a further method of distinguishing low-renin hypertensive from other hypertensive patients.

None of the hypertensive patients when sodium deprived showed a fall in lying or standing blood pressure with saralasin infusion, even though, in some of them, angiotensin II and PRA had increased into the same range as that of the normal subjects. It appears therefore that angiotensin II is not directly maintaining blood pressure in these patients when sodium deprived, and is very unlikely to be playing any direct role in maintaining their blood pressure on their normal sodium intake.

References


