SHORT COMMUNICATION

INCREASE OF PLASMA RENIN-SUBSTRATE CONCENTRATION AFTER INFUSION OF ANGIOTENSIN IN THE RAT

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SUMMARY

1. Compared with sixteen control animals infused with saline, plasma renin-substrate concentration increased twofold \( (P<0.001) \) in twenty-two rats following infusion of angiotensin II at a mean rate of 191 ng kg\(^{-1}\) min\(^{-1}\) for 13 h.

2. The change was not attributable to an overall increase of plasma protein concentration.

Key words: plasma renin-substrate, angiotensin.

Although a variety of stimuli lead to large changes in the plasma concentration of renin-substrate, the mechanisms involved are not fully understood (see Helmer & Judson, 1967; Carretero & Gross, 1967a, b; Bing & Poulsen, 1969). Increased plasma renin-substrate concentration (PRSC) is sometimes found in renal hypertension (Helmer & Judson, 1963; Gould, Skeggs & Kahn, 1966), and in a recently reported case, plasma concentrations of angiotensin II and renin-substrate increased and decreased in parallel as the condition advanced and regressed (Brown, Düsterdieck, Fraser, Lever, Robertson, Tree & Weir, 1971).

The experiments reported here were undertaken because this observation raised the possibility that angiotensin might stimulate the production or release of renin-substrate. Measurements of PRSC were made in rats before and after infusion of angiotensin II.

METHODS

Male Wistar rats (235–300 g) were anaesthetized with diethyl ether and a blood sample (1 ml) was taken from the femoral vein into a syringe previously flushed with 0·1 m-EDTA. A polyethylene catheter (internal diam. 0·5 mm) was inserted into the jugular vein and brought to the surface at the back of the neck. On recovery from anaesthesia the animals were studied in two groups.

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Twenty-two rats were infused intravenously with [Val\textsuperscript{15}]-angiotensin II (CIBA) in 0.15 M-NaCl at a constant rate of 0.12 ml/h for 13 h. Allowing for differences of weight, the rate of angiotensin infusion varied between 167 and 221 (mean 191) ng kg\textsuperscript{-1} min\textsuperscript{-1}. On stopping the infusion the rats were anaesthetized again and a second blood sample was taken from the opposite femoral vein. A further sixteen rats made up a control group; these were studied in the same way and at the same time, the only difference being that 0.15 M-NaCl without angiotensin II was infused.
Plasma renin-substrate after angiotensin

Measurements of plasma renin-substrate concentration (Carretero & Gross, 1967b), packed cell volume (Hawksley) and plasma protein concentration (Autotechnicon) were made on the samples of femoral venous blood. The substrate method was modified slightly in that aliquots were taken from the incubation mixture at 15 and 120 min to show that a plateau of angiotensin concentration had been reached. Forty of the plasma samples were incubated and assayed in duplicate by independent observers. The duplicate measurements of PRSC had a coefficient of variation of 6.7%.

RESULTS

Plasma renin-substrate concentration rose by an average of 27% in control and 124% in experimental animals infused with angiotensin (Fig. 1). The difference was highly significant (Mann-Whitney U-Test, $R_1 = 164$, $R_2 = 573$, $P<0.001$).

Packed cell volume increased slightly in animals infused with angiotensin and decreased slightly in saline-infused controls (Fig. 1). Although the changes in each group were not significant at the 5% level a significant difference between groups developed after infusion ($t = 2.50$, $P<0.02$). Changes of plasma protein concentration were comparable in the two groups (Fig. 1).

DISCUSSION

Plasma renin-substrate concentration increased slightly in control animals infused with saline. This could have resulted from previous anaesthesia and surgery (see Romero, Lazar & Hoobler, 1970). As compared with the control group, there was a significantly greater increase of PRSC after infusion of angiotensin. Because angiotensin causes haemoconcentration (Cuthbert & Peart, 1970) increased PRSC could be a manifestation of an overall increase of plasma protein concentration. This possibility is excluded by the measurements of plasma protein concentration.

Other explanations for the rise of PRSC include increased synthesis or release of substrate and a decrease in its rate of clearance. Further experiments are needed to distinguish these possibilities. On theoretical grounds it is likely that decreased clearance or consumption of renin-substrate will contribute to the effect: substrate is consumed by renin in vivo and the decrease of circulating renin that occurs after infusion of angiotensin (Vander & Geelhoed, 1965) is likely to raise PRSC provided substrate production remains constant. Although contributory, this is unlikely to be the whole explanation since infusion of renin in a small amount (which presumably raises plasma levels of renin and angiotensin together) also increases PRSC in the rat (Carretero & Gross, 1967b). The increase of substrate concentration with angiotensin may not be a direct consequence of the peptide; indirect effects resulting from increased blood pressure or from altered corticosteroid production could equally well be responsible.

Though high, the rate of angiotensin infusion was within the range used to demonstrate other pharmacological effects of the peptide in the rat (Barraclough, 1965; Peters, 1965; Cuthbert & Peart, 1970). The relevance of these and other experiments on angiotensin to physiological and even pathological effects of the endogenous peptide has yet to be agreed. Similar reservations apply to the results reported here. Angiotensin is unlikely to be an over-
riding stimulus to substrate, since concentration of renin (and probably angiotensin) change in an opposite direction to PRSC after bilateral nephrectomy (see Bing & Poulsen, 1969), sodium deprivation (Carretero & Gross, 1967b; Rosset & Veyrat, 1971) and adrenocortical deficiency (Helmer & Griffith, 1951; Carretero & Gross, 1967b; Brown, Fraser, Lever Robertson, James, McCusker & Wynn, 1968; Tree, 1972).

As noted above, Carretero & Gross (1967b) found an increase of PRSC after injection of small amounts of renin. If the effect was due to the angiotensin formed, it would be consistent with the present observations. Injection of larger amounts of renin, by contrast, tend to decrease PRSC, particularly after bilateral nephrectomy (Carretero & Gross, 1967b). As the authors suggest this probably represents consumption of substrate by renin.

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REFERENCES


