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THE EFFECT OF ANGIOTENSIN II INFUSION ON PLASMA CORTICOSTEROID CONCENTRATIONS IN NORMAL MAN

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SUMMARY

Angiotensin II infusion at graded rates into sodium replete, normal male subjects caused marked increases in the plasma concentrations of 18-hydroxycorticosterone and aldosterone. The magnitude of the increase was similar for each compound and plasma concentrations correlated closely with concurrent plasma angiotensin II concentration. No clear evidence of changes in the plasma concentrations of the other aldosterone precursors, DOC and corticosterone, was obtained and levels of cortisol, 11-deoxycortisol and 18-hydroxy-DOC were unaffected by angiotensin II infusion.

INTRODUCTION

Aldosterone is synthesised in the adrenal zona glomerulosa by a pathway which includes 11-deoxycorticosterone (DOC), corticosterone and 18-hydroxycorticosterone [1]. DOC and corticosterone are also synthesised in the zona fasciculata, which is the main source of 18-hydroxy-DOC, 11-deoxycortisol and cortisol (Fig. 1). Sodium depletion raises the plasma concentrations of 18-hydroxycorticosterone [2, 3] and aldosterone significantly in normal subjects, but has little effect on the circulating levels of other corticosteroids [e.g. 4, 5]. The response of aldosterone to sodium depletion is thought to be secondary to the increase in plasma angiotensin II concentration which also occurs at this time. Exogenous angiotensin II does indeed increase plasma aldosterone levels [6, 7].

Previous studies of the locus of action of angiotensin II in the biosynthesis of aldosterone have led to the conclusion that the octapeptide, like ACTH [8], acts early in the pathway [1]. Recently it has become possible to measure the concentrations of all the major corticosteroids in human peripheral plasma by means of gas–liquid chromatography [2, 9–11]. This study describes an attempt to locate the effect of angiotensin II on adrenocortical biosynthesis by comparing the changes in plasma concentration of each corticosteroid mentioned above using these new techniques.

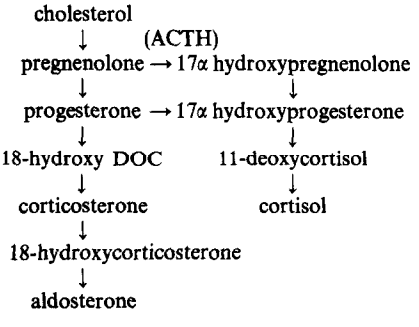

Fig. 1. Biosynthesis of corticosteroids.

SUBJECTS AND METHODS

Seven normal male volunteers aged between 24 and 39 years took a controlled diet for three days. Sodium content was adjusted to the taste of the individual and varied between subjects from 145 to 200 mEq/day. Potassium was also fixed for each subject, varying from 71 to 108 mEq/day between subjects.

All experiments commenced between 08.00 and 09.00 h with the subject recumbent and fasting. Intravenous infusions of 1-Asp NH_2-5-Val angiotensin II in 5% dextrose were given at rates of 0, 2, 4 and 8 ng/kg/min by means of a motor-driven syringe, each rate being continued for 1 h as previously described [7]. Blood samples for the estimation of plasma angiotensin II [12] and corticosteroid [3, 9–11] concentrations were taken from a vein in the opposite arm by means of an indwelling plastic cannula, just before the end of each infusion period. Plasma and urine electrolytes were measured by flame photometry.

RESULTS

The mean urine excretion of sodium and potassium for the 24 h prior to the infusion was 138.5 ± 58.7 (SD) and 73.8 ± 35.6 mEq respectively. Plasma sodium and potassium concentrations at the beginning of the infusion were 139.2 ± 2.6 (SD) and 4.2 ± 0.2 mEq/l respectively. The relationships between the plasma concentrations of each corticosteroid and their concurrent plasma angiotensin II

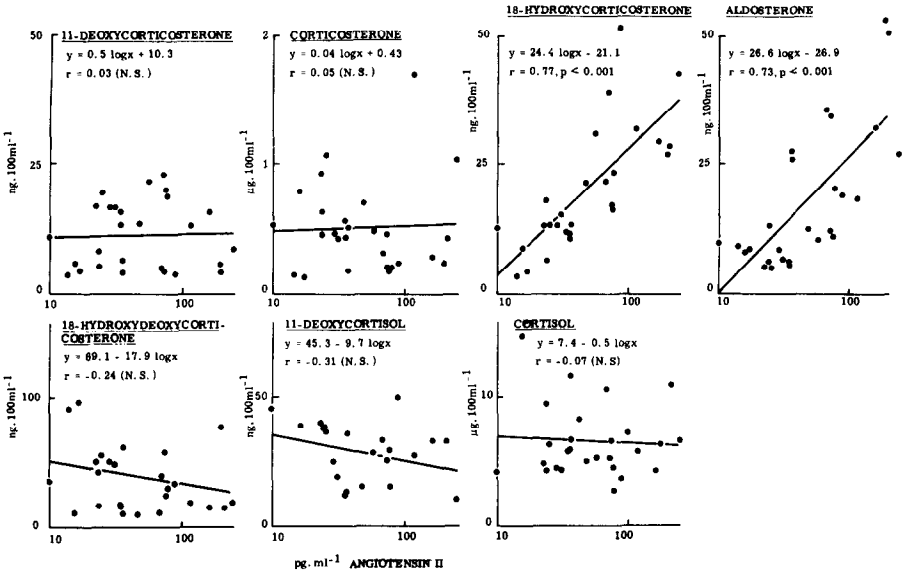

Fig. 2. Relationships between the plasma concentrations of angiotensin II and individual corticosteroids. The lines are linear regressions.

levels are shown in Fig. 2. Angiotensin II infusion markedly raised the concentrations of both 18-hydroxycorticosterone and aldosterone. Correlation coefficients were positive and highly significant in both cases. Correlation coefficients for the relationship between plasma angiotensin II concentration and the remaining corticosteroids failed to reach statistical significance ($P < 0.05$).

DISCUSSION

Although plasma corticosterone and cortisol concentrations may respond to high rate angiotensin II infusion in the dog [13, 14] there is no evidence of a similar effect in man [6]. Plasma DOC [4, 15], adrenal vein 18-hydroxy-DOC [5] and plasma 11-deoxycortisol [16] are likewise unaffected. In the current studies, the relationships between the peripheral plasma concentrations of cortisol, 11-deoxycortisol and 18-hydroxy-DOC and concurrent angiotensin II concentrations were all inverse but did not achieve statistical significance ($P < 0.05$). The secretion of these corticosteroids is ACTH dependent and plasma levels would be expected to fall across the period of the experiment due to the normal diurnal pattern of ACTH release. However, the possibility of inhibition of ACTH release by angiotensin II infusion [17] cannot be excluded.

There was a direct but again insignificant correlation between plasma angiotensin II and DOC or corticosterone levels. In addition to synthesis in the zona fasciculata, the zona glomerulosa contributes a significant but relatively small proportion of the total secretion [18]. It is possible that some stimulation of this latter component, which may show very small responses to sodium depletion [18], may have occurred but was either technically undetectable or alternatively partially compensated by a fall in the zona fasciculata contribution due to suppression of ACTH secretion via negative feedback action on the anterior pituitary.

There was a positive and highly significant relationship between plasma angiotensin II and plasma aldosterone concentration which confirms previous experience [7, 19, 20]. The effects of angiotensin II on aldosterone secretion have recently been reviewed [21] and there seems little doubt that the peptide is a major controlling factor in man. The effect of angiotensin II infusion on plasma 18-hydroxycorticosterone, not previously studied in man, was also positive and highly significant. The regression for steroid on log. plasma angiotensin II concentration was parallel to that for aldosterone on angiotensin II (Fig. 2), the ranges of concentration for the two corticosteroids being similar. Although not direct evidence, this is compatible with the conclusion that the angiotensin II-mediated increases in 18-hydroxycorticosterone and aldosterone are respectively cause and effect.

Thus, of the steroid precursors of aldosterone, only the plasma concentration of the immediate precursor, 18-hydroxycorticosterone, increases significantly. This information may throw some light on the locus of action of angiotensin II in the zona glomerulosa only if secretion, and therefore plasma concentration, is in direct proportion to adrenal tissue steroid concentrations. If this is indeed the case, the results indicate that at least one point of action is prior to the 18-hydroxylation reaction (Fig. 1). However, the exact point between cholesterol and 18-hydroxycorticosterone cannot be established with certainty. In multienzyme biosynthetic pathways, substrate concentrations of enzyme catalysed reactions distal to the locus of stimulation, providing that the reactions are not rate limiting, need not necessarily increase. Thus, failure

to demonstrate clear increases in DOC and corticosterone concentrations does not exclude the possibility that stimulation occurs prior to 21-hydroxylation as has previously been suggested [1]. However, the marked increase in 18-hydroxycorticosterone levels may indicate that the final conversion to aldosterone is rate limiting and may require a different stimulus such as, for example, changes in potassium status [1, 23]. It would also seem probable that the rise in 18-hydroxycorticosterone secretion rate [22] and plasma concentration [2, 3] following sodium depletion is secondary to the rise in angiotensin II concentration seen in this situation.

REFERENCES

1. Müller J.: *Regulation of Aldosterone Biosynthesis.* Springer-Verlag, Berlin (1971).
2. Wilson A., Mason P. A. and Fraser R.: *J. Endocr.* **68** (1976) 24–25.
3. Mason P. A., Fraser R., Morton J. J., Semple P. F. and Wilson A.: submitted for publication.
4. Brown R. D. and Strott C. A.: *J. clin. Endocr. Metab.* **32** (1971) 744–750.
5. Melby J. C., Dale S. L., Grekin R. J., Gaunt R. and Wilson T. E.: *Recent Prog. Horm. Res.* **28** (1972) 287–339.
6. Fraser R., James V. H. T., Brown J. J., Isaac P., Lever A. F. and Robertson J. I. S.: *Lancet* **2** (1965) 989–991.
7. Oelkers W., Brown J. J., Fraser R., Lever A. F., Morton J. J. and Robertson J. I. S.: *Circ. Res.* **34** (1974) 69–77.
8. Stone D. and Hechter O.: *Archs Biochem. Biophys.* **51** (1954) 457–469.
9. Wilson A., Mason P. A. and Fraser R.: *J. steroid Biochem.* **7** (1976) 611–613.
10. Wilson A. and Fraser R.: *J. Endocr.* **51** (1971) 557–567.
11. Mason P. A. and Fraser R.: *J. Endocr.* **64** (1975) 277–288.
12. Düsterdieck G. and McElwee G.: *Eur. J. clin. Invest.* **2** (1971) 32–38.
13. Slater J. D. H., Barbour B. H., Henderson H. H., Caspar A. G. T. and Bartter F. C.: *Clin. Sci.* **28** (1965) 219–236.
14. Ganong W. F., Biglieri E. G. and Mulrow P. J.: *Recent Prog. Horm. Res.* **22** (1966) 381–429.
15. Wilson A.: Ph.D. Thesis: University of Glasgow (1973).
16. Brown R. D., Strott C. A. and Liddle G. W.: *J. clin. Invest.* **51** (1972) 1413–1418.
17. Rayyis S. S. and Horton R.: *J. clin. Endocr. Metab.* **32** (1971) 539–546.
18. Tan S. Y. and Mulrow P. J.: *J. clin. Endocr. Metab.* **41** (1975) 126–130.
19. Oelkers W. O., Schöneshöfer M., Schulze G., Brown J. J., Fraser R., Morton J. J., Lever A. F. and Robertson J. I. S.: *Circ. Res.* **36, 37,** suppl. I (1975) 49–56.
20. Hollenberg N. K., Chenitz W. R., Adams D. F. and Williams G. H.: *J. clin. Invest.* **54** (1974) 34–42.
21. Brown J. J., Fraser R., Lever A. F., Morton J. J. and Robertson J. I. S.: *Textbook of Hypertension.* (Edited by J. Genest, E. Koiw and O. Küchel) Montreal. McGraw Hill, in press.
22. Ulick S., Nicholis G. L. and Vetter K. K.: *Aldosterone, a Symposium* (Edited by E. E. Baulieu and P. Robel). Blackwell, Oxford (1964) pp. 3–17.
23. Hollenberg N. K., Williams G., Burger B. and Hooshmand I.: *Clin. Sci. Mol. Med.* **49** (1975) 527–534.