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18-HYDROXY-11-DEOXYCORTICOSTERONE RESPONSE TO INSULIN IN NORMAL MAN

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SUMMARY

The response of 18-hydroxy-11-deoxycorticosterone (18-OH-DOC) to insulin induced hypoglycemia has been studied in eight normal volunteers.

Following insulin, a marked increase was observed in 18-OH-DOC which was more significant and rapid than plasma corticosteroids but disappeared earlier. The good correlation between 18-OH-DOC and the plasma corticosteroids pattern during hypoglycemia further demonstrated the ACTH dependence of this compound which appears to be highly sensitive to stress.

INTRODUCTION

The enhancement of mineralocorticoids other than aldosterone, such as 11-deoxycorticosterone (DOC) and 18-hydroxy-11-deoxycorticosterone (18-OH-DOC), following stress or other stimuli has recently being hypothesized as a cause of arterial hypertension [1]. Taking into account the significant increase of plasma corticosteroids after insulin administration (2–4) and the correlation between these and 18-OH-DOC [5], an ACTH-dependent steroid product of the zona fasciculata of the adrenal cortex, investigations were carried out to study the response of 18-OH-DOC to hypoglycemic stress induced by insulin.

MATERIALS AND METHODS

Eight normal male volunteers, aged between 20 and 25 years, were studied. Insulin tolerance test was performed by injecting i.v. 0.1 U of regular insulin per kg of body weight, between 0080 and 0090. Blood samples were collected before and 30, 45, 60 and 90 min after the injection.

18-OH-DOC was evaluated by the radioimmunoassay method of Sulon and Sparano[6]. Normal values are 6–15 ng/dl. Plasma corticosteroids were determined by the competitive protein binding technique of Murphy[7] (normal values are 6–18 ng/dl) which measures cortisol, corticosterone and 11-deoxycortisol.

Human growth hormone (hGH) was assayed by a radioimmunoassay method [8] (normal values are 0.5–5 μU/ml).

RESULTS AND DISCUSSION

Following insulin injection a rapid fall in plasma glucose to minimal values of 40–50 mg/dl at either 30 or 45 min was recorded in all cases. The response of 18-OH-DOC, plasma corticosteroids and hGH to insulin is given in Fig. 1.

In basal conditions plasma 18-OH-DOC (mean ± S.E.) is 8.3 ± 2.3 ng/dl, reaching values of 22.1 ± 6.3 ($P = 0.025$), 38.2 ± 6.5 ($P < 0.0005$), 40.4 ± 7.7 ($P < 0.0025$), 30, 45 and 60 min, respectively, after insulin administration, decreasing to 11.4 ± 2.7 at 90 min.

Maximum values (ng/dl) of 18-OH-DOC after insulin are: 31 at 45 min in case 1; 44.1 at 45 min in case 2; 28.9 at 60 min in case 3; 38.8 at 60 min in case 4; 34.9 at 60 min in case 5; 21.8 at 45 min in

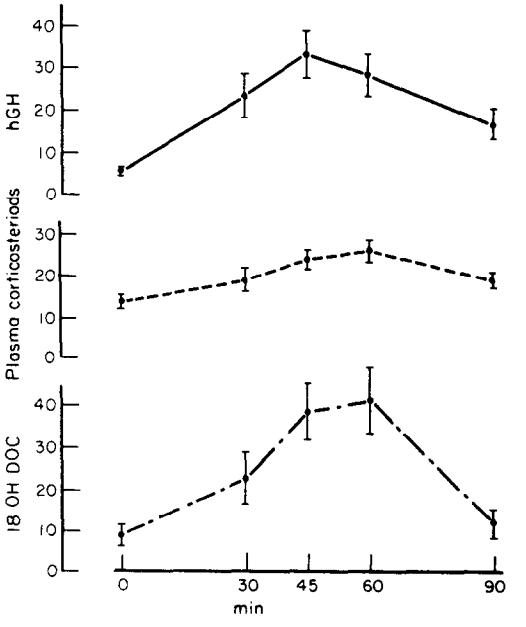

Fig. 1. 18-OH-DOC (ng/dl), plasma corticosteroids (μg/dl), and hGH (μU/ml) mean (±S.E.) values in eight normal subjects, before and after 30, 45, 60 and 90 min of insulin administration (0.1 IU/kg of body weight).

Table 1. Individual correlation coefficients (r) with P values between plasma corticosteroids and hGH, plasma corticosteroids and 18-OH-DOC, and hGH and 18-OH-DOC.

Cases:		1	2	3	4	5	6	7	8
Plasma corticosteroids -hGH	r	0.746	0.780	0.810	0.777	0.319	0.556	0.760	0.892
	P	<0.01	<0.01	<0.01	<0.01	>0.1	<0.1	<0.01	<0.001
Plasma corticosteroids -18-OH-DOC	r	0.942	0.976	0.578	0.511	0.956	0.963	0.815	0.876
	P	<0.001	<0.001	<0.05	=0.1	<0.001	<0.001	<0.01	<0.001
hGH-18-OH-DOC	r	0.854	0.832	0.747	0.879	0.054	0.490	0.953	0.998
	P	=0.001	=0.001	<0.01	<0.001	>0.1	>0.1	=0.001	<0.001

case 6; 52.9 at 30 min in case 7 and 88.2 at 60 min in case 8.

Similarly, plasma corticosteroids which, in basal conditions, present values (μg/dl $\pm$ S.E.) of 12.3 $\pm$ 1.4 increase to 17.6 $\pm$ 2.6 ($P < 0.05$), 22.3 $\pm$ 2.1 ($P = 0.0025$) and to 24.5 $\pm$ 2.2 ($P = 0.0005$) at 30, 45 and 60 min, respectively, after insulin administration. After 90 min plasma corticosteroids decrease to 17.5 $\pm$ 1.5 ($P = 0.01$).

Finally, the basal levels of hGH (μU/ml $\pm$ S.E.) are 4.9 $\pm$ 1.0, reaching concentrations of 22.3 $\pm$ 4.9 ($P < 0.0025$), 31.8 $\pm$ 5.4 ($P < 0.0005$) 26.9 $\pm$ 5.1 ($P < 0.0005$) and 15.1 $\pm$ 3.5 ($P < 0.01$) at 30, 45, 60 and 90 min, respectively, after insulin injection.

Correlation coefficients with P values of 0.001 were obtained between 18-OH-DOC and plasma corticosteroids ($r = 0.3447$) and between hGH and 18-OH-DOC ($r = 3604$), whereas between hGH and plasma-corticosteroids ($r = 2108$) P values of 0.05 were obtained. When these three parameters are compared in each single subject a good correlation is observed in all cases between 18-OH-DOC and plasma corticosteroids with the exception of case 4. Similarly, 18-OH-DOC and hGH, and plasma corticosteroids and hGH are well correlated, with the exception of cases 5 and 6 (Table 1).

These data further confirm the ACTH-dependence of 18-OH-DOC [9–12] since the insulin induced hypoglycemia is responsible for corticotropin release [4, 13]. Previous findings have in fact demonstrated a 20-fold or even greater increase in 18-OH-DOC after corticotropin administration [9–12] and a synchronous pulsatile activity between 18-OH-DOC and F during a 24 h study period [5].

Moreover, the present results show that the increase in 18-OH-DOC is more significant and rapid than plasma corticosteroids, disappearing at 90 min, whereas plasma corticosteroids levels remain more elevated.

In fact the slope of the calculated linear regression curves for 18-OH-DOC and plasma corticosteroids (where x = minutes and y = plasma steroid concentrations) are 0.5736 and 0.2108, respectively, from 0 to 60 min and -0.6484 and -0.1280, respectively, from 45 to 90 min.

Similarly, a more marked increase in 18-OH-DOC with respect to plasma cortisol and aldosterone has recently been observed [12] during ACTH administration at increasing infusion rate.

In conclusion, it is evident that 18-OH-DOC is controlled by the pituitary corticotropin and is highly sensitive to exogenous stimuli inducing ACTH-hypersecretion such as hypoglycemia. Intermittent elevations of this and/or other minor mineralocorticoids in these conditions could be, in our opinion, of some importance, if we consider the possible role of the minor mineralocorticoids in the pathogenesis of essential hypertension, as suggested by Fraser *et al.*[1].

It remains to be established whether, and to what extent, hGH is capable of enhancing 18-OH-DOC following insulin induced hypoglycemia.

REFERENCES

1. Fraser R., Brown J. J., Brown W. C., Ferriss J. B., Kennedy A., Lever A. F., Mason P. A., Morton J. J., Nicholls M. G., Ramsay L. E., Robertson J. I. S., Schelekamp M. A. D. and Wilson A.: The adrenal cortex and hypertension: some observations on a possible role for mineralocorticoids other than aldosterone. *J. steroid Biochem.* **7** (1976) 963–970.
2. Landon J., Wynn V. and James V. H. T.: The adrenocortical response to insulin-induced hypoglycemia. *J. Endocr.* **27** (1963) 183–190.
3. Greenwood F. C., Landon J. and Stamp T. C. B.: The plasma sugar, free fatty acid, cortisol and growth hormone response to insulin. I. The control subjects. *J. clin. Invest.* **45** (1966) 429–436.
4. Demura R., Demura H., Nunokawa T., Baba H. and Mivra K.: Response of plasma ACTH, GH, LH and 11-hydroxycorticosteroids to various stimuli in patients with Cushing's syndrome. *J. clin. Endocr. Metab.* **34** (1972) 852–859.
5. Sulon J., Sparano F., Sciarra F., Giaquinto G. and Genard P.: 24 h pattern of 18-hydroxy-11-deoxycorticosterone in normal supine men, relationship with cortisol and aldosterone. *Clin. Endocr.* **8** (1978), 367–372.
6. Sulon J. and Sparano F.: A non-chromatographic radioimmunoassay of 18-hydroxy-11-deoxycorticosterone in human plasma. *J. steroid Biochem.* **9** (1978) 253–256.
7. Murphy B. E.: Some studies on the protein binding of steroids and their application to the routine micro-ultra-micro-measurements of various steroids in body fluids by competitive protein binding radioassay. *J. clin. Endocr. Metab.* **27** (1967) 973–990.
8. Molinatti G. M., Massara F., Pennisi F., Scassellati G. A., Strumia E. and Vancheri L.: Radioimmunoassay of growth hormone. *J. nucl. Biol. Med.* **13** (1969) 26–36.

9. Melby J. C., Dale S. L., Grekin R. J., Gaunt R. and Wilson T. E.: 18-hydroxy-11-deoxycorticosterone (18-OH-DOC) secretion in experimental and human hypertension. *Recent Prog. Horm. Res.* **28** (1972) 287–351.
10. Williams G. M., Braley L. M. and Underwood R. H.: The regulation of plasma 18-hydroxy-11-deoxycorticosterone in man. *J. clin. Invest.* **58** (1976) 221–229.
11. Dale S. L., Komanicky P., Pratt J. M. and Melby J. C.: Radioimmunoassay of 18-hydroxy-11-deoxycorticosterone in plasma. *J. clin. Endocr. Metab.* **43** (1976) 803–809.
12. Tuck M. L., Chandler D. W. and Mayes D. M.: The influences of ACTH, dietary sodium, upright posture and angiotensin II on plasma 18-hydroxy-11-deoxycorticosterone levels in normal subjects. *J. clin. Endocr. Metab.* **45** (1977) 893–902.
13. Ichikava Y., Mishikai M., Kawagof M., Yoshida K. and Homma M.: Plasma corticotropin, cortisol and growth hormone responses to hypoglycemia in the morning and evening. *J. clin. Endocr. Metab.* **34** (1972) 895–898.