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Circadian Adrenal Rhythm in Diabetics

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Summary. The circadian rhythm of adrenocortical secretion in 18 diabetic subjects was normal as judged by serial plasma 11-OH-corticosteroid levels. Mild episodes of hypoglycaemia induced a rise in the plasma 11-OH-corticosteroid in 12 diabetic patients on insulin therapy.

Rythme circadien des surrénales chez des diabétiques

Résumé. Le rythme circadien de la sécrétion corticosurrénale de 18 diabétiques était normal, comme on a pu en juger par les taux plasmatiques en série des 11-OH-corticostéroïdes. Des épisodes d'hypoglycémie modérée ont provoqué une augmentation des 11-OH-corticostéroïdes du plasma chez 12 patients diabétiques sous thérapeutique insulinique.

Der Tagesrhythmus der Nebennierenrinde bei Diabetikern

Zusammenfassung. Bei 18 Diabetikern wurde durch Serienbestimmung der Plasma-11-OH-Corticosteroidspiegel ein normaler Tagesrhythmus der Nebennierenrinden-Sekretion gefunden. Leichte Hypoglykämien bewirkten einen Anstieg der 11-OH-Corticosteroidspiegel im Plasma bei 12 insulinbehandelten Diabetikern.

Key-words: Diabetes, Circadian, Adrenal, Rhythm, Hypoglycaemia, 11-OH, Corticosteroid, Insulin Therapy.

The circadian rhythm of adrenocortical activity in normal subjects and in disease states has been studied by following the variations in plasma corticosteroid levels [14]. Both physical and emotional stimuli may cause an acute increase in adrenocortical secretion and this response is superimposed on the basic thythm. Pathological states such as heart failure [3, 5] and cerebrovascular disease or other central nervous system lesions [10], have caused marked alterations in the adrenal circadian rhythm. Diabetes mellitus is of particular interest with regard to adrenocortical activity since it has been speculated that some diabetic complications might be related to excess adrenocortical secretion [1]. So far, the adrenal status in patients with diabetes has been judged principally from the urinary steroid output, but a moderate disturbance of the normal plasma adrenocortical rhythm in patients with diabetes has been reported [5]. The effect of insulin treatment requires consideration since hypoglycaemia is a potent stimulus to the pituitaryadrenal axis. It therefore seemed worthwhile to study the plasma 11-OH-corticosteroid levels of diabetic subjects on insulin therapy to determine if the disease, or its therapy, induced any alteration in the circadian rhythm.

Material and Methods

We have studied the circadian rhythm in 18 diabetic subjects, all on insulin therapy (age range 24—63 years). Plasma 11-OH-corticosteroids were measured by the method of MATTINGLY [12]. Blood sugar was measured by a ferricyanide method modified for the Auto-Analyser. Venous blood was drawn in the early morning at 7.00 a.m. (before breakfast and administration of insulin) and at 12.30 p.m., 5.30 p.m. and 10.00 p.m. on the same day. Eleven non-diabetic patients of comparable age and from the same hospital population were studied as controls under a relatively similar ward routine. In addition, 12 diabetic subjects were studied at the time of the occurrence of a hypoglycaemic insulin reaction. These hypoglycaemic reactions had occurred inadvertently in the course of their diabetic management and were not specifically induced. Blood samples were obtained as soon as possible after the onset of symptoms of hypoglycaemia, before the patient was given oral glucose, and also 30 min later, after such therapy.

Results

The plasma 11-OH-corticosteroid values for the 18 diabetic subjects and the mean value for the controls is shown in Table 1. The mean value in the diabetics at 7.00 a.m. was 20.5 ± 7.3 μg/100 ml, and at 10.00 p.m. was 11.5 ± 4.5 μg/100 ml. The control subjects showed a similar morning-evening pattern, mean value at 7.00 a.m. 22.3 ± 5.6 μg/100 ml and at 10.00 p.m. 8.0 ± 4.8 μg/100 ml. There was no significant difference between the mean plasma 11-OH-corticosteroid levels at these times between control and diabetic subjects, although there was a tendency for the diabetic patients to have slightly higher evening (both 5.30 p.m. and 10.00 p.m.) plasma 11-OH-corticosteroid levels than the controls. The mean blood sugar values in the diabetics are also shown in the lower half of Table 1. When individual plasma 11-OH-corticosteroid and blood sugar values were correlated, there was no significant relationship ($r = 0.05$). In the four patients who showed the least satisfactory "control" of their diabetes in that blood sugars were in the range 200—400 mg/100 ml, plasma 11-OH-corticosteroid values were slightly higher throughout the day. The mean value for these four patients was 7.9 μg/100 ml

Table 1. *Circadian rhythm of plasma 11-OH-corticosteroids in patients with diabetes and in controls*

	Levels	7.00 a. m.	12.30 p. m.	5.00 p. m.	10.00 p. m.
18 Diabetic Patients	Plasma 11-OH-corticosteroids (μg per 100 ml)	19.5	21.5	28.0	20.5
		16.0	16.0	10.0	9.5
		20.0	22.5	17.0	14.0
		22.5	27.5	18.0	14.5
		26.0	23.0	28.5	13.5
		16.5	10.0	14.0	4.0
		38.0	21.0	20.0	13.5
		30.0	17.0	13.0	6.5
		18.0	20.5	19.0	14.0
		29.5	16.5	15.0	16.5
		18.0	13.0	21.5	—
		19.0	14.0	—	16.5
		7.0	8.0	6.5	10.5
		17.5	—	17.5	10.5
		22.0	10.5	9.0	12.5
		27.5	12.5	15.5	10.0
		8.0	4.0	14.0	6.5
		17.0	7.0	5.5	5.5
	Mean$\pm$S.D.	20.5$\pm$7.3	15.6$\pm$6.6	16.0$\pm$6.6	11.5$\pm$4.5
	Blood sugars (mg per 100 ml) Mean $\pm$ S.D.	175$\pm$84	224$\pm$85	197$\pm$78	185$\pm$85
11 Control Patients	Plasma 11-OH-corticosteroids (μg per 100 ml) Mean $\pm$ S.D.	22.3$\pm$5.6	15.0$\pm$3.7	10.0$\pm$3.3	8.0$\pm$4.8
	Blood sugars (mg per 100 ml) Mean $\pm$ S.D.	95$\pm$13	99$\pm$29	102$\pm$13	93.5$\pm$6.5

above the mean for the entire group when the four times of estimation were pooled.

Twelve patients were studied at the first symptom of mild hypoglycaemia. The mean blood sugar at this time was 59 mg/100 ml. The mean plasma 11-OH-corticosteroid was 29.0 μg/100 ml and 30 min later was 30.5 μg/100 ml. When the patients were divided into those experiencing a reaction between early morning and midday and those in whom the hypoglycaemic symptoms occurred in the afternoon or evening, the mean values of plasma 11-OH-corticosteroid were 33.4 μg/100 ml and 35.7 μg/100 ml at zero and 30 min respectively in the morning group, and 25.9 and 26.7 μg/100 ml in the afternoon group. To apply statistical tests to these figures the morning and afternoon values have been pooled. The mean morning plasma 11-OH-corticosteroid (7.00 a.m. and 12.30 p.m.) in the normal subjects was 18.7 μg/100 ml, in the diabetic subjects 18.2 μg/100 ml, and for those experiencing hypoglycaemia during the morning (initial and 30 min values), 34.5 μg/100 ml. For the afternoon and evening period the respective figures were 9.0 μg/100 ml (normals) 14.1 μg/100 ml (diabetics) 26.3 μg/100 ml (hypoglycaemic patients). Although the groups are small these mean levels in the hypoglycaemic patients are significantly increased (t-tests, $P < 0.001$ in each case).

Recently we have studied a patient with prolonged and severe hypoglycaemia due to sulphonylurea therapy, where blood sugar levels fell to below 25 mg/

Table 2. *Plasma 11-OH-corticosteroids (μg per 100 ml) during hypoglycaemic symptoms*

Time of symptoms	Plasma 11-OH-corticosteroids (μg per 100 ml)	
	At onset of hypoglycaemic symptoms	30 minutes later
a. m.	35.0	40.0
	60.0	52.0
	25.0	20.0
	22.5	34.0
	24.5	32.5
Mean	33.4	35.7
p. m.	36.5	40.0
	39.0	26.5
	21.5	23.0
	9.5	25.0
	30.5	34.5
	22.0	19.5
	22.5	18.5
Mean	25.9	26.7
Mean overall total	29.0	30.5

100 ml during the evening and night. At 5.30 p.m. the 11-OH-corticosteroid level was 25 μg/100 ml; hypoglycaemic symptoms occurred at 6.00 p.m. At 6.30 p.m. the 11-OH-corticosteroid level was 28 μg/100 ml, and at 7.00 p.m. 31 μg/100 ml. At 1.00 a.m. the same night, when hypoglycaemic symptoms recurred, the 11-OH-corticosteroid level in the plasma was still 39 μg/100 ml.

Discussion

Our finding of a normal circadian rhythm in diabetic subjects is in keeping with earlier studies showing normal adrenal function in diabetes [15]. The study by these workers revealed no evidence of adrenal cortical hyperfunction in patients with uncomplicated diabetes, or in those with diabetic retinopathy and nephropathy. It has been shown that diabetic ketosis elicits an increased adrenocortical response [11, 16], but sufficiently severe ketotic states are an uncommon phenomenon in the average diabetic life. Mild or clinically occult hypoglycaemia is not so uncommon and might involve increased adrenal activity consequent to ACTH release, although other authors have found in normal subjects that severe hypoglycaemia is necessary to activate the adrenal-pituitary system [2, 4, 8, 17].

The plasma 11-OH-corticosteroid results in the 12 hypoglycaemic patients show that this stimulus causes an increased adrenocortical secretion even when the level of blood sugar is only slightly below normal. Several workers [6, 9, 13] have suggested that it is not the absolute value of the blood sugar but the rate and extent of its fall that is responsible for pituitary adrenal activation. It is worth stressing that the hypoglycaemic symptoms experienced in this group of patients were minimal and consisted of such complaints as weakness, sweating and mild disturbance of cerebration, and no patient became unconscious. Infrequent transient stimulation of adrenocortical activity of this order seems unlikely to have major pathological significance, but it may be worth while to study this phenomenon forther in excessively brittle diabetics in whom a cumulative effect of frequent episodes of rapid onset might have some influence. The levels of plasma 11-OH-corticosteroid achieved during morning and evening reactions are not very different considering that the baseline plasma 11-OH-corticosteroid in the morning is at a higher level. However, the peak level of plasma 11-OH-corticosteroids attained is less and whether this would have any clinical significance with regard to the ability of a patient to recover more rapidly from hypoglycaemia during the morning as opposed to later in the day is not known.

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