Impaired ACTH and glucagon response to hypoglycaemia in an insulin-treated diabetic

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Summary

A 32-year-old woman who had been diabetic for 24 years presented with frequent, oligosymptomatic episodes of hypoglycaemia. Investigations showed that she had attenuated adrenocortical and pancreatic A-cell response to hypoglycaemia. Her plasma ACTH response to hypoglycaemia was also impaired but there was normal adrenocortical response to the injection of synthetic ACTH. Plasma glucagon response to intravenous arginine was also normal.

It is concluded that the blunted plasma cortisol response to insulin-induced hypoglycaemia in some long-standing diabetics is due to a pituitary or higher dysfunction, rather than adrenocortical dysfunction.

Introduction

Counter-regulatory hormonal response to hypoglycaemia has been reported to be impaired in diabetics by several workers (Goldfien *et al.*, 1961; Molnar *et al.*, 1971; Campbell *et al.*, 1979; Skyler, 1979). The absent or impaired plasma glucagon response to hypoglycaemia has been better documented in these subjects (Maher *et al.*, 1977). The lack of an adequate response of the pancreatic A-cells has been attributed to the decreased sensitivity to glucose by these cells. The degree of impairment of response of plasma cortisol and growth hormone has been controversial. Some workers have found no significant relationship between counter-regulatory hormonal changes and glucose recovery from insulin-induced hypoglycaemia in diabetics (Gale, Kurtz and Tattersall, 1980). On the other hand Campbell *et al.* (1979) found significantly less hormo-

nal response to hypoglycaemia in long-standing and unstable diabetics than in normal subjects. The majority of opinion appears to favour the view that there is impairment of hormonal response to hypoglycaemia in some long-standing diabetics. The level at which there is such impairment to glucose sensing has not been well defined in relation to the hypothalamo-pituitary-adrenal axis. We report a case in which there was evidence that the impaired response of plasma cortisol was due to a dysfunction at the pituitary or higher level.

Case report

A 32-year-old nurse who had been diabetic for over 24 years was admitted because of frequent oligosymptomatic episodes of hypoglycaemia. Episodes of hypoglycaemia occurred without warning. She was on a twice daily regime of soluble and lente insulin, at a mean daily dose of 1.0 u./kg body weight.

On admission she weighed 56 kg and was 165 cm tall. Systemic examination was essentially normal except for the presence of an ejection systolic murmur which was shown to be due to a bicuspid aortic valve.

Her blood count and serum biochemistry were normal as was the chest radiograph. Her autonomic nervous system function was kindly assessed by Dr D. J. Ewing of the Royal Infirmary, Edinburgh. Her supine and erect blood pressures were 125/75 mmHg and 120/75 mmHg respectively. The Valsalva ratio (ratio of the R-R interval after the manoeuvre to the shortest R-R interval during the manoeuvre), the rise in diastolic blood pressure during a sustained hand grip and the heart rate response (R-R interval variation) to standing were all within normal limits. Her exocrine pancreatic function tests as assessed by

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a five-day faecal fat collection and tryptic activity after a test meal were normal. Thyroid function tests were also within normal limits.

Serial overnight urinary cortisol/creatinine ratios (UCCR) ranged from 9.2 to 18.4 (normal mean $\pm$ s.d. = 8.5 ± 3.8). The blood glucose levels observed during an overnight monitoring of blood variables are shown in Table 1.

TABLE 1. Biochemical findings during an overnight study of patient

Time (Hr)	Blood glucose (mmol/litre)	Plasma cortisol (nmol/litre)	Plasma growth hormone (mu./litre)
2300	5.8	200	2.6
0100	2.3	130	1.9
0200	1.3	98	38.5
0300	1.1	390	49.6
0400	1.6	420	42.8
0500	1.5	410	28.0
0700	2.0	520	10.4

Plasma glucagon was below assay sensitivity level (< 5 pmol/litre).

During the period of about 5 hr when she was biochemically hypoglycaemic, she showed few signs of hypoglycaemia. Her maximum pulse rate during the night was 72 beats/minute and she had an apparently comfortable sleep.

In order to assess her hypothalamo-pituitary-adrenal axis in a more standard way, she had an insulin stress test done as well as the short tetracosactrin (Synacthen) test. The findings during the standard intravenous insulin stress test were similar to those of the night study and are shown in Table 2.

During the insulin stress test she quietly lapsed into hypoglycaemic pre-coma and she had to be resuscitated with intravenous glucose. Plasma glucagon, cortisol and ACTH responses were absent or blunted. Her UCCR on the day of the night study and after the insulin stress test were similarly attenuated at 18.4 and 18.9 respectively (normal mean $\pm$ s.e. post insulin-stress test UCCR in our laboratory is 54 ± 6).

Following the short Synacthen test, there was a

brisk and adequate response of plasma cortisol from a basal level of 270 nmol/litre to a peak of 800 nmol/litre at 45 min. She also responded normally to intravenous infusion of arginine; plasma glucagon levels rose from less than 5 pmol/litre at 0 min to 20 pmol/litre at 45 min. During the periods when she was hyperglycaemic (blood glucose > 8.0 mmol/litre), there was no measurable C-peptide in her plasma on two occasions.

When her insulin was reduced from 1.0 u./kg/24 hr to 0.57 u./kg/24 hr, she improved symptomatically. There was also a marked fall in her mean UCCR from 13.7 ± 1.3 to 6.7 ± 0.81 , which was well within the normal range for the laboratory.

Discussion

The clinical and biochemical findings in this patient are very similar to the cases described by Gale and Tattersall (1979). Of their 22 insulin-treated diabetics with nocturnal hypoglycaemia, only one was awoken by hypoglycaemic symptoms. The features of over-insulinized diabetics are well reviewed by Rosenbloom and Giordano (1977), Skyler (1979) and Gale and Tattersall (1979).

The failure of glucose recovery during hypoglycaemia in some diabetics has been attributed to the diminished response of the anti-insulin hormones (growth hormone, glucagon, cortisol and the catecholamines). The diabetic subjects with such impaired counter-regulatory mechanisms tend to be more labile. However, Gale *et al.* (1980) found no significant difference in the response of plasma cortisol and growth hormone in diabetics with post-hypoglycaemic rebound and those without rebound hyperglycaemia.

The role of chronic hypoglycaemia in the causation of impaired counter-regulatory hormonal response to insulin-induced hypoglycaemia is not clear. However, the phenomenon of impaired hormonal response to hypoglycaemia appears common among insulin-treated diabetics (Skyler, 1979; Campbell *et al.*, 1979).

TABLE 2. Biochemical findings during insulin tolerance test in the same patient

Time (mins)	Blood glucose (mmol/litre)	Plasma cortisol (nmol/litre)	Plasma ACTH (pmol/litre)	Plasma growth hormone (mu./litre)
-15	0.49	240	5.8	0.37
0	4.1	220	5.5	0.37
30	2.6	480	5.7	32.2
60	0.8	400	5.5	31.2
90	**4.5	235	5.5	22.3
120	3.2	193	19.8	6.7

Plasma glucagon was below assay sensitivity level (< 5 pmol/litre).

**After 50 ml of 50% dextrose given at 60 min.

The impaired response of the pancreatic A-cells to hypoglycaemia but with normal response to other stimulants like arginine in insulin-treated diabetics is well known (Campbell *et al.*, 1979). The explanation is unclear but Ohneda *et al.* (1969) have suggested that arginine has a powerful stimulatory action on the A-cells and may be too strong a stimulant to detect partial glucagon deficiency. A central (hypothalamo-pituitary) cause is also possible as it is known that insufficiency of either growth hormone or the adrenocortical steroids leads to a blunting of the endocrine pancreatic response to changing blood glucose concentrations (Van Lan *et al.*, 1974).

Using plasma cortisol changes in response to insulin-induced hypoglycaemia, the adrenocortical response could be taken as borderline or equivocal in this patient. However, the blunted adrenocortical response to hypoglycaemia was more clearly shown by the relatively low urinary cortisol-creatinine ratio after the insulin stress test. This measurement may be more discriminatory between normal and subnormal adrenocortical response to insulin-induced hypoglycaemia (Ohwovoriole *et al.*, 1982).

Though several workers have commented on the blunted plasma cortisol response to hypoglycaemia in long-standing diabetics, information on the ACTH response in these patients is scanty. Campbell *et al.* (1979) suggested that this acquired defect in counter-regulatory control is probably of central origin. Boden *et al.* (1981) have recently described a case similar to the one in this report and they also suggest that the dysfunction is at the hypothalamic or low brainstem level. The finding of a normal adrenocortical response to synthetic ACTH in the patient described by Boden *et al.* (1981) and in this patient reinforces this suggestion.

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