Counterregulation of insulin-induced hypoglycaemia in primary hypothyroidism

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Abstract. Hypothyroidism has been alleged to modulate insulin action and influence the secretion of growth hormone and catecholamines. We recently investigated the influence of hypothyroidism on glucose counter-regulatory capacity and the hormonal responses to insulin-induced hypoglycaemia in 6 patients with primary hypothyroidism (age 32–52 years, TSH-values 66–200 mU/l). Hypoglycaemia was induced in the hypothyroid state and again when the subjects were euthyroid. After an overnight fast a constant rate infusion of insulin (2.4 U/h) was given for 4 h. Glucose was measured every 15 min and insulin, C-peptide, glucagon, epinephrine, norepinephrine, growth hormone and cortisol every 30 min for 5 h.

During insulin infusion somewhat higher concentrations of the hormone were obtained in the hypothyroid state and simultaneously glucose levels were 0.5 mmol/l lower. As expected, basal norepinephrine levels were higher in hypothyroidism. However, no increase in circulating norepinephrine during hypoglycaemia was registered in the two experiments. The responses of counterregulatory hormones showed an enhanced response of cortisol, similar responses of growth hormone and epinephrine while the glucagon response was paradoxically impaired. Our findings suggest that hypothyroidism alters insulin metabolism, and that the glucagon response to hypoglycaemia is impaired in this condition.

Hypoglycaemia may appear spontaneously in severe hypothyroidism (Forester 1963) and hypoglycaemic episodes are a clinical sign of this condition in insulin-treated diabetics. The underlying mechanism for this is not fully understood. Thyroid hormones have been alleged to influence glucose absorption from the gastrointestinal tract (Müller & Seitz 1984), endogenous glucose production (Okajima & Ui 1979) and the peripheral utilization of glucose (Oppenheimer 1979), all of which may affect blood glucose levels. Furthermore the glycogen content in liver and muscle is decreased (Baldwin et al. 1980) and the mobilization of glycogen by glucagon delayed in hypothyroidism (Levy et al. 1970).

Hypoglycaemia is prevented by hormones counteracting the effects of insulin. Among these hormones glucagon and epinephrine are important for immediate glucose counterregulation. Thus in the absence of these two hormones glucose recovery fails to occur. The present study was designed to characterize the glucagon, epinephrine, norepinephrine, cortisol and growth hormone responses to hypoglycaemia in a group of non-diabetic patients with primary hypothyroidism.

Materials and Methods

The study was performed on 6 patients, 4 women and 2 men, aged 32–52 years, with primary hypothyroidism. In four cases we found evidence of chronic thyroiditis and in one hypothyroidism was due to lithium therapy. One case was considered as idiopathic primary myxoedema. At diagnosis TSH-values ranged from 66–200 mU/l. The patients participated in hypoglycaemic expe...
riments when diagnosed and again 16–24 weeks later on replacement therapy with l-thyroxine (Levaxin, Nyegaard, Norway) and euthyroid. By then plasma-thyroxine levels had increased from $15 \pm 6$ to $134 \pm 8$ nmol/l (normal range 54–122 nmol/l). After l-thyroxine treatment their mean body weights decreased by 3% from $67.5 \pm 3.9$ to $65.5 \pm 3.5$ kg ($P < 0.05$). All patients had normal fasting blood glucose on both occasions. The patients gave their informed consent to the study which had been approved by the Ethics Committee of the Karolinska Hospital. The hypoglycaemic experiments were started at 8 a.m. After an overnight fast short teflon catheters were inserted in a brachial vein in each arm, one for blood sampling, the other for insulin administration by a constant rate volume controlled pump. The infused volume was 100 ml/h and the dose of insulin given was 2.4 U/h (Actrapid. Novo Industries, Denmark) for 4 h. Blood pressure and pulse rate were registered every 30 min. The subjects were resting in a supine position throughout the experiment. Glucose was measured every 15 min and insulin, C-peptide, norepinephrine, epinephrine, growth hormone, cortisol and glucagon every 30 min. In order to study glucose recovery after hypoglycaemia blood glucose was measured during an additional period of 60 min after the insulin infusion was stopped.

Blood glucose was measured by test-sticks and reflometer (Reflo-test-hypoglycemia and Reflomat, Boehringer Mannheim, West Germany). Radioimmunoassay techniques were used for the determination of growth hormone (Cerasi et al. 1966), glucagon (Faloona & Unger 1974), insulin (Herbert et al. 1965), and C-peptide (Heding 1975). Thyroxine, triiodothyronine and TSH were determined by commercially available kits. Cortisol was measured by fluorometry (de Moor et al. 1960) and catecholamines by high pressure liquid chromatography with electrochemical detection (Hallman et al. 1978). The areas under the curves were calculated and the statistical significance evaluated by means of Student's $t$-test for paired observations.

![Fig. 1. Blood glucose, C-peptide, insulin and norepinephrine levels during (0–240 min) and after insulin infusion. Open circles indicate hypothyroidism, filled circles euthyroidism. Mean $\pm$ SEM (n = 6). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.](downloaded from Bioscientifica.com at 11/24/2018 01:42:08PM via free access)
Results

Basal insulin and glucose concentrations were similar in hypo- and euthyroidism. The infusion of insulin raised the circulating levels of the hormone to approximately 40 μU/ml. In the hypothyroid state significantly higher levels of insulin appeared during the second half of the infusion period and the area under the insulin curve was significantly larger in hypothyroidism (237 ± 7 vs 176 ± 17, P < 0.05). Simultaneously endogenous insulin secretion was suppressed as evaluated by the determination of plasma C-peptide. The decrease of C-peptide levels was almost identical in the two experiments (Fig. 1). When insulin infusion was stopped, the insulin levels in the low basal range were registered within 30 min. In euthyroidism insulin infusion lowered blood glucose to about 2.5 mmol/l during the initial 60 min period, whereafter blood glucose remained at this level until the insulin infusion was stopped. In hypothyroidism the rate of the initial blood glucose fall was similar but the steady state glucose levels were approximately 0.5 mmol/l lower when compared with euthyroidism. After the termination of insulin infusion blood glucose increased in both experiments, normoglycaemia being reached earlier in the euthyroid state (Fig. 1).

As expected, a tendency towards higher basal levels of norepinephrine was noted in hypothyroidism. During hypoglycaemia the circulating levels of norepinephrine did not increase in either experiment (Fig. 1). Epinephrine and growth hormone responses were not significantly altered in hypothyroidism while the cortisol response, when expressed as area under the curve, was enhanced in this condition (1967 ± 657 vs 583 ± 21, P < 0.05). In contrast the glucagon response evaluated as area under the hormone curve was significantly lower in hypothyroidism (506 ± 107 vs 730 ± 124, P < 0.05) (Fig. 2).

Blood pressure and pulse rate recordings revealed only minor changes during the experiments. In the euthyroid state diastolic blood pres-
Blood pressure and pulse rate during insulin-induced hypoglycaemia. Open circles indicate hypothyroidism, filled circles euthyroidism. Mean ± SEM (n = 6). *P < 0.05.

Discussion

We demonstrate here that when given iv insulin patients with hypothyroidism develop a more marked hypoglycaemic reaction. However, the rapidity with which blood glucose returned to normal was not affected. Therefore the somewhat delayed recovery of blood glucose was a consequence of the lower steady state levels. These observations are consistent with previous findings (Shah et al. 1975). Several metabolic events related to hypothyroidism can be held responsible for this effect. Firstly this study demonstrated that during a constant rate infusion higher circulating levels of insulin were obtained in hypothyroidism than in the euthyroid state. This was not due to interference with endogenous insulin, since the suppression of circulating C-peptide levels was close to identical in hypo- and euthyroidism. Insulin metabolism has previously been demonstrated as normal in hypothyroidism by Shah and coworkers (Shah et al. 1975). It should however, be emphasized that these investigators studied insulin kinetics in connection with a rapid iv bolus of the hormone while in the present study insulin was infused over several hours. Possibly the effects of hypothyroidism on insulin kinetics cannot be disclosed unless examined under steady state conditions. The significance of the higher circulating insulin levels in hypothyroidism for the metabolic response to insulin must be questioned since the exaggerated hypoglycaemic reaction occurred before the higher circulating insulin levels were observed. Furthermore the more pronounced hypoglycaemic effect of insulin could not be attributed wholly to insulin metabolism as Shah and coworkers also registered a more marked hypoglycaemic reaction in spite of any effect on circulating insulin levels. Moreover it has been demonstrated, in miniature pigs, that thyroid hormone induced alterations in whole body glucose turnover are independent of endogenous insulin (Müller et al. 1983) suggesting that other factors than insulin could be of major importance.

An alternative explanation would be an altered sensitivity to the effects of insulin. Using isolated fat cells from normoglycaemic hypothyroid patients Arner and coworkers demonstrated that the insulin receptor number was increased by 70% and simultaneously the sensitivity to insulin as determined by glucose oxidation was increased 4-fold (Arner et al. 1984). The lower steady state level of glucose achieved in hypothyroidism in the present study does not allow any estimation of total insulin sensitivity since hormones counteracting the effects of insulin were simultaneously released in excess. The responses of these coun-
terregulatory hormones to hypoglycaemia must however, be viewed in the light of the more marked hypoglycaemia evoked by insulin in hypothyroidism and particularly so regarding catecholamines since their release is closely related to ambient glucose levels (Christensen 1979). A series of studies have revealed that hypothyroid patients have higher circulating basal levels of norepinephrine, while those of epinephrine are within the normal range (Christensen 1972). In response to hypoglycaemia however the urinary excretion of epinephrine was decreased (Leak et al. 1962). In our study the rise of circulating epinephrine during hypoglycaemia was similar in hypo- and euthyroidism. The lower ambient glucose levels under which epinephrine levels were measured in hypothyroidism suggest, however, that the epinephrine response to hypoglycaemia was moderately impaired in hypothyroidism. While most previous studies have shown impaired response of growth hormone in hypothyroidism (Brauman et al. 1973) some investigators reported normal GH secretory patterns (Iwatsubo et al. 1967). In the present study the growth hormone response to hypoglycaemia was similar in hypo- and euthyroidism. Again considering the differences in nadir glucose levels we interpret our data as demonstrating a reduction of the pituitary responsiveness as to growth hormone secretion in hypothyroidism.

The cortisol response to hypoglycaemia registered in the present study suggests that the pituitary-adrenal axis is not affected in hypothyroidism. Circulating cortisol levels have previously been shown to be normal in this condition, and it has been suggested that a decreased synthesis of cortisol appearing in hypothyroidism is balanced by decreased removal of the steroid from circulation (Peterson 1958). Our findings may place this hypothesis in question. Taken together, the impairment of the pituitary's capacity to secrete growth hormone and the simultaneously normal cortisol responsiveness suggest that thyroid hormone deficiency influences pituitary function in a complex way.

The capacity of the pancreatic alpha-cells to secrete glucagon in response to hypoglycaemia has not previously been investigated in hypothyroidism. In response to fasting glucagon secretion is known to increase normally in hypothyroidism, and in response to arginine the glucagon response may even be enhanced (Seino et al. 1977). Against this background our finding that the glucagon response to hypoglycaemia is impaired in hypothyroidism is somewhat unexpected, and its significance is not obvious to us. Recently thyroid hormones have been shown to regulate glucagon receptors (Madsen & Sonne 1976) which may explain the decreased sensitivity of target tissues to glucagon in hypothyroidism (Levy et al. 1970). Since epinephrine secretion in response to hypoglycaemia is decreased in hypothyroidism the simultaneous glucagon deficiency may be of particular importance as the combined deficiency of these counterregulatory hormones is known to impair the recovery of glucose from hypoglycaemia (Gerich et al. 1980).

From the present study we would conclude that glucose recovery is impaired in hypothyroidism and that this may be the result of multiple metabolic consequences of this disorder, such as decreased metabolism of insulin, deficiencies in the secretion of counterregulatory hormones and altered sensitivity of tissues to insulin and counterregulatory hormones. Our finding that the glucagon response to hypoglycaemia is blunted in this condition may be of particular importance because of the simultaneous relative impairment of epinephrine secretion.

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References


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