Case report

Insulin resistance in a case of coexisting insulinoma and type 2 diabetes

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Abstract. Hyperinsulinaemia due to pancreatic β-cell tumours has been reported to lead to insulin resistance. A possible contribution of dysregulated insulin receptors to the impaired insulin action of insulinoma has not been explored. Therefore, we studied insulin receptor function in a patient with insulin-producing adenoma. This patient was rather unusual in that she was found to have a very large tumour and strikingly high circulating levels of insulin. In addition, her previous history included type 2 (non-insulin-dependent) diabetes mellitus. We confirmed decreased glucose utilization and metabolic clearance rate for glucose in presence of marked endogenous hyperinsulinaemia (~2000 pM). 125I-labelled insulin binding capacity and receptor affinity for insulin were normal in her intact blood monocytes and erythrocytes. Insulin receptors were purified from the patient's tumour as well as from the pancreas, omental fat, liver and erythrocytes. All parameters of insulin binding to these receptors were normal. Thus, no evidence of receptor downregulation due to the marked hyperinsulinaemia was found. As expected, addition of insulin in vitro stimulated receptor autophosphorylation and tyrosine kinase activity of the receptors isolated from the liver, fat and erythrocytes. However, the basal tyrosine kinase activities of the tumour and pancreatic receptors were very high when isolated and further addition of insulin in vitro increased the protein kinase activity only slightly. These results demonstrate that: (1) insulin receptor downregulation does not necessarily occur in the face of chronic endogenous hyperinsulinaemia; and (2) insulin resistance of insulinoma is not due to any structural or functional defect of the insulin receptors and is thus probably related to defect(s) at a level distal to the receptor function.

Key words: Insulinoma – Insulin receptor – Insulin resistance

Introduction

The concept of insulin resistance has been invoked to explain such diverse clinical conditions as obesity, hypertension, dyslipidaemia, glucose intolerance and type 2 (non-insulin-dependent) diabetes mellitus [1]. There are no clinically useful tests currently available to determine insulin action in vivo, however. The degree of hyperinsulinaemia has been used, therefore, as a surrogate measure for estimating the degree of insulin resistance. Yet the relationship between insulin resistance and hyperinsulinaemia has not been clarified. There is considerable confusion in the literature and the mere presence of hyperinsulinaemia is sometimes taken as evidence of insulin resistance.

Traditionally, hyperinsulinaemia has been considered to be a compensatory secretory response to diminished peripheral insulin action [2]. However, the opposite scenario – that is of experimental hyperinsulinaemia leading to insulin resistance – has also been amply demonstrated [3, 4]. Rizza et al. [5] and McGee et al. [6] took advantage of natural cases of hyperinsulinaemia (i.e. patients with insulinomas) and studied measures of glucose metabolism utilizing [3-3H]glucose infusion and the euglycaemic clamp technique, respectively. In the former report [5], insulin-mediated suppression of hepatic glucose production was the primary cause of hypoglycaemia while no defect in glucose utilization was found in these patients. In the latter study, however, patients with β-cell tumours exhibited insulin resistance (lower glucose utilization) before surgery [6]. Significantly, in periods of up to 2 years after removal of the tumour, the glucose utilization rates remained below those of healthy controls subjected to exogenous hyperinsulinaemia of the same magnitude as the patients (~300 pM insulin). Chronic endogenous hyperinsulinaemia of insulinoma was thought to lead to defects in peripheral glucose utilization which were only partly resolved after removal of the tumour. The mechanisms responsible for this finding were not elucidated. In the discussion, the authors postulated [6] a combination of receptor and postreceptor defects
due to downregulation of receptors as a consequence of the chronic hyperinsulinaemia. However, no studies of insulin receptors were actually conducted to support that hypothesis.

In this report we present a patient who was initially treated for type 2 diabetes mellitus and who developed a large insulin-producing tumour resulting in extremely high serum insulin levels. If McGee et al.'s hypothesis were correct, this would be a patient with insulin resistance due to receptor downregulation. However, such a receptor defect was not observed in tissues from this patient.

Case report

A 65-year-old white woman with a history of hypertension, hypercholesterolaemia, obesity and glaucoma presented in February 1989 with transient episodes of dizziness and weakness relieved by eating. A random blood glucose measurement on presentation was 12 mM. Diagnosis of diabetes mellitus was confirmed by a 75 g oral glucose tolerance test: at 0 min her plasma glucose was 4.8 mM; at 30 min, 7.8; at 60 min, 12.0; at 120 min, 11.9; and at 180 min, 9.0 mM. Fasting serum insulin was 75 PM (normal range 30–150 PM). She was placed on a daily regimen of oral glyburide (Diabeta, Hoechst) 2.5 mg and a 5880 kJ (1400 kcal) American Diabetes Association diet. However, her spells of dizziness, weakness and palpitation persisted unless she ate at least every 3 h. Glyburide was discontinued. In May 1989 her random plasma glucose was 2.9 mM, insulin 1380 PM, glycated haemoglobin 7.5% (normal range 4.4–8.2%), thyroid stimulating hormone 2.53 mIU/l (0.15–3.2), total cholesterol 6.14 mM (<6.24) and high density lipoprotein 1.04 mM (0.91–1.17). She remained on the daily 5880 kJ diet spread over five or six meals. Eight weeks later, fasting plasma glucose was 3.2 mM and serum insulin 714 PM; fasting plasma glucose after another 2 weeks was 1.6 mM and serum insulin 1536 PM. Random capillary blood glucose values at home ranged between 2.2 and 4.2 mM. She continued to complain of episodes of diaphoresis and tachycardia if she did not eat every 3 h.

At admission to the hospital she denied weakness, anorexia, abdominal pain, fever, salt craving, or changes in skin pigmentation. She denied use of insulin, sulphonylureas, tobacco, ethanol or illicit drugs. She took only her prescribed medications: oral (long-acting) propranolol 120 mg daily and ophthalmic drops (pilocarpine 4% and timolol maleate 0.5%). She had no known access to insulin or other drugs. There was no family history of diabetes mellitus.

She was afebrile, pulse was 84/min and regular, respirations 12/min and blood pressure was 150/100 mmHg sitting, without orthostatic changes. Her height was 1.52 m and weight 88.5 kg (BMI = 38.3 kg/m²). No abdominal masses were palpated due to her obesity. She had no apparent complications of diabetes (normal retinal examination, no peripheral neuropathy, no signs of autonomic neuropathy, normal EKG and normal beat-to-beat variation, normal urinary creatinine clearance, no albuminuria). Laboratory values, including haematological profile, electrolytes, renal and hepatic functions were normal. A screen for sulphonylureas in her urine was negative.

An overnight fast resulted in symptomatic hypoglycaemia (Table 1). Additional plasma values revealed normal levels of glucagon, ionized calcium, parathyroid hormone (N-terminal 11 pg/ml, C-terminal/mid-region 380 pg/ml), insulin-like growth factor I (somatomedin-C, 1.54 U/ml), and α-subunit human choriionic gonadotrophin (1.0). Examination of 24 h urine revealed normal levels of free cortisol (64 µg), creatinine (0.7 g), vanillylmandelic acid (7 µg), metanephrine (0.5 µg), total catecholamines (165 µg), noradrenaline (27 µg), adrenaline (7 µg), and dopamine (131 µg).

Table 1. Fasting protocol

<table>
<thead>
<tr>
<th>Time</th>
<th>Glucose (3.88–5.83 nM)</th>
<th>Insulin (30–150 pM)</th>
<th>C-peptide (0.16–0.99 nM)</th>
<th>Glucagon (50–200 ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0630</td>
<td>3.33</td>
<td>1416</td>
<td>3.97</td>
<td>690</td>
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<tr>
<td>0730</td>
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<tr>
<td>1100</td>
<td>2.17</td>
<td>1530</td>
<td>3.14</td>
<td>770</td>
</tr>
</tbody>
</table>

The test was stopped at 1100 hours after the patient became symptomatic with tachycardia, diaphoresis, nausea and weakness.

The patient underwent euglycaemic studies on three separate occasions: on the day before her surgery, the day after surgery, and 5 months postoperatively (Fig. 1 shows results of the preoperative studies only).

The patient was kept euglycaemic on the day before her operation by 10% dextrose infusion via an antecubital vein. The protocol of McGee et al. [6], taking advantage of endogenous hyperinsulinaemia, was intentionally followed for purposes of comparison with their patients. Capillary blood glucose was obtained every 10 min and plasma glucose every 60 min. Blood glucose was kept between 95 and 100 mg/dl for 3 h by adjusting the dextrose infusion rate every 10 min. Blood serum insulin and C-peptide measurements were obtained every 30 min (Fig. 1).

Glucose utilization rate (M) was calculated as in [6] and expressed in mg/kg per minute, using the rate of dextrose infusion as

Materials and methods

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