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The hyperinsulinaemic hypoglycaemias in infancy: a study of six cases

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Abstract. The aim of the present study was to evaluate various functional tests for the differentiation of hyperinsulinaemic hypoglycaemia. The pathophysiological and histological findings in six infants, aged 2–7 months, with persistent hyperinsulinaemic hypoglycaemia are described. Islet cell adenoma was found in four infants and pancreatic nesidioblastosis in two others. Circulating levels of blood glucose (BG), immunoreactive insulin and C-peptide immunoreactivity were measured under basal conditions and during both stimulation and suppression. The diagnosis of hyperinsulinaemia was made by estimation of the BG/serum insulin ratio, which was the most important diagnostic criterion of hyperinsulinism. Control subjects of comparable age showed a ratio of 8.3 ± 4.4 (range 4.1–13.3), whereas the six patients had values between 0.3 and 5.1. At least four determinations with ratios lower than 2.6 were necessary for confirming the diagnosis. Preoperatively we performed oral glucose tolerance, diazoxide infusion, somatostatin infusion and C-peptide suppression tests. It is suggested that the various function tests, especially the suppression tests, do not differentiate hyperinsulinism caused by an adenoma from that caused by diffuse pancreatic nesidioblastosis.

Key words: Hypoglycaemia – Hyperinsulinaemia – Insulinoma – Nesidioblastosis

Introduction

The differential diagnosis of persistent hypoglycaemia in newborns and young infants requires more elaborate diagnostic measures tan in adults [6, 20]. Other causes of hypoglycaemia in infants include congenital defects of gluconeogenesis and glycogenolysis, disorders of amino acid metabolism, growth hormone deficiency or adrenal insufficiency.

Hypoglycaemia due to hyperinsulinism may be transient as in infants of diabetic mothers, in infants with erythroblastosis fetalis or in the Wiedemann-Beckwith syndrome [1, 20]. Persistent hyperinsulinaemic hypoglycaemia can be caused either by diffuse abnormal distribution of B-cells (nesidioblastosis, endocrine cells dysplasia) or by abnormal local distribution of endocrine cells (islet cell adenoma, insulinoma) of the endocrine pancreas [11, 13, 20].

Modern laboratory techniques including sonography, computered tomography and angiography cannot differentiate between these two forms of hyperinsulinaemia [6, 7]. In adults, transhepatic portal vein catheterization has become a reliable diagnostic technique to identify hormone-producing pancreatic tumours [3, 6, 7]. In infants, this procedure is technically difficult and not without risks.

Early diagnosis and effective medical or surgical treatment are absolutely necessary in order to prevent brain damage and mental retardation [8, 16, 20].

We evaluated the ability of several functional tests to differentiate between various forms of hyperinsulinaemic hypoglycaemia in infants.

Patients and methods

Patients

Clinical details of the six infants are summarized in Table 1. All were children of non-diabetic mothers and there was no history of diabetes or multiple endocrine neoplasia. The pancreatic adenomata were enucleated and 95% resection of the pancreas was done in cases of nesidioblastosis. Portions of resected pancreas were examined histologically. Recurrent hypoglycaemia was seen in only one patient with nesidioblastosis (patient 6) despite 85%–90% pancreatic resection in the initial operatin.

Histological data

The histological diagnoses are summarized in Table 1. The tissue samples were fixed in formalin or Bouin's fluid, embedded in paraffin, stained with haematoxylin-eosin, Goldner, PAS, Congo red, acridine orange, aldehyde fuchsin and Grimelius argyrophily, respectively. The insulinomas contained diffusely distributed argyrophil cells. Aldehyde-fuchsin staining showed that tumour cells reacted far less than regular islets. In the two cases with pancreatic nesidioblastosis, no adenoma but hyperplasia of the endocrine tissue, giant islets, confluent islets and minute endocrine cell complexes was found. Staining with aldehyde-fuchsin was variable and various degrees of argyrophilia, budding of endocrine celkls from the ductal epithelium, and frequently islets in the vicinity of exocrine ducts were also found [14].

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Abbreviations: IRI = Immunoreactive insulin; BG = blood glucose; CPR = C-peptide immunoreactivity; HCP = human C-peptide; BW = body weight

Table 1. Clinical and histological characterization of six infants with pancreatic hypoglycaemia

Patient no.	Sex	Weight at birth (g)	Diagnosis
1	F	3150	Ductoinsular insulinoma, size 8 × 8 mm, diagnosed at age 6 months
2	F	3140	Mixed islet-acinar adenoma, size 5 × 12 × 20 mm, diagnosed at age 5 months
3	F	3500	Ductoinsular insulinoma, size 5 × 6 mm, diagnosed at age 3 months
4	M	4750	Focal nesidioblastosis (nesidioblastoma), size 7 × 8 mm, diagnosed at age 2 months
5	F	3500	Diffuse nesidioblastosis, diagnosed at age 7 months
6	M	4250	Diffuse nesidioblastosis, diagnosed at age 2 months, recurrence after 90% resection of the pancreas

Biochemical methods

Venous blood samples were collected in heparinized glass tubes, centrifuged within 60 min and the plasma stored at −20°C until assayed. The patients' plasma samples were drawn exclusively prior to surgery. Plasma glucose was determined by the glucose oxidase method. Plasma immunoreactive insulin (IRI) was estimated by radioimmunoassay using commercial kits (Isocommerz, GDR) and a porcine insulin standard (Novo, Copenhagen, Denmark). Human C-peptide (HCP) was measured by radioimmunoassay according to Heding [10]. HCP standard and ^{125}I-labelled HCP were from Novo (Copenhagen, Denmark); the HCP antiserum was a gift of Dr. Beischer (University of Ulm, Ulm, FRG). Cross-reactivity of the antiserum with biosynthetic human proinsulin was indistinguishable from that with synthetic HCP. There was no cross-reaction with reduced human proinsulin or native insulin.

Control subjects

Blood glucose (BG) and plasma immunoreactive insulin (IRI) were determined in six healthy infants of normal body weight, aged 1–9 months after a 12-h fasting period. The infants were admitted either on account of minor ailments or for observation. Informed consent was obtained from the parents. Due to a risk of hypoglycaemia the fasting period was limited to 12 h. BG was 3.54 ± 0.26 mmol/l (range 3.2–3.9) or 65.5 ± 4.8 mg/100 ml (range 59.2–72.2). IRI was 0.026 ± 0.03 nmol/l (range 0.028–0.1) or 10.1 ± 4.9 μU/ml (range 4.6–16.4).The quotient BG (mg/100 ml) to IRI (μU/ml) was 8.3 ± 4.4 (range 4.1–13.3).

Function test

Oral glucose tolerance test. (oGTT) The oGTT was performed by administration of 2.0–2.5 g/kg body weight (BW) glucose via a gastric tube. Blood samples were taken as indicated in Fig. 1.

Table 2. Biochemical characterization of six infants with pancreatic hypoglycaemia

Patient no.	Ratio BG (mg/100 ml) : IRI (μU/ml)	
	Individual values	Mean ± SD
1	2.6/2.7/2.4/0.7/0.9/0.6/1.0/1.8/0.9	1.5 ± 1.0
2	2.9/3.5/1.4/5.1/2.8/2.2/4.6/1.4/0.8	2.7 ± 1.4
3	1.1/1.0/1.2/1.2/0.8/0.7/0.8/1.0/1.0	1.0 ± 0.2
4	0.9/1.0/1.3/1.2/0.8/1.0/0.8/2.2/1.0/0.8/0.9	1.1 ± 0.4
5	2.8/1.9/2.1/4.7/3.2/3.3/2.6/2.2/2.3	2.9 ± 0.8
6	1.7/2.1/0.7/0.3/0.8/0.9/0.9/1.2	1.1 ± 0.5

Diazoxide test. Diazoxide (Proglicem, Shering, Bloomfield, U.S.A.) was given as an intravenous bolus of 1 mg/kg BW at the time 0 min followed by a continuous infusion of 300 mg/m^2 over a period of 60 min. Blood samples were taken as indicated in Fig. 2.

Somatostatin test. Somatostatin (Stilamin, Serono, Freiburg, FRG) was administered in a 0.9% saline solution containing 1% human serum albumin. An intravenous bolus of 2 μg/kg BW was given at time 0 min followed by 100 μg/m^2 over 60 min. At this time a dose of 6 μg/kg BW was administered and infusion continued at a dose of 300 μg/m^2 over a second 60-min period. Blood samples were taken as indicated in Fig. 3.

C-peptide suppression test. C-peptide suppression was performed by intravenous injection of 0.15 IU MC(Monocomponent)-insulin/kg BW (Actrapid, Novo, Copenhagen, Denmark). Blood samples were taken as indicated in Fig. 4.

Results

Ratio of blood glucose to plasma insulin

The ratio BG (mg/100 ml) to IRI (μU/ml) in the six patients is shown in Table 2. In four patients, all individual values showed inapropriately high plasma IRI levels when compared with the BG values, whereas in two patients (nos. 2 and 5) only after measuring four individual values was the diagnosis confirmed.

Oral glucose tolerance tests

The oGTT gave varying results, ranging from delayed and unchanged to exaggerated IRI and HCP release (Fig. 1). Peak levels for both IRI and HCP were attained 60–120 min after starting oral loading.

Diazoxide tests

The hormone response during diazoxide infusion was different (Fig. 2). While both IRI and HCP were paradoxically increased in the two insulinoma patients (nos. 1 and 2), the decrease of HCP in patient 3., who also had an adenoma, was only transient. In contrast, IRI stimulation associated with a weak inhibition of HCP release was observed in patient 4 with nesidioblastosis. Only in ony patient with diffuse nesidioblastosis (no. 6) were both IRI and CPR suppressed over the whole test period.

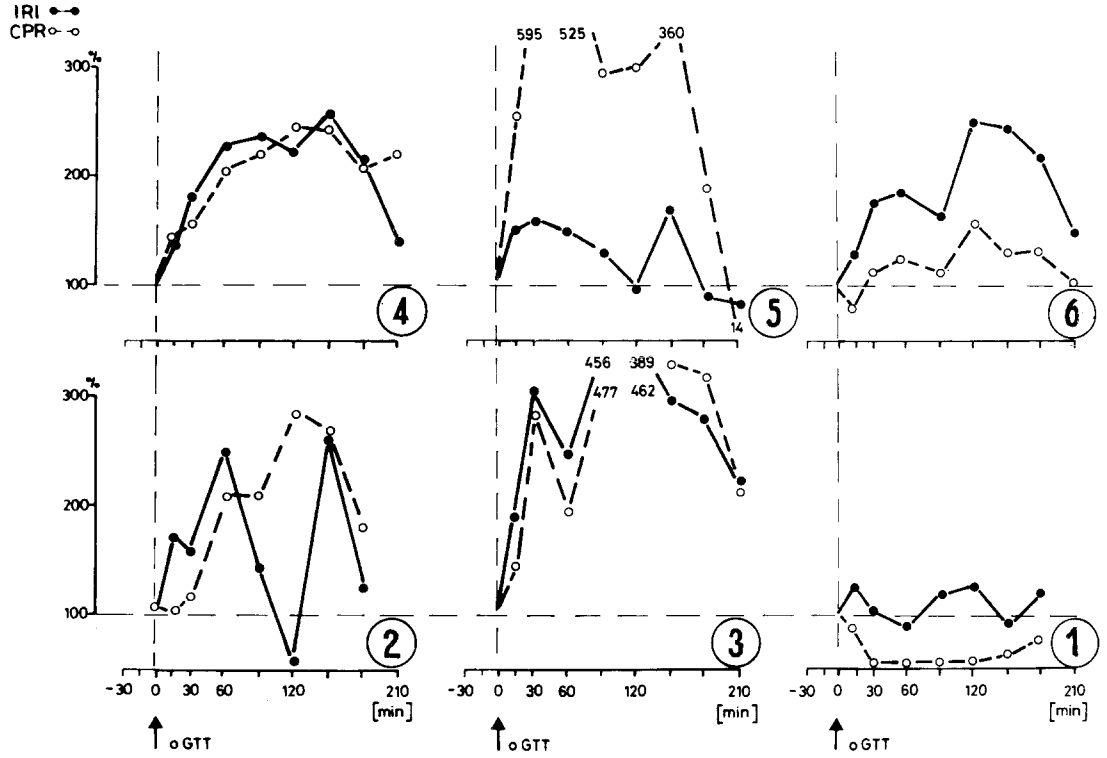

Fig. 1. Effects of oral glucose load on *IRI and* CPR in patients with pancreatic hypoglycaemia. Values are expressed as a percentage of basal concentration

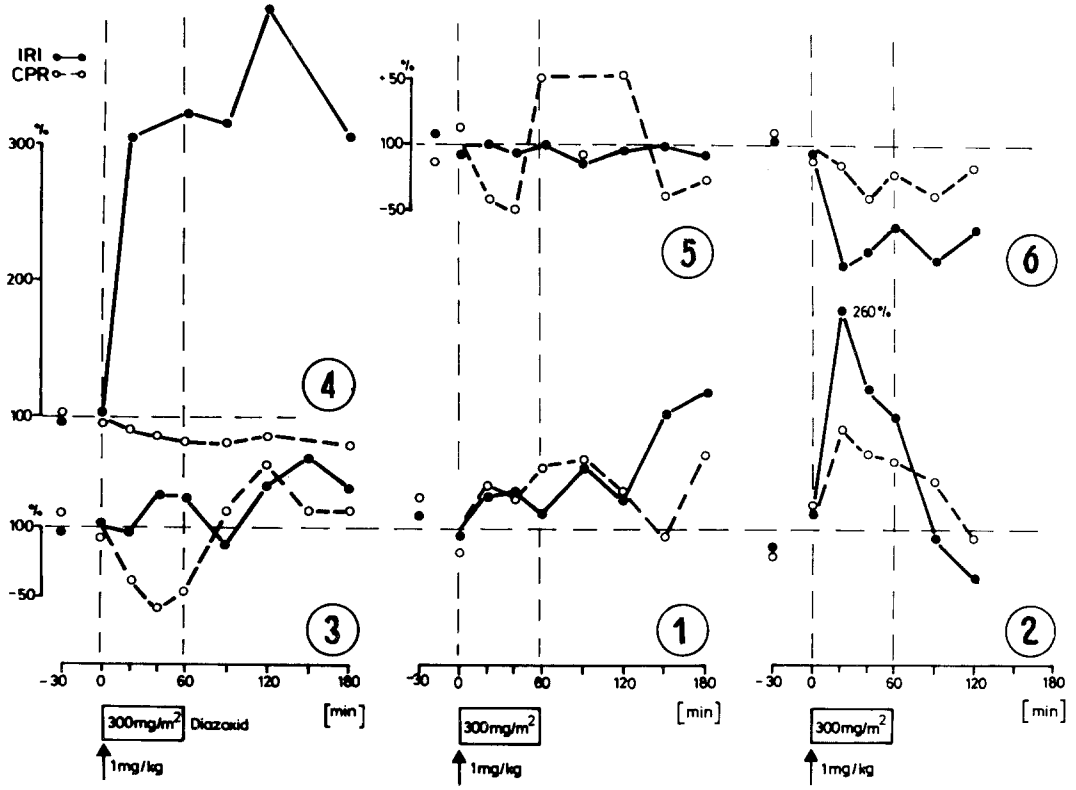

Fig. 2. Effects of diazoxide infusion on *IRI* and *CPR* in infants with pancreatic hypoglycaemia. Values are expressed as a percentage of basal concentration

Somatostatin tests

Both IRI and HCP secretion were suppressed in both insulinoma and nesidioblastosis patients (Fig. 3). After stopping the infusion, the hormone concentrations returned to basal levels. Depression of HCP was more prominent than inhibition of IRI secretion, but both were inhibited in a dose-dependent manner. During the somatostatin infusion a decrease of growth hormone immunoreactivity below 0.6 ng/ml (1.2 μU/ml) was observed.

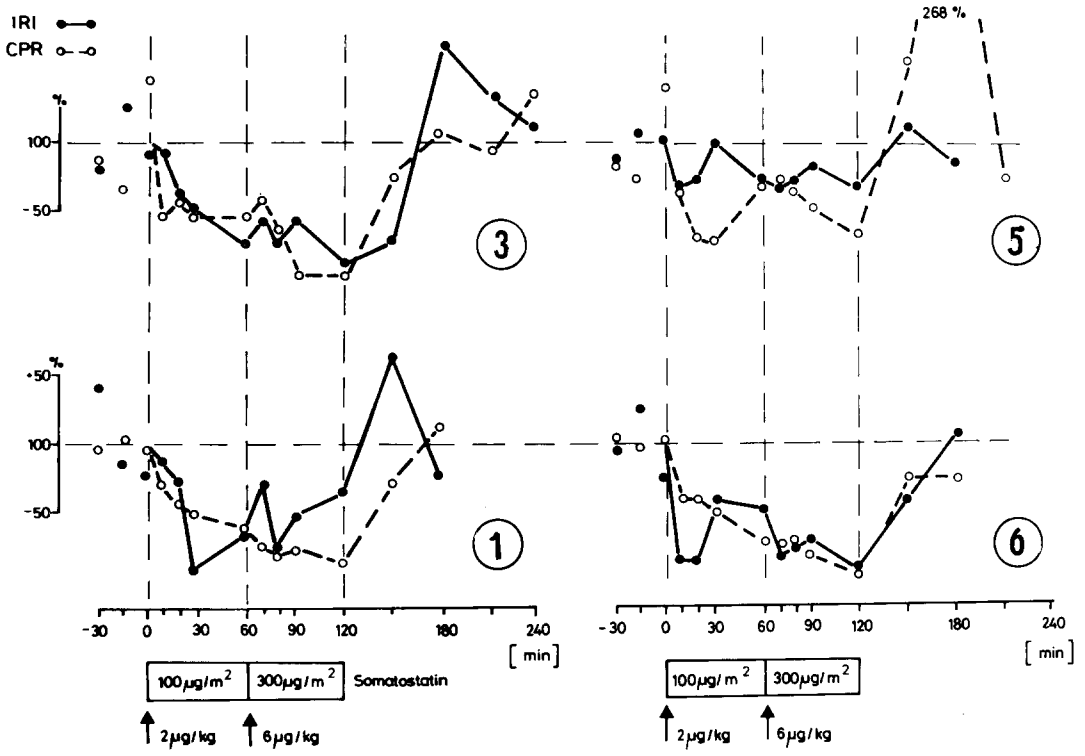

Fig. 3. Effects of somatostatin infusion on *IRI* and *CPR* in infants with pancreatic hypoglycaemia. Values are expressed as a percentage of basal concentration

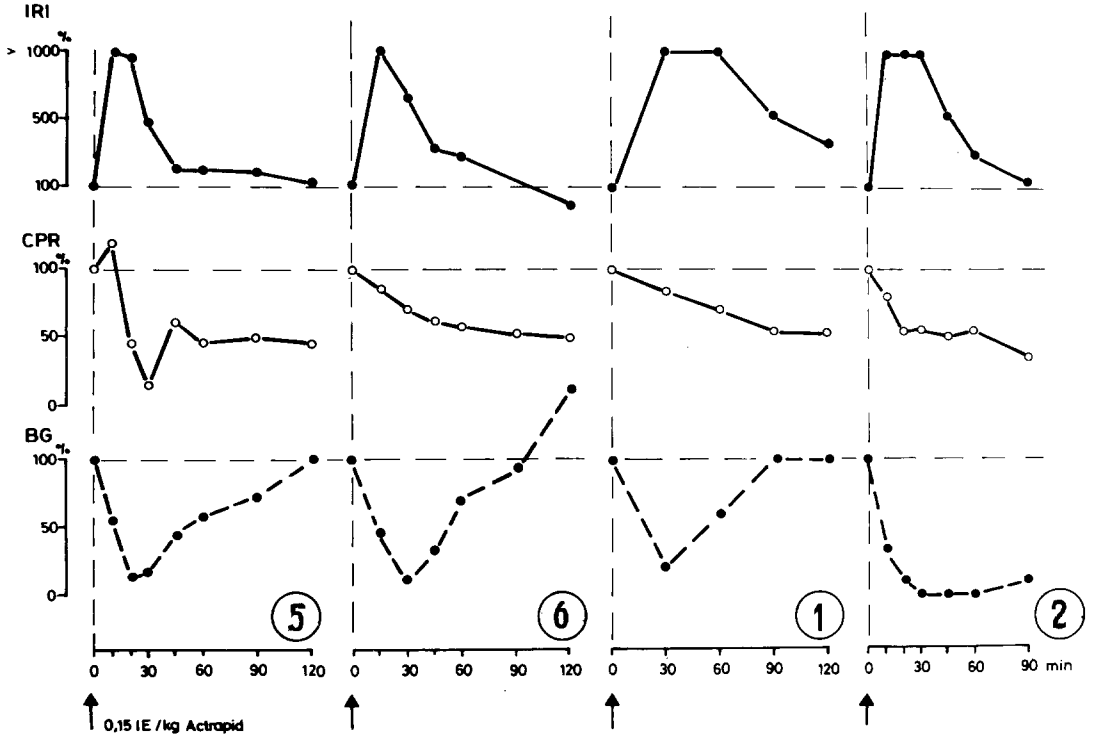

Fig. 4. *IRI, CPR* and *BG* changes after intravenous injection of Actrapid. Values are expressed as a percentage of basal concentration

C-peptide suppression tests

As shown in Fig. 4, intravenous injection of a short-acting insulin preparation (Actrapid) in two patients with nesidioblastosis and two patients with insulinoma produced an 80% decrease of basal BG. Inhibition of HCP release was 86%, 60%, 46% and 65% of basal levels (from left to right in Fig. 4). Insulin concentrations increased to over 1000% of basal levels. Under the same conditions six tall healthy children (age 9–14 years) demonstrated a 50% drop in blood glucose and 88%–85% suppression of CPR.

Table 3. Basal values of immunoreactive insulin (nmol/l; first value; above) and C-peptide immunoreactivity (nmol/l; second value; below) of the different functional tests

Patient no.	Oral glucose tolerance tests	Diazoxide tests	Somatostatin	C-peptide suppression tests
1	0.070	0.130	0.044	0.106
	0.380	0.600	0.240	0.340
2	0.057	0.167		0.109
	0.320	0.960		0.450
3	0.069	0.062	0.099	
	0.227	0.218	0.481	
4	0.073	0.144		
	0.190	0.177		
5	0.038	0.036	0.036	0.069
	0.178	0.315	0.260	0.240
6	0.220	0.110	0.083	0.058
	1.610	0.580	0.245	0.500

Basal concentrations of IRI and CPR

In the Fig. 1–4 only reactive patterns of hormone concentrations are demonstrated. The basal values of IRI and CPR are shown in Table 3.

Discussion

The aetiopathogenesis of diffuse or focal abnormalities of the insulin-producing B-cells is still unknown [1, 17, 20]. Hypoglycaemia during the 1st year of life is a potent cause of brain damage and mental retardation. Early diagnosis and effective medical or surgical treatment is necessary.

The most important biochemical change in hyperinsulinaemic hypoglycaemia is the inappropriately elevated plasma insulin concentration in relation to blood glucose [6, 20, 21]. By using a rapid radioimmunoassay for insulin [2], it seems possible to confirm the diagnosis of hyperinsulinism within a few hours. Measurements of CPR or proinsulin immunoreactivity are not useful in differentiating between diffuse nesidioblastosis or a discrete adenoma, the two causes of pancreatic hypoglycaemia [20].

Our study showed that the repeated estimation of the ratio BG to IRI is of high value in the diagnosis of hyperinsulinaemic hypoglycaemia. It is necessary to assay more than one blood sample at different times because of fluctuating pancreatic hormone secretion [21]. A minimum of five measurements seems to be necessary for the diagnosis of hyperinsulinaemic hypoglycaemia. A BG:IRI ratio less than 2.6 is pathological. The oGTT gave different results, ranging from delayed or unchanged to high insulin release. These tests were without diagnostic value. Diazoxide causes hyperglycaemia by inhibition of insulin release, and it has been shown that in healthy subjects, as well as in cases of insulinoma, insulin secretion was inhibited [12]. In one case with nesidioblastosis CPR and IRI were suppressed. Two of our insulinoma patients showed a paradoxical increase of CPR and IRI. Moreover, patient 4 with nesidioblastosis responded during diazoxide infusion with a dramatic increase of IRI, whereas CPR levels remained almost unchanged. Whether the ifferences seen in CPR and IRI secretion or especially the paradoxical increase of insulin levels after diazoxide infusion are of diagnostic value awaits further investigation.

In adults, somatostatin administration was thought to be a useful diagnostic test for hyperinsulinaemia [19], but this could not be confirmed by the present data. Suppression of CPR was more prominent than inhibition of insulin release, but both were inhibited by somatostatin in a dose-dependent manner. This is in accordance with the results of other investigators who administered 7 µg/kg per hour and 20 µg/kg per hour, respectively [5, 18, 19]. In normal probands 10 µg somatostatin has been reported to be effective in suppressing insulin secretion [4]. It is possible that the somatostatin dose in the present study was too high.

Administration of insulin has been shown to inhibit CPR secretion in healthy adults [9, 15]. This was confirmed in our control subjects. Variable results in adults with insulinoma are reported in the literature [9]. In one of our insulinoma patients a diminished suppression was seen; in the others it was similar to that of healthy children. Due to the variation in results in the literature, our own negative experience and the risk of precipitating cerebral lesions, we abandoned this test.

Preoperative differentiation of the two forms of pancreatic hypoglycaemia was not possible with the different function tests. The diagnosis was only established by histological examination after surgery.

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