Normal proinsulin processing despite beta-cell dysfunction in persistent hyperinsulinaemic hypoglycaemia of infancy (nesidioblastosis)

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Summary Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is a genetic disorder which causes severe hypoglycaemia in the neonate. The beta cells fail to respond to changes in blood glucose levels in all the stages of the disease, which often ends with NIDDM. Fasting insulin, intact proinsulin and des 31,32 split proinsulin levels were measured in PHHI patients with active disease, patients after partial pancreatectomy, and those in clinical remission. All but one of the pancreatectomized patients developed diabetes and were hyperglycaemic on evaluation. Fasting insulin was comparable in pancreatectomized and medically treated patients. Des 31,32 split proinsulin levels were much higher in pancreatectomized compared to non-pancreatectomized patients (10.7 ± 2.5 vs 3.4 ± 0.8 pmol/l, $p = 0.001$) and age-matched control subjects (3.8 ± 1.4 pmol/l, $p = 0.018$). Also the ratio of des 31,32 split proinsulin to total insulin plus proinsulin-like peptides was higher in pancreatectomized patients (18.7 ± 2.8 vs $7.2 \pm 0.8\%$ in non-pancreatectomized patients, $p = 0.001$, and $6.8 \pm 2.1\%$ in normal control subjects, $p = 0.004$). Furthermore, des 31,32 split proinsulin was the dominating species of proinsulin-like molecules in the pancreatectomized patients ($62.7 \pm 1.6\%$ vs $45.5 \pm 3.8\%$, and $49.0 \pm 3.2\%$ in non-pancreatectomized patients and control subjects, respectively, $p = 0.001$ and $p = 0.0002$). Intact proinsulin levels, and the proinsulin percentage, tended to be higher

in pancreatectomized patients; however, the differences did not reach statistical significance. All parameters were similar in non-pancreatectomized patients and age-matched control subjects. Subgroup analysis showed comparable proinsulin-like peptide levels in patients with active disease and those in apparent clinical remission. Fasting levels of insulin and proinsulin-like peptides were also measured in a larger group of healthy children and young adults. Insulin and des 31,32 split proinsulin increased with age, the differences being most prominent when the young age group (0–8 years) was compared to the older groups (8–16 and > 16 years). The fasting levels of plasma insulin were correlated with those of intact proinsulin and des 31,32 split proinsulin ($r = 0.82$ and 0.81 , respectively). Fasting insulin, intact proinsulin and des 31,32 split proinsulin were correlated with BMI ($r = 0.55$, 0.56 and 0.53 , respectively). In summary, relative hyperproinsulinaemia was noted only in PHHI patients with increased secretory demand following pancreatectomy, but not in patients with active disease or those in spontaneous clinical remission. These findings suggest that abnormal proinsulin processing is not an intrinsic feature of PHHI despite the severe beta-cell dysfunction. [Diabetologia (1996) 39: 1338–1344]

Keywords Nesidioblastosis, hypoglycaemia, infancy, proinsulin, pancreatectomy.

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Abbreviations: PHHI, Persistent hyperinsulinaemic hypoglycaemia of infancy; PLP, proinsulin-like peptides; SUR, sulphonylurea receptor; IRMA, immunoradiometric assay.

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI, also called nesidioblastosis) is the most common cause of severe non-transient hypoglycaemia in the neonatal period. In vitro, pancreatic tissue from surgical specimens releases insulin at high rates even in the absence of nutrients; nevertheless,

Table 1. Clinical, metabolic and biochemical characteristics of patients with PHHI

Patient number	Age (years)	Sex	Body mass index (kg/m ²)	Px	Remission ^a	Medical Rx	Diabetes (Rx)	IVGTT	C-peptide ^b suppression
1	12	F	18.6	+	+		+ (Diet)	Diabetic	Abnormal
2	17	M	20.6	+	+		+ (Insulin)	Diabetic	Abnormal
3	16	F	23.3	+	+		+ (Insulin)	Diabetic	Abnormal
4	14	F	21.5	+	+		+ (Insulin)	Diabetic	Normal
5	32	M	25.3	+	+		+ (Insulin)		
6	17	M	19.4	+	+		+ (Diet)	Diabetic	Abnormal
7	2	M	16.3	+	+		–		
8	2	F	18.1	–	–	Octreotide	–		
9	3	M	18.5	–	–	Octreotide + Diazoxide	–		
10	3	F	15.7	–	–	Diazoxide	–		
11	3	M	14.2	–	+/-	Diet	–		
12	5	M	17.0	–	–	Diazoxide	–		
13	5	F	16.3	–	+/-	Diet	–		
14	6	F	14.4	–	–	Diet	–		
15	7	F	17.5	–	+		–		
16	8	F	16.3	–	+		–	Normal	Abnormal
17	9	M	16.0	–	+		–	Diabetic	Abnormal
18	11	M	19.0	–	+		–	FIR	
19	13	F	18.5	–	+		–	Normal	
20	13	F	20.6	–	+		–	Normal	Normal
21	22	M	27.1	–	+		+	Diabetic	

Px, Partial pancreatectomy; Rx, current treatment; IVGTT, intravenous glucose tolerance test; FIR, flat insulin response and normal K_g value (> 1 % · min⁻¹)

^a +/-, Patients without current hypoglycaemia but still treated with frequent carbohydrate-rich meals

^b C-peptide levels higher than 80 pmol/l during prolonged hypoglycaemia were considered abnormal

insulin is secreted through the regulated pathway since it is calcium-dependent and responsive to modulation by hormones [1]. It has recently been shown that mutations in the sulphonylurea receptor (SUR) gene are responsible for the disease in the majority of patients [2, 3]. However, this is not the case for all patients, and the relationship between pathogenesis and the SUR mutation remains to be fully clarified.

Remission from hypoglycaemia is observed several months to years after diagnosis in most patients with PHHI, independent of the mode of treatment during infancy [4–6]. We have shown, however, that children with PHHI retain the impaired insulin response to glucose, and fail to suppress endogenous insulin secretion during induced hypoglycaemia several years after clinical remission [7]. Thus, the beta-cell defect responsible for the disease during infancy is not corrected with time, despite disappearance of symptoms. Moreover, most patients treated by partial pancreatectomy as neonates developed diabetes during puberty [7]. The mechanism of this transition from hyperinsulinaemic hypoglycaemia to hypoinsulinaemic hyperglycaemia is not clear.

Efficient processing of proinsulin to mature insulin is one of the hallmarks of normal beta-cell function. The plasma ratio of proinsulin-like peptides (PLP) to insulin permits assessment of the proinsulin conversion efficiency, and has been used to characterize beta-cell functional disturbances in such diverse conditions as non-insulin-dependent diabetes mellitus

(NIDDM) and insulinoma [8, 9]. In this study, we determined the fasting levels of insulin, proinsulin and des 31,32 split proinsulin in PHHI patients with active disease or in clinical remission, with or without overt diabetes mellitus. Since the normal range of PLP has not been established in the paediatric population, it was measured in healthy infants, children and young adults.

Materials and methods

Subjects. We studied 21 patients with PHHI, diagnosed on the basis of recurrent hypoglycaemia, inappropriately high insulin levels, and augmented glucose requirements [4, 10, 11]. All patients had severe PHHI; in most (19 patients), hypoglycaemia appeared during the first hours/days after birth. Genetic evaluation revealed point mutations in both alleles of the SUR gene in 13 patients (numbers 1–4, 6, 8–10, 12–14, 17, 21), in one allele in 6 patients (numbers 5, 11, 15, 18–20), while no mutation was found in 2 patients (numbers 7 and 16) [3]. Clinical and biochemical details of the patients are given in Table 1. The data on ten of these patients has previously been reported in another context [7]. Seven patients (numbers 1–7) required early partial (80–90 %) pancreatectomy; six of these developed clinical diabetes during puberty. Fourteen patients were treated conservatively: two (numbers 10 and 12) received diazoxide, one (8) was on octreotide, one (9) on combined octreotide/diazoxide, and three (11, 13 and 14) treated with frequent carbohydrate-rich meals without medication. Seven patients (14–21) were in clinical remission. Patient 21 had normal fasting blood glucose levels but diabetic oral glucose tolerance

Table 2. Fasting insulin and proinsulin-like peptide levels in normal children and young adults

	Age range (years)			p-value		
	0–8	8–16	> 16	1	2	3
<i>n</i>	17	16	14			
Age	5.6 ± 0.6	12.3 ± 0.5	21.6 ± 1.2			
Body mass index (kg/m ²)	15.7 ± 0.7	19.0 ± 1.3	24.2 ± 1.3	0.05	0.0001	0.02
Glucose (mmol/l)	4.8 ± 0.3	4.9 ± 0.2	4.6 ± 0.1	NS	NS	NS
Insulin (pmol/l)	18.1 ± 3.4 (11.0–25.2)	72.3 ± 13.3 (44.0–100.6)	85.5 ± 19.2 (44.3–126.7)	0.0001	0.0001	NS
Proinsulin (pmol/l)	3.8 ± 0.6 (2.5–5.2)	4.6 ± 0.8 (2.9–6.3)	5.9 ± 1.4 (2.9–8.8)	NS	NS	NS
Des 31,32 proinsulin (pmol/l)	3.4 ± 0.9 (1.5–5.2)	7.7 ± 1.7 (4.0–11.3)	11.8 ± 2.5 (6.4–17.1)	0.01	0.004	NS
Insulin ratio (%)	73.8 ± 3.0 (67.2–80.3)	83.4 ± 2.1 (78.8–87.9)	79.6 ± 2.7 (73.7–85.5)	0.02	NS	NS
Proinsulin ratio (%)	12.9 ± 2.1 (8.4–17.4)	6.5 ± 0.9 (4.5–8.5)	7.1 ± 1.0 (4.9–9.4)	0.006	0.02	NS
Des 31,32 proinsulin ratio (%)	13.3 ± 2.6 (7.5–19.0)	10.2 ± 1.4 (7.2–13.1)	13.2 ± 1.9 (9.0–17.4)	NS	NS	NS
Des 31,32 proinsulin as % of PLP	47.4 ± 5.0 (36.4–58.3)	60.5 ± 2.7 (54.7–66.3)	63.4 ± 3.4 (55.9–70.8)	0.02	0.008	NS

Data are arithmetic means ± SEM (95% confidence interval). P1 refers to differences between age groups 0–8 and 8–16 years; P2 between age groups 0–8 and > 16 years; P3 between age groups 8–16 and > 16 years. Statistical analysis was performed using the Kruskal-Wallis test

Peptide ratio indicates peptide percentage of sum of insulin, intact proinsulin and des 31,32 split proinsulin

test; he showed symptoms of hypoglycaemia only after prolonged fasting. None were hypoglycaemic when evaluated for the present study.

Blood samples of 21 age and sex-matched control subjects were used for comparison with the PHHI group. The control group was then enlarged to 48 patients for better characterizing PLP levels in normal children and young adults. Thirty-two control subjects were Ashkenazi Jewish, 15 Sephardic Jewish, and one was Arab. Insulin and PLP levels being comparable in the different ethnic groups, PHHI patients and control subjects were not matched for ethnic origin. Adiposity was assessed by body mass index (BMI, kg/m²) [12]. Blood samples were collected after an overnight fast, plasma separated immediately, frozen, transported to Cambridge, UK on dry ice, and stored at –70°C until analysed. In diabetic PHHI patients treated with insulin, blood was drawn prior to the morning injection, 12–14 h following the night injection (Insulatard; Novo Nordisk, Bagsvaerd, Denmark, or Humilin N, Lilly, Fegersheim, France). The study was approved by the institutional ethics committee.

Laboratory methods. Plasma glucose was measured by glucose oxidase (Beckman, Berkeley, Calif., USA), plasma insulin by immunoenzymatic assay (Medgenix Diagnostics SA, Fleurus, Belgium) which has performance characteristics indistinguishable from our previously used immunoradiometric assay (IRMA) [13]. Intact proinsulin and des 31,32 split proinsulin were measured by two-site IRMA [13]. The assay for des 31,32 split proinsulin does not discriminate between this intermediate and des 32 split proinsulin or 32,33 split proinsulin. However, comparison of IRMA for plasma proinsulin and split proinsulins with assays combined with HPLC shows that split proinsulin IRMA predominantly measures des 31,32 proinsulin [14]. The insulin IRMA had an interassay coefficient of variation less than 12%, the minimal detection limit being 8

pmol/l. The intact proinsulin and des 31,32 split proinsulin assays had interassay coefficients of variation less than 13%, the minimal detection limit being 1.25 pmol/l. The cross-reactivity of proinsulin in the assay is determined by direct analysis for each batch of reagents. The corrected des 31,32 split proinsulin is equivalent to the measured des 31,32 split proinsulin minus 84% of the measured proinsulin. Insulin antibodies were absent in insulin-treated patients, therefore interference in the assay is unlikely.

Statistical analysis. Results are expressed as mean ± SEM. Samples of pancreatectomized vs non-pancreatectomized patients and of PHHI patients and their matched control subjects were compared using the unpaired Mann-Whitney U-test. The Kruskal-Wallis test for one-way analysis of variance was used to compare insulin and PLP values in different control age groups. Correlations between age, BMI, glucose, insulin, intact proinsulin and des 31,32 split proinsulin were tested by multivariate analysis.

Results

Beta-cell function in PHHI (Table 1).

Pancreatectomy group. Six patients who underwent partial pancreatectomy in infancy developed diabetes during puberty, with significant fasting hyperglycaemia and elevated glycated haemoglobin values, but without ketoacidosis. Four patients (2–5) were treated with insulin, while two (1, 6) were controlled with diet alone. C-peptide suppression in response to

Table 3. Fasting insulin and proinsulin-like peptide levels in patients with PHHI and age-matched control subjects

	Px	Medical Rx	Control P	Control M	<i>p</i> -value		
					1	2	3
<i>n</i>	7	14	7	14			
Age (years)	15.7 ± 3.4	7.8 ± 1.5	15.6 ± 3.4	8.3 ± 1.5			
Body mass index (kg/m ²)	22.3 ± 1.2 (19.4–25.2)	18.0 ± 0.9 (16.1–19.9)	19.2 ± 1.2 (16.2–24.5)	16.6 ± 1.0 (14.5–18.7)	0.004	NS	NS
Fasting glucose (mmol/l)	10.7 ± 1.5 (4.0–14.3)	4.6 ± 0.2 (4.2–5.0)	5.0 ± 0.6 (3.5–6.6)	5.1 ± 0.4 (4.3–5.8)	0.003	0.018	NS
Insulin (pmol/l)	42.4 ± 9.0 (20.5–64.4)	39.1 ± 7.0 (24.1–54.2)	43.7 ± 11.8 (14.8–72.6)	36.4 ± 9.1 (16.8–56.0)	NS	NS	NS
Proinsulin (pmol/l)	6.7 ± 1.8 (2.4–11.0)	3.3 ± 0.4 (2.4–4.2)	3.9 ± 1.0 (1.5–6.2)	3.3 ± 0.6 (2.1–4.5)	0.056	NS	NS
Des 31,32 proinsulin (pmol/l)	10.7 ± 2.5 (4.6–16.7)	3.4 ± 0.8 (1.6–5.2)	3.8 ± 1.4 (0.5–7.2)	3.9 ± 0.8 (2.1–5.8)	0.001	0.018	NS
Proinsulin ratio (%)	11.9 ± 2.0 (7.0–16.9)	8.5 ± 1.0 (6.4–10.5)	7.8 ± 1.6 (4.0–11.6)	10.3 ± 1.4 (7.4–13.3)	NS	0.097	NS
Des 31,32 proinsulin ratio (%)	18.7 ± 2.8 (11.9–25.6)	7.2 ± 0.8 (5.6–8.8)	6.8 ± 2.1 (1.7–11.8)	11.0 ± 2.2 (6.2–15.9)	0.001	0.004	NS
Insulin ratio (%)	69.0 ± 4.7 (57.5–80.5)	84.3 ± 1.3 (81.4–87.2)	83.9 ± 3.1 (76.4–91.4)	78.6 ± 2.7 (72.9–84.3)	0.007	0.026	0.066
Des 31,32 proinsulin as % of PLP	62.7 ± 1.6 (58.8–66.5)	45.5 ± 3.8 (37.2–53.8)	49.0 ± 3.2 (41.2–56.7)	50.6 ± 4.2 (41.6–59.7)	0.001	0.0002	NS

Data are arithmetic means ± SEM (95 % confidence interval)
Px, Pancreatectomy; Rx, treatment; PLP, proinsulin-like peptides

Control P, age-matched control subjects for pancreatectomized patients; Control M, age-matched control subjects for medically treated patients

P1 refers to differences between pancreatectomized and medically treated patients; P2 between pancreatectomized patients and age-matched control subjects; P3 between medically treated patients and age-matched control subjects. Statistical analysis was performed using the Mann-Whitney U-test

Peptide ratio indicates peptide percentage of sum of insulin, intact proinsulin and des 31,32 split proinsulin

induced hypoglycaemia was inadequate in four of the five patients tested. Patient 7 was 2 years old and therefore no dynamic test was performed.

Non-pancreatectomy group. Seven patients (8–14) had active disease and were not subjected to dynamic tests. Among the 6 patients in clinical remission two (16, 17) failed to suppress the plasma C-peptide level during insulin-induced hypoglycaemia. Five patients had an intravenous glucose tolerance test: three (16, 19, 20) had normal plasma insulin responses, one (18) had a flat insulin curve, while one (17) showed a blunted response with borderline diabetic K_g value ($1\% \cdot \text{min}^{-1}$). Patient 21 had normal fasting blood glucose levels, but was diabetic by oral glucose tolerance test (16.7 mmol/l at 120 min); his insulin response was blunted, increasing only from 144 to 260 pmol/l. The test protocols and detailed results were recently reported [7].

Insulin precursor levels in healthy children and young adults. Seventeen healthy children aged 0–8 years, 16 aged 8–16 years, and 15 older than 16 years were studied. Table 2 shows their plasma glucose, insulin and PLP levels. Plasma insulin was significantly lower in the youngest than in the older age groups ($p = 0.0001$), also des 31,32 split proinsulin was significantly

lower ($p = 0.01$ and 0.004 compared to the age groups 8–16 and > 16 , respectively), while proinsulin levels were comparable among the three groups. By multivariate analysis, fasting insulin levels strongly correlated with intact proinsulin and des 31,32 split proinsulin ($r = 0.82$ and 0.81 , respectively). The correlations between BMI and fasting insulin, intact proinsulin and des 31,32 split proinsulin ($r = 0.55$, 0.56 and 0.53 , respectively) were weaker, and no correlation was found between BMI and age or fasting glucose.

Insulin and insulin precursor levels in PHHI. Table 3 presents the plasma levels of glucose, insulin and PLP in patients with PHHI. Pancreatectomized patients had significantly elevated fasting glucose levels (10.7 ± 1.5 mmol/l) compared to matched control subjects (5.0 ± 0.6 mmol/l, $p = 0.018$). Fasting insulin was similar in pancreatectomized and non-pancreatectomized patients and in age-matched control subjects. Intact proinsulin was slightly higher in pancreatectomized than in non-pancreatectomized patients ($p = 0.056$). Des 31,32 split proinsulin in pancreatectomized patients was significantly higher than in non-pancreatectomized patients and control subjects (10.7 ± 2.5 vs 3.4 ± 0.8 and 3.8 ± 1.4 pmol/l; $p = 0.001$ and 0.018 , respectively). In pancreatectomized patients, intact proinsulin and des 31,32 split proinsulin

comprised 11.9 ± 2.0 and $18.7 \pm 2.8\%$ of total insulin plus PLP, respectively. For comparison, these percentages were 8.5 ± 1.0 and $7.2 \pm 0.8\%$ in non-pancreatectomized patients, and 7.8 ± 1.6 and $6.8 \pm 2.1\%$ in normal children. The differences between pancreatectomized and non-pancreatectomized patients and healthy control subjects regarding des 31,32 split proinsulin ratios were statistically significant (Table 3). These differences may have been underestimated, since the intact insulin values in insulin-treated patients may partly reflect the intermediate-acting insulin injected the night before sampling. Indeed, the fasting C-peptide levels in these patients were low ($39\text{--}116$ pmol/l), compatible with decreased secretion of fully processed insulin. In non-pancreatectomized patients and normal control subjects, des 31,32 split proinsulin represented 45.5 ± 3.8 and $49.0 \pm 3.2\%$ of total proinsulin-related molecules; this proportion was significantly increased in pancreatectomized patients ($62.7 \pm 1.6\%$, $p = 0.001$ and 0.0002 , respectively).

In order to determine whether the disease state of the patients affects insulin processing, medically treated patients were divided into two groups: those with active disease, and those in clinical remission (Fig. 1). The insulin, proinsulin and des 31,32 split proinsulin levels and ratios were comparable between these two groups. The differences in proinsulin and des 31,32 split proinsulin between the pancreatectomized and non-pancreatectomized groups noted above were accentuated when the latter group was limited to patients with active disease.

Discussion

Following a period of variable duration with hypoglycaemic episodes, most patients with PHHI enter clinical remission, despite the persistence of beta-cell dysfunction. This is evidenced by occurrence of mild hypoglycaemia during intercurrent disease, failure to suppress endogenous insulin release in response to induced hypoglycaemia, and abnormal beta-cell response to glucose loading [7]. The medical and surgical interventions required to control hypoglycaemia may also influence the evolution of the disease. Thus, most patients treated by subtotal pancreatectomy during infancy develop diabetes around puberty. However, this may also reflect the natural history of the disease, as shown in two of the older medically treated patients (17, 21) who showed diabetic glucose tolerance tests, albeit without fasting hyperglycaemia.

In this study we evaluated the efficiency of proinsulin processing in various stages of the disease, as reflected by the plasma levels of proinsulin and des 31,32 split proinsulin. Des 31,32 split proinsulin was elevated only in patients who had undergone pancreatectomy. Since the majority of these had diabetes, it is impossible to conclude if the increase in insulin

Fig. 1A–C Fasting plasma insulin (A), proinsulin (B) and des 31,32 split proinsulin (C) in PHHI patients after pancreatectomy (Px), patients with active disease undergoing medical treatment or diet, and those in clinical remission. * $p = \text{NS}$; ** $p = 0.01$; *** $p = 0.0006$; **** $p = 0.038$

precursors is due to hyperglycaemia, or to the compensatory hyperfunction of the residual pancreas. One young patient (7) who underwent partial pancreatectomy but had not yet developed diabetes also had high levels of partially processed proinsulin, supporting the latter alternative. Non-pancreatectomized patients had des 31,32 split proinsulin levels comparable to those of age-matched normal control subjects. Even the two patients with impaired glucose tolerance but without fasting hyperglycaemia had normal proinsulin levels. Subgroup analysis revealed no difference between patients in clinical remission and those with active disease, whether they were medically treated or treated by diet alone. It must be remembered, however, that PLP measurements pertain to the fasting state; thus, subtle defects in proinsulin processing would not be detected in our study.

Our finding of normal levels of proinsulin-related peptide in all non-pancreatectomized, non-hyperglycaemic patients suggests that abnormal proinsulin processing is not an intrinsic element in PHHI. This conclusion is strengthened by the finding that non-pancreatectomized patients with active disease, when analysed separately, showed the lowest proinsulin levels of all groups. These findings are surprising if one takes into consideration the severity of the beta-cell dysfunction in this disorder. Partial pancreatectomy also induces hyperproinsulinaemia in presumably healthy people [15]. In that sense the situation is similar to that found in insulin-resistance syndromes [16, 17] and in identical twins discordant for NIDDM [18]. Reduction of hyperglycaemia corrects the proinsulin secretion in NIDDM [19, 20]; however hyperproinsulinaemia is also found in impaired glucose tolerance and in relatives of NIDDM patients in the absence of hyperglycaemia [21–24]. Excessive secretion of insulin precursors also characterized and predicted gestational diabetes before the appearance of hyperglycaemia [25]. In contrast to these, in patients with active PHHI, in whom insulin hypersecretion is driven by a defective SUR rather than metabolic demand, hypersecretion of precursors was not seen. In most insulinoma patients, proinsulin secretion is elevated [9]; thus, the pathophysiology of insulin hypersecretion in these tumours seems to be different from that of PHHI.

Proinsulin is processed sequentially, first by the convertase PC1 which cleaves the molecule at the 32,33 site, then by PC2 which cleaves at the 64,65 site to produce mature insulin [26]. Under stress conditions PC2 cleavage becomes rate-limiting, leading to the accumulation of des 31,32 split proinsulin [26]; therefore, increase in des 31,32 split proinsulin may be a more specific correlate of beta-cell dysfunction. In support of the above, pancreatectomized patients had only a modest elevation of intact proinsulin concentrations, contrasting with the highly significant augmentation of des 31,32 split proinsulin. A similar trend was observed in impaired glucose tolerance [27], NIDDM [28] and gestational diabetes [25].

PHHI is a monogenic disorder, associated with mutations in the SUR gene which result in persistent depolarization of the beta-cell membrane and hence autonomous insulin hypersecretion [2]. Variability in SUR gene mutations, and the relatively small number of PHHI patients available for study, make it impossible to provide correlation between clinical findings and the nature of the mutation. Nevertheless, our findings suggest that insulin hypersecretion under these conditions is not associated with abnormalities in proinsulin processing, while failure of this function appears when the islets are exposed to the stress of partial pancreatectomy and/or hyperglycaemia.

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