Acta Diabetol (1996) 33: 1–6

ORIGINAL

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Increased insulin sensitivity and basal insulin effectiveness in postprandial reactive hypoglycaemia

Received: 23 March 1995 / Accepted in revised form: 3 November 1995

Abstract Glucose clamp experiments have shown that patients with reactive postprandial hypoglycaemia (PRH) frequently have an increased glucose disposal, but the relative involvement of insulin sensitivity (SI) and glucose effectiveness (Sg) in this process remains unknown. The minimal model approach was used to compare 13 patients in whom moderate reactive hypoglycaemia (<3.3 mmol) had been previously diagnosed and 13 matched controls. The intravenous glucose tolerance test (IVGTT, 0.5 g/kg glucose IV) with 0.02 U/kg insulin given at the 19th min and frequent sampling over 180 min shows that PRH patients exhibit a higher glucose tolerance coefficient Kg (2.99 ± 0.26 vs 2.19 ± 0.12; $P<0.02$), higher SI [22.9 ± 6.4 vs 7.18 ± 0.14 $min^{-1}/(\mu U/ml) \cdot 10^{-4}$; $P<0.01$] and higher Sg (3.84 ± 0.35 vs 2.92 ± 0.79 $min^{-1} \cdot 10^{-2}$; $P<0.05$). The increase in Sg is explained by an increase in its component basal insulin effectiveness (BIE: 1.2 ± 0.27 $min^{-1} \cdot 10^{-2}$ in PRH subjects vs 0.58 ± 0.07; $P<0.05$) rather than an increase in Sg at zero insulin. The increase in BIE results from the high values of SI. In 4 PRH subjects SI and Sg were within the normal range, and the increase in Kg evidenced in the 9 others was explained by an increase in SI alone in 3 cases, in Sg alone in 1 case, and both SI and Sg in 5 cases. Thus, in sedentary subjects, the previously reported rise in tissue glucose assimilation is mainly explained by an increased insulin-mediated glucose disposal rather than non-insulin-mediated glucose disposal.

Key words Insulin sensitivity · Glucose effectiveness · Intravenous glucose tolerance test · Reactive hypoglycaemia

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Introduction

Postprandial reactive hypoglycaemia (PRH) has been a controversial topic for many years [1–3]. This syndrome was first described in 1924 by Harris [4] who postulated that hypoglycaemia (caused by high insulin or increased insulin activity) represented a counterpart to diabetes mellitus (resulting from low insulin or reduced insulin activity). The major cause of controversy is the oral glucose tolerance test (OGTT) which was too frequently employed for diagnosing this syndrome. It has been well demonstrated that this test normally induces falls in glycaemia below 2.8 mmol/l in more than 10% of normal subjects [5]. If correct criteria are applied, PRH occurs less frequently than believed by patients, but is not a rare condition [6]. Ambulatory glycaemic control demonstrates its occurrence in 46% of patients referred for postprandial signs [7], and hypoglycaemia can be reproduced after a standardized hyperglucidic breakfast test in 47% of such patients [8]. Thus, there is evidence that excessive postprandial drops in blood glucose levels really occur in some individuals. In that case a simple dietary correction may markedly improve the quality of life for these patients [9].

Such bona fide PRHs can be theoretically explained by three mechanisms which may sometimes be associated: excessive insulin response, deficient counterregulation, and increased glucose uptake by tissues [10]. The third mechanism, i.e. an increase in insulin sensitivity (SI), was suspected 20 years ago [11] and has been more recently demonstrated with the glucose clamp technique [12]. However, the clamp measurement which was employed in that study does not allow measurement of the important effect of glucose itself independent of insulin, on the glucose utilisation rate. This parameter, termed glucose effectiveness (Sg) [13], is markedly increased in some sportsmen suffering from exercise hypoglycaemia [14]. Thus, whether the previously reported increase in glucose uptake in PRH results only from increases in SI or is also related to changes in Sg remains to be determined. Theoretically, increases in Sg or SI may be related to different pathophy-

siological processes, which would imply different dietary approaches. Therefore, we aimed at analysing PRH with the minimal model in order to determine: (a) whether this procedure detects an increase in SI as previously found with the glucose clamp; (b) whether there are also changes in Sg in these patients.

Subjects and methods

Subjects

Thirteen patients were selected for the study after the diagnosis of PRH had been made on the basis of two criteria:

- Spontaneous occurrence of a plasma glucose level lower than 3.3 mmol/l in daily life (ambulatory control with a commercial glucose analyser) and/or after a standardized hyperglucidic breakfast test as previously reported [8];
- Complaint of spontaneous signs of hypoglycaemia according to the list given by the consensus symposium of Rome [6]. This questionnaire looks for signs of neuroglucopenia: blurred vision, headache, confusion, depression, paraesthesia; and sympathetic signs: tremors, anxiety, hunger, palpitations, sweating, nausea, dizziness and weakness. Patients were asked to give all signs a scale value (from 0 to 5).

Subjects presenting with pituitary, thyroid and adrenal insufficiencies were excluded from the study. No patient in this series either had insulinoma or had undergone gastrectomy. Markedly obese subjects (body mass index, BMI >31 kg · m^{-2}) and patients with impaired glucose tolerance according to the WHO criteria were excluded from the study.

Thirteen subjects matched for age, sex and BMI were also studied (Table 1). All subjects gave their informed consent prior to inclusion in the study. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Intravenous glucose tolerance test

Subjects underwent the intravenous glucose tolerance test (IVGTT) after a 12-h fast. At 9:00 a.m., a cannula was set in the cephalic vein at the level of the cubital fossa for blood sampling at various times, while glucose was injected in the contralateral cephalic vein. Glucose (0.5 g/kg, solution at 30%) was slowly injected over 3 min. Insulin (0.02 units/kg body weight, i.e. 1 or 2 units) was injected intravenously immediately after time 19. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 min following the onset of the glucose injection. Times 1 and 3 were used for the determination of the insulin early secretory phase [15]. The other times were necessary for minimal model calculations [16, 17]. Giving insulin bolus at time 19 improves the reliability of the measurements, since a marked increase of plasma insulin above baseline (area under the curve higher than 1000 μU · ml^{-1} · min) is needed for a correct calculation of SI [13].

Table 1 Characteristics of study subjects and controls (*BMI* body mass index). No significant differences for these data between the two groups

	Controls (n=13)	Hypoglycaemic subjects (n=13)
Age (years)	31 ± 2.37	38.46 ± 3.62
Sex (M/F)	5/8	4/9
Weight (kg)	65.6 ± 2.68	65.88 ± 3.28
Height (cm)	169.3 ± 1.76	167.27 ± 1.7
BMI (kg/m^2)	22.94 ± 0.98	23.42 ± 0.97

Laboratory measurements

All samples were analysed for plasma insulin by radioimmunoassay (kit SB-INSI-5 from the international CIS) and plasma glucose with a Beckman glucose analyser. The within-assay coefficient-of-variation (CV) for insulin was determined by repetitive measurements of the same sample and ranged from 8.6% (low values) to 9.7% (high values). The between-assay CV for insulin ranged from 12.5% (low values) to 14.4% (high values). The sensitivity (lowest detectable value) was 2 μU/ml.

Glucose assimilation coefficient

The least square slope of the log of the absolute glucose concentration between 4 and 19 min after the glucose bolus was used as an index of glucose tolerance, Kg_{4-19}. This Kg value describes glucose assimilation by tissues and depends on three factors: insulin release, insulin sensitivity, and glucose effectiveness independent of insulin. We did not use the more classic Kg_{10-30} (i.e. the same measurement made between 10 and 30 min) which may be influenced by the insulin injection at the 19th min, while Kg_{4-19} is not.

Measurement of insulin sensitivity and glucose effectiveness

Minimal model analysis of IVGTT was done according to Bergman [13, 16] with the software 'TISPAG' from the Department of Physiology of the University of Montpellier I, France [14, 18], which uses a non-linear least square estimation. This program gave the values of SI and Sg as calculated from the following equations:

$$dG(t)/dt = -[p1 + X(t)]\,G(t) + p1\,Gb$$
$$G(0) = Go$$
$$dX(t)/dt = -p2\,X(t) + p3\,[I(t) - Ib]$$
$$X(0) = 0$$

where $G(t)$ and $I(t)$ are plasma glucose and insulin concentrations, $X(t)$ is the insulin in a compartment remote from plasma ("insulin action"), and $p1$–$p3$ are model parameters. Go is the glucose concentration that one would obtain immediately after injection, if there were instantaneous mixing in the extracellular fluid compartment. Gb and Ib are basal values of glucose and insulin. Parameter $p1$ represents Sg, i.e. the fractional disappearance rate of glucose, independent of any insulin response, and $p3$ and $p2$ determine the kinetics of insulin transport, respectively, into and out of the remote insulin compartment where insulin action is expressed. SI is an index of the influence of plasma insulin to change glucose's own effect on glucose concentration. Thus, SI is equal to $-p3/p2$.

Sg was divided into its two components [14]: the contribution of hyperglycaemia per se to tissue glucose utilization and the effect of basal insulin on glucose uptake. The basal insulin component of Sg is termed basal insulin effect (BIE) and can be calculated as the product of basal insulin Ib and SI: BIE = $Ib \times SI$. Thus, the contribution of non-insullin-dependent glucose uptake (glucose effectiveness at zero insulin, GEZI) to glucose uptake is the difference between total Sg and BIE: GEZI = Sg – ($Ib \times SI$).

The validity of our procedure using a reduced number of samplings has been tested on 10 IVGTTs with values of SI ranging between 0.56 and 16.94 $min^{-1}/\mu U(ml) \times 10^{-4}$. We compared the results given by the software with a classical protocol including 26 samples (1, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, 180 min) and with the reduced number of samples proposed by Steil and Bergman [16] and used here. Values of Sg (r=0.996; slope 0.966; intercept 0.046) and SI (r=0.971; slope 0.875; intercept 0.983) were highly correlated. The mean relative deviation (defined as the percentage of difference between parameters calculated from the full sample protocol and parameters calculated from the reduced sample protocol) was –1.95% ± 1.15% for Sg and 2.55% ± 4.23% for SI.

Assessment of beta-cell function

First-phase insulin secretion [15] was calculated by the sum of insulin concentration at 1 and 3 min after the end of glucose injection (I_{1+3}). The AIRglc was also calculated, i.e. the mean of insulinaemia as above baseline between 1 and 10 min [20]. A product AIRglc×SI was also calculated, as a glucose tolerance index according to Kahn and coworkers [19, 20]. Since exogenous insulin was added at time 19, the second-phase insulin secretion could not be measured.

Statistics

Results are presented as mean ± SE. Modifications of glycaemia and insulinaemia after IVGTT and comparisons of these curves between the two groups were investigated with analysis of variance (ANOVA) with the Neumans Keuls procedure. Parameters of glucose assimilation were compared with the Mann-Whitney test. Significance was defined as $P<0.05$.

Results

Fasting values of plasma glucose and insulin were different between the two groups. In patients examined for PRH, glycaemia was lower at time 0 (4.34 ± 0.12 vs 4.92 ± 0.13 mmol/l; $P<0.01$) as well as baseline insulinaemia at time 0 (6 ± 0.266 vs 8.5 ± 0.843 µU/ml; $P<0.02$).

Comparison of IVGTT curves of blood glucose and insulin (Figs. 1 and 2) showed significant differences between controls and subjects referred for PRH. Blood glucose was significantly lower in PRH than controls at times 0 ($P<0.01$), 3 ($P<0.05$), 4 ($P<0.001$), 10 ($P<0.01$), 15 ($P<0.02$), 19 ($P<0.01$), 22 ($P<0.02$) and 24 ($P<0.05$). Insulin curves showed on the whole lower values (ANOVA $P<0.01$) in PRH (see Fig. 2). These values were significantly different (lower in PRH than controls) at times –15 ($P<0.05$), 0 ($P<0.0$), 22 ($P<0.05$), 30 ($P<0.05$), 41 ($P<0.05$), 90 ($P<0.01$) and 180 ($P<0.02$).

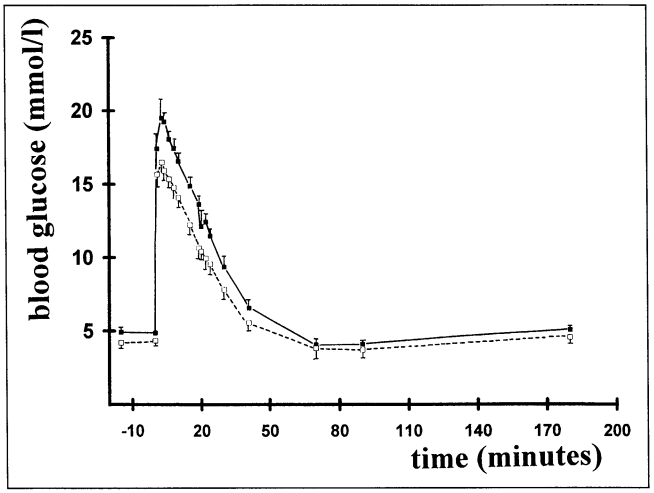

Fig. 1 Blood glucose response to the intravenous glucose tolerance test (IVGTT) in patients referred for postprandial signs of hypoglycaemia (PRH, $n=13$, *lower curve*) compared with 13 matched control subjects. Values are mean ± SEM. Glycaemia is significantly lower in the PRH group at times 0 ($P<0.01$), 3 ($P<0.05$); 4 ($P<0.001$), 10 ($P<0.01$), 15 ($P<0.02$), 19 ($P<0.01$), 22 ($P<0.02$) and 24 ($P<0.05$)

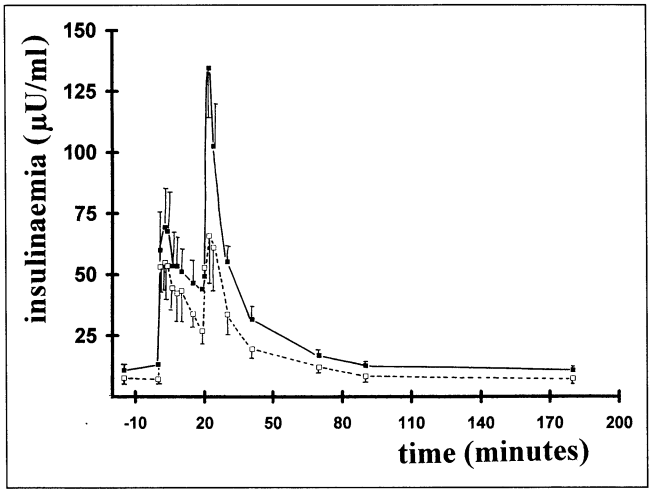

Fig. 2 Insulinaemic response to the IVGTT in patients referred for postprandial signs of hypoglycaemia ($n=13$, *lower curve*) compared with 13 matched control subjects. Values are mean ± SEM. Insulinaemia is significantly lower at times –15 ($P<0.05$), 0 ($P<0.01$), 22 ($P<0.05$), 30 ($P<0.05$), 41 ($P<0.05$), 90 ($P<0.01$) and 180 ($P<0.02$)

Parameters of glucose assimilation

Parameters of glucose assimilation are shown in Table 2. Compared with controls PRH subjects had higher Kg (+36.5%; $P<0.02$), higher SI (+218.9%; $P<0.01$) and higher Sg (+31.5%; $P<0.05$). The insulin first-phase response was not different, either expressed as I_{1+3} or as AIRglc. The glucose tolerance factor AIRglc×SI was also not different, due to a large overlap between the values of the two groups.

When Sg was divided into its two components BIE and GEZI, an increased value of BIE was observed in PRH subjects (+108.33%; $P<0.05$), while GEZI was not statistically different between the two groups. Values of Sg in the PRH group were correlated to values in BIE ($r=0.663$; $P<0.05$) and GEZI ($r=0.685$; $P<0.05$). BIE and GEZI were not correlated to each other ($r=-0.127$; NS) and were thus independent determinants of Sg, each of them accounting for 43% of the total variance of this parameter (as indicated by the square of r values). BIE was strongly correlated to SI ($r=0.933$; $P<0.001$), while GEZI was not ($r=-0.33$).

If individual values of PRH subjects are compared with the range of controls, the minimal model evidenced a marked increase in glucose assimilation in 9 of 13 subjects: SI in 8, Sg in 6. An increase in SI alone was found in 3 cases, in Sg alone in 1 case, in SI and Sg in 5 cases. In 4 cases SI and Sg were within the control range.

Table 2 Parameters of glucose tolerance calculated from IVGTT in study subjects and controls. [*Kg* coefficient of glucose assimilation, i.e the slope of exponential decrease of glycaemia between 4 and 19 min ($min^{-1} \cdot 10^{-2}$); *SI* insulin sensitivity ($min^{-1}/(\mu U/ml) \cdot 10^{-4}$); *Sg* glucose effectiveness ($min^{-1} \cdot 10^{-2}$); I_{1+3} insulin first-phase response (μU/ml); *AIRglc* mean of insulinaemias above baseline between 1 and 10 min; *AIRglc* × *SI* glucose tolerance index measuring the balance between SI and insulin response ($min^{-1} \cdot 10^{-2}$)]

	Controls ($n=13$)	Hypoglycaemic subjects ($n=13$)	Comparison
Kg	2.19 ± 0.12	2.99 ± 0.26	$P<0.02$
Sg	2.92 ± 0.79	3.84 ± 0.35	$P<0.05$
SI	7.18 ± 0.14	22.9 ± 6.4	$P<0.01$
I_{1+3}	87.38 ± 8.11	100.41 ± 13.08	NS
AIRglc	49.2 ± 12.2	41.29 ± 10.04	NS
AIRglc × SI	4.3 ± 2.13	11.8 ± 6.87	NS
BIE	0.58 ± 0.07	1.2 ± 0.27	$P<0.05$
GEZI	2.3 ± 0.19	2.65 ± 0.28	NS

Discussion

There are very few studies on insulin sensitivity in patients referred for idiopathic reactive hypoglycaemia. To our knowledge, this study is the first one which investigates this topic with the minimal model, and the second which investigates differences in insulin-induced glucose disposal in these subjects. We can confirm that they, on the whole, have an increased glucose assimilation, as indicated by an increase in Kg. Minimal model analysis shows that an increase in SI and/or Sg is a common biological finding in these patients. The increase in Sg mainly depends on its component BIE, which reflects the effect of increased insulin sensitivity: thus, increased SI is the most important cause of the increased glucose assimilation in this sample of patients. However, there was one case of an unusually high value of GEZI which was responsible for an increase in Sg, with SI remaining within the range of control values.

Thus, as previously postulated by Luyckx and Lefebvre [11], and demonstrated by Tamburrano et al. with the glucose clamp [12], increased SI appears to be a frequent finding in PRH. In 9 of our 13 subjects, SI and/or Sg is unusually high, resulting in an overall increased value of both parameters in the group of PRH compared with matched controls.

The most frequent finding in the subjects of this sample is a higher SI, i.e. an increased effectiveness of insulin when it rises above baseline values. This is fully consistent with the previous report of Tamburrano et al. [12]. More recently, the same team has further analysed this point in detail and indicated that the increase in insulin effect was mainly due to a rise in non-oxidative carbohydrate metabolism [21]. Thus, putting our results together with previous reports, increased Sg clearly appears to be a major feature of patients with PRH.

However, with the minimal model technique, other aspects which could not be clearly detected with the glucose clamp are stressed. First, Sg is also commonly increased in these patients. This means that, even without a change in insulinaemia, any increase in blood glucose is more rapidly cleared. The distinction between glucose disposal modifications induced by insulin and glucose disposal which occurs when insulin remains unchanged may be potentially important for the management of these patients. The glucose clamp procedure, which in its usual form does not clearly discriminate SI from Sg, had not elucidated this point. An analysis of Sg as the sum of two parameters termed BIE and GEZI has been developed [19]. It is interesting to note that in most cases the factor responsible for increased Sg is BIE, but that GEZI is also the only increased part of Sg in several cases. Since BIE is equal to $Ib \times SI$ and *Ib* is not increased in these subjects, an increase in BIE is only the consequence of an unusually high value of SI. By contrast, when GEZI is increased, this probably reflects non-insulin-mediated glucose clearance, which is another possible mechanism for hypoglycaemia, yet it has not been frequently reported. Whether an increased GEZI would result in falls in glycaemia after a meal appears unlikely on a theoretical basis, since the increase in glucose uptake in that case would be expected to be unrelated to meals. However, changes in GEZI may be compensated by changes in insulin levels. Thus, increased Sg may be compensated during a fast and induce hypoglycaemia in situations where the steady state is broken, i.e. during exercise of after a meal when the compensatory reduction in insulin is no longer observed because insulin increases. In sportsmen suffering from hypoglycaemic events during exercise, we reported preliminary evidence that a rise in GEZI (and thus Sg) was a frequent finding [14] and could reflect an increased glucose assimilation by muscles submitted to frequent exercise. In this study on sedentary subjects, such a mechanism may be also involved. However, the most frequent mechanism appears to be an increased SI, which in turn may increase BIE and thus Sg.

The calculation of AIRglc×SI provides an interesting index given by the minimal model for evaluating glucose tolerance [20]. It has been reported to be a biological constant, representative of the physiological reciprocal feedback relationship between insulin sensitivity and insulin secretion. In our control group, it is twofold higher than reported by Kahn et al. [20] who indicated a mean value of 2.24×10^{-2}. This is not surprising, since our dose of IV glucose (0.5 g/kg) is higher than their dose (0.3 g/kg) and thus represents a stronger glucose stimulus responsible for a higher AIRglc. Although there is a trend towards a higher value of AIRglc×SI in PRH subjects, the difference fails to be significant, because of a marked overlap. With a higher number of subjects, a significant difference could perhaps be detected. However, this tendency is rather weak and contrasts with the marked difference which is found for Sg and SI. This finding suggests that the physiological balance between SI and insulin secretion is to some extent maintained, with values of AIRglc×SI which remain within a normal range. According to the concept of the feedback between SI and AIRglc [13, 20], a compensatory reduction in AIRglc tends to prevent excessive falls in gly-

caemia when SI is increased. Since patients do undergo hypoglycaemic events, we can speculate that this homeostatic mechanism is not adequate. When looking at individual values, three subjects exhibited AIRglc×SI values higher than $10 \cdot 10^{-2}$, which could correspond to cases of imbalance between insulin sensitivity and insulin secretion. This aspect of the pathophysiology of PRH will require further investigations of larger series of patients.

Some comments should be made on the definition of PRH patients in this study. First, the diagnostic criteria is not OGTT but the spontaneous fall in blood glucose level in patients complaining about signs of hypoglycaemia. On the other hand, a blood glucose level <3.3 mmol/l is considered moderate hypoglycaemia, ad most textbooks or reviews on this subject define hypoglycaemia as a value of blood glucose lower than 2.8 or 2.2 mmol/l [5]. However, the recent literature provides a large body of evidence that values of plasma glucose between 3.3 and 2.8 mmol/l can induce symptoms of hypoglycaemia [7, 22–29]. In a recent review on this subject, PJ Lefebvre writes, "at plasma glucose values around 3.2 mmol/l, palpitations, tremor and sweating may be slightly uncomfortable" [10]. Moreover, although moderate, hypoglycaemic events in this range of values cause significant impairment in some complex tasks like driving a car [24] and need to be diagnosed and corrected. Therefore, although a plasma glucose value of 3.3 mmol/l is surely normal after OGTT [5], it can no longer be considered as a perfectly physiological one after meal ingestion or in everyday life, as sometimes stared in textbooks. In a recent paper, we pointed out this cut-off value of 3.3 mmol/l after a standardized hyperglucidic breakfast test [8]. In that case such a value is not physiological, but reflects a situation associated with the occurrence of hypoglycaemic postprandial events. In a study using ambulatory glucose sampling [7], the same value of 3.3 mmol/l is also found as a boundary between normal blood glucose values and values associated with symptoms of PRH.

It should also be pointed out that the symptoms of hypoglycaemia are rather aspecific and are difficult to use alone as diagnostic criteria. This is the reason why we employed a standardized list given by the consensus statements [6] which helps to analyse them rigorously, and to quote them as a numerical score. Such an analysis of symptoms further confirms that moderate PRH below 3.3 mmol/l, although to some extent a borderline aspect of "normal" glucose homeostasis, is really a disabling situation which cannot be considered a fully physiological one.

In conclusion, this study shows that minimal model measurements in most subjects with PRH detect highly increased values of SI and Sg. This procedure, which is technically simple to perform, may be useful for the biological characterization of this syndrome. Clearly, most of the controversies concerning PRH come from the fact that it cannot be well explored with the usual tests (e.g. OGTT) [1, 2, 5, 6]. Our data suggest that IVGTT with minimal model analysis helps to find a pathophysiological mechanism for PRH. The usefulness and limits of this approach should be further explored with larger series of patients.

An attractive working hypothesis which is under investigation in our units is that PRH resulting from increased SI, PRH from increased Sg, PRH from deficient counter-regulation, and PRH from hyperinsulinism are different diseases and that the dietary approach to them can vary.

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Diabetologia
Clinical and Experimental Diabetes and Metabolism
Journal of the European Association for the Study of Diabetes (EASD)

Vol. 39, No. 1, 1996

Indexed in Current Contents and Index Medicus

DBTGAJ 39 (1) 1–128 (1996)
Printed on acid-free paper