POSTPRANDIAL REACTIVE HYPOGLYCEMIA

J.F. BRUN, C. FEDOU, J. MERCIER

SUMMARY - Postprandial reactive hypoglycemia (PRH) can be diagnosed if sympathetic and neuroglucopenic symptoms develop concurrently with low blood sugar (< 3.3 mmol). Neither the oral glucose tolerance test (OGTT) nor mixed meals are suitable for this diagnosis, due to respectively false positive and false negative results. They should be replaced by ambulatory glycemic control or, as recently proposed, an hyperglucidic breakfast test. PRH patients often suffer from an associated adrenergic hormone postprandial syndrome, with potential pathologic consequences such as cardiac arrhythmia. PRH could result from (a) an exaggerated insulin response, either related to insulin resistance or to increased glucagon-like-peptide 1; (b) renal glycosuria; (c) defects in glucagon response; (d) high insulin sensitivity, probably the most frequent cause (50-70%), which is not adequately compensated by hypoinsulinemia and thus cannot be measured by indices of insulin sensitivity such as the homeostatic model assessment. Such situations are frequent in very lean people, or after massive weight reduction, or in women with moderate lower body overweight. PRH is influenced by patient’s alimentary habits (high carbohydrate-low fat diet, alcohol intake). Thus, diet remains the main treatment, although α-glucosidase inhibitors and some other drugs may be helpful.

Key-words: hypoglycemia, insulin sensitivity, exercise, glucagon, GLP-1, breakfast-test.

RÉSUMÉ - Hypoglycémie réactionnelle post-prandiale. Le diagnostic d’hypoglycémie réactionnelle (HR) nécessite l’observation simultanée d’une glycémie basse (< 3.3 mmol/l) et des signes sympathiques et neuroglucopéniques. L’hyperglycémie provoquée per os et les repas tests mixtes entraînant respectivement de fréquents faux positifs et faux négatifs n’ont aucune valeur pour le diagnostic et sont à remplacer par l’autocontrôle glycémique ou, comme récemment proposé, par un petit déjeuner hyperglycémiique. Les HR s’associent souvent à une hypersensibilité adrénergique postprandiale. Les HR s’expliquent par (a) une décharge excessive d’insuline, due à une insulino-résistance ou au glucagon-like-peptide 1, (b) des glycosuries, (c) une déficience de réponse du glucagon, et (d) une sensibilité élevée à l’insuline (mécanisme probable de 50-70 % des HR). Cette dernière non compensée par un hypoinsulinisme est indétectable par les index basés sur l’insulinémie à jeun. Les HR sont fréquentes en cas de forte maigreur, d’adiposité gynocidée modérée, ou d’amaigrissement important. Les habitudes alimentaires influençant la survenue des HR, le régime est la thérapeutique de base, associé parfois à des médicaments (inhibiteurs des α-glucosidases).

Mots-clés : hypoglycémie, insulino-sensibilité, exercice, glucagon, GLP-1, petit-déjeuner-test.
Low values of blood glucose, reaching the range where symptoms of hypoglycemia can be observed, are not uncommon [1-2]. While the differential diagnosis with "organic" causes of hypoglycemia [3] should always be carefully discussed, most of these cases reflect a situation on the boundaries of physiology where glucose counterregulation becomes unable to totally balance glucose disposal [1]. This situation was first evidenced by Harris [4] who reported in 1924 five cases of hypoglycemia following a meal, that he called reactive hypoglycemia. Harris postulated that reactive hypoglycemia was some kind of counterpart to diabetes mellitus: while the latter was considered to result from hypoinsulinism, or at least impaired insulin action, hypoglycemia was expected to be due to hyperinsulinism or dysinsulinism. Symptoms fully similar to those occurring during insulin-induced hypoglycemia were observed at blood-glucose values below 0.7 g/100 l [4].

Later, this issue became for decades a matter of considerable controversy [5-6], due to a lack of consensus in definitions and to the inappropriate use of the oral glucose tolerance test [7-8]. In addition, hypoglycemia has become a fashionable and overdiagnosed disorder in several countries, due to its popularization in the lay literature, so that a host of patients used to describe signs suggestive for hypoglycemia without any clinical evidence for low blood glucose, a situation that Cahill [5] and Yager [6] proposed to call "non-hypoglycemia". In agreement with them, Charles [9] who found that such patients never exhibited hypoglycemia after a mixed meal concluded that this situation has no relation to glycemia and should rather be termed "post prandial idiopathic syndrome". The number of terms applied to reactive hypoglycemia have added to the confusion: these included functional hyperinsulinism, essential hypoglycemia, functional hypoglycemia, dysinsulinism, hypoglycemic fatigue, insulinogenic hypoglycemia, and relative hypoglycemia [10-11].

Consensus conferences were held to clarify this question. Chairmen of the Third International Symposium on Hypoglycemia (22-23 September 1986) in Rome [8] published a consensus statement indicating that, although the disease was generally overdiagnosed, there was no doubt that "some patients exhibit postprandial symptoms suggesting hypoglycemia in everyday life and that, if these symptoms are accompanied by blood glucose levels between 2.8 and 2.5 mM or below (determined by a specific method on capillary or arterialized venous blood, respectively) the diagnosis of postprandial, or reactive, hypoglycemia may be correct. In these patients, every effort should be made to document hypoglycemia under their everyday-life conditions.". Another important conclusion of that conference was that the oral glucose tolerance test (OGTT) should not be employed for this diagnosis.

This conference provided thus the basis for a novel approach of this disease on better defined bases. Since that time, several interesting advances have been performed in the understanding and treatment of the disease. It is the purpose of this review to discuss postprandial reactive hypoglycemia (PRH) and its pathogenesis, diagnosis, and treatment. Another usual situation very close from reactive hypoglycemia is exercise hypoglycemia, which is also "functional" in nature and is frequently associated with an increased occurrence of reactive postprandial decrease in blood glucose. It will not be reviewed in this article since we will review it in a separate paper.

**WHICH ARE THE BOUNDARIES BETWEEN HYPOGLYCEMIA AND NORMOGLYCEMIA?**

While in his initial description Harris [4] reported that symptoms of hypoglycemia occurred at blood-glucose values below 0.7 g/l (3.9 mmol/l) the blood glucose value defining hypoglycemia has fluctuated since this time [10-13]. Some authors defined hypoglycemia as a decrease of more than 0.2 g/l [10] or 10% to 20% [12-13] below the fasting blood glucose level. Such definitions are no longer accepted since the rate of relative decrease does not modify physiological responses [14-17] which are set at fixed values, so that hypoglycemia should be defined on a level of blood glucose [11, 18]. Physiological studies aiming at more closely defining "normoglycemia" in everyday life [2] can help to define this level. Marks [2] studied 30 healthy volunteers (aged 25-55 years), in whom he determined capillary blood glucose levels 17-18 times a day during the ordinary everyday life, i.e., a total of 498 values. The crude mean of all blood glucose values was 4.2 ± 0.8 (S.D.) mmol/l, but there was a physiological nadir at 17.00 hours (3.9 ± 0.6 mmol/l) while the highest level was found in samples collected at 14.00 hours which averaged 4.9 ± 1.0 mmol/l. This study demonstrated that 5% of blood glucose values of this sample were below 3.0 mmol/l and 2.8% below 2.8 mmol/l (0.5 g/l). Values < 3 mmol were found in 33% of subjects and values < 2.8 in 17% of them. Since ninety-five percent of all blood glucose values were above 3 mmol/l (0.54 g/l) hypoglycemia could be defined biochemically as a blood glucose level below this level [2]. However, consensus statements proposed a lower cut-off value at 0.4 g/l (= 2.2 mmol/l) on whole blood and 0.5 g/l (= 2.8 mmol/l) on plasma [8]. This definition was questionable since it did not take into account the fact that symptoms physiologically occur at threshold values comprised between 3 and 3.5 mmol [19-23]. These thresholds have been carefully described on arterialized blood by Mitrakou et Cryer [24] who...
found at 3.7 mmol the onset of counterregulatory hormonal response (glucagon, epinephrine, norepinephrine and growth hormone), at 3.2 mmol the onset of the sympathetic response and at 2.8 mmol/l the onset of neuroglucopenic symptoms. Deterioration in cognitive function tests began at 2.7 mmol/l. In venous blood, thresholds are less precisely defined, but are interesting to assess since blood glucose is usually measured on venous blood. Consistent with this literature [20-24], we found on whole venous blood that symptoms occur as soon as 3.5 mmol, with a mean value at 3 mmol for adrenergic symptoms and neuroglucopenic symptoms [25]. This value of 3 mmol/l is the same as that reported by PJ Lefèbvre [1] in a paper reviewing studies performed in healthy volunteers in whom mild hypoglycemia was induced with an insulin infusion. At this precise value of 3 mmol/l, the symptoms included weakness, difficulty in thinking and concentrating, diaphoresis, palpitations and tremor. Values at which neurophysiological testing is impaired range between between 2.2 and 3.5 mmol/l while objective electrophysiological testing has been demonstrated to already show alterations already at 4 mmol/l [26]. More recently, studies on driving performance when blood glucose levels decrease have also given evidence for early disturbances in several neurological functions at levels of blood glucose higher than 3 mmol. For instance, Cox [27] evidences important alterations between 3.3 and 2.8 mmol, but also finds that between 4 and 3.3 mmol there is already a significant disturbance of driving performance at high speed and a higher feeling of difficulty in this task. These values are defined on venous blood. Thus, in contrast to the classical statements defining hypoglycemia below 2.8 mmol, there is a large body of evidence that indicates important alterations, that may disturb everyday life, in the range of 3-4 mmol. Although these values are not likely to be at risk for neurological damage, they could result in marked discomfort and difficulties for intellectual or psychomotor tasks. Thus, defining hypoglycemia as a blood glucose value below 2.8 mmol (0.5 g/l), as classically done [10], is probably too restrictive [3]. Based upon these physiological data a cut-off value around 3.3 (onset of counterregulatory responses) seems to be more accurate [3].

First, diagnosis based upon symptoms, (including the usual self-diagnosis by patients themselves), is seldom confirmed by accurate investigations [30]. Recent consensus statements [8] emphasize the importance of interpreting the patient’s symptoms in respect to the blood glucose determination.

Despite their lack of specificity, symptoms could be analyzed with a questionnaire [24] and quoted from 0 to 5 (Table I). If clinical exploration reproduces the hypoglycemic event, it is interesting to compare symptoms of the laboratory event and the self-reported symptoms. Note that more recently the classification of these symptoms has been readressed with a multifactorial analysis [31] leading to a slightly different list of symptoms. According to these authors, signs of hypoglycemia cluster into three sets: autonomic (sweating, palpitation, shaking and hunger), neuroglucopenic (confusion, drowsiness, odd behavior, speech difficulty and incoordination), and malaise (nausea and headache). However, this description has not, as far as we know, resulted in a new standardized questionnaire and the classical one is still employed by teams working in this field.

However, unusual clinical presentations are not rare. For instance, in the study of Lev Ran [32], there was one of the patients who suffered from arthritis of the hip with a sharp increase in pain after meals rich in sugar. He did not suspect he was hypoglycemic, but during glucose tolerance testing he recorded hip pain when his plasma glucose reached a nadir of 0.44 g/l. A low carbohydrate diet significantly decreased his pain during the 18 months that he was followed [32]. Due to this lack of specificity of symptoms, blood glucose measurement should be performed in association with this clinical interrogatoire.

Permutt [33] recommended that the reproduction of symptoms of hypoglycemia occurring in the home situation during an OGTT at the time of plasma glucose level of less than 0.50 g/l (2.8 mmol) is sufficient for the diagnosis of reactive hypoglycemia. However, it has been obvious since more than twenty years that

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Table I. Standardized list of symptoms of hypoglycemia. Each sign could be quoted from 0 to 5 allowing the calculation of a "score". After [20, 24, 26].
this could lead to most cases of misdiagnosis [11], since plasma glucose nadirs below 2.8 mmol/l are usual in healthy persons after OGTT, while symptoms are not specific [1, 7, 8, 11]. Therefore, the OGTT has been repeatedly demonstrated to be not suitable at all for this diagnosis, although it surely remains the most widely employed procedure in this context. The probably most convincing demonstration of this was given by Lev Ran and Anderson [32] who studied the decrease in blood glucose after OGTT in 650 patients who were entirely free from hypoglycemic symptoms, either before and during testing. They found that 10% of the patients had plasma glucose nadirs of 0.47 g/l (2.6 mmol/l) or below and 2.5% had values of 0.39 g/l (2.15 mmol/l) or less. Similarly, in a large group of military draftees tested 2 h after glucose challenge, Fariss [34] found plasma glucose concentrations below 0.49 g/l (2.7 mmol/l) in 7.4%, and below 0.29 g/l (1.6 mmol/l) in 14%. Since most nadirs occur later than 2 h after glucose load, it is probable that their true incidence is even higher than Fariss reports. In another study [10], Hofeldt noted that 48% of normal subjects had nadirs below 0.50 g/l (2.8 mmol/l). Occasionally, values as low as 0.35 g/l (1.9 mmol/l) are found in healthy persons. [11, 35]. Thus, reactive hypoglycemia is quite a “normal” finding after OGTT, whether or not subjects suffer hypoglycemia after meals during their everyday life. Pure glucose appears to be an unphysiologic stress, seldom encountered outside the clinical laboratory [7], and that induces a rather different glucose kinetics than a mixed meal [36]. It is clear that a 75-g glucose load is a much stronger stimulus to insulin secretion and, therefore, is much more likely to provoke reactive hypoglycemia than any meal [7]. Although the upper limits of normal for glucose tolerance testing are standardized internationally, there is no agreement concerning the clinical significance of lower values obtained during testing. Clearly, considering nadirs below 0.50 g/l (2.8 mmol/l) abnormal leads to overdiagnosis of PRH [11]. All consensus statements emphasize that the glucose tolerance test alone is not a reliable means for diagnosing reactive hypoglycemia.[8] By contrast, it is suggested that this test could still be employed for further investigation (insulin response, glucose tolerance, relationships between symptoms and blood glucose values, counterregulation) after the diagnosis has been made [1, 30].

“The hypoglycemic index”

The hypoglycemic index [37] is the drop of plasma glucose during the 90 min preceding the nadir divided by the nadir value. It is reputedly above 0.8 in all symptomatic patients, and was said to be especially valuable for patients with nadirs below 0.65 g/l (3.6 mmol/l). Lev Ran, consistent with Johnson and others [11] concluded that the hypoglycemic index is of no value in the diagnosis of functional hypoglycemia [34] and should thus not be recommended.

The golden standard (?): ambulatory glucose sampling

Clearly, accurate diagnosis of hypoglycemia requires that symptoms develop concurrently with low blood sugar and that they are absent at other times. Low plasma glucose must be considered only if it occurs in correlation with symptoms. By the past, this diagnosis needed to be performed in an hospital unit. Nowadays, ambulatory glycemie control may give the means to measure glycemia in everyday life and to confirm, when symptoms occur, whether or not they are associated to a low blood glucose value. Palardy et al [38] investigated 28 patients referred for suspicion of this disorder with ambulatory glycemie control and found at the time when symptoms occurred values of blood glucose < 3.3 mmol in 46% of the subjects, and < 2.8 mmol in 18% of them. This study provided a milestone in the history of PRH since it first demonstrated a rather high (46%) occurrence of bona fide hypoglycemia in patients referred for this diagnosis, and proposed the accurate tool for performing the diagnosis. Patients have to be carefully educated to the use of glucose analyzers and should be asked to write their blood glucose values, their association with signs, and whether sugar ingestion reverses them [19]. However, this procedure is not always conclusive and it is sometimes difficult to affirm that signs are due to low blood glucose values. Presumably, when signs occur, counterregulation has already started to operate and glycemia is not as low as expected because it is increasing in order to recover from the hypoglycemic event. Thus, although considered as the “gold standard” for diagnosis of PRH, glycemic control is probably not devoid of false negative results and there is room for an alternative approach as indicated below.

The breakfast test

Theoretically, a standardized breakfast test could be a more accurate test than OGTT since it mimics everyday life habits. If a patient undergoes hypoglycemia after such a meal, this is not likely to be an artifact as for the OGTT. On the other way about, such a response would demonstrate that hypoglycemia can occur in the patient’s everyday life. However, this issue was extensively studied at the beginning of the 1980 [9, 39-44] and all studies concluded that after a mixed meal patients referred for PRH almost never demonstrate a fall in blood glucose. Charles [9] concluded that PRH actually did not exist or at least should be considered as a “postprandial syndrome” that had nothing to do with glycemia. In fact all authors used rather equilibrated mixed meals which reproduce the dietary correction of the PRH rather
than the hyperglucidic meal that induced the fall in glycemias. It is very likely that, in contrast to OGTT which is too sensitive, mixed breakfast test are too balanced, and that this is the reason why they almost never evidence hypoglycemia in subjects referred for suspicion of PRH [9, 39-44].

We thus developed [45] a new “hyperglucidic breakfast test” which mimics more closely than the above the dietary habits of people prone to PRH. This meal is composed of bread (80 g), butter (10 g), jam (20 g), skimmed concentrated milk (80 ml), sugar (10 g) and powder coffee (2.5 g), which corresponds to 2070 kilojoules with 9.1% proteins, 27.5% lipids, and 63.4% carbohydrates. Thus, the test provides an almost equivalent amount of carbohydrates as the standardized hyperglucidic breakfast. Since this test more closely mimics the spontaneous situation in which hypoglycemia is typically reactive and occurs after a meal [48]. However, there remains probably in some cases a possibility to fail to detect an insulinoma if the 48 hr fast is not performed. This is clearly demonstrated by a recent case report of insulinoma presenting as a late post-prandial hypoglycaemia in a patient who had previously undergone subtotal gastrectomy [49]. This case report supports the use of the fasting test in some cases of PRH, when they appear to be severe and to resist to dietary prescription. However, in our opinion, the fasting test should not be initially applied to the subjects referred with a typical tableau of PRH.

A STILL IMPORTANT DIFFERENTIAL DIAGNOSIS: INSULINOMA

The diagnosis of insulinoma, a rather rare tumor, the incidence of which is estimated to be four cases per 1 million person-years [47] is generally difficult and is based upon the 48 to 72 hr fast test [19, 47]. Due to the low frequency of insulinoma, it is thus questionable in terms of health cost policy to perform a prolonged fast in all patients referred for suspicion of hypoglycemia, and even more when this hypoglycemia is typically reactive and occurs after a meal [48]. Another explanation of the past confusion concerning PRH is the disturbed psychological background most often found in patients. The psychiatric literature related hypoglycemia to life situations, emotions, tension, depression, neurosis, and asthenic syndromes and to a condition of pernicious inertia [10]. Subsequently, reactive hypoglycemia became associated with a number of disease states that included behavioral disturbances, criminal behavior, alcoholism, allergies, rheumatoid conditions, neurological disturbances, neurocardiac disturbances, and asthenic syndromes [10]. In addition, in a recent report [50] Kurlan suggests that postprandial reactive hypoglycemia and restless leg syndrome might be related disorders.

Harris, in his initial publication, also observed low blood-pressure readings in all but two of the nondiabetic patients who had symptoms of reactive hypoglycemia and postulated that there may be an association between the altered insulin secretion and abnormalities in secretory disorders of the thyroid, pituitary, or adrenal gland [4]. A mild deficiency in adrenal or pituitary counterregulatory response was then suggested, leading to some treatments with gland extracts which were clearly not recommended by experts [10]. Hypoglycemia should also be distinguished from Ménière’s syndrome, idiopathic hypertrophic subaortic stenosis, migraine, functional bowel disorder, mitral valve prolapse, factitious thyrotoxicosis [32]. In fact, the nonspecific symptoms of reactive hypoglycemia can be seen in a host of paroxysmal disorders that present as adrenergic mediated syndromes: anxiety neurosis, seizure disorders, pheochromocytoma, carcinoid syndrome, hyperthyroidism, cardiac arrhythmias,
dumping syndrome, and beta-adrenergic hyperresponsive state (De Costa’s syndrome) [10].

PJ Lefèvre [1] proposes the term of “Adrenergic hormone postprandial syndrome” to describe autonomic symptoms (anxiety, palpitations, sweating, irritability, tremor...) that are experimentally observed after insulin infusion, at plasma glucose levels of about 3.7 mmol/l. It is likely that, in some individuals, after a meal, such autonomic counterregulation may occur. This counterregulatory response induces symptoms but also prevents biochemical hypoglycemia being achieved [19]. In such cases, since low blood glucose levels do not occur, the term “postprandial” or “reactive” hypoglycemia should thus be avoided.

However, it is clear that patients with bona fide reactive hypoglycemic states may manifest an abnormal personality profile as determined, for instance, by the Minnesota Multiphasic Personality Inventory (MMPI) [11]. These patients’ personality profiles are characterized by hypersomatization and hypochondriacal complaints. Therefore, it would surely be erroneous to consider as fully different syndromes the true postprandial or reactive hypoglycemia and this adrenergic hormone postprandial syndrome. Several lines of evidence suggest that these mechanisms frequently coexist, explaining to some extent the specific psychological and behavioural pattern of the bona fide PRH prone patients. This issue has been investigated by Berlin [51] who studied eight patients with suspected postprandial hypoglycemia in whom he evaluated beta-adrenergic sensitivity with the isoproterenol sensitivity test. While plasma epinephrine and norepinephrine responses after OGTT were similar than those of controls, both heart rate and systolic blood pressure were significantly higher (albeit remaining within the normal range) compared to controls. Moreover, after glucose intake, seven patients had symptoms (palpitations, headache, tremor, generalized sweating, hunger, dizziness, sweating of the palms, flush, nausea, and fatigue), whereas in the control group, one subject reported flush and another palpitations, tremor, and hunger. Psychological analysis showed that patients had emotional distress and significantly higher anxiety, somatization, depression, and obsessive-compulsive scores than controls. This study shows that such patients with suspected postprandial hypoglycemia most often exhibit an increased beta-adrenergic sensitivity and emotional distress.

We investigated [25] this association between bona fide PRH and postprandial syndromes by determining at which levels of venous blood glucose adrenergic and neuroglucopenic symptoms were found in subjects either complaining of PRH or without this complaint. When hypoglycemia is artificially induced by an insulin infusion, symptoms occur at the following levels: vertiges 3.5 mmol; sweating 3.3; tremor: 3.3; blurred vision 3.2; anxiety 3.2; weakness 3.1; nausea 3; headache 3; hunger 2.9 [25]. By contrast, when symptoms are quoted during a PRH reproduced with the hyperglucidic breakfast test, these thresholds are not at the same levels: respectively: 4; 4; 4; 3.9; 3.9; 3.8; 4.7; 4; 4.1 mmol. Thus, symptoms of PRH are reported at a higher blood glucose levels than symptoms of hypoglycemia artificially induced by insulin in non PRH prone individuals. Adrenergic symptoms are found at 4 ± 0.1 vs 3 ± 0.1 mmol and neuroglucopenic symptoms at 4 ± 0.2 vs 3 ± 0.1 mmol. These differences are highly significant (p < 0.001) [25]. Clearly, thresholds of appearance of hypoglycemic symptoms are shifted towards higher blood glucose levels in patients with bona fide PRH. This is even more striking for the autonomous signs. Thus, pseudo-hypoglycemia may be associated with true PRH, so that the diagnosis of PRH could not be fully excluded in patients with an obvious tableau of pseudo-hypoglycemia and adrenergic hormone postprandial syndrome.

This adrenergic hormone postprandial syndrome is likely to be of clinical relevance, since Rokas and coworkers [52] published a case report of a patient with refractory atrioventricular nodal reentry tachycardia in whom it was possible to document that reactive hypoglycemia was the trigger for aggravation of arrhythmia. Over a period of 6 years, a series of electrophysiological studies revealed that, when the patient was in a hypoglycemic state, initiation of tachycardia was easy and most importantly that tachycardia termination by extra-stimulus pacing always failed. Furthermore, atrial fibrillation was inducible or spontaneously occurred only when the blood glucose level was reduced by IV insulin administration [52].

### PHYSIOLOGICAL BASIS

Hypoglycemia is basically an unbalance between glucose influx to the circulation (from endogenous glucose production or exogenous glucose delivery) and glucose efflux [53]. While external losses may be a cause of hypoglycemia in the case of massive renal glycosuria [54], glucose efflux is generally almost equivalent to glucose utilisation by tissues. This balance between glucose influx and efflux is controlled by a complex equilibrium of glycogulated hormones that may undergo various disturbances.

Normoglycemia is physiologically maintained by a complex set of regulatory mechanisms, which are thus likely to be impaired in various situations. First, insulin suppresses hepatic glucose production and, at higher levels, stimulates glucose utilisation by insulin-sensitive tissues. Glucagon and epinephrine stimulate both glycogenolysis and gluconeogenesis. Insulin, glucagon, and epinephrine act rapidly (in minutes). Over a longer time frame (3-4 h), cortisol and growth hormone both limit glucose utilisation and stimulate glucose production. Among the counterregulatory hor-
mones, glucagon initially plays a primary counterregulatory role. Epinephrine is not normally critical unless glucagon secretion is deficient, so that hypoglycemia will occur in situations where both glucagon and epinephrine are deficient while insulin is present, even when all other glucose counterregulatory systems are intact [55]. While glucagon, in terms of effects on glucose metabolism, acts mostly on hepatic glucose production, epinephrine decreases glucose nonoxidative utilization [55].

Therefore decrements in insulin and increments in glucagon and, in the absence of glucagon, epinephrine, play important roles in the prevention and correction of hypoglycemia. This has been demonstrated in the postprandial state, after overnight and 3-day fasts, and during moderate physical exercise in humans. Hypoglycemia develops over the short term under all of these conditions when both glucagon and epinephrine are deficient and insulin is present. The roles of growth hormone and cortisol in the prevention of hypoglycemia are less easy to understand because they are rather long-lasting (12 hr). Thus they are not likely to impair recovery from hypoglycemia [47] while some roles can be inferred from the fact that fasting hypoglycemia sometimes develops in patients (particularly young children) with chronic deficiencies of these hormones.

Besides, there is evidence that glucose autoregulation modulates hepatic glucose production as an inverse function of plasma glucose concentration independent of hormonal and neural regulatory factors in humans [53]. Autoregulation appears to be important only during severe hypoglycemia (1.7 mmol/l) and not during more moderate hypoglycemia (2.8 mmol/l) in humans.

Skeletal muscle has also been reported to contribute to defense against hypoglycemia. During hypoglycemia, muscle markedly decreases (80%) its rate of glucose uptake [56-58], via a reduction in glycogen synthase activity [56, 59] and in fractional velocity for glycogen synthase [60]. Epinephrine has been shown to reduce overall insulin sensitivity via beta-adrenergic receptors [61] and this effect is mostly due to a reduction in nonoxidative glucose utilization via an inhibition of insulin-mediated glycogenogenesis [62]. Therefore, it is likely that muscular insulin resistance in muscle during hypoglycemia is an important defense against hypoglycemia and is to some extent due to catecholamines. This mechanism has been reported to be more prominent during prolonged hypoglycemia, while stimulation of glucose production is predominant initially [53]. By contrast, this mechanism is limited by the fact that glucose transport across the muscular cell membrane, which is critical in insulin action [63-65] is up-regulated in situations of hypoglycemia [66-67], and is not reduced by epinephrine [68].

On the whole mechanisms by which blood glucose returns after 2-3 hours to a steady state value after a meal appear to be a remarkably integrated mechanism which results in a smooth transition from exogenous glucose delivery to endogenous glucose production. The complexity of this coordinated process explains why some degree of unbalance among insulin release, insulin sensitivity and counterregulatory response may result in a fall of blood glucose concentration below the usual levels.

### MECHANISMS OF PRH

Although some aspects require further investigation, most of the pathophysiology of PRH is nowadays elucidated and it is no longer correct to state that this is an undefined entity whose mechanisms (and existence) remain elusive.

**Exaggerated insulin response**

A role for exaggerated insulin response was suspected until the first reports by Harris [4]. The term “functional hyperinsulinism” (proposed by Conn [69]) has been utilized for describing the syndrome. With the appearance of extensive utilization of methods for the assay of plasma insulin, studies have been undertaken to confirm this hypothesis. Consistent with classical assumptions, a study conducted by Luyckx and Lefebvre [54] on forty-seven patients demonstrated to suffer from reactive hypoglycemia (<45 mg/100 ml) evidenced an exaggerated insulin response as the major abnormality explaining hypoglycemia, either in obese with impaired glucose tolerance or in isolated PRH. A characteristic pattern was when the release of insulin is sluggish and the insulin peak delayed with respect to the peak value for blood glucose.

While the most usual cause of an increased insulin response is most often assumed to be insulin resistance-related hyperinsulinemia [10, 54], there may be other mechanisms for hyperinsulinemia. For example there has been an anecdotic report of reactive hypoglycemia (0.34 g/l) with an unusually exaggerated insulin secretion (more than 1000 µU/ml) which seems to be explained by an exaggerated response of glucagon-like-peptide-1 (GLP-1) [70].

Interestingly, hyperinsulinemia has been reported to enhance epinephrine, norepinephrine and cortisol secretion in response to hypoglycemia [71], while it does not modify glucagon and GH responses. Thus, excess insulin may be a factor involved in the postprandial adrenergic syndrome whose link with PRH is discussed above.

**Alimentary hypoglycemia**

The PRH due to accelerated stomach emptying has been proposed to be termed alimentary hypoglycemia.
It is frequent in totally or partially gastrectomized patients [54, 72-73]. Most generally this variety of hypoglycemia is related to an excess insulin response [54]. Recent advances in the understanding of this specific cause of hypoglycemia should be briefly mentioned here. A study of gastric emptying in 27 tumor-free totally gastrectomized patients provided convincing evidence that a rise in GLP-1 inducing both insulin release and inhibition of pancreatic glucagon explains the reactive hypoglycemia encountered in some patients following gastric surgery. The peak postprandial concentration of GLP-1 averaged 44 pmol/l in controls, 172 in gastrectomized patients without reactive hypoglycemia, and 302 in patients whose glucose fell below 3.8 mmol/l during the second postprandial hour. Rapid emptying seems to be one causative factor for the exaggerated response of gastrointestinal insulin-stimulating hormones [74]. This issue has been more recently investigated by Toft Nielsen [75] who reproduced the glucose and hormone profiles of the patients with reactive hypoglycemia in healthy volunteers with an i.v. infusion of glucose, associated or not with i.v. GLP-1 infusion, or alternatively the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP). These procedures after termination of i.v. glucose achieved different glucose concentrations. Clearly the lowest was after GLP-1 (2.4 mmol/l) while they were 3.7 with low GIP, 3.3 with high GIP and 4.5 for glucose alone. Thus, the exaggerated GLP-1 response to nutrients in patients with accelerated gastric emptying is very likely to be responsible for their high incidence of postprandial reactive hypoglycemia [75].

PRH without hyperinsulinism: renal glycosuria, increased insulin sensitivity, or defects in counter-regulation

Abnormalities in circulating plasma insulin do not explain all cases of reactive hypoglycemia, and about half of patients in all published series have normal insulin response [54, 76]. This led several authors to speculate on the existence of an inadequate counter-regulation in these subjects or of a possibility of a relatively exaggerated sensitivity to insulin [1, 29, 30, 54].

The first well-defined mechanism of reactive hypoglycemia without hyperinsulinism has been renal glycosuria [77-78]. In some series it could represent 15% of the patients [54]. Actually, an excess insulin response during OGTT has been described in certain cases of renal glycosuria [77-78]. This hyperinsulinism is apparently not involved in the pathogenesis of reactive hypoglycemia [54]. An excess renal loss of glucose is likely to result in a slight unbalance between glucose production and disappearance, since the insulin response is related to the amount of the carbohydrate load while an important part of this load is actually lost in urine [54].

A major cause of PRH is surely high insulin sensitivity [1, 29, 30, 54]. This mechanism was postulated many years before the tools for demonstrating it were made available [4]. It has been demonstrated by Tamburrano [79] using the glucose clamp procedure. In 10 of 16 patients in whom PRH was diagnosed with ambulatory glucose testing, the clamp evidenced an elevated insulin-stimulated glucose uptake. Further, the same team [80] evidenced an increased nonoxidative glucose metabolism that appears to explain most of this increased glucose disposal as evidenced in clamp experiments. They investigated eight patients with PRH compared to eight controls during an euglycemic-hyperinsulinemic clamp associated with indirect calorimetry and found a similar rate of glucose oxidation in PRH subjects and controls, either in basal conditions and during the clamp studies, but the nonoxidative glucose disposal was significantly higher (± 63%) in PRH than in controls. They also report a lower rate of fat oxidation during insulinization in PRH, while the glucagon response to clamp (that is normally found in controls) is blunted in PRH patients. Thus, increased insulin-mediated glucose disposal appears to be due to an increase in nonoxidative glucose metabolism. For these authors, it is clear that an increase in insulin sensitivity associated with a deficiency in glucagon secretion can widely explain the occurrence of hypoglycemia in the late postprandial phase in these patients [80].

We investigated this question with the minimal model technique [81] and also found a high insulin sensitivity explaining more than 50% of our cases of confirmed PRH. Interestingly, only the insulin-dependent component of glucose disposal was increased, while the non-insulin dependent component of glucose effectiveness termed glucose effectiveness at zero insulin was not significantly increased. This contrasts with exercise hypoglycemia where this parameter mostly explains the increased glucose disposal.

It should be reminded that GLP-1 stimulates glycogen storage in muscle, [82] i.e., a component of nonoxidative glucose disposal that has been shown to be increased in patients with PRH [79-80]. Thus this gastro-intestinal hormone may also play a role in this increased insulin sensitivity.

Thus, it seems well demonstrated by two different teams and with the two most accurate techniques that increased insulin sensitivity is the most usual mechanism of PRH. It probably explains fifty to seventy percent of the cases [79, 81]. However, it is not likely that increased insulin sensitivity alone can induce hypoglycemia, since high values like those found in PRH are found in young, lean people who never report suffering PRH. The team of RN Bergman has developed the concept of an homeostatic balance between insulin sensitivity and insulin secretion, so that when insulin sensitivity increases, insulin levels
Defects in counterregulation

Defects in counterregulatory response resulting in a lack of compensation of the hypoglycemic effect of insulin has been long suspected. In a series of nineteen patients Mirouze [89] reported that postprandial reactive hypoglycaemia is associated with a low response in glucagon to OGTT while this response is high in people who do not suffer from this symptom. In addition, he found that treatment with pectin protected against falls in blood glucose after OGTT, increasing the glucagon response in the late period of the test [89].

Consistent with this work, more recent reports support the involvement of a defect in glucagon in the pathogenesis of PRH. As indicated above, Leonetti [80] demonstrated a blunted response of glucagon to the glucose clamp in PRH patients, suggesting that a deficiency in glucagon secretion, associated to high insulin sensitivity, explained the occurrence of postprandial hypoglycemia. In a further paper [90] she performed in 12 PRH subjects (compared with 12 controls) a two-step hyperinsulinemic euglycemic glucose clamp. When only insulin and glucose were infused the PRH patients required 20% higher glucose infusion rates to maintain euglycemia than controls. However this difference disappeared during second step of the clamp when basal glucagon was restored by a glucagon perfusion. Thus, the glucagon defect seems to play a role in the increased glucose disposal. Glucagon may protect against hypoglycemia via some degree of insulin resistance that it induces [90].

The abnormality of glucagon in PRH seems to include also some degree of glucagon resistance, as shown by Ahmadpour [91] who reported 2.5 fold higher values of basal glucagon in PRH subjects than in controls while, during a protein meal, its response was 2.5 fold lower. This basal hyperglucagonemia with normal glucose concentration may suggest the presence of a hyposensitivity of the glucagon receptor in PRH while the blunted response to hypoglycemia and to a protein meal reflected an altered glucagon secretion. These authors conclude that in PRH subjects both glucagon sensitivity and secretion are impaired and that these mechanisms are involved in the pathogenesis of PRH [91].

A case of severe PRH with hyperinsulinaemia and absent glucagon response to hypoglycaemia due to a defect in hepatic glucose-6-phosphatase enzyme system has been reported by Pears [92] who considers this case as an example of disordered pancreatic islet cell paracrine regulation.

On the whole, the importance of a defect in glucagon secretion in reactive hypoglycemia now appears well demonstrated. By contrast, very little is known about abnormalities of other counterregulatory hormones in this disease [1, 73].

### INFLUENCE OF BODY COMPOSITION

Very lean people are prone to hypoglycemia, a condition that could trigger accidents at work through errors in judgment by impairing cognitive function in some countries: this is clearly shown in a study on 77 “healthy” volunteers conducted in India [93]. In this study 22.4% of the 76 subjects experienced biochemical hypoglycemia (less than 3.3 mmol/l) as demonstrated by multiple blood glucose determinations. This underestimated situation may have important consequences in occupational health in developing countries [93].

Similarly, slimming increases insulin sensitivity [94-95]. Since fat mass (mostly intraabdominal) linearly decreases insulin sensitivity in either diabetics or nondiabetics [96] it is not surprising to observe that massive weight reduction increases the occurrence of reactive hypoglycemia. After massive weight reduction, rates of insulin-stimulated nonoxidative glucose disposal accounted for the majority of the improvement in insulin sensitivity [95]. Interestingly, above a certain threshold of weight loss, improvement in insu-
Carbohydrate-low fat diet increases insulin sensitivity

Some physiological literature indicates that high body weight which is well known to decrease SI, lower body overweight is associated with values of SI within the upper range. This situation seems to be associated with a lower incidence of diabetes and high values of HDL cholesterol [100], suggesting a possible protective effect of tight fat [100]. We measured insulin sensitivity by the minimal model procedure in lower-body overweight women and compared matched women with a similar degree of upper-body obesity and control women. Insulin sensitivity averaged 11.2 min⁻¹(µU/ml) × 10⁻⁴ in lower-body obesity vs 2.6 in upper-body obesity and 6.1 in controls. This finding was assumed to be explained by the fact that lower-body obesity could be associated with a reduced free fatty acids-induced inhibition of insulin action by the Randle mechanism [98]. In addition, the marked effects of the balance between estrogens and progesterone on insulin sensitivity may explain some of this specific aspect, since it has been demonstrated twice that insulin sensitivity is twofold higher in follicular than in luteal phase [101-102]. Thus, lower body overweight seems to have a metabolic pattern opposite to upper body obesity [100] and to be beneficial for carbohydrate and fat metabolism [98-100]. However, these women frequently describe hypoglycemic symptoms late in the morning [98] which seem to result in carbohydrate craving and further weight gain [98].

Another situation where reactive hypoglycemia is frequently found is women with moderate lower body overweight. In contrast to upper body overweight which is well known to decrease SI, lower body overweight is associated with values of SI within the upper range [98]. This situation seems to be associated with a lower incidence of diabetes [99] and high values of HDL cholesterol [100], suggesting a possible protective effect of tight fat [100]. We measured insulin sensitivity by the minimal model procedure in lower-body overweight women and compared matched women with a similar degree of upper-body obesity and control women. Insulin sensitivity averaged 11.2 min⁻¹(µU/ml) × 10⁻⁴ in lower-body obesity vs 2.6 in upper-body obesity and 6.1 in controls. This finding was assumed to be explained by the fact that lower-body obesity could be associated with a reduced free fatty acids-induced inhibition of insulin action by the Randle mechanism [98]. In addition, the marked effects of the balance between estrogens and progesterone on insulin sensitivity may explain some of this specific aspect, since it has been demonstrated twice that insulin sensitivity is twofold higher in follicular than in luteal phase [101-102]. Thus, lower body overweight seems to have a metabolic pattern opposite to upper body obesity [100] and to be beneficial for carbohydrate and fat metabolism [98-100]. However, these women frequently describe hypoglycemic symptoms late in the morning [98] which seem to result in carbohydrate craving and further weight gain [98].

It is interesting to remind that, on the whole, women have been classically reported to be frequently prone to marked decreases in glycemia in situations such as prolonged fasting. In approximately 40% of women, blood glucose levels decrease to less than 0.4 g/l (2.22 mmol/l) in a 72-hr fast. Of these, one third had values as low as 0.3 g/l (1.7 mmol/l) [103-104].

**Influence of Diet**

There is no doubt that patient’s alimentary habits have a major role in the occurrence of hypoglycemia. However, we are not aware of specific studies on nutritional habits of these patients, and well-conducted studies on this subject appear to be almost lacking. Some physiological literature indicates that high carbohydrate-low fat diet increases insulin sensitivity [105], and this pattern is frequently found in PRH patients. In addition, two-weeks very-low-energy diets alter some aspects of the counterregulatory response to falling plasma glucose concentrations as mostly evidenced by growth hormone peaks. This results in an accelerated decline in plasma glucose. Therefore, patients on a very-low-energy diet may be at risk for abnormally low plasma glucose concentrations when ingesting high carbohydrate loads [106]. Clearly, there is very few literature on this subject.

A lot of literature has been devoted to the role of alcohol in the occurrence of hypoglycemia. While it is well known that alcohol intake at fast inhibits hepatic glucose output (via a blunting of gluconeogenesis) [107], there is also a large body of literature indicating that ethanol may induce hypoglycemia in the post-prandial period [108]. An experiment by O’Keefe and Marks [109] in ten volunteers shows that alcohol intake (equivalent of three gin-tonics) increases insulin response to sucrose, resulting in a lower nadir of glycemia (when compared to sucrose alone). In four subjects the nadir was below 2.5 mmol/l and signs of neuroglucopenia were reported in three subjects. Similarly the association of glucose (50 g) and ethanol (50 g) induces a higher insulin response which may result in hypoglycemia while glycemia does not decrease below 4 mmol/l if ethanol is associated to corn starch instead of glucose [110]. Note that other works confirm the increase in insulin response but not the reactive hypoglycemia [111] after an association of sucrose and ethanol.

These effects are due to the stimulatory effect of ethanol on insulin response to both sucrose and glucose [108, 112-117]. This effect is found with either oral [112-115] or intravenous [116-117] glucose. In addition ethanol blunts hepatic glucose output [118] by inhibiting both glycogenolysis and gluconeogenesis and induces a peripheral insulin resistance [119-120]. Effects on glucose counterregulation are more controversial: Kolaszynski [121] reported that ethanol reduced the response of cortisol, epinephrine, GH and glucagon to hypoglycemia. However, insulin resistance seems to limit the consequences of this effect [121]. Other investigators failed to report a defect in counterregulation [122] but a recent paper [123] confirms that in otherwise healthy individuals a combination of gin and regular tonic can induce reactive hypoglycemia, due to an inhibiting effect of acute ethanol ingestion (0.5 g/kg) on epinephrine and growth hormone response to a fall in blood glucose levels. After the ingestion of three gin tonics, the blood glucose nadir (3.35 mmol/l) was lower compared to that with tonic alone without alcohol alone (3.87 mmol/l) and after gin, subjects reported typical hypoglycemic symptoms. Partial prevention of these alcohol-induced postprandial hypoglycemas can be obtained by a reduction of glucose or saccharose in
these drinks, or, alternatively, by replacing these carbohydrates by fructose [124].

Some old literature also suggests an association of reactive hypoglycemia with calcium status. Reactive hypoglycemia has been reported to be frequent in hypocalcemic patients [10, 125], to be corrected by calcium infusion [126], and to be unrelated to glucagon [127].

### DIETARY TREATMENT

Harris, in his first paper [4], advocated treating PRH with a low-carbohydrate diet and frequent small split meals. This dietary approach remains the first treatment of this disorder [1, 10, 28-30, 73].

The first important point is to add small meals at the middle of the morning and of the afternoon, when glycemia would start to decrease. If adequate composition of the meal is found, the fall in blood glucose is thus prevented.

The second cornerstone of this diet is that patients should avoid rapidly absorbable sugars and thus avoid popular soft drinks rich in glucose or sucrose. They should also be cautious with drinks associating sugar and alcohol, mainly in the fasting state.

If the breakfast is hyperglucidic, adding proteins to it frequently reduces its insulin response and thus its power to induce further excessive falls in blood glucose [45].

Addition of soluble dietary fibers that lower the glycemic and the insulinenic index has a similar effect and has thus been recommended. Soluble fibers as pectin and guar delay gastric emptying and prolong the intestinal transit time. Mirouze [89] reported in a series of nineteen patients that treatment with pectin protected against falls in blood glucose after OGTT by increasing the glucagon response in the late period of the test [89]. The addition to the meal of 5 to 10 g hemicellulose, guar or pectin often improves postprandial hypoglycemia. Dietary fibers are mainly interesting when PRH is associated with decreased glucose tolerance or occurs after gastric surgery [29].

As shown above, the risk of reactive hypoglycemia is markedly enhanced by the simultaneous ingestion of ethanol and sucrose or glucose, mainly in the fasting state. Decreasing the amount of sucrose (glucose) ingested or replacing it with either saccharin or the noninsulinotropic carbohydrate fructose has been shown to prevent this kind of hypoglycemia [108].

In most patients with idiopathic-reactive hypoglycemia, diet alone is sufficient; but one should be alerted for the aggravation of symptoms on a low-carbohydrate diet. If this occurs, one should suspect fructose 1-6 diphosphatase enzyme deficiency, and the diet should be increased in carbohydrates [10].

### PHARMACOLOGIC APPROACH

When symptoms persist despite a correctly prescribed (and adequately followed ...) diet, a pharmacological approach is justified [29]. The treatment of choice seems to be intestinal alpha-glucosidase inhibitors which delay starch and sucrose digestion and therefore reduce the insulin response to sugar or to a mixed meal [128, 129]. Satisfactory results in reactive hypoglycemia have been reported for both acarbose [130-133] and miglitol [134], the latter being poorly tolerated. However their long-term use in this indication has not been firmly established by controlled studies [128]. Acarbose can also be employed in the dumping syndrome [135-137] and in PRH related to alcohol intake [111, 138].

Biguanides have been shown to alleviate PRH [10, 139]. Metformin can be useful associated to diet at a dose of 500 to 850 mg orally taken with the meals [29]. There are also reports on the anticholinergic drugs Atropine (0.25 mg) and Probanthine (7.5 mg), taken before the meals [29, 140]. Phenytoin has been shown to improve also PRH [141-142]. Calcium gluconate infusions [126-127] have also been shown to modify the OGTT curve, suppressing the postload fall in blood glucose [127] and thus to be of some efficiency in PRH. Supplemental chromium, which exerts some insulin-sensitizing effects, has also been proposed [143]. By down-regulating beta-cell activity, chromium may be assumed to increase glucagon secretion [143].

Diazoxide is a major treatment of organic hypoglycemia [144] that can also be employed in some very severe cases of reactive hypoglycemia [145]. Since it is generally not well tolerated (water retention, hypertrichosis, digestive disorders) its use remains limited in PRH [144-145] but it could sometimes provide an efficient alternative in the case of failure of other treatments.

In exceptional cases, somatostatin analogues can be interesting, as first shown in 1981 by Mirouze [146] who demonstrated that an infusion of somatostatin in PRH patients slowed down the initial rise in blood sugar and thus delayed the occurrence of hypoglycemia. Given the increase in glycemia that reached 13 mmol, this drug appeared to be frankly diabetogenic. However, somatostatin analogues gave more interesting results in cases of PRH resisting to all other treatments [147]. Somatostatin controls the secretion of gastrointestinal hormones and lowers insulin levels in both basal and stimulated conditions [147]. In a case of severe PRH due to a defect in hepatic glucose-6-phosphatase [92], a good response to a single dose (100 micrograms IM) of the somatostatin analogue octreotide was found. In fact this treatment, given its cost and its side effects, should be used only in exceptional cases.

Other drugs proposed in PRH include propranolol and calcium antagonists such as nifedipine, diltiazem,
and nicardipine but controlled studies appear to be still lacking to assess their interest [10]. Since a low adrenal activity was initially assumed to explain the disease, its treatment by adrenal extracts got some popularity, leading the American Diabetes Association and the American Medical Association to issue a joint statement on the necessity of critical evaluation of hypoglycemic states and to discourage the usage of the biologically inactive adrenocortical extracts as therapy for these disorders [10].

CONCLUSION

The so-called functional hypoglycemic states have suffered from the past difficulty to diagnose and the lack of knowledge regarding their mechanisms. They thus are still considered by many physicians as examples of “non disease” [148]. However, there are now both standardized tools to perform the diagnosis and pathophysiological data explaining the mechanisms. These states represent minor disturbances of the balance between glucose utilization and glucose supply in situations like meals or exercise which suddenly disturb carbohydrate homeostasis. Most generally, these hypoglycemias occur in situations of high insulin sensitivity, i.e., the opposite of syndrome X and diabetes. While this metabolic situation is potentially beneficial, a fall of blood glucose below the usual levels will result in rather uncomfortable symptoms (palpitation, tremor, sweating, dizziness, blurred vision) and in dangerous disturbances in reaction time in some usual tasks like driving a car or performing a specific exercise. Generally, the patient is disturbed by the recurrence of these events and many physicians will rather consider him as as neurotic and send him to the psychiatrist. However, we have seen that the specific psychological pattern of "pseudohypoglycemia" which is mostly characterized by an increase in sympathetic tone, is also found in bona fide hypoglycemia, probably in part because this is a very stressful situation. In fact, just like the other metabolic diseases, postprandial hypoglycemia can now be approached scientifically and thus treated, so that the patient’s quality of life can be improved.

REFERENCES


