EXERCISE HYPOGLYCEMIA IN NONDIABETIC SUBJECTS

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SUMMARY - Hypoglycemia during exercise is a common event due to an unbalance between training volume, nutrition, and external influences such as chronobiology, temperature or altitude, in subjects characterized by an acute and chronic increase in glucose effectiveness and insulin sensitivity. While it is preventable by adequate pre-exercise feeding with carbohydrates, it can also be induced by a prior carbohydrate meal with high glycemic index. Adequate training induces resistance to hypoglycemia via a shift in the balance of oxidized substrates and marked hormonal adaptations, but overtraining, by partially reversing this adaptation, favors hypoglycemia. Exercise hypoglycemia is a cause of fatigue or exercise cessation, but also impairs thermoregulatory adaptation and is assumed to fragilize muscles and tendons for traumatic events.

Key-words: hypoglycemia, adults, exercise, blood glucose, dietary carbohydrates, insulin sensitivity, glucose effectiveness, overtraining.

REVIEW

RÉSUMÉ - Hypoglycémie lors de l’exercice chez les patients non diabétiques.
Les hypoglycémies à l’exercice (HE) surviennent chez des sujets présentant des valeurs élevées d’insulino-sensibilité et d’efficience glucidique, en raison d’erreurs diététiques, de surentraînement sportif, ou de circonstances particulières (écarts thermiques, altitude, rythme circadien).

Mots-clés : hypoglycémie, adulte, exercice, insulin, insulino-sensibilité, efficience glucidique, surentraînement.
since muscle is responsible for almost 90% of body’s glucose uptake, as demonstrated in euglycemic hyperinsulinemic clamp experiments [1] it is not surprising to frequently observe cases of exaggerated decrease in blood glucose in athletes in situations of increased glucose processing by exercising muscles. Although an epidemiological study showing their exact prevalence among athletes is still lacking, low values of blood glucose, reaching the range where symptoms of hypoglycemia can be observed, are surely not infrequent [2]. Like the postprandial reactive hypoglycemias [3] these events, which should be carefully differentiated from all ‘organic’ causes of hypoglycemia [4] are likely to reflect in most of the cases a situation on the boundaries of physiology [5] where glucose counterregulation becomes unable to totally balance glucose disposal [6].

There is no doubt that endurance performance can be influenced by altering the availability of blood glucose during exercise [7]. Blood glucose levels seem to be a at least a marker of this muscular glucose availability [8, 9]. In addition, hypoglycemia, although only occasionally severe enough to result in fatigue from neuroglucopenia, has been assumed to cause fatigue by limiting blood glucose (and therefore total carbohydrate) oxidation [10-12]. Actually, this issue has long been controversial since it appears that in most of the cases the reduction of glycogen stores rather than hypoglycemia by itself explains fatigue [2]. Clearly, because of its limited storage, depletion of muscle glycogen is one factor responsible for fatigue and exhaustion during prolonged exercise. [13]. However, an experimental approach of this issue in rats [14] has recently challenged this controversy. In rats infused with insulin the duration of running until exhaustion is reduced, and even more reduced if rats are also fasting, when compared to saline-infused fed animals. Intravenous infusion of glucose at the time of fatigue produces an immediate recovery, allowing the formerly fatigued animals to run 20 min without development of fatigue. The interest of this experiment is to confirm the importance of blood glucose itself in the mechanism of fatigue, regardless glycogen stores. Although other mechanisms of exhaustion can be described such as hyperthermia or acidosis, severe exercise hypoglycemia can thus be, experimentally, a major cause of fatigue.

Whether athletes prone to hypoglycemia are also “fragilized” for traumatic events of muscles and tendons at exercise is a quite usual belief among sports physicians but there is no clear scientific evidence in the literature to demonstrate this assumption. Actually, this point of view is supported by a host of indirect and theoretical data [15].

In fact, most of the controversies about exercise hypoglycemia are likely to be due, just like what occurs for postprandial reactive hypoglycemia [3], to the lack of standardized and widely recognized diagnostic tools for this situation.

By contrast, literature about the physiological mechanisms of exercise hypoglycemia and its dietary treatment is not so reduced, and its size has been rapidly growing over the last years. Thus, in this review, we will try to summarize the available information about exercise hypoglycemia and to propose some guidelines for its clinical management.

**THE PHYSIOLOGICAL BACKGROUND: ACUTE EFFECTS OF MUSCULAR EXERCISE ON CARBOHYDRATE HOMEOSTASIS**

At rest muscle mostly oxidizes fat [16]. By contrast, carbohydrate, principally glycogen, appears to be the preferred fuel for muscular activity [17] although fats and protein contribute also to a lesser extent to energy demands of exercise [18].

Basically, glucose homeostasis during exercise is modified by an increase in both glucose muscular uptake and glucose supply by the blood stream. The problem of glycemia during exercise is to maintain the balance between these two parameters that undergo dramatic modifications. In addition, the effect of exercise on glycemia is dependent upon the level of work intensity, which affects the mechanisms by which glucose fluxes are regulated [19].

In the case of moderate-intensity exercise, glucoregulatory response resembles glucoregulation in the basal state, eg, glucose release from the liver is controlled by glucagon and insulin, and blood glucose levels are tightly controlled.

During high-intensity exercise, on the other way about, glucoregulatory response is similar to that of a classical stress response. Blood glucose levels are no longer closely regulated, and increase, due to an unbalance between the marked stimulation of glucose production and a a somewhat smaller increment in its utilization. This appears to be due to a disproportionate increase in plasma catecholamine while the increase in glucagonemia is rather moderate [19, 20].

Another major mechanism explaining exercise-related changes in blood glucose levels is the changes in peripheral glucose disposal. In humans, acute exercise increases insulin sensitivity and glucose effectiveness [21], independent of insulin. It is important to point out that these effects are less transient than those of insulin, resulting in a risk of late hypoglycemia. A usual example of this mechanism is the case of diabetics that have exercised during the day and suffer an unexpected hypoglycemia during the night. Insulin sensitivity is thus increased for at least 16-48 hr after a bout of exercise in humans. The major mechanism of these changes in glucose disposal has been shown to be the transmembrane transport of glucose mediated by glucose transporter (GLUT) 4. This transporter is
expressed mainly in skeletal muscle, heart and adipose tissue and mediates glucose transport stimulated by either insulin or muscular exercise which both act via separate synergistic pathways. GLUT-4 glucose transporters are able to migrate to the plasma membrane of skeletal muscle from intracellular stores [22, 23]. Whether muscle GLUT4 is or not a major determinant of insulin sensitivity and glucose effectiveness has been a controversial issue in recent studies with transgenic animals. First experiments with homozygous whole-body GLUT4 knockout (GLUT4-null) mice demonstrated only mild perturbations in glucose homoeostasis, while muscle-specific inactivation of the insulin receptor results in almost undetectable changes in glucose tolerance. This was surprising since, on the other hand, transgenic mice overexpressing human GLUT4 in muscle and fat exhibit greater muscle glycogen content at rest, and during exercise they metabolize more carbohydrate. An increased glyco-
genolysis rate can be measured in muscle and liver. Overall, overexpressing human GLUT4 in muscle and fat results in a predominant use of carbohydrate as a fuel source, even in cases of experimental hypoglycemia and increased availability of free fatty acids [24]. In fact, a more recent report of selective disruption of GLUT4 in mouse muscles [25] has clearly demonstrated the importance of these transporters in glucose homoeostasis. This mutation results in a profound re-
duction in basal glucose transport and a near-absence of stimulation by insulin or muscular contraction. Mice are severely insulin resistant and exhibit a glucose intolerance [25]. Interestingly, in contrast with older literature emphasizing the key role of muscle glycogen synthase as a limiting step in the regulation of muscle glucose use [26-28] these transgenic animal models demonstrate that the GLUT4-mediated glu-
cose transport is actually an even more important rate-limiting mechanism, governing to a large extent the pivotal role of muscle in the maintenance of glu-
cose homoeostasis [25].

A cellular mechanism that may explain the simul-
taneous activation in exercising muscle of so many different metabolic pathways such as free fatty acid oxidation, glycogenogenesis, GLUT-4 processing, hexokinase, and mitochondrial enzymes, has been re-
cently been suggested to be a protein kinase activated by adenosine monophosphate (AMP) and termed the AMP- activated protein kinase (AMPK). As recently reviewed by Rennie [28]. AMPK, which is activated by the production of contraction-induced metabolites, is likely to be a “cellular fuel gauge” which monitors the energy status of the cell and thereby activates intracellular energy supply to the contractile structures. However, AMPK does not appear to mediate the migration of GLUT4 to the cell membrane [28].

On the whole, it can be considered that during exercise the absolute work rate determines the total quantity of fuel required, while relative exercise inten-
sity sets the proportions of carbohydrate and fat oxid-
dized by working muscles. As relative exercise intensity is increased, there is a decrease in the proportion of the energy requirement derived from fat oxidation and an increase in that provided by carbohydrate oxidation [29-31]. Increasing intensity and/or duration of exercise thus increases the amount of glucose handled and oxidized by muscles and coming from both the glycogen stores and the blood [19]. This increase, although sometimes represented as displaying an ex-
ponential slope [31], is proportional to the exercise intensity [32] and can be considered as almost linear [33, 34], allowing the calculation of a constant of a glucose oxidation rate which averages 0.22 mg.min⁻¹ kg⁻¹.watt⁻¹ and is rather reproducible among individuals tested twice (paired coefficient of variation = 15.9%). Thus, exercise intensity is a major determinant of glucose uptake in muscles.

Immediately after the end of exercise there is an increase in glycemia accompanied by a parallel in-
crease in insulinemia [20, 35]. This postexercise re-
bound has been reported to play a role in postexercise “glycogen supercompensation” in muscles, ie the very large increase in muscle glycogen concentration which occurs in response to carbohydrate feeding following prolonged, glycogen depleting exercise, resulting in a glycogen muscular content far above the level found in well-fed sedentary individuals. This “glycogen su-
percompensation” has been recently shown to be markedly enhanced by endurance exercise training, due to an increase in the GLUT4 isoform of the glucose transporter in skeletal muscle [29]. However, this large increase in carbohydrate uptake by muscles after exercise may favorize postexercise hypoglyce-
mia.

WHAT MAKES GLYCEMIA DECREASE AT EXERCISE

Given the factors reviewed above, several distur-
bances in this exquisite regulation may occur and result in an unbalance between glucose production and muscular glucose use.

The duration of exercise

Clearly, the situation which is the most likely to decrease glycemia is prolonged, low intensity exercise (55-75% VO₂max). This kind of exercise is moder-
ately strenuous and can thus be maintained for 90 minutes or longer. Given the reduced size of car-
bohydrate stores, glycogen depletion can gradually occur. To avoid this depletion, there appears to be an adaptive mechanism resulting in a progressive de-
cline in the proportion of energy derived from muscle glycogen and a progressive increase in plasma fatty acid oxidation. This mechanism is improved by train-
ing, resulting in a marked sparing of carbohydrate during exercise, with an increased proportion of the energy being provided by fat oxidation [29]. The mechanisms by which training decreases utilization of blood glucose are not well understood. A possible link between the relative lack in carbohydrate and the increased use of fats may be intramuscular malonyl-CoA concentrations [36]. This metabolite inhibits carnitine acyltransferase I (mostly in the muscle) and is an important regulator of fatty acid oxidation and ketogenesis in the liver. Fluctuations in muscle malonyl-CoA may thus regulate the rate of fatty acid oxidation in muscle during exercise. During long duration exercise, the decline in malonyl-CoA occurs before muscle glycogen depletion and before the onset of hypoglycemia. This exercise-induced decrease in malonyl-CoA may be thus a signal triggering an increase in muscle fatty acid oxidation during exercise. In addition, supply of free fatty acids by lipolysis is stimulated by an increase in sympathetic tone in conditions of low insulin [37]. While the precise nature of defects in this process remains poorly defined, it is clear that if fat-derived energy cannot supply to the lack of carbohydrates, hypoglycemia can occur, as frequently observed in sports medicine practice [19].

**Hepatic glucose production**

Therefore, during prolonged exercise, the increased rate of glucose utilization by the working muscle would lead to hypoglycemia were it not accompanied by compensatory mechanisms. Beside the shift towards a higher utilization of fat, there is also an increase in hepatic glucose production.

The participation of both hepatic glycogenolysis and gluconeogenesis to the glycemic changes promoted by exercise has been well described. Hepatic glycogen has a crucial role to determine hyperglycemia during exercise, as shown by experiments where hypoglycemia developed during exercise when glycogen was depleted [37].

However, the ability of the liver to produce glucose from gluconeogenic substrates (L-lactate, glycerol and L-glutamine, but apparently not L-alanine) is increased during exercise when hepatic glycogen stores are depleted [37]. Thus, during exercise, there is an increased capacity to produce glucose in the liver. At least in experimental rats, this mechanism seems to be the most important metabolic adaptation to protect against severe hypoglycemia [38]. Moreover, during exercise, protein synthesis is depressed and this change leaves amino acids available for both catabolic processes and gluconeogenesis. The rate of leucine oxidation is increased during exercise. There is a movement of amino acids, mostly in the form of alanine, from muscle to liver where the rate of gluconeogenesis is increased as a result of exercise. These changes in protein metabolism are probably physiologically significant in at least three ways: amino acid conversion to citric acid cycle intermediates enhances the rate of oxidation of acetyl-CoA generated from glucose and fatty acid oxidation, oxidation of some amino acids may provide energy for muscular contraction, increased conversion of amino acids to glucose helps to prevent hypoglycemia [39].

By contrast with the increase in glucose uptake which is normally driven by mechanisms that are primarily independent of the action of insulin and other hormones [22, 23], the response of the liver appears to be closely controlled by the endocrine system [19].

### The key role of insulin and glucagon

The most important hormone in this regulation is probably insulin, which blunts hepatic glucose production. In human islet clamp studies during moderate exercise (approximately 60% peak O2 consumption for 60 min), when insulin and glucagon are held constant, there is a substantial exercise-associated decrement in plasma glucose i.e., from 5.5 to 3.4 mmol/l which shows that these pancreatic hormones are critical for preventing hypoglycemia [40]. Experimentally in rats an infusion of excess insulin during a treadmill exercise induces a progressive decline in blood glucose, either if rats are fasting or fed at libitum. Even more, in the last case, exercise accelerates the rate of development of hypoglycemia while in fasting rats the rate of decline in blood glucose was not influenced by exercise, probably because it was already maximal [41]. There is a large body of evidence, in humans, supporting this concept. Clearly, a meal taken 1 hr before exercise results in high insulin levels during exercise which favorize hypoglycemia, probably because it blunts hepatic glucose production [42, 43]. Even if the carbohydrate meal is taken in several small feedings, it can produce transient hypoglycemia near the onset of exercise. The magnitude of this hypoglycemic response is unrelated to either the amount of carbohydrate ingested or the insulin response [42].

Several sophisticated islet clamp experiments using somatostatin infusion in normal human volunteers have been performed during light prolonged exercise (40-60% maximal oxygen consumption). Despite some discrepancies in the results and mostly in their interpretation they clearly show that there must be a reduction in insulin and/or an increase in glucagon concentration if plasma glucose homeostasis is to be maintained. If such changes do not occur, hypoglycemia, and hence exhaustion occurs [44, 45]. Actually if exercise intensity is very low, decrements in insulin are not fully critical to the prevention of hypoglycemia even if the sympathochromaffin counterregulatory response is blunted if there is a glucagon response [46]. On the other way about, somatostatin-induced glucagon suppression clearly results in hypoglycemia both during rest and exercise and the glucagon/insulin molar ratio is the best correlate of the rate of glucose
hepatic production during exercise. Glucagon is likely to control approximately 70% of the increase of glucose production during exercise [47].

Other counterregulatory hormones

In studies where insulin and glucagon are kept constant during moderate prolonged exercise, the blood glucose level decreases, but reaches then a steady state, indicating that, beyond pancreatic hormones, there is an additional compensatory mechanism preventing deep hypoglycemia [40, 45]. It is known that, beside the decreased plasma insulin, there is an increase in catecholamines, glucagon, cortisol, and growth hormone. All of them are likely to contribute to (but are thought to be not fully essential) for the increased hepatic output of glucose during exercise [2]. The regulation of these hormonal responses to moderate exercise is due to exercise itself with a synergistic effect of hypoglycemia for sympathoadrenal and GH response, while the peripheral glucagon response is entirely glucose dependent. The epinephrine response to hypoglycemia can be dissociated from that to exercise, suggesting differing control mechanisms. Accordingly, the activation of counterregulatory hormones during exercise is regulated by glucose-independent mechanisms, although these responses may be augmented by concurrent hypoglycemia [48].

Actually, the normal matching of glucose utilization by increased glucose production has been suggested to be due to a redundant effect of glucoregulatory systems including sympathochromaffin activation and changes in pancreatic islet hormone secretion. Accordingly, the occurrence of exercise hypoglycemia requires both a sufficient action of catecholamines and a lack of response in islet hormones [49]. In adrenalectomized rats as compared to sham-operated controls, during exercise, hypoglycemia occurs earlier and is more pronounced. Besides, exercise-induced mobilization of glycogen in exercising muscles is diminished and the breakdown of liver glycogen is accelerated [50]. Therefore, sympathochromaffin activation plays an important glucoregulatory role. Presumably catecholamines act by limiting glucose utilization as well as stimulating glucose production, so that in case of catecholamine deficiency decrements in insulin and increments in glucagon become critical for avoiding exercise hypoglycemia [49].

In fact, adrenergic blockade during exercise only results in a very initial and limited decrease in plasma glucose (from 5 to 4.4 mmol/L). Sympathochromaffin activation plays a minor role when insulin and glucagon are operative, and a catecholamine, probably epinephrine, becomes critical to the prevention of hypoglycemia during exercise only when changes in insulin and glucagon do not occur [40]. The marked increase in plasma epinephrine that occurs in fasted exercising rats has probably an important physiological relevance, as demonstrated by the marked reduction in endurance run times of adrenomedullectomized rats. Epinephrine seems to induce glycogenolysis in contracting type I and noncontracting type II muscle fibers, providing essential quantities of lactate for hepatic gluconeogenesis in fasted exercising rats. [51]. Experiments of adrenomedullectomy also show that adrenomedullary catecholamines including epinephrine are not critical to glucoregulation during moderate exercise in humans even when changes in insulin and glucagon are prevented. Thus sympathetic neural norepinephrine is likely to be the operative catecholamine in the prevention of hypoglycemia during exercise in humans [49].

Consistent with this physiological literature, the effects of beta blockade in humans may include hypoglycemia, associated with impaired mobilization of free fatty acids and decreased breakdown of glycogen in skeletal muscle. Most of these metabolic beta-adrenergic effects are thought to be beta 2 in nature. However, two populations of receptors (mixed beta 1 and beta 2) may explain some controversial findings [52].

Less information is available about the involvement of the other counterregulatory hormones in the prevention of exercise hypoglycemia. However cortisol and growth hormone, which are important for preventing hypoglycemia [53] are likely to play also this role during prolonged exercise, as evidenced, for instance, by correlations between postexercise lipid oxidation rate and the magnitude of growth hormone response to exercise [32] which show that this GH response may be a determinant of the shift towards a greater reliance of lipids in order to spare carbohydrates. In addition, it has been experimentally demonstrated that decreases in blood glucose concentration below to a critical level of 3.3 mM trigger the pituitary-adrenocortical axis to enhance secretion of ACTH and cortisol during low-intensity prolonged exercise in humans [54]. Growth hormone [48] and catecholamine [55] responses to exercise are also enhanced by hypoglycemia. This potentiation by hypoglycemia of the physiological response to exercise of hyperglycemicant hormones, which are well known as major stimulators of hepatic glucose output, may indicate that it plays a role in glucose homeostasis during exercise.

Therefore, hepatic glucose production during exercise, which is initially supported by the breakdown of hepatic glycogen and subsequently by an increase in gluconeogenesis, is necessary to compensate for the marked increase in glucose uptake by muscle. If there is a failure in this complex regulatory process and hepatic glucose output becomes inadequate, hypoglycemia may result [2]. More precisely, hypoglycemia can develop, both when catecholamine action is deficient and when changes in islet hormones do not occur during exercise in humans [49].
MECHANISMS OF HYPOGLYCEMIA DURING PROLONGED EXERCISE

Increased insulin sensitivity and glucose effectiveness

Kuipers [43] observed that in 30% of athletes fed with glucose 30 min before exercise plasma glucose levels dropped transiently below 3.0 mmol/l. On the basis of lower plasma glucose levels despite similar insulin levels, he postulated that these hypoglycemia-prone athletes had a higher insulin sensitivity. On the whole the occurrence of hypoglycemia appeared to be determined by a combination of a high insulin sensitivity, a small amount of ingested glucose, and a low symptomatic activity.

This conclusion about insulin sensitivity is questionable. Actually, high insulin sensitivity is a very common feature in athletes [56-58], although exercise intensification does not appear to further increase this parameter above physiological levels [59]. While increased insulin sensitivity is clearly a major mechanism of postprandial reactive hypoglycemia [3], [60, 61], we reported in a previous paper that exercise hypoglycemia was rather associated with a higher glucose effectiveness, i.e., the non-insulin dependent component of glucose disposal [62]. While insulin sensitivity is proportional to aerobic capacity and to the degree of training [63, 64] this is not the case of glucose effectiveness [65] even if it can be further increased by intense training [59]. We think therefore that Kuiper’s finding of a low glucose despite unchanged insulin rather reflect a higher glucose effectiveness. It should be stressed that crude values of insulin and glucose can be helpful for evaluating insulin sensitivity in some populations like sedentary obese individuals [66], but are absolutely unreliable in athletes [67].

Clearly, however, Kuiper’s paper [43] points out the importance of preexercise conditions on the occurrence of exercise hypoglycemia. The question of the previous meal is critical. As already discussed, any meal which can result in high insulin levels during exercise is at risk for inducing hypoglycemia [42]. Glucose or high glycemic index carbohydrates are not the only sugars that can induce exercise hypoglycemia. In fact, as demonstrated by Mitchell [68], hypoglycemia measured during a 10-km treadmill run decreases less after fast than if subject were fed with either an 8 g 100 ml⁻¹ high fructose corn syrup solution, a 6 g 100 ml⁻¹ glucose solution, a 6 g 100 ml⁻¹ sucrose/glucose mixture, or banana with water. This means that a wide variety of carbohydrates are actually able to induce exercise hypoglycemia. Trained athletes have been reported to have an accelerated carbohydrate uptake (despite a lower carbohydrate oxidation) after a high carbohydrate meal [69].

Another condition previous to exercise that may impair defense against exercise hypoglycemia is an antecedent hypoglycemia during the preceding day. A prior hypoglycemia can blunt hormonal (glucagon, insulin, catecholamines) and metabolic (endogenous glucose production, lipolysis, ketogenesis) responses to exercise, and thus favorize the occurrence of hypoglycemia [70].

Finally, the hour at which exercise is performed may markedly influence the risk for hypoglycemia. Scheen [71] demonstrated a marked effect of daytime on neuroendocrine and metabolic responses to a 3-h exercise period (40-60% maximal O₂ uptake) in men. When comparing exercise performed during early morning, during on, and around midnight it appeared that the exercise-induced glucose decrease was 50% greater around midnight, when cortisol was minimal and not stimulated by exercise, than in the afternoon or early morning. These circadian variations are likely to explain some hypoglycemic events in athletes exercising after a transcontinental flight with an important jet lag. Presumably, if an athlete’s body is chronobiologically set at midnight at the time of exercise, glucose regulation is likely to be impaired.

Altitude

In altitude there may be a dramatic increase in the utilization of carbohydrate, fluid, and in some instances protein. These increased requirements may then not be covered. Insufficient replacement of carbohydrate may lead to hypoglycemia, altered protein metabolism, central fatigue and exhaustion. Inadequate carbohydrate and protein intake leads to a negative nitrogen balance, which over the long term will lead to a loss of muscle mass [72].

Overtraining

Overtraining is defined as an increase in training volume and/or intensity of exercise resulting in performance decrements [73]. Recovery from this condition often requires many weeks or months [74]. A shorter or less severe variation of overtraining is referred to as overreaching, which is easily recovered from in just a few days. [75]. Overtraining consists of a spectrum of psychological, endocrinological, physiological, and immunological symptoms that all play a role in the failure to recover from exercise. While the hormonal and metabolic adaptation of the human body to endurance training includes a host of mechanisms that prevent hypoglycemia, in situations on the edge of the overtraining syndrome, most of adaptive hormonal mechanisms described during training are reversed [76]. More precisely, responses of growth hormone and cortisol to both insulin-induced hypoglycemia [77] and exercise [78] are impaired, so that counter-regulation may become less efficient. Accordingly, hypoglycemia is often mentioned among the symptoms of overtraining [76, 79]. In fact, this tendency to
hypoglycemia seems to be a very early symptom of overtraining, as demonstrated by a study on four weeks of daily exhaustive exercise (six days/week) which reduced blood glucose, even if hypoglycemia is not clinically significant, as a result of depletion of carbohydrate storage. [80]. Alterations in the pattern of circulating binding proteins for the growth factor IGF-I may explain this tendency to hypoglycemia in overtrained athletes, since an increase in the ratio IGF-I/IGFBP-3 [81] and possibly a decrease in baseline IGFBP-1 have been observed in samples of overtrained athletes and are likely to increase free circulating levels of IGF-I, a well-known hypoglycemia -inducing hormone.

The special case of ultra-short supramaximal work loads

Supramaximal exercise is likely to represent the ultimate example of short and very intense exercise, ie, the variety of exercise which rather increases glycemia. In fact, this kind of exercise has been shown in one study to result in hyperglycemia, followed by a rapid return to normal exercise blood glucose and insulin values within 10-30 min after exercise. In this case such an exercise was not likely to induce hypoglycemia [82]. By contrast, we recently observed that, if a series of supramaximal work loads is preceded by a standard breakfast, glycemia markedly decreases, due to a lack of insulin suppression despite the huge waste of glucose by muscles [83].

**HYPOGLYCEMIA AND THERMOREGULATION**

Temperature at which exercise is performed may influence the balance of substrates, as shown by an experiment consisting of a 30-min swim in thermal water cooled to 25 degrees C. Swimming in cooled water depletes muscle and liver glycogen and slightly decreases heart glycogen. Under these conditions, plasma insulin decreases and hypoglycemia occurs [84]. On the other hand, when rats exercised in the heat (35.5 degrees C) until hyperthermic exhaustion, food deprivation resulted in severe hypoglycemia following exercise. Although short-term endurance capacity is unaltered by this hypoglycemia, it is associated with hypertriglycerideremia, hyper lactacidemia, and more severe dehydration, demonstrating a close relationship between the availability of sugars and thermoregulatory adaptation to exercise. [85]. In addition, hypoglycemia influences the thermoregulatory responses to a temperature change. When a blood glucose level of 2.8 mM is achieved, it decreases the core temperature threshold for shivering during cold exposure [86]. In fact, some reports indicate that in humans hyperglycemia can attenuate the rise in exercise core temperature. Elevation of plasma glucose in previously dehydrated volunteers prior to submaximal exercise attenuates hyperthermia. This effect is unrelated to any change in heat production, total body sweating, serum electrolytes and osmolality, or exercise-induced hypoglycemia. Its mechanism is assumed to be an enhanced peripheral blood flow that could enhance body heat loss [87]. A similar experiment in rats [88] also shows that endurance is increased by hyperglycemia when exercising in hyperthermic conditions.

**MECHANISMS PROTECTING AGAINST EXERCISE HYPOGLYCEMIA**

**Improved hypoglycemic resistance following regular training**

Endurance training has long been known to improve the individual’s resistance to exercise-induced hypoglycemia, . While sedentarity increases the reliance on carbohydrates as a source of energy [16] beside an increase in fat storage, training, on the opposite, increases the ability to use lipids as a preferential fuel during submaximal exercise [89]. The improved hepatic gluconeogenic capacity of endurance trained individuals, at least in rats, is critical to this resistance to exercise-induced hypoglycemia [38]. Training-induced reductions in both hepatic glycogenolysis and gluconeogenesis are probably largely due to alterations in the glucoregulatory hormone response to exercise, and possibly to other factors such as changes in hepatic hormone sensitivity and/or responsiveness. Epinephrine responses to insulin-induced hypoglycemia have indicated that athletes have a higher adrenal medullary secretory capacity than untrained subjects. Long-term endurance training increases responsiveness of the adrenal medulla to exercise, indicating increased secretory capacity. During maximal exercise this may contribute to higher glucose production, lower glucose clearance, hyperglycemia, and higher lypolysis [90].

In addition, it has been more recently reported that, at least in humans, training also reduces muscle glucose transport. This adaptation seems to be related to the training-induced increase in muscle mitochondrial respiratory capacity. It has been described to be often quantitatively just as important as the decline in muscle glycogen utilization in accounting for the overall carbohydrate-sparing effect of training [91]. In addition, since during exercise the protein synthesis is depressed, amino acids become more available for catabolic processes, as indicated by an increased rate of leucine oxidation. Besides, there is a movement of amino acids, mostly in the form of alanine, from muscle to liver. In the liver, these substrates are thus available for gluconeogenesis. On the whole, these metabolic changes are likely to participate to the pre-
vention of hypoglycemia by three major mechanisms: first, they provide energy for muscular contraction; then, they may enhance the rate of oxidation of acetyl-CoA generated from glucose and fatty acid oxidation; finally, these amino acids are processed by gluconeogenesis and help to maintain it and thus to supply glucose to tissues [39]. All these training-induced adaptations in glucose production and substrate balance are likely to minimize the possibility of hypoglycemia.

Training-induced alteration in counterregulatory hormones response

Classically, during exercise, glucagon is directly responsible for 80% of the increment of glucose production and controls glucose uptake by the muscle indirectly. Glucagon spares muscle glycogen by increasing hepatic glucose production. Epinephrine infusion transiently increases glucose production and induces a sustained inhibition of glucose clearance, resulting in hyperglycemia. Accordingly, glucagon suppression diminishes hepatic responsiveness to epinephrine [92].

On the whole, the effects of regular training on hormones of glucose homeostasis are now well described. LeBlanc [93] analyzed the response to insulin injection in athletes compared to non-trained subjects and observed, beside a greater fall in plasma glucose due to high insulin sensitivity, a higher raise in epinephrine and growth hormone in trained subjects. Similarly, the increase of growth hormone (GH) was greater in the trained subjects. Tremblay [94] investigated counterregulatory response to insulin-induced hypoglycemia in trained and nontrained healthy individuals, and showed that increases in plasma glucagon, epinephrine, norepinephrine, and growth hormone were at least 50% lower in trained than in nontrained subjects. Interestingly, trained subjects are characterized by a normal recovery from hypoglycemia despite a reduced response of counterregulatory factors to insulin-induced hypoglycemia [93]. In fact, the picture is somewhat different when considering hormonal responses to exercise. Although some aspects had remained controversial for a long time, it is now well established that endurance training increases epinephrine, GH [95] and beta-endorphin [96] responses to exercise, while it decreases ACTH [96, 97], cortisol [96, 97], and possibly glucagon while this latter hormone has been less studied [98]. Besides, insulin (baseline and postchallenge) is lowered. All this pattern is associated with an increase in lipid oxidation that helps to spare carbohydrate stores [30, 31, 89]. In addition, Insulin-like Growth Factor – binding protein 1 (IGFBP-1) which is regulated by both insulin and cortisol and increases in case of hypoglycemia, potentially serves to prevent the hypoglycemic effects of free IGFs [99].

Significant, sexual dimorphisms exist in counterregulatory responses to exercise, as well as commonly occurring stresses, such as hypoglycemia, fasting, and cognitive testing. The question of whether counterregulatory responses differ during exercise in healthy men and women remains controversial. During exercise, men have increased autonomic nervous system (epinephrine, norepinephrine, pancreatic polypeptide), cardiovascular (systolic, mean arterial pressure) and certain metabolic (carbohydrate oxidation) counterregulatory responses, but that women have increased lipolytic (glycerol, nonesterified fatty acids) and ketogenic (beta-hydroxybutyrate) responses. Women may compensate for diminished SNS activity during exercise by increased lipolytic responses [70].

Training increases secretion of growth hormone, beta endorphin, and epinephrine while it decreases glucagon and insulin exercise-induced changes [see a review in 30, 31]. Therefore this specific endocrine pattern of trained athletes is likely to contribute also to a lower reliance upon carbohydrates and a higher utilization of lipids, which may prevent the risk of hypoglycemia. A recent study by Zinker and coworkers [55] supports this concept. This investigator reported that, during hyperinsulinemic euglycemic and hypoglycemic clamps combined with treadmill exercise, the exercise-induced increases in insulin action are negated during hypoglycemia by the counterregulatory response. The decreased need for exogenous glucose during hypoglycemic compared with euglycemic exercise is due to stimulation of endogenous glucose production, which accounts for approximately 30% of the decrease, and reduction of glucose utilization, which accounts for approximately 70%. The insulin-stimulated nonoxidative glucose metabolism is unaffected by exercise or hypoglycemia, whereas insulin-stimulated oxidative glucose metabolism is selectively increased by exercise and decreased by hypoglycemia. Thus, under insulin-induced hypoglycemic conditions, there is a profound increase in counterregulation which correctly counteracts the increase in muscular glucose use. The effectiveness of the potent insulin counterregulatory response may be important in decreasing the magnitude and frequency of exercise-induced hypoglycemia [55]. As shown above, a reversal of this training-related pattern during the overtraining syndrome may explain the increased occurrence of hypoglycemia in this situation.

Melatonin at 2.0 mg/kg preserves glycogen stores in exercised rats through changes in carbohydrate and lipid utilization [100]

IGFBP-1

The plasma concentration of the binding protein for somatomedins IGFBP-1 increases during acute exercise, at least in some exercise protocols [95] and after endurance training [J Manetta, in press]. Since IGFBP-1 traps IGF-1 and thus inhibits its insulin-like
effects, these exercise-related IGFBP-1 increments have been suggested to protect against delayed onset hypoglycemia [101]. Accordingly, some preliminary reports indicated that early stages of overtraining are associated with a reduction in baseline plasma IGFBP-1 levels [95].

**Influence of exercising muscle mass and location**

Muscle mass and location influence glucose regulation: for example, glucose uptake by the working knee extensors is decreased when arm cranking is added to knee extensions. This decrease in glucose uptake is not compensated for by increased uptake of free fatty acids but is accompanied by decreases in plasma insulin and increases in plasma epinephrine and norepinephrine. It may thus be elicited by neuroendocrine adjustments or lactate-induced inhibition of glycolysis and may represent a mechanism for protecting against premature hypoglycemia during prolonged exercise [102].

**Metabolic adaptations limiting glucopenia**

Circulating ketone-body and lactate levels, which increase several-fold during hypoglycemia associated with prolonged fasting or strenuous exercise, have been reported to diminish symptoms of hypoglycemia. Experimentally, infusion of B-hydroxybutyrate and lactate increases the glycemic thresholds, i.e., the required greater hypoglycemia for initiation of autonomic and neuroglycopenic symptoms, counterregulatory hormone responses, and cognitive dysfunction. In addition the magnitude of symptoms and physiological responses to hypoglycemia also reduced. Therefore, lactate appears to contribute to the protection against the effects of low blood glucose values [103].

On the other hand, just after exercise, during recovery, there is a rapid decrease in muscular glucose uptake, despite persisting high values of glucose effectiveness. This decrease is probably due to catecholamines. The physiological postexercise rebound in insulinemia is required for this response and to return plasma glucose concentrations to preexercise levels, [32]. Carbohydrate supplementation, provided with exercise, increases GLUT-4 protein expression after exercise by increasing translational efficiency [104]. Conversely, postexercise fasting appears to upregulate GLUT-4 mRNA. This could lead to amplify GLUT-4 protein expression on an increase in glucose availability [104]. These regulatory mechanisms may help control muscle glucose uptake in accordance with glucose availability and protect against postexercise hypoglycemia [104].

**THE MANAGEMENT OF EXERCISE HYPOGLYCEMIA**

Surprisingly, despite the important physiological literature on the regulation of blood glucose and substrate balance at exercise, there are very few practical papers describing the clinical management of exercise hypoglycemia.

From a pure clinical viewpoint, it is clear that prolonged exercise (i.e., greater than 2 hours) often results in a failure of hepatic glucose output to keep pace with muscle glucose uptake. As a result, blood glucose concentration frequently declines below 2.5 mmol/L. However, despite this hypoglycemia, Coyle reports that fewer than 25% of subjects display symptoms suggestive of central nervous system dysfunction [105]. Presumably a more careful clinical assessment would detect more hypoglycemics. However, just as what is admitted for postprandial reactive hypoglycemia, diagnosis needs both the measurement of a low blood glucose value and the occurrence of clinical symptoms of neuroglycopenia and sympathetic activation. We are not aware of the use of standardized questionnaires of hypoglycemia such as those reported for postprandial reactive hypoglycemia in patients referred for exercise hypoglycemia.

The use of standardized questionnaires to detect early signs of overtraining [79] is inexpensive and appears useful to detect athletes on the edge of this syndrome, before chronicization. Clearly, some work is needed forstandardizing the clinical approach of exercise hypoglycemia in sports medicine.

**Diagnostic tests?**

Similarly, concerning laboratory investigations, there is no standardized diagnostic test for exercise hypoglycemia in athletes. Some years ago we proposed a standardized exercise-test [106] which is routinely used in our unit. The interest of this test is to measure the kinetics of glycemia (which normally increases but shows marked decreases in patients describing hypoglycemic events). In addition hormonal responses can be measured and compared to those of control athletes.

More recently Kuipers [43] reported an experimental procedure which can also provide the basis for a laboratory test. Subjects first had to ingest 50 grams of glucose dissolved in water around noon after having a normal breakfast in the early morning followed by a 4-hour fast. This ingestion of glucose was followed by 30 minutes 30 minutes. After that, subjects cycled for 40 minutes at 60% of the predetermined maximal power output. Every 10 minutes blood was sampled for determination of glucose, catecholamines, and insulin concentrations. In a group of trained cyclists this exercise protocol was able to induce a transient hypoglycemia in one third of the subjects, who were consid-
ered as hypoglycemia-prone athletes. Such exercise-tests need to be more extensively investigated as diagnostic tools for exercise hypoglycemia. Their specificity and sensibility for this purpose has to be defined.

Actually, while most athletes prone to exercise hypoglycemia exhibit postprandial falls in glucose during the standardized hyperglucidic breakfast test [3], it is generally difficult to reproduce during a standardized exercise test in laboratory the hypoglycemic event, for instance in athletes in whom it occurs after several hours of exercise. Obviously, the OGTT is of no value and should be avoided, since it induces falls in blood glucose in normal subjects that are absolutely devoid of any clinical significance [3].

Another issue is the detection of situations characterized by high insulin sensitivity and/or glucose disposal. We proposed some years ago to use the minimal model analysis of intravenous glucose tolerance tests [62] for detecting such values. Clearly, high values of glucose effectiveness (and more precisely its component termed glucose effectiveness at zero insulin (GEZI)) were a characteristic finding in athletes complaining of hypoglycemia during exercise. Since surrogate indices of insulin sensitivity based on baseline insulin and glucose are unreliable in subjects with high values of insulin sensitivity, including athletes [75], they should be avoided for this diagnosis. However, insulin sensitivity and glucose effectiveness are increased by training [59, 107, 108] and the boundaries between “normal” and “excess” elevated values of glucose disposal parameters are not well delineated.

Differential diagnosis

Of course, like postprandial reactive hypoglycemia, exercise hypoglycemia should be differentiated from other causes of fatigue in athletes [109]. For example, recently, Backer and coworkers investigated exertional heat illness in summertime hikers in Grand Canyon National Park and found that 16% of exhausted patients referred for heat exertion with clinically significant symptoms actually had hyponatremia (sodium levels < 130 mmol/L). This hyponatremia was likely to result from hyperhydration. During prolonged exercise in the heat hyponatremia is thus a differential diagnosis of hypoglycemia, which is characterized by an altered mental status and by seizures without hyperpyrexia [110].

Prevention by adequate feeding with carbohydrates

Finally, the best known aspect of the clinical management of exercise hypoglycemia is its dietary prevention. While preexercise feeding with carbohydrates is clearly a situation at risk for hypoglycemia [42, 68], adequate carbohydrate feeding during moderate intensity exercise postpones the development of fatigue by apparently slowing the depletion of muscle glycogen. [105].

Investigations on pre-exercise supplements and carbohydrate feedings during exercise in this context have given conflicting results. Notwithstanding some disagreements among investigators, there appears to be an increasing evidence [111] suggesting that carbohydrates may be consumed before exercise with beneficial effects on performance. Reactive hypoglycemia due to a rise in insulin can be avoided by several procedures. According to Coggan [111] a first important aspect is the size and the timing of the meal. First, ingesting a large amount (eg, 200-350 g) of carbohydrates 3-6 h before exercise clearly appears to improve performance. In that case the meal may maximize muscle and/or liver glycogen stores or, alternatively, supply carbohydrates from the small intestine during exercise itself [111]. By contrast, if the preexercise meal is smaller (50-200 g of carbohydrates ingested 30-60 min before exercise) there should be a transient hypoglycemia early in exercise. Actually, this hypoglycemia does not usually cause overt symptoms of hypoglycemia neither it appears to affect the rate of muscle glycogen. Besides, the effects on performance are unclear and conflictual. Probably, such a preexercise meal is not very interesting for athletes [111]. In fact, there appears to be several procedures in order to avoid rebound hypoglycemia. First, carbohydrate-containing beverages (either sucrose, fructose, maltodextrin, or glucose) or a placebo) could be ingested during warming-up, followed by a 7-min break before exercise. In that case there is no rebound hypoglycemia during prolonged cycling, whatever the amount of ingested sugars. On the other way about, blood glucose increases [112]. Another aspect is the insulinogenic index of the ingested carbohydrates. For instance white rice, which has a low insulinogenic index contrasting with its rather elevated glycemic index [113], when taken 20 min before exercise, is able to maintain glycemia and to postpone fatigue during an endurance exercise performed after glycogen depletion [114].

However, the best demonstrated procedure for avoiding exercise hypoglycemia is the ingestion of carbohydrates during the exercise session itself. There is general agreement that this procedure can maintain plasma glucose availability and oxidation during the later stages of exercise and thus improve performance [111]. Exogenous glucose has been shown to allow a sparing of endogenous carbohydrates stores [115, 116]. Thus, very little muscle glycogen is used for energy during the 3-4-h period of prolonged exercise when fed carbohydrate. At this time, exogenous glucose disposal exceeds 1 g/min (i.e., 16 mg·kg⁻¹·min⁻¹) as evidenced by the intravenous glucose infusion rate which is required for maintaining normoglycemia. However, obviously, such a car-
Carbohydrate supplementation during exercise delays fatigue by 30–60 min, but does not prevent fatigue. In addition, ingesting carbohydrates during exercise after the onset of fatigue is generally ineffective to restore both plasma glucose availability for oxidation, and exercise tolerance [111]. Whether these carbohydrates are provided under a solid or a liquid form is not likely to be important provided that sufficient water is also consumed when ingesting carbohydrates in solid form [111]. No apparent differences exist between glucose, sucrose, or maltodextrins in their ability to improve performance [111].

The issue of fructose is more conflictual. A general consensus may be that ingesting fructose during exercise does not markedly improve performance and may cause gastrointestinal distress [111]. However, Fructose ingested before exercise is utilized at least as well as glucose and allows a more stable glycemia [117]. When ingested sixty minutes prior to exercise, fructose significantly increases endurance exercise duration until exhaustion and allows a better stability of blood glucose compared to placebo. It can be concluded that this sugar provides an alternative carbohydrate source to contracting muscles, which helps to spare glucose sources, and is thus helpful to prevent transient hypoglycemia [118]. Although its effects seem to be modest, fructose is likely to be an additional tool for preventing hypoglycemia and thereby delaying the onset of fatigue. However, recent developments in literature suggest that some of these anti-hypoglycemic effects of fructose may be due to its deleterious effects on insulin sensitivity which are classical in animals, where fructose feeding is a traditional model for inducing insulin resistance [119–121], but appear to be also fully relevant in humans [122].

A practical example of the importance of carbohydrate supplementation during exercise has been given in soccer, a sport where glycogen depletion is frequent and thus carbohydrate supply is critical. Carbohydrate intake during a match, when compared to placebo, has been found to result in muscle glycogen sparing (39%), greater second-half running distances, and more goals being scored with less conceded [123]. It is interesting to point out that carbohydrate feeding during exercise is beneficial even if subjects have been already carbohydrate-loaded before exercise, since increases in glycogen content of working muscle at the start of exercise have no effect on the rates of plasma glucose oxidation during exercise [124].

Carbohydrate feeding should also be considered after exercise, since the most sensitive period for glycogen resynthesis appears to be within the first few hours after exercise. Optimal recovery from an exhaustive exercise bout may depend on a reasonably rich carbohydrate diet soon after the exercise, in order to replenish muscle and liver glycogen stores [13]. Complex, low glycemic index carbohydrates such as pasta are usually considered as the most interesting sugars at this time. High glycemic index carbohydrates such as sucrose are not likely to be interesting after exercise, as shown by experiments on rats where sucrose was administered immediately after exercise. While this sugar increased liver glycogen content and prevented early postexercise hypoglycemia, there was a slight hypoglycemia seven hours later. Accordingly, sucrose is probably not an ideal postexercise sugar in order to ensure a complete refilling of the hepatic glycogen store [125]. The importance of these postexercise meals has been emphasized in the case of sports like soccer which implies heavy demands on endogenous muscle and liver glycogen stores, as demonstrated by a marked muscle glycogen depletion and frequent case of hypoglycemia. Thus carbohydrate stores must be rapidly replenished. Since daily carbohydrate intakes are often insufficient to replenish muscle glycogen stores, carbohydrate supplementation has been recommended in this sport not only prior to and during matches, but also after them [123].

Finally, everyday’s diet is also important, since when an athlete’s diet is low in carbohydrate, little glycogen is resynthesized between training sessions, leaving the individuals with low muscle glycogen and a state of chronic fatigue [13].

On the whole, a careful nutritional management of athletes is of course fundamental for their performance, and even more if they are known to be prone to hypoglycemia. In that case, carbohydrate is necessary to the hypoglycemic individual as a means of supercompensating glycogen stores prior to (and throughout) endurance performance [126].

**Training**

Adequate training, as reviewed above, results in an hormonal and metabolic adaptation of the human body to endurance training includes a host of mechanisms for preventing hypoglycemia, so that hypoglycemia during exercise, albeit very usual, reflects a failure in this homeostasis. The overtraining syndrome is an example of this failure, since there is increasing evidence that most of the adaptive hormonal mechanisms described during training and protecting against the risk of hypoglycemia are reversed. Thus, reassessment of the training programme is probably an important issue in the hypoglycemic athlete, although standardized statements are lacking. First, training should avoid excess work loads resulting in progression of the overtraining syndromes. In addition, levels of muscular activity aiming at improving the ability to oxidize fat rather than carbohydrates should probably be favored in order to decrease reliance on carbohydrates. Probably, as shown in obese sedentary whom this reliance on carbohydrates is an important biological feature [127], training intensification at a level where individuals oxidize mostly fat will result in a shift of this level towards higher intensities [128] thereby decreasing the tendency to waste glucids [30,
Examine hypoglycemia is an example of functional disorders on the edge of physiology that can induce discomfort and, in the case of athletes or workers who need to do a hard physical task, failure in exercise performance. Most of the time, this disorder is related to rates of glucose disposal in the upper range of normal values, i.e., a theoretically beneficial situation on the opposite of the insulin resistance syndrome. This metabolic characteristic is unlikely to explain alone the fall in blood glucose, and additional factors such as alimentary mistakes, overtraining, chronobiological disturbances, altitude, or unusual ambient temperature, should also be present. This situation has generated some fundamental literature, but there appears to be surprisingly few practical papers aiming at determining how to diagnose and to manage this problem. Probably, just as postprandial reactive hypoglycemia which is a very close situation, this disorder suffers from a lack of standardized tools for defining and investigating it.

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