

Reactive Hypoglycemia- is it a real phenomena among endurance athletes?

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Are you an athlete that periodically experiences episodes of extreme hypoglycemia (low blood sugar) or dropping blood pressure, which leads to light-headedness or even experiences of passing-out? Sometimes this might happen during an easy morning run, or even during an extreme race situation. Furthermore, do you experience these conditions at what seem totally random times, and under, what you perceive normal dietary conditions? If so, you might be among about 30% of athletes that appear to be incredibly sensitive to having reactive hypoglycemia (Kuipers *et al.*, 1999). But, there are certainly some recommendations, in terms of phasing your diet and exercise, which will assist in alleviating these symptoms and episodes.

Reactive hypoglycemia is a condition in which low blood sugar (below blood glucose levels of ~3 mmol/L, with some individuals being symptomatic already at blood sugar values of ~4 mmol/L) is induced by a combination of the timing of an athletes dietary intakes and the types of dietary intake, in conjunction with the timing of subsequent exercise. Increased sensitivity to episodes of reactive hypoglycemia also appears to be related to a complex interaction of training status, timing and type of previous nutritional intake, time of the day, previous hypoglycemic events, hydration status, anxiety/stress, gender, a lowered sympathetic nervous system activity, blood pressure and the athletes individual sensitivity to low glucose and counter-regulatory hormones of insulin and glucagon.

Physiological mechanisms explaining reactive hypoglycemia in endurance athletes

To understand why well-trained endurance athletes might experience hypoglycemic episodes, an understanding of some basic blood glucose handling is necessary. Hypoglycemia will occur when there is a greater blood glucose uptake than compared to glucose supply, via either the diet sources or liver gluconeogenesis (making of glucose). First, skeletal muscle is responsible for nearly 90% of the entire body's glucose uptake and disposal and athletes have a greater ratio of lean skeletal muscle to total body weight than most non-athletes. Furthermore, as described below, athletes also have a much more enhanced and sensitive glucose handling and uptake mechanisms than non-athletes. Thus, it is not surprising to observe periodic cases of exaggerated decreases in blood glucose in athletes in conjunction with exercising muscles.

The major mechanism for skeletal muscle glucose uptake and disposal involves the transmembrane transporter of glucose, which is called glucose transporter (GLUT4). GLUT4 needs to be present at the surface of the skeletal muscle cell (membrane) to bring glucose into the muscle. It has been shown that GLUT4 are stored in intercellular pools, and can migrate to the skeletal muscle membrane by two primary mechanisms: 1) insulin or 2) contraction. Further, it appears there are two pools of GLUT4 transporters, one that are induced to the membrane by insulin, and ones that are induced by skeletal muscle contraction (ie. exercise). So it is easy to hypothesize that in situations when a well-trained athlete consumes a large amount of simple carbohydrates (high glycemic index carbohydrates), which induces a very high insulin level coupled with muscle contraction, both pools of GLUT4 transporters migrate to the surface of the skeletal muscle membrane. This extreme concentration of GLUT 4 transporters at the skeletal muscle membrane then causes a rapid uptake of blood glucose, which causes an acute and immediate drop in blood glucose, causing hypoglycemia. Normally, situations of decreasing blood glucose are offset by the counter-regulatory hormone glucagon, which increases the livers production of glucose into the blood stream to maintain a normal blood glucose concentration. However, the sensitivity to this situation is highly individual and some athletes will still

experience acute bouts of hypoglycemia prior to the effects of glucagon increasing blood glucose again.

Possibly exacerbating this situation, is that well-trained endurance athletes not only have more GLUT4 transporters, but their GLUT4 transporters actually work more efficiently than non-trained individuals (ie. are more sensitive to insulin and contraction induced translocation to the skeletal muscle membrane). In other words, some athletes might actually have induced a state of over-adaptation in handling glucose, in that their GLUT4 transporters actually work too well! This is the exact opposite of type II diabetic and/or obese populations, where insulin sensitivity is diminished since GLUT4 transporters do not work efficiently, and thus these populations tend to have chronically high blood sugar levels. Several good references explaining the complex interactions leading to hypoglycemia in non-diabetics and athlete include: (Kuipers *et al.*, 1999; Brun *et al.*, 2001).

An n=1 experiment examining reactive hypoglycemia

We had the opportunity at Maastricht University, Netherlands to examine first hand the mechanisms at play in inducing reactive hypoglycemia in an elite endurance athlete (HS) that has had previous hypoglycemia events. The athlete (HS) was at the end of her summer racing season (Sept, 2006) during a short period of rest from serious training. For her, most previous hypoglycemic episodes nearly always occurred in the morning, after an overnight fast, in which she went out for a fasted morning run. According to her, a hypoglycemic episode was most likely to occur immediately upon stopping her morning run or within 30 to 60 min after eating post exercise. Thus, we attempted to mimic this scenario, and actually induce a hypoglycemia reaction in a laboratory setting, while taking blood samples to measure both blood glucose and insulin levels.

HS came into the laboratory in the morning (8.00AM) after an overnight fast. At this point, a catheter was inserted into her arm to allow for easy and multiple blood sampling over time. First, a baseline resting and fasted blood draw was taken (Fig. 1).



Figure 1. Insertion of catheter to allow for easy and multiple blood sampling over time.

HS then proceeded to the laboratory treadmill and underwent 25 min of easy running between 10-12 km/hr (Fig.2). Throughout the run, continual monitoring and caution was taken to ensure that the subject was feeling like she had euglycemia (normal blood sugar). If she felt an impending hypoglycemic episode occurring, exercise would stop; the athlete would proceed back

to the hospital bed under assistance and a blood sample taken, and then oral carbohydrate administered to counteract the hypoglycemia.



Figure 2. Athlete undertakes 25 min of fasted, easy running at ~10-12 km/hr.

If hypoglycemia did not occur during the fasted run (Fig. 2), the athlete would then proceed back to the hospital bed and proceed with an oral glucose tolerance test (OGTT- when 1 gram of glucose per kg body weight is given, and then blood glucose and insulin is monitored over the subsequent 2 hrs. An OGTT is primarily used by practitioners as a way to assess glucose and insulin insensitivity in diabetic and/or obese populations. However, an OGTT can also be used to monitor extreme insulin sensitivity in athletic populations, possibly leading to hypoglycemia). For HS, 50 grams of glucose in solution was acutely consumed orally, and then blood samples were taken every 30 min over 2 hrs post-exercise to assess blood glucose and insulin concentrations.

Major findings

The measured blood glucose and insulin concentrations are shown in figure 3. As expected, despite a 10⁺hr overnight fast, the athlete came in with baseline blood glucose within normal values due to adequate overnight liver gluconeogenesis (making of new glucose from liver glycogen stores). However, contrary to our hypothesis this normal blood glucose concentration was adequately maintained throughout the fasted 25min exercise period, as skeletal muscle contraction induced GLUT4 translocation did not cause a significant drop in blood glucose levels. After post-exercise carbohydrate consumption (50 grams), there was a small rise in blood glucose which was immediately counteracted by a large 3-fold increase in plasma insulin. This caused a slight over-adjustment in plasma glucose concentration at the 60 min mark, as glucose dropped nearly 40%, from a value of ~7 to ~4 mmol/L. By 90min post carbohydrate ingestion, blood glucose was back to baseline values

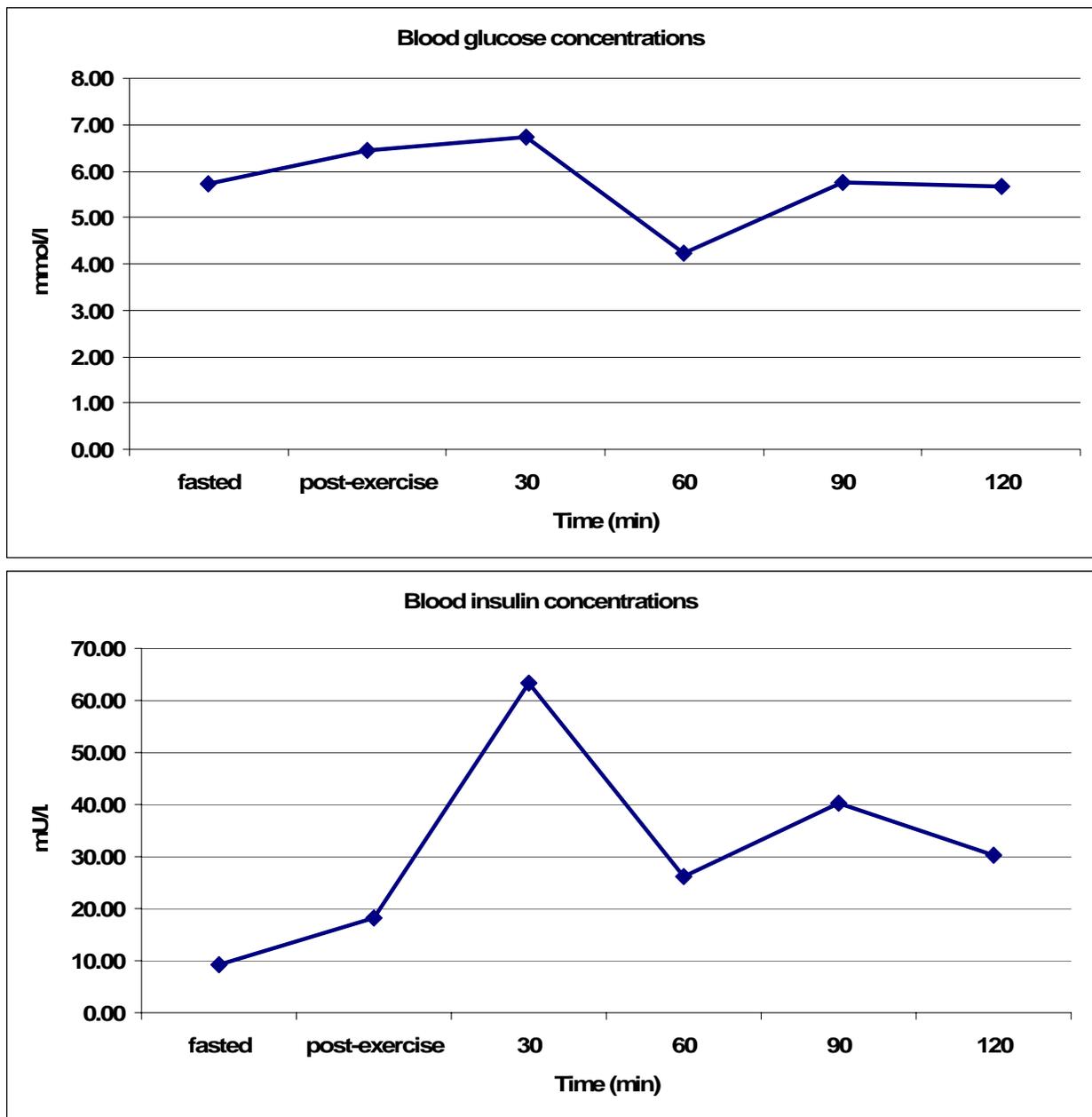


Figure 3. Blood glucose and insulin concentrations taken prior to and post-exercise, and every 30 min for 2 hrs following an OGTT post-exercise.

Interestingly, despite trying to induce a hypoglycemia event with an individualized protocol that the athlete deemed was most likely to succeed, this specific dietary and exercise situation resulted in no hypoglycemia felt by the athlete, or observed from the blood glucose data. Why was this? There are several possible explanations for we why did not necessarily find anything with this single acute examination. Again, this has to do with the complex interaction of a myriad of physiological and psychological factors, outlined below.

Recommendations to prevent reactive hypoglycemia

Again, it should be made clear that most endurance athletes do not have a problem with reactive hypoglycemia. Further as further described below, athletes that have experienced periodic episodes may only have acute situations which might increase the likelihood of an episode. So,

for the majority of athletes, reactive hypoglycemia is not a problem. But, for those of you that do have experience this periodically, then the following recommendations should help alleviate the likelihood of this occurring. However, if you consistently experience hypoglycemic situations, despite following these recommendations, then you should consult both a medical and nutritional specialist. As outlined above, it is very difficult to pinpoint the exact mechanisms in each individual responsible for situations of hypoglycemia and/or low blood pressure, leading to light-headedness or fainting. Episodes of reactive hypoglycemia appear to be related to a complex interaction of training status, timing and type of previous nutritional intake, time of the day, previous hypoglycemic events, hydration status, anxiety/stress, gender, a lowered sympathetic nervous system activity, blood pressure and the athlete's individual sensitivity to low glucose and counter-regulatory hormones of insulin and glucagon. However, scientific studies and anecdotal evidence suggest the following recommendations will assist in keeping blood sugar levels more constant.

- Avoid initiating exercise when having not eaten in the previous 4hrs (ie. overnight or racing in the late afternoon after only eating in the morning). This might dictate that an athlete needs to get up earlier for a morning run and eating a small amount of complex carbohydrates to help stabilize blood sugar and liver glycogen levels prior to exercise.
- The consumption of *just* simple sugars in the 1-2 hrs prior to exercise (high glycemic index, resulting in high insulin levels) are more likely to induce hypoglycemia during exercise, than the consumption of more complex carbohydrates or carbohydrates with other foods (ie. having a whole-grain bagel with some peanut-butter is much better than drinking a cola prior to a run).
- Once exercise has been initiated for at least 20min, and during prolonged training and racing situations (1hr⁺), the consumption of sports-drinks will drastically reduce the likelihood of hypoglycemia by maintaining blood glucose concentrations.
- Anecdotal reports suggest that more females than compared to males suffer from reactive hypoglycemia. However, it remains to be resolved as to whether this is really a gender difference, or the fact that more females may enter an exercise/race situation with less than optimal carbohydrate stores (liver and muscle glycogen) and already low blood glucose levels.
- Training status also may play a role in hypoglycemia, as an overtrained athlete often mentions bouts of hypoglycemia as one of the symptoms of overtraining. In fact, bouts of hypoglycemia may be one of the first physiological symptoms and signs of overtraining.
- It appears that the hour in which exercise is undertaken can markedly influence the risk for hypoglycemia. One study showed that the exercise induced drop in blood glucose was 50% greater when exercise was performed at midnight, than compared to the morning or afternoon. This correlates to when the circadian hormone cortisol was the lowest and was not stimulated by exercise. Obviously, with a multi-time zone flight, an athlete might undertake exercise when their body is chronobiologically still set at midnight from the previous time zone, and cause an increased risk for hypoglycemia.
- Also performing exercise within close proximity of a previous hypoglycemic event puts the athlete at risk for another bout of hypoglycemia. Prior hypoglycemia can blunt the normal hormonal (glucagon, insulin, catecholamines) and metabolic (endogenous glucose production, lipolysis) responses to exercise. However, for how long a previous hypoglycemic episode compromises these normal counter-regulatory

- mechanisms remains to be examined. But, certainly the athlete will be at risk for at least 24 to 48 hrs after a serious hypoglycemic event.
- Finally, antecedent reports indicate that there appears to be a complex interaction between dehydration, low blood-pressure, and anxiety/stress in inducing hypoglycemic events that remains to be fully elucidated.

Acknowledgements

A big thank-you needs to be made to former work colleagues, and continued friends, at the M³-Maastricht Muscle Metabolism Group at Maastricht University, Netherlands for supporting this small experimental intervention. Specifically: group leader Dr. Luc van Loon and Dr. Milou Beelen and PhD Candidate Ralph Manders for their direct assistance during the experimental trial, and the technicians Joan Senden and Jos Stegen for measuring the blood glucose and insulin concentrations.

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