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Review article

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POST-EXERCISE MUSCLE GLYCOGEN REPLETION IN THE EXTREME: EFFECT OF FOOD ABSENCE AND ACTIVE RECOVERY

Paul A. Fournier ✉, Timothy J. Fairchild, Luis D. Ferreira and Lambert Bräu

School of Human Movement and Exercise Science, University of Western Australia, Crawley, WA, 6009, Australia

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ABSTRACT

Glycogen plays a major role in supporting the energy demands of skeletal muscles during high intensity exercise. Despite its importance, the amount of glycogen stored in skeletal muscles is so small that a large fraction of it can be depleted in response to a single bout of high intensity exercise. For this reason, it is generally recommended to ingest food after exercise to replenish rapidly muscle glycogen stores, otherwise one's ability to engage in high intensity activity might be compromised. But what if food is not available? It is now well established that, even in the absence of food intake, skeletal muscles have the capacity to replenish some of their glycogen at the expense of endogenous carbon sources such as lactate. This is facilitated, in part, by the transient dephosphorylation-mediated activation of glycogen synthase and inhibition of glycogen phosphorylase. There is also evidence that muscle glycogen synthesis occurs even under conditions conducive to an increased oxidation of lactate post-exercise, such as during active recovery from high intensity exercise. Indeed, although during active recovery glycogen resynthesis is impaired in skeletal muscle as a whole because of increased lactate oxidation, muscle glycogen stores are replenished in Type IIa and IIb fibers while being broken down in Type I fibers of active muscles. This unique ability of Type II fibers to replenish their glycogen stores during exercise should not come as a surprise given the advantages in maintaining adequate muscle glycogen stores in those fibers that play a major role in fight or flight responses.

KEY WORDS: Glycogen synthase, glycogen phosphorylase, Cori cycle, glyconeogenesis.

INTRODUCTION

Glycogen is a fuel of major importance for the support of the energy demands of muscle during intense physical activity (Hargreaves et al., 1995). Despite its importance, it is generally the case in humans and all animal species investigated so far that very little glycogen is stored in skeletal muscle and liver (Fournier et al., 2002). In fact, we store just enough glycogen to sustain our energy demands for only a few hours of intense aerobic exercise (Gollnick et al., 1973; Ivy, 1991), and so little

glycogen is stored in our muscles that close to a third to half of these stores can be depleted within a few minutes of a maximal sprint effort (Gollnick et al, 1973; Fairchild et al., 2003). As a result, active individuals are at increased risks of experiencing a fall in their ability to engage not only in intense aerobic exercise (Ivy, 1991), but also in short sprint effort under situations eliciting fight or flight responses (Balsom et al., 1999; Fournier et al., 2002). One obvious way to prevent the sustained depletion of muscle glycogen stores after exercise is to ingest carbohydrate-rich food to replenish rapidly these stores. It is not surprising, therefore, that there has been a large volume of research aimed at developing dietary strategies to optimise glycogen synthesis before and after exercise (Ivy, 1991; Robergs, 1991; Burke et al., 2004). What has not received the same level of attention, however, is how muscles replenish their glycogen stores when exposed to conditions expected to be highly unfavourable to glycogen synthesis. It is our objective here to review some of the most recent developments in this area.

Post-exercise glycogen repletion in the absence of food intake

One extreme dietary condition that would be expected to impair the synthesis of muscle glycogen during recovery from exercise is the absence of food. Is it possible for our muscles to re-build at least part of their glycogen stores after exercise if food is not available? This is a situation likely to have had a major impact on the survival of our ancestors who, as a result of their hunter-gatherers life-style, were at increased risks of experiencing regular episodes of prolonged fast. This notion that skeletal muscles might have the capacity to replenish their glycogen independently of food intake is not a novel one as it was central to the work of the Nobel Laureat, Otto Meyerhof, who, nearly a hundred years ago, provided evidence, based on the use of isolated frog muscle preparations, that skeletal muscles have such a capacity (Fournier et al., 2002). It is only over the past 30 years, however, that experiments have been performed in humans and a wide range of animal species to establish if this is also the case in intact animals. The general consensus is that, after exercise, skeletal muscles in humans have the capacity to replenish at least part of their glycogen stores without food intake, irrespective of whether they are recovering from prolonged aerobic exercise (Hultman and Bergstrom, 1967; Maehlum et al., 1978) or from high intensity exercise (Hermansen and Vaage, 1977; Peters-Futre et al., 1987; Astrand et al., 1986; Bangsbo et al., 1991, 1997; Fairchild et al., 2003). Moreover, we have also shown that this resynthesis occurs across all muscle fiber types (Fairchild et al. 2003).

This capacity to replenish muscle glycogen stores without food intake is not unique to our species, since it is now well established from our work and that of others that fish, amphibians, reptiles and other mammals have also the capacity to replenish their glycogen under these conditions (reviewed in Gleeson, 1996; Milligan, 1996, Palmer and Fournier, 1997; Fournier et al., 2002). It is important to note, however, that until recently, there was some evidence that the rat was the only exception to this generalisation. Although, during recovery from prolonged exercise of moderate intensity, rats have been shown to possess the capacity to replenish a large proportion of their stores of muscle glycogen without food intake (Fell et al., 1980; Brooks and Gaesser, 1980; Gaesser and Brooks, 1980; Favier et al., 1987), an earlier study performed by Brooks and colleagues (1973) reported that, in contrast to humans and other animals species, no muscle glycogen is replenished in the absence of food intake in rats when recovering from high intensity exercise. These findings are somewhat problematic because they suggest that the rat cannot be adopted as an animal model for the study of this process. For this reason, we have re-examined the suitability of the rat as an experimental model (Nikolovski et al., 1996; Peters et al., 1996; Bräu et al., 1997; Ferreira et al., 2001) as well as that of another rodent species native to Western Australia, the Western Chestnut mouse (Bräu et al., 1999), and showed that, in response to a short bout of high intensity exercise, a large proportion of the glycogen stores is replenished during recovery in the rat (Nikolovski et al., 1996; Bräu et al., 1997; Ferreira et al., 2001; Raja et al., 2003), in contrast to what has been reported previously (Brooks et al., 1973). Similarly, there is also resynthesis of muscle glycogen stores during recovery from a short sprint in the Western Chestnut mouse (Bräu et al., 1999), but with the difference that all the glycogen mobilised during exercise is completely replenished during recovery (Bräu et al., 1999).

Carbon sources for post-exercise glycogen repletion in the absence of food

The observation that humans and other animal species can replenish at least part of their glycogen stores after exercise while fasting raises the question of the nature of the endogenous carbon sources recruited for this process. This depends to a large extent on the type of exercise from which one is recovering (Fournier et al., 2002). For instance, in response to prolonged exercise of moderate intensity resulting in only a marginal accumulation of lactate or glycolytic intermediates, these carbon sources

play a role of marginal importance in the resynthesis of muscle glycogen in humans and rats, with most of the accumulated lactate being oxidised (Brooks and Gaesser, 1980; Gaesser and Brooks, 1984; Favier et al., 1987). There is strong evidence that, under these conditions, glycogen resynthesis occurs primarily at the expense of amino acids (Favier et al., 1987). In response to a sprint, on the other hand, a large proportion of muscle glycogen stores is converted into lactate and, to a lesser extent, to glycolytic intermediates. In humans and across all animal species studied to date, there is strong evidence that lactate, either directly or indirectly via its conversion to glucose, is a major carbon source for glycogen repletion under these conditions (reviewed in Fournier et al., 2002), although a large proportion of it is oxidised (Hatta et al., 1988). We and others have also shown that the glycolytic intermediates can also contribute to glycogen repletion in humans and rats, but to a much lower extent (Astrand et al., 1986; Nikolovski et al, 1996; Pascoe and Gladden, 1996). What about other carbon sources such as the amino acids derived from the pool of free amino acids or protein breakdown and the glycerol released from the hydrolysis of triglycerides? Although there is evidence that late into recovery these carbon sources might play some role in the replenishment of muscle glycogen (Fournier et al., 2002), their relative contributions remain to be established.

Muscle glycogen repletion during active recovery from intense exercise

The finding that lactate can be a major carbon source for the replenishment of muscle glycogen stores raises an intriguing question. What if recovery from high intensity exercise were to occur under even less favourable conditions, where an increased proportion of the accumulated lactate is oxidised? This is normally what is observed if mild exercise is performed during recovery from a sprint, a protocol of recovery known as active recovery. More lactate is oxidised during active recovery, in part, because lactate is used as a fuel by skeletal muscles under these conditions (Bangsbo et al., 1994; Pascoe and Gladden, 1996). Since, as a result, less lactate is expected to be available for glycogen synthesis, this extreme type of recovery protocol would be predicted to impair glycogen repletion in the muscles of fasted individuals. This is an issue that has been examined in several studies (Peters-Futre et al., 1987; Nordheim and Vollestad, 1990; Bangsbo et al., 1994; Choi et al., 1994; Fairchild et al., 2003). Interestingly, contrary to predictions, two of these studies reported that active recovery has no effect on muscle glycogen levels (Peters-Futre et al., 1987; Bangsbo et al., 1994). In one of these studies (Bangsbo et al., 1994), however, there was no net glycogen repletion in response to both active and passive recovery, a finding best explained on the basis that recovery lasted only 10 min (Bangsbo et al., 1994), which is likely to be much too short for the detection of significant increases in muscle glycogen levels. Moreover, as pointed out by Bangsbo and colleagues (1997), suboptimal lactate accumulation might have contributed to the observed lack of glycogen deposition during recovery. This was not a limitation shared by the only other study which reported that active recovery is without any effect on glycogen synthesis (Peters-Futre et al., 1987). However, the statistical power of this latter study might have been too low for the detection of significant differences in glycogen levels between recovery protocols, given that glycogen accumulation in response to passive recovery was reported to be 37.8 as opposed to 24 $mmol \cdot kg^{-1}$ in response to active recovery (Peters-Futre et al., 1987).

In support of the view that active recovery inhibits glycogen resynthesis is the observation that glycogen repletion in individuals fed carbohydrate post-exercise is impaired during active recovery (Bonen et al., 1985). Moreover, a more recent study also supports indirectly the view that glycogen synthesis is inhibited during active recovery (Choi et al., 1996), with a combination of active and passive recovery being accompanied by a lower extent of glycogen synthesis than with passive recovery alone in overnight fasted individuals (Choi et al., 1996). Unfortunately, the impact of active recovery *per se* on glycogen synthesis was not examined in this study because no muscle sampling was performed at the end of the active recovery period (Choi et al., 1996). Also, since all the muscle biopsies were obtained through the same incision site in this study, and that this has been shown to impair glycogen synthesis (Costill et al., 1988), the extent of glycogen accumulation post-exercise might have been underestimated (Choi et al., 1996).

One major limitation shared by all of the above mentioned studies on the effect of active recovery on glycogen repletion is that their focus is on changes in total muscle glycogen levels as a whole rather than across the individual muscle fiber types. This can be a problem because the pattern of change in average muscle glycogen level can differ markedly from those of individual muscle fibers. For this reason, we have examined recently the response of muscle glycogen to active and passive recovery in humans, and shown, in agreement with others, that glycogen synthesis is impaired in the quadriceps muscle during active recovery, with glycogen remaining at stable levels (Fairchild et al., 2003). However, a distinct pattern of change in glycogen levels occurs at the level of the individual muscle

fibers (Fairchild et al., 2003). In comparison to passive recovery, where glycogen levels increase across all muscle fiber types, active recovery has no inhibitory effect on glycogen synthesis in type II muscle fibers, but causes a net glycogen breakdown in Type I muscle fibers (Fairchild et al., 2003). The observation that the average glycogen levels in the quadriceps muscle remain stable during active recovery is explained on the basis that Type I and II muscle fibers are present in comparable proportions in this muscle and the extent of net glycogen synthesis in Type II fibers matches that of glycogen breakdown in type I fibers (Fairchild et al., 2003), the net result being the apparent lack of change in average glycogen content in this muscle. These findings thus show quite clearly that the pattern of change in total muscle glycogen during active recovery informs us little about the patterns of glycogen response across the individual muscle fibers. Moreover, the fall in muscle glycogen in Type I fibers is consistent with these fibers being preferentially recruited in response to exercise performed at intensities comparable to those adopted for active recovery (Vøllestad and Bloom, 1985). It is important to note that, in an earlier study, Nordheim and Vollestad (1990) reported that Type I and II muscle fibers also respond differently to active recovery, but no control group subjected only to passive recovery was included in this study, which makes it difficult to estimate the degree to which active recovery affects glycogen metabolism in these fibers.

The absence of any effect of active recovery on the replenishment of glycogen stores in Type II muscle fibers is surprising given the unfavourable hormonal environment associated with this recovery mode. Indeed, we have shown that active recovery is associated with lower plasma glucose and insulin levels together with higher catecholamines concentrations than during passive recovery (Fairchild et al., 2003). These conditions associated with active recovery should be unfavourable to glycogen synthesis because the stimulation of glucose transport and glycogen synthesis in skeletal muscle is not as marked if the levels of plasma glucose and insulin are reduced, whereas high catecholamines inhibit insulin-stimulated glucose uptake (Chiasson et al., 1981; Lee et al., 1997) and activate glycogen breakdown at rest and during exercise (Chiasson et al., 1981; Richter et al, 1982). It has been argued that the lower H^+ levels during active recovery might counter the inhibitory effects of low insulin and high catecholamines levels because high H^+ levels have been reported by some to inhibit glucose transport in skeletal muscles (Kristiansen et al., 1994; Fairchild et al., 2003). Finally, the glycogenic drive associated with low intramuscular glycogen stores (Richter, 1996) might be of such a magnitude that it overrides the impact of the unfavourable environment associated with active recovery on glycogen synthesis. More research work will be required to test these hypotheses.

The ability of Type II muscle fibers to replenish their glycogen stores under conditions expected to be highly unfavourable, such as food absence or active recovery, suggests that the maintenance of adequate glycogen stores in these fibers is of paramount importance. Given that Type II muscle fibers are recruited mainly during intense exercise (Vøllestad and Blom, 1985), and that the depletion of muscle glycogen stores can affect one's capacity to engage in a maximal sprint effort (Balsom et al., 1999), the absence of mechanisms to replenish the glycogen stores of Type II muscle fibers under unfavourable conditions could limit one's capacity to engage as effectively in flight or fight responses. This capacity to replenish muscle glycogen stores might not be a major issue in our modern societies, but for hunter-gatherers this is likely to have been of key importance to their survival

Metabolic pathways responsible for the conversion of lactate into muscle glycogen

Given the evidence that lactate is likely to be the major carbon source mobilised for the synthesis of muscle glycogen during passive, and maybe, active recovery, this raises the question of the metabolic pathway responsible for its conversion into muscle glycogen. In theory, the synthesis of muscle glycogen from lactate could occur via two metabolic pathways, muscle lactate glyconeogenesis and the Cori cycle. These pathways have already been the object of numerous reviews (McDermott and Bonen, 1992; Pascoe and Gladen, 1996; Palmer and Fournier, 1997; Donovan and Pagliassotti, 2000; Fournier et al., 2002), and for this reason will be discussed only briefly here. The former pathway involves only the participation of skeletal muscles, and it differs from hepatic gluconeogenesis in that there is no intra-mitochondrial step involved, and the most recent evidence point to the reversal of the reaction normally catalysed by pyruvate kinase as being responsible for the conversion of pyruvate into PEP (Palmer and Fournier, 1997; Dobson et al., 2002). The Cori cycle, on the other hand, differs in many respects from lactate glyconeogenesis in that more than one organ are involved. Indeed, following its release from skeletal muscle, lactate is removed by the liver or kidneys where it is converted via gluconeogenesis into glucose. Once produced, glucose is released into the blood before being taken up and stored as glycogen in skeletal muscles.

Although, there is a general agreement that the former pathway plays the major role in glycogen synthesis from lactate in fish, amphibians and reptiles (reviewed in Gleeson, 1996; Fournier et al., 2002), the relative contributions of muscle lactate glyconeogenesis and Cori cycling to the resynthesis of muscle glycogen in humans and rats have been a controversial issue. Earlier studies in humans and rats have identified muscle lactate glyconeogenesis as the primary route responsible for lactate conversion into muscle glycogen (Hermansen and Vaage, 1977; Astrand et al., 1986; Nikolovski et al., 1996), but those findings have been subsequently challenged (Gaesser and Brooks, 1984; Bangsbo et al., 1991; Palmer and Fournier, 1997), with more recent evidence indicating that the Cori cycle plays also an important role (Bangsbo et al., 1991, 1997). What is still unclear, is the relative contributions of both pathways to the recycling of lactate into muscle glycogen (reviewed in Fournier et al., 2002).

Regulation of post-exercise glycogen repletion in the absence of food intake

It is noteworthy that under conditions expected to be highly unfavourable to glycogen synthesis following high intensity exercise, such as food absence or active recovery, the rates of muscle glycogen synthesis in humans and rats are among the highest reported in the literature (Pascoe and Gladden, 1996; Nikolovski et al, 1996; Fairchild et al., 2003). This raises the issue of the mechanisms responsible for such a marked activation of muscle glycogen synthesis in fasted individuals. Arguably, the activation of glycogen synthase is expected to play a major role, irrespective of the pathways responsible for the conversion of lactate or other carbon sources into muscle glycogen. In support of this view, we have shown that, in response to an intense sprint effort, the pattern of changes in the fractional velocity of glycogen synthase in the rat suggests that this enzyme undergoes a dephosphorylation-mediated activation at the onset of recovery (Bräu et al., 1997; Ferreira et al., 2001). As recovery progresses, the phosphorylation state of this enzyme returns to basal levels, at which point no further glycogen is being deposited (Bräu et al., 1996; Ferreira et al., 2003). As discussed previously (Bräu et al., 1997), several factors are likely to be responsible for the acute activation of glycogen synthase, namely the stimulation of contraction-mediated activation of glucose transport, the hyperinsulinemia and hyperglycaemia associated with a maximal sprint effort (Kruszynska et al., 1986; Pascoe and Gladden, 1996; Fairchild et al., 2003), the low post-exercise glycogen levels (Richter, 1996), the elevated levels of H^+ and glucose 6-phosphate levels (Bräu et al., 1997), the inhibition of glycogen synthase kinase 3 (Markuns et al., 1999) and the activation of phosphoprotein phosphatase (Kida et al., 1989).

For the marked increase in the net rate of glycogen synthesis to occur during recovery from intense exercise, one might argue that it is important not only to activate glycogen synthase, but also to inhibit glycogen phosphorylase. In agreement with this view, the pattern of change in the activity ratios of glycogen phosphorylase at the onset of recovery from high intensity exercise suggests that this enzyme experiences a transient dephosphorylation–mediated inhibition of its activity (Bräu et al., 1997), and that its state of phosphorylation increases progressively throughout recovery until it reaches pre-exercise levels, at which point no more glycogen is deposited. This raises the question of the role of this transient dephosphorylation of glycogen phosphorylase. This is an important question, since under other physiological conditions, such as during the starved-to–fed transition, it is possible to observe a rapid synthesis of glycogen despite the absence of any change in the phosphorylation state of glycogen phosphorylase (James et al., 1998). Under these conditions, a large fraction of glycogen phosphorylase is in its active phosphorylated form, but this is probably not enough for net glycogenolysis to occur because the levels of its activators or substrate (AMP, IMP, Pi) must also be elevated to activate glycogen phosphorylase (Chasiotis, 1983). Since the onset of recovery from a short sprint is characterised by the accumulation of high levels of Pi, AMP and IMP in the cytosol, the transient dephosphorylation of glycogen phosphorylase might be one mechanism that prevents these metabolites from increasing glycogenolysis and substrate cycling between glycogen and glucose 1-phosphate, which otherwise would probably occur in the presence of elevated levels of these metabolites (Bräu et al., 1997). Moreover, the elevated levels of inhibitors of glycogen phosphorylase at the onset of recovery, such as H^+ and glucose 6-phosphate, might help to prevent further the marked activation of glycogenolysis, and thus favour optimal rates of glycogen deposition (Bräu et al., 1997).

Since as discussed above, the Cori cycle plays an important role in the replenishment of muscle glycogen stores during recovery from high intensity exercise, it is not surprising that glucose transport in skeletal muscles is also activated under these conditions (Kawanaka et al., 1998). Although, as discussed above, the elevated catecholamine levels at the start of recovery would be expected to inhibit glucose transport, several factors are likely to counter their effects and contribute to the activation of glucose transport, namely the contraction-

stimulated translocation of GLUT4 to the plasma membrane, the hyperinsulinaemia associated with a maximal sprint effort (Pascoe and Gladden, 1996; Fairchild et al., 2003), the low post-exercise muscle glycogen levels (Richter, 1996), and the hyperglycaemia that typically accompanies high intensity exercise, which can act via both a mass action ratio effect and a glucose-mediated activation of glucose transport (Bandyopadhyay et al., 2001).

The acute activation of glucose transport in skeletal muscles is also one of several mechanisms that might contribute indirectly to the activation of glycogen synthesis at the onset of recovery from high intensity exercise. Indeed, there is compelling evidence that glucose transport has the capacity to control, at least in part, the rates of glycogen synthesis in skeletal muscles by altering glucose 6-phosphate levels (Bloch et al., 1994; Chase et al., 2001). Elevated levels of glucose 6-phosphate have the capacity to cause a fall in the phosphorylation state of glycogen synthase and phosphorylase because the binding of glucose 6-phosphate to these enzymes enhances their susceptibility to net dephosphorylation (Bräu et al., 1997). It is important to stress, however, that this does not explain the patterns of change in the phosphorylation state of these enzymes throughout most of the recovery period, since the rates of glycogen synthesis and phosphorylation state of glycogen synthase and phosphorylase change markedly and well after glucose 6-phosphate levels return to pre-exercise levels (Bräu et al., 1997; Ferreira et al., 2001). Overall, although the patterns of response of glucose transport, glycogen synthase and phosphorylase following high intensity exercise might explain, at least in part, the high rates of muscle glycogen synthesis post-exercise in fasting individuals, it is not clear which component plays the most important role in controlling these high rates of glycogen synthesis

CONCLUSIONS

In conclusion, during recovery from exercise, it is possible for skeletal muscles to replenish their glycogen stores under conditions expected to be highly unfavourable to glycogen synthesis such as fasting or active recovery. The rates of muscle glycogen synthesis can be very high under these conditions, most probably because of the acute activation of glucose transport and glycogen synthase and inhibition of glycogen phosphorylase. This capacity of skeletal muscles to replenish their glycogen stores under extreme conditions is clearly advantageous as it allows muscles to maintain adequate levels of glycogen stores for fight or flight responses.

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AUTHORS BIOGRAPHY

Paul A. FOURNIER
Employment
Exercise biochemist and physiologist
Degree
PhD
Research interests
Carbohydrate metabolism in health and diseases
Email: fournier@cyllene.uwa.edu.au

Timothy J. FAIRCHILD
Employment
PhD student
Degree
BSc (Hns)
Research interests
Carbohydrate metabolism in health and diseases
Email: timf@cyllene.uwa.edu.au

Luis D. FERREIRA
Employment
Exercise Biochemist
Degree
PhD
Research interests
Type 1 and 2 diabetes, with particular emphasis on both insulin resistance and glucose dyshomeostasis in exercise.
Email: ferreira@cyllene.uwa.edu.au

LAMBERT BRÄU
Employment
Molecular biologist
Degree
PhD
Research interests
Microbiology and exercise biochemistry
Email:lbrau@central.murdoch.edu.au

KEY POINTS

- Even in the absence of food intake, skeletal muscles have the capacity to replenish some of their glycogen at the expense of endogenous carbon sources such as lactate.
- During active recovery from exercise, skeletal muscles rich in type II fibers replenish part of their glycogen stores even in the absence of food intake.
- Post-exercise muscle glycogen synthesis in the fasted state is facilitated, in part, by the transient dephosphorylation-mediated activation of glycogen synthase and inhibition of glycogen phosphorylase.

✉ **Dr. Paul A. Fournier**
School of Human Movement and Exercise Science, University of Western Australia, Crawley, WA, 6009, Australia