

Muscle glycogen and metabolic regulation

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Muscle glycogen is an important fuel for contracting skeletal muscle during prolonged strenuous exercise, and glycogen depletion has been implicated in muscle fatigue. It is also apparent that glycogen availability can exert important effects on a range of metabolic and cellular processes. These processes include carbohydrate, fat and protein metabolism during exercise, post-exercise glycogen resynthesis, excitation–contraction coupling, insulin action and gene transcription. For example, low muscle glycogen is associated with reduced muscle glycogenolysis, increased glucose and NEFA uptake and protein degradation, accelerated glycogen resynthesis, impaired excitation–contraction coupling, enhanced insulin action and potentiation of the exercise-induced increases in transcription of metabolic genes. Future studies should identify the mechanisms underlying, and the functional importance of, the association between glycogen availability and these processes.

Glycogen: Skeletal muscle: Exercise

The importance of muscle glycogen for endurance exercise capacity has been recognised since the study of Bergström and colleagues in the late 1960s (Bergström *et al.* 1967). Soon afterwards, it was demonstrated that alterations in muscle glycogen availability have marked effects on muscle substrate utilisation and exchange during exercise (Pernow & Saltin, 1971; Gollnick *et al.* 1972, 1981). While some of these effects may have been secondary to changes in the plasma levels of substrates and hormones (Steensberg *et al.* 2002), there are also intracellular factors related to the availability of glycogen that influence muscle metabolism and function. Morphological studies have characterised a heterogeneous intramuscular distribution of glycogen and its association with the sarcolemma, sarcoplasmic reticulum, mitochondria and myofibrils (Marchand *et al.* 2002). Furthermore, glycogen granules are physically associated with a number of proteins (including glycogen phosphorylase, phosphorylase kinase, glycogen synthase, glycogenin and phosphatases) that are involved in the metabolism of glycogen itself and other substrates such as glucose. This information implies that glycogen is not only a substrate for exercise metabolism, but may also have an important role in metabolic regulation. The present paper will briefly summarise the influence of muscle glycogen on exercise metabolism, post-exercise glycogen synthesis, excitation–contraction coupling, insulin action and gene

transcription. In most cases, reference will be made to studies conducted in human subjects; however, when necessary animal studies will also be cited.

Exercise metabolism

Higher muscle glycogen availability before exercise results in greater glycogenolysis during subsequent exercise (Gollnick *et al.* 1972; Hargreaves *et al.* 1995; Weltan *et al.* 1998*a,b*; Shearer *et al.* 2001; Wojtaszewski *et al.* 2003). While this outcome is most evident at the extremes of pre-exercise muscle glycogen availability (Wojtaszewski *et al.* 2003), there is a linear relationship between pre-exercise muscle glycogen levels in the range of 50–120 mmol/kg wet mass and its subsequent utilisation during exercise (Hargreaves *et al.* 1995). It is known that glycogen can bind to glycogen phosphorylase and increase its activity, and this process represents the most likely explanation for the enhanced glycogenolysis during exercise with elevated glycogen (Shearer *et al.* 2001). Muscle glucose uptake during exercise may also be influenced by pre-exercise muscle glycogen availability, although studies are equivocal (Gollnick *et al.* 1981; Hargreaves *et al.* 1995; Weltan *et al.* 1998*a,b*; Blomstrand & Saltin, 1999; Watt & Hargreaves, 2002; Wojtaszewski *et al.* 2003). The divergent results are probably related to the potential

Abbreviation: AMPK, AMP-activated protein kinase.

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confounding effects of the pre-trial exercise and dietary manipulations used to produce differences in muscle glycogen (Steensberg *et al.* 2002). Alterations in plasma glucose, NEFA, insulin and catecholamine concentrations, secondary to high dietary carbohydrate or fat intakes, can modulate the effects of muscle glycogen availability on glucose uptake. Conversely, manipulating muscle glycogen by previous exercise introduces the potential residual effects of this exercise. These effects are largely eliminated in the perfused rat hindlimb model, in which an inverse relationship between muscle glycogen and glucose uptake and transport during contractions has been clearly demonstrated (Hespele & Richter, 1990). Translocation of GLUT4 (Derave *et al.* 1999; Kawanaka *et al.* 2000) and the increase in AMP-activated protein kinase (AMPK) activity (Kawanaka *et al.* 2000; Wojtaszewski *et al.* 2003) are enhanced in low muscle glycogen states and these mechanisms potentially mediate glycogen effects on glucose uptake. In relation to AMPK, it has recently been demonstrated that the β subunit of AMPK has a glycogen-binding domain that targets AMPK to glycogen (Polekhina *et al.* 2003). Whether GLUT4 also associates with glycogen has not been definitively proven. An early study, and other subsequent studies, observed an inverse relationship between leg glucose uptake during exercise and the intramuscular glucose-6-phosphate concentration (Gollnick *et al.* 1981), implying that elevated muscle glycogen may also inhibit glucose uptake via effects on hexokinase and glucose metabolism.

Lipid oxidation during exercise is increased when pre-exercise muscle glycogen is low (Hargreaves *et al.* 1995; Weltan *et al.* 1998a,b; Blomstrand & Saltin, 1999; Wojtaszewski *et al.* 2003), as a result of increased plasma NEFA uptake (Blomstrand & Saltin, 1999; Wojtaszewski *et al.* 2003) that is secondary to the higher plasma levels, as NEFA clearance during exercise does not differ between low and high glycogen conditions (Wojtaszewski *et al.* 2003). Presumably the higher plasma NEFA levels are a result of increased adipose tissue lipolysis as a consequence of lower plasma insulin levels and increased sympathetic activity, as reflected by higher catecholamine levels (Galbo *et al.* 1979; Weltan *et al.* 1998a,b). Increased β acetyl-CoA carboxylase phosphorylation, mediated via increased AMPK activity, may contribute to enhanced fat oxidation (Wojtaszewski *et al.* 2003). The influence of muscle glycogen on intramuscular triacylglycerol utilisation has not been studied to date. Low glycogen availability has also been shown to increase net protein degradation, at least as measured by tyrosine and phenylalanine release (Blomstrand & Saltin, 1999), and is associated with greater activation of the branched-chain oxoacid dehydrogenase in skeletal muscle (Jackman *et al.* 1997), implying increased amino acid oxidation.

Post-exercise glycogen resynthesis

Depletion of muscle glycogen during exercise activates glycogen synthase (Nielsen & Richter, 2003), and this activation is greater when muscle glycogen is lower (Zachwieja *et al.* 1991), resulting in a faster rate of glycogen resynthesis in the early post-exercise period.

The absence of glycogen degradation during exercise in patients with McArdle's disease is associated with a slight decrease in glycogen synthase activity (Nielsen *et al.* 2002b). The link between glycogen and glycogen synthase may be mediated by protein phosphatase 1, which is targeted to the glycogen molecule. The regulatory or glycogen-targeting subunit of protein phosphatase 1 is essential for the exercise-induced activation of glycogen synthase in skeletal muscle (Aschenbach *et al.* 2001).

Excitation–contraction coupling

As glycogen is associated with the sarcoplasmic reticulum (Marchand *et al.* 2002), it is possible that glycogen has a key role in excitation–contraction coupling. It has been shown that low muscle glycogen following fatiguing contractions is associated with reduced sarcoplasmic reticulum Ca^{2+} release (Chin & Allen, 1997). Furthermore, the capacity of skinned fibres to respond to T-system depolarisation is directly related to the muscle glycogen level, even under conditions in which glycogen is not required for energy production (Stephenson *et al.* 1999; Barnes *et al.* 2001). It has been suggested 'that glycogen has a protective role in maintaining fibre excitability' (Barnes *et al.* 2001), describing another potential role of glycogen availability in the aetiology of muscle fatigue.

Insulin action

Exercise increases insulin-stimulated glucose uptake (insulin sensitivity) in the post-exercise period, and the increase in glucose uptake is correlated with the magnitude of glycogen utilisation during exercise (Richter *et al.* 2001). Furthermore, there is an inverse relationship between muscle glycogen and both basal and insulin-stimulated glucose uptake (Jensen *et al.* 1997). Insulin-stimulated GLUT4 translocation is greater under low glycogen conditions (Kawanaka *et al.* 1999; Derave *et al.* 2000), while protein kinase B activity (Derave *et al.* 2000) and phosphorylation (Kawanaka *et al.* 2000) are higher, in the absence of changes in the activity of the upstream phosphatidylinositol 3-kinase. In patients with McArdle's disease, with elevated muscle glycogen levels, insulin-stimulated glucose uptake in the rested state is approximately 30% lower than that in age-matched control subjects (Nielsen *et al.* 2002a). While absolute protein kinase B phosphorylation is similar in the two groups, the increase in response to insulin is lower in the patients with McArdle's disease. Taken together, these results indicate that muscle glycogen availability can modulate insulin-stimulated glucose uptake.

Gene transcription

Exercise has potent effects on the transcription of metabolic genes, with the most pronounced changes often observed in the post-exercise recovery period. Recent studies have demonstrated that the exercise-induced increase in transcription rates and mRNA levels of a number of genes are potentiated by low pre-exercise muscle

glycogen availability (Keller *et al.* 2001; Febbraio *et al.* 2002; Pilegaard *et al.* 2002). The mechanisms linking muscle glycogen availability with gene transcription remain to be fully elucidated, although the recent observation of exercise-induced nuclear translocation of AMPK in human skeletal muscle (McGee *et al.* 2003) may provide a potential mechanism, given that AMPK may target nuclear transcription factors and/or kinases. Indeed, it has recently been observed that exercise-induced nuclear AMPK translocation is greater when pre-exercise muscle glycogen levels are reduced (SL McGee, MJ Watt, MA Febbraio and M Hargreaves, unpublished results).

Summary

In summary, in addition to being an important metabolic fuel during prolonged strenuous exercise and implicated in the aetiology of muscle fatigue, glycogen may also play a key role in the regulation of metabolic and cellular processes within skeletal muscle. Future studies should focus on the potential mechanisms linking glycogen availability to these processes.

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