PERSPECTIVES

Muscle glycogen: where did you come from, where did you go?

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Muscle glycogen is an important fuel source during exercise. Inadequate glycogen availability results in reduced endurance exercise capacity and an inability to continue exercise because of impaired excitation–contraction coupling once glycogen stores are depleted. The glycogen utilization rate depends on exercise intensity and is greatest at maximal dynamic or static contractions. The spherical glycogen molecules are located in three distinct subcellular compartments within skeletal muscle: (i) intermyofibrillar glycogen, which accounts for approximately three-quarters of total glycogen and is situated near mitochondria between the myofibrils, mainly near the I-band, (ii) subsarcolemmal glycogen, which accounts for ∼5–15% of all glycogen, and (iii) intramyofibrillar glycogen, which also accounts for ∼5–15% of total glycogen (Fridén *et al.* 1989; Nielsen *et al.* 2011; Kent *et al.* 2016). During prolonged exercise, glycogen in all three compartments is used but only intramyofibrillar glycogen becomes depleted. This depletion of intramyofibrillar glycogen is thought to provide the link between low muscle glycogen and muscle fatigue because intramyofibrillar glycogen is involved in the control of sarcoplasmic Ca^{2+} release (Ørtenblad *et al.* 2011).

In this issue of *The Journal of Physiology*, Gejl and colleagues (Gejl *et al.* 2016) evaluated site- and fibre-type-specific depletion of glycogen stores in elite male cross-country skiers following repeated sprint exercise, which relies heavily on muscle glycogen as fuel (Fig. 1). Each skier completed four consecutive 4-min treadmill skiing sprint time trials (STT1–4) with 45 min rest between trials during which they consumed 1.2 g carbohydrates per kilogram body weight per hour. Muscle biopsies from the triceps brachii, a very active muscle during cross-country skiing, which was composed of ∼40% type 1 (slow twitch) and 60% type 2 (fast twitch) fibres, were taken before and after STT1 and before and after STT4 to measure total glycogen content (enzymatically) and subcellular glycogen storage pool sizes (by using electron microscopy). They found site- and fibre-type-specific differences in glycogen depletion that differed between STT1 and STT4. During STT1, intermyofibrillar and subsarcolemmal glycogen stores decreased by ∼20–35% each, both in type 1 and type 2 fibres, whereas intramyofibrillar glycogen stores were not affected in type 2 fibres and decreased by 50% in type 1 fibres. The absolute decline in intramyofibrillar glycogen in type 1 fibres, however, was much less than the decline in intermyofibrillar glycogen due to the smaller intramyofibrillar glycogen pool size. During STT4, intermyofibrillar glycogen stores decreased to the same extent (absolute amount) as in STT1, both in type 1 and type 2 fibres, whereas subsarcolemmal and intramyofibrillar glycogen stores did not change. These results suggest a well-coordinated hierarchical breakdown of muscle glycogen from different locations and a greater reliance of type 1 compared with type 2 fibres on intramyofibrillar glycogen during very intense exercise.

The mechanisms responsible for the site- and fibre-type-specific preferential use of muscle glycogen during repeated very intense exercise and its implications for performance remain unclear. Carbohydrate ingestion during the rest periods between each of the four STTs did not restore muscle glycogen stores in the study by Gejl and colleagues (Gejl *et al.* 2016); hence, intermyofibrillar and subsarcolemmal muscle glycogen stores in type 1 and type 2 fibres and intramyofibrillar glycogen stores in type 1 fibres were significantly less before STT4 than before STT1. Total glycogen use was also ∼35% less during STT4 than during STT1, and the authors attributed this to the reduced initial glycogen availability during STT4 because they found an

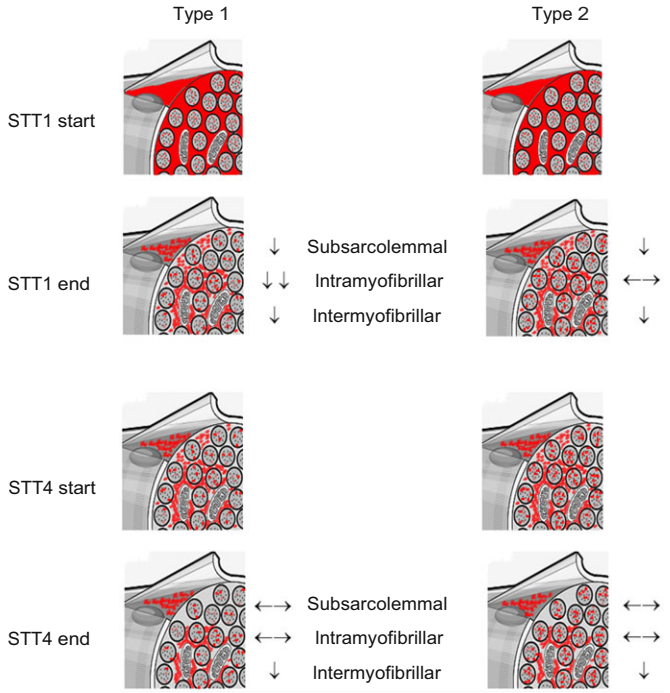

Figure 1. Muscle glycogen use during repetitive sprint trials
Site- and fibre-type-specific changes in skeletal muscle glycogen volume in male elite cross-country skiers during the 1st and 4th of four consecutive 4-min cross-country skiing sprint trials (STT), which were separated by 45 min during which the athletes consumed 1.2 g carbohydrates per kilogram body weight per hour.

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inverse relationship between the size of the glycogen store before beginning the exercise and the reduction in its size during exercise. Reduced reliance on glycogen as a fuel source during STT4 compared with STT1, however, did not affect performance. One could speculate that sparing intramyofibrillar glycogen, once these stores reach a critically low value, might help preserve performance due to the small size of the intramyofibrillar glycogen store, which was depleted by half during SST1, and its critical role for maintaining sarcoplasmic Ca^{2+} release and excitation–contraction coupling. It remains unclear, however, why subsarcolemmal glycogen was also preserved during STT4. If glycogen breakdown precisely matches glycogen use as fuel, these findings suggest that muscle relied on different fuel sources during STT1 and STT4. The most likely alternative source of fuel would have been plasma glucose derived either directly from the carbohydrate drink consumed between the STTs or liver glycogen (both previously stored or newly synthesized) because liver, unlike muscle glycogen, is rapidly refilled with refeeding (Burke *et al.* 2016). This is consistent with the observation that time to fatigue can be prolonged past the point of glycogen depletion if an alternative supply of glucose, via intravenous infusion, is made available (Coyle *et al.* 1986) and raises the question of what would have happened if carbohydrates were not ingested between the four STTs. It is also intriguing that type 2 intramyocellular glycogen was not used at all (either during STT1 or STT4) because type 2 fibres are the classical glycogen-using muscle fibres. It may be that during the very short bouts of exercise performed in the study by Gejl and colleagues, creatine phosphate, which is more abundant in type 2 than type 1 fibres (Tesch *et al.* 1989), was primarily used as the energy source in type 2 fibres. Answering these questions will be critical to determine the significance of the results reported by Gejl and colleagues. In addition, it will be important to evaluate the preferred sources of glycogen in less trained or even untrained persons during both prolonged exhaustive and very intense exercise, and to determine whether there is a hierarchy in the repletion of glycogen stores after exercise and how it might affect site- and fibre-type-specific glycogen use and performance during repeat exercise on a subsequent day or several days later.

In summary, the study by Gejl and colleagues adds an important piece in our understanding of glycogen utilization in trained athletes and beautifully demonstrates that glycogen use is a highly dynamic and complex process. Uncovering the precise regulatory pathways and control mechanisms that govern glycogen breakdown in a site- and fibre-type-specific manner may have important implications to enhance exercise performance and muscle function not only in athletes, but also in the general population and in people with glycogen storage diseases. In the future, it may turn out that exercise training and nutritional strategies that ensure the right amount of glycogen in the right place at the right time are more important to enhance muscle function and performance than simply maximizing muscle glycogen loading.

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Additional information

Competing interests

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