Detailed Study Notes: Episode 456
Prof. Glenn McConell

Table of Contents

Introduction to this Episode

Exercise improves metabolic control both via increasing muscle glucose uptake during muscle contractions by insulin-independent mechanisms and by increasing skeletal muscle insulin sensitivity after physical activity. A reduction in skeletal muscle insulin sensitivity is an early event in the development of not only prediabetes, metabolic syndrome, and type 2 diabetes but is also associated with other conditions such as cardiovascular disease and some cancers.

One of the researchers that has been at the forefront of research in this area for many years is Professor Glenn McConell. In this episode, we discuss glucose uptake during and after exercise, looking at both insulin-dependent and insulin-independent mechanisms. In addition, we discuss the crucial importance of muscle insulin sensitivity and some important research breakthroughs on the topic.

Connection to Previous Episodes

- In episode 385, we explored the causes of insulin resistance, and the dietary modifications that may help those with insulin resistance.
- In episode 286, James Morton, PhD discussed the use of carbohydrate periodization in elite sport setting, as well as the concept of 'fueling for the work required'.
- In episode 282, Professor Louise Burke compared LCHF vs. High Carbohydrate vs. Periodized Carbohydrate diets for performance.
- In episode 185, Trent Stellingwerff, PhD was on the podcast to discuss nutritional considerations for the endurance athlete.

Background Context

- Exercise can improve metabolic control by increasing:
    - muscle glucose uptake during muscle contractions by *insulin-independent* mechanisms
    - skeletal muscle insulin sensitivity after physical activity.
- A reduction in insulin sensitivity *in the muscle* occurs early in the processes which lead to the development of prediabetes, metabolic syndrome, and type 2 diabetes.
    - It is also associated with the risk of cardiovascular disease and some cancers.

Exercise-stimulated Glucose Uptake

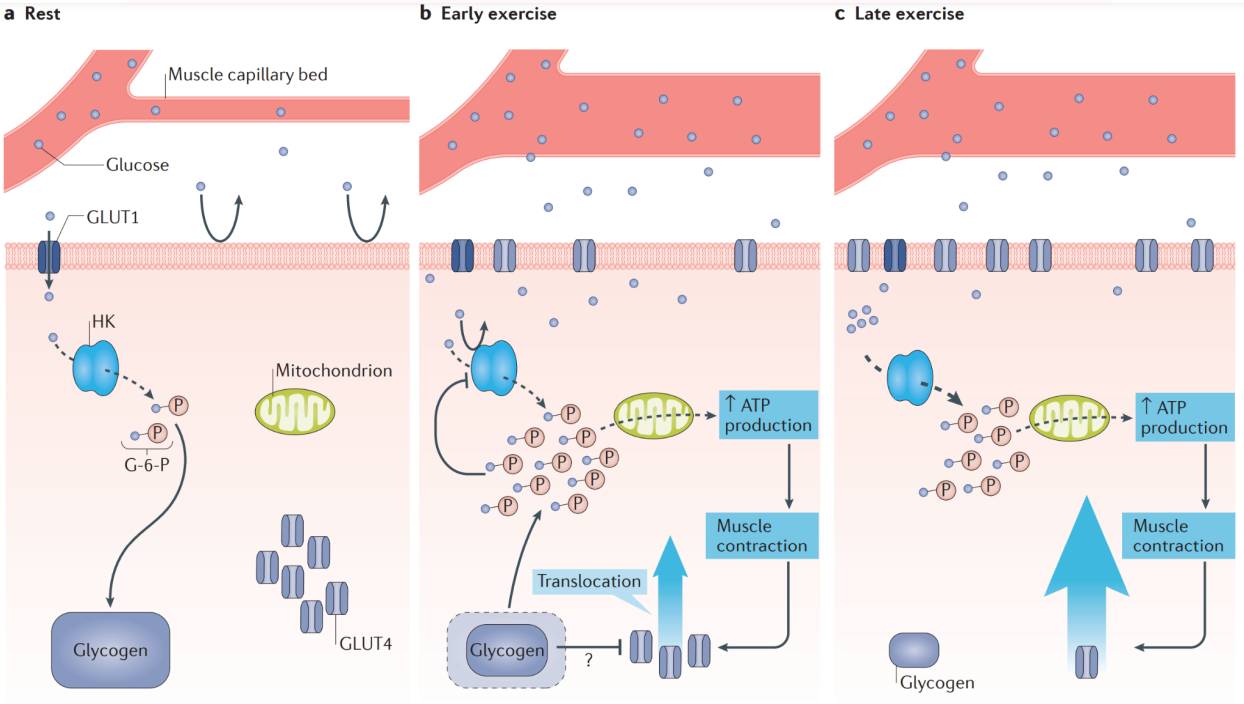


Figure from: Sylow et al., Nature Reviews Endocrinology volume 13, pages133–148 (2017)

It is useful to think of exercise-stimulated glucose uptake in three phases, as per the diagram above. As shown, we can see the following important events at each phase:

A: At Rest

1. Requirements for glucose are extremely low when the muscle is at rest.
    a. So at this time, glucose delivery is low.

2. At rest, there is a relatively low amount of glucose transport from the blood to the muscle occuring.
    a. As shown in the diagram, there is a low absolute number of glucose transporters in the plasma membrane of the cell.
    b. Glucose transporter type 4 (GLUT4) transporters are still “embedded” within the cell (and not at the cell surface).
3. For any of the glucose that does enter the muscle at this time, there are two potential fates:
    a. Stored as glycogen
    b. Metabolized to generate ATP (via glycolysis and oxidative phosphorylation).

B: Early Exercise

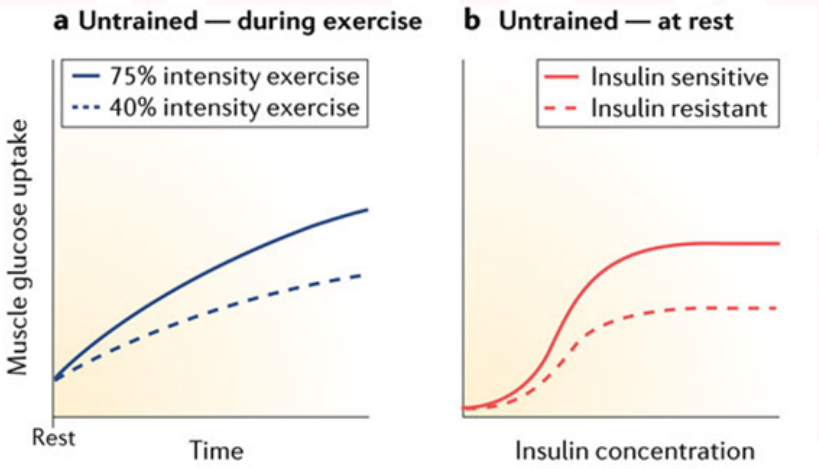
- For exercise of sufficiently high intensity, glucose will be required to generate ATP in order to meet the energetic demands of the activity.
- As such exercise starts, initially, the muscle will preferentially use the glycogen already stored in the muscle to supply this glucose for ATP generation.
    - Therefore, glucose from the blood is being spared, as rather than taking up this glucose and “burning” it for fuel, the muscle is breaking down glycogen in glucose and metabolizing this instead.
- Other aspects of metabolism at this time also help to spare blood glucose. For example:
    - Free glucose then accumulates in the muscle, which decreases the gradient required for glucose entry and, therefore, overall transport rates.
    - The presence of high amounts of glycogen may also inhibit the movement (translocation) of GLUT4 from the inner cell to the plasma membrane.
- So the net result is that, although both delivery and transport of glucose are increased, blood glucose is spared at the expense of the internal glucose (glycogen) stores.

C: Late Exercise

- As exercise continues, glycogen continues to be broken into glucose and metabolized to meet the metabolic demands of the exercise.
- So glycogen levels become progressively depleted.
- The rate of depletion is related to the exercise intensity.
- As glycogen stores become more and more depleted, the glucose supply gradually shifts from glycogen to blood glucose uptake, to generate the required amount of ATP.

Exercise Enhances Insulin Sensitivity

- Exercise exerts acute effects on glucose uptake in muscle (graph A below).
    - While insulin stimulates glucose uptake, there are also ***insulin-independent*** processes that can increase glucose uptake.
    - Muscle contraction is one potent stimulator of glucose uptake that occurs independently of insulin action.
        - This drives increased GLUT4 translocation.
    - Therefore, this means that it will lead to increased glucose uptake in both healthy and insulin-resistant muscle.
- If the muscle is insulin resistant, this can lead to issues.
    - With insulin resistant muscle there is a lower amount of insulin-induced GLUT4 translocation and a lower amount of microvascular recruitment.
    - Therefore, there is lower muscle glucose uptake in insulin resistant muscle (graph B).



Delivery	↑ Microvascular recruitment and blood flow	↓ Microvascular recruitment in insulin resistance
Transport	↑ GLUT4 translocation	↓ GLUT4 translocation by insulin in insulin resistance
Metabolism	↑ Glycolysis ↑ Oxidative phosphorylation	↓ HK expression in insulin resistance

Figure from: Sylow et al., Nature Reviews Endocrinology volume 13, pages133–148 (2017)

- The sensitivity of muscle to insulin is increased for up to 48 hours following a single bout of exercise (graph C below).
    - So in the post-exercise period, glucose uptake is increased for both those who are insulin sensitive and insulin resistant.
- Exercise also has long-term effects (graph D).
    - Consistent exercise/training over time improves the effect of insulin on glucose uptake in muscle.
    - Therefore, in cases where there is dysfunctional insulin signaling, exercise can help overcome this to some degree.
    - So exercise can be seen as a very useful means of increasing glucose uptake in insulin-resistant muscle and thus helping to normalize glycaemic control.

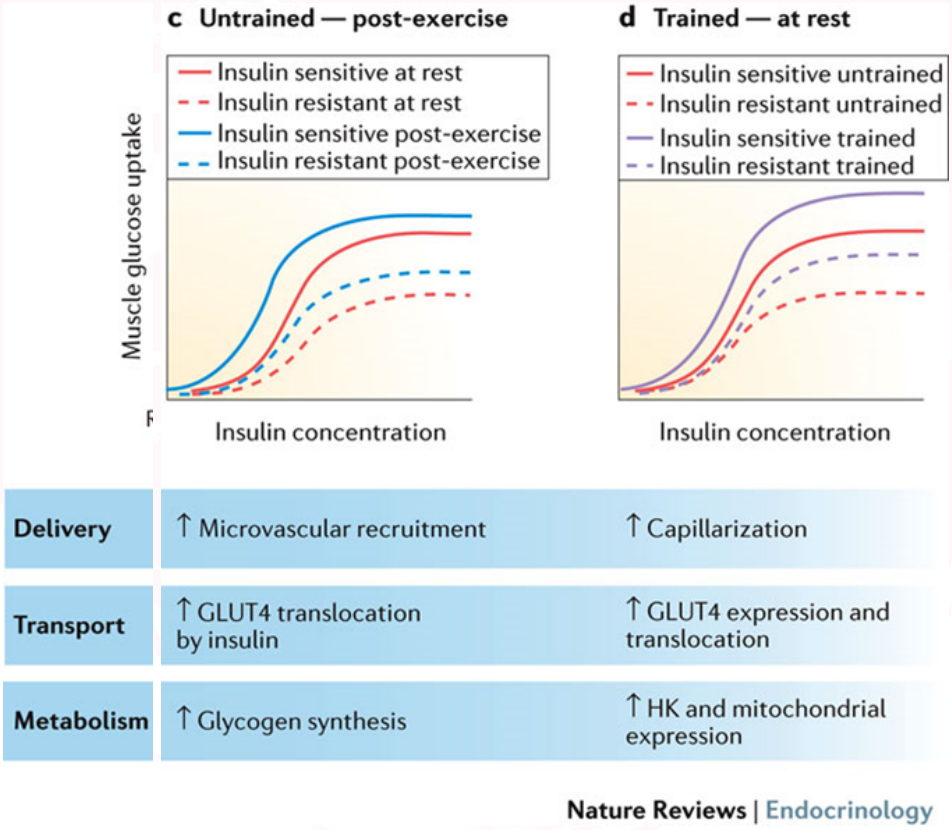


Figure from: Sylow et al., Nature Reviews Endocrinology volume 13, pages133–148 (2017)

Role of AMPK in Muscle Metabolism & Exercise

- Late 1990s: Muscle AMP-activated protein kinase (AMPK) activity was shown to be increased during exercise.
- AMPK is activated during moderate or harder exercise in humans. But has also been suggested it increases fat oxidation.
- Indeed, as Prof. McConell mentioned in this episode, most papers related to AMPK state in the 'Introduction' section that AMPK regulates glucose uptake *and* fat oxidation during exercise.
- However, Prof. McConell has long argued that AMPK cannot simultaneously act as a primary regulator of both glucose uptake *and* free fatty acid oxidation during exercise because there are situations whereby *increases* in glucose uptake are accompanied by simultaneous *decreases* in fat oxidation, and vice versa (McConell, 2020).
    - For example:
        - increases in exercise intensity
        - pre- versus posttraining exercise
        - high versus low carbohydrate diets
- Of course, activation of AMPK during exercise appears to be critical for adaptations after exercise. And it can play a role in glucose uptake or fat oxidation.
- However, AMPK activation is not *necessary* for increases in glucose uptake or fat oxidation during exercise.

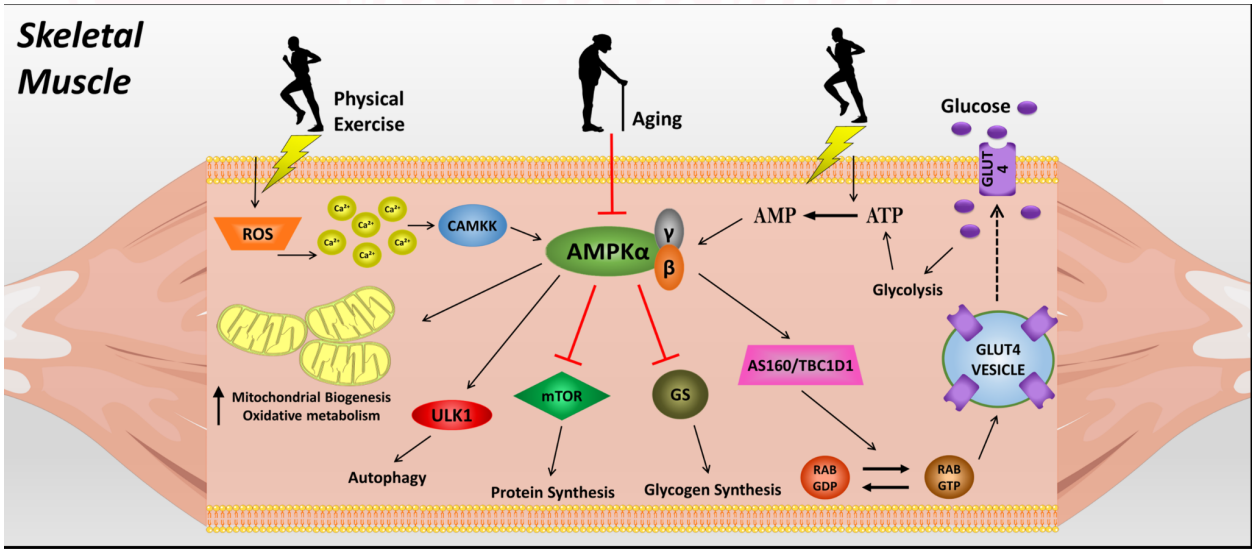
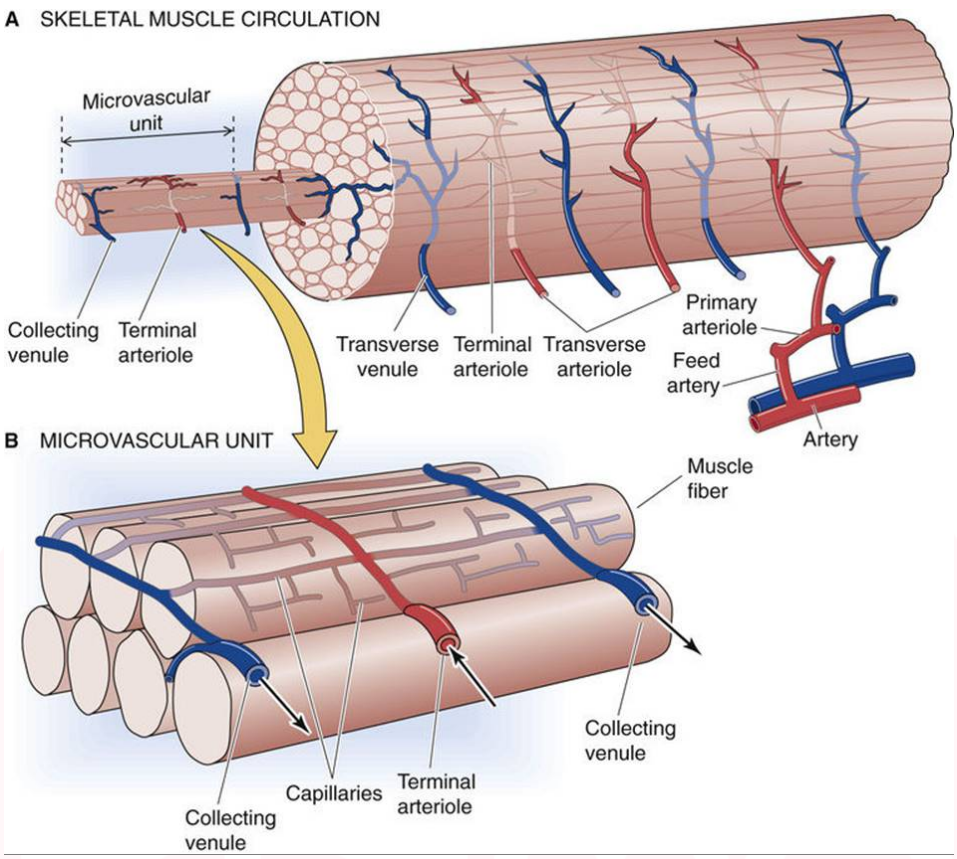


Image from: Vieira et al., 2020

Microvascular Perfusion

Context:

1. The microvasculature is defined as vessels with a diameter <150 µm in diameter and includes arterioles, capillaries, and venules.
    a. [While the macrovasculature relates to arteries and veins]
2. During exercise, blood flow increases to augment oxygen delivery and uptake to the contracting muscle.
    a. This is an increase in both total limb and microvascular blood flow.
3. While arteries do transport blood (with oxygen) towards the muscle, it is the microvasculature that is in direct contact, i.e.,
    a. Macrovasculature flow is responsible for feeding the capillary network (ie, large arteries, feed arteries, and arterioles)
    b. Microvasculature flow feeds the muscle bed, thus is responsible for nutrient and hormone exchange.
4. However, the macrovascular and microvascular blood flow responses to muscle contraction, insulin infusion, and meal ingestion, can be changed **independently** of each other.
5. This is important to note as the majority of techniques used to measure changes in blood flow are unable to distinguish between macrovasculature flow and microvasculature flow (Broatch et al., 2021).
6. Prof. McConell has been involved in much of the work that looks as the microvascular flow and separates out their effects.



Source: doctorlib.info

Sjoberg et al., 2017 - **Exercise Increases Human Skeletal Muscle Insulin Sensitivity via Coordinated Increases in Microvascular Perfusion and Molecular Signaling**

- The aim of this study was to determine whether the insulin-sensitizing effect of prior acute exercise is associated with increases in muscle microvascular perfusion.
- Thirteen healthy male volunteers, aged 24-26
    - Note: For a variety of reasons mentioned in the methods section of the paper, the data presented are n = 12 for leg balance data, n = 9 for muscle specimen data, and n = 6 for the microvascular perfusion data.

Methods:

- Before the day of the experiement, subjects refrained from exercise training for 48 hours.
- At 5 a.m on the morning of the experimental day, subjects consumed a breakfast containing 40 g of oatmeal and 150 mL of low-fat milk.
- Subjects arrived at the laboratory by public transportation at 6:45 a.m.
- They performed 60-min of a knee extensor exercise workout.
- Subjects then rested for 4 hours.

- A euglycemic-hyperinsulinemic clamp was initiated 4 hours after the exercise bout was completed.
    - The euglycemic-hyperinsulinemic clamp is the gold-standard method for detecting insulin sensitivity and glucose utilization in humans.
- In 9 of the 13 subjects, muscle biopsies were obtained from the vastus lateralis muscle (largest part of the quadriceps) of both legs.

Findings:

- The ability of insulin to increase microvascular perfusion is augmented several hours after acute exercise.
- Importantly, this response was necessary to improve insulin sensitivity for glucose uptake in muscle after exercise.
- This suggests that a bout of exercise primes the muscle for greater postexercise insulin-stimulated glucose uptake.
- Despite similar blood flow in the two legs 4 hours after exercise, microvascular perfusion was 40% higher in the exercised leg than in the rested leg.