Chapter 1
A Brief History of Exercise Metabolism

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Abstract The source of energy utilized during physical activity has been of intense scientific interest for at least two centuries. This chapter briefly describes how (and why) each of the three major macronutrients—i.e., protein, carbohydrate, and fat—has alternately had their moments in the sun. Specifically, although until the 1860s protein was considered to be the only fuel used during exercise, first carbohydrate, then fat, and then again carbohydrate held sway from the 1860s until World War II, from World War II until the late 1960s, and from the late 1960s to ca. 1990, respectively. It is now widely recognized, however, that contracting muscle relies upon a mixture of carbohydrate, fat, and even a small amount of protein to provide its energy needs, with the relative importance of each varying with the exercise intensity and duration, the characteristics (e.g., nutritional state, physical fitness) of the individual, etc. Thus, although substrate metabolism during exercise is now understood in greater detail than ever before, the overall picture has come full circle to that described by Zuntz at the start of the twentieth century.

Keywords Scientific history · Physical activity · Substrate oxidation · Muscle energetics · Macronutrient metabolism

1.1 Introduction

Precisely how skeletal muscle obtains the energy needed to support contractile activity, i.e., physical exercise, has been of keen interest for at least 150 years. This chapter briefly traces the historical development of our modern understanding of the answer to this question, focusing primarily upon macronutrient metabolism,

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i.e., the utilization of protein, carbohydrate, and fat (lipids) during exercise in humans. For a more detailed discussion of this and related issues, readers are referred to a previous review (Coggan 2014).

1.2 Exercise Metabolism, Late Eighteenth Century to the 1860s: Protein Reigns Supreme

Early perspectives on substrate metabolism during exercise arose in parallel with broader developments in science and especially biochemistry. In particular, the recognition of proteins as a distinct class of chemicals by de Fourcroy (1789), their careful study in the early 1800s by luminaries such as Mulder (1838), and their ultimate naming by Berzelius in 1838 (Harold 1951) initially led to the hypothesis that muscle obtained its energy primarily from consumption of its own substance. This was an extension of the common belief among chemists and physiologists of the time, such as Voit or von Haller, that "flesh becomes flesh" (Bischoff and Voit 1860; Holmes 1963). Leibig in particular asserted that protein was the only true nutrient and that carbohydrates and fats were combusted only to prevent excess O_2 from entering the body during ventilation, one major purpose of which was simply to cool the "metabolic furnace" (von Liebig 1842; Carpenter 2003). In 1862, however, Smith (1862) demonstrated that laboring for 8 h/d on a treadwheel did not increase the 24 h urea excretion of four British prisoners, thus seemingly ruling out protein as a major source of energy for muscular work. These findings were confirmed shortly thereafter by Fick and Wislicenus (1866), who measured their own urea excretion during and after a day-long mountain hike during which they consumed only protein-free snacks and beverages (including some beer and wine). They ascended nearly 2000 m during the climb, but the amount of protein that was oxidized could have provided only about half of the energy required by the vertical work that they performed, even if their muscles were 100% efficient. This led Fick and Wislicenus (1866) to conclude that "the burning of protein cannot be the only source of muscular power." Similarly, upon reviewing these and other results (e.g., von Pettenkofer and Voit 1866), Fick's brother-in-law, Edward Frankland, concluded that:

> Like every other part of the body the muscles are constantly being renewed; but this renewal is not perceptibly more rapid during great muscular activity than during comparative quiescence. After the supply of sufficient albuminized matter [protein] in the food to provide for the necessary renewal of the tissues, the best materials for the production, both of internal and external work, are non-nitrogenous material. . . . (Frankland 1866)

Thus, almost as quickly as it began, the reign of protein (whose name is derived from the Greek word πρώτειος (proteios), meaning "primary" or "of the first rank") as a major, much less the only, source of energy during exercise was over.

1.3 Exercise Metabolism, 1860s to World War II: Carbohydrate Is King

Even as protein was enjoying its brief time in power, other events were transpiring that would eventually see carbohydrate anointed—mistakenly, as it turns out—as its successor as the singular substrate fueling exercise. Major findings leading to this conclusion included the following observations:

1. Lactate levels were higher in the non-paralyzed vs. the paralyzed muscles of hunted stags (Berzelius and Berzelius 1806–1808).
2. Contractile activity resulted in an increase in water-soluble and a decrease in alcohol-soluble substances in the muscle, apparently as a result of lactate formation via degradation of glycogen (von Helmoltz 1845).
3. Muscle contractions were accompanied by tissue acidification, again presumably as a result of glycogenolysis to form lactate plus protons (du Bois-Reymond 1859; Heidenhain 1864).
4. Direct demonstration that electrically stimulated contractions resulted in a decrease in muscle glycogen content (Weiss 1871).

As discussed by Zuntz (1911), these observations led to the erroneous belief that the energy required to support muscle contractions was derived entirely from carbohydrate. Major proponents of this theory, which persisted in various forms until almost the middle of the twentieth century, included Chauveau himself and, subsequently, Archibald Vivian (A.V.) Hill.

Chauveau based his belief in part on measurement of the respiratory exchange ratio (RER; i.e., whole-body CO_2 production divided by whole-body O_2 uptake) during strenuous exercise lasting about an hour, which revealed a value close to unity, commensurate with oxidation of strictly carbohydrates (Chauveau 1896). He therefore proposed that fat could only contribute to the energy needs of contracting muscle if it were first converted to carbohydrate in the liver, a process that he estimated would increase the overall energy cost of exercise by approximately 30%.

In contrast to Chauveau, Hill's perspective was primarily based on biochemical and biophysical studies of isolated amphibian muscle, including his mentor Fletchers' definitive demonstration of lactate production during electrical stimulation (Fletcher and Hopkins 1907) and his own measurements of the effects of O_2 availability on the heat released during and after such evoked contractions (Hill 1910, 1913, 1914). These studies, for which Hill eventually shared the Nobel Prize in Physiology or Medicine with Meyerhof in 1922, demonstrated that although a fixed amount of heat was always liberated during the contractile activity, the presence of O_2 led to additional heat being released afterward. Hill interpreted these results to mean that lactate formation was directly responsible for force production by the muscle, with oxidative resynthesis of glycogen occurring during recovery.

Regardless of the somewhat different basis for their reasoning, the adamancy of Chauveau and Hill that carbohydrate was the only fuel used by muscle during

exercise held considerable sway for decades. This was so even though other data available at the time, including Zuntz's own measurements of RER in exercising horses (Zuntz 1898) and humans (Zuntz and Schumberg 1901), indicated that fat could also be oxidized. As discussed previously (Coggan 2014), the refusal of Chauveau and Hill to accept this conclusion may have stemmed in part from the inability to consistently demonstrate utilization of lipids by the muscle. For example, Leathes (1906) did not find any changes in the total fat content of amphibian muscle following electrical stimulation. In contrast, Lafon (1913) found that electrical stimulation to fatigue decreased the total muscle fat content in two rabbits. Lafon also found a net uptake of fat by muscle at rest and especially during exercise in one horse and two donkeys, but not in three dogs. As emphasized by Zierler (1976), these variable results were probably due to (1) the relatively crude biochemical methods available at the time and (2) the simultaneous uptake of fatty acids by muscle and release by adipose tissue (as recognized by Lafon: ". . .variations could be due to the possibility that blood, at the same time in which it loses fat to muscle, replenishes [it] from reserves"). Indeed, uncertainty about the precise source and nature of the lipids oxidized by exercising muscle persisted until almost the end of the twentieth century, as will be discussed.

As a result of Chauveau's and Hill's stature as scientists, studies of exercise metabolism in the early 1900s were largely devoted to testing their hypotheses, especially Chauveau's. Often, this entailed manipulating an individual's diet in an attempt to alter bodily carbohydrate stores and then determining the effect of such an intervention on RER and efficiency during exercise (e.g., Heinemann 1901; Frentzel and Reach 1901; Benedict and Cathcart 1913; Krogh and Lindhard 1920; Marsh and Murlin 1928). Benedict and Cathcart (1913), for example, used this approach to test Chauveau's ideas, relying primarily on a professional cyclist as their subject. However, despite inducing a marked shift in substrate utilization, as evidenced by a decrease in RER of 0.10–0.15 units, Benedict and Cathcart were unable to demonstrate any significant decrease in thermodynamic efficiency. Krogh and Lindhard (1920), though, were mistrustful of these data, because Benedict and Cathcart used a mouthpiece and nose clip to collect expired air, which can lead to errors due to hypo- or hyperventilation. They therefore built and carefully validated a respiration chamber large enough to enclose a cycle ergometer, and essentially repeated Benedict and Cathcart's experiments. Unlike this prior study, Krogh and Lindhard found that subjects were 10–11% less efficient during exercise when oxidizing purely fat versus purely carbohydrate. Similarly, using a young boxing instructor as their subject, Marsh and Murlin (1928) found a 11–12% difference in efficiency after at least 3 days of a high-fat diet.

The results of Krogh and Lindhard, Marsh and Murlin, and previously also Frentzel and Reach (working in Zuntz's lab), were therefore all remarkably consistent in demonstrating a roughly 10% difference in efficiency depending upon the substrate being oxidized, which was clearly less than the 30% difference predicted by Chauveau or even the slightly lower figure calculated by Zuntz. However, Krogh and Lindhard did not consider such data to be definitive, stating that they were ". . .not convinced of the validity of any of these summary methods of calculating the

waste of energy incidental to the conversion of fat into sugar. . . .” Marsh and Murlin, on the other hand, were somewhat more confident, concluding that “we cannot account for the lower efficiency [based] on Chauveau’s theory.” In contrast, Hill interpreted these results to “. . .suggest[s] strongly that the primary breakdown is of carbohydrate, and that fat is used only in a secondary manner, e.g., to restore the carbohydrate which has disappeared. . .” (Hill 1924). Thus, the question of whether muscle could use fat directly during exercise remained unsettled for some time.

Carbohydrate’s grip on the battlefield as the sole substrate utilized by the contracting muscle only really began to loosen after further biochemical advances in the late 1920s and early 1930s led to what Hill himself described as a “revolution in muscle physiology” (Hill 1932). These breakthroughs, which have been reviewed in greater detail by Maruyama (1991), included:

1. The contemporaneous discovery of “phosphagen” and its identification as phosphocreatine (PCr) by Eggleton and Eggleton (1927) and Fiske and SubbaRow (1927), respectively.
2. Establishment of PCr’s high heat of hydrolysis by Meyerhof and Suranyi (1927).
3. Subsequent near-simultaneous and independent discovery of “pyrophosphate” by Lohman (1929) and “adenosine triphosphonic ester” by Fiske and SubbaRow (1929), which were almost immediately recognized to be the same compound. Originally called “adenylpyrophosphate” in Meyerhof’s lab where Lohman worked, this was changed to adenosine triphosphate (ATP) by Barrenscheen and Filz (1932).
4. The recognition by Lohman (1934)
   that ATP served as the immediate source of energy during muscle contractions, with the ATP utilized being rapidly resynthesized via the hydrolysis of PCr.

Combined with the demonstration by Lundsgaard (1930a, b, 1931, 1932) that blocking glycolysis and hence lactate production using iodoacetic acid did not prevent frog muscle from contracting, these findings finally put to rest the Hill and Meyerhof “lactic acid” theory of muscle contraction.[1]

[1] Even so, Hill seemed to stubbornly cling to his and Meyerhof’s original beliefs, first proposing in 1933 that the “lactacid” portion of post-exercise O_2 consumption was due to the resynthesis of glycogen from lactate Margaria et al. (1933) and then in 1950 emphasizing that direct proof of ATP hydrolysis during contractions was still lacking:

> In the lactic acid era the evidence that the formation of lactic acid was the cause and provided the energy for contraction seemed pretty good. In the phosphagen era a similar attribution to phosphagen appeared even better justified. Now, in the adenosinetriphosphate era lactic acid and phosphagen have been relegated to recovery and ATP takes their place. Those of us who have lived through two revolutions are wondering whether and when the third is coming. (Hill 1950)

Hill’s famous “challenge to biochemists” was only finally met in 1962, when Cain and Davies (1962) were able to demonstrate small but significant and reciprocal changes in ATP and adenosine diphosphate (ADP) in contracting frog muscle by inhibiting creatine kinase using 1-fluoro-2,4-dinitrobenzene.

Thus, in the years leading up to World War II, it gradually became accepted that along with carbohydrates, fats could also be used for fuel during exercise. However, it was still thought that this could only occur via some indirect pathway (Lundsgaard 1938; Steinhaus 1941; Gemmill 1942). For example, Lundsgaard wrote that "it is probable that the high-molecular fatty acids are not attacked, or not readily attacked oxidatively in the muscles." Instead, Lundsgaard hypothesized that fatty acids were converted into ketone bodies by the liver, which were then utilized by the muscle. In support of this hypothesis, Blixenkrone-Møller observed avid uptake of ß-hydroxybutyrate by resting and especially contracting perfused cat hindquarters (Blixenkrone-Møller 1938). Drury and coworkers also found significant ketone body extraction by muscle in various species, including humans (Barnes and Drury 1937), and shortly thereafter reported that exercise had a temporary ketone-lowering effect in both rats and humans (Drury et al. 1941). Similar results were obtained in guinea pigs and humans by Neufeld and Ross (1943). Ketone bodies therefore shared the arena with carbohydrates for approximately 15–20 years, until they were displaced by non-esterified fatty acids as described below.

1.4 Exercise Metabolism, World War II to the Late 1960s: Lipids Have Their Heyday

As described previously (Coggan 2014), research into exercise metabolism slowed during and immediately after the Second World War, due to (1) the negative impact of the conflict on the lives of important scientists and (2) a shift in emphasis in exercise physiology research toward more pragmatic studies of heat and altitude acclimation, fitness testing, ergogenic aids, etc. However, metabolic research then began to accelerate again in the 1950s, on the heels of major advances in biochemistry, driven in part by the availability of ^{14}C-labeled tracers in the new nuclear age (Krebs 1964). Such advancements soon led to the realization that long-chain fatty acids, not ketone bodies, were the plasma lipid substrate normally utilized by resting and contracting skeletal muscle. Specifically, in 1958, Fritz and colleagues used ^{14}C-labeled palmitate to demonstrate that electrical stimulation resulted in a doubling in the rate of fatty acid oxidation by isolated rat skeletal muscle (Fritz et al. 1958). Shortly thereafter, Friedberg, Estes, and coworkers reported that exercise increased the rate of clearance of a bolus of ^{14}C-labeled palmitate from plasma in humans (Friedberg et al. 1960, 1963). Friedberg and Estes also used ^{14}C-labeled palmitate to quantify the rate of $^{14}CO_2$ production across the human forearm and found that it increased during contractions (Friedberg and Estes 1961). This study therefore provided the first direct evidence that exercise increases the rate of fatty acid utilization by the human skeletal muscle. Subsequent experiments using continuous infusion of various ^{14}C-labeled fatty acids essentially confirmed this conclusion and firmly established the importance of plasma-borne fatty acids as an

energy substrate during exercise (Carlson and Pernow 1961; Havel et al. 1963, 1964, 1967; Issekutz Jr et al. 1965).

This muscling aside of ketone bodies by fatty acids finally broke carbohydrate's iron-like grip as "the" source of energy during exercise. In fact, the see-saw nature of the battle between carbohydrate and fat actually seemed to swing too far the other way, with at least some scientists of the era apparently believing that the latter was equally the dominant metabolic fuel, writing that "free fatty acids are the major circulating metabolites burned by working muscle in the postabsorptive state" (Havel et al. 1963), "fatty acid oxidation is considered the primary if not the sole energy source in exercising men" (Rowell et al. 1965), and "muscular work, performed aerobically in the post-absorptive state, depends mainly on utilization of fat" (Jones and Havel 1967).[2] Glycogen was relegated to a role as an emergency substrate used only during high-intensity "anaerobic" exercise, whereas the contribution from plasma glucose as an energy source during any form of exercise was considered to be relatively unimportant (e.g., "glucose uptake from the blood [is] negligible" (Bergström and Hultman 1966b), "the rates of turnover and oxidation of plasma glucose play only a minor role in exercise metabolism" (Paul and Issekutz Jr 1967), "the amount of glucose extracted [. . .] does not amount to more than 5-6% of all energy production of the skeletal muscles at submaximal or maximal work levels" (Keul et al. 1967)).

1.5 Exercise Metabolism, Late 1960s to ca. 1990: Carbohydrates Mount a Comeback

Just when it seemed that fatty acids had prevailed in the struggle for supremacy as the most important fuel during exercise, carbohydrates launched a counterattack. This was largely the result of the resurrection of Duchenne's percutaneous needle muscle biopsy technique (Charrière and Duchenne 1865)[3] by Bergström and Hultman (1966a). Application of this "new" method quickly revealed that the glycogen content of the *v. lateralis* declined significantly even during low intensity exercise (i.e., 30 min of supine cycling at 50 W) (Bergström and Hultman 1966b). Even greater utilization of glycogen was observed during more prolonged or intense cycling (Ahlborg et al. 1967; Bergström et al. 1971), Nordic skiing (Bergström et al.

[2] Although studies using ^{14}C-labeled fatty acids highlighted their own importance as an energy source during exercise, they also resurrected the long-standing question of the role played by tissue (muscle) lipid stores. Specifically, oxidation of plasma fatty acids was generally found to account for only about half of the total amount of fat oxidized during exercise, as determined via indirect calorimetry (e.g., Havel et al. 1967). However, similar to earlier studies (Leathes 1904, Lafon 1913), attempts in the 1950s and 1960s to directly demonstrate utilization of muscle lipids during contractions were met with mixed success (Volk et al. 1952; George and Naik 1958; Neptune et al. 1960; Masoro et al. 1966; Carlson 1967).

[3] For a full history of the method, see Waclawik and Lanska (2019).

1973) or distance running (Costill et al. 1971, 1973). Perhaps most importantly, it was shown that an individual's time to fatigue during moderate-intensity exercise was highly correlated with their initial muscle glycogen level, as manipulated using variations in activity and diet (Bergström et al. 1967). These and other studies therefore cemented the importance of muscle glycogen as an energy source during exercise, especially at higher intensities typical of many athletic competitions.

During this same period, a number of studies also showed that contrary to previous suggestions, plasma glucose could also be an important source of energy during exercise. Using the arteriovenous balance approach, for example, Ahlborg et al. (1974) found that during prolonged, low-intensity cycling glucose uptake by the legs could account for 30–40% of total energy expenditure. Even though muscle glycogen utilization increases at higher exercise intensities, plasma glucose was found to account for a similar fraction of overall energy production during exercise at 60–70% of VO_2max (Wahren et al. 1971; Martin et al. 1978). Comparable results were subsequently obtained using other methods, i.e., isotopic tracer infusion or the glucose clamp technique (see Coggan 1991 for review). It was also demonstrated that fatigue during prolonged, moderate-intensity exercise was often the result of both muscle glycogen depletion and hypoglycemia, and not just glycogen depletion alone (Coyle et al. 1986; Coggan and Coyle 1987), thus aiding carbohydrate's revival as a key substrate.

This reemergence of carbohydrates forced lipids to surrender their position as the chief, if not only, metabolic fuel during exercise. Nonetheless, they retained a position of importance, especially during lower-intensity, more prolonged exercise. Indeed, the period from the 1960s to approximately 1990 was marked by an increasingly sophisticated understanding of the overall pattern of substrate utilization during exercise. For example, it was during this period that it was finally accepted that along with plasma-borne fatty acids, intramuscular triglycerides could also be an important source of energy during exercise (Watt et al. 2002). Notably, this was not the result of any single study, but rather was simply due to the accumulation of evidence over the previous 100 years. This deeper appreciation of the nuanced nature of substrate choice by contracting muscle was aided along the way by the development and application of newer, less invasive methods than muscle biopsy or arteriovenous balance sampling, such as stable isotopic tracer techniques (see Coggan 1999a, b for review) and ^{31}P, ^{1}H, and ^{13}C magnetic resonance spectroscopy, used to assess high-energy phosphate, muscle triglyceride, and muscle and liver glycogen metabolism, respectively (see Kemp and Radda 1994 for review).

The period from the 1960s to ca. 1990 was also marked by an explosion of research into the biochemical responses and adaptations to exercise at the cellular level. Spearheaded by work from the laboratory of John Holloszy (Hagberg et al. 2019), such studies demonstrated how muscle mitochondrial respiratory capacity plays a key role in determining the rates of muscle and liver glycogen utilization during exercise (Fitts et al. 1975). Research using rats by Holloszy and coworkers (Holloszy 1967; Holloszy et al. 1970; Molé and Holloszy 1971; Baldwin et al. 1972) and others such as Pette (reviewed by Pette and Vrbová 2017) and using humans by

Varnauskas et al. (1970), Morgan et al. (1971), Gollnick et al. (1972, 1973), etc. also revealed the remarkable adaptability of skeletal muscle in response to changes in demand imposed by voluntary or involuntary (i.e., electrically stimulated) contractile activity. These findings paved the way for subsequent more in-depth studies of the molecular underpinnings of the metabolic responses to acute and chronic exercise in the 1990s and beyond, as discussed previously (Coffey and Hawley 2007; Röckl et al. 2008; Hawley et al. 2015).

1.6 Exercise Metabolism, ca. 1990 to Present: Détente Prevails

Approaching the end of the twentieth century, the overall pattern of substrate utilization during exercise, at least in young, healthy male subjects, had been well described. Thus, after this point, research into exercise metabolism became increasingly focused on additional factors that might modify this pattern, as previously noted (Coggan 2014). Although space precludes a detailed discussion of the impact of such "special circumstances" on the utilization of various fuels, a brief discussion of some of them is provided below. For additional details, readers are again referred to previous reviews (e.g., Holloszy and Coyle 1984, Coggan and Williams 1995, Coggan 1996, 1999a, b, Tarnopolsky and Ruby 2001, Mittendorfer and Klein 2001, Devries 2016, etc.).

1.6.1 Endurance Training

It was widely recognized in the early years of the twentieth century that trained athletes are less dependent than untrained individuals on carbohydrate metabolism during exercise, as evidenced by their lower RER and blood lactate levels. However, it was generally assumed that this was due to an athlete's muscles being less "anaerobic," or more vaguely ascribed to their greater "skill," with the only formal study of this adaptation being a longitudinal training of three men conducted by McNelly (1936). The previously described boom in exercise/metabolic research in the 1960s and thereafter, however, brought renewed attention to this question. Key *human* experiments during this period included the first cross-sectional (Hermansen et al. 1967; Evans et al. 1979) and longitudinal (Saltin et al. 1976; Karlsson et al. 1974) studies demonstrating that training reduces the rate of muscle glycogen utilization during exercise. Subsequently, it was also shown that training reduces utilization of plasma glucose as well (Coggan et al. 1990; Mendenhall et al. 1994), with this lesser demand associated with slower rates of hepatic glycogenolysis and gluconeogenesis (Coggan et al. 1995a). Conversely, the rate of intramuscular triglyceride utilization was shown to be increased (Hurley et al. 1986). All of these

adaptations were found to be evident not only at the same absolute exercise intensity but even at the same relative intensity, i.e., the same percentage of VO_2max (Coggan et al. 1995b, 2000). On the other hand, utilization of plasma free fatty acids, which was initially thought to not only compensate for the slower rate of carbohydrate utilization but also to at least partially cause it via the glucose-fatty acid cycle (Holloszy 1973), was found to actually be lower during exercise at the same absolute intensity after training (Martin 3rd et al. 1993). This is due to a slower rate of sympathetically mediated adipose tissue lipolysis in the trained state, as training increases not only the maximal capacity of muscle to oxidize fatty acids but also the maximal capacity for inward transport as well (Talanian et al. 2010). Consequently, during exercise at the same relative intensity, when activation of the sympathetic nervous system is comparable, utilization of plasma free fatty acids is higher in the trained state (Coggan et al. 2000).

1.6.2 Aging

Measurement of RER and blood lactate levels in older vs. younger subjects during incremental exercise provided the first evidence that aging results in an increase in carbohydrate utilization and a decrease in fat utilization during exercise (Robinson 1938; Durnin and Mikulicic 1956; Åstrand 1958). It was only many years later, however, that this issue was studied in any great detail. Specifically, using stable isotopic tracers, Sial et al. (1996) determined the rates of whole-body glucose and free fatty acid turnover while also measuring the overall rates of carbohydrate and fat oxidation via indirect calorimetry in older and younger men and women exercising at both the same absolute and the same relative intensity. At the same absolute intensity, carbohydrate oxidation was higher in older subjects, with this difference being apparently due to a higher rate of muscle glycogen utilization (as glucose kinetics were similar). Conversely, the overall rate of fat oxidation was lower, despite a higher turnover and especially a higher concentration of free fatty acids in the older subjects. Differences in relative rates of substrate oxidation were minimized during exercise at the same relative intensity, but free fatty acid concentrations were still higher in older subjects, due to their much lower rate of free fatty acid clearance. These age-related changes in substrate metabolism are undoubtedly the result of a complex interaction of a host of factors, including decreases in VO_2max with aging, which confounds the basis on which subjects of varying fitness have conventionally been compared. Another important factor, however, is age-related changes in the skeletal muscle itself, especially a decline in mitochondrial content and hence in respiratory capacity (Coggan et al. 1992), which results in a greater disturbance in muscle energetics during contractile activity, even when accounting for the age-related decrease in muscle mass (Coggan et al. 1993).

1.6.3 Sex

Due to societal norms that discouraged mass participation of women in physical activity and sports, possible sex-related differences in substrate metabolism during exercise were the last battlefront to be confronted. In 1979, however, Costill and colleagues studied male and female distance runners matched for both training volume and VO_2max and found no difference in RER during submaximal exercise (Costill et al. 1979). Similar results were obtained by Powers et al. (1980) and Helgerud et al. (1990), whereas Froberg and Pedersen (1984) and Blatchford et al. (1985) found RER to be lower in women. The first in-depth study, however, was performed by Tarnopolsky et al. (1990), who used indirect calorimetry and the muscle biopsy technique to compare substrate metabolism in men and women matched for training and volume and VO_2max while also controlling for menstrual status and diet. Supporting a sex-related difference in substrate preference, they found both RER and muscle glycogen utilization to be lower in the women. Although follow-up studies from the same group as well as others have yielded somewhat mixed results (Phillips et al. 1993; Tarnopolsky et al. 1995, 1997), the bulk of the evidence indicates that women do rely somewhat more on fat as fuel during exercise. As with the effects of aging, multiple mechanisms almost certainly contribute to this subtle difference, including sex-related differences in gonadal and catecholamine hormone levels, type II muscle fiber volume, muscle glycolytic/glycogenolytic enzyme activities, etc. (Coggan 1999a, b).

1.6.4 Obesity and Type 2 Diabetes

Also reflecting societal trends, a number of relatively recent studies have determined the effects of obesity or diabetes on substrate metabolism, primarily at rest but also in response to exercise. As reviewed by Houmard (2008), these studies have demonstrated that although the overall rate of fatty acid uptake by muscle is increased, the capacity to oxidize such fatty acids is actually reduced. This leads to intramuscular accumulation of lipid metabolites (triglycerides, ceramides, diacylglycerol, etc.) that are thought to play a leading role in the muscle insulin resistance in such disease states. Interestingly, this reduced capacity to oxidize fatty acids is not reversed by weight loss (Thyfault et al. 2004), suggesting that genetics may play a significant role in its etiology.

1.7 Summary

During the last 150 years, tremendous advances have been made in understanding the pattern of substrate metabolism during exercise. The picture that has emerged is that of muscle as a metabolic omnivore, capable of utilizing carbohydrates, fats, and even to some extent protein to fulfill its energy needs, with the precise mixture of substrates being oxidized depending upon the exercise intensity and duration and the individual's diet, fitness, age, sex, etc. Future studies will undoubtedly provide even greater detail and lead to an even deeper mechanistic basis for these findings.

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