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Review

Carbohydrate and fat utilization during rest and physical activity

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SUMMARY

The energy used in post-prandial state during rest and physical activity is derived predominantly from the oxidation of carbohydrate (CHO) and fat. Although protein can also serve as a source of energy, amino acids oxidation is usually tightly adjusted to amino acids intake and their contribution to total energy expenditure is rather insignificant in healthy subjects. Blood glucose, glycogen, plasma fatty acids and intramuscular triglycerides, on the other hand, present major sources for energy production.

The amount of energy stored in the form of fat is large, representing 92–98% of all endogenously stored energy with CHO contributing only about 2–8%. Fat is at the bottom of an oxidative hierarchy that determines fuel selection, and its oxidation is governed by the presence or absence of the other macronutrients. In addition, the rate at which it can be oxidized depends on intensity of energy expenditure. In contrast, CHO elicit strong auto-regulatory adjustments in their oxidation.

This review aims at summarizing the current state of knowledge on CHO and fat body storage, hierarchy of fuel utilization during resting state, anaerobic and aerobic pathways for energy production during exercise, and the effects of exercise mode, intensity, duration, and training on CHO and fat utilization.

1. Introduction

On average, resting metabolic rate (RMR) accounts for about 60–70% of TEE, the remainder being accounted for by diet-induced thermogenesis (10%) and physical activity (~20–30%).

The RMR corresponds to the energy required by the body to maintain post absorptive homeostatic functions in resting subjects. It is usually measured in the morning, in a subject who has fasted overnight and who has rested quietly for around 30 min in a thermo-neutral environment.[1–3]

Indirect calorimetry allows to measure a volume of gas exchange (CO_2 production, O_2 consumption), and to determine the proportion of different nutrients oxidized and calculate the energy released from each nutrient. In a resting subject consuming an average diet (e.g. 35% fat, 12% protein, and 53% CHO), studied in the post absorptive state, about 4.8 kcal are expended per liter O_2 consumed (Table 1).[4]

Thus, at rest, an average person consumes about 3.5 ml O_2/kg body weight/min or expends about 1 kcal/kg body weight/hr. This rate of energy expenditure is expressed as 1 metabolic equivalent (MET).[5] Using these common values, it can be calculated that a resting 70 kg man expends around 1680 kcal/d.

The value equating 1 MET was first derived from the resting O_2 consumption of one person, a 70 kg, 40 year old man, and is nowadays widely used as a physiological concept for expressing energy cost of physical activities as multiples of RMR. Nevertheless, it should be noted that the MET was developed to standardize intensities of physical activities rather than to indicate precise estimates of physical activity energy costs. An error in estimating resting O_2 consumption from 1 MET increases with increasing adiposity, i.e. measured resting O_2 consumption decreases with increased body fat. This does not mean obese individuals have lower metabolic rate that normal weight subjects, but rather confirms that expressing O_2 consumption per kg body weight is inappropriate.[6,7]

The respiratory quotient (RQ) is the ratio CO_2 production/O_2 consumption. A RQ of 1 indicates 100% CHO oxidation, while a general value of 0.7 indicates 100% fatty acid oxidation (the value ranges between 0.69 and 0.73, depending on the oxidized fatty acid' carbon chain length) (Table 1). The average resting RQ of 0.82 thus reflects that the human body derives more than half of its energy from fatty acids and most of the rest from glucose (Table 1). The amount of fatty acids released from adipose tissue during rest typically exceeds daily energy needs (fatty acid appearance into plasma is approximately twice the rate of fatty acid oxidation).[8] Therefore, only one portion of the fatty acid flux is oxidized for fuel, the rest being re-esterified back into triacylglycerols, principally by the liver. The body stores of energy fuels are presented in a Table 2.

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Table 1
Substrate utilization during resting state.

Food	Complete oxidation of food in bomb calorimeter (kcal/g)	Complete oxidation of absorbed or stored fuel in body[b] (kcal/g)	Physiological value of consumed food[c](kcal/g)	O_2 (kcal/l)	CO_2 (kcal/l)	RQ[a] (V_{CO_2}/V_{O_2})
Carbohydrate	4.1	4.1	4	5.05	5.05	1.00
Protein	5.4	4.2	4	4.46	5.57	0.80
Fat	9.3	9.3	9	4.74	6.67	0.71[d]
Alcohol	7.1	7.1	7	4.86	7.25	0.67
Average				4.83	5.89	0.82

Adapted from Stipanuk HM.[4]
[a] RQ = Respiratory quotient = volume of CO_2 produced/volume of O_2 consumed.
[b] Complete oxidation of food component in bomb calorimeter. N is excreted as urea, which has an energy content of 5.4 kcal/g N. All energy in urine is attributed to N excretion in the calculation of fuel values, and the correction factor is 7.9 kcal/kg N, or 1.25 kcal/g protein.
[c] Physiological fuel value of consumed food adjusted for digestibility (incomplete absorption).
[d] RQ = 0.71 for oleic acid (RQ for fat ranges between 0.69 and 0.73, depending on the oxidized fatty-acid' carbon chain length).

Most of the overall RMR (~60%) arises from four organs: liver, kidney, heart and brain, although they represent only ~5% of body weight (Table 3).[9] Their metabolic rates are 15–40 times greater than that of the equivalent weight of muscle mass (~10–15 kcal/kg/day) and 50–100 times greater than that of adipose tissue (~4.5 kcal/kg/day). When summed up, the RMR/kg of these organs remains remarkably stable during growth, in contrast to the changes in RMR/kg body weight.

The higher RMR/kg body weight of infants and children compared to adults can be largely explained by the increased proportion of metabolically active tissues. For example, the brain, which account for almost 50% of TEE of the infant, decreases in size in proportion to body weight during growth.[9] On the other hand, skeletal muscle, which is less metabolically active than the brain and other organs, increases in proportion to body weight during growth. In adult life, the muscle mass presents the largest tissue of the whole body and accounts for about 40–50% in an ordinary lean man. As such, it has a major effect on RMR, energy expenditure, and nutritional requirements.

Other factors like age,[10–12] sex,[13] growth,[14] hormones, genotype,[15] physiological stress,[4] pregnancy[16] and hypothermia[17] can also influence RMR and they are presented in Fig. 1.

After the body's needs during rest are met, additional energy is needed for diet-induced thermogenesis (DIT) and physical activity. DIT increases energy expenditure following food intake and is associated with the digestion, absorption and metabolism of food and nutrients. It accounts for 5–10% of TEE and is influenced by the amount and type of meal ingested. The measured thermogenesis of nutrients related to total calorie intake are 0–3% for fat, 5–10% for CHOs, and 20–30% for proteins,[18] indicating that a high protein and/or CHO diet induces a greater thermic response compared to a high-fat diet. The reason for this difference is the higher energy cost of storing amino acids as protein and glucose as glycogen, compared to the cost of processing and storing fatty acids as fat. As caloric intake increases, peak DIT increases and occurs later after meal ingestion. In addition, the magnitude of the DIT is greater and the duration of the DIT is prolonged.[13] DIT measurements lasting 6 h indicate that DIT is unchanged when comparing lean and obese men for a given caloric intake, although the shape of the DIT is affected, i.e. the peak DIT decreases and occurs at a later time as the body fat content of a subject increases (either amount or percent).[19,20] Duration of DIT measurements should thus be adequately long in order to assure that these differences are taken into account. Too short measurements would be likely to give different DIT values between lean and obese subjects.[20,21] Analyses of 131 DIT tests performed by Reed GW and Hill J indicate that DIT measurements lasting as short as 3 h can miss more than 40% of the total DIT, while 4 h DIT measurements can miss up to 22.5% of the total DIT.[20] Although factors other than the duration of DIT measurements were reported to play a role in the reduction of DIT in obesity (most notably insulin resistance, impaired insulin mediated glucose disposal, impaired activation of the sympathetic nervous system and of the sodium-potassium pump[22–25]), no consensus exists in the literature in this respect.[21] The blunted DIT in the obese is more likely to be a consequence rather than a cause of obesity.[24] The small energy deficit related to blunted thermogenesis does not seem to play an important role in energy balance as it can be easily offset by higher cost of physical activity associated with the increased weight gain of the obese.

Physically active persons have been shown to have either higher[24,26–30] or lower[31–34] DIT response compared to sedentary controls. More studies are needed to confirm the effect of physical activity on DIT.

2. Post-prandial substrate utilization

The nitrogen balance has a high priority in the body's metabolism regulation. Although its regulation is not fully understood, protein oxidation is tightly adjusted to protein intake in healthy individuals. On the other hand, CHO and fat oxidation are modifiable and their utilization depends on glucose availability.

High CHO intake, as a single load or with a mixed meal, stimulates CHO oxidation and promotes glucose storage as glycogen.[35] Stimulation of CHO oxidation after high CHO meals increases insulin concentration and suppresses fat oxidation. This is in accordance

Table 2
Body stores of energy fuels.

	Body stores (g)[a]	kcal
Carbohydrates		
Liver glycogen	110	451
Muscle glycogen	500	2050
Glucose in body fluids	15	62
Fat		
Subcutaneous and visceral	7800	72,540
Intramuscular	161	1497

Adapted from Wilmore JH and Costill DL.[54]
[a] These estimates are based on an average body weight of 65 kg with 12% body fat.

Table 3
Contribution of different organs and tissues to resting metabolic rate.

Organ	Metabolic rate (kcal/kg/day)	Weight (kg)	Organ metabolic rate (kcal/day)	% BMR
1) Brain	240	1.4	336	20
2) Liver	200	1.8	360	21
3) Heart	440	0.3	132	8
4) Kidney	440	0.3	132	8
Total (1–4)	330	3.8	960	57
5) Muscle	13	28	364	22
Total (1–5)			1324	79
70 kg man		32	1680	100.0

Adapted from Kinney JM and Tucker NH.[9]

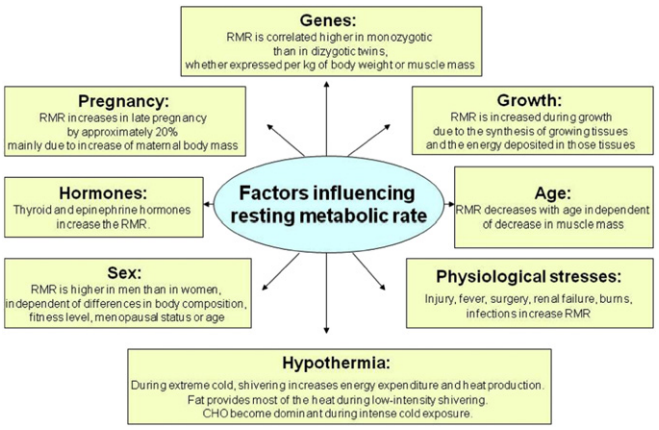

Fig. 1. Influence of various factors (age, sex, growth, hormones, genetics, physiological stress, pregnancy or hypothermia) on RMR.

with the normal understanding of post-prandial metabolism, that ingestion of CHO stimulates insulin release, which in turn suppresses the release of fatty acids from adipose tissue, and stimulates fat storage by activation of adipose tissue lipoprotein lipase.[36,37]

Nevertheless, dietary CHO does not generally increase an individual's fat storage by *de novo* lipogenesis, even after ingestion of CHO-rich diet for 3 days,[38] and fat deposited in the adipose tissue comes mainly from ingested lipids. Only after 7 days CHO overfeeding, body glycogen stores increase by ~500 g, and appreciable *de novo* lipogenesis begins.[38] After 7 days on high-CHO low-fat diet (CHO 77%, lipid 5%, and protein 18% kcal), about 50% of the CHO intake (~500 g) is oxidized and the remaining 50% is used for *de novo* lipogenesis.[39] Nevertheless, such large amounts of CHO are usually not spontaneously eaten, because such bulky food with its great satiating effect reduces desire for overconsumption and limits the energy intake. Thus, the human body can easily accommodate the daily ingestion of relatively large amounts of CHO without having a need to convert CHO to fat.

In contrast to the high CHO diet that stimulates CHO oxidation, high-fat diet does not stimulate fat oxidation. A supplement of 50 g margarine (containing 40 g fat) to a breakfast providing 75 g CHO and 20 g protein fails to promote the use of fat as a metabolic fuel.[40] Fat utilization does not appear to be regulated acutely, and fat added to a relatively normal meal is largely stored.

Although fat is one of the main fuels of the body in the post absorptive state, there is a rapid shift to CHO when feeding begins, regardless of the fat content of the food consumed.[41] This can be explained by the fact that several organs and tissues, for example the brain, have an obligatory requirement for glucose. Trembley et al.[42] believe that the occurrence of satiety coincides with a level of CHO intake that is sufficient to satisfy the expected body CHO needs. They suggest that, as long as the CHO requirements are not met, food intake increases.[42] In the case of low-CHO, high-fat diet, this can cause hyperphagia and induce a long term increase in adiposity, as reflected by higher levels of body fatness in high-fat consumers.[43]

A self-regulating effect after high-fat meals, which promotes compensatory lower energy fat intake, has not been demonstrated so far. Nevertheless, the problem of food intake is complicated and many more additional factors may play a role in food selection. A weak action of fat on satiation, specific preference or altered variety of food may also correlate with amounts or type of food selection.[44–46]

An individual at rest can accommodate CHO intakes from ~100–500 g/day, and fat intakes from ~40–200 g/day, without displacing macronutrient stores as long as the total amount ingested does not exceed the subject's energy requirements.[47] Nevertheless, fat oxidation can be stimulated by certain metabolic conditions including stress (fasting, severe trauma, sepsis), or exercise of long duration and moderate intensities.[48] Chronic conditions such as obesity or type II diabetes also increase lipolysis.[49]

In obesity, expansion of the fat mass is a prerequisite to an adaptive increment in fat oxidation. This expansion has to be substantial in order for fat oxidation to be achieved.[50] For each 10-kg increase in fat mass, there is an expected increase in fat oxidation that averages 0.8 g/h or ~20 g/day. This implies that an excess fat intake of 20 g/day or 180 kcal/day would lead to an increase in body fat of ~10 kg before lipid balance would be achieved with a corresponding increase in fat oxidation.[50]

In summary, one of the important factors determining post-prandial substrate utilization in healthy subjects is the availability of substrates. While proteins and CHOs elicit strong auto-regulatory adjustments in their oxidation in response to changes in intake, fat is at the bottom of an oxidative hierarchy that determines fuel selection.[47] This response is governed by a relatively small storage capacity of protein and CHO, a need to maintain glucose homeostasis within tight limits, and infinite body capacity for fat storage.[47]

3. Anaerobic and lactic acid pathway for energy production during exercise

As the body shifts from rest to exercise, an individual's energy demands increase. The extra energy required can be supplied through anaerobic (independent on oxygen O_2) and aerobic metabolism (dependent on O_2). Which metabolic system will be used depends on the intensity, duration, and type of physical activity imposed. During light exercise, the required energy is provided almost exclusively by the aerobic system. As the intensity of exercise increases, the role of the anaerobic systems becomes more important.

The energy required for work is not derived directly from the macronutrients eaten. Instead, this energy becomes released and funneled through an energy rich compound adenosinetriphosphate (ATP) to power cellular need. The ATP molecule consists of adenosine (a molecule of adenine joined to a molecule of ribose) combined with three inorganic phosphate (P_i) groups. Adenine is a nitrogenous base and ribose is a five-carbon sugar. In presence of water and the enzyme ATPase the last phosphate group of the ATP splits away (hydrolyzes of ATP to ADP (adenosine-diphosphate)) and releases approximately 7.3 kcal of free energy (i.e. energy available for work):

$$\mathrm{ATP} + \mathrm{H_2O} \xrightarrow{\mathrm{ATPase}} \mathrm{ADP} + \mathrm{Pi} + 7.3\ \mathrm{kcal\ per\ mol}$$

The ATP breakdown generates energy for rapid use and does not require O_2. Energy transfer increases about four-fold in the transition from sitting in a chair to walking. However, the transition from walking to an all-out sprint almost immediately accelerates the energy transfer rate about 120 times within active muscle.[51] Generating significant energy output almost instantaneously demands ATP availability and a means for its rapid resynthesis.

Although energy rich, only a small amount of ATP is present within the muscle cells, amounting to about 5 mmol/kg muscle cells or 3.4 g/kg muscle cells. An average person with, for example, 28 kg muscle mass thus contains around 95 g of ATP.[52]

The rate of turnover of ATP in a sprinting human is approximately 2.7 mmol/kg/s; in a high jump it may be as high as 7 mmol/kg/s.[53] With only 5 mmol/kg of ATP available, it has to be quickly resynthesized in order to support exercise that lasts for more than a few seconds.

The second source of readily available energy is present in the form of creatine phosphate (CP). The CP, present within the muscle

cell at a concentration about 3–4 times that of ATPs (~ 17 mmol/kg muscle cells), can be considered as a "reservoir" of high-energy phosphate bonds. Unlike ATP, energy released by the breakdown of CP is not used directly to accomplish cellular work. Instead, it rebuilds ATP to maintain a relatively constant supply. The resynthesis of ATP from ADP by transfer of a phosphate group from CP is catalyzed by the enzyme creatine kinase.

$$CP + ADP \overset{\text{Creatine kinase}}{\leftrightarrow} C + ATP$$

This reaction is extremely rapid, does not require O_2, can supply energy at a very high rate and produce metabolic power above 4000 W.[53] During the first few seconds of intense muscular activity, such as sprinting, tennis serve or weight lift, ATP is maintained at a relatively constant level, but the CP level declines steadily as it is used to replenish the depleted ATP. After around 5–10 s of intense exercise activity, CP storage is exhausted and an alternative fuel must be used.

The ATP concentration is 5 mmol/kg muscle cells, and the one of CP is 17 mmol/kg. The potential total energy of the ATP-CP immediate energy system is approximately 4.3 kcal for a man with 20 kg muscle mass.[53] It has been estimated, however, that the energy cost of a 100 m sprint is about 8 kcal, and if the duration of the sprint is 10 s, the power is 3300 W.[14] So even if the ATP and CP of the entire muscle mass could be used for the sprint, there would be a remaining deficit in energy which has to be provided by glycolysis with the formation of lactic acid.

CHOs (blood glucose and glycogen from muscle or liver) are the only macronutrients whose potential energy can generate ATP anaerobically as well as aerobically.[51] The anaerobic process of glucose/glycogen utilization occurs within the cell's cytoplasm, outside of the mitochondrion, and is called "anaerobic glycolysis" or "lactic acid pathway for energy production".

Before either glucose or glycogen can be used to generate energy, it must be converted into a compound called glucose-6-phosphate (Fig. 2). Conversion of a molecule of glucose requires one molecule of ATP. In the conversion of glycogen, glucose-6-phosphate is formed directly from glucose-1-phosphate with no need for extra energy expenditure. The anaerobic glycolysis begins once the glucose-6-phosphate is formed and involves its transformation to pyruvic acid that is converted to lactic acid as an end product. During this process, 3 molecules of ATP are formed from each glucose residue originated from glycogen or 2 molecule of ATP for each molecule of glucose (Fig. 2).

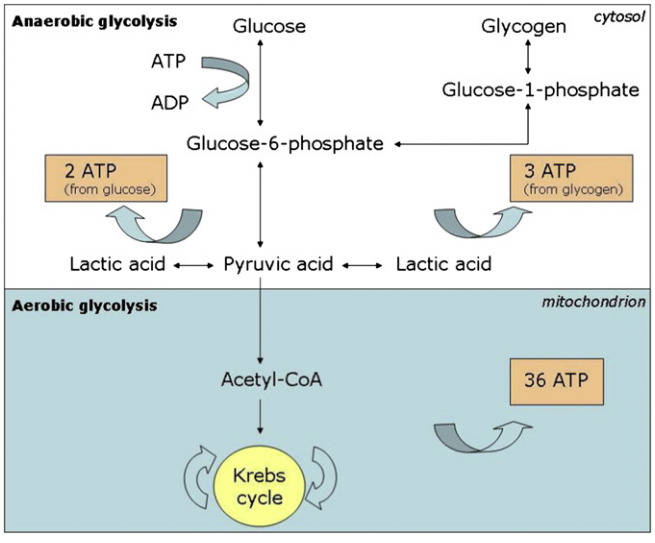

Fig. 2. The derivation of energy (ATP) via glycolysis. Conversion of a 1 mol of glucose into glucose-6-phosphate requires 1 mol of ATP. In the conversion of glycogen, glucose-6-phosphate is formed directly from glucose-1-phosphate. The anaerobic glycolysis begins once the glucose-6-phosphate is formed and produces pyruvic acid that is converted to lactic acid as an end product. During this process, 3 mol of ATP are formed from each mole of glycogen or 2 mol of ATP for each mole of glucose.

The anaerobic glycolysis contributes energy during an all-out effort lasting up to several min, and may produce power of around 2000 W.[53] Unfortunately, this energy system does not produce larger amounts of ATP and cannot generate energy for longer duration activities. Furthermore, the lactic acid production impairs glycolytic action and decreases the muscle fibers' calcium binding capacity which may impede muscle contraction.[54] Production of energy in amounts sufficient to support continued muscle activity for longer duration requires the input of O_2.

With the onset of prolonged submaximal exercise, O_2 uptake increases gradually and reaches a steady state within 3–5 min, indicating that the aerobic system is supplying all the energy required by the muscles. However, until the steady state is reached, muscles require more energy than can be provided by the aerobic system. That portion of the exercise for which the aerobic system is unable to provide sufficient ATP is termed *O_2 deficit*. During that period, the immediate ATP-CR and anaerobic glycolytic systems continue to supply energy to the muscles.

4. Aerobic pathway for energy production

The anaerobic reaction of glycolysis release only about 10% of the energy within the original glucose molecule, the rest being released when pyruvate enters the aerobic pathway of energy production where it is converted to Acetyl-CoA and degraded within mitochondria in the Krebs cycle (Fig. 3). The complete oxidation of 1 mol of glucose produces 36 mol of ATP.

The aerobic pathway can also provide ATP by metabolizing fats and proteins. Fat energy reserves are stored in the human body as triglycerides. To release energy, triglycerides must be hydrolyzed (lipolysis) to fatty acids and glycerol as follows:

$$\text{Triglyceride} + 3H_2O \xrightarrow{\text{Lipase}} \text{Glycerol} + 3\ \text{Fatty acids}$$

Fatty acids released from adipose tissue are transported to the muscle in the plasma where they are bound to albumin. At the muscle site, fatty acids bound to albumin or stored in the core of chylomicrons and very low density lipoproteins (VLDL) have to be

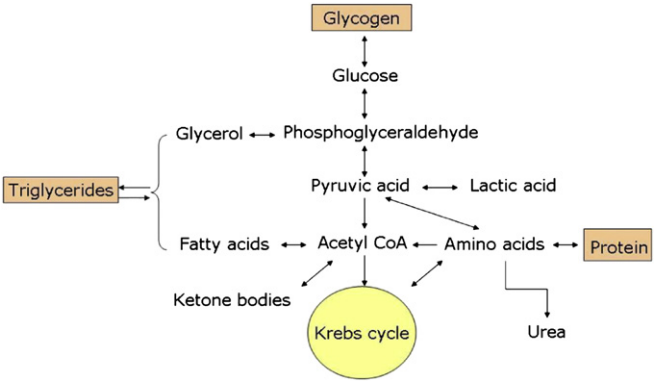

Fig. 3. The metabolism of CHO, fat, and protein. To release energy, triglycerides must be hydrolyzed (lipolysis) to fatty acids and glycerol. Glycerol can also be used to yield a small amount of energy. Transformed to 3-phosphoglyceraldehyde, it can degrade to pyruvate and enter the Krebs cycle. Glycerol also provides carbon skeletons for glucose synthesis. Amino acids can be converted to acetyl-CoA to enter the Krebs cycle, or be synthesized to glucose when glycogen reserves run low. Under normal conditions, protein oxidation accounts for not more than 5% of the energy requirements during prolonged exercise.

released prior to transport across the membrane. In the case of VLDL and chylomicrons, this is achieved by the lipoprotein lipase enzyme. Inside the mitochondrion, the fatty acid molecule transforms to acetyl-CoA during β-oxidation reaction and enters the Krebs cycle (Fig. 3). For each 18-carbon fatty acid molecule, 147 ATP are produced. As triglyceride molecule contains three fatty acid molecules, 441 ATP are formed from one triglyceride.[51]

However, to produce the same amount of ATP, oxidation of fatty acids requires more oxygen than the oxidation of CHO. For example, the complete oxidation of one molecule of glucose requires 6 molecules of oxygen, while the complete oxidation of stearic acid requires 26 molecules of oxygen.

Glycerol can also be used to yield a small amount of energy. Transformed to 3-phosphoglyceraldehyde, it can degrade to pyruvate and enter the Krebs cycle. Glycerol also provides carbon skeletons for glucose synthesis (Fig. 3).

Although the primary fuels contributing to oxidative metabolism during prolonged exercise are fats and CHOs, proteins (amino acids) can be used as a source of substrate oxidation. The use of amino acids as a fuel is increased when other substrates, especially CHO, are not available. Under normal conditions, nevertheless, protein oxidation accounts for not more than 5% of the energy requirements during prolonged exercise.[51] Amino acids can be converted to acetyl-CoA to enter the oxidative process, or be synthesized to glucose when glycogen reserves run low (Fig. 3).

In order to enter the pathways for energy release, amino acids must be converted to a form that readily enters the Krebs cycle. This conversion requires removing nitrogen from the amino acid molecule. The nitrogen is converted into urea and excreted in the urine. The conversion requires the use of ATP. Because some energy is spent in this process, the metabolized protein yields 4.1 kcal/g, which is less than the energy released from the complete protein oxidation in the laboratory calorimetry bomb (5.6 kcal/g) (Table 1).

In summary, aerobic pathway of energy production, i.e. Krebs cycle provides energy for the prolonged exercise. CHO, fats and proteins can be used as a source of aerobic substrate oxidation.

5. Exercise intensity and substrate utilization

5.1. Substrate utilization during exercise in fasted state

CHOs (muscle glycogen and plasma glucose) and fats (plasma fatty acids and intramuscular triglyceride) are thus the primary energy sources during exercise. The proportions of their contribution to energy expenditure are determined largely by the intensity and duration of substrate utilization.

In fasted state during low intensity exercise (25% of maximal O_2 uptake (VO_2max)), which corresponds to walking at 4–5 km/h, most of the energy need is provided by oxidation of fatty acids of which more than 85% is derived from plasma.[55] At this intensity, the rate of appearance of fatty acids in plasma is very similar to the rate of fatty acid oxidation (i.e. lipolysis from adipocytes) (~26 μmol/kg/min). The rate of fatty acid oxidation is determined from direct measures of the rate of appearance (Ra) of glycerol, which is an index of lipolysis (defined as 3 × glycerol Ra, as 3 fatty acids and 1 glycerol molecule are released from 1 triglyceride during lipolysis).

As the exercise intensity increases to a moderate level (65% VO_2max), use of plasma fatty acids decrease while the intramuscular triglycerides oxidation increases (Fig. 4). At this level, plasma fatty acids and intramuscular triglycerides contribute equally to total fat oxidation. Although the total fat oxidation is highest at this exercise level (>40 μmol/kg/min), fat cannot be oxidized at sufficiently high rates to provide all the energy required. Consequently, about one-half of the total energy is simultaneously derived from CHO oxidation (muscle glycogen and blood glucose).[56]

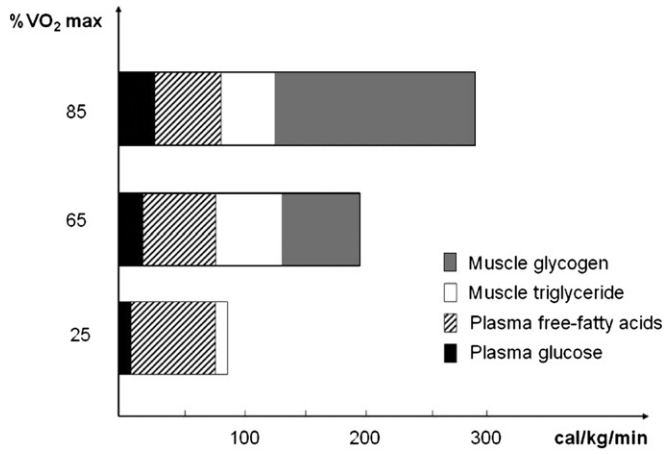

Fig. 4. CHO and fat contribution to energy expenditure at different levels of physical exercise. Adapted with permission from Romijn JA, Coyle EF, Sidossis LS et al. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. Am J Physiol 1993;265:E380–E391.[56]

At high exercise intensities level (85% of VO_2max), the rate of plasma fatty acid oxidation is decreased below the value at 65% of VO_2max, and intramuscular triglycerides become the major source of fatty acids for oxidation. The intramuscular triglycerides release fatty acids directly into the cytosol of working muscle, avoiding having to transfer the muscle plasma membrane, which makes them a very attractive potential energy source. Concerning long-chain fatty acids, they become trapped in adipose tissue as exercise intensity increases, presumably because of insufficient albumin delivery to carry them from adipose tissue into the systemic circulation.[57] It cannot be excluded that during high intensity exercise free carnitine (which transports the long-chain fatty acids into the mitochondria so they can be oxidized) concentration declines to a value that could limit carnitine palmitoyl transferase activity and reduce the long-chain fatty-acid oxidation.[58] The oxidation of medium chain fatty acids (i.e. those primarily containing fatty acids with 8–10 carbon atoms) seems to be less inhibited because they are transported differently into the mitochondria by using a different enzyme complex (carnitine octanoyl transferase). As a consequence, part of the medium chain fatty acids can freely diffuse into the mitochondria.[59]

The availability of plasma fatty acids decreases despite a maintained high rate of lipolysis from adipocytes. When the intensity of exercise reaches 85% VO_2max, the absolute rate of fat oxidation decreases (from >40 to 30 μmol/kg/min), and the CHO oxidation provides more than two-thirds of the energy required. The advantage of CHO metabolism during high intensity exercise lies in its two times more rapid energy transfer capacity compared with fatty acids.[51] These data have been collected in endurance trained subjects after 10–12 h fast and 30 min exercise.

5.2. Substrate utilization during exercise in non-fasted state

CHO meals and their importance for exercise performance have been recognized since the classic respiratory exchange studies of Christensen and Hansen in the late 1930s,[60] and the biopsy studies of Bergstrom et al. in 1967.[61]

Typically, the rate of CHO oxidation is elevated during prolonged exercise after a CHO meal compared with exercise after fasting.[62] The ingestion of a CHO-rich meal before exercise has been shown to increase muscle glycogen, blunt fatty acid mobilization and enhance exercise performance.[60,63–65] The improvements in performance following CHO ingestion were shown to result from the maintenance of blood glucose late in exercise. In particular, low

glycemic index (GI) foods, in comparison to high GI foods, were observed to prolong endurance during strenuous exercise by inducing less post-prandial hyperglycemia and hyperinsulinemia, to lower levels of plasma lactate before and during exercise, and to maintain plasma glucose and fatty acid at higher levels during exercise.[64,66,67]

The combination of a pre-exercise CHO meal and CHO ingestion during exercise may further enhance exercise performance. Ingested CHO can be oxidized at rates of up to 1 g/min (the apparent maximal oxidation rate of this exogenous substrate),[68] thus increasing performance during prolonged exercise. Ingesting a large quantity of medium chain triacylglycerol (as a strategy to increase plasma fatty acids) prior to exercise and/or together with CHO during exercise does not significantly affect total rates of CHO and fat oxidation and has no positive effect on performance.[69–71]

In summary, during low intensity exercise, fat predominates as energy substrate, whereas during high intensity exercise, CHO presents the major fuel for utilization. In absolute terms, CHO oxidation in fasted state gradually increases with exercise intensity, while fat oxidation increases from low to moderate exercise intensities and then decreases from moderate to high exercise intensities. Ingestion of a CHO meal before or during exercise enhances CHO utilization and endurance performance.

5.3. Exercise duration and substrate utilization

The pattern of substrate utilization changes with time, even when the exercise intensity remains constant. The longer the time spent exercising, the higher the contribution of fat as an energy substrate.

During low intensity exercise lasting longer than 2 h, the substrate utilization is not significantly altered as compared to those utilized during shorter bouts of low intensity exercise. On the other hand, during higher intensity levels, there is a progressive increase in reliance on plasma fatty acids.[56]

In prolonged exercise, plasma fatty acid oxidation increases in parallel with the depletion of glycogen storage in the working muscle.[52] The increased rate of fat oxidation is due to an increase in circulating level of catecholamine (adrenalin and noradrenalin), and a decrease in the circulating level of insulin. The catecholamines play a role in stimulating, and the insulin, in inhibiting the process of lipolysis.

Once the glycogen stores become depleted, blood glucose becomes the primary source of the limited CHO energy and is unable to support the required rate of energy production. The inability to maintain a desired level of performance (fatigue) is usually referred to as “hitting the wall”, where liver and muscle glycogen levels decrease severely, even with sufficient O_2 available to the muscles and almost unlimited potential energy from stored fat.

5.4. Effect of training on substrate utilization

Repeated episodes of physical activity performed over a longer period of time cause adaptations in the pulmonary, cardiovascular and neuromuscular systems that improve the delivery of O_2 to the mitochondria and enhance the control of metabolism within the muscle cells. These changes enable physically trained persons to exercise for longer at a given absolute exercise intensity, or to exercise at a higher exercise intensity for a given duration.[72]

The adaptations in metabolic and physiologic systems depend on the type of exercise overload imposed. The adaptation of the anaerobic training include increased intramuscular levels of anaerobic substrates (adenosine triphosphate (ATP), phosphocreatine, glycogen), increased quantity and activity of enzymes that control the anaerobic phase of glucose breakdown (phosphofructokinase, lactate dehydrogenase) and increased capacity to generate high blood lactate levels during maximal exercise.[51]

Likewise, regular aerobic training elicits specific endurance-training adaptations. For many years, it was thought that increased exercise capacities are exclusively the result of cardiovascular adaptations to exercise (enlarged left ventricular cavity of the heart, enhanced blood and stroke volume, increased cardiac output and decreased resting and submaximal exercise heart rate),[72] and thus improved O_2 delivery to the working muscles.

However, there is an increasing body of evidence, showing that endurance-training adaptations also involve an increase in mitochondrial size and number in aerobically-trained skeletal muscles (which improves their capacity to generate ATP by oxidative phosphorylation),[73] an increase in the level of aerobic system enzymes (which enables lower lactate accumulation during exercise), improved ability to oxidize triglycerides stored within active muscle, and proportional decrease in muscle glycogen and blood glucose utilization.[51,74]

Strikingly, most recent evidence shows that high intensity sprint interval training can induce remarkably similar changes in exercise capacity and selected muscle adaptations as traditional endurance-training.[75] Studies performed by Gibala et al. indicate that as little as 6 sessions of high intensity training over 2 weeks or a total of around 15 min of very intense exercise ($\sim$140 kcal) can increase skeletal muscle oxidative capacity and alter metabolic control during aerobic-based exercise.[75–77]

5.5. Exercise mode and fat utilization

Recent studies showed that fat oxidation during exercise can be influenced by the type of exercise performed. Maximal fat oxidation rates are shown to be significantly higher during running compared to the same intensity of cycling.[78,79] Women oxidize more fat than men at around 40% of VO_2max,[80,81] although gender difference does not seem to occur at higher intensities.[80] Fat oxidation was also shown to be augmented in exercise that combines aerobic and resistance training. Training that combines both aerobic and high intensity resistance exercise augments fat utilization during subsequent aerobic exercise compared to aerobic training only or training that combines aerobic and low-intensity resistance exercise.[82]

6. Conclusion

Carbohydrates and fats are oxidized simultaneously, but their relative contribution depends on a variety of factors. In healthy subjects, substrate utilization during rest is highly dependent on carbohydrate availability. During exercise, changes in substrate utilization are highly influenced by exercise duration and intensity. The longer the time spent exercising, the higher the contribution of fat as an energy substrate. With increasing intensity, the contribution of carbohydrates to energy expenditure increases and the contribution of fatty acids to energy expenditure decreases. Substrate utilization under the same exercise intensity is affected by the exercise mode, with fat oxidation being higher in running compared to cycling. Utilization of carbohydrates and fats during rest and exercise remains an important object of further investigation.

Conflict of interest

The author has no conflict of interest.

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