brief review

Balance of carbohydrate and lipid utilization during exercise: the "crossover" concept

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Brooks, George A., and Jacques Mercier. Balance of carbohydrate and lipid utilization during exercise: the "crossover" concept. *J. Appl. Physiol.* 76(6): 2253–2261, 1994.—The "crossover" concept represents a theoretical means by which one can understand the effects of exercise intensity and prior endurance training on the balance of carbohydrate (CHO) and lipid metabolism during sustained exercise. According to the crossover concept, endurance training results in muscular biochemical adaptations that enhance lipid oxidation as well as decrease the sympathetic nervous system responses to given submaximal exercise stresses. These adaptations promote lipid oxidation during mild- to moderate-intensity exercise. In contrast, increases in exercise intensity are conceived to increase contraction-induced muscle glycogenolysis, alter the pattern of fiber type recruitment, and increase sympathetic nervous system activity. Therefore the pattern of substrate utilization in an individual at any point in time depends on the interaction between exercise intensity-induced responses (which increase CHO utilization) and endurance training-induced responses (which promote lipid oxidation). The crossover point is the power output at which energy from CHO-derived fuels predominates over energy from lipids, with further increases in power eliciting a relative increment in CHO utilization and a decrement in lipid oxidation. The contemporary literature contains data indicating that, after endurance training, exercise at low intensities ($\leq$45% maximal O_2 uptake) is accomplished with lipid as the main substrate. In contrast, the literature also contains reports that are interpreted to indicate that during hard-intensity exercise ($\sim$75% maximal O_2 uptake) CHO is the predominant substrate. Seen within the context of the crossover concept these apparently divergent results are, in fact, consistent. Because in their training and competition most athletes perform at intensities that elicit >70–75% of maximum aerobic power, they are dependent on CHO for energy. Furthermore, lipid becomes the predominant fuel during recovery from exercises that result in glycogen depletion.

exertion; free fatty acids; glycogen; glucose; mitochondrial adaptations; sympathetic nervous system; recovery

WE PROPOSE a unifying concept that reconciles apparently conflicting interpretations of data on the balance of substrate [carbohydrate (CHO) and fat] metabolism during exercise in well-nourished individuals. According to the "crossover concept," prior endurance training results in muscular biochemical adaptations that enhance lipid oxidation as well as decrease the sympathetic nervous system (SNS) response to given submaximal exercise stresses. These adaptations promote lipid oxidation during mild- to moderate-intensity exercise. In contrast, increases in exercise intensity are conceived to increase contraction-induced muscle glycogenolysis, alter the pattern of fiber type recruitment, and increase SNS activity. Therefore the pattern of substrate utilization in an individual at any point in time depends on the crossover between the exercise intensity-induced responses (which increase CHO utilization) and the endurance training-induced responses (which promote lipid oxidation). The crossover point is identified as the power output at which energy derived from oxidation of CHO-based fuels predominates over that derived from lipids, with further increases in power eliciting a relative increment in energy from CHO utilization and a relative decrement in energy from lipid oxidation (Fig. 1). Specifically, by "CHOs" we refer to endogenous energy sources that include muscle and liver glycogen; blood glucose; and blood, muscle, and

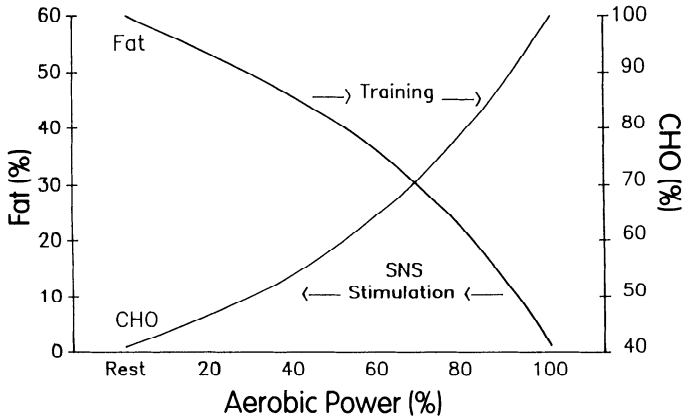

FIG. 1. Relative increase in energy derived from carbohydrate (CHO) utilization and decline in energy from oxidation of lipid (fat) utilization as function of relative power output. At crossover point, increments in relative exercise intensity result in increasingly greater dependence on CHO and less dependence on fat. Even though on absolute scale training results in rightward curve shifts, on relative basis training probably has minimal effects on curves relative to aerobic power. See text for explanation. SNS, sympathetic nervous system.

liver lactate. By "lipids" we refer to adipose and intramuscular triglycerides (TGs) as well as blood-borne free fatty acids (FFAs) and TGs. By "amino acids" we refer to free amino acids in blood, muscle, and liver pools, as well as the protein stores in which they are at equilibrium.

Throughout this brief review we use qualitative descriptors of exercise intensity. Specifically, "moderate"-intensity exercise is defined as a leg power output that elicits 50–55% of whole body maximal O_2 uptake ($\dot{V}O_{2\,max}$). "Mild"-intensity exercise elicits a lesser metabolic response (e.g., $\leq$45% $\dot{V}O_{2\,max}$), whereas "hard" exercise elicits a greater metabolic response than moderate-intensity exercise (e.g., $\geq$65% $\dot{V}O_{2\,max}$). Unless otherwise stated, by "training" we mean regularly performed endurance exercise at an intensity sufficient to induce both central circulatory and peripheral muscle mitochondrial adaptations. By "utilization" we mean disposal (disappearance) from blood or other energy substrate storage compartments. Utilization of CHOs can involve disposal through anaerobic glycolysis, gluconeogenesis, or oxidation. Disposal of lipids can involve oxidation or reesterification. Disposal of amino acids can involve oxidation or incorporation into protein. By "anaerobic glycolysis" we mean glycogenolysis or glycolysis leading to net lactate accumulation in blood, skeletal muscle, or some other compartment. By "oxidation" we mean oxidative decarboxylation and excretion in breath. By "gluconeogenesis" we mean conversion or reconversion to blood glucose. By "reesterification" we mean incorporation or reincorporation of fatty acids into TG. By incorporation into protein we mean amino acid flux into polypeptide and protein synthesis. Here the perspective is that, even though other pathways of substrate utilization are physiologically important during exercise, substrate disposal through oxidation is energetically by far the most important. Because, in terms of energy supply, catabolism of glucose and glycogen can yield energy anaerobically as well as aerobically, whereas lipid catabolism can yield energy only aerobically, we refer to lipid oxidation and CHO utilization.

As a necessary first step in developing our concept we have likely oversimplified the presentation of a complex problem. However, if a consensus can be achieved on the basic factors regulating crossover of substrate flux during exercises of graded intensities, then it will be possible to perform experiments necessary to describe how specific factors such as training and nutritional histories, environment, muscle fiber type, gender, hormone levels, and sensitivities to those hormones affect the pattern of substrate flux during exercise. In this brief review we cannot attempt an extensive survey of the effects of exercise intensity, exercise duration, training, environment, or dietary status on CHO-lipid interactions during exercise. Rather, we refer to the more extensive reviews of others (9, 48). In this paper we identify the significant work that we believe supports our concept.

HISTORICAL BACKGROUND

Since the "classic period" of exercise biochemistry that began in the late 1960s and progressed through the mid-1980s, a vast volume of data has accumulated that has been interpreted to mean that endurance exercise training increases the subject's capacity to oxidize lipids during exercise. Mainly the data can be described as offering indirect support for the conclusion of a training effect on the mix of energy substrates used during mild- to moderate-intensity exercise. Nevertheless, it is widely believed that an increased capacity of trained muscle to oxidize blood-borne FFAs and TGs, along with an increased capacity to access intramuscular TGs, results in glycogen sparing and increased exercise endurance (21, 28–30, 45, 47). The perspective articulated here is that, even though the data supporting the general conclusion are valid, their interpretation needs to be confined to the circumstances of mild- to moderate-intensity exercise. Likely, at the higher exercise intensities and power outputs used by athletes in training and competition, the absolute oxidation rates of all classes of energy substrates increase, with CHOs being the primary energy sources (21, 35, 43, 46, 52, 57). Dependence on lipids as fuels likely occurs in trained individuals during recovery from exercise that results in glycogen depletion.

In this brief review, emphasis is on CHO and lipid oxidation during submaximal (mild- to hard-intensity) exercise where the precision of measuring flux rates is probably greater and this interplay between lipid and CHO utilization occurs. However, some amino acids play important roles in supporting the substrate utilization patterns sustaining exercise (4, 37). In terms of overall energy flux during submaximal efforts, it can be stated that utilization rates of most amino acids are not affected during exercise. Of the several classes of amino acids, branched-chain amino acid oxidation increases during exercise, whereas the overall flux rates change little (27, 44). Training increases leucine oxidation during exercise, but the contribution to overall substrate oxidation is small ($\sim$1%) and the relative contribution to overall fuel supply decreases as exercise intensity increases (27). Amino acid metabolism during exercise has been reviewed separately, and the reader is encouraged to consult those sources (4, 37, 51, 56).

EFFECTS OF EXERCISE AND TRAINING ON GLUCOSE-FATTY ACID CYCLE ACTIVITY: SUBSTRATE FLUX AND THE CROSSOVER CONCEPT

The conceptual basis to understanding the balance of CHO and lipid metabolism during exercise as well as the interactions between exercise intensity and training status is that factors related to increments in exercise intensity act to increase relative utilization of CHO-derived fuels (Fig. 1). In contrast, prior endurance training results in muscular biochemical adaptations that enhance lipid oxidation and decrease SNS activity in response to given exercise stresses; these adaptations enhance the ability to oxidize all energy substrates, but overall the adaptations promote lipid, in contrast to CHO, oxidation. The factors that operate at high exercise power outputs include contraction-induced (adenosine 3′,5′-cyclic monophosphate-independent) muscle glycogenolysis, increased recruitment of more skeletal muscle including a greater proportion of fast glycolytic muscle fiber types, and increased SNS activity. Norepinephrine may stimulate hepatic glucose production (5) as well as stimulate lipolysis (47). Epinephrine amplifies the contraction-induced rate of muscle glycogenolysis leading to lactate formation (7, 14), thus supporting the use of lactate as a fuel source and gluconeogenic precursor (40, 57). Also, the acidic effect of lactate accumulation inhibits FFA mobilization (32), thus reducing muscle FFA uptake.

Central to the crossover concept is recognition of the essential role of flux rate on the pattern of substrate utilization during exercise. As exercise intensity increases from mild to moderate and then to greater levels of effort, depending on the form of exercise (i.e., running, swimming, cycling), energy demand increases as a power function of speed and work rate. The requirement that energy release meet the need at high exercise power outputs serves to cause a crossover to CHO-based fuels. This shift is due in part to the relatively greater abundance of glycolytic as opposed to lipolytic enzyme systems in all skeletal muscle. The shift to CHO at high power outputs is also due in part to a change in the pattern of fiber recruitment to involve fast glycolytic motor units (21). The increased metabolism in fibers of these motor units will not involve a proportional increase in fat oxidation but rather glycogenolysis and glycolysis leading to net lactate production (3, 14).

In the range of mild- to high-intensity continuous exercise, oxidative metabolism provides almost all of the energy transduction needed. In human subjects studied at rest and during graded exercise, arterial lactate appearance rate increases as a power function of O_2 uptake ($\dot{V}O_2$) (52). However, in the range of moderate- to hard-intensity exercise, muscle and blood lactate are elevated above resting levels but blood lactate concentration can be constant despite increased turnover and oxidation. Because most (70–80%) of the lactate appearing in the blood and blood-exchangeable pools is disposed of through oxidation (18, 43), $\dot{V}O_2$ represents most of the energy required for performance of muscle work. Therefore, energy production not represented in $\dot{V}O_2$ (i.e., "anaerobic" energy production) is minimal at exercise intensities less than the lactate threshold (6).

In the range of maximal intensity exercise, muscle and blood lactate levels rise continuously until the cessation of exercise. In this range of power output, anaerobic energy production occurs to a much greater extent than in hard exercise, but it is difficult to quantitate anaerobic energy production in maximal exercise as the mass and distribution of accumulated lactate are not measurable with current technology. However, for purposes of the present discussion, increasing lactate accumulation can be taken to represent increased CHO utilization and, thus, crossover to CHO dependency.

TRAINING INCREASES CAPACITY TO UTILIZE LIPIDS AS ENERGY SOURCES AT MODERATE EXERCISE INTENSITIES

In general, four sets of findings support the idea that prior endurance training increases lipid oxidation during sustained submaximal intensity exercise of defined duration. These are that training increases mass of the mitochondrial reticulum (15, 28, 29, 39), decreases the respiratory gas exchange ratio ($R = CO_2$ output/$\dot{V}O_2$) (21), spares muscle glycogen (1, 21, 36), and lowers circulating blood catecholamine and lactate levels during given exercise power outputs (3, 11, 12, 17, 22, 40, 59).

Training and muscle mitochondrial reticulum. At the level of skeletal muscle, training increases mitochondrial mass (28, 29), which we interpret to be an elaboration of the mitochondrial reticulum (15, 39), resulting in an increased capacity to oxidize fatty acids (45, 47). As recognized initially by Molé et al. (45), training increases the enzymes of FFA translocation, the tricarboxylic acid cycle, the β-oxidation pathway, and components of the electron transport chain necessary to oxidize fatty acids. More recently, it has become recognized that increased mass of the mitochondrial reticulum due to training allows increased lipid oxidation and given rates of tissue $\dot{V}O_2$ to be accomplished with higher ATP-to-ADP concentration ratios and citrate and acetyl-CoA levels. The net result of these training-induced effects is superior cellular "respiratory control," a downregulation of cytoplasmic phosphofructokinase kinase and pyruvate dehydrogenase, decreased net glycolytic flux, and increased lipid oxidation (14, 20). In terms of allosteric regulation, training may affect intramuscular levels of fructose 2,6-bisphosphate and malonyl-CoA, putative regulators of glycolysis (59). In other words, increasing the mitochondrial mass and capacity to utilize activated fatty acids should promote activity of the "glucose-fatty acid cycle" of Randle et al. (50). According to the crossover concept, during submaximal exercise at a given, or greater, power output, the relative oxidation of lipid will increase and of CHO will decrease after training.

Training and R. Observation of a lower gas exchange for exercise at a given submaximal power output after training is a highly reproducible observation (21). However, interpretation of the finding is dependent on several assumptions. One is that R equals the tissue respiratory quotient (RQ), which in turn equals the nonprotein RQ. In support of using R to evaluate training effects on the balance of fuel utilization during exercise, it is noted that after training blood lactate falls and pH is higher

and more stable, indicating a lesser disturbance to the body's bicarbonate pools (18). Although analysis of the effects of training on R seldom is accompanied by attempts to model changes of bicarbonate kinetics during exercise, use of "steady-state" conditions with stable Rs and blood lactate concentrations ensures that R approximates RQ. The data obtained under steady-state conditions showing a downward shift in R probably represent the strongest data available supporting the conclusion of enhanced lipid oxidation after training (21).

Muscle glycogen sparing. Biopsies of rat (1) and human (21, 36) limb skeletal muscle, before and after given exercise bouts, indicate that net muscle glycogen breakdown is less after than before training. This blunting of glycogenolysis due to training is most prominent during the rest-to-exercise transition than later in exercise. Overall a large volume of data indicates that training spares muscle glycogen during prolonged exercise (21).

Although the basic observation of glycogen sparing due to prior exercise training is well documented, studies on the mechanisms explaining the lesser net change are lacking. For instance, glycogen synthesis has been observed during exercise (J. L. Azevedo, S. L. Lehman, and G. A. Brouns, unpublished data), but the phenomenon is little studied. Similarly, little attention has been given to evaluating the pathways of glycogen metabolism during exercise before and after training. Recently, Donovan and Sumida (19) have challenged the concept that glycogen sparing is associated with increased lipid metabolism, and they have supplied data to indicate that increased uptake of blood glucose explains most of the muscle glycogen sparing observed in trained rats during moderate- to hard-intensity exercise.

Blood lactate after endurance training. After training, blood lactate concentration is lower at a given submaximal exercise power output than before training (3, 18, 22, 52, 57). Additionally, after training the net change in active muscle glycogen during a given exercise task is less than before training (21). These results are usually taken as evidence that lipid energy sources substitute for CHOs (i.e., muscle glycogen and blood glucose) and thereby spare glycogen and decrease lactate production. A decrease in glycogenolysis and attendant decrease in CHO utilization during exercise of a given or greater power output due to reduced SNS stimulation after training are illustrated by a leftward curve shift in the CHO oxidation curve and a rightward shift in the lipid oxidation curve (Fig. 1).

PROBLEMS WITH THE CONCEPT THAT ENDURANCE TRAINING INCREASES RELATIVE LIPID UTILIZATION AT ALL EXERCISE INTENSITIES

Palmitate turnover in men during hard-intensity exercise. Despite widespread belief that in trained individuals lipids represent important fuel sources for exercise, the literature contains a paucity of data relevant to this issue. Initially, published reports utilized dogs as experimental models (32–34). Dogs are highly aerobic carnivorous animals adapted for lipid and amino acid metabolism, making extrapolation of data from these studies to humans difficult. In contrast, despite extensive use of the laboratory rat as an experimental model, we know of no published reports showing increased FFA turnover and oxidation in exercise-trained vs. untrained rats. Despite initial progress (26), the literature on FFA turnover in trained vs. untrained humans is not much better, with two reports (25, 35) generally ignored. In physically fit subjects cycling at 70% $\dot{V}O_{2\,max}$, Jones et al. (35) observed a decrease in palmitate turnover compared with at rest. This result is consistent with those of Issekutz and Miller (32), who showed that there is decreased lipolysis and FFA turnover when lactic acidosis occurs in running dogs. Similarly, in men engaged in marathon running, Hall et al. (25) observed only a minor rise in palmitate turnover when the rate of glucose appearance increased twofold over resting values. Because in both of these reports on fit men engaged in moderate- to hard-intensity efforts $\dot{V}O_2$, CO_2 output, and total CHO oxidation increased ~15-fold compared with at rest, the relative contribution of FFAs, as indicated by palmitate turnover, to the overall metabolic response actually decreased during exercise. A small absolute increase but relative decline in lipid oxidation at relatively high power outputs, even in highly trained individuals, is predicted by the crossover concept.

Selection of the exercise paradigm. Critical to evaluating the effect of prior exercise training on patterns of substrate utilization during exercise is selection of the exercise testing paradigm. Specifically, it has often been the practice (e.g., see Refs. 11–13) to study subjects at the same absolute (as opposed to relative) power output before and after training. In such studies, R declines after training. Similarly, in the single published report on the subject, Coggan et al. (11) provided data to suggest that, as the result of training, glucose turnover declines in humans during mild- to moderate-intensity exercise. In our view these results showing a lower R, blood lactate accumulation, and rate of glucose appearance after training are due to the specific exercise protocols employed to date that have emphasized mild to moderate exercise intensities and have, therefore, missed the crossover to CHO dependency by not testing subjects at higher exercise intensities (Fig. 1).

Training-induced cellular adaptations that favor increased glucose utilization and glycogen sparing. As already noted, endurance exercise training increases the capacity to use all classes of energy substrates, not just lipids. With regard to blood glucose utilization, after endurance training muscle GLUT-4 concentration (31) and hexokinase activity (2) are increased. Most recently, it has been demonstrated that, after training, the capacity for gluconeogenesis is improved in rat livers studied in situ (53). Extrapolation of these data to the in vivo situation would predict that, at power outputs sufficient to raise arterial glucose concentration above resting levels, training adaptations that increase insulin action and hexokinase activity in muscle should favor glycogen sparing by increased blood glucose, not lipid, utilization (19, 57).

EFFECTS OF ENDURANCE TRAINING ON GLUCOREGULATORY HORMONE LEVELS

Whereas prolonged exercise leading to low blood glucose levels elicits strong SNS responses, exercise training dampens the initial endocrine responses to submaximal exercise (17, 24). Consequently, during exercise in highly trained subjects presented with given submaximal intensity exercise bouts, insulin falls less and glucagon and catecholamines rise less than before training (12, 17, 24, 42). These endocrine responses should spare muscle glycogen by increasing blood glucose utilization.

Effects of exercise and training on catecholamines. Of the many factors that affect substrate utilization, epinephrine is likely one of the most important. In resting individuals, it is known that there is a hierarchy of metabolic effects of epinephrine (10), with lipolytic, glycogenolytic, and insulin-suppressive effects occurring in sequence. Although the hierarchical effects of epinephrine are less well documented during exercise than during rest, it is known that during exercise of mild to moderate intensity circulating epinephrine levels rise little, if at all, compared with levels at rest (42). Moreover, for a given exercise power output, circulating epinephrine is lower in trained than in untrained subjects (17). As a result, during prolonged mild- to moderate-intensity exercise the lipolytic effects of epinephrine and other lipolytic hormones [e.g., growth hormone (54)] predominate in favor of lipid oxidation. However, at moderate- to hard-intensity exercise in the trained state, SNS stimulation occurs and catecholamines rise (17, 23, 24, 40, 42), with the rise in catecholamines being greater in highly trained than in less fit individuals (40). Under these conditions, epinephrine stimulates muscle glycogenolysis. Lactate is produced as the result of mass action (14), and gluconeogenesis is facilitated by availability of a gluconeogenic precursor. Concurrently, lactic acidosis acts to inhibit lipolysis (32). At the same time, norepinephrine rises, possibly stimulating hepatic glucose production (5, 7, 8), and epinephrine suppresses insulin release, allowing the gluconeogenic effects of glucagon on hepatic function to predominate. For these reasons, epinephrine likely plays a powerful role in determining the crossover point.

The view of a crossover effect on substrate utilization is supported by results recently provided by Green et al. (22). They observed a significant change in pattern of substrate utilization (i.e., lower lactate and R) after only a few exercise training bouts before circulatory or muscle mitochondrial adaptations occurred. Although Green et al. did not report catecholamine responses during exercise before and after minimal training, they did succeed in uncoupling changes in patterns of substrate utilization from mitochondrial or cardiovascular adaptations. In terms of the crossover concept, the results of Green et al. provide opportunity for insight into metabolic regulation. If with minimal training there is insufficient time for mitochondrial or circulatory adaptations to occur and yet SNS activity is suppressed, the pattern of substrate utilization will nevertheless change with crossover occurring at a higher power output than before training. Thus, with SNS downregulation more lipid will be used during moderate-intensity exercise even without benefit of other structural adaptations.

Interactive effects of epinephrine, insulin, and mitochondrial adaptations after endurance training. The crossover concept may be useful in terms of understanding the antagonistic effects of glucoregulatory hormones on substrate utilization after training. For instance, adipocytes from trained individuals demonstrate enhanced lipolysis in response to epinephrine (16). Additionally, it may be that training increases the sensitivity of intramuscular type L hormone-sensitive lipase activity to epinephrine (47, 48). However, it has also been observed in rats that after training the effect of insulin on suppressing plasma FFA concentration is increased (41). Therefore, resolution of these apparently conflicting effects of training on FFA mobilization and oxidation during exercise remains to be achieved. The crossover concept would predict that because during exercise at a given power output insulin will be higher (i.e., fall less than before training), glucagon will be lower, and epinephrine will rise less (possibly not increase above resting levels during an exercise at an intensity eliciting 40–50% of posttraining $\dot{V}O_{2\,max}$), enhancement of lipid oxidation would be dependent on intramuscular adaptations.

As a consequence of dampened glucoregulatory hormone responses after training (17, 24), during exercise at a given mild- to moderate-intensity power output circulating FFA concentration is less (11). Because FFA disposal rate is known to be concentration dependent (32–34), lower circulating FFAs after training would tend to hamper FFA uptake and oxidation. Therefore, increased capacity for lipid oxidation for a given submaximal power output after training may depend on ability of the expanded mitochondrial reticulum to suppress glycolysis and increase uptake of fatty acyl-CoA from intracellular TG stores (see above).

The effects of prior endurance training that enhance lipid oxidation during mild- to moderate-intensity exercise illustrate the intricacy of metabolic regulation. By suppressing SNS activity and providing for superior respiratory control in skeletal muscle, training acts to facilitate lipid oxidation, suppress muscle glycogenolysis, and avoid dependence on muscle glucose uptake during mild- to moderate-intensity exercise. However, it has been noted previously (58), and reconfirmed more recently (46), that athletes train to compete at high power outputs and intensities where CHO-derived fuels, not lipids, predominate. When individuals are stressed to perform at high levels of effort, then SNS stimulation and alterations in muscle fiber type recruitment result in crossover to predominant dependence on glucose, glycogen, and lactate as fuel sources regardless of training state (Fig. 1).

DOES ENDURANCE TRAINING INCREASE CAPACITY FOR GLUCONEOGENESIS?

The crossover concept may be of use with regard to apparently conflicting data over the effects of endurance training on blood glucose appearance rate and the rate of hepatic gluconeogenesis during exercise. The literature

contains at least two reports (19, 57) that indicate the blood glucose appearance rate is higher in trained than in untrained rats during sustained submaximal exercise. It is also known that during exercises eliciting ≥60% $\dot{V}O_{2\,max}$ arterial glucose concentration and rate of appearance are higher in trained than in untrained men (40). After training, insulin falls less during a given exercise task than before training (13, 17, 24) and insulin action is greater (38). Again, after training, muscle GLUT-4 concentration (31) and hexokinase activity (2) are increased and the hepatic capacity for gluconeogenesis is improved (53). These training adaptations favor increased blood glucose utilization and glycogen sparing, not increased lipid oxidation.

On the basis of the results just described, it is reasonable to conclude that after endurance training blood glucose appearance rate and the rate of hepatic gluconeogenesis are increased during exercise. However, after training, when men exercised at 50% of the pretraining $\dot{V}O_{2\,max}$ (now 40–45% of posttraining $\dot{V}O_{2\,max}$), blood glucose concentration and turnover rate were decreased compared with pretraining values (11). How then are these apparently conflicting results to be reconciled?

According to the crossover concept, if after training the relative intensity of the exercise task were reduced, sympathoadrenal responses to exercise would also be reduced. Lower circulating epinephrine levels will attenuate glycogenolysis, glycolysis, and lactate production. Lower circulating lactate will result, and the liver will not have available an increased supply of its main gluconeogenic precursor, lactate. Therefore, according to the hypothesis under discussion, after training mild to moderate exercise will be accomplished with lesser rates of glycogenolysis and gluconeogenesis. Overall, metabolism of lipids will be facilitated at these exercise intensities.

The limited data available at present support the view that at exercise intensities above the crossover point sympathoadrenal responses are as great or greater than before training (40). However, even though high-intensity exercise appears to be associated with little change in lipid metabolism in comparison to rest (24, 34), necessary experiments to establish effects of SNS stimulation in shifting the balance of substrate utilization from lipid to CHO have not yet been done.

LACTATE ACCUMULATION AND THE CROSSOVER POINT

As already suggested, exercise power outputs defined as hard to maximal are accompanied by increases in SNS stimulation and increased recruitment of more skeletal muscle and an increased proportion of fast twitch fibers. These factors act to stimulate glycogenolysis, glycolysis, and lactate production. In exercises requiring continually increasing power outputs, there will occur a point where the lactate disposal rate will be unable to keep pace with rising lactate production. As a consequence of disposal being less than production, the lactate threshold is reached, with muscle and blood accumulation increasing with degree of effort (3).

Potential for using blood lactate accumulation (i.e., the lactate threshold) as a marker for the crossover point may be found in the results of a recent report (12) in which the investigators described differences in blood glucose kinetics between subjects with "low" and "high" lactate thresholds. High-threshold subjects were defined as those who experienced a steep rise in blood lactate only in response to relatively high-intensity exercise, whereas low-threshold subjects were those who responded with a rise in blood lactate in response to mild- to moderate-intensity exercise. Although SNS responses were not reported, the data obtained are consistent with heightened sympathoadrenal responses in low-threshold subjects who demonstrated higher blood glucose turnover than did high-threshold subjects. Similarly, in another recent report employing similar experimental design (13), the same group of investigators found elevated levels of citrate in muscles of trained subjects exercising at a power output that elicited 50% of the pretraining $\dot{V}O_{2\,max}$. However, muscle glucose 6-phosphate levels were unchanged compared with pretraining levels, leading the investigators to conclude that an attenuation in the glycolytic flux before the phosphofructokinase step resulted from training. This result is consistent with a lesser epinephrine response to a given exercise task after training. The results are also inconsistent with the suggested training effect of raising glucose-fatty acid cycle activity in humans.

At present, the precise meaning of changes in blood lactate concentration in response to exercise or environmental conditions is extremely complex, and it is clear that lactate flux rates cannot be determined solely from changes in blood concentration (3, 7, 43, 52). Arterial lactate concentration rises in response to progressive intensity exercise (42), but sustained exercise at the power output that elicits the lactate or ventilatory thresholds during progressive exercise is not likely to result in a constant elevated lactate concentration. It will remain to be determined which, if any, blood lactate concentration or change in blood lactate concentration will correlate with the crossover point.

GLYCOGEN DEPLETION AND THE CROSSOVER POINT

During prolonged exercise, even in the trained state, hepatic and skeletal muscle glycogen depletion occurs (21). Regardless of training state, a reduction in glycogen reserves as the result of prolonged exercise, or inadequate preexercise nutrition, may limit glycolytic flux during subsequent exercise. According to the crossover concept (Fig. 1), the effect of glycogen depletion on the balance of substrate utilization during exercise would be illustrated by a leftward shift in the CHO oxidation curve and a corresponding rightward shift in the fat oxidation curve. For both trained and untrained individuals, glycogen depletion will be accompanied by a decrease in the power output that can be sustained.

In addition to prolonged exercise leading to glycogen depletion and a consequent shift toward fat metabolism, it is also known that high-fat diets containing adequate calories can result in physiological adaptations to increase lipid oxidation during rest and exercise (49). In humans, this adaptation period of minimal CHO consumption requires several weeks, if not months. Subjects

adapted to high-fat diets can apparently maintain blood glucose homeostasis during prolonged submaximal exercise (49), but it is unclear that adaptation to a high-fat diet would permit exercises of sustained high power output such as used in athletic competition.

IS THE FLUX OF ENERGY SUBSTRATES DIFFERENT IN WOMEN AND MEN?

It has been proposed that, in comparison to men, women possess superior capacities for lipid oxidation and exercise endurance. Such ideas apparently stem from notable improvements in marathon and ultramarathon running by women and the ability of contemporary female swimmers to surpass the times of men a generation ago. Moreover, the abilities of women to carry fetuses to term, to endure labor, and to nurse infants for extended periods is not within the experience of men. Physiological and anthropometric differences between the sexes as well as differences in lifestyles have made comparisons of lipid oxidation in men and women extremely difficult. As emphasized by Tarnopolsky et al. (55), male-female comparisons require matching of subjects' training status and exercise performance, standardizing diet, and testing of females during a standard (e.g., midfollicular) phase of their menstrual cycles. With attention to these important parameters, but recognizing the impossibility of matching subjects on the basis of absolute power outputs, Tarnopolsky et al. have observed in trained women compared with men a lower R, a lower circulating epinephrine level, and lesser muscle glycogen depletion during running 90–101 min at 65% $\dot{V}O_{2\,max}$. Despite previous reports that yielded conflicting results, it may be that women possess a blunted sympathetic response to exercise and are, therefore, less apt to demonstrate crossover to CHO energy dependency during exercise than men. Unfortunately, with regard to our concept, we know of no published attempts to measure and differentiate metabolite flux rates in men and women during exercise. Such data need to be supplied.

RECENT REPORTS

Several reports have appeared recently that support the crossover concept as articulated here. In brief, results of those reports are summarized below.

Van Baak et al. (57a) gave Intralipid and heparin to male subjects during exercise at 70% $\dot{V}O_{2\,max}$. Although Intralipid and heparin treatment increased circulating levels of nonesterified fatty acids and glycerol several times over those in saline infusion control experiments, exercise endurance was not significantly improved when circulating FFA levels were raised. Seen within context of the crossover concept, the result is not surprising because during exercise at 70% $\dot{V}O_{2\,max}$ the relative effort is in the range of hard exercise, which is primarily dependent on CHO energy sources. Thus, the lack of effect of an extremely large increase in FFA delivery to working muscle is understood because muscles were CHO dependent at the exercise intensity studied.

In their paper, Romijn et al. (51a) reported on glucose, glycerol, and FFA kinetics in five highly trained men exercising at 25, 65, and 85% $\dot{V}O_{2\,max}$. Highly trained subjects were used to obtain sufficient exercise endurance to obtain reliable isotope tracer data during hard exercise and also to optimize the ability to utilize lipids as energy sources. Consistent with the crossover concept, plasma FFA appearance decreased and glucose appearance increased in direct proportion to exercise intensity. Furthermore, despite a threefold increase in energy expenditure, total fat oxidation (as measured by indirect calorimetry) was no different during exercise at 85% than at 25% $\dot{V}O_{2\,max}$. Thus, in their report Romijn et al. not only demonstrate the effect of exercise intensity in changing the balance of lipid and CHO but also show that even highly trained subjects shift to CHO energy sources during hard-intensity exercise.

Finally, in their report, Martin et al. (42a) studied the effects of training on FFA turnover in 10 men and 3 women during an exercise power output that elicited (from their Tables 1 and 2) 58% $\dot{V}O_{2\,max}$ before training and 46% $\dot{V}O_{2\,max}$ after training. According to our paradigm, subjects were studied at moderate-intensity exercise before training and mild-intensity exercise after training. During exercise after training, the exercise respiratory R decreased, which was interpreted to indicate increased total lipid oxidation. However, after training, plasma FFA turnover and oxidation also decreased. The investigators concluded that the training-induced decreases in plasma FFA concentration and turnover were due to a reduction in sympathetic stimulation during exercise at the same external power output. Because of divergent results obtained using indirect calorimetry and tracer palmitate, the investigators also concluded that after training the increased ability to oxidize lipid was due to increased utilization of intramuscular lipid. No data on SNS responses or lipolytic rate were available, but the data from indirect calorimetry demonstrate that shifting the exercise intensity to a relatively lesser level increases total lipid oxidation if not FFA oxidation.

As with the results contained in previous reports, seen within the context of the crossover concept, the apparently divergent results reported recently by van Baak et al. (57a), Romijn et al. (51a), and Martin et al. (42a) are consistent with each other as well as with results contained in previous reports of the effects of exercise intensity and endurance training on the balance of lipid and FFA oxidation.

SUMMARY

In summary, the crossover concept may explain and reconcile seemingly divergent results in the literature concerning the balance of CHO and lipid metabolism during exercise. During rest and mild- to moderate-intensity exercise, lipids predominate as energy sources, especially in the endurance-trained state. However, as exercise intensity increases, there occurs a shift in substrate utilization toward CHO, even in the trained state. Thus the pattern of substrate utilization during exercise depends on several factors, one of which is the exercise intensity relative to the crossover point where SNS-initiated responses predominate or where fast glycolytic fibers are recruited. Ultimately, to support increased energy substrate flux rates necessary to support muscle con-

traction in hard exercise, SNS-initiated events along with those initiated by actions of insulin and glucagon, blood lactate level, dietary and exercise histories, size of glycogen depots, cardiac output, blood flow distribution, muscle recruitment, and muscle mitochondrial mass interact to determine coarse and fine settings of substrate utilization patterns during exercises of graded intensities. Our recognition that at low relative exercise power outputs humans depend on lipid oxidation, whereas at high power outputs there occurs a shift toward increased CHO utilization has been made previously (9). In view of recent developments, our observations and summary may lay the basis for future experiments to measure glucose, glycerol and FFA kinetics, glycogen depletion patterns, and the levels of glucoregulatory hormones and putative regulators of substrate flux during exercises of graded intensities after short- and long-term training. Such experiments are required to substantiate the crossover concept. During the interim, the concept represents a theoretical construct with which apparently conflicting data can be reconciled.

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