Mol. Cells, Vol. 23, No. 3, pp. 272-279

Minireview

Molecules and Cells

Regulation of Blood Glucose Homeostasis during Prolonged Exercise

Sang-Hoon Suh*, Il-Young Paik, and Kevin A. Jacobs[1]

Laboratory of Sports Physiology and Medicine, Department of Physical Education, Yonsei University, Seoul 120-749, Korea;
[1] Department of Exercise and Sport Sciences, University of Miami, 5202 University Drive, FL 33146, USA.

(Received March 16, 2007; Accepted April 2, 2007)

The maintenance of normal blood glucose levels at rest and during exercise is critical. The maintenance of blood glucose homeostasis depends on the coordination and integration of several physiological systems, including the sympathetic nervous system and the endocrine system. During prolonged exercise increased demand for glucose by contracting muscle causes to increase glucose uptake to working skeletal muscle. Increase in glucose uptake by working skeletal muscle during prolonged exercise is due to an increase in the translocation of insulin and contraction sensitive glucose transporter-4 (GLUT4) proteins to the plasma membrane. However, normal blood glucose level can be maintained by the augmentation of glucose production and release through the stimulation of liver glycogen breakdown, and the stimulation of the synthesis of glucose from other substances, and by the mobilization of other fuels that may serve as alternatives. Both feedback and feedforward mechanisms allow glycemia to be controlled during exercise. This review focuses on factors that control blood glucose homeostasis during prolonged exercise.

Keywords: Exertion; Glucose Kinetics; Homeostasis; Oxygen Consumption; Training.

Introduction

Under normal circumstances, many physiological control mechanisms ensure that there is a relatively close matching of the uptake of glucose (i.e., glucose rate of disappearance; R_d) by tissues and the appearance of glucose (i.e., glucose rate of appearance; R_a) in the bloodstream. This matching of uptake and appearance, reflected by a relatively constant blood glucose concentration over a wide range of circumstances, is controlled by regulatory factors governing both uptake and production (Wolfe, 1992). The maintenance of nearly normal blood glucose levels is always of primary importance. Normal blood glucose concentrations are in the range of 4–5.5 mM (90–100 mg/dl) and are required for optimal function of the brain and nervous system. Exercise causes increased glucose uptake from the blood. During exercise, blood glucose level can be maintained or increased by augmented release of glucose from the liver and kidneys into blood, as well as by the mobilization of other fuels that may serve as alternatives (Brooks *et al.*, 2005). The increase in hepatic glucose output is accomplished through a combination of feedback (Geor *et al.*, 2000; McConell *et al.*, 2000) and feedforward (Kjaer *et al.*, 1986; 1991) regulatory controls. The coordinated physiological response to maintain blood glucose homeostasis during exercise is governed by hormonal regulation, autonomic nervous system, and alterations in enzyme activities (Brooks *et al.*, 2005).

This review focuses on factors that control blood glucose homeostasis during prolonged exercise. Especially, it will include the following aspects: 1) regulation of skeletal muscle glucose uptake, 2) regulation of hepatic glucose production, and 3) effects of endurance training on glucose kinetics.

Regulation of skeletal muscle glucose uptake during exercise

Exercise is a potent stimulus for skeletal muscle glucose uptake. In healthy, post-absorptive individuals, glucose uptake from the blood satisfies 15–30% of the energy requirement of the working muscle during moderate exercise (Wahren *et al.*, 1971), which can increase to 40% during high intensity exercise. The work rate-dependent

* To whom correspondence should be addressed.
Tel: 82-2-2123-6187; Fax: 82-2-2123-6187
E-mail: ssh@yonsei.ac.kr

increase in glucose uptake is disproportionately greater at intensities greater than 50% $\dot{V}O_{2max}$ (Cooper *et al.*, 1989; Wahren *et al.*, 1971). The increase in skeletal muscle glucose uptake during exercise results from a coordinated increase in rates of glucose delivery, membrane glucose transport, and intracellular substrate flux through glycolysis (Rose and Richter, 2005). The magnitude of the increase in muscle glucose uptake is influenced by both exercise intensity and duration. Probably, the most influential factor for the magnitude of increase in muscle glucose uptake during exercise in the post-absorptive state is exercise intensity, with skeletal muscle glucose uptake being greater at higher exercise intensities (Romijn *et al.*, 1993; Wahren *et al.*, 1978). This is probably due to a combination of greater fiber recruitment (Gollnick *et al.*, 1974) as well as higher metabolic stress on active muscle fibers (Ihelemann *et al.*, 1999a; 1999b) at higher exercise intensities. During exercise, the major metabolic fate of blood glucose after entry into skeletal muscle cells is glycolysis (Williams *et al.*, 1995; Zinker *et al.*, 1993) and subsequent oxidation (Jeukendrup *et al.*, 1999a; Zinker *et al.*, 1993).

Glucose transport across the muscle cell membrane occurs by facilitated diffusion in a process that is not energy dependent and exhibits Michaelis-Menten saturation kinetics, thereby suggesting the presence of a membrane carrier of transporter. Muscle glucose transport capacity sets the rate of membrane glucose transport at any transmembrane glucose gradient. Skeletal muscle expresses multiple isoforms of glucose transporters. During exercise the most important glucose transporter is GLUT4, because systemic (Ryder *et al.*, 1999) and muscle-specific (Zisman *et al.*, 2000) GLUT4 knockout abolishes contraction-stimulated glucose uptake, at least when studied *in vitro*. Several studies suggest that glucose transport is rate limiting for glucose uptake into muscle during exercise. Membrane transport capacity depends upon the number and possibly intrinsic activity of the glucose transporter proteins in the sarcolemma. Many studies have demonstrated that increase in glucose transport is due to an increase in the number of GLUT4 transporter proteins in the plasma membrane, as a result of translocation from and intracellular storage site (Goodyear *et al.*, 1990; 1991). Because the increase in muscle glucose transport and uptake is often larger than the increase in plasma membrane glucose transporter number, it has been suggested that there is also an increase in the intrinsic activity of glucose transporter (Goodyear *et al.*, 1990).

Contraction and insulin both increase the transport of glucose into muscle cells. Constable *et al.* (1988) have observed that the effects of insulin and contraction in muscle are additive, implying that insulin and exercise activate glucose transport via different mechanisms. There is evidence that there are distinct contraction and insulin-responsive GLUT4 vesicle pools in skeletal muscle (Douen *et al.*, 1990; Lemieux *et al.*, 2000; Ploug *et al.*, 1988) and that the molecular signals that trigger increased glucose transport and surface membrane GLUT4 (Fig. 1) are different when comparing insulin and contraction stimulation (Ihelemann *et al.*, 1999a; Wright *et al.*, 2004). Exercise increases the sensitivity of skeletal muscle to the action of insulin, which together with increased insulin flow due to enhanced muscle flow, may overcome a reduction in plasma insulin levels. Furthermore, insulin affects muscle glucose uptake via its inhibitory effects on adipose tissue lipolysis and muscle glycogenolysis (Yamatani *et al.*, 1992).

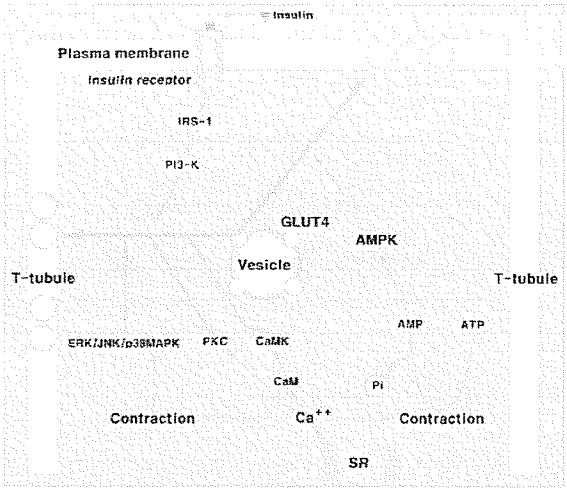

Fig. 1. Potential mechanisms by which insulin and contractions stimulate GLUT4 translocation from intracellular pools to the plasma membrane and transverse tubules (T-tubules) in skeletal muscle. Insulin-stimulated GLUT4 translocation may involve insulin receptor substrate 1 (IRS-1) and phosphatidylinositol 3-kinase (PI 3-K). Contraction-stimulated GLUT4 translocation may involve mitogen-activated protein kinase (MAPK; ERK, JNK, p38 MAPK). The contraction signal is probably initiated by release of calcium (Ca^{++}) from sarcoplasmic reticulum (SR) and may involve calmodulin (CaM), Ca^{++}-CaM dependent protein kinase (CaMK), and protein kinase C (PKC).

Recent studies using genetic manipulation to alter the expression of proteins involved in glucose transporter and metabolism have shed some light on the possible limiting steps in glucose uptake during exercise. It has been demonstrated that neither GLUT4 overexpression nor partial knockout alter exercise-stimulated increases in skeletal muscle glucose uptake *in vivo* (Fueger *et al.*, 2004a; 2004b), suggesting that only a percentage of the total GLUT4 pool is required for the increase in surface membrane permeability with exercise. Further studies using mice with skeletal muscle hexokinaseII (HKII) overexpression or partial knockout implicate an important role for HKII in the regulation of glucose uptake by working murine muscle *in vivo* (Fueger *et al.*, 2003; 2004a; 2004b).

However, there is little evidence that skeletal muscle HK activity is altered by acute contractile activity or exercise, and that there have not been studies examining the relationship between HK activity and glucose uptake with exercise.

Despite considerable research, relatively little is known about how exercise regulates skeletal muscle glucose transport. Calcium (Ca^{++}) has been recognized as a stimulator of glucose transport in muscle (Holloszy, 2003), although the down stream events that ultimately increase glucose transport have not been fully described. Ca^{++} may act via signaling pathways sensitive to Ca^{++} such as the conventional isoforms of protein kinase C (PKC α, β, γ) and the calcium/calmodulin-dependent protein kinase (CaMK). It has recently been demonstrated that exercise increase CaMK activity in human skeletal muscle (Rose and Hargreaves, 2003) and that inhibiting CaMK reduces glucose transport during contractile activity in incubated muscle (Wright *et al.*, 2004). The signaling through CaMK isoforms is probably related to the motor nerve activity and could be regarded as a feedforward regulation. Recently, much evidence has accumulated that the decrease in high-energy phosphates (~P) induced by contractions plays a major role in the activation of muscle glucose transport. This effect is mediated by AMP-activated protein kinase (AMPK) by the decrease in phosphocreatin (PCr) and adenosine triphosphate (ATP) and the increase in adenosine monophosphate (AMP) during contractions (Hayashi *et al.*, 2000; Mu *et al.*, 2001).

Another signal that potentially regulates glucose transport in muscle during exercise is mitogen-activated protein kinases (MAPK). MAPK kinases, including extracellular regulated kinases (ERK) and the stress-activated protein kinases, JNK and p38 MAPK, are activated by insulin and exercise (Ryder *et al.*, 2001; Sakamoto and Goodyear, 2002). Although ERK activation has been implicated in the stimulation of glucose transport by 5-aminoimidazole-4-carboxamide 1-β-D-ribofuranoside (AICAR) and exercise (Chen *et al.*, 2002), inhibiting a kinase upstream from ERK does not affect glucose transport during muscle contraction (Wojtaszewski *et al.*, 1999). More studies are required to elucidate the importance of MAPK pathways in activating glucose transport during exercise.

Regulation of hepatic glucose production during exercise

Maintaining adequate blood glucose supply is critical during exercise because it constitutes an appreciable fraction of the fuel for the working muscle and, as is the case at rest, supplies virtually all the fuel for the central nervous system. During the early stages of exercise, muscle glycogen is the chief source of energy for contraction, whereas circulating glucose and non-esterified fatty acids become essential with increasing exercise duration. An increase in exercise intensity amplifies the need for carbohydrates, and intra- and extra-muscular sources of glucose are utilized at greater rates (Brooks and Mercier, 1994). Despite the reliance of the working muscle on glucose, arterial levels are generally constant.

The liver plays an important regulatory role in maintaining blood glucose homeostasis by matching the increased rate of muscular glucose utilization with a quantitatively equal rate of glucose production. The tracer methodology to measure glucose flux (production and utilization) is shown in Fig. 2. This task takes on added complexity during prolonged exercise, since the energy requirement at a given work intensity is constant, but hepatic glycogen stores decrease. Thus, to maintain glucose homeostasis and sustain glucose delivery to muscle under these conditions, the liver must conserve carbon-based compounds, such as lactate, glycerol, and certain amino acids by channeling them into the gluconeogenic pathway.

During moderate intensity exercise, the blood glucose level remains relatively constant, despite a marked exercise-induced rise in peripheral uptake of glucose in contracting muscle uptake (Kjaer *et al.*, 1991), and a major drop in blood glucose is not observed unless exercise is prolonged for several hours (Ahlborg *et al.*, 1974). This indicates that the exercise-induced rise in hepatic glucose output matches the increased glucose uptake by contracting skeletal muscle as long as sufficient stores of glycogen are present in the liver. In contrast, if exercise becomes more intense, blood glucose is usually found to increase in humans, indicating that the hepatic glucose output exceeds the peripheral glucose uptake (Kjaer *et al.*, 1991). This confirms the hypothesis that mechanisms other than feedback regulation to maintain euglycemia are involved in the mobilization of glucose from the liver during exercise.

Hepatic glucose production during exercise: glycogenolysis and gluconeogenesis

In the transition from rest to exercise, liver glucose production increases due to an enhancement of both glycogenolysis and gluconeogenesis. In the early stages of fasting and during the initial stages of moderate and high intensity exercise, almost the entire increase in splanchnic glucose output is caused by an accelerated hepatic glycogenolysis (Hultman and Nilsson, 1971; Sonne *et al.*, 1987). Liver glycogenolysis occurs following the activation of glycogen phosphorylase and simultaneous inactivation of glycogen synthase through a series of phosphorylation reactions initiated by hormones such as glucagon and norepinephrine. The contribution of glycogenolysis is demonstrated by an exercise-induced reduction in liver glycogen content both in the rats (Sonne *et al.*,

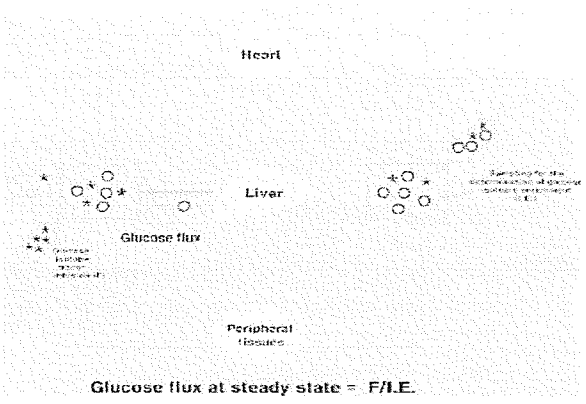

Fig. 2. Tracer methodology to measure glucose flux. With the continuous infusion of isotope tracer, such as [6,6-^{2}H]glucse, and [^{13}C]glucose, and by measuring the plasma glucose isotopic enrichment at steady state, it is possible to determine the glucose rate of appearance (glucose R_a) from the dilution of the infused glucose isotope tracer. If the tracee (i.e., endogenously produced glucose) concentration does not change over time, glucose rates of appearance and disappearance (glucose R_d) are the same.

1987) and in humans (Hultman and Nilsson, 1971). The liver glycogen content influences the magnitude of glucose output during exercise. During treadmill running a correlation was found between the rise in hepatic glucose output and liver glycogen levels, indicating that liver glycogen concentration is an important determinant of liver glycogenolysis and, therefore, of glucose production (Sonne and Galbo 1986; Sonne *et al.*, 1987). In trained men, liver glycogen contents are larger compared with physically untrained counterparts (Galbo *et al.*, 1975). Hepatic glucose output during exercise was greater in trained than in untrained rats (Brooks and Donovan, 1983) and greater in endurance trained athletes than in untrained healthy control subjects when groups were compared at identical relative workloads (Kjaer *et al.*, 1987). Therefore, the glycogenolytic activity and thereby the glucose mobilization from the liver during exercise is dependent on the glycogen of the liver.

Hepatic gluconeogenesis is as important as glycogenolysis. It has been estimated that gluconeogenesis accounts for ~20% of glucose production at rest and during low-to moderate-intensity exercise in humans (Stanley *et al.*, 1988) but accounts for 40–70% glucose production under similar conditions in rats (Brooks and Donovan, 1983). The increase in liver gluconeogenesis during prolonged exercise is important for the conversion of glycerol, lactate, and amino acids into glucose in order to delay depletion of liver and muscle glycogen. The rate of gluconeogenesis is mainly controlled by the activities of the unidirectional enzymes, phosphoenol pyruvate carboxylase (PEPCK), fructose 1,6-bisphosphatase (FP2ase), and glucose 6-phosphatase (G6Pase). (Raddatz and Ramadori, 2007). The gene transcription of these gluconeogenic enzymes is controlled by hormones, mainly insulin, glucagons, and glucocorticoids. While insulin inhibits gluconeogenesis by suppressing the expression of PEPCK and G6Pase, glucagons and glucocorticoids stimulate gluconeogenesis, thereby hepatic glucose production by inducing these genes (Raddatz and Ramadori, 2007). When gluconeogenesis is blocked in rats by administration of mercaptopicolinic acid (MPA), exercise endurance time is diminished by approximately 30% in both trained and untrained rats (John-Adler *et al.*, 1986). Turcotte *et al.* (1990) have demonstrated that MPA-treated rats have no measurable glucose recycling, and decreased blood glucose concentration (35%) and increased lactate concentration (160%) during exercise.

The absorptive state of the organism influences the relative importance of gluconeogenesis. While glycogenolysis occurs within 2–6 h after a meal, gluconeogenesis has a greater importance with prolonged fasting. In subjects who fasted for 60 h, almost all of the increase in splanchnic glucose output during mild exercise is due to uptake gluconeogenesis precursors (Bjorkman *et al.*, 1981). In contrast, if subjects receive glucose before exercise, a diminished splanchnic uptake of gluconeogenesis precursors is observed, most likely resulting in a reduced contribution of gluconeogenesis (Ahlborg and Felig, 1977).

Feedback regulation

Feedback mechanisms have been considered to be very important for a precise matching of hepatic glucose output to the increased glucose requirements of contracting muscles. It has been suggested that a major regulating mechanism is a change in blood glucose levels per se, reflecting changes in need for substrate mobilization. In support of this, infusion of glucose during exercise, in order to mimic the exercise-induced increase in hepatic glucose production in control experiments, resulted in an abolition of the endogenous glucose production during moderate intensity exercise [60% maximal oxygen consumption ($\dot{V}O_{2max}$)] in both humans (Jenkins *et al.*, 1985) and rats (Vissing *et al.*, 1988). The fact that glucose infusion in these experiments resulted in only a very moderate change in plasma glucose (4–5 mg%) indicates that hepatic glucose production is very sensitive to feedback signals and furthermore, that signals that contribute to an exercise-induced increase in glucose production can be inhibited by glucose infusion. Some studies using glucose ingestion have shown total abolishment of glucose production in exercising humans (Jeukendrup *et al.*, 1999b), some have shown a reduction in the exercise-induced increase in R_a (Geor *et al.*, 2000; McConell *et al.*,

2000), and finally some have shown an absence of exercise-induced hepatic glucose production under hyperthermic conditions (Angus *et al.*, 2001). This indicates that feedback signals are active during muscular contraction, and are responsible for the exercise-induced increase in mobilization of glucose.

Feedforward regulation

Several studies have found that glucose concentration dose not decrease, but rather increase, during intense exercise. This has been found to be caused by an exercise-induced rise in hepatic glucose production that exceeds the rise in peripheral glucose uptake in both exercising rats (Sonne and Galbo, 1985) and humans (Kjaer *et al.*, 1986; 1991). This mismatch between glucose production and peripheral glucose uptake is more pronounced with increasing work intensity (Kjaer *et al.*, 1986; 1991) and early in exercise compared with late in exercise (Kjaer *et al.*, 1987; Sonne and Galbo, 1985). This indicates that mobilization of hepatic glucose in response to exercise is determined, in part, by activity in motor centers in the central nervous system (central command) and that glucose production is subject to feedforward rather than feedback regulation.

It is apparent that there are numerous mechanisms that may activate glucoregulatory processes during exercise. One of the main difficulties in deciphering the contributions of feedback and feedforward regulation is that more than one mechanism may act simultaneously. As a consequence, the effect of an absence of one mechanism, whether it is abolished experimentally or through disease or injury, may be difficult to identify because of compensation from an alternate pathway.

Effects of endurance training on glucose kinetics

Both longitudinal and cross-sectional exercise training studies reveal that glucose utilization during exercise is decreased compared to the untrained state at the same absolute exercise intensity (Carter *et al.*, 2001; Coggan *et al.*, 1995; Miller *et al.*, 2002; Richter *et al.*, 1998; van Loon *et al.*, 1999). Recently, several longitudinal studies reported that endurance training at the same relative exercise intensity results in similar whole body glucose kinetics (Bergman *et al.*, 1999; Friedlander *et al.*, 1997; 1998; Miller *et al.*, 2002). Furthermore, by using arterial-venous (a-v) balance the same investigators showed that active skeletal muscle was largely responsible for reducing glucose R_d at the same absolute workload post-training, but that at the same relative workload, the active muscle actually took up approximately the same amount of glucose as it did in pre-training (Bergman *et al.*, 1999). These observations (Bergman *et al.*, 1999) are important because they confirm that the endurance training-induced reduction in glucose R_d was due to a reduced uptake of glucose by skeletal muscle.

While endurance training decreases glucose kinetics, the skeletal muscle GLUT4 protein content (Houmard *et al.*, 1993; Kristiansen *et al.*, 2000; Phillips *et al.*, 1996; Ploug *et al.*, 1990; Richter *et al.*, 1998) paradoxically increases during exercise. This indicates that factors, such as translocation, other than total skeletal muscle GLUT4 content are involved in the regulation of glucose uptake during exercise.

The overall rate of carbohydrate oxidation, as determined by indirect calorimetry, was also lower throughout exercise after endurance training. Quantitatively, this decrease was greater than the accompanying reduction in glucose R_d, indicating that muscle glycogen utilization must have been lower after endurance training. In fact, during the first 30 min of exercise most of the carbohydrate-sparing effect of training appeared to have been due to a showing of muscle glycogen utilization. After this time reduced glucose turnover is as important. Coggan *et al.* (1995) demonstrated that the lower glucose R_a during exercise is mostly due to a slower rate of hepatic glycogenolysis. Reductions in muscle and liver glycogen utilization therefore contributes roughly equally to the overall carbohydrate-sparing effect of endurance training, at least during moderate exercise at same absolute workload.

Summary

The maintenance of normal blood glucose levels depends on the integrated functioning of several systems. This integration is affected by transmitter substances released from the sympathetic nervous system and the endocrine system. During prolonged exercise, the increased demand for glucose by contracting muscle causes to increase glucose uptake to working skeletal muscle.

The increase in glucose uptake during exercise arises from both an increase in glucose delivery to contracting muscle, as a result of elevated skeletal muscle blood flow, and an increase in glucose extraction, as measured by the arteriovenous glucose difference. Increased glucose extraction by contracting muscle is due to enhanced membrane glucose transporter and activation of the glycolytic and oxidative pathways responsible for glucose disposal.

During exercise the glucose production is derived mainly from liver glycogenolysis, and only a small part (10–20%) is explained by gluconeogenesis. With increasing exercise duration (several hours) the contribution of gluconeogenesis rises to about 50% of the total liver glucose production. This rise occurs in parallel with a decline in liver glycogen stores and an increase in supply of glu-

coneogenic precursors to the liver.

Both feedforward and feedback mechanisms allow glycemia to be controlled during exercise. At the onset of exercise, and during moderate to hard intensity exercise, feedforward mechanisms operate to maintain or increase circulating blood glucose. The central mechanisms coupled to the degree of motor center activity are responsible for an increase in glucose mobilization that exceeds the peripheral glucose uptake, resulting in a rise in blood glucose level during intense exercise. However, if blood glucose concentration falls during prolonged exercise, then powerful feedback response are elicited to maintain blood glucose levels. The control of glycemia during exercise is a multi-component and highly redundant system.

Endurance training reduces glucose flux during exercise at a given power output. However, when expressed at a given relative power output, endurance training does not affect glucose kinetics. In addition, endurance training may enhance to utilize lipids during mild to moderate exercise, but the transition to hard exercise appears to result in a crossover to predominantly carbohydrate utilization regardless of training status.

References

Ahlborg, B. and Felig, P. (1977) Substrate utilization during prolonged exercise preceded by ingestion of glucose. *Am. J. Physiol.* **233**, E188–E194.

Ahlborg, B., Felig, P., Hagenfeldt, L., Hendler, R., and Wahren, J. (1974) Substrate turnover during prolonged exercise in man. *J. Clin. Invest.* **53**, 1080–1090.

Angus, D. J., Febbraio, M. A., Lasini, D., and Hargreaves, M. (2001) Effect of carbohydrate ingestion on glucose kinetics during exercise in the heat. *J. Appl. Physiol.* **90**, 601–605.

Bergman, B. C., Butterfield, G. E., Wolfel, E. E., Lopaschuk, G. D., Casazza, G. A., *et al.* (1999) Muscle net glucose uptake and glucose kinetics after endurance training in men. *Am. J. Physiol.* **277**, E81–E92.

Bjorkman, O., Felig, P., Hagenfeldt, L., and Wahren, J. (1981) Influence of hypoglucagonemia on splanchnic glucose output during leg exercise in man. *Clin. Physiol.* **1**, 43–57.

Brooks, G. A. and Donovan, C. M. (1983) Effect of endurance training on glucose kinetics during exercise. *Am. J. Physiol.* **244**, E505–E512.

Brooks, G. A. and Mercier, J. (1994) Balance of carbohydrate and lipid utilization during exercise: the "crossover"concept. *J.Appl. Physiol.* **76**, 2253–2261.

Brooks, G. A., Fahey, T. D., and Baldwin, K. M. (2005) Exercise Physiology: Human Bioenergetics and Its Applications. New York: McGraw-Hill.

Carter, S. L., Rennie, C., and Tarnopolsky, M. A. (2001) Substrate utilization during endurance exercise in men and women after endurance training. *Am. J. Physiol.* **280**, E898–E907.

Chen, H. C., Bandyopadhyay, G., Sajan, M. P., Kanoh, Y., Standaert, M., *et al.* (2002) Activation of the ERK pathway and atypical protein kinase C isoforms in exercise- and aminoimidazole-4-carboxamide-1-β-D-riboside(AICAR) stimulated glucose transport. *J. Biol. Chem.* **277**, 23554-23562.

Coggan, A. R., Swanson, S. C., Mendenhall, L. A., Habash, D. L., and Kien, C. L. (1995) Effect of endurance training on hepatic glycogenolysis and gluconeogenesis during prolonged exercise in men. *Am. J. Physiol.* **268**, E375–E383.

Constable, S. H., Favier, R. J., Cartee, G. D., Young, D. A., and Holloszy, J. O. (1988) Muscle glucose transport: interactions of in vitro contractions, insulin and exercise. *J. Appl. Physiol.* **64**, 2329–2332.

Cooper, D. M., Barstow, T. J., Bergner, A., and Lee, W. P. (1989) Blood glucose turnover during high- and low- intensity exercise. *Am. J. Physiol.* **257**, E405–E412.

Douen, A. G., Ramlal, T., Rastogi, S., Bilan, P. J., Cartee, G. D., *et al.* (1990) Exercise induces recruitment of the "insulin-responsive glucose transporter": evidence for distinct intracellular insulin- and exercise-recruitable transporter pools in skeletal muscle. *J. Biol. Chem.* **265**, 13427–13430.

Friedlander, A. L., Casazza, G. A., Horning, M. A., Huie, M. J., and Brooks, G. A. (1997) Training-induced alterations of glucose flux in men. *J. Appl. Physiol.* **82**, 1360–1369.

Friedlander, A. L., Casazza, G. A., Horning, M. A., Huie, M. J., Piacentini, M. F., *et al.* (1998) Training-induced alterations of carbohydrate metabolism in women: women respond differently from men. *J. Appl. Physiol.* **85**, 1175–1186.

Fueger, P. T., Heikkinen, S., Bracy, D. P., Malabanan, C. M., Pencek, R. R., *et al.* (2003) Hexokinase II partial knockout impairs exercise-stimulated glucose uptake in oxidative muscles of mice. *Am. J. Physiol.* **285**, E958–E963.

Fueger, P. T., Bracy, D. P., Malabanan, C. M., Pencek, R. R., and Wasserman, D. H. (2004a) Distributed control of glucose uptake by working muscles of conscious mice: roles of transport phosphorylation. *Am. J. Physiol.* **286**, E77–E84.

Fueger, P. T., Hess, H. S., Posey, K. A., Bracy, D. P., Pencek, R. R., *et al.* (2004b) control of exercise-stimulated muscle glucose uptake by GLUT4 is dependent on glucose phosphorylation capacity in the conscious mouse. *J. Biol. Chem.* **279**, 50956–50961

Galbo, H., Holst, J. J., and Christensen, N. J. (1975) Glucagon and plasma catecholamine responses to graded and prolonged exercise in man. *J. Appl. Physiol.* **38**, 70–76.

Geor, R. J., Hinchcliff, K. W., and Sams, R. A. (2000) Glucose infusion attenuates endogenous glucose production and enhances glucose use of horses during exercise. *J. Appl. Physiol.* **88**, 1765–1776.

Gollnick, P. D., Piehl, K., and Saltin, B. (1974) Selective glycogen depletion pattern in human muscle fibres after exercise of varying intensity and at varying pedalling rates. *J. Physiol.* **241**, 45–47.

Goodyear, L. J., Hirshman, M. F., King, P. A., Hotrod, E. D., Thompson, C. M., *et al.* (1990) Skeletal muscle plasma membrane glucose transport and glucose transporters after exercise. *J. Appl. Physiol.* **68**, 193–198.

Goodyear, L. J., Hirshman, M. F., and Horton, E. S. (1991) Exercise-induced translocation of skeletal muscle glucose transporters. *Am. J. Physiol.* **261**, E795–E799.

Hayashi, T., Hirshman, M. F., Fujii, N., Habinowski, S. A., Witters, L. A., *et al.* (2000) Metabolic stress and altered glucose transport. Activation of AMP-activated protein kinase

as a unifying coupling mechanism. *Diabetes* **48**, 527–531.

Holloszy, J. O. (2003) A forty-year memoir of research on the regulation of glucose transport into muscle. *Am. J. Physiol.* **284**, E453–E467.

Houmard, J. A., Shinebarger, M. H., Dolan, P. L., Legget-Frazier, N., Bruner, R. K., *et al.* (1993) Exercise training increases GLUT-4 protein concentration in previously sedentary middle-aged men. *Am. J. Physiol.* **264**, E896–E901.

Hultman, E. and Nilsson, L. H. (1971) Liver glycogen in man. Effect of different diets and muscular exercise. *Advan. Exp. Med. Biol.* **11**, 143–151.

Ihelemann, J., Galbo, H., and Ploug, T. (1999a) Calphostin C is an inhibitor of contraction, but not insulin-stimulated glucose transport, in skeletal muscle. *Acta Physiol. Scand.* **167**, 69–75.

Ihelemann, J., Ploug, T., Hellsten, T., and Galbo, H. (1999b) Effect of tension on concentration-induced glucose transport in rat skeletal muscle. *Am. J. Physiol.* **277**, E208–E214.

Jenkins, A. B., Chisholm, D. J., James, D. E., Ho, K. Y., and Kraegen, E. W. (1985) Exercise-induced hepatic glucose output is precisely sensitive to the rate of systemic glucose supply. *Metabolism* **34**, 431–441.

Jeukendrup, A. E., Raben, A., Gijsen, A., Stegen, J. H., Brouns, F., *et al.* (1999a) Glucose kinetics during prolonged exercise in highly trained human subjects: effect of glucose ingestion. *J. Physiol.* **515**, 579–589.

Jeukendrup, A. E., Wagenmakers, A. J., Stegen, J. H., Gijsen, A. P., Brouns, F., *et al.* (1999b) Carbohydrate ingestion can completely suppress endogenous glucose production during exercise. *Am. J. Physiol.* **276**, E672–E683.

John-Adler, H. B., Mcallister, R. M., and Terjung, R. L. (1986) Reduced running endurance in gluconeogenesis-inhibited rats. *Am. J. Physiol.* **251**, R137–R142.

Kjaer, M., Farrell, P. A., Christensen, N. J., and Galbo, H. (1986) Increased epinephrine response and inaccurate glucoregulation in exercising athletes. *J. Appl. Physiol.* **61**, 1693–1700.

Kjaer, M., Secher, N. H., Bach, F. W., and Galbo, H. (1987) Role of motor center activity for hormonal changes and substrate mobilization in humans. *Am. J. Physiol.* **253**, R687–R695.

Kjaer, M., Kiens, B., Hargresves, M., and Richter, E. A. (1991) Influences of active muscle mass on glucose homeostasis during exercise in humans. *J. Appl. Physiol.* **71**, 552–557.

Kristiansen, S., Gade, J., Wojtaszewski, J. F., Kiens, B., and Richter, E. A. (2000) Glucose uptake is increased in trained vs. untrained muscle during heavy exercise. *J. Appl. Physiol.* **89**, 1151–1158.

Lemieux, K., Han, X. X., Dombrowski, L., Bonen, A., and Marette, A. (2000) The transferrin receptor defines two distinct contraction-responsive GLUT4 vesicle population in skeletal muscle. *Diabetes* **49**, 183–189.

McConell, G. K., Canny, B. J., Daddo, M. C., Nance, M. J., and Snow, R. J. (2000) Effect of carbohydrate ingestion on glucose kinetics and muscle metabolism during intense endurance exercise. *J. Appl. Physiol.* **89**, 1690–1698.

Miller, B. F., Fattor, J. A., Jacobs, K. A., Horning, M. A., Suh, S. H., *et al.* (2002) Metabolic and cardiorespiratory responses to "the lactate clamp". *Am. J. Physiol.* **283**, E889–E898.

Mu, J., Brozinick, J. T. Jr., Valladares, O., Bucan, M., and Birnbaum, M. J. (2001) A role for AMP-activated protein kinase in contraction- and hypoxia-regulated glucose transport in skeletal muscle. *Mol. Cell* **7**, 1085–1094.

Phillips, S. M., Han, X. X., Green, H. J., and Bonen, A. (1996) Increments in skeletal muscle GLUT-1 and GLUT-4 after endurance training in humans. *Am. J. Physiol.* **270**, E456–E462.

Ploug, T., Stalkecht, B. M., Pedersen, O., Kahn, B. B., Ohkuwa, T., *et al.* (1990) Effect of endurance training on glucose transport capacity and transporter expression in rat skeletal muscle. *J. Physiol.* **259**, E778–786.

Ploug, T., van Deurs, B., Ai, H., Cushman, S. W., and Ralston, E. (1988) Analysis of GLUT4 distribution in whole skeletal muscle fibers: identification of distinct storage compartments that are recruited by insulin and muscle contractions. *J. Cell. Biol.* **142**, 1429–1446.

Raddatz, D. and Ramadori, G. (2007) Carbohydrate metabolism and the liver: actual aspects from physiology and disease. *Z. Gastroenterol* **45**, 51–62.

Richter, E. A., Jensen, P., Kiens, B., and Kristiansen, S. (1998) Sarcolemmal glucose transport and GLUT-4 translocation during exercise are diminished by endurance training. *Am. J. Physiol.* **274**, E89–E95.

Romijn, J. A., Coyle, E. F., Sidossis, L. S., Gastaldelli, A., Horowitz, J. F., *et al.* (1993) Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. *Am. J. Physiol.* **265**, E380–E391.

Rose, A. J. and Hargreaves, M. (2003) Exercise increases Ca^{2+}/calmodulin-dependent protein kinase II activity in human skeletal muscle. *J. Physiol.* **553**, 303–309.

Rose, A. J. and Richer, E. A. (2005) Skeletal muscle glucose uptake during exercise: How is it regulated? *Physiol.* **20**, 260–270.

Ryder, J. W., Chibalin, A. V., and Zierath, J. R. (2001) Intracelluar mechanisms underlying increases in glucose uptake in response to insulin or exercise in skeletal muscle. *Acta Physiol. Scand.* **171**, 249–257.

Ryder, J. W., Kawano, Y., Galuska, D., Fahlman, R., Wallberg-Henriksson, H., *et al.* (1999) Postexercise glucose uptake and glycogen synthesis in skeletal muscle from GLUT4-deficient mice. *FASEB J.* **13**, 2246–2256.

Sakamoto, K. and Goodyear, L. J. (2002) Invited review: intracellular signaling in contraction skeletal muscle. *J. Appl. Physiol.* **93**, 369–383.

Sonne, B. and Galbo, H. (1985) Carbohydrate metabolism during and after exercise in rats: studies with radioglucose. *J. Appl. Physiol.* **59**, 1627–1639.

Sonne, B. and Galbo, H. (1986) Carbohydrate metabolism in fructose-fed and food-restricted running rats. *J. Appl. Physiol.* **61**, 1457–1466.

Sonne, B., Mikines, K. J., and Galbo, H. (1987) Glucose turnover in 48-hour-fasted running rats. *Am. J. Physiol.* **252**, R587–R593.

Stanley, W. C., Wisneski, J. A., Gertz, E. W., Neese, R. A., and Brooks, G. A. (1988) Glucose and lactate interrelations during moderate-intensity exercise in humans. *Meta. Clin. Exp.* **37**, 850–858.

Turcotte, L. P., Rovner, A. S., Roark, R. R., and Brooks, G. A. (1990) Glucose kinetics in gluconeogenesis-inhibited rats during rest and exercise. *Am. J. Physiol.* **258**, E203–E211.

van Loon, L. J., Jeukendrup, A. E., Saris, W. H., and Wagen-

makers, A. J. (1999) Effect of training status on fuel selection during submaximal exercise with glucose ingestion. *J. Appl. Physiol.* **87**, 1413–1420.

Vissing, J., Sonne, B., and Galbo, H. (1988) Role of metabolic feedback regulation in glucose production of running rats. *Am. J. Physiol.* **255**, R400–R406.

Wahren, J., Felig, P., Ahlborg, G., and Jorfeldt, L. (1971) Glucose Metabolism during leg exercise in man. *J. Clin. Invest.* **50**, 2715–2725.

Wahren, J., Felig, P., and Hagenfeldt, L. (1978) Physical exercise and fuel homeostasis in diabetes mellitus. *Diabetologica* **14**, 213–222.

Williams, B. D., Plag, I., Troup, J., and Wolfe, R. R. (1995) Isotopic determination of glycolytic flux during intense exercise in humans *J. Appl. Physiol.* **78**, 483–490.

Wojtaszewski, J. F. P., Lynge, J., Jakobsen, A. B., Goodyear, L. J., and Richer, E. A. (1999) Differential regulation of MAP kinase by contraction and insulin in skeletal muscle: metabolic implications. *Am. J. Physiol.* **277**, E724–E732.

Wolfe, R. R. (1992) Radioactive and stable isotope tracers in biomedicine: principles and practice of kinetic analysis. New York: Wiley-Liss.

Wright, D. C., Hucker, K. A., Holloszy, J. O., and Han, D. H. (2004) Ca^{2+} and AMPK both mediate stimulation of glucose transport by muscle contractions. *Diabetes* **53**, 330–335.

Yamatani, K., Shi, Z. Q., Giacca, A., Gupta, R., Fisher, S., *et al.* (1992) Role of FFA-glucose cycle in glucoregulation during exercise in total absence of insulin. *Am. J. Phsiol.* **263**, E646–E653.

Zinker, B. A., Lacy, D. B., Bracy, D., Jacobs, J., and Wasserman, D. H. (1993) Regulation of glucose uptake and metabolism by working muscle. An *in vivo* analysis. *Diabetes* **42**, 956–965.

Zisman, A., Peroni, O. D., Abel, E. D., Micheal, M. D., Mauvais-Jarvis, F., *et al.* (2000) Targeted disruption of the glucose transporter 4 selectively in muscle causes insulin resistance and glucose intolerance. *Nat. Med.* **6**, 924–928.