Mobilization of Glucose From the Liver During Exercise and Replenishment Afterward

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Abstract/Résumé

The liver is anatomically well situated to regulate blood glucose. It is positioned downstream from the pancreas, which releases the key regulatory hormones glucagon and insulin. It is also just downstream from the gut, permitting efficient extraction of ingested glucose and preventing large excursions in systemic glucose after a glucose-rich meal. The position of the liver is not as well situated from the standpoint of experimentation and clinical assessment, as its primary blood supply is impossible to access in conscious human subjects. Over the last 20 years, to study hepatic glucose metabolism during and after exercise, we have utilized a conscious dog model which permits sampling of the blood that perfuses (portal vein, artery) and drains (hepatic vein) the liver. Our work has demonstrated the key role of exercise-induced changes in glucagon and insulin in stimulating hepatic glycogenolysis and gluconeogenesis during exercise. Recently we showed that portal venous infusion of the pharmacological agent 5’-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside leads to a marked increase in hepatic glucose production. Based on this, we propose that the concentration of AMP may be a component of a physiological pathway for stimulating hepatic glucose production during exercise. Insulin-stimulated hepatic glucose uptake is increased following exercise by an undefined mechanism that is independent of liver glycogen content. The fate of glucose taken up by the liver is critically dependent on...
hepatic glycogen stores, however, as glycogen deposition is greatly facilitated by prior glycogen depletion.

La judicieuse position anatomique du foie lui permet de contrôler le glucose sanguin. En effet, il est situé en aval du pancréas qui libère les hormones importantes de la régulation du glucose: le glucagon et l’insuline. Aussi en aval de l’intestin, il peut donc extraire efficacement du glucose alimentaire et limiter la diffusion massive de glucose dans la circulation après un repas riche en glucose. Cependant d’un point de vue expérimental et clinique, le foie n’est pas si bien situé, car son principal réseau sanguin est impossible d’accès chez des sujets humains conscients. Au cours des 20 dernières années, des échantillons de sang dans l’artère et la veine porte de même que dans la veine hépatique ont été prélevés d’un chien conscient afin d’étudier le métabolisme du glucose hépatique pendant et après un exercice physique. Nos travaux ont démontré le rôle majeur de la modification du glucagon et de l’insuline associée à l’activité physique dans la stimulation de la glycogénolyse et de la gluconéogenèse hépatiques au cours de l’exercice physique. Récemment, nous avons démontré que l’infusion d’un agent pharmacologique, le 5’-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside, élève la production de glucose hépatique. À la lumière de ces résultats, nous pensons que la concentration d’AMP est un élément du processus physiologique stimulant la production hépatique de glucose au cours de l’exercice. La captation hépatique du glucose à l’aide de l’insuline est accrue à la suite de l’exercice par un mécanisme indépendant du contenu hépatique de glycogène. L’issue du glucose capté par l’insuline est liée étroitement aux réserves hépatiques de glycogène; cependant, le stockage du glycogène est de beaucoup favorisé par une déplétion préalable du glycogène.

Introduction

It was shown over 100 years ago that glucose uptake is increased in contracting skeletal muscle (Chaveau and Kaufmann, 1887). Subsequent studies confirmed that carbohydrate oxidation is increased as a result of muscular work (Christensen and Hansen, 1939). Research conducted in the 1930s from the Harvard Fatigue Laboratory described the glycemic response to different exercise conditions (Dill et al., 1932; 1935; Edwards et al., 1934). Dill et al. and Edwards et al. showed that (a) during light to moderate exercise of limited duration (< 90 min), blood glucose is usually unchanged from resting levels; (b) exercise of prolonged duration (> 90 min), however, can lead to a gradual fall in blood glucose levels; while (c) heavy exercise results in a rise in blood glucose. These researchers surmised that for blood glucose not to fall precipitously with short-duration exercise, the liver must break down its stored glycogen at an increased rate to compensate for accelerated glucose usage.

With the development of tools sensitive enough to measure circulating hormone concentrations in the 1970s, the endocrine response to exercise was defined and studies into the control of endogenous glucose production were initiated (Galbo, 1983). The purpose of this review is twofold. The first is to summarize and update the continuing investigation into the regulation of endogenous glucose production during exercise. The second is to describe recent work examining the newly emerging concept that the liver, like the muscle, adapts to an acute bout of prior exercise by increasing its ability to take up and store glucose.
Control of Endogenous Glucose Production During Exercise

An extensive series of experiments conducted in a dog model have illustrated that the exercise-induced decrease in insulin and the increase in glucagon are the primary mechanism by which hepatic glycogenolysis and gluconeogenesis are increased during moderate intensity muscular work (Wasserman, 1995). This work is summarized in Figure 1. These findings in the dog are consistent with results showing the importance of changes in insulin and glucagon obtained in human subjects (Hirsch et al., 1991; Kjaer et al., 1993; Lavoie et al., 1997; Wolfe et al., 1986). Also consistent with the important roles of insulin and glucagon are data from human subjects, dogs, and rats showing that epinephrine and norepinephrine seem to play little or no role during the physiological response of the liver to moderate exercise (Howlett et al., 1999; Marker et al., 1991; Wasserman, 1995).

![Figure 1](image-url)

**Figure 1.** Contributions of the fall in insulin and rise in glucagon as well as the rise in epinephrine to endogenous glucose production. During prolonged exercise, the rise in glucagon and fall in insulin are primarily responsible for the increase in endogenous glucose production. As exercise continues, epinephrine stimulation of gluconeogenic pathways begins to contribute to glucose production (modified from Wasserman, 1995).

Researchers attempting to assess the role of glucoregulatory hormones from changes in peripheral or arterial concentrations have underestimated the role of glucagon and overestimated the role of epinephrine. This is because changes in the peripheral levels of these hormones with exercise differ from those in the hepatic portal venous blood which perfuses the liver. Figure 2 shows that at 150 min of exercise in the dog, glucagon rises twofold more in the portal vein than in an artery. The increase in portal vein epinephrine, however, is only 10% of that seen in artery. A more detailed discussion of the control of endogenous glucose production during moderate intensity exercise is found in Wasserman (1995) and Wasserman and Cherrington (1996).

There are instances such as high intensity exercise or exercise in specific populations when the adrenergic response is unusually high while the pancreatic
Mobilization of Glucose • 295

hormone response is not (Wasserman and Cherrington, 1996). For this reason the regulation of endogenous glucose production under such conditions has been postulated to be different. It has been hypothesized that during exercise of high intensity there may be a shift in the control of glucose production away from the pancreatic hormones to the catecholamines (Marliss et al., 1991). This is based on two observations. First, circulating blood norepinephrine and epinephrine can increase by 10- to 20-fold, whereas the increase in the glucagon-to-insulin ratio in peripheral blood is considerably less (Marliss et al., 1992), and in some cases is undetectable (Kjaer et al., 1993). Second, when high-intensity exercise is superimposed on a preexisting pancreatic clamp, endogenous glucose production increases normally even though the increase in glucagon is blunted and the fall in insulin is absent (Sigal et al., 1995). Nevertheless, all studies that have attempted to directly assess the role for catecholamines in stimulating endogenous glucose production during high intensity exercise (>80% maximum O₂ uptake) have yielded negative results (Kjaer et al., 1993; Marliss et al., 1992; Sigal et al., 1994).

Adrenergic blockade studies in humans have been difficult to interpret due to the lack of specificity of these pharmacological agents. A method was recently developed in the dog that allows for selective hepatic adrenergic blockade (Coker et al., 1997b). The approach uses an intraportal propranolol and phentolamine infusion to create a local hepatic adrenergic blockade. By infusing into the portal vein directly, the blocker dose can be greatly reduced. Moreover, the liver extracts approximately 90% of the infused blockers on a first pass. As a consequence, intraportal hepatic adrenergic blockade can be achieved without extrahepatic effects. It is notable, in this regard, that intraportal blocker infusion does not affect heart rate, arterial blood pressure, or arterial concentrations of glycerol, lactate, or free fatty acids at rest or during exercise (Coker et al., 1997b). The completeness of the blockade can be verified using suprapharmacological intraportal norepinephrine and epinephrine infusions, which have minimal extrahepatic actions.

The selective hepatic α- and β-adrenergic receptor blockade technique has been applied in the dog to study the effect of high intensity treadmill exercise that

![Figure 2. Changes in arterial and portal vein plasma glucagon, norepinephrine, and norepinephrine levels from basal levels at 150 min of exercise. *Significantly different values from the changes in arterial levels, p < 0.05.](image-url)
results in a threefold increase in hepatic norepinephrine spillover (Coker et al., 1997a). Hepatic adrenergic blockade did not significantly impair the increase in endogenous glucose production or affect blood glucose homeostasis under this condition. It was concluded from these experiments that the exaggerated increase in sympathetic drive during heavy exercise is not an important controller of endogenous glucose production (Figure 3) (Coker et al., 1997b). Similar results are seen in alloxan-diabetic dogs. Alloxan-diabetic dogs with poor metabolic control have approximately a sevenfold higher rate of hepatic norepinephrine spillover than nondiabetic dogs during prolonged exercise of moderate intensity (Coker et al., 1997c). Despite this difference, selective hepatic adrenergic receptor blockade did not affect the exercise-induced increase in endogenous glucose production (Coker et al., 2000). Thus, endogenous glucose production is not reliant on hepatic adrenergic receptor stimulation even under a pathological condition, such as diabetes, associated with excessive sympathetic drive.

Coker et al. (2002) recently conducted experiments in the dog model in which the role of hepatic adrenergic receptor stimulation was assessed during moderate intensity exercise in the absence of the primary stimulus to endogenous glucose production, changes in glucagon and insulin. Glucagon and insulin were fixed at basal levels using the pancreatic clamp technique (somatostatin + basal glucagon and insulin replacement) in the presence and absence of hepatic adrenergic receptor blockade. Exercise with pancreatic hormones fixed at basal levels resulted in a gradual fall in blood glucose of about 30 mg/dl over a 2-hr period. Despite the absence of exercise-induced changes in glucagon and insulin, endogenous glucose

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*Significant difference from control, p < 0.05 (from Coker et al., 1997b, *Am. J. Physiol. Endocrinol. Metab.* Used with permission from The American Physiological Society).
production still rose by about 30% of the response seen when the pancreatic hormone response was intact. Preventing the fall in blood glucose completely attenuated the compensatory increase in endogenous glucose production, while hepatic adrenergic blockade did not affect it at all.

These studies illustrate that hepatic adrenergic stimulation does not drive endogenous glucose production even when primary controlling factors such as increased glucagon and decreased insulin are eliminated. It is notable, however, that a stimulus related to the gradual decline in blood glucose did provide increased glucose production during exercise in the absence of the known hormonal signals. This suggests that hepatic autoregulation is an important line of defense against exercise-induced hypoglycemia. The specific nature of the apparent autoregulatory stimulus requires further elucidation.

Recent reports have given valuable insight into possible intracellular signaling mechanisms that could lead to the increase in hepatic glucose production during exercise. The 5’-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR) is a compound avidly consumed by cells, in which it is converted to the nucleotide ZMP. ZMP is normally in low concentrations in the body, but at higher concentrations it mimics the allosteric effects of AMP. Portal venous AICAR infusion was used to create high ZMP concentrations in the liver of conscious dogs (~3 µmol/g tissue) without creating high ZMP concentrations in nonhepatic tissues (Camacho et al., 2005; Pencek et al., 2005). Portal venous AICAR potently stimulated hepatic glucose production to rates comparable to those seen during exercise in the conscious dog (Camacho et al., 2005). Remarkably, AICAR’s effect on the liver occurred despite hyperinsulinemia great enough to suppress the hepatic effects of glucagon at doses that elicit a maximal increase in glucagon-stimulated hepatic glucose production (Camacho et al., 2005).

There are two important implications of this work. First, these studies suggest that nucleotides could be physiological regulators of hepatic glucose production. Second, AICAR or a related compound could be a useful pharmacological agent for countering insulin-induced hypoglycemia, since it does not seem suppressible by hyperinsulinemia (Camacho et al., 2005).

**Hepatic Adaptations to Prior Exercise**

It is well established that prior exercise increases skeletal muscle insulin action, leading to enhanced rates of net muscle glucose uptake and glycogen synthase (Richter, 1996). These adaptations have been studied in great detail and much has been learned about the mechanisms involved (Richter, 1996). Despite the integral role of the liver in fuel homeostasis and the added metabolic demands placed on it by exercise described in the preceding paragraphs, very little is known about how this organ functions during recovery from exercise.

Galassetti et al. (1999a) demonstrated for the first time, using direct measurements of net hepatic glucose uptake, that prior exercise increases the liver’s capacity to consume glucose. These studies were conducted in the chronically catheterized dog under carefully controlled conditions. Experiments consisted of 150 min of exercise or rest, a 30-min control period, and a 100-min period during which glucose was infused into the portal vein at 3.5 mg·kg⁻¹·min⁻¹ and in the
vena cava to clamp arterial glucose at ~185 mg/dl. During the glucose load, somatostatin was infused in a peripheral vein and insulin (fourfold basal) and glucagon (basal) were replaced in the portal vein. Exercised dogs had a net hepatic glucose output of 4.1 ± 0.3 mg·kg⁻¹·min⁻¹ prior to the glucose load compared to normal basal rates in sedentary dogs of 1.9 ± 0.2 mg·kg⁻¹·min⁻¹. With a glucose load of twofold basal and an arterial-portal venous (a-pv) glucose gradient of ~20 mg/dl, net hepatic glucose uptake was 3.3 ± 0.4 and 1.8 ± 0.2 mg·kg⁻¹·min⁻¹ in exercised and sedentary dogs, respectively (Figure 4). Not only was net hepatic glucose uptake nearly twofold greater in exercised dogs, but the total shift from net output to net uptake was also twofold greater: 7.4 ± 0.7 and 3.7 ± 0.5 mg·kg⁻¹·min⁻¹ in exercised and sedentary dogs, respectively.

These data suggest that the increased glucose disposal in the postexercise state is due to an improved ability of both muscle and liver to take up glucose. The results were consistent with indirect assessments in the anesthetized rabbit which concluded that liver deposition of 3-fluoro-3-deoxyglucose via either an oral bolus or a continuous 120-min intraportal infusion was greater after hindlimb contraction (Matsuhisha et al., 1998). These data are also consistent with studies using

Figure 4. Net hepatic glucose balance following either 150 min of moderate treadmill exercise (closed bars) or an equivalent period of rest (open bars). Data are mean ± SE; n = 6 per group. After baseline measurements following either rest or exercise, insulin levels were fixed at ~30 μU/ml using somatostatin with intraportal insulin replacement, and arterial blood glucose was clamped at ~130 mg/dl. The portal to arterial glucose gradient was ~19 mg/dl during hyperinsulinemic, hyperglycemic periods in both groups. Measurements made in the presence of a hyperglycemic, insulin-stimulated state were taken after a 60-min equilibration period during which a steady state was achieved. *Significantly greater values than corresponding sedentary period, p < 0.05 (modified from Galassetti et al., 1999a).
$^{13}$C magnetic resonance spectroscopy which showed that ingestion of glucose immediately after completion of prolonged moderate exercise increased liver glycogen resynthesis by $\sim 0.7$ mg·kg$^{-1}$·min$^{-1}$ over a period of 4 hrs of postexercise recovery (Casey et al., 2000).

The mechanism for the added stimulation of net hepatic glucose uptake during an intraportal glucose load after exercise remains to be elucidated. Cherrington et al. (1987) have defined three variables that stimulate glucose uptake by the liver: the a-pv glucose gradient, hepatic glucose delivery (i.e., glucose effectiveness), and plasma insulin. Galassetti et al. (1999b) recently tested whether the increase in the liver’s ability to take up glucose was due to a sensitization of the liver to the stimulatory effects of the a-pv glucose gradient. This was assessed by studying dogs during an intravenous glucose infusion designed to increase the glucose load twofold, either in the presence or absence of a negative a-pv glucose gradient. As expected, the presence of a negative a-pv glucose gradient led to a marked stimulation of glucose uptake by the liver, but the gradient was no more effective after exercise than it was in sedentary dogs (Galassetti et al., 1999b).

We have recently turned our attention to the question of whether the liver is more insulin sensitive after exercise and, if so, whether it could explain the improved ability of the liver to take up glucose. Recent experiments showed that during a hyperinsulinemic (1 mU·kg$^{-1}$·min$^{-1}$) euglycemic clamp, net hepatic glucose output was suppressed to a greater extent following 150 min of exercise in dogs compared to their sedentary controls (Koyama et al., 2002). These results provide a basis for the hypothesis that hepatic insulin sensitivity could be the cause of increased net hepatic glucose uptake during a hepatic glucose load when the liver is in a storage mode. This was subsequently addressed by Pencek et al. (2003a), who compared hepatic glucose uptake in sedentary and exercised dogs during a hyperglycemic clamp (180 mg/dL) with either basal (0.2 mU·kg$^{-1}$·min$^{-1}$) or elevated insulin (1.2 mU·kg$^{-1}$·min$^{-1}$). The increase in net hepatic glucose uptake and fractional extraction with hyperinsulinemia was approximately 50% greater in exercised compared to sedentary dogs. The results of that study provide a physiological basis for advocating exercise for patients with insulin resistance, since it appears the liver is one of the tissues affected in patients with this syndrome.

Endocrine responses during exercise, depletion of fuel stores, alterations in hepatic enzyme activity, or a combination of these factors all could conceivably alter the hepatic uptake of glucose after exercise. Some or all of these adaptations to exercise may accentuate the hepatic response to insulin. As discussed in the preceding section, the exercise-induced increase in glucagon and/or decrease in insulin are the major stimuli for the accelerated mobilization of glucose from the liver. We hypothesized that by depleting hepatic glycogen stores, exercise-induced changes in pancreatic hormones could increase the ability of the liver to consume glucose and store it as glycogen after exercise. This would be consistent with a role for glycogen stores in regulation of liver glucose uptake, such as has been proposed in skeletal muscle (Richter, 1996).

To address the role of the exercise-induced changes in insulin and glucagon to adaptations of the liver following exercise, dogs were exercised and endogenous glucagon and insulin release was suppressed using somatostatin and pancreatic hormones which were either replaced at basal rates or at exercise-simu-
lated rates (Pencek et al., 2004). Blood glucose was clamped at basal during the exercise period under both conditions. When the glucagon and insulin responses to exercise were prevented, glucose was not mobilized from the liver, i.e., glycogen breakdown was not increased. Simulation of the glucagon and insulin responses to exercise resulted in a threefold increase in the rate of hepatic glucose output, i.e., increased glycogen breakdown. Despite the differences in glycogen mobilization in the two protocols, NHGU was increased equally in response to a glucose load, exceeding the rate of NHGU evident in sedentary dogs.

It is noteworthy, however, that when pancreatic hormone responses were simulated and hepatic glucose output was accelerated during exercise, a greater fraction of the glucose consumed by the liver was directed to glycogen (Pencek et al., 2004). Thus a factor other then those adaptations resulting from the exercise-induced increase in glucagon and decrease in insulin are responsible for the increased insulin-stimulated NHGU during a glucose load. However, this endocrine response to exercise is a critical determinant of the fate of glucose consumed by the liver.

Exercise also leads to a number of other endocrine changes. It is possible, for example, that the glucocorticoid response to exercise may prime the liver to take up more glucose since high doses of this hormone can stimulate hepatic glycogen deposition (Long et al., 1940). The general belief, however, is that the time course for the full glucocorticoid effect requires a longer interval than that used for studying the hepatic adaptations to prior exercise (Galassetti et al., 1999a; 1999b; Pencek et al., 2003a). Exercise has persistent effects on processes and enzymes involved in liver glucose metabolism which are sustained well after the cessation of exercise (Dohm et al., 1985). It is possible that some facet of the exercise response activates enzymes involved in hepatic glucose uptake and metabolism.

The effect of prior exercise on the fate of glucose once the liver extracts it has received very little attention. A greater fraction of the glucose taken up by the liver after prolonged exercise in dogs is metabolized nonoxidatively, with proportionally less being oxidized (Hamilton et al., 1996). A similar result is seen after a prolonged, glycogen-depleting fast (Galassetti et al., 1999c). The mechanism for this diversion of glucose carbons to glycogen (direct pathway for hepatic glycogen synthesis) has not been studied, nor has the potential contribution of carbons diverted from the gluconeogenic pathway (indirect pathway for hepatic glycogen synthesis).

Clearly there are effects of prior exercise directly at the liver that facilitate hepatic glucose uptake and glycogen storage. It is important to consider the integrated response of the body when examining the physiological response to actual ingestion of glucose. In this regard, replenishment of hepatic glycogen stores is facilitated by intestinal adaptations that cause an increase in absorption of glucose into the portal circulation. Hepatic glucose uptake after exercise is facilitated by an increased absorption of ingested glucose (Hamilton et al., 1996; Pencek et al., 2003b). Through the use of the isotopic glucose analogues 3-O-[^3]H]methylglucose (absorbed via transporter-mediated and passive processes) and L-[^14]C]glucose (absorbed passively), it was determined that the increase in gut glucose absorption seen following exercise was primarily due to an increase in passive absorption across the intestinal cell wall (Pencek et al., 2003b).
The liver is ideally situated anatomically to regulate blood glucose. It is positioned downstream from the pancreas, which releases the key regulatory hormones glucagon and insulin. It is also just downstream from the gut, permitting efficient extraction of ingested glucose and preventing large excursions in systemic glucose after a glucose-rich meal. From the standpoint of experimentation and clinical assessment, however, the position of the liver is unfortunate as it and its primary blood supply are impossible to access in conscious human subjects. As a consequence, continued advancements in our understanding of hepatic metabolism during exercise will be driven in large part by continued use of existing animal models and emerging new animal models, such as those created by genetic manipulation of key metabolic enzymes, hormones, receptors, and signaling proteins.

Acknowledgments

Work described in this paper was supported by NIH R01 DK50277.

References


Received June 19, 2002; accepted in final form January 18, 2003.