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Exercise Effects on Muscle Insulin Signaling and Action Selected Contribution: Evidence that the decrease in liver glycogen is associated with the exercise-induced increase in IGFBP-1

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Lavoie, Jean-Marc, Yovan Fillion, Karine Couturier, and Pierre Corriveau. Selected Contribution: Evidence that the decrease in liver glycogen is associated with the exercise-induced increase in IGFBP-1. *J Appl Physiol* 93: 798–804, 2002. First published May 3, 2002; 10.1152/jappphysiol.00125.2002.—The purpose of the present study was to test the hypothesis that the exercise-induced increase in insulin-like growth factor binding protein (IGFBP)-1 is not always linked to a decrease in blood glucose level and to examine whether the decreasing levels of liver glycogen during exercise may be associated with the increase in IGFBP-1. Three groups of rats were submitted to a 70-min treadmill exercise. One group of rats was fed normally, and the two other groups had their food intake restricted by 50% (50% fast) the night before the experiment. One of these two 50% fasted groups of rats was infused (intravenously) with glucose throughout exercise to maintain euglycemia. Exercise in noninfused 50% fasted rats, compared with the normally fed rats, resulted in significantly lower blood glucose (*minute* 70) and insulin levels, significantly lower liver glycogen content, no change in IGF-I, and significantly higher increases in free fatty acid, glycerol, β -hydroxybutyrate, and IGFBP-1. Maintenance of euglycemia during exercise in glucose-infused 50% fasted rats reduced to a large extent the decrease in insulin levels but only slightly attenuated the lipid response and the IGFBP-1 response seen in noninfused 50% fasted rats. Comparisons of all individual liver glycogen and IGFBP-1 values revealed that liver glycogen values were highly ($P < 0.001$) predictive of the IGFBP-1 response during exercise ($R = 0.564$). The present results indicate that the IGFBP-1 response during exercise is not always linked to a decrease in plasma glucose and suggest that the increase in IGFBP-1 during exercise may be related to the decrease in liver glycogen content.

hypoglycemia; free fatty acids; glucose infusion; insulin-like growth factor binding protein-1

INSULIN-LIKE GROWTH FACTOR I (IGF-I) is a small polypeptide whose actions *in vitro* are either acute anabolic effects on protein and carbohydrate metabolism or longer-term effects on cell replication and differentiation. The insulin-like actions of IGF-I are best appreciated in the *in vivo* studies of the effects of IGF-I administration (see review in Ref. 14). In normal rats, IGF-I infusion causes hypoglycemia, primarily by stimulating peripheral glucose uptake (12). Major differences between the effects of insulin and IGF-I *in vivo* are related to the presence of IGF binding proteins (IGFBPs), which prolong IGF actions and buffer the acute hypoglycemic effects of IGF-I (14). The importance of IGFBPs is, therefore, related to the modulation of IGF's actions through IGF bioavailability and bioactivity (32).

Approximately 75% of IGF-I in plasma is bound to IGFBP-3 and a non-IGF binding component termed acid labile subunit, which forms a 150-kDa ternary complex that is unable to leave the endothelial barrier. The lower-molecular-mass forms of IGFBPs that are present in plasma in concentrations sufficient to alter IGF action include IGFBP-1, IGFBP-2, and IGFBP-4. Of all the currently identified IGFBPs, IGFBP-1 is the only one to show rapid and marked fluctuation in human plasma and dynamic regulation in relation to substrate activity (21, 22). An increase in levels of IGFBP-1 is usually related to a reduction in free IGF-I, and this may serve as a mechanism to adjust IGF-I bioactivity to the actual fuel supply (2, 32).

Most studies have noted an absence of increase in IGF-I during prolonged exercise (13, 16). However, a large increase in IGFBP-1 during prolonged exercise has been repeatedly observed in humans and rats (1,

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11, 16, 27, 30). The mechanisms for such high circulating concentrations during exercise and their physiological role remain unclear. It has been proposed that IGFBP-1 may have an important role in gluco-regulation during exercise by neutralizing the insulin-like activity of IGF-I (11, 16). The decrease in insulin and glucose, to which IGFBP-1 has been shown to respond rapidly, has been proposed to explain the large increase of IGFBP-1 during exercise. However, this view has been challenged in two recent reports. Ingestion of a glucose polymer solution during exercise to maintain plasma glucose and insulin levels did not prevent plasma IGFBP-1 levels from rising in humans (11). Similarly, oral administration of a meal immediately after 2 h of exercise in rats, thus elevating plasma insulin and glucose concentrations, did not prevent IGFBP-1 concentrations to remain elevated (1). The first purpose of the present study was to reexamine the changes in IGFBP-1 during exercise in relation to glucose, insulin, and IGF-I by maintaining euglycemia during exercise through an intravenous glucose infusion.

In recent years, our group has published some data showing a parallel between the decreasing level of hepatic glycogen content and some of the metabolic responses to prolonged exercise (18, 31). Because the liver is the primary source of circulating IGFBP-1, which can act as a gluco-regulatory factor (11, 16), it is tempting to draw a similar parallel between the decreasing level of liver glycogen during exercise and the increase in IGFBP-1. The second purpose of the present study was to investigate the possibility that the decreasing levels of hepatic glycogen during exercise might be associated with the increasing levels of IGFBP-1. To do that, liver glycogen concentration was decreased by a food restriction protocol and the time course of the decrease in liver glycogen was compared with the increase in IGFBP-1.

METHODS

Animal care. Male Sprague-Dawley rats (Charles River, St. Constant, PQ), weighing 220–240 g, were housed in individual cages and allowed pellet rat chow and tap water ad libitum for 14–16 days after they were received in our laboratory. The lighting schedule was such that lights were on from 7:00 AM until 7:00 PM; the room temperature was maintained at 20–23°C. Two days after their arrival, rats underwent a habituation running protocol on a motor-driven rodent treadmill consisting of six sessions over an 8-day period beginning with 20 min/day at 15 m/min and progressively increased to 60 min/day at 26 m/min (0% grade), so that they were well accustomed to running and being handled.

Surgery. Five days before experimentation, all rats underwent a right jugular vein cannulation under pentobarbital sodium (40 mg/kg ip) anesthesia. After insertion, the catheter was filled with saline containing heparin (500 U/ml; Fisher Scientific) and the external portion was capped with the crunched shaft of a blunted 23-gauge needle. Subsequently, 3 days were allocated for recovery. The catheter was used for the glucose or saline infusion and to anesthetize the animals at the end of the experiment.

Groups and exercise protocol. The day before experimentation, rats were divided into three dietary groups: two food-restricted groups and one normally fed group. The food-restricted rats received only 50% (10 g) of their daily food intake the night before experimentation (50% fasted rats). During the exercise protocol, one group of food-restricted rats was infused with glucose to maintain euglycemia, whereas the other groups received an equivalent infusion of isotonic saline. The three groups of rats were subdivided into subgroups killed in the resting state and after 30, 45, and 70 min of exercise. Because there was no need to infuse glucose in the resting state to maintain euglycemia, the same resting data were used for food-restricted rats with or without glucose infusion. The exercise protocol consisted of running on a motor-driven rodent treadmill at 26 m/min.

On the day of the experiment, food was removed from cages of fed rats at 7:00 AM, and the exercise tests were run between 9:00 AM and 12:00 PM. The catheters of the jugular vein were connected to tubing extensions to be used for glucose or saline infusions. After this procedure, rats were returned to their cages for a 30-min stabilization period. Afterward, rats were either submitted, at random, to the exercise protocol for a specific duration or were kept at rest for 70 min, while still infused with saline. The intravenous infusion of either glucose (25% dextrose solution) or isotonic saline (0.9%) was made with a microinfusion pump (model 55-2222, Harvard Apparatus). Glucose infusion, for all glucose-infused rats, started after the 15th min of exercise and was maintained at a rate of 6 μ l/min (8.33 μ mol/min of glucose) for the remainder of the exercise period. The appropriateness of this glucose infusion rate to maintain euglycemia during exercise was determined in a pilot study, based on previous experiments from our laboratory (19, 31). At the end of exercise, the animals were quickly anesthetized (while still running) through the venous catheter with pentobarbital sodium (20 mg/kg). Immediately after, the abdominal cavity was opened, and ~7 ml of blood were withdrawn from the abdominal vena cava. The whole liver was then immediately taken frozen with aluminum block tongs cooled to liquid-nitrogen temperature. Nonexercised rats were treated in the same manner as the exercised rats and were killed at approximately the same time.

Analytic methods. Peripheral blood was collected into 5-ml syringes with 7% EDTA. A small portion of this blood was used for serum IGF-I determinations. The remaining portion was immediately centrifuged (Eppendorf centrifuge, no. 5415), and the plasma was stored for subsequent glucose, insulin, free fatty acids (FFAs), β -hydroxybutyrate, and IGFBP-1 determinations. All tissue and blood samples were stored at -78°C until analyses were performed.

Plasma glucose concentrations were determined with the use of a glucose analyzer (Yellow Springs Instruments 2300, Yellow Springs, OH). Insulin and IGF-I concentrations were determined with commercially available radioimmunoassay kits (Radioassay System Laboratory, and ICN Biomedicals, Costa Mesa, CA; distributed by Immunocorp, Montreal, PQ, and Diagnostic Systems Laboratories-2900, respectively). FFAs and β -hydroxybutyrate were assessed enzymatically with the use of reagents kits from Boehringer Mannheim Laboratories (distributed by Immunocorp). Liver glycogen concentrations were determined by use of the phenol-sulfuric acid reaction (25). Plasma IGFBP-1 protein content was determined by Western blotting. All samples were separated on a 12% SDS-polyacrylamide gel followed by protein transfer to a polyvinylidene difluoride membrane by electroblotting. The membrane was blocked in 5% (wt/vol) skim milk in PBS (100 mM Na₂HPO₄, 100 mM NaCl, pH 7.5) for 1 h at

room temperature before overnight incubation with a rat IGFBP-1 (M-19) polyclonal antibody (Santa Cruz Biotechnology, Santa Cruz, CA) diluted to 0.5 $\mu\text{g/ml}$ in 0.1% BSA and 0.5% Tween 20 in PBS (PBS-T). After three washes in PBS-T, the membrane was incubated for 1 h with an anti-goat horseradish peroxidase antibody (Sigma Chemical, St. Louis, MO). The membrane was washed three times for 10 min each time in PBS-T before a chemifluorescence substrate (enhanced chemiluminescence, Amersham, Baie D'Urfé, PQ) was applied to the membrane. The resulting signal was detected on enhanced chemiluminescence film (Amersham), scanned with the use of Agfas Arcus II, and quantified with Imagepro 4.0 software (Media Cybernetics, Silver Spring, MD).

Statistics. Statistical analyses were performed by a two-way ANOVA non-repeated-measures design. Fisher's post hoc test was used in the event of a significant ($P < 0.05$) F ratio. Relationships between parameters were evaluated by linear regression analysis.

RESULTS

Hepatic glycogen concentrations were significantly ($P < 0.01$) decreased after exercise in all three conditions (Fig. 1A). On the whole, however, liver glycogen

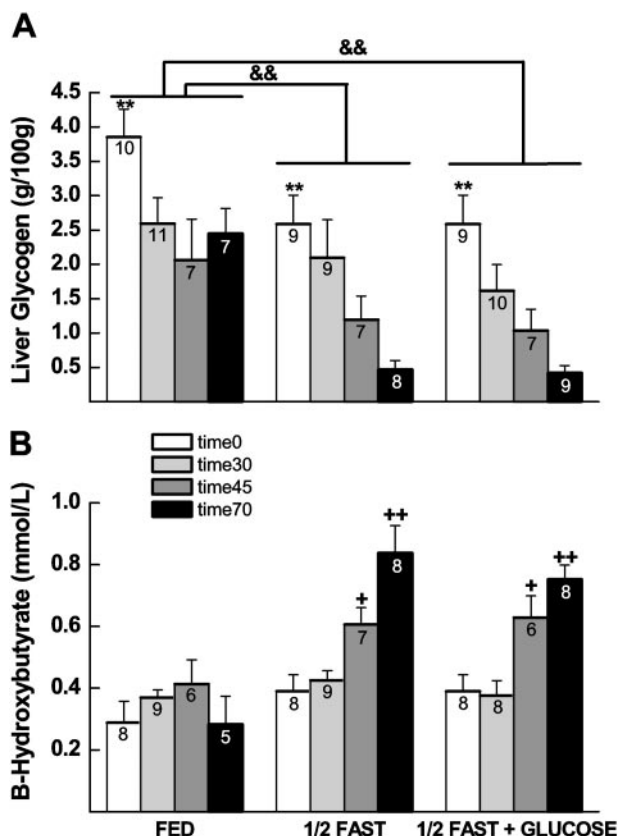


Fig. 1. Liver glycogen (A) and β -hydroxybutyrate (B) concentrations at rest and after exercise in normally fed, 50% fasted (1/2 fast), and 50% fasted rats with glucose infusion (1/2 fast + glucose). Values are means \pm SE. The number of rats in each group is indicated within bars. **Significantly different from all corresponding exercise values, $P < 0.01$. &&Significantly different between indicated groups, $P < 0.01$. +Significantly different from corresponding rest and 30-min values and from corresponding values in the 2 other groups, $P < 0.05$ and ++ $P < 0.01$.

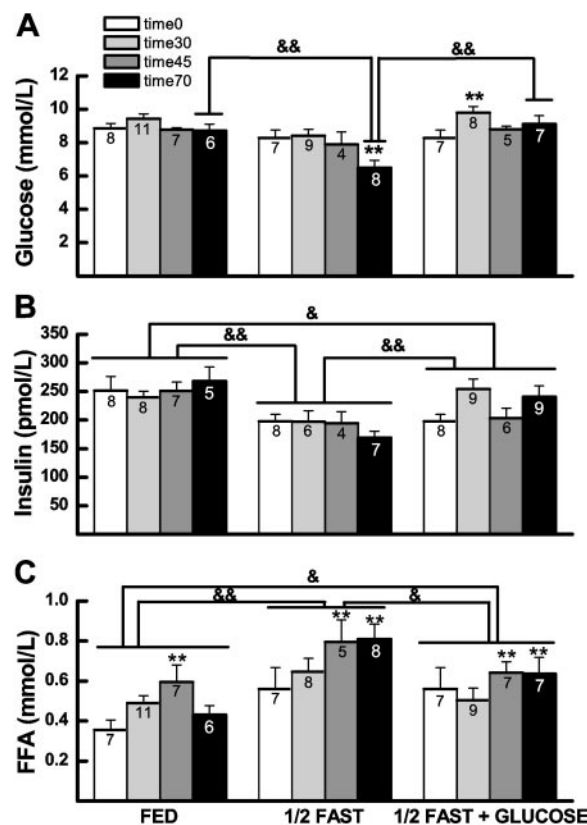


Fig. 2. Plasma glucose (A), insulin (B), and free fatty acid (FFA; C) concentrations at rest and after exercise in normally fed, 50% fasted, and 50% fasted rats with glucose infusion. Values are means \pm SE. The number of rats in each group is indicated within bars. **Significantly different from corresponding rest values, $P < 0.01$. &&Significantly different between indicated groups, $P < 0.01$ and & $P < 0.05$.

content was significantly ($P < 0.05$) higher in normally fed rats than in the two other groups of 50% fasted rats. There were no effects of glucose infusion on liver glycogen breakdown during exercise. Plasma β -hydroxybutyrate concentrations were increased significantly ($P < 0.05$) after 45 and 70 min of exercise only in the 50% fasted rats, whether with or without glucose infusion (Fig. 1B). Consequently, values of plasma β -hydroxybutyrate were significantly ($P < 0.05$) lower in normally fed rats during exercise (minutes 45 and 70) than in the two other groups.

Blood glucose concentrations were decreased significantly ($P < 0.05$) after 70 min of exercise only in the group of rats that were 50% fasted without glucose infusion (Fig. 2A). There was no significant decrease in plasma glucose during exercise in the glucose-infused 50% fasted rats, but a significant ($P < 0.01$) increase was measured in the first 30 min of exercise. There were no statistical effects of exercise on plasma insulin concentrations on any of the three groups (Fig. 2B). On the whole, however, insulin concentrations were different from one group to another, the values of the 50% fasted glucose-infused rats being intermediate between the two other groups. FFA concentrations were significantly ($P < 0.01$) increased during exercise in all three groups (Fig. 2C). On the whole, however, values

for FFA concentrations, as above-reported for insulin levels, were all different from one group to another, the values of the 50% fasted glucose-infused rats being intermediate between the two other groups.

Plasma IGF-I concentrations were not affected by either the dietary or the exercise stimuli (Fig. 3A). Plasma IGFBP-1 levels, on the other hand, were largely increased in all three conditions after 45 and 70 min of exercise. Intergroup comparisons revealed that the exercise-induced increase in IGFBP-1 was larger ($P < 0.01$) in the 50% fasted rats than in the fed rats (*minute 70*). Infusion of glucose during exercise in 50% fasted rats only partially reduced the increase in IGFBP-1, the values at *minute 70* of exercise being intermediate between the normally fed and the 50% fasted rats (Fig. 3B). Figure 4 shows the association between the level of liver glycogen and the plasma insulin values and between the level of liver glycogen and the IGFBP-1 response for all subjects throughout the whole experiment. This comparison reveals a weak association between the level of liver glycogen and the plasma insulin values ($R = -0.159$; not significant), whereas IGFBP-1 response was significantly ($P < 0.001$) increased as liver glycogen concentration was progressively decreased ($R = -0.564$). A significant ($P < 0.001$) negative correlation was also found be-

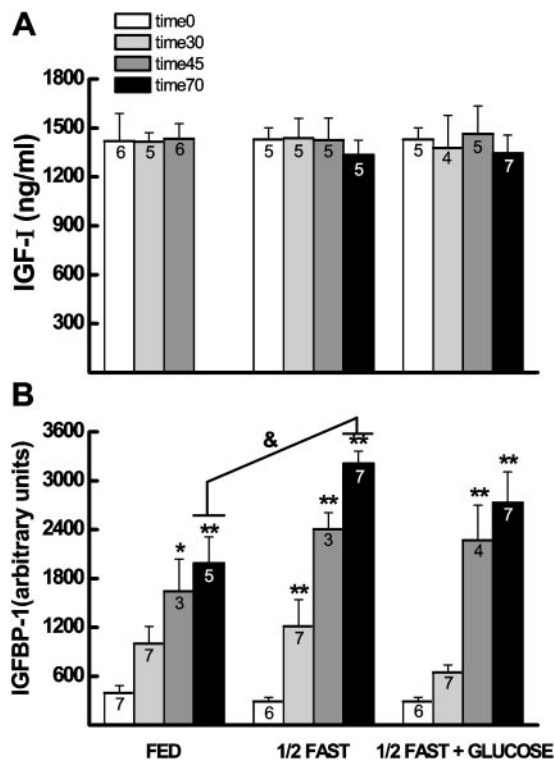


Fig. 3. Insulin-like growth factor I (IGF-I; A) and insulin-like growth factor binding protein-1 (IGFBP-1; B) at rest and after exercise in normally fed, 50% fasted, and 50% fasted rats with glucose infusion. Values are means \pm SE. The number of rats in each group is indicated within bars. **Significantly different from corresponding rest values, $P < 0.01$ and * $P < 0.05$. &Significantly different between indicated groups, $P < 0.05$. IGFBP-1 was measured by Western blotting and expressed as arbitrary units.

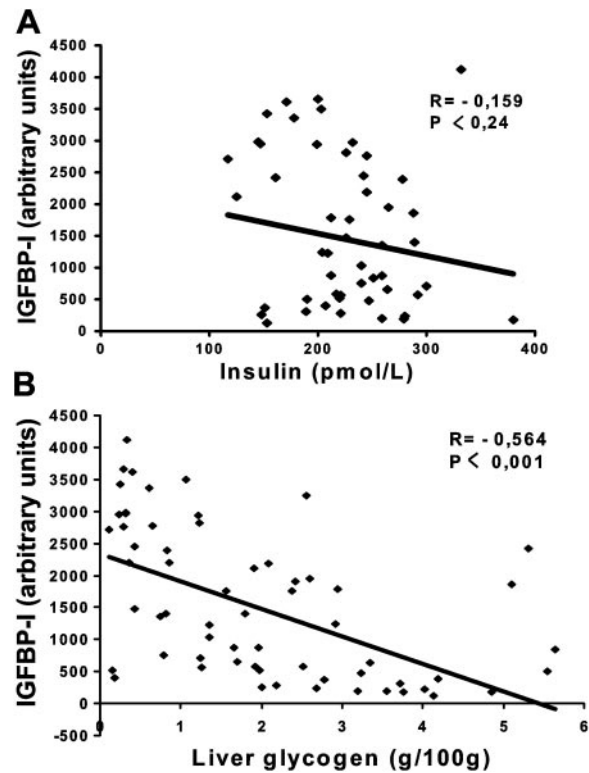


Fig. 4. Relationship between liver glycogen concentrations and IGFBP-1 ($n = 49$, not significant; B) and between liver glycogen concentrations and plasma insulin values ($n = 59$, $P < 0.001$; A) for all rats in all dietary and activity conditions. IGFBP-1 was measured by Western blotting and expressed as arbitrary units.

tween the level of liver glycogen and the plasma FFA concentrations ($R = -0.474$; Fig. 5).

DISCUSSION

Results of the present study show clearly that maintenance of euglycemia, through glucose infusion (intravenous), during a period of prolonged exercise did not prevent plasma IGFBP-1 levels from rising. This is in agreement with what has been reported previously in work that studied consumption of a carbohydrate drink

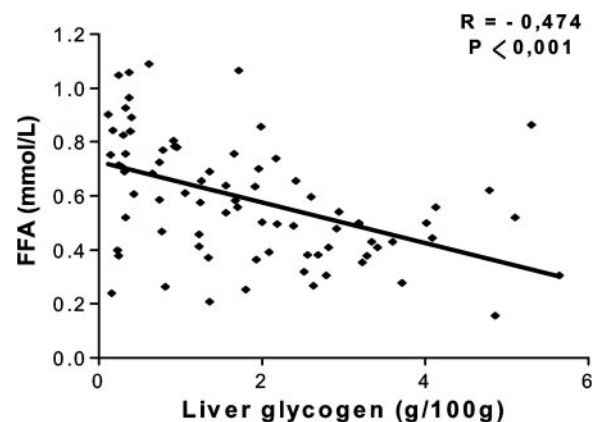


Fig. 5. Relationship between liver glycogen concentrations and plasma FFA concentrations ($n = 78$, $P < 0.001$) for all rats in all dietary and activity conditions.

during cycling exercise in humans (11) and ingestion of a meal after a treadmill exercise in rats (1). It is also noteworthy to mention that, in the normally fed condition, IGFBP-1 was steadily increased during exercise (*minutes 45 and 70*), although blood glucose levels were not decreased. Besides glucose, insulin has been proposed to be a primary regulator of circulating IGFBP-1 under several physiological conditions (22). In the exercise situation, however, this view has been questioned in several recent reports in humans (11, 16) as well as in rats (1). In the present study, insulin levels in the fed rats were not significantly decreased during exercise. As expected, however, overall insulin levels were lower in 50% fasted rats than in the normally fed rats. In addition, there is a tendency for insulin to be decreased after 70 min of exercise, compared with resting values, in the 50% fasted rats. Infusion of glucose largely attenuated the low insulin levels measured in 50% fasted rats, but the values, on the whole, were lower ($P < 0.05$) than those measured in the normally fed rats. This overall pattern of response is similar to the one obtained for IGFBP-1. Therefore, it can be argued that the contribution of insulin levels as a factor responsible for the increase in IGFBP-1 during exercise could be used to explain the overall difference in IGFBP-1 between the three dietary conditions. However, plotting together all insulin and IGFBP-1 values revealed that insulin was a weak predictor of IGFBP-1 response (Fig. 4). The present data, therefore, support the previously reported contention (11, 16, 30) that plasma concentrations of insulin do not predict circulating levels of IGFBP-1 during exercise.

In recent years, our laboratory has gathered evidence showing that the liver may act as an afferent organ contributing to the metabolic and hormonal regulation of exercise (see review in Ref. 17). In this context, our laboratory (6) recently reported that a low initial level of glycogen content, brought about by a series of glucagon injections, resulted in a higher plasma FFA concentration during a subsequent period of exercise. It was postulated in the latter study that a decrease in liver glycogen may afferently stimulate an increase in lipid mobilization. It is interesting to note that, if in the present study the infusion of glucose in the 50% fasted rats attenuated the plasma FFA response during exercise, this response was still more elevated than in the normally fed rats. This suggests that the lower level of liver glycogen content in the 50% fasted rats infused with glucose may have contributed to the larger FFA levels found in this group. This is further supported by the strong negative correlation found between the level of liver glycogen and the plasma FFA concentrations (Fig. 5). On the other hand, the infusion of glucose in the 50% fasted rats did not attenuate the response of β -hydroxybutyrate (*minutes 45 and 70* of exercise). This indicates that the livers of both 50% fasted groups of rats were in a similar metabolic state even though blood glucose was maintained at normal levels in one of these two groups. Similarly to the FFA response, the overall IGFBP-1 response in 50% fasted rats was only attenuated by the infusion of

glucose. This as such is a good indication that the level of liver glycogen may be involved in IGFBP-1 secretion by the liver. This interpretation is further supported by the strong correlation found between the present decrease in liver glycogen concentrations and the increase in plasma IGFBP-1 levels (Fig. 4). The hypothetical construct would be that the liver is able to sense the progressive decrease in liver glycogen content during exercise and stimulates a counterregulatory response, including the increased secretion in IGFBP-1 before blood glucose falls. On the other hand, IGFBP-1 response was largely increased during exercise in the fed state but not in the resting state of both 50% fasted groups, despite a similar decrease in liver glycogen levels in all these groups. This suggests that this postulated liver glycogen-IGFBP-1 regulatory mechanism was mainly operating during exercise. It is possible that the rapid decrease in liver glycogen in the exercise situation, as opposed to a more progressive decrease during the 50% fast, resulted in acute metabolic changes inside the hepatic cells that triggered the secretion in IGFBP-1. A longer period of fasting (24–48 h), resulting in a larger decrease in liver glycogen, would be necessary to stimulate an increase in IGFBP-1 secretion. Finally, the present data do not preclude the possibility that a contingent decrease in blood glucose and insulin levels may add to the stimulus of decreasing liver glycogen levels.

Besides exercise, the other physiological situation where a decrease in liver glycogen may be associated with an increased secretion of IGFBP-1 is fasting. It has been reported that IGFBP-1 levels increase during fasting and are normalized within 2–3 h of refeeding (8, 24). Although changes in plasma glucose and insulin levels always accompanied the fasting situations, the normalization of IGFBP-1 levels with refeeding is not always followed by an increase in insulin levels (8). Alternatively, because the liver is the primary source of circulating IGFBP-1, plasma IGFBP-1 has been suggested to reflect portal rather than peripheral insulin levels (3, 22). Supporting this view, C-peptide levels have been reported to be strongly correlated with serum IGFBP-1 levels in a fasting-refeeding situation (8). Interestingly, there has been reported evidence of a direct neural link between the availability of carbohydrates in the liver and the portal insulin concentrations, whether in a resting or an exercise situation (19, 20). Altogether, if portal insulin is a good predictor of the IGFBP-1 increase in the fasting situation (8) because this is what the liver sees, one has to realize that fasting by definition is associated with a decrease in liver glycogen. In other words, the missing factor regulating IGFBP-1 secretion during acute conditions such as fasting and exercise (1, 4) could be the liver glycogen content. It is possible, however, that in more chronic situations of metabolic disturbances such as obesity, diabetes, or liver cirrhosis other mechanisms may be involved in the regulation of IGFBP-1 secretion.

The possibility that liver glycogen content may be involved in the regulation of the secretion of IGFBP-1

by the liver raises the question as to what mechanism links these two factors. Because a decrease in liver glycogen during exercise has been suggested to influence some of the hormonal responses (i.e., glucagon; Ref. 31), it is possible that low levels of liver glycogen may be linked to an increased secretion of IGFBP-1 during exercise through some extrahepatic regulation. However, it is also possible that these two metabolic events are linked inside the hepatocyte. Although it remains highly speculative, one of the candidates for such a link would be the decrease in energy charge level (i.e., liver ATP levels). A decrease in liver glycogen during exercise has been associated with a decrease in ATP levels (9). This could lead to the activation of a number of signal transduction pathways. One of them, the AMP-activated protein kinase, which acts as a metabolic sensor of the AMP-to-ATP ratio, has recently been reported to stimulate IGFBP-1 secretion in rat hepatoma cells in short-term culture (23). AMP-activated protein kinase activity in liver, which has been reported to increase with exercise (5), might in turn act to stimulate gene expression. It seems that IGFBP-1 gene may be expressed rapidly and markedly in rat liver (26). Interestingly, fasting (7), prolonged exercise (9), and partial hepatectomy (19), all known to decrease liver glycogen content and liver ATP levels, are all associated with an increase in IGFBP-1 levels.

Besides glucose and insulin, there are other factors that may be responsible for the increase in IGFBP-1 during exercise. It has been shown in isolated hepatic cells that the nonavailability of amino acids induces IGFBP-1 expression (15). However, it has been reported that consumption of a protein-containing meal immediately after exercise did not blunt circulating IGFBP-1 compared with exercise-food-deprived animals (1). The same authors (1) also suggested that the increase in corticosterone during exercise may be an important factor in the IGFBP-1 response. This was based on the fact that the IGFBP-1 promoter contains a glucocorticoid response element (22). Cortisol or corticosterone responses were not measured in the present experiment. Therefore, no conclusive statement can be made from the present data regarding the contribution of the glucocorticoid hormones to the increase in IGFBP-1 during exercise. It is, however, doubtful that glucocorticoid levels would still be elevated 1 h after exercise, at a time where IGFBP-1 has been reported to be still elevated, even with feeding a postexercise meal (1).

In summary, results of the present experiment showed that the maintenance of euglycemia, through an intravenous glucose infusion, did not prevent IGFBP-1 levels to raise during a prolonged bout of exercise. On the basis of the strong negative correlation found between liver glycogen and plasma IGFBP-1 levels, it is suggested that the increase in IGFBP-1 levels during exercise is linked to the decrease in liver glycogen content.

The importance of a better knowledge of the factors regulating IGFBP-1 secretion is highlighted by the recent demonstration of a close relation between

IGFBP-1 and some risk factors for diabetes and cardiovascular disease (10), not to mention that IGFBP-1 has also been associated with insulin resistance in prepubertal obesity and in cirrhosis (28, 29).

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