Swim Training Increases Glucose Output From Liver Perfused In Situ With Glucagon in Fed and Fasted Rats

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The effect of endurance swim training (3 hours per day, 5 days/week, for 10 weeks) on hepatic glucose production (HGP) in liver perfused in situ for 60 minutes with glucagon and insulin was studied in Sprague-Dawley rats. The experiments were performed in fed rats and in rats fasted for 24 hours, but with lactate (8 mmol/L) added to the perfusion medium. Liver glycogen content was significantly lower in fasted than fed rats (fasted untrained and trained: 14 ± 4 and 11 ± 3 μmol glycosyl U/g of liver wet weight (WW); fed untrained and trained: 205 ± 11 and 231 ± 11 μmol glycosyl U/g of liver WW; not significantly different in trained and untrained rats). Glucagon increased HGP in the 4 experimental groups, but the increases were more rapid and pronounced in trained than in untrained rats in both fed and fasted states. HGP values (area under the curve [AUC] in μmol/g of liver WW) were significantly higher in trained fed (112.1 ± 7.1 *v* 85.9 ± 12.2 in untrained rats) than in trained fasted rats (50.8 ± 4.4 *v* 34.7 ± 3.6 in untrained rats). When compared with untrained rats, the total amount of glucose released by the liver in response to glucagon in trained rats was approximately 30% higher in the fed state and approximately 45% larger in the fasted state. These results indicate that endurance training increases the response of both glycogenolysis and gluconeogenesis to glucagon.

HEPATIC GLUCOSE production (HGP) increases in response to prolonged exercise in humans[1,2] and rats[3,4] and appears to be primarily controlled by a reduction in the insulin-to-glucagon ratio (I/G).[5-8] Following endurance training, plasma glucose homeostasis during exercise is improved despite a higher I/G both in humans[9-12] and rats,[3,13,14] and this is mainly due to an increase in HGP.[13,14] These observations are in line with data from Cheeks et al,[15] Podolin et al,[16] and Drouin et al[17] indicating a higher HGP in response to glucagon in trained than untrained rats[15,16] and humans.[17] Drouin et al[17] have reported, at rest, following an 8-hour fast, a higher HGP within 10 minutes following initiation of glucagon infusion in trained than in untrained subjects. As for the preliminary report by Cheeks et al,[15] these investigators observed a larger HGP from liver perfused in situ when stimulated with counterregulatory hormones, including glucagon and a mixture of glucose precursors, in trained than untrained fasted rats. Finally, Podolin et al[16] reported a higher gluconeogenic capacity from lactate in liver slices from trained than untrained rats when incubated with glucagon. Recent data also show a higher density[18] and affinity[19] of glucagon receptors in plasma membranes isolated from hepatocytes in trained rats.

The purpose of the present experiment was to compare HGP from liver perfused in situ with glucagon in untrained and endurance swim trained rats. HGP under glucagon stimulation was measured in fed rats, with large glycogen stores, and in rats fasted for 24 hours, with very low glycogen stores, but perfused with lactate as a glucose precursor. Depletion of liver glycogen stores with a 24-hour fasting period minimizes HGP from glycogenolysis and, thus, allows to specifically observe HGP from gluconeogenesis.[13,20-22] In contrast, in fed rats, with high liver glycogen stores, HGP is mainly due to glycogenolysis.[20,23] We hypothesized that HGP during glucagon infusion will be higher in trained than in untrained rats both in fed and fasted conditions.

MATERIALS AND METHODS

Animals

The experiment was conducted on male Sprague-Dawley rats (Anilab, Ste-Foy, Québec, Canada), which were kept in individual cages at 20°C and 55% relative humidity with a 12-hour light/12-hour dark cycle, in a facility that met the Canadian Council on Animal Care guidelines. They had free access to a standard rat chow, and tap water ad libitum. The Animal Care Committee of the Université du Québec à Trois-Rivières approved the protocol.

Training and Experimental Groups

The animals were randomly assigned to either the untrained or endurance-trained group. Trained animals swam in 60 × 90 cm tanks filled with 50 cm of water at 37°C under constant supervision to prevent underwater swimming. The duration of each training session was progressively increased to 3 hours over the first 2 weeks. For the following 8 weeks, the rats trained between 8 AM and 11 AM, 5 days per week. The animals assigned to the untrained group were handled daily.

The experiments were conducted between 8 AM and 11 AM, 48 hours following the last bout of exercise for the trained group, either after an overnight with free access to food and water (fed animals), or after a 24-hour fast with only access to tap water (fasted animals). Trained and untrained animals were randomly assigned to the fed (trained, n = 8; untrained, n = 8) or fasted groups (trained, n = 9, untrained, n = 9).

Liver Perfusion

The animals were anesthetized with sodium pentobarbitate (50 mg/kg body weight [BW] intraperitoneal [IP]). The rectus femoris (right leg) was removed, frozen in liquid nitrogen, and stored at − 80°C

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Table 1. Liver Glycogen Content (μmol Glycosyl U/g of Liver WW) Before and After Stimulation With Glucagon in Untrained and Trained Fed and Fasted Rats

	Untrained		Trained	
	Fed	Fasted	Fed	Fasted
Before	205 ± 11	14 ± 4†	231 ± 11	11 ± 3†
After	146 ± 14*	ND	58 ± 24*‡	ND

NOTE. Values are mean ± SEM.

Abbreviation: ND, not detectable.

Significantly different from before (*), from fed rats (†), and from untrained rats (‡), $P < .05$.

for subsequent analysis. The portal vein and the inferior vena cava, as well as the bile duct were, then, cannulated.[24] The liver was perfused in situ at 8 mL · min^{-1} · 100 g^{-1} BW (Minipuls 3; Mandel Scientific, Guelph, Ontario, Canada)[24] in single pass using Krebs-Henseleit buffer (pH 7.4) saturated with an oxygen/carbon dioxide mixture (95/5%), albumin (2%), and glucose (5 mmol/L) at 37°C. To prevent lactate appearance in the influent perfusate, no erythrocytes were added to the perfusion medium.[24,25] However, in the fasted group, lactate (8 mmol/L) was added to the perfusate as a glucose precursor. When the flow through the liver had been established, the animal was killed by sectioning the aorta.

Following a 40-minute washout period, a small sample (5 to 10 mg in order to limit injury to the organ) of the left lobe of the liver was removed for the measurement of glycogen content and of glycogen phosphorylase activity and content (in fed rats, only). The liver was then stimulated for 60 minutes with a combination of insulin and glucagon (Harvard Apparatus 22, St-Laurent, Quebec, Canada; Insulin and glucagon kindly provided by Eli Lilly, Mississauga, Ontario, Canada). The concentration of insulin and glucagon in the perfusate was 45.7 ± 2.2 pmol/L and 63.7 ± 3.1 pg/mL, respectively (radioimmunoassays: KTSP #11001 from Immunocorp, Québec, Canada and KGNDI double antibody from Inter-medico, Markham, Ontario, Canada). No liver damage occurred over the period of perfusion, as evidenced by steady bile flow (gravimetry; range, 0.33 ± 0.03 to 0.76 ± 0.05 mg · min^{-1} · g of $liver^{-1}$) and by the low alanine aminotransferase concentration (range, 1.2 ± 0.4 to 3.3 ± 1.1 U/L; threshold concentration for tissue damage >100 U/L[24]) in the effluent of the perfused liver.[24,26] In addition, pH values (Accumet pHmeter 910; Fischer Scientific, Nepean, Ontario, Canada) of the effluent perfusate remained close to 7.4 in the 4 experimental conditions (fasting state: 7.36 ± 0.02 and 7.38 ± 0.01; fed state: 7.37 ± 0.03 and 7.38 ± 0.01 in the untrained and trained groups, respectively). At the end of perfusion, the liver was quickly removed, weighted, frozen in liquid nitrogen, and stored at −80°C for subsequent analysis.

Measurements

Glucose, lactate, and alanine aminotransferase concentration (spectrophotometric assays, Sigma Diagnostics, St Louis, MO) were measured in blood withdrawn from the vena cava before initiating the perfusion, and in the effluent from the perfused liver at regular intervals during the course of perfusion. Liver glycogen content was measured following acid hydrolysis according to the method described by Passoneau and Lauderdale[27] and expressed in wet weight (WW).[31] Liver glycogen phosphorylase concentration and activity ratio in the absence or presence of 5 mmol/L of 5′ adenosine monophosphate (5′AMP) was determined according to the procedure of Gilboe et al.[28] The activity of citrate synthase, as a marker of the training status, was determined in the rectus femoris, according to Srere.[29]

Liver net glucose release and lactate extraction (μmol · min^{-1} · g^{-1} of liver wet weight) was computed as the product of the perfusion rate (mL · min^{-1} · g of $liver^{-1}$) by the glucose or lactate concentration gradient across the liver (portal vein *v* vena cava) in micromoles per milliliter.

Statistics

Data are presented as mean ± SEM. The main effects of time and treatments (fed *v* fasted and trained *v* untrained) as well as time-treatment interactions were tested by analysis of variance with repeated-measures over time. Newman Keuls post hoc tests were used to identify the location of significant differences ($P \leq .05$) when appropriate.

RESULTS

At the time of experiment, body mass was not significantly different between trained (fed: 447 ± 11 g; fasted: 442 ± 11 g) and untrained animals (fed: 453 ± 17 g; fasted: 420 ± 10 g) and was not significantly modified by the overnight fast. Liver mass was not significantly different in trained and untrained rats, but was significantly lower in fasted rats (2.79% ± 0.05% *v* 3.62% ± 0.13% body mass, $P < .05$). Citrate synthase activity in the rectus femoris was not modified by the overnight fast, but was 36% higher in trained than in untrained rats (27.9 ± 1.6 *v* 20.5 ± 2.5 μmol · min^{-1} · g^{-1}, $P \leq .05$). Basal liver glycogen content before initiation of perfusion with glucagon was not significantly different in trained and untrained fed rats, but was much higher in fed than fasted rats (Table 1). Glycogen phosphorylase concentration and activity ratio were not modified by glucagon, but were significantly higher in liver from trained animals both before and after stimulation with glucagon (Table 2).

Basal HGP before initiation of perfusion with glucagon was much higher in fed than fasted rats, but no significant difference was observed between trained and untrained rats, in fed (0.42 ± 0.10 and 0.63 ± 0.18 μmol · min^{-1} · g^{-1} of liver WW in trained and untrained rats, respectively) as well as in fasting state (0.24 ± 0.10 and 0.09 ± 0.05 μmol · min^{-1} · g^{-1} of liver WW in trained and untrained rats, respectively, Fig 1). Glucagon significantly increased HGP in the 4 experimental groups (Fig 1), but the increase was more pronounced in trained than in untrained rats. In addition, when compared with untrained rats, the increase in HGP upon stimulation with glucagon occurred more quickly in fed and fasted trained rats (fed: 5 minutes *v* 15 minutes; fasted: 5 minutes *v* 10 minutes). Peak HGP values were higher in fed than in fasted rats and were higher in trained than in untrained rats in both fed and fasted conditions (Fig 1).

Table 2. Liver Glycogen Phosphorylase Concentration and Activity Before and After Stimulation With Glucagon in Untrained and Trained Fed Rats

	Concentration (IU/g liver WW)		Activity Ratio	
	Untrained	Trained	Untrained	Trained
Before	15.0 ± 1.6	19.7 ± 1.1*	0.81 ± 0.02	0.87 ± 0.01*
After	11.7 ± 1.9	19.2 ± 0.9*	0.77 ± 0.04	0.86 ± 0.02*

NOTE. Ratio I/I + D, where I and D are respectively the fraction of phosphorylase not activated and activated by 5′AMP[28]

*Significantly different from untrained rats: $P < .05$.

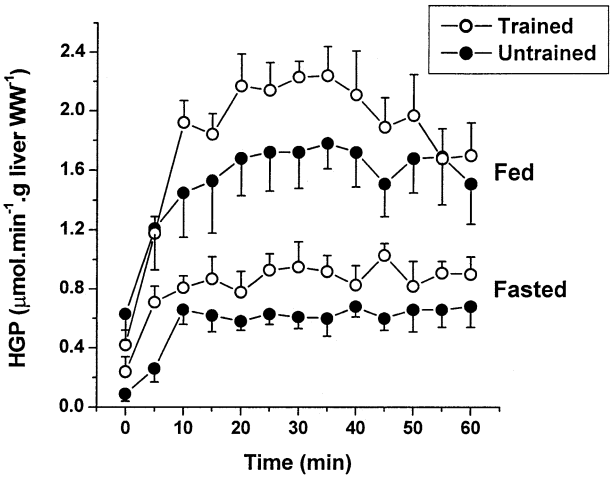

Fig 1. Glucose production in response to glucagon in perfused liver from trained and untrained, fed or fasted rats. Values are means ± SEM. Glucagon significantly increased HGP in all groups; the values observed in trained rats were significantly higher than those observed in untrained rats in both conditions; the values observed in fed rats were significantly higher than those observed in fasted rats in both untrained and trained conditions (main effects; $P < .05$).

Over the 60 minutes of perfusion with glucagon, the total amount of glucose released by the liver, computed from the area under the curve (AUC) of HGP (Fig 2A), was significantly higher in trained than in untrained rats both fed (+31%: 112.1 ± 7.1 *v* 85.9 ± 12.2 μmol/g of liver WW) and fasted (+46%: 50.8 ± 4.4 *v* 34.7 ± 3.6 μmol/g of liver WW, Fig 2B). In addition, the total amount of glucose released from the liver over the 60-minute period of perfusion with glucagon, both in untrained and trained rats, was approximately 60% higher in fed (34.7 ± 3.6 *v* 85.9 ± 12.2 μmol/g of liver WW) than fasted rats (50.8 ± 4.4 *v* 112.1 ± 7.1 μmol/g of liver WW). At the end of the period of stimulation with glucagon, liver glycogen content was much lower in fed trained than untrained rats (Table 1). Changes in glycogen content in liver from fasted rats, if any, over the period of stimulation with glucagon were below the limit of detection of the method (~10 μmol glycosyl U/g of liver WW).

In fasted animals, the mean lactate extraction across the liver during glucagon stimulation was significantly 30% ($P < .05$) higher in trained than untrained rats (2.69 ± 0.14 *v* 2.06 ± 0.13 $\mu mol \cdot min^{-1} \cdot g^{-1}$ of liver WW, respectively).

DISCUSSION

Results from the present study indicate that when compared with untrained rats, the increase in HGP in response to glucagon is higher from liver from endurance-trained rats in fasted as well as in fed states. These observations suggest that endurance training increases the response of both liver glycogenolysis and gluconeogenesis to glucagon.

We are not aware of any data concerning possible changes in liver glycogenolysis and/or its response to glucagon following training. In contrast, several studies have shown that liver gluconeogenesis from various precursors is increased following training.[14,21,35,36] However, there are only 3 reports on the effect of glucagon on the response of liver gluconeogenesis following training.[15-17] Drouin et al[17] have shown that when the secretion of endogenous insulin and glucagon were suppressed by somatostatin, HGP in response to insulin and glucagon infusion (I/G = 2.4 to 2.7) was 53% higher in endurance-trained than untrained subjects, at rest, following an 8-hour fast. Podolin et al[16] using liver slices from endurance trained rats incubated with high amounts of glucagon (10^{-7} mol/L) have reported a 47% increase in gluconeogenic capacity from lactate. Finally, preliminary data from Cheeks et al,[15] using liver perfused in situ, indicate that gluconeogenesis from a mixture of precursors was respectively 1.2, 1.9, and 3.5 times higher upon stimulation with glucagon at increasing concentration (50, 500, and 5,000 pmol/L, respectively), infused along with norepinephrine (3.0 nmol/L), and epinephrine (2.0 nmol/L) in liver from endurance-trained rats, following a 24-hour fast.

In the present study, livers from both fed and fasted animals were perfused with insulin and glucagon at concentrations within the physiologic range,[30] with an I/G ratio of 2.9 ± 0.1 or approximately 30% the basal values observed in untrained and trained fed animals.[18] With similar value of I/G (~2.4;

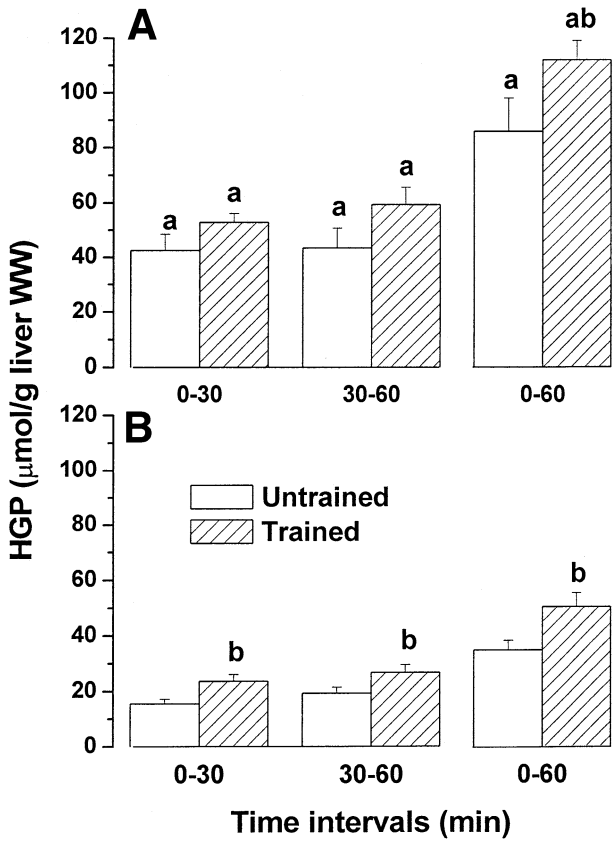

Fig 2. Total glucose production computed from the AUC in response to glucagon in perfused liver from trained and untrained, fed (A) or fasted (B) rats. Values are means ± SEM; [a]significantly higher than fasted rats and [b]untrained rats ($P < .05$).

glucagon concentration = 88 pg/mL), Shiota et al[30] have reported a net 2.2-fold increase in HGP in perfused liver from untrained fed rats, with peak values 30 minutes following the onset of glucagon administration. Results reported in the present study are well in line with these findings with an approximate 2.5-fold increase in HGP upon stimulation with glucagon in fed untrained rats. The response of HGP was rapid (peak HGP at 1.78 ± 0.17 $\mu mol \cdot min^{-1} \cdot g^{-1}$ of liver at minute 35), but was not sustained over the entire period of glucagon stimulation and was associated with a marked 29% decrease in liver glycogen content. In contrast, in untrained animals fasted for 24 hours and, accordingly, with very small liver glycogen stores, administration of glucagon resulted in a slow increase in HGP which leveled-off at 15 minutes and remained sustained thereafter. The cumulative glucose output, computed from the total AUC of HGP in untrained fasted animals, was 35 ± 4 μmol glucose/g of liver WW over the 60-minute period of stimulation with glucagon (Fig 2B). This value is more than double the amount of glucose present under the form of glycogen (Table 1) at the beginning of the experiment (14 ± 4 μmol glycosyl U/g of liver WW). These observations confirm that glycogenolysis and gluconeogenesis, respectively, were the main source of the glucose released under stimulation with glucagon in fed and fast animals.

As for the effect of the 10-week endurance swim-training program on the stimulation of HGP by glucagon, observations made in fed rats indicate that when compared with untrained rats, HGP was faster and higher in trained rats upon stimulation with glucagon. As expected, this was associated with a larger decline in liver glycogen content (66% *v* 29% in the untrained group). The overall glucose release (Fig 2) and liver glycogen breakdown (Table 1) in response to glucagon were, respectively, 31% and 38% higher in fed trained than untrained animals. Cherrington et al,[32] in anesthetized dogs, and Vissing et al,[33] in exercising rats, have shown that liver glycogen breakdown upon stimulation with glucagon[32] or in response to exercise[33] was increased when liver glycogen content was increased. However, this mechanism cannot account for the observation made in the present experiment in fed rats, because the initial liver glycogen content was similar in untrained and trained animals. The larger glycogen breakdown observed in liver from trained than untrained rats, although the initial glycogen contents were similar in both groups, indicates that liver glycogenolysis was more responsive to glucagon following endurance training.

When livers from trained fasted animals were stimulated with glucagon, the total increase in HGP was 46% larger than from liver from their untrained counterparts. This was associated with a 30% significant larger lactate uptake. As discussed previously for the untrained animals, the very small glycogen content (Table 1) at the beginning of stimulation with glucagon cannot account for the large HGP observed in trained animals (11 ± 3 μmol glycosyl U/g of liver WW). The larger HGP observed in trained than untrained animals thus confirms that endurance training increases the response of liver gluconeogenesis to glucagon as already suggested in a preliminary report by Cheeks et al[15] using perfused liver and by data from Podolin et al[16] using incubated liver slices.

Liver glucose output has been shown to be larger during exercise after endurance training,[13,14] and this could be due to a higher response of the liver to glucagon. Recently, Bergman et al[34] reported a 2-fold increase in gluconeogenesis from lactate in fasted humans at rest after a 9-week endurance training. In addition, several investigators have shown that endurance training increases gluconeogenesis in perfused liver or isolated hepatocytes from various glucose precursors without any hormonal stimulation.[14,21,35,36] However, except for the studies by Podolin et al[16] and Cheeks et al,[15] we are not aware of any data concerning the respective changes in the response of liver glycogenolysis and/or gluconeogenesis to glucagon following endurance training. Results from the present experiment confirm that endurance training not only increases basal gluconeogenesis, but also basal glycogenolysis and the response of both gluconeogenesis and glycogenolysis to glucagon.

The precise mechanisms by which endurance training increases HGP from glycogenolysis and gluconeogenesis, both in the basal state and upon stimulation with glucagon, remains to be determined. There is paucity of data concerning possible changes in key enzymes regulating liver glycogenolysis following endurance training. Data from Lamb et al[37] and Galbo et al[38] indicate, respectively, that in liver from endurance trained rats, the activity of glucose-6-phosphatase is unchanged, and that of glycogen phosphorylase is decreased. In the present study, in contrast to the report by Galbo et al,[38] both the concentration and activity of glycogen phosphorylase were significantly higher in liver from trained fed rats. However, this did not translate into a higher HGP before stimulation with glucagon. In addition, glycogen breakdown, and the response of HGP to glucagon observed in both untrained and trained rats, was not associated with an increased activity of glycogen phosphorylase. As for gluconeogenesis, several studies have failed to show any increase in the activity of key enzymes regulating this pathway.[36,37,39-41] Results from Burelle et al[35] suggest that an increased capacity of alanine transport and an increased transamination of alanine into pyruvate in isolated hepatocytes could be responsible for the larger gluconeogenic flux observed from alanine in endurance-trained rats. However, the concentration of alanine transporter(s) and the concentration or activity of alanine transaminase was not directly determined. Recent data from Légaré et al[18] and Podolin et al[19] indicate, respectively, a 39% higher density and a 2-fold greater affinity of glucagon receptors in plasma membranes purified from liver in trained than untrained rats. These changes in glucagon receptors are well within the range of those observed in the present experiment for HGP in response to glucagon following swim training, both in the fed and fasted states. It could thus be suggested that the increased response of both liver glycogenolysis and gluconeogenesis to glucagon following endurance training could be mainly due to the increased density and affinity of glucagon receptors.

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