Effect of oral glutamine on whole body carbohydrate storage during recovery from exhaustive exercise

J. L. BOWTELL, K. GELLY, M. L. J ACKMAN, A. PATEL, M. SIMEONI, and M. J. RENNIE
1Department of Anatomy and Physiology, University of Dundee, Dundee, United Kingdom DD1 4HN; and 2Department of Electronics and Informatics, University of Padua, 35131 Padua, Italy

Effect of oral glutamine on whole body carbohydrate storage during recovery from exhaustive exercise. J. Appl. Physiol. 86(6): 1770–1777, 1999.—The purpose of this study was to determine the efficacy of glutamine in promoting whole body carbohydrate storage and muscle glycogen resynthesis during recovery from exhaustive exercise. Postabsorptive subjects completed a glycogen-depleting exercise protocol, then consumed 330 ml of one of three drinks, 18.5% (wt/vol) glucose polymer solution, 8 g glutamine in 330 ml glucose polymer solution, or 8 g glutamine in 330 ml placebo, and also received a primed constant infusion of [1-13C]glucose for 2 h. Plasma glutamine concentration was increased after consumption of the glutamine drinks (0.7–1.1 mM, P < 0.05). In the second hour of recovery, whole body nonoxidative glucose disposal was increased by 25% after consumption of glutamine in addition to the glucose polymer (4.48 ± 0.61 vs. 3.59 ± 0.18 mmol/kg, P < 0.05). Oral glutamine alone promoted storage of muscle glycogen to an extent similar to oral glucose polymer. Ingestion of glutamine and glucose polymer together promoted the storage of carbohydrate outside of skeletal muscle, the most feasible site being the liver.

Glutamine synthesis; glucose oxidation; insulin resistance

Glutamine is a glucogenic, nonessential amino acid that can be synthesized within the tissues of the body, with skeletal muscle (13) and liver (16) being the most quantitatively important producers. There is considerable evidence to suggest that the size of the intramuscular glutamine pool exerts a controlling influence over whole body protein balance (for review, see Ref. 28). For example, during various catabolic conditions such as after surgery the pool size is reduced (37) and in the anabolic state it is increased (23, 24). There is also some evidence to suggest that a relative immunodeficiency that is symptomatic of “overtraining syndrome” may be one consequence of glutamine depletion (for review, see Ref. 31), because glutamine is a favored fuel and nitrogen source for macrophages and lymphocytes (2).

It has also been reported that glutamine stimulates the activity of hepatic glycogen synthase, possibly through a cell-swelling-mediated action (2, 26). Glutamine is readily taken up into skeletal muscle via the high-capacity, sodium-dependent system Nm (1), resulting in an increased intramuscular glutamine concentration and thus promoting cell swelling (22). Meijer et al. (26) found that both hepatocyte swelling and a rise in glutamate concentration (both of which would result from an increased systemic glutamine concentration) stimulate glycogen synthase phosphatase and hence cause an activation of glycogen synthase through dephosphorylation (19). Work from our laboratory suggests that, in vitro, myotube glycogen synthesis is also modulated by cell volume changes, independently of changes in glucose uptake (21). In recent studies (36), our laboratory also found the intravenous adminstration of glutamine to promote muscle glycogen synthesis during recovery after exhaustive exercise, possibly because glutamine was acting as a glucogenic substrate and/or through an activation of glycogen synthase.

The purposes of the present study were threefold. First, we wanted to determine whether the oral provision of glutamine may also be successful in promoting muscle glycogen resynthesis during recovery from exhaustive exercise. Glutamine is readily utilized by the gut mucosal cells (15), and the oral route of administration may thus prove problematic if the gut removes glutamine for its own use in a first-pass effect. Second, in a protocol involving the consumption of glucose polymer with or without glutamine supplementation, we investigated whether the stimulatory effects of glutamine and of glucose polymer on postexercise muscle glycogen resynthesis are additive. Third, to determine the effects of glutamine on whole body glycogen storage and (by comparison with the effects in muscle) on hepatic glycogen storage, we used a glucose tracer labeled with the stable, nonradioactive isotope 13C was used.

METHODS

Seven male subjects [weight: 76.2 ± 3.4 kg, height: 1.78 ± 0.03 m, body fat: 16.0 ± 3.6%, and maximal O2 uptake (V̇O2max): 38.9 ± 3.2 ml·kg–1·min–1] participated in three trials, in each of which they received one of three different drinks by systematic rotation: 18.5% (wt/vol) glucose polymer solution (containing dextrose, maltose, maltotriose, tetrasaccharide, pentasaccharide, and higher sugars; SmithKline Beecham Consumer Healthcare, Gloucestershire, UK); a placebo containing 8 g glutamine; or 18.5% glucose polymer containing 8 g glutamine. Their V̇O2max values were determined in the week preceding each trial, to control for any changes that may have occurred in the intervening month. An incremental exercise test on an electrically braked cycle ergometer (Monark) using the criteria of Taylor et al. (33) was adopted for the measurement of V̇O2max. Respiratory gases were measured by using on-line gas analysis (Morgan Benchmate Exercise Test, P. K. Morgan, Gillingham, Kent, UK). The study was approved by the Tayside Ethics Committee, and all subjects gave their informed consent.

Subjects were instructed to refrain from exercise and the consumption of alcohol on the day preceding each trial. After an overnight fast, the subjects completed an exercise protocol designed to deplete both type I and II muscle fibers of glycogen as validated by Vollestad et al. (38). Subjects cycled on the ergometer at 70% V̇O2max for 30 min; the workload was...
then doubled, and they completed 6 × 1-min bursts of activity separated by 2 min of rest. This burst of high-intensity activity was designed to deplete type II fibers of glycogen. Finally, they cycled for a further 45 min at 70% \( \dot{V}O_2 \)max to ensure both a further depletion of glycogen in type I fibers and a low plasma lactate concentration at the end of exercise to minimize glycogen resynthesis from lactate during recovery. Subjects were allowed to consume water ad libitum during the exercise period.

Immediately after exercise, cannulas were inserted into the antecubital vein of each forearm, one for blood sampling and the other for the infusion of [1-\(^{13}\)C]glucose (99 atoms % MassTrace, Somerville, MA). Two basal blood samples were then taken, and expired air for \(^{13}\)CO\(_2\) analysis was collected into a 1-liter bag, from which two aliquots were removed and stored in 10-ml evacuated glass tubes (Exetainers, Europa Scientific, Crewe, UK). A muscle biopsy was taken from quadriceps femoris by conchotheric forceps under local anesthetic (lignocaine, 1%, wt/vol, Phoenix Pharmaceuticals, Gloucester, UK) (12) within 15 min of the end of exercise. Once these postexercise samples had been collected, a 2-h, primed, constant [1-\(^{13}\)C]glucose infusion was begun, always within 20 min of the cessation of exercise. The plasma glucose pool was primed with a 9 mg/kg bolus of [1-\(^{13}\)C]glucose to facilitate the rapid attainment of a steady state of plasma glucose \(^{13}\)C labeling. The [1-\(^{13}\)C]glucose was then infused at a rate of 8.5 mg·kg\(^{-1}\)·h\(^{-1}\) for the first 30 min. The subject then consumed a drink (330 ml), 18.5% glucose polymer, a placebo containing 8 g glutamine, or 18.5% glucose polymer containing 8 g glutamine, within 2 min of the start of the infusion. The rate of [1-\(^{13}\)C]glucose infusion was increased to 10 mg·kg\(^{-1}\)·h\(^{-1}\) for the final 90 min to minimize the changes in the tracer-to-tracee ratio (see below).

Samples of blood and expired air were collected every 15 min during the glucose tracer infusion. Respiratory gas exchange was measured for 10 min every 30 min by using a Deltatrac metabolic monitor (Datex, Helsinki, Finland). Second and third quadriceps femoris muscle biopsies were taken during recovery, 1 and 2 h after the start of the [1-\(^{13}\)C]glucose infusion. \(^{13}\)CO\(_2\) labeling was determined by using an automatic nitrogen and carbon analyzer coupled to a Tracermass 20:20 isotope ratio mass spectrometer (Europa Scientific); results were expressed as per thousand change (‰) in \(^{13}\)C-labeled Pee Dee Belemnitella-1 (PDB-1) in comparison with the international standard (PDB-1). The \(^{13}\)C-labeling (moles percent excess) was obtained by using the isotope ratios as described previously, and the resultant values for \(^{13}\)CO\(_2\) were multiplied by six to obtain \(^{13}\)C labeling of the glucose molecule to correct for dilution by the hexose carbons. The tracer-to-tracee mass ratios were then calculated from these values (9).

For measurement of muscle glycogen concentration, the muscle tissue was frozen immediately in liquid nitrogen and stored at −70°C until the analyses could be performed. Muscle glycogen concentration was determined by a method previously described by Varnier et al. (36). In brief, 30–40 mg muscle tissue cleaned of blood and connective tissue were homogenized in 250 µl distilled water by using a Teflon glass Potter-Elvehjem homogenizer on ice. The homogenate was transferred to screw-topped glass hydrolysis tubes containing 50 µl 6 M hydrochloric acid and incubated in a boiling water bath for 2 h. After cooling, the mixture was neutralized by using 2 M potassium hydroxide and then centrifuged, and the supernatant was assayed for glucose (Sigma Chemical).

The rate of glucose appearance (R\(_a\)) and disappearance (R\(_d\)) were estimated by using Steele’s equations (32)

\[
R_a(t) = \left[ R_s(t) - V_s \frac{dz(t)}{dt} \right] z(t)
\]

\[
R_d(t) = R_s(t) - V_s \frac{dg(t)}{dt}
\]

where \(V_s\) is Steele’s volume, \(g(t)\) is glucose concentration, \(z(t)\) is tracer-to-tracer ratio, and \(R_s\) is the tracer infusion rate. Steele’s volume was assumed equal to 130 ml/kg (7). Note that to reduce the effect of model error on \(R_a\) and \(R_d\) estimations (7, 8), variations of tracer-to-tracee ratio were minimized by adopting a two-step tracer-administration format.

Whole body glucose oxidation was calculated as the product of total \(^{13}\)CO\(_2\) produced (i.e., \(\dot{V}CO_2 \times F^{13}\CO_2\)) divided by plasma glucose \(^{13}\)C labeling, where \(\dot{V}CO_2\) is \(^{13}\)CO\(_2\) production. A correction factor (F) was used to correct for the retention of \(^{13}\)C within the bicarbonate pool. A mean correction factor (46%) was used. This was derived from the pooling of data from two of our studies, in which the retention of \(^{13}\)C label within the bicarbonate pool during recovery from exercise (6, 20) was determined. This value is considerably lower than the 81% figure frequently used to calculate substrate oxidation in postabsorptive subjects in the resting state. However, during the postexercise period, sequestration of bicarbonate carbon for various metabolic processes such as ureagenesis and gluconeogenesis is increased, thus reducing \(^{13}\)C label recovery. Nonoxidative glucose disposal was calculated as the difference between \(R_d\) and oxidation.
The average net rate of muscle glycogen storage was calculated as the difference between muscle glycogen concentration in the biopsies obtained after 2 h of recovery and immediately after exercise.

Data were analyzed by using repeated-measures ANOVA to establish the presence of a significant difference among trials, and then a post hoc Tukey test was used to locate the site of the difference.

**RESULTS**

All subjects completed the exercise protocol, although in some cases the resistance had to be reduced for the final 10 min. Plasma glucose was increased by consumption of the glucose polymer-containing drinks ($P < 0.0005$, Fig. 1). Plasma lactate concentrations at the end of exercise were only slightly higher than normal resting values (1.8 ± 0.2 mM, data not shown) and were not different among trials at any time during recovery. Plasma insulin was increased by the consumption of the glucose polymer-containing drinks ($P < 0.005$, Fig. 2). Plasma insulin concentration was lower in the subjects who had consumed the glutamine-only drink than in those who had consumed the glucose polymer-containing drinks ($P < 0.05$). There was a tendency for plasma insulin concentration to be higher after consumption of the glucose polymer + glutamine rather than the glucose polymer-only drink.

Plasma glutamine concentration was elevated after consumption of the glutamine-containing drinks ($P < 0.05$, Fig. 3). Plasma glutamate concentration (normally 70–90 µM) was not different between trials (data not shown).

$R_a$ changed over time ($P < 0.005$, Table 1) and was higher during the glucose polymer + glutamine than the glutamine-only trials at 82.5 and 112.5 min. In the final hour of recovery, $R_a$ tended to be higher during the glucose polymer + glutamine than the glucose polymer-only trial. $R_d$ changed over time ($P < 0.0005$, Table 1) and was higher during the glucose polymer + glutamine than the glutamine-only trials at 82.5, 97.5, and 112.5 min. $R_a$ tended to be higher during the second hour of recovery in the glucose polymer + glutamine than the glucose polymer-only trial.

There was no statistical difference in whole body glucose oxidation among trials (0.64 ± 0.13, glutamine-only; 0.40 ± 0.07, glucose polymer-only; and 0.49 ± 0.06, glucose polymer + glutamine; all mmol·kg$^{-1}$·h$^{-1}$). Whole body nonoxidative disposal of glucose changed over time ($P < 0.005$, Fig. 4) and was significantly
Table 1. Effect of glutamine, glucose polymer-only, and glucose polymer + glutamine drinks on the rate of appearance and disposal of glucose during 2-h recovery from fatiguing exercise

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Ra (mmol·kg⁻¹·h⁻¹)</th>
<th>Rd (mmol·kg⁻¹·h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5</td>
<td>Gln</td>
<td>3.46 ± 0.67</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>2.44 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>GP + Gln</td>
<td>2.95 ± 0.46</td>
</tr>
<tr>
<td>22.5</td>
<td>Gln</td>
<td>2.94 ± 0.69</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>3.38 ± 0.27</td>
</tr>
<tr>
<td></td>
<td>GP + Gln</td>
<td>3.45 ± 0.24</td>
</tr>
<tr>
<td>37.5</td>
<td>Gln</td>
<td>3.84 ± 1.02</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>4.12 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>GP + Gln</td>
<td>4.59 ± 0.69</td>
</tr>
<tr>
<td>52.5</td>
<td>Gln</td>
<td>3.74 ± 0.98</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>4.31 ± 0.31†</td>
</tr>
<tr>
<td></td>
<td>GP + Gln</td>
<td>4.32 ± 0.25</td>
</tr>
<tr>
<td>67.5</td>
<td>Gln</td>
<td>3.47 ± 0.92</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>4.20 ± 0.27†</td>
</tr>
<tr>
<td></td>
<td>GP + Gln</td>
<td>4.51 ± 0.52</td>
</tr>
<tr>
<td>82.5</td>
<td>Gln</td>
<td>2.82 ± 0.78*</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>3.79 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>GP + Gln</td>
<td>4.87 ± 0.80‡</td>
</tr>
<tr>
<td>97.5</td>
<td>Gln</td>
<td>3.30 ± 0.94</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>3.41 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>GP + Gln</td>
<td>4.83 ± 0.97‡</td>
</tr>
<tr>
<td>112.5</td>
<td>Gln</td>
<td>2.74 ± 0.76*</td>
</tr>
<tr>
<td></td>
<td>GP</td>
<td>3.12 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>GP + Gln</td>
<td>4.52 ± 0.87</td>
</tr>
</tbody>
</table>

Values are means ± SE in mmol·kg⁻¹·h⁻¹; n = 7 subjects in each group. Ra and Rd, rate of appearance and disappearance, respectively; Gln, glutamine; GP, glucose polymer. Significantly different from values after consumption of GP + Gln drink: *P < 0.05. Significantly different from values after 7.5-min recovery during GP-only trial (†P < 0.05) and during GP + Gln trials (‡P < 0.05).

higher during the glucose polymer + glutamine than the glutamine-only trial at 52.5 min (4.22 ± 0.22 vs. 1.97 ± 0.45), 82.5 min (4.70 ± 0.82 vs 2.19 ± 1.64), and 97.5 min (4.72 ± 0.86 vs 2.63 ± 0.74; all mmol·kg⁻¹·h⁻¹). The area under the curve of the nonoxidative disposal graph was calculated to provide a measure of whole body carbohydrate storage during the first and second hours of recovery. The area under the curve was significantly higher in the second hour of recovery in all trials (P < 0.05, Fig. 5), but the average rate of net muscle glycogen storage during the 2 h of recovery was not different among trials (4.10 ± 1.08, glutamine-only; 5.04 ± 1.13, glucose polymer-only; 4.51 ± 1.88, glucose polymer + glutamine; all mmol·kg⁻¹·h⁻¹).

**DISCUSSION**

There is evidence that up to 53% of a tracer dose of glutamine is removed on the first pass through the splanchnic bed, accompanied by a large increase in the rate of glutamine oxidation, presumably in the splanchnic viscera (15). However, in the present study, provision of glutamine orally was successful in elevating plasma glutamine at the peak concentration by 46%, which suggests that a substantial proportion of the oral

![Fig. 4. Rate of whole body nonoxidative glucose disposal during recovery from exhaustive exercise. Values are means ± SE (n = 7). Significantly different from values after consumption of glucose polymer-only drink (P < 0.05) and from values after consumption of glucose polymer + glutamine drink (P < 0.05) and during GP-only trial (†P < 0.05) and glutamine-only trials (§P < 0.05).](http://jap.physiology.org/)
load escaped utilization by the gut mucosal cells and uptake by the liver and kidneys. If the entire glutamine dose had been distributed within the blood (8% body wt) and extracellular fluid (20% lean body mass) compartments, then a 3-mM rise in blood glutamine concentration might have been expected, whereas plasma glutamine concentration was only observed to rise by 0.3 mM. This might suggest that only 10% of the oral dose reached the extracellular fluid compartments; however, this interpretation is certainly complicated by the relative distribution of the glutamine between plasma and erythrocytes in the blood.

Glutamine is transported across the intestinal brush border by both sodium-dependent and -independent systems (34). Because of this cotransport, it has been suggested that glutamine may promote more rapid fluid absorption in the gut; the inclusion of glutamine within oral rehydration solutions has been found to increase sodium absorption and therefore bulk water flow (30, 35). However, as far as could be ascertained with the limited sensitivity of the sampling protocol used in the present study, peak plasma glucose concentration was achieved 45 min after consumption of both of the glucose polymer-containing drinks. This would tend to suggest that the consumption of glutamine in addition to glucose polymer did not increase the rate of substrate absorption.

The exogenous glucose polymer has three possible fates: oxidation, storage as glycogen, or storage as fat after glycolysis to acetyl-CoA; the formation of alphaglycerophosphate and storage as glycogen in triglyceride is also a possibility. The first two and the fourth possibilities are likely to be the most important quantitatively in adult human beings used to eating a high-fat diet (18). Thus we have calculated whole body net carbohydrate storage as whole body glucose disposal minus oxidation. There was no statistical difference in whole body glucose oxidation or total carbohydrate oxidation (as calculated by indirect calorimetry) among trials. However, the rate of whole body glucose disposal was elevated in those trials in which exogenous glucose polymer was provided; thus nonoxidative disposal of glucose was therefore elevated relative to the glutamine-only trial. This nonoxidative disposal of glucose (i.e., carbohydrate storage or glycogen synthesis) accounted for 80, 89, and 91% of total glucose disposal in the glutamine, glucose polymer, and glucose polymer+glutamine trials, respectively. Although the addition of glutamine to the glucose polymer beverage did not significantly alter the proportion of glucose turnover composed of storage, the total amount of carbohydrate stored in the whole body during recovery was higher after consumption of the glucose polymer+glutamine drink than after the glucose polymer-only drink, because of the higher whole body glucose flux. This is unlikely to be attributable to the study design because, although glutamine was provided in addition to the glucose polymer, the energetic difference was only 10%, whereas the difference in total carbohydrate storage over the 2-h period was 20%.

The rates of muscle glycogen storage were not different among trials, which is surprising because it would have been expected that the provision of 61 g glucose polymer (1,125 kJ) as opposed to 8 g glutamine (140 kJ) should result in a greater muscle glycogen synthesis. The resultant increase in both glucose and insulin availability, after consumption of the glucose polymer-containing drinks, should tend to increase glucose uptake by the muscle both via increased glucose delivery and a translocation of GLUT-4 to the sarcolemmal membrane (14) and also via the activation of glycogen synthase (10).

However, when the results from the present study are directly compared with those obtained by Varnier and colleagues (36), in a study carried out in our laboratory and using an identical experimental protocol in similar subjects, oral glutamine does appear to promote net resynthesis of muscle glycogen stores relative to control subjects in whom saline or alanine+glycine were infused. We found that after the subjects’ consumption of the glutamine-only drink, the rate of muscle glycogen storage was 4.1 ± 1.1 mmol·kg wtx−1·h−1, whereas Varnier and colleagues found that the rate of net muscle glycogen storage after infusion of either saline or alanine+glycine fell within the range 0.5–1.0 mmol·kg wtx−1·h−1, which is consistent with previously reported results. The effect of glutamine may be due to one or both of two possibilities: first, glutamine has been shown to be an effective substrate for hepatic glycogen synthesis in 72-h fasted rats, i.e., when glycogen is severely depleted (27); such a scenario could also occur in postexercise muscle in which glycogen is low and in which all of the required transporters and enzymes exist. In skeletal muscle, the exogenous glutamine will be rapidly taken up through system Nm (1), where it can be deaminated to form glutamate and then 2-oxoglutarate through the action of either glutaminase and glutamate dehydrogenase or glutamine transaminase and ω-amidase. It is possible, then, for the 2-oxoglutarate to enter the TCA cycle and be removed at the level of malate (by the action either of malate dehydrogenase or of the malic enzyme plus phosphoenolpyruvate carboxykinase and pyruvate kinase); the malate can be converted to oxaloacetate, phosphoenolpyruvate, and finally pyruvate, which may then be used in the glycogenic pathway by reversal of glycolysis to fructose 1,6-bisphosphate. This pathway may be particularly active at the end of exercise, when both the availability of glycogenic metabolites and muscle glycogen concentration are low; comparisons may be drawn to the physiological state in the starved condition, when glutamine has proved to be an effective glycogenic substrate in rat muscle (27). However, only 55 mmol of glutamine were ingested, of which, at most, probably only 47% reached the systemic circulation (15); thus the resultant glycogenic precursor would be of minor importance relative to the 119 mmol of muscle glycogen storage that occurred during the 2-h recovery period.
It is more likely that the promotion of muscle glycogen storage by glutamine consumption occurs via an activation of glycolgen synthase (19), which catalyzes the rate-limiting step in the glycogen synthesis pathway. This may be a result of glutamine-induced cell swelling (21, 26), which is thought to stimulate glycolgen synthase phosphatase. The pool of muscle glutamine is depleted after exercise (29); therefore, provision of glutamine immediately postexercise may be particularly effective in promoting a relative cell swelling and thus glycolgen synthase activity. Any increase in intracellular fluid volume would tend to cause an underestimation of muscle glycogen concentration, because the glycolgen assay was performed in wet muscle. However, in vitro work using primary rat myotubes suggests that cell swelling is a transient response that disappeared 15 min after the removal of glutamine from the incubation media (22). The rate of muscle glycogen storage is therefore unlikely to have been underestimated. The signaling effect induced by cell swelling is a much more long-lived response, with the peak response in glycolgen synthesis occurring 1 h after osmotic swelling (21). One might therefore expect to observe any effect of glutamine supplementation on carbohydrate storage during the second hour of recovery. Indeed, the increase in muscle glycogen concentration is greater during the second hour of recovery for the glutamine-only trial (Fig. 5). In contrast, muscle glycogen storage is more rapid during the first hour of recovery in the glucose polymer-only trial, presumably because of the higher availability of glucose as indicated by plasma glucose concentration.

The addition of glutamine to the glucose polymer drink did not further promote muscle glycogen storage. Glutamine alone did appear to promote muscle glycogen resynthesis (possibly via an activation of glycolgen synthase), but in the presence of elevated insulin concentrations the activity of glycolgen synthase might be expected to be maximally stimulated (10). Although insulin stimulates glycogen synthase phosphatase and thus activates glycogen synthase, it has been suggested that an additional part of insulin’s action may be mediated through cell swelling and the mitogen-activated protein-kinase-activated protein kinase pathway, as well as via the tyrosine kinase-initiated phosphorylation cascade (17). The mechanism of the glutamine-induced activation of glycogen synthase in liver and muscle is also proposed to occur via cell swelling (3, 21, 26). If both mechanisms were fully activated by insulin, this would explain why there does not appear to be an additive increase in glycogen storage when the glutamine+glucose polymer drink was consumed.

Despite the apparent absence of a stimulatory effect of the gluclumine and glucose polymer drink on muscle glycogen resynthesis, whole body carbohydrate storage was elevated by the addition of glutamine. Total glycogen storage in the exercised leg muscle over the 2 h of recovery was calculated on the basis that 40% body weight is composed of skeletal muscle and that leg muscle contributes 50% of total skeletal muscle mass (i.e., 14.5 ± 0.8 kg). After the subjects’ consumption of glutamine-only and glucose polymer-only drinks, 35 and 37% whole body carbohydrate storage can be attributed to glycogen storage in the exercised muscles, respectively. However, for glucose polymer+glutamine trials, only 25% carbohydrate storage occurred within the exercised muscle, although total glycogen stored in muscle was probably greater than this (exercised and nonexercised). The most likely site of the increased carbohydrate storage associated with glutamine supplementation is the liver, but without further investigation using liver biopsies or $^{13}$C or proton NMR it will not be possible to confirm or refute this hypothesis. Nevertheless, it is puzzling why, if similar mechanisms for stimulation of glycogen synthesis by glutamine, or at least their potential, exists in both skeletal muscle and liver, only nonmuscle sites are stimulated to store exogenous glucose in the presence of glutamine.

One explanation is offered by the results of recent in vitro work using rat skeletal muscle (4), which suggest that glucosamine, a product of glucose metabolism via the hexosamine pathway, induces insulin resistance by causing an impairment of the translocation of GLUT-4 from an insulin-sensitive intracellular pool to the sarcolemmal membrane. The amination of fructose-6-phosphate to form glucosamine-6-phosphate catalyzed by glutamine-fructose-6-phosphate amidotransferase, with glutamine acting as the amido donor, is the rate-limiting step in the hexosamine biosynthetic pathway (11). It is possible, therefore, that the increase in intracellular glutamine and glucose induced by the consumption of the glucose polymer+glutamine beverages stimulated flux through this rate-limiting step and hence the hexosamine pathway as a whole. Impaired GLUT-4 translocation in skeletal muscle would act to reduce skeletal muscle glucose uptake and hence limit muscle glycogen synthesis despite any activation of glycogen synthase. Glucose uptake in the liver, however, is via the non-insulin-dependent glucose transporter, GLUT-2, so that a compensatory increase in liver glucose uptake and hence hepatic glycogen synthesis could feasibly occur. The restoration of muscle glycogen in the postexercise recovery period is normally prioritized at the expense (presumably) of liver glycogen resynthesis (25). The addition of glutamine to the glucose polymer drink appears to facilitate a resynthesis of both liver and muscle glycogen stores, with the potential benefit of prolonging the availability of glucose in the blood for use by the central nervous system and thus possibly endurance time in a subsequent bout of exercise.

This hypothesis suggests that the eating of protein and thus a glutamine-rich mixed meal containing carbohydrate may be more efficient in storing glycogen than consumption of a pure carbohydrate meal alone. Indeed, Zawadzki and colleagues (39) found that postexercise muscle glycogen storage was promoted by the consumption of protein in addition to a carbohydrate meal. Unfortunately, the test meals in this study were
not isoenergetic; thus further work in this area is required to determine whether protein may elicit a true stimulatory effect.

In conclusion, ingestion of glutamine alone appeared to promote muscle glycogen resynthesis during recovery from exhaustive exercise, relative to that expected from studies in which no substrate was provided. The promotion of muscle glycogen synthesis by consumption of glucose polymer and of glutamine was not additive. However, the addition of glutamine to the glucose polymer drink resulted in a greater storage of carbohydrate in sites other than skeletal muscle, the most likely candidate being the liver.

This work was supported by SmithKline Beecham Consumer Healthcare and the University of Dundee.

Address for reprint requests and other correspondence: J. L. Bowtell, Dept. of PE/SS/RM, Loughborough Univ., Loughborough, Leics LE11 3TU, UK (E-mail: J.L.Bowtell@lboro.ac.uk).

Received 22 October 1997; accepted in final form 23 February 1999.

REFERENCES


