L-Glutamine Supplementation of a High Fat Diet Reduces Body Weight and Attenuates Hyperglycemia and Hyperinsulinemia in C57BL/6J Mice1,2,3

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ABSTRACT C57BL/6J (B/6J) mice are genetically predisposed to become overweight and develop hyperglycemia if raised on a high fat diet. The purpose of the present study was to explore the effect of dietary supplementation of L-glutamine (Gln), an inhibitor of fatty acid oxidation, on the development of hyperglycemia and excessive weight gain. Groups of 10 age- and weight-matched male B/6J mice were raised on one of four diets: 1) a low fat, low sucrose (LL), studied separately, 2) a high fat, low sucrose (HL) diet alone, 3) high fat, low sucrose supplemented with L-glutamine (HL + Gln) and 4) high fat, low sucrose supplemented with L-alanine (HL + Ala). Energy intake, body weight, plasma glucose and insulin concentrations were monitored over time. We found no difference in energy intake per unit body weight between any groups after the first 2 wk of feeding. However, the mean ± SEM for body weight (27.1 ± 0.6 g) of the LL group measured at 16 wk was lower (P < 0.05) than that of the HL group at 37.9 ± 1.9 g. Also, after 5.5 mo, the mean ± SEM for plasma glucose and insulin concentrations in the LL group of mice were 6.9 ± 0.4 mmol/l and 146 ± 30 pmol/l, which were lower (P < 0.05) than those in the HL group at 10.1 ± 0.9 mmol/l and 438 ± 84 pmol/l, respectively. Although both amino acids caused a 10% reduction (P < 0.05) in body weight compared with HL feeding at wk 16, only Gln supplementation resulted in persistent reductions in both plasma glucose and insulin concentrations over 5.5 mo. In another experiment, when Gln was added to the high fat (HL) diet of heavy hyperglycemic animals for 2 mo, body weight gain, hyperglycemia and hyperinsulinemia were attenuated. In conclusion, supplementing glutamine to a high fat diet reduces body weight and attenuated hyperglycemia and hyperinsulinemia in B/6J mice. J. Nutr. 126: 273–279, 1996.

INDEXING KEY WORDS:
- L-glutamine • antidiabetic • antioesity
- weight maintenance • mice

Most individuals with noninsulin-dependent diabetes mellitus [NIDDM]5 or Type 2 diabetes suffer from obesity [Caro et al. 1989]. However, the effect of obesity on glucose tolerance is poorly understood. Recent studies have shown that obesity and insulin resistance can be induced by high fat feeding [Bray et al. 1992, Storlien et al. 1986, Surwit et al. 1988]. Considerable evidence indicates, however, that obesity and Type 2 diabetes have a strong genetic component that controls the metabolic response to dietary fat [Bray et al. 1992, Laws et al. 1989, Surwit et al. 1988, 1991 and 1995, West et al. 1992]. For example, previous studies from our laboratory have shown that when two strains of mice, the A/J and C57BL/6J (B/6J), are fed a high fat diet for 4 mo, the B/6J but not the A/J mice become obese and develop Type 2 diabetes (Surwit et al. 1988, 1991 and 1995).

Some studies have suggested that in susceptible individuals, consumption of a high fat diet induces the expansion of fat stores and a commensurate increase in the oxidation of fat for energy [Astrup et al. 1994,....]

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3 The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 USC section 1734 solely to indicate this fact.
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5 Abbreviations used: ECE, energy conversion efficiency; HL, high fat, low sucrose; HL + Gln, high fat, low sucrose supplemented with L-glutamine; HL + Ala, high fat, low sucrose supplemented with L-alanine; LL, low fat, low sucrose; NIDDM, noninsulin-dependent diabetes mellitus.
Flatt et al. 1987, Randle et al. 1963). Randle et al. (1963) hypothesized that in this situation, there is an inverse relationship between fatty acid oxidation and glucose oxidation resulting in impaired glucose utilization. This hypothesis recently received considerable attention (McGarry 1992). It is generally held that increased levels of intermediates and products of fatty acid oxidation including acetyl CoA, citric acid, ATP and lipid peroxides inhibit glucose metabolism at several steps of the glycolytic pathway (Arslanian and Kalhan 1994, Baron et al. 1989, Foley 1992, Groop et al. 1991, Opara and Hubbard 1993a, Randle et al. 1963, Sako and Grill 1990, Saloranta et al. 1993). The strongest support for this concept has come from studies showing that inhibition of fatty acid oxidation with pharmacologic agents can prevent fatty acid-induced impairment of glucose oxidation and the associated pathophysiologic response, in vivo and in vitro (Foley 1992, Opara and Hubbard 1993a, Sako and Grill 1990). It is not clear if nutrients that inhibit fatty acid oxidation can be useful in preventing and/or treating impaired glucose regulation induced by dietary fat.

Over the last decade, there has been interest in L-glutamine (Gln) because of its numerous metabolic effects (Lowe et al. 1990, Newsholme 1994, Souba and Wilmore 1985). Among these are inhibition of fatty acid oxidation (Malaisse et al. 1980), inhibition of lipolysis (Cersosimo et al. 1986, Dechellotte et al. 1991), stimulation of glycogen and protein synthesis (Rennie et al. 1994) and enhancement of glutathione biosynthesis (Hong et al. 1992). Glutamine has been used to inhibit linoleic acid oxidation and thus prevent its desensitization effect on response to glucose stimulation in isolated perfused islets (Opara et al. 1993b). The present study was designed to examine the effect of Gln supplementation during high fat feeding on the development of excessive body weight and hyperglycemia in the B/6J mouse.

MATERIALS AND METHODS

Animals and dietary regimens. Weight-matched B/6J male mice were obtained from Jackson Laboratories (Bar Harbor, ME) at 4 wk of age. The animals were housed five per cage in a temperature-controlled room with a 12-h light-dark cycle. Groups of 10 mice had free access to water and were weaned onto one of the following diets: a high fat, low sucrose diet alone (HL), the high fat diet supplemented with L-glutamine (HL + Gln) and the high fat diet supplemented with L-alanine (HL + Ala). A control group, studied separately, was raised on a low fat, low sucrose (LL) diet, and all animals had free access to food and water. The HL + Ala diet was designed to assess the specificity of the effect of Gln supplementation in the diabetogenic high fat diet. All diets obtained from Research Diets, New Brunswick, NJ, contained at least 16.5% protein and met the AIN requirements for mice with regard to mineral and vitamin content (Surwit et al. 1995). The low fat diet is composed of fat as 10.5% and carbohydrate as 73% of total energy compared with 45.4% fat in the high fat diets. The Gln was supplemented as 2.87%, whereas alanine was 3.5% of total energy in the respective high fat diets. The carbohydrate concentrations in the three high fat diets were adjusted between 34.6 and 38.1% of total energy, to make all diets nearly isocaloric. The detailed composition of each of these diets is shown in Table 1. The animals were maintained on their specified diets for 5.5 mo. Body weight for each animal was determined biweekly, and food intake was measured individually once per week, during a 24-h housing of one mouse per cage. Energy intake was determined using an energy density of 17.09 kJ/g and 21.29 kJ/g, for the low fat diet and each of the three high fat diets, respectively. The individual percent energy conversion efficiency (ECE) defined as weight gained divided by kJ consumed multiplied by 100, was determined in each animal after 16 wk of diet treatment.

Additionally, in a follow-up study, two groups (10 per group), which had been fed the high fat diet alone for 4 mo, were used to evaluate the therapeutic effect of Gln in heavy hyperglycemic animals. One group was maintained on the high fat diet alone while the other was switched to the glutamine-supplemented

<p>| TABLE 1 |
| Composition of experimental diets1 |</p>
<table>
<thead>
<tr>
<th>Diet</th>
<th>LL</th>
<th>HL</th>
<th>HL + Gln</th>
<th>HL + Ala</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient, g/kg</td>
<td>17.1</td>
<td>21.3</td>
<td>21.3</td>
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<tr>
<td>Casein</td>
<td>228</td>
<td>228</td>
<td>228</td>
<td>228</td>
</tr>
<tr>
<td>Di-methionine</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>L-glutamine, 19.2%N</td>
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<td>0.0</td>
<td>0.0</td>
<td>40</td>
</tr>
<tr>
<td>L-alanine, 15.5%N</td>
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<td>0.0</td>
<td>0.0</td>
<td>48.9</td>
</tr>
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<td>Corn starch</td>
<td>835</td>
<td>350.5</td>
<td>310.5</td>
<td>301.6</td>
</tr>
<tr>
<td>Maltodextrin 10</td>
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<td>170</td>
<td>170</td>
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<td>Coconut oil</td>
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<td>240.5</td>
<td>240.5</td>
<td>240.5</td>
<td>240.5</td>
</tr>
<tr>
<td>Sucrose</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Salt mix (AIN-76)2</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>10.5</td>
<td>10.5</td>
<td>10.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Vitamin mix (AIN-76A)2</td>
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<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Choline bitrate</td>
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<td>2</td>
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<td>2</td>
</tr>
<tr>
<td>FDC dye #40</td>
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<td>0.05</td>
<td>0.00</td>
<td>0.1</td>
</tr>
<tr>
<td>FDC blue dye #1</td>
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<td>0.05</td>
<td>0.1</td>
<td>0.00</td>
</tr>
<tr>
<td>FDC yellow dye #5</td>
<td>0.1</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

1 LL, low fat, low sucrose; HL, high fat, low sucrose; HL + Gln, high fat, low sucrose with L-glutamine supplementation; HL + Ala, high fat, low sucrose with L-alanine supplementation.

2 (AIN, 1977).
high fat diet. The two groups were monitored further over 2 mo of glutamine supplementation. The dietary protocols for raising these animals as well as the method for blood sample collection were approved by the Duke University Institutional Animal Care and Use Committee.

Analytical procedures. Blood was collected at monthly intervals beginning after 1-mo exposure to the diets. The blood was drawn following an 8-h period of food deprivation, via retro-orbital sinus puncture in nonanesthetized mice. Plasma glucose concentrations were determined using a Beckman glucose analyzer 2 (Brea, CA), and plasma insulin concentrations were measured with a double-antibody RIA kit (Linco Research, St. Louis, MO), with rat insulin as standard. The primary antibody in this RIA kit is specific against rat insulin. Plasma triglyceride and total free fatty acids were determined spectrophotometrically, using the respective kit assays (Wako kit #990-75401 and #997-69801, Wako Pure Chemical Industries, Richmond, VA).

At mo 5, fecal fat output was determined after a 72-h collection of fecal specimens from each mouse fed the LL, HL and HL + Gln diets. Using specially designed Nalgene metabolic cages (Fischer Scientific, Pittsburgh, PA) that allow for separate collection of urine and feces from experimental rodents, mice were housed individually in each cage, and fecal samples were collected for 72 h. After weighing, fecal material was first homogenized with water and placed in a glass tube containing the Dole extraction mixture [Dole and Meinertz 1960], with a homogenate to solvent ratio of 1:8. After a 4-d incubation at 4°C, the contents of the test tubes were thoroughly mixed by stirring.

Heptane (4 ml) and 4 ml of water were added to each tube, which was then capped and vortexed. The caps were promptly removed and replaced by parafilm before centrifuging the tubes at 200 × g for 10 min at 4°C. Two milliliters of the upper phase was carefully aspirated and placed in preweighed aluminum boats and allowed to evaporate under the hood for at least 24 h. The boats were then weighed again, and the differences in weight were recorded. The fat content in the fecal sample was calculated as percent fat using a routine procedure [Tietz 1976].

Statistical analysis. All data are presented as means ± SEM. In the evaluation of data obtained within this study, a one-way ANOVA computer program (Graphpad Software, San Diego, CA) was used and when data obtained from separate studies were compared, a repeated measures ANOVA was performed. In both cases, depending on the outcome of ANOVA, the Bonferroni method (Ingelfinger et al. 1994) was used to assess the significance of differences among groups. A value of *P < 0.05* was considered significant.

Results

Food intake and effect of diets on body weight. At wk 2 of exposure to the diets, energy intake per unit body weight from HL + Gln and LL diets were less (*P < 0.05*) than from HL and HL + Ala diets (Fig. 1). After wk 2, energy intake from all four diets did not differ significantly among the dietary groups of B/6J mice (Fig. 1). As previously reported (Surwit et al. 1995), mice fed a high fat diet were significantly heavier (*P < 0.05*) than mice fed a low fat diet (Fig. 2).

**FIGURE 1** Energy intake per gram body weight in B/6J mice fed a low fat diet or a high fat diet with or without supplemental Gln or Ala. Abbreviations used: HL, high fat, low sucrose; HL + Gln, high fat, low sucrose with l-glutamine supplementation; HL + Ala, high fat, low sucrose with L-alanine supplementation; LL, low fat, low sucrose (studied separately). Values are means ± SEM, *n* = 10. Different letters at wk 2 indicate significant differences among groups, *P < 0.05*.

**FIGURE 2** Body weights of B/6J mice fed a low fat diet or a high fat diet with or without supplemental Gln or Ala. Values are means ± SEM, *n* = 10. The error bars were so small that they are not visible in most data points. Means at a particular time point with different letters are significantly different, *P < 0.05*. Abbreviations used: HL, high fat, low sucrose; HL + Gln, high fat, low sucrose with l-glutamine supplementation, HL + Ala, high fat, low sucrose with L-alanine supplementation, LL, low fat, low sucrose.
However, at wk 8, animals fed the HL + Gln or HL + Ala gained 10% less [P < 0.05] weight than those fed HL and the lower body weights in the two amino acid-supplemented groups persisted for 16 wk (Fig. 2).

The mean body weight of the mice fed the LL diet at wk 16 was 27.1 ± 0.6 g, which was lower [P < 0.01] than those of the animals fed the amino acid-supplemented high fat diets (Fig. 2).

To examine the possibility that amino acid supplementation could affect dietary fat absorption, fecal fat output in one of the amino acid-supplemented groups, the Gln-supplemented group, was assessed and compared with those of the LL and HL groups. Table 2 shows that the reduction in body weight was not due to amino acid-induced fat malabsorption, because percent fecal fat output was the same for animals fed the HL diet alone and those that received glutamine supplementation. However, fecal fat output in the LL group was significantly lower [P < 0.05] than in these groups. The ECE in the LL group was the same as in the HL + Gln group but was lower [P < 0.05] than that of the animals fed the HL diet (Table 2).

**Plasma glucose, insulin and lipid concentrations.** At 3 mo, the mean plasma glucose concentration was elevated [P < 0.01] in the HL-fed mice compared with that in the group fed the LL diet, and the higher plasma glucose level in the HL group was maintained for more than 5 mo (Fig. 3). Although both amino acids appeared to be equally potent in reducing plasma glucose concentrations over the first 3 mo, only glutamine had a normoglycemic effect lasting for more than 5 mo because plasma glucose levels in the LL and HL + Gln groups were not different at 5.5 mo (Fig. 3). At 5.5 mo, the mean plasma glucose concentration in the HL + Ala group was similar to that in the HL group but higher [P < 0.05] than in the LL and HL + Gln groups. Hyperinsulinemia, which occurred with HL but not LL feeding, was attenuated [P < 0.05] by supplementation with either alanine or glutamine in the high fat diet (Fig. 4). Plasma lipid levels were not assessed in the HL + Ala group and although plasma triglyceride concentrations measured in the other three groups were similar, plasma-free fatty acid concentrations were higher [P < 0.01] in animals fed the LL diet than in those fed the HL diet with or without glutamine supplementation (Table 3). Plasma-free fatty acid concentrations were not different between the group

### Table 2

<table>
<thead>
<tr>
<th>Diet</th>
<th>ECE</th>
<th>Fecal fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL</td>
<td>14.56 ± 1.42&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.1 ± 0.10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HL + Gln</td>
<td>11.43 ± 0.90&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.0 ± 0.01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>LL</td>
<td>10.17 ± 0.88&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.1 ± 0.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM, n = 10 mice per group. At mo 5, fecal fat output was determined after a 72-h collection of fecal specimens from each mouse fed the following diets: HL, high fat, low sucrose; HL + Gln, high fat supplemented with L-glutamine; LL, low fat, low sucrose.

2 Values in a column with different superscripts are significantly different [P < 0.05].

3 Studied separately.

**Figure 3** Effects of a low fat diet or a high fat diet with or without Gln or Ala supplementation on plasma glucose in B/6J mice. Data are means ± SEM, n = 10. Different letters at 5.5 mo indicate significant differences among groups. Abbreviations used: HL, high fat, low sucrose; HL + Gln, high fat, low sucrose with 1-glutamine supplementation; HL + Ala, high fat, low sucrose with 1-alanine supplementation; LL, low fat, low sucrose.

**Figure 4** Effects of a low fat diet or a high fat diet with or without Gln or Ala on plasma insulin concentrations in B/6J mice. Data are means ± SEM, n = 10. Different letters at 5.5 mo indicate significant differences among groups. Abbreviations used: HL, high fat, low sucrose; HL + Gln, high fat, low sucrose with 1-glutamine supplementation; HL + Ala, high fat, low sucrose with 1-alanine supplementation; LL, low fat, low sucrose.
TABLE 3

Effect of dietary lipid concentration and glutamine supplementation on plasma lipids in mice.1,2

<table>
<thead>
<tr>
<th>Diet</th>
<th>Triglycerides (mmol/L)</th>
<th>Free fatty acids (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL</td>
<td>0.83 ± 0.05</td>
<td>0.77 ± 0.07b</td>
</tr>
<tr>
<td>HL + Gln</td>
<td>0.95 ± 0.05</td>
<td>0.82 ± 0.08b</td>
</tr>
<tr>
<td>LL3</td>
<td>0.91 ± 0.05</td>
<td>1.26 ± 0.09a</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM, n = 10.
2 Values in a column with different superscripts are significantly different (P < 0.05).
3 Studied separately.

HL, high fat, low sucrose; HL + Gln, high fat supplemented with L-glutamine; LL, low fat, low sucrose.

Glutamine supplementation (Fig. 7). The reduced plasma concentration of insulin in previously hyperinsulinemic mice was maintained throughout the period of glutamine therapy, which also resulted in normoglycemia because the plasma glucose concentration at the end of therapy (8.6 ± 0.6 mmol/L, d 65 after change; Fig. 6) and that in prehyperglycemic animals (7.1 ± 0.3 mmol/L, mo 2 before change, Fig. 6) were not significantly different.

DISCUSSION

We previously showed that dietary fat interacted with genetic factors to cause obesity and diabetes in B/6J mouse (Surwit et al. 1991 and 1995). In the pres-
ent study, we found that dietary glutamine supple-
dmentation during high fat feeding prevented the de-
velopment of overweight and hyperglycemia in this 
mouse model. Furthermore, we observed that 2 mo of 
glutamine supplementation can reduce weight gain 
and attenuate hyperglycemia and hyperinsulinemia in
overweight hyperglycemic mice even with continuous 
high fat intake. The efficacy of glutamine and alanine 
in reducing body weight gain does not appear to be 
due to an inducement of fat malabsorption but may 
be related to the effect of the amino acids on the 
conversion and storage of consumed energy [Ivy et al.
1994]. The short-term beneficial effect of alanine on 
the development of impaired glucose regulation that 
we have seen in the B/6J mouse model is also consist-
tent with observations in studies performed with py-
ruvate, a metabolite of Ala and its analog, pyruvate-
glycine, in obese Zucker rats [Ivy et al. 1994]. How-
ever, it is not clear why alanine failed to regulate 
plasma glucose concentrations after 3 mo of supple-
mentation during high fat feeding, in contrast to the 
long-lasting effect of glutamine. Both amino acids are 
classified as nonessential and are interconvertible 
through the generation of common intermediates in 
the Krebs cycle, although glutamine can produce more 
alanine than vice versa [Moskovitz et al. 1994]. While 
the L-alanine concentration in the diet was slightly 
higher than that of Gln, it is possible that the level of 
alanine supplementation used in the present study did 
not generate enough glutamine to block the deleterious 
effect of long-term high fat feeding on glucose home-
ostasis. These data suggest a specific therapeutic 
effect of Gln on the development of diet-induced hy-
perglycemia in the B/6J mouse. The present study uti-
лизирован Gln on the basis of previous studies showing that 
this amino acid is an inhibitor of fatty acid oxidation 
(Malaisse et al. 1980), since it has been reported that 
hibition of fatty acid oxidation with pharmaceutical 
agents was efficacious in the treatment of Type 2 di-
abetes [Foley 1992]. These findings are consistent with 
the present observations. However, the mechanism by 
which glutamine causes a reduction in body weight 
gain during high fat feeding is not clear. It has recently 
been proposed that insulin resistance may be a pre-
dictor of body weight gain [Odeleye et al. 1995], 
therefore, one possible mechanism of glutamine action 
on body weight reduction could involve its attenuation 
of insulin resistance induced by fat. Other possibilities 
may include glutamine-induced changes in the par-
tioning between oxidation, storage and or alterations 
in membrane structure, which appear to play a role in 
dietary fat-induced obesity [Pan et al. 1994].

It is noteworthy that plasma-free fatty acid concen-
trations were higher in low fat-fed animals than in the 
high fat-fed groups but the low fat-fed mice did not 
develop hyperglycemia. Although the low fat diet was 
low in sucrose, it had a high content of complex car-
bohydrate (corn starch). A low fat, high carbohydrate 
diet causes hyperlipidemia in normal and diabetic 
states [Bierman and Hamlin 1961, Reaven et al. 1979]. 
The low fat, high carbohydrate-induced hyperlipid-
emia has been classified as neutral fat [Bierman and 
Hamlin 1961]. The mechanism whereby an excessive 
carbohydrate intake would cause hyperlipidemia in 
comparison with high fat consumption is presently 
not clear. However, the pathway of dietary fat oxida-
tion differs from that of endogenous fat synthesis. 
Whereas high fat consumption inhibits endogenous 
metabolism in the face of increased fat utilization, a 
high carbohydrate intake promotes increased fat syn-
thesis in the liver and carbohydrate utilization by tis-
sues [Lehninger et al. 1993]. In this scenario, elevated 
plasma lipid concentrations, representing endoge-
nously synthesized lipids being transported for storage 
in the adipose tissue, may occur with excessive car-
bohydrate intake [Lehninger et al. 1993]. Further stu-
dies are required to determine the regulatory factors 
that are involved in maintaining normoglycemia in 
the presence of hyperlipidemia in B/6J mice fed a low 
fat, high carbohydrate diet.

In conclusion, the present study shows that dietary 
glutamine supplementation attenuated the develop-
ment of excessive weight gain and prevented hyper-
glycemia and hyperinsulinemia in B/6J mice fed a high 
fat diet. Because Gln, even at very high doses, has been 
shown to be safe in humans [Lowe et al. 1990], our 
data suggest the possibility that this amino acid may 
be useful as an antiobesity and antidiabetic agent in 
prediabetic and diabetic subjects.

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tions on fecal fat determination and Pamela McAuley 
for editorial assistance.

LITERATURE CITED

American Institute of Nutrition (1977) Report of the AIN ad hoc 
committee on standards for nutritional studies. J. Nutr. 107:
1340–1348.

acid and glucose metabolism. Potential explanation of insulin 

Astrup, A., Buemann, B., Western, P., Toubro, S., Raben, A. & 
Christensen, N. J. (1994) Obesity as an adaptation to a high-

fatty acids and ketone bodies on in vivo non-insulin-mediated 
glucose utilization and production in humans. Metabolism 38:
1056–1061.

low-fat, high carbohydrate diet in diabetic subjects. Diabetes 10:
432–437.


