INTRODUCTION

Glutamine (Gln) is a non-essential amino acid that plays a relevant role as a central metabolite for amino acid transamination and is a crucial constituent of proteins. Gln, the most abundant amino acid in human plasma, accounts for almost 6% of bound amino acids (1). Its primary source is the skeletal muscle from where it is released and transported to different organs (2, 3). Gln promotes and maintains the function of different cells and tissues, including the intestines (4), liver (5), neurons (6), lymphocytes (7), and kidney (8). Gln is a precursor of proteins, peptides, amino sugars, purines, and pyrimidines involved in nucleic acids and nucleotide synthesis (9). Gln is synthesized ubiquitously into cell cytoplasm predominantly from glutamate and branched-chain amino acids. Gln is an important stimulator of immune function, and in particular, it stimulates lymphocyte proliferation (10). Gln depletion blocks the lymphocyte cell cycle during differentiation (11) and impairs cellular stress responses (12). Gln also influences monocyte differentiation (13) and is one of the most important precursors of glutathione, thereby influencing the redox potential of the cell (14). Gln carbon is utilized as a precursor for lipid synthesis in adipocytes (15). Fatty acids produced from Gln are incorporated into triacylglycerol in incubated adipocytes (7). Gln plays an important role in cell proliferation activating nucleotide synthesis (16), and it increases contractile protein synthesis and, in particular, extracellular matrix proteins (17). The direct effect of Gln on collagen biosynthesis includes a dose-dependent increase of collagen types I and III (17).

Gln regulates the expression of a group of proteins essential for cellular survival during several stress conditions, referred to as heat shock proteins, by enhancing the stability of mRNA. In experimental and human studies, Gln has already been indicated as a non-nutritive amino acid with potential positive effects on glucose metabolism and on insulin resistance (1).

Aim of this review is to analyze the specific role of Gln in the regulation of glucose and insulin metabolism. We will consider both experimental and human data for any possible implications of Gln in the clinical approach to insulin resistance.
GLUTAMINE AND GLUTAMINE HOMEOSTASIS

In humans, Gln plasma concentrations are twice those of alanine which is considered the most important gluconeogenic amino acid (18, 19). Gln basal turnover in the postabsorptive state of normal subjects is greater than that of alanine (20, 21). In vivo and in vitro studies showed that Gln is the major gluconeogenic precursor in the kidney. The Gln carbon skeleton derives mainly from other amino acids and proteins and is the major contributor to the newly synthesized glucose pool (21). Gln plasma levels are determined by its release into, and uptake from, plasma by cells and tissues. The most important tissue releasing Gln into plasma is the skeletal muscle. Kidney and gut are the principal organs controlling Gln uptake. Liver regulates Gln homeostasis and, in association with muscle, may increase its uptake. Unlike gluconeogenesis from other substrates, Gln mediated–gluconeogenesis represents an exergonic reaction with a net yield of 8 mol adenosine triphosphate (ATP) per mole of synthesized glucose (22, 23).

GLUTAMINE AND INSULIN METABOLISM

Gln enhances glucose-stimulated insulin secretion via the metabolism of the gamma-glutamyl cycle, glutathione synthesis and mitochondrial function (24). It has already been demonstrated that Gln modulates the glucose-induced loss of maximal insulin responsiveness (25). In fact, hexosamine, a product of glucose and Gln metabolism, is involved in the development of insulin resistance (25). Gln, in association with insulin and glucose, increases the activity and mRNA levels of pyruvate kinase involved in glucose metabolism (26).

EXPERIMENTAL DATA ON THE ROLE OF GLUTAMINE ON GLUCOSE/INSULIN PROFILE

Infusion of 28 g/4 hours of Gln, resulting in 3-fold increased Gln plasma levels, caused a 7-fold increase in glucose formation with no alterations in insulin and glucagon plasma concentrations (27). Opara et al demonstrated that dietary Gln supplementation during high fat feeding prevented the development of overweight and hyperglycemia in a mouse model. In particular, 2 months of Gln supplementation reduced weight gain and attenuated hyperglycemia and hyperinsulinemia in overweight hyperglycemic mice even with continuous high fat intake. The mechanisms by which Gln causes these effects are still uncertain (28).

In another animal study, it was hypothesized that Gln plays a critical role as a signaling molecule in amino acid– and glucose-stimulated insulin secretion, and that β-cell depolarization and subsequent intracellular calcium elevation are required for this Gln effect to occur (29).

HUMAN DATA REGARDING THE METABOLIC ROLE OF GLUTAMINE IN GLUCOSE/INSULIN PROFILE

Infusion of insulin in normal volunteers suppressed systemic Gln gluconeogenesis by 50%. The fact that Gln-based gluconeogenesis in the liver was reduced by 25%, whereas that in the kidney was reduced by almost 75%, indicates that renal Gln gluconeogenesis is more sensitive to insulin than hepatic (30).

The stimulatory effect of Gln on glycogen synthesis is attributed not only to liver but also to muscle. In humans whose muscle glycogen and Gln stores were depleted by exercise, infusion of Gln increased net muscle glycogen storage 3-fold compared with saline infusion, but had not effect on the fractional rate of blood glucose incorporation into glycogen (31).

GLUTAMINE AND INSULIN RESISTANCE IN CRITICAL ILLNESS

A multicenter, randomized, double-blind, controlled trial of surgical and trauma intensive care unit patients (n = 114) demonstrated that supplementation of total parenteral nutrition with l-alanyl-l-Gln dipeptide led to a significant reduction in hyperglycemia and a significant reduction in the number of patients requiring insulin; patients also had reduced infectious complications in association with the amelioration of glucose intolerance (32). Bakalar et al specifically investigated the role of Gln supplementation in 40 trauma patients and found an improvement in insulin sensitivity with a parenteral supplementation of 0.4 g of Gln/ kg body weight per day (33). Several mechanisms could explain these effects in critically ill patients. In particular, Gln can influence intestinal and immune function, decreasing intestinal permeability in stressed patients (34) leading to a possible reduction of glucose plasma levels. Experimental evidence indicates that Gln modulates inflammatory cytokine production by decreasing gut mucosa interleukin-8 levels (35) or increasing antiinflammatory cytokines such as interleukin-10 (36).

All of these clinical results appear to be in agreement and
focus on the positive role of Gln supplementation in critically ill patients. On the other hand, recent data suggest that the relationship between Gln and insulin resistance could be bidirectional, the former influencing the latter and vice versa. Indeed, Biolo et al showed that euglycemia in cancer patients undergoing surgery improves skeletal muscle protein metabolism, resulting in increased de novo muscle glutamine synthesis and plasma glutamine concentrations (37). These results question whether tight glycemic control would prevent the need for Gln supplementation in critically ill patients, or whether Gln may confer per se some clinical benefits. More studies are needed to solve this issue, but the available evidence suggests that we cannot ignore exogenous glutamine provision, and that perhaps Gln and tight glycemic control are complementary, with each facilitating the other (38).

GLUTAMINE AND DIABETES MELLITUS

In type 1 diabetes, plasma Gln concentrations are not reduced (39-41). In type 2 diabetes, increased Gln conversion to glucose and to alanine was observed, but decreased oxidation was also demonstrated (42). In a recent elegant clinical study, type 2 diabetes patients, obese individuals, and obese nondiabetic control subjects were given oral Gln supplementation. Gln increased circulating glucagon-like peptide 1 (GLP-1), glucose-dependent insulino-tropic polypeptide, and insulin concentration (43). Interestingly, the GLP-1 response to Gln was not different in the diabetic group compared with the obese and the lean control subjects, suggesting that it might be possible to circumvent the diabetes-associated GLP-1 secretory defect with agents that target alternative pathways in the L-cells releasing GLP-1 (43). The mechanism by which Gln stimulates GLP-1 release in vivo remains uncertain. These data are consistent with a study of Reiman et al investigating cell cultures. In this setting, supplementation with Gln was demonstrated to represent a more potent GLP-1 secretagogue than glucose or other amino acids (44). Similarly, another experimental study showed that insulin and Gln attenuate the expression of inflammatory cytokines such as tumor necrosis factor- and interleukin-8, and reduce the oxidative stress of hyperglycemia (45).

CONCLUSION

Gln is the major metabolic source of the gut and has positive effects on GLP-1, glucagon, and insulin release. Both animal and human studies have shown several benefits of Gln supplementation on insulin resistance and hyperglycemia. This glucose-ameliorating effect may be related to a specific Gln effect on fat metabolism, such as the inhibition of fatty acid oxidation and lipolysis (46). Also, Gln in association with insulin is significantly more effective in reducing the expression of proinflammatory cytokines and oxidative stress than insulin or Gln alone. Considering the results of these experimental and human data, the clinical relevance of Gln supplementation becomes self-evident. In particular, considering the elevated number of patients affected by different diseases associated with insulin resistance, such as type 2 diabetes, metabolic syndrome, obesity, critical illness, etc., it appears to be essential to give this information to clinicians. Evidence has shown that both parenteral and enteral Gln administration are effective in glucose and insulin metabolism. An interesting role may be found for oral L-Gln supplementation, which can be prescribed in individuals and patients preserving oral nutrition. L-Gln might be useful in association with traditional pharmacological approaches to improve patients’ glucose and insulin profiles. We strongly recommend larger controlled clinical trials to investigate the efficacy and safety of Gln administration.

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REFERENCES