REVIEW

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The role of glutamine and α-ketoglutarate in gut metabolism and the potential application in medicine and nutrition

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Abstract: An amino acid, Glutamine (Gln), is abundant in both the human body and diet. Gln and its derivatives are important factors affecting intestinal function, growth and development as a main source for energy and structure component. The importance to metabolism is evident during stress. During the past 2 decades, an increased understanding has been gained into its role in metabolism. Gln is currently classified as a conditionally essential amino acid; however, it is unstable in water solution and produces toxic byproducts on decomposition, which has led to the commercialization of its precursor - AKG. Apart from its nutritive role, Gln and AKG possess certain pharmacologic and/or immunologic effects. The article presents the role of Gln and AKG in gut metabolism and, on the basis of clinical trials and animal experiments, discusses their potential usefulness in medicine and nutrition.

Key words: alpha-ketoglutarate, glutamine, nutrition

INTRODUCTION

In situations such as extensive weight reduction, intensive exercise, different illnesses or trauma, surgery, quantitative changes in nutritional intake may not be sufficient or in practice impossible to introduce. Therefore, it is particularly important to identify the substances which, as delivered substrates, play key functions in the regulation of protein metabolism under different physiological and/or pathological conditions. Poor nutritional status may be assessed by body weight, body mass index and other anthropometric measures, low plasma albumin, as well as severe loss of nitrogen and functional tissue. In the case of existing external or internal conditions leading to malnutrition, which may be accompanied also by hormonal stress, the human body turns to the increase of protein degradation, and a decrease in protein synthesis, or both [1, 2]. Both processes, even if occurring separately, may lead to the growth retardation and/or a variety of disturbances in organ and tissue functions, including the intestine. Negative energy balance leads to an increased excretion of nitrogen in the urine [3], which is a direct result of the increased protein breakdown and/or decreased synthesis of proteins with a related increase in oxidation of amino acids. A good example of this seems to be lasting for even several weeks alteration of protein metabolism after surgery [4, 1, 5]. However, despite sufficient amounts of energy and protein given total per- and post-operative parenteral nutrition (TPN), the appearance of negative nitrogen balance may impede post-surgery recovery [6].

In normal conditions, the GI tract is capable of absorbing the necessary nutrients selectively. It is also the largest reservoir of bacteria in the body, which produces a great quantity of different toxins [7]. They are not taken in by the intestine because of the presence of the mucosal barrier, which consists of three parts: mechanical, biological and immnunological. Any etiological factors that impair these barriers would cause bacterial/endotoxin translocation [8]. Intestinal obstruction, haemorrhagic and necrotic enteritis, chemotherapy, radiotherapy and some drugs (e.g. NSAIDs) may destroy the mechanical barrier which consists of intestinal epithelial cells [9]. The immune barrier is composed of intra-epithelial secreting IgA, intra-mucosal lymphocytes, Payer's nodules and mesenteric lymph nodes (gut-associated lymphoid tissue, GALT). Any conditions interfering with the organism immunity, such as protein malnutrition, leukemia, HIV infection, intensive chemotherapy would damage the immune barrier [10]. The biological barrier consists of normal inhabitant bacterial flora in the GI tract, and may be described as having a preserving effect on the intrinsic flora protecting the surface of intestinal mucosa against harmful bacteria from any that may colonize the large intestine. The colonization resistance would be destroyed by the diseases that cause alterations of inhabitant bacteria in the bowel such as bacterial enteritis, ileus (bacterial overbreeding), antibiotic enteritis (double infection) [11].

Gln and its derivatives, such as α-ketoglutarate (AKG), are known as crucial molecules in protein metabolism, gene and cellular redox regulation, as well as amino acids transport across membranes [12] (Fig. 1). Post-operative and post-traumatic catabolism leads to depleted skeletal muscle glutamine as well as an increased use of glutamine by the intestine [13]. Gln has been proved to be an important metabolic factor to counteract functional and metabolic disorders induced by trauma and, therefore, has become an important diet supplement, e.g. for injured patients [14]. However, two unfavourable physical-chemical properties prevent the widespread use of free glutamine in nutrition. These properties are: poor stability due to the quantitative decomposition of aqueous Gln to the cyclic product associated with ammonia liberation, and its

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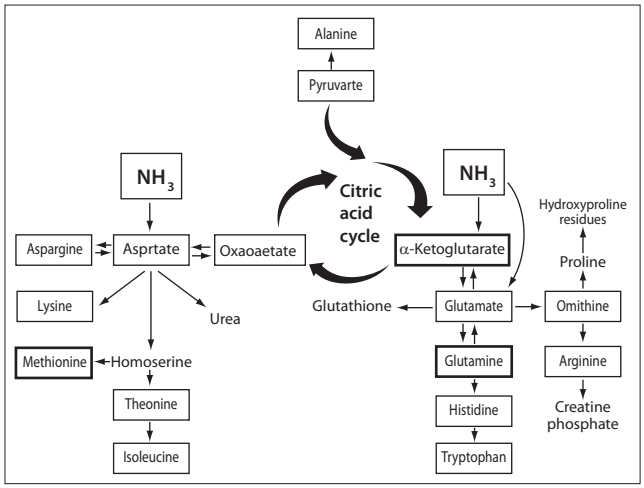

Figure 1 Amino acids synthesis and metabolism.

limited solubility in water [15]. This probably justifies recent increased interest in AKG, which has been shown to be an efficient nutrient in trauma conditions such as burns [16, 17], exerts beneficial effect on nitrogen metabolism [18]; reduces the toxicity levels of ammonium ions in the body [19, 20], and protects the gut mucosa against bacterial dissemination after severe injury [21].

The aim of the review is to present the role of Gln and AKG *in* gut metabolism and, on the basis of clinical trials and animal experiments, to discuss their potential usefulness in medicine and nutrition.

Glutamine (Gln)

Gln is the most abundant free amino acid in the body, in both extracellular fluid and in the free amino acid pool. Gln constitutes about 25% of the total amino acids in extracellular fluid and more than 60% of the free amino acid pool in skeletal muscle [22]. It is avidly consumed by growing and rapidly dividing cells, such as those lining the gut lumen. This is because its 5-carbon skeleton can provide energy while the nitrogen molecules support the synthesis of nucleic acids.

Gln is an essential amino acid for proper growth in most cells and tissues, and in several studies it has been demonstrated that Gln is important for determining and guarding normal metabolic processes of the cell [23, 24, 25]. Endogenous Gln storage and synthesising capabilities may not be sufficient to meet the needs of the organism during long-term stress, hypercatabolic and hypermetabolic states, or during prolonged starvation, as demonstrated in a number of studies [26, 27, 28, 29], and for that reason, Glu is considered a "conditionally essential" amino acid. Instead of playing a key role as a precursor for protein synthesis, Gln is an intermediate in various metabolic pathways and takes part in the regulation of acid-base balance [31]. Gln is a source of nitrogen in purines, pyrimidines, nucleotides and amino sugars synthesis, and may be also considered a nitrogen transporter between various cells and tissues. Due to unique diverse transamination reactions, Gln plays an essential role in amino acid homeostasis [31].

The human GI tract is a major site of Gln utilization, accounting for more than half of the net splanchnic utilisation of Gln from systemic circulation, and therefore dietary Gln seems to be less essential. However, in case of the lack of any other amino acids, including Gln, both dietary Gln and glutamate (Glu) can become crucial for proper gut function. Since the results of both human and animal studies show that some growth factors and specific nutrients may accelerate growth, adaptation, and repair of the intestinal mucosa [32], Gln becomes an object of considerable interest as a gut-targeted nutrient due to its proposed key role in the maintenance of intestinal structure and function.

Gln seems to be indispensable as a metabolic fuel to be fully oxidised by the intestinal mucosa [33] and an important nitrogen source for the enterocytes. Gln is the principal metabolic fuel for both growing and mature enterocytes, even when compared to glucose [34, 35]. It has been shown that 94% of the enteral [U-^{13}C] Gln but only 6% of the enteral [U-^{13}C] glucose is utilised in the first pass by the portal drained viscera (PDV) in fed piglets, which extracted 6.5% of the arterial flux of [U-^{13}C] glucose and 20.4% of the arterial flux of [U-^{13}C] Glu. Gln is also important for maintaining mucosal cell integrity and gut barrier function [24, 36]. Using the rat model, total parental nutrition and transplanted small intestine, Gln was shown to improve mucosa structure (i.e. mucosal villus height, surface area) [37]. Although Gln increases TGF-α activity on epithelial proliferation in cell culture [38], it was also shown that in the IPEC-J2 cell line (neonatal pigs), Gln itself enhances gene transcription by increasing mitogen activated protein kinase activity [39]. Oral Gln supplementation causes a jejunal lamina propria depth (LPD) increase, which is an indicator of crypt depth and increased number of less mature cells; it may therefore be concluded that Gln plays a role in enhancing the maturation of intestinal crypt cells [40]. However, no effect was found in the duodenal villi height, which may reflect the difference in Gln action and cell proliferation between porcine duodenum and jejunum [41]. Instead of exerting its effect on gut maturation, Gln may also protect intestinal mucosa from injury if administrated prior to chemotherapy [42] and radiotherapy, which may decrease both morbidity and mortality after those procedures [42, 43].

Considering the link between Gln and GALT, it was shown that Gln may stimulate lymphocyte and macrophage function in the mesenteric lymph nodes which were suppressed by irradiation [44, 45]. Gln supplemented TPN may also enhance the gut immune system by s-IgA levels normalization, which results in the decrease in bacterial adherence to enterocytes, and therefore lower gut permeability for bacteria.

Significant decrease in the dietary supply of nutrients due to minimal feed intake during the first postweaning week may result in intestinal atrophy, which occasionally appears to be a clinical problem in both human and animal medicine. Gln supplementation prevented jejunal atrophy during the first postweaning week and increased the gain/feed ratio by 25%, and additionally significantly increased plasma concentrations of aspartate, glutamate and alanine [41]. Gln supplemented to TPN solutions significantly improved recovery of the intestine from starvation atrophy and dysfunction that accompanies starvation also in rat model [46, 47]. There are also evidences that Gln serves the liver as a source of several essential substrates as well as for the whole body, and may be an important source of citrulline and arginine [48].

The emerging interest of clinicians in practical Gln application has resulted in at least 17 clinical studies with enteral Gln supplemented in a number of clinical situations (Table 1). According to Fürst et al. (2001) [49], patients with the following diseases/conditions may benefit from Gln therapy: acute or chronic infection, burn/trauma, surgery, bone marrow transplantation, inflammatory bowel

Table 1 Clinical studies with enteral Gln and Gln dipeptide supplemented parenteral nutrition [49]

Enteral Gln	
Cancer, response to chemotherapy	Bozzetti et al. 1997, Earl et al. 1995 [102, 103]
Chemotherapy in cancer disease, efficacy	Conversano et al. 1995, Nattakom et al. 1995 [84, 85]
Veno-occlusive disease	Nattakom et al. 1995 [85]
Premature infants, outcome and immunity	Neu et al. 1997, Roig et al. 1995 [86, 87]
Chemotherapy, efficacy	Rubio et al. 1998 [88]
Peptic ulcer, healing	Furst et al. 1999, Shive et al. 1957 [89, 90]
Stomatitis, duration and severity	Anderson et al. 1998, Skubitz and Anderson 1996 [91, 92]
Critically ill patients	Jones et al. 1999 [93]
Morbidity in multiple trauma	Schloerb and Amare 1993, Houdijk et al. 1998, Houdijk 1998 [94, 95, 96]
IBD, intestinal permeability	Zoli et al. 1995 [97]
Pouchitis	Wischmeyer et al. 1993 [98]
Chemotherapy, intestinal barrier function	Yoshida et al. 1998 [99]
Duchenne muscular dystrophy, protein breakdown	Hankard et al. 1998 [100]
Reconstruction of body Gln pool	Fish et al. 1997 [101]
Premature infants, plasma Gln levels	Roig et al. 1996 [104]
Bone marrow transplantation, outcome	Schloerb and Skikne 1999 [105]
Parenteral Gln dipeptide	
Muscular Gln concentration	Stehle et al. 1989, Hammarqvist et al. 1990, Karner et al. 1989, Furst et al. 1990 [106, 107, 108, 15]
Nitrogen balance	Furst et al. 1990, Stehle et al. 1989, Morlion et al. 1998 [15, 106, 109]
Protein synthesis	Hammarqvist et al. 1990, Petersson et al. 1991, Barua et al. 1992 [107, 110, 11]
Trauma related intestinal atrophy	Van der Hulst et al. 1993 [112]
Weight gain in hematological patients	Van Zaanen et al. 1994 [113]
Length of hospital stay	Morlion et al. 1998 [109]
Release of proinflammatory cytokines (IL8, TNF-α)	de Beaux et al. 1998 [114]
Expression of anti-inflammatory cytokines (IL-10)	Morlion et al. 1997 [115]
Lymphocyte proliferation	de Beaux et al. 1998 [114]
Immunity	Morlion et al. 1997, Morlion et al. 1998, O'Riordain et al. 1994 [115, 114, 116]

disease, intestinal immaturity or necrotizing enterocolitis, infectious enteritis, short bowel syndrome, mucosal damage after chemotherapy and radiotherapy, immunodeficiency syndromes, immune system dysfunction associated with critical illness or bone marrow transplantation, advanced malignant disease and cancer cahexia [49].

Glutamine dipeptides

Because of the low solubility and poor stability, Gln-containing TPN solutions must be freshly prepared under strict aseptic conditions and stored at 4°C. Gln concentration in such solution should not exceed 2.5%, due to the risk of precipitation. This means that provision of adequate amounts of Gln to injured or critically ill patients represents a severe burden, especially in volume-restricted situations. Therefore, parenteral use of free Gln is reserved for controlled clinical trials, and only in countries allowing nonheat-sterilized solutions [49, 50]. Glu water solution is stable; however, it hardly passes through cell membranes and is suspected of being neurotoxic. The above- mentioned limitations resulted in an intensive search for alternative Gln sources and precursors. Among them, dipeptides appeared to be a reasonable candidates because the dipeptide molecule with Gln at the C-terminal position fulfills all chemical and physical criteria needed for approval by the authorities for the composition of parenteral solutions. The

Table 2 Clinical studies with AKG, Ca-AKG and OKG supplementation in parenteral or enteral nutrition.

AKG	
Postoperative muscle catabolism	Wernerman et al. 1990 [16]
Protein synthesis and free glutamine concentration in skeletal muscle after surgery	Hammarqvist et al. 1991 [81]
Growth retardation in children due to gastrointestinal diseases	Moukarzel et al. 1994 [83]
Protein synthesis and muscle free glutamine concentration after total hip replacement	Blomqvist et al. 1995 [59]
Cardioprotection during blood cardioplegia	Kjellman et al. 1997 [117]
Renal effects after coronary operations	Jeppsson et al. 1998 [118]
Postoperative nitrogen balance and muscle catabolism	Wiren et al. 2002 [58]
Ca-AKG	
Ammonia, pyruvic and lactic acid blood levels in patients with cirrhosis	Salerno et al. 1983 [63]
Amino acid metabolism in undernourished hemodialysis patients	Riedel et al. 1996 [61]
Secondary hyperparathyroidism	Zimmermann et al. 1996 [119]
Hyperphosphataemia in patients on maintenance haemodialysis	Bro et al. 1998 [120]
Hyperphosphataemia in patients on maintenance haemodialysis	Birck et al. 1999 [62]
Bone metabolism in postmenopausal women with osteopenia	Filip et al. 2007 [76]
OKG	
Postoperative muscle protein synthesis as assessed by ribosome analysis and nitrogen balance	Wernerman et al. 1987 [121]
Effect of the loss of muscle glutamine after surgical trauma	Wernerman et al. 1989 [122]
Metabolism after enteral administration in burn patients	le Bricon et al. 1997 [80]
Metabolism after enteral administration in burn patients	de Bandt et al. 1998 [123]
Substrate fuel kinetics in enterally fed trauma patients	Jeevanandam et al. 1999 [124]
Nutritional and clinical efficacy of in severe burn patients	Donati et al. 1999 [125]
Anaplerosis and oxidative energy delivery in human skeletal muscle	Bruce et al. 2001 [126]
HIV infection: effects on muscle, gastrointestinal, and immune functions	Karsegard et al. 2004 [127]

Gln containing dipeptides L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine are commercially available and today are an integral part of routine clinical practice [49].

Ala-Gln is capable of providing the organism with readily available Gln, because of relatively high hydrolase activity in the body which facilitates rapid realise of Gln from Ala-Gln. During parenteral administration, only trace amounts of Ala-Gln are present in the blood, but undetectable in tissues and urine. Easy hydrolysis, together with subsequent utilisation in body fluids, avoids the risk of undesirable pharmacological and physiological side effects. An additional positive effect of Ala-Gln is that alanine is readily metabolised via the gluconeogenic pathway, and thereby may spare endogenous body proteins. Ala-Gln, like Gln, is capable of stimulating crypt cell proliferation in the ileum, and proximal and distal colon in humans [51]. Ala-Gln supplementation preventss bacteria translocation, similar to genistein (soybean), and enhances recovery of trasmucosal resistance [52]. Example clinical trials with Gln-dipeptides are presented in Table 1.

α–ketoglutarate (AKG)

AKG has a good water solubility, is non-toxic and relatively stabile in water solutions, and thus appeared to be the most preferable of Gln derivatives. It can be rapidly transaminated (by glutamate dehydrogenase) to Glu, which can be further aminated (by glutamine synthetase) to form Gln. AKG, due to conversion to succinate with the loss of CO_2 and formation of NADH, is considered a key intermediate in oxidative metabolism. Moreover, by formation of Glu via transamination and scavenging free ammonia, also plays an important role in nitrogen metabolism. AKG is capable of replacing dietary dispensable amino acids by shunting ammonium back into the dispensable amino acid pool; it was therefore reasonable to include AKG in nutritional formulas [53]. In a number of animal experiments and clinical studies, AKG shows similar metabolic effects when compared to Gln. Arginine-AKG treated rats showed increased use of arginine for metabolic purposes, including an efficient urea cycle operation (rat trauma model induced by femur fracture) [54]. On the other hand, in an animal model (rabbit) it was also shown to facilitate the transport of organic anions in the kidney [55]. AKG also enhanced the metabolism of fats which can suppress oxygen radical generation and thus prevent lipid peroxidative damage, and exerts an influence on non-enzymatic oxidative decarboxylation during hydrogen peroxide decomposition. This effect was confirmed in two different experiments (ammonium acetate and ethanol intoxication rat models) [56, 57]

Instead of experiments with animal models studying the influence of AKG different metabolic pathways, human clinical studies were also performed (Table 2). In some studies, beneficial effects of AKG and Gln in clinical nutrition with respect to intestinal mucosa integrity were reported [36]. In the early postoperative phase, enteral AKG improved gut integrity and in that way reduced infectious complication [58]. AKG supplementation prevented the decrease of muscle free Gln concentration and influenced protein synthesis after hip replacement [59]. AKG has also been shown to have a positive influence on muscle protein synthesis in postoperative patients [60] and to improve amino acid metabolism in hemodialyzed patients [61]. Calcium salt of AKG (Ca-AKG) administered to patients during pre- and hemodialysis was shown to increase the amino acids metabolism, with the calcium functioning as a phosphate binder [62]. Pyridoxine-AKG in patients with liver cirrhosis reduced the ammonia levels [63].

Pharmacokinetics studies showed that large amounts of AKG are metabolized in first-pass by the splanchnic tissues (80% intake); however, nonoxidative pathways predominate over complete metabolism to CO_2 [64, 65, 66]. Some AKG present in the diet is metabolized to proline, which justifies its possible application in the treatment of bone metabolic diseases, e.g. osteoporosis [67, 68]. AKG increased plasma proline levels together with enhancement of both mineralization and mechanical properties of bone tissue in turkeys [69, 70], piglets [71] and lambs [72, 73]. The positive effect of AKG on bone tissue was also observed in ovariectomized rats with developing and established osteopenia [74, 75]. Human studies suggest the potential usefulness of AKG in preventing bone loss in postmenopausal women. Ca-AKG induced a significant decrease in bone turnover (monitored by C- terminal Crosslinked Telopeptide of Type I Collagen CTX), which is consistent with the preservation of bone mass in the lumbar spine [76].

Ornithine α–ketoglutarate (OKG)

The salt OKG might exert a synergistic effect on both its constituents. It contains one molecule of AKG and two molecules of ornithine. It is not clear, however, to what extent the exerted metabolic effects of OKG can be attributed to either ornithine or AKG; however, both ornithine and AKG may increase the formation of Gln [77]. The results of several studies indicate that after enteral OKG administration, gut morphology and function improve, trauma-induced immune dysfunction is alleviated, and there are anabolic/anticatabolic actions on protein metabolism [78, 79]. Positive effects on muscle protein synthesis have been observed in trauma and burned patients after enteral administration [79, 80]. After intravenous administration, improved nitrogen balance and improved protein synthesis have been found [81]. There are also studies, however, in which no direct beneficial effects have been demonstrated of ornithine or OKG on gut structure, function or outcome [82], in contrast to Gln and AKG, although patients with GI tract diseases may also benefit from the OKG treatment. In prepubertal children, retarded in growth due to intestinal diseases, OKG supplementation concomitantly increased the plasma levels of Gln, Glu and insulin like growth factor 1 (IGF-1) which was followed by a significant increase of growth rate [83].

CONCLUSIONS

In vitro experiments, together with animal model experiments, have elucidated many important aspects of Gln metabolism as well as other biological features important for practical application of these molecule in medicine and nutrition. Gln and its derivatives are important factors affecting intestinal function, growth and development as a main source for energy and structure components. Gln is currently classified as a conditionally essential amino acid; however, it is unstable in water solution and produces toxic byproducts on decomposition, which has led to the commercialization of its precursor – AKG. Apart from its nutritive role, Gln and AKG possess certain pharmacologic and/or immunologic effects. Clinical studies reveal evidence that the currently applied concept of these molecules is beneficial in the case of e.g.

burn/trauma, surgery, inflammatory bowel disease, intestinal immaturity or necrotizing enterocolitis, infectious enteritis, short bowel syndrome, mucosal damage after chemotherapy and radiotherapy, immunodeficiency syndromes, immune system dysfunction associated with critical illness or bone marrow transplantation, osteopenia, advanced malignant disease and cancer cahexia.

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