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Dietary glutamine supplementation modulates Th1/Th2 cytokine and interleukin-6 expressions in septic mice

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Abstract

Glutamine (Gln) has been demonstrated to have benefit in the modulation of systemic immunity in sepsis. However, the effects of Gln on local immunity and intra-lymphocyte cytokine expression have not been investigated in mice with gut-derived sepsis. This study evaluated the influence of a Gln-enriched diet on interleukin (IL)-6 expression in organs and Th1/Th2 type cytokine production within lymphocytes in septic mice. Male ICR mice were assigned to control and Gln groups. The control group was fed a semi-purified diet, while in the Gln group, Gln replaced part of the casein. After feeding the respective diets for 3 weeks, sepsis was induced by cecal ligation and puncture (CLP). Mice were sacrificed at 0, 6, 12 and 24 h after CLP and their organs were harvested for further analysis. Results showed that IL-6 levels in the liver were decreased, whereas levels were increased in the lungs, kidneys and intestines with the progression of sepsis in both groups. Also, intra-lymphocyte interferon (IFN)-γ expression decreased and IL-4 expression increased during sepsis. Compared to the control group, the Gln group had higher levels of IL-6 in the liver and lower levels in other organs at various time points. Lymphocyte IFN-γ expression in the Gln group was higher, and IL-4 levels were lower than those of the control group after CLP. These results suggest that Gln supplementation decreased IL-6 production in non-hepatic organs, while reducing intra-lymphocyte IL-4 and enhancing IFN-γ expressions. This change may reverse the Th2 type response to a more-balanced Th1/Th2 response during sepsis.

Keywords: Sepsis; Glutamine; Interleukin-6; Interleukin-4; Interferon-γ

1. Introduction

Despite the usage of potent antibiotics and strong medical support, sepsis and multiple organ failure remain the leading causes of death in surgical intensive care units. Sepsis is initiated by bacteria and their related toxins. When a host is exposed to bacterial toxins, a variety of endogenous mediators are produced. Tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 are major pro-inflammatory mediators in the septic condition [1]. IL-6 is a cytokine produced by a number of cell types in response to a variety of external stimuli. IL-6 induces the synthesis of acute-phase proteins in hepatocytes, the activation of T cells and the attraction of neutrophils to the site of inflammation [2,3]. Several studies have shown that elevated plasma IL-6 levels are associated with vulnerability to septic shock or multiple organ dysfunction syndrome (MODS) and raise the mortality of patients with sepsis [4–6]. However, IL-6 knockout mice did not show improved survival in a cecal ligation and puncture (CLP)-induced sepsis model [7], and the absence of IL-6 expression may impair immune

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and acute-phase responses in mice [8]. A proper expression of IL-6 during the period of sepsis may thereby play a substantial role in successful intervention.

Cytokine profiles are associated with and related to the severity of various types of infection. The cytokine profiles are determined by two functional subsets of T lymphocytes, Th1 and Th2. IL-2 and interferon (IFN)-γ are produced by Th1 lymphocytes. Th1 cytokines enhance cell-mediated immunity. Th2 cytokines, including IL-4 and IL-10 enhance humoral immunity. The effects of Th1 and Th2 lymphocytes are counter-regulatory [9]. Studies have shown that there is a marked depression in cell-mediated immunity after the onset of sepsis, and the Th2 cytokine, IL-4, is responsible for the suppression and death associated with polymicrobial sepsis [10–12].

Glutamine (Gln) is the most-abundant free amino acid in the circulation and serves as an important energy source for many rapidly proliferating cells, especially enterocytes and immune cells [13,14]. Gln deficiency can occur during periods of critical illness. In patients with catabolic diseases, plasma and muscle Gln levels are dramatically reduced, which correlates with the poor prognosis and high degree of protein catabolism in those patients [15]. A previous study showed that Gln supplementation attenuated pro-inflammatory cytokine release, protected against organ damage, and decreased mortality in a lipopolysaccharide (LPS)-treated rat model [16]. Studies done by our laboratory also showed that preventive use of a Gln-supplemented enteral diet before CLP or intravenous Gln supplementation after CLP had the effects of promoting proliferation of total lymphocyte in gut-associated lymphoid tissue, enhancing IgA secretion, and maintaining T lymphocyte populations in Peyer's patches [17,18]. Gln is considered to be an essential amino acid during certain disease conditions and to have beneficial effect on reducing inflammatory reactions [15,19]. However, there is no study, so far, investigating the regulatory role of Gln on the Th1/Th2 response in sepsis. Therefore, the aim of this study was to investigate the effect of enteral Gln supplementation on intra-lymphocyte IL-4 and IFN-γ expressions in sepsis. Since IL-6 promotes IL-4 production and Th2 differentiation, we analyzed IL-6 levels in organs to understand the local immune response of septic mice administered with Gln.

2. Results

2.1. Food intake and body weight gain

There was no difference in food intake among the groups. The initial body weights and body weigh gain during the experimental period did not differ across the groups (data not shown).

2.2. IL-6 expressions in the liver, lung, kidney, and intestine

IL-6 levels in liver homogenate decreased with the progression of sepsis in both groups. However, IL-6 levels in the Gln group were significantly higher than those of the corresponding control group at various time points after CLP, and showed no difference from the normal and 0 h groups when sepsis was induced for 24 h (Fig. 1). IL-6 levels in the lungs, kidneys and intestines increased after CLP in both groups. Compared with the control group, the Gln group had lower IL-6 concentrations 6 h after CLP in those 3 organs. Also, IL-6 levels in the Gln group 12 and 24 h after CLP were lower than those in the lungs and kidneys of the control group. IL-6 levels in the lung, kidney, and intestinal homogenates 24 h after CLP showed no differences between the Gln and NC groups (Table 1).

2.3. Intra-lymphocyte IFN-γ and IL-4 distributions

The intra-lymphocyte interferon (IFN)-γ distribution decreased, whereas that of IL-4 increased in both groups as sepsis progressed. Lymphocyte IFN-γ expression in the Gln groups was significantly higher, and IL-4 levels were lower than those of the control group at various time points after CLP. There was no difference in lymphocyte IL-4 levels 24 h after CLP between the Gln and NC groups (Fig. 2).

3. Discussion

IL-6 is an important mediator in the early phase of infection. IL-6 has been demonstrated to be associated with septic mortality and is an inducer of the systemic inflammatory response syndrome [20,21]. A previous study showed that IL-6 expression in the lungs and

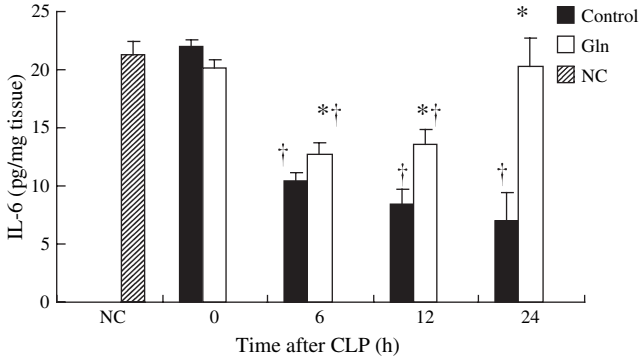

Fig. 1. Concentration of IL-6 in liver homogenate during sepsis. CLP, cecal ligation and puncture; NC, normal control group; *significantly different from the corresponding group at the same time point; †significantly different from the NC group and time 0 h in the same group.

Table 1
Concentrations of IL-6 in lung, kidney, and intestinal tissue homogenates during sepsis

	Lung (pg/mg tissue)	Kidney (pg/mg tissue)	Intestines (pg/mg tissue)
Normal control	1.33 ± 0.24	12.1 ± 0.90	1.05 ± 0.73
0 h			
Control	1.99 ± 0.56	12.35 ± 0.97	1.01 ± 0.25
Gln	1.70 ± 0.56	11.56 ± 2.33	1.57 ± 1.68
6 h			
Control	28.34 ± 7.18[a,b,c]	31.6 ± 1.08[a,b,c]	27.1 ± 0.86[a,b,c]
Gln	11.94 ± 1.7[b,c]	28.91 ± 3.04[b,c]	15.1 ± 2.88[b,c]
12 h			
Control	13.84 ± 3.18[a,b]	26.96 ± 0.75[a,b]	3.50 ± 0.66[b]
Gln	5.54 ± 2.54	18.10 ± 0.91[b]	4.03 ± 0.82[b]
24 h			
Control	15.14 ± 2.47[a,b]	20.27 ± 0.61[a,b]	3.58 ± 0.8[a]
Gln	1.23 ± 0.03	13.98 ± 1.44	2.08 ± 1.32

[a] Significantly different from the corresponding group at the same time point.
[b] Significantly different from the normal control group and time 0 h in the same group.
[c] Significantly different from the same group at various time points.

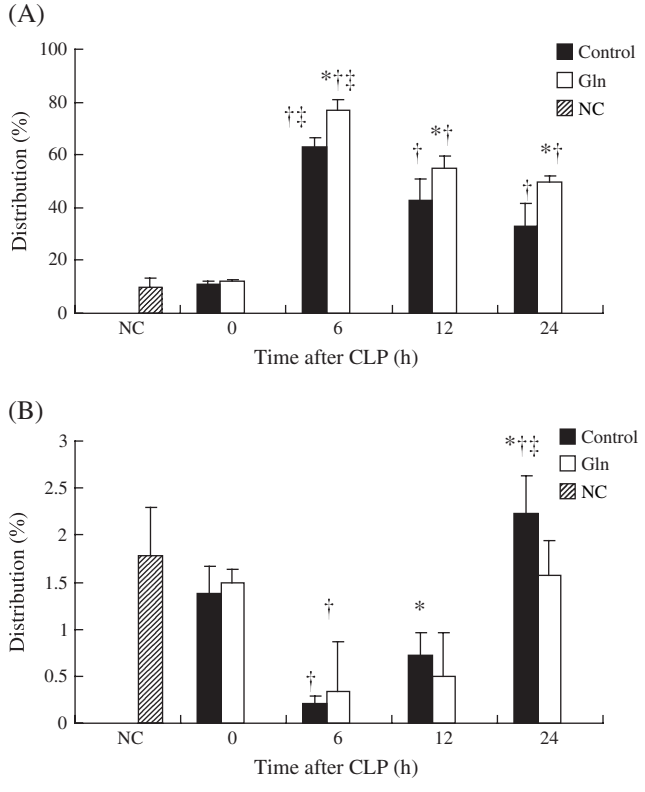

Fig. 2. Distributions of intra-lymphocyte IFN-γ (A) and IL-4 (B) expressions at the time indicated after CLP. CLP, cecal ligation and puncture; NC, normal control group. *Significantly different from the corresponding group at the same time point; †significantly different from the NC group and time 0 h in the same group; ‡significantly different from the same group at various time points.

kidneys was enhanced after surgery with sepsis induced by LPS [22]. In this study, we found that IL-6 levels in the lungs, kidneys and intestines in the Gln group were lower than those of the control group at various time points. These results may indicate that Gln administration attenuate the inflammatory reaction in non-hepatic organs. This finding is similar to that of a report by Coëffier et al. [23], which showed that Gln down regulates IL-6 protein in human intestinal mucosa. In this study, we observed that hepatic IL-6 levels were diminished as sepsis progressed in both groups. The Gln group had higher hepatic IL-6 levels than the corresponding group at various time points after CLP, and IL-6 levels 24 h after CLP in the Gln group had no difference from that of the NC group. This result indicates that Gln supplementation in septic mice helped maintain IL-6 expression in the liver 24 h after CLP. The findings were consistent with our previous study. In that study, we observed that IL-6 levels in plasma and peritoneal lavage fluid were diminished after induction of sepsis and recovered 24 h after CLP [24]. However, this finding was inconsistent with reports by others [25–27], in which they found that IL-6 mRNA expression and IL-6 levels were increased in septic rodents. In our study, the cecum of the mice was punctured twice to induce gut-derived sepsis. This model of peritonitis was found to result in an irreversible hepatic dysfunction [28]. It is possible that the ability of hepatic IL-6 production impaired after CLP under the present experimental condition. IL-6 is a cytokine with many functions. Hepatic IL-6 production is very important in the host defense against infection: it enhances the hepatic acute-phase response, activates T and B cell differentiation and antibody production [23,29]. A previous study showed that loss of intrahepatic IL-6 activity was associated with poor outcomes in a fecal peritonitis rat model [27]. We propose that IL-6 expression has an organ-specific response, and maintenance of IL-6 protein levels in the liver as shown in the Gln group may have beneficial effects in regulating the immune response under a septic condition.

Previous studies have shown that a shift from a Th1 to a Th2 type response occurs during sepsis [10–12]. Lymphocytes from the spleens of septic mice express increased levels of Th2 cytokines, which may directly or indirectly suppress the Th1 cytokine response [11,30]. Marked depression in cell-mediated immunity results in increased mortality in sepsis [10–12]. In this study, we directly measured intra-lymphocyte Th1/Th2 cytokine production. The result showed that in accordance with the progression of sepsis, a predominant Th2 type response was observed in the control group. In contrast, Gln supplementation reversed the predominant T cell response. Compared with the control group, Gln administration enhanced IFN-γ and suppressed IL-4 production during sepsis. This may consequently reverse

the predominant Th2 response to a more-balanced Th1/Th2 response and may benefit the prognosis of sepsis. Since IL-6 is positively correlated with IL-4 production and Th2 differentiation [31], this finding is comparable to the lower IL-6 levels in the Gln group observed in non-hepatic organs. Gln is a major energy source for immune cells, particularly lymphocytes [13,14]. Yaqoob and Calder [32,33] found that Th1 cytokine production depends on Gln present in the culture medium. Th1, but not Th2, cytokine responses require the presence of optimal concentrations of Gln [34]. In this study, we did not observe a survival benefit in the Gln group 24 h after CLP (8 survivors of 12 mice in the Gln group vs. 8 of 14 in the control group). Since survival was only observed for 24 h in the present study, determining whether Gln supplementation improves survival over a longer period requires further investigation.

In summary, this study showed that IL-6 levels in non-hepatic organs increased, whereas hepatic IL-6 levels decreased during sepsis, and a predominant Th2 type response was observed in polymicrobial sepsis. Gln supplementation decreased IL-6 secretion in non-hepatic organs, while reducing intra-lymphocyte IL-4 and enhancing IFN-γ expressions. This change may reverse the Th2 type response to a more-balanced Th1/Th2 response during sepsis.

4. Materials and methods

4.1. Animals

Male ICR mice weighing 20–25 g were used in this experiment. All mice were housed in temperature- and humidity-controlled rooms and allowed free access to a standard chow diet and water for 1 week before the study. The care of the laboratory animals was established by Taipei Medical University, and protocols were approved by the Animal Care Committee.

4.2. Study protocol

Mice were randomly assigned to a normal group (NC) ($n = 8$), a control group ($n = 36$), or the Gln group ($n = 38$). Mice in the normal group were fed a chow diet. The control group was fed a common semi-purified diet, and the Gln group part of the casein was replaced by Gln, which provided 25% of the total amino acid nitrogen. This amount of Gln is known to have an immunomodulating effect in rodents [18,35]. The 2 diets were isonitrogenous and identical in energy and nutrients distribution (Table 2). After feeding the respective diets for 3 weeks, polymicrobial sepsis by CLP was induced in the mice in the control and Gln groups, because CLP is clinically relevant and is considered a simple and reproducible model of gut-derived sepsis in mice [36]. CLP was performed as previously described by Ayala et al. [11]. Mice were lightly anesthetized with ether. A midline incision (1.5–2.0 cm) was made below the diaphragm, exposing the internal organs. The cecum was isolated and a 3-0 silk ligature was placed around it, ligating the cecum just below the ileocecal valve. The cecum was then punctured in 2 places with a 22-gauge needle and replaced into the abdomen. The abdominal wound was closed in 2 layers. Eight mice each of the control and Gln groups were sacrificed 0, 6, 12, and 24 h after CLP, respectively. Mice in the NC group were sacrificed at the time CLP was performed in the experimental groups. All mice were anesthetized and sacrificed by cardiac puncture. Blood samples were collected in tubes containing heparin for analysis of intra-lymphocyte IL-4 and IFN-γ levels. Tissues including the lungs, kidneys, liver, and intestines were immediately harvested and stored at −70 °C for further analysis.

Table 2
Composition of the experimental diets (g/kg)

Component	Control	Glutamine
Soybean oil	100	100
Casein	200	150
Glutamine	0	41.7
Salt mixture[a]	35	35
Vitamin mixture[b]	10	10
Methyl cellulose	31	31
Choline chloride	1	1
Methionine	3	3
Corn starch	620	628.3

[a] The salt mixture contained the following (mg/g): calcium phosphate diabasic, 500; sodium chloride, 74; potassium sulfate, 52; potassium citrate monohydrate, 20; magnesium oxide, 24; manganese carbonate, 3.5; ferric citrate, 6; zinc carbonate, 1.6; cupric carbonate, 0.3; potassium iodate, 0.01; sodium selenite, 0.01; and chromium potassium sulfate, 0.55.

[b] The vitamin mixture contained the following (mg/g): thiamin hydrochloride, 0.6; ricoflavin, 0.6; pyridoxine hydrochloride, 0.7; nicotinic acid, 3; calcium pantothenate, 1.6; D-biotin, 0.05; cyanocobalamin, 0.001; retinyl palmitate, 1.6; DL-α-tocopherol acetate, 20; cholecalciferol, 0.25; and menaquinone, 0.005.

4.3. Measurements of IL-6 concentrations in organ tissues

Individual organs including the lungs, kidneys, liver, and intestines (from the proximal, middle, and distal small intestine) were removed and placed in 10 ml of lysis buffer containing protease inhibitors (2 mM phenylmethysulfonyl fluoride, and 2 μg/ml of leupeptin, pepstatin A, and aprotinin; Sigma, St. Louis, MO) at 4 °C. Samples were homogenized and ultracetrifuged at 15,000 rpm for 45 min at 4 °C. The levels of IL-6 in the supernatants were determined with a commercially available enzyme-linked immunosorbent assay (ELISA) kit. Antibodies specific for mice IL-6 were coated onto

the wells of the microtiter strips provided (BioSource, Camarillo, CA, USA). The sensitivity of the ELISA kit specific for mice IL-6 measurement we used is <2 pg/ml. The within-run coefficient of variation was 5.1% in this study.

4.4. Analysis of IL-4 and IFN-γ distributions in T lymphocytes

The proportions of T cell IL-4 and IFN-γ expressions in fresh blood were analyzed. Briefly, 50 μl of fresh blood was incubated with 100 μl Leucoperm (Serotec, Oxford, UK) reagent A for 15 min at room temperature to fix the leukocytes, then 5 ml phosphate-buffered saline (PBS) was added and the mixture was centrifuged for 5 min at 300 *g*. After removing the supernatants, 100 μl Leucoperm reagent B was added to the cell pellet to penetrate the leukocytes, then 10 μl of fluorescein-conjugated rat monoclonal anti-mouse IFN-γ (Serotec) and 5 μl phycoerythrin-conjugated rat monoclonal anti-mouse IL-4 (Serotec) were incubated for 30 min at room temperature. Cells were washed with PBS. After removing the supernatant and resuspended cells in the sheath fluid, T lymphocytes capable of IL-4 and IFN-γ expression were assessed using dual intracellular cytokine staining and flow cytometry (Coulter, Miami, FL, USA). The results were presented as percentage of cytokine producing cells in 1×10^5 lymphocytes.

4.5. Statistical analysis

Data are expressed as the means ± standard deviation. Differences among groups were analyzed by two-way analysis of variance with Fisher's test. $P < 0.05$ was considered statistically significant.

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