

## 添加魚油之全靜脈營養對胃切除大鼠細胞性免疫反應之影響

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本研究探討在胃切除之後在全靜脈營養 ( TPN ) 液中添加富含 n-3 脂肪酸之魚油脂肪乳劑對手術後細胞性免疫反應之影響。實驗將 Wistar 雄性老鼠分為三組，一組為控制組，兩組實驗組，三組均進行頸靜脈插管以 TPN 供給營養，在插管同時實驗組進行全胃切除手術，控制組則只剖腹但不做胃切除。實驗組一組給予一般黃豆油脂肪乳劑(SO)，一組則給予黃豆油、魚油各半之脂肪乳劑(FO)，控制組配方與 SO 相同，三組為等熱量、等氮量，營養素分佈比例相同，只有脂肪乳劑不同，醣類：脂肪：蛋白質比例為 60：20：20，TPN 共維持 2 或 4 天視實驗分組而定。術後 1 天和 3 天每組分別犧牲半數老鼠，取全血和腹腔沖洗液分析淋巴球分佈、細胞激素分泌及巨噬細胞吞噬能力。結果顯示，FO 組在術後一天 CD4 顯著較 SO 組高而與控制組無差異。在術後 3 天 FO 組 CD4 顯著較 SO 及控制組高，SO 則 CD8 顯著較其他兩組高，CD4/CD8 比例不論術後 1 天或 3 天 FO 組均顯著較高。在淋巴球中 interferon- $\gamma$  術後 3 天 FO 組顯著較其他兩組高，interleukin-4 則無差異。術後 3 天 FO 組腹腔巨噬細胞吞噬能力較控制組高，SO 則與控制組無差異。本實驗結果顯示，在腹腔手術之後給予富含 n-3 脂肪酸之 TPN 可促進 Th1 細胞激素分泌，並增進 CD4 分佈比例及巨噬細胞吞噬能力，應有助於恢復術後之細胞性免疫反應。

關鍵詞：胃切除，魚油乳劑，全靜脈營養，淋巴球分佈，細胞激素，巨噬細胞

## Effects of parenterally infused n-3 fatty acid on cellular immunity in rats with gastrectomy

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This study investigated the effect of n-3 fatty acid (FA)-containing parenteral nutrition on lymphocyte distribution and macrophage phagocytic activity in rats undergoing gastrectomy. Normal rats with internal jugular catheters were assigned to one control and 2 experimental groups and received total parenteral nutrition (TPN). At the same time, total gastrectomy was performed in the experimental groups, while the control group underwent a sham operation. The TPN solutions were isonitrogenous and identical in nutrient compositions except for differences in fat emulsion. The control and one experimental group received soybean oil emulsion (SO), and the other experimental group received 50% soybean oil emulsion and 50% fish oil emulsion (FO). TPN was maintained for 2 or 4 days of the group according to the sacrifice schedule of the rats. Half of the rats in the respective group were sacrificed 1 or 3 d after surgery or sham operation to examine their immune response. The results showed that The FO group had higher CD4<sup>+</sup> proportion and CD4<sup>+</sup>/CD8<sup>+</sup> ratio than those of the SO and control groups postoperatively. The phagocytic activity of peritoneal macrophages was higher in the FO group than in the control group, whereas no difference was found between SO and the control groups 3 d after surgery. Monocyte chemoattractant protein (MCP)-1 levels in peritoneal lavage fluid were lower in the FO group than in the SO group on postoperative d 3. The intra-lymphocyte interferon (IFN)- $\gamma$  distribution increased in both groups after gastrectomy. Lymphocyte IFN- $\gamma$  expression in the FO group was higher than those of the SO group on postoperative d 3. These results suggest that parenterally infused fish oil enhances phagocytic activity and reduces the production of MCP-1 at the site of injury. Also, n-3 FA supplementation promotes lymphocyte Th1 cytokine production and enhances cellular immunity in rats with total gastrectomy.

Key words: n-3 fatty acid, gastrectomy, lymphocyte distribution, phagocytosis

飲食中添加精胺酸對敗血症免疫黏著分子及器官中 myeloperoxidase 活性的影響

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本實驗探討在飲食中添加精胺酸(Arginine, Arg)對敗血症老鼠整合素、細胞黏著分子及器官中 MPO 表現的影響。實驗動物為雄性 ICR mice, 實驗分為兩組,一組為控制組餵食 semi-purified 飲食,實驗組餵食含 Arg 的 semi-purified 飲食,其中 Arg 含量為總熱量之 2%,兩組飲食為等熱量及等氮量,經過三週不同飲食的餵養,給予盲腸結紮並穿刺(cecal ligation and puncture,CLP)手術引致敗血症,CLP 後的 0、6、12 及 24 小時將老鼠犧牲。結果顯示 Arg 組白血球上 CD11a/CD18 及 CD11b/CD18 之表現在 CLP 後的 6、12 及 24 小時明顯高於控制組,可溶性(soluble) sICAM-1 在 CLP 後的 6 及 12 小時 Arg 組老鼠血液中的濃度明顯高於控制組,肝臟、小腸及肺中 MPO 的活性則在 CLP 後 24 小時 Arg 組明顯高於控制組,Arg 組老鼠的腎臟組織中 MPO 活性則在 12 及 24 小時時明顯高於控制組。此結果顯示,敗血症時 Arg 之添加可能使發炎反應介質的表現增加而使發炎反應更為嚴重。

關鍵詞：敗血症、精胺酸、黏著分子、myeloperoxidase 活性

Effects of dietary arginine supplementation on cellular adhesion molecule expression and myeloperoxidase activity in septic mice

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This study investigated dietary arginine (Arg) supplementation before sepsis induction on cellular adhesion molecule expressions (integrins including CD11a/CD18 and CD11b/CD18) on neutrophil and organ myeloperoxidase activity in septic mice. Male ICR mice were divided into control and Arg groups. Control group received semipurified diet and Arg group had part of the casein replaced with 2% of total calorie as Arg. The diets were isonitrogenous and identical in nutrient composition except for the difference in amino acid content. After 3 weeks, sepsis was induced by cecal ligation and puncture (CLP), and mice were sacrificed 0、6、12 and 24 h respectively after CLP. The results showed that integrin expressions on neutrophil were significantly higher in Arg group than those in control group at 6, 12 and 24 h after CLP. The Arg group had significantly higher plasma soluble ICAM-1 levels than the control group at 6 and 12 h after CLP. Compared with the control group, MPO activity of liver, intestine, kidney and lung in Arg group were significantly higher at 24 h. The enzyme activity in kidney was also higher in the Arg group than that of the control group at 12 h after CLP. This finding may indicate that Arg administration aggravate the inflammatory response in sepsis under the present experimental condition.

Keywords: arginine, sepsis, cellular adhesion molecule, myeloperoxidase

飲食中補充 glutamine 對敗血症小鼠體內 Th1/Th2 平衡的改變及器官中 IL-6 表現的影響

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過去的研究顯示，在發生敗血症時會使 Th1/Th2 平衡偏向 Th2，本實驗探討飲食中添加 Glutamine (Gln)，對敗血症後器官組織中細胞激素 IL-6 的濃度變化，及淋巴球中 Th1/Th2 平衡改變的情形。雄性 ICR 小鼠分為正常組餵食 chow 飲食、控制組餵食 semipurified 飲食及 Gln 組餵食部分胺基酸由 Gln 取代的飲食。經過三週的餵食，將控制組及實驗組老鼠利用盲腸結紮並穿刺手術引致敗血症，引致敗血症後的 0、6、12 及 24 小時將老鼠犧牲，而正常組則不引致敗血症。結果顯示，肝中 IL-6 在敗血症發生後其濃度會下降，而控制組下降的情形明顯大於 Gln 組，Gln 組肝中 IL-6 濃度在敗血症後 24 小時則恢復至與正常組相同，而在腎臟、肺臟及小腸中 IL-6 的濃度在敗血症後兩組皆提高，但在敗血症後 6 小時 Gln 組三個器官中 IL-6 的濃度明顯低於控制組，在敗血症後 12 及 24 小時 Gln 組肺及腎臟中 IL-6 濃度持續的低於控制組，Gln 組老鼠淋巴球中的 IFN- $\gamma$  表現量在敗血症後的各個時間點明顯高於控制組，而 IL-4 則明顯的低於控制組，但其 IL-4 的濃度與正常組相較則無差異。給予 Gln 的補充可減輕小鼠在發生敗血症時肝外器官如：肺、腎臟及小腸組織中 IL-6 的濃度，但可維持肝臟中 IL-6 的濃度，對於淋巴球中 Th1 的細胞激素 IFN- $\gamma$  有促進，而 Th2 之細胞激素 IL-4 則有抑制的現象，此結果顯示 Gln 的補充在敗血症時會使偏向 Th2 的反應回復至偏向 Th2。

關鍵字：敗血症、麩醯胺、interleukin-6、Th1/Th2 平衡

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

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This study evaluated the influence of Gln enrich-diet on interleukin (IL)-6 expression in organs and Th1/Th2 type cytokine expression within lymphocytes in septic mice. Male ICR mice were assigned to normal (NC) group, Control group and Gln group. NC group provide normal chow diet, the Control group fed a semi-purified diet and the Gln group supplied Gln enrich-diet with part of casein replaced by Gln. After feeding mice the respective diets for 3 weeks, sepsis was induced by cecal ligation and puncture (CLP) except NC group. Mice were sacrificed 0, 6, 12 and 24h after CLP and organs were harvested immediately for further analysis. The results showed that IL-6 levels in liver homogenate were decreased in accordance with the progress of sepsis in both groups. However, Gln group had higher IL-6 levels than the control group at various time points and had no difference from the NC group 24 h after CLP. IL-6 levels in lung, kidney and intestine were increased after CLP in both groups. Compared with the control group, Gln group had lower IL-6 concentrations 6h after CLP in the 3 organs, and 12h and 24h after CLP in lung and kidney. Intra-lymphocytes interferon (IFN)- $\gamma$  expression was decreased whereas IL-4 was increased in both groups during sepsis. Lymphocyte IFN- $\gamma$  expression in Gln group was higher, and IL-4 levels were lower than Control group at various time points after CLP. There was no difference in lymphocyte IL-4 levels between Gln and NC groups. The findings suggest that Gln supplementation decreased IL-6 secretion in non-hepatic organs, maintained intra-lymphocyte IL-4 expression and IL-6 levels in liver. This alteration may reverse the Th2 type response to a more balance Th1/Th2 response during sepsis.

Keywords: sepsis, glutamine, interleukin-6, Th1/Th2 cytokine

## 麩醯胺對砷暴露內皮細胞黏著分子表現與白血球遷移之影響

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本研究探討砷 (As) 暴露老鼠血漿中麩醯胺 (GLN) 的濃度，並以砷刺激內皮細胞 (ECs)，評估麩醯胺濃度是否會影響內皮細胞黏著分子的表現以及嗜中性白血球 (PMNs) 的遷移。實驗一：將老鼠分成控制組 (飲用去離子水) 與砷水組 (飲用砷水)，兩組的飲食中再分成補充或不補充 GLN，飼養五週後犧牲老鼠，分析血漿中 GLN 濃度。實驗二：人類臍靜脈內皮細胞 (HUVECs) 與 PMNs 以不同濃度的 GLN (0、300、600、1000 $\mu$ M) 培養 24 小時後，HUVECs 用 0.5 $\mu$ M 的砷刺激 3 小時，再加入 PMNs 遷移 2 小時。分析 HUVECs 細胞黏著分子與 PMNs 之 integrin (CD11b) 及 Interlukin (IL)-8 接受器表現量；並分析 PMNs 遷移的程度。結果顯示，砷暴露組老鼠血漿中的濃度比控制組低，補充 GLN 可以改善此現象。細胞實驗中，砷暴露組的細胞黏著分子與 integrin 表現量均高出控制組；以 600 $\mu$ M 和 1000 $\mu$ M 培養的砷暴露組，其血管細胞黏著分子-1、CD11b、IL-8 與 IL-8 接受器均低於 300 $\mu$ M 培養者，而 300 $\mu$ M GLN 培養的砷暴露組，其 PMNs 遷移程度最高。以上結果顯示，ECs 與 PMNs 受砷的刺激而活化，低濃度的 GLN 增加黏著分子表現量與 PMNs 遷移程度。給予生理濃度以上的 GLN 可以減少砷刺激後 IL-8 與黏著分子的表現，並降低 PMNs 遷移的程度。

關鍵詞：砷暴露，麩醯胺，黏著分子表現，Interleukin-8，嗜中性白血球遷移

Effects of glutamine on adhesion molecule expression and leukocyte transmigration in endothelial cells exposed to arsenic

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This study analyzed plasma glutamine (GLN) concentrations in mice exposed to arsenic. Also, we evaluated whether GLN concentration was related to endothelial surface molecule expression and the migration of polymorphonuclear neutrophils (PMNs) through endothelial cells (ECs) stimulated by arsenic. Experiment 1: Mice were assigned to either a control (drank deionized water) or an arsenic group (drank water with arsenic). Each control and arsenic group was divided into subgroups with or without GLN. Five weeks later, mice were sacrificed for plasma GLN analysis. Experiment 2: Human umbilical vein endothelial cells (HUVECs) and PMNs were treated with different GLN concentrations (0, 300, 600, and 1000  $\mu$ M) for 24 h. After that, we stimulated HUVECs for 3 h with 0.5  $\mu$ M arsenic and PMNs were allowed to transmigrated to through ECs for 2 h. HUVEC surface expressions of cell adhesion molecules and integrin (CD11b) and interleukin (IL)-8 receptor expressions on PMNs were measured. The results demonstrated that ECs and PMNs were activated after arsenic stimulation. A low GLN concentration resulted in higher adhesion molecule expression and greater transendothelial migration of neutrophils. GLN administration at levels similar to or higher than physiologic concentrations reduced IL-8 and adhesion molecule expression, PMN transmigration was also decreased after stimulation with arsenic.

Keywords: Arsenic, Glutamine, Adhesion molecule, Interleukin-8, neutrophils transmigration



