n-3 脂肪酸對糖尿病或高膽固醇血症併發敗血症時發炎反應之影響

Effects of n-3 Fatty Acid on Inflammatory Response in Diabetic or Hypercholesterolemic Condition with Sepsis

中文摘要

本研究旨在探討 n-3 脂肪酸對糖尿病或高膽固醇血症合併敗血症時發炎反應之影響，本研究共分成兩個動物實驗及一個體外實驗。動物實驗主要探討與黃豆油(SO)飲食相較，魚油(FO)飲食介入對於糖尿病或高膽固醇血症合併敗血症小鼠發炎反應介質表現之影響。另外亦分析器官中骨髓過氧化酶（myelopoeroxidase；MPO）作爲器官被白血球浸潤之指標。糖尿病以注射 streptozotocin 誘發產生；高膽固醇血症以高油高膽固醇飲食引致；敗血症則以盲腸結紮及穿刺術（cecal ligation and puncture，CLP）引致，動物實驗中魚油飲食之 n-3 和 n-6 比例均調整成 1 : 2。在糖尿病合併敗血症的動物模式中，結果顯示，魚油可以降低 CLP 後腹腔沖洗液中 prostaglandin (PG)E2 及 tumor necrosis factor (TNF)-α 的含量，魚油組在敗血症的早期白血球上整合素之表現量較低，同時亦發現在敗血症後 FO 組各器官中 MPO 活性較低。在高膽固醇血症併發敗血症的實驗中，結果顯示 FO 之給予可以減少白血球細胞內 interferon-γ /interleukin-4 比例，且腹腔沖洗液中 monocyte chemoattactant protein (MCP)-1 分泌較低，其免疫調節反應趨向 Th1。白血球上整合素之表現量在魚油組也較低。高膽固醇血症會使器官中 MPO 的活性增加，而各器官中 MPO 之活性在 SO 組與 FO 組相較均無顯著差異，此實驗中顯示給予高膽固醇血症小鼠魚油飲食，在合併敗血症時並不會有免疫抑制現象；與 SO 比較，FO 可以降低黏著分子表現和受傷部位之發炎反應之介質，主要影響的時間點在敗血症的早期而非晚期。體外實驗研究 EPA 或 DHA 對於 RAW 264.7 培養在高或低葡萄糖的培養液中以 LPS-刺激後之發炎介質分泌及 peroxisome proliferators-activated receptor (PPAR)-γ 表現之影響。結果顯示不論是 EPA 或是 DHA 均可以減少細胞在 LPS 刺激後 TNF-α 、MCP-1 以及 nitric oxide 之分泌，然而 EPA 與 DHA 對於細胞中 PPAR-γ 的表現與其所分泌的發炎反應介質濃度並無一致的相關性。此體外實驗顯示，EPA 或 DHA 不論在高或低葡萄糖的環境中均可減少經 LPS 刺激後所產生之發炎介質，然而此正面之影響並非透過活化 PPAR-γ 來調控。

英文摘要

This study investigated the effect of n-3 fatty acids on inflammatory response in diabetic or hypercholesterolemic condition with sepsis. There were two animal experiments and one in vitro experiment in this study. The animal studies compared the effect of fish oil (FO) with soybean oil (SO) on inflammatory mediator expressions in diabetic or hypercholesterolemic mice complicated with sepsis.

Myeloperoxidase (MPO) activities in organs were analyzed to identify the extent of tissue injury resulting from neutrophil infiltration. Diabetes was induced by a streptozotocin injection, hypercholesterolemia was induced by a high fat high cholesterol diet and sepsis was induced by cecal ligation and puncture (CLP). The ratio of n-3/n-6 fatty acid was 1:2 in the FO diet in the animal studies. The results of the diabetes-sepsis study showed that FO administration decreased the prostaglandin (PG)E2 and tumor necrosis factor (TNF)-α levels in peritoneal lavage fluid (PLF) after CLP. Leukocyte integrin expressions were lower in FO groups at early stage of sepsis. The FO group also had lower organ MPO activities at various time-points after CLP. In the hypercholesterolemia with sepsis study, the results showed that the mice fed with FO had a higher intracellular interferon-γ/interleukin-4 ratio and lower TNF-α and monocyte chemoattractant protein (MCP)-1 concentrations in PLF at early stage of sepsis. Leukocyte integrin expressions were also lower in the FO group. Hypercholesterolemia resulted in higher tissue MPO activities, but there were no differences in MPO activities in various organs between SO and FO groups. These results suggest that hypercholesterolemic mice fed FO did not exhibit immunosuppression when complicated with sepsis. FO administration reduced adhesion molecule expressions and inflammatory-related mediators at the site of injury at an early but not a late stage of sepsis. The in vitro study investigated the effect of EPA and DHA on inflammatory mediator secretion and peroxisome proliferators -activated receptor (PPAR)-γ expression in LPS-stimulated RAW 264.7 marcophage under high or low glucose concentrations in the culture medium. The results showed that both EPA and DHA attenuated TNF-α, MCP-1 and nitric oxide (NO) secretion after LPS stimulation. However, the PPAR-γ expressions and these mediators did not have consistent alteration patterns when EPA or DHA was administered. These results suggest that EPA or DHA administration decreased inflammatory mediator production in LPS-stimulated RAW 264.7 cells regardless high or low glucose concentrations in the culture medium. However, PPAR-γ expression may not be responsible for the beneficial effect of n-3 fatty acid-mediated immune regulation in this in vitro study.