

# 行政院國家科學委員會專題研究計畫 成果報告

## 深海魚油對於大鼠在強迫游泳試驗之作用

計畫類別：個別型計畫

計畫編號：NSC94-2314-B-039-027-

執行期間：94年08月01日至95年07月31日

執行單位：中國醫藥大學附設醫院精神科

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報告類型：精簡報告

報告附件：出席國際會議研究心得報告及發表論文

處理方式：本計畫可公開查詢

中 華 民 國 95 年 9 月 25 日

## 一、摘要

中文：

強迫游泳試驗 (Forced Swim Test, FST) 是目前憂鬱症的動物模型中最常被運用的模型之一，具有極佳之信效度。本研究的目的在了解攝取富含 n-3 脂肪酸飲食對於大白鼠在 FST 中產生具有類似憂鬱症行為的影響，藉以了解 n-3 脂肪酸在憂鬱症的角色。

本實驗以 Sprague Dawley 品系大白鼠為實驗動物，依照所攝取的油類不同分為 2 大組—魚油組 (富含 n-3 族脂肪酸) 和橄欖油組 (富含 n-9 族脂肪酸)。實驗動物於餵食實驗飼料六週後進行憂鬱症行為之誘導，誘導後二日，在行為測試評估之後立即以斷頭法犧牲。行為測試以計算動物在水中五分鐘內靜止時間及奮力掙扎時間長短來反應其類似憂鬱的嚴重程度。實驗動物於實驗期初、類似憂鬱症行為誘導前後各採集尾靜脈血一次，犧牲後取出腦組織，所有檢體取得後進行脂肪酸定性及定量分析。

本研究結果發現，魚油組在 FST 中的 immobility time 顯著低於橄欖油組 (218±16 vs. 183±19 sec., p=0.001)，而且其腦中的 DHA (50% increase) 和 ALA (alpha-linolenic acid, 63% increase) 及血中的 EPA (27% increase) 顯著高於於橄欖油組。有趣的是，大腦中 DHA 濃度和 immobility time 有顯著性的負相關 (r = -0.654, p = 0.006)。

本研究佐證了 n-3 脂肪酸在憂鬱症的臨床治療上的結果，本研究團隊亦已將結果整理投稿於 Journal of Psychiatric Research (Impact factor: 3.3)，已經被該期刊所接受刊登。

關鍵詞：omega-3 多不飽合脂肪酸 (omega-3 fatty acids)、魚油、重鬱症、強迫游泳試驗 (Forced Swim Test, FST)

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English Abstract:

Based on the findings of epidemiological data and recent clinical trials, omega-3 fatty acids seem to have a preventive and therapeutic effect on depression.

We examined the effect of omega-3 fatty acids on the forced swimming test (FST) in two groups of Sprague-Dawley rats after a six-week treatment with two different diets. Behavioral responses were observed and recorded during the 5-minute test. The fatty acid composition from the whole brain tissue and the RBC membrane of the rats were analyzed.

Comparing to control diet, omega-3 fatty acid diet significantly decreased the immobility time (218±16 vs. 183±19 sec., p=0.001) and increased behaviors of swimming (32±7 vs. 45±9 sec., p=0.012) and climbing (50±10 vs. 73±14 sec., p=0.011) during the FST. The group in omega-3 fatty acid diet had higher levels of docosahexaenoic acid (DHA, 50% increase) and alpha-linolenic acid (ALA, 63% increase) in the brain, and of eicosapentaenoic acid (EPA, 27% increase) in the peripheral RBC membrane. The level of brain DHA is negatively correlated to the immobility time (r = -0.654, p = 0.006) and is positively correlated to the swimming time (r = 0.69, p = 0.003).

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The result shows that omega-3 fatty acids have a beneficial effect on preventing the development of depression-like behaviors in rats with the FST.

Keywords: Omega-3 polyunsaturated fatty acids (PUFAs), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), depression, forced swimming test (FST)

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## 二、緣由與目的

Based upon the evidence from epidemiological data, biological studies in human, and recent clinical trials, omega-3 polyunsaturated fatty acids (PUFAs) seem to be related to the mechanisms underlying the pathogenesis and treatment of depressive disorders (Su et al. 2000; Peet and Horrobin 2002; Su et al. 2003). The abnormalities in PUFA composition in cell membranes can alter membrane microstructure, which could result in abnormal signal transduction and immunological dysregulation, and possibly can increase the risk of developing depression (Horrobin and Bennett 1999; Su et al. 2003; Chiu et al. 2003). Several clinical trials have been reported to show an antidepressant effect of PUFAs (Puri et al. 2001; Su et al. 2003; Nemets et al. 2002; Peet and Horrobin 2002). Recently, Carlezon and his colleagues (Carlezon, Jr. et al. 2005) reported that dietary supplementation with omega-3 fatty acids reduced immobility in the FST when given for 30 days, but not for 3 or 10 days. Unfortunately, the lipid profiles of brain and RBC were not reported

in their study. In the present study, we examined the effect of omega-3 fatty acids on the FST and on fatty acid compositions of brain tissue and erythrocyte membrane after six-week treatment with two different diets.

## 三、結果與討論

Compared to the control diet, the immobility time was significantly lower ( $218 \pm 16$  sec. vs.  $183 \pm 19$  sec.,  $p=0.001$ ) and the times of swimming ( $32 \pm 7$  sec. vs.  $45 \pm 9$  sec.,  $p=0.012$ ) and climbing are significantly higher ( $50 \pm 10$  sec. vs.  $73 \pm 14$  sec.,  $p=0.011$ ) in the group of omega-3 fatty acid diet. The levels of docosahexaenoic acid (DHA, 50% increase) and alpha-linolenic acid (ALA, 63% increase) in the brain, and that of eicosapentaenoic acid (EPA, 27% increase) in the peripheral RBC membrane were higher in the group of omega-3 fatty acid diet. There was no difference found in omega-6 PUFAs neither in the brain nor erythrocyte membrane.

Our finding of the potential antidepressant effect of omega-3 fatty acids is consistent with the recent study reported by Carlezon and his colleagues (2005). The methodological differences are the duration of 42-day dietary supplementation in our study, while it was 3-10 days in Carlezon's, and the measurements of brain and erythrocyte lipid compositions in our study, which were not used in Carlezon's. The other important finding of our study is the significant effect of omega-3 fatty acid diet on the levels of brain and erythrocyte fatty acids, while the effect is inconsistent on

brain and erythrocyte tissues. It is the DHA and ALA increased, but not EPA in the brain; and the EPA increased, but not ALA and DHA in the peripheral RBC. Our study limitation was that PUFA levels were assessed after FST; therefore, we could not clarify whether this inconsistency between the brain and erythrocyte was result from the effects of diets or the stress of FST.

One of the mechanism of omega-3 PUFAs' antidepressant effect is that the change of fatty acid concentration could alter serotonergic and dopaminergic neurotransmission in the brain (Carlezon, Jr. et al. 2005; Su et al. 2003). Another mechanism is that omega-3 PUFAs play an important role in the mechanism of mood stabilization by targeting parts of the "arachidonic acid (AA) cascade" (Rapoport and Bosetti 2002). AA is the major substrate for prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), which is important in the development of animals' sickness behavior, a series of behavioral changes that resemble depressive symptoms (Maddock and Pariante 2001). It has been reported that omega-3 PUFA treatment could reduce PGE<sub>2</sub> synthesis, and attenuate cytokine-induced sickness, stress and anxiety-like behaviors (Song et al. 2004).

#### 四、計畫成果自評

By granted from the National Science Council (NSC89-2320-B-038-046, 90-2320-B-038-046, 91-2320-B-039-010, 92-2320-B-039-002, 91-2320-B-039-017, 92-2320-B-039-003), our research team has been achieved some preliminary results and published in the international journals on the

field of omega-3 fatty acids in depressive disorders.

Our result here shows that omega-3 fatty acids have a beneficial effect on preventing the development of depression-like behaviors in rats with the FST. This is important to support the causal relation between the pathogenesis of depressive disorders and omega-3 fatty acids. Along with our previous studies of omega-3 fatty acids effects on patients with major depression, the diet and red blood cell levels of omega-3 fatty acids in patients with major depression and bipolar disorder, the results from this study is original.

In addition, the result of this study is accepted to be published in the *Journal of Psychiatric Research* (Impact factor: 3.3).

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