UNIVERSITI PUTRA MALAYSIA

EFFECTS OF HIGH POLYUNSATURATED FATTY ACIDSUPPLEMENTATION OF DIET ON SPATIAL MEMORY AND PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR EXPRESSION IN RATS

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By

TOKTAM HAJJAR

Thesis Submitted to the School of Graduate Studies, UniversitiPutra Malaysia, in Fulfilment of the Requirements for the Degree ofDoctor of Philosophy

April 2012

DEDICATION

To

My father for his encouragement

My mother for her kindness

My husband for his support

My son for his help

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

EFFECTS OF HIGH POLYUNSATURATED FATTY ACID SUPPLEMENTATION OF DIET ON SPATIAL MEMORY AND PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR EXPRESSION IN RATS

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TOKTAM HAJJAR

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Chair: Associate ProfessorGoh Yong Meng, PhD

Faculty: Veterinary Medicine

The n-3 and n-6 polyunsaturated fatty acids (PUFAs) are essential dietary nutrients. The n-3 fatty acids are the most abundant fatty acid in the mammalian central nervous system and played important role in brain growth and function. DietaryPUFA have effects on membrane composition and regulation of gene expression. The PUFA-activated transcription factors regulate the genes involved in synaptic plasticity to improve memory formation.

The aim of this research was to study the effects of diets supplemented with menhaden fish oil (source of n-3) and soybean oil (source of n-6) on the fatty acid profiles of the plasma and hippocampus, cognitive function developments, and expression of transcription factors associated with changes in morphological aspects of neurons in rats.

In this study, forty male rats were randomly allotted into 4 groups of ten animals each namely CTRL (control) standard diet plus 7% butter (w/w), LMO (low menhaden fish oil) standard diet plus 0.23 % menhaden fish oil + 6.77 % soybean oil (w/w) with a n-6:n-3 ratio of 26:1, MMO (medium menhaden fish oil) standard diet plus 1 % menhaden fish oil + 6 % soybean oil (w/w) with a n-6:n-3 ratio of 22:1 and HMO (high menhaden fish oil) standard diet plus 3.5 % menhaden fish oil + 3.5 % soybean oil (w/w) with a n-6:n-3 ratio of 4.5:1.

The fatty acid profiles of the diets, plasma and hippocampus of the rats were determined using standard extraction, methylation and gas-liquid chromatographic procedures. Results showed that docosahexaenoic acid (DHA)content and total n-3 PUFA in the plasma of the MMO and HMO groups were significantly higher and their n-6:n-3 ratio lower than CTRL group (P<0.05). HMO animals also had significantly higher DHA content, total n-3 PUFA, and less n-6:n-3 ratio in the hippocampus compared with CTRL group (P<0.05).

The effects of above-mentioned changes in fatty acid composition on cognitive function were assessed for their spatial memory performance using the Morris Water Maze (MWM) test. The MWM test was performed in four phase namely spatial acquisition, probe trial, spatial reversal, and reversal probe trial. The results showed that the HMO and MMO rats had better spatial learning and re-learning compared with LMO and CTRL animals, indicating spatial memory abilities are related to the brain n-3 PUFAs status.

The effect of increased brain n-3 fatty acids on hippocampus morphology was analyzed based on the changes in amount of presynaptic protein synaptophysin in hippocampus and the size of hippocampal neurons. Results indicated that the size of CA1 neurons was significantly increased in the HMO group compared to the CTRL group ($P<0.05$). Moreover, the expression of synaptophysin was increased in the rats supplemented with n-3 and n-6 fatty acids.

The expressions of PPARα, PPARγ and c-Fos genes were assessed by real-time quantitative PCR method. Results showed that the dietary menhaden fish oil- and soybean oil supplementation upregulated PPARα and PPARγ genes expression ($P<0.05$) in the MMO and HMO groups compared to the CTRL group. However, the expression of c-Fos gene was not differentially expressed between animals fed the menhaden oil and soybean oil when compared with CTRL group.

In conclusion, the dietary supplementation with higher level of n-3 fatty acids led to increased DHA and n-3 PUFAs content of the plasma and hippocampus, and PPARs upregulation. The increased n-3 PUFAs content in the hippocampus resulted in improved spatial memory in the rat, which may be also related to the alteration in synaptic protein and neuronal morphologic changes. The higher expression of

PPARs suggests the association of these transcription factors in protein synthesis involved in the synaptic mechanisms that mediate the formation of spatial memory.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysiasebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KESAN PEMBERIAN SUPLEMEN ASID LEMAK POLITAKTEPU YANG TINGGI KE MEMORI RUANG DAN ATAS EKSPRESI PPAR PADA TIKUS

Oleh

TOKTAM HAJJAR

April 2012

Pengerusi: ProfesorMadya Goh Yong Meng, PhD

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Asid lemak politaktepu n-3 dan n-6 merupakan nutrien pemakanan yang wajib.Asid lemak n-3 juga merupakan asid lemak yang terbanyak dalam sistem saraf pusat haiwan mamalia, dan memainkan pernan yang penting dalam tumbesaran dan fungsi otak. Asid lemak politaktepu mampu mempengaruhi komposisi membran serta ekspresi gen. Malah, faktor transkripsi yang diaktifkan oleh asid lemak politaktepu mengawalatur gen yang terlibat dalam plastisiti sinaps yang bertanggungjawab untuk memapankan pembentukan ingatan.

Tujuan penyelidikan ini adalah untuk mengkaji kesan makanan yang ditambah dengan minyak ikan Menhaden (sumber n-3) dan minyak kacang soya (sumber n-6), ke atas profil asid lemak pada plasma serta hipokampus, pembangunan fungsi kognitif, dan ekspresi faktor transkripsi yang berkait dengan perubahan morfologi neuron tikus.

Kajian ini menggunakan empat puluh ekor tikus jantan yang diagihkan secara rawak ke dalam empat kumpulan rawatan, yakni CTRL, LMO, MMO dan HMO. Kumpulan ini masing-masingnya menerima makanan tikus yang ditambah dengan 7 % mentega (b/b), 0.23% minyak ikan Menhaden + 6.77 % minyak kacang soya (b/b), 1 % minyak ikan Menhaden + 6 % minyak kacang soya (b/b) dan 3.5 % minyak ikan Menhaden + 3.5 % minyak kacang soya (b/b). Campuran ini menghasilkan nisbah n-6:n-3 pada 65:1, 26:1, 22:1 dan 4.5:1.

Profil asid lemak makanan, plasma dan hipokampus tikus telah ditentukan menggunakan kaedah kromatografi gas. Keputusan menunjukkan bahawa asid lemak DHA dan jumlah asid lemak politaktepu n-3 pada plasma MMO dan HMO adalah tinggi, dan nisbah n-6:n-3 yang rendah serta berbeza dengan signifikan daripada kumpulan CTRL ($P<0.05$). Kumpulan HMO juga mencatatkan kandungan asid lemak DHA, jumlah asid lemak n-3 dan nisbah n-6:n-3 yang rendah pada hipokampus berbanding kumpulan CTRL ($P<0.05$).

Untuk menilai kesan langsung diet ke atas fungsi kognitif, fungsi ingatan ruangan tikus telah diuji dengan menggunakan ujian Morris Water Maze (MWM). Ujian ini telah dilakukan dalam empat peringkat, yakni ujian pembelajaran ruangan, ujian prob, ujian penerbalikan ruangan, ujian penerbalikan prob. Keputusan menunjukkan bahawa kumpulan HMO dan MMO menunjukkan keupayaan pembelajaran dan pembelajaran semula ruangan yang lebih baik berbanding kumpulan LMO dan

CTRL. Keputusan ini secara langsung menunjukkan perkaitan antara kecekapan fungsi ingatan ruangan serta status n-3 otak.

Kesan ke atas morfologi neuron hipokampus oleh tahap n-3 yang meningkat dalam otak dinilai berdasarkan perubahan ke atas tahap protein sinaptofisin dalam hipokampus, serta saiz neuron.Keputusan menunjukkan bahawa saiz neuron CA1 pada kumpulan HMO adalah lebih besar berbanding kumpulan CTRL ($P<0.05$).Malahan, ekspresi sinatofisin juga meningkat di kalangan tikus yang menerima asid lemak n-3 dan n-6 tambahan dalam makanan mereka.

Ekspresi PPARα, PPARγ dan gen c-Fos telah diukur menggukan kaedah PCR kuantitatif masa nyata (RT-PCR). Kumpulan yang menerima minyak ikan Menhaden serta minyak kacang soya dalam diet telah menunjukkan peningkatan ekspresi PPARα dan PPARγ di kalangan MMO dan HMO, berbanding kumpulan CTRL ($P<0.05$).Walaubagaimanapun, ekspresi c-Fos tiada bezanya di antara semua kumpulan.

Kesimpulannya, penambahan asid lemak n-3 pada tahap yang lebih tinggi telah meningkatkan kandungan DHA dan asid lemak n-3 pada plasma dan otak, serta mengakibatkan peningkatan ekpresi PPAR.Tahap n-3 yang tinggi dalam hipokampus terlibat secara langsung dalam peningkatan tahap fungsi ingatan ruangan pada tikus.Peningkatan ini mungkin juga berkait rapat dengan perubahan pada protein sinaps dan perubahan morfologi neuron.Tahap ekspresi PPAR yang lebih tinggi menujukkan kemungkinan faktor transkripsi ini memainkan peranan menerusi mekanisme sinaps yang menjadi pengantara kepada pembentukan ingatan ruangan.

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I certify that a Thesis Examination Committee has met on 20 April 2012 to conduct the final examination of Toktam Hajjar on her thesis entitled "Effects of High Polyunsaturated Fatty Acid Supplementation of Diet on Spatial Memory and Peroxisome Proliferator Activated Receptor Expression in Rats" in accordance with the Universities and University College Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and hasbeen accepted as fulfilment of the requirement for the degree of **Doctor of Philosophy**. The members of the Supervisory Committee were as follows:

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DECLARATION

I declare that the thesis is my original work except for quotations and citationswhich have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti PutraMalaysia or at any other institution.

TOKTAM HAJJAR

Date: 20th April 2012

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AA	arachidonic acid
ACh	acetylcholine
ACO	acyl-CoA oxidase
ACS	acyl-CoA synthase
ALA	α- linolenic acid
CA	cornu ammonis
CaM-KII	calcium-calmodulin-dependent protein kinases II
CNS	central nervous system
DG	dentate gyrus
DHA	docosahexaenoicacid
EFA	essential fatty acid
EPA	eicosapentaenoic acid
FTTP	fatty acid transport protein
GABA	gamma-aminobutyric acid
IEG	immediate early gene
IL	interleukin
LA	linoleic acid
LCPUFA	long chain polyunsaturated fatty acid
LPL	lipoprotein lipase
LTP	long term potentiation
MUFA	monounsaturated fatty acid
MWM	Morris water maze
n-6: n-3 ratio	total n-6 PUFA to total n-3 PUFA ratio
NE	north east
NMDA	N-methyl-D-aspartat
NO	nitric oxide
NW	north west
PKC	protein kinase C

PPAR	peroxisome proliferatoractivated receptor
PPRE	peroxisome proliferator response elements
PUFA	polyunsaturated fatty acid
RAR	retinoic acid receptor
rCBF	regional cerebral blood flow
RXR	retinoid X receptors
SE	south east
SFA	saturated fatty acid
SW	south west
TNF	tumor necrosis factor
UFA	unsaturated fatty acid

CHAPTER 1

INTRODUCTION

Two majorfamilies of polyunsaturated fatty acids (PUFAs) are n-3 PUFA and n-6 PUFA.Both n-3 and n-6 compete for the samemetabolic enzymes in the lipid desaturation and elongation pathways(Gurr, 1999). This necessitates that n-3 and n-6 be consumed in a balanced proportion.This is particularly important when considering the abundance of n-6 fatty acids and the scarcity of n-3 fatty acids in common diets (Simopoulos, 1999).

Studies suggest the evolutionary human diet, rich in game animals, seafood, and other sources of n-3, may have been provided at a healthy ratio of n-6:n-3(Simopoulos, 2003; Simopoulos et al., 2000) and have been caunsed health benefits including reducing the risk of cognitive dysfunction because of its content of PUFAs(Hashimoto et al., 2009; Simopoulos, 2003; Simopoulos et al., 2000).

The n-6 and n-3 fatty acidsare two important fatty acids for the brain.The essentiality of these fatty acids to the brain functions is well reflected in the high PUFA lipid composition of the mammalian brain, which is unique from other tissues (Gamoh et al., 1999). The brain is an organ rich in n-3 PUFAs, particularly docosahexaenoicacid (DHA; 22:6n-3). The n-3 PUFAsare essential for plasma membrane structure and played an important role in cellular functioning and normal brain development cognitive functions including learning and memory(Birberg-thornberg et al., 2006; Calderon and Kim, 2004).Several clinical and epidemiologic studies have reported low plasma n-3 fatty acid status in individuals with dementia, personality disorder, depression, and bipolar disorder (Peet and Stokes, 2005; Timonen et al., 2004).The n-6 fatty acids are also important in proper brain function because they affect neurotransmitter release.

The n-3 PUFAs aremajor structural components of all cell membranes, andthe proposed mechanisms for health benefits of n-3 fatty acids are related to the incorporation of the fatty acids into membrane phospholipids (Clandinin et al., 1994). The n-3 PUFAs contribute to the modulation of membrane properties like fluidity, selective permeability(Yehuda, 2003),and membrane-associated activities of transporters, enzymes andreceptors(Smit et al., 2004).PUFAs are also precursors for eicosanoids, growth regulators, and are components of membrane phospholipids involved in signal transduction (Spector, 1999). Studies have demonstrated thatthese fatty acids inhibit neuronal apoptosis (Lau et al., 2000)and controlthe activity of some enzymes(Chanez, 1994), neural signalling (Kim andEdsall, 1999) and ionic channels(Leaf et al., 1996).

There are many reports on the detrimentaleffects of n-3 PUFA deficiency in mental ability development. Animal studies have shown that low dietary n-3 PUFAs and low plasma DHA concentration leads to decreased levels of n-3 PUFAs in the brain, which in turn resulted in behavioral defects in development and reduced visual ability (Conquer et al., 2000; Noaghiul andHibbeln, 2003).On the other hand, the recent studies have shown that a high lipid content diet (16% saturated fat) is harmful to cognitive ability by increasing serum cholestrol level and affecting thebrain's fatty acid composition(Hooijmans andKiliaan, 2008; Yu et al., 2010), while n-3 PUFAs can improve spatial memory (Hooijmans andKiliaan, 2008; Privitera et al., 2011).

Dietary PUFA have effects on diverse physiological processes impacting normal health and chronic diseases, such as the regulation of plasma lipid levels, cardiovascular function, insulin action and neuronal development. PUFA supplementation affects on membrane composition and function, cellular signaling and regulation of gene expression. The n-3 fatty acids incorporated into neuron membrane increase synaptic protein expression resulting in strengthen hippocampal synaptic plasticity to improve memory formation (Su, 2010).Expression of proteins involved in neural plasticity at synapses is modulated by transcription factors**.**

The transcription factors peroxisome proliferatoractivated receptor (PPAR) play a critical physiological role as lipid sensors and regulators of lipid metabolism, being activated by fatty acids (Berger and Moller, 2002; Hihi et al., 2002). The PPARsplay an essential role in neuromodulation, by regulation of genes involved in synaptic plasticity(Moreno et al., 2004).

The transcription factor c-Fos also haskey functions in synaptic plasticity underlying learning and memory formation (Alberini, 2009; Kandel et al., 2000). It can regulate the expression of genes involved in the replenishment of synaptic vesicles (Kaczmarek, 2000).

Hypothesis

It was hypothesized that dietary n-3 PUFAs will alter the plasma and hippocampus fatty acid composition in the rat, leading to the upregulation PPARs and c-Fos expression, as well as inducingmorphologic neuronal changes, which eventually contributed to the improvement of spatial memory.

Objectives

The objectives of the present study were:

1. To determine the extent of fatty acid profiles changes in the hippocampus and plasma following dietary PUFA supplementation.

2. To assess the differential effects of n-6:n-3 fatty acid ratios on cognitive function developments in rats.

3. To determine extent of morphologic neuronal alteration following n-3 and n-6 fatty acids supplementation.

4. To investigate the effects of n-3 and n-6 fatty acids supplementation on PPAR up-regulation andc-Fos expressions that are associated with changes in cognitive function.

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