UNIVERSITI PUTRA MALAYSIA

ANTIDEPRESSANT-LIKE EFFECTS OF MENHADEN FISH OIL IN POSTPARTUM-INDUCED MODEL OF DEPRESSION IN RATS

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FPSK(M) 2014 15

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

March 2014

DEDICATION

I dedicate this thesis to my beloved parents for their unconditional love and support

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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Chair: Mohamad. Taufik Hidayat Baharuldin, PhD
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Postpartum depression (PPD) is a psychiatric disorder that defined as a subtype of major depressive disorder (MDD) which may result from reproductive hormone fluctuations subsequent to childbirth. Approximately 10-15% of women experience postpartum depression (PPD) after baby delivery. It is hypothesized that the depression symptoms may be attenuated with omega-3 fatty acids. In order to examine this hypothesis, ovariectomized female rats underwent hormone-simulated pregnancy (HSP) regimen and received progesterone and estradiol benzoate or vehicle for 23 days, mimicking the actual rat's pregnancy. Forced feeding of menhaden fish oil (rich in omega-3) with three doses of 1, 3 and 9 g/kg/d, fluoxetine (an antidepressant drug) 15mg/kg/d and distilled water 2ml/d per rat started in six experimental groups on postpartum day 1 and continued for 15 consecutive days. On postpartum day 2, 8 and 15 all groups were tested in the forced swimming test (FST) and open field test (OFT). The seventh experimental group (normal control), which had not experienced neither ovariectomy nor injection, received only distilled water 2ml/d through oral gavage for 15 consecutive days and underwent the same behavioral tests as well. Animals were sacrificed by decapitation on postpartum day 15 following exposure to behavioral tests and blood and brain samples were collected. Plasma samples were utilized to assay levels of corticosterone and pro-inflammatory cytokines using ELISA and Procarta immunossay technique respectively. The corticosterone levels of hippocampus were measured by ELISA as well. Significant differences between groups were evaluated using one-way analysis of variance (ANOVA), followed by the post hoc Tukey's multiple comparison test when appropriate $P<0.05$ was considered significant. The results showed that following 15 consecutive days' treatment with three different doses of menhaden fish oil, the immobility time of animals seen in FST was reduced compared to negative control group. The effect was found to be dose dependent where menhaden fish oil 3g and 9g/kg/d have shown significant reduction in immobility time. Furthermore, menhaden fish oil did not change locomotor activity; therefore, the decrease of immobility time observed in FST

following menhaden fish oil supplementation is due to its ability to attenuate depression. The results of biochemical analysis showed that the plasma levels of corticosterone, interleukin 1-β and interferon-γ were decreased significantly following menhaden fish oil treatment at doses of 3 and 9 g/kg/d. In addition, supplementation with 9 g/kg menhaden fish oil significantly decreased the plasma levels of tumor necrosis factor-α and hippocampal levels of corticosterone. However, menhaden fish oil at 1 g/kg produced a slight reduction ($p>0.05$) in immobility time in FST and in the levels of corticosterone and pro-inflammatory cytokines. Taken together, these results suggest that menhaden fish oil, rich in omega-3, exerts beneficial effect on postpartum depression and decreases the biomarkers related to depression.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Sarjana Sains

KESAN ANTI-KEMURUNGAN MINYAK IKAN MENHADEN KEATAS TIKUS MODEL KEMURUNGAN POSTPARTUM

Oleh

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Kemurungan postpartum (PPD) ialah gangguan psikiatri yang berlaku selepas kelahiran anak. PPD didefinisikan sebagai satu bentuk gangguan kemurungan (MDD) disebabkan oleh ketidakstabilan hormon reproduktif selepas kelahiran anak. Hampir 10-15% wanita mengalami PPD setelah kelahiran bayi. Adalah dihipotesiskan bahawa simptom-simptom kemurungan boleh dikurangkan dengan pengambilan asid omega 3 lemak. Untuk mengkaji hipotesis ini, tikus betina yang diaruh ovariektomi disimulasi kehamilan oleh hormon (HSP) melalui pemberian benzoat progesteron dan estradiol atau bahan kawalan selama 23 hari, bagi menyerupai tempoh kehamilan tikus sebenar. Pemberian secara oral minyak ikan menhaden (kaya dengan omega-3) dengan tiga dos 1, 3 dan 9 g/kg/d, 15mg/kg/d fluoxetine (dadah antidepresan) dan 2mL/d air suling setiap tikus dimulakan keatas 6 kumpulan eksperimen pada hari pertama pospartum dan berterusan untuk 15 hari berikutnya. Pada hari ke-2, 8 dan 15 pospartum, semua kumpulan diuji dengan ujian paksa-renang (FST) dan lapangan terbuka (OFT). Kumpulan uji kaji ketujuh, yang tidak diaruh ovariektomi mahupun suntikan hormon, menerima 2mL/d air suling secara oral untuk 15 hari berturut-turut serta menjalani ujian tingkahlaku yang sama. Haiwan dikorbankan dengan dipenggal lehernya pada hari ke-15 pospartum selepas ujian tingkahlaku serta sampel darah dan hipokampus diambil. Sampel plasma digunakan untuk ujian kortikosteron dan sitokin pro-inflamatori menggunakan ELISA dan teknik ujian imun Procarta. Tahap kortikosteron hipokampus diukur menggunakan ELISA. Perbezaan yang signifikan antara kumpulan dinilai menggunakan ANOVA, diikuti dengan ujian perbandingan pelbagai Tukey post hoc. Setelah 15 hari rawatan dengan tiga dos minyak ikan menhaden, masa immobiliti haiwan ketika FST lebih pendek berbanding kumpulan kawalan negatif. Dos 3g dan 9g/kg/d minyak ikan menhaden menunjukkan pengurangan yang signifikan terhadap masa immobiliti haiwan. Tambahan pula, pengambilan minyak ikan menhaden tidak mengubah aktiviti lokomotor; maka, pengurangan masa immobiliti haiwan ketika FST mencadangkan bahawa pengambilan minyak ikan menhaden berupaya mengurangkan kemurungan.

Keputusan analisis biokimia menunjukkan aras kortikosteron plasma, interleukin1-β dan interferon-γ menurun dengan signifikan pada kumpulan rawatan 3 dan 9 g/kg/d minyak ikan menhaden. Pengambilan 9 g/kg minyak ikan menhaden juga mengurangkan aras plasma nekrosis tumor faktor α dan kortikosteron hipokampus dengan signifikan. Walaubagaimanapun, minyak ikan menhaden 1g/kg menunjukkan sedikit penurunan ($p>0.05$) terhadap tempoh imobiliti FST dan paras kortikosteron serta sitokin. Oleh itu minyak ikan menhaden, yang kaya dengan omega-3, dicadangkan mempunyai kesan antidepresan serta berupaya mengurangkan paras penunjuk biologi keatas tikus-tikus yang diaruh PPD.

ACKNOWLEDGEMENTS

First of all, I would like to thank God for giving me this opportunity. I am honored and grateful to have the full support and commitment from a number of people during my study. I would like to express my sincere appreciation and gratitude to my supervisor Assoc. Prof. Dr. Mohamad. Taufik Hidayat Baharuldin, my co-supervisor Assoc. Prof. Dr. Mohamad. Aris Mohamad. Moklas and member of the Supervisory Committee Assoc. Prof. Dr. Sharida Fakurazi for their kindness, support and guidance all throughout my study.

I am also indebted to the staffs of Anatomy laboratory, Department of Human Anatomy of FMHS for helping me to set up the behavioral room and assisted during the laboratory work. I would like to express special thanks to Dr. Sani Ismaila Muhammad for his technical support regarding surgery on rats and Mr. Ramli Suhaimi and staffs of Animal Unit for their kind support. I am also thankful to Mr. Ariyo Movahedi and Mr. Sobhan Ghafourian for their technical support.

Last but not least, I would like to express my deepest thanks to my beloved family and parents for their patience, continuous support and encouragement.

I certify that a Thesis Examination Committee has met on 19 March 2014 to conduct the final examination of Leila Arbabi on her thesis entitled "Antidepressant-Like Effects of Menhaden Fish Oil in Postpartum-Induced Model of Depression in Rats" in accordance with the Universities and University Colleges 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 Master of Science.

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LIST OF ABREVIATIONS

AA	Arachidonic Acid
ACTH	Adrenocorticotropic Hormone
ACUC	Animal Care and Use Committee
ALA	Alpha-Linolenic Acid
ANOVA	Analysis Of Variance
C	Centigrade
CORT	Corticosterone
CRF	Corticotropin-Releasing Factor
d	day
DHA	Docosahexaenoic Acid
EB	Estradiol
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
EPA	Eicosapentaenoic Acid
FLX	Fluoxetine
FSH	Follicle-Stimulating Hormone
FST	Forced Swim Test
g	gravitational acceleration
GnRH	Gonadotropin-Releasing Hormone
GR	Glucocorticoid Receptor
HPA	Hypothalamic-Pituitary-Adrenal
HSP	Hormone-Simulated Pregnancy
i.m.	Intramuscular
IDO	Indoleamine 2,3-dioxygenase
IL	Interleukin
INF-γ	Interferon gamma
IRS	Inflammatory Response System
JHU	John Hopkins University
LA	Linoleic Acid
LCPUFA	Long Chain Polyunsaturated Fatty Acids
LH	Luteinizing Hormone
MAP	Multi-Analyte Profiling beads
MD	Major Depression
MDD	Major Depression Disorder
MFO	Menhaden Fish Oil
mL	milliliter
MR	Mineralocorticoid Receptor
MSc	Master of Science
N	Number
ng	nanogram
NK	Natural killer
OFT	Open Field Test

OVX	Ovariectomy
p	probability
PBS	Phosphate Buffered Saline
PG	Prostaglandin
Pg	picogram
PLA2	Phospholipases A2
PP	Postpartum
PPD	Postpartum Depression
PUFA	Polyunsaturated Fatty Acids
PVN	Paraventricular Nucleus
s.c.	subcutaneous
SEM	Standard Error of the Mean
SIDS	Sudden Infant Death Syndrome
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressants
TNF-α	Tumor Necrosis Factor alpha
UPM	Universiti Putra Malaysia
USA	United States of America
W	Watt

CHAPTER 1

INTRODUCTION

1.1 Introduction

Postpartum depression (PPD) is a psychiatric disorder, which occurs following childbirth. PPD is defined as a subtype of major depressive disorder (MDD) with several symptoms such as depressed mood, loss of interest in activities, loss of pleasure, sleep and appetite disturbance, guilty feeling, lack of concentration, and thought of suicide (Pearlstein *et al.*, 2009).

The onset of PPD occurs within the first 2-3 month after baby delivery and may last one year (Cuijpers *et al.*, 2008). Mood disorder is the most frequent morbidity for mothers during postpartum period (Stocky & Lynch, 2000).

Dramatically changes in reproductive hormones in all women at parturition results in "baby blues" with an estimated rate of 75 % of mothers (Moses-Kolko *et al.*, 2009). Symptoms of baby blues, which are similar to PPD, occur in the first week following baby delivery, peaked on the 5^{th} day, and usually diminish by the 12^{th} day. If the symptoms of baby blues last more than two weeks, it will be considered as postpartum depression (Leitch, 2002). It has been reported that 10-15% women suffer from PPD following childbirth (Halbreich, 2005).

Although the underlying etiology of postpartum depression remained unknown, scientists suggest a number of possible theories in this respect. Biological, psychological and social factors or combination of them may contribute to cause and progress of PPD (Berggren-Clive, 1998). One of the most potent hypotheses of its etiology is the hormonal hypothesis. Abrupt changes in reproductive hormones that women undergo in post-delivery period may cause postpartum depression (Moses-Kolko *et al.*, 2009; O'Hara, 2009; Parry *et al.*, 2003). In addition to the role of estrogen and progesterone, some other biological factors such as hypothalamic-pituitary-adrenal (HPA) axis hormones, altered immune system and cytokines, and altered fatty acids have been proposed to play a role in causing postpartum depression (Corwin & Pajer, 2008; Zonana & Gorman, 2005).

Not diagnosing and treating postpartum depression has significant adverse effects on depressed individuals and their families (Dennis, 2004). Increased risk for marital disruption and divorce as well as child abuse, infanticide and maternal suicide are some of the problems of untreated PPD (Sit *et al.*, 2006). Besides, children from depressed mothers have a high rate of cognitive and behavioral problems and have lower vocabulary skills (Jones & Venis, 2001).

Generally, two main classes of antidepressant drugs, prescribed to decrease PPD symptoms, are serotonin-specific reuptake inhibitor (SSRIs) and tricyclic antidepressants (TCAs). The best example for the former is fluoxetine (Prozac) and for the latter are amitriptyline (Elavil) and imipramine (Tofranil). Due to side effects of medical treatment on breastfed infants and negative effects of untreated depression, mothers face dilemma over how to deal with depression symptoms. Therefore, another alternative treatment should be considered to lessen depressive symptoms with lower side effects for both mother and baby.

The benefits of omega-3 to attenuate depression symptoms have been reported in previous studies. There are many reasons indicating an inverse relationship between omega-3 fatty acids and depression. This link is seen in both observational and experimental research (Hallahan & Garland, 2005; Frasure-Smith *et al.*, 2004; Tiemeier *et al.*, 2003; Maes *et al.*, 1999).

Omega-3 fatty acids are long chain polyunsaturated fatty acids (LCPUFA). Alpha-linolenic acid (ALA) is the precursor for omega-3 fatty acids and it is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) through elongation (Nettleton, 1995). EPA (20:5 n-3) and DHA (22:6 n-3) which are both vital compounds should be supplied via individuals' diet since the human body cannot convert ALA to EPA and DHA efficiently (Pawlosky *et al.*, 2001). Fish and fish oil, which are rich in omega-3 fatty acids, are the best dietary sources of EPA and DHA (McGregor *et al.*, 2001).

In the nervous system, omega-3 has vital functions such as controlling membrane function (Tinoco, 1982), acting as antioxidant, reducing cerebral lipid peroxides (Choi-Kwon *et al.*, 2004; Hossain *et al.*, 1999) and protecting cells from toxicants (Baker, 2007). Immune system, vision and motor skills are the other parts of the body which are affected by omega-3 (Baker, 2007).

Although it is believed that omega-3 plays a vital role in the body and particularly in the nervous system and mood disorder, the mechanism involved is poorly understood. While numerous studies have been done to evaluate the effects of omega-3 on depression and other mood disorders, researches carried out to determine the effects of omega-3 on postpartum depression are few and the results are inconsistent.

Due to the contradictions among the results of previous researches in this regard, the present study was performed to clarify these discrepancies by investigating the effects of menhaden fish oil (rich in omega-3) on postpartum-induced rats. In this study, the locomotore activity and antidepressant-like effect of omega-3 was evaluated using standard behavioral tests, OFT and FST respectively. In addition, corticosterone levels in plasma and hippocampus were assayed and to determine the relation between omega-3 and immune system responses, plasma levels of pro-inflammatory cytokines were also measured.

1.2 Problem statement

Due to disadvantages of using antidepressant drugs such as costs and side effects on mother and breastfed infant, another alternative treatment should be considered to lessen depressive symptoms with lower drawbacks.

1.3 Hypothesis

Menhaden fish oil (rich in omega-3 fatty acids) have antidepressant-like effects on postpartum model of depression in rats.

1.4 Objectives

1.4.1 General objectives

To investigate the beneficial effects of menhaden fish oil (rich in omega-3 fatty acids) on behavioral activity, corticosterone levels and immunological indicators in rat model of postpartum depression.

1.4.2 Specific objectives

1. To determine the effects of menhaden fish oil on behavioral activity in forced swimming test (FST) and locomotor activity in PPD-induced rats
2. To measure levels of corticosterone in the hippocampus and plasma of PPD-induced rats following menhaden fish oil treatment
3. To measure plasma levels of IL1-β, TNF-α and INF-γ in PPD-induced rats following menhaden fish oil treatment.

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