UNIVERSITI PUTRA MALAYSIA

EFFECTS OF PRENATAL AND POSTNATAL TOCOTRIENOL- RICH FRACTION SUPPLEMENTATION ON COGNITIVE FUNCTION DEVELOPMENT IN F1 MALE RATS

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By

GOWRI A/P NAGAPAN

Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in fulfillment of the Requirement for the Degree of Master of Science

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

EFFECTS OF PRENATAL AND POSTNATAL TOCOTRIENOL- RICH FRACTION SUPPLEMENTATION ON COGNITIVE FUNCTION DEVELOPMENT IN F1 MALE RATS

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August 2014

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The intake of specific nutrients during the critical period in early life influence cognitive and behavioural development profoundly. Antioxidants such as vitamin E have been postulated to be pivotal in this process, as vitamin E is able to protect the growing brain from oxidative stress. Currently, tocotrienols are gaining much attention due to their potent antioxidant and neuroprotective properties. It is thus compelling to look at the effects of prenatal and early postnatal tocotrienols supplementation, on cognition and behavioural development among offspring of individual supplemented with tocotrienols. Therefore, this study was aimed to investigate potential prenatal and early postnatal influence of Tocotrienol-Rich Fraction (TRF) supplementation on vitamin E content in plasma and tissues; fatty acid profiles in brain and cognitive function developments in male F1 rats.

Eight-week-old adult female Sprague Dawley (SD) rats (F0 generation) were randomly assigned into five groups of two animals each. The animals were fed either with the base diet as control (CTRL), base diet plus vehicle (VHCL), base diet plus docosahexanoic acid (DHA), base diet plus Tocotrienol-Rich fraction (TRF), and base diet plus both docosahexaenoic acid, and tocotrienol rich fraction (DTRF) diets for two weeks prior to mating. The F0 females were maintained on their respective treatment diets throughout the gestation and lactation periods. Pups (F1 generation) derived from these dams were raised with their dams from birth till four weeks post natal. The male pups were weaned at eight weeks postnatal, after which they were grouped into five groups of ten animals each, and fed with the same diets as their dams for another eight weeks. Learning and behavioural experiments were conducted only in F1 male rats using the Morris water maze (MWM).

The vitamin E content of the diets, plasma and tissues of the male F1 rats were determined using standard extraction and High Performance Liquid Chromatography procedures. Results showed that vitamin E content, α-tocopherol and α-tocotrienol were found increased in the plasma, brain and liver of the TRF and DTRF groups than CTRL group (P<0.05). δ-Tocotrienol was found increased in the adipose of TRF and DTRF groups than CTRL group (P<0.05). Results also showed that the DHA content and total n-3 PUFA in the brain of the DHA and DTRF groups were significantly higher and their n-3: n-6 ratio significantly lower than CTRL group (P<0.05). TRF supplementation had no detectable effects on the PUFA profiles of the brain tissues of male F1 rats. Animals supplemented with either DHA and/or TRF such as DHA, TRF and DTRF groups demonstrated better spatial learning and re-learning ability compared to the CTRL animals (P<0.05). The cognitive parameters of TRF supplemented animals from the current study were comparable to that of the DHA group which was a positive control for this experiment.

In conclusion, the current study demonstrated that prenatal and postnatal intake of TRF increases the α-tocotrienol level in the progeny's brain. This results in better behavioural performance and cognitive function development in the F1 progeny.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN SUPLEMENTASI PECAHAN KAYA-TOKOTRIENOL (TRF) SEMASA PRANATAL DAN PASCANATAL KE ATAS PERKEMBANGAN FUNGSI KOGNITIF PADA TIKUS JANTAN F1

Oleh

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Pengambilan nutrien khusus mempengaruhi perkembangan kognitif dan tingkah laku dalam kehidupan awal. Antioksidan seperti vitamin E memainkan peranan penting dalam proses ini. Ini kerana vitamin E dapat melindungi otak daripada tegasan oksidatif. Tokotrienol semakin banyak mendapat perhatian sebagai komponen penting antioksidan dan pelindung saraf pada masa ini. Sehunbungan itu, adalah penting untuk mengkaji kesan suplementasi tokotrienol semasa pranatal dan pascanatal pada perkembangan fungsi kognitif. Kajian ini bertujuan untuk menyelidik kesan pengambilan pecahan kaya-tokotrienol (*Tocotrienol-rich fraction, TRF*) semasa pranatal dan pascanatal pada tahap vitamin E, profil asid lemak dalam tisu dan plasma, serta kesannya ke atas perkembangan fungsi kognitif pada progeni tikus jantan F1.

Tikus betina Sprague Dawley (SD) dewasa berumur lapan minggu telah dibahagikan secara rawak kepada lima kumpulan yang terdiri daripada dua haiwan setiap kumpulan. Tikus ini diberi makan diet rawatan yakni, diet asas (CTRL), diet ditambah dengan pengantara (VHCL), diet ditambah dengan asid dokosaheksanoik (DHA), diet dengan pecahan kaya-tokotrienol (TRF), dan diet ditambah dengan asid dokosaheksaenoik serta pecahan kaya-tokotrienol (DTRF) selama dua minggu sebelum mengawan denagan tikus dewasa jantan. Tikus betina generasi F0 diberi makan diet rawatan masing sepanjang tempoh bunting dan laktasi. Progeni tikus jantan dicerai susu pada masa lapan minggu. Selepas itu tikus jantan F1 telah dikumpulkan ke dalam lima kumpulan dengan sepuluh haiwan setiap kumpulan, dan dirawat dengan diet yang sama seperti induk tikus masing-masing selama lapan minggu lagi . Penilaian

fungsi kognitif hanya dijalankan pada progeni jantan F1 menggunakan Instrumen Pagar Sesat Air Morris (*Morris Water Maze*, MWM).

Tahap kandungan vitamin E dalam diet, plasma dan tisu tikus jantan F1 ditentukan menggunakan kaedah Kromatografi Cecair Berprestasi Tinggi (*High Performance Liquid Chromatography*, HPLC). Keputusan menunjukkan bahawa tahap vitamin E, α - tokoferol dan α - Tokotrienol didapati meningkat dalam plasma, otak dan hati pada kumpulan TRF dan DTRF berbanding kumpulan CTRL ($P<0.05$). δ-tokotrienol didapati meningkat dalam tisu adipos daripada kumpulan TRF dan DTRF berbanding CTRL ($P<0.05$). Keputusan juga menunjukkan bahawa kandungan DHA dan asid lemak poli tak tepu n-3 (PUFA n-3) telah meningkat dalam otak haiwan dari kumpulan DHA dan DTRF dengan nisbah PUFA n-3 : PUFA n-6 yang lebih rendah berbanding kumpulan CTRL ($P < 0.05$). Suplementasi TRF juga tidak memberi kesan signifikan kepada profil asid lemak politaktepu otak tikus jantan F1. Hasil kajian menunjukkan bahawa haiwan yang diberi makan sama ada DHA dan/atau TRF menunjukkan prestasi fungsi kognitif yang lebih baik berbanding dengan haiwan CTRL ($P < 0.05$). Tahap fungsi kognitif kumpulan TRF daripada kajian ini juga setanding dengan kumpulan DHA yang merupakan haiwan kawalan positif dalam eksperimen ini.

Kesimpulannya, kajian ini menunjukkan bahawa suplementasi TRF semasa pranatal dan pascanatal meningkatkan tahap α -tocotrienol dalam tisu otak. Ini seterusnya berkait dengan peningkatan fungsi kognitif di kalangan progeni jantan F1.

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I certify that a Thesis Examination Committee has met on 26 August 2014 to conduct the final examination of **Gowri Nagapan** on her thesis entitled " **Effects of Prenatal and Postnatal Tocotrienol- Rich Fraction Supplementation on Cognitive Function Development in F1 Male 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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ABC	ATP binding cassette
AD	Alzheimer's disease
APO B	apolipoprotein B
BDNF	Brain derived neurotropic factor
CA	Cornu ammonis
CEHC	Carboxyethyl hydroxychroman
CNS	Central nervous system (CNS)
EDTA	Ethylene-diamine-tetra-acetate
FAC	Fatty acid composition
FAME	Fatty Acid Methyl Esters
GC	Gas-liquid chromatography
GRAS	Generally regarded has safe
HDL	High-density lipoproteins
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HO-3	heme oxygenase 3
HPLC	High Performance Liquid Chromatography
L1	LINE-1
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
LTD	Long-term depression
LTM	Long- term memory
LTP	Long-term potentiation
MDR2	multidrug resistance 2 GeneTransporter glycoprotein
MWM	Morris water maze
NaCl	Sodium chloride
PMC	2, 2, 5, 7, 8-pentamethyl-6-hydroxychroman
ppm	Parts per million

PUFA	Polyunsaturated fatty acid
ROS	Reactive oxygen species
SREBPs	Sterol regulatory element binding protein
STM	Short- term memory
VLDL	Very-low-density lipoprotein
α-CEHC	2,5,7,8-tetramethyl-2(2'carboxyyethyl)-6-hydroxychroman
α-TTP	α-tocopherol-transfer protein
γ-CEHC	2,7,8-trimethyl-2(2'carboxyyethyl)-6-hydroxychroman
α-	Alpha
β-	Beta
γ-	Gamma
δ-	Delta

CHAPTER 1

INTRODUCTION

1.1 Overview

The brain requires adequate nutrition for optimum growth, development and maturation. Several micronutrients and polyunsaturated fatty acids (PUFAs) are known to be essential for proper structure of brain tissue, healthy neurochemistry and maturation of the brain (Bourre, 2006a; Bourre, 2006b). Adequate intake of these nutrients results in proper cognitive development. As the brain development occurs during foetal and early postnatal life, inadequate maternal intake of nutrition not only alters the brain development, but also causes impact on cognitive abilities that can have long lasting and irreversible effect (Lucas *et al*., 2001a). In the developing brain, macronutrients such as proteins and PUFAs are critically important for the synthesis of nucleic acids, neurotransmitters, growth factors and formation of cell membranes, synapse and myelin (Bourre, 2006b). Micronutrient such as vitamin E is important in developing brain as an antioxidant to protect the vulnerable brain cells from lipid peroxidation and also for normal neurological function (Ramakrishna, 1999).

The brain develops very rapidly during the last trimester of foetal life (prenatal) and the first two years (postnatal) of childhood (Rassin *et al*., 2003). Research has shown that exposure to certain conditions such as diseases (gestational diabetes, hypertension), nutrient deficiency, exposure to alcohol and smoking can have long lasting effects on cognition (Roseboom *et al*., 2012). Specifically, n-3 fatty acids, iodine, iron and choline have been shown to influence brain development and impact cognitive ability and behaviour in human and animals (Lucas *et al*., 2001b). Animal studies have shown that low n-3 PUFAs intake leads to decrease levels of n-3 PUFAs in the brain and in turn resulted in memory impairment and behavioural depression (Su H.M., 2010; Watanabe *et al*., 2004). Other nutrient such as vitamin E also had demonstrated significant neuroprotective properties (Khanna *et al*., 2003, 2005; Sen *et al*., 2000, 2003). The brain is highly susceptible to oxidative damage as it rich in PUFAs that form plasma membrane of neural cells. Vitamin E has been regarded as an important component of biological membrane as it may act as chain-breaking antioxidant to protect lipid membrane from oxidative damage (Suzuki *et al*., 1993). Tocotrienols in particular have been reported to exert antioxidant activity in many *in vitro* and *in vivo* systems (Ghafoorunissa *et al*., 2004; Nesaretnam *et al*., 1993; Noguchi *et al*., 2003; Yoshida *et al*., 2003; Yoshida *et al*., 2007; Qureshi *et al*., 2000). Tocotrienols may quench lipid radicals and in the process become radicals themselves, albeit less reactive ones. These radicals then reduced back to native form by vitamin C or indirectly by thiol antioxidants (glutathione and lipoic acid) (Rimbach *et al*., 2002).

Vitamin E is a lipid soluble natural antioxidant, which comprised of two major families of tocopherols and tocotrienols. The tocotrienols are the major form of vitamin E found in palm oil with the ratio of 30 % tocopherols and 70 % tocotrienols (Aggarwal *et al*., 2012). Accumulation of tocotrienol in tissue has very tangible health benefits. Studies have shown that tocotrienols have potent antioxidant (Azlina *et al*., 2005), cardioprotective (Das *et al*., 2008), hypocholesterolemic (Qureshi et al.,1986, 1991, 2000, 2001) anti-cancer (Sundram *et al.*, 1989; Komityama *et al.*, 1989; Nesaretnam *et al*., 2004, 2008;) and neuroprotective (Khanna *et al*., 2003, 2005; Sen *et al*., 2000, 2003) properties that are not exhibited by tocopherols. Tocotrienol also is a nutrient certified as GRAS (generally regarded as safe) by the U.S. Food and Drug Administration (US FDA) GRAS notice number (GRN) 307 in April 2010 (Park *et al*., 2011).

The integrity of the neural membrane is crucial to the neural functions. For living beings, the nervous system acts as a central coordinating centre for the various physiological, locomotor, and cognitive functions central to an animal's survival. Cognition refers to the mental processes involve in memory and learning (Wainwright & Colombo, 2006). Various factors such as nutrition, environment and genetic have strong influences on memory and learning. Nutrition affects cognition and mental health as brain structure and function are dependent on nutritional inputs (Dauncey & Bicknell, 1999). Various dietary factors such as n-3 fatty acids, antioxidants vitamins, minerals, curcumins and flavonoids have been identified as having beneficial effects on cognition (Gomez, 2008). This is because these dietary factors can affect multiple brain processes by regulating neurotransmitter pathways, synaptic transmission, membrane fluidity and signal transduction pathways associated with synaptic plasticity (Gomez, 2008). In contrast, diets rich in saturated and trans fats are known to affect cognition adversely. This is typically attributed to the role of these fats in reducing the synaptic plasticity mediated by the hippocampal brain derived neurotropic factor (BDNF) mediated synaptic plasticity (Molteni, 2002).

Accumulation of tocotrienols in the brain is required to protect vulnerable neurons from oxidative stress, enhance existing neuronal function and stimulate neuronal regeneration. Long-term oral supplementation was reported to be effective in delivering tocotrienols to vital organs without dependence on tocopherol-transfer protein (TTP) (Khanna *et al*., 2005). The delivery was more pronounced in the fetal brain when pregnant rats were fed with tocotrienols (Roy *et al*., 2002). Previous animal studies on cognition have focused on role of tocotrienols on improvement and prevention of cognitive impairments caused by diabetes (Kuhad *et al*., 2009), alcoholism (Tiwari *et al*., 2009), oxidative stress (Tiwari *et al*., 2009) and aging (Taridi *et al*., 2011, 2014). The roles of tocotrienols in neuroprotection have been reported in a number of studies. However, their exact contribution to neuroprotection afforded by the dam to her developing foetus and subsequent generations remained to be investigated. Aptly so, there are limited numbers of scientific publications in the trans-generational influence of tocotrienols supplementation on cognition and behaviour development. Thus, this study attempted to investigate the potential trans-generational

effects of maternal TRF supplementation on cognitive function development in the F1 males at maturity.

1.2 Hypothesis

It was hypothesized that continuous maternal TRF supplementation during gestation, lactation and post-weaning will improve cognitive function development in the F1 rats.

1.3 Objectives

The objectives of the present study were:

a) To investigate the prenatal and postnatal effects of TRF supplementation on the brain fatty acids profile and vitamin E content in plasma and tissues of the F1 male rats.

b) To investigate the prenatal and postnatal effects of TRF supplementation on cognitive function development in F1 male rats.

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