UNIVERSITI PUTRA MALAYSIA

MODULATION OF NMDA AND AMPA/KAINATE RECEPTORS BY TOCOTRIENOL-RICH FRACTION AND α-TOCOPHEROL IN GLUTAMATE- INDUCED INJURY OF PRIMARY ASTROCYTES

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FPSK(M) 2017 17

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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 2017

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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March 2017

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Neurodegenerative diseases such as Huntington`s, Alzheimer`s, Parkinson's disease and stroke are the most common diseases suffered by the aged population. Glutamate is considered as a main excitatory amino acid neurotransmitter in the mammalian central nervous system which can be excitotoxic, playing a key role in series of chronic neurodegenerative diseases. The Vitamin E which consist of tocopherol and tocotrienols, are different in their side chain either in saturated or unsaturated phytyl tail. Previous studies have demonstrated that tocopherol and tocotrienol have protective effects against glutamate toxicity in an astrocytic cell line. The aim of current study is to demonstrate the potential of tocopherol and tocotrienol in protecting glutamate injured primary astrocytes. For this purpose, the primary astrocytes were isolated from mixed glial cells of C57BL/6 mice by using the Easysep Mouse CD11b positive selection kit and cultured in supplemented DMEM. Mixed glial cultures were treated with 50-75 mM L-leucine methyl ester (LME) for 60-90 minutes to improve purity of cultures. The purity of primary astrocytes was measured by flow-cytometer and is approximately 79.4%. The IC_{20} and IC_{50} values of glutamate were determined by MTT assay at 10 mM and 100 mM respectively. Cell were induced injury at IC_{20} and IC_{50} of glutamate and the effects of tocopherol and tocotrienol rich fraction (TRF) was determined.in pre and post-treatment study. For the high yield of RNA, the IC_{20} of glutamate was used in the experiment. Exposure to 100 mM of glutamate in primary astrocytes reduced cell viability by approximately 64.75 % and 61.10 % in pre and post treatment study respectively. The mitochondrial membrane potential (MMP) detected in primary astrocytes were assessed with 100, 200 and 300 ng/ml concentration of TRF and α-Tocopherol. The results depicted that pre-treatment with TRF and α-Tocopherol caused the mitochondrial activity to achieve 88.46%, 82.42%, 80.74% and 93.31%, 87.51%, 83.70%, respectively. In post-treatment study, with increase of TRF (100, 200 and 300 ng/ml) concentration causes the increase to 61.21%, 73.01%, 78.43% of MMP value. Similarly, increase of MMP value from 66.12%, 76.46%, and 81.22% was observed with increasing

concentration of α-Tocopherol. Then the expression of ionotropic glutamate receptors genes was elucidated using Real-time PCR. The gene of interest consists of the Gria2 (Glutamate Receptor, Inotoropic AMPA), GRIK1 (Glutamate Receptor, Ionotropic, kainate1) and Grin2A (Glutamate Receptor, Ionotropic, N-Methyl D-Aspartate 2A). The results showed that in both pre and post studies, the ionotropic glutamate receptors genes were down regulated after the treatment and α- tocopherol played an important role in down regulating the genes. The most affected genes were Gria2, GriK1 and Grin2A respectively in both pre and post studies. Decreased intracellular calcium concentration also was observed indicating the present of vitamin E altered the polarization of astrocytes. As a conclusion, this study shown that α- tocopherol is more effective and only required low concentration of α- tocopherol for prophylactic purposes compared to post-treatment in primary astrocytes cells.

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

MODULASI RESEPTOR-RESEPTOR NMDA & AMPA/ KAINATE OLEH FRAKSI-KAYA TOKOTRIENOL DAN TOKOFEROL DI DALAM SEL PRIMER ASTROSIT YANG DIRANGSANG KECEDERAAN OLEH GLUTAMAT

Oleh

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Penyakit neurodegeneratif seperti Huntington's, Alzheimer's dan Parkinson's dan strok adalah penyakit yang sering dialami oleh populasi golongan warga tua. Glutamate merupakan neurotransmiter utama asid amino bagi sistem saraf pusat mamalia yang boleh menyebabkan eksitotoksik dan ia memainkan peranan penting dalam siri penyakit kronik neurodegeratif. Vitamin E terdiri daripada tokoferol dan tokotrienol yang mempunyai perbezaan dari segi struktur rantai sisi lemak tidak tepu dan lemak tepu. Berdasarkan kajian sebelum ini, tokoferol dan tokotrienol didapati mempunyai kesan pelindung terhadap toksisiti glutamat di dalam sel astrosit. Tujuan kajian ini dilakukan adalah bagi melihat potensi Vitamin E dalam melindungi sel astrosit primer daripada kecederaan yang disebabkan oleh glutamate. Dengan ini, sel primer astrosit telah dipencilkan daripada campuran sel glial tikus C57BL/6 dengan menggunakan kit pemilihan positif Easysep Mouse CD116 dan dikulturkan di dalam media *DMEM* yang mengandungi supplemen. Kultur campuran glial dirawat selama 60-90 minit dengan 50-75 mM L-leucine methyl ester (LME) bagi tujuan memperbaiki ketulenan kultur tersebut. Ketulenan sel astrosit yang diperolehi adalah 79.4% dengan menggunakan "flow-sitometer". Nilai IC_{20} dan IC_{50} glutamate ditentukan dengan menggunakan MTT asai iaitu 10 mM dan 100 Mm. Sel dicederakan dengan glutamat pada aras IC_{20} dan IC_{50} untuk kesan tokoferol dan fraksi kaya tokotrienol (TRF) dan ditentukan di dalam pra dan pasca rawatan. Bagi tujuan menghasilkan RNA yang tinggi, eksperimen dijalankan dengan menggunakan glutamat pada IC_{20}. Pada kepekatan 100 mM glutamat di dalam sel astrosit utama menyebabkan pengurangan sel hidup dengan anggaran 64.75% dan 61.10% di dalam pra dan pasca rawatan. Potensi membran mitokondria (MMP) mengesan sel utama astrosit pada kepekatan 100, 200 dan 300 ng/ml untuk fraksi kaya tokotrienol (TRF) dan α-tokoferol. Hasil kajian pra-rawatan dengan menggunakan TRF dan α-tokoferol menyebabkan aktiviti mitokondria telah mencapai sebanyak 88.46%, 82.42%, 80.47% bagi TRF dan 93.31%, 87.51%, 83.70% untuk tokoferol. Dalam kajian pasca-rawatan

pula, pertambahan kepekatan TRF pada 100, 200 dan 300 ng/mL menyebabkan kenaikan nilai MMP kepada 61.21%, 73.01% dan 78.43%. Kenaikan yang serupa bagi nilai MMP daripada 66.12%, 76.46% ke 81.22% diperhatikan apabila kepekatan α-tokoferol meningkat. Ekspresi reseptor gen ionotropik glutamat juga telah dikenalpasti menggunakan "Real-time PCR". Gen-gen tersebut ialah Gria2 (Reseptor gluatamate, Ionotropic AMPA), GRIK1 (Reseptor Glutamate, Ionotropik, Kinate 1) dan Grin2A (Reseptor Glutamate, Ionotropik, N-Methyl-D-Aspartate 2A). Kajian didapati, kedua-dua pra dan pasca rawatan menunjukkan reseptor ionotropik glutamate menurun selepas rawatan, dan ini menunjukkan keberkesanan α-tokoferol dalam mengawal selia gen-gen tersebut. Gen yang paling terkesan dalam pra dan paska rawatan kajian, adalah Gria2, Grik1 dan Grin2A. Penurunan kepekatan kalsium pada intraselular menyebabkan perubahan polarisasi pada sel astrosit dengan kehadiran vitamin E. Kesimpulannya, kajian ini menunjukkan α-tokoferol adalah lebih berkesan dan memerlukan hanya kepekatan yang rendah bagi tujuan profilaktik berbanding penggunaannya dalam pasca rawatan di dalam sel primer astrosit

ACKNOWLEDGEMENTS

I humbly thank Allah Almighty, the Beneficent and the Merciful, who gave me health, thoughts and co-operative people to enable me to achieve this goal.

This work would not be accomplished without the help of so many people. In the following lines is a brief account of some but not all who deserve my thanks.

First, I offer my sincerest gratitude to my supervisor, Dr. Huzwah Khaza'ai for taking the burden of supervising this research. Her theoretical insight and her relentless enthusiasm assisting in creating such inspiration to make this direction and finally, to succeed in this study. Without her, this thesis would not have been completed.

I am also delighted to convey my appreciations to my co-supervisor, Assoc. Prof. Dr. Sharmili Vidyadaran, for her unwavering efforts in reviewing this thesis and other supporst. Appreciate from Miss Tan Shi wei for her valuable assist to complate the section 3.2.2.1 in Immonolgy lab.

My warmest gratitude goes to all my friends: Dr. Atabak Kheirkhah, Dr. Hamid Reza Abolkheir, Dr. Kambiz Yousefi Talooki and Dr. Thilaga Rati Selvaraju for their endless patient, support, understanding and encouragement.

My heartfelt thanks go to all my family member, especially my parents Mr.Hossein Abedi and Mrs.Fatima Abedi for their endless love and support in all my life, with all nice memory that I could never forget.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AB	Amyloid beta
ROS	Reactive oxygen species
NOS	Nitric oxide synthetase
PARP	Poly ADP ribose polymerase
AIF	Apoptosis- inducing factor
TRF	Palm tocotrienol-rich fraction
α-TCP	A-tocopherol
HGA	Homogentisate
HPT	HGA phytyltransferase
GSH	Glutathione
DMBA	7, 12-dimethyl benz[α] anthracene
EBV	Epstein-Barr virus
LDL	Low-density lipoprotein
HMG-CoA	3-hydroxy-3-methylglutaryl coA
RNS	Reactive nitrogen species
ALS	Amyotropic lateral sclerosis
HUVEC	Human umbilical vein endothelial cells
TBARS	Thiobarbituric acid reactive substances
12-Lox	12-lipoxygenase
AD	Alzheimer's disease
NFT	Neurofibrillary tangles
APP	Amyloid precursor protein
BBB	The blood-brain barrier
CNS	Central nervous system
NSA1DS	Non-steroidal anti-inflammatory drugs
SNpc	Substantia nigra pars compact
HD	Huntington's disease
ALS	Amyotropic lateral sclerosis
PNS	Peripheral nervous system
GABA	Γ-aminobutyric acid
ATP	Adenosine triphosphate
AMPA	A-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid
NMDA	N-methyl-D-aspartate
GSH	Glutathione
TAC	Tricarboxylic acid
MPT	Mitochondrial permeability transition
NSE	Neuron specific enolase
GFAP	Glialfibrillary acidic protein
MBP	Myelin basic protein
TBI	Traumatic brain injury
DMEM	Dulbecco's modified eagle medium
DMSO	Dimethyl sulfoxide
Rlio 123	Dye rhodamine 123
Day in vitro	Div
GFAP	Glial fibrillary acidic protein
BSO	Buthionine sulfoximine
AHS	Ammon's horn sclerosis
iGluR	Ionotropic glutamate receptor

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Neurodegenerative diseases such as Alzheimer's disease and Parkinson as well as stroke are some of the common diseases among the aged individuals. In neurodegenerative diseases in mammals, cell death occurs in the brain due to two reasons: either the accumulation of amyloid beta (AB) protein or oxidative glutamate toxicity that causes neuronal cell death (Murphy et al., 1990).

The endogenous chemicals which transmit a signal from one neuron to another neuron across a synapse are referred to as neurotransmitters. These transmitters bind to a receptor in postsynaptic membrane where depolarization is caused by an excitatory neurotransmitter. In contrast, hyper-polarization in the postsynaptic membrane occurs as a result of an inhibitory neurotransmitter. It is assumed that glutamate, which is the main amino-acid neurotransmitter stimulant in the mammals' central nervous system can be excitotoxic at higher concentration, which mainly responsible for neurodegenerative diseases.

Glutamate which is considered as an important excitatory amino acid neurotransmitter plays a key role in the mammals' central nervous system. It can be excitotoxic and is assumed to be a cause of most types of neurodegenerative diseases (Zou & Crews, 2005). According to (Coyle & Puttfarcken, 1993), glutamate toxicity is a kind of brain-cell death which is associated with many types of chronic neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases.

There are two reasons for the occurrence of glutamate toxicity: receptor-originated excitotoxicity and non-receptor mediated toxicity. In the former type, excitotoxicity is caused by the activation of glutamate receptors, while in the latter it is the result of a series of disturbances, which reduce and oxide homeostasis in the cells. There are two main types of glutamate receptors: ionotropic receptors that are ligand-gated ion channels and metabotropic receptors, which are coupled with second messenger systems by G proteins (Hollmann & Heinemann, 1994). Cell death caused by excitotoxicity is due to the lack of three functional families of ionotropic glutamate receptors known as N-Methyl-D- Aspartate (NMDA) receptor, α-Amino-3-Hydroxy-5-Methyl-4- isoxazolepropionic acid (AMPA) receptor and Kainate receptor. These receptors are considerably penetrable to Ca^{2+} ions as well as Na^{+} and K^{+}. Thus, the increase in $[Ca^{2+}]$ through this receptor–gated channels is essential for physiological function and Excitotoxicity (Choi et al., 2005; Singh et al., 2003).

When a neuron and glial cell injury occur , as a result of their deprivation of oxygen and glucose, ATP decreases rapidly and becomes depolarized which leads to the release of glutamate from nerve terminals and eventually caused reduction of glutamate uptake by glial cells (SIESJÖ et al., 1995).

Additionally, glutamate accumulation over-excites the post-synaptic NMDA and AMPA receptors leading to an intracellular overload of Ca^{2+} (Sattler & Tymianski, 2001). Furthermore, increased of Ca^{2+} uptake into mitochondria due to strong loading, which can disrupt their function and lead to the release of damaging reactive oxygen species (ROS)(Dowling, 2001). Ca^{2+} loading may also lead to the generation of ROS through other mechanisms, such as the activation of nitric oxide synthetase (NOS), resulting in nitric oxide production, and the activation of NADPH-oxidase producing superoxide in mitochondria (Brennan et al., 2009). The generated ROS can induce DNA damage, which causes the activation of Poly ADP ribose polymerase (PARP) enzyme, capable of injuring neurons via NAD^{+} depletion, causing glycolytic block, ATP depletion, and induction of apoptotic signaling pathway through the release of apoptosis- inducing factor (AIF) from mitochondria (Alano et al., 2010).

In the case of a cerebral insult, the role of astrocytes in improving neuronal survival and recovery is increasingly recognized. The large body of recent studies on neuroprotection has focused on improving the neuron survival (Chang et al., 2009); however, a main simultaneous effect of ischemic infarction is the death of glia, especially astrocytes.

When an astrocyte is damaged, reduction of astrocytes function can lead to loss of CNS and the overall pathology related to the excitatory amino acids (Chen et al., 2000). Thus, it is essential to identify the responsible mechanisms in astrocytes death after insults and it should result in developing strategies with the specific aim of promoting astrocytes survival. Many studies have shown astrocytes damage after neurodegenerative disorders (Landis, 1994; Liu et al., 1999). For example, a study by Chen (2000)(Chen et al., 2000) showed that stimulating astrocytes with glutamate cause cell swelling and cell death.

With regard to the significance of the astrocyte survival in the occurrence of glutamate insult, it is highly desirable to find treatments to prevent excitotoxicity that causes cell death. It has been shown that astrocytes treated with vitamin E were able to resist glutamate excitotoxicity (Chen et al., 2001). The neuroprotective properties of Vitamin E composed of eight different isoforms, four tocopherols (α-,β-,γ-,δ-) and four tocotrienols (α-,β-,γ-,δ-) have been identified (Aggarwal et al., 2010).

Structurally, tocopherols and tocotrienols are different, in which the former possesses a saturated phytyl tail, while the latter has an unsaturated isoprenoid side chain. Palm tocotrienol-rich fraction (TRF) which is extracted from palm oil contains 75% tocotrienols and 25% α-tocopherol. It was illustrated that TRF has potent antioxidant (Maniam et al., 2008; Serbinova & Packer, 1994), anti-inflammatory (Wu et al., 2008), anticancer (Goh et al., 1994; Takahashi & Loo, 2004; WU & Ng, 2007),

neuroprotection (Osakada et al., 2004; Sen et al., 2000) and cholesterol-lowering effects(Minhajuddin et al., 2005; Mutalib et al., 2003; Qureshi et al., 1995).

Most of the studies have focused on the neuronal cell protection rather than astrocytes (Pettmann & Henderson, 1998; Wang et al., 2005). Hence, the present study attempts to investigate the effects of tocotrienols and tocopherols in preventing glutamate excitotoxicity in astrocytes. Besides promoting astrocytes survival, advanced neuroprotection would be expected. The prophylactic and preventive properties of tocotrienols and tocopherol in neurodegeneration are expected to be achieved and an alternative therapeutics based on nutrition would be offered.

1.2 Research Problem

Glutamate excitotoxicity in astrocytes cells leads to the release of Ca^{2+} and reactivation of free radicals by over-activation of glutamate receptors that eventually cause neuronal neurodegeneration and cell death. Controlling the receptor activity and inhibition of Ca^{2+}, release of glutamate and free radicals from astrocyte cells may be an effective method for preventing neurodegeneration. Does neuroprotective action of tocotrienol and tocopherols prevent astrocyte cells death induced glutamate?

1.3 Research Objectives

1.3.1 General Objective

To determine the role of tocotrienols and tocopherols in the prevention of glutamate toxicity in injured primary astrocytes.

1.3.2 Specific Objectives

- To determine the IC_{20} and IC_{50} values of glutamate in primary astrocyte cells.
- To determine the effect of tocotrienols and tocopherols on cell viability in primary astrocytes injured by glutamate.
- To determine the effect of tocotrienols and tocopherols on NMDA receptors in primary astrocytes injured by glutamate.
- To determine the effect of tocotrienol and tocopherols on the activation of Ca^{2+}permeabililty in AMPA/Kainate receptors in primary astrocytes injured by glutamate.
- To determine the effect of tocotrienol and tocopherols on Ca^{2+} ion influx in primary astrocytes injured by glutamate.

1.4 Hypotheses

Tocotrienols and tocopherols are capable of modulating glutamate receptors and Ca^{2+} influx in increasing survivability of primary astrocytes.

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