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EFFECTS OF GSK-3 INHIBITION ON LPS-INDUCED NEUROINFLAMMATION AND IL-10 PRODUCTION IN MICROGLIA

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By

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Microglia are resident macrophages of the central nervous system (CNS) that play a role in the immune surveillance system against various pathogenicities. However, excessive inflammation resulting from activation of microglia has been implicated in the neurodegenerative diseases such as multiple sclerosis. The protein kinase, Glycogen Synthase Kinase (GSK) 3, is involved in many cellular functions including microglial activation. Previously, inhibition of GSK-3 has been shown to reduce inflammation due to decreased production of pro-inflammatory cytokines and increased production of IL-10 in LPS-induced endotoxin shock animal model. Thus, this study was performed to elucidate the possible immunoregulatory effects of GSK-3 inhibitors on activated microglia. We hypothesized that inhibition of GSK-3 would reduce the exaggeration of inflammation in LPS-induced microglial activation with associated increased of IL-10 production. The optimal concentration of LPS and incubation period were optimized and determined by measuring the level of nitric oxide (NO) produced by BV-2, microglia cell lines, without compromising their effect on cell viability. The GSK-3 inhibitors, including lithium chloride (LiCl), SB216763, NP12 and CHIR99021 were used to block GSK-3 activities in the BV-2 cells. All GSK-3 inhibitors tested have shown their efficacy in reducing production of pro-inflammatory molecules, such as NO, glutamate, MCP-1 and cytokines (TNF-α and IL-6). Interestingly, reduction of pro-inflammatory molecules via GSK-3 inhibition was associated with significant increase in IL-10 production. Furthermore, treatment with GSK-3 inhibitor reduced expression of microglial activation markers, CD11b, while increased expressions of microglial inhibitory markers, CD200R, which confirmed the ability of GSK-3 inhibitor in inhibiting microglial activation. These results indicate that GSK-3 inhibitors effectively reduced pro-inflammatory molecules via inhibition of microglial activation. Moreover, these inhibitors could potentially reduce the severity of neuroinflammation by enhancing IL-10 production.

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

KESAN PERENCATAN GSK-3 KEATAS KERADANGAN NEURON YANG DIRANSANG LPS DAN PENGHASILAN IL-10 DALAM MICROGLIA

Oleh

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Mikroglia ialah makrofaj yang terdapat di dalam sistem saraf pusat (CNS) yang memainkan peranan di dalam sistem pengawasan imun terhadap pelbagai penyakit disebabkan patogen. Walaubagaimanapun, keradangan yang berlebihan hasil dari pengaktifan mikroglia telah dikaitkan dalam penyakit-penyakit yang melibatkan kemerosotan neuron seperti sklerosis berbilang. Glycogen synthase kinase (GSK) 3, iaitu salah satu daripada protein kinase, terlibat dalam banyak fungsi selular termasuk pengaktifan mikroglia. Sebelum ini, perencatan GSK-3 telah menunjukkan pengurangan keradangan disebabkan pengurangan penghasilan sitokin pro-radang dan peningkatan penghasilan IL-10 dalam model haiwan kejutan endotoksin yang dirangsang oleh LPS. Kami telah membuat hipotesis bahawa perencatan GSK-3 akan meningkatkan penghasilan IL-10 dan seterusnya mengurangkan keradangan yang keterlaluan pada mikroglia yang dirangsang oleh LPS. Dengan tu, kajian ini telah dijalankan untuk menunjukkan potensi pengawalan imun oleh perencat GSK-3 terhadap mikroglia yang aktif. Kami telah membuat hipotesis bahawa perencatan GSK-3 dapat mengurangkan keradangan yang keterlaluan dalam pengaktifan mikroglia yang diransang oleh LPS disebabkan peningkatan penghasilan IL-10. Kepekatan optimum LPS dan masa inkubasi telah ditentukan dengan menyukat tahap nitrik oksida (NO) dihasilkan oleh sel BV-2, sel mikroglia, dengan mengambil kira kesannya terhadap jumlah sel hidup. Perencat-perencat GSK-3 termasuk lithium klorida (LiCl), SB216763, NP12, dan CHIR99021 telah digunakan untuk menyekat aktiviti GSK-3 dalam sel BV-2. Semua perencat GSK-3 yang diuji telah mengesahkan keberkesanannya dalam mengurangkan penghasilan molekul-molekul yang menyebabkan keradangan seperti NO, glutamat, MCP-1 dan sitokin pro-radang (TNF-α dan IL-6). Menariknya, pengurangan penghasilan molekul pro-radang melalui perencatan GSK-3 adalah berkaitan dengan peningkatan penghasilan IL-10 yang ketara.

Tambahan pula, rawatan dengan perencat GSK-3 telah mengurangkan ekspresi penanda pengaktifan mikroglia, CD11b dan meningkatkan ekspresi penanda perencatan, CD200R, yang telah mengesahkan kemampuan perencat GSK-3 dalam mengurangkan pengaktifan mikroglia. Keputusan-keputusan ini menunjukkan bahawa perencat GSK-3 dapat mengurangkan molekul-molekul pro-radang secara berkesan melalui perencatan pengaktifan mikroglia. Lebih lebih lagi, perencat-perencat ini berpotensi untuk mengurangkan tahap keterukan keradangan neuron dengan meningkatkan penghasilan IL-10.

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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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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

α	alpha
β	beta
γ	gamma
^{o}C	degree celcius
M	molar
mL	mililitre
µL	microlitre
µg	microgram
µg/mL	microgram per mililitre
nm	nanometer
mM	milimolar
µM	micromolar
mg/mL	milligram per mililitre
mL/L	mililitre per litre
g/L	gram per litre
U/mL	unit per mililitre
RT	room temperature
hrs	hours
min	minute
Sec	second
rpm	revolutions per minute
1X	one time
AD	alzheimer's disease
ALS	amyotrophic lateral sclerosis
APCs	antigen presenting cells
Aβ	beta amyloid
BBB	blood brain barrier

BSA	bovine serum albumin
CNS	central nervous system
dH_2O	distilled water
DMEM	Dulbecco's Modified Eagle Medium
DMSO	dimethyl sulfoxide
EAE	Experimental autoimmune encephalomyelitis
EDTA	ethylene diamine tetraacetic acid
ELISA	enzyme linked immunosorbent assay
FBS	fetal bovine serum
FITC	fluorescein isothiocyanate
GSK-3	glycogen synthase kinase 3
H_2O	water
H_2O_2	hydrogen peroxide
HD	huntington's disease
IFN	interferon
IL	interleukin
LPS	lipopolysaccharide
MAPK	mitogen activated protein kinase
MCP-1	monocyte chemotactic protein-1
MHC II	major histocompatibility complex class II
MS	multiple sclerosis
$NaNO_2$	sodium nitrite
NED	N-1- napthylenediamine dihydrochloride
NF-κB	nuclear factor kappa B
NO	nitric oxide
PBS	phosphate buffer saline
TNF-α	tumour necrosis factor-alpha
TLR-4	toll like receptor-4

CHAPTER 1

INTRODUCTION

Microglia are the macrophages of the innate immune system in the central nervous system (CNS). Upon activation of peripheral and central immune system, microglia play their role by receiving the inflammatory signals and propagate the inflammation (Huang et al., 2009; Nguyen et al., 2002). Microglia are derived from primitive myeloid progenitors constituting almost 10-15% of the total CNS cell population (Ginhoux et al., 2010). In normal homeostatic condition, microglia are quiescent, ramified in shape and moves along parenchyma constituting immune surveillance system by monitoring homeostatic changes in CNS tissue and providing mechanical and trophic support to neurons (McGeer et al., 1987). Once activated, the morphology shift to amoeboid in shape and possess macrophage-like capabilities such as phagocytosis, antigen presentation to CD4 T helper cells and release of cytokines or chemokines (Goldmann & Prinz, 2013). Intense and continuous microglia activation induces neuroinflammation and contributes to neurodegenerative disease such as multiple sclerosis. Activation of microglia can be induced by various stimuli such as lipopolysaccharide (LPS) and interferon (IFN)-γ which promotes pro-inflammatory cytokines production including tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, and other inflammatory components such as nitric oxide (NO) and glutamate (Nakajima & Kohsaka, 2001).

Stimulation of microglia with LPS able to stimulate expression of inducible nitric oxide synthase (iNOS) (Heneka & Feinstein, 2001; Murphy, 2000). Expression of iNOS induce production of high NO level (Bal-Price & Brown, 2001; Bal-Price et al., 2002) which further inhibits mitochondrial cytochrome oxidase that can cause neuronal cell death (Bal-Price & Brown, 2001; Brown & Cooper, 1994). NO competes with oxygen for cytochrome oxidase causing respiratory inhibition which cause neuronal depolarization and production of glutamate (Bal-Price & Brown, 2001; Golde et al., 2002; Jekabsone et al., 2007; McNaught & Brown, 1998; Stewart et al., 2002). On the other hands, production of glutamate inflicts an amplified metabolic demand on neurons. Inhibition of respiratory metabolism by NO, for example, can cause the cells to be pushed over some toxic state and lead to neuronal cell death. Glutamate is the major excitatory neurotransmitter in CNS that plays an important role memory and learning (Featherstone, 2009; Reis et al., 2009). Overproduction of glutamate may cause an imbalance in CNS homeostasis which could lead to neuronal cells death. Studies have shown that excessive production of NO and glutamate propagates inflammation in the CNS and induces neuronal cell death (Goldmann & Prinz, 2013).

Glycogen Synthase Kinase (GSK-3) is a protein kinase which gets its name from their function in phosphorylating glycogen synthase. GSK-3 also phosphorylates more than 50 substrates which contribute to many cellular

processes (Woodgett, 1990). GSK-3 consists of two isoforms, GSK-3α and GSK-3β. Both are structurally similar but different in their functions. GSK-3β is profoundly involves in inflammatory response. Constitutively active GSK-3β is negatively regulated by phosphorylation of serine residue at position 9 (Ser9), which may result in a decrease in pro-inflammatory cytokines and an increase in anti-inflammatory cytokine, IL-10 (Hu et al., 2006; Rehani et al., 2009). A study conducted by Hoeflich et al (2000) discovered that in GSK-3β knockout mice suffered from degenerative liver (Hoeflich et al., 2000) while GSK-3α knockout mice were still viable but increased glucose and insulin sensitivity with reduced fat mass (MacAulay et al., 2007). This may indicate that GSK-3β is more important in regulating the immune response. GSK-3 plays a prominent role in promoting inflammation through production of pro-inflammatory cytokines and increased microglial migration (Yuskaitis & Jope, 2009). Regulation of inflammatory transcription factor NF-κB may promote pro-inflammatory actions of GSK-3 via activation of toll-like receptors (Beurel, 2011).

IL-10 is a cytokine with anti-inflammatory properties produced by different types of immune cells including T lymphocytes, macrophages, dendritic cells, natural killer (NK) cells and mast cells. Production of IL-10 by almost all cells in the immune system indicates its crucial role in limiting the exaggeration of pro-inflammatory cytokines and to maintain normal homeostasis (Saraiva & O'Garra, 2010). IL-10 was initially known as cytokine synthesis inhibitory factor (CSIF) since it was first documented to inhibit activation of Th1 and the production of its associated cytokines (Fiorentino et al., 1989). Nuclear factor kappa B (NF-κB) is a transcription factor that regulates the inflammatory responses via activation of toll-like receptor (TLR) and GSK-3 signaling (Rehani et al., 2009). Activation of this transcription factor caused depletion of CBP/p300, which essential in cyclic AMP response element (CREB) to produce IL-10 (Hofmann et al., 2012). Limited amounts of available CBP/p300 to bind with CREB binding protein lead to inhibition of IL-10 production which will promote inflammation. IL-10 inhibits inflammatory effects of T lymphocytes by interrupting the action of antigen presenting cells (APC) (Hofmann et al., 2010). The roles of anti-inflammatory effects of IL-10 have been studied to control the production of cytokines that promote pathogenicity of neuroinflammation particularly IFNγ and IL-17, produced by Th1 and Th17, respectively (Couper et al., 2008). In addition, the inhibitory action of IL-10 towards inflammatory effects of T lymphocytes could limit secretion of various pro-inflammatory cytokines and reduce activation and differentiation of macrophages, B cells and T cells (Shachar & Karin, 2013). GSK-3 also promotes activation of STAT3 to produce a high level of IL-6, which may contribute to Th17 development. (O'Shea & Paul, 2010). Many studies reported that Th17 is critical in the pathogenesis of various autoimmune diseases particularly in multiple sclerosis (MS) (Aranami & Yamamura, 2008; Maddur et al., 2012; Rothhammer et al., 2011). Other studies reported that inhibition of GSK-3 in monocytes and microglia also increased production of IL-10 (Huang et al., 2009; Wang et al., 2011). Furthermore, it has been suggested that inhibition of GSK-3 might provide a new intervention in treating autoimmune disease. In this study, we

hypothesize that GSK-3 inhibitor has protective effects against inflammatory action induced by LPS in microglia via upregulation of IL-10 production.

Rationale of the study

Continuous activation of microglia with a retained pro-inflammatory phenotype has been implicated in causing profound neuronal damage within the CNS parenchyma. Detection of activated microglia at the injury sites of neurodegenerative diseases including Alzheimer's disease (AD) and MS, underscore microglia activation as an important pathophysiological component of inflammatory and degenerative CNS conditions. Therefore, modulation of microglia responses is an active target for therapeutics of these degenerative diseases.

The GSK-3 inhibitor was found to exert anti-inflammatory properties on macrophage by limiting microglia to produce pro-inflammatory molecules including IL-6, TNF-α, glutamate, Monocyte chemoattractant protein-1 (MCP-1), and NO (Martin et al., 2005). We suggest that GSK-3 inhibitors may also modulate microglia inflammatory response. Although lithium chloride (LiCl) has potent anti-inflammatory effects, they might give adverse effects as LiCl has a low therapeutic index (Beurel et al., 2013) which makes SB216763, NP-12 and CHIR99021 ideal candidates among the GSK-3 inhibitors family for microglia modulation. To date, there are many kinds of literature concerning the modulatory effects of GSK-3 inhibitors on microglia responses. However, there are very limited studies that relate the ability of microglia in reducing production of pro-inflammatory cytokines with the expressions of activation and inhibitory state of microglia. Since GSK-3 plays an important role in propagating inflammation, we hypothesize that GSK-3 inhibitors can limit the excessive immune response by microglia activation and reverse the imbalance of homeostasis in the CNS.

Objectives of the research

The general objective of this project is to inhibit GSK-3 signalling in microglia in order to reduce microglial activation.
Whilst the specific objectives are:

1. To study the potential role of LPS in the production of NO and glutamate in microglia.
2. To evaluate the efficacy of GSK-3 inhibitors (LiCl, SB216763, NP-12 and CHIR99021) in limiting the production of pro-inflammatory components (e.g. NO, glutamate, IL-6, TNF-α, and MCP-1) in microglia.
3. To determine the anti-inflammatory effects of GSK-3 inhibition on IL-10 production in microglia.
4. To determine microglia activation status by expressions of CD11b and CD200R during inhibition of GSK-3
5. To determine the effects of GSK-3 inhibitors on the phosphorylation of GSK-3β protein expressions.

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LIST OF PUBLICATIONS

Poster

Zuhaida Md Zain, Sharmili Vidyadaran and Masriana Hassan. Production of IL-10 in BV-2 cell lines reduces neuroinflammation via inhibition of GSK-3. Faculty Excellent Month (FEM) 2015. Universiti Putra Malaysia, Malaysia. 2015. (Poster presentation)

Full paper

Zuhaida Md Zain, Sharmili Vidyadaran and Masriana Hassan. Inhibition of GSK-3 in microglia reduces inflammation and upregulates IL-10 production.

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