UNIVERSITI PUTRA MALAYSIA

INFLUENCE OF DIETARY POLYUNSATURATED FATTY ACIDS ON GLUCOSE SENSITIVITY, INSULIN RESISTANCE AND COGNITIVE FUNCTION IN A RAT MODEL

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By

TAN AI LI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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

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July 2014

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Insulin resistance (IR) occurs when there is an impaired response to insulin-dependent glucose regulation in the body. Hallmarks for insulin resistance include persistent hyperinsulinaemia and hyperglycaemia. In this present study, we are able to understand how insulin resistance occur in the molecular pathway because most studies are focusing on factors that cause insulin resistance such as diet and exercise rather than more in depth work. The objectives of this study were to investigate the changes in insulin sensitivity, body fat accretion and circulating leptin level in the body due to different ratio of n-6 and n-3 polyunsaturated fatty acids (PUFAs) supplementation. The histological changes in the liver will also be determined. The roles and expression levels of the relevant genes involved in fat metabolism such as peroxisome proliferator-activated receptor, (PPAR), selected adipokines and glucose transporters were examined in the rat model. At the end of the study, the rats were also examined to determine if there is any plausible link between cognitive ability, insulin resistance and dietary fatty acid supplementation in the test subjects.

Male Sprague Dawley rats were used in this feeding trial which lasted more than 24 weeks. The animals were fed either a diet fortified with additional 10 % of fat made up primarily of either n-3 PUFA from Menhaden oil (MCD), n-6 PUFA from soybean oil (SCD), saturated butter fat (BCD) or an unsupplemented base diet (CD). Plasma insulin, glucose and the relevant adipokine levels were monitored at week 0, 10 and 22 of the experiment to determine the onset of insulin resistance. Liver histology examination was performed to determine the possible pathologies associated with long-term fat supplementation. Muscle and liver tissue samples were also sampled to determine the level of PPAR, tumor necrosis factor (TNF)-α, glucose transporter (GLUT) 1 and GLUT4 gene expressions. The expression of the glucose transporter

and selected biomarkers of insulin resistance was evaluated by real-time reverse transcription polymerase chain reaction method. The study was capped with cognitive ability evaluation of the rats using the Morris Water Maze.

Results indicated that high n-3 PUFA supplementation in MCD rats delayed the onset of IR. MCD rats also had lower fat mass and fat percentage in the body, and moderate levels of leptin compared to other groups. This was due to the positive correlation between fat mass and leptin secretion. In BCD rats, they exhibited insulin resistance characteristic with high glucose and insulin level. This was due to the high saturated fat accumulation in their body. Other than that, PPARα and PPARγ genes were lowly expressed, as well as negligible levels of GLUT4 and GLUT1 readings in the liver and muscle cells. However, TNF-α gene expression were significantly higher in the insulin resistant BCD group, but much lower among the MCD and SCD groups. In addition the, the liver section of the BCD group showed lipid vacuolation in and between the hepatocytes. This will lead to the pathogenesis of liver pathology. The profound effects of dietary fatty acids on the functions of the central nervous system during cognition, memory and learning ability was evident in this study. Animals that were supplemented with saturated fats which were insulin resistant at this stage fared poorly in the Morris Water Maze Test. Contrastingly, non-insulin resistant animals from the MCD group fed with n-3 PUFA and normal animals from the CD group performed significantly better. In conclusion, this study demonstrated that high n-3 PUFA dietary fats delayed the onset of insulin resistance and reduces body fat accretion. Furthermore, it also highlights the high expression of PPARα, PPARγ, GLUT1 and GLUT4 genes while reducing the pro-inflammatory gene (TNF-α). High n-3 PUFA also exerts protective effect in the brain to enhance spatial learning and cognitive performance.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

PENGARUH PEMAKANAN ASID LEMAK POLITAKTEPU TERHADAP KEPEKAAN GLUKOSA, KERINTANGAN INSULIN DAN FUNGSI KOGNITIF PADA MODEL TIKUS

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Kerintangan insulin (IR) berlaku apabila terdapat kepincangan gerak balas terhadap proses pengawalaturan glukosa yang dikawal selia oleh insulin. Ciri-ciri kerintangan insulin adalah hiperinsulinemia dan hiperglisemia. Kerintangan insulin kerap berlaku beberapa tahun sebelum kemunculan Diabetes Mellitus Jenis II (T2DM). Di dalam kajian ini, kita dapat memahami bagaiman kerintangan insulin berlaku pada tahap molekular kerana kebanyakan kajian sebelum ini hanya memberi tumpuan kepada faktor-faktor yang menyebabkan kerintangan insulin seperti menerusi diet dan senaman. Objektif kajian ini ialah untuk memerhatikan perubahan pada insulin sensitivi, pengumpulan lemak badan dan tahap pengedaran leptin di dalam badan disebabkan oleh perbezaan nisbah n-6 dan n-3 asid lemak poli tak tepu. Perubahan histologi di hati juga akan ditentukan. Peranan dan tahap ekspresi gen yang terlibat dalam metabolisme lemak seperti peroksisom proliferator-diaktifkan penerima (PPAR), adipokin yang dipilih dan pengangkutan glukosa diperiksa dalam model tikus. Pada akhir kajian, tikus juga telah diperiksa untuk menentukan sama ada terdapat hubungan yang munasabah antara keupayaan kognitif, rintangan insulin dan akibat suplementasi asid lemak dalam tikus kajian.

Tikus Sprague Dawley jantan telah digunakan dalam eksperimen pemakanan ini yang telah mengambil masa 24 minggu. Tikus diberi makan diet yang ditambah dengan 10 % lemak tambahan yang terdiri sama ada daripada lemak yang majoritinya asid lemak n-3 dari minyak Menhaden (kumpulan MCD), asid lemak n-6 dari minyak kacang soya (kumpulan SCD), asid lemak tepu dari mentega (kumpulan BCD), dan kumpulan kawalan (CD) yang tidak ditambah lemak tambahan. Tahap insulin, glukosa, dan adipokin terpilih dalam plasma telah diukur dalam minggu 0, 10 dan 22 untuk menentukan kemunculan fenomena kerintangan insulin. Kajian histology hati telah dibuat untuk menentukan perubahan patologi pada hati akibat suplementasi lemak yang berterusan. Tisu otot dan hati turut diambil untuk

mengukur tahap ekspresi gen PPAR, TNFα, GLUT1 dan GLUT4. Ekspresi pengangkut glukosa dan penanda-bio untuk kerintangan insulin telah diukur menggunakan teknik RT-PCR. Keupayaan kognitif pada tikus ini turut dinilai menggunakan teknik pagar sesat Morris.

Keputusan menunjukkan bahawa suplementasi n-3 PUFA yang tinggi pada tikus MCD melambatkan permulaan IR. Tikus MCD juga mempunyai pengumpulan lemak dan peratusan lemak yang lebih rendah dalam badan, dan tahap leptin juga sederhana berbanding dengan kumpulan lain. Ini disebabkan oleh korelasi positif antara jumlah lemak badan dan rembesan leptin. Pada tikus BCD, mereka menunjukkan ciri-ciri rintangan insulin seperti tahap glukosa dan insulin yang tinggi. Ini disebabkan oleh pengumpulan lemak tepu yang tinggi di dalam badan mereka. Selain daripada itu, expresi gen PPARα dan PPARγ berada pada tahap yang rendah, manakala tahap expresi GLUT4 dan GLUT1 pula berada pada tahap yang boleh diabaikan. Tetapi, expresi gen TNF-α adalah lebih tinggi pada kumpulan BCD manakala kimpulan MCD dan SCD jauh lebih rendah. Selain itu, histologi hati kumpulan BCD menunjukkan vakoulasi lipid dalam dan di antara hepatosit. Ini akan membawa kepada patogenesis patologi hati. Kesan mendalam pemakanan asid lemak terhadap fungsi sistem saraf pusat dalam kognisi, ingatan dan pembelajaran adalah terbukti dalam kajian ini. Haiwan yang disuplementasi dengan lemak tepu yang mempunyai kerintangan insulin akan mempunyai perfomasi yang lebih lemah. Manakala, haiwan yang tidak mempunyai kerintangan insulin dari kumpulan MCD yang disuplementasi dengan n-3 PUFA dan haiwan biasa dari kumpulan CD mempunyai performasi jauh lebi baik. Kesimpulannya, kajian ini menunjukkan bahawa suplementsai n-3 PUFA yang tinggi akan melambatkan permulaan kerintangan insulin dan mengurangkan pertambahan lemak badan. Tambahan pula, ia juga menyebabkan expresi gen PPARα, PPARγ, GLUT1 dan GLUT4 yang tinggi. Di samping itu, mengurangkan expresi gen pro-radang (TNF-α). Suplementsai n-3 PUFA yang tinggi juga memberikan kesan perlindungan kepada otak untuk mempertingkatkan pembelajaran dan prestasi kognitif.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREBRIATIONS

Abbreviation	Definition
AA	Arachidonic acid
ACH	Acetylcholine
ALA	Alpha-linolenic acid
AMPK	AMP-activated protein kinase
ARC	Arcuate nucleus
AUC	Area under the curve
BBB	Blood-brain barrier
BF_3	Boron trifluoride
BMI	Body mass index
CA	*Cornu Ammonis*
cDNA	Complementary DNA
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic acid
DPA	Docosapentaenoic acid
EFA	Essential fatty acid
EIA	Enzyme immunoassay
EPA	Eicosapentaenoic acid
FA	Fatty acid
FAME	Fatty acid methyl ester
FFAs	Free fatty acids
FM	Fat mass

GLA	Gamma-linolenic acid
GLUT	Glucose transporter
HDL	High density lipoprotein
IL-1	Interleukin-1
IL-6	Interleukin-6
IPGTT	Intraperitoneal glucose tolerance test
IPITT	Intraperitoneal insulin tolerance test
IR	Insulin resistance
IRS	Insulin receptor substrate
IRS-PI3-K	Intrinsic receptor substrate-phosphatidylinositol 3-kinase
KATP	ATP-sensitive K+
LA	Linoleic acid
MCP	Monocyte chemotatic protein
MEC	Medial entorhinal cortex
MUFA	Monounsaturated fatty acid
n-3 PUFA	Omega-3 polyunsaturated fatty acid
n-6 PUFA	Omega-6 polyunsaturated fatty acid
NAFLD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NE	Northeast
NPY	Neuropeptide Y
NW	Northwest
PCR	Polymerase chain reaction
POMC	Proopiomelanocortin

PPAR	Peroxisome proliferator-activated receptor
PPAR-α	Peroxisome proliferator-activated receptor- α
PPAR-γ	Peroxisome proliferator-activated receptor- γ
PUFA	Polyunsaturated fatty acid
PUFA	Polyunsaturated fatty acid
RNA	Ribonucleic acid
RXR	Retinoid X receptor
S	South
SE	Southeast
SFA	Saturated fatty acid
SFA	Saturated fatty acid
SOC-3	Suppressor of cytokine signalling-3
SW	Southwest
T1D	Type-1 diabetes
T2D	Type-2 diabetes
TNF-α	Tumor necrosis factor- α
VF	Visceral fat
W	West
α-MSH	Alpha melanocyte-stimulating hormone

CHAPTER 1

INTRODUCTION

Insulin resistance has received more attention recently not only because it precludes type-2 diabetes (T2D) but also as a predictor of increased risk for cardiovascular disease such as coronary heart disease and hypertension. The coexistence of these diseases has been known as metabolic syndrome and an estimated 250 million people worldwide will be affected by T2D by the year 2020. Even though the primary factors causing this disease are still unknown, there is an indication that insulin resistance played a vital part in the development of these metabolic diseases. This is due to evidence showing the relationship between insulin resistance and T2D. The state of insulin resistance is achieved when normal insulin production does not commensurate with the insulin response by the body. Hence, any defect of the insulin signalling pathway can in fact lead to insulin resistance.

Generally, the public has misconception that insulin resistance only happens to those who are overweight, or those with high levels of sugar intake. In reality, insulin resistant can also happen to normal weighted person of any age group. Insulin resistance can be prevented and even reversed by changing to a healthy lifestyle by eating healthy and incorporating an exercise regime.

Insulin resistance is on the rise because of the poor dietary balance and lack of physical activities among affluent societies of the 21st century. Early human societies at the dawn of time focused in hunting and gathering food and this simple act comprises of two key elements: obtaining whole foods straight from the environment and exercising hard in the process of gathering food. In modern society, ready availability of foods led to reduced physical movements. Modern process foods had lesser nutritional value and most contained highly refined carbohydrate, preservatives, pesticides, trans-fats, toxins and high sugar level which becomes factors that contribute to insulin resistance (Draznin, 2003).

Insulin resistance is an important sign pointing to the dysregulation of glucose metabolism. A 2006 survey showed that there are more than 371 million people worldwide affected by diabetes of which in Malaysia, about 1.2 million adults aged from 30 years and above was affected. From this number, about 98% Malaysians with diabetes suffer from T2D (Wan Nazaimoon *et al.*, 2013). Approximately 1 in 3 Malaysians are suffering from, or at risk of being diabetic. This number continued to increase from year to year as shown by the survey done by The 2011 National Health & Morbidity Survey (NHMS). It is estimated that by 2020, Malaysia will have approximately 4.5 million people with diabetes. In the first report from NHMS in year 1986, the results showed that 6.3% of the population aged 30 and above were suffering from diabetes. Ten years later in 1996, the percentage rose to 8.3 and in 2006 to 14.9%. Recently in year 2011, the number increased to 20.8%. This is an alarming situation with the proposition of population with diabetes increase

exponentially. In the United States, 25.8 million people or about 8.3% of the United States population suffers from diabetes (Centers for Disease Control and Prevention, 2011). Type-2 diabetes typically develops after the age of 30 and the risk increases with age. It is not obvious until the patient is been treated for one of its serious complications.

The onset of insulin resistance can be prevented or reversed by understanding the role of insulin in modulating the uptake of glucose in the body. This is because insulin plays a role in directing the cells to take in glucose from bloodstream and excess glucose intake will be stored as glycogen. It is crucial to understand the roles of dietary factors, such as fatty acids and their inter-relationships with insulin resistance. The findings will be invaluable as these will potentially elucidate how body fats and body composition play their role in the regulation of blood glucose, as well as understanding the potential changes in the liver when insulin resistance sets in. The current study was capped with a segment investigating whether insulin resistance had any plausible link to cognition and spatial memory as the brain is very much dependent on glucose as a primary fuel source.

Hypothesis

It was postulated that the increased presence of omega-3 polyunsaturated fatty acid (n-3 PUFA) in the body will reduce fat accretion and subsequently reduce the leptin level in the body. Futhermore, incorporating n-3 PUFA will increase membrane fluidity and this consequently improves insulin sensitivity. It is also further hypothesised that diets high in n-3 PUFA will result in the up-regulation of PPAR activities, and facilitated GLUT expression on cellular membrane, leading to better glucose sensitivity despite higher dietary fat intake. The net effects of these developments will be the delayed onset of insulin resistance. Cognitive performance and spatial memory was not hypothesised to be affected by insulin resistance within the framework of this study.

Research objectives

1. To determine the associated changes in insulin sensitivity, changes in body fat accretion and circulating leptin levels due to n-6 and n-3 PUFA supplementation.
2. To determine the histological changes in liver associated with insulin resistance, and as a result of dietary intervention.
3. To investigate the effects of dietary fatty acid intake on TNF-α, PPAR-α and PPAR-γ gene expression in the onset of insulin resistance.
4. To examine the effects of different dietary fatty acid intake on the expression of GLUT1 and GLUT4 on cellular membranes.
5. To determine the effects of n-6 and n-3 PUFA supplementation through dietary intervention on cognitive performance and spatial memory learning in the rat model.

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