EXPERIMENTAL MODEL OF MATERNAL DYSLIPIDEMIA AND TAURINE SUPPLEMENTATION ON PREVENTING METABOLIC DISORDERS IN OFFSPRING

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รูปแบบการทดลองของแม่หนูที่มีภาวะไขมันในเลือดสูงและการได้รับทอรีนเสริมต่อการป้องกันการบกพร่องของเมแทบอลิซึมในลูกหนู

นางสาวชลธิชา แตงน้อย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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ชลธิชา แตงน้อย : รูปแบบการทดลองของแม่หนูที่มีภาวะไขมันในเลือดสูงและการได้รับทอรีนเสริมต่อการป้องกันการบกพร่องของเมแทบอลิซึมในลูกหนู (EXPERIMENTAL MODEL OF MATERNAL DYSLIPIDEMIA AND TAURINE SUPPLEMENTATION ON PREVENTING METABOLIC DISORDERS IN OFFSPRING). อาจารย์ที่ปรึกษา : อาจารย์ ดร.อัจฉราพร แถวหมอ, 120 หน้า.

การศึกษาครั้งนี้ได้ทดสอบสมมติฐานที่ว่าการให้ทอรีนเสริมในระยะปริกำเนิด-แรกเกิดช่วยป้องกันภาวะไขมันในเลือดสูงกับโรคความดันโลหิตสูงในลูกหนูเพศผู้โตเต็มวัยที่มีแม่มีภาวะไขมันในเลือดสูง โดยหนูเพศเมียพันธ์วิสตาร์ได้ถูกเลี้ยงด้วยอาหารและน้ำบริสุทธิ์ แบ่งเป็นกลุ่มที่ไม่มีภาวะไขมันในเลือดสูงและกลุ่มที่มีภาวะไขมันในเลือดสูง ซึ่งถูกกระตุ้นด้วยไทรทัน ดับบลิว อาร์-1339 โดยการฉีดเข้าช่องท้อง ก่อนการตั้งครรภ์ จากนั้นนำไปผสมพันธุ์ เพื่อให้ตั้งครรภ์ ระหว่างตั้งครรภ์ แม่หนูจะถูกแบ่งเป็น กลุ่มแม่หนูที่ได้รับทอรีนเสริม 3% ในน้ำบริสุทธิ์ [กลุ่มควบคุม+เสริมทอรีน (T) กลุ่มที่มีแม่มีภาวะไขมันในเลือดสูง+เสริมทอรีน (DT)] และกลุ่มแม่หนูที่ได้รับน้ำบริสุทธิ์ [กลุ่มควบคุม+ได้รับน้ำบริสุทธิ์ (C) กลุ่มที่มีแม่มีภาวะไขมันในเลือดสูง+ได้รับน้ำบริสุทธิ์ (D)] หลังจากหย่านมลูกหนูทุกกลุ่มจะได้รับอาหารและบริสุทธิ์ จนกระทั่งสิ้นสุดการทดลอง เมื่ออายุครบ 4 สัปดาห์ ลูกหนูในแต่ละกลุ่มจะถูกแบ่งออกเป็นกลุ่มที่ไม่ได้ออกกำลังกาย [กลุ่มควบคุม+ได้รับน้ำบริสุทธิ์ (C) กลุ่มควบคุม+เสริมทอรีน (T) กลุ่มที่มีแม่มีภาวะไขมันในเลือดสูง+ได้รับน้ำสะอาด (D) กลุ่มที่มีแม่มีภาวะไขมันในเลือดสูง+เสริมทอรีน (DT)] และกลุ่มที่ออกกำลังกาย [กลุ่มควบคุม+ออกกำลังกาย (Ex) กลุ่มควบคุม+เสริมทอรีน+ออกกำลังกาย (TEx) กลุ่มที่มีแม่มีภาวะไขมันในเลือดสูง+ได้รับน้ำบริสุทธิ์+ออกกำลังกาย (DEx) กลุ่มที่มีแม่มีภาวะไขมันในเลือดสูง+เสริมทอรีน+ออกกำลังกาย (DTEx)] กลุ่มที่ออกกำลังกายลูกหนูจะถูกบังคับให้ว่ายน้ำในอ่างทรงกระบอกเป็นเวลา 12 สัปดาห์ จนกระทั่งหนูเพศผู้ทุกกลุ่มอายุ 16 สัปดาห์ ได้ถูกนำมาศึกษาค่าเคมีในเลือดและพารามิเตอร์เกี่ยวกับระบบหัวใจร่วมหลอดเลือด ซึ่งการศึกษาพบว่า ค่าน้ำหนักตัว หัวใจ และไต ไม่แตกต่างกันอย่างมีนัยสำคัญระหว่างกลุ่ม นอกจากนี้ คอเลสเตอรอลและไตรกลีเซอไรด์ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในขณะที่ลูกหนูเพศผู้โตเต็มวัยจากแม่มีภาวะไขมันในเลือดสูง (D) แสดงให้เห็นว่า แอลดีแอลและการแสดงออกของ แอนจิโอเทนซิน II รีเซพเตอร์ชนิดที่ 1 เพิ่มขึ้น เมื่อเทียบกับกลุ่มอื่น ๆ นอกจากนี้ในกลุ่มลูกหนูเพศผู้โตเต็มวัยที่ออกกำลังกาย (กลุ่ม TEx DEx DTEx) เอ็ชดีแอลที่เพิ่มขึ้น เมื่อเทียบกับกลุ่มอื่นที่ไม่ได้ออกกำลังกาย และเมื่อเทียบกับกลุ่มควบคุมพบว่า ค่าความดันโลหิตแดงเฉลี่ยและอัตราการเต้นของหัวใจเพิ่มขึ้นอย่างมี

นัยสำคัญ และการตอบสนองของบาโรรีเซพเตอร์ ลดลงในกลุ่มที่มีแม่มีภาวะไขมันในเลือดสูง+ได้รับน้ำบริสุทธิ์ (D) อีกด้วย ถึงแม้ว่าการเสริมทอรีนในระยะปริกำเนิด-แรกเกิด จะไม่ส่งผลต่อค่าพารามิเตอร์ที่วัดได้ในกลุ่มควบคุม แต่ก็ลดผลกระทบจากภาวะไขมันในเลือดสูงจากแม่หนูในแง่ของการตอบสนองของบาโรรีเซพเตอร์ และป้องกันความเสียหายของกล้ามเนื้อและตับโดยการลดซีรั่มเอนไซท์กลูตาเมตไพรูเวททรานส์อะมิเนสในกลุ่มการออกกำลังกายได้และการออกกำลังกายสามารถลดผลข้างเคียงของภาวะไขมันในเลือดสูงจากแม่หนู ซึ่งมีผลต่อความดันโลหิต อัตราการเต้นของหัวใจและการแสดงออกของแอนจิโอเทนซิน II รีเซพเตอร์ ชนิดที่ 1 ในลูกหนูเพศผู้โตเต็มวัย การศึกษาในปัจจุบัน แสดงให้เห็นว่าแม่ที่มีภาวะไขมันในเลือดสูง ทำให้เกิดภาวะไขมันในเลือดสูงและความดันโลหิตสูงในลูกหนูเพศผู้โตเต็มวัยได้ และผลข้างเคียงเหล่านี้สามารถป้องกันได้โดยการเสริมด้วยทอรีนในระยะปริกำเนิด-แรกเกิด และการออกกำลังกาย

สาขาวิชาปรีคลินิก
ปีการศึกษา 2560

ลายมือชื่อนักศึกษา_____
ลายมือชื่ออาจารย์ที่ปรึกษา_____
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม_____
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CHONTHICHA TANGNOI : EXPERIMENTAL MODEL OF MATERNAL DYSLIPIDEMIA AND TAURINE SUPPLEMENTATION ON PREVENTING METABOLIC DISORDERS IN OFFSPRING. THESIS ADVISOR : ATCHARAPORN THAEOMOR, Ph.D. 120 PP.

TAURINE / EXERCISE / DYSLIPIDEMIA / METABOLIC DISORDERS

This study tested the hypothesis that perinatal-neonatal taurine supplementation prevents dyslipidemia and hypertension in male adult offspring of maternal dyslipidemia rats. Female Wistar rats were fed normal rat chow and reverse osmosis water (RO) without dyslipidemia (Control groups) or with dyslipidemia (Dyslipidemia groups) induction by intraperitoneal Triton-WR 1339 injection before pregnancy. After that, rats were allowed to mate for the pregnancy. During pregnancy, they were supplemented with 3% taurine in water [Control+T (T), Dyslipidemia+T (DT) groups] or water alone [Control+RO (C), Dyslipidemia+RO (D) groups]. After weaning, male offspring were fed normal rat chow and RO throughout the study. At 4 weeks of age in male offspring in each group were divided into non-exercise [Control+RO (C), Control+T (T), Dyslipidemia+RO (D), Dyslipidemia+T (DT) groups] and exercise groups [Control+Ex (Ex), Control+T+Ex (TEx), Dyslipidemia+RO+Ex (DEx), Dyslipidemia+T+Ex (DTEx) groups]. In male offspring, exercise group was forced to swim in the cylinder tank for 12 weeks. Blood chemistry and cardiovascular parameters were studied at 16 weeks of age. Body, Heart, and Kidney weights were not significantly different among groups. Further, cholesterol, triglyceride were not significantly different among groups, while male adult offspring from maternal

dyslipidemia (D) displayed an increase LDL and expression of an AT_1 receptor when compared to other groups. Moreover, in male adult offspring exercise groups (Ex, TEx, DEx, DTEx groups) displayed an increase in HDL when compared to another non-exercise group. Compared to control, mean arterial pressure and heart rate significantly increased and baroreflex sensitivity decreased in D groups. Although perinatal-neonatal taurine supplementation did not affect any measured parameters in Control groups, it prevented the adverse effects of maternal dyslipidemia on baroreflex sensitivity and protect muscle and liver damage by reduced SGPT in exercise groups. Exercise can prevente the adverse effects of maternal dyslipidemia on blood pressure, heart rate, and AT1 receptor expression in adult male offspring. The present study indicates that maternal dislipidemia induced dyslipidemia and hypertension in male adult offspring. These adverse effects can be prevented by taurine supplementation during a perinatal-neonatal period and exercise.

School of Preclinic

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LIST OF ABBREVIATIONS

cm.	=	Centimeter
mmHg	=	A millimeter of mercury
mg/dl	=	milligram per deciliter
mmol/L	=	Millimoles per liter
yr	=	Year
h	=	Hour
kg/m^2	=	Kilogram per square metre
kg	=	Kilograms
MC4R	=	melanocortin 4 receptor gene
α- MSH	=	α -melanocyte-stimulating hormone
γ-MSH	=	γ -melanocyte-stimulating hormone
NO	=	Nitric oxide
Na+	=	Sodium
ATI	=	Angiotensin II (AII) receptor type 1
AT2	=	Angiotensin II (AII) receptor type 2
eNOS	=	Endothelial NOS
Cu/ Zn-SOD	=	Copper- and zinc-containing superoxide dismutase
Mn- SOD	=	Manganese-dependent superoxide dismutase
°C	=	Degrees Celsius

LIST OF ABBREVIATIONS (Continued)

g	=	Gram
L	=	Litre
pH	=	Potential of Hydrogen ion
mg/kg BW.	=	Milligrams per kilogram of body weight
Ca^{2+}	=	Calcium ions
PIP2	=	Lipid phosphatidylinositol 4,5-bisphosphate
IP3	=	Inositol 1,4,5-trisphosphate
DAG	=	1,2-Diacylglycerol
PL-C	=	Phospholipase C
RO water	=	Reverse Osmosis water
BUN	=	Blood Urea Nitrogen
i.p	=	Intraperitoneal injection
Cr	=	Creatinine
ALT	=	Alanine transaminase
AST	=	Aspartate transaminase
NaF	=	Sodium fluoride
RIPA buffer	=	Radioimmunoprecipitation assay buffer
NaCl	=	Sodium chloride
DDW	=	Deuterium-depleted water

CHAPTER I

INTRODUCTION

1.1 Rational of the study

Metabolic syndrome is leading cause of death among people around the world. Dyslipidemia and hypertension are common disorders among them. Genetics, food, habits, race, gender, improper behavior, socio-economy, and environment are all complicated to the pathogenesis and severity of the diseases. In addition, previous studied have been suggested that maternal environment and behavior during pre-pregnancy and pregnancy has long-term and short-term can cause development dyslipidemia and hypertension in adult offspring. This perinatal environment influences not only growth and development of the fetus and newborn, but the phenotypic expression of the adult offspring is also modified. For examples, inhibition of the renin-angiotensin system since conception throughout life or shortly at the perinatal period attenuates or prevents hypertension and other related damage in spontaneously hypertensive rats at later life (Wyss, 1992). Moreover, Studying in dyslipidemia rats shown that an increase in leptin level has been influenced by nitric oxide production and sodium excretion in urine, and along with chronic sympathetic activation, especially, it may lead to sodium retention in kidney, systemic vasoconstriction so they are all complicated to blood pressure elevation. Consequently, obesity and leptin are an important role in the development of hypertension (Perez-Bravo et al., 1996).

In addition to maternal dyslipidemia may contribute to the obesity in childhood epidemic through fetal metabolic programming, although the mechanism(s) of these effects is still unclear, abnormalities of inflammation and blood lipids, which can have profound effects on the developing embryo and the fetus in utero. Fetal exposure to excess blood lipids, particularly saturated fatty acids, can activate proinflammatory pathways, which could impact substrate metabolism and mitochondrial function, (Hall et al., 2014) as well as an increase leptin level in maternal obesity during pregnancy, all of which affect organ development and the response to the postnatal environment.

In both human and animal models found that fetal environment in utero has a significant impact on adult health and disease (Barker, 2002). Previous studied found that leptin resistance induces metabolic disorders in adults, including coronary vascular diseases, hypertension, insulin resistance, diabetes mellitus, dyslipidemia, obesity and renal damage. Obesity appears to be related to hypertension and diabetes mellitus developed in the later life. The obesity is the common cause of cardiovascular diseases particularly hypertension. Obesity or insulin resistance predispose the adult hypertension. Obesity is associated with high leptin levels, effects of leptin in obesity, is a result of a leptin-resistance mechanism. Nevertheless, obesity is associated with increased sympathetic nerve activity, and leptin has been proven to participate in autonomic nervous system control, in part, by increasing renal sympathetic nerve activity (RSNA). Therefore, it is implied that, in the presence of a leptin resistance state, the hormone can contribute to the sympathetic activation seen in obesity (Hall et al., 2010).

Taurine is a sulphur containing beta-amino acid that plays many essential roles from prenatal throughout life (Sturman, 1988). Its function includes intracellular volume

regulation, cell membrane stabilization, neuromodulation, antioxidative stress, vasodilation, cardiac performance, learning and memory, renal growth and differentiation, hypoglycemic action, anti-dyslipidemia, anti-leptin resistance, reduce fat accumulation, increase activity, sympathoinhibition, and inhibition of the renin-angiotensin system. Body taurine content is highest during fetal life and gradually declines after birth (Akahori, 1986). During lactation, it appears to be an essential amino acid in animals and humans, since taurine synthesis is minimal and the main source of taurine in these organisms is from maternal milk. Several lines of evidence indicate that perinatal taurine exposure programs cells for adult function, including those related to the metabolic syndrome. Moreover, taurine is an important role on program adult function and disease at the early life. In the previous study shown that taurine depletion in the early life induces low birth weight newborns and these offspring will develop obesity, diabetes mellitus, and hypertension in the later life but in another study found the adverse effects of perinatal taurine supplementation prevents hypertension in SHR. Previous experiments indicate that either taurine depletion or supplementation in early life alters renal function and autonomic nervous control of arterial pressure in adult, male rats. Their renal hemodynamics and excretory function are also modified by the level of perinatal taurine exposure. (El Idrissi et al., 2013). Exercise induces enhance energy expenditure, lipolysis and improves leptin sensitivity in the hypothalamus (Flores et al., 2006). There is thus great interest in identifying the exact mechanisms by which maternal excess leptin or excess blood lipid may lead to diseases in the offspring later in life for the development of strategies to prevent this destructive cycle of metabolic dysfunction through generations. The present study indicates that taurine supplementation in the perinatal-neonatal period on maternal

dyslipidemia may be having anti-dyslipidemia and anti-hypertension in the later life offspring.

1.2 Research objectives

The experiments were designed to clarify the following:

1. To study the effect of taurine supplementation on the metabolic disorder in male rats offspring.
2. To study the effect of exercise on the metabolic disorder in male rats offspring.
3. To explore the relationship between taurine supplementation and exercise on the metabolic disorder in male rats offspring.

1.3 Research hypothesis

Taurine supplementation in the perinatal-neonatal period on maternal dyslipidemia and exercise could prevent the development of metabolic disorder in male rats offspring.

1.4 Expected results

1.4.1 The findings will provide the new evidence of the beneficial effects of taurine supplementation in a perinatal-neonatal period to control of serum lipid profile level, and blood pressure.

1.4.2 The findings will provide the exercise relating to control of serum lipid profile level, leptin levels, and blood pressure.

1.4.3 The findings will provide interaction between taurine supplementation in a perinatal-neonatal period and exercise to control of serum lipid profile level, leptin levels, and blood pressure.

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CHAPTER II

LITERATURE REVIEWS

2.1 Fetal origin of adult disease hypothesis

A new paradigm for obesity prevention has emerged from the idea that nutritional and other environmental factors in early life have a profound influence on lifelong health. This notion is gaining increasingly great interest since the development of Barker's hypothesis of the "fetal origin of adult diseases" (Barker, 1990). In this regard, the word "programming", first introduced by (Lucas, 1991), has been adopted to describe the linkages between fetal life and long-term consequences (Gluckman and Hanson, 2004). It involves the notion that a stimulus that operates within a critical or sensitive period of development can lead to lasting or permanent effects on the structure or function of the body (Lucas, 2000). Gestation and lactation are disclosed as critical periods, and both food restriction and overnutrition can lead to lasting effects in the offspring, thereby changing propensity to obesity and related metabolic alterations in adult life (Cottrell and Ozanne, 2008; McMillen and Robinson, 2005; Sánchez et al., 2012). Adaptive responses occurring in early life to face an adverse environment may result in new physiological set points intended to maximize immediate changes for survival. The "predictive adaptive response" hypothesis proposes that a mismatch between the pre- and postnatal environment is a major determinant of subsequent disease (Gluckman and Hanson, 2004). (Figure 1)

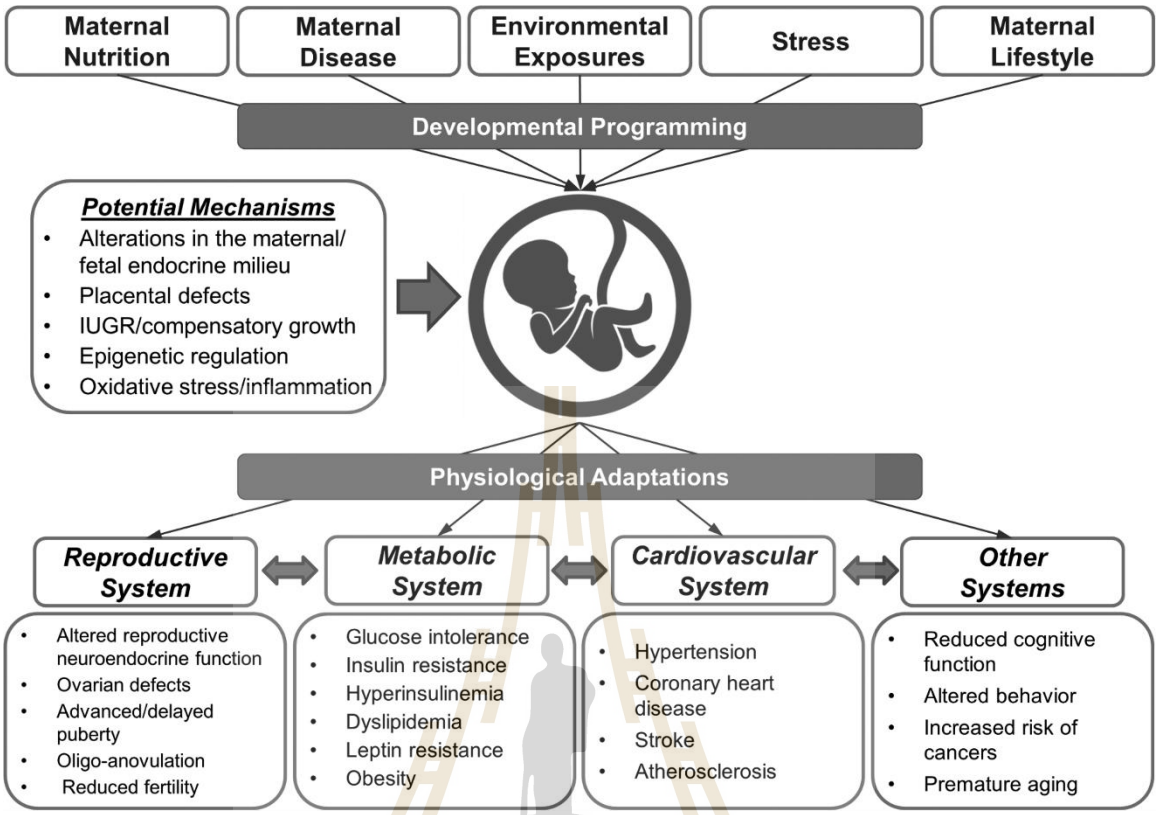

Figure 1 Impact of perinatal insults in programming adult pathologies in the offspring (Padmanabhan et al., 2016).

Maternal health prior to and at the time of conception can have detrimental effects on the pregnancy and the subsequent health of the child. In particular, obesity and insulin resistance during pregnancy have been consistently shown to negatively impact the metabolic health of the offspring. Obesity and insulin resistance often co-exist and are common metabolic conditions of pregnancy with an estimated 33% of all pregnancies complicated by maternal obesity. The relationship between obesity and insulin resistance in pregnancy and the impact on obesity, type 2 diabetes (T2D), and metabolic syndrome in the offspring may be due to permanent alterations in glucose-insulin metabolism in the offspring, causing reduced capacity for insulin secretion and insulin resistance (Fan et al., 2013). In fact, maternal obesity and insulin resistance have

been shown to confer insulin resistance as early as the embryonic stage in animal models (Cardozo et al., 2011). Maternal insulin resistance can negatively impact the developing embryo due to impaired glucose transport (Doblado and Moley, 2007).

In a study of the umbilical cords of lean pregnant women compared to obese pregnant women, maternal obesity was associated with significantly increased leptin and insulin levels in maternal plasma and cord plasma (Thakali et al., 2014). These differences were accompanied by differential umbilical cord gene expression between lean and obese mothers. A study of 99 offspring of diabetic mothers evaluated cardiovascular risk factors in childhood and adolescence. They observed a significant increase in E-selectin, vascular cell adhesion molecule 1 (VCAM1), and leptin levels in offspring of diabetic mothers compared to offspring of non-diabetic mothers, increased body mass index and waist circumference and decreased ADIPOQ. E-selectin and VCAM1 are markers of endothelial function and atherosclerosis and leptin and ADIPOQ are regulators of hunger and metabolism (West et al., 2011). Increased leptin and decreased ADIPOQ levels are likely due to the increased body mass index and waist circumference (West et al., 2011).

Maternal obesity is associated with epigenetic changes in the offspring, which mediate the metabolic disturbances seen in these offspring. In a mouse model of obesity, triglyceride and leptin levels were significantly elevated in offspring of obese mothers compared to offspring of mothers with normal metabolism (Li et al., 2013). These changes were accompanied by reduced expression of two mitochondrial genes, ATPASE6 and CYTB, and widespread changes in methylation patterns. These changes were exacerbated in offspring of obese mothers who were then fed a high-fat diet postnatally, compared to offspring fed a normal diet. The results of this study provide

further evidence of the effect of the maternal metabolic state on the metabolic health of the offspring, and demonstrate the additionally detrimental effects of a high-fat postnatal diet following exposure to maternal obesity (Li et al., 2013).

Studies of experimental induction of obesity in animal models provide causal evidence in support of detrimental effects of maternal overnutrition on the offspring's health. For instance, offspring of female rats fed a high-fat diet during gestation manifest increased overall adiposity, reduced insulin sensitivity, and hypertension (Ainge et al., 2011; Khan et al., 2005). Similarly, increased feed consumption before and during pregnancy in sheep was found to program glucose intolerance in the offspring (Long et al., 2010). In nonhuman primates, chronic consumption of a high-fat diet during gestation was found to increase adiposity and lipotoxicity in the liver (McCurdy et al., 2009), and increase anxiety in the offspring (Sullivan et al., 2010). Interestingly, there are several common traits such as hyperphagia, increased adiposity, reduced insulin sensitivity, and hypertension (Alfaradhi and Ozanne, 2011) in the offspring's phenotypic outcomes among the various animal models implicating common mechanistic pathways between the different animal models.

2.2 Metabolic syndrome

Metabolic syndrome (Xu et al.) is a chronic condition consisting of a number of disorders such as abdominal obesity, high blood glucose, high triglycerides, low high-density lipoprotein (HDL) cholesterol and elevated blood pressure that occur together in individuals. MetS have emerged a major clinical and public health problem. It contributes to doubling the incidence risk of cardiovascular disease within five to ten

years (Mottillo et al., 2010) a major cause of death, not only in developed countries but also in urban communities of developing countries, including Thailand.

The prevalence of MetS is increasing worldwide. Metabolic risk factors are associated with high prevalence of MetS (Grundy et al., 2005) and include high levels of fasting glucose, triglycerides and blood pressure, low HDL cholesterol, and central obesity. These risk factors require treatment for control, and include waist circumference to ≤ 80 cm in women or ≤ 90 cm in men, reduced systolic and diastolic blood pressure to ≤ 130/85 mmHg, reduced fasting plasma glucose to ≤ 100 mg/dl, reduced plasma to triglyceride level ≤ 150 mg/dl and raised HDL cholesterol level to ≥ 50 mg/dl in women or ≥ 40 mg/dl in men (Tan et al., 2004). This control is undertaken by means of lifestyle changes, particularly eating behavior and physical activity.

Promoting healthy eating behaviors and physical activity are required strategies for controlling MetS, however these are difficult to change due to many barriers, including personal, cultural, environmental, and societal factor (Kohinor et al., 2011). Changing people's behaviors by providing traditional health education or simple approaches such as information transference, general advice, and prescribing dietary or/and exercise regimens is difficult to achieve. Traditional health education usually focuses on teaching disease-specific skills and compliance to prescribed advice from health care providers (Coleman and Newton, 2005). Provision of information and skills is mainly based on health care providers' agendas rather than people's needs. Thus, adherence to medical treatment may be the issue.

Furthermore, the focus of traditional health education is often not based on problem-solving behavioral change issues. When patients encounter problems and obstacles, they neither solve them nor maintain new behaviors. Therefore, a new

approach is needed for changing unhealthy behaviors and should focus on teaching and training problem-solving skills.

2.2.1 Dyslipidemia

Dyslipidemia is an elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein level that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary. Diagnosis is by measuring plasma levels of total cholesterol, TGs, and individual lipoproteins. Treatment involves dietary changes, exercise, and lipid-lowering drugs.

Cause of dyslipidemia. Primary (genetic) causes and secondary (lifestyle and other) causes contribute to dyslipidemias in varying degrees. For example, in familial combined hyperlipidemia, expression may occur only in the presence of significant secondary causes. Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of TG and LDL cholesterol, or in underproduction or excessive clearance of HDL. The names of many primary disorders reflect an old nomenclature in which lipoproteins were detected and distinguished by how they separated into alpha (HDL) and beta (LDL) bands on electrophoretic gels.

Secondary causes contribute too many cases of dyslipidemia in adults. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans fats are polyunsaturated or monounsaturated fatty acids to which hydrogen atoms have been added; they are used in many processed foods and are as atherogenic as saturated fat.

Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (Vallance et al.), stroke, and

peripheral arterial disease. High levels of TGs (> 1000 mg/dL [> 11.3 mmol/L]) can cause acute pancreatitis.

Dyslipidemia is suspected in patients with characteristic physical findings or complications of dyslipidemia (eg, atherosclerotic disease). Primary lipid disorders are suspected when patients have physical signs of dyslipidemia, an onset of premature atherosclerotic disease (at <60 yr), a family history of atherosclerotic disease, or serum cholesterol > 240 mg/dL (> 6.2 mmol/L). Dyslipidemia is diagnosed by measuring serum lipids. Routine measurements (lipid profile) include total cholesterol (TC), TGs, HDL cholesterol, and LDL cholesterol.

Lipid profile measurement. TC, TGs, and HDL cholesterol are measured directly. TC and TG values reflect cholesterol and TGs in all circulating lipoproteins, including chylomicrons, VLDL, intermediate-density lipoprotein (Catar et al.), LDL, and HDL. TC values can vary by 10% and TGs by up to 25% day-to-day even in the absence of a disorder. TC and HDL cholesterol can be measured in the nonfasting state, but most patients should have all lipids measured while fasting (usually for 12 h) for maximum accuracy and consistency.

Testing should be postponed until after resolution of acute illness because TG and lipoprotein (a) levels increase and cholesterol levels decrease in inflammatory states. Lipid profiles can vary for about 30 days after an acute MI; however, results obtained within 24 h after MI are usually reliable enough to guide initial lipid-lowering therapy.

LDL cholesterol values are most often calculated as the amount of cholesterol not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5 because the cholesterol

concentration in VLDL particles is usually one fifth of the total lipid in the particle. Thus,

This calculation is valid only when TGs are < 400 mg/dL and patients are fasting, because eating increases TGs. The calculated LDL cholesterol value incorporates measures of all non-HDL, nonchylomicron cholesterol, including that in IDL and lipoprotein (a) [Lp(a)].

LDL can also be measured directly using plasma ultracentrifugation, which separates chylomicrons and VLDL fractions from HDL and LDL, and by an immunoassay method. Direct measurement may be useful in some patients with elevated TGs, but these direct measurements are not routinely necessary.

The role of apo B testing is under study because values reflect all non-HDL cholesterol (in VLDL, VLDL remnants, IDL, and LDL) and may be more predictive of CAD risk than LDL cholesterol. Non-HDL cholesterol (TC - HDL cholesterol) may also be more predictive of CAD risk than LDL cholesterol.

2.2.2 Obesity

Obesity is defined as an excess accumulation of body fat associated with increased fat cell size and number (Ali and Crowther, 2005). In terms of body mass index (BMI), the World Health Organization (Nwafor and Owhoji) and the U.S. National Institute of Health (NIH) define overweight as a BMI of 25 to 29.9 kg/m^2 and obesity as a BMI of 30 kg/m^2 or greater. The prevalence of overweight and particularly obesity continues to rise and is reaching epidemic proportions in both developed and developing nation (Ali and Crowther, 2005). Additionally, the National Heart, Lung and Blood Institute (Panel) recommends that a waist circumference of 88 cm or more (35 in. or more) in women or 102 cm or more (40 in. or more) in men, or alternatively,

a waist-to-hip ratio (WHR) higher than 0.80 in women or 0.95 in men, is used as an adjunct to BMI to classify high-risk obesity (Panel, 1998). The current state of a rapidly increasing prevalence of obesity appears to have emerged largely from increased intake of calorie-dense foods, highly palatable diet and a technology driven life of convenience and leisure at a time when physical activity is minimized (Nieves et al., 2003). A growing of obesity epidemic appears to be associated with an increasing prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus, includes hypertension and reduced glucose tolerance (Kahn et al., 2001). Also, obesity has been identified as the key etiological condition that predisposes to the development of the metabolic syndrome (Kahn and Flier, 2000), which is present in 25-50% of United Stated population. This constellation of metabolic abnormalities includes glucose intolerance (type 2 diabetes, impaired glucose tolerance, or impaired fasting glycemia), insulin resistance (IR), central obesity, dyslipidemia and hypertension, all well-documented risk factor for cardiovascular disease (CVD) (Eckel et al., 2005). Thus, obesity is now recognized as a serious health problem worldwide.

2.2.2.1 Health conditions associated with obesity

Excess body fat is associated with an increased risk of health problem, including hypertension and diabetes mellitus. Diseases associated with obesity maybe arise from two mechanisms: from the metabolic changes associated with excess fat, as type 2 diabetes mellitus and cardiovascular disease, or from the increased fat mass itself, as it is clearly the case for joint diseases. Obesity can affect almost all organs causing a multitude of clinical problems. (Formiguera and Cantón, 2004; Khaodhiar et al., 1999)

Obesity and hypertension are comorbid risk factors for the development of cardiovascular disease. In adults with a BMI > 30 kg/m2, the prevalence of high blood pressure (BP) were 38% in men and 32% of women, as compared with 18% of men and 16% of women with a BMI < 25 kg/m^2 (Khaodhiar et al., 1999). It was estimated that a 1 kg increase in weight is associated with a 5% increase in risk. An additional 10 kg in body weight was associated with higher BP, with increases of 3.0 mmHg in systolic and 2.3 mmHg in diastolic BP (Afridi et al., 2003).

The development of hypertension associated with obesity is related to a combination of increased sodium retention, increased sympathetic nervous system activity, alterations of the rennin-angiotensin-aldosterone system and insulin resistance.

In obesity-related hypertension, the cardiovascular abnormalities produced by sodium retention and intravascular volume expansion, which induces an increase in venous return and cardiac output, as well as an increase in peripheral vascular resistance, are well described. The maintenance of hypervolemia with hypertension implies a resetting of pressure toward higher BP. These changes in the cardiovascular system and the kidney may be related to insulin resistance, the enhancement in sympathetic nervous activity, and the activation of the renin-angiotensin-aldosterone system. In addition, the renal medulla of obese persons demonstrates histologic changes including interstitial cell proliferation and deposition of a noncellular matrix, which can lead to compression of tubules and vasa recta, increased sodium reabsorption (Formiguera and Cantón, 2004; Khaodhiar et al., 1999).

2.2.2.2 Leptin

Obesity is a disease that has a causes a wide range of factors including genetic factors, behavior, environment and culture (Krassas and Pontikides,

2004). From the previous study stated that Obesity is a disease caused by heredity. And obesity occurring in children are often influenced by genetic factors as much as 30-70 percent (Bouchard, 1991). In general, the study of genetics is mainly conducted to determine the changes or mutations in genomic DNA of a variety of genes or a nearby gene (genetic polymorphism, single nucleotide polymorphism (SNPs), CA repeat microsatellites) (Clément, 2006). So it shows that genetic factors are important to obesity. Obesity that may arise from gene mutations, only a single gene, called "monogenic obesity" is an example of a gene, including genes leptin (LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC), prohormone convertase. 1 (PC1), melanocortin 4 and 3 receptors. The mutations in the genes that interfere with the function of the hypothalamus part of the brain that controls hunger and satiety. When these genes are sequences nucleotide changes. Or mutation can affect the function of the gene for the disorder. And affect the expression of characteristics (phenotype) that is associated with eating behavior. And may develop into a more severe obesity from a young age (Hainerová et al., 2007).

Leptin gene is located on chromosome 7 the position q 31.3 consists of 3 exons (Tatti et al., 2001). The function of the leptin gene Affect the hormone leptin (Paracchini et al., 2005). Leptin is a peptide hormone secreted from adipose tissue in direct proportion to adipose tissue mass. This protein, which is produced by fat tissue of the body (Trayhurn and Beattie, 2001). Hormone leptin causes severe obesity. Because it is important for the transmission of nerve signals that make decreases appetite. As a result of the accumulation of body fat and body weight. Hormone leptin works to decrease food intake and increase energy metabolism in the body (Baratta, 2002). Previous studies have found that Mutations of the leptin gene causes obesity and

diabetes in an animal. The result of the condition in human beings, such as eating more than usual. (Hyperphagia) a condition in which the body cannot burn calories or burn a little. (Hypothermia), etc. (Chen and Garg, 1999). Although mutations of the leptin gene are found not much. However, previous studies have demonstrated the importance of leptin gene that controls the balance of power in human (Froguel and Boutin, 2001). So when leptin gene disorders to make the hormone leptin change. As a result, people do not feel satiety, body burn less energy, the fat is accumulated in the body. Obesity and serious consequences. However, even just find the nucleotide sequence of leptin gene and nearby genes (SNPs), but that is associated with obesity. Or the appearance of expression in obese people. This position is part of the gene. Also known as a promoter Leptin gene affects the function of the tissue with fat (Miller et al., 1996).

Thus, knowledge of mutation or modification of nucleotide sequences in a gene leptin and vicinity. It is important to study obesity in humans (Paracchini et al., 2005). Detection of blood samples for genetic mutations or changes in the leptin gene has enormous potential. Because of the causes of obesity at the molecular level. On that note, there is an abnormal gene anticonvulsant thin, it will be a self-care and weight control.

2.2.2.3 Hyperleptinemia with hypertension

Hyperleptinemia is another possible link between obesity and the development of hypertension. The close relationship of hyperleptinemia with hypertension is further supported by observations obtained in obese leptin-deficiency mice, which are obese but do not exhibit hypertension. Obesity does not invariably increase BP in mice and probably also in human beings and the arterial pressure response to obesity may depend critically on the underlying genetic and neuroendocrine

mechanisms (Mark et al., 1999). Mutations might reduce the functional activity of leptin. MC4R deficiency abolished the cardiovascular and metabolic actions of leptin in obese MC4R (−/−) mice and possibly in human beings. BP levels have been reported significantly lower in MC4R-deficient subjects than in control subjects (Greenfield et al., 2009). Thus, a functional MC4R is essential for the chronic cardiovascular and metabolic actions of leptin (Tallam et al., 2006). MSHs have an important function in feeding, energy metabolism and inflammation. Both α- and γ-MSH acutely elevated BP and heart rate through central stimulation of sympathetic nervous outflow (Humphreys, 2007). This action of α-MSH is mediated by the MC4R, whereas γ-MSH deficiency or disruption of MC3R in rodents leads to salt-sensitive hypertension possibly through a central mechanism. This salt-sensitive hypertension is accompanied by the development of insulin resistance. SNS-stimulating actions of leptin are mainly shown in the kidneys, adrenal glands, and brown adipose tissue. SNS stimulation is not the only mediator through which hyperleptinemia leads to cardiovascular reactions. Endothelial dysfunction has also been reported as another important aspect of leptin's effects (Knudson et al., 2008; Korda et al., 2008). Leptin is believed to promote direct endothelium toxicity by causing an alteration in the expression of endothelial NO synthase. Finally, it should be considered that perivascular adipose tissue is an additional source of leptin.

2.2.3 Hypertension

Hypertension is a state of arterial pressure higher than normal pressure for a long time or all time. In generally blood pressure of normal person while a state in rest about 120/80 mmHg if measure over 120/80 mmHg but less than 140/90 mmHg be within the scope of start to high blood pressure (prehypertension) and if blood pressure

more than or equal to140/90 mmHg considered be hypertension (Table 2). The patient should control blood pressure below 140/90 mmHg but if a patient has another congenital disease along such as diabetes, nephropathy they should be control blood pressure level not above 130/80 mmHg (Chobanian et al., 2003).

Table 1 Blood Pressure Levels adults aged 18 years and over.

Blood Pressure Classification	**Systolic Blood Pressure (mmHg)**		**Diastolic Blood Pressure (mmHg)**
Normal	<120	and	<80
Prehypertension	120-139	or	80-89
Hypertension			
Stage 1	140-159	or	90-99
Stage 2	≥160	or	≥100

Adapted from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 2003

Hypertension divided by the following 2 type:

Essential hypertension is hypertension not known the cause of the disease found about 90-95% of a patient be hypertension. The cause of disease were many factors to

be increased risk occur hypertension in age older make aorta harder follow by age increase. Resistance to circulation increasing effect to high blood pressure, heredity, gender, obesity, lack of exercise, under stress , smoking , drink alcohol beverage (Klabunde et al., 2005; Malhotra et al., 2003).

Secondary hypertension is hypertension know the cause of the disease found about 5-10 % of hypertension patient which curing caused helping blood pressure come back to normal state. Caused by hypertension such as nephropathy, a patient who has renal artery stenosis tumor at adrenal gland make generate aldosterone or hormone catecholamines excess. Abnormality of heart since was born, aorta anomaly (coarctation of the aorta), to receive some type of medicine too much such as contraceptives toxemia of pregnancy etc. (Klabunde et al., 2005; Malhotra et al., 2003).

2.3 Blood pressure

Blood pressure is pressure reaction to blood vessel walls occurs when heart contraction for send blood to any part of a body. The maximum pressure while the heart compression called systolic (systolic pressure).The minimum pressure while heart relaxes called diastolic (diastolic pressure)

2.3.1 Blood pressure control mechanisms

Due to blood pressure is direct variation with heart blood flow rate outlet (cardiac output, CO) and total end part vessel resistance (total peripheral resistance, TPR). Therefore blood flow rate changing of cardiac output (CO) or total peripheral resistance, TPR) either or both effect to blood pressure change too (Widmaier, 2004). When blood pressure changing from a normal mechanism of body adjust blood pressure

constantly which each mechanism has a period and the size of the response not equal. (Figure 1) divided into two groups by the following:

2.3.1.1 Mechanism to control blood pressure in short term

When lower or higher blood pressure than normal mechanism occur immediately to adjust for help blood pressure to be normal fast in the second or minute this is working of autonomic nervous systems via reflex by adjusting heart working and vessel in conjunction with hormone secretion such as epinephrine, angiotensin and vasopressin that effect to heart working and vessel (Guyton and John; Widmaier et al.).

2.3.1.1.1 Baroreceptor reflex

Baroreceptor reflex is reflex the most importance to control blood pressure by baroreceptor with was stretched baroreceptor found in aorta wall around carotid sinus and aortic arch (Figure 1) When stimulating carotid baroreceptor will send nerve signals into carotid sinus nerve which process of glossopharyngeal nerve (CN9). Aortic baroreceptor will send nerve signal import from both of nerve into nucleus tracts solitaries in medulla oblongata to control heart working and blood vessel (Klabunde et al., 2005). Working of baroreceptor reflex (Sino aortic baroreceptor reflex) when blood pressure higher than normal make stretching of arterial vessel stimulate arterial baroreceptor at carotid sinus area and aortic arch send nerve signal into nucleus tracts solitariness in medulla make depressor response by prohibit sympathetic nervous system sending to heart and blood vessel and stimulate vagus nerve pass through heart make heart rate decrease and vessel expansion all around body (vasodilation, vasodilation) effect to CO and TPR decrease, blood pressure in normal level . In the other hand if blood pressure decrease below normal blood pressure as

baroreceptor was decreased stimulated, send nerve signal to medulla decrease will occur pressure response make vagus nerves system work more will increase heart rate and contraction of vessel all around body (vasoconstriction) effect to increase CO and TPR blood pressure Increased to normal levels. (Mohrman and Haller, 2003)

Carotid baroreceptor to respond to changes in blood pressure in range 60-180 mmHg by the best response rate in mean article pressure about 95 mmHg. The changing of blood pressure in a little bit range will effect to a response of baroreceptor reflex more, but aortic baroreceptor has a response similar to carotid baroreceptor (Klabunde et al., 2005). *Baroreceptor reflex* is important in control blood pressure to constantly all time by responsive of baroreflex (sensitivity or gain) will decrease follow age. High blood pressure or atherosclerosis occur due to a vessel wall of arteries will harder, reflexibility decrease (Grassi et al., 2006; Klabunde et al., 2005; Thrasher et al., 2005). Furthermore, baroreflex was adjusted for response of baroreflex (setting of the reflex or setpoint) in some state by adjusting in 2 factor

Central resetting is changing nerve signal into nucleus tracts solitaries such as when a body is going to exercise make high blood pressure increase scale to exercise level, but heart rate does not decrease due to reflex increase set point level while exercising (Levick, 2013).

Peripheral resetting to adjust responsive of baroreceptor by threshold of baroreceptor will increase when blood pressure high for more 15 minutes which adjust new blood pressure make response at old blood pressure lower than comparative with normal state (Levick, 2013) baroreceptor reflex cannot control blood pressure in long-term because of adjust set point reduce baroreceptor of central nerve system will not

recognize data which blood pressure changing for a long time so that baroreceptor reflex is important to control blood pressure in short-term .

2.3.1.1.2 Cardiopulmonary reflex

Cardiopulmonary reflex has a receptor (cardiopulmonary receptor) that is stretch receptor was found stimulated when blood pressure or blood volume in an atrium and central venous pool increase. Furthermore cardiopulmonary reflex is important for kidney to control liquid volume in body for example when volume and pressure in vein increase vagus effect to suspense sympathetic nervous system which working at heart, vessel and kidney make vessel expansion, heart rate decrease, blood pressure decrease, kidney secretion renin decrease make angiotensin II (Ang II) and aldosterone decrease, increase diuretic effect to blood volume decrease and blood pressure decrease (Klabunde et al., 2005).

2.3.1.1.3 Bainbridge reflex

Bainbridge reflex response of cardiopulmonary receptor was stimulated from increase blood volume and venous return makes medullary center of sympathetic efferent activity at SA node effect to increase heart rate (Ganong and Coleman, 2005).

2.3.1.1.4 Chemoreceptor reflex

Chemoreceptor divided by central chemoreceptor and peripheral chemoreceptor by central chemoreceptor was found at medulla, peripheral chemoreceptor was found at a carotid body and aortic body by chemoreceptor was stimulated while oxygen in blood decrease (hypoxemia). Increasing carbon dioxide in the blood (hypercapnia) and concentrate of hydrogen ion increase or high acidity (acidosis).When chemoreceptor was stimulated send nerve signal to stimulate pressor region at medulla effect to increase sympathetic nervous system to work at heart and

vessel make vessel constriction effect to increase blood pressure (Klabunde et al., 2005).

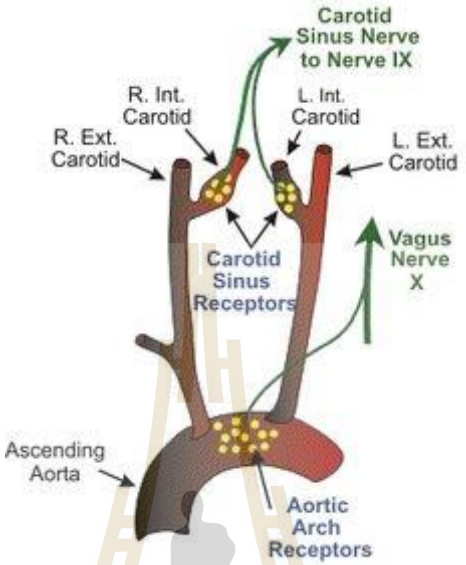

Figure 2 show a position of baroreceptor found around carotid sinus and aortic arch when was stimulated carotid sinus receptor will send nerve signal import to sinus nerve and then into glossopharyngeal nerve and aortic baroreceptors will send nerve signal into vagus nerve signal import from both nerve into medulla (Klabunde et al., 2005).

2.3.1.2 Mechanism to control blood pressure in long term

The mechanism in long term starts slowly working and time to work longer in day or week make blood pressure will come back to normal state (Guyton et al., 2006) this mechanism need kidney function to work with certain hormones for adjusting the volume of fluid and blood in the body properly (Widmaier, 2004). When a body has increased blood pressure or decrease will stimulate reflex to work make blood pressure into normal scale. In some case mechanism occurs immediately and

have short term efficiency cannot correct blood pressure and circulation to the normal state must using a long time as day or week for adjusting blood pressure to normal scale. Body will control blood pressure in long-term by control liquid volume, adjust blood in a body (blood volume) due to when blood volume changing in body effect to blood pressure change along with kidney work as adjust removal of water and minerals from the body. Decreased blood volume, blood pressure is reduced to normal levels or when the body's blood pressure dropped, it will be a mechanism to adjust blood pressure On the other hand (Bullock et al., 1995; Guyton et al., 2006). Renal function to adjust blood pressure is a result of the work of hormones following:

2.3.1.2.1 Renin-Angiotensin-Aldosterone system

Renin-Angiotensin-Aldosterone system is an important role in controlling blood pressure, heart working and vessel and blood pressue in body when blood pressure decrease effect to secretion of renin from juxtaglomerular cells at kidney. Moreover stimulating to sympathetic at kidney and reduce concentrate of Na+ at ureter even secretion renin too effect to generate angiotensin II (Ang II) activate by catch up with ATI receptor show in table 1 effect to occurring vasoconstriction ,stimulate secretion of aldosterone from adrenal cortex include stimulate feeling thirsty , increase Na+ reabsorption at renal tubule , decrease renal blood flow , increase vasopressin , stimulate sympathetic nervous system to working and increase action of noradrenergic. The result which occurs when Ang II stimulate is vasoconstriction, liquid volume of an outer cell (extracellular fluid, ECF) and blood volume increasing effect to increase blood pressure. Furthermore, Ang II when catch up with receptor still effects in stimulation to cell growth occur and proliferation in vascular smooth muscle cells, cardiomyocytes and coronary endothelial cells effect to pathology all circulatory

system, kidney and brain such as ventricular hypertrophy, cardiac arrhythmias, atherosclerosis, glomerulosclerosis, stroke and dementia (Unger, 2002).

Table 2 Actions of Ang II at AT1 and AT2 receptor (Unger, 2002).

AT1 receptor	**AT2 receptor**
-Vasoconstriction	- Fetal tissue development
- Aldosterone synthesis and secretion	- Inhibition of cell growth/proliferation
- Renal tubular sodium reabsorption	- Vasodilation
- Increased vasopressin secretion	- Modulation of extracellular matrix
- Decreased renal blood flow	- (Neuronal) regeneration
- Renal renin inhibition	- Cell differentiation
- Cardiac hypertrophy	- Apoptosis
- Cardiac contractility	
- Vascular smooth muscle cell proliferation	
- Augmentation of peripheral Noradrenergic activity	
- Modulation of central sympathetic nervous system activity	
- Central osmocontrol	
- Extracellular matrix formation	

2.3.1.2.2 Vasopressin (Antidiuretic Hormone, ADH)

Stimulator to secretion vasopressin from posterior pituitary gland such as Ang II, an addition of osmolarity, decrease signal from the aterial receptor (atrial receptor firing) and stimulate sympathetic nervous system working by vasopressin action to increase reabsorption of water at kidney to make blood volume increase. Moreover, vasopressin that high concentration activate vasoconstrictor make vasoconstriction occur increase blood pressure (Klabunde et al., 2005).

2.3.1.2.3 Artrial Natriuretic Peptide (ANP)

When a wall of the atrium was stretched, stimulating sympathetic nerve system, addition of Ang II and endothelin will stimulate atrial myocytes secretion ANP which action to a suspension of renin secretion, Ang II and aldosterone increase filtration rate at Kidney, increase eject Na^+ and water at kidney effect to decrease blood volume. Moreover, ANP suspense secretion and activate of norepinephrine make vasodilation of blood pressure decrease (Bullock et al., 1995; Klabunde, 2005).

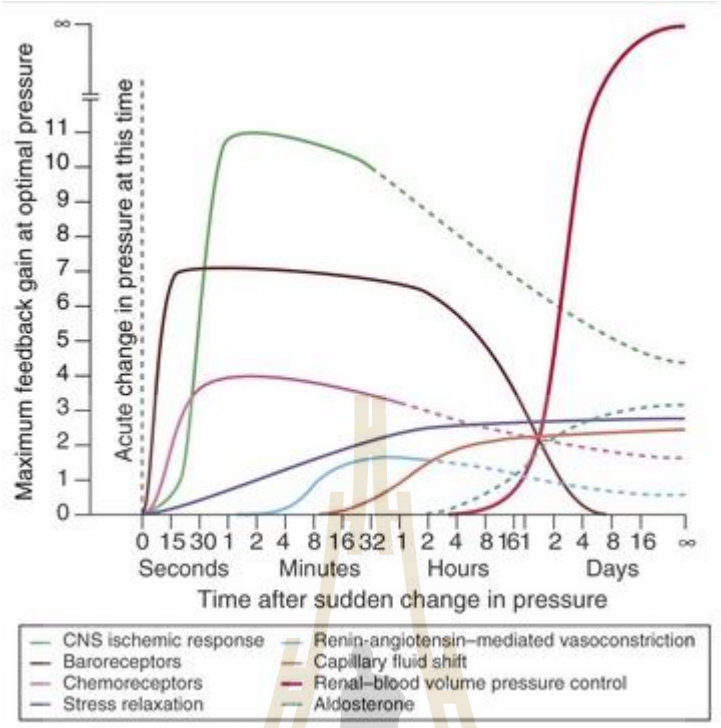

Figure 3 demonstrate mechanism and time period to control blood pressure which differentiates control blood pressure by time length to change blood pressure (Guyton et al., 2006).

2.4 Taurine

Taurine is a semi-essential amino acid (conditionally essential) that is known as a sulfur-containing beta-amino acid due to its structure. It comprises over 50% of the free amino acid pool of cardiac tissue (highly prominent) (Jacobsen and Smith Jr, 1968; Pansani et al., 2012) but is located systemically in lower concentrations, particularly the testicles where it is the most important free amino acid (Higuchi et al., 2012; Yang et al., 2010) In general, taurine is present in excitable tissues more than others (Huxtable, 1992) although as its transporter is expressed ubiquitously it could be assumed taurine is omnipresent in the human body (Uchida et al., 1992). Unlike other

amino acids and more like beta-amino acids, taurine is not a structural component of any quaternary proteins or peptide bonds and resembles a peptide neurotransmitter (like adrenaline or dopamine) more than general dietary proteins (Bouckenooghe et al., 2006).

Processing taurine from trans-sulfuration, taurine produce directly from cysteine by oxidation reaction or by a path to change methionine to cysteine and then change to taurine. Moreover, taurine can be produced from a cysteic acid by decarboxylation (cysteic acid produced from accumulation inorganic sulfate and serine). Furthermore, accumulation of sulfate and serine processing cysteamine which oxidized cystein to homocysteine and taurine, but almost produce taurine by oxidizing cysteine conversion into cysteine sulfinic acid (CSA) in procedure by use enzyme called cystathionine synthase, cystathionase and cysteine sulfinic acid decarboxylase (CASD). figure 4

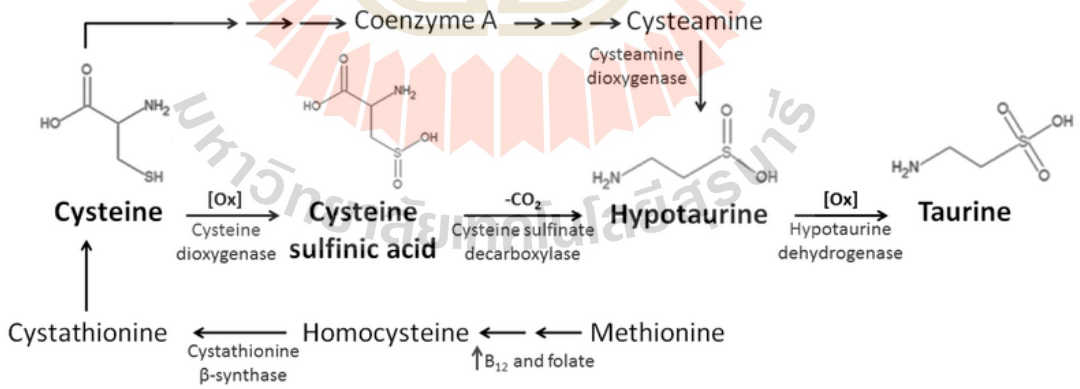

Figure 4 Biosynthetic route of taurine from amino acids cysteine and methionine (De Luca et al., 2015).

2.4.1 Interactions with Cardiovascular Health

Cardiac muscle has taurine more than 50% of free amino acid in heart.Taurine influence positive inotropic with cardiac muscle and reduce and reduce blood pressure. Effect of taurine to cardiac muscle caused by taurine could control a quantity of calcium in heart prevent heart disease to maintain heart working when a body has calcium higher or less by taurine control calcium and potassium pump (Satoh, 1994).

2.4.1.1 Hypertension

In the year 1987 study about the taurine effect to blood pressure and catecholamine in plasma by double-blind controlled study in patients that have borderline hypertension was found blood pressure systolic and diastolic decrease more than a placebo group. The treatment taurine group has epinephrine in plasma decrease legibly in essential hypertension patient (Fujita et al., 1987). Body reject taurine into urine less than the normal person [708 (SD 57) vs 1594 (SD 143) micromole/day] and taurine clearance and taurine/creatinine ratio decreased sharply in infants who are neonatal physiologic aminoaciduria (Kohashi and Katori, 1983). Body reject lots of taurine into urine because renal tubular system working not well so that reabsorb taurine not much in infant give birth more premature and lack of taurine. Infants still reject lots of taurine into urine because of tubular cell working not well cannot reabsorb taurine, but Infants preterm give birth and have body weight > 1,700 g can reabsorb taurine make quantity of taurine in urine decrease (Geggel et al., 1985; Rassin et al., 1977).

2.4.2 Interactions with cholesterol level

2.4.2.1 Reduce cholesterol level in blood

From metabolism of cholesterol effect to be cholic acid and cheno-deoxycholic acid that bacteria in intestine transform to deoxycholic acid and lithocholic acid, respectively. Bile acid both conjugated by taurine and glycine produce bile salt corporate catch with cholesterol to reject into feces. Study single-blind placebo-controlled method in male age 18-29 years divide two groups eat cholesterol foods along 3 weeks. The first group receives taurine supplement, the second group receive placebo that has total cholesterol and low-density lipoprotein cholesterol (LDL) higher than the first group (Mizushima et al., 1996). The result was found taurine could reduce cholesterol in the blood by bile acid conjugation.

2.4.2.2 Fatty liver

In the year 1996, Obinata and Maruyama giving taurine to obesity have fatty liver was found alanine transaminase (Peters et al.) to normal level can control body weight better. Glycine/taurine ratio in bile decrease (Obinata et al., 1996).

2.4.3 Pharmacokinetics of Oral Taurine

Taurine is occasionally used in therapeutics as a medicine, the pharmacokinetics and effects of oral taurine in a human. Some foods or drinks, for example, energy drink (Alford et al., 2001), contain a considerable amount of taurine (Gupta et al., 2005). Little is known of the pharmacokinetics of taurine in man after oral administration. Such information is essential if a regimen for administration of this agent to patients is designed. A literature review revealed report concerning the pharmacokinetics of taurine performed by (Zhang et al., 1998) using 200 mg IV injection form of taurine in six patients with hypertension, but the paper was brief and

only available in mandarin. And another one from previously studied the pharmacokinetics and effects of oral taurine in healthy volunteers that would be useful in the future studies of taurine in pharmacology and nutrition from (MohammadReza et al., 2010) showed that endogenous plasma taurine levels (mmoL) in eight healthy volunteers following administration of 4 g (32 mmoL) oral taurine before taking the taurine capsules ranged from 0.03 to 0.06 mmoL. (Figure 4) Time to reach maximum concentration ranged from 1 to 2.5 hr (absorption phase). The mean maximum plasma taurine concentration was 0.57 ± 0.05 mmoL.

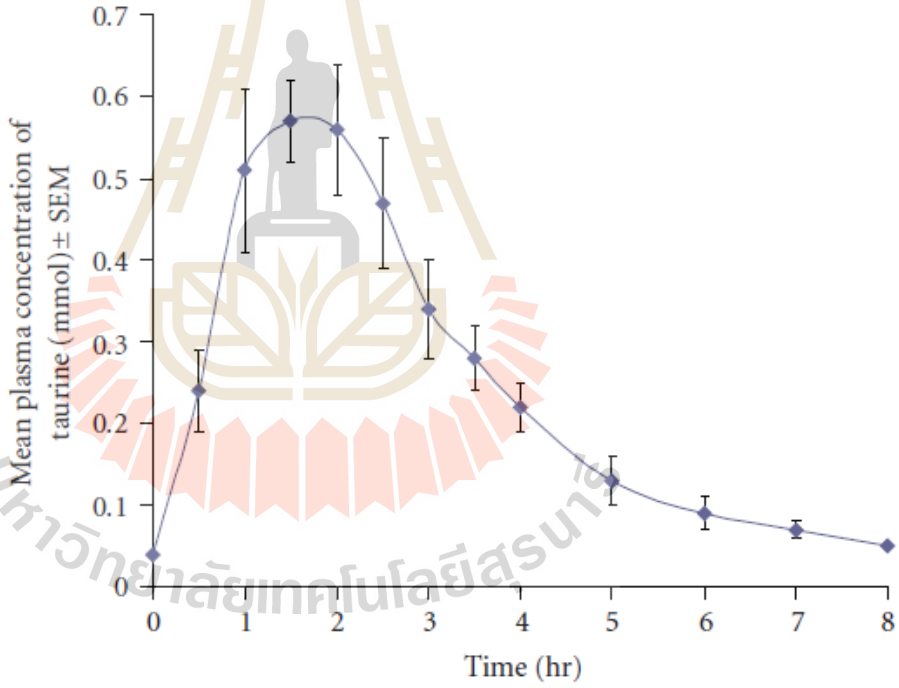

Figure 5 Linear plot of mean plasma taurine levels (mmoL) in eight healthy volunteers following administration of 4 g (32 mmoL) oral taurine.

Total body taurine is regulated by the kidney. Taurine is a major urinary amino acid in humans because the capacity of renal uptake is low (Sturman and Gaull, 1975).

Daily taurine losses in urine are diet-dependent but generally range from 65 to 250 mg (0.5–2.0 mmoL) (Chesney et al., 1985). Studies have demonstrated that taurine, even in high doses, is generally free of any serious adverse effects.

2.4.4 Taurine Benefits of Exercise

The benefits taurine has on muscle and during exercise. Taurine has been shown to increase the mechanical threshold for skeletal muscle fiber contraction, meaning muscle fibers can withstand greater stresses for long periods of time. This is related to the modification of the excitation-contraction coupling process, which in turn alters the calcium handling ability of the sarcoplasmic reticulum (SR) inside cells. Ultimately, this allows for the re-synthesis of energy in muscles and means taurine can help to stimulate the body to work harder (Satoh and Kang, 2009).

From the previous study found the benefits taurine has on muscle damage. The studies started in laboratory rats to assess the potential benefits seen when taurine was ingested by the animals before endurance exercise: in this case, running on little rat treadmills (De Luca et al., 1996). First, it was observed that skeletal muscles had a reduced concentration of taurine following endurance running, thus indicating that the taurine was utilized by the muscle tissue. However, the reduction in taurine concentration was significantly less in those animals who had been provided taurine (vs the control group who were not given taurine). On top of the reduced rate of taurine depletion, the duration of time before exhaustion was also significantly increased by taurine supplementation. This would indicate that oral consumption of taurine increases the capacity of endurance and slows fatigue. This study is even more interesting as it also demonstrated that the rats consumed taurine prior to exercising had lesser amounts of creatinine, creatine, and 3-MH in their urine, which are all indicators of muscular

damage. This may indicate that the means by which taurine is able to increase endurance is by reducing exercise-induced muscle damage and fatigue, and therefore assisting recovery from exercise.

The benefits taurine has on muscle recovery. These benefits are considered to occur by modulating ion channels, cell membrane excitability (Yatabe et al., 2003) and protection of muscle cells against a response which facilitates atrophy (wastage) (Camerino et al., 2004). Additionally, taurine reduces some of the oxidative stress markers induced by exercise and behaves in a manner to scavenge free radicals in various tissues (Dawson Jr et al., 2002; Ra et al., 2013). This would then reduce the degree of substances created by protein degradation and energy metabolism, and maintain normal muscle morphology. These results are further supported by studies in human participants where time to exhaustion, VO_2 max and maximal workload on an exercise bike were all enhanced by oral taurine supplementation (Dawson Jr et al., 2002). Another really interesting study showed that muscle damage as a consequence of high intensity, eccentric exercise is reduced delayed onset muscle soreness when taurine supplements and branch chain amino acids (BCAAs) are combined (Zhang et al., 2004).

The benefits taurine has on the reduction of oxidative stress. Previous studies have suggested that the mechanisms for the taurine-mediated enhancement in exercise performance might involve the reduction of exercise-induced oxidative stress (Dawson et al., 2002; Miyazaki et al., 2004; Zhang et al., 2004), increased cardiac contractility during exercise (Baum and Weiss, 2001), inhibition of exercise-induced blood lactate acid production (Imagawa et al., 2009; Manabe et al., 2003), or decreased exercise-induced muscular damage (Manabe et al., 2003). In addition, a recent study

demonstrated that acute taurine supplementation in humans just before exercise produced significant increases in total whole-body fat oxidation, suggesting the possible mechanism of taurine to shift relative fuel utilization (Rutherford et al., 2010). Therefore, it is suggested that there might be other possible roles of taurine on metabolism associated with carbohydrate, lipid, and amino acids for energy production. During endurance exercise, certain amino acids themselves may be utilized as fuel sources through the gluconeogenesis pathway. The best-characterized system in gluconeogenesis is the glucose-alanine cycle in which muscle alanine is catabolized in the liver for glucose homeostasis. In addition, branched-chain amino acids (BCAA); leucine, isoleucine, and valine, can be oxidized as fuels in skeletal muscle during prolonged exercise (Rennie et al., 2006).

2.5 Exercise Training

Exercise training is an activity or moving a body to make organ working harder than normal activity especially skeleton system, circulatory system, respiration system and nerve system that working related to being appropriate. Exercise for developing body performance depend on the intensity of exercise, time to spending (duration) and frequency of time often in exercise) (McArdle et al., 2007; Plowman and Smith, 2013) which exercise must do continuous and always. If stop exercising will decrease body performance and will invert to a state before exercise like nothing to exercise. Exercising can divide by the following:

2.5.1 Divide by using oxygen

Aerobic exercise is exercise by using oxygen in combustion energy by burning energy from glycogen and fat. This exercising using large muscle to working continuously have enough time will contribute to developing circulatory system working. This exercising using energy from fat that accumulated in body effect to decrease body mass such as brisk walk, running, jogging, ride bicycle, swimming and aerobic dance etc.

Anaerobic exercise is exercise by not use oxygen to combustion energy but using energy from muscle inform glycogen disintegrate to be energy by not use oxygen encourage to combustion. Characteristics of this exercise will occur rapidly, a short term such as jogging on short length way, weight lifting.

2.5.2 Divide by muscle working

Isometric exercise to exercise by type of muscle contraction imply length of muscle not change make body which exercising do not moving, tension of muscle will increase for resist with resistance force. This exercising can be doing in anywhere anytime for example exert to push the wall, exert to squeeze the object.

Isotonic exercise is exercising in type of stretching of muscle in length of muscle change and organs or joint moving. Can divided this exercise by muscle working in 2 type are concentric which has stretching of muscle in type of length short stretch make mass move closer to body such as weight lift mass close to body and eccentric type which stretching of muscle which contraction and length muscle increase such as life mass further of body.

Isokinetic exercise is an exercise in a type of stretching of muscle against resistant with constant velocity. This exercise may be using exercise tools to setting hard life of activities of users such as running on a treadmill and step test.

2.5.3 Effect of exercising training on hypertension.

Exercise by continuously effect to healthy due to exercising help prevent or reduce pathology from any in current disease such as hypertension, coronary artery disease, diabetes Parkinson's disease, Alzheimer's disease, osteoporosis and atherosclerosis (Zanesco and Antunes, 2007) in patients with essential hypertension were found aerobic exercise encourage reduce lethal rate and rate of pathogenesis in circulatory system (Higashi and Yoshizumi, 2004). Many researches showed the results of aerobic exercise which reduce blood pressure in hypertension patients type of essential hypertension (Bittner and Oparil, 1994; Moreira and Goldemberg, 1999; O'Sullivan and Bell, 2000; Peters et al., 2005).

Mechanism of reducing blood pressure in person that is the result of exercise maybe occur many factors such as reduced sympathetic nervous system working and/ or increase parasympathetic nervous system (O'Sullivan and Bell, 2000). Increasing the number of vessels in skeletal muscle. Increasing endothelial function by increase secretion NO from endothelial cell cooperate with up-regulation of eNOS.Reducing of NO inactive from up regulations of antioxidant in the body make antioxidant level in body increase both Cu/ Zn-SOD, Mn- SOD, extracellular SOD, glutathione peroxidase and catalase. Moreover, aerobic exercise reduces working of NAD(P)H oxidase. These results effect to decrease ROS level, NO increase. Working of endothelial cell better. Figure 5 (Green and Nuechterlein, 2004; Higashi and Yoshizumi, 2004) report the results of exercise to reduce blood pressure in rats Spontaneously hypertensive rat

(SHR) to by these results indicated about exercise can increase aortic baroreceptor gain sensitivity (Brum et al., 2000) increasing stimulating eNOS , increasing generated and NO working.

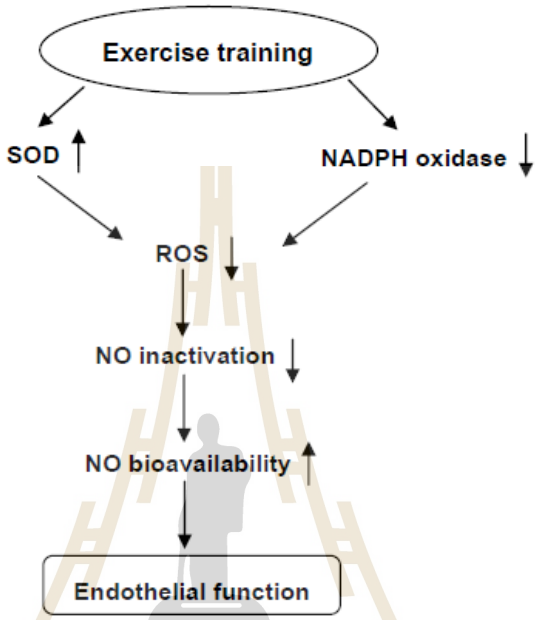

Figure 6 Showed mechanism of exercise increase SOD and reduce NADPH oxidase make ROS decrease effect to NO inactive reduce, NO bioavailability increase, endothelial cell be better (Higashi and Yoshizumi, 2004).

2.5.4 Effect of exercising training on lipid profile.

Exercise is one method to reduce cholesterol. Exercise in obesity namely well know about fat people have incidence in some disease higher than normal people for example hypertension, diabetes, and dyslipidemia these diseases relate to heart disease. Evidence to assure about abnormality would be better if fat people have exercise always. Even though exercising not encourage to lose weight but it can help to control weight body to reach higher than not exercise (Miller et al., 1997) cause make a fat ratio of body decrease especially around an abdominal surface. And if people

exercise and control foods quantity coexisting was contributed to preventing or reduce aggressive of diabetes disease, hypertension, and dyslipidemia to reduce risk for coronary artery disease (Blair et al., 1996). Furthermore, exercise increases strength of muscle and relax too. The effect of exercise with fat in the blood level of people who exercise always (neither fat nor slim) lead to triglyceride decrease and ratio HDL to total cholesterol increase but hardly to confirm that result carry overweight decrease and eating behavior changes. So that exercise program in fat people is important to be equal to lose weight program by control eating foods. Was see more clearly result in a patient who has tendency about can lose weight when enter to exercise program.

The regular physical activity can alter endothelial phenotype and function in vasculatures per fusing the nonworking skeletal muscle, brain, viscera, and skin. Although limited, there is also recent evidence that exercise training can alter the vasculature perfusing bone (Dominguez et al., 2010). Although the mechanisms driving exercise training-induced endothelial adaptations beyond the active muscle beds are not established at this time, we propose hemodynamic forces (i.e., shear stress and cyclic strain) and/or circulating factors released from adipose tissue and skeletal muscle as likely signals responsible for the endothelial adaptations in these vasculatures (Figure 6). Given that localized exercise training (i.e., a single arm or leg) does not exert systemic effects on the vasculature, it is possible that there is a threshold for hemodynamic forces and circulatory factors that may only be reached when exercise involves large muscle groups. Further research is warranted to shed light on our understanding of the exercise-mediated signals for endothelial adaptation and to determine how these signals synergistically interact in the systemic modulation of endothelial phenotype and function.

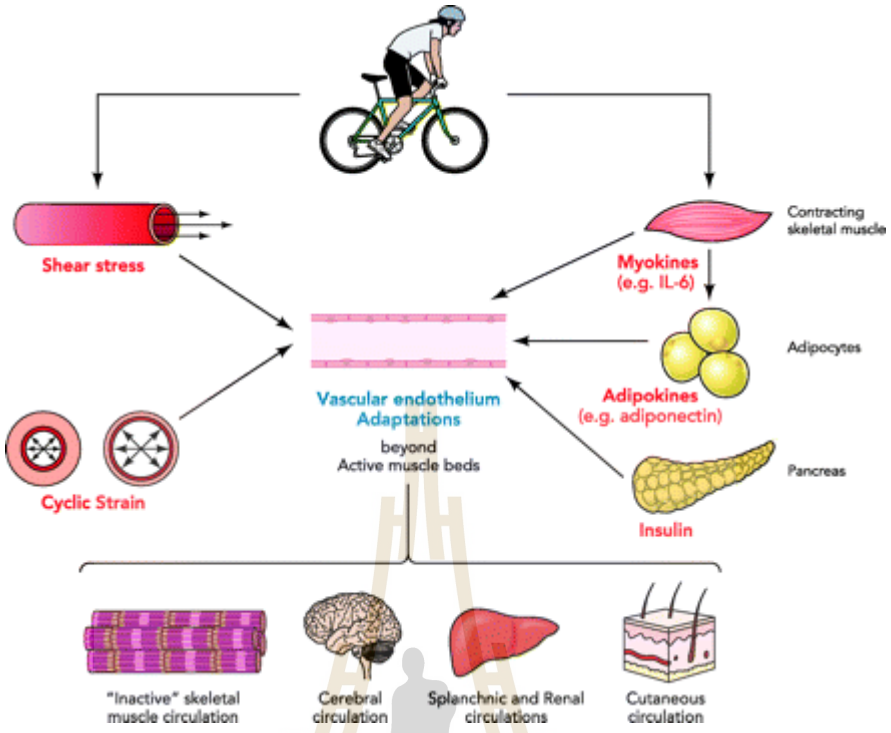

Figure 7 Summary of proposed mechanisms by which exercise training may alter endothelial cell phenotype and function beyond the active muscle beds (Padilla et al., 2011).

2.6 Tyloxapol (Triton WR-1339)

Triton WR-1339 (formaldehyde;oxirane;4-(2,4,4-trimethylpentan-2-yl)phenol) is a non-ionic detergent.Triton WR-1339 has been widely used to produce acute dyslipidemia in animal models in order to screen natural or chemical drugs (Schurr et al., 1972) and to study cholesterol and triacylglycerol metabolism (Ghatak and Panchal, 2012). The accumulation of plasma lipids by this detergent appears to be especially due to the inhibition of lipoprotein lipase activity (Scharwey et al., 2013).

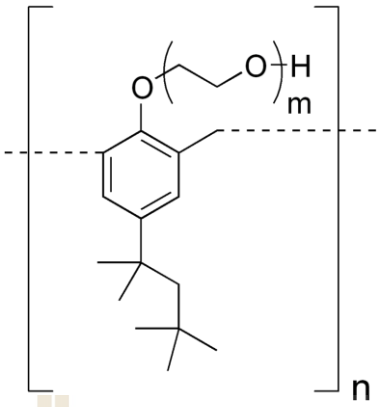

Figure 8 Chemical Structure of Tyloxapol (Kim et al., 2015).

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CHAPTER III

MATERIALS AND METHODS

3.1 Materials

3.1.1 Animals preparation

Maternal rats were bred at the animal unit of Suranaree University of Technology and maintained at constant humidity (60 ± 5%), temperature (24 ± 1 ^{o}C), and light cycle (06.00-18.00 h). Maternal rats were fed normal rat chow and reverse osmosis water (RO) ad libitum. Maternal rats were divided into two groups: the first group is non-dyslipidemia rats and another group is dyslipidemia rats. Maternal dyslipidemia rats were injected with Triton WR-1339 (400 mg/ 2.5 ml. / kg, i.p.) every 3 days over a 4-week period (Huterer et al., 1975; Zarzecki et al., 2014). The serum lipid profile was confirmed which blood sampling from the lateral tail vein in the rat (Lee and Goosens, 2015). Then, these animals were subjected to a mating procedure. After pregnancy, all maternal non-dyslipidemia and maternal dyslipidemia rats were divided into a treat with RO and 3% taurine in RO water until their offspring weaning. After weaning, all male rat offspring were treated with normal diet and RO water until the end of an experiment. After weaning, male rat offspring were fed with the normal rat chow and RO water ad libitum throughout the experiment. All experimental procedures were preapproved by the Universities Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health. At 4 weeks of age of all male rats offspring in each group were divided into non-exercise and exercise

group. In exercise groups were forced exercise for 12 weeks. At 16 weeks of age, all male rat offspring in each group was started to measure under Nembutal anesthesia (30 mg/kg, i.p), then was implanted with femoral arterial and venous catheters. And then arterial pressure pulses was continuously recorded (Power Lab) in an unconscious condition before and during infusion of phenylephrine (increased arterial pressure) or sodium nitroprusside (decreased arterial pressure), respectively. At the end of the experiment, fasting blood samples was collected arterial blood samples was obtained for BUN, creatinine, and leptin levels, lipid profile. This study design for 8 groups, 7 rats per group amount total 56 rats (Charan and Kantharia, 2013).

Group 1: Adult male offspring from maternal non-dyslipidemia were fed with RO water (Control group; C).

Group 2: Adult male offspring from maternal non-dyslipidemia were treated with 3% taurine in RO water (Taurine group; T).

Group 3: Adult male offspring from maternal non-dyslipidemia and force to exercise (Exercise group; Ex).

Group 4: Adult male offspring from maternal non-dyslipidemia rats were treated with 3% taurine in RO water and force to exercise (Taurine with Exercise group; TEx).

Group 5: Adult male offspring from maternal dyslipidemia rats (Dyslipidemia group; D).

Group 6: offspring from maternal dyslipidemia rats were treated with 3% taurine in RO water (Dyslipidemia and Taurine group; DT).

Group 7: Adult male offspring from maternal dyslipidemia rats were fed with RO and force to exercise (Dyslipidemia with Exercise group; DEx).

Group 8: Adult male offspring from maternal dyslipidemia rats were fed were treated with 3% taurine in RO water and force to exercise (Dyslipidemia and Taurine with Exercise Group; DTEx).

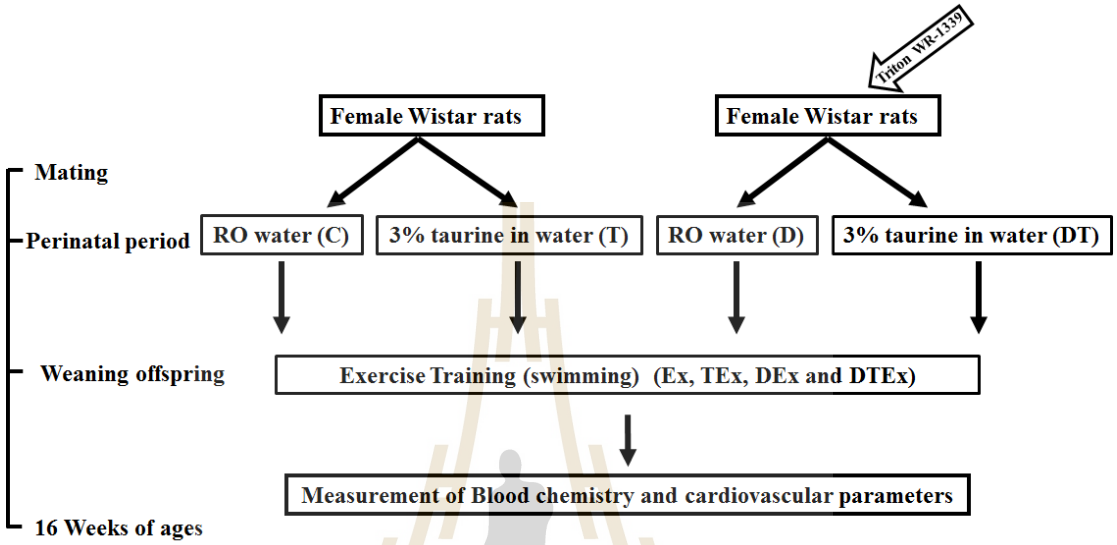

Figure 9 Summary diagram of experiment design.

3.1.2 Exercise Training Protocol

At 4 weeks of age, rats were transported to a treatment room, the exercise groups were forced to swim in a cylindrical tank with a diameter and height of 60 and 100 cm, respectively, in water at a depth of 30–45 cm. Water temperature was monitored and maintained at 36 °C. Initially, rats were forced to swim 15 minute per day (5 days/week). Thereafter, rats were swimming 1 hour/day, 3 day/week, for an additional period of 11 weeks. After weeks 12 of exercise, exercised rats were sacrificed 48 hours after the last bout of exercise (Flores et al., 2006).

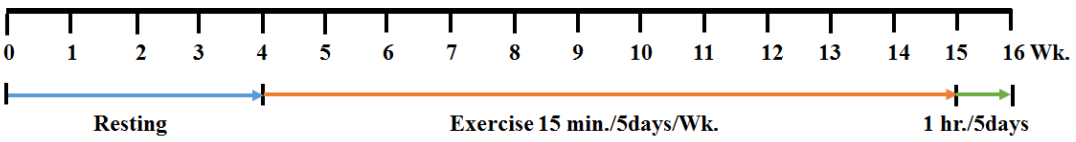

Figure 10 Experimental sequence of the physical exercise program (swimming).

3.1.3 Experimental procedure

At 16 weeks of age, all rats were anesthetized with Nembutal (30 mg/kg, i.p), implantation with femoral arterial and venous catheters, and arterial pressure and heart rate continuously recorded by Power Lab (Pty ADInstrument Ltd., Lab Chart 5, Australia) (Parasuraman and Raveendran, 2012), After baseline data recording, a baroreflex sensitivity control of heart rate was measured by an intravenous infusion of phenylephrine (to increase arterial pressure) and sodium nitroprusside (to decrease arterial pressure). Then, blood samples were collected for blood chemistry measuring blood urea nitrogen (BUN), Creatinine (Cr), and blood leptin level, and lipid profile. Retroperitoneal adipocytes were collected for study histological photograph and sizes. Finally, all rats were a sacrifice by a high dose of anesthesia and heart and kidney weights were collected.

3.2 Methods

3.2.1 Experimental techniques

Rats was anesthetized with Nembutal (30 mg/kg, i.p). After hair shaving, the femoral sheath was exposed through skin incision. The femoral nerve, artery, and vein was then isolated from the connective tissues by arterial forceps. Both femoral artery and vein were inserted with PE-10 fused to PE-50 tubes containing 0.9% NaCl and heparin (20 units/ml) into blood vessels about 2-3 centimeters for monitoring arterial pressure and intravenous infusion, respectively (Parasuraman and Raveendran, 2012).

Figure 11 The arterial catheter (PE-10 fused to PE-50 tubes).

Figure 12 Cannulation of femoral vein and artery.

3.2.2 Determination of mean arterial pressure and heart rate

Mean arterial pressure and heart rate was offline analyzed from the record arterial pressure using the Lab Chart software version 5 About 20 min length of continuous tracing was used to average the baseline data and at least a minute length for others.

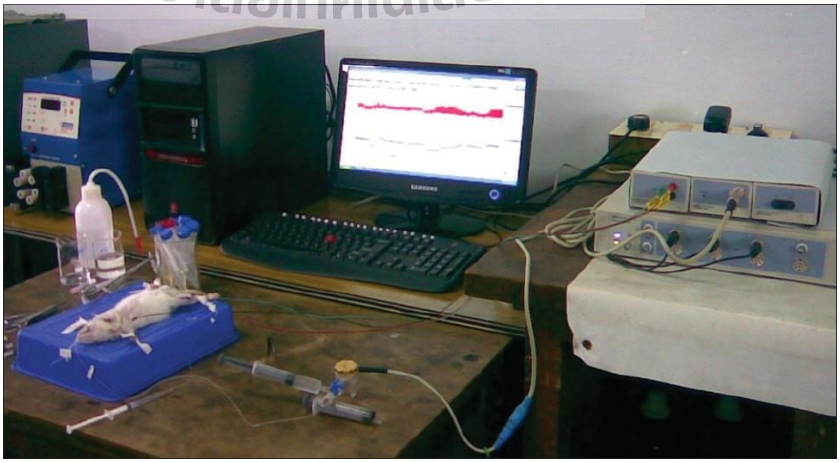

Figure 13 Blood pressure measurement by Power Lab.

3.2.3 Determination of baroreflex sensitivity

After catheterization, all adult male rat offspring was tracheotomized and tracheal tube insertion in a supine position, femoral arterial and venous catheters was flushed with heparinized saline. The arterial catheter was connected to a pressure transducer and PowerLab system to record arterial pressure and the venous one for fluid and drug injection as mentioned earlier. Body temperature was controlled the heating lamp over the animal.

Then, the arterial catheter was connected to a pressure transducer that connected to the PowerLab for continuous recording of the arterial pulse. The venous catheter was connected to syringe pump for saline and drug administration. After 30 minutes resting, phenylephrine, a specific alpha-adrenergic agonist (100 mg/ml in saline) was intravenously infused at a rate of 0.02 ml/min for 2 minutes or until mean arterial pressure increased about 20-30 mm Hg. The animal was allowed to rest until arterial pressure returned to baseline (20-30 minutes). Then, sodium nitroprusside (25 mg/ml in saline) was similarly infused until the mean arterial pressure down to 20-30 mm Hg. Baroreflex sensitivity during hypertensive or hypotensive responses was estimated offline by Chart 5 (PowerLab System, CA, USA). Baroreflex sensitivity control of heart rate was estimated by a slope of the simultaneous changes of heart rate to mean arterial pressure during the drug infusion (Swenne, 2013). The autonomic nervous system activity before and during arterial pressure responses to drug infusion was then estimated by arterial pulse power spectrum analyses.

3.2.4 Determination of blood chemistry assay

At the end experiment. Blood was collected and centrifuged at 3000rpm for 20 minutes and collected supernatant. After that, all serum was kept in frozen -20 ºC until further assay for the serum parameters.

The serum triglyceride (Freiberg et al.), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), glucose, Blood Urea Nitrogen (BUN), Creatinine (Cr), Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic-pyruvic Transaminase (SGPT), was measured by automatic blood analyzer (Transasia Bio-Medicals Ltd, Germany) (Jeon and Kim, 2006).

3.2.5 Determination of Leptin level

The serum samples was measured leptin level by using MOUSE LEPTIN ELISA KIT (96-Well Plate Assay: Cat. # EZML-82K) (Merck KGaA, Darmstadt, Germany)

3.2.5.1 Preparation of sample

Whole bloods were directly drawn into a centrifuge tube that contains no anti-coagulant and kept at room temperature for 30 min. After that, Tube blood clots were centrifuged at 2,000 to 3,000 x g for 15 minutes at 4± 2 ºC. Serum samples were transferred in separate tube and kept at -20 ºC, respectively.

3.2.5.2 Assay procedure

Pre-warm all reagents to room temperature prior to setting up assay. The 10X concentrated HRP wash buffer (50mM Tris buffered saline containing Tween-20) was diluted concentrate 10-fold by mixing the entire content of each bottle of wash buffer with 900 mL de-ionized water (Luo et al.). The required number of strips was

removed from the microtiter assay plate. Unused strips should be resealed in the foil pouch and stored at 2-8 ^{o}C. Assemble strips in an empty plate holder and wash each well 3 times with 300 µL of dilute wash buffer per wash. Wash buffer was decanted and removed the residual amount from all wells by inverting the plate and tapping it smartly onto absorbent towels several times. Do not let wells dry before proceeding to the next step. 30 µL of assay buffer (0.05 M phosphosaline pH 7.4, 0.025M EDTA, 0.08% sodium azide 0.05% Triton X-100 and 1% BSA) was added to each of the background, standard and leptin in QC buffer (QC1 and QC2) wells and 40 µL of assay buffer was added to sample wells follow by 10 µl Rat/Mouse matrix solution (matrix containing 0.08% Sodium Azide) to the background, standard and QC1 and QC2 wells. After that, 10 µl of Mouse Leptin standards was added in duplicate in the order of ascending concentration to the appropriate wells. Next, 10 µl of duplicate was added to the appropriate wells. After that, 10 µl QC1 and 10 µl QC2 were added to the appropriate wells, respectively. Next, 10 µl of samples were added of the unknown samples in duplicates to remaining wells follow by 50 µl of Antiserum solution. The plate was covered with plate sealer and incubated at room temperature for 2 hours on an orbital microtiter plate shaker set to rotate at moderate speed, about 400 to 500 rpm. After that, plate sealer was removed and decanted solutions from the plate. Tap as before to removed residual solutions in well. Wells were washed 3 times with diluted wash buffer, 300 µL per well per wash. Decant and tap after each wash to removed residual buffer. 100 µL of Rat/Mouse Leptin Detection Antibody Solution (Pre-titered streptavidin-horseradish peroxidase conjugate in buffer) was added to each well. Plate was covered with sealer and incubated with moderate shaking at room temperature for 30 min on the microtiter plate shaker. After that, sealer was removed and decant

solutions was removed from the plate and tap plate to the residual fluid. Next, wells were washed 3 times with diluted Wash Buffer, 300 µl per well per wash. Decant and tap after each wash to remove residual buffer. 100 µl of Enzyme Solution was added (3, 3', 5, 5'- tetramethylbenzidine in buffer) to each well, plate with sealer was removed and shake in the plate shaker for approximately 5 to 20 mins. Blue color should be formed in wells of Leptin Standards with intensity proportional to increasing concentrations of Leptin. Next, Sealer was removed and added 100 µl stop solution (0.3M HCl) and shake plate by hand to ensure complete mixing of solution in all wells. The blue color should turn into yellow after acidification. Finally, the bottom of the microtiter plate was wiped to remove any residue prior to reading on plate reader. Read absorbance at 450 nm and 590 nm in a plate reader within 5 minutes and ensure that there are no air bubbles in any well. The difference of absorbance units was recorded (Hoggard et al., 1997; Price et al., 2012).

3.2.6 Determination of AT1 receptor expression

The heart, and kidney was separated and detected AT1 receptor expression by western blot (Benicky et al., 2012).

Preparation of sample. Heart and kidney were fixed with liquid nitrogen and kept at -20 ^{o}C and then organ was kept in cool (dry ice) and prepared for homogenization by a breakdown organ to small size. Fix solution was prepared for homogenize organ by phosphatase inhibitor (cocktail 1:100, 100mM NaF 1:100, 100mM NaV_2O_5 1:100, 500mM ß-glycol phosphate 1:100 and RIPA (50mM Tris-base pH 8.0, 150 mM NaCl pH 8.0, 0.5% DOC, 1% NP-40, 0.1% SDS). Next, phosphatase solution was put into a test tube and put all sample break down into same tube were homogenized. Next, a sample was kept in cool. 30 minutes later, homogenize sample

was transferred to new microtube and centrifuged at 12,000 g for 20 minutes and then supernatant was transferred onto new microtube and 2-5 µl of supernatant was separated for measuring spectrum absorbent by microplate reader for calculating the concentration of protein in supernatant and how to know the quality of protein to in the running gel. After measuring absorbent, all sample have calculated a concentration of protein. Next, calculation protein was removed to new microtube and mixed with RIPA (50mM Tris-base pH 8.0, 150 mM NaCl pH 8.0, 0.5% DOC, 1% NP-40, 0.1% SDS) and mixed with dye (1:5) by vortex. Finally, all sample was boiled by heat for 10 minutes and kept cool down, respectively.

Preparation of gel for running. Lower gel: 10% Persulfate was prepared (Ammonium Persulfate 30 mg, H_2O 270 µl). Next, solution was mixed for preparing 12% gel (DDW 4.3 ml, 40% acrylamide 3.0 ml, Lower buffer 2.6 ml (1.5M Tris base pH 8.8 18.16 g, 0.4% SDS 0.4 g, DDW 100 ml), Persulfate 0.20 ml, TEMED 0.004 mL) total volume 100 ml and then lower gel was loaded into block and isopropanol was loaded into the same block (get rid of bubble) and waited for 20 minutes for stronger gel. A gel was rinsed by DW for 3 times after gel stronger. After that, 5% stacking gel was prepared (upper gel) (DDW 3.1 ml, 40% acrylamide 0.62 ml, Upper buffer 1.26 ml (0.5 M Tris base pH 8.8 6.055 g, 0.4% SDS 0.4 g, DDW 100 ml), Persulfate 50 µl,) total volume 5 ml. Next, a stronger gel was rinsed by DW and an upper gel was loaded into the same gel for upper gel. The comb was put into the upper gel and wait for until the upper gel strong. Finally, a sample was loaded into well (marker was loaded into the first and the last well 5 µl each well). The block was closed and opened the electricity (100 V).

Preparation of transfer AT1 process. Sponge, filtration paper, transfer paper (PVDF) were stained in transfer buffer (Glycine 14.4 g, Trizma base 3.03 g, DW 800 ml, Methanol 200 ml). A sandwich was prepared for each gel from bottom to top consist of a black cassette, sponge, filter paper, gel, membrane paper (PVDF), sponge and white cassette, respectively. The sandwich was placed into the black/red holder (black cassette facing the black side of the container). A container was filled with transfer buffer and ice pack and then switch on run transfer at 100 V for 1 hour. Next, milk blocking solution was prepared (150 ml/membrane: PBS pH 7.4 150 ml, non-fat dry milk 7.5 g, 0.1% Tween 150 µl) and mixed in a beaker with stirring bar. At the time to finish, ice pack, transfer buffer, cassette were removed, and the membrane paper was taken to stain in Ponceau stain for 1 minute. Next, the stain was removed and rinsed with DW several times. After that, the membrane was cut into the smaller size and put the cut membrane into a rectangular plastic container and 10 ml milk blocking solution was added to it. The milk blocking solution was changed every 15 minutes for 1 hour. The container was put on the rocker (speed level 4) then milk was discarded. Next, an antibody was added (Rabbit Anti-AT_1 receptor affinity purified polyclonal antibody: 1:500, AB15552-50UL, Millipore, USA) into milk solution and then applied to the membrane and incubated at 4 ^{o}C overnight. Next, milk was discarded and changed the milk solution every 15 minutes for 1 hour and then secondary antibody was added (a goat anti-rabbit IgG, Peroxidase conjugated: 1:5,000, AP132P, Millipore, USA) into milk solution and incubated at room temperature for 1 hour on a rocker (speed level 2). Next, Transfer membrane was washed with milk solution every 15 minutes for 45 minutes followed by TBS (25mM Tris pH 7.5, 150mM NaCl) every 15 minutes for 30 minutes. Chemiluminescent reagent 1X ECL reagent was prepared (12630, Cell

Signaling Technology, USA) by diluting one part 2X Reagent A and part 2X Reagent B(for 10 ml, add 5 ml Reagent A and 5 ml Reagent B) and mixed well. TBS solution was discarded and chemiluminescent reagent was dropped into transfer membrane for 1 minute and kept membrane paper to develop box and took a photo.

Preparing of transfer actin process. The same transfer membrane was put into a rectangular plastic container and 10 ml of milk blocking solution was added to it. The milk blocking solution was changed every 15 minutes for 1 hour. The container was put on the rocker (speed level 4)[t] and then discarded milk. Next, Anti-Actin, clone 4 was added (Monoclonal: 1:500, MAB1501, Millipore, USA) with milk blocking solution and incubated at room temperature for 2 hours on a rocker (speed level 2) Next, milk was discarded and transfer membrane was washed for 3 times with. TBS (25mM Tris pH 7.5, 150mM NaCl) for 3-5 minutes each wash. Next, The transfer membrane was incubated with secondary antibody (A goat anti-mouse IgG (H+L) HRP conjugated, 1:5,000: AP124P, Millipore, USA) in TBS with milk solution for 60 minutes at room temperature and the transfer membrane was washed 3 times in TBS for 3-5 minutes each wash. Finally, the chemiluminescent reagent was used for detection band of actin. Analysis of intensities of AT1 expression was conducted using image J software. The experiment was repeated using tissue from 3 different individuals. The intensities were shown as mean ± S.D. The means among the group were compared using one-way analysis of variance (ANOVA), Followed by a Duncan's Multiple Range test. The probability value less than 0.05 ($P \leq 0.05$) was used to indicate a significant difference.

3.2.7 Determination of histology in retroperitoneal adipocytes tissue

Histological photograph of adipose tissue was analyzed based on the paraffin method using a light microscope. Fresh tissues were fixed immediately in 4% paraformaldehyde solution for 6-12 hours and then fixed tissue was washed under running water. After being dehydrated through different grades of alcohol, the tissues were embedded in paraffin block at 60 °C. Eight μm sections were cut and mounted on glass slides coated with an egg albumin and then the paraffin was removed with xylene and alcohol. The glass slides were stained with hematoxylin and eosin. After being dehydrated and cleared by alcohol and xylene, the glass slides were mounted in Canada Balsam. Photomicrographs were taken with a Zeiss Axiolab light microscope equipped with a Nikon Microflex HFX microscope camera (20X). The size of retroperitoneal adipocyte was calculated by stochastic 10 cells with Image-Pro Plus 6.0 (Media Cybernetics, Maryland, USA) and the results were expressed as pixels per retroperitoneal adipocyte.

3.3 Data analysis

1. Cardiovascular parameter: blood pressure and heart rate. These data was recorded and analysed by Power lab and Lab chart program.

2. The baroreflex sensitivity (ΔHR/ΔBP), as measured by the changes in heart rate (ΔHR) and mean blood pressure (ΔBP)

Baroreflex sensitivity was measured by the IV injection of phenylephrine and sodium nitroprusside as described previously. The changes in heart rate (ΔHR) and mean blood pressure (ΔBP) after the injection was measured.

The baroreflex sensitivity was then calculated as the change in heart rate divided by the change in blood pressure (ΔHR/ΔBP).

3.4 Statistical analysis

All data are expressed as mean ± SEM. Statistical comparisons among the eight groups were performed by using one-way ANOVA followed by the *post hoc* Duncan's Multiple Range test (StatMost32 version 3.6, Dataxiom, CA, USA). The probability value less than 0.05 ($P \leq 0.05$) was used to indicate a significant difference.

3.5 References

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CHAPTER IV

RESULTS

4.1 Body weights and organ weight in their male rat offspring.

At 16-18 weeks of age, in adult male offspring from maternal dyslipidemia rats group (Dyslipidemia group; D), body weight (BW) was significantly increased compared to other groups. And BW in adult male offspring from maternal non-dyslipidemia was fed with RO water group (Control group; C) was shown no significant differences when compared with adult male offspring from maternal non-dyslipidemia was treated with 3% taurine in RO water group (Taurine group; T). However, when compared with adult male offspring from maternal dyslipidemia rats were treated with 3% taurine in RO water (Dyslipidemia and Taurine group; DT) and in adult male offspring from maternal dyslipidemia rats were fed were treated with 3% taurine in RO water and forced to exercise group (Dyslipidemia and Taurine with Exercise group; DTEx) groups shown significantly increase (367.14 ± 19.67 versus 408.14 ± 11.77 and 418.86 ± 3.29, $P \leq 0.05$, in Table 4). and when compared with adult male offspring from maternal non-dyslipidemia rats were treated with 3% taurine in RO water and forced to exercise group (Taurine with Exercise group; TEx) found that BW was shown significantly decrease (367.14 ± 19.67 versus 314 ± 1.91, $P \leq 0.05$, in Table 4).

In addition, when adult male offspring from maternal non-dyslipidemia and force to exercise group (Exercise group; Ex) found that BW has shown a significant decrease when compared with control group (C) (316.29 ± 4.46 versus 359.14 ± 13.18,

P≤0.05, in Table 4). In contrast, when treated with 3% taurine in RO water and forced to exercise group (Taurine with Exercise group; TEx) was shown no significant differences (P≤0.05, in Table 4). While In adult male offspring from maternal dyslipidemia rats were fed with RO water and forced to exercise group (Dyslipidemia with Exercise group; DEx) and in dyslipidemia and taurine with exercise group (DTEx) shown significantly increase (417.71 ± 5.56 and 418.86 ± 3.29 versus 316.29 ± 4.46, P≤0.05, in Table 4).

From this experiments show that the effect of dyslipidemia disease in groups of adult male rat offspring from maternal dyslipidemia treated with taurine on a perinatal-neonatal period (DT) and adult male rat offspring from maternal dyslipidemia force to exercise and treated with taurine supplementation group (DTEx) can increase BW. In contrast, taurine supplementation with forced to exercise from maternal non-dyslipidemia (TEx) was shown a decrease in BW. While adult male rat offspring from maternal non-dyslipidemia forced to exercise alone (Ex) can increase BW than the adult male rat offspring from maternal dyslipidemia both in the forced to exercise (DEx) and exercise treated with taurine supplementation group (DTEx).

The absolute weights of the kidney in a group that treated with 3% taurine in RO water (Taurine group; T) were shown no significant differences when compared with control (C), taurine with exercise group (TEx) and adult male offspring from maternal dyslipidemia rats group (Dyslipidemia Group; D). And in dyslipidemia and taurine group (DT) was shown a significant decrease (1.26 ± 0.05 versus 1.18 ± 0.03, P≤0.05, in Table 4). In contrast, in dyslipidemia and taurine with exercise group (DTEx) and dyslipidemia with exercise group (DEx) was shown a significant increase in this groups (1.26 ± 0.05 versus 1.42 ± 0.03, and 1.43 ± 0.03, P≤0.05, in Table 4).

In addition, when forced to exercise (exercise group; Ex) has shown no significant differences when compared with control (C) and taurine with exercise groups (TEx) In contrast, The data of this experiment showed a significant increase when compared with dyslipidemia and taurine with exercise group (DTEx) and dyslipidemia with exercise group (DEx) (1.30 ± 0.05 versus 1.42 ± 0.03, and 1.43 ± 0.03, $P \leq 0.05$, in Table 4).

From this experiments show that the effect of taurine supplementation and exercise on a perinatal-neonatal period in adult male rat offspring from maternal dyslipidemia both in forced to exercise (DEx) and non-exercise group (DTEx) can increase KW. In contrast, the effect of taurine supplementation in adult male rat offspring from maternal dyslipidemia (DT) was shown a decrease in KW.

The absolute weights of the heart (HW) in a group that treated with 3% taurine in RO water (Taurine group; T) were shown significantly increase compared to control (C) and other that treated with 3% taurine in RO water groups (DT, TEx, and DTEx). In contrast, when forced to exercise (exercise group; Ex) has shown no significant differences when compared with other groups that forced to exercise (TEx, DEx, and DTEx). From this experiments show that the effect of taurine supplementation can increase HW.

Moreover, a ratio of kidney weight to body weight (KW/BW) and Heart weight to body weight (HW/BW) in dyslipidemia group (D) was significantly decreased compared to other groups. In contrast, the group that treated with 3% taurine in RO water (Taurine group; T) was shown significantly increase compared to control (C). While significantly decrease compared to other that treated with 3% taurine in RO water groups (DT, TEx, and DTEx). In addition, when forced to exercise (exercise group; Ex)

has shown a significant decrease compared to control (C) and other that treated with 3% taurine in RO water groups (DT, TEx, and DTEx). From this experiments show that the effect of exercise can decrease KW/BW and HW/BW.

4.2 Blood Chemistry in their male rat offspring.

The serum leptin levels was measured enzyme-linked immunosorbent assay (Elisa) were no significant differences in this studies ($P \leq 0.05$, in Table 4).

The concentrations of serum Total cholesterol (TC), and low-density lipoprotein (LDL) in the group that treated with 3% taurine in RO water (Taurine group; T) and when forced to exercise (exercise group; Ex) were no significant differences compared with their control ($P \leq 0.05$, in Table 5). That means both taurine and exercise does not affect these parameters. While TC, triglyceride (TG) and LDL in dyslipidemia group (D) was significantly increased compared to other groups. This implies that as a result of the disease. In addition, High-density lipoprotein (HDL) showed in exercise groups were significantly increased compared to non-exercise groups. Exercise alone has effects of increasing the concentration of HDL ($P \leq 0.05$, in Table 6).

Blood urea nitrogen (BUN), and Creatinine (Cr) in the group that treated with 3% taurine in RO water (Taurine group; T) and when forced to exercise (exercise group; Ex) were no significant differences compared with their control ($P \leq 0.05$, in Table 6). That means both taurine and exercise does not affect these parameters. While serum glutamic oxaloacetic transaminase (SGOT) was no significant difference in all treatment ($P \leq 0.05$, in Table 6). Serum glutamic pyruvic transaminase (SGPT) in the group that treated with 3% taurine in RO water (Taurine group; T) was shown significantly increase compared to taurine with exercise group (TEx) and dyslipidemia

and taurine with exercise group (DTEx) ($P \leq 0.05$, in Table 6). The present study indicates that taurine can be abolished the adverse effects of maternal dyslipidemia on protecting muscle and liver damage by reduced SGPT in exercise groups.

Table 3 Body weights (BW), Kidney weight (KW), Heart weight (HW) and Leptin in their male rat offspring.

Treatment	Body weight; BW (g)	Kidney weight; KW (g)	Heart weight; HW (g)	KW/BW (%)	HW/BW (%)	Leptin (ng/mL)
C	359.14±13.18^{c}	1.31±0.13^{b}	1.34±0.07^{b}	0.37±0.04^{b}	0.37±0.02^{b}	6.97±1.40^{a}
T	367.14±19.67^{c}	1.26±0.05^{bc}	1.29±0.04^{c}	0.34±0.02^{c}	0.35±0.02^{c}	6.61±1.41^{a}
D	507.14±10.11^{a}	1.24±0.04^{cd}	1.41±0.03^{a}	0.24±0.01^{e}	0.28±0.01^{e}	6.43±1.38^{a}
DT	408.14±11.77^{b}	1.18±0.03^{d}	1.36±0.05^{b}	0.29±0.01^{d}	0.33±0.01^{d}	6.69±0.95^{a}
Ex	316.29±4.46^{d}	1.30±0.05^{bc}	1.40±0.01^{a}	0.41±0.02^{a}	0.44±0.01^{a}	6.45±0.79^{a}
TEx	314±1.91^{d}	1.24±0.04^{bc}	1.41±0.03^{a}	0.40±0.01^{a}	0.45±0.01^{a}	6.64±0.76^{a}
DEx	417.71±5.56^{b}	1.42±0.03^{a}	1.41±0.02^{a}	0.34±0.01^{c}	0.34±0.01^{cd}	6.33±0.62^{a}
DTEx	418.86±3.29^{b}	1.43±0.03^{a}	1.42±0.03^{a}	0.34±0.01^{c}	0.34±0.01^{cd}	6.35±1.28^{a}

Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$). (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

Table 4 Total cholesterol (CHO), plasma triglyceride (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) in their male rat offspring.

Treatment	CHO (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
C	80.57±13.39^{b}	122.14±15.37^{ab}	62.86±3.29^{c}	102.43±16.60^{b}
T	80.71±7.13^{b}	123.00±11.73^{ab}	60.00±4.76^{c}	100.14±16.24^{b}
D	95.00±6.73^{a}	131.43±14.99^{a}	60.71±3.99^{c}	137.00±18.39^{a}
DT	81.14±5.84^{b}	121.00±14.09^{ab}	62.00±4.65^{c}	106.71±12.92^{b}
Ex	85±7.90^{ab}	123.43±8.68^{ab}	75.43±6.53^{a}	102±6.08^{b}
TEx	86.43±7.44^{ab}	118.14±4.95^{ab}	75.14±6.44^{a}	107.86±6.12^{b}
DEx	87.71±11.21^{ab}	112±7.75^{b}	68.71±6.55^{b}	99.29±7.80^{b}
DTEx	90.29±6.52^{ab}	112.57±5.97^{b}	69.14±4.47^{b}	102.71±8.34^{b}

Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$). (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

Table 5 Blood urea nitrogen (BUN), Creatinine (Cr), Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT) in their male rat offspring.

Treatment	BUN (mg/dL)	Cr (mg/dL)	SGOT (U/L)	SGPT (U/L)
C	25.29±1.50^{ab}	0.46±0.13^{a}	137.86±13.64^{a}	34.43±2.57^{c}
T	24.43±1.72^{abc}	0.41±0.09^{ab}	134.86±12.42^{a}	35.14±1.95^{c}
D	23.71±2.81^{bc}	0.40±0.08^{ab}	135.71±17.35^{a}	35.71±2.14^{c}
DT	24.86±1.77^{ab}	0.36±0.10^{ab}	131.57±11.73^{a}	35.29±2.50^{c}
Ex	25.71±1.98^{ab}	0.47±0.11^{a}	136.86±11.84^{a}	52.71±7.02^{a}
TEx	26.71±1.11^{a}	0.37±0.11^{ab}	145.71±10.97^{a}	44±5.89^{b}
DEx	23.86±1.95^{bc}	0.31±0.09^{b}	136±13.07^{a}	46.57±7.02^{b}
DTEx	22.29±2.43^{c}	0.39±0.17^{ab}	133.71±13.02^{a}	45.86±6.96^{b}

Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group (P≤0.05). (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

4.3 Mean arterial pressure in their male rat offspring.

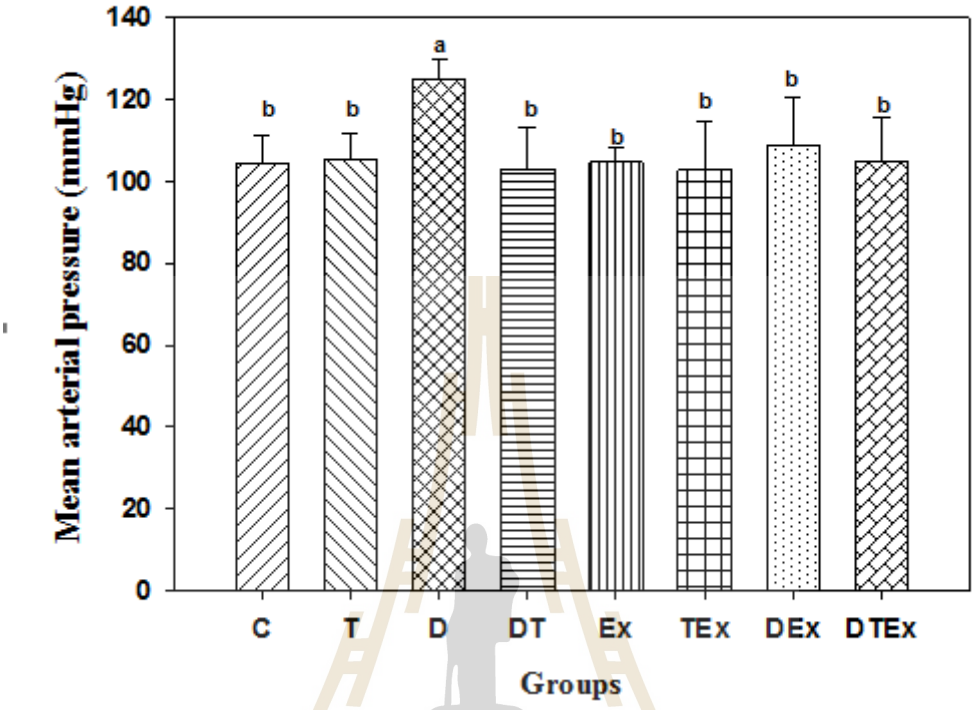

Figure 14 Mean arterial pressure (MAP). All data expressed as means ± SEM. Each treated group was compared one-way ANOVA followed by the *post hoc* Duncan's Multiple Range test. [a,b] Means superscripted with different letters are significantly different at ($P \leq 0.05$). (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

4.4 Heart Rate in their male rat offspring.

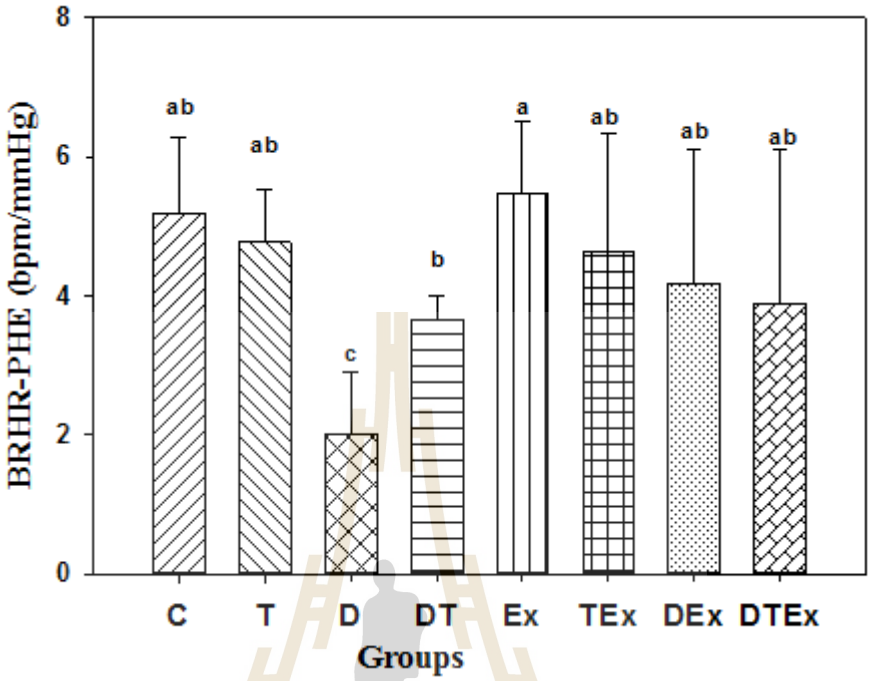

Figure 15 Heart Rate (HR). All data expressed as means ± SEM. Each treated group was compared one-way ANOVA followed by the *post hoc* Duncan's Multiple Range test. [a,b,c,d,e] Means superscripted with different letters are significantly different at ($P \leq 0.05$). (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

4.5 Baroreflex sensitivity in their male rat offspring.

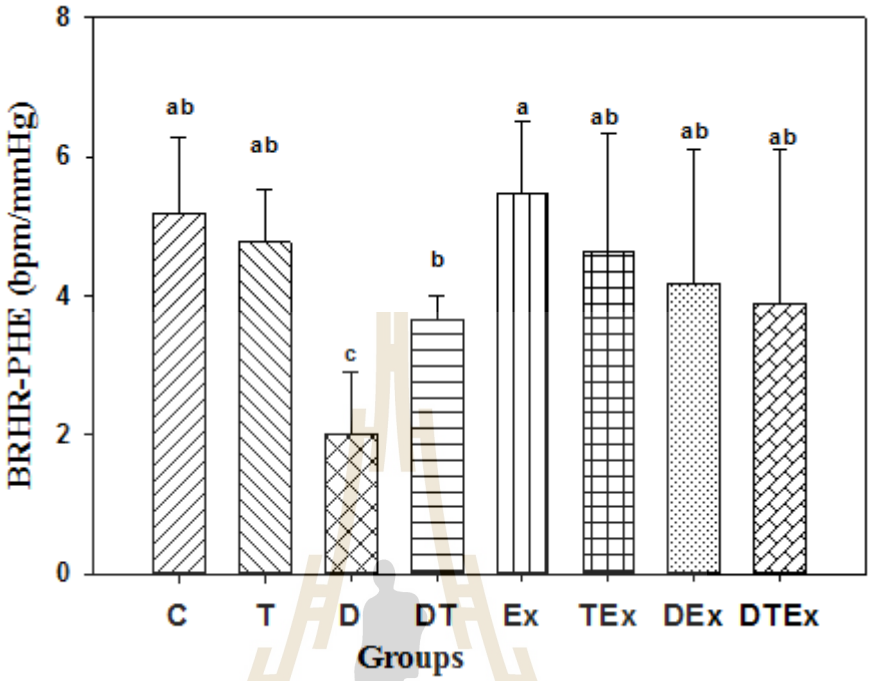

Figure 16 Baroreflex sensitivity of heart rate response to phenylephrine. All data expressed as means ± SEM. Each treated group was compared one-way ANOVA followed by the *post hoc* Duncan's Multiple Range test. ^{a,b,c} Means superscripted with different letters are significantly different at ($P \leq 0.05$). (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

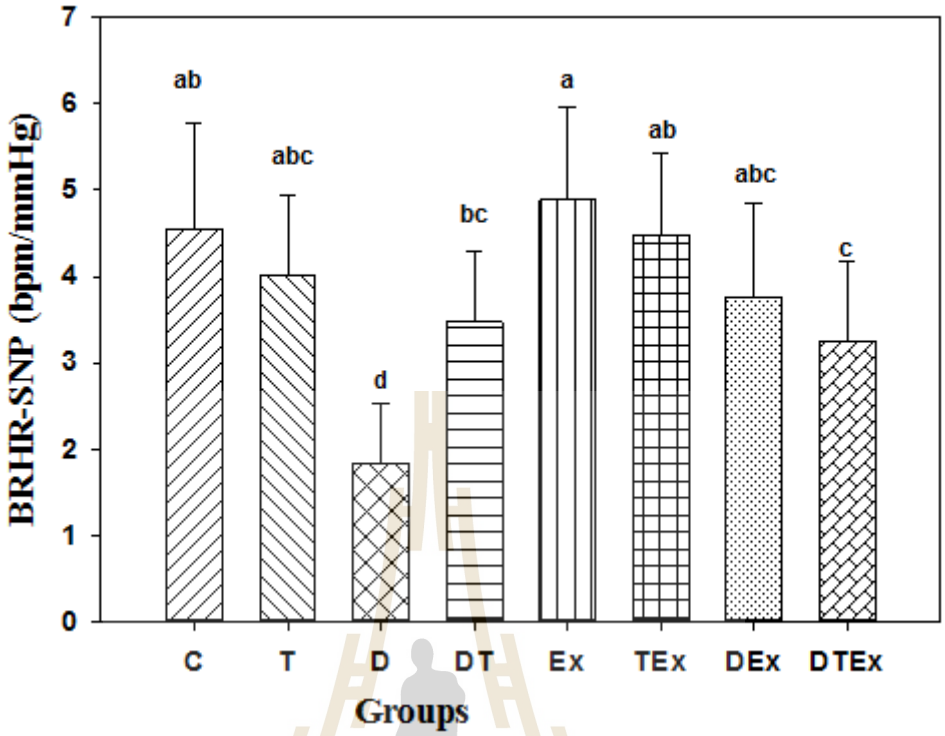

Figure 17 Baroreflex sensitivity of heart rate response to sodium nitroprusside. All data expressed as means ± SEM. Each treated group was compared one-way ANOVA followed by the *post hoc* Duncan's Multiple Range test. [a,b,c] Means superscripted with different letters are significantly different at ($P \leq 0.05$). (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

Mean arterial pressures (MAP) difference increased significantly in offspring from maternal dyslipidemia rats (D) when compared with another group. Taurine supplementation and exercise can maintain mean arterial pressures not to exceed. While heart rates (HR) difference decreased significantly in exercise-groups when compared with non-exercise groups. While heart rates (HR) difference decreased significantly in exercise-groups when compared with non-exercise groups. However, we found that no significant differences in HR were observed in offspring from maternal dyslipidemia (D) and offspring from maternal dyslipidemia rats were fed with 3% taurine in RO water (DT), The baroreflex sensitivity control of heart rate induced by either phenylephrine (PHE) or sodium nitroprusside (SNP) infusion difference was lower than in dyslipidemia group when compared with another group. On the other hand, perinatal taurine supplementation abolished these adverse effects of maternal dyslipidemia without any effect on hemodynamic parameters in the control groups. While Baroreflex sensitivity difference was higher than in exercise groups when compared with non-exercise groups.

4.6 Retroperitoneal adipocytes.

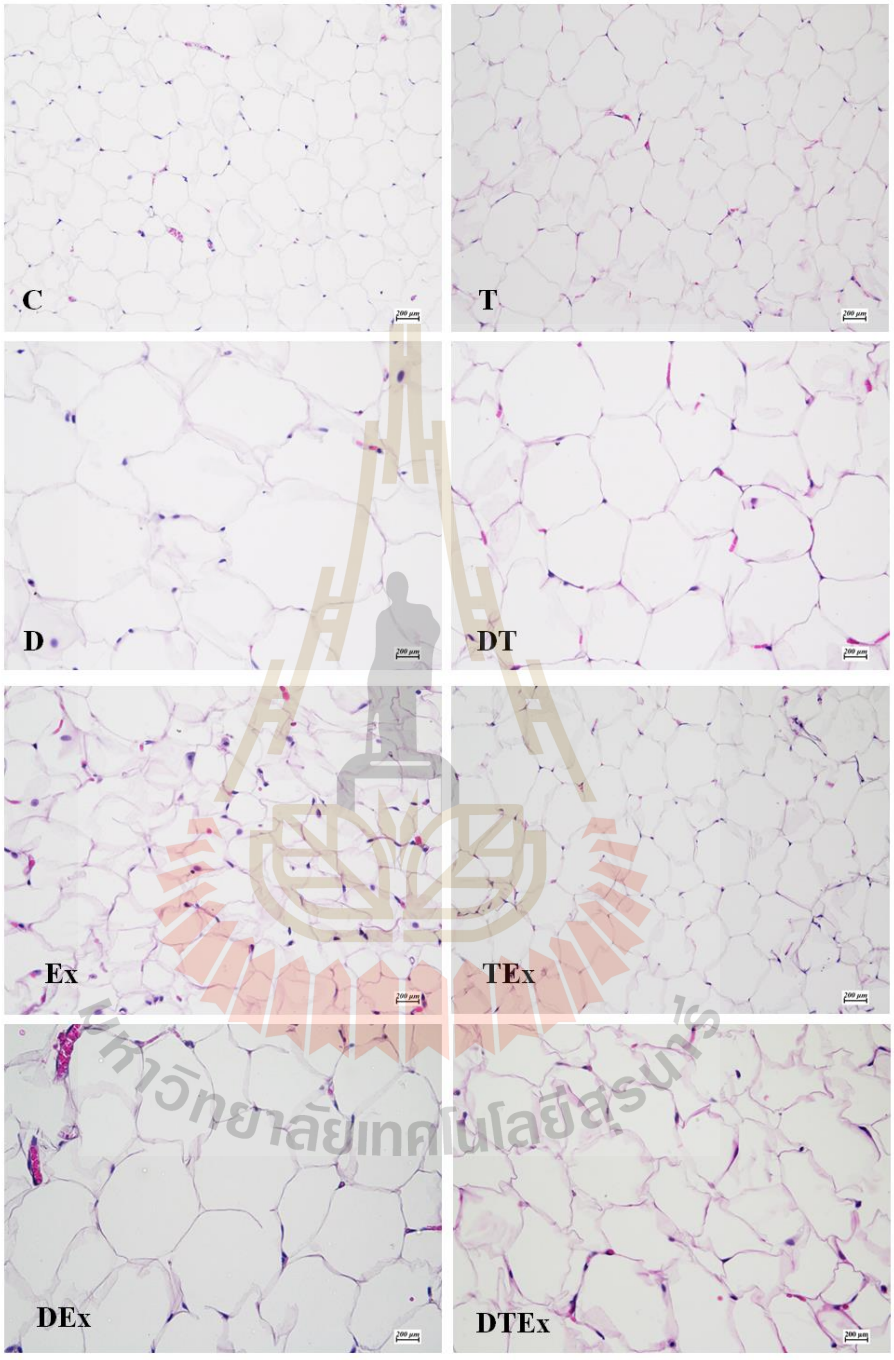

Figure 18 Histological photograph of retroperitoneal adipocytes. Magnification × 200.

4.7 Sizes of retroperitoneal adipocytes in their male rats offspring.

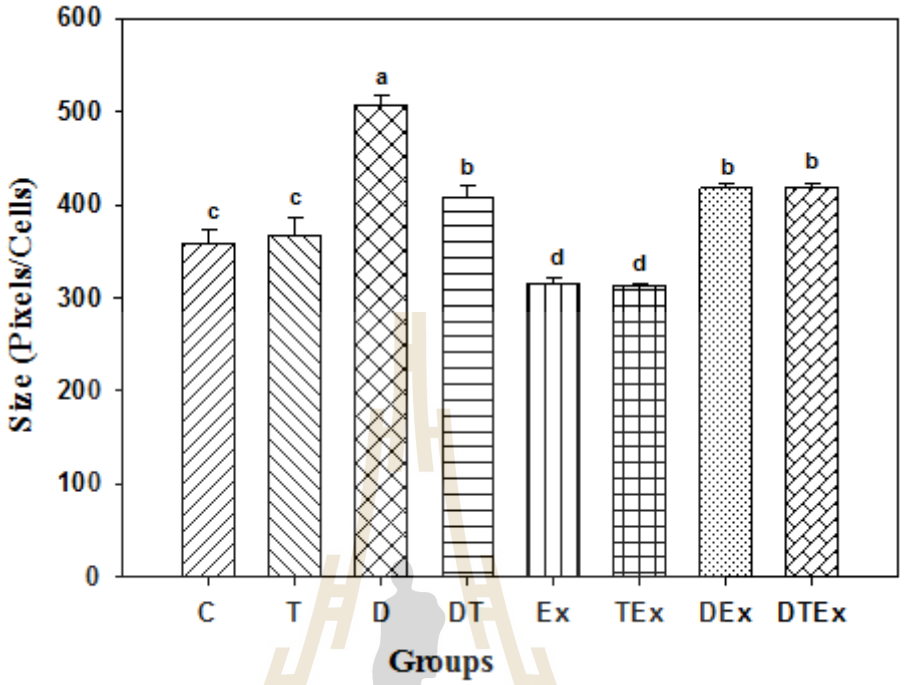

Figure 19 Sizes of retroperitoneal adipocytes. Calculation by stochastic 10 cells by Image-Pro Plus 6.0. Data were presented as mean ± SE. Values with different superscripts are significantly different at P≤0.05 by Duncan's multiple range tests. [a,b,c,d,e] Means superscripted with different letters are significantly different at (P≤0.05). (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

Excessive growth of adipose tissue results in a metabolic syndrome which includes two growth mechanisms: hyperplastic (cell number increase) and hypertrophic

(cell size increase) (Björntorp and Sjöström, 1971). The histological appearance of retroperitoneal adipocytes was a morphological change in dyslipidemia and taurine group (DT) compare to another group. However, this morphological change did not appear in control (C) and taurine (T) groups (Figure 17). The sizes of retroperitoneal adipocytes were significantly increased in dyslipidemia (D) group compared to another group and in exercise (Ex) and taurine with exercise (TEx) groups showed adipocyte size smaller than other groups (Figure 18). These results suggest that exercise alone or with taurine supplementation can inhibit lipid accumulation in retroperitoneal adipocytes tissue.

4.8 The expression of AT1 receptor in kidney.

The relative density of an expression of angiotensin II type 1 (AT1) receptor and actin difference increased significantly in offspring from maternal dyslipidemia rats (D) when compared with another group ($P \leq 0.05$, one way ANOVA, Figure 20).

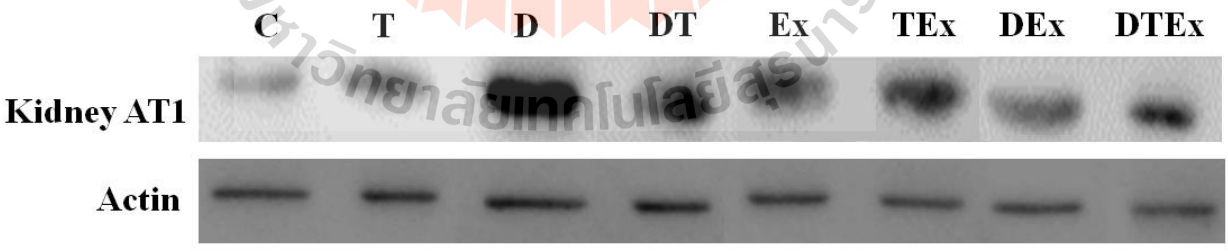

Figure 20 Expression of AT1 receptor in kidney.

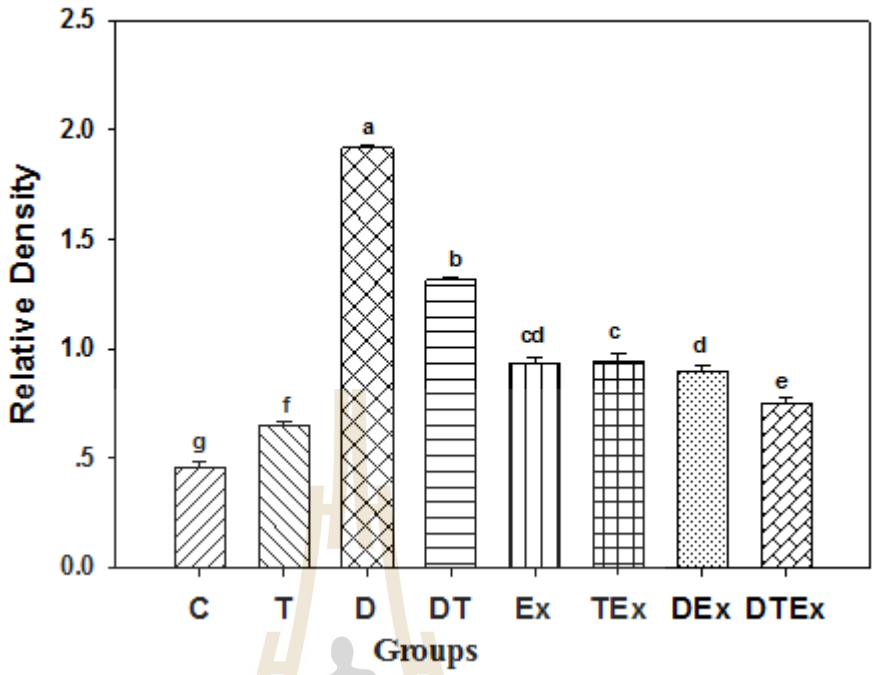

Figure 21 Western blot analysis detected expression of angiotensin II type 1 (AT1) receptor in Kidney. (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

4.9 The expression of AT1 receptor in heart.

The relative density of an expression of angiotensin II type 1 (AT1) receptor and actin difference increased significantly in offspring from maternal dyslipidemia rats (D) when compared with another group ($P \leq 0.05$, one way ANOVA, Figure 22).

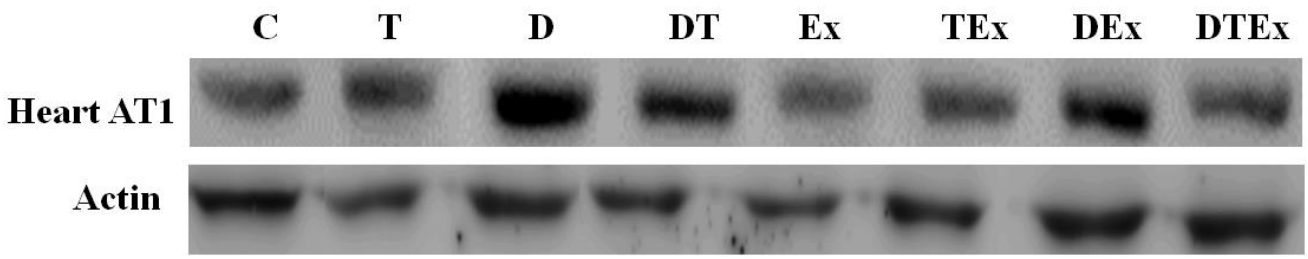

Figure 22 Expression of AT1 receptor in heart.

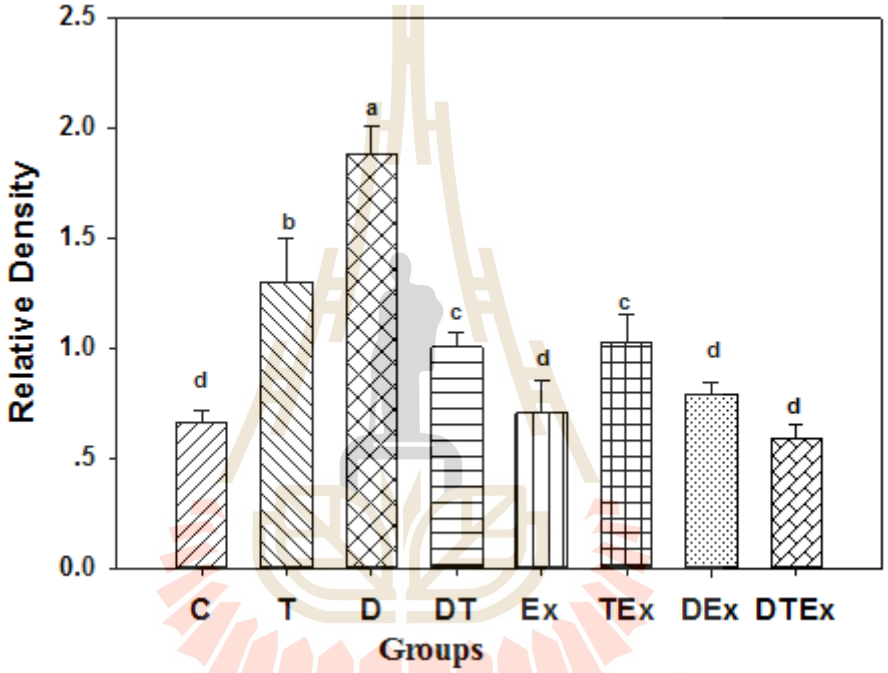

Figure 23 Western blot analysis detected expression of angiotensin II type 1 (AT1) receptor in Heart. (C, Control; T, Taurine; D, offspring from maternal dyslipidemia rats; DT, offspring from maternal dyslipidemia rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-dyslipidemia rats were fed with 3% taurine and exercise; DEx, offspring from maternal dyslipidemia rats were fed with RO and exercise; DTEx, offspring from maternal dyslipidemia rats were fed with 3% taurine and exercise).

4.10 References

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CHAPTER V

DISCUSSION AND CONCLUSION

5.1 Body weights and organ weight in their male rat offspring

The present study, body weight (BW) of their male rats offspring are increased in Dyslipidemia group. Dyslipidemia is commonly seen with excess weight (Grundy et al., 2002). Similarly, in a study from Helvaci and co-worker found that excess weight and dyslipidemia showed highly significant increases in prevalence during passing to the fourth decade of life ($P<0.001$ in all), and interestingly while the prevalence of excess weight was decreasing in the eight decades significantly, the prevalences of dyslipidemia decreased, too ($P<0.05$ in all). So dyslipidemia may be a pioneer sign of a tendency of body weight either to increase or decrease (Helvaci et al., 2008). Similarly, the relationship between the excess weight and hypertension is also described under the heading of the metabolic syndrome, and clinical manifestations of the syndrome include abdominal obesity, dyslipidemia, hypertension, and insulin resistance. In addition to hypertension, the prevalences of high fasting plasma glucose, high serum total cholesterol, and low HDL, and their clustering were all raised with increases in body mass index (BMI) (Zhou et al., 2002). Excess weight leads to both structural and functional abnormalities of many systems of the body, and it is important in medical terms to specify the excess weight not only as one of the risk factors but as “obesity disease”. For example, individuals with excess weight will have an increased circulating blood volume as well as an increased volume of cardiac output, thought to

be the result of increased oxygen demand of the extra body tissue. The prolonged increase in circulating blood volume can lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of hypertension. Similarly, the relationship between the excess weight and hypertension is also described under the heading of the metabolic syndrome, and clinical manifestations of the syndrome include abdominal obesity, dyslipidemia, hypertension, insulin resistance, and pro-inflammatory as well as pro-thrombotic states. In addition to hypertension, the prevalence of high fasting plasma glucose, high serum total cholesterol, and low HDL, and their clustering were all raised with increases in BMI (Zhou et al., 2002). The combination of these cardiovascular risk factors will eventually lead to an increase in left ventricular stroke work with a higher risk of arrhythmias, cardiac failure, or even sudden cardiac death. So the above prospective cohort study showed that the BMI is one of the independent risk factors for stroke and congenital heart disease (CHD) (Zhou et al., 2002). Similarly, the incidences of CHD and stroke, especially ischemic stroke, have increased with an elevated BMI in other studies (Zhou, 2002). Eventually, the risk of death from all causes increases with excess weight in all age groups (Calle et al., 2000).

In this study, found that taurine supplement and/with exercise may act synergistically to decrease BW. The NCEP guidelines recommend dietary modification, exercise and weight control as the foundation of treatment of dyslipidemia (Grundy, 1994). These basic interventions may provide sufficient treatment for up to 90 percent of persons with dyslipidemia according to the NCEP cut points (Yeshurun and Gotto Jr, 1995). A reduction in total cholesterol by 1 percent may decrease a person's risk of developing coronary heart disease by 2 percent

(Investigators, 1992). Reduction of other modifiable risk factors is essential aspects of prevention of coronary heart disease (Ahmed et al., 1998). Patients are more likely to comply with exercise programs that are tailored to meet individual goals, interests, and needs. Most patients benefit from aerobic exercise that targets large muscle groups, performed for 30 minutes four or more times a week (Blake and Triplett, 1995). Shorter, but more frequent, aerobic exercise sessions provide similar benefits. Overweight patients should engage in low-intensity exercise more frequently and for longer durations. During exercise, mechanical work associated with muscle contractions clearly requires energy. As a result of the associated loss of energy as heat during ATP synthesis in the mitochondria and ATP hydrolysis during muscular contraction, the energetic capacity of working muscles is about 25%. (Li et al., 2009). Therefore, physical exercise will increase energy expenditure above the basal energy expenditure. Taurine does not directly cause weight loss in the traditional sense, as it does not increase body's energy expenditure or calorie-burning ability. Additionally, researchers who published a study in the August 2008 edition of Journal of Applied Physiology found that taurine supplementation did not increase fat or calorie burning during exercise (Galloway et al., 2008). While using taurine alone will not produce weight loss, it may help you get the most out of exercise sessions. The previous study found that taurine consumption promoted increased endurance (Yatabe et al., 2009). This can help to exercise longer and burn more calories, which would be beneficial for weight loss.

In this study, kidney weight and heart weight in exercise-groups were increased compared with non-exercise groups. Effect of exercise on kidney weight. In general, exercise training ameliorates renal function by improving metabolic factors such as

plasma lipids, blood glucose, blood pressure, and body weight. It is also known to improve renal histology without altering metabolic factors (Poortmans, 1984). Exercise can increase blood flow and oxygen supply (Tschakovsky and Joyner, 2007) and exercise training alters the vascular reactivity, enhances endothelium-dependent and -independent renal vasodilation (De Moraes et al., 2004). Literature also indicated that nitric oxide can play an alternative role affecting the blood flow (Tschakovsky and Joyner, 2007). In general, exercise training ameliorates renal function by improving metabolic factors such as plasma lipids, blood glucose, blood pressure, and body weight. It is also known to improve renal histology without altering metabolic factors (Ishikawa et al., 2012). Effect of exercise on heart weight. A result of regular exercise is cardiac hypertrophy. Cardiac hypertrophy is where the heart increases in size and blood volume (Tardiff, 2006). This is good for athletes or people who exercise regularly because they can continue with their level of exercise and fitness. This is positive because when cardiac hypertrophy occurs more blood can be pumped around the body which means more energy and oxygen can be transported around the body for use. When we exercise the wall of the left ventricle thickens (chamber size increases) which strengthens the beat of the heart. This means more blood can be pumped through the body, this is because the force of the contraction is stronger. This benefits the athlete because the more blood pumped around the body the more oxygen the athlete receives when exercising.

5.2 Blood chemistry in their male rat offspring

In their male rats offspring that have maternal with dyslipidemia, in this study show data level of leptin in serum unaltered when compared with another group. It is generally known that serum leptin concentration is related to the size of adipose tissue mass in the body (Klein et al., 1996; Maffei et al., 1995). On the other hand, Serum leptin concentration is not only dependent on the size of adipose tissue mass, since fasting decreases leptin concentration without marked changes in the body lipid content. A decrease of 10% in body weight was associated with 53% reduction in serum leptin (Considine et al., 1996). This large change in serum leptin concentration in the presence of a small reduction in adipose tissue mass suggests that leptin secretion is regulated by factors unrelated to adipose tissue mass. One important factor is caloric intake; a reduced energy intake is accompanied by a lower fasting serum insulin concentration, which may alter serum leptin secretion both in experimental animals and in humans (Boden et al., 1996; Trayhurn et al., 1995). The decline in leptin levels could be responsible for the decrease in energy expenditure that is induced by weight loss (Leibel et al., 1995). The decrease of leptin expression and levels in starvation leads to energy conservation by decreasing thyroid hormone-induced thermogenesis and gonadotrophin secretion while at the same time increasing secretion of glucocorticoids that mobilize energy stores (Ahima et al., 1996). This adaptation to fasting seems to require a decline in leptin levels.

In this study, increased levels of total cholesterol (TC), triglycerides (Freiberg et al.), low-density lipoprotein (LDL) and a decreased level of high-density lipoprotein (HDL) in dyslipidemia group. Dyslipidemia is as known as disorder of lipoprotein metabolism. Dyslipidemia is a state of excessive accumulation of one or more of the

major lipids in plasma, as a manifestation of metabolic abnormalities or lipid transport. In clinical, dyslipidemia is expressed as hypercholesterolemia, hypertriglyceridemia, or a combination of both. Fat (also called lipids) is an important component of cell membranes, the nerve sheath that envelopes nerve cells and bile. The 2 major fats in the blood are cholesterol and triglycerides. Fats bind themselves to certain proteins that can follow the bloodstream; this combination of fat and protein is called lipoprotein. Plasma fats are transported within the lipoprotein complex. Metabolic disorders that cause an increase in any type of lipoprotein. The main lipoprotein is Chylomicron, VLDL (very low-density lipoproteins), LDL (low-density lipoprotein) and HDL (high-density lipoprotein). The body regulates lipoprotein levels in a several ways (Xu et al., 2015). For example, reduce the formation of lipoproteins and reduce the number of lipoproteins that enter the blood and increase or decrease the rate of removal of lipoproteins from the blood. Abnormal fat levels in the blood circulation (especially cholesterol) can cause long-term problems (Fesus, 1993). Excessive LDL can precipitate in blood vessel walls that will result in narrowing and hardening of the arteries, or called atherosclerosis (the formation of plaque on blood vessel walls). When this narrowing and hardening is severe enough, there is not enough blood supply to the heart muscle, and there is a pain or chest pain called angina and, if it continues, will result in the death of cardiac muscle tissue called myocardial infarction. If this is widespread, it will lead to a condition called heart failure. If this blockage attacks the blood vessels of the brain, a stroke will occur. This is where cholesterol (especially LDL) plays a negative role in health and should always be controlled. LDL is dangerous so often referred to as bad cholesterol. LDL carries the most cholesterol in the blood. Excessive LDL will cause it to easily adhere to the walls of the blood vessels. LDL will

penetrate the inner walls of blood vessels that can cause the walls of blood vessels to narrow. LDL is a major risk factor for coronary heart disease as well as a major target in treatment. HDL is often also called good cholesterol because it cleans the excess cholesterol from the blood vessel wall to be carried away and thrown in the gallbladder. HDL has less fat content and has a higher density, making it heavier. HDL prevents cholesterol from depositing in the arteries and protects blood vessels from the process of Atherosclerosis (the formation of plaque on blood vessel walls) (Gunstone, 1958). In addition to LDL and HDL, which is important to know also is Triglycerides, which is one type of fat contained in the blood and various organs in the body. Increased levels of triglycerides in the blood can also increase cholesterol levels. A number of factors can affect blood triglyceride levels such as obesity, alcohol consumption, sugar, and fatty foods. High levels of triglycerides (Freiberg et al.) can be controlled with low-carbohydrate diets.

In this study, shows the blood urea nitrogen (BUN) in dyslipidemia group was no significant difference with another group and in Dyslipidemia with Taurine supplement and Exercise (DTEx) group were significantly decreased compared to another group. A study from Foran et al. showed elevated BUN levels 4 hours after exercise as a result of dehydration and decreased renal perfusion (Foran et al., 2003). In this study, showed the opposite results to Foran et al.'s study (Foran et al., 2003) regarding blood urea concentrations. A subject had diminished levels of urea. Urea is a waste product of amino acid catabolism. Consequently, its plasma concentration is directly related to the amount of protein in the diet (Schutz, 2011). This study showed that the observed alterations in blood urea levels were not dependent on a high or low protein diet. Urea is excreted by the kidneys. Urea is filtered by the glomerular

capillaries, and it enters the renal tubule. Approximately half of urea is reabsorbed passively by diffusion, but the remainder is excreted in the urine. Lower blood urea levels suggest increased glomerular filtration and excretion in the urine or diminished reabsorption in the tubules. All these processes may result from changes in the electrical, aqueous environment in humans who are earthed. Urea is passively reabsorbed in the renal tubules. The rate of transport is determined by the electrochemical gradient for diffusion of the substance across the membrane and the permeability of the membrane for the substance. Additionally, glomerular filtration depends on the negative charge of the basement membrane of podocytes, which restrict large negatively charged molecules (Guyton and Hall, 1991; 2006). Changes in the electrical potential of the membrane of tubular and glomerular cells can affect filtration and absorption. Another waste product of metabolism is creatinine (Cr), which is a larger molecule than urea and is impermeant to the tubular membrane. Therefore, almost all of the creatinine filtered by the glomerulus is excreted in the urine (Guyton and Hall, 1991; 2006). In our study, in contrast to the changes in urea, we did not observe altered levels of creatinine in the exercise phase. Lower creatinine concentrations at the end of the recovery phase in earthed subjects may have resulted from increased kidney filtration.

In the present study, Creatinine serum (Cr) in dyslipidemia group unaltered when compared with another group but in Exercise group shown an increase when compared to dyslipidemia conjunction with exercise group. Serum creatinine level closely reflects skeletal muscle mass, and changes with it (Heymsfield et al., 1983). Creatinine-level-based estimated glomerular filtration rate (eGFR) has a limitation, that is, the weight-loss-associated decrease in skeletal muscle increases eGFR apparently.

Kanda et al. demonstrated that the males with low normal BMIs or who were underweight (BMI < 22 kg/m2) showed tendencies their eGFR tended to increase with a decreasing BMI change (Kanda et al., 2015). From considering previous studies, these findings may reflect the decrease in muscle mass. On the other hand, in the males with high normal BMIs, this increasing eGFR change was not observed with a decreasing BMI change in line with our present study. Which demonstration that BW in dyslipidemia group increased when compared to dyslipidemia conjunction with exercise group. A possible reason for this inconsistency was the actual decrease in kidney function caused by weight loss affected eGFR to a great extent than the apparent improvement of serum creatinine level due to the decrease in muscle mass. In the overweight males, instead of certain effects of a decrease in muscle mass, the kidney function may have improved actually.

In the present study, shows serum glutamic oxaloacetic transaminase (SGOT) was no significant difference in all treatment and Serum glutamic pyruvic transaminase (SGPT) in exercise-groups was significantly increased compared to non-exercise groups. Serum glutamate pyruvate transaminase (SGPT), now called Alanine aminotransferase (ALT), is a liver enzyme that is vital for energy production. It is present in different tissues such as the liver, skeletal muscles, and heart, but is found with the highest concentration in the liver. When the liver is damaged, SGPT leaks out of the cells and into your blood. Normal SGPT level ranges from 7 to 56 units per liter of blood. High levels of SGPT in the blood may indicate liver problems and damage, but they may also be elevated due to strenuous exercise. Strenuous exercise has resulted in increased serum transaminase levels (Malinoski, 1992). From the previous study provides some scientific data to support this concept (Uadia et al., 2016). The results

obtained indicate that physical exercise could be of immense benefit to an individual's health. SGPT used as an indicator for liver injury, showed an increase in the post-exercise values as against the pre-exercise values, although this decrease was not statistically significant ($P \leq 0.05$). This suggests that the pattern, intensity, and duration of the exercise regimen did not cause damage to the liver which is the major source of SGPT. This is in agreement with Davries et al. (Devries et al., 2008). In addition, past studies indicate that increasing plasma SGPT is associated with increased adiposity and risk of the metabolic syndrome. Several possible mechanisms have been proposed to explain how hepatic enzymes are markers for the risk of developing the metabolic syndrome. Dyslipidemia has been identified as an important factor contributing to elevated serum levels of hepatic enzymes (Adler and Schaffner, 1979; Angulo, 2002; Galambos and Wills, 1978) and Marchesinia reported an association between SGPT activity and dyslipidemia, insulin resistance in type 2 diabetes (Marchesini et al., 2005). One study has also correlated SGPT activity with increased hepatic fat (Cho et al., 2007). Moreover, Atiba et al. investigated that increased SGPT and SGOT with dyslipidemia in patients from Nigeria were diagnosed with type 2 diabetes (Atiba et al., 2013).

5.3 Mean arterial pressure and heart rate in their male rat offspring

In the present study, shows mean arterial pressure (MAP) significantly increase in dyslipidemia group when compared with another group. Mean arterial pressure (MAP) was calculated as the multiply of cardiac output (CO) and total peripheral vascular resistance (PVR). Although a simplification, this emphasizes that an elevation of mean blood pressure can only come about as a result of an increase in cardiac output

(CO), an increase in total peripheral vascular resistance (PVR), or a combination of both. MAP equally predict incident cardiovascular disease (CVD) events and may provide additional insight into the underlying pathophysiology of high blood pressure (BP). MAP is determined by MAP is determined by serving as an indicator of peripheral resistance and cardiac output (Franklin et al., 2009). Dyslipidemia decreases the distensibility of large elastic arteries and it is also associated with endothelial dysfunction (Chowienczyk et al., 1992; Wilkinson et al., 2002) which, in turn, increases BP. Which there is evidence that cholesterol induces endothelial dysfunction in experimental (Hayakawa and Raij, 1999) and clinical studies, even at normal (Creager and Selwyn, 1997) or high-to-normal (Vallance et al., 1989) ranges by reducing the bioavailability of endothelium-derived nitric oxide. Endothelium-dependent vasodilation, in fact, correlates inversely with total cholesterol levels (Vallance et al., 1989)

In the present study, shows heart rate decreasing significantly in exercise-groups when compare with non-exercise groups and in dyslipidemia group was significant increase compared to another group. From the previous study, the data reported demonstrating that heart rate correlates with atherogenic blood lipid fractions in the general population. The results extend previous studies that showed positive correlations between serum cholesterol and heart rate"' or blood pressure (Bonaa and Thelle, 1991; Criqui et al., 1980). By showing that heart rate and blood pressure are independently related to non-HDL cholesterol levels. Heart rate correlated with sex, anthropometric variables, but these relations could not explain the association between heart rate and blood lipid levels. The association between the usual heart rate and serum lipid levels. Persons participating in physical training have generally lower heart rate,

and their blood lipid levels may differ from those of sedentary persons. Like many large surveys, this study is hampered by an imprecise a measure of physical activity, and residual effects of physical fitness can remain after adjustments. However, three of the covariates used in the analyses, i.e., body mass index, and a simple measure of physical activity, are valid estimators of physical fitness assessed by treadmill work capacity (Blair et al., 1989) or bicycle ergometry (Løchen and Rasmussen, 1992). In addition, although moderate or intense physical training may increase HDL cholesterol and decrease triglyceride levels in men, (Thompson et al., 1988) the effect is less certain in women, (Brownell et al., 1982) and it appears that exercise produces little change in total or LDL cholesterol levels (Fletcher et al., 1992). Finally, a smaller study showed that heart rate was significantly related to serum lipoprotein levels also when maximum aerobic power was controlled for. On the basis of this background, this may infer that the association between heart rate and blood lipids reported here is not a consequence of physical activity.

5.4 Baroreflex sensitivity in their male rat offspring

In the present study, shows a baroreflex sensitivity of heart rate response to phenylephrine and baroreflex sensitivity of heart rate response to sodium nitroprusside was significantly decreased in dyslipidemia group compared to another group. Hypertension and dyslipidemia are important risk factors for cardiovascular disease. Population-based epidemiological studies have also reported that gradual increases in blood pressure (BP) or prevalence of hypertension are associated with increases in blood lipid levels (Ebrahim et al., 2006; Elias et al., 2005; Freiberg et al., 2008; Okamura et al., 2007). One possible explanation for these relationships is that

hypertension and dyslipidemia share common pathophysiological etiologies, such as obesity and the resulting dysregulation of adipocytokine release from adipose tissue (McGill et al., 2009). Furthermore, dyslipidemia adversely affects functional and structural arterial properties and promotes atherosclerosis (Casino et al., 1993; Creager et al., 1990; Wilkinson et al., 2002). These changes may impair BP regulation, which, in turn, predisposes individuals with dyslipidemia to development of hypertension. Dyslipidemia may predispose individuals to the development of hypertension by reducing baroreflex sensitivity (Li et al., 1996; Piccirillo et al., 2001). The baroreflex is the regulation of BP by a negative feedback loop; baroreceptors, located in blood vessels, activate the parasympathetic nervous system, which counteracts any changes in BP. Third, dyslipidemia decreases the distensibility of large elastic arteries (Wilkinson et al., 2002). This decrease may reduce the windkessel effect (Westerhof et al., 2009), which, in turn, increases BP, in particular, systolic BP. Last, physical inactivity and a high-fat diet promote obesity and dyslipidemia. In obese individuals, adipose tissue excessively secretes adipocytokines, such as leptin, thereby inducing insulin resistance and subsequent activation of the sympathetic nervous system and the renin-angiotensin system (McGill et al., 2009). These biological changes may, in turn, raise BP. In the present study, the multivariate analyses were adjusted for several potential confounding factors, including BMI. However, other adiposity-related residual confounders may be involved in the association between dyslipidemia and risk of hypertension.

5.5 Histological of retroperitoneal adipocytes

In the present study, shows the sizes of retroperitoneal adipocytes were significantly increased in dyslipidemia group compared to another group and dyslipidemia with taurine (DT) and dyslipidemia with taurine and exercise (DTEx) group showed adipocyte size smaller than other groups. Adipose tissue is the major site for storage of excess energy in the form of triglycerides, and it contains multiple cell types, including mostly adipocytes, pre-adipocytes, endothelial cells and immune cells. During positive energy balance, adipose tissue stores excess energy as triglycerides in the lipid droplets of adipocytes through an increase in the number of adipocyte (hyperplasia) or an enlargement in the size of adipocytes (hypertrophy) (Hausman et al., 2001). The number of adipocytes is mainly determined in childhood and adolescence and remains constant during adulthood in both lean and obese subjects, even after marked weight loss (Spalding et al., 2008). Hence, an increase in fat mass in adulthood can primarily be attributed to hypertrophy. Adipose tissue expansion that occurs during the development of dyslipidemia initially is characterized by fat cell hypertrophy (Bonnet, 1981; Brook et al., 1972). Adipocytes do not have an unlimited capacity for expansion, however, and increases in fat cell number occur even during adulthood (Bonnet, 1981; Brook et al., 1972). When adipose tissue development in genetic or diet-induced obese animals is monitored over time, it is generally observed that increases in fat cell size precede increases in fat cell number (Björntorp et al., 1982; Faust et al., 1978; Hill et al., 1993; Johnson et al., 1978; Lemonnier, 1972). However, a recent study has reported that normal-weight adults can expand lower-body subcutaneous fat, but not upper-body subcutaneous fat, via hyperplasia in response to overfeeding (Tchoukalova et al., 2010), suggesting hyperplasia of adipocytes can also

occur in adulthood. When energy is needed between meals or during physical exercise, triglycerides stored in adipocytes can be mobilized through lipolysis to release free fatty acids into circulation and the resulting free fatty acids are transported to other tissues to be used as an energy source. However, circulating free fatty acid concentrations do not increase in proportion to fat mass and do not predict the development of metabolic syndrome (Byrne et al., 1999; Cho et al., 2012; Reeds et al., 2006).

5.6 The expression of AT1 receptor in kidney and heart

In the present study, shows the relative density between an expression of angiotensin II type 1 (AT1) receptor and actin in dyslipidemia group showed noticeable of expression of angiotensin II type 1 (AT1) receptor more than another group both in kidney and heart. Dyslipidemia is the activation of the renin-angiotensin system (RAS). Angiotensin II is the most powerful biologically active product of RAS and activates at least two types of cell-surface receptors, type 1 receptor (AT1) and type 2 receptor (AT2). Angiotensin II directly constricts vascular smooth muscle cells, enhances myocardial contractility, stimulates sodium and water retention, stimulates the release of catecholamines from the adrenal medulla and sympathetic nerve endings, and increases sympathetic nervous system activity, which results in increased blood pressure (Kobori et al., 2007). Increasing evidence reveals cross-talk between dyslipidemia and RAS activation in cardiovascular diseases (Hamden et al., 2011; Singh and Mehta, 2001). Upregulates angiotensin-converting enzyme (ACE) and AT1 expression in human endothelial cells (Catar et al., 2007; Luo et al., 2011). In vitro studies have shown that incubation of vascular smooth muscle cells with LDL increases expression of the AT1 receptor (Nickenig et al., 1997). Li et al. (Li et al., 2000)

examined the expression of angiotensin II receptors in human coronary artery endothelial cells and observed that Oxidized low-density lipoprotein (Ox-LDL) increases the mRNA and protein for AT1 receptor but not AT2 receptor, implying that ox-LDL increases AT1 expression at the transcriptional level. In this process, activation of the redox-sensitive transcription factor NF-κB (nuclear factor kappa B) plays a critical role. To define the relationship of RAS and lipids in humans, Nazzaro et al. 1999 administered angiotensin II in normocholesterolemic and hypercholesterolemic men and found that increase in blood pressure was exaggerated in the hypercholesterolemic group and that this response could be blunted by LDL-C–lowering agents (Nazzaro et al., 1999). Furthermore, these investigators found that there was a linear relationship between AT1 receptor density on platelets and LDL-C concentration in plasma.

In conclusion, perinatal exposure of the taurine health program and adult disease. Maternal dyslipidemia has long-term effects on adult offspring, including metabolic and cardiovascular diseases. This study shows that offspring are more sensitive to maternal dyslipidemia. However, the taurine supplementation perinatal period prevents maternal blood pressure dysregulation and metabolic by induced dyslipidemia. Therefore, our studies indicate that taurine supplementation in the perinatal period on maternal dyslipidemia may be having anti-dyslipidemia and anti-hypertension in the later life offspring.

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