รูปแบบการทดลองของแม่หนูเบาหวานและการได้รับทอรีนเสริม ต่อการป้องกันความผิดปกติทางเมแทบอลิซึมในลูกหนู

นายปุญญพัฒน์ แตงเผือก

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาชีวเวชศาสตร์
มหาวิทยาลัยเทคโนโลยีสุรนารี
ปีการศึกษา 2559

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

Punyaphat Teangphuck

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science in Biomedical Sciences

Suranaree University of Technology

Academic Year 2016

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

Suranaree University of Technology has approved this thesis submitted in partial fulfillment of the requirements for a Master's Degree.

Thesis Examining Committee

G. Eumkeb.

(Assoc. Prof. Dr. Griangsak Eumkeb)

Chairperson

Atcharaporn T.

(Dr. Atcharaporn Thaeomor)

Member (Thesis Advisor)

Sajeera Kupittayanant

(Assoc. Prof. Dr. Sajeera Kupittayanant)

Member

Rungrudee Srisawat

(Asst. Prof. Dr. Rungrudee Srisawat)

Member

(Prof. Dr. Santi Maensiri)

Vice Rector for Academic Affairs and Internationalization

(Asst. Prof. Dr. Worawat Meevasana)

Dean of Institute of Science

ปุญญพัฒน์ แตงเผือก : รูปแบบการทดลองของแม่หนูเบาหวานและการได้รับทอรีนเสริมต่อการป้องกันความผิดปกติทางเมแทบอลิซึมในลูกหนู (EXPERIMENTAL MODEL OF MATERNAL DIABETES AND TAURINE SUPPLEMENTATION ON PREVENTING METABOLIC DISORDERS IN OFFSPRING) อาจารย์ที่ปรึกษา : อาจารย์ ดร.อัจฉราพร แถวหมอ, 163 หน้า.

การศึกษาครั้งนี้ทดสอบสมมุติฐานของการให้ทอรีนเสริมในแม่หนูช่วงปริกำเนิด-ทารกแรกเกิดและการออกกำลังกายในลูกหนูเพศผู้ ต่อการป้องกันเบาหวานและความดันโลหิตสูงในลูกหนูที่แม่มีภาวะเป็นเบาหวาน หนูแรทเพศเมียจะได้รับอาหารปกติและน้ำอาร์โอ (กลุ่มควบคุม) ที่ไม่ได้ชักนำให้เป็นเบาหวาน หรือถูกชักนำให้เป็นเบาหวาน (กลุ่มเบาหวาน) โดยฉีดสเตรปโตโซโตซิน ผ่านทางช่องท้องก่อนการตั้งครรภ์ หลังจากตั้งครรภ์แม่หนูถูกแบ่งออกเป็น กลุ่มที่ได้รับ 3% ทอรีนร่วมกับน้ำอาร์โอ (กลุ่มควบคุมได้รับทอรีน (T) กลุ่มเบาหวานได้รับทอรีน (DMT) และกลุ่มที่ได้รับน้ำอาร์โออย่างเดียว (กลุ่มควบคุมได้รับน้ำอาร์โอ กลุ่มเบาหวานได้รับน้ำอาร์โอ (DM) จนกระทั่งลูกหนูหย่านม 4 สัปดาห์ ลูกหนูถูกแบ่งออกเป็น 2 กลุ่ม กลุ่มไม่ออกกำลังกาย (กลุ่มควบคุม+ได้รับน้ำอาร์โอ (C) กลุ่มควบคุม+ได้รับทอรีน (T) กลุ่มเบาหวาน+ได้รับน้ำอาร์โอ (DM) กลุ่มเบาหวาน+ทอรีน (DMT)) และกลุ่มออกกำลังกาย (กลุ่มควบคุม+ออกกำลังกาย (Ex) กลุ่มควบคุม+ได้รับทอรีน+ออกกำลังกาย (TEx) กลุ่มเบาหวาน+ได้รับทอรีน+ออกกำลังกาย (DMTEx)) ในกลุ่มออกกำลังกายให้หนูออกแรงว่ายน้ำในถังน้ำ 12 สัปดาห์ เมื่อลูกหนูอายุ 16 สัปดาห์ ทำการวัดค่าข้อมูลทางสรีรวิทยา ค่าเคมีในเลือดและแองจิโอเทนซิน รีเซพเตอร์ ชนิดที่ 1 จากผลการทดลองพบว่า ค่าน้ำหนักตัวของลูกหนูที่เกิดจากแม่เป็นเบาหวานลดลงอย่างมีนัยสำคัญ เมื่อเปรียบเทียบกับกลุ่มอื่น ๆ ในขณะที่น้ำหนักหัวใจและไต ในกลุ่มออกกำลังกายเพิ่มขึ้นอย่างมีนัยสำคัญ เมื่อเปรียบเทียบกับกลุ่มที่ไม่ออกกำลังกาย นอกจากนี้ ค่าคอเลสเตอรอล ไตรกลีเซอไรด์ ค่าแอลดีแอล และน้ำตาลในกลุ่มลูกหนูที่แม่เป็นเบาหวานเพิ่มขึ้นอย่างมีนัยสำคัญ เมื่อเปรียบเทียบกับกลุ่มอื่น ๆ แต่ค่าเอชดีแอลและอินซูลินลดลงอย่างมีนัยสำคัญ อย่างไรก็ตาม ค่าเฉลี่ยความดันเลือดแดงเพิ่มขึ้นอย่างมีนัยสำคัญ ในขณะที่อัตราการเต้นของหัวใจและการตอบสนองของบาโรรีเซพเตอร์ ในกลุ่มลูกหนูที่แม่เป็นเบาหวานลดลงอย่างมีนัยสำคัญ เมื่อเปรียบเทียบกับกลุ่มอื่น ๆ แองจิโอเทนซิน รีเซพเตอร์ ชนิดที่ 1 เพิ่มขึ้นอย่างมีนัยสำคัญ แต่ไอส์เลตออฟลังเกอร์ฮันส์ลดลงอย่างมีนัยสำคัญ ในกลุ่มออกกำลังกายอัตราการเต้นของหัวใจลดลงอย่างมีนัยสำคัญ เมื่อเปรียบเทียบกับกลุ่มที่ไม่ออกกำลังกาย จากการศึกษาในปัจจุบันพบว่า แม่ที่เป็นเบาหวานมีความเสี่ยงต่อการเกิดความผิดปกติทางเมแทบอลิซึมในลูกหนูเพศผู้ ผลของศึกษาครั้งนี้พบว่า การให้ทั้งทอรีนเสริมในแม่หนูช่วงปริกำเนิด-ทารกแรกเกิดหรือการออกกำลังกายในลูก สามารถป้องกันผลกระทบของโรคที่

เกิดจากแม่ที่เป็นเบาหวาน ต่อการเกิดภาวะไขมันผิดปกติ การตอบสนองของบาโรรีเซพเตอร์ ความดันเลือด อัตราการเต้นของหัวใจ การแสดงออกของแองจิโอเทนซินรีเซพเตอร์ และการเป็นเบาหวานในลูก

สาขาวิชาปรีคลินิก
ปีการศึกษา 2559

ลายมือชื่อนักศึกษา_____
ลายมือชื่ออาจารย์ที่ปรึกษา_____
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม_____
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม_____

PUNYAPHAT TEANGPHUCK : EXPERIMENTAL MODEL OF MATERNAL DIABETES AND TAURINE SUPPLEMENTATION ON PREVENTING METABOLIC DISORDERS IN OFFSPRING.
THESIS ADVISOR : ATCHARAPORN THAEOMOR, Ph.D. 163 PP.

TAURINE SUPPLEMENTATION /EXERCISE /MATERNAL DIABETES/ METABOLIC DISORDERS /BAROREFLEX SENSITIVITY

This study tested the hypothesis that perinatal-neonatal period taurine supplementation and exercise in male offspring prevents diabetes mellitus and hypertension in adult offspring of maternal diabetes rats. Female Wistar rats were fed normal rat chow and reverse osmosis (RO) without (Control group) or with diabetes induction by intraperitoneal streptozotocin injection (Diabetes group) before pregnancy. Then, they were supplemented with 3% taurine in water (Control + Taurine (T) and Diabetes + T group (DMT)) or water alone from conception to weaning. After weaning, at 4 weeks of age male rats offspring each group were divided to non-exercise (Control + RO, (C), Control + Taurine, (T); Diabetes + RO, (DM); Diabetes + T (DMT) groups) and exercise group (Control + Ex, (Ex); Control + T + Ex (TEx); Diabetes + T + Ex (DMTEx). In exercise groups were forced to swim in cylinder tank for 12 weeks. At 16 weeks of age, all rats were measured physiological data, Blood chemistry and angiotensin II receptor type I (AT_1 receptor). The results showed, Body weight in male offspring from maternal diabetes mellitus (DM) group significantly decreased when compared to another group while heart and kidney weight in exercise group significantly increased when compared to non-exercise. In addition, cholesterol,

triglyceride, LDL and glucose were significantly increased in offspring from maternal diabetes group (DM) when compared to another group but HDL and insulin were significantly decreased. However, mean arterial pressure were significantly increased while heart rate and baroreflex sensitivity were significantly decreased in DM group when compared to another group. AT_1 receptor were significantly increased but islet of Langerhans were significantly decreased in DM group. Exercise group were significantly decreased in heart rate when compared to non-exercise. The present study show that maternal diabetes mellitus is associated with an increased risk of metabolic dysfunction in male offspring. These data show either taurine supplementation in perinatal-neonatal period or exercise can be prevented the adverse effect of maternal diabetes on dyslipidemia, baroreflex sensitivity, blood pressure, heart rate, AT_1 receptor expression and diabetes in offspring.

School of Preclinic

Academic Year 2016

Student's Signature Punyaphat

Advisor's Signature Atcharaporn T.

Co-Advisor's Signature Rungaudee Sirisawat

Co-Advisor's Signature Sajeeva Kupittayanant

ACKNOWLEDGEMENTS

I would like to express my gratitude to my advisor, Dr. Atcharaporn Thaeomor, for her supervision, guidance, much more suggestion, kindness, and patience which enable me to carry out this thesis successfully. I would like to extend many thank to my co-advisor, Asst. Prof. Dr. Rungrudee Srisawat for supporting transducer used for blood pressure measurement that is presented in this thesis.

I would also like to thank Assoc. Prof. Dr. Griangsak Eumkeb and Assoc. Prof. Dr. Sajeera Kupittayanant for taking the time to serve on my thesis committee. I also wish to express my gratitude to the staff member of the Center for Scientific and Technological Equipment, Suranaree University of Technology of providing facilities and helpful suggestions during the investigation.

In addition, I am grateful for suggestions and helps from all teachers in Biomedical Science Program and Miss Chonticha Tangnoi.

Finally, I want to extend huge thanks to my family for their encouragement, understanding, endless love, and support throughout my life.

Punyaphat Teangphuck

CONTENTS

CONTENTS (Continued)

Page

CONTENTS (Continued)

Page

CONTENTS (Continued)

Page

CONTENTS (Continued)

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES (Continued)

LIST OF ABBREVIATIONS

µg	Microgram
µg/ml	Microgram per milliliter
µm	Micrometer
ACE	Angiotensin converting enzyme
ADA	American diabetes association
ADH	Antidiuretic hormone
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Ang	Angiotensinogen
ANS	Autonomous nervous system
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AT_1	Angiotensin II receptor type 1
AT_2	Angiotensin II receptor type 2
BUN	Blood urea nitrogen
Ca^{2+}	Calcium ion
Cm	Centimeter
CO_2	Carbon dioxide
Cr	Creatinine

LIST OF ABBREVIATIONS (Continued)

CV	Cardiovascular
DAB	Diaminobenzidine
DBP	Diastolic blood pressure
DI	Distilled water
DM	Diabetic mellitus
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial nitric oxide synthase
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucose-like-1 peptide
GLUT2	Glucose transporter 2
H^+	Hydrogen ion
HDL	High-density lipoprotein cholesterol
hr	Hour
HRV	Heart rate variability
HTN	Hypertension
IDDM	Insulin-dependent diabetes mellitus
IDM	Infant diabetes mother

LIST OF ABBREVIATIONS (Continued)

IGF-1	Insulin-like growth factor 1
IGF-2	Insulin-like growth factor 2
IGT	Impaired glucose tolerance
IR	Insulin resistance
K	Potassium
KATP	ATP-sensitive K+ channel
LBW	Low birth weight
LDCV	Large dense-core vesicle
LDL	low-density lipoprotein cholesterol
LGA	large of gestational age
lgG	lgG immunoglobulin
L-NAME	L-nitro-arginine
M	Molar
MAP	Mean arterial pressure
min	Minute
ml	Milliliter
mm	millimeter
mM	Millimolar
mmHg	millimeters of mercury
Na^+	sodium ion

LIST OF ABBREVIATIONS (Continued)

Na_2CO_3	Sodium carbonate
NaCl	Sodium chloride
NDDG	National data group diabetes
ng/ml	Nanogram per milliliter
NGT	Normal glucose tolerance
NIDDM	Non-insulin-dependent diabetes mellitus
NIH	National institutes of health
nm	Nanometer
NO	Nitric oxide
NTS	Nucleus of the tract solitaries
^oC	Degree Celsius
PAI-1	Inhibit plasminogen activator-1
PBS	Phosphate buffered saline
PGDM	Pre-gestational diabetes mellitus
pH	Potential of hydrogen ion
PI3	Phosphoinostide 3-kinase
PVDF	Polyvinylidene difluoride
QC1	Quality control 1
QC2	Quality control 2
RAS	Renin-angiotensin system

LIST OF ABBREVIATIONS (Continued)

RO	Reverse osmosis
SBP	Systolic blood pressure
SD	Standard definition
SNP	Sodium nitroprusside
STZ	Streptozocin
SUR	Sulfonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TauT	Taurine transporter
TBS	Tris-buffered saline
TC	Total cholesterol
TG	Triglyceride
TMB	3, 3', 5, 5'-Tetramethylbenzidine
VCAM	Vascular cell adhesion molecule
VLDL	Very low-density lipoprotein cholesterol
VSCC	Voltage- sensitive calcium channels
VSMC	Vascular smooth muscle cell
WHO	World Health Organization

CHAPTER I

INTRODUCTION

1.1 Background/Problem

Maternal diabetes mellitus, the most common medical complication and metabolic condition during pregnancy, which leads to insulin resistance and abnormality in glucose metabolism changing to meet the nutritional demands of the mother and fetus causes an increased susceptibility to diabetes and hypertension later in the life of the offspring (Reece et al., 2009). In order to maintain proper glucose metabolism, the amount of insulin secreted from β-cells increases during pregnancy (Lain et al., 2007). The perinatal environment *in utero* significantly impacts on health and disease of the fetus, the infants, and the adult offspring (Harding, 2001; Norma et al., 2008; Osmond et al., 1993).

Maternal malnutrition or imbalanced food consumption, especially protein in the perinatal period can lead to low birth weight and subsequently induces several disorders, including insulin resistance, diabetes mellitus, and hypertension in adult offspring, and via epigenetic mechanisms, these can transfer to the next generation (Barker et al., 2002; Forrester, 2004). Maternal diabetes mellitus during pregnancy may increase the risk of diabetes and hypertension in their offspring due to many reasons such as genetic and environmental factors, mainly from the lifestyle such as diet, foods that contain protein (Ferrara, 2007; Beischer et al., 1991; Ishak and Petocz, 2003; Thorpe et al., 2005; Zargar et al., 2004).

Taurine (2-aminoethansulfonic acid) is amino sulfonic acid found at a high concentration in many organs including brain, heart, liver, muscle, kidneys, and reproductive organs (Bouckenooghe et al., 2006; Huxtable, 1992). In general, taurine content in these organs is highest during perinatal and early postnatal life, and it gradually declines after birth (Aerts and van Assche, 2002). During lactation, mothers transfer taurine to their embryos or fetuses via the placenta and to the newborn via the maternal milk (Tosh et al., 2010). During perinatal period, taurine supplementation is commonly used as a dietary supplement (McPherson and Hardy, 2011; Wu, 2009; Yamori et al., 2010). Previous results indicate that dietary taurine supplementation during perinatal period not only decreases or protects against spontaneous hypertension in adult animal and human models (Nara et al., 1978; Fujita and Sato 1984; Wyss et al., 1994; Anuradha and Balakrishnan, 1999; Militante and Lombardini, 2002) but also stimulates postnatal growth and reduces insulin resistance in adult offspring (Hultman et al., 2007). While the effects of adult taurine exposure are modest, altered exposure during the perinatal period can have lifelong effects on adult function and disease (Sturman, 1993).

A close relationship between muscular taurine content and exercise performance is suggested by studying a depletion of taurine in the skeletal muscle as well as other organs. The exogenous taurine is needed during the transient deficiency of endogenous taurine transport, which caused by exercise performances (Ito et al., 2008; Warskulat et al., 2004). In rat, skeletal muscle taurine concentration was decreased after exhaustive exercise (Matsuzaki et al., 2002). Furthermore, exogenous taurine supplementation prevented the exercise-induced taurine reduction in the rat gastrocnemius (Sullivan and Armstrong, 1978), and consequently, significantly enhanced exercise performance

(Miyazaki et al., 2004). Therefore, the muscular taurine content might be lowered by exercise, and compensated by exogenous taurine supplementation.

Although the mechanism(s) of these effects still unclear, the evidence found that the mechanisms for the taurine-mediated enhancement in exercise performance might involve increased cardiac contractility during exercise (Baum and Weiss, 2001). In the diabetic rats, previous reports demonstrated that taurine supplementation helps to maintain blood sugar level concentrations during prolong exercise and improved hyperglycemia or insulin resistance with increased muscular glycogen content (Ishikura et al., 2011; Harada et al., 2004). This study focuses on the effect of perinatal taurine supplement action in maternal diabetes mellitus, and exercise on prevention of diabetes and hypertension via glucose-Insulin interaction in the adult male offspring.

1.2 Research objectives

The experiments are designed to clarify the followings:

1. To study the effect of taurine supplementation on metabolic disorder in their offspring.

2. To study the effect of exercise on metabolic disorder in their offspring.

3. To explore the relationship between taurine supplementation and exercise on metabolic disorder in their offspring.

1.3 Research hypothesis

Taurine supplementation in the perinatal period on maternal diabetes mellitus and exercise prevents the development of metabolic disorder in their offspring.

1.4 Expected results

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

1.4.2 The findings will provide the exercise relating to control of blood glucose, insulin levels and blood pressure control.

1.4.3 The findings will provide interaction between taurine supplementation in perinatal-neonatal period and exercise to control of blood glucose, insulin levels and blood pressure control.

CHAPTER II

LITERATURE REVIEW

2.1 Programming hypothesis

The hypothesis as Pedersen found that hyperglycemia in maternal diabetes mellitus or gestational diabetes mellitus and affect to fetus hyperglycemia also. This phenomenon helps explain several anomalous structures and changes in newborns (Pedersen, 1967). There is abundant data supporting the hypothesis of Pedersen. For example, the cordon umbilical insulin concentrations are strongly correlated with fetal growth in humans and animal studies. Schwartz to the reported fetal size was significantly correlated with umbilical total insulin, free insulin and C-peptide (Schwartz et al., 1994). Hyperglycemia was recently completed and study of adverse pregnancy outcome showed a linear relationship between increased maternal glucose and C-peptide in cord birth weight. (HAPO Study Cooperative Research Group, 1996). Several in vivo animal models also support the hypothesis of Pedersen. Twelve hours after injection of insulin in fetuses of rats, significantly increased compared to saline injection controls (Ogata et al., 1988). The authors concluded increased fetal insulin, even in the presence of normal breast substrate concentrations was the development promotion in non-human primates (Susa et al., 1984). Studies could link of glucose maternal greater to an increase of weight in the birth of the child as well as different degrees of morbidity, among others things the incidence of malformations of

morbidity, among others things the incidence of malformations congenital, supporting the hypothesis, that even glucose moderately growing of the blood in the absence of diabetes influences positively on the growth of the fetus (Macfarlane and Tsakalakos, 1988; Robert and Lindsay, 2009). In 1952 the Pedersen, formulated the hypothesis that maternal hyperglycemia during pregnancy can cause fetal hyperglycemia, which exposes the fetus to high insulin levels. This would result in an increased risk of fetal macrosomia and neonatal hypoglycemia. The glucose concentration of blood in humans depends on diet, especially energy intake and the proportion of carbohydrates in the diet. High glucose in the blood of pregnant women cause to an intensified transfer of nutrients to the fetus, increased fetal growth (Kerssen et al., 2007). Subsequently carried out modifications to the hypothesis of Pedersen: nutrients other than sugar and its linkage to the fetal overgrowth in diabetic pregnancy were taken into account; but however, emphasized the crucial role of the hyperinsulinism fetal and maternal glucose monitoring. Recent studies indicated that diabetes in the mother in their offspring increases the risk of obesity and diabetes type 2 (Robert et al., 2010).

The "Barker hypothesis", or thrifty phenotype, found the effect of on adult health conditions during pregnancy. Associated risk of lifelong diseases, including cardiovascular disease, type 2 diabetes, obesity and hypertension. Babies who are born lighter weight appear to have a higher mortality rate of babies who are born with a heavier weight (Bateson, 2001). The "Barker Hypothesis" also known as "the hypothesis of fetal programming." "Program" Programming is the idea that the critics of the early days of the development of the fetus, persistent changes in the structure and function of the body are caused by irritation of the environment. This is related to

the concept of plasticity of the development where our genes can express different ranges of states physiological or morphological in response to the conditions environmental during the development fetal. However, the environment during childhood and fetal life appears to be strongly related to risk of non-communicable diseases in adulthood (Barker, 2004). To explain these apparently the causal relationships is proposed that adaptations during critical phases of growth and development can guarantee the maintenance of homeostasis and thus survival, when the environment commits (Gluckman and Hanson, 2004). Variation in the supply of nutrients during the development early seems to be a strong signal to initiate these adaptive processes. Media through which described events in early life permanent trigger responses such as nutritional or metabolic programming (Lucas, 1991).

These terms describe the process through that, causes a stimulation or an insult during a critical period of fetal or child development Permanent responses that produce long-term changes in the structure of the tissue or function. The programming is the consequence of the innate ability to develop tissues to adapt to the conditions that prevail during the first years of life, which for almost all types in all organs of the cell is a skill it is present for a short period of the time of birth. This constantly evolving concept is now described as the origins of health and disease development hypothesis.

The origins of health and disease development the hypothesis was originally developed to explain associations between patterns of fetal and infant growth and major States of disease in human populations, but he has received strong support from experimental studies in animals. Thus, If the mother has an inadequate diet, then points to the baby that the condition of life, in the long run, to be poor. Accordingly,

the baby adapts to changing their body size and metabolism to prepare for the harsh conditions of food scarcity after the birth. Physiological and metabolic processes in the body undergo changes in the long term as a result of restricted growth. When the environment condition of malnutrition to a society of abundance of nutrients, this exposes the infant to a rich environment which goes against what your body is designed for and this puts your baby at increased risk for diseases of adult later in adulthood (Barker, 2004). Similarly, if the fetus grows in a healthy mother's womb is exposed to the famine extended after birth, the baby would be less adaptive to the harsh environment that baby of low weight at birth.

2.2 Diabetes mellitus and classifications

World Health Organization (WHO) describes Diabetes mellitus as a metabolic disorder of multiple characterized hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (World Health Organization, 1998). The chronic hyperglycemia of diabetes is associated with damage to long-term, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. The American Diabetes Association (ADA) suggests that divided general classification forms of diabetes are: 1) Type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes mellitus; and 4) the specific type of diabetes due to other causes (Alexandria and Virginia, 2016).

1) Type 1 diabetes (T1DM) or Insulin-dependent diabetes mellitus (IDDM) is a disease in which the pancreas does not produce any insulin, results from a cellular mediated autoimmune destruction of the β cells of the pancreas. Can be diagnosed at any age, but mostly develops in a baby. Change in the genetic background and the

results environmental factor can increase the incidence and prevalence of T1DM (Gillespie, 2006).

2) Type 2 diabetes (T2DM) or Non-insulin-dependent diabetes mellitus (NIDDM) is represented insulin resistance resulting from the body cannot produce enough insulin or not- respond action of insulin. The pathogenesis of T2DM reduces the sensitivity to insulin and insulin action as a function of hyperglycemia. Including obesity, impaired insulin action and decreased insulin secretion can cause metabolic abnormalities that these individual factors have before the onset or during the development of diabetes. All these factors favor the progression of normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) and ultimately diabetes (Weyer et al., 1999). Insulin resistance (IR) in muscle and liver and β-cell deficiency represent the main pathophysiological defects in the development of type 2 diabetes. Age, genes, IR, lipotoxicity, glucotoxicity, amyloid deposition, Abnormal insertion are factors that play a role in progressive β-cell dysfunction. The progressive decrease in insulin secretion, decreased mass and β-cell function of the pancreas and the presence of IR contribute to changing the status of dysglycemia from normal glucose tolerance and glucose tolerance.

3) Gestational diabetes mellitus (GDM) is a variable degree of hyperglycemia in diabetes during pregnancy. Most women with GDM appear to have β-cell dysfunction already indicated before pregnancy on a background of resistance to chronic insulin. In less than 10% of patients with gestational diabetes, β-cell dysfunction is caused by an autoimmune destruction of pancreatic β-cells, such as in intolerance diabetes glucose type 1 occurs normally during pregnancy, especially in the third trimester.

4) Another class of glucose regulation is diabetes that cannot be classified into a single class, such as pancreatic dysfunction, high blood glucose level during pregnancy, progressive exocrine pancreas injuries chemical induced diabetes, β-cell destroyer from certain virus's infection, inflammation mediated diabetes.

2.2.1 Diagnosis criteria for diabetes mellitus

Several tests are available for diabetic patients who directly measure the glucose levels in the blood. According to the guidelines of the American Diabetes Association (ADA) in 2010, fasting plasma glucose (FPG) overnight, and the values of 2 hours of testing blood glucose test and tolerance against oral glucose testing (OGTT) were submitted after high glucose consumption.

In addition, the classic symptoms of diabetes (especially polyuria, polydipsia, and weight loss) are precarious with the concentration of glucose in the plasma of time in the time in each provisional period. Show with the glucose concentration in the plasma rare every day, regardless of the time since the last above the intake of 200 mg/dl overnight for at least 8 hours the blood glucose level higher than 126 mg/dl or an oral glucose tolerance test of 200 mg/dl a glucose load with 75 g, according to the protocol of the World Health Organization. As impaired fasting glucose level (IFG) is between 100-125 mg/dl and as impaired glucose tolerance (IGT) between 140-199 mg/dl, risk factors for future diabetes are altered and under increased account "pre-diabetes" (American Diabetes Association, 2010).

2.2.2 Diabetes and pregnancy

During a normal pregnancy, as many physiological changes, they increase hormone release, which regulates the glucose level in the blood, as a "leakage" of glucose to the fetus, the slow emptying of gastric excretion of glucose through the

kidney, and the resistance of the cells versus insulin. The risk of the fetus developing maternal diabetes includes miscarriage, restriction of growth, acceleration of growth, fetal obesity (macrosomia), mild neurological deficits (Meaghan et al., 2008), polyhydramnios and birth defects. An environment, maternal hyperglycemia also has been associated with newborn infants are increased risk for the development of the negative results in health as future obesity, resistance to insulin, diabetes mellitus type 2 and metabolic syndrome (Christine et al., 2011). The effect of pregnancy on the metabolism of diabetic fuel is one of the under-utilization of exogenous fuel in the fed state (reduced anabolism ease) and the overproduction of the fasting endogenous source (hyper-accelerated hunger). The first sign of pregnancy in a diabetic (especially in type 1 diabetes) and in the first week of pregnancy and even before nausea or vomiting is set in the early morning hours ketonuria. A smaller proportion of women does not have the necessary β-cells reserves to maintain normal blood glucose levels during pregnancy and to develop impaired glucose tolerance (IGT). The insulin responses are significantly lower at 30 and 60 minutes after glucose exposure by oral glucose tolerant compared to control, while insulin sensitivity is similar to that in the second trimester (Nicholls et al., 1995).

Reaction intravenous glucagon C-peptide was also significantly reduced in women with IGT during pregnancy, while the increase in serum proinsulin. The need for insulin therapy in gestational diabetes mellitus (GDM) is associated with an increased circulating levels of proinsulin, which means that the β-cell dysfunction increases leads to poor glucose intolerance. (Dornhorst et al., 1991). The need for treatment of insulin in gestational diabetes mellitus (GDM) is associated with elevated levels of proinsulin circulating, implying that greater dysfunction β-cells lead to the

worst glucose intolerance (Nicholls et al., 1994). Glucose intolerance during pregnancy may vary in intensity, but also mild degrees, accompanied by other abnormalities, including disorders of the metabolism of glycerin and nonesterified fatty acid metabolism (Coppack et al., 1999). Women with a previous history of GDM that become tolerant to postpartum glucose to see continuous B-cell dysfunction, characterized by the release of insulin in response to oral glucose and lipolysis deteriorated despite the normal insulin sensitivity impaired (Chan et al., 1992; Dornhorst et al., 1990). This shows a decrease in the function of β-cells in GDM women, which makes them susceptible to the future development of type 2 diabetes (Dornhorst, 1993). Carbohydrate intolerance worsens in pregnancy in women with diabetes early, in parallel with the physiological decrease in insulin sensitivity. Women with type 1 diabetes are dependent on the dose of insulin to increase glycemic control. On average, from 12 weeks to 37 weeks of pregnancy, weekly increments of 6% of the dose of insulin may require your preconception dose. Late pregnancy is associated with a triple incidence of type 1 diabetes newly introduced (Takizawa et al., 2003). This may occur because the insulin resistance of pregnancy imposes an additional burden on the woman's β-cells that are in the prolonged phase, but subclinical prediabetes with active insulitis, but enough mass of residual β-cells to prevent "obvious hyperglycemia beyond pregnancy. Maternal diabetes also affects the placenta, both structurally and functionally. Placental glycogen content and insulin binding capacity is higher in pregnancies pre-gestational in non-diabetic pregnancies (Gernot et al., 2007). Lipolysis induced by pregnancy caused type 1 diabetes women are more prone to diabetic ketoacidosis. It can develop quickly and with relatively mild hyperglycemia. Untreated, it can lead to the death of the unborn child. Mother

with type 2 diabetes also has to increase the production of insulin to compensate for the insulin resistance associated with pregnancy. Prior to the pregnancy these women had reduced sensitivity to insulin. Additional requirements for their β-cell impaired because the cell function in most women with insulin regimen require type 2 (oral antidiabetics or in parts of the world where insulin is not available) in the early pregnancy.

2.2.3 Classification of diabetes in pregnancy

Always uniform diabetic pregnancies epidemiological and clinical classification needs necessary. Both the World Health Organization (WHO) (WHO Diabetes Mellitus, 1985) and the National Data Group Diabetes (NDDG) (National Diabetes Data Group, 1979) of the National Institutes of Health (NIH) have approved a classification based on etiology. The WHO classification differs only in recognition of glucose intolerance before pregnancy. It is simple, but no prognostic value.

Classification of maternal diabetes during pregnancy: Existing diabetes:

1. Type 1 or type 2 pre-existing or secondary
2. Pregnancy diabetes diagnosis is made after pregnancy; normal glucose tolerance
3. Any type of diabetes that occurs, pregnancy

2.2.4 Pre-gestational diabetes mellitus (PGDM)

This term refers to a diabetic already performed during pregnancy. Time, it was known that the incidence of maternal and fetal complications is strongly influenced by the severity of maternal diabetes. Diabetes duration, the age of the mother at the beginning of diabetes, the presence or absence of vascular complications and treatment methods: the severity, the following factors must be

considered. Based on the prejudice of factors, Priscilla White established a clinical classification procedure in 1949 (White, 1949) and was amended in 1965 and 1971. This division has tried to predict the outcome of pregnancy among various metabolic, obstetric and other factors and prognosis A (best) to F (worst). Subsequently, the classification attempts to update and ischemic heart disease and kidney transplant take for general use were too heavy (Hare and White, 1980). Another classification system is used prognostically unfavorable signs of pregnancy, found on the basis of the risk factors during pregnancy. It is toxemia, pyelonephritis clinically manifest, severe acidosis, lack of patient cooperation and markedly negative social conditions. A combination of these two ratings predicts more fetal prognosis accurately, but its complexity has become superfluous. Effects of changes in fuel metabolism diabetic pregnancy. If hyperglycemia occurs in the first three months, when organogenesis occurs, birth defects can occur. It is said that the incidence is as high as 8% of pregnancies without diabetic complications (uncontrolled during the first 8 weeks of pregnancy), which is two to three times higher in the general population. Defects often affect the heart and the central nervous system and are potentially fatal. In addition to birth defects, there may be an early fetal loss due to miscarriage (Hanson et al., 1990). Contrary to the previous assumption that due to altered hypoglycemia early pregnancy maternal organogenesis Pedersen found a significant negative correlation between the onset of birth defects and severe hypoglycemia that occurred in the first trimester of pregnancy (Sadler, 1989).

Table 1 Fetal problems associated with maternal hyperglycaemia after trimesters.

Frist trimester	**Second trimester**	**Third trimester**
Malformations	Hypertrophic	Hypoglycemia
Growth	cardiomyopathy	Hypocalcemia
Retardation	Polyhydramnios	Hyperbilirubinemia
Fetal wastage	Erythremia	Respiratory distress
	Placental	syndrome
	Insufficiency	Macrosomia
	Preeclampsia	Hypomagnesemia
	Fetal loss	Intrauterine death
	Low IQ	

(Sadler et al., 1989).

In addition to breast hypoglycemia, several other factors may be involved in the development of malformations due to maternal diabetes. The role of other factors has been ketonemia maternal, fetal zinc depletion and inhibited the effect of somatomedin in animal experiments (Sadler, 1989; Lewis, 1983; Goldman, 1985; Sadler et al., 1986). The role of the genetically determined vulnerability requires further clarification. It seems likely that the high incidence of malformations in newborns of diabetic mothers is multifactorial. Defects develop in individuals genetically predisposed to follow a number of teratogenic factors.

Hyperglycaemia in the second quarter may result in intellectual disability in the performance of the offspring. The fetal pancreas is able to insulin 8-11 weeks of

pregnancy size. Maternal glucose passes through the placenta stimulates the β-cells, and mixed nutrients have similar effects (Figure 1). Accordingly, the activity of the β-cells of the fetus depends on the level of glucose and amino acids in the maternal blood. Once stimulated the pancreas continues to secrete insulin fetal autonomously, independently of glucose stimulation. Maternal-fetal hyperinsulinemia and glucose produce macrosomia (weight> 4 kg) and hypokalemia, the latter producing deadly cardiac arrhythmias. Unequaled stillbirth in the third trimester, although rare, may be due to fetal hypoxia (placental insufficiency). This potentially lethal metabolic state could be prevented by maintaining maternal euglycemia throughout the duration of pregnancy.

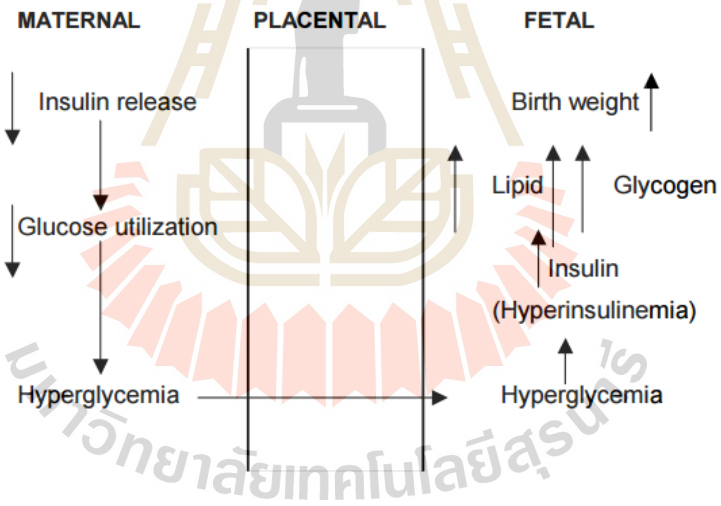


Figure 1 The result of altered assumption of maternal hyperglycemia by Pedersen hypothesis (Pedersen, 1967).

Hypoglycemia because endogenous hyperinsulinemia and suppression of endogenous glucose production, the infant diabetic mother (IDM) is an increased risk of hypoglycemia between 1 and 3 hours after birth. The factor that primarily protects against fetal hypoglycaemia is the optimal control of maternal hypoglycaemia,

especially during the third trimester and during work. It has been shown in the past four hours in a diabetic mother that leads to an increased incidence of newborn hypoglycemia that shows the average maternal glucose> 6 mmol /L About 25% IDM may have serum calcium <7 mg/dl, which can remain largely asymptomatic and is usually detectable in the second and third day of birth.

2.3 The Effects of hyperglycemic intrauterine environment due to offspring disorders

2.3.1 Growth and adiposity

Offspring of diabetic mothers have an excess of macrosomia of growth resulting and large for gestational age (LGA), contribute to an increased risk of caesarean section or traumatic birth (Jansson et al., 2006). This excess fetal growth is caused by the increased availability of nutrients from the mother caused by the placenta to the fetus. Maternal serum glucose, which is the main excess nutrients in these circumstances, free the placenta happens while not native insulin. Hyperglycaemia fetal when fetal pancreas, while immature is able to produce a higher level of insulin, which in turn acts as a growth hormone and promotes growth and fatness in the following induced fetus (Ashworth et al., 1973). The degree of hyperglycemia appears to determine the metabolic effects of the newborn (Lain and Catalano, 2003). The addition of an excess of glucose, changes in the supply of amino acids and an over-expression of placental transport systems also contribute to increasing fetal growth (Jansson et al., 2006; Ericsson et al., 2007). In particular, exposure to the diabetic intrauterine environment leads to changes in the growth pattern of the fetus, which predispose these children to overweight and obese even later in life, even in the absence of macrosomia in birth (Pettitt et al., 1987). Insulin

seems to play an important role, as the levels of insulin in the third quarter correlates independently with obese infants (Silverman et al., 1991).

2.3.2 Glucose tolerance disturbance

Many studies have shown that the offspring of diabetic mothers have a statistically higher impaired glucose tolerance (IGT), which is a known pre-diabetic condition (Silverman et al., 1995). In the case of gestational diabetes, it was shown that offspring decreased insulin secretion, whereas, in the case of pre-existing diabetes, it was shown that offspring insulin had high resistance, perhaps a display small difference in the underlying mechanisms (Plagemann et al., 1997). Earlier studies have shown that children were shown in all groups exposed to utero hyperglycemia age, the incidence of diabetes was higher compared to children of mothers without diabetes, although some of these even develop diabetes in the future (Dana, 2007). Therefore, diabetes is mainly progeny after exposure to diabetic intrauterine environment, and genetic susceptibility.

2.3.3 Cardiovascular abnormalities

The main problem is whether these metabolic abnormalities in the offspring increase the risk of cardiovascular disease later in life-threatening diseases because such a discovery closer to their mothers with diabetes could lead to glycemic control and monitoring possible next own offspring as a high- Population. However, few studies have investigated the effect of intrauterine environment diabetes on cardiovascular risk factors in the offspring (Figure 2) Still, since it is known that obesity and diabetes increase the risk of cardiovascular disease, it is believed that the cardiovascular effects occur in children of mothers with diabetes (Halfon et al., 2012). The detection of cardiovascular changes of pregnancies complicated by diabetes is

already evident in the third quarter of life in utero. The fetal heart shows ventricular contractility reduced compared to pregnancies complicated by diabetes, even if they were complicated by hypertensive disease (Hibbard, 2002). These results suggest that the diabetic intrauterine environment induces biochemical changes in the cardiovascular system that affect their function and that these changes differ from those of other poor intrauterine environments as observed in the hypertensive pregnancies observed. Furthermore, systolic blood pressure, a known risk factor for cardiovascular disease, for children born diabetic mothers was significantly higher than that of those born of nondiabetic mothers (Silverman et al., 1991). Research data also show that exposure to a diabetic intrauterine environment during pregnancy is associated with an increase in dyslipidemia, vascular inflammation, and subclinical processes of endothelial dysfunction in offspring that are linked to the development of diseases related cardiovascular in later life. Dyslipidemia leads to an increase in total cholesterol and low-density lipoprotein cholesterol (LDL). Vascular inflammatory and endothelial dysfunction inhibitors have been shown to inhibit plasminogen activator-1 (PAI-1), vascular adhesion molecule 1 (VCAM), molecule-1 intercellular adhesion (ICAM) E-selectin, Insulin-like growth factor 1 (IGF-1) and other (Manderson et al., 2002). Consequently, women with gestational diabetes and their fetuses show changes in the marker for endothelial NOS (eNOS) uncoupling, oxidative stress, and endothelial dysfunction, and these changes are correlated with the levels of hyperglycemia (Mordwinkin et al., 2012).

Experimental Diabetes Research

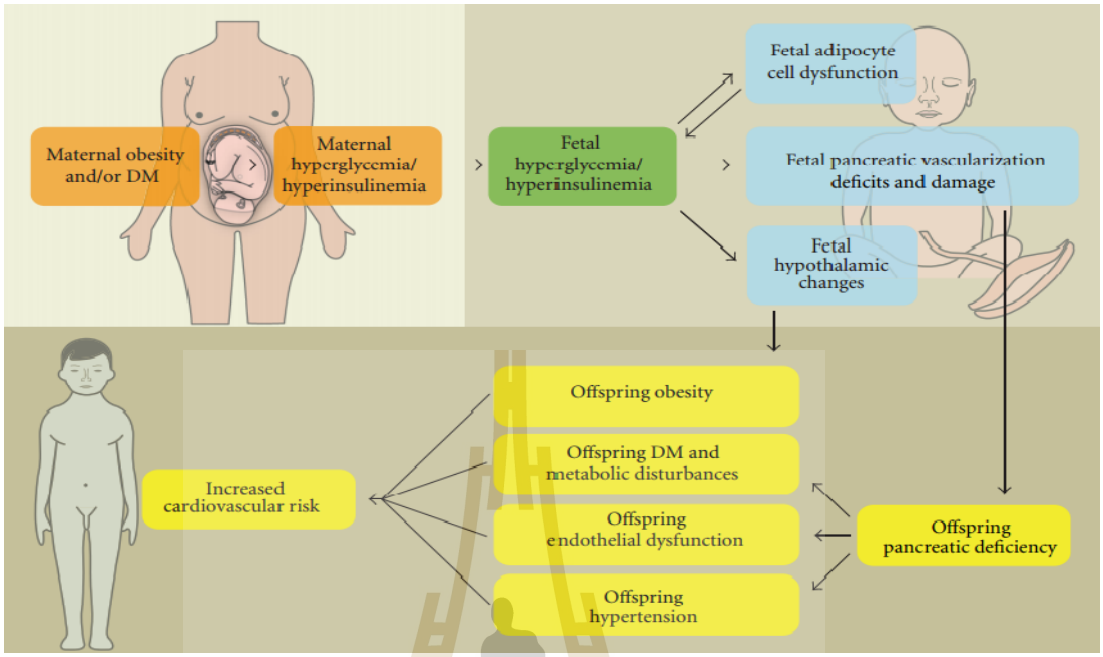


Figure 2 Maternal hyperglycemia, hyperinsulinemia and hyperglycemia, therefore, fetal and hyperinsulinemia affects the function of every step in the fetal metabolism, including the hypothalamus, the pancreas, and adipose tissue. These metabolic disorders are passed on to offspring and can eventually increase the cardiovascular risk in young adults (Vrachnis et al., 2012).

2.4 Glucose homeostasis

Most of the tissues and organs need glucose constantly, as an important source of energy. Low blood glucose concentrations may cause convulsions, loss of consciousness and death. On the other hand, long-lasting increase in the concentration of glucose can cause that the blindness, renal failure, cardiovascular disease, etc. must, therefore, blood glucose concentrations within narrow limits to be held. The process of maintaining the glucose in the blood to a stationary level called glucose homeostasis (DeFronzo, 1988). This is accomplished by the finely-regulation of

hormones of absorption of glucose, peripheral glucose uptake and the production of hepatic glucose during the ingestion of carbohydrates (Szablewski, 2011).

2.4.1 Mechanisms of glucose homeostasis

To avoid fasting hypoglycemia, postprandial hypoglycemia, the body can adjust the levels of glucose by secreting two hormones, insulin, and glucagon in opposition one to another. During periods of high blood sugar, the β-cell, the pancreatic islets of Langerhans cells secrete more insulin. Insulin is synthesized in β-cells of the pancreas in response to a rise in blood glucose and amino acid after a meal. The main function of insulin to counteract the procedures involved for a number of hyperglycemia-generating hormones to maintain low blood glucose levels. It also plays an important role in regulating the metabolism of glucose. This hormone that regulates the metabolism of glucose, in many areas, reducing liver glucose output, through decreased gluconeogenesis and glycogenolysis, facilitates the transfer of glucose in striated muscle and adipose tissue and inhibits glucagon secretion. Insulin is not secreted if the concentration in the blood is less than or equal to 3 mmol/L, but is secreted in increasing amounts, as glucose concentrations increase beyond this limit (Gerich, 1993). When blood glucose levels increase over the approximately 5 mmol/l β-cells increase their production of insulin. Glucagon production α-cells of the pancreas the islets of Langerhans remained calm, holding those hormones. It is to note that postprandially, insulin secretion occurs in two phases. An initial rapid release of insulin preshaped, followed by insulin increased synthesis and release in response to glucose in the blood. Long-term insulin release occurs if glucose levels remain high (Aronoff et al., 2004; Cryer, 1992). On the other hand, during periods of low blood sugar, the alpha of the pancreatic islets of Langerhans cells secrete glucagon more. It

is the main hormone responsible for maintaining glucose in plasma inappropriate levels during periods of higher demand functional (Cryer, 2002). This hormone counteracts the hypoglycemia and opposes actions of insulin stimulating hepatic glucose production. It induces a catabolic effect, mainly activating hepatic glycogenolysis and gluconeogenesis, resulting in the release of glucose into the bloodstream, thus increasing blood glucose levels. Digestion and absorption of nutrients that are also associated with increased excretion of multiple intestinal hormones that Act distal targets. There are more than 50 intestinal hormones and peptides are synthesized and released from the gastrointestinal tract. These hormones are synthesized by specialized enteroendocrine cells are found in the epithelium of the stomach, small intestine, and large intestine. It was demonstrated that ingest foods caused more potent insulin release from glucose is injected intravenously (Wook and Josephine, 2008). This effect, called the Incretin effect suggests that the signals of the gut are important in the hormonal regulation of the disappearance of glucose. The Incretin hormones are secreted peptide hormones from the intestine and specific criteria have to be met so that an agent called an Incretin. They have a number of important biological effects, as for example, the release of insulin, inhibition of glucagon and β-cells mass maintenance and feeding inhibition. Various Incretin hormones have been characterized, but currently (glucose-dependent insulin tropic polypeptide) GIP and GLP-1 (Glucagon-Like-1 peptide) are the only known incretins. GLP-1 and GIP are secreted in a nutrient-dependent manner and stimulate glucose-dependent insulin secretion. The hormones in the intestine are secreted at low basal levels in the fasting State. The secretion of hormones in the gut is regulated, at least in part, by nutrients. Intestinal hormones most plasma levels rise rapidly within minutes

of absorption of nutrients and they fall quickly thereafter mainly because they are eliminated by the kidney and are inactivated enzymatically (Drucker, 2007).

2.5 Hyperglycemia

Hyperglycemia is the technical term for the high blood glucose (sugar). It develops when there is too much sugar in the blood. High blood glucose occurs when the body has too little insulin or when the body does not use insulin properly. Hyperglycemia is a serious health problem for people with diabetes. In people with diabetes, there are two specific types of hyperglycemia that appear. Hyperglycemia fasting is defined as a larger 90-130 mg/dl (5-7.2 mmol/l) blood sugar after fasting for at least 8 hours. Postprandial (Hyperglycemia after eating) is defined as a blood sugar tends to be higher than 180 mg/dl (10 mmol/l). Hyperglycemia in diabetes can be caused by skip or forget oral or insulin glucose - lowering medicine, eating too many grams of carbohydrates by the amount of administered insulin, eating too much food and have many calories, infection, disease, increased stress, decreased activity or exercise less unusual physical activity, intense.

Early signs and symptoms of hyperglycemia include increased thirst, headaches, difficulty concentrating, blurred vision, frequent urination, fatigue (feeling of weakness, fatigue), weight loss, blood sugar more than 180 mg/dL (10 mmol/L), high levels of sugar in the urine. Prolonged hyperglycemia in diabetes may lead to vaginal and skin infections, slow-healing cuts and sores, low vision, nerve damage causing the painful cold or unfeeling legs, stomach and intestinal problems. In people without diabetes postprandial or meta-meal sugar rarely go above 140 mg/dL (7.8 mmol/L), but sometimes, after a big meal, a 1 2-hour glucose levels can reach 180 mg/dL (10 mmol/L). Blood glucose levels may vary from day to day. An occasional high level

(above 10 mmol/L) is not problem, provided it returns to normal (under 7 mmol/L; 126 mg/dL) within 12-24 hours. Persistently high levels of blood glucose (above 15 mmol/L; 270 mg/dL) for more than 12-24 hours may result in symptoms of hyperglycemia (Carroll et al., 2003).

2.6 Insulin

The Figure 3 shows the structure of insulin then. C-chain, connecting chains A and B is released together with insulin after the breakdown of the proinsulin. Insulin monomers aggregate to form dimers and hexamers (Bell et al., 1980). Zn Hexamer is composed of three associated insulin regulators in the triple symmetric pattern. Insulin is synthesized in the pancreas β-cells in the form of pre-proinsulin that is the precursor end the same gene is located on chromosome 11 near of Insulin-like growth factor 2 (IGF-2) (Bliss, 1993). Within a minute after the composition being discharged in external space of rough endoplasmic reticulum where it is cleaved to proinsulin by proteolytic enzymes. Proinsulin with a C string (which connects) to the chains A and B is then transported by macrovesicles to the golgi apparatus. Insulin is secreted from β-cells in response to various stimuli such as glucose, arginine, sulfonylureas, though physiologically the glucose is the main determinant. Several neural, endocrine and pharmacological agents may also be stimulated effect. Glucose is taken from β-cells through glucose transporter 2 (GLUT2) receptors. After entering the β-cell, glucose is oxidized by the glucokinase, which acts as a glucose sensor. Below 90 mg/dl glucose concentration does not cause the release of insulin.

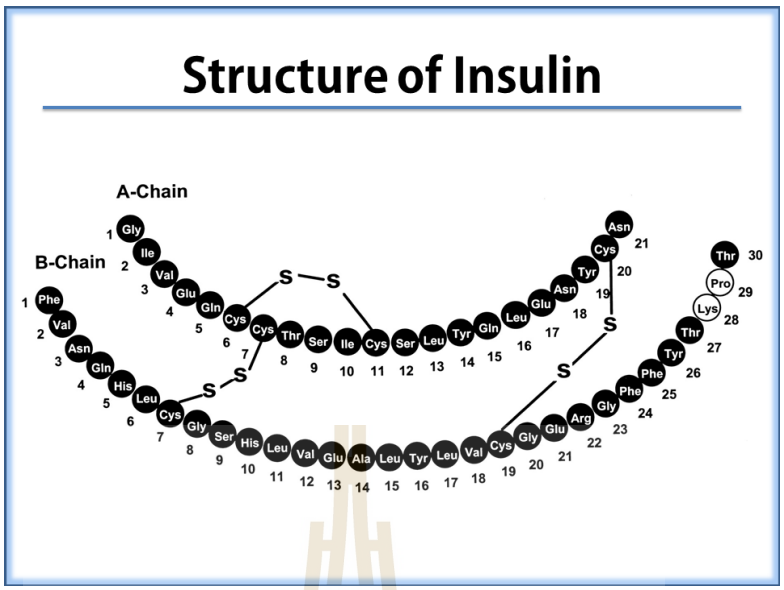


Figure 3 Structure of insulin (Bell et al., 1980).

Proinsulin is released into the vesicles. Conversion of proinsulin to insulin continues in the process of maturing the granules through the action of the prohormone converts 2 and 3 and carboxypeptidase H. Mature granules are translated with the help of microtubules and microfilaments. At such concentrations of glucose ATP-sensitive K^+ channel (KATP channel) through the open of flow keep the cell membrane potential a negative β-cell that channels unbound calcium (Ca^{2+}) voltage-gated are closed. As there is the increase of glucose in plasma, the absorption of glucose and β-cell metabolism is higher. An increase in the result of the concentration of ATP in the closure of the KATP channel, leads to a depolarization of the membrane, an opening of voltage-gated channels Ca^{2+}, Ca^{2+} influx, an increase of intracellular calcium concentration and, ultimately, exocytosis of insulin granules.

Structurally, the pancreatic KATP channel consists of two unrelated subunits: a sulfonylurea (SUR1) receiver and a channel subunit of potassium (Kir6.2) that form the central ion-conducting pathway (Figure 4). The mature KATP channel exists as a

steamer of SUR1 Kir6.2 and subunits in a stoichiometry 4:4 (Figure 4). A subunit c site-specific co specifies the pancreatic KATP channel, confers an advantage on the other secretagogues, sulphonylurea, glimepiride. Drugs sulfonylureas and not sulfonylureas act as secretagogues insulin closing those channels KATP preventing the metabolism of the β-cell. Diazoxide is a potassium channel opener and inhibits the secretion of insulin, independent of blood glucose levels (Gribble et al., 2003; Ashcroft and Gribble, 1999). Glucose and insulin secretion. β-cells respond to many nutrients in the circulation of the blood, such as glucose, other monosaccharides, amino acids and fatty acids. Glucose is evolutionarily the main stimulus for the release of insulin in some animal species since it is a major component of food and can accumulate immediately after the ingestion of food. In fact, in rodents and humans, the amplitude of the glucose-induced insulin secretion is much higher in comparison with that stimulated by protein or fat. Oral ingestion of 75g of glucose will cause insulin to plasma Ascend from a baseline level (20-30 pmol/l) 250-300 mmol/l in 30 min, while the intake of a similar amount of fat or a diet of fat and protein will increase by only 50 to 60 mmol/l plasma insulin levels respectively, in human subjects (Bakari and Onyemelukwe, 2004).

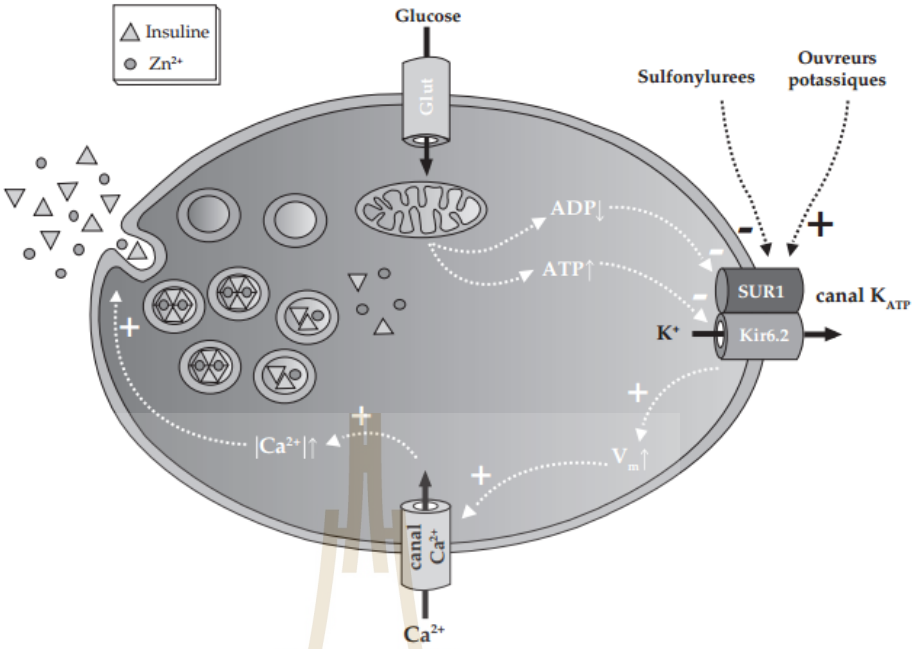


Figure 4 β-cell schematic (Gribble et al., 2003).

Glucose is the fuel supply forces for neurons, including the β-cells can be used other cells, alternative sources of fuel during brief periods of starvation, an adaptation that could predispose to glucolipotoxicity. β-cells do not seem to contain receptors for glucose of membrane - bound but they have several devices sensors that measure glucose in circulation. Glucose transporter 2 (GLUT2) is constitutively expressed in β-cells, is first found in the β-cells glucose sensor. Most of the glucose in the by facilitated diffusion GLUT2-mediated β-cell. GLUT2 is the glucose transporter expressed only in β-cells. Also, it is expressed in the liver and to a lesser extent in renal and intestinal absorption cells. Unlike the GLUT4, which is expressed mainly in the muscle and fat cells, GLUT2 mobilization to the plasma membrane is independent of insulin and the transporter protein shows a low affinity for the substrate, ensuring high glucose influx. After entering the β-cells, glucose is phosphorylated by the enzyme glucokinase speed limitation, a subtype of hexokinase. Glucokinase is

expressed in only four types of mammalian cells: liver cells, β-cells, enterocytes, and glucose-sensitive neurons. Two important properties enable glucokinase function as a sensor of glucose β-cells, differentiating it from other hexokinases. The first property is its relatively low affinity for glucose than other hexokinases. The second property is that not is inhibited by its product, often a regulatory feature in metabolism. This feature allows your ongoing activity despite a high load glycolysis. Glucokinase is the rate-limiting step in the metabolism of glucose of β-cells and is considered an important glucose sensor (Suckale and Soliman, 2008).

The insulin human is produced now by deoxyribonucleic acid (DNA) recombinant technology. Several companies differ in their methodology but the basic principle is the introduction of insulin human or genes of proinsulin in organisms such as E. coli or yeast. The technology of base of the yeast can provide physics-chemical structural and protein folding advantages although this may not be clinically significant. Agencies continue multiplying and in turn produce insulin or proinsulin becoming insulin by enzymatic cleavage. Dry human insulin is a crystalline powder with a molecular weight of 5808. Insulin rushes to its isoelectric 5.4 pH, whereas it is soluble at a pH of 2-3.1 IU of insulin corresponds to 38.5 g of dry matter. Insulin is available in the market the strength of 40 U and 100 U: 40 U/ml and 100 U/ml respectively. U500 is even available in the united states and U10 is sometimes formulated individually for use in infants with diluent provided by the manufacturer. Life half of injected Insulin is around 40 min.

2.7 Insulin resistance

Insulin resistance (IR) is a medical condition in which cells fail to respond properly to the hormone insulin. The body produces insulin when glucose begins to be released into the bloodstream from the digestion of carbohydrates in the diet. Normally this response to insulin causes glucose taken into the cells of the body, to be used for energy, and inhibits the body uses fat for energy. The level of glucose in the blood decreases, as a result, is within the normal range, even when a lot of carbohydrates consumed. When the body produces insulin in insulin-resistant conditions, the cells are resistant to insulin and it is unable to effectively use, leads to hyperglycemia. In the pancreas β-cells subsequently increase their production of insulin, contributing further to a high blood level of insulin. What often remains undetected and may contribute to the diagnosis of type 2 diabetes or latent autoimmune diabetes of adults (Chiu et al., 2007). Although this type of chronic insulin resistance is harmful, during the acute illness is actually a well-evolved mechanism for protection. Recent investigations have revealed that the insulin resistance helps keep the supply of glucose to the brain prevents the muscles take excessive glucose (Wang and Guanyu, 2014). Insulin resistance should be strengthened even under severe metabolic conditions such as pregnancy, during which the increased fetal brain requires more glucose. One of the functions of insulin is to regulate the supply of glucose to the cells to provide energy. Insulin resistant cells cannot take in glucose, amino acids, and fatty acids. So, glucose, fatty acids and amino acids "leaked" out of the cells. The decline in the proportion of insulin/glucagon inhibits glycolysis, which in turn reduces energy production. The

resulting increase in blood glucose may raise levels outside the normal range and cause adverse health effects, depending on nutritional conditions.

Certain types of cells such as fat and muscle cells require insulin to absorb glucose. When these cells do not respond properly to the circulation of insulin, blood glucose levels rise. The liver helps to regulate glucose levels by reducing the secretion of glucose in the presence of insulin. This normal reduction in the production of glucose from the liver cannot occur in people with insulin resistance. Insulin resistance in muscle and fat cells reduces the absorption of glucose (and also storage of glucose as glycogen and triglyceride, respectively), while the resistance to insulin in the liver cells results in the reduction of glycogen synthesis and storage and also a failure to suppress the production of glucose and released into the blood. Insulin resistance usually refers to reduced insulin glucose lowering effects. However, other functions of insulin may also be affected.

For example, resistance to insulin in the fat cells reduces the normal effects of insulin on lipids and results in the reduction of lipid absorption and greater hydrolysis of triglycerides stored in circulation. Greater mobilization of stored lipids in these cells elevates the free fatty acids in the blood plasma. Concentrations of fatty acids high blood (associated with resistance to insulin and type 2 diabetes mellitus), reduced muscle glucose uptake and increased hepatic glucose production contribute to high levels of glucose. High plasma levels of insulin and glucose due to insulin resistance are an important component of the metabolic syndrome. If there is resistance to insulin, more insulin needs to be secreted by the pancreas. If there is this compensatory increase, the concentrations of blood glucose. Is the most common type

of insulin resistance associated with overweight and obesity in a condition known as Metabolic syndrome.

Insulin resistance often develops into full type 2 diabetes mellitus (T2DM) or latent autoimmune diabetes in adults (Behme et al., 2003). This is often seen when hyperglycemia develops after a meal when pancreatic β-cells are not able to produce enough insulin to keep blood sugar levels normal blood against insulin resistance. The inability of β-cells produces insulin enough in a condition of Hyperglycemia is what characterizes the transition from resistance to insulin to T2DM (McGarry, 2002).

2.8 Mechanism of blood pressure regulation

One of the most important factors for the cardiovascular function of blood pressure. The blood pressure is defined as the force or pressure of the blood against the walls of the vessels of the cardiovascular system. The blood pressure is transient and fluctuates due to the pulse cycle. When the heart contracts to increase the blood from the heart and the vessels of the cardiovascular system, the blood pressure, and the maximum pressure in the container is known as the systolic blood pressure (SBP). However, if the heart relaxes between heartbeats (pulse), the pressure in the vessels decreases and the lowest pressure is the diastolic blood pressure (DBP). Clinically systolic and diastolic blood pressures are called systolic pressure on diastolic pressure. For example, a systolic pressure of 120 mmHg and a diastolic pressure of 80 mmHg are designated 120/80. Although the pressure can be recorded in many different units, clinically, blood pressures are measured in millimeters of mercury (mmHg).

Systolic and diastolic pressures are two or more independent values representing the cardiovascular performance of the heart. Clinically, these two values can be combined into an average arterial pressure, the mean arterial pressure called,

reflecting the influence of systolic pressure and diastolic pressure in the cardiovascular system. The other designation known as mean arterial pressure (MAP) is considered as an integrated blood pressure parameter. The mean arterial pressure can be calculated using the following formula:

$$MAP = DBP + 1/3 (SBP - DBP)$$ (Lee et al., 2006)

The calculation of the main blood pressure is a good way to assess stress on the vessel walls. This new parameter can be useful to quickly estimate the excessive burden on the cardiovascular system in the future. Although the various body tissues are able to regulate their own blood flow, the blood pressure should remain constant enough that the blood changes from one area of the body to another. The mechanisms used to regulate blood pressure depends on whether short- or long-term adjustment needs.

2.8.1 Short-term regulatory

Short - term regulatory mechanisms of blood pressure that work for a few minutes or hours are designed to correct transient imbalances in blood pressure, as during movement and changes in the body position occurs. These mechanisms are also responsible for maintaining the blood pressure levels in survival situations that endanger life, as in the case of an acute bleeding incident. The short-term regulation of blood pressure is mainly based on neuronal and humoral mechanisms, including fast neural mechanisms.

2.8.1.1 Neural Mechanisms

Neural control centers for regulating the blood pressure in the reticular formation of the cord and the lower third of the bridge, with the integration and modulation of the autonomous nervous system (ANS) reactions occurring. This area of the brain contains vasomotor and heart monitoring centers and is often referred to collectively as the cardiovascular center. The cardiovascular parassimpáticos center sends impulses to the heart via the vagus nerve and compassionate heart and blood vessels into the spinal cord and the peripheral sympathetic nerve impulses. Heart stimulation leads to a decrease in heart rate while the causes of sympathetic stimulation increased heart rate and contractility of the heart. The blood vessels are selectively innervated by the sympathetic nervous system. Increased sympathetic activity causes a narrowing of the small arteries and arterioles with a resulting increase in peripheral vascular resistance. Autonomic nervous system blood pressure control is mediated by intrinsic blood flow reflexes, superior reflexes, and extrinsic neuronal control sites. Individual reflexes, including baroreceptor and chemoreceptor reflexes, are arranged in the circulatory system and are designed for fast regulation and short-term blood pressure. Extrinsic sensors reflections from traffic. They include reactions in the blood pressure associated with factors such as pain and cold. The nerve pathways of these reactions are more diffuse and reactions are less uniform than the intrinsic reflexes. Many of these reactions are channeled by the hypothalamus, which plays a crucial role in the control of the sympathetic nervous system reactions. Among the top middle of the answers are those caused by changes in mood and emotion. Baroreceptors are sensitive to pressure in the walls of the blood vessels and heart receptors. The carotid and the aorta

baroreceptors are removed in strategic positions between heart and brain. Respond to changes in the area of the vessel wall by sending pulses to the cardiovascular center in the brain stem to make appropriate changes in heart rhythm and vascular tone of the smooth muscle. For example, the blood pressure drop occurs when moved from the rest position to the standing position causing a decrease in the stretch baroreceptor, with a resulting increase in heart rate and induced sympathetic vasoconstriction, which causes an increase in peripheral vessel resistance. Baroreceptor resetting refers to the activation of a receptor in the direction in the pressure threshold to a change in the prevalence of MAP (Krieger, 1986; Lohmeier et al., 2004). During the restoration, the baroreceptor mechanism is set to a high pressure, thus maintaining performance rather than suppressing hypertension. There seem to be two different forms of adaptation that are characterized by the underlying mechanism primarily causing the variation of the pressure threshold. The first form is called acute baroreceptor reversal. It begins with rapid changes in the pressure to which the receptors are exposed for a short period of time, usually 20 minutes or less (Munch et al., 1983).

This initial variation of the threshold voltage remains stable for at least one hour, without changing the sensitivity of the receivers, and is completely reversible. The second type is called Chronic Wielder, in which the sensitivity of the baroreceptor decreases. The pressure threshold will be moved in the direction of the pressure change, but this time the changes are not easily reversible (Sleight et al., 1977). The first proof that adapted Baroreceptors appeared in 1956 (McCubbin et al., 1956). At this time, a study of nerve receptors and sinus nerve aorta in dogs with renal hypertension has been shown to induce baroreceptor burning and high pressure a high-pressure threshold at which the shot was continuous; This was significant

compared to normal controls. To confirm that the baroreflex remained functional over these dogs, a separate set of experiments was performed to document pressure responses to occlusive arteria carotid before and during the development of renal hypertension, weekly. There was no pressure response Carotid occlusion attenuation increased as hypertension, suggesting that the channel baroreflex dogs was intact in renal hypertension. Subsequent studies have confirmed the presence of re-regulation receptors in the aorta wall and carotid sinus (Sleight et al., 1977). The underlying mechanisms for the adaptation and the relative importance of chronic acute baroreceptor adjustment and are hardly understood. Myelinated fibers are in the possibilities of baroreceptors neuro rules and are connected to a rapid recovery, while unmyelinated fibers seem to be re-launched chronic hypertonia models (Seagard et al., 1992; jones et al., 1977). It has also been shown that in general the size of the adjustment does not seem to correlate with the degree of change in the MAP (Munch et al., 1983). Adjustments in the context of chronic hypertension have been attributed to a damage to the receptors, lead to a change in the coupling between the recipient and the vessel walls, certain receptors themselves have genetic properties and reduced compliance the vessel walls, and the receivers are integrated. (Aars, 1968; Brown et al., 1976). This last option is particularly advantageous as the prevalence of arteriosclerosis and hypertension coexists. It appears that adherence to the wall, which is an activation susceptibility factor large baroreceptor, decreases when compliance with the blood vessels decreases. However, the threshold pressure at which the baroreceptor is activated depends on the blood pressure and other factors that are not yet defined (Andresen, 1984). Arterial baroreceptor controls the sympathetic drive to the heart and peripheral blood vessels. Constantly adjust to maintain systemic changes

in the blood pressure sympathetic activity relative homeostasis. Based on this mechanism, it was thought that the separation of the result of the baroreceptor afferent to chronically increased sympathetic activity, suggesting hypertension, was confirmed by a number of early experiments (Ferrario et al., 1969). Subsequent work confirmed, however. In animal studies, dogs with sinoaortic baroreceptor denervation (SAD) was conducted in a very labile MAP in response to environmental irritation and physical movements, but only a slight increase in MAP in terms of controls (Cowley et al., 1973). In addition, it significantly reduces the ability to maintain a stable blood pressure after hemorrhage. Similar effects of SAD are reported by transient MAP without significant persistent hypertension in rats, rabbits, cats and monkeys (Osborn et al., 1990; Saito et al., 1986; Ramirez et al., 1985). It was then done hypertension and decreased sympathetic nervous system (SNS) activity. Several mechanisms have been proposed to explain long-term baroreceptor unregulated MAP. One of the most popular theories involved the reset baroreceptor phenomenon discussed in the previous section. Another explanation is that in addition to the carotid sinus and baroreceptors aortic cardiopulmonary receptors are actively involved in the control of blood pressure, which is involved in the short term, as evidenced by the fact that the combined denervation SAD receptor and cardiopulmonary MAP increases dogs. A third explanation relates to evidence that the enhancement of the baroreceptor control system was not sufficient to account for the long-term consistency of the blood pressure. Studies on narcotized dogs and rabbits, for example, have shown that the baroreceptors show only 65-75% for a particular blood pressure (Cowley, 1992) change arterial. It was assumed that one mechanism was the last possible loss-inducing baroreceptor activation after SAD. The loss of this duration impulse leads to

a modification of the neuronal process in the nucleus of the tract solitaries (NTS) or another route baroreflex nuclei, as shown by experiments on animal models SAD (Alan et al., 1997). Arterial chemoreceptors are chemosensitive cells that control the oxygen content, carbon dioxide, and hydrogen blood. They are found in the body of the carotid, at the crotch of the two organs of the common carotid artery and the aorta in the aorta. Because of its location, these chemoreceptors are always in close contact with arterial blood. Although the main function of chemoreceptors is regular airing as they can communicate with cardiovascular centers in the brainstem and induce a generalized vasoconstriction. Every time the blood pressure falls below a critical threshold, the chemoreceptors are stimulated due to the decrease in oxygen and carbon dioxide ion storage and hydrogen.

2.8.2 The long-term regulatory

The long-term regulatory mechanisms control the daily, weekly and monthly blood pressure. Although the neural and hormonal mechanisms in fast-term of the measure of the blood pressure rule, they are not able to maintain their effectiveness over time. Instead, the long-term regulation of blood pressure is largely attributed to the kidneys and their role in the regulation of extracellular fluid volumes. After the late Arthur Guyton, a well-known physiologist, the extracellular volume, and blood pressure are regulated around the equilibrium that is the normal pressure for a particular individual. When the body contains an excess of extracellular fluid due to an increased intake of water and salt, at which the pressure rises in the blood and the rate that kidney is excreted through the kidney (pressure diuresis) and salt (ie, natriuresis). Therefore, there are two ways to increase the blood pressure with the design: one is the removal of salt and water to a higher-pressure level and the second

modification of the fluid level change extracellular wherein diuresis and natriuresis occur. The role of the kidney in long-term regulation of blood pressure can be influenced by a number of factors. For example, excessive activity of the sympathetic nerve or release of vasoconstrictors can affect kidney transmission of blood pressure. Similarly, changes in neural control of humoral and renal function may cause the diuretic-natriuretic process to move to a fluid level or higher pressure, thereby initiating an increase in blood pressure. There are two general mechanisms by which an increase in the fluid volume can increase blood pressure. It is a direct effect on the delivery and the other indirect self-control of the blood flow and its effect on the peripheral vessel resistance. In the distribution of the blood flow in different body tissues according to their metabolism needs auto regulation mechanisms. If the blood flow to a specific tissue bed is too high, narrow the local blood vessels, and if the flow is small, local vessels dilate. In situations of increasing the extracellular fluid volume and causing an increase in cardiac output, all body tissues are exposed to the same throughput increase. The result is a generalized exacerbation of the arteries and an increased peripheral vascular resistance and blood pressure. The role of the kidney in the regulation of blood pressure is demonstrated by the fact that many antihypertensive drugs produce their effect of lowering blood pressure by increasing the excretion of sodium and water.

2.8.2.1 Humoral Mechanisms

Several humoral mechanisms contribute pressure to the regulation of blood, including the renin-angiotensin-aldosterone system and vasopressin. Other humoral substances such as adrenaline released from a sympathetic neurotransmitter from the adrenal gland directly stimulate an increase in heart rate, cardiac contraction,

and vascular tone. The renin-angiotensin system plays a central role in the regulation of blood pressure. Renin is an enzyme that is synthesized and released from the juxtaglomerular cells of the kidney in response to increased sympathetic nervous system activity or a decrease in blood pressure, extracellular fluid concentration, or extracellular sodium concentration. Most renin is released to the kidney and acts in the bloodstream, where it converts the plasma protein excellently enzymatically inactive called angiotensinogen into angiotensin I. Angiotensin I is then converted by angiotensin II. This transformation is almost completely in the lungs, such as blood catalyzed by the small vessels of the lungs, through an enzyme called angiotensin-converting enzyme flowing through which is present in the endothelium of the pulmonary vessels. Although II angiotensin has a half-life of only a few minutes, renin persists in the circulation for 30 minutes to 1 hour and continue to produce angiotensin II during this time. Angiotensin II regulation works both short- and long-term blood pressure. It is a potent vasoconstrictor, especially arteries and to a lesser extent, veins. Constriction of arterioles increases the peripheral vascular resistance and thus contributes to the short-term regulation of the blood pressure. Angiotensin II also decreases the excretion of sodium, increasing sodium reabsorption by the kidney proximal tubules. A second important role of angiotensin II, the stimulation of aldosterone secretion by the adrenal gland, contributes to the long-term regulation of the increase in salt retention and water by the kidneys, blood pressure. Vasopressin, also known as antidiuretic hormone (ADH), is released by the posterior pituitary in response to decreased blood volume and blood pressure, an increase in osmolality of body fluids and other stimuli. Vasopressin has a direct vasoconstrictor effect,

especially in the vessels of splanchnic circulation, which provides the abdominal organs.

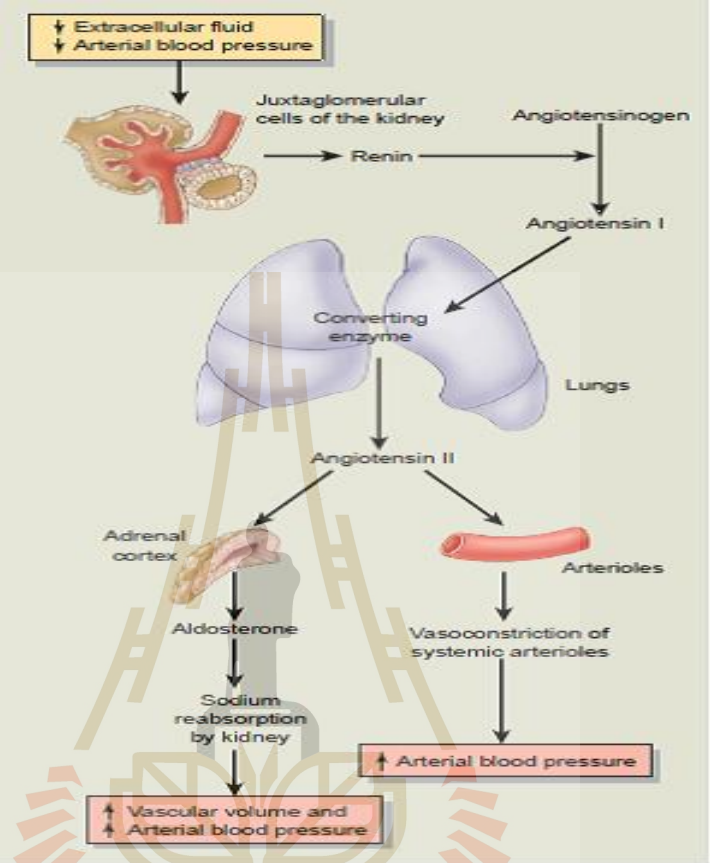


Figure 5 The blood pressure regulation by the renin-angiotensin system. Renin converts angiotensinogen plasma protein enzyme of angiotensin I; The converting enzyme inhibitors in the lung transformation of angiotensin I to angiotensin II; And angiotensin II causes vasoconstriction and increases the retention of water and salt by direct action on the kidney and increasing aldosterone secretion from the adrenal cortex (Paul et al., 2006).

However, long-term vasopressin does not increase the blood pressure can maintain, and make the induced hypertension vasopressin does not increase hormones sodium retention or other vasoconstrictor substances. It has been suggested that

vasopressin plays a permissive role in hypertension due to its water retention properties or as a neurotransmitter that alters the function of ANS.

2.9 Effect of insulin resistance on cardiovascular disease

Insulin resistance modified reveals a biological response to insulin. In the early stages of insulin resistance is a compensatory increase in insulin concentration. Although persistence hyperinsulinemia can compensate for some of the biological effects of insulin, in tissues can lead to overexpression of actions that keep normal insulin sensitivity or altered minimally. In addition, high insulin concentrations can act by receptor insulin-like-growth-factor 1 (IGF-1). Thus, stressing certain insulin resistance actions with other concurrent actions results in different symptoms and effects of resistance syndrome in clinical insulin.

Insulin and IGF-1 stimulation increases the amount of PI3 -kinase associated with IRS, and the binding process is associated with increased activity of the enzyme. Activation of the enzyme is crucial for transducing the actions of these peptides in cardiovascular (CV) tissue (Sowers et al., 1997; Sowers, 1997) as well as conventional insulin-sensitive tissues (Hunter et al., 1998) (Figure 6).

The insulin and the IGF-1 and a functional homology sensitive tissue CV insulin and classic adipose tissue such as skeletal muscle and. IGF-1 in contrast to insulin is synthesized by vascular smooth muscle cells (VSMCs) and cardiomyocytes (Sowers, 1997; Sowers 1996). The production of IGF-1 in the CV tissue stimulated by mechanical stress, insulin, angiotensin II (Ang II) and other growth factors. Insulin and IGF-1 reduce vascular tone, because of the effects on the metabolism of partial cations (Figure 6).

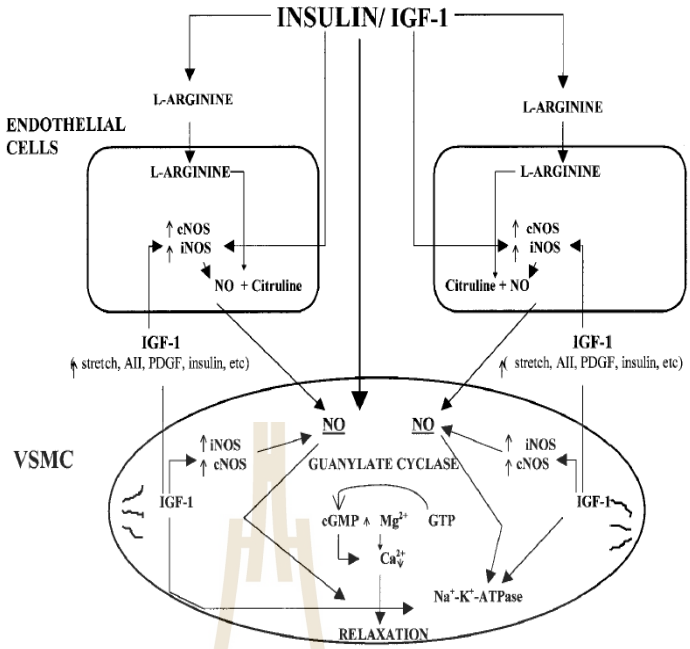


Figure 6 The actions of insulin and IGF-1 on cationic metabolism and vascular tonus (Samy et al., 2001).

Both peptides reduce calcium influx in vascular smooth muscle cells (VSMC) currents to reduce mediated Ca^{2+} activated receptor voltage channel and associated with contraction responses VSMC. Both peptides increase the Ca^{2+} adenosine triphosphate activity of Ca^{2+} ATPase in the plasma membranes and intracellular organelles and activated potassium channels dependent Ca^{2+}.

Since no active K-dependent Ca^{2+} channels, the effect of insulin / IGF-1 in these channels are partly mediated by the increased production of NO by endothelial cells and VSMCs. Another mechanism by which insulin / IGF-1 reduces Ca^{2+}/ intracellular VSMC vasoconstriction by stimulating the Na^+, K^+ ATPase pump, by transcriptional and post-translational modifications of the pump. That the Na^+, K^+ ATPase stimulates the transport of Na^+ and K^+ ions against concentration gradients, energy must be provided by hydrolysis of ATP. The ATP generated by aerobic glycolysis is preferably

used for this procedure, suggesting that the glucose transport mediated by insulin / IGF-1 is a possible mechanism by which these peptides stimulate the activity of the pump. Recently, it has been shown that the activation of insulin strains / IGF-1 Phosphoinositide 3-kinase (PI3K) has been crucial for the ability of these peptides to stimulate the pump. Therefore, PI3K responses modified insulin / IGF-1 might explain the decreased ability of these peptides to mediate vasodilatation in patient's resistant to insulin. As shown, Ang II interferes with the activation of PI3 in VSMC and cardiomyocytes, the over-expression of the renin-angiotensin system (RAS) is one of the main factors of resistance to CV / IGF-1 (Figure 8).

Classically sensitive tissues such as muscles and adipose tissue. PI3 kinase average increases in the ability of NO, Na^{+}, K^{+}, and sensitivity to myofilament calcium (Ca^{2+}) increase in traffic and the translocation of NO synthase and pumping and conveyors of glucose units. Therefore, the resistance to the action of insulin and IGF-I occurs in these tissues whenever it is a diminished activation of PI3K.

Several studies have shown a close relationship between the use of insulin-dependent glucose and increase in blood flow in response to insulin muscles. Peripheral vasodilatation, which occurs in the systemic infusion of insulin, is eliminated by the administration of inhibitors of the NO synthase enzyme, a crucial role for NO in the vasodilating response to normal insulin. The effect of insulin vascular NO production induces (Chen et al., 1998). In fact, significant evidence suggests that the insulin sensitivity is selectively impaired in extrahepatic tissues, the development of hypertension associated with increased salt sensitivity (Ferri et al., 1998).

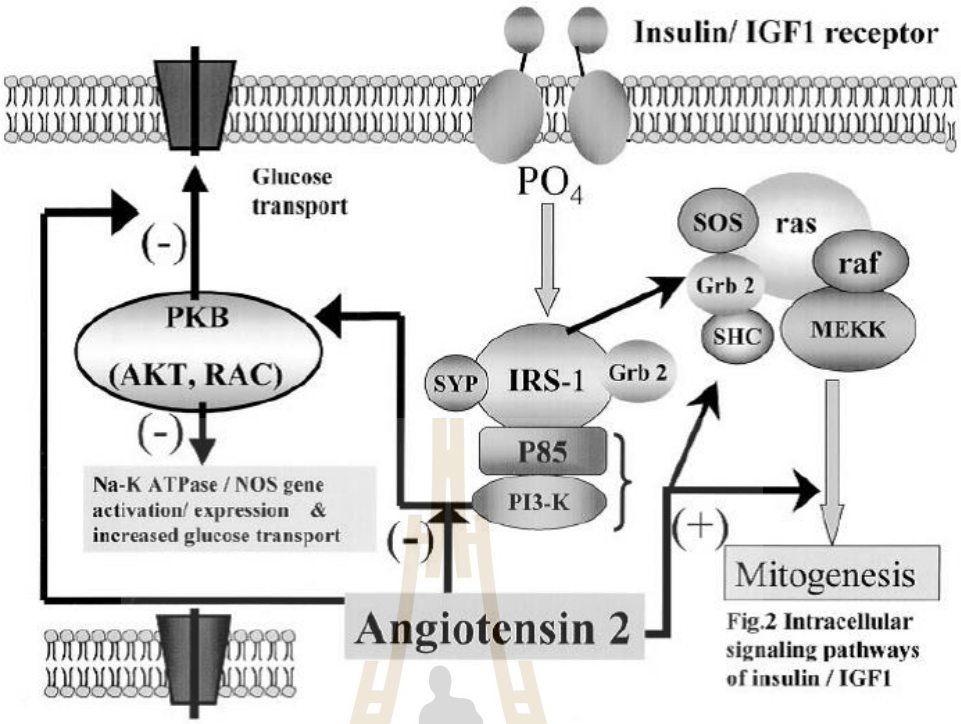


Figure 7 The interaction of insulin / IGF-1 and RAS in cardiovascular tissues shows insulin / IGF-1 signaling steps inhibited by Ang II (Samy et al., 2001).

2.10 Effect of insulin resistance on renin-angiotensin system (RAS)

The renin-angiotensin system (RAS) is traditionally known for its role in the regulation of blood pressure, fluid balance, and electrolytes (Schmieder et al., 2007). Angiotensinogen (Ang), the main RAS peptide precursor undergoes enzymatic cleavage by renin and angiotensin converting enzyme (ACE) to form angiotensin II (Ang II), the main system effector peptide (Castrop et al., 2010). Ang II exerts its physiological effects by two receptors with the G protein-coupled Ang II receptor type 1 (AT_1) and types 2 (AT_2). In addition to the systemic RAS, there are also several local organs such as brain tissue, pancreas, heart and obese. Since Ang II blood pressure is increased by AT_1, ACE inhibitors (ACE inhibitors) and angiotensin

receptor blocker (ARB) are used clinically as antihypertensive agents (Jones et al., 1997; Paul et al., 2006). The evidence for the role of systemic and local RAS in hypertension, renal function, and cardiovascular disease was previously investigated, RAS and cardiovascular disease; Adipose RAS and cardiovascular disease; RAS brain and hypertension; Endocrine and paracrine RAS; RAS fat and metabolic disorders (Thatcher et al., 2009). Interestingly, epidemiological studies have shown that patients with ACE inhibitors or ARBs have a lower risk of developing compared to those treated with another antihypertensive type 2 diabetes. Angiotensin is cleaved by renin-angiotensin I (Ang I) enzyme. Renin is mainly caused by the kidneys and their secretion is the main limiting factor in the regulation of the systemic RAS step. Renin receptor can also come to recognize the renin/prorenin recently and increase the efficiency of the catalytic formation of angiotensin I. Angiotensin I is then cleaved by the angiotensin-converting enzyme, which is currently mainly present in the vascular endothelium of the lung, Angiotensin II. Alternatively, angiotensin II can also be formed by the action of chymase and cathepsin, in particular, local RAS (Figure 10).

From this observation, we also showed that mice overexpressed renin in the liver develop glucose intolerance. Also, recently, he showed that adipous RAS specific overactivation leads to intolerance and resistance to systemic insulin to glucose (Kalupahana et al., 2011). Overall, this shows that the systemic or chronic overactivation of obese RAS led to systemic insulin resistance.

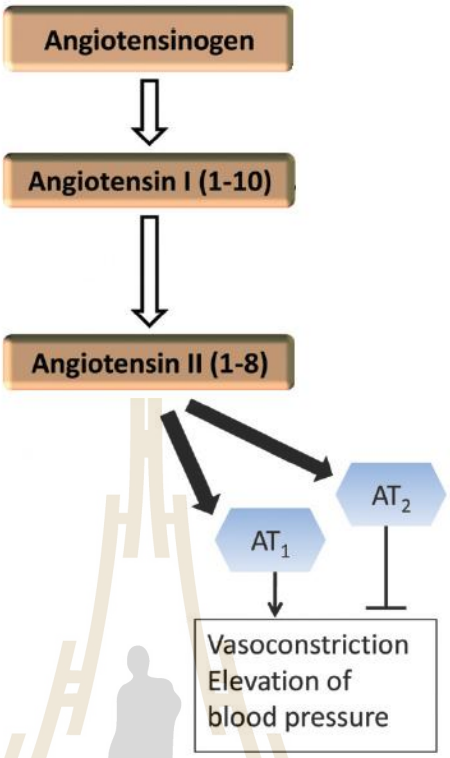


Figure 8 Angiotensinogen is cleaved by renin and angiotensin converting enzyme (ACE), angiotensin II (Ang) I and II, respectively. Ang II acts through Ang II type 1 receptor (AT_1) and type 2 (AT_2) its physiological effects (Schmieder et al., 2007).

2.11 Effect of renin-angiotensin system on blood pressure control

The systemic system function Renin-angiotensin (RAS) in the regulation of blood pressure and volume homeostasis and the pathophysiology of hypertension (HTN) has been the subject of several decades. Increased accessibility activity is also an important factor in many disease states due to angiotensin II (Ang II) increases aldosterone and blood pressure and contributes to the development of lesions in the final body effects directly on the heart tissue, vascular and kidney (Paul et al., 2006). As is generally known, Angiotensin II is systematically generated. RAS substrate Ang is released from the liver and is cleaved by reining circulating by the juxtaglomerular

kidney secreted to Angiotensin I. Further, Angiotensin I is easily activated by Angiotensin II converting enzyme (ACE) High concentrations on the surface of the endothelial cells in the pulmonary circulation (Ichihara et al., 2004).

Angiotensin II, which is the strongest RAS active product, affects it on specific receptors. Note that this vision of RAS is expanded by newer results that increase the complexity of the system. They described a different receptor and signaling pathways. Routes, additional peptides were recognized as a 1-7 and the proposed substitutions for the formation of Angiotensin II, for example, serine protease chymase (Figure 11). The change from our inspection of the RAS became the concept of "local" RAS or substance). Among them, the pathophysiological effects of intracranial RAS were the main target in the pathogenesis of HTN and progressive renal damage. Many data are available that support the central role of internal RAS exerts various pathological effects on the development and progression of HTN and kidneys. The large proportion of Angiotensin II at the cellular level, such as cell growth and apoptosis, may be important factors important physiological stimuli. Over-expression transgenic and knockout models as genes of animals showed a functional role of RAS in prenatal development (Brand et al., 2006; Takahashi et al., 2005). In addition, many epidemiological and experimental studies have provided a strong RAS involvement in fetal programming of hypertension and sick adults (Woods et al., 2001). Programming during fetal life occurs with an unfavorable fetal environment and leads to long-term adaptation reactions that lead to structural and physiological changes and the further development of HTN (Barker et al., 1989; Brenner et al., 1988). Thus, we will summarize the physiological effects of angiotensin II, including the internal renin angiotensin system (RAS) and the latest results related to its role in the pathogenesis

of HTN. Evidence for the effects of internal RAS in fetal programming regarding HTN is also discussed.

2.11.1 Physiologic actions of angiotensin II (Ang II)

Physiological effects are a renin-angiotensin system (RAS) critical to manipulating the stability of the blood pressure and the homeostasis of the extracellular fluid. Most of these actions are performed by RAS Angiotensin II with its receptor in a variety of organs and tissues. Angiotensin II is one of the most potent vasoconstrictors known and affects the heart, vascular system, nervous system, digestive system, skin, reproductive system, sense organs, tissue, lymph, adipose tissue, adrenal glands, and kidneys. It seems likely that local and systemic effects of the RAS must be integrated into the concerted action. Vasoconstrictor responses of arterioles afferents angiotensin II mediated by angiotensin II-1_A (AT_{1a}), and 1_B (AT_{1B}), while responses to vasoconstrictor angiotensin blood-derived arterial II are mediated by only AT_{1a} receptors in the mouse kidney (Harrison et al., 2002). Angiotensin II also reduces the coefficient increases while the resistance to glomerular filtration and laxative arterioles, which contributes to the reduction of the glomerular filtration rate. Acute infusion of Angiotensin II is sufficient to alter the cause of the proteinuria renal hemodynamics. However, sustained increases in Angiotensin II-induced intracranial proteinuria induced by progressive injury to the glomerular filtration barrier, which consists of products of the endothelial glomerular membrane and the basal glomerular (Whaley et al., 2006). The pharmacological effect of Ang II is the glomerular filtration rate (GFR) is blocking variable, either increased, decreased or unchanged. Most clinical studies show that the GFR is introduced during the blockade of angiotensin II remains stable. II increases the nephron GFR single currency and single

nephron plasma when the blood pressure significantly reduces angiotensin blockage. On the contrary, often a significant reduction in the glomerular filtration rate was observed in patients with renal disease. Presumably, the lowering of the blood pressure by blocking Angiotensin II stimulates the sympathetic nervous activity, a vasodilator.

Angiotensin II also has a modulating effect on the sensitivity to a tubuloglomerular feedback mechanism which ensures equilibrium between resorption tubules of the filtered load and GFR setting. Transgenic mice analysis showed micropuncture in a substantial role of Angiotensin II in the regulation feedback tubuloglomerular mediated AT_{1a} receptor (Schnermann, 1999). Ang II is involved in the regulation of the renal excretion of sodium and water not only by the effects on renal hemodynamics, GRF and the regulation of the secretion of aldosterone, but also by direct effects on the transport of renal tubules. In addition, it stimulates the secretion of H^+ and HCO3 in the proximal and distal tubular reabsorption and regulates cell H^+ ATPase activity intercalated in the collection tube (Valles et al., 2005). The activation of the Na Exchange +/H^+ apical and basolateral Na+ /HCO3 cotransport basolateral Na^+, K^+ -ATPase and apical H^+ -ATPase is involved in the absorption of sodium and bicarbonate-induced transcellular Angiotensin II in the proximal tubule, while the exchange of Na^+ H^+ and H^+ -ATPase contributes to the absorption of sodium and bicarbonate in the distal tubule. In addition, it was shown that the metabolism of water abnormally absents in mice the AT_{1a} receptor, suggesting that Angiotensin II stimulates the urinary concentrating mechanism in the internal medullary collection line, which leads to an increase in the absorption of water.

Important data provide convincing evidence that Angiotensin II impacts the growth of the kidney cells. The fact that Angiotensin II-mediated proliferation or hypertrophy of kidney cells is rather dependent. All components of the RAS are regulated in the kidney organogenesis and the RAS in the development of renal blockage shows serious renal abnormalities and abnormal cell renewal (Kang et al., 2003). The effects of Angiotensin II-induced growth is also present in the development of glomerulosclerosis and tubule-interstitial fibrosis, and anger these effects is a primary goal of the renoprotection way in clinical Nephrology.

2.11.2 Angiotensin II receptor

In different regions, segments of nephrons and types of cells in the kidney, Angiotensin II receptors play an important role in the complex actions and stretches of Angiotensin II on renal function. AT_1 receptors (subtypes 1A and 1B) and Angiotensin II type 2 (AT_2) receptors are two major types of receptors Angiotensin II. The AT_1 receptor is primarily responsible for most of the actions of Angiotensin II and has been widely distributed by the kidney. In hypertension Angiotensin II-dependent glomerular vessel and AT_1 receptors are down-regulated, but the proximal tube receivers will either be adjusted or altered. Deficient mice AT_{1a} receptors showed a predominant role of AT_{1a} receptors and a limited role of the AT_{1B} receptor in the regulation of blood pressure and renal responses to the administration of angiotensin II in the long run.

The expression of the AT_2 receptor is found in the proximal tubule, collecting channel, glomerular epithelial cells and a part of the vascular system. The AT_2 receptor significantly increases during fetal life and decreases greatly after birth. It is believed that the activities mediated by the AT_2 receptor are generally performed

against those of the AT_1 receptor while the functions of the AT_2 receptor are largely unknown. The absence of the AT_2 receptor leads to renal vascular disease and hypersensitivity to angiotensin II, including anti-Natriuretic, hypertension, suggesting that the AT_2 receptor plays a protective role in the regulation of bradykinin-mediated and nitric oxide against anti-Natriuretic actions and angiotensin II- Pressor.

2.11.3 Role of renin-angiotensin system - fetal programming of hypertension

Fetal programming is the process by which the negative effects of environmental damage can predispose to adult disease early in life, especially in the uterus prenatal death (Barker et al., 1989). He confirmed for the first time an inverse association with a birth weight and the death of cardiovascular disease in the adult age, which shows that some components of the prenatal environment, partly related to the death of the mother, can "program" the individual into one Increased cardiovascular risk. Since then, several studies have provided a strong link between events and the following intrauterine conditions such as glucose tolerance, type 2 diabetes, obesity, and chronic renal disease. Among them, the programming of hypertension has been the most studied. Both epidemiological and experimental data have shown strong evidence that the prenatal environment can alter blood pressure in adults. Linkage mechanisms with low birth weight (LBW) with hypertension appear to be multifactorial and involve changes in natural systems of regulation and renal function that affect long-term control of blood pressure. Burner suggested that the HTN is associated with congenital loss of the number of neurons that would result in reduced sodium renal excretion and increased sensitivity to sustain (Brenner et al., 1988). This assumption is based on the understanding that in the context of the loss of neurons, compensatory hypertrophy and hyper in the remaining glomeruli occurs the

proper renal function. Although not the exact mechanism of reducing the number of neurons has been clarified possible causes suggested program; DNA methylation changes, the increase in apoptosis in the development of the kidneys, renal RAS activity, and increased fetal exposure to glucocorticoids. It is known that all the components of the RAS play present in the kidney and the development an important role in nephrogenesis. Several experimental models have shown that the reduced expression of RAS components during nephrogenic time helps to reduce the number of neurons and HTN in later life. Specifically, Woods noted that the restriction of the strain protein during pregnancy was associated with renal renin mRNA and Angiotensin-II levels in the tissues of the offspring at birth in rats (Woods et al., 2001). RAS suppression of this model was associated with a reduction in the glomerular count, increased blood pressure and a decrease in GFR.

2.12 Taurine

Figure 9 Chemical structure of Taurine.

Taurine (2-aminoethanesulfonic acid) is a sulfur-containing amino acid in condition synthesized in the body as a result of cysteine metabolism (Figure 12). This amino acid passes the blood-brain barrier and is distributed in the brain, heart, skeletal muscle, intestine, bile, liver, kidney, retina, leukocytes, thrombocytes and 0.1% of

total body weight (Bidri and Choay, 2003). In premature infants, the enzymes that cause cystathionine to cysteine are lacking in its deficiency. For this reason, taurine supplementation is necessary for small children. Taurine-containing energy products are Red Bull, AMP Energy, Celsius, Full Gas, 5 Hour Energy, Monster Energy, Rockstar, and Venom (Bidri and Choay, 2003).

Taurine deficiency causes a reduction in oxygen consumption and the synthesis of adenosine triphosphate, causing superoxide formation and generating an oxidative stress. A number of conditions, including the abnormalities in the central, epilepsy, myopathy, hypertension, cardiovascular diseases such as arrhythmias, cardiomyopathy and heart failure, high cholesterol levels, liver disorders, mucoviscidosis, retinal degeneration, cancer, immune deficiency, development of nervous system growth and development Associated with taurine deficiency (Yamori et al., 2010). It is reported that supplementing the diet taurine prevents the progress of hypertension, coronary heart disease, and endothelial dysfunction in young men, type 1 diabetes, hepatitis and high cholesterol. This amino acid has a different pharmacological activity. Taurine is an anxiolytic effect of the activation of the glycine receptor and exerts anti-depressants, anti-inflammatory, anti-apoptotic and antioxidant activity.

Taurine increases the development of nerve tissue and is important for synaptic transmission in the central nervous system. Protects against seizures and glutamate excitotoxicity. Hypoxia glutamate brain released very rapidly, which leads to the opening of calcium channels and its concentration in nerve cells to increase. Taurine plays a neuroprotective role by interacting with the GABA receptor (Yamori et al., 2010) and regulating the homeostasis of cytoplasmic and mitochondrial calcium

mirrors due to the inhibition of the Ca^{2+} influx induced by glutamate through channels L-, P/Q- and calcium channel N-type with the closed voltage (Oja and Saransaari, 2007).

The facts reported in patients with Alzheimer's disease have lower levels of taurine and this amino acid increases the level of acetylcholine in the brain by showing animals that have taurine positive effects on Alzheimer's disease and other neurological disorders caused by β-amyloid neurotoxicity GABA receptors (Oja and Saransaari, 2007). The normal function of dopaminergic neurons is controlled by NMDA receptors. Its overactivity leads to the accumulation of dopamine and neuronal death. Taurine reduces the release of dopamine receptor antagonists as NMDA acts (Yamori et al., 2010). Taurine is important for preventing cardiovascular and cardiovascular function because it improves the left ventricular function, cardiotropic effect lowers blood pressure, stabilizes heart rate, prevents platelet aggregation and regulates the osmotic pressure. It affects the heart, nervous system, blood vessels and the kidney to help regulate blood pressure (Roysommuti and Wyss, 2012). The antihypertensive effect of this amino acid is based on the fact that with essential hypertension after 6 weeks of treatment was reduced in patients mean systolic blood and diastolic. Oral supplementation of taurine induces antihypertensive effects in animal models of hypertension due to both central and peripheral effects. CNS effects include amino-specific mediation baroreflex modulation and regulation of the activity of hypothalamic neurons involved in the secretion of vasopressin (Roysommuti and Wyss, 2012). The vasodilation and blood pressure lowering effect of taurine associated with peripheral medium following mechanisms are:

1) Reduction of plasma catecholamines adrenaline and norepinephrine.

2) Improve natriuresis, the volume of urine and secretion of kallikrein.

3) The effect as osmoregulation in vascular endothelial and smooth muscle cells.

4) Increased expression of endothelial nitric oxide synthetase, which leads to the production of nitric oxide vasodilator, and stimulates the release of the vascular endothelium.

5) Minimize serum cytokine, endothelin, and thromboxane B2 neuropeptide Y

6) Modulation of the activity-aldosterone system renin-angiotensin.

In endothelial cells, the anti-apoptotic effect of this amino acid is mediated by its anti-inflammatory effect and its ability to inhibit reactive oxygen species. Taurine also has help people with congestive heart failure, has been shown to increase the strength and effectiveness of cardiac muscle contractions (Abebe and Mozaffari, 2011).

Taurine supplementation is probably beneficial for the prevention of atherosclerosis, coronary heart disease, and hepatic impairment, the secretion of apolipoprotein B100, which is a structural component of very low-density lipoprotein (VLDL) and LDL (Yanagita et al., 2014). This amino acid prevents the development of atherosclerosis and vascular disease caused by the following mechanisms: 1) Reduction of serum lipids and lysophosphatidic acid, a lipid component of the atherosclerotic plaques; 2) reduce the oxidation of LDL (Roysommuti and Wyss, 2012); 3) inhibition of thrombocyte aggregation, thereby reducing the risk of arterial thrombus formation. Taurine reacts with hypochlorous acid derivatives from the training phagocyte autocleaning. This compound inhibits the synthesis of interleukins 6 and 8 and suppresses the physiological activation of matrix metalloproteases secreted by macrophages of the intima and the cells of the foam. This results in the

inhibition of proteolysis of collagen fibers and other proteinaceous components of the intracellular matrix and reduces the rupture of the atherosclerotic plaques (Abebe and Mozaffari, 2011). It is reported that the myeloperoxidase inhibits taurine expression of the enzyme derived by this mechanism hypochlorous acid and phagocytes which reduce the risk of coronary heart disease and myocardial infarction. It acts as a diuretic to keep potassium and magnesium in the cell and the excess sodium outside the cell (Roysommuti and Wyss, 2012). This amino acid lowers the blood glucose and prevents microangiopathy with diabetes and nephropathy (Das and Sil, 2012). The antioxidant effect of taurine in biological systems is the result of its ability to capture the reactive oxygen species, bio-membranes and reduce the production of lipid peroxidation. Also reduces oxidative stress, which inhibits the formation of products glycation end. It acts as an antioxidant and protects against the toxicity of lead and cadmium and many tissues prevented by a toxic injury induced by oxidants. Supplementation with taurine prevents oxidative stress induced by movement (Bidri and Choay, 2003). This amino acid is important in early embryonic development, the immune system and the function of the skeletal muscle (Silva et al., 2011). Taurine has a positive effect in the eyes of the dystrophic processes in the retina to protect and the development of diabetic cataract, senile or traumatic radiative (Bidri and Choay, 2003).

This amino acid is found in high concentrations in the skeletal muscle, the modulus of contractile function and increases the production of energy, which increases by accumulation and release from the sarcoplasmic reticulum calcium (Gwacham and Wagner, 2012). Taurine helps cell proliferation and the viability and stability of membranes. Physiologically plays an important role in abnormal

metabolism and promotes the repair of tissue process. This amino acid improves energy processes, detoxifies some xenobiotics, and regulates the rate of calcium ions in the blood hypolipidemic activity for its role metabolism exerts fat metabolism products (Bidri and Choay, 2003). Taurine is involved in the regulation of secretion of vasopressin and oxytocin secretion. It has been shown cultured to have a protective effect on human hair follicles in vitro (Bidri and Choay, 2003).

2.12.1 Taurine synthesis

The synthesis of taurine is important because the substance plays several functional roles in the body, which can be improved by supplementation. It is for this reason that the chemical synthesis of taurine has been developed as an industrial process that allows for the increased uptake of the amino acid. Taurine is an amino acid present in many foods and its intake to a daily dose of about 58 mg, depending on the individual plan. In particular fish and meat products have a high content of taurine and individuals on a vegetarian or vegan diet tend to have lower consumption values. In addition, taurine is naturally present in some parts of the body, including the gastrointestinal tract, muscle tissue and bile. This taurine is synthesized in the pancreas of cysteic acid via sulfonic acid as the biosynthesis of taurine. It is the oxidation of the thiol group of cysteine, followed by a decarboxylation reaction and a final spontaneous reaction to form taurine. Taurine also occurs in adult male testes. There are two streams that are often used for chemical reactions of taurine. The first involves a reaction between ethylene oxide and sodium bisulphite oxidized to form is thionic acid, which is then used as the synthetic taurine. The second uses the chemical reaction between aziridine and sulphur to taurine in a single process acid transporter.

Taurine can be synthesized from the precursor amino acid, cysteine, by a variety of mechanisms (Huxtable, 1989). In the central nervous system, however, taurine synthesis proceeds from cysteine to cysteine sulfinate, hypotaurine, and finally taurine, a sequence commonly called the cysteine sulfinate decarboxylase (CSD) route (Tappaz et al., 1992). Contributions to taurine synthesis via cysteamine or cysteine are very minor or insignificant. The taurine-synthesizing enzymes, cysteine dioxygenase (CDO) and CSD, have been identified and characterized in the rat brain (Misra and Olney, 1975; Remy et al., 1990). In addition, Ohkuma (Ohkuma, 1984). demonstrated conversion of cysteine to cysteine sulfinic acid, hypotaurine, and taurine in rat whole brain homogenates. In hyperosmotic hypernatremia, contents of a number of organic osmolytes including polyamines, polyalcohol sugars, and amino acids are elevated in brain tissue (Heilig et al., 1989; Lien et al., 1990). In some animal models, accumulation of taurine accounts for as much as 50% of the additional osmolytes needed for brain volume regulation (Trachtman et al., 1988). Tissue culture studies of cerebral astrocytes have demonstrated increased cellular contents and rates of the influx of taurine (Olson et al., 1990) and inositol (Strange et al., 1994) during hyperosmotic exposure. However, in situ, enhanced cellular accumulation of taurine only serves to sequester available taurine intracellularly, as unidirectional transport from blood to the brain is not elevated by acute hyperosmotic treatment (Strange et al., 1994). Thus, activation of de novo synthesis of taurine may play an important role in the brain's adaptation to hyperosmotic conditions.

2.12.2 Taurine transfer and metabolism

Most amino acids are provided from the maternal circulation to the fetus by active transport across the placenta. (Regnault et al., 2005). Dependent transporter amino acid of energy is expressed in both maternal surfaces and the surfaces of fetal trophoblast in the human placenta. There are several different transport systems specific groups transfer according to their charge and structure of amino acids (Regnault et al., 2002). The final transfer rate for a single amino acid depends on the relative concentrations of amino acids in maternal plasma and abundance and the activity of transport systems. In addition, there is amino acids shuttle between the fetal liver and placenta exchange serine glycine and glutamate for glutamine. These exchanges result in net uptake of serine and glutamate from the fetus by the placenta (Christensen, 1990). However, with the exception of serine and glutamate, under normal conditions, net absorption of amino acids from the placenta of the fetus (Rozance et al., 2009). Since amino acids are also released into the fetal circulation fetal tissue, total rates of the occurrence of amino acids in the fetal plasma (which are the removal rate of the fetal amino acid in the form equal to steady state) are greater than the net-detection rate of the placenta of the fetus. Removing fetal amino acids in direct flow to the placenta and flow to fetal tissues. For most amino acids, the stream is further divided into protein synthesis and the oxidation of amino acids. The synthesized proteins can be degraded, and the difference between syntheses and protein degradation is the net charge of protein accumulation. The relative contribution of each of these sets (fetal placenta plasma flow rate, protein synthesis and oxidation) to the safe elimination of fetal amino acids varies for each particular amino acid (Anderson et al., 1997; Carver et al., 1997; Chien et al., 1997; Guyton et

al., 1993; Lemons et al., 1976; Liechty et al., 1999). However, accumulation of the total protein in late pregnancy is estimated to be 2-4 g / day (Van et al., 2009). Taurine supplementation has many physiological functions and development. It is considered essential for the fetus and newborn amino since the de novo synthesis fetuses at this age are not enough. The specific effects of taurine in the developing pancreas are highlighted by a series of examinations of a particular model of intrauterine growth restriction rat characterized by progressive loss of beta cells and functional disorders. Maternal fed a low protein isocaloric diet (8% vs. 20% dietary protein) throughout gestation gave birth to pups with lower birth weight and reduced β-cell mass and function compared to controls (Snoeck et al., 1990; Boujendar et al., 2003). Plasma taurine was lower in low protein maternal and their fetuses, and taurine supplementation to the low protein maternal during pregnancy normalized β-cell mass and insulin secretion (Sodoyez et al., 1979). However, fetal and pup body weights were not corrected. Despite the persistently low body weights in the low protein fetuses and pups, which in this particular model is almost certainly due to deficiency of other amino acids, the improvement in β-cell mass and function with taurine supplementation has important potential implications for the design of future therapeutic interventions (Kimball et al., 1998).Thus, with an adequate supply of nutrients, the fetus taurine supplementation has the potential to improve beta cell function and insulin secretion, the necessary increase in anabolic hormones allows the fetal growth to improve fetus.

2.12.3 Effect of taurine on glucose metabolism

In the pancreas, taurine is found mainly in most positive glucagon-positive cell cells and some somatostatin, while it is absent in the insulin-positive

cells. The role of taurine in the pancreas is not clearly understood. Although a hypoglycemic effect of taurine was observed in 1930 until the 1990s, only a few studies have investigated the possible role of taurine in the regulation of glucose metabolism. The amino acid appears to increase gluconeogenesis and glycolysis glucose oxidation and the glucose uptake in the liver and the heart of adult rats. Some reports show that taurine increases the activity of insulin, probably by binding to the insulin receptors. However, the effect of taurine on the endocrine pancreas seems to depend on age, and adults appeared insulin secretion (Lucas et al., 2001), while in the fetal pancreas stimulated the release of insulin by reducing leucine and arginine (Cherif et at., 1998).

2.12.4 Effect of taurine on insulin

Taurine has a variety of biological effects, including antioxidation, modulation of movement of ions, osmoregulation, modulation of neurotransmitters, and conjugation of bile acids that can maintain physiological homeostasis. Furthermore, supplementation against insulin-dependent diabetes, non-insulin-dependent, and insulin resistance (Franconi et al., 2004; Hansen 2001; Schaffer et al., 2009). Taurine plays a role in the modulation of cardiovascular function, acting not only in the brain but also in peripheral tissues. The above data have shown that GABA taurine assets are shown. The functional involvement of the $GABA_A$ receptor is the relaxation of arterial vessels, vasodilatation and reduced blood pressure. In the preparations of the aorta, taurine vasorelaxation can be induced mainly $GABA_A$ receptors expressed on smooth muscle cells. In addition, taurine acts as an agonist of GABA receptors (Idrissi et al., 2009). In cardiac muscle cells, taurine inhibits the increase in Ca^{2+} induced by the β-adrenergic receptor stimulating agent (Failli et al., 1992). This could be mediated

cardiomyocyte level (e.g regulation of calcium homeostasis and contraction properties) or by the interaction of taurine with the autonomic nervous system (ANS) innervation of the heart. Taurine also proved to be a potent agonist of the GABA receptors, and the activation of these receptors was demonstrated to affect the cardiovascular function and the peripheral resistance.

Taurine effects are mediated by the GABAA receptors. The source of taurine and GABA in such an environment can result from the release of these substances that result from the pancreas. It has been shown that the pancreas contains taurine and GABA. Therefore, GABA or taurine can be released through the pancreas and cause tonic relaxation of the smooth muscle cells in the aorta. Taurine independently affects insulin release from the pancreatic β-cells. First, taurine is taken up by the taurine transporter (TauT) on the β-cells. Once in the cytoplasm, taurine inactivates the ATP-sensitive K^+ channel. Taurine binds to the sulfonylurea receptor (SUR) portion of the channel and inhibits the ATP-sensitive K^+-channel leading to the opening of voltage-sensitive calcium channels (VSCC) or alternately the efflux of calcium from intracellular stores. Ultimately, the increase in cytoplasmic calcium concentration results in the exocytotic release of the large dense-core vesicle (LDCV) containing insulin and GABA.

2.12.5 Taurine and diabetes mellitus

It has recently been shown that taurine has positive effects in experimental models of DM (Trachtman et al., 1988). In the initial experimental studies, the positive effect of taurine occurs without any significant change in blood glucose. However, two long-term studies during more than 6 months have shown that taurine supplementation glucose, eventually lowers blood levels in rats with

streptozotocin (Franconi et al., 1999). There are no clear explanations for this taurine effect; it probably improves the spontaneous regeneration of the pancreas, which occurs after the injection of streptozotocin. Furthermore, in the above study Odetti, the taurine administration will not modify the extended products of glycosylation in the kidney and the skin and does not affect the glomerular disease. This is in contrast to other studies that have shown that taurine partially prevents diabetic glomerulopathy. However, Trachtman showed that taurine did not inhibit in vitro glycation of albumin and an inhibitory effect on the renal accumulation of glycosylation end products. In the rat skin, streptozotocin-injected effects of taurine compared with vitamin E and selenium. Interestingly, the decrease in lipid peroxidation and the maintenance of the activity of taurine supplementation-induced sodium pump are more stable than in the treated groups with vitamin E and selenium (Leo et al., 2003). While the treatment of diabetic patient's leads to a lower incidence of diabetic complications and ultimately lowers mortality, whether taurine reduces the mortality in diabetics by streptozotocin via induced rat is vitamin E plus selenium. Although supplementation does not decrease the mortality rate, the former has significantly increased the survival rate (Franconi et al., 2004). The main cause of mortality and morbidity associated with DM and insulin-resistant condition are long-term vascular complications; thus, taurine can reduce cardiovascular mortality. Clinically patients with insulin-dependent diabetes mellitus and insulin-dependent taurine in plasma and blood platelets decreased (Luca et al., 2001).

Several studies have shown that taurine peroxidation products induced in plasmalipid-induced type 1 diabetes can prevent hyperglycemia in taurines also reported in type alloxan-induced diabetic rabbits. Otsuka Long Evans Tokushima

Fatty in rat model of non-insulin-dependent diabetes with hyperglycemia and insulin resistance and abdominal fat was compared to normal rats accumulated. It has been shown that taurine supplementation improves insulin resistance and hyperglycemia (Harada et al., 2004; Nakaya et al., 2000). Furthermore, an inverse correlation was found between the logarithm of the plasma taurine and glycated hemoglobin. In addition, in insulin-dependent diabetic patients, reduced taurine supplementation platelet aggregation, restored its own plasma levels and platelets (Franconi et al., 2004) and removed to the inverse correlation between the logarithmic taurine and glycosylated hemoglobin. However, in a double-blind study with a duration of 1 year, taurine does not improve kidney associated with type 2 diabetes-associated complications (Hansen, 2001), which agrees with the results of Odetti (Odetti et al., 2002). Therefore, the effect of taurine in the reported tissue can be specific.

2.12.6 Taurine and fetal programming on development of type 2 Diabetes Mellitus

The hypothesis that changes in the endocrine pancreas "programming" system persist in fetal life and childhood throughout life, creates the risk of later development of type 2 DM (Hales and barker, 1992). Many data show that taurine is important for fetal development, including pancreatic function (Sturman, 1993). A fetus is provided by the mothers, and when the activity of the placenta is reduced, fetal tissue becomes depleted of taurine. In diets, low protein diet reduces the level of taurine in the fetus (Cherif et al., 1998) and induces maternal DM, changes in the endocrine fetal pancreas (Oliver et al., 2001), and glucose tolerance in adult offspring.

Cultured fetal pancreatic islets obtained from fetuses under our showed a defect in insulin secretion which was not repaired by in vitro exposure to taurine but

could be restored by filling mothers with taurine that confirmed taurine has an effect on the maturation of taurine B-cells of the fetus (Cherif et al., 1998). Maternal taurine supplementation reduced the rate of apoptosis by IL-1-induced pancreatic islets (Merezak et al., 2004) and fetal on the DNA synthesis, which prevents the abnormal development of the endocrine pancreas. The plasma taurine content was low in diabetic pregnant rats and their offspring in the course of life and in fetuses of the next generation (Aerts and Van, 2001). The above results suggest that it is time to conduct detailed studies on the involvement of taurine in "fetal programming" to determine if this amino acid should be supplemented during pregnancy, to prevent insulin resistance and other metabolic damage up to adult and second generation.

2.12.7 Effect of taurine on sympathetic nervous system (SNS)

It is reported that GABA blood pressure in test animals and people after systemic and its main administration or suggested that the depressive effect is lowered by systemic administration of GABA-induced blockage of the sympathetic ganglion (Takahashi et al., 2005). It has been reported that GABA inhibits sympathetic neurotransmission in the artery by presynaptic GABA-B receptor subtype and GABA acts to remove GABA receptors presynaptic neurotransmitter release (and thereby attenuate renal vasoconstriction) upon activation of the sympathetic nervous system. While the sympathetic nervous system caused vasoconstriction proportional to the level of activation of adrenergic receptors, GABAerge system-mediated vasodilatation. Isolated thoracic aorta rings of rats that exacerbate chronic β-alanine internal taurine to norepinephrine showed reactions rich in potassium and contraction and improved the relaxant response to sodium nitroprusside (SNP) and acetylcholine (Abebe and Mozaffari, 2011). Thoracic aorta rings of rats isolated chronic taurine,

showed a reduction of norepinephrine and rich in potassium contraction reactions of nonspecific (Abebe and Mozaffari, 2000).

2.12.8 Effects of taurine on the renin-angiotensin system and insulin

The Renin-angiotensin system plays an important role in blood pressure homeostasis, the body's fluid and electrolyte balance, as well as the activation of the renin-angiotensin contributes to hypertension in several animal models. Taurine reduces hypertrophic cardiac effects of angiotensin II in the adult rat (Schaffer et al., 2009). However, taurine deficiency in adult animals exacerbates many adverse effects of angiotensin II in the heart, blood vessels and kidneys (Cross et al., 2000). Angiotensin II induces heart hypertrophy in vivo and in vitro and taurine can inhibit these adult rats (Schaffer et al., 2010).

In adult animals, taurine supplementation or the inhibition of the angiotensin converting enzyme, hypertension induced by high carbohydrate can prevent or reduce. A hypoglycemic effect of taurine reduced or delayed diabetes mellitus (Kim et al., 2007) and prevented by sugar induced hypertension (Harada et al., 2004). The hypoglycemic effects of taurine include insulin sensitivity increased and the secretion of pancreatic insulin. Therefore, the antihypertensive effect of taurine can be by decreasing the insulin resistance or inhibiting the renin-angiotensin system in the sugar-induced hypertension.

2.13 Effect of exercise on diabetes mellitus

The present study is that moderate-intensity aerobic exercise for 10 weeks in combination with a high-fructose diet, which prevents adverse effects of fructose-induced hemodynamic overload, regional and metabolic rate. However, studies in humans have shown that the consumption of fructose can induce weight gain, reduces

insulin sensitivity, dyslipidemia, and hypertension (Elliott et al., 2002). Although calorie intake was similar between the groups, it is clear that a chronic consumption of fructose product causes a change in production and secretion of hormones and peptides appetite regulators such as ghrelin, leptin, and peptide YY, thereby contributing to an increase in fat and weight. In addition, in obese subjects have identified plasma catecholamine levels, cardiovascular abnormalities, and autonomic activation increased in the renin-angiotensin system several studies (Simona, 2013; Zouhal et al., 2010).

In addition, the sympathetic nervous system appears to play an important role in metabolic and cardiovascular disorders in metabolic syndrome. In addition, sympathetic hyperactivity leads to insulin resistance, which can lead to the activation of the α_1-adrenergic receptors. This sympathetic activation reduces the blood flow causing and thus a reduction in the administration of glucose into the skeletal muscle. The regular exercise program can improve metabolic and chronic cardiovascular adjustments. It is known that regular exercise glucose, lipid profile (Durstine and Haskell, 1994) and sensitivity to insulin improves body weight and improves the absorption of glucose by the muscle. In diabetic and hypertensive rats, physical training has played an important role in the treatment of metabolic disorders and self-improvement of nervous disorders heart rate variability (HRV) baroreflex sensitivity, modulation of vagal pressure and blood. In addition, physical training can influence the metabolism, hemodynamics, and hypertension. Self-control, even in healthy persons (Laterza et al., 2007). In addition, chronic low stimulation rates in vivo or in vitro caused muscle induction of GLUT4 expression above the baseline level. Exercise training increases the use of glucose-mediated insulin whole body of the

human being, an adjustment in the muscle caused by dependent mechanisms of local contraction. Physical training in humans does not alter the function of the muscle insulin receptor, but increases the muscle GLUT4 content (Houmard et al., 1991; Dela et al., 1994). Similarly, chronic exercise improves the expression of GLUT4 in the muscle of rats (Ploug et al., 1990). In fact, it seems that a single training unit that improves the expression of GLUT4 in the muscles. Furthermore, chronic movement also increases the content of GLUT4 in insulin resistant skeletal muscle obese sugar rats (Snyder et al., 1990). GLUT4 is translocated site of the intracellular cell surface of muscle fibers in response to insulin or exercise (Zorzano et al., 2015).

It is also shown that insulin promotes significant recruitment of GLUT4 to the carriers of the cell surface in cardiac myocytes. In fact, GLUT4 was recruited in response to the combination of insulin and exercise. The conclusion is a feature of the muscle cells that involve two different cell surfaces, namely the sarcomeres and T-tubules involved in GLUT4 recruitment in response to insulin or exercise. Therefore, a sensitive intracellular GLUT4 movement bath of subcellular fractionation of rat skeletal muscle was identified; this group does not show the insulin sensitivity of GLUT4 indicating that different groups can be responsible for the translocation of GLUT4 movement dependent and insulin.

weaning (DM and Control groups). After weaning, male offspring were fed the normal rat chow and RO throughout the experiment (n = 8 each group).

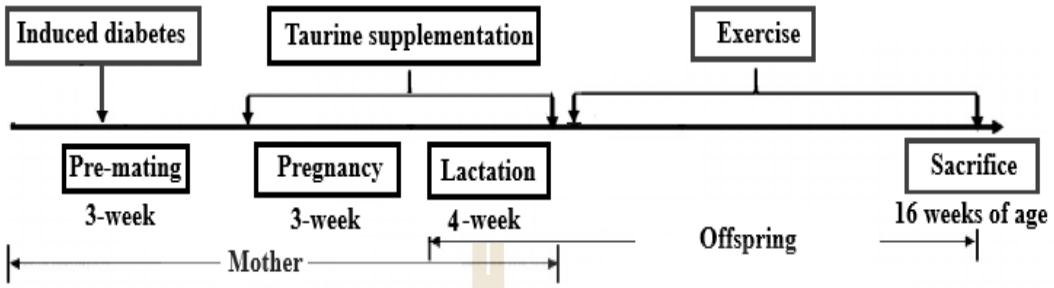


Figure 10 Flow chart showing experiment timeline.

- Group 1: Adult male offspring from maternal non-diabetes rats were fed with RO ad libitum (C).
- Group 2: Adult male offspring from maternal non-diabetes rats were fed with 3% taurine in RO ad libitum (T).
- Group 3: Adult male offspring from maternal diabetes rats were fed with RO ad libitum (DM).
- Group 4: Adult male offspring from maternal diabetes rats were fed with 3% taurine in RO ad libitum (DMT).
- Group 5: Adult male offspring from maternal non-diabetes rats were fed with RO ad libitum and exercise (Ex).
- Group 6: Adult male offspring from maternal non-diabetes rats were fed with 3% taurine in RO ad libitum and exercise (TEx).
- Group 7: Adult male offspring from maternal diabetes rats were fed with RO ad libitum and exercise (DMEx).

CHAPTER III

MATERIALS AND METHODS

3.1 Material

3.1.1 Animal preparation

Male and female Wistar rats (weight 250-300 g) 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). All rats were fed normal rat chow and water RO (Reverse Osmosis) ad libitum. Female rats were divided into two groups: the first group is non-diabetic mellitus (Non-DM) rats and another group is a diabetic mellitus (DM) rats. Female rats were induced by a single intraperitoneal injection of freshly prepare Streptozocin (STZ) 50 milligram (mg)/ kilogram (kg)/of body weight was dissolved in 0.1 M cold citrate buffer solution, pH 4.5 and prepared freshly before immediately use within 10 min by intraperitoneal injection (IP) followed by 20% glucose in RO for 24 hour (hr) (to prevent initial drug-induce hypoglycemic mortality). Three days later, fasting blood glucose (FBS) was confirmed to be 280-350 mg/dl (Gajdosik et al., 1999). Then, these animals were subjected to a mating procedure. The control group were similarly treated without diabetic induction (Control group). In experiment, the pregnant rats were caged individually and supplemented with 3% taurine in RO (Control plus taurine supplementation, T; Diabetes plus taurine supplementation, DMT) or RO alone until

- Group 8: Adult male offspring from maternal diabetes rats were fed with 3% taurine in RO ad libitum and exercise (DMTEx).

3.1.2 Exercise protocol

The exercise group after weaning, rats were transported to a treatment room, where exercise rats were forced to swimming in cylindrical tank with a diameter and height of 60 and 100 cm, respectively, in water at a depth of 30–45 centimeter (cm). Water temperature was monitored and maintained at 36°C. At 4 weeks of age, rats were forced swimming for 10 minutes (min)/5 days/ week (wk). At five to eleventh weeks forced swimming for 15 min/5 day/ wk. and since the twelve weeks is the end swimming for 1 hr/ 5 days/ wk. (Santos et al., 2010). All experimental procedures were approved by the universities animal care and use committee and were conducted in accordance with the National Institutes of Health.

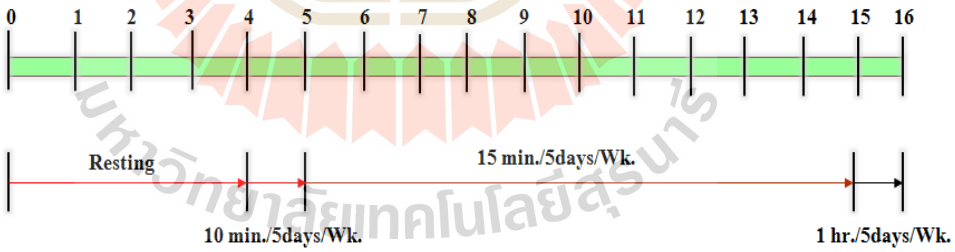


Figure 11 showing exercise protocol.

3.1.3 Experimental designs

At 16 weeks of age, fasting blood glucose and plasma insulin levels were determined from blood samples drawn from rat tail vein. Two days later, all rats were anesthetized with Nembutal (30 mg/kg of body weight, IP), 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) (Chen et al., 1998), 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 sugar level, insulin level, and lipid profile. Pancreas were collected for study morphology of Islet of Langerhans. Finally, all rats were sacrifice by a high dose of anesthesia and heart and kidney weights were collected.

3.2 Methods

3.2.1 Experimental techniques

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

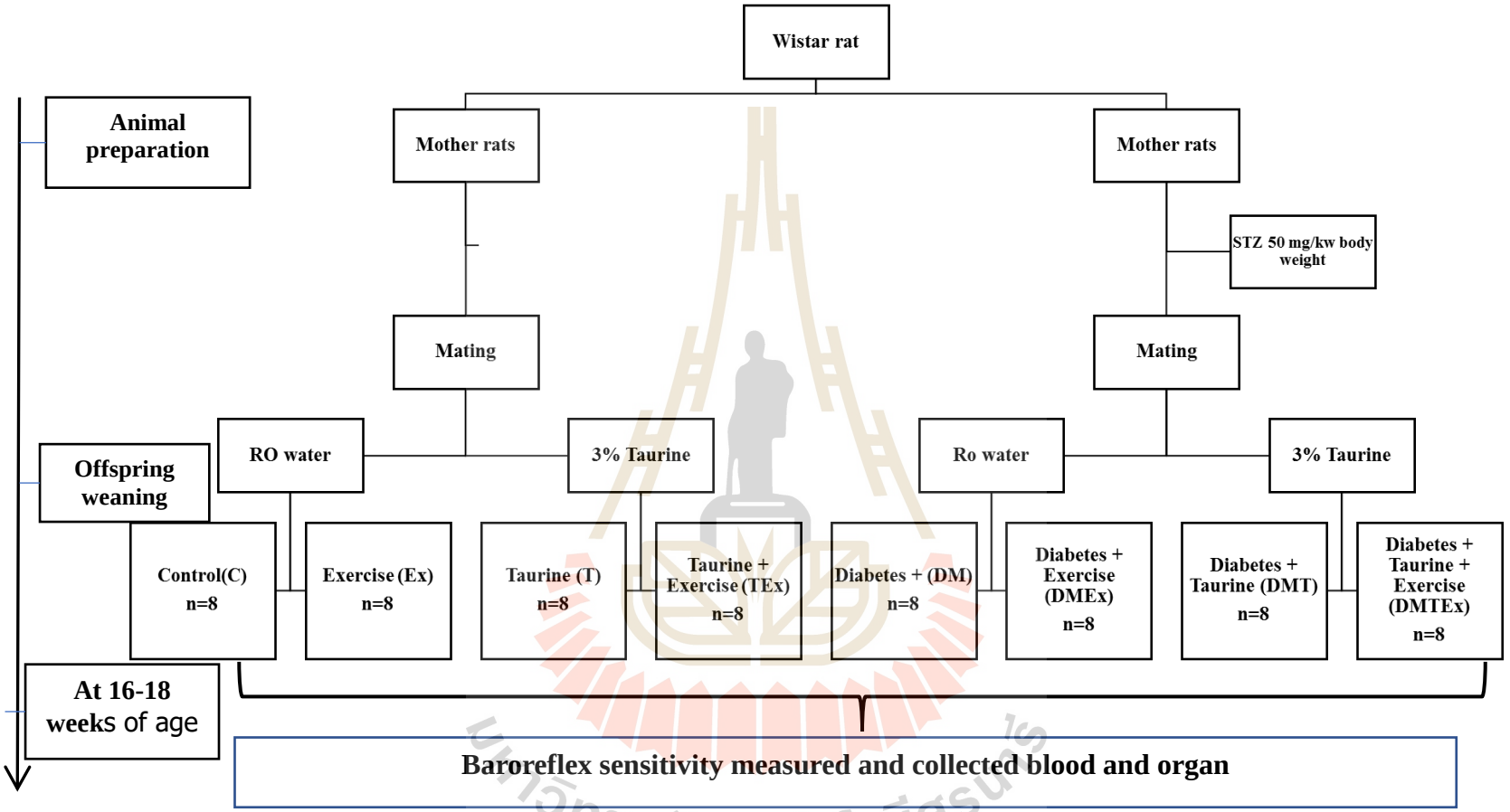


Figure 12 Flow chart showing experiment design.

3.2.2 Determination of baroreflex sensitivity

After catheterization, all adult male rats offspring were tracheotomized and tracheal tube insertion in a supine position, femoral arterial and venous catheters were flushed with heparinized saline. The arterial catheter was connected to a pressure transducer and Power Lab system to record arterial pressure and the venous one for fluid and drug injection as mentioned earlier. Body temperature were controlled the heating lamp over the animal. Then, the arterial catheter was connected to a pressure transducer that connected to the power lab for continuous recording of arterial pulse. Venous catheter was connected to syringe pump for saline and drug administration. After 30 mins resting, phenylephrine, a specific α-adrenergic agonist (100 mg/ml in saline) were intravenously infused at a rate of 0.02 ml/min for 2 mins 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 mins). Then, sodium nitroprusside (25 mg/ml in saline) were similarly infused until the mean arterial pressure down to 20-30 mmHg. Baroreflex sensitivity during hypertensive or hypotensive responses were estimated offline by Chart 6 (Power Lab System, CA, USA). Baroreflex sensitivity control of heart rate were estimated by a slope of the simultaneous changes of heart rate to mean arterial pressure during the drug infusion (Swenne, 2013). Mean arterial pressure and heart rate were offline analyzed from the record arterial pressure using the Chart software version 6. About 20 min length of continuous tracing were used to average the baseline data and at least a minute length for others.

3.2.3 Determination of blood chemistry assay

At the end experiment. Blood were collected and centrifuged. After that all serum plasma were kept in frozen -20 degree celsius until further assay for the plasma parameters such as plasma triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), Blood Urea Nitrogen (BUN), Creatinine (Cr), Alanine Aminotransferase (ALT) and Aspartate aminotransferase (AST) were measured by automatic blood analyzer (Jeon and Kim, 2006) by Suranaree University of Technology hospital.

3.2.4 Determination of insulin level

3.2.4.1 Preparation of sample

Whole blood was directly drawn into a centrifuge tube that contains no anti-coagulant kept at room temperature for 30 min and centrifuged the blood clotted at 2,000 g for 15 mins at 4 degrees Celsius serum samples were transferred in separate tube and kept at -20 degrees Celsius.

3.2.4.2 Assay procedure

Pre-warm all reagents to room temperature prior to setting up assay. the 10X wash buffer was diluted (50mM Tris buffered saline containing Tween-20) concentrate 10-fold by mixing the entire content of each bottle of wash buffer with 450mL de-ionized water (DW). (Dilute both bottles with 900 ml deionized water). 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°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. 10 µL of assay buffer was added (0.05 M phosphosaline pH 7.4, 0.025M EDTA, 0.08% sodium azide and 1% BSA) follow by 10 µl matrix solution (Charcoal stripped pooled mouse serum) to each of the blank standard and control wells. After that, 10 µl of rat insulin 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 Rat/Mouse insulin quality control 1 (QC1) and 10 µl Rat/Mouse insulin quality control 2 (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 80 µl of Detection Antibody (Pre-titered biotinylated anti-insulin antibody). 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, per well per wash. Decant and tap after each wash to removed residual buffer. 100 µL of Enzyme Solution was added (Pre-titered streptavidin-horseradish peroxidase conjugate in buffer) 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 6 times with diluted Wash Buffer, 300 µl per well per wash. Decant and tap after each wash to remove residual buffer. 100 µl of Substrate 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 Insulin Standards with intensity proportional to increasing concentrations of insulin. 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 (Tulin et al., 2012; Nakagawa et al., 2011; Zhen et al., 2011).

3.2.5 Determination of AT_1 receptor expression

3.2.5.1 Preparation of sample

Heart and Kidney were fixed with liquid nitrogen and kept at -20 degree celsius and then organ was kept in cool (dry iced) and prepared for homogenization by break down 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 β-glycophosphate 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 test tube and put all sample break down in to same tube were homogenized. Next, sample was kept in cool. 30 mins later, homogenize sample was transferred to new microtube and centrifuged at 12,000 g for 20 mins and then supernatant was transferred onto new microtube and 2-5 µl of supernatant was separated for measuring spectrum absorbent by microplate reader for calculation the concentration of protein in supernatant and how to know the quality of protein to in the running gel. After measuring absorbent, all sample were calculated 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 mins and kept cool down, respectively.

3.2.5.2 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 mins for stronger gel. 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, stronger gel was raised by DW and upper gel was loading into the same gel for upper gel. The comb was put into the upper gel and wait for until the upper gel strong. Finally, 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).

3.2.5.3 Preparation of transfer AT_1 process

Sponge, filtration paper, transfer paper polyvinylidene difluoride (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 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 hr. Next, milk blocking solution was prepared (150 ml/membrane: PBS pH7.4 150 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 wear removed, and the membrane paper was taking to stain in Ponceau stain for 1 min. Next, the stain was removed and rinsed with DW several times. After that, the membrane was cut into 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 mins for 1 h. The container was put on the rocker (speed level 4) then milk was discarded. Next, 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 degrees Celsius overnight. Next, milk was discarded and changed the milk solution every 15 mins for 1 h 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 hr on a rocker (speed level 2). Next, Transfer membrane was washed with milk solution every 15 min for 45 mins follow by tris-buffered saline (TBS) (25mM Tris pH 7.5, 150mM NaCl) every 15 min for 30 mins. 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 min and kept membrane paper to develop box and take a photo.

3.2.5.4 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 mins for 1 hr. The container was put on the rocker (speed level 4) 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 hr. 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 mins 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 mins at room temperature and the transfer membrane was washed 3 times in TBS for 3-5 mins each wash. Finally, chemiluminescent reagent was used for detection band of actin. Analysis of intensities of angiotensin II type 1 (AT_1) expression was conducted using image J software. In each band, 5 areas were randomly selected and the intensities were then analyzed. The experiment was repeated using tissue from 5 different individuals. The intensities were show as mean ± S.D. The means among 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<0.05) was used to indicate a significant difference.

3.2.6 Determination of histology in pancreas tissue

The pancreatic were harvested from the sacrificed rat after dissection and weight, washing with saline. The specimens were stretched on filter paper and 4% paraformaldehyde. The specimen was fixed and into the processed for dehydration,

after that embedded in paraffin blocks. The paraffin section was thinner 4 micrometer (µm) paraffin by a rotary microtome. The sections were stained with hematoxylin and eosin (H&E) The sections were stained with H&E using the traditional method, sections were infused in xylene for clear up of paraffin. The sections were rehydrated by infuse graded series of alcohol (100-70%) and then distilled water, followed by staining with hematoxylin for 3-5 mins wash in running tap water until sections is blue color for 5 mins or less, differentiate in 1% acid alcohol (1% HCl in 70% alcohol) for 5 mins. washing in running tap water until the sections are again blue by dipping in an alkaline solution (eg. ammonia water) followed by tap water wash. stain in 1% eosin Y for 10 mins washing in tap water for 1-5 mins and dehydrate for increasing concentration of alcohols and clear in xylene. Finally, the samples mount in mounting media (Rahier et al., 2008; Longnecker, 2014). and observe under microscope.

The percentages of number islet of Langerhans were calculated. From each section, 10 microscopic fields were photographed. The percentages of number islet of Langerhans were then calculated as described below.

$$Percentage\ of\ number\ islet\ of\ Langerhans = \frac{Number\ islet\ of\ Langerhars}{Total\ number\ islet\ of\ hangerhans} \times 100$$

3.3 Data analysis

1. Cardiovascular parameter: Blood pressure and heart rate. These data were recorded and analyzed 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).

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

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

3.4 Statistical analysis

All data are expressed as mean ± SD. 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.

CHAPTER IV

RESULTS

4.1 Body weight, organ weight and blood chemistry

In adult male rats offspring, at 16-18 weeks of age, body weights differences decreased significantly in offspring from maternal diabetes rats (DM) when compared with control group (C) (384 ± 15.27 versus 357 ± 7.55, $P \leq 0.05$) and then differences decreased significantly in the exercise group compared with a non-exercise group. While heart and kidney weight differences increased significantly in the exercise groups compared with non-exercise groups (Table 1). FBS and TG differences increased significantly in offspring from maternal diabetes rats (DM) when compared with control group (C) (116.1 ± 12.30 versus 82.5 ± 6.04, $P \leq 0.05$) (166.6 ± 19.80 versus 130.0 ± 14.45, $P \leq 0.05$). While, plasma insulin level differences decreased significantly in offspring from maternal diabetes rats (DM) compared with control group (C) (7.2 ± 1.81 versus 10.1 ± 13.00, $P \leq 0.05$). FBS and TG differences decreased significantly in exercise groups when compared with non-exercise groups. While insulin level differences increased significantly in exercise groups when compared with non-exercise groups. No significant differences in cholesterol were observed among groups. HDL levels differences decreased significantly in offspring

from maternal diabetes rats (DM) compared with control group (C) (51.7 ± 6.20 versus 62.0 ± 3.89, $P \leq 0.05$). In contrast to LDL level difference increased significantly in offspring from maternal diabetes rats (DM) compared with control group (C) (122.0 ± 15.91 versus 106.6 ± 5.50, $P \leq 0.05$) (Table 2). The level of HDL increased and LDL decreased in exercise groups. Blood urea nitrogen (BUN) difference decreased significantly in offspring from maternal diabetes rats (DM) compared with control group (C) (23.1 ± 3.60 versus 25.1 ± 1.40, $P \leq 0.05$). No significant differences in serum creatinine were observed among group. While, SGOT difference increased significantly in offspring from maternal diabetes rats (DM) compared with control group (C) (106.3 ± 9.91 versus 134.8 ± 15.18, $P \leq 0.05$) and SGPT difference decreased significantly in offspring from maternal diabetes rats (DM) compared with control group (C) (33.5 ± 6.40 versus 44.7 ± 7.10, $P \leq 0.05$) (Table 3). SGOT and SGPT increased in taurine supplementation with exercise group (TEx).

Table 4.1 Body weight, heart weight, kidney weight.

Treatment	Body weight (g)	Heart weight (g)	Kidney weight (g)	HW/BW (%)	KW/BW (%)
C	384 ± 15.27^{a}	1.29 ± 0.09^{b}	1.38 ± 0.13^{a}	0.34 ± 0.02^{d}	0.36 ± 0.04^{b}
T	386 ± 19.80^{a}	1.29 ± 0.09^{b}	1.27 ± 0.10^{b}	0.34 ± 0.01^{d}	0.33 ± 0.01^{c}
DM	357 ± 7.55^{b}	1.33 ± 0.09^{b}	1.15 ± 0.08^{c}	0.37 ± 0.03^{c}	0.32 ± 0.02^{c}
DMT	347 ± 14.63^{b}	1.30 ± 0.11^{b}	1.14 ± 0.08^{c}	0.38 ± 0.03^{c}	0.33 ± 0.02^{c}
Ex	322 ± 3.70^{c}	1.42 ± 0.01^{a}	1.37 ± 0.04^{a}	0.44 ± 0.01^{b}	0.43 ± 0.01^{a}
TEx	313 ± 4.70^{cd}	1.43 ± 0.01^{a}	1.38 ± 0.05^{a}	0.46 ± 0.03^{ab}	0.44 ± 0.01^{a}
DMEx	298 ± 4.34^{e}	1.37 ± 0.01^{ab}	1.30 ± 0.03^{ab}	0.46 ± 0.01^{ab}	0.44 ± 0.03^{a}
DMTEx	304 ± 5.02^{de}	1.42 ± 0.01^{a}	1.36 ± 0.01^{a}	0.47 ± 0.01^{a}	0.45 ± 0.02^{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; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).

Table 4.2 Blood chemistry.

Treatment	Fasting blood sugar (mg/dl)	Insulin level (ng/ml)	Triglyceride (mg/dl)	Total cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
C	82.5 ± 6.04^{c}	10.1 ± 13.00^{ab}	130.0 ± 14.45^{b}	80.3 ± 13.84^{a}	62.0 ± 3.89^{b}	106.6 ± 5.50^{b}
T	82.4 ± 3.34^{cd}	14.5 ± 3.41^{ab}	124.5 ± 11.60^{b}	77.8 ± 9.53^{a}	60.6 ± 4.74^{b}	105.6 ± 8.89^{b}
DM	116.1 ± 12.30^{a}	7.2 ± 1.81^{c}	166.6 ± 19.80^{a}	85.2 ± 18.79^{a}	51.7 ± 6.20^{c}	122.0 ± 15.91^{a}
DMT	85.3 ± 4.51^{c}	10.7 ± 2.61^{bc}	132.6 ± 19.20^{b}	80.2 ± 15.30^{a}	61.5 ± 4.14^{b}	102.0 ± 9.65^{b}
Ex	76.6 ± 7.60^{d}	16.0 ± 5.23^{a}	121.0 ± 10.50^{b}	82.2 ± 10.60^{a}	74.1 ± 7.07^{a}	103.7 ± 7.40^{b}
TEx	77.8 ± 8.01^{d}	15.6 ± 5.12^{a}	121.6 ± 10.80^{b}	84.1 ± 9.40^{a}	74.0 ± 6.78^{a}	106.0 ± 7.70^{b}
DMEx	92.6 ± 5.02^{b}	14.5 ± 4.11^{ab}	123.0 ± 6.70^{b}	90.7 ± 13.90^{a}	75.0 ± 8.51^{a}	108.3 ± 15.30^{b}
DMTEx	81.1 ± 5.80^{cd}	14.6 ± 5.41^{ab}	120.0 ± 11.60^{b}	83.5 ± 9.10^{a}	76.7 ± 10.56^{a}	102.0 ± 11.70^{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; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).(HDL, high density lipoprotein; LDL, low density lipoprotein)

Table 4.3 Blood Urea Nitrogen, Serum creatinine, SGOT and SGPT.

Treatment	Blood Urea Nitrogen (mg/dl)	Serum creatinine (mg/dl)	SGOT (µ/l)	SGPT (µ/l)
C	25.1 ± 1.40^{ab}	0.45 ± 0.11^{a}	134.8 ± 15.18^{a}	44.7 ± 7.10^{a}
T	24.7 ± 1.80^{ab}	0.43 ± 0.10^{a}	142.1 ± 15.68^{a}	41.8 ± 6.70^{b}
DM	23.1 ± 3.60^{c}	0.41 ± 0.11^{a}	106.3 ± 9.91^{b}	33.5 ± 6.40^{c}
DMT	25.1 ± 1.91^{ab}	0.41 ± 0.08^{a}	134.3 ± 14.90^{a}	35.8 ± 7.10^{c}
Ex	26.2 ± 2.31^{a}	0.49 ± 0.11^{a}	133.7 ± 14.00^{a}	50.6 ± 8.70^{a}
TEx	26.1 ± 1.92^{a}	0.40 ± 0.13^{a}	143.0 ± 12.70^{a}	45.2 ± 6.41^{a}
DMEx	23.3 ± 3.20^{ab}	0.39 ± 0.12^{a}	125.1 ± 9.50^{a}	44.7 ± 6.90^{a}
DMTEx	24.7 ± 3.20^{ab}	0.43 ± 0.07^{a}	135.8 ± 10.60^{a}	41.5 ± 6.61^{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; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise)

4.2 Mean arterial pressures and baroreflex sensitivity

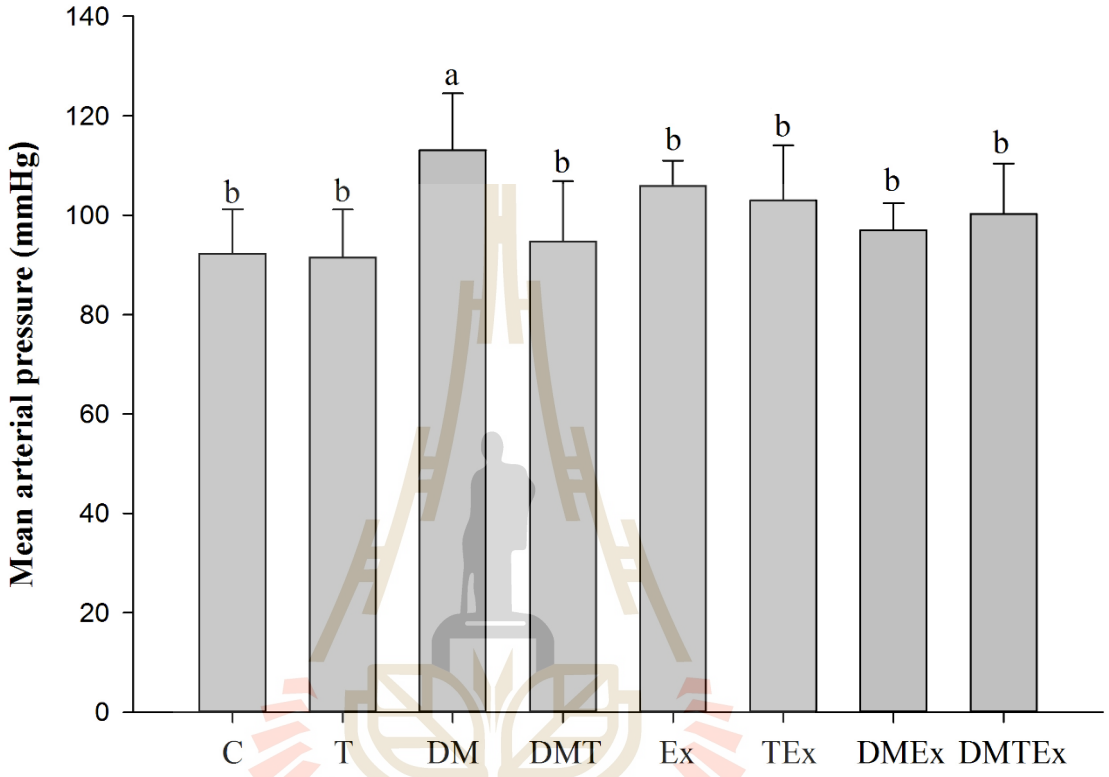


Figure 13 Mean arterial pressures (Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$). (C, Control; T, Taurine; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).

Mean arterial pressures (MAP) difference increased significantly in offspring from maternal diabetes rats (DM) when compared with another groups. 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. However, we found that no significant differences in HR were observed in offspring from maternal diabetes rats (DM) and offspring from maternal diabetes rats were fed with 3% taurine (DMT), In contrast, offspring from maternal diabetes rats were fed with 3% taurine and exercise (DMTEx) decreased MAP and HR when compared with non-exercise groups.

MAP, the baroreflex sensitivity control of heart rate induced by either phenylephrine (PHE) or sodium nitroprusside (SNP) infusion difference were lower than in diabetes group when compared with another group. On the other hand, Perinatal taurine supplementation abolished these adverse effects of maternal diabetes mellitus without any effect on hemodynamic parameters in the control groups. While Baroreflex sensitivity difference were higher than in exercise groups when compared with non-exercise groups.

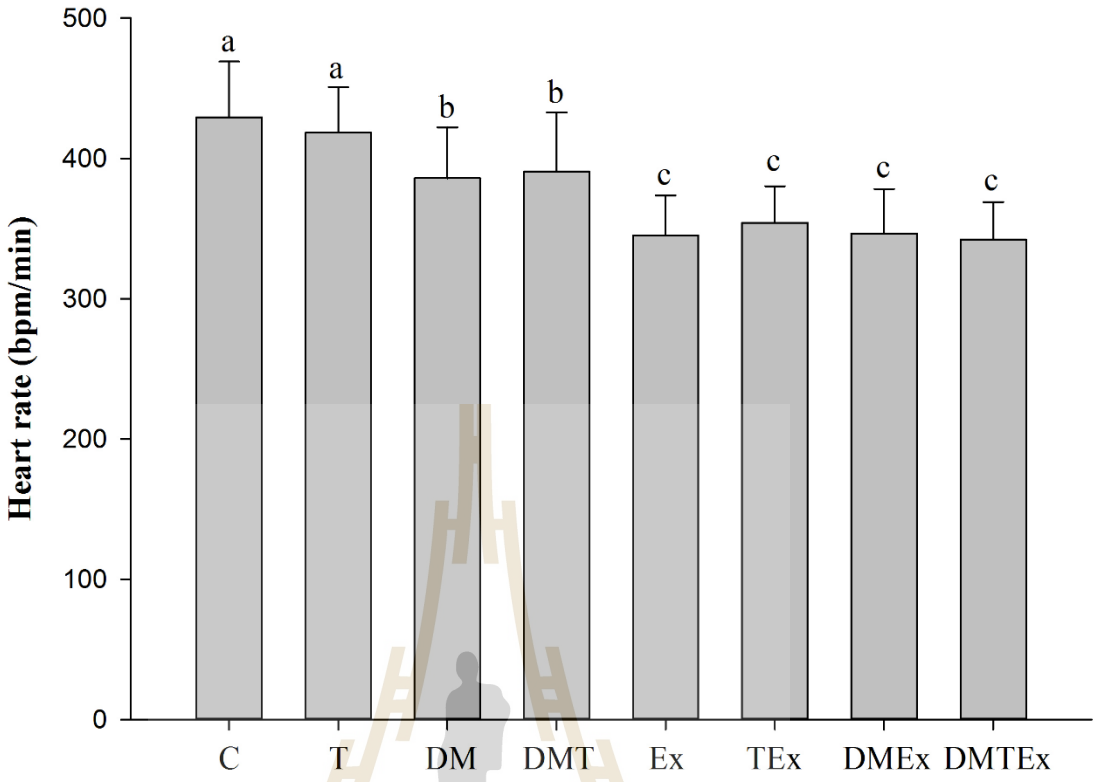


Figure 14 Heart rates (Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$). (C, Control; T, Taurine; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).

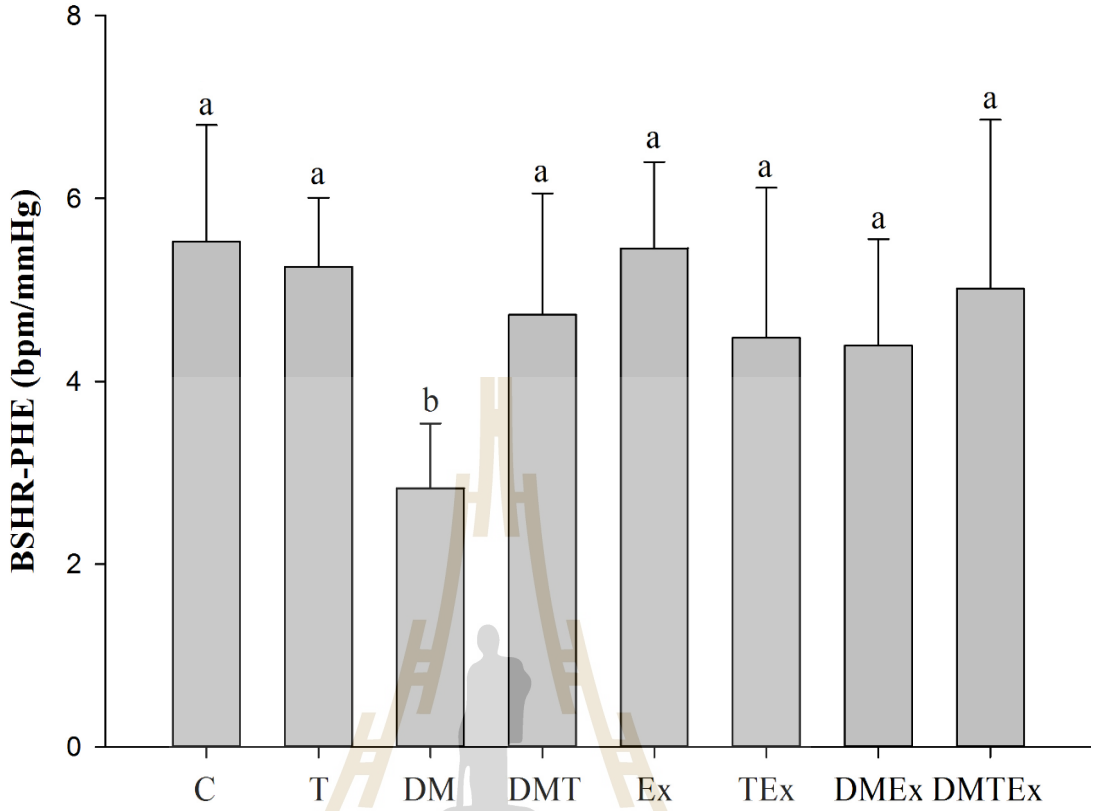


Figure 15 Baroreflex sensitivity of heart rate response to phenylephrine. (Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$) (C, Control; T, Taurine; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).

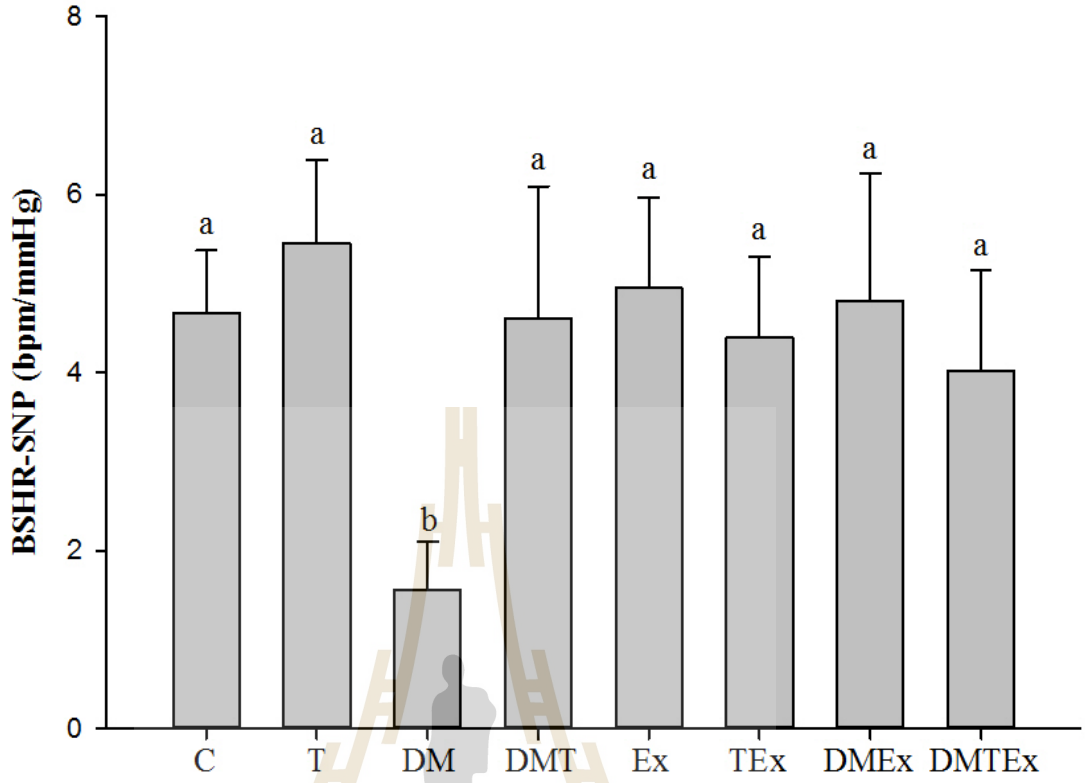


Figure 16 Baroreflex sensitivity of heart rate response to sodium nitroprusside. (Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$). (C, Control; T, Taurine; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).

4.4 Islet of Langerhans of pancreas

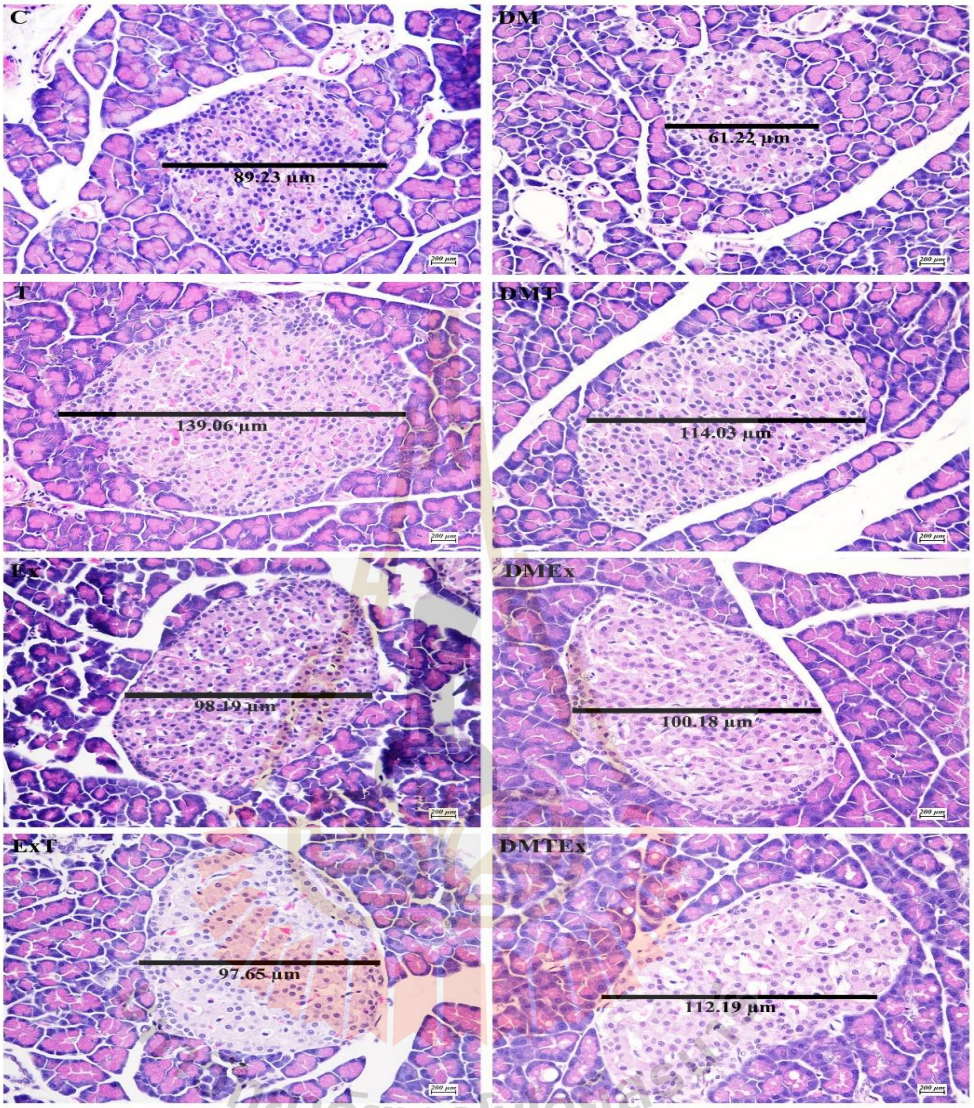


Figure 17 Islet of Langerhans of pancreas stained by H&E. Scale Bars = 200 µm.

Islet of Langerhans of pancreas stained by H and E (Figure 17) observe in offspring from maternal diabetes rats (DM) was smaller size of Islet of Langerhans when compared with control group (62.22 versus 89.23 µm). When taurine

supplementation with exercise can maintain body size or increased body size islet of Langerhans.

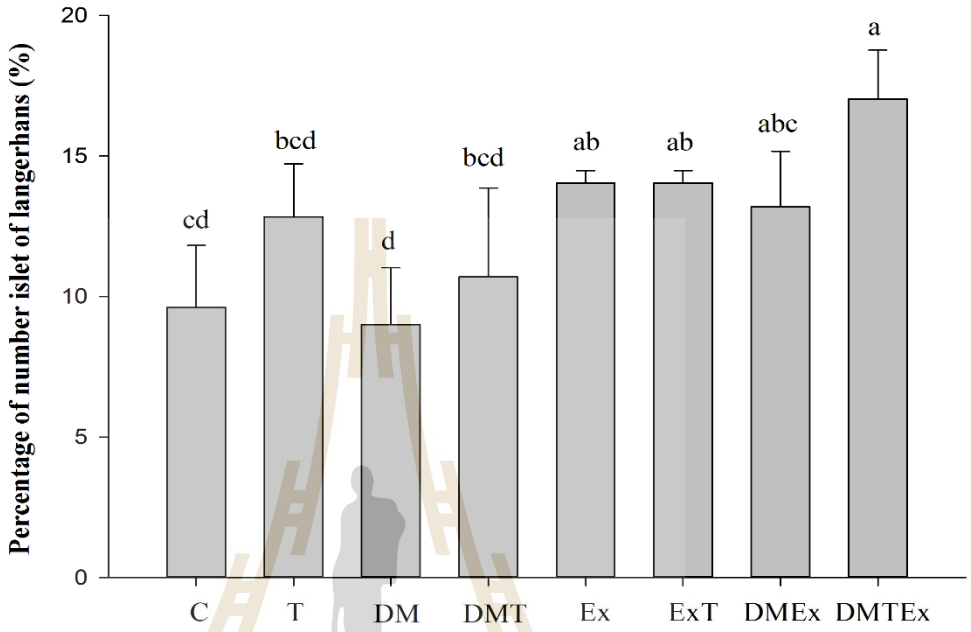


Figure 18 Percentage of number islet of Langerhans. (Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$). (C, Control; T, Taurine; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).

The percentage of islet of Langerhans number no significant differences in offspring from maternal diabetes rats (DM) when compared with control groups. The

percentage of islet of Langerhans number difference were higher than in taurine supplementation with exercise group when compared with another group.

4.5 Expression of AT_1 receptor in heart and kidney

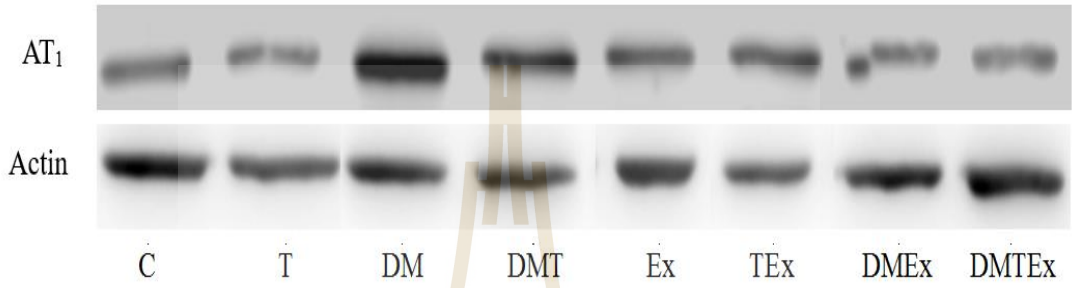


Figure 19 Expression of AT_1 receptor in heart.

Percentages expression of AT_1 receptor in heart difference increased significantly in offspring from maternal diabetes rats (DM) when compared with control groups (61.33 ± 1.53% versus 40.66 ± 2.52%, $P \leq 0.05$). When offspring from maternal diabetes rats (DMT) plus taurine, offspring from maternal diabetes rats with exercise (DMEx), and offspring from maternal diabetes rats plus taurine with exercise (DMTEx), expression of AT_1 receptor in heart difference were lower than in offspring from maternal diabetes rats (DM).

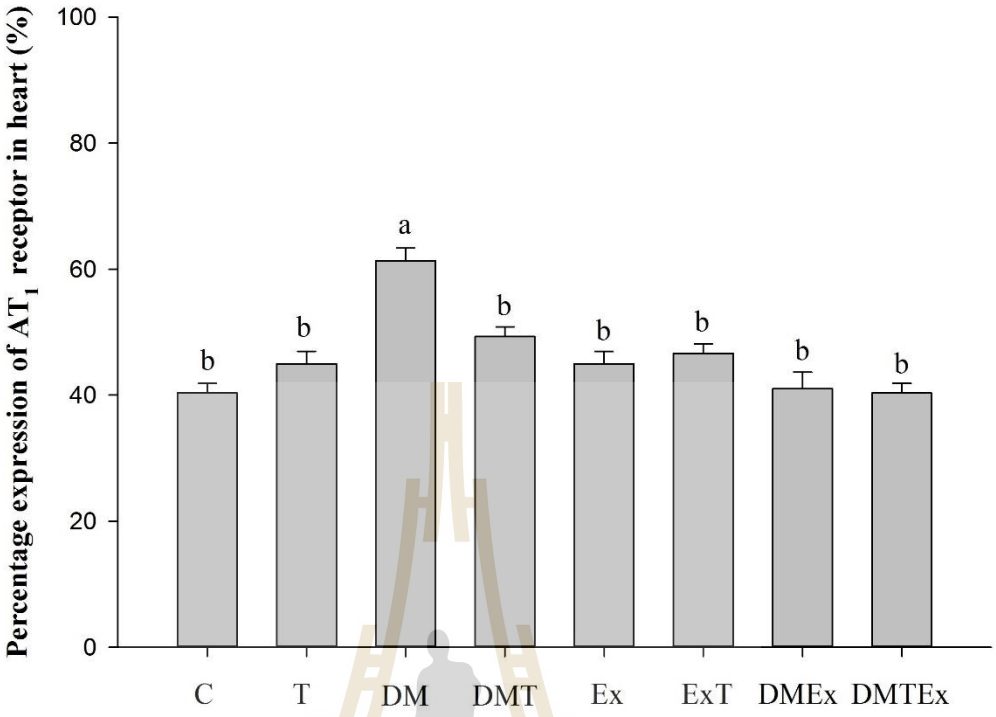


Figure 20 Percentage expression of AT_1 receptor in heart (Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$). (C, Control; T, Taurine; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).

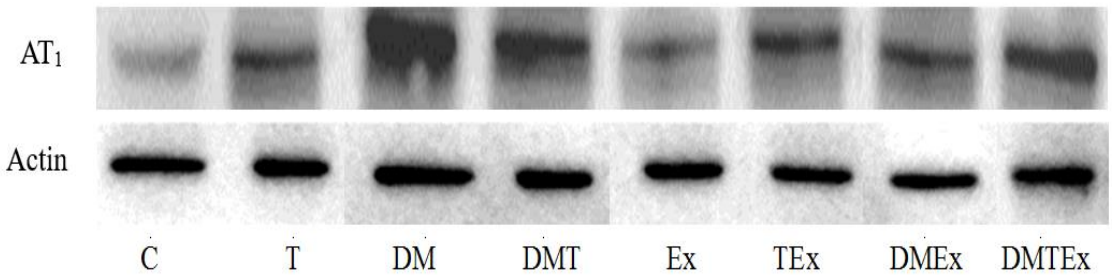


Figure 21 Expression of AT_1 receptor in kidney.

Percentages expression of AT_1 receptor in kidney difference increased significantly in offspring from maternal diabetes rats (DM) when compared with control groups (65.05 ±2.53% versus 41.94 ±1.78%, $P<0.05$). When offspring from maternal diabetes rats (DMT) plus taurine, offspring from maternal diabetes rats with exercise (DMEx), and offspring from maternal diabetes rats plus taurine with exercise (DMTEx), expression of AT_1 receptor in heart difference were lower than in offspring from maternal diabetes rats (DM).

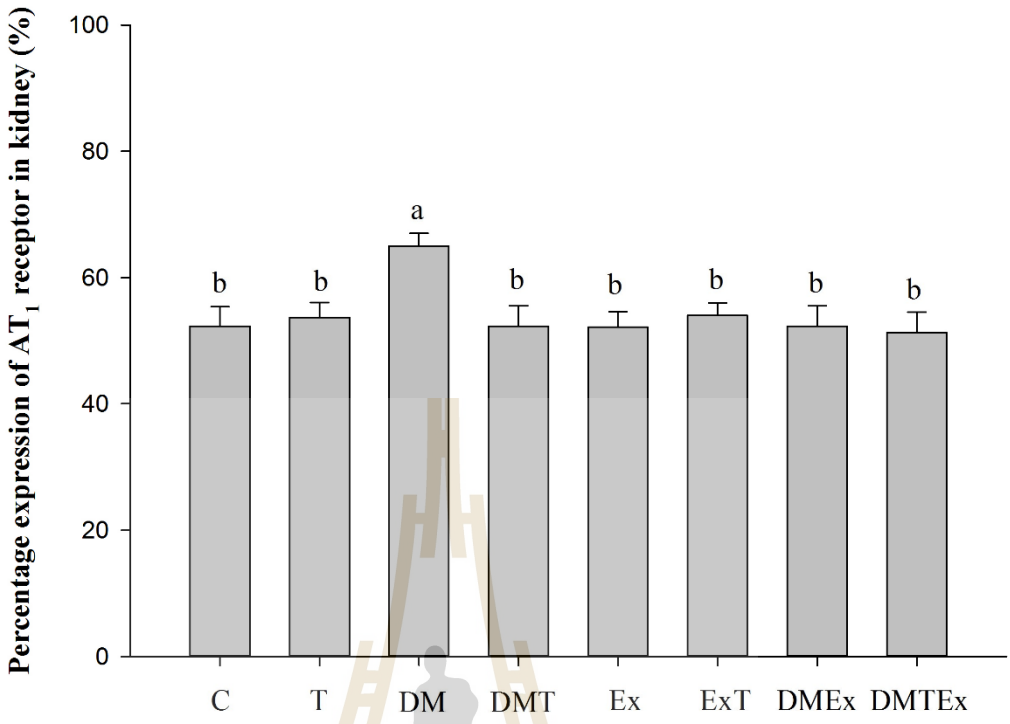


Figure 22 Percentage expression of AT_1 receptor in kidney. (Each value is mean ± SD for eight rats in each group. ANOVA followed by post hoc Duncan's multiple range test. Different letters indicate different values among group ($P \leq 0.05$) (C, Control; T, Taurine; DM, offspring from maternal diabetes rats; DMT, offspring from maternal diabetes rats were fed with 3% taurine; Ex, Exercise; TEx, offspring from maternal non-diabetes rats were fed with 3% taurine and exercise; DMEx, offspring from maternal diabetes rats were fed with RO and exercise; DMTEx, offspring from maternal diabetes rats were fed with 3% taurine and exercise).

CHAPTER V

DISCUSSION AND CONCLUSION

5.1 Body weight and organ weight

The present study, body weights differences decreased significantly in offspring from maternal diabetes rats (DM) when compared with control group (384 ± 15.27 versus 357 ± 7.55, $P \leq 0.05$). The previous study found that diabetes is an autoimmune damage of pancreatic β cells brings to a defect of insulin secretion that goes to be the metabolic disorder about with diabetes. In additional various biochemical mechanisms that report for damage of tissue response to insulin. Imperfection in insulin advance to uncontrolled lipolysis and high levels of free fatty acids in the plasma, which are repressed glucose metabolism have the affected to peripheral tissues, which are involved the weight loss such as skeletal muscle (muscle weakness) (Westerblad et al., 2010). Insulin resistance is reduced glucose uptake in peripheral tissues leads into reduced rate of glucose metabolism. However, the level of hepatic glucokinase is controlled by insulin secretion. Therefore, a lower rate of glucose phosphorylation in hepatocytes bring to high delivery to the plasma (Westerblad et all., 2010). In addition, body weights differences decreased significantly in all exercise groups compared with non-exercise groups. It was observed that the final body mass of rats trained with moderate intensity exercises were smaller after 12 weeks period of physical training, suggesting increase in the energy use in these animals. The processes of metabolic are suggesting increase in the energy use in these animals.

The processes of metabolic are responsible for creating adenosine triphosphate (ATP), the energy source for all muscle action. ATP is created by three basic energy systems.

First, the ATP-phosphocreatine (ATP-PCr) system, second is the glycolytic system and third is the oxidative system. In each system supply to energy production in every type of exercise. The corresponding addition of each will base on influence such as the energy of activity rate at the start of exercise and the show of oxygen in the muscle. The processes of metabolic adaptations appear in skeletal muscle in response to endurance training. Adaptation combined with the high in capillaries and muscle blood flow in the trained, highly enlarge the oxidative capacity of the endurance-trained muscle. Endurance training also enlarges the capacity of skeletal muscle to store glycogen (Kiens et al., 1993). The understanding of trained muscles to use fat as an energy source is also improved, and this high dependence on fat spares glycogen stores (Kiens et al., 1993). The high capacity to use fat succeeding endurance training results from an enlarger can be to activate free-fatty acids from fat store and an enhanced capacity to oxidize fat consistent to the high in the muscle enzymes important for fat oxidation (Jack et al, 1994).

Heart weight differences increased significantly in all exercise groups compared with non-exercise groups. Moreover, infinite variables may lead cardiac hypertrophy in rats present to physical exercises, such as the density, intensity and period of the physical training series, over and above the training program period. Another influence consists of star the age at the onset of the training, sex and group of animals used in the physical training (James et al., 1974). Therefore, the results show in this investigation linked to the heart's corresponding weight after low and high intensities training, allow with the previous mentioned above. Furthermore, low intensity

exercises did not affect for increase in the heart weight of trained rats, in corresponding to the non-trained. Yet, there was increase in the related weight of these organs and myocytes hypertrophy, expose through the histopathological investigation of the rats trained at high intensity.

Kidney weight differences increased significantly in all exercise groups compared with non-exercise groups. According to Shizuru (Shizuru et al., 1991), the renal responses to physical exercises are related to their intensity, therefore, exercises performed at low intensities increase the urinary flow and the sodium excretion, while at high intensities, these two parameters considerably decrease. Maybe such decrease is due to the high plasmatic indices of aldosterone, hormone which progressively increases, reaching up to six times more than the indices observed in resting bodies, as means of keeping the body liquids and the homeostasis. Actually, Carla (Carla et al., 2016) reported that the primary function of the kidneys is to regulate the volume and composition of the extra cellular liquid, and hence, these alterations that occur during the performance of physical exercises may generate hemodynamic changes and changes in the sodium and water excretion. It may be coming from the changes mechanism in the homeostatic mechanism such as increased cardiac output and blood pressure during stress have the effected to contributed increased kidney weight after stress (Chang et al., 1995). Stress were inducing adrenal hypertrophy is a well-established phenomenon. Strong stimulation of the adrenal glands during prolonged stress situations is known to cause adrenal hyperplasia and hypertrophy (Marti et al., 1993; Tuli et al., 1995). The regular and appropriate exercise is believed to be beneficial to overall health and has a positive effect on various organs, heart and liver

in particular. However, exhaustive exercise may result in organ damage in the liver and kidney as was first demonstrated by Fojt (Fojt et al., 1976).

5.2 Blood chemistry

FBS and TG differences increased significantly in offspring from maternal diabetes rats (DM)when compared with control group (116.1 ± 12.30 versus 82.5 ± 6.04, $P \leq 0.05$) (166.6 ± 19.80 versus 130.0 ± 14.45, $P \leq 0.05$). While, plasma insulin level differences decreased significantly in offspring from maternal diabetes rats (DM) compared with control group (7.2 ± 1.81 versus 10.1 ± 13.00, $P \leq 0.05$). According Schalaan found to increase significantly in FBS in maternal diabetes rats could be due to the destruction of the pancreatic β-cell by STZ in rat mothers that affect to children could cause plasma insulin levels to decrease (Weyer et al., 2000; Wohaieb et al., 1987). Elevation of blood glucose may be attributed to the reduced entry of glucose to peripheral tissues, muscle and adipose tissue (Beck-Nielsen, 2002), increased glycogen breakdown (Gold, 1970) and increased gluconeogenesis and hepatic glucose production (Raju et al., 2001). In a group of diabetic rats were have taurine combination with exercise, there was a significant reduction in blood glucose levels and increased insulin levels in adult rats. Similarly, to Miyazaki the serum glucose level in the exercise without taurine group was significantly decreased compared to that in the non-exercise without a taurine group (Miyazaki et al., 2004). The study found that exercise improves insulin sensitivity. As a result, glucose uptake, the greater per unit of insulin. It the flow of blood to the working muscles to increase the size of perfused capillary and the number of insulin receptors are present (Wahren et al., 1971) and exercise can facilitate the glycemic control by increased insulin sensitivity, improved fuel for oxidation, and increased storage of muscle glycogen

(Doi et al., 1979). The previous study found that taurine supplementation diabetes during pregnancy reduced the rate of apoptosis by IL-1-induced pancreatic islets (Merezak et al., 2004) and fetal on the DNA synthesis, which prevents the abnormal development of the endocrine pancreas (Sangeeta et al., 2007). The plasma taurine content was low in diabetic pregnant rats and their offspring in the course of life and in fetuses of the next generation (Aerts and Van, 2002). The above results suggest that it is time to conduct detailed studies on the involvement of taurine in "fetal programming" to determine if this amino acid should be supplemented during pregnancy, to prevent insulin resistance and other metabolic damage up to adult and second generation. In addition, taurine administration for 4 weeks enhances both the growth of the β-cell islets of the pancreas and the degree of insulin secretion (Idrissi et al., 2009) and protects the β-cells from death or a functional defect induced by several stresses, such as hyperglycemia and hyperlipidemia (Oprescu et al., 2007; Chang, 2000; Tang et al., 2007).

HDL levels differences decreased significantly in offspring from maternal diabetes rats (DM) when compared with control group (51.7 ± 6.20 versus 62.0 ± 3.89, $P \leq 0.05$). In contrast to LDL level difference increased significantly in offspring from maternal diabetes rats (DM) when compared with control group (122.0 ± 15.91 versus 106.6 ± 5.50, $P \leq 0.05$). Effect insulin production apolipoprotein regulates the enzyme lipoprotein lipase and cholesterol ester transport protein, which is causing the fat with diabetes. The previous study found that insulin deficiency reduces the activity of hepatic lipase and lipoprotein lipase. Hypertriglyceridemia occurs by decreased HDL cholesterol, important feature of the plasma lipid abnormalities found in diabetes. (Grundy et al., 2004; Wang et al., 2012). Hypertriglyceridaemia, caused of

very low-density lipoprotein (VLDL) triglyceride lipoproteins and increased nutrient levels in the secretion of free fatty acids and triglycerides glucose (Ginsberg, 2005). The report also states that it will result in a pattern in high blood lipid levels (elevation of serum triglycerides, cholesterol, LDL-C, reduction in HDL), triglycerides and cholesterol accumulated in the liver associated with a reduction in liver glycogen content as supported by previous studies (Schaalan et al., 2009). Clinical characteristics related to hepatic steatosis disease include obesity, hyperlipidemia, and diabetes, all of which are attributable to insulin resistance. (Harrison et al., 2002).

In the present study, rats swimming for exercise group showing differences increased significantly in high-density lipoprotein (HDL) levels, but decreased significantly in lipoprotein, low density (LDL). Our observations support the idea that exercise affects lipid and lipoprotein metabolism. (Oyelola and Rufai, 1993). The previous studies have reported that body training regularly promotes increased plasma concentrations of HDL (Thompson et al., 2001) and decrease in its concentration of LDL cholesterol (Silva et al., 2011).

In this study, shows the blood urea nitrogen (BUN) and serum glutamate pyruvate transaminase (SGOT) were increased in a groups of taurine supplement with exercise. Our results are in accordance with previous studies where prolonged exercise swimming has been shown to increase plasma levels of SGOT and BUN, caused of damages in skeletal muscle, liver, and kidney (Bowers et al., 1987; Decombaz et al., 1979; Raimondi et al., 1975; Riley et al., 1975; Soloman, 1979). In addition, regular exercise aggravated renal damage in hypertensive animals (Kuru et al., 2005). The previous study found that activities of SGOT, SGPT and ALP (Alkaline phosphatase) in serum were altered in DM. In offspring from maternal

diabetes rats (DM), the changes in the levels of SGOT, SGPT and ALP are directly related to changes in metabolism in which the enzymes are involved. The increased activities of transaminases, which are active in the absence of insulin due to the availability of amino acids in the blood of diabetes mellitus and are also responsible for the increased gluconeogenesis and ketogenesis (Kumaresan et al., 2014).

5.3 Mean arterial pressures and baroreflex sensitivity

In the present study, mean arterial pressures are increased in offspring from maternal diabetes rats (DM). According to previous studies in a diabetes group the pressures and heart rate are increased (Brands et al., 1996). The heart rate is non-changes, for understood this mechanism. However, the study reported that induction of poor glycemic control increased mean arterial pressure (Michael and Sharyn, 2001). Despite the modest amplitude of the pressure rise, several additional features of the response were noteworthy. First, the increase in pressure was rapid in onset, consistent with peripheral vasoconstriction. Second, the increase occurred despite significant urinary sodium and volume losses: the increase in arterial pressure may have contributed to the natriuresis, but it still could be predicted that elimination of the urinary losses may have yielded a greater increase in arterial pressure. Third, arterial pressure decreased rapidly with the restoration of good glycemic control and reversed, rising with equal rapidity, with the onset of a second diabetic period (Brands and Hopkins, 2001). Those results indicated that the onset of diabetes could affect systemic hemodynamics directly, and also suggested there was underlying vasoconstriction. In addition, cardiac output decreased progressively during the first week of diabetes, due in part to the significant decrease in sodium balance. Total peripheral resistance increased markedly, however, and the changes in cardiac output

and sodium balance during the diabetic and recovery periods suggested that there was a vasoconstrictor influence associated with the period of poor glycemic control (Michael et al., 2001).

In the present study are decreased baroreflex sensitivity (BRS) and depressed heart rate variability (HRV) in offspring from maternal diabetes rats (DM). Autonomic dysfunction with increased sympathetic activation expressed by the low value of BRS along with depressed HRV is the characteristic feature of metabolic syndrome. In diabetes to reduces the resistance of insulin and increases sympathetic tone. As a result, low value of baroreflex sensitivity (Dela et al., 1994). In addition, in diabetic patients, BRS and HRV can be considered as early signs of cardiovascular autoimmune disease, a fivefold increase in mortality and morbidity.

While BRS were improved in exercise groups when compared with non-exercise groups. MAP increases in response to dynamic exercise, largely owing to an increase in systolic blood pressure, because diastolic blood pressure remains at near-resting levels. Systolic blood pressure increases linearly with increasing rates of work, reaching peak values of between 200 and 240 mmHg in normotensive persons. Because MAP is equal to cardiac output times total peripheral resistance, the observed increase in mean arterial pressure results from an increase in the cardiac output that outweighs a concomitant decrease in total peripheral resistance. This increase in mean arterial pressure is a normal and desirable response, the result of a resetting of the arterial baroreflex to a higher pressure (Brooks et al., 1996). A program of mild-intensity exercises would be enough to show some improvement in the autonomic function of healthy adults (Uusitalo et al., 2002). or those with chronic heart failure (Malfatto et al., 2002), even without direct training supervision (Radaelli et al., 1996),

changes on vagal activity caused by physical training would be central, possibly directly on baroreflex, whereas the sympathetic activity would be primarily related to peripheral changes (vasoconstriction) (Radaelli et al., 1996). The previous study found that BRS increase after exercise training, increases in markers of vagal activity (LaRovere et al., 2002). Some studies found that exercise can improve diabetes, cardiovascular and nervous system disorders. (Howorka et al., 1997; Frattola et al., 1997; Soška et al., 2001). In addition, studies have also show that increased interest in the effects of hypoglycemia has been reported by studies showing the relationship between severe hypoglycemia and blood vessel disease in type 2 diabetic, which are shown that increased interest in the effects of hypoglycemia (Zoungas et al., 2010) and by large-scale clinical studies showing an association between intensive glycemic control and adverse cardiovascular events (Gerstein et al., 2008; Patel et al., 2008; Duckworth et al., 2009). Multiple processes associated with cardiovascular injury or dysfunction are induced during hypoglycemia are including increased activation of the renin-angiotensin-aldosterone system, endothelial dysfunction, decrease in the spontaneous baroreflex, and increased sympathetic nerve activity. All of these factors have a role in the adverse clinical outcomes associated with hypoglycemia (Adler et al., 2010; Joy et al., 2015; Limberg et al., 2014).

5.4 Histological study in islet of Langerhans

In the present study in the pancreas show smaller size of islet of Langerhans in offspring from maternal diabetes rats (DM) when compare the control group. Similarly, with Saito (Saito et al., 1979). The islet of Langerhans is smaller are may be the mechanism is oxidative stress and decreased protective superoxide dismutase enzymes. The presence of amyloid deposits in type 2 diabetes had led to the

suggestion that it is causal for diabetes since islets with amyloid deposits are decreased the percentage of β-cells, and islet amyloid polypeptide (IAPP) fibrils have been shown to induce apoptosis (Lorenzo et al., 1994).

Maternal has received the taurine supplements have the resulting islet of Langerhans size are increased, also the taurine has the affected to increase insulin secretion, and in inhibition of apoptosis (Huxtable, 1992; Hansen, 2001). Moreover, taurine also seems to have plasma improves insulin sensitivity (Nakaya et al., 2000). In maternal fed a low-protein diet, insulin secretion in vitro from islets of Langerhans show from the offspring was reduced. When taurine was added to the drinking water of low-protein-fed, the release of insulin from fetal islets was restored to normal levels (Cherif et al., 1998). Although, taurine supplementation in maternal fed low protein has been reported to normalize the vascularization and beta-cell mass in the fetal endocrine pancreas (Boujendar et al., 2003). The present, it was reported that taurine supplementation during pregnancy and lactation in rats fed low protein starve collected, a less in beta-cell working in vivo in the old offspring (12-week) (Merezak et al., 2004). The effect of maternal taurine supplementation on beta-cell function in old offspring was present studied in maternal fed a control or fed low protein (Merezak et al., 2004).

5.5 The expression of AT_1 receptor in heart and kidney

In the present study shows that percentages expression of AT_1 receptor in heart and kidney difference increased significantly in offspring from maternal diabetes rats (DM)when compared with control groups. The study found that maternal dietary protein restriction or diabetes during pregnancy is associated with renal morphological and physiological changes. Different mechanisms can contribute to

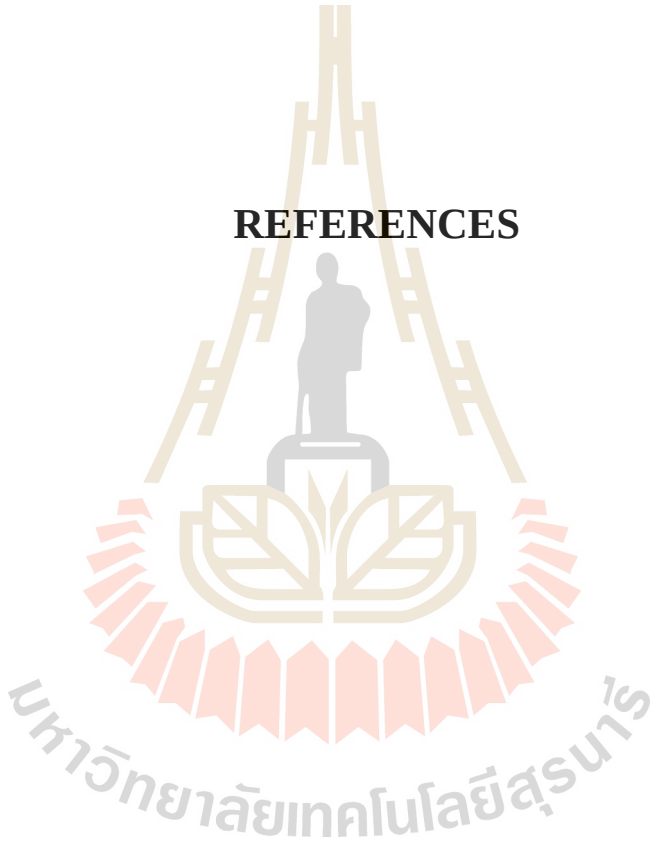
this phenotype: exposure to fetal glucocorticoid, alterations in the components of the RAS, apoptosis, and DNA methylation. A maternal protein restriction diet or diabetes during gestation decreases the activity of placental 11ß-hydroxysteroid dehydrogenase, exposing the fetus to glucocorticoids and resetting the hypothalamic pituitary- adrenal axis in the offspring. The abnormal function/ expression of AngII receptors during any period of life may be the consequence or cause of renal adaptation. (José et al., 2015). The previous study found that mechanism of AngII has also been implicated in insulin resistance and inhibits insulin-mediated GLUT4 translocation in this skeletal muscle model through a transient activation of mitogen-activated protein (MAP) kinases ERK1/2 inhibiting insulin receptor substrate 1/2 (IRS-1/2) and through a direct inhibitory nitration of Akt. It induces tyrosine phosphorylation of IRS-1 by Janus kinase 2 associated with AT_1 receptor stimulation which attenuates insulin-induced activation of phosphatidylinositol-3-kinase associated with IRS-1, leading to decreased insulin sensitivity (Kifor et al., 1991). The mechanism of AT_1, AT_1 receptor stimulation leads to renal arterial vasoconstriction, tubule epithelial sodium reabsorption, augmentation of tubulo–glomerular feedback sensitivity, and inhibition of pressure-natriuresis (Carey et al., 2003) can cause hypertension (Ferrario et al., 2006; Goldblatt et al., 1984). Conversely, AT_2 receptor activation exerts the opposite effects with respect to cardiovascular hemodynamics and cell growth. AT_2 receptor activation stimulates BK and NO production, vasodilatation, and modulates the vasoconstrictor action mediated by the AT_1 receptor through endothelium-dependent vasodilatation (Zhang et al., 2003).

When offspring from maternal diabetes rats (DM) plus taurine, offspring from maternal diabetes rats with exercise (DMEx), and offspring from maternal diabetes

rats plus taurine with exercise (DMTEx), expression of the AT1 receptor in heart and kidney difference was lower than in offspring from maternal diabetes rats (DM). The previous study found that training exercise, causing changes in circulating RAS. The reduction of circulating ACE activity and AngII concentrations are essential. Increasing of arterial renal sympathetic nerve activity, depending AngII are reduce in plasma. (Liu et al., 2001) However, it is possible that exercise training reduced AngII in circulatory system because the AT_1 expression was substantially lower in the exercise-trained rats.

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

REFERENCES



REFERENCES

Aars, H. (1968). Aortic baroreceptor activity in normal and hypertensive rabbits. **Acta Physiologica Scandinavica.** 72(3): 298–309.

Abebe, W. And Mozaffari, MS. (2011). Role of taurine in the vasculature: an overview of experimental and human studies. **American Journal of Cardiovascular Disease.** 1: 293–311.

Abebe, W. and Mozaffari, MS. (2011). Role of taurine in the vasculature: an overview of experimental and human studies. **American Journal of Cardiovascular Disease.** 1(3): 293–311.

Abebe, W. and Mozaffari, MS. (2011). Role of taurine in the vasculature: an overview of experimental and human studies. **American Journal of Cardiovascular Disease.** 1(3): 293–311.

Aditya, G. and Ajay, KS. (2017). The Pharmacological Potential of Rutin. **Pharmaceutical Journal.** 149–164.

Adler, GK., Bonyhay, I., Curren, V., Waring, E. and Freeman, R. (2010). Hypoglycaemia increases aldosterone in a dose-dependent fashion. **Diabetic Medicine.** 27: 1250–1255

Aerts and van Assche. (2002). Taurine and taurine-deficiency in the perinatal period. **Journal of Perinatal Medicine.** 30(4): 281–286.

Aerts, L. and Van Assche, FA. (2006). Animal evidence for the transgenerational development of diabetes mellitus. **The International Journal of Biochemistry & Cell Biology.** 38: 894–900

Alan, F., Sved, M., Schreihofer, O. and Curtis, K. (1997). Blood Pressure Regulation in Barorecptor-Denervated Rats**. Clincal and exeperimental.** 11: 1440–1681.

Allen, AM. (2011) Role of angiotensin in the rostral ventrolateral medulla in the development and maintenance of hypertension. **Current Opinion in Pharmacology.** 11: 117–123.

American Diabetes Association. (2011). Diagnosis and Classification of Diabetes Mellitus. **Diabetes Care.** 34(1): S62–S69.

Anderson, AH., Fennessey, PV., Meschia, G., Wilkening, RB. and Battaglia, FC. (1997). Placental transport of threonine and its utilization in the normal and growth-restricted fetus. **American Journal of Physiology - Endocrinology and Metabolism.** 272: E892–E900.

Andresen, MC. (1984). Short - and long-term determinants of baroreceptor function in aged normotensive and spontaneously hypertensive rats. **Circulation Research.** 54(6): 750–759.

Andresen, MC., Kuraoka, S. and Brown, AM. (1980). Baroreceptor function and changes in strain sensitivity in normotensive and spontaneously hypertensive rats. **Circulation Research.** 47(6): 821–828.

Antunes-Neto, JM., Toyama, MH., Carneiro, EM., Boschero, AC., Pereira-daSilva, L. and Macedo, DV. (2006). Circulating leukocyte heat shock protein 70 (HSP70) and oxidative stress markers in rats after a bout of exhaustive exercise. **Archives of Pathology & Laboratory Medicine.** 107–115.

Anuradha, CV. and Balakrishnan, SD. (1999). Taurine attenuates hypertension and improves insulin sensitivity in the fructose-fed rat, an animal model of

insulin resistance. **Canadian Journal of Physiology and Pharmacology** 77(10): 749–754.

Arima, S. and Ito, S. (2000). Angiotensin II type 2 receptors in the kidney: evidence for endothelial-cell-mediated renal vasodilatation. **Nephrol Dial Transplant.** 15(4): 448–451.

Aronoff, SL. (2004). Glucose metabolism and regulation: beyond insulin and glucagon. **Diabetes Spectrum.** 17(3): 183–189, 1040–9165.

Ashcroft, FM. and Gribble, FM. (1999). ATP-sensitive K^+ channels and insulin secretion: their role in health and disease. **Diabetologia.** 42(8): 903–919.

Ashworth, MA., Leach, FN. and Milner, RD. (1973). "Development of insulin secretion in the human fetus," **Archives of Disease in Childhood**. 48(2): 151–152.

Atkinson, MA., George, S., Eisenbarth, MD., Aaron, W. and Michels, MD. (2015). Type 1 diabetes. **Lancet.** 383(9911): 69–82.

Bakari, AG1. and Onyemelukwe, GC. (2004). Plasma insulin response to oral glucose tolerance test in type-2 Nigerian diabetics. **East African Medical Journal.** 81: 463–467.

Baker, L. and Piddington, R. (1993). Diabetic embryopathy: a selective review of recent trends. **Journal of Diabetes and its Complications.** 7: 204–212.

Barker, DJ. (2004). The developmental origins of chronic adult disease. **Acta Paediatrica.** 93: 26–33.

Barker, DJ. (2007). Obesity and early life. **Obesity Reviews.** 1: 45–49.

Barker, DJ., Eriksson, JG., Forsen T., and Osmond, C. (2002). Fetal origins of adult disease: strength of effects and biological basis. **International Journal of Epidemiology.** 31: 1235–1239.

Barker, DJ., Winter, PD., Osmond, C., Margetts, B. and Simmonds, SJ. (1989). Weight in infancy and death from ischaemic heart disease. **Lancet.** 2(8663): 577–580.

Bateson, P. (2001). Fetal experience and good adult designa. **International Journal of Epidemiology.** 30(5): 928–934.

Baum, M. and Weiss, M. (2001). The influence of a taurine containing drink on cardiac parameters before and after exercise measured by echocardiography. **Amino Acids.** 20(1): 75–82.

Beck-Nielsen, H. (2002). Insulin resistance: organ manifestations and cellular mechanisms. **Ugeskrift for Laeger.** 164: 2130–2135.

Bedford, JJ. and Leader, JP. (1993). Response of the rat to anisosmotic conditions. **American Journal of Physiology.** 264.

Behme, MT., Dupre, J., Harris, SB., Hramiak, IM. and Mahon, JL. (2003). Insulin resistance in latent autoimmune diabetes of adulthood. **Annals of the New York Academy of Sciences.** 1005: 374–377.

Beischer, NA. Oats, JN. Henry, OA. Sheedy, MT. and Walstab, JE. (1991). Incidence and severity of gestational diabetes mellitus according to country of birth in women living in Australia. **Diabetes.** 40(2): 35–38.

Bell, GI., Pictet, RL., Rutter, WJ., Cordell, B., Tischer, E. and Goodman, HM. (1980). Sequence of the human insulin gene. **Nature**. 284: 26–32.

Bemben, DA. and Bemben, MG. (2000). Effects of resistance exercise and body mass index on lipoprotein lipid patterns of postmenopausal women. **Journal of Strength and Conditioning Research.** 14: 80–85.

Benicky, J., Hafko, J., Sanchez-Lemus, E., Aguilera, G. and Saavedra, JM. (2012). Six Commercially Available Angiotensin II AT1 Receptor Antibodies are Non-specific. **Cellular and Molecular Neurobiology.** 32(8): 1353–1365.

Bidri, M. and Choay, P. (2003). Taurine: a particular aminoacid with multiple functions. **Pharmaceutiques Françaises.** 61(6): 385–391.

Bidri, M. and Choay, P. (2003). Taurine: a particular aminoacid with multiple functions. **Annales Pharmaceutiques Francaises.** 61: 385–391.

Bliss, M. (1993). The history of insulin. **Diabetes Care.** 16: 4–7.

Bouckenooghe, T., Remacle, C. and Reusens, B. (2006). Is taurine a functional nutrient? **Current Opinion in Clinical Nutrition and Metabolic Care.** 9(6): 728–733.

Boujendar, S., Arany, E., Hill, D., Remacle, C. and Reusens, B. (2003). Taurine supplementation of a low protein diet fed to rat dams normalizes the vascularization of the fetal endocrine pancreas. **Journal of Nutrition.** 133: 2820–2825.

Bowers, WDJ., Hubbard, RW., Leav, I., Daum, R., Conlon, M., Hamlet, MP., Mager, M. and Brandt, P. (1987). Alterations of rat liver subsequent to heat overload. **Archives of Pathology & Laboratory Medicine.** 102: 154-157.

Bradley, RL., Jeon, JY., Liu, FF. and Maratos-Flier, E. (2007). Voluntary exercise improves insulin sensitivity and adipose tissue inflammation in diet induced

obese mice. **American Journal of Physiology - Endocrinology and Metabolism.** (3): 586–94.

Brand, M., Lamande, N., Sigmund, CD., Larger, E., Corvol, P. and Gasc, JM. (2006) Angiotensinogen modulates renal vasculature growth. **Hypertension** 47: 1067–1074.

Brands and Hopkins, MF. (2001). Arterial Pressure Control at the Onset of Type I Diabetes: The Role of Nitric Oxide and the Renin-Angiotensin System. **American Journal of Hematology.** 14: 126S–131S.

Brands, MW. and Hopkins, TE. (1996). Poor glycemic control induces hypertension in diabetes mellitus. **Hypertension.** 27: 735–739.

Brenner, BM., Garcia, DL. and Anderson, S. (1988). Glomeruli and blood pressure. Less of one, more the other. **American Journal of Hypertension.** 1: 335–347.

Brooks, GA., Fahey, TD. and White, TP. (1996). Exercise physiology human bioenergetics and its applications. 2nd edition. Mountain View, CA: **Mayfield Publishing Company.**

Brown, AM., Saum, WR. and Tuley, FH. (1976). A comparison of aortic baroreceptor discharge in normotensive and spontaneously hypertensive rats. **Circulation Research.** 39(4): 488–496.

Bunt, JC., Antonio, Tataranni, P. and. Salbe, AD. (2005). “Intrauterine exposure to diabetes is a determinant of hemoglobin A1c and systolic blood pressure in pima indian children,” **Journal of Clinical Endocrinology and Metabolism.** 6: 3225–3229.

Carey, RM. and Siragy, HM. (2003). The intrarenal renin-angiotensin system and diabetic nephropathy. **Trends in Endocrinology and Metabolism.** 14(6): 274–281.

Carla, G., Sandra, A., Patrícia, P., Olívia. P., Pedro G., João, B., Rute, S. and Pedro, M. (2016) Sodium and potassium urinary excretion and dietary intake: a cross-sectional analysis in adolescents. **Genes & Nutrition Journal.** 60: 10–34.

Carroll, MF., Burge, MR. and Schade, DS. (2003). Severe hypoglycemia in adults**. Reviews in Endocrine and Metabolic Disorders.** 4(2): 149-157, 1389–9155.

Carver, TD., Quick, AA., Teng, CC., Pike, AW., Fennessey, PV. and Hay, WW. Jr. (1997). Leucine metabolism in chronically hypoglycemic hypoinsulinemic growth-restricted fetal sheep. **American Journal of Physiology - Endocrinology and Metabolism.** 272: E107–E117.

Castrop, H., Höcherl, K., Kurtz, A., Schweda, F., Todorov, V. and Wagner, C. (2010). Physiology of kidney renin. Format: **Abstract Send to Physiological Reviews.** 90(2): 607–673.

Chan, SP., Gelding, SV. and McManus, RJ. (1992). Abnormalities of intermediate metabolism following a gestational diabetes pregnancy. **Clinical Endocrinology.** 36: 417–420.

Chang, KJ. and Kwon, W. (2000). Immunohistochemically localization of insulin in pancreatic beta-cells of taurine-supplemented or taurine-depleted diabetic rats. **Advances in Experimental Medicine and Biology.** 483: 579–587.

Chang, LT., Kras, K., Suzuki, K., Strasburg, G., Rodger, CD. and Schemmel, RA. (1995). Voluntary running in S5B/P1 Ras rats fed high fat or high carbohydrate diets. **Physiology & Behavior.** 57: 501–508.

Chang, TW. and Goldberg, AL. (1978). The metabolic fates of amino acids and the formation of glutamine in skeletal muscle. **The Journal of Biological Chemistry.** 253: 3685–3693.

Chen, M., Walia, R. and Hao, DE. (1998)). Sp_1 sites mediate activation of the plasminogen activator inhibitor-1 promotor by glucose in vascular smooth muscle cells. **The Journal of Biological Chemistry.** 273: 8225– 8231.

Cherif, H., Reusens, B., Ahn, MT., Hoet, JJ. and Remacle, C. (1998). Effects of taurine on the insulin secretion of rat fetal islets from dams fed a low-protein diet. **Journal of Endocrinology.** 159: 341–348.

Chien, PF., Smith, K., Watt, PW., Scrimgeour, CM., Taylor, DJ. and Rennie, MJ. (1993). Protein turnover in the human fetus studied at term using stable isotope tracer amino acids. **American Journal of Physiology.** 265: E31–E35.

Chiu, HK., Tsai, EC. and Juneja, R. (2007). "Equivalent insulin resistance". **Diabetes Research and Clinical Practice.** 77: 237–244.

Christensen, HN. (1990). Role of amino acid transport and counter transport in nutrition and metabolism. **Physiological Reviews.** 70: 43–77.

Christine, A., White, MD., Ayub Akbari, MD., Hari Talreja, MD., Neha Lalani, BSc., Greg, A. and Knoll. (2016). MD2 Classification of Kidney Transplant Recipients Using a Combination of Estimated GFR and Albuminuria Reflects Risk. **Transplant Direct.** 2(8): e96.

Christine, MB., Michael, S., Susan, O., Barbara, T. and Alexander. (2011). Impact of Maternal Obesity and Diabetes on Long-Term Health of the Offspring. **Experimental Diabetes Research.** 163438.

Clausen, TD., Mathiesen, ER. and Hansen, T. (2008). High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. **Diabetes Care.** 31: 340–346.

Clausen, TD., Mathiesen, ER. and Hansen, T. (2009). Overweight and the metabolic syndrome in adult offspring of women with diet treated gestational diabetes mellitus or type 1 diabetes. **The Journal of Clinical Endocrinology & Metabolism.** 94: 2464–2470.

Coppack, SW., Persson, M., Judd, RL. and Miles, JM. (1999). Glycerol and nonesterified fatty acid metabolism in human muscle and adipose tissue in vivo. **American Journal of Physiology.** 276: 233–240.

Cowley, AW Jr. (1992). Long-term control of arterial blood pressure. **Physiological Reviews.** 72(1): 231–300.

Cowley, AW Jr., Liard JF. and Guyton, AC. (1973). Role of baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. **Circulation Research.** 32(5): 564–576.

Cross, SE., Bacon, PL. and Morris, ML. (2000). The relational-interdependent self-construal and relationships. **Journal of Personality and Social Psychology**. 78(4): 791–808.

Cryer, P. (2001). The prevention and correction of hypoglycemia. In: Handbook of physiology: Section 7, the endocrine system. Vol. II. **The endocrine pancreas and regulation of metabolism.** 1057–1092.

Cryer, PE. (1992). Glucose homeostasis and hypoglycemia, **In: William's Textbook of Endocrinology. J.D. Wilson, D.W. Foster (Ed.).** 1223–1253.

Dabelea, D. and Pettitt, DJ. (2001). "Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility," **Journal of Pediatric Endocrinology and Metabolism.** 8: 1085–1091.

Dabelea, D., Hanson, RL. and Lindsay, RS. (2000). Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. **Diabetes.** 49: 2208–2211.

Dana, D. (2007). The Predisposition to Obesity and Diabetes in Offspring of Diabetic Mothers. **Diabetes Care.** S169–S174.

Das, J. and Sil PC. (2012). Taurine ameliorates alloxan-induced diabetic renal injury, oxidative stress-related signaling pathways and apoptosis in rats. **Amino Acids.** 43(4): 1509–1523.

Das, J. and Sil, PC. (2012). Taurine ameliorates alloxan-induced diabetic renal injury, oxidative stress-related signaling pathways and apoptosis in rats. **Amino Acids.** 43(4): 1509–23.

David, L. and Peter, A. (1982). Insulin and non-esterified fatty acids. **Biochemical Journal.** 204: 433–439.

Decombaz, J., Reinhardt, P. and Anantharaman, K. (1979). Biochemical changes in a 100-km run: free amino acids, urea, and creatinine. **European Journal of Applied Physiology.** 41: 61–72.

DeFronzo, R.A. (1988). The triumvirate: beta cell, muscle, liver – a conclusion responsible for NIDDM. **Diabetes.** 667–684.

Dela, F., Ploug, T. and Handberg, A. (1994). Physical training increases GLUT-4 protein and mRNA in patients with NIDDM. **Diabetes.** 43: 862–865.

Desoye, G., Hauguel. de., Mouzon, S. and Shafrir, E. (2003). The placenta in diabetic pregnancy. **Diabetes and pregnancy.** 26–147.

Doi, K., Prentki, M., Yip, C., Muller, W., Jeanrenaud, B. and Vranic, M. (1979). Identical biological effects of pancreatic glucagon and a purified moiety of canine gastric glucagon. **The Journal of Clinical Investigation.** 63: 525–531.

Dornhorst, A. and Beard, RW. (1993). Gestational diabetes: a challenge for the future. **Diabetes Medical.** 10: 897–905.

Dornhorst, A., Bailey, PC. and Anyakou, V. (1990). Abonormalities of glucose tolerance following gestational diabetes. **The Quarterly Journal of Medicine.** 284(77): 1219–1228.

Dornhorst, AN., Simon, G., Edwards, M., Jonathan SD., Nicholls, Victor Anyaoku, Duncan, M.L., Kirsten, E., Heslop, Robert, S., Elkeles, Richard, W. and Desmond, G. (1991). A defect in insulin release in women at risk of future non-insulin-dependent diabetes. **Clinical Science.** 81: 195–199.

Drucker, DJ. (2007). The role of gut hormones in glucose homeostasis**. The Journal of Clinical Investigation.** 117(1): 24–30, 0021–9738.

Duarte, FO., Sene-Fiorese, M., Manzoni, MS., de Freitas, LF., Cheik, NC., Garcia, Oliveira Duarte, de., AC. (2008). Caloric restriction and refeeding promoted different metabolic effects in fat depots and impaired dyslipidemia profile in rats. **Nutrition.** 24(2): 177–186.

Duckworth, W., Abraira, C. and Moritz, T. (2009). VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. **The New England Journal of Medicine.** 360: 129–139.

Durstine JL. and Haskell, WL. (1994). Effects of exercise training on plasma lipids and lipoproteins. **Exercise and Sport Sciences Reviews.** 22: 477–521.

Elliott, R., Bohart, AC., Watson, JC. and Greenberg, LS. (2011). Empathy. **Psychotherapy.** 48(1): 43-49.

Ericsson, A., Saljo, KE. and ostrand, Sj. (2007). "Brief hyperglycaemia in the early pregnant rat increases fetal weight at term by stimulating placental growth and affecting placental nutrient transport," **Journal of Physiology.** 3: 1323–1332.

Estadella, D., Oyama, LM., Damaso, AR., Ribeiro, EB., Oller, Do. and Nascimento, CM. (2004). Effect of palatable hyperlipidic diet on lipid metabolism of sedentary and exercised rats. **Nutrition.** 20(2): 218–24.

Failli, P., Fazzini, A. and Franconi, F. (1992). Taurine antagonizes the increases in intracellular calcium concentration induced by o~-adrenergic stimulation in freshly isolated guinea-pig cardiomyocytes. **Journal of Molecular and Cellular Cardiology.** 24: 1253–1265.

Ferrara, A. (2007). Increasing prevalence of gestational diabetes mellitus: A public health perspective. **Diabetes Care.** 30: S141–S146.

Ferrario, CM. and Strawn, WB. (2006). “Role of the renin-angiotensinaldosterone system and proinflammatory mediators in cardiovascular disease,” **American Journal of Cardiology.** 98(1): 121–128.

Ferrario, CM., McCubbin, JW. and Page, IH. (1969). Hemodynamic characteristics of chronic experimental neurogenic hypertension in unanesthetized dogs. **Circulation Research.** 24(6): 911–922.

Ferri, C., Bellini, C., Desideri, G., Giuliani, E., De., Siati, L., Cicogna, S. and Santucci, A. (1998). Clustering of endothelial markers of vascular damage in human salt-sensitive hypertension: influence of dietary sodium load and depletion. **Hypertension.** 32(5): 862–868.

Fojt, E., Ekelund, LG. and Hultman, E. (1976). Enzyme activities in hepatic venous blood under strenous physical exercise. **Pflügers Archiv.** 361: 287–296.

Forrester, T. (2004). Historic and early life origins of hypertension in Africans. **Journal of Nutrition.** 134(1): 211–216.

Franconi, F., Di, Leo, MA., Bennardini, F. and Ghirlanda, G. (2004). Is taurine beneficial in reducing risk factors for diabetes mellitus. **Neurochemical Research.** 29: 143–150.

Fraser, A. and Lawlor, DA. (2014). Long-term health outcomes in offspring born to women with diabetes in pregnancy. **Current Diabetes Reports.** 14: 489.

Frattola, A., Parati, G. and Gamba, P. (1997). Time and frequency domain estimates of spontaneous baroreflex sensitivity provide early detection of autonomic dysfunction in diabetes mellitus. **Diabetologie.** 40: 1470–1475.

Fujita, T. and Sato, Y. (1984). The antihypertensive effect of taurine in DOCA-salt rats. **Journal of Hypertension.** 2(3): 563–565.

Gajdosik, A., Gajdosikova A., Stefek M., Navarova, J. and Hozova, R. (1999). Streptozotocin-Induced Experimental Diabetes in Male Wistar Rats. **General Physiology and Biophysics.** 18: 54–62.

Gerich, JE. (1993). Control of glycemia. Baillier's Best Practice and Research in Clinical **Endocrinology & Metabolism.** 551–586: 0145–7217.

Gernot, D. and Sylvie, HDM. (2007). The Human Placenta in Gestational Diabetes Mellitus. **Diabetes Care.** 2: S120–S126.

Gerstein, HC., Miller, ME. and Byington, RP. (2008). Action to Control Cardiovascular Risk in Diabetes Study Group Effects of intensive glucose lowering in type 2 diabetes. **The New England Journal of Medicine.** 358: 2545–2559.

Gillespie, KM. (2006). Type 1 diabetes: pathogenesis and prevention. **Canadian Medical Association Journal.** 175(2): 165–170.

Ginsberg, HN., Zhang, YL. and Hernandez-Ono, A. (2005). Regulation of plasma triglycerides in insulin resistance and diabetes. **Archives of Medical Research.** 36: 232–240.

Gluckman, PD. and Hanson, MA. (2004). Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. **Pediatric Research.** 56(3): 311–317.

Gluckman, PD. And Hanson, MA. (2004). Living with the past: evolution, development, and patterns of disease. **Science.** 17: 1733–1736.

Gold, AH. (1970). The effect of diabetes and insulin on liver glycogen synthetase activation. **The Journal of Biological Chemistry.** 245: 903–905.

Goldblatt, HJ., Lynch, R., Hanzal, F. and Summerville, WW. (1984). “Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia,” **The Journal of Experimental Medicine.** 59(3): 347–379.

Goldman, AS. (1985). Hyperglycemia induced teratogenesis is mediated by a functional deficiency of arachoid acid. **Proceedings of the National Academy of Sciences of the United States of America.** 82: 8227.

Gribble, FM., Williams, L., Simpson, AK. and Reimann, F. (2003). A novel glucose-sensing mechanism contributing to glucagon-like peptide-1 secretion from the GLUTag cell line. **Diabetes.** 52: 1147–1154.

Grossman, G., Schwentikowski, M., Keck, FS., Hoher, M., Steinbach, G., Osterhues, H. and Hombach, V. (2004). Signal-averaged electrocardiogram in patients with insulin-dependent (type 1) diabetes mellitus with and without diabetic neuropathy. **Diabetic Med.** 14: 364–369.

Grundy, SM., Brewer, HB., Jr., Cleeman, JI., Smith, SC., Jr. and Lenfant, C. (2004). Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. **Circulation.** 109: 433–438.

Guyton, TS., De Wilt, H., Fennessey, PV., Meschia, G., Wilkening, RB. and Battaglia, FC. (1993). Alanine umbilical uptake, disposal rate, and decarboxylation rate in the fetal lamb. **American Journal of Physiology.** 265: E497– E503.

Gwacham, N. and Wagner, DR. (2012). Acute effects of a caffeine-taurine energy drink on repeated sprint performance of American college football players.

International Journal of Sport Nutrition and Exercise Metabolism. 22: 109–116.

Gwacham, N. and Wagner, DR. (2012). Acute effects of a caffeine-taurine energy drink on repeated sprint performance of American college football players. **International Journal of Sport Nutrition and Exercise Metabolism.** 22(2): 109–116.

Hales, CN. and Barker, DJ. (2001). The thrifty phenotype hypothesis. **British Medical Bulletin.** 60: 5–20.

Halfon, N., Verhoef, PA. and Kuo, AA. (2012). "Childhood antecedents to adult cardiovascular disease," **Pediatrics in Review.** 2: 51–60.

Hansen, SH. (2001). The role of taurine in diabetes and the development of diabetic complications. **Diabetes/Metabolism Research and Reviews.** 17: 330–346.

Hanson, U., Persson, B. and Thunell, S. (1990). Relationship between haemoglobin A1C in early type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. **Diabetologia.** 33: 100–104.

Harada, N., Ninomiya, C., Osako, Y., Morishima, M., Mawatari, K., Takahashi, A. and Nakaya, Y. (2004). Taurine alters respiratory gas exchange and nutrient metabolism in type 2 diabetic rats. **Obesity Research and Clinical Practice.** 12(7): 1077–1184.

Haralambie, G. and Berg, A. (1976). Serum urea and amino nitrogen changes with exercise duration. **European Journal of Applied Physiology.** 36: 39-48.

Harder, T., Aerts, L., Franke, K., Van Bree, R., Van Assche, FA. and Plagemann, A. (2001). Pancreatic islet transplantation in diabetic pregnant rats prevents

acquired malformation of the ventromedial hypothalamic nucleus in their offspring. **Neuroscience Letters.** 299: 85–88.

Harding, JE. (2001). The nutritional basis of the fetal origins of adult disease. **International Journal of Epidemiology.** 30(1): 15–23.

Harrison, SA., Kadakid, S., Lang, KA. and Schenker, S. (2002). Nonalcoholic steatohepatitis: what we know in the new millennium. **The American Journal of Gastroenterology.** 97: 2714–2724.

Heilig, CW., Stromski, ME., Blumenfeld, JD., Lee, JP. and Gullans, SR. (1989). Characterization of the major brain osmolytes that accumulate in salt-loaded rats. **American Journal of Physiology.** 257.

Hibbard, JU. (2002). Hypertensive disease and pregnancy. **Journal of Hypertension.** 20: 29–33.

Houmard, JA., Wheeler, WS., McCammon, MR., Wells, JM., Truitt, N., Hamad, SF., Holbert, D., Israel, RG. and Barakat, HA. (1991). An evaluation of waist to hip ratio measurement methods in relation to lipid and carbohydrate metabolism in men. **International Journal of Obesity.** 15(3): 181–188.

Howorka, K., Pumprla, J. and Haber, P. (1997). Effects of physical training on heart rate variability in diabetic patients with various degrees of cardiovascular autonomic neuropathy**. Cardiovascular Research.** 34: 206–214.

Hultman, K., Alexanderson, C., Mannerås, L., Sandberg, M., Holmäng, A. and Jansson, T. (2007). Maternal taurine supplementation in the late pregnant rat stimulates postnatal growth and induces obesity and insulin resistance in adult offspring. **The Journal of Physiology.** 579(3): 823–833.

Hunter, SJ. and Garvey, T. (1998). Insulin action and insulin resistance: diseases involving defects in insulin receptors, signal transduction and glucose transport effector system. **American Journal of Physiology.** 5: 331–346.

Huxtable, R. and Barbeau, A. (1976). Taurine. New York: Raven Press.

Huxtable, R., Franconi, F. and Giotti, A. (1987). The biology of taurine. Methods and mechanisms. New York: Plenum Press.

Huxtable, RJ. (1976). The metabolism and function of taurine in the heart. In: Huxtable RJ, Barbeau A (eds) Taurine. **Ravan press.** P99.

Huxtable, RJ. (1989). Taurine in the central nervous system and the mammalian actions of taurine. **Progress in Neurobiology.** 32: 471–533.

Huxtable, RJ. (1992). Physiological actions of taurine. **Physiological Reviews.** 72(1): 101–163.

Hyung Eun Yim, MD. and Kee Hwan Yoo, MD. (2008). Renin-Angiotensin System - Considerations for Hypertension and Kidney. **Department of Pediatrics, Korea University College of Medicine, Seoul, Korea.** 6: 42–50.

Ichihara, A., Kobori, H., Nishiyama, A. and Navar, LG. (2004). Renal renin-angiotensin system. **Contributions to Nephrology.** 143: 117–130.

Idrissi, El., Boukarrou, L., Heany, W., Malliaros, G., Sangdee, C. and Neuwirth, L. (2009). Effects of taurine on anxiety-like and locomotor behavior of mice. **Advances in Experimental Medicine and Biology.** 643: 207–215.

Ishak, M. and Petocz, P. (2003). Gestational diabetes among Aboriginal Australians: prevalence, time trend, and comparisons with non-Aboriginal Australians. **Ethnicity & Disease.** 13: 55–60.

Ishikura, K., Miyazaki, T., Ra., SG., Endo, S., Nakamura, Y., Matsuzaka, T, Miyakawa, S. and Ohmori, H. (2011). Effect of taurine supplementation on the alterations in amino Acid content in skeletal muscle with exercise in rat. Journal of Sports Science and Medicine. 10(2): 306–314.

Ito, S. and Sved, AF. (1997). Influence of GABA in the nucleus of the solitary tract on blood pressure in baroreceptor-denervated rats. **American Journal of Physiology.** 273(5): R1657–R1662.

Ito, T., Kimura, Y., Uozumi, Y., Takai, M., Muraoka, S., Matsuda, T., Ueki, K., Yoshiyama, M., Ikawa, M., Okabe, M., Schaffer, S., Fujio, Y. and Azuma, J. (2008). Taurine depletion caused by knocking out the taurine transporter gene leads to cardiomyopathy with cardiac atrophy. **Journal of Molecular and Cellular Cardiology.** 44: 927–937.

Jack, HW., David, L. and Costill. (1994). Physiology of Sport and Exercise**. Exercice - Aspect physiologique.** 549.

James, S., Somsong, P. and Ashok, KB. (1974). Experimental observations on the effects of physical training upon intrinsic cardiac physiology and biochemistry. **American Journal of cardiology.** 33(6): 744–751

Jansson, T., Cetin, I. and Powell TL. (2006). "Placental transport and metabolism in fetal overgrowth—a workshop report," **Placenta.** 27: 109–113.

Jeon, JA. and Kim, H. (2006). In vitro endothelial potential of human UC blood-derived mesenchymal stem cells. **Cytotherapy.** 8(3):215-227.

Jespersen, B., Knupp, L. and Northcott, CA. (2012). Femoral Arterial and Venous Catheterization for Blood Sampling, Drug Administration and Conscious

Blood Pressure and Heart Rate Measurements. **Journal of Visualized Experiments.** e3496.

Jones, BH., Standridge, MK., Taylor, JW. and Moustaïd, N. (1997). Angiotensinogen gene expression in adipose tissue: analysis of obese models and hormonal and nutritional control. **American Journal of Physiology.** 273(1): 236–242.

Jones, JV. and Thoren, PN. (1977). Characteristics of aortic baroreceptors with non-medullated afferents arising from the aortic arch of rabbits with chronic renovascular hypertension. **Acta Physiologica Scandinavica.** 101(3): 286–293.

Jong, HR., Ko, GJ., Wasowska, BA. and Rabb, H. (2009). The interaction between ischemiareperfusion and immune responses in the kidney. **Journal of Molecular Medicine.** 87: 859–864.

José, ES., Marcelo, CL., Agnes, L., Ize, PL, Flávia FM., Daniele, BT., Patrícia, AB. and José, ARG. (2015). Impact of taurine supplementation on blood pressure in gestational protein restricted offspring: Effect on the medial solitary tract nucleus cell numbers, angiotensin receptors, and renal sodium handling. **Journal of the Renin-Angiotensin- Aldosterone System.** 16(1): 47–58.

Joy, NG., Tate, DB., Younk, LM. and Davis, SN. (2015). Effects of acute and antecedent hypoglycemia on endothelial function and markers of atherothrombotic balance in healthy humans. **Diabetes.** 64: 2571–2580.

Kalupahana, NS., Massiera, F., Quignard-Boulange, A., Ailhaud, G., Voy, BH., Wasserman, DH. and Moustaid-Moussa, N. (2012). Overproduction of angiotensinogen from adipose tissue induces adipose inflammation, glucose intolerance, and insulin resistance. **Obesity.** 20(1): 48–56.

Kang, NS., Yim, HE., Bae, IS., Choi, JH., Choi, BM. and Yoo, KH. (2003). ACE inhibition modulates transforming growth factor-β receptors in the young rat**.** **Pediatric Nephrology.** 18: 865–871.

Kerssen, A., de Valk, HW., Visser, GH. (2007). Increased second trimester maternal glucose levels are related to extremely large-for-gestational-age infants in women with type 1 diabetes. **Diabetes Care.** 30(5): 1069–1074.

Kiens, B., Éssen-Gustavsson, B., Christensen, NJ. and Saltin, B. (1993). Skeletal muscle substrate utilization during submaximal exercise in man: effect of endurance training. **Journal of Physiology.** 469: 459–478.

Kifor, I., Moore, TJ. and Fallo, F. (1991). Potassium-stimulated angiotensin release from superfused adrenal capsules and enzymatically dispersed cells of the zona glomerulosa. **Endocrinology.** 129(2): 823–831.

Kim, YC., Lee, HG. and Han, KA. (2007). D1 dopamine receptor dDA1 is required in the mushroom body neurons for aversive and appetitive learning in Drosophila. **Journal of Neuroscience.** 27(29): 7640–7647.

Kimball, SR., Horetsky, RL. and Jefferson, LS. (1998). Implication of eIF2B rather than eIF4E in the regulation of global protein synthesis by amino acids in L6 myoblasts. **The Journal of Biological Chemistry.** 273: 30945– 30953.

Klitgaard, H., Marc, R., Brunet, A., Vandewalle, H. and Monod, H. (1989). Contractile properties of old rat muscles: Effect of increased use. **Journal of Applied Physiology.** 67: 1401–1408.

Krieger, E. (1986). Neurogenic mechanisms in hypertension: resetting of the baroreceptors. **Hypertension.** 8: 7–114.

Kumaresan, P., Jeyanthi, KA. and Kalaivani, R. (2014). Biochemical evaluation of anti-diabetic activity of aqueous extract of Gmelina arborea in Alloxan induced albino rats. **International Journal of Herbal Medicine.** 2(2): 90–94.

Kuriyama, K., Ida, S. and Ohkuma, S. (1984). Alteration of cerebral taurine biosynthesis in spontaneously hypertensive rats. **Journal of Neurochemistry.** 42: 1600–1606.

Kuru, O., Sentürk, ÜK., Gülkesen, H., Demir, N. and Gündüz, F. (2005). Physical training increases renal injury in rats with chronic NOS inhibition. **Renal Failure.** 27: 459–463.

La Rovere. MT., Bersano, C., Gnemmi, M., Specchia, G. and Schwartz, PJ. (2002). Exercise- induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. **Circulation.** 106: 945–949.

Lain, KY. and Catalano, PM. (2007). Metabolic changes in pregnancy. **Clinical Obstetrics and Gynecology.** 50(4): 938–948.

Lampl, M. and Jeanty. P. (2004). "Exposure to maternal diabetes is associated with altered fetal growth patterns: a hypothesis regarding metabolic allocation to growth under hyperglycemic-hypoxemic conditions," **American Journal of Human Biology.** 16(3): 237–263.

Langley-Evans, SC., Langley-Evans, AJ. and Marchand MC. (2003). Nutritional programming of blood pressure and renal morphology. **Archives of Physiology and Biochemistry.** 111(1): 8–16.

LaRovere, MT., Bersano, Ch. and Gnemmi, M. (2002). Exercise inducted increase in baroreflex sensitivity predicts improved prognosis after myocardial Infarction. **Circulation.** 106: 945–949.

LaRovere, MT., Bigger, JT. and Marcus, FI. (1998). Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. **Lancet.** 351: 478–484.

Laterza, MC., de Matos, LD., Trombetta, IC., Braga, AM., Roveda, F., Alves, MJ., Krieger, EM., Negrão, CE. and Rondon, MU. (2007) Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. **Hypertension.** 49(6): 1298–1306.

Lemons, JA., Adcock, EW. III, Jones, MD., Jr., Naughton, MA., Meschia, G. and Battaglia, FC. (1976). Umbilical uptake of amino acids in the unstressed fetal lamb. **The Journal of Clinical Investigation.** 58: 1428–1434.

Levine, AS., Rogers, B. and Kneip, J. (1983). Effects of centrally administered corticotropic releasing factor (CRF) on multiple feeding paradigms. **Life Sciences.** 22: 337–339.

Lewis, NJ. (1983). Teratogenesis from bata hydroxybutyrete in rat embryo organ culture and enhancenebt by subteratogenic glucose. **Diabetes.** 32(1): 11.

Liechty, EA., Boyle, DW., Moorehead, H., Auble, L. and Denne, SC. (1999). Aromatic amino acids are utilized and protein synthesis is stimulated during amino acid infusion in the ovine fetus. **Journal of Nutrition.** 129: 1161–1166.

Lien, YH., Shapiro, JI. and Chan L. (1990). Effects of hypernatremia on organic brain osmolytes. **The Journal of Clinical Investigation.** 85: 1427– 1435.

Limberg, JK., Taylor, JL. and Dube, S. (2014). Role of the carotid body chemoreceptors in baroreflex control of blood pressure during hypoglycemia in humans. **Experimental Physiology.** 99: 640–650.

Lisa, AC., Mark, J., Graham. and Erin, LD. (2015). Modeling Course-Based Undergraduate Research Experiences: An Agenda for Future Research and Evaluation. **CBE-Life Sciences Education.** 14.

Liu, JL., Pliquett, RU., Brewer, E., Cornish. KG., Shen, YT. and Zucker, IH. (2001). Chronic endothelin-1 blockade reduces sympathetic nerve activity in rabbits with heart failure**. American journal of physiology.** 280(6): R1906-R1913.

Lohmeier, TE., Irwin, ED. and Rossing, MA. (2004). Prolonged activation of the baroreflex produces sustained hypotension. **Hypertension.** 43(2): 306–311.

Longnecker, D. (2014). Anatomy and Histology of the Pancreas.Pancrea pedia: **Exocrine Pancreas Knowledge Base.** 6(3): 441–444.

Lorenzo, A., Razzaboni, B., Weir, GC. and Yankner, BA. (1994). Pancreatic islet cell toxicity of amylin associated with type-2 diabetes mellitus. **Nature.** 368: 756–760.

Lucas, A. (1991). Programming by early nutrition in man. **Ciba Foundation Symposium.** 156: 38–50.

Macfarlane, CM. and Tsakalakos, N. (1988). The extended Pedersen hypothesis. **Clinical Physiology and Biochemistry.** 6(2): 68–73.

Malfatto, G., Branzi, G., Riva, B., Sala, L., Leonetti, G. and Facchini, M. (2002) Recovery of cardiac autonomic responsiveness with low-intensity physical training in patients with chronic heart failure. **European Journal of Heart Failure.** 4: 159–166.

Manderson, J., Mullan, B., Patterson, C., Hadden, D., Traub, A. and McCance, D. (2002). “Cardiovascular and metabolic abnormalities in the offspring of diabetic pregnancy,” **Diabetologia.** 7: 991–996.

Marti, O., Gavalda, A., Jolin, T. and Armario, A. (1993). Effect of regulatory exposure to chronic immobilization stress on the circadian pattern of pituitary adrenal hormones, growth hormone and thyroid stimulating hormone in the adult male rat**. Psychoneuroendocrinol.** 18: 67-77.

McCubbin, JW., Green, JH. and Page, IH. (1956). Baroceptor function in chronic renal hypertension. **Circulation Research.** 4(2): 205–210.

McGarry, JD. (2002). "Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes". **Diabetes.** 51(1): 7–18.

McPherson, RA. and Hardy, G. (2011). Clinical and nutritional benefits of cysteine-enriched protein supplements. **Current Opinion in Clinical Nutrition and Metabolic Care.** 14(6): 562–568.

Meaghan, AL., Michael, LP. and Jay S. (2008). The Impact of Maternal Obesity on Maternal and Fetal Health. **Reviews in Obstetrics and Gynecology.** 1(4): 170–178.

Merezak, S., Reusens, B., Renard, A., Goosse, K., Kalbe, L., Ahn, MT., Tamarit-Rodriguez, J. and Remacle, C. (2004). Effect of maternal low-protein diet and taurine on the vulnerability of adult Wistar rat islets to cytokines. **Diabetologia.** 47: 669–675.

Michael, W., Brands, Sharyn, M. and Fitzgerald. (2001). Arterial Pressure Control at the Onset of Type I Diabetes: The Role of Nitric Oxide and the Renin-Angiotensin System. **American Journal of Hematology.** 14: 126S–131S.

Militante, JD. and Lombardini, JB. (2002). Treatment of hypertension with oral taurine: experimental and clinical studies. **Amino Acids.** 23(4): 381–393.

Misra, CH. and Olney, JW. (1975). Cysteine oxidase in the brain. **Brain Research.** 97: 117–126.

Miyazaki, T., Matsuzaki, Y., Ikegami, T., Miyakawa, S., Doy, M., Tanaka, N. and Bouscarel, B. (2004). "Optimal and effective oral dose of taurine to prolong exercise performance in rat," **Amino Acids.** 27: 291–298.

Mordwinkin, NM., Ouzounian, JG., Yedigarova, L., Montoro, MN., Louie, SG. and Rodgers, KE. (2013). "Alteration of endothelial function markers in women with gestational diabetes and their fetuses," **Journal of Maternal-Fetal and Neonatal Medicine.**

Munch, PA., Andresen, MC. and Brown, AM. (1983). Rapid resetting of aortic baroreceptors in vitro. **American Journal of Physiology.** 244(5): H672–H680.

Nagaraja, HS. and Jeganathan, PS. (1999). Forced swimming stress induced changes in the physiological and biochemical parameters in albino rats. **Indian Journal of Physiology and Pharmacology.** 43: 5359.

Nakagawa, P., Fujita, K., Shoji, I., Miyazawa, N. and Lipids, T. (2011). Amadori-glycated phosphatidylethanolamine, a potential marker for hyperglycemia, in streptozotocin-induced diabetic rats. **Phumon Sookwong.** 46: 943–952.

Nakaya, Y., Minami, A., Harada, N., Sakamoto, S., Niwa, Y. and Ohnaka, M. (2000). Taurine improves insulin sensitivity in the Otsuka Long-Evans Tokushima Fatty rat, a model of spontaneous type 2 diabetes. **The American Journal of Clinical Nutrition.** 71: 54–58.

Nara, Y., Yamori, Y. and Lovenberg, W. (1978). Effect of dietary taurine on blood pressure in spontaneously hypertensive rats. **Biochemical Pharmacology.** 27(23): 2689–2692.

Nicholls, JSD., Ali, K. and Gray, IP. (1994). Increased maternal fasting proinsulin as a predictor of insulin requirement in women with gestational diabetes. **Diabetes medical.** 11: 57–61.

Nicholls, JSD., Chan, SP., Ali, KR., Beard, W. and Dornhorst, A. (1995). Insulin Secretion and Sensitivity in Women Fulfilling WHO Criteria for Gestational Diabetes**. Diabetes medicine.** 12: 56–60.

Norma, B., Ojeda, Daniela, G. and Barbara, TA. (2008). Intrauterine Growth Restriction: Fetal programming of hypertension and kidney disease. **Advances in Chronic Kidney Disease.** 15(2): 101–106.

Ogata, ES., James, W., Collins, Jr. and Sandra Finley. (1988). Insulin injection in the fetal rat: Accelerated intrauterine growth and altered fetal and neonatal glucose homeostasis. **Metabolism.** 37(7): 649–655.

Ohkuma, S. (1984). Characteristics of taurine transport in rat hepatocytes in primary culture. Cell Biochemistry and Function. 2(2): 71–77

Oja, SS. and Saransaari, P. (2007). Pharmacology of taurine. **Proc West Pharmacol Soc.** 50: 8–15.

Oja, SS. and Saransaari, P. (2007). Pharmacology of taurine. **Proceedings of the Western Pharmacology Society.** 50: 8–15.

Oliveira, AO., Fileto, C. and Melis, MS. (2004). Effect of strenuous maternal exercise before and during pregnancy on rat progeny renal function. **Brazilian Journal of Medical and Biological Research.** 37: 907–911.

Oliverio, MI., Delnomdedieu, M., Best, CF., Li, P., Morris, M. and Callahan, MF. (2005). Abnormal water metabolism in mice lacking the type 1A receptor for ANG II. **American Journal of Physiology.** 278: 75–82.

Olson, JE. and Goldfinger, MD. (1990). Amino acid content of rat cerebral astrocytes adapted to hyperosmotic conditions in vitro. **Journal of Neuroscience.** 27: 241–246.

Olubobokun, TH., Aluko, EO. and Iyare, EE. (2013). Anyaehie UB: *Dioscorea alata* L. reduces body weight by reducing food intake and fasting blood glucose level. **British Journal of Medicine and Medical Research.** 3: 1871–1880.

Onsri, J. and Srisawat, R. (2016). Effects of Taurine Supplement in Conjunction with Exercise on Body Weight, Organ Weights and Blood Chemistry Parameters in Aged Rats. **Int'l Journal of Advances in Chemical Engg & Biological Sciences (IJACEBS).** 3(1): 2349–1507.

Oprescu, AI., Bikopoulos, G., Naassan, A., Allister, EM., Tang, C., Park, E., Uchino, H., Lewis, GF., Fantus, IG. and Rozakis-Adcock, M. (2007). Free fatty acid-induced reduction in glucose-stimulated insulin secretion: evidence for a role of oxidative stress in vitro and in vivo. **Diabetes.** 56: 2927–2937.

Ornoy, A., Wolf, A., Ratzon, N., Greenbaum, C. and Dulitzky, M. (July 1999). "Neurodevelopmental outcome at early school age of children born to mothers with gestational diabetes". **Archives of Disease in Childhood: Fetal and Neonatal Edition.** 81(1): 10–14.

Osborn, JW. and England, SK. (1990). Normalization of arterial pressure after barodenervation: role of pressure natriuresis. **American Journal of Physiology.** 259(6): R1172–R1180.

Osmond, C., Barker, DJP., Winter, PD., Fall, CHD. and Simmonds, SJ. (1993). Early growth and death from cardiovascular disease in women. **British Medical Journal.** 307: 1519–1524.

Oyelola, OO. and Rufai, MA. (1993). Plasma lipid, lipoprotein and apolipoprotein profiles in Nigerian university athletes and nonathletes. **British Journal of Sports Medicine.** 27: 271–274.

Patel, A., MacMahon, S. and Chalmers, J. (2008). ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. **The New England Journal of Medicine.** 358: 2560–2572.

Paul, M., Poyan, Mehr, A. and Kreutz, R. (2006). Physiology of local renin-angiotensin systems. **Physiological Reviews.** 86(3): 747–803.

Pedersen, J. (1967). The pregnant diabetic and her newborn. **Problems and management.**

Perley, MJ. and Kipnis, DM. (1967). Plasma insulin response to oral and intravenous glucose studies in normal and diabetic studies. **The Journal of Clinical Investigation.** 46(12): 1954–1962.

Pettitt, DJ., Knowler, WC. and Bennett, PH. (1987). “Obesity in offspring of diabetic Pima Indian women despite normal birth weight,” **Diabetes Care.** 1: 76–80.

Plagemann, A., Harder, T., Kohlhoff, R., Rohde, W. and Dorner, G. (1997). “Glucose tolerance and insulin secretion in children ¨ of mothers with pregestational IDDM or gestational diabetes,” **Diabetologia.** 9: 1094–1100.

Ploug, T., Stallknecht, BM., Pedersen, O., Kahn, BB., Ohkuwa, T., Vinten, J. and Galbo H. (1990). Effect of endurance training on glucose transport capacity

and glucose transporter expression in rat skeletal muscle. **American Journal of Physiology.** 259: E778–E786.

Radaelli, A., Coats, AJ., Leuzzi, S., Piepoli, M., Meyer, TE. and Calciati A. (1996). Physical training enhances sympathetic and parasympathetic control of heart rate and peripheral vessels in chronic heart failure. **Clinical Science.** 91: S92–94.

Rahier, J., Guiot, Y., Goebbels, RM., Sempoux, C. and Henquin, JC. (2008). Pancreatic beta-cell mass in European subjects with type 2 diabetes. **Diabetes, Obesity and Metabolism.** 32–42.

Raimondi, GA., Puy, RJ. and Raimondi, AC. (1975). Effects of physical training on enzymatic activity of human skeletal muscle. **Biomedicine.** 22: 496–501.

Raju, J., Gupta, D., Rao, AR., Yadava, PK. and Baquer, NZ. (2001). Trigonella foenum graecum (fenugreek) seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reserving the altered glycolytic, gluconeogenic and lipogenic enzymes. **Molecular and Cellular Biochemistry.** 224: 45–51.

Raju, SM. and Raju, B. (2010). Illustrated medical biochemistry. 2nd Edition. **Jaypee Brothers Medical Publishers (P) Ltd.** 645.

Ramirez, AJ. Bertinieri, G. and Belli, L. (1985). Reflex control of blood pressure and heart rate by arterial baroreceptors and by cardiopulmonary receptors in the unanaesthetized cat. **Journal of Hypertension.** 3(4): 327–335.

Rasanen, J., and Kirkinen, P. (1987). “Growth and function of human fetal heart in normal, hypertensive and diabetic pregnancy,” **Acta Obstetricia et Gynecologica Scandinavica.** 4; 349–353.

Reece, EA., Leguizamon, G. and Wiznitzer, A. (2009). Gestational diabetes: The need for a common ground. **Lancet.** 373(9677): 1789–1797.

Regnault, TR., de Vrijer, B. and Battaglia, FC. (2002). Transport and metabolism of amino acids in placenta. **Endocrine.** 19: 23–41.

Regnault, TR., Friedman, JE., Wilkening, RB., Anthony, RV. and Hay, WW. Jr. (2005). Fetoplacental transport and utilization of amino acids in IUGR-a review. **Placenta.** 26 A: S52–S62.

Regnault, TR., Marconi, AM., Smith, CH., Glazier, JD., Novak, DA., Sibley, CP. and Jansson, T. (2005). Placental amino acid transport systems and fetal growth restriction--a workshop report. **Placenta.** 26 A: S76–S80.

Remy, A., Henry, S. and Tappaz, M. (1990). Specific antiserum and monoclonal antibodies against the taurine biosynthesis enzyme cysteine sulfinate decarboxylase: identity of brain and liver enzyme. **Journal of Neurochemistry.** 54: 870–879.

Riley, WJ., Pyke, FS. and Roberts, AD. (1975). The effects of long-dis- tance running on some biochemical variables. **Clinica Chimica Acta.** 65: 83–89.

Robert, S. and Lindsay. (2009). Many HAPO Returns Maternal Glycemia and Neonatal Adiposity: New Insights from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study. **Diabetes.** 58(2): 302–303.

Robert, S., Lindsay, FR., Scott, M., Nelson, MR., James, D., Walker, FR., Stephen, A., Greene, FR., Gillian Milne, BSC., Naveed S., and Donald, W. (2010). Programming of Adiposity in Offspring of Mothers with Type 1 Diabetes at Age 7 Years**. Diabetes Care.** 33(5): 1080–1085.

Rougier, G. and Babin, JP. (1975). A blood and urine study of heavy muscular work on ureic and uric metabolism in man. **The Journal of Sports Medicine and Physical Fitness.** 15: 212–222.

Roysommuti, S. and Wyss, JM. (2012). Perinatal taurine exposure affects adult arterial pressure control. **Amino Acids.**

Roysommuti, S. and Wyss, JM. (2012). Perinatal taurine exposure affects adult arterial pressure control. **Amino Acids.** 46(1): 57–72.

Rozance, PJ., Crispo, MM., Barry, JS., O'Meara, MC., Frost, MS., Hansen, KC., Hay WW. Jr. and Brown, LD. (2009). Prolonged maternal amino acid infusion in late-gestation pregnant sheep increases fetal amino acid oxidation. **American Journal of Physiology - Endocrinology and Metabolism.** 297: E638–E646.

Sachetelli, S., Liu, Q., Zhang, SL., Liu, F., Hsieh, TJ. and Brezniceanu, ML. (2006). RAS blockade decreases blood pressure and proteinuria in transgenic mice overexpressing rat angiotensinogen gene in the kidney. **Kidney International.** 69: 1016–1023.

Sadler, TW. (1986). Somatomedin inhibitors from diabetic rat serum after growth and development of mouse embtyos in culture. **Diabetes.** 35: 861.

Sadler, TW., Hunter, ES. and Wynn, RE. (1989). Evidence for multifactorial origin of diabetes-induced embryopathies. **Diabetes.** 38: 70.

Saito, K., Yaginuma, N. and Takahashi, T. (1979). Differential volumetry of A, B, and D cells in the pancreatic islets of diabetic and non-diabetic subjects. **The Tohoku Journal of Experimental Medicine.** 129: 273–283.

Saito, M., Terui, N. and Numao, Y. (1986). Absence of sustained hypertension in sinoaortic-denervated rabbits. **American Journal of Physiology.** 251: H742–H747.

Sakai, K. and Sigmund, CD. (2005). Molecular evidence of tissue renin-angiotensin systems: a focus on the brain. **Current Hypertension Reports.** 7(2): 135–140.

Samy, I., Mcfarlane, Maryann, B. and James, R. (2001). Insulin Resistance and Cardiovascular Disease. **The Journal of Clinical Endocrinology & Metabolism.** 86: 2–6

Sangeeta, D., Senta, G. and Anil, B. (2007). Formation and regeneration of the endocrine pancreas. **Current Opinion in Cell Biology.** 19(6): 634–645.

Santos, D., JW., Mello, D. and Mar. (2010). Endurance Swimming Periodized Training in Rats. **Official Research Journal of the American Society of Exercise Physiologists (ASEP).** 1097–9751.

Schaalan, M., El-Abhar, HS., Barakat, M. and El-Denshary, ES. (2009). Westernized-like-diet-fed rats: effect on glucose homeostasis, lipid profile, and adipocyte hormones and their modulation by rosiglitazone and glimepiride. **Journal of Diabetes Complications.** 23: 199–208.

Schaffer, SW., Azuma, J. and Mozaffari, M. (2009). Role of antioxidant activity of taurine in diabetes. **Canadian Journal of Physiology and Pharmacology.** 87: 91–99.

Schmieder, RE, Hilgers, KF., Schlaich, MP. and Schmidt, BM. (2007). Renin-angiotensin system and cardiovascular risk. **Lancet.** 369(9568): 1208–1219.

Schnermann, J. (1999). Micropuncture analysis of tubuloglomerular feedback regulation in transgenic mice. **Journal of the American Society of Nephrology.** 10: 2614–2619.

Schreihofer, AM. and Sved, AF. (1992). Nucleus tractus solitarius and control of blood pressure in chronic sinoaortic denervated rats. **American Journal of Physiology.** 263: R258–R266.

Schwartz, J. (1994) Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. **Environmental Research.** 65(1): 42–55.

Seagard, JL., Gallenberg, LA. and Hopp, FA. (1992). Acute resetting in two functionally different types of carotid baroreceptors. **Circulation Research.** 70(3): 559–565.

Semrád, B., Honzíková, N. and Fišer, B. (1994). Metody určení rizika náhlé srdeční smrti u nemocných po infarktu myokardu. **Cor Vasa.** 36: 295–298.

Sene-Fiorese, M., Duarte, FO., Scarmagnani, FR., Cheik, NC., Manzoni, MS. and Nonaka KO. (2008). Efficiency of intermittent exercise on adiposity and fatty liver in rats fed with high-fat diet. **Obesity.** 16(10): 2217–2222.

Shizuru, EM., Freud, BJ., Hashiru, GM. and Clay-Baugh, JR. (1991). Hormonal electrolyte and renal responses to exercise are intensity dependent. **Journal of Applied Physiology.** 70: 900–906.

Shoukry, A., El-Sherbieny, I. and Swelam, E. (2012). Association of insulin resistance, insulin and leptin levels with coronary in-stent restenosis. **The Egyptian Heart Journal.** 64: 35–42.

Silva, CA. and Lima, WC. (2000). Efeito Benéfico do Exercício Físico no Controle Metabólico do Diabetes Mellitus Tipo 2 à Curto Prazo. **Arq Bras Endocrinol Metab.** 46: 550–556.

Silva, LA., Silveira, PC., Ronsani, MM., Souza, PS., Scheffer, D., Vieira, LC., Benetti, M., De Souza, CT. and Pinho, RA. (2011). Taurine supplementation decreases oxidative stress in skeletal muscle after eccentric exercise. **Cell Biochemistry and Function.** 29(1):43–49.

Silverman, BL., Metzger, BE., Cho, NH. and Loeb, CA. (1995). "Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism," **Diabetes Care.** 5: 611–617.

Silverman, BL., Rizzo, T. and Green, OC. (1991). "Long-term prospective evaluation of offspring of diabetic mothers," **Diabetes.** 2: 121–125.

Simona F. (2013). Comment on: Straznicky et al. Neuroadrenergic Dysfunction Along the Diabetes Continuum: A Comparative Study in Obese Metabolic Syndrome Subjects. **Diabetes.** 62(1): e1.

Sleight, P., Robinson, JL. and Brooks, DE. (1977). Characteristics of single carotid sinus baroreceptor fibers and whole nerve activity in the normotensive and the renal hypertensive dog. **Circulation Research.** 41(6): 750–758.

Snoeck, A., Remacle, C., Reusens, B. and Hoet, JJ. (1990). Effect of a low protein diet during pregnancy on the fetal rat endocrine pancreas**. Biology of the Neonate.** 57: 107–118.

Snyder, SJ., Karzel, RP., Del Pizzo, W., Ferkel, RD. nad Friedman, MJ. (1990). SLAP lesions of the shoulder. Arthroscopy. 6(4): 274-279.

Sodoyez-Goffaux, F., Sodoyez, JC., Vos De, CJ. and Foa, PP. (1979). Insulin and glucagon secretion by islets isolated from fetal and neonatal rats. **Diabetologia.** 16: 121–123.

Soloman, JG. (1979)."Abnormal" laboratory results in runners. **The Latest Medical Research, Reviews, and Guidelines.** 241: 2262.

Soška, V. (2001) Poruchy metabolizmu lipidů. Diagnostika a léčba. **Grada Publishing.** 166s.

Sowers, JR. (1996). Effects of insulin and IGF-I on vascular smooth muscle glucose and cation metabolism. **Diabetes.** 45: 47–51.

Sowers, JR. (1997). Insulin and insulin-like growth factor in normal and pathological cardiovascular physiology. **Hypertension.** 29: 691–699.

Stevenson, JAF., Box, BM, Feleki, V. and Beaton, JR. (1966). Bouts of exercise and food intake in the rat. **Journal of Applied Physiology.** 2: 118–122.

Strange, K., Emma, F., Paredes, A. and Morrison, R. (1994). Osmoregulatory changes in myo-inositol content and Na^+/myo-inositol cotransport in rat cortical astrocytes. **Glia** 12: 35–43.

Stummer, W., Betz, AL., Shakui, P. and Keep, RF. (1995). Bloodbrain barrier taurine transport during osmotic stress and in focal cerebral ischemia. **Journal of Cerebral Blood Flow & Metabolism.** 15: 852–859.

Sturman, JA. (1993) Taurine in development. **Physiological Reviews.** 73: 119–147.

Suckale, J. and Solimena, M. (2008). Pancreas islets in metabolic signaling focus on the beta cell. Frontiers in Bioscience: **a journal and virtual library.** 1(13): 7156–7171.

Suckale, J. and Solimena, M. (2008). Pancreas islets in metabolic signaling – focus on the β-cell. **Molecular Cell Biology.** 13: 7156–7171.

Sullivan, TE. and Armstrong, RB. (1978). Rat locomotory muscle fiber activity during trotting and galloping. **Journal of Applied Physiology.** 44(3): 358–363.

Susa, JB., Neave, C., Sehgal, P., Singer, DB., Zeller, WP. and Schwartz, R. (1984). Chronic hyperinsulinemia in the fetal rhesus monkey: effects of physiological hyperinsulinemia on fetal growth and composition. **Diabetes.** 33: 656–660.

Svačinová, H., Siegelová, J. and Olšovský, J. (2001). Effect of exercise training on baroreflex sensitivity in patients with type 2 diabetes mellitus. **Journal of Hypertension.** 191: 14.

Swanston-Flatt, SK., Day, C., Flatt, PR., Gould, BJ. and Bailey, CJ. (1989). Glycemic effects of traditional European plant treatments for diabetes, Studies in normal and Streptozotocin diabetic mice**. Diabetes Review.** 10: 69–73.

Swenne, CA. (2013). Baroreflex sensitivity: mechanisms and measurement. **Netherlands Heart Journal.** 21(2): 58–60.

Szablewski, L. (2011). Glucose homeostasis and insulin resistance, **Bentham E-Books**, 978–1–60805–189–2.

Takahashi, N., Lopez, ML, Cowhig, JE., Jr., Taylor, MA., Hatada, T. and Riggs, E. (2005). Ren1c homozygous null mice are hypotensive and polyuric, but heterozygotes are indistinguishable from wild-type. **Journal of the American Society of Nephrology.** 16: 125–132.

Takizawa, M., Kaneko, T., Kohno, K., Fukada, Y. and Hoshi, K. (2003). The relationship between carbohydrate intake and glucose tolerance in pregnant women. **Acta Obstet Gynecol** Scand. 82(12): 1080–1085.

Tang, C., Han, P., Oprescu, AI., Lee, SC., Gyulkhandanyan, AV., Chan, GN., Wheeler, MB. and Giacca, A. (2007). Evidence for a role of superoxide generation in glucose-induced beta-cell dysfunction in vivo. **Diabetes.** 56: 2722–2731.

Tappaz, M., Almarghini, K., Legay, F. and Remy, A. (1992). Taurine biosynthesis enzyme cysteine sulfinate decarboxylase (CSD): the long and tricky trail to identification. **Neurochemical Research.** 17: 849–859.

Thatcher, S., Yiannikouris, F. and Gupte, M. and Cassis, L. (2009). The adipose renin-angiotensin system: role in cardiovascular disease. **Molecular and Cellular Endocrinology.** 302(2): 111–117.

The HAPO Study Cooperative Research Group. (2008).**The New England Journal of Medicine.** 358.

Thompson, PD., Crouse, SF., Goodpaster, B., Kelley, D., Moyna, N. and Pescatello, L. (2001) The acute versus chronic response to exercise. **Medicine and Science in Sports and Exercise.** 33: 438–445.

Thorpe, LE. Berger, D. Ellis, JA. Bettegowda, VR. Brown, G. and Matte, T. (2005) Trends and racial/ethnic disparities in gestational diabetes among pregnant women in New York City, 1990-2001. **American Journal of Public Health** 95: 1536–1539.

Tosh, DN., Fu, Q., Callaway, CW., McKnight, RA., McMillen, IC., Ross, MG., Lane, RH. and Desai, M. (2010). Epigenetics of programmed obesity: alteration in

IUGR rat hepatic IGF1 mRNA expression and histone structure in rapid vs. delayed postnatal catch-up growth. **American Journal Gastrointestinal and Liver of Physiology.** 299(5): 1023–1029.

Trachtman, H., Barbour, R., Sturman, JA. and Finberg, L. (1988). Taurine and osmoregulation: taurine is a cerebral osmoprotective molecule in chronic hypernatremic dehydration. **Pediatric Research.** 23: 35–39.

Tuli, JS., Smith, JA. and Morton, DB. (1995). Effects of acute and chronic restraint on the adrenal gland weight and serum corticosterone concentration of mice and their fecal output of oocyst after infection with eimueria apionodes. **Research in Veterinary Science.** 59: 82-86.

Tulin, OP., Vijay, E., William, AB., Nuran, E. and Gul, NS. (2012). Topiramate treatment protects blood-brain barrier pericytes from hyperglycemia-induced oxidative damage in diabetic mice. Banks, **Nuran Ercal,Gul N Shah Endocrinology.** 153.

Uusitalo, ALT., Laitinen, T., Väisänen, SB., Länsimies, E. and Rauramaa, R. (2002) Effects of endurance training on heart rate and blood pressure variability Clinical **Physiology and Functional Imaging**. 22: 173–179.

Valles, P., Wysocki, J. and Batlle, D. (2005). Angiotensin II and renal tubular ion transport. **ScientificWorldJournal** 5: 680–690.

Van den Akker, CH., Schierbeek, H., Dorst, KY., Schoonderwaldt, EM., Vermes, A., Duvekot, JJ., Steegers, EA. and van Goudoever JB. (2009). Human fetal amino acid metabolism at term gestation. **The American Journal of Clinical Nutrition.** 89: 153–160.

Vermes, E., Ducharme, A., Bourassa, M.G., Lessard, M., White, M. and Tardif, JC. (2003). Studies of Left Ventricular Dysfunction. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies of Left Ventricular Dysfunction (SOLVD**). Circulation.** 107(9): 1291–1296.

Vitoratos, N., Vrachnis, N., Valsamakis, G., Panoulis, K. and Creatsas, G. (2010). "Perinatal mortality in diabetic pregnancy," **Annals of the New York Academy of Sciences.** 1205: 94–98.

Vrachnis, N., Augoulea, A., Iliodromiti, Z., Lambrinoudaki, I., Sifakis, S. and Creatsas, G. (2012) "Previous gestational diabetes mellitus and markers of cardiovascular risk," **International Journal of Endocrinology**. 458610: 6.

Vrachnis, N., Belitsos, P. and Sifakis, S. (2012). "Role of adipokines and other inflammatory mediators in gestational diabetes mellitus and previous gestational diabetes mellitus," **International Journal of Endocrinology**. 549748: 12.

Wahren, J., Felig, P., Ahlborg, G. and Jorfeldt, L. (1971). Glucose metabolism during leg exercise in man. **The Journal of Clinical Investigation.** 50: 2715–2725.

Wang J. and Guanyu H. (2014). "Raison d'être of insulin resistance: the adjustable threshold hypothesis". **Journal of The Royal Society Interface.** 11(101): 20140892.

Wang, J., Stancakova, A. and Soininen, P. (2012). Lipoprotein subclass profiles in individuals with varying degrees of glucose tolerance: a population-based study of 9399 Finnish men. **Journal of Internal Medicine.** 272: 562–572.

Warskulat, U., Flögel, U., Jacoby, C., Hartwig, H.G., Thewissen, M., Merx, M.W., Molojavyi, A., Heller-Stilb, B., Schrader, J. and Häussinger, D. (2004). Taurine transporter knockout depletes muscle taurine levels and results in severe skeletal muscle impairment but leaves cardiac function uncompromised. **Federation of American Societies for Experimental Biology.** 18(3): 577–579.

Westerblad, H., Place, N. and Yamada, T. (2010). Mechanisms of skeletal muscle weakness. **Advances in Experimental Medicine and Biology.** 682: 279-296.

Weyer, C., Bogardus, C., Mott, DM. and Pratley, RE. (1999). The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. **The Journal of Clinical Investigation.** 104(6): 787–94.

Weyer, C., Hanson, RL., Tataranni, PA., Bogardus, C. and Pratley RE. (2000). A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance: evidence for a pathogenic role of relative hyperinsulinemia. **Diabetes.** 49(12): 2094-2101.

Weyer, C1., Hanson, RL., Tataranni, PA., Bogardus, C. and Pratley, RE. (2000). A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance: evidence for a pathogenic role of relative hyperinsulinemia. **Diabetes.** 49(12): 2094-2101.

Whaley-Connell, AT., Chowdhury, NA., Hayden, MR., Stump, CS., Habibi, J. and Wiedmeyer, CE. (2006). Oxidative stress and glomerular filtration barrier

injury: role of the renin angiotensin system in the Ren2 transgenic rat. **American Journal of Physiology.** 291: 1308–1314.

White, P. (1949). Pregnancy complicating diabetes. **American Journal of Medicine.** 7:609–616.

Wilmore, JH. and Costill, DL. (1994). Physiology of sport and exercise. Champaign, IL: **Human Kinetics.**

Wohaieb, SA. and Godin, DV. (1989). Alterations in free radical tissue defense mechanism in streptozotocin induced diabetes in rat. **Diabetes**. 36: 1014–1018.

Woods, LL., Ingelfinger, JR., Nyengaard, JR. and Rasch, R. (2001). Maternal protein restriction suppresses the newborn reninangiotensin system and programs adult hypertension in rats. **Pediatric Research.** 49: 460–467.

Wook, K. and Josephine, ME. (2008). The Role of Incretins in Glucose Homeostasis and Diabetes Treatment. **Pharmacological Reviews.** 60(4): 470–512.

Wu, G. (2009). Amino acids: metabolism, functions, and nutrition. **Amino Acids.** 37(1): 1–17.

Wyss, JM., Roysommuti, S., King, K., Kadisha, I., Regan, CP. and Berecek, KH. (1994). Salt-induced hypertension in normotensive spontaneously hypertensive rats. **Hypertension.** 23(6–1): 791–796.

Xin Zhao, David Ho, Shumin Gao, Chull Hong, Dorothy, EV., Stephen, F. and Vatner. (2011). Arterial Pressure Monitoring in Mice**. Current Protocols in Mouse Biology.** 1: 105–122.

Yamori, Y., Taguchi, T., Hamada, A., Kunimasa, K., Mori, H. and Mori, M. (2010). Taurine in health and diseases: consistent evidence from experimental and epidemiological studies. **Journal Biomed Science.** 17(1): 6.

Yanagita, M., Kojima, Y., Kubota, M., Mori, M., Yamashita, M., Yamada, S., Kitamura, M. and Murakami, S. (2014). Cooperative Effects of FGF-2 and VEGF-A in Periodontal Ligament Cells. **Journal of Dental Research.** 93(1): 89–95.

Zargar, AH., Sheikh, MI. and Bashir, M. (2004). Prevalence of GDM in Kashmiri women in Indian subcontinent. **Diabetes Research and Clinical Practice.** 66(2): 139–145.

Zeng, G. and Quon, MJ. (1996). Insulin-stimulated production of nitric oxide is inhibited by wortmannin. Direct measurement in vascular endothelial cells. **Journal of Clinical Investigation.** 98: 894–898.

Zhang, C., Hein, TW., Wang, W. and Kuo, L. (2003). Divergent roles of angiotensin II AT1 and AT2 receptors in modulating coronary microvascular function. **Circulation Research.** 92(3): b322-329.

Zhen, Y., Fu, W., Jiang, Z., Liu, J., Belardinelli, D. and Dhalla AK, L. (2011). Ranolazine increases β-cell survival and improves glucose homeostasis in low-dose streptozotocin-induced diabetes in mice. **Ning The Journal of pharmacology and experimental therapeutics.** 337: 50–58.

Zorzano, A. and Claret M. (2015). Implications of mitochondrial dynamics on neurodegeneration and on hypothalamic dysfunction. **Frontiers in Aging Neuroscience.** 7: 101.

Zouhal. H., Jabbour, G., Jacob, C., Duvigneau, D., Botcazou, M., Ben, Abderrahaman. A., Prioux, J. and Moussa, E. (2010). Anaerobic and aerobic energy system contribution to 400-m flat and 400-m hurdles track running. **The Journal of Strength and Conditioning Research.** 24(9): 2309–2315.

Zoungas, S., Patel, A. and Chalmers, J. (2010). Severe hypoglycemia and risks of vascular events and death. **The New England Journal of Medicine.** 363: 1410–1418.

APPENDIX

APPENDIX

THE PREPARATIONS OF REAGENTS

Phosphate buffer saline pH 7.4

Chemicals

Sodium chloride (NaCl)	8 g
Potassium chloride (KCl)	0.2 g
Disodium hydrogen phosphate (Na_2HPO_4)	1.44 g
Potassium dihydrogen Phosphate (KH_2PO_4)	0.24 g
Distilled water	1 L

Preparation

Add chemical compounds one by one into 800 ml of distilled water. Adjust the pH to 7.4 with HCl. Add distilled water to a total volume of 1 liter. Sterilization by autoclaving (20 min, 121-degree Celsius, liquid cycle). Store at room temperature.

Lysis Buffer

Chemicals

10 mM TRIS hydrochloride (Tris-HCl) pH 7.2	0.16 g
150 mM Sodium chloride (NaCl)	0.87 g
1 mM Ethylenediaminetetraacetic acid (EDTA)	0.04 g

0.5% Triton X-100	25 µl
1mM Phenylmethylsulfonyl fluoride (PMSF)	50 µl
Distilled water	100 ml

Preparation

Prepare stock solution by adding Tris-HCl, NaCl, and EDTA into 80 ml distilled water. Adjust pH to 7.2 and then add distilled water to a total volume of 100 ml. Sterilization by autoclaving (20 min, 121°C, liquid cycle program). Prepare working solution by adding PMSF and Triton X-100 into 4.945 ml stock solution.

Electrophoresis Buffer pH 8.3

Chemicals

Tris (hydroxymethyl) aminomethane (Tris base)	3.02 g
Glycine	14.4 g
Sodium dodecyl sulfate (SDS)	1 g
Distilled water	1 L

Preparation

The total chemical compounds were mixed in 1000 mL distilled water.

Transfer Buffer

Chemicals

Tris (hydroxymethyl) aminomethane (Tris base)	2.93 g
Glycine	5.81 g
Sodium dodecyl sulfate (SDS)	0.375 g
Methanol	200 ml

Distilled water	1 L

Preparation

The total chemical compound was mixed in distilled water. Ready for use.

Separating gel

Chemicals

Autoclaved H_2O	5.68 ml
30% acrylamide	12 ml
Separating gel buffer	6 ml
10% Sodium dodecyl sulfate (SDS)	240 µl
10% Ammonium persulfate (APS)	120 µl
(N, N, N, N, -tetramethyl ethylenediamine) TEMED	8 µl

Preparation

Mix all chemical compounds together, except TEMED which was added at the final process.

Stacking gel

Chemicals

Autoclaved H_2O	6 ml.
30% acrylamide	1.34 ml.
Stacking gel buffer	2.5 ml.
10% Sodium dodecyl sulfate (SDS)	100 µl.
10% Ammonium persulfate (APS)	50 µl.
(N, N, N, N, -tetramethyl ethylenediamine) TEMED	5 µl.

Preparation

Mix all chemical compounds together, except TEMED which was added at the final process.

Gel Setting

Reagents	12.5% separating gel		15% separating gel		4% stacking gel	
	2 sides	4 sides	2 sides	4 sides	2 sides	4 sides
1. 30% acrylamide	5 ml.	10 ml.	6 ml.	12 ml.	0.67 ml.	1.34 ml.
2. Separating gel buffer	3 ml.	6 ml.	3 ml.	6 ml.	-	-
3. Stacking gel buffer	-	-	-	-	1.25 ml.	2.5 ml.
4. 10% SDS	120 µl.	240 µl.	120 µl.	240 µl.	50 µl.	100 µl.
5.Autoclaved H_2O	3.84 ml.	7.68 ml.	2.84 ml.	5.68 ml.	3 ml.	6 ml.
6. 10% APS	60 µl.	120 µl.	60 µl.	120 µl.	25 µl.	50 µl.
7. TEMED	4 µl.	8 µl.	4 µl.	8 µl.	2.5 µl.	5 µl.

CURRICULUM VITAE

Name	Punyaphat Teangphuck
Date of birth	Sep 22, 1989
Place of Birth	Uthai Thani, Thailand
Education	Suranaree University of Technology, 2005-2011 Bachelor of Science (Sports Sciences)
Home Address	105/393 Sura Sawat Land village, Suranaree, Muang Nakhon Ratchasima, Nakhon Ratchasima, 30000
Publication	Teangphuck, P., Srisawat, R., Roysommuti, S. and Thaeomor, A. (2016). Taurine supplementation in perinatal period on maternal Diabetes mellitus prevents development of diabetes mellitus (DM) And hypertension in the offspring during adulthood. (Poster) **Proceeding of the 20th International Taurine Meeting Conference.** May, 23-27, 2016, Seoul, Korea.