β_2 ADRENERGIC RECEPTOR GENE POLYMORPHISMS IN HYPERTENSIVE PATIENTS

BY

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A dissertation submitted in partial fulfilment of the requirements for the degree of Master of Medical Sciences

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ABSTRACT

Background: Polymorphisms within Beta$_2$-adrenergic receptor (β_2AR) gene have been repeatedly linked to hypertension. Among the β_2AR polymorphisms detected, Arg16Gly and Gln27Glu codons were considered the two most important variations. Arg16Gly especially, has been found to be significantly associated with hypertension in Caucasian and Black subjects. The amino acid substitution at this codon may lead to abnormal regulation of β_2AR activity. The aim of the present study was to assess the association between β_2AR polymorphisms and hypertension. Methods: This case-control study consisted of 100 unrelated subjects (50 hypertensive and 50 matched normal controls). Arg16Gly and the Gln27Glu polymorphisms were analyzed by polymerase chain reaction-restriction fragment length polymorphism assay. Results: There were no significant evidence of association in allelic and genotypes distribution of Arg16Gly and Glu27Gln with hypertension. Conclusion: These findings suggest that the variation within codon 16 and 27 of β_2AR gene were unlikely to confer genetic susceptibility for hypertension in our population samples.

Key words:

β_2-adrenergic receptor, single nucleated polymorphism, hypertension.

ملخص البحث

المقدمة: الاشكال المتعددة داخل جين مستقبلات بيتا $_2$ الادرينالية ارتبط وبشكل متعدد بضغط الدم, ومن بين الاشكال المتعددة المكتشفة, ارجنين16 جلايسين و جلوتامين 27 حمض الجلوتاميك اعتبرو اكتر المتغيرات اهمية. ارجنين16 جلايسين بالاخصية وجد له ارتباطية مؤترة بضغط الدم في الافراد القوقازيين والسود. تغير حمض اميني عند هذا الموقع قد يؤدي الي تنظيم غير طبيعي لنشاطات مستقبل بيتا $_2$, الهدف من هده الدراسة كان لتقييم العلاقة بين الاشكال المتعددة لمستقبلات بيتا $_2$ وضغط الدم. الطريقة: هده دراسة 100 مرضي واناس طبيعيين (50 مرضي و50 اناس طبيعيين). الاشكال المتعددة لي ارجنين16 جلايسين و جلوتامين 27 حمض الجلوتاميك تم تحليلهم بواسطة فحص تفاعل التسلسل البوليميريزي_الاشكال المتعددة المتقطعة الجزئية. النتيجة: لم نجد دليل مؤتر علي وجود علاقة بين توزيع الاليل و الانماط الجينية لي ارجنين16 جلايسين و جلوتامين 27 حمض الجلوتاميك مع ارتفاع ضغط الدم و حالة ضغط الدم. الخلاصة: هده النتائج تقترح ان التغييرات في كودون 16 و 27 لي جين بيتا$_2$ ليست لها علاقة بحدوث ضغط الدم في عينات سكاننا.

مفتاح الكلمات: الاشكال المتعددة لمستقبلات بيتا$_2$_أرتفاع ضغط الدم.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of Medical Sciences.

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DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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β2 ADRENERGIC RECEPTOR GENE POLYMORPHISM IN

HYPERTENSIVE PATIENTS

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LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring.
AHA	American Heart Association.
ASO	Allele-specific oligonucleotide.
ASPE	Allele-specific primer extension.
BMI	Body mass index.
BP	Blood pressure.
BSA	Bovine serum albumin.
cAMP	Adenosine 3' – 5' cyclic monophosphate.
CDC	Centers for Disease Control and Prevention.
CHD	Chronic heart disease.
DAG	Diacylglycerol.
dATP	Deoxyadenosin triphosphates.
DBP	Diastolic blood pressure.
dCTP	Deoxycytocine triphosphate.
ddNTPs	Dideoxynucleoside triphosphates.
dGTP	Deoxyguanosine triphosphate.
DMSO	Dimethyl sulfoxide.
DNA	Deoxyribo Nucleic Acid.
dNTPs	Deoxynucleoside triphosphates.
dTTP	Deoxythyamine triphosphate.
EDTA	Ethylenediaminetetraacetic acid.
ELISA	Enzyme-linked immune absorbent assay.
Gln27Glu	Glutamine27Glutamic acid.
Gly16Arg	Glycine16Arginine.
HWE	Hardy–Weinberg equilibrium.
IEDD	Impaired endothelium-dependent dilatation.
IL-6	Interleukin-6.
IP3	Inositol trisphosphate.
KPB	Kilo base pairs.
LDL-C	Low density lipoprotein.
MALDI-TOF	Matrix-assisted laser desorption/ionization–Time-off light.
mM	Milimolar.
OBP	Office blood pressure.
PCR	Polymerase chain reaction.
PKA	Protein kinase.
RAS	Rennin angiotensin system.
RE	Restriction endnuclease.
RFLP	Restriction fragment length polymorphism.
RNA	Ribo Nucleic Acid.
SBE	Single base extension.
SBP	Systolic blood pressure.
SNPs	Single nucleotide polymorphisms.
SPSS	Statistical Product and Service Solutions.

TBE	Tris-borate-EDTA.
Thr164Ile	Threonine164Isoleucine.
TM	Melting temperature.
TNF-α	Tumor necrosis factor-α.
U	Unit.
URL	Upper reference limit.
UV	Ultraviolet.
Val34Met	Valine34Methionine.
β_2AR	Beta-$_2$-adrenergic receptors.

CHAPTER ONE

INTRODUCTION

Hypertension, which affects 4.8 million of Malaysian individuals (Ministry of Health Malaysia, 2008), is associated with significant comorbidities, such as stroke, cardiac dysfunction, infarction, heart failure and renal failure (Mosterd et al., 1999). It is a complex trait, influenced by multiple environmental and genetic factors with estimated 30% heritability (Ward et al., 1990). Though it is known that environmental factors, such as exercise and salt intake affect blood pressure, not much data is known about genetic factors that predispose individuals to hypertension.

Genetic linkage and gene association studies have implicated several loci and genes in the predisposition to hypertension (Krushkal et al., 1998). Defective β_2-adrenergic receptor (β_2AR) mediated vasodilatation has been implicated in the pathogenesis of salt-sensitive hypertension (Skrabal et al., 1989). Studies concerning β_2AR locus relation to hypertension are not consistent. The locus has been linked to essential hypertension in white Americans, African Americans, African Caribbeans and Northern Europeans (Bray et al., 2000).

The human β_2-adrenergic receptor is a G-protein-coupled receptor found in a wide variety of tissue types and is a target for many β_2-adrenoreceptor agonists and antagonists currently used in the treatment of many disorders. Individual variations in physiological responses, expression and function of the receptor, as well as individual differences in response to drugs that act on these receptors may relate to polymorphic variants of the receptor (Brodde et al., 1999).

The β_2-adrenergic receptor is encoded by an intronless gene (β_2AR) located on chromosome 5 (5q31-q32). At least nine different allelic variants have been identified, three are more frequent resulting in the substitution of Glycine for Arginine at codon 16 (Arg16Gly), the substitution of Glutamic acid for Glutamine at codon 27 (Gln27Glu), and substation of isoleucine for threonine at codon 164 (Thr164Ile). Numerous studies have associated these polymorphisms with differences in the prevalence, severity and response to drugs used in disorders like arterial hypertension, heart failure, coronary disease and sudden cardiac death (Barbato et al., 2007). They have been shown to alter the receptor function in the cardiovascular and respiratory systems. Arg16Gly substitution exaggerates agonist-mediated receptor down-regulation, whereas Gln27Glu reduces it (Liggett S.B., 1997). The Thr164Ile causes decreased affinity for β_2AR agonists (Brodde et al., 2001). Both SNPs of β_2AR have been associated with the prevalence of hypertension and systolic BP (Ranade et al., 2001; Ge D, 2005, Kazuko Masuo et al., 2005). However, some studies have found no association (Jia et al., 2000; Herrmann et al., 2000; Xie H.G, 2000, Candy et al., 2000; Norihiro et al., 2001).

The distribution of β_2AR mutations were mostly investigated in patients suffering from hypertension and compared with healthy reference subjects (Bray et al., 2000). Taking into account that β_2AR is an important target of many drugs and endogenous substances, inter-ethnic differences in this receptor may explain differences in drug response and disease susceptibility (Evans et al., 2001).

Therefore, we undertook an association study in our population by using 3 β_2AR polymorphisms (Arg16Gly, Gln27Glu, and Thr164Ile). The relevance of β_2AR polymorphisms to hypertension was tested in a case-control study conducted on 50

hypertensive and 50 normotensive subjects by using PCR-RFLP assay. The significance of an association between the SNPs was tested by χ^2 test.

This study was approved by the ethics committee of our faculty, and written informed consent was obtained from all patients before inclusion.

CHAPTER TWO

LITERATURE REVIEW

2.1 HYPERTENSION

Essential hypertension has a multifactorial etiology that includes interaction of many genetic and environmental factors acting through the intermediate systems regulating blood pressure (BP) control (Lifton et al., 1993). A complex and diverse array of metabolic and physiologic processes can cause hypertension, which interact with the environmental factors to ultimately determine blood pressure levels and diseases. However, the identification of genes related to hypertension is complicated by the heterogeneity of its etiology and the likelihood that several genes acting in a context dependent manner, influence blood pressure and the occurrence of hypertension (Molly et al., 2002).

2.1.1 Definition of Blood Pressure and High Blood Pressure

Blood pressure is the pressure exerted by the blood against the walls of the blood vessels, especially the arteries. Arterial BP is the pressure inside large arterial vessels. It is controlled by cardiac output and peripheral resistance. When the left ventricle of the heart contracts to eject blood to large arteries, the highest pressure inside the vessels is systolic, and the lowest pressure just before systole is called diastolic BP (Guyton et al., 1991).

Hypertension is a state of chronically elevated BP. Based on epidemiological studies, high BP can be defined as a repeatedly elevated blood pressure exceeding 140 over 90 mmHg, a systolic pressure above 140 with a diastolic pressure above 90

(Lifton et al., 2001). According to the 2007 report of the Malaysian society of hypertension, BP can be classified into optimal, normal, and high normal, while hypertension is divided into; hypertension grade I, grade II, and grade III (Table 2.1).

Table 2.1
Categories of hypertension

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal	<120	and	<80
Normal	<120-129	and	<80-84
High normal	130-139	or	85-89
Hypertension			
Stage 1	140-159	or	90-99
Stage 2	160-179	or	100-109
Stage 3	> or =180	or	> or =110

2.1.2 Prevalence of Hypertension

Hypertension affects about 25% of adult population in western countries (Lifton et al., 1993). It has been estimated that almost one billion individuals worldwide (Hajjar et al., 2003), and 4.8 million in Malaysia (Ministry of Health, Malaysia, 2008) are affected. It contributes to more than one-third of premature mortality due to chronic heart disease (CHD) and a greater proportion due to stroke (NHMS2 Conference, 1997). It is also an important risk factor for premature mortality in heart and kidney failures (Ministry of Health, Malaysia, 2008).

2.1.3 Causes of Hypertension

There is no single specific cause of primary hypertension. Multiple pathophysiological mechanisms are probably involved, including gene-gene and gene-environment interaction. Between 30-60% of blood pressure variation is determined by genetic factors (Lifton et al., 1993). It has been assumed that common genetic variants (polymorphisms) in that system are involved in the regulation of blood pressure, thus the response to specific antihypertensive therapy (Lifton et al., 1993).

2.1.4 Pathophysiology of Hypertension

Substantial effort has been devoted to define the role of various factors in the pathogenesis of blood pressure variation. Epidemiologic studies have documented the impact of many factors, including age, gender, and body mass index (Stanton et al., 1982). Diet, salt, potassium, and calcium have also been implicated and suggested as important factors (Appel et al., 1997).

A variety of physiological systems have been found to affect blood pressure. These included baroreceptors that sense acute changes in pressure in vessels; natriuretic peptides produced by the brain and heart in response to increased pressure in these organs; the kinin-kallikrein system, which affects vascular tone and renal salt handling; the renin-angiotensin-aldosterone system, which influences vascular volume homeostasis and vascular tone; the adrenergic receptor system, which influences heart rate, vascular tone, and cardiac contraction, and factors produced by blood vessels that cause vasodilatation, such as nitric oxide, or contraction, such as endothelia. These systems act in complete manner to ensure adequate perfusion of all tissues (Richard et al., 2001).

2.1.5 Blood Pressure Regulation

Optimal BP maintains tissue perfusion with oxygen and nutrients. Under normal circumstances, arterial BP deviates 10 to 15% from its usual level (Guyton et al., 1991). The body has several mechanisms to maintain BP within optimal level. The most important two systems are the central nervous system, by adjusting the diameter of blood vessels and the heart rate, and the kidneys, by regulating water and electrolyte homeostasis. The central nervous system controls circulatory system mainly by autonomous nervous system, the affect of which are mediated by adrenaline and noradrenaline, renin-angiotensin system (RAS), and water electrolyte balance (Guyton et al., 1991). Electrolyte homeostasis is regulated by the sodium transporters along the nephrons which include Na+/H+ exchangers in the proximal tubule, Na+/K+/Cl2 co-transporters in the thick ascending limb of Henle, Na+/Cl co-transporters in distal convoluted tubule, and epithelial sodium channel (ENaC) in the distal tubule and collecting duct (Su YR et al., 2001).

2.1.6 Blood Pressure Measurement

Office blood pressure (OBP) measurement is routinely used in evaluating BP level. It is measured by a doctor or a nurse mainly by using a device called sphygmomanometer. At least two measurements spaced by 1 to 2 minutes per visit are recommended (Mancia et al., 2007). Self measurement of BP at home is an alternative for OBP measurement. It has the advantages of being practical, enable recordings of BP on different days and allow for a longer follow up period. In addition to reducing the white coat effect (WCE), home BP measurements may predict cardiovascular events more accurately than OBP measurements (Mancia et al., 2007). Furthermore, OBP measurements may overestimate BP levels, compared with

self made measurements at home, and underestimate the control achieved with antihypertensive medication. Therefore, some experts recommended the use of home measurements as an important aid in clinical practice a part from the OBP (Niiranen et al., 2006).

24-hour ambulatory blood pressure measurements (ABPM) provide additional information of daytime and night time average BP levels. ABPM is usually lower than OBP. ABPM is recommended in cases when there is an inconsistency between OBP and home measurements, when there is a large variability in OBP measurements during the same or different visits, or when there is a suspicion of resistance to drug treatment or occurrence of hypotensive episodes (Mancia et al., 2007). BP values at night time have an important prognostic value. ABPM also predicts better organ damages than OBP. In adjustment of antihypertensive drug treatment, ABPM and home measurements were comparable, when using the same BP target (Niiranen et al., 2006).

2.1.7 Hypertension as a Risk Factor

Hypertension has been shown to shorten life-expectancy (Tsevat et al., 1991). Mortality rates are constantly higher with increased pulse pressure across all levels of mean blood pressure and all age groups. This is especially true for CHD but not stroke (Benetos et al., 1997). Of all atherosclerotic cardiovascular events, 35% may be attributable to hypertension (Kannel et al., 1996). Recently, it appears that systolic blood pressure is more important as a predictor of risk for cardiovascular events than is diastolic pressure (Kannel et al., 2000). Hypertension is the most important risk factor for stroke (Collins et al., 1990). A difference of 6 mmHg in diastolic blood pressure is associated with a 36% difference in the risk for stroke (Macmahon et al.,

1989). When the severity of hypertension increases, the proportion of strokes due to atherosclerotic brain infarction increases along with a decrease in the proportion due to subarachnoid haemorrhage and cerebral emboli, but the proportion due to intracerebral haemorrhage is unchanged (Kannel et al., 1996).

It has been analyzed that systolic blood pressure and pulse pressure are positively associated with coronary heart disease risk, whereas diastolic pressure is negatively associated with risk at any level of systolic pressure above 120 mmHg (Kannel et al., 1996). Moreover, hypertensive men have a 2-fold and women a 3-fold risk for developing congestive heart failure in 14 years compared with risks in normotensives (Levy et al., 1996). An increase of 20 mmHg in blood pressure elevates risk for left ventricular hypertrophy by 43% in men and 25% in women (Levy et al., 1996). Left ventricular hypertrophy occurs in 23 to 56% of hypertensives, whereas the occurrence among normotensives is less than 10% (Devereux et al., 1987). Increases in pulse pressure have been associated with an elevated C reactive protein level (Abramson et al., 2002), known to be a marker of future risk for coronary heart disease and myocardial infarction (Ridker et al., 2000).

2.1.8 Genetic Predisposition to Hypertension

Hypertension and cardiovascular disease are known to run in families. Several reports support the inherited nature of hypertension, showing that blood pressure is more similar between related individuals than between unrelated (Hamilton et al., 1954). The similarities in blood pressure within families are not restricted to hypertensives, but to all levels of blood pressure (Miall et al., 1963).

Researchers in USA show that as much as 40 – 70 % of blood pressure variance can be explained by genetic factors (Ditto et al., 1993). Study of

monozygotic twins brought up in separate environments shows that 34 - 44% of the variance in blood pressure is explained by genetic factors (Hong et al., 1994). Based on the blood pressure distribution of hypertensive patients and their siblings, Platt launched the "single gene theory" (Platt et al., 1947). He postulated that the presence of an important gene like angiotensinogen in homozygous form would cause severe hypertension, while in heterozygous form, moderate hypertension (Platt et al., 1947). This theory was opposed by Pickering who believes in polygenetic inheritance, which is also reflected in current consensus (Pickering et al., 1959). However, there are many factors that complicate the attribution of blood pressure as a genetic trait. The individual genetic contributions are most likely not independent, due to gene-gene and gene-environment interaction (Kannel et al., 1996). In summary, primary hypertension is most likely not a singular disease but a clinical syndrome attributable to a variety of underlying pathophysiological mechanisms, genes and genetic variants interacting with environmental factors.

2.2 β_2 ADRENERGIC RECEPTOR AND ITS POLYMORPHISMS

2.2.1 Adrenergic Receptor

Adrenoceptor is a term widely used to describe receptors that respond to catecholamines such as epinephrine and norepinephrine. Two main groups of adrenergic receptors have been discovered (Table 2.2), α and β, with several subtypes; α receptors have the subtypes α_1 (a G_q coupled receptor) and α_2 (a G_i coupled receptor). Whereas, β receptors have the subtypes β_1, β_2 and β_3 (G_s coupled proteins which are linked to adenylate cyclase) (Joel et al., 2001).

Table 2.2
Adrenergic receptor types and their locations

Receptor Name	Typical Locations	Result of Ligand Binding
α_1	Postsynaptic effector cells, especially smooth muscle	Formation of Inositol trisphosphate (IP3) and diacylglycerol (DAG), Increased intracellular calcium
α_2	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cyclic adenine mono-phosphate (cAMP)
β_1	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals	Stimulation of adenylyl cyclase, increased cAMP
β_2	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP.
β_3	Postsynaptic effector cells, especially lipocytes	Stimulation of adenylyl cyclase and increased cAMP

(Goodman & Gilman's the Pharmacological Basis of Therapeutics, 9th Edition, 2001)