



THE ROLE OF CATECHOLAMINES IN THE
PATHOGENESIS OF ESSENTIAL HYPERTENSION

BY

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ABSTRACT

BACKGROUND: Even though essential hypertension has been known for over a century, its pathophysiology and management remains a problem. It has been suggested that adrenaline plays a role in the pathogenesis of essential hypertension. According to the adrenaline hypothesis, excessive stimulation of the adrenomedullary hormonal system can contribute to the development of essential hypertension by augmenting sympatho-neuronal noradrenaline release. However, current literature on the admissability of the adrenaline hypothesis as a cause for hypertension is mixed and at times conflicting. **OBJECTIVES:** The aim of this study is to demonstrate that the adrenaline hypothesis is a workable theory that underpins hypertension. It comprises of three substudies, the first study involves humans as a model, while the second and the third studies involve spontaneously hypertensive rats (SHR) as models for experimentation. It aims to prove the presence of sympathetic over-activity in young, pre-hypertensive and young, mildly hypertensive Malaysians. It also intends to prove that removal of circulating adrenaline via adrenal demedullation or the administration of an adrenaline synthesis enzyme-inhibitor, Phenylethanolamine-N-methyltransferase (PNMTI) will result in reduced blood pressure in SHRs. **METHODS:** The study comprises of three arms, one human and two animal studies. 484 subjects were screened from a primary outpatient medical facility, 97 subjects and age-matched controls were recruited into our human study. Simple demographic data were recorded, blood samples taken for plasma catecholamine and other cardiovascular risk factor variables and blood pressure recordings were observed. 2 groups of spontaneously hypertensive rats were then put through either adrenal demedullation or PNMTI administration along with age- and weight-matched controls. **RESULTS:** Our study has shown that there is increased plasma adrenaline in young, pre- and mildly hypertensive subjects. Our study have also shown that adrenal demedullation and administration of PNMTI will consistently result in sustained blood pressure reduction as proposed by our hypotheses. We have also shown that the cardiovascular risk factor variables associated with hypertension were significantly increased in our pre- and mildly hypertensive subjects compared to our age- and BP-matched controls. **IMPORTANCE:** This study shows that adrenaline over-activity is associated with mild hypertension in the young and that removal of the adrenaline drive will result in sustained blood pressure reduction. It has wide-ranging implications especially towards the clinical application of measures to reduce circulating adrenaline levels in order to treat hypertension.

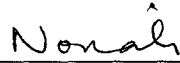
خلاصة البحث

خلفية البحث: بالرغم من أن فرط ضغط الدم الأساسي قد عُرف منذ أكثر من قرن مضى، فإن خطوات علاجه مازالتتشكل مشكلة ما. إنه لمن المعروف أن مادة الأدرينالين تلعب دوراً هاماً في حدوث هذا المرض؛ وحسب نظرية الأدرينالين "كسبب رئيسي لفرط ضغط الدم" فإنالتحفيز الزائدللجهاز الهرموني لُب الكظر يساهم في ازدياد الإفراز الودي-العصبي لمادة النورأدرينالين؛ بيد أنه لمن المقبول في الأدبيات المعاصرة للبحث العلمي أن هنالك تضارب في افتراض الأدرينالين كمسبب لفرط ضغط الدم.

أهداف البحث: إن الهدف الرئيسي لهذه الدراسة هو الإثبات بالدليل العملي القاطع صحة افتراضية الأدرينالين. وتشمل هذه الافتراضية ثلاثة محاور حيث يشمل المحور الأول المرضى كنموذج؛ بينما يشمل المحور الثاني والثالث دراسة تجريبية على الفئران المصابة بالفرط التلقائي لضغط الدم. وتهدف كذلك هذه الدراسة إلى اثبات النشاط الودي الزائد في الشباب المالميزي ألمصاب بجدية فرط ضغط الدم وكذلك المصابون بفرط ضغط الدم البسيط. ويهدف هذا البحث أيضاً إلى أن نزع الأدرينالين المتواجد في الدم إما بإستئصال جزء من لُب الغدة الكظرية، أو تعاطي العقاقير المثبطة لهرمون الأدرينالين مثل فينايل إيثانولامين-ن-ميثيل ترانسفيريز والمؤدي إلى انخفاض فرط ضغط الدم في الفئران المصابة بالفرط التلقائي لضغط الدم. **الطرق المستعملة في البحث:** لقد تم تقصي 494 حالة من العيادة الخارجية و 97 حالة طبيعية (لاتعاني من فرط ضغط الدم) من نفس الفئة العمرية للمناظرة. أما بالنسبة للدراسة التجريبية على الفئران فقد تم تعريف مجموعتين من الفئران المصابة بالفرط التلقائي لضغط الدم إما بإستئصال جزء من لُب الغدة الكظرية، أو تعاطي العقاقير المثبطة لهرمون الأدرينالين؛ هذا بالإضافة إلى المجموعة المناظرة من نفس الفئة العمرية. وقد دُونت البيانات الإحصائية البسيطة؛ فدُون ضغط الدم وأُخذت عينات من كاتيكولامين البلازما والمواد الأخرى الخطره على الجهاز القلبي الوعائي. **نتائج البحث:** لقد توصلنا في هذا البحث إلى الوجود الزائد لمادة الإدرينالين في الشباب المعرض للإصابة بفرط ضغط الدم المرتفع، وكذلك المصابين بفرط ضغط الدم البسيط. ولقد أكدنا في نتائج هذه الدراسة أن استئصال أجزاء من لُب الغدة الكظرية، أو تعاطي العقاقير المثبطة لهرمون الأدرينالين يؤدي إلى انخفاض فرط ضغط الدم كما توقعنا في فرضية البحث. وقد أظهرت النتائج أن العواملالمتغيرة ذات الخطورة للجهاز القلبي الوعائي المتعلقة بفرط ضغط الدم كانت ذات قيمة إحصائية عالية. **أهمية البحث:** لقد أبرزت نتائج البحث في المرضى المعرضين لفرط ضغط الدم وكذلك المصابين بفرط ضغط الدم البسيط أهمية العوامل الخطرة المتغيرة في الجهاز القلبي الوعائي والملازمة لفرط ضغط الدم وذلك عند مقارنتهم بحالات المستخدمة للمناظرة.

APPROVAL PAGE

The thesis of Aszrin Bt. Abdullah has been approved by the following:



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DECLARATION

I hereby declare that this thesis 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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Signature

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I dedicate this thesis to my parents,

Banon Rajab and Abdullah Omar

my parents-in-law,

Zaleha Ibrahim and Mohd Shah Ali

my children,

Ameera

Asma'

A'isha

'Ammar

Ayman

and to my beloved husband,

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TABLE OF CONTENTS

Abstract.....	ii
Abstract in Arabic.....	iii
Approval Page	iv
Declaration Page.....	v
Copyright Page	vi
Dedication.....	vii
Acknowledgements	viii
List of Tables	xii
List of Figures.....	xiv
List of Abbreviations	xvi
CHAPTER ONE: INTRODUCTION.....	1
1.1 Epidemiology of Hypertension.....	2
1.2 Definition of Hypertension.....	2
1.3 Blood pressure Control and Hypertension.....	3
1.3.1 Haemodynamic Basis of Hypertension	3
1.3.2 Blood Pressure Regulation Under Basal Conditions.....	4
1.3.3 Autonomic Nervous System and Autoregulation of Blood Pressure .	6
1.3.3.1 Parasympathetic Nervous System and Blood Pressure	
Control	6
1.3.3.2 Sympathetic Nervous System and Blood Pressure	
Control	7
1.3.4 Sympathetic Receptors and Blood Pressure Regulation.....	12
1.4 Pathophysiology of Essential Hypertension	16
1.4.1 Neurohumoral Role of Adrenaline in Essential Hypertension	17
1.4.2 Peripheral Dopamine in Essential Hypertension	21
1.5 Essential Hypertension and SNS Enhancement	22
1.6 Sympathetic Nervous System Enhancement and Adrenal Medulla in Essential	
Hypertension.....	26
1.7 Phenylethanolamine-N-methyltransferase Inhibition in Essential Hypertension	27
1.8 Sympathetic Nervous System Enhancement in Pre-Hypertensive, Young	
Adults	28
1.9 Sympathetic Nervous System Enhancement, Central Blood Pressure and CV	
Risk Assesment.....	30
1.10 Research Hypotheses	32
1.11 Objectives	32
1.11.1 Primary Objectives	32
1.11.2 Secondary Objectives.....	33
CHAPTER TWO: METHODOLOGY	34
2.1 Human Study Design.....	34
2.1.1 Sample Recruitment	34

2.1.1.1 Inclusion Criteria	34
2.1.1.2 Exclusion Criteria	35
2.1.2 Study Protocol	36
2.1.2.1 Visit 1	36
2.1.2.2 Visit 2	37
2.1.2.3 Mildly Hypertensive Patients	37
2.1.3 Measurements	38
2.1.3.1 Blood Pressure	38
2.1.3.2 Blood Biochemical Analysis	39
2.1.3.3 Plasma Catecholamine Measurement	40
2.1.3.4 Assessment of Sympathetic Activity	46
2.1.3.5 Central Aortic Systolic Pressure Measurement	46
2.1.3.6 Framingham 10-year CV Risk Score	49
2.1.4 Human Study Protocol Flow Chart	50
2.2 First Animal Study Design	50
2.2.1 Adrenal Demedullation and Blood Pressure in SHR's	50
2.2.1.1 Rat Selection	50
2.2.1.2 Blood Pressure Measurement	51
2.2.1.3 Plasma Catecholamine Measurement	55
2.2.1.4 Bleeding Technique in SHR's	56
2.2.2 Bilateral Adrenal Demedullation	56
2.2.3 Sham Operation	62
2.2.4 Post-operative Care	62
2.2.5 Histological Assessment of Adrenal Demedullation	63
2.3 Second Animal Study Design	64
2.3.1 Phenylethanolamine-N-methyltransferase (PNMT) Effect on Blood Pressure in SHR's	64
2.3.1.1 Rat Selection, BP and CA Measure, Bleeding	64
2.3.1.2 PNMT Inhibition	64
2.4 Animal Study Protocol Flow Chart	65
2.5 Sample Size Calculation	66
2.5.1 Human Study	66
2.5.2 Animal Study	66
2.6 Statistical Analysis	67
CHAPTER THREE: RESULTS	68
3.1 Human study	68
3.1.1 Characteristics of Study Participants	68
3.1.2 Biochemistry Values	70
3.1.3 Plasma Catecholamine Levels	73
3.1.4 Correlations	75
3.2 Bilateral Adrenal Demedullation	79
3.2.1 Body Weight	80
3.2.2 Heart Rate	81
3.2.3 Systolic Blood Pressure	82
3.2.4 Histological Assessment	84
3.2.5 Plasma Catecholamine Levels and Adrenal Demedullation	85
3.3 PNMT Inhibition	87

3.3.1 Body Weight.....	87
3.3.2 Heart Rate	88
3.3.3 Systolic Blood Pressure	89
3.3.4 Plasma Catecholamine Levels and PNMTI.....	91
3.4 Other Parameters Monitored Throughout Treatment Period.....	92
CHAPTER FOUR: DISCUSSION.....	93
4.1 Role of Adrenaline in Hypertension Pathogenesis	93
4.2 Human Study	93
4.2.1 Adrenaline and Early Hypertension Development.....	93
4.2.2 Adrenomedullary System and SNS Enhancement.....	96
4.2.3 Adrenomedullary System, SNS Enhancement and Behaviour.....	98
4.2.4 Dopamine, Young Pre-Hypertensive and Mild Hypertension.....	99
4.2.5 Central BP and CV Risk Assessment of Young Adults	101
4.2.6 10-year CV Risk Assessment of Young Hypertensives	102
4.2.7 Plasma Catecholamines: A Method for Screening Young Adults.....	103
4.2.8 Biochemical Values and Assessment of Young Adults.....	105
4.3 Animal Study.....	106
4.3.1 Adrenal Demedullation and Sustained BP Reduction.....	107
4.3.2 Phenylethanolamine-N-Methyltransferase and BP Reduction.....	110
4.4 Limitations to Study	112
4.5 Future Prospectives.....	112
4.6 Conclusion	113
BIBLIOGRAPHY.....	114
APPENDIX I: Information Sheet For Research Participants	132
APPENDIX II: Consent Form	137
APPENDIX III: Case Record Form	140
APPENDIX IV: Framingham’s Cardiovascular Risk Assessment Form.....	157
APPENDIX V: Guidelines Prior To Blood Taking.....	158
APPENDIX VI: Framingham’s Cardiovascular Risk Questionnaire	160
APPENDIX VII: Accepted Abstracts.....	161

LIST OF TABLES

<u>Table No.</u>		<u>Page No.</u>
1.1	Stages of hypertension	2
1.2	Major effects mediated by neurotransmitters and their receptors	16
1.3	Principal techniques for the assessment of sympathetic activity	26
1.4	Age-dependent normal CASP ranges	31
2.1	Factors that influence catecholamine levels	41
3.1	Characteristics of human study subjects	70
3.2	Characteristics of human study subjects according to blood pressure classification	71
3.3	Biochemical profile of subjects	72
3.4	Biochemical profile of subjects according to blood pressure classification	73
3.5	Plasma catecholamine levels of subjects	74
3.6	Plasma catecholamine levels of subjects according to blood pressure classification	74
3.7	Correlation between adrenaline, NA, dopamine with SBP, DBP, MAP and CASP	76
3.8	Association between other variables in all subjects	78
3.9	Association between Mean BP and other variables	79
3.10	Baseline characteristics of SHRs	80
3.11	Group 1 weekly body weight	80
3.12	Group 2 weekly body weight	81
3.13	Group 1 weekly heart rate	81
3.14	Group 2 weekly heart rate	82

3.15	SBP of sham-operated control SHR	83
3.16	SBP of SHR post-adrenal demedullation (Group 2)	83
3.17	Weekly SBP comparisons	84
3.18	Plasma adrenaline levels comparison	86
3.19	Plasma noradrenaline levels comparison	86
3.20	Plasma dopamine levels comparison	86
3.21	Baseline characteristics of SHR	87
3.22	Body weight comparison between groups	87
3.23	Treated SHR group's weekly heart rate	88
3.24	Control SHR group's weekly heart rate	88
3.25	Treated SHR group SBP	89
3.26	Treated SHR group SBP, pre- and post- comparison to baseline	90
3.27	Control SHR group SBP	90
3.28	SBP comparison between groups	90
3.29	Plasma adrenaline levels pre- and post-PNMTI	91
3.30	Plasma noradrenaline levels pre- and post-PNMTI	92
3.31	Plasma dopamine levels pre- and post-PNMTI	92

LIST OF FIGURES

<u>Figure No.</u>		<u>Page No.</u>
1.1	Factors affecting mean arterial pressure	4
1.2	Autonomic nervous system and control of the cardiovascular system	5
1.3	Biosynthesis of NA and adrenaline in sympathetic nerve endings	8
1.4	The hypothalamic-adrenal axis in adrenaline production	11
1.5	Factors contributing to hypertension	17
1.6	Steps involved in the adrenaline hypotheses	18
2.1	Applanation tonometer in radial pulse wave analysis	47
2.2	Features of an arterial pulse waveform in a healthy adult	48
2.3	Sensor assembly; tail-cuff and LED	52
2.4	Hatteras equipment console	53
2.5	Normal arterial pulse wave forms in rats denoting good, consistent wave amplitudes	54
2.6	Localising the hump in the ventral position	57
2.7	Midline incision	58
2.8	Exposing tissue down to the spinal muscles	58
2.9	Scoring of the dorso-lateral abdominal muscles	59
2.10	Localising the left adrenal gland	60
2.11	Lifting the adrenal gland	60
2.12	Incising the adrenal cortex	60
2.13	Enucleating the adrenal medulla	61
2.14	Enucleated adrenal medulla	61
2.15	Surgical equipment	62

3.1	Correlations between MAP and catecholamines	77
3.2	Example of adrenal tissue [H&E stain, 10x (Lt) and 40x (Rt)]	85

LIST OF ABBREVIATIONS

NHMS	National Health and Morbidity Survey
WHO	World Health Organisation
BP	Blood Pressure
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
TPR	Total Peripheral Resistance
CO	Cardiac Output
ANS	Autonomic Nervous System
CNS	Central Nervous System
SNS	Sympathetic Nervous System
PNS	Parasympathetic Nervous System
SA	Sinoatrial
AV	Atrioventricular
ACh	Acetylcholine
NA	Noradrenaline
Na ⁺	Sodium Ion
DOPA	Dihydroxyphenylalanine
CRH	Corticotrophin-Releasing Hormone
ACTH	Adrenocorticotrophic Hormone
PNMT	Phenylethanolamine-N-Methyltransferase
COMT	Catechol O-Methyltransferase
MAO	Monoamine Oxidase
AH	Adrenaline Hypothesis
LBNP	Lower Body Negative Pressure
NA-SOR	NA Spill Over Rate
SHR	Spontaneously Hypertensive Rats
JNC	Joint National Committee on Hypertension
CASP	Central Aortic Systolic Pressure
CAD	Coronary Artery Disease
MAP	Mean Arterial Pressure
LDL	Low Density Lipoprotein
HDL	High Density Lipoprotein
URTI	Upper Respiratory Tract Infection
HPLC	High Performance Liquid Chromatography
EDTA	Ethylenediaminetetraacetic Acid
PWF	Arterial Pulse Waveform
CV	Cardiovascular
LED	Light-Emitting Diode
THIQ _{1,2,3,4}	Tetrahydroisoquinoline
BMI	Body Mass Index
TC	Total Cholesterol
TG	Triglyceride
BPM	Beats Per Minute
HPT	Hypertension

CHAPTER ONE

INTRODUCTION

1.1 EPIDEMIOLOGY OF HYPERTENSION

Hypertension or high blood pressure, is a condition that has a significant impact on the world's population morbidity and mortality (Chobanian et al., 2003; Levenson, Skerrett, & Gaziano, 2002; Padwal, Straus, & McAlister, 2001). It was estimated in 2000 that 26.4% of the world's adult population had hypertension, 34.3 % in developed countries and 65.7 % in economically developing countries (Kearney et al., 2005). Malaysia's third National Health and Morbidity Survey (NHMS III) in 2006 reported that hypertension afflicted 43% of adults over the age of 30, compared to 33% in the second NHMS in 1996 (Institute for Public Health, 2008; Lim T.O., 2004). The high prevalence of hypertension during this survey proved that hypertension was becoming an important health problem in Malaysia.

The World Health Report 2002, stated that high blood pressure caused 7.1 million deaths throughout the world, which was approximately 13% of total deaths worldwide (WHO, 2002). It also reported that suboptimal blood pressure, i.e. a systolic blood pressure (SBP) of more than 115mmHg, was responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease worldwide. Moreover, the Framingham Heart Study showed that young individuals with high-normal blood pressure (diastolic blood pressure of 85-89 mm Hg) were two-to-threefold more likely to develop hypertension than those with normal blood pressure (DBP less than 85 mm Hg) (Leitschuh, Cupples, Kannel, Gagnon, & Chobanian, 1991).

Furthermore, cardiovascular events such as angina, myocardial infarction, heart failure, stroke and even death, were hypertension-related and propelled the need for earlier diagnosis and intervention. This resulted in the introduction of the new classification, “pre-hypertension” (Chobanian et al., 2003; Hypertension Guideline Working Group, 2008; WHO, 2002) or “high normal blood pressure” (B Williams et al., 2004; Zanchetti et al., 2003) in the classification of hypertension. In addition, hypertension was increasingly identified in the younger population although the prevalence was not as high as in the adult population (Gan, Loh, & Seet, 2003; William, Kimberly, Kevin, Samuel, & Bonita, 2002). The United States National Health Survey 2008 for example, found 9.2 % of the population young adult males aged 20-34 years old were diagnosed with hypertension between 2003-2006, compared to 7.1% between 1988-1994 (National Center for Health Statistics, 2008).

1.2 DEFINITION OF HYPERTENSION

Hypertension is defined as persistent elevation of the blood pressure. The systolic blood pressure is 140 mmHg or more and/or the diastolic blood pressure is 90 mmHg or more at least on 2 different occasions (Hypertension Guideline Working Group, 2008; WHO, 2002). It is further subclassified as illustrated in the Table 1.1 below;

Table 1.1
Stages of Hypertension

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

[Adapted from: Hypertension Guideline Working Group, 2008]

In 90-95% of patients presenting with hypertension, when the elevated blood pressure could not be attributed to any known cause, the hypertension is termed essential (or primary) hypertension (Hypertension Guideline Working Group, 2008; WHO, 2002). The remaining 5-10% of patients with hypertension results from other diseases such as renal disease, endocrine disorders, or other identifiable causes. This form of hypertension is called secondary hypertension (Hypertension Guideline Working Group, 2008; WHO, 2002).

1.3 BLOOD PRESSURE CONTROL AND HYPERTENSION

1.3.1 Haemodynamic Basis of Hypertension

Arterial blood pressure is influenced by several factors. The diagram on the following page summarizes the main homeostatic factors that control arterial pressure. In general, despite its causes, the raised arterial pressure in hypertension is the result of an increase in Total Peripheral Resistance (TPR) or Cardiac Output (CO). TPR is determined by the arterial tone (state of vessel constriction), whereas the CO is influenced by heart rate and stroke volume. Stroke volume is in turn, affected by the heart contraction strength and pressure within the heart ventricle (Boron & Boulpaep, 2008). [Figure 1.1 summarizes the factors that affect CO and TPR and the conditions that could lead to raised CO and TPR]

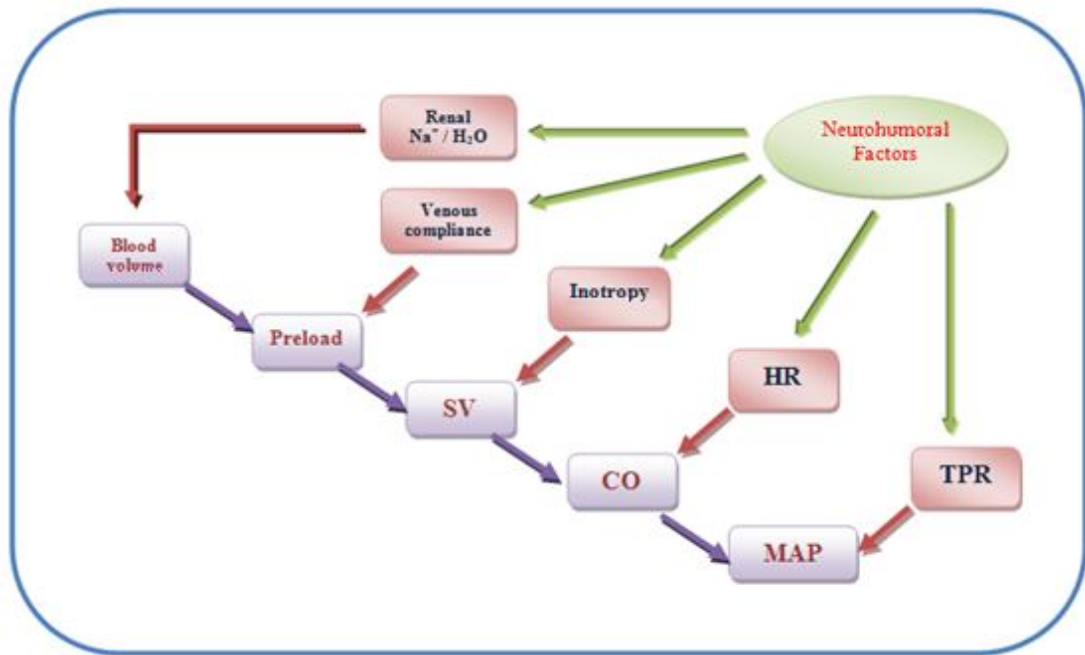


Figure 1.1: Factors affecting mean arterial pressure
 [Adapted from: Boron & Boulpaep, 2008]

1.3.2 Blood Pressure Regulation Under Basal Conditions

The body's arterial blood pressure control depends on short-term (time frame of seconds to minutes) and long-term (hours or days) mechanisms. Short-term BP regulation is mediated by the autonomic nervous system (ANS) targeting the heart, vessels, and adrenal medulla. Long-term BP regulation is primarily mediated by humoral factors through pathways targeting on the blood vessels and the kidneys, for the control of extracellular fluid volume (Boron & Boulpaep, 2008).

The hypothalamus is the major integration centre for the ANS. Output from the hypothalamus influences the medulla (located within the central nervous system, CNS) which is the major cardiovascular control centre. The medulla coordinates response according to inputs received from higher CNS centres (hypothalamus and cerebral cortex) or the peripheral sensors (baroreceptors and also chemoreceptors). The baroreceptors which are found primarily at the aortic arch and carotid artery

monitor the arterial pressure. The chemoreceptors (the carotid bodies and the aortic bodies) which are located close to the baroreceptors, monitor changes in the blood P_{O_2} , P_{CO_2} , and pH. The medullary cardiovascular control centre elicits response through the neurons of the peripheral nervous system, the autonomic or somatic (voluntary control of body functions) systems. Figure 1.2 below shows the cardiovascular system control centre at the medulla.

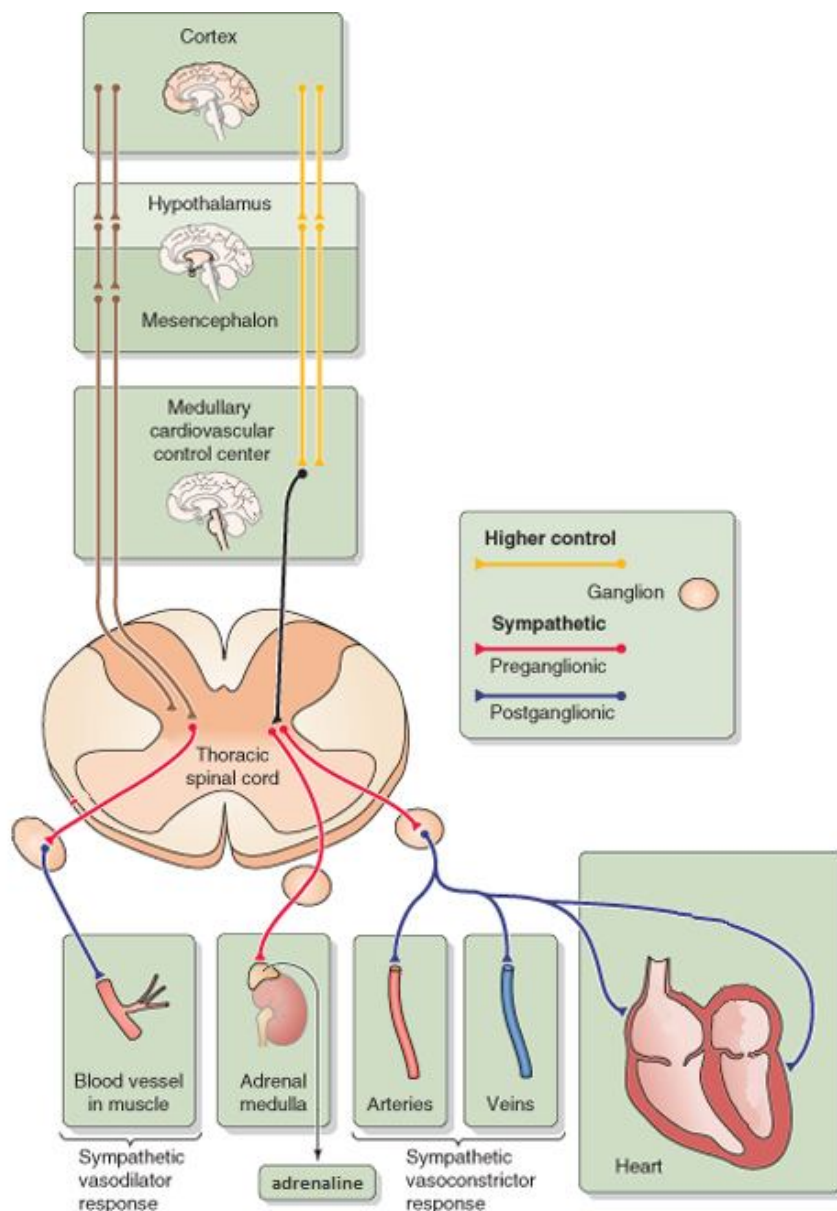


Figure 1.2: Autonomic nervous system and control of the cardiovascular system.
[Adapted from: Klabunde RE, 2005]

1.3.3 ANS and Autoregulation of Blood Pressure

The ANS is the peripheral nervous system that autoregulates visceral functions. It plays an important role in the cardiovascular system, regulating the blood pressure and cardiac function. ANS is further divided into the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) which complements each other functionally. Generally, the SNS stimulates the heart and constricts the blood vessels (vasoconstriction) resulting in a rise in arterial pressure while the PNS depresses cardiac function and dilates selected blood vessels (vasodilatation) causing reduction of the arterial pressure (Boron & Boulpaep, 2008).

1.3.3.1 Parasympathetic Nervous System and Blood Pressure Control

The cardiovascular effects of parasympathetic (vagal) activation are primarily seen in the heart (Boron & Boulpaep, 2008; Considine, 2004). Vagal nerves innervate the heart's pacemaker cells (sinoatrial [SA] and atrioventricular [AV] nodes). The postganglionic vagal nerve fibres that synapse to the heart cells (myocytes) release Acetylcholine (ACh) as a neurotransmitter. The binding of ACh to muscarinic receptors of the myocytes decreases the heart rate, therefore CO is reduced (Boron & Boulpaep, 2008; Considine, 2004). The parasympathetic effect on blood vessels is very minimal and if any, it influences the muscarinic receptors, causing a dilatation of the blood vessels (vasodilatation), hence reducing the TPR and the blood pressure (H.P Rang, Dale, Ritter, & Moore, 2003).

1.3.3.2 Sympathetic Nervous System and Blood Pressure Control

Sympathetic neurotransmitter synthesis and release

The catecholamines adrenaline, noradrenaline (NA) and dopamine have a key role in the sympathetic control of blood pressure. They are synthesized in a common biosynthetic pathway from tyrosine, through dopa, dopamine and NA, to adrenaline [Figure 1.3]. Adrenaline is predominantly synthesized from NA in the cytosol of chromaffin cells in the adrenal medulla (comprising 80% of adrenal glands' total secretion) (Price, 1966; Shah, Tse, Clutter, & Cryer, 1984; Wurtman, Pohorecky, & Baliga, 1972).

However, there is evidence that shows adrenaline being synthesized from chromaffin cells found outside the adrenal medulla (extra-adrenal), such as the kidneys and heart tissues (Caramona & Soares-da-Silva, 1985; Sudo, 1985, 1987a, 1987b; Ziegler, Bao, Kennedy, Joyner, & Enns, 2002). It has been shown that adrenaline: NA tissue concentration ratio is greater (1:50) in the heart and kidneys (Caramona & Soares-da-Silva, 1985; Sudo, 1985). Adrenaline is classically known for its humoral function, acting on a distant target after its release into the bloodstream.

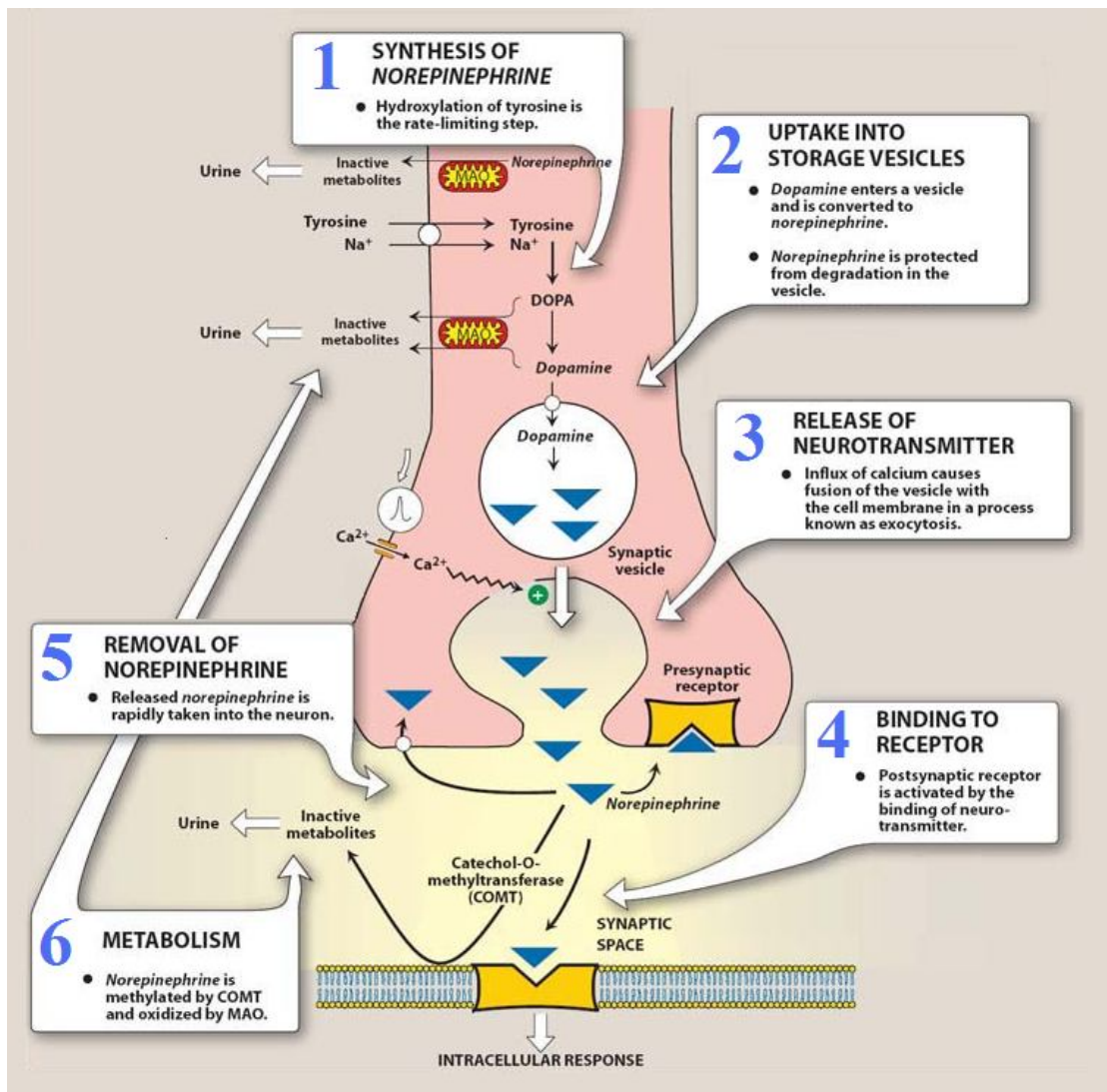


Figure 1.3: Biosynthesis of NA and adrenaline in sympathetic nerve endings
 [Adapted from: Harvey RA, 2009]

Meanwhile, 2.0-7.5% of circulating NA in humans is also released from the adrenal medulla and could have a humoral function (D. S. Goldstein, McCarty, Polinsky, & Kopin, 1983a; Price, 1966; Silverberg, Shah, Haymond, & Cryer, 1978). Nonetheless, NA's main function is as the primary neurotransmitter in the sympathetic nervous system for blood pressure regulation at the postganglionic sympathetic nerve endings, where 92-98% of circulating NA is derived from under basal conditions (D. S. Goldstein et al., 1983a; Pohorecky & Wurtman, 1971; Silverberg et al., 1978). NA