# 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 لِلُب 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 الإفتراضية 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 الماليزي ألمصاب بحدية فرط ضغط الدم وكذلك المصابون بفرط ضغط الدم البسيط. ويهدف هذا البحث أيضاً إلي أن نزع الأدرينالين المتواجد في الدم إما بإستئصال جزء من لُب الغدة الكظرية، أو تعاطي العقاقير المثبطة لهرمون الأدرينالين مثل فينايل إثانولامين-ن-ميثايل 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 تعريض مجموعتين من الفئران المصابة بالفرط التلقائي لضغط الدمإما 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؛ فدُوِّن 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، و كذلك المصابين بفرط ضغط الدم البسيط. ولقد أكدنا في نتائج هذه الدراسه 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:

Noriah Mohd Noor
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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.

Aszrin Abdullah

Signature ..... Date .....

INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

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**THE ROLE OF CATECHOLAMINES IN THE PATHOGENESIS OF HYPERTENSION**



Affirmed by AszrinBinti Abdullah.

..... .....

Signature Date

*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,*

***Azarisman Shah Mohd Shah***

*Thank you for all your patience, support and du'a.*

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# 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 | Adrenocorticotropic 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]

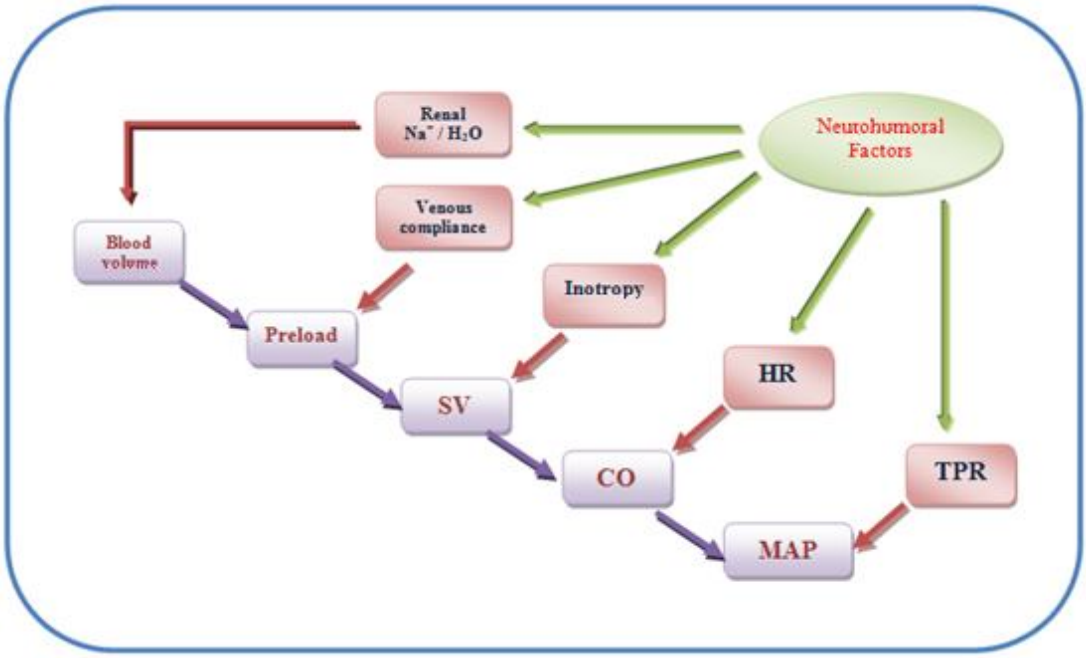


Figure 1.1: Factors affecting mean arterial pressure
[Adapted from: Boron & Boulpaep, 2008]

### 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 $P_{O2}$, $P_{CO2}$, 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.

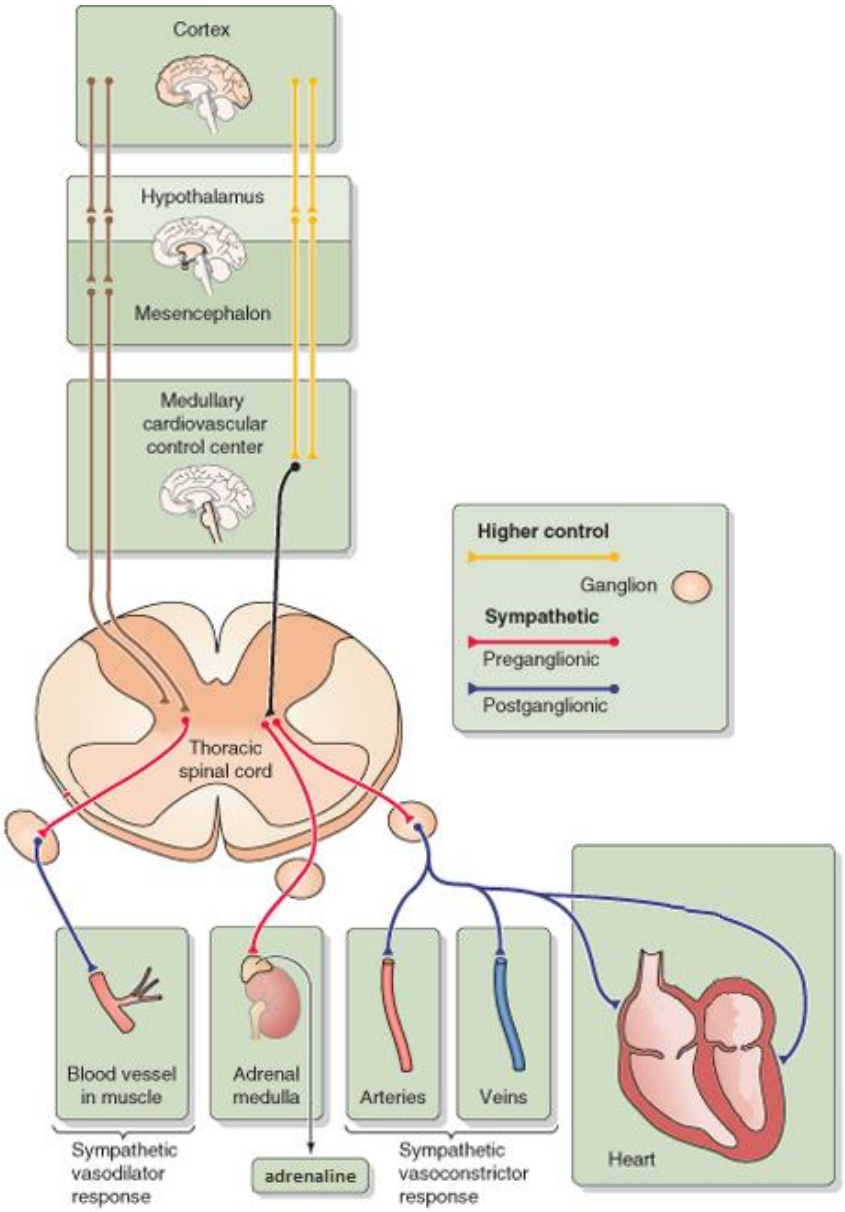


Figure 1.2: Autonomic nervous system and control of the cardiovascular system. [Adapted from: Klabunde RE, 2005]

### 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.

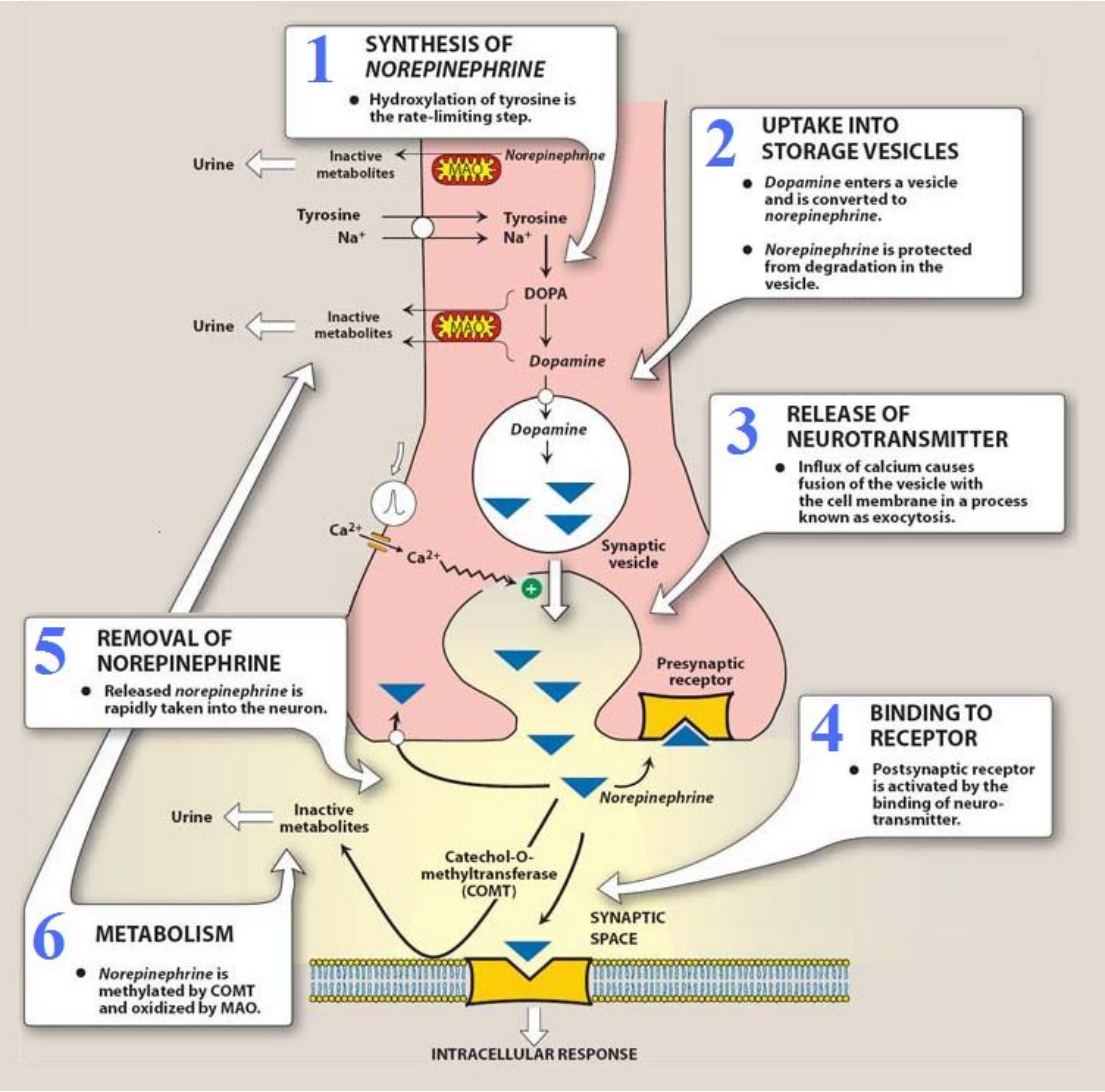


Figure 1.3: Biosynthesis of NA and adrenaline in sympathetic nerve endings [Adapted from: Harvey RA, 2009]

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