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(Clin.Pharm)

BARORECEPTORS and NUCLEUS TRACTUS SOLITARY

A Forgotten Potential Targets to Treat Hypertension

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Words of Wisdom

"*Allowing physiological functions for a while to maintain hemodynamics while supporting lifestyle modifications is a crucial aspect of treatment*"

Dr. apt. Yedy Purwandi Sukmawan. M.Si (Clin. Pharm)

FOREWORDS

By the grace and blessing of Allah SWT, the author has been able to complete this book entitled 'Baroreceptors and Nucleus Tractus Solitary: A Forgotten Potential Targets to Treat Hypertension'. Peace and blessings be upon the Prophet Muhammad SAW. The author would like to express his sincere gratitude to his parents, wife, Ai Teni Alfianti, S.Pd, and his children, Atsna Adhkan Fawwaz Sukmawan, Fayzha Samha Saufa Sukmawan, and Adnan Faiz Sukmawan.

The author delves into the author's thoughts on developing new treatments for hypertension by targeting the under-explored baroreceptor-Nucleus Tractus Solitary pathway. This pathway is crucial for detecting abnormalities in blood pressure and maintaining blood pressure homeostasis. Dysfunction or damage to this pathway can lead to

hypertension. Various receptors and neurotransmitters within this pathway can be targeted for the treatment of hypertension. Additionally, the book presents non-pharmacological approaches to maintain and repair this pathway.

The author acknowledge that this work is not without its flaws. It is our hope that this book will make a significant contribution to the field and beyond.

The author

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SECTION 1
Introduction to Hypertension

1. Definition, Prevalence, and Global Health Impact.

Hypertension is defined as an elevation of blood pressure above the normal range (Gabb, 2020). Based on several guidelines, such as The Joint National Committee – 7 and the European Society of Cardiology, hypertension is defined as systolic/diastolic blood pressure ≥ 140/90 mmHg (Mancia et al., 2023; Sica, 2004). This disease is often referred to as the silent killer due to its ability to cause sudden death without preceding symptoms (Mensah, 2019). According to the World Health Organization (WHO) report in 2023, the prevalence of hypertension has reached over 1 billion people worldwide (Kario, Okura, Hoshide, & Mogi, 2024). Moreover, there has been a continuous increase of 41% from 1990 to 2019 in Europe and the Americas, and 144% in

Southeast Asia and the Western Pacific region (Kario et al., 2024).

The WHO has set a target of reducing the global prevalence of hypertension by 33% from 2010 to 2030 (Kario et al., 2024). However, given the continued increase in hypertension prevalence, particularly in Asia, achieving this target is highly unlikely without a significant improvement in public awareness of hypertension risk factors. Fostering community awareness requires a collaborative effort from healthcare professionals worldwide. Hypertension poses a significant burden on global health, contributing to a range of serious conditions such as cardiovascular, cerebrovascular, and renovascular diseases, which are leading causes of mortality globally (Mills, Stefanescu, & He, 2020).

The cardiovascular diseases that developed from hypertension include :

a. Left Ventricular Hypertrophy (LVH).
b. Arrhytmias.
c. Coronary arterial disease (CAD) (Masenga & Kirabo, 2023).

LVH develops due to various mechanisms, including overexpression of the fatty acid transporter cluster of differentiation 36 (CD36), redox-sensitive Protein Kinase C (PKC), increased oxidative stress, increased matrix metalloproteinase-2 (MMP-2) activity, abnormal Ca2+ homeostasis, increased activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway, apoptosis, and abnormal regulation of junctional proteins (Masenga & Kirabo, 2023; Scioli et al., 2020).

The physiological function of CD36 is to uptake long-chain fatty acids from albumin and high-triglyceride lipoproteins, including chylomicrons and very low-density lipoprotein (VLDL). Overexpression of CD36 can have

detrimental effects due to enhanced uptake of fatty acids by the heart, leading to the accumulation of fatty acids in the heart, induced lipotoxicity, enhanced formation of reactive oxygen species (ROS), altered substrate preference towards fatty acids compared to glucose (which is more efficient for ATP production), and ultimately, ischemic conditions in the heart (Masenga & Kirabo, 2023; Scioli et al., 2020).

Arrhythmias involve complex mechanisms including structural changes in the heart (hypertrophy), activation of fibroblasts and collagen deposition in the heart, ion channel dysfunction, overactivation of the sympathetic nervous system, decreased parasympathetic activity, oxidative stress, alterations in gene and epigenetic expression, all of which ultimately lead to abnormalities in the heart's electrical conduction pathways (Antzelevitch &

Burashnikov, 2011; Lei, Salvage, Jackson, & Huang, 2024).

Coronary arterial diseases involve various mechanisms including increased shear stress on the endothelial lining of arteries, reduced nitric oxide (NO), increased secretion of pro-inflammatory cytokines and adhesion molecules, increased oxidative stress, dysregulation of lipid metabolism including the promotion of LDL cholesterol oxidation, overactivation of growth factors and matrix metalloproteinases (MMPs), and arterial stiffness (Simon & Vijayakumar, 2013).

The cerebrovascular diseases that developed from hypertension include:

a. Transient ischemic stroke (TIA).
b. Ischemic stroke (IS).
c. Hemmorhagic stroke (HS).
d. Vascular dementia.

e. Lacunar infarcts
f. Encelopathy
g. Kidney dysfunction (Webb & Werring, 2022).

The various cerebrovascular diseases are caused by a variety of mechanisms such as atherosclerosis formation, weakening of blood vessel walls leading to rupture (aneurysm), and failure of cerebral autoregulation (Webb & Werring, 2022). Meanwhile, renovascular diseases include renal arterial stenosis, nephrosclerosis, acute kidney injury (AKI), and chronic kidney disease (CKD) (Textor, 2017).

The development of renovascular diseases is also influenced by various contributing factors, including reduced blood flow to the kidneys due to the long-term release of renin (endothelial dysfunction), damage to small blood vessels in the glomeruli, the formation of oxidative stress and the release of pro-inflammatory cytokines,

arterial stiffness, and vascular remodeling, including thickening and reduced elasticity (Textor, 2017).

2. Pathophysiology of Hypertension.

The pathophysiology of hypertension is quite challenging to understand. Based on available evidence, it involves a multitude of factors, and until recently, the exact determinant of hypertension remains elusive. Hypertension is classified into two types including primary hypertension and secondary hypertension (Ma & Chen, 2022). Primary hypertension is hypertension without an identifiable underlying cause, with a prevalence of 90-95%. Secondary hypertension is hypertension with an identifiable underlying cause, with a prevalence of 2-10% (Ma & Chen, 2022).

A comprehensive discussion of the pathophysiology of hypertension will encompass all potential factors involved, such as:

a. Renin angiotensin aldosterone system (RAAS).
b. Central nervous system (CNS).
c. Sodium and water retention.
d. Vascular endothelial dysfunction.
e. Inflammatory and immune system processes.
f. Metabolism syndrome.
g. Genetic predisposition.
h. Microbiome (Ryousuke, Harrison, & L. Gabriel, 2018).

3. The Renin Angiotensin Aldosterone System (RAAS)

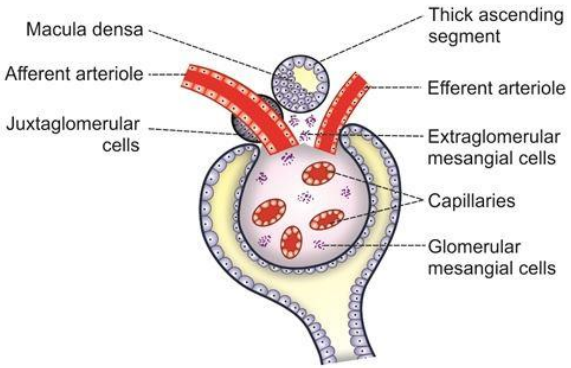
Renin

Renin is an endopeptidase enzyme produced by specialized cells in the kidneys

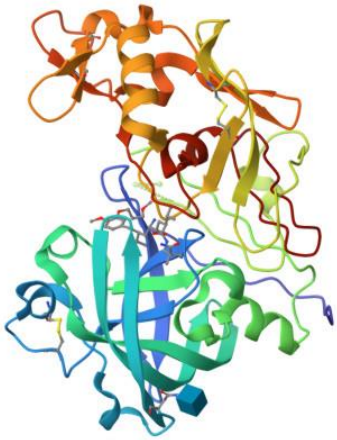
known as juxtaglomerular cells (Kanugula, Kaur, Batra, Ankireddypalli, & Velagapudi, 2023). These cells are located in the walls of the afferent arterioles, which supply blood to the glomerulus (Figure 1). The renin gene is located on chromosome 1, designated as 1q32.1, and translates into a protein of 406 amino acids with a mass of 37 kDa (Figure 2) (Kanugula et al., 2023). The normal reference range for renin released into the blood is approximately 0.6 to 4.3 ng/mL/hour (Gaddam et al., 2008; Kanugula et al., 2023).

There are two primary factors that stimulate renin elevation include direct stimulation and indirect stimulation (Zheng et al., 2020). Direct stimulation includes a drop in blood flow to the kidney and a decrease in sodium delivery to the macula densa, a specialized region of the distal tubule. Indirect stimulation includes activation of the sympathetic nervous system and

angiotensin II deficiency. Factors that activate the sympathetic nervous system include stress, exercise, and hemorrhage. Additionally, conditions such as hypokalemia and the release of prostaglandins, particularly PGE2, can also stimulate renin release(Zheng et al., 2020).



Picture 1. Juxtaglomerular cells location (Sembulingam and Sembulingam, 2010)



Picture 2. Structure of Renin (Protein Data Bank, 2024)

Angiotensinogen

Angiotensinogen is a protein primarily produced by the liver (Figure 3) (Lu, Cassis, Kooi, & Daugherty, 2016). While the liver is the main source, other tissues also contribute to angiotensinogen production, albeit in smaller quantities, including adipose tissue, the heart, the brain, and the kidneys (Lu et al., 2016).

Angiotensinogen consists of 485 amino acids and serves as a crucial precursor for renin to be converted into its active form.(Lu et al., 2016; Mancia et al., 2023) The normal reference range for plasma angiotensinogen is 745 to 2340 pmol/mL (Lu et al., 2016; Mancia et al., 2023). Several factors influence angiotensinogen concentrations, including:

a. Physiology.
b. Genetic.
c. Environments (Lu et al., 2016; Mancia et al., 2023).

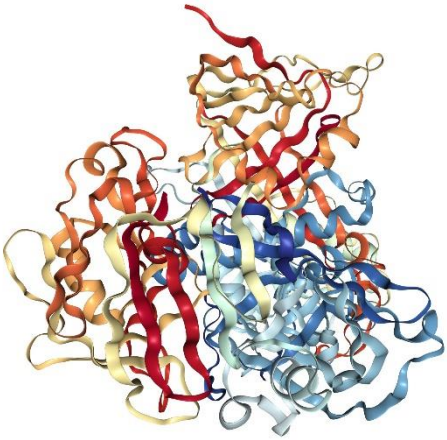
The physiology factors that influence angiotensinogen concentration including liver function, hormonal influences (estrogen and corticosteroid), inflammation, and nutritional status (Ryousuke et al., 2018). The liver function has a clear impact to the angiotensinogen concentration due to the primarily sites for generating angiotensiongen. Estrogen has an

impact to the increased of angiotensinogen if the estrogen level is increased through the upregulation of the angiotensinogen gene expression (Ryousuke et al., 2018). Corticosteroid has an impact to the increased of angiotensinogen through direct stimulation and indirect stimulation (Hunter, Ivy, & Bailey, 2014). The direct stimulation through stimulate hepatocytes to produce angiotensinogen, meanwhile indirect stimulation through influence RAAS pathway such as stimulation to increase aldosterone, water retension, and vascular reactivity (Ayari et al., 2014; Hunter et al., 2014).

Genetic factors play a significant role in angiotensinogen production. Genetic polymorphisms or variations in the gene encoding angiotensinogen can influence its expression. Individuals with a family history of hypertension often have elevated

angiotensinogen levels compared to the general population (Gorący et al., 2022).

Environmental factors also contribute to angiotensinogen production . A high-salt diet is a well-established factor associated with increased angiotensinogen levels. Infections and toxins that can cause liver damage can also influence angiotensinogen production, as the liver is the primary site of its synthesis (Zheng et al., 2020). Chronic stress can activate the hypothalamic-pituitary-adrenal axis, leading to increased cortisol levels and ultimately stimulating angiotensinogen production (Ramachandran, 2009).



Picture 3. *Structure of Angiotensinogen (SinoBiological, 2024)*

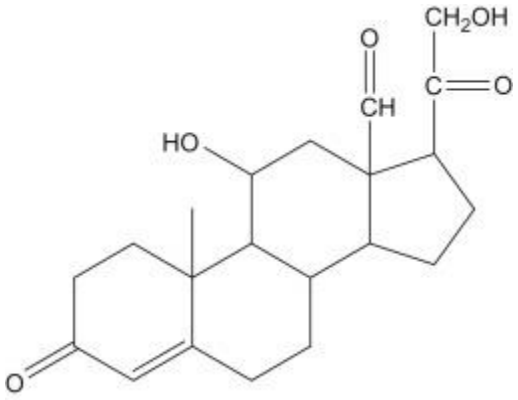
Aldosterone

Aldosterone is a steroid hormone produced by the adrenal cortex, the outer layer of the adrenal glands located above the kidneys (Taves, Gomez-Sanchez, & Soma, 2011). It has the chemical formula C21H28O5 (Figure 4, Figure 5). The primary function of aldosterone is to regulate the body's salt and water balance, which ultimately affects blood pressure. While its

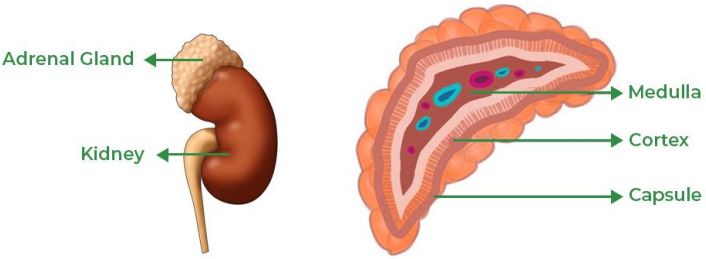
primary target organ is the kidney, aldosterone also influences other organs, such as the sweat glands and salivary glands (Bollag, 2014; Taves et al., 2011).

The primary function in the salt balance including promote the reabsorption of sodium from the kidney back into the bloodstream, and the potassium excreted to the urine (Bollag, 2014; Taves et al., 2011). The reabsorption effects to the sodium cause the water retention in the body. The factors stimulate the aldosterone release are:

a. Decrease of blood volume,
b. Decrease of blood pressure,
c. Low sodium level
d. High potassium level
e. Drugs (diuretics, and ACE-I) (Taves et al., 2011; Hattangady et al., 2012; Bollag et al 2014)



Picture 4. Chemical Structure of Aldosterone (Feher, 2017).



Picture 5. Adrenal Cortex (https://www.geeksforgeeks.org/adrenal-gland/).

1.2.3 The role of RAAS to Hypertension

RAAS is a complex hormonal system primarily responsible for regulating blood pressure and fluid balance in the body (David G; et al., 2018). Renin, angiotensinogen, and aldosterone are proteins produced by the kidney, liver, and adrenal glands, respectively (David G; et al., 2018; Martyniak & Tomasik, 2023). The RAAS pathway is activated in response to a drop in blood pressure or blood volume, which leads to decreased perfusion of the kidneys (David G; et al., 2018; Martyniak & Tomasik, 2023). This condition stimulates the release of renin from juxtaglomerular cells in the kidneys. Renin cleaves the N-terminal of angiotensinogen, converting it into angiotensin I (Ang I) (David G; et al., 2018). Angiotensin I is further converted into angiotensin II (Ang II) by angiotensin-converting enzyme (ACE), which removes two C-

terminal residues (David G; et al., 2018; Martyniak & Tomasik, 2023).

Ang II is a potent vasoconstrictor that binds to the angiotensin II type 1 receptor (AT1R), leading to increased blood pressure, cardiac contractility, myocardial metabolism, and mitogenic responses. Additionally, Ang II stimulates the release of aldosterone, which directly promotes water retention, sodium reabsorption, and potassium excretion. Aldosterone also plays a role in vascular remodeling by promoting the deposition of collagen and other extracellular matrix components, which ultimately increase peripheral resistance and arterial stiffness (David G; et al., 2018; Martyniak & Tomasik, 2023).

1.2.3 The role of the sympathetic nervous system in blood pressure regulation

The sympathetic nervous system (SNS) is a division of the autonomic nervous system, responsible for controlling involuntary bodily functions (Waxenbaum, Reddy, & Varacallo, 2024). It originates in the spinal cord (T1-L2), where preganglionic neurons send signals to sympathetic ganglia (paravertebral and prevertebral) (Waxenbaum et al., 2024). These ganglia house postganglionic neurons, which release the neurotransmitters acetylcholine and norepinephrine. These neurotransmitters influence various bodily functions, including heart rate, blood pressure, and pupil dilation (Forstenpointner et al., 2022).

Preganglionic neurons use acetylcholine, while postganglionic neurons release norepinephrine. The SNS is often called the "fight-or-flight" response, preparing the body for action

in stressful situations. It increases heart rate, blood pressure, and breathing rate, dilates pupils, releases adrenaline and cortisol, and shunts blood away from non-essential areas like the digestive and reproductive systems (Waxenbaum et al., 2024).

The activation process of SNS initially with the perceives of potential threat in the brain, specifically the amygdala . The process is continued by the hypothalamus activation that activated the SNS system that cause neurotransmitter release norephineprine and epinephrine to result physiological changes (Waxenbaum et al., 2024). Moreover, the SNS activation is also stimulate the adrenal medulla to release additional epinephrine and norepinephrine, part of the adrenal glands, amplifying the effects of the SNS (Picture 6) (Waxenbaum et al., 2024).