Physiological Response to Dietary Salt: A Review on Salt Sensitivity Hypertension

Lee Mei Tan, Mohd Makmor Bakry, Adyani Redzuan*

Quality Use of Medicine Research Group, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia

ABSTRACT

High blood pressure is a major medical condition concerning public health, economical and disease burden worldwide. Elevated intake of dietary salt as a modifiable risk factor for high blood pressure, has been reported to be one of the increasing threats to the world's health. Evidence from various scientific researches including animal, genetic, epidemiological and interventional studies is suggesting that salt reduction could improve blood pressure level and subsequently, decrease the cardiovascular events. Despite the potential lead, the result is sometimes inconsistent and not reproducible. One key justification behind such irregularity could be due to heterogeneity of salt sensitivity. This review attempts to accumulate and reassess information and knowledge pertaining to pathogenesis of salt-sensitive hypertension for better understanding of the trait. Salt sensitivity in individual patients should be acknowledged when deciding treatment options, especially pharmacological therapy to maximise its effectiveness, and hence reducing unwanted side effects and medical costs.

Key Words: Dietary Salt, Salt-Sensitive, Hypertension, Treatment

eIJPPR 2018; 8(2):8-20

HOW TO CITE THIS ARTICLE: Lee Mei Tan, Mohd Makmor Bakry, Adyani Redzuan. (2018). "Physiological response to ditary salt: a review on salt sensitivity hypertension" , International Journal of Pharmaceutical and Phytopharmacological Research, 8(2), pp.8-20.

1. INTRODUCTION

High blood pressure or hypertension, defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg [1], is a major medical condition concerning public health, economical and disease burden worldwide. Global burden of disease (GBD) study ranked hypertension as the top risk factor attributed to almost 200 thousand disability-adjusted life-years (DALYs) [2,3]. Consequences of uncontrolled hypertension combined with cardiovascular diseases remain the leading cause of death, accounting for 46% of non-communicable diseases (NCD) death [4] in addition to total economic burden of estimated US$73.4 billion [5]. Year 2015 sees 22% of global prevalence of hypertension [6] which is projected to increase to 29% in 2025 as hypertension increases with age consistently in all world regions [7].

In recent years, there has been an increasing number of research on the potential benefits of salt reduction in improving hypertension and subsequently lowering cardiovascular events. Although, most of the findings are positive and encouraging, the results remain equivocal. A revisited of INTERSALT 1988 research [8] was done following Salt Institute's objection to the initial result and methodology [9]. Unfortunately, even the second result was not well-received [10]. Contrasting findings in Cochrane's (2013) systematic review on the effects of the salt reduction made headlines in the news, leaving many in disarray [11, 12]. Despite that, multiple randomized controlled trials (RCTs) and meta-analysis have continuously demonstrated positive linear relationship between sodium intake and blood pressure across diverse population with varying level of sodium intake and susceptibility. In this review, we discuss the physiological responses to dietary salt that directly or

Corresponding author: Adyani Redzuan
Address: Quality Use of Medicine Research Group, Faculty of Pharmacy, National University of Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia.
E-mail: ✉ adyani @ ukm.edu.my
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest .
Received: 05 October 2017; **Revised:** 16 February 2018; **Accepted:** 23 March 2018

indirectly cause hypertension, whether salt sensitivity is inherited or induced, as well as the management of antihypertensive drugs and non-drug therapy on this special class of hypertensive patients.

History of Salt

History of salt dates back to the ancient time when salt production was scarce. For millenniums, salt has notably been regarded as a person's social status, economical dominance and political supremacy. Salt was historically used as an exchange currency. It was a highly valuable trade commodity, so that a 'salt route' was created for the purpose of its transportation. Salting was a symbol of a fine culture and traditional etiquette which was uncommonly observed unless among the wealthy and during religious offerings. In fact, salt is thought to be the cause of wars and protests in many regions of the world, angered by salt taxes and monopolies from the major political powers [13, 14].

Life since then, has evolved to depend so much on salt for sustainability. Thus, resulted to Dahl's (1960) proposition that, "perhaps it is the ancient valuation of salt as a precious possession that may have contributed to the modern notion that the addition of salt to food is necessary or even beneficial" [15]. This practise of adding salt to food which occurred 5000 years ago is nevertheless considered as a quite recent evolution in human dietary pattern [16]. Anthropological evidences have indicated that throughout the human civilization, ancestral diet has a characteristically low level of sodium [11], that sodium was acquired naturally from food products, and that the daily intake was only about 10 mmol/day [17].

Salt and Hypertension Relationship

The first written record on the association of blood pressure to salt intake traces back to 2000 years ago in an ancient Chinese medical text book. It reads, "if a large amount of salt is taken, the pulse will stiffen and harden" [18]. This salt hypothesis has led to the inquisition on the role of salt on blood pressure. In the early 20th century in 1904, Ambard and Beaujard revived the salt hypothesis and stated that salt is necessary for the genesis of essential hypertension [19]. Their research looked at implication of chloride restriction on hypertension but failed to consider the function of sodium because of the confusion in the methodology used. In 1923, Frederick Allen [101] used salt restriction diet to treat hypertension. His work received much opposition from Goldring and Chasis (1994) who argued that the restriction of salt is un-called for and that such restriction with potential effect on blood pressure has not been substantiated, suggesting that a salt restriction diet to treat hypertension is merely a personal conjecture without sufficient proof or evidence [20].

It was Louis Dahl's (1960) unprecedented linear graph demonstrating positive relationship between prevalence of hypertension and mean salt intake across five population groups in 1960 that made a remarkable breakthrough on salt-hypertension research. Five important bases were incorporated in Dahl's paper [21]. First, he found that the average daily intake of salt by white American men and northern Japanese farmers was 10 g and >26 g respectively, due to the exceptionally high rate of hypertension and stroke of the Japanese at that time. He noted the vast variability of an individual's dietary salt consumption, and many predicaments of measuring a person's salt intake level. Nonetheless, he recommended that the most accurate method to estimate a person's daily salt intake level is by measuring 24-hour urinary sodium excretion. Dahl (1960) also proposed that low sodium consumption can be gradually adapted without suffering from any medical side effect due to the reason that salt appetite in humans is induced rather than being innate. In his animal study, Dahl (1960) demonstrated that hypertension can be induced in rats, in dose-dependent sodium ingestion over a period of time. Lastly, Dahl acknowledged that the risk of diseases, particularly hypertension is dependable on a cumulative effect of risk factors including salt intake and genetic susceptibility. These findings and theories on salt and hypertension relation remain influential to the research community to this day [21].

Following Dahl's (1960) momentous salt-hypertension research findings, many international investigation bodies attempted to further investigate the possibility of salt reduction on its potential to improve blood pressure. INTERSALT, a notable international study investigated the relation between electrolyte excretion and blood pressure in 10079 individuals in 52 centres across 32 countries. They found significant positive relation between 24 hour urinary sodium excretion and median systolic pressure in individual participants after standardization with age and sex [8]. Positive results from Intersalt study were supported by subsequent successful experiment in vitro animal study [22] as well as trials in human intervention [9]. Trials of Hypertension Prevention (TOHP), a study designed to investigate the short-term feasibility and efficacy of non-pharmacologic interventions in persons with higher than normal blood pressure found weight, and sodium reduction interventions were the most effective method for reducing blood pressure. When sodium is reduced by 44 mmol/day, a reduction of

systolic pressure 1.7 mmHg and diastolic pressure 0.9 mmHg was observed, besides, a 25% lower risk of cardiovascular event among those in the intervention group was noticed. In addition, various systematic reviews including gold-standard Cochrane review and meta-analysis have repeatedly shown positive evidence for the effect of salt reduction on lowering blood pressure [23-25].

Salt and Physıology

Chemically, salt is an ionic compound that may be resulted from a number of chemical reactions such as the neutralization of acid and base, reaction between a metal and a non-metal or a metal with an acid. Sodium chloride is the most common form of dietary salt. It is composed of elements sodium (Na^+) and chloride (Cl^-) thus is abbreviated by chemical formula NaCl. Each element carries a positive and negative charge respectively, hence are bound together through an ionic bond due to the oppositely charged ions. Sodium makes up about 39.337% of NaCl while chloride makes up 60.663%. Separately, these two electrolytes display distinctly different properties. Sodium belongs in alkali metal group that carries a positive charge when contacting with water, while chloride is a negatively charged halogen. It is important to note that sodium is approximately 0.25% of salt [26].

Sodium is an essential mineral abundantly available in the daily diet. Fresh and unprocessed farm products such as fruits, vegetables; grain products, dairy and meat contain very little sodium. On the contrary, most sodium in our diet comes from discretionary salt with salt in processed food, contributing the highest total intake of 77%, 11.6% derived from sodium inherent to food, 6.2% from salt added at the table while the remaining 5.1% was salt added during cooking [27]. The body also reproduces tiny amount of sodium from metabolic activity during catabolism of bone matrix and nucleic acids.

Physiologically, humans need approximate 1g of salt or 17 mmol sodium per day [21, 28]. Sodium is prevailing when referring to dietary salt due to its major presence in the extracellular fluid (ECF). Approximately 75% of exchangeable sodium in a human body can be found in the extracellular fluid being plasma and interstitial fluid whilst the remaining 25% of non-exchangeable sodium resides in tissues, or bound to inorganic salt of bone and cartilages. Because sodium is the predominant solute in the extracellular fluid, its concentration is considered as a determinant of the total body water (TBW) content [29]. Change in TBW in a closed circulatory system has a major influence on the blood pressure.

A normal range of plasma sodium concentration is between 135 – 145 mmol/L [30]. Beside its significance in TBW content and blood pressure, sodium concentration directly affects electrolytes' balance, water movement, cells structure and the plasma osmolality. It assists in osmo-regulation by moving water molecules towards the region of higher concentration, thereby maintaining a state of equilibrium, and an optimal range of plasma osmolality, and consequently blood pressure. Steady intracellular water and osmolality are in turn necessary for cell membrane integrity and cellular processes [31]. In addition, sodium along with potassium, calcium and their respective anions accounts for the great majority of cell membrane polarization which is essential for conduction of electrical nerve impulses and for contraction of muscle fibers [32].

Sodium homeostasis is regulated via an intrinsic system of renal mechanism that includes cascade of hormonal system with renin-angiotensin-aldosterone system (RAAS) being the most prominent. The renal sympathetic nervous system (SNS) and a family of sodium transport proteins function as an expression of the formers. Ingested sodium goes through digestive tract, and is absorbed largely in the intestine. Most excess sodium is removed through urine, small amount via sweat and, tears or faeces [33]. Defect or malfunction in any of these body systems are said to cause irregularity in sodium balance which resulted in salt-sensitive hypertension. These factors shall be discussed in more details in the next sections.

Salt Sensıtıvıty: Definıtıon and Prevalence

In theoretical context, salt-sensitivity is defined as an appropriate elevation or fall in blood pressure in response to alteration in salt intake [34]. Dahl postulated in his 1960 paper that humans show a range of response to salt intake level. His hypothesis was proven in the animal model through a series of breeding experiments where he fed his in-bred strains of salt-sensitive rats (Dahl-S rats) with diet high in salt which subsequently developed hypertension and stroke. In contrary, in-bred Dahl-R rats, which were resistant to salt alteration did not show sign of raised blood pressure, despite the same high salt diet [35, 36]. A series of human experiments further strengthen the conviction of salt-sensitive hypertension [37]. A total of 19 hypertensive subjects were observed through a period of normal (109 mmol/d), low (9 mmol/d) and then high (249 mmol/d) sodium intake. Blood pressure fell significantly with dietary salt restriction and rose significantly back to baseline level after the high salt phase. Individual blood pressure responses to salt

alteration were compared and further separated into two groups: salt-sensitive (n=9) for those who demonstrated at least a 10% increase in mean arterial pressure when the low and high salt pressures were compared, and alternately, the salt resistant group (n=10) [38]. The same observation was extended to normotensive population where 16 normotensive men were subjected to an increment range of sodium intake from 10 to 1500 mmol/d over a period of 3 weeks. Blood pressure rose significantly from the lowest to the highest salt intake. However, individual responses were variable and ranged from an increase of 1.5% to 34% indicating heterogeneity of blood pressure responsiveness to alteration in dietary sodium intake [39].

Due to difficulties and lack of uniformity of the technique used to identify salt sensitivity [40], its precise definition and relation to pathogenesis of hypertension remains controversial. One method most commonly used to distinguish salt sensitivity was proposed by Weinberger *et al*. (1996) who concluded that salt-sensitivity state is persistent and reproducible over time [37]. Weinberger's (1996) method is based on the intravenous administration of high (2L 0.9% saline at 500 ml/hr) and low (10 mmol/day) sodium content coupled with oral furosemide (3 doses of 40 mg each). Individuals with ≥10 mmHg blood pressure difference upon the administration were categorized as salt-sensitive, whereas individuals with ≤5 mmHg difference were defined as salt resistant. Those with a decrease in blood pressure between 6 and 9 mm Hg were considered indeterminate [37].

Using the same approach, Weinberger (2001, 1996) discovered that about 26% of normotensive population is salt-sensitive and the figure is higher (51%) in hypertensive population [37, 43]. Salt sensitivity is also prevailing in older generation and in blacks, with African American encompassing 73% of the total salt-sensitive population. Obese patients or those with concomitant diabetes mellitus also appear to be commonly sensitive to salt intake [42]. Weinberger (2001) also further suggested an association of salt sensitivity to increased mortality independent of blood pressure. In his long term (27 years) observation in a group of normotentive and hypertensive individuals, he found normotensive salt-sensitive subjects aged >25 years when initially studied have a cumulative mortality similar to that of hypertensive subjects, contrary to higher survival in salt-resistant normotensive subjects [43]. His observations were supported by Frohlich (2007) who noted that in salt-sensitive patients, salt-loading does not simply raise arterial pressure, but may trigger local hormone system stimulation in response to elevated sodium, thereby promoting severe damage to the cardiac, vascular and renal structural and functional derangement [44].

Pathogenesis of Salt-Sensitive Hypertension

A commentary by Frohlich (2007) is that salt sensitivity should not be observed solely on the effect of salt loading on patients' blood pressure, but rather on the overall hypertension disease process including nonhemodynamic factors such as aging, gender, race, genetic, environmental, pharmacological, coexistent morbid and disease factors as well as irregularity in the endocrine and homeostasis system resulted from excessive salt intake [44]. Due to its critical role in maintaining sodium balance and body fluid volume, the kidney is the primary organ where blood pressure regulation is concerned. It is said that hypertension travels with the donor kidney. The most compelling evidence to justify this statement, comes from cross-transplantation studies between two strains of rats with opposite genetic propensities to hypertension. Dahl noticed that when the recipient animal and its renal homograft came from the same strain, blood pressure was not significantly affected. However, animals from the hypertension-resistant strain with a renal homograft from the hypertension-prone strain had higher pressures whereas hypertension-prone rats with a homograft from the hypertension-resistant strain had lower pressures than their respective controls [45, 46]. Dahl went on to inter-transplant kidneys from salt-induced hypertensive and normotensive rats. Elevated BP as reduced to normal level by normotensive homograft in hypertensive recipient, and that hypertensive homograft raised the blood pressure of a normotensive host [47].

Homeostasis in sodium-water balance:

The body homeostatic mechanism works in an integrated fashion to maintain equilibrium in a system allowing a range of salt and water intake without large fluctuation in total body fluid volume and the resulting blood pressure. It has been hypothesized that excessive salt intake or sodium retention by the kidneys and the resulting plasma volume expansion eventually lead to a raised blood pressure [37]. This relation between blood pressure and natriuresis was described by Arthur Guyton (1991) with a shift to the right of the pressure-natriuresis curve. In the excess of salt, ECF volume expands which increases cardiac output hence, results in a rise in tissue perfusion exceeding metabolic demands. Due to the surplus of blood supply, the body autoregulatory response then initiates

vasoconstriction and peripheral vascular resistance resulting to a higher arterial pressure [48]. This phenomenon of resetting a body system is caused by an alteration in kidney function to maintain steady state homeostasis following persistent high intake of dietary salt. The result is a long-term rise in blood pressure as proposed by Guyton and Coleman nearly five decades ago that hypertension can be developed when consistent excessive salt intake impairs the excretory ability of the kidneys [49].

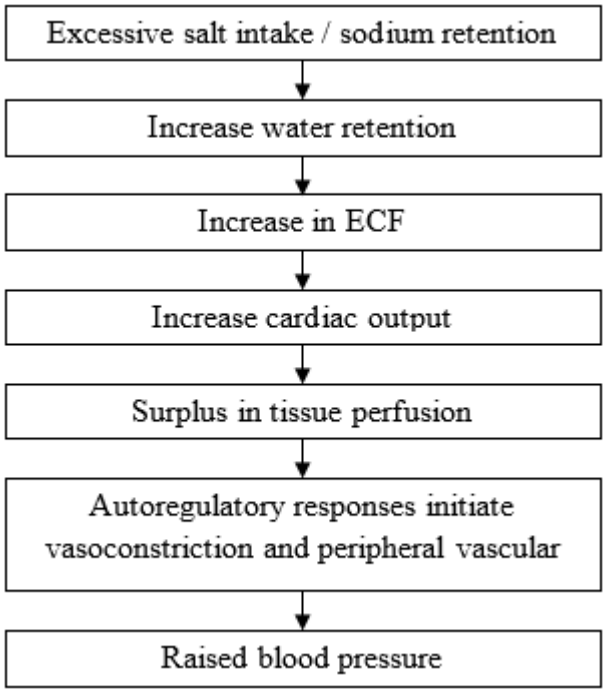

Fig. 1: Guyton's blood pressure-natriuresis mechanism. ECF = extracellular fluid.

Functional units in the kidney that regulate homeostasis in sodium-water balance encompass a family of sodium transport proteins and the Juxtaglomerulus apparatus. A number of sodium transport proteins are embedded along the apical membrane renal tubules (Figure 2) including the Na+H+ exchanger (NHE) and Na+ phosphate co-transporter (NaPi2) in the proximal tubules, Na+K+2Cl- co-transporter (NKCC2) and NHE in the Loop of Henle, Na+Cl- co-transporter (NCC) in the distal tubules as well as the epithelial Na+ channel (ENaC) in the collecting ducts [50]. Na+K+ATPase pump, on the other hand is present abundantly in the basolateral membrane of the renal tubules. The Na+K+ATPase pump is a membrane bound enzyme that carries out active electrogenic translocation of sodium and potassium ions across the plasma membrane, thereby maintaining an optimum sodium gradient in the ECF and cellular volume, which as discussed is a major determinant of blood pressure. It also indirectly controls cell ionic balance and epithelial transport [50].

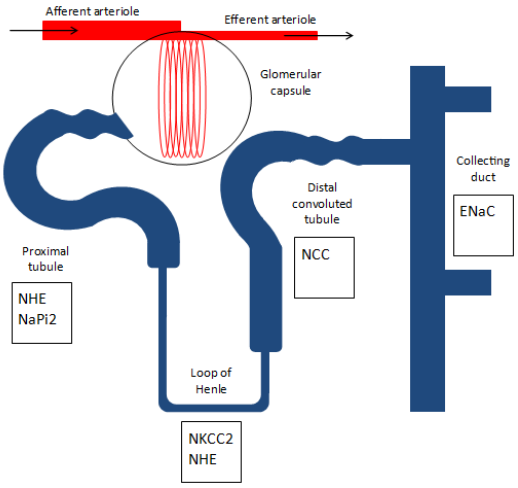

Fig. 2: A schematic diagram on sodium transport protein along the nephron.

NHE = Na+H+ exchanger, NaPi2 = Na+ phosphate co-transporter, NKCC2 = Na+K+2Cl- co-transporter, NCC = Na+Cl- co-transporter, ENaC = epithelial Na+ channel. Adapted from [53]

Mutation or malfunction of any of these proteins may lead to disruption on the sodium-water homeostasis that could further result in salt-sensitive hypertension. Blaustein et al. (2006) reported endogenous ouabain (EO), a compound synthesized and secreted by adrenal glomerulosa cells stimulated by chronic salt intake inhibits the α2Na+K+ATPase pump. Increase in cytosolic sodium due to the inhibition hence resulted in elevation of cytosolic calcium via sodium calcium exchanger (NCX). Excess cytosolic calcium augments arterial contractibility causing raise in blood pressure. EO, which has both cardiotonic and vasotonic properties were elevated in approximate 40% of essential hypertension patients. In animal study, increased level of EO was also observed in salt-dependent hypertensive rats [51].

The Juxtaglomerular apparatus is composed of three components: (1) macula densa (MD) cells denotes the beginning of distal convoluted tubules, (2) Juxtaglomerular cells near the afferent arteriols, and (3) flatted and elongated extraglomerular mesangial cells. All three components are located adjacent to one another in the proximity of Glomerulus capsules, and are closely related physiologically in terms of their function in regulating the blood pressure. The MD cells are of particular importance in the pathogenesis of salt-sensitive hypertension due to their role in detecting NaCl concentration. In fact, the Juxtaglomerular apparatus works in a synchronized affecter and effecter events, termed as tubuloglomerular feedback mechanism (TGF), to control the arterial pressure within normal limit when there are changes in salt intake. In the short term, fast and random changes in NaCl concentration of tubular fluid is detected by the MD cells, positive or negative TGF mechanism then causes vasodilation or vasoconstriction respectively of the afferent arterioles resulting in change in glomerular

filtration rate (GFR) which returns NaCl delivery in distal tubule to the normal level [52]. In the long term, MD cells respond to a chronic shift in the NaCl concentration by signalling renin secretion in the Juxtaglomerular cells, thereby adjusting the generation of angiotension II to a level that is appropriate for the maintenance of sodium homeostasis.

Salt-sensitive hypertension could possibly occur due to irregularity in TGF mechanism resulted from the generation of nitric oxide (NO) from neuronal nitric oxide synthese (NOS) in MD. Synthesis for NOS is activated by tubular fluid reabsorption that mediates a vasodilating effect on the TGF negative response [53]. Increases in sodium intake has shown to cause an increase in renal medullary nNOS protein in salt-resistant Sprague-Dawley rats. In another animal study, nNOS protein was inhibited via intravenous 7-nitroindazole resulted in salt-resistant rats to become salt-sensitive [54]. The result suggests that nNOS may prevent salt-sensitive hypertension, and that decrease in nNOS may be the cause of salt sensitivity [54]. Recently, Wang et al. (2016) demonstrated that the mice with deletion of NOS, NOS1 specifically from the MD developed salt-sensitive hypertension [55] with NOS1β acting as a primary NOS1 isoform expressed in the MD that regulates the TGF response, the natriuretic response to acute volume expansion, and the development of salt-sensitive hypertension [56]. Therefore, suggesting that NOS1B may be a salt-sensitive isoform in the MD that modulates TGF response, promotes sodium excretion, and protects against the development of salt-sensitive hypertension [57].

Renin-angiotensin aldosterone system (RAAS):

The RAAS is a cascade of hormonal mechanism that assists in regulation of blood pressure and body fluid balance. The system is activated with the biosynthesis of renin from the Juxtaglomerular cells that lines the renal afferent arterioles (AA). This action is triggered by a number of stimuli: (1) a decreased perfusion volume due to decrease in AA pressure following reduction in plasma volume; (2) a reduced NaCl delivery in renal distal tubules detected by stretched macula densa cells in Juxtaglomerular apparatus (3) an increase in sympathetic activity [58].

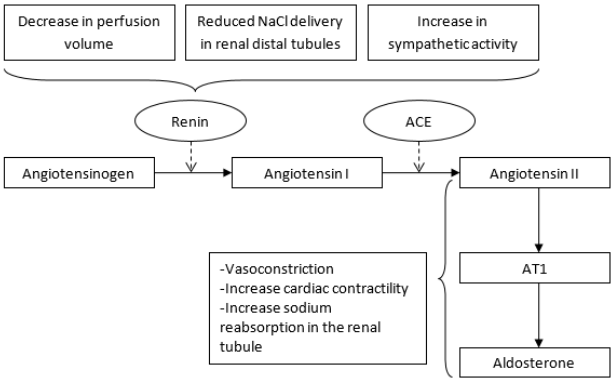

Fig. 3: Cascade for the activation of the renin-angiotensin-aldosterone system (RAAS).

NaCl = sodium chloride, ACE = angiotensin converting enzyme, AT1 = angiotensin receptor subtype 1. Adapted from [61]

In the extracellular space, the renin activates the biological inert circulating angiotensinogen to angiotensin I, which in turn is converted into angiotensin II by an angiotensin converting enzyme (ACE). Angiotensin II is the primary active product of RAAS. A vasoconstrictor itself, angiotensin II and its receptor subtype 1 (AT1) play a key role in restoring or maintaining circulatory homeostasis, and mediates most of the physiological and pathophysiological functionalities of RAAS system including vasoconstriction, an increased blood pressure, and increased cardiac contractility. On top of that, angiotensin II also increases sodium reabsorption in the renal proximal tubule by stimulating NHE, thereby inhibits further release of renin, besides stimulating the production of aldosterone from adrenal cortex which role is essential in regulating sodium balance [58].

It is well-established that changes in urinary sodium excretion or natriuresis are chiefly the function of aldosterone [59, 60]. Aldosterone is the final active product of RAAS, and is produced in the zona glomerulosa of the adrenal cortex in the presence of angiotensin II. Aldosterone plays a critical role in promoting the expression of sodium transport channels and pumps particularly the ENAC and the basolateral Na+K+ATPase pump [50]. Approximately, 2% of filtered sodium is reabsorbed in the renal distal tubule when aldosterone is present, hence absence of aldosterone would result in renal loss of sodium in excess of 500mmols/day. Conversely, if aldosterone is secreted in excess, final urine sodium concentration will be close to zero [31].

Blaustein (2006) suggested that aldosterone hormone and its receptor, mineralcorticoid receptor (MR) enables reabsorption of sodium and water back into the plasma vessel, hence increasing the extracellular fluid volume causing a rise in blood pressure. Persistent rise in blood pressure stimulates a pressure natriuresis so that normal ECF is restored at the expense of an elevated blood pressure [51]. His hypothesis was clarified by Ando and Fujito (2012) that production of aldosterone is also observed in some types of hypertension in the absence of primary aldosteronism, a secondary hypertension disease where the plasma aldosterone concentration (PAC) is increased due to overproduction of aldosterone. They postulated that aldosterone and MR may be overactivated in salt-sensitive hypertension from increase in PAC and Rac1 activity due to obesity and excessive salt intake respectively. As a result, sodium is retained, and salt-sensitive hypertension is developed [61].

Paradoxically in a separate study, Thomson et al. observed an unexpected increase of angiotensin II in event of excessive salt, more so with an increased activity of aldosterone [60]. Ritz concluded that high salt intake could induce aldosterone secretion [59] by looking at experimented animals that are normotensive on low salt but hypertensive when serum potassium is low with an increased epithelial sodium channel activity on high salt [62]. Fujita (2007) concluded that salt could be the culprit behind aldosterone-induced MR activation and subsequent hypertension [63]. He credited this claim from an animal study where salt-induced MR activation in obese hypertensive rats was observed as a result of inappropriate secretion of aldosterone from adipose tissues [64].

Renal Sympathetic Nervous System:

A few studies have discussed the implication of renal sympathetic nervous system in the regulation of renal excretory function and blood pressure control [65]. There is a considerable evidence for sympathetic nerve activity being elevated in hypertensive patients contributing to the development of hypertension. Blood pressure is the product of cardiac output and peripheral vascular resistance, which is most likely the effect of over activation of renal sympathetic nervous system. The renal sympathetic nerves innervate the kidney, i.e. the vascular cells, tubular epithelial cells and Juxtaglomerular cells [65]. Changes in these nerves may influence the kidney function in maintaining sodium-water balance resulted in blood pressure change.

Campese *et al*. (1982) observed a higher level of stress hormone norepinephrine in salt-sensitive hypertensive individuals compared to normotensive individuals [66]. Fujita (2007) concluded that this is due to a persistent autonomic drive in salt-sensitive individual to salt loads [63]. Several effects can be observed from an increased renal sympathetic nervous activity resulted from increased level of norepinephrine: (1) Increasing sodium and water retention from the distal tubules, (2) decreasing renal blood flow and glomerular filtration rate due to vasoconstriction of renal blood vessel, (3) increasing secretion of renin from the Juxtaglomerular cells. These actions contribute to long-term arterial pressure elevations by shifting the pressure-natriuresis curve to the right as mentioned by Guyton in the pathogenesis of salt-sensitive hypertension [67].

Some evidence has also suggested that over-activation of renal sympathetic nervous system may cause a compromised arterial baroreceptor reflex function that leads to salt-sensitive hypertension [67]. In contrary, several etiological experiments have identified a reduced renal dopamine production in salt-sensitive hypertension [68, 69]. Dopamine is a vasodilator with natriuretic effect on the kidney [41].

Other Factors Influencing Salt-Sensitive Hypertension

Hereditary and genetic factors:

Although salt intake level may be a risk factor, Joossens and Geboers (1983) argued that other factors, primarily genetics might contribute to the expression of the salt induced hypertension [70]. Luft *et al*. (1979) and Weinberger (1996) both reported hereditary factor as associated with salt-sensitive hypertension. Homozygous haptoglobin phenotype (HP 1-1) may predispose individuals to become salt-sensitive hypertensive [37, 71]. In a separate genetic study, Drenjancevic-Peric *et al*. (2011) identified different haplotype distributions between normotensive individuals and hypertensive individuals with regards to the renin gene [72]. This suggests that genetic variations in genes involved in the sodium homeostasis such as RAAS may predispose salt sensitivity hence results in salt-sensitive hypertension.

Demographic factors:

In addition to all factors discussed above, hypertension is well-known to be highly associated to old age and obesity [37, 41, 71]. A national study of 16,440 hypertensive patients in Malaysia showed the prevalence of hypertensive increases with age in both men and women [73]. Weinberger (1991) reported that when salt-sensitive normotensive individuals were followed over a duration of time, their blood pressure slowly increased [74]. There is also report that salt sensitivity increases at menopause [16]. These evidences seem to suggest that salt sensitivity expression increases with age and weight.

Meneton (2005) noted that salt sensitivity in old age is due to reduced capacity of the human kidney to excrete sodium, thus small increases in salt intake may induce a pronounced rise in blood pressure [16]. On the other hand, Luft et al. (1991) concluded that older subjects, usually with a decreased in renal function, were more sluggish in their natriuretic responses, hence a delayed sodium excretion occurs [71]. Among differing backgrounds, it is clearly documented that hypertension is most prevalent among the Blacks in the continent of Africa [6] as reported by Weinberger (1996) that 73% of black hypertensive patients were salt-sensitive [37]. Meneton (2005) attributed this to notable deterioration in GFR or kidney function in the black population [16]. According to Luth *et al*. (1991) however, salt-sensitive hypertension in different races is largely because of altered sodium transport regulation at cellular level. These include irregularity in Na^+K^+ATPase activity, decreased Na^+Li^+ counter-transport activity, increased parathyroid hormone values and augmented Na^+H^- anti-transported activities [71].

Treatment of Salt-Sensitive Hypertension

Studies on novice and existing available treatment targeting on salt-sensitive hypertension are still scarce despite the increased amount of research on the role of salt in pathogenesis of hypertension. Salt-sensitive hypertension is not specifically categorized or defined in a broader context of hypertension. As such, patients

continue to be treated as any other hypertensive patients disregarded of their salt sensitivity status.

Non-pharmacological approaches:

Healthy lifestyle including dietary salt restriction is known to be the first line of defence for hypertension [75]. This move was also strongly encouraged in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension where lifestyle modification is prescribed for all hypertensive and prehypertensive patients which include weight reduction, dietary sodium reduction, increasing physical activity and reduction of alcohol consumption. In Trial of Hypertension Prevention TOHP Phase 1, three lifestyles (weight reduction, sodium restriction and stress management) and four nutrition supplements' (calcium, magnesium, fish oil and potassium) single factor intervention aimed at lowering blood pressure were compared. Among the seven non-pharmacologic interventions, weight reduction (DBP -2.3mm Hg, SBP -2.9mm Hg, $P<0.01$) and salt restriction (DBP -0.9mm Hg, SBP -1.7mm Hg, $P<0.01$) were found to be the most effective [76], hence supporting the notion that sodium reduction should be implemented as a population strategy for hypertension prevention [77].

Because of the intimate relationship of salt-sensitive hypertension and dietary salt, long before the invention of antihypertension medication, dietary modification that includes reduction in sodium content was already available. Kempner rice diet was an accidental innovation from Dr Walter Kempner in 1930s. It consists of only white rice and fruit with characteristically low level of salt content. Prolonged dietary treatment with Kempner diet has shown improvement on blood pressure, a decrease in heart size, and noticeable improvement on eye damage [78]. As a matter of fact, various meta-analysis and systematic analysis on dietary salt reduction trials revealed that salt restriction resulted in reduced blood pressure with the most improvement noted in older hypertensive patients [24, 25]. Furthermore, studies suggest that decreased dietary sodium intake not only reduces blood pressure, but also may be associated with a reduced need for antihypertensive drug therapy. DASH, a study on Dietary Approaches to Stop Hypertension compared the dietary pattern of three different approaches on blood pressure. 459 study participants were put on a 3 weeks of control diet before randomization, and were subsequently subjected to 8 weeks of control diet, diet high in fruits and vegetables, and the DASH diet. On overall, blood pressure reduced by 5.5/3.0 mmHg but most significantly, on hypertensive patients where 11.6/5.3 mmHg blood pressure reduction was observed while in non-hypertensive patients, a moderate reduction of 3.5/2.2 mmHg was observed. In African American population, pronounced for its salt sensitivity characteristic, blood pressure was reduced by 6.9/3.7mmHg when DASH diet was introduced [79, 80]. Diet high in fruits and vegetable also reduced blood pressure but to a lesser extent. Separately, in another study comparing the three diets in hypertensive patients, DASH diet reduced blood pressure of hypertensive patients significantly by 11.4/5.5 mmHg while diet high in fruits and vegetable also reduced blood pressure by 7.2/2.8 mmHg. These improvements were observed merely 2 weeks after patients were given the diets regimen. After 8 weeks, 70% of patients eating DASH diet have their blood pressure controlled under 140/90 mmHg while 45% on diets high in fruits and vegetables [81].

Pharmacological agents:

Besides, non-pharmacological remedy by reducing consumption of dietary salt, hypertension is a chronic disease that requires a lifelong pharmacological intervention. Various effective antihypertensives are available on the current market, and each varies according to their mechanisms of action.

Diuretics*:*

Diuretic is one of the first antihypertensive agents that have been used to control blood pressure since the development in 1950s. Termed as water pill, it works on total body fluid by flushing out water and salt via urine excretion thus relaxing the blood vessels. Diuretic is an effective natriuretic agent that directly counteracts the tendency for salt and water retention [51]. It targets the luminal side of renal epithelial cells by blocking various sodium transport protein hence disabling electrolyte reabsorption in the renal tubules [82]. In short term, diuretic reduces blood volume by promoting sodium excretion. In the long run, it works excellently to decrease peripheral vascular resistance [83]. Diuretic has been reported to be highly effective in salt-sensitive hypertensive groups, particularly the elderly and African descents with resistant hypertension [84, 85]. Conversely, Grossman *et al.* (2011) reviewed diuretic treatment of hypertension. He concluded that for prevention of hypertension mortality and morbidity, diuretic is superior to other antihypertensive drugs attributing it to several large meta-analysis studies [86-88] where he observed a 51% stroke risk reduction compared to only 29% when hypertension is treated with β-blocker [89].

Calcium channel blocker (CCB):

Another effective antihypertensive agent for salt-sensitive hypertensive patients is the calcium antagonist as reported by Weir and colleagues (1998). They did a single-blind study on 21 hypertensive patients where 5 were determined to be salt-sensitive (mean blood pressure difference ≥5mmHg). Comparisons were made between salt-sensitive and non-salt-sensitive hypertensive participants in both high and low salt diet. After titration with isradipine, improvement on blood pressure was most profound in salt-sensitive hypertensive patients with high salt diet where a blood pressure difference of -18.7/-19.6mmHg was observed from 157.2/102.9mmHg. He concluded that calcium antagonist has robust antihypertensive

properties in high salt setting [90]. Calcium antagonist or CCB relaxes the blood vessel by inhibiting the entry of calcium into the muscle cells of the arteries. Along with diuretics, CCB works better on salt-sensitive hypertension in lowering blood pressure which has characteristically low renin activity [91].

Angiotensin Converting Enzyme Inhibitor (ACEI):

ACEI is commonly recommended to hypertensive patients with organ complication and diabetes mellitus but not to salt-sensitive hypertensive patients. As monotherapy drug, ACEI displayed limited effectiveness on salt-sensitive hypertensive patients due to the low level of renin distinctive to this group of patients [92, 93]. In a separate study to compare the influence of race and dietary salt on the antihypertensive efficacy of ACEI and CCB in salt–sensitive hypertension, it was found that enalapril exerted less blood pressure control among salt-sensitive hypertension as compared to isradipine. The study compared efficacy of enalapril and isradipine on 3 races (Black, Hispanic and White) on high and low salt diet. Blacks who are known to be salt-sensitive population displayed less blood pressure differences when treated with enalapril (-10.3/-8.6 mmHg) contrary to isradipine (-15.9/-12.1 mmHg) (P=0.01) [94]. However, the effectiveness of ACEI in salt-sensitive hypertension may be enhanced by a reduction in dietary salt intake coupled with a combination of drug therapy with diuretics [91]. This was confirmed from the work of Fliser and his colleagues (1993) who concluded that blood pressure reduction after acute ACEI is a function of salt intake [95]. One obvious drawback of ACEI is coughing which is observed in about 15% of patients. Taking ACEI for long term may prevent worsening of kidney function, and delay the onset of heart failure [96].

Angiotensin Receptor Blocker (ARB):

Similar to ACEi, ARB helps the improvement of hypertension by working on the RAAS. It binds to angiotensin II, thereby renders it to be inactive [83]. With reduced angiotensin II, aldosterone secretion is inhibited, as a result of a decreased vasoconstriction activity and lower blood pressure level. ARB is usually the first choice for patients with heart and kidney complication or diabetes mellitus. Though ARB may work as a monotherarapy treatment, Endo and his colleagues (2009) has shown in their animal study that ARB olmesartan when combined with hydrochlorothiazide is highly effective even under high salt diet [97]. His work was supported by Ando (2009) who did a clinical trial on hypertensive patients whose blood pressure is not controlled by amlodipine, and subsequently switched to combination therapy of telmisartan with low dose hydrochlorothiazide. After 12 weeks of treatment in both groups, a significant blood pressure improvement was seen in patients taking the combined medication as compared to amlodipine alone (-9.9±11.4 mmHg vs -3.7±8.9 mmHg; P<0.02) [98]. On a separate study, Yamamoto *et al.* (2012) examined the possible differences between combination therapies of ARBs with CCBs or diuretics on salt-loaded stroke-prone spontaneously hypertensive rats (SHRSP). He found that olmesartan in presence of azelnidipine provide better vascular protection in improving hypertension than do olmesartan and hydrochlorothiazide despite that both combinations provide a comparable blood pressure lowering effect [99]. Recent breakthroughs have successfully shown that ARB is able to prevent salt-sensitive and renal oxidation stress in Type 2 Diabetes patients hypertension, with or without comorbidity [100]. Beside reducing blood pressure, it can directly prevent organ damage caused by hypertension complication.

CONCLUSION

Increasing results from epidemiological, experimental and interventional studies have shown the emergence of a special hypertensive group: the salt-sensitive hypertension. Although the exact mechanism remains inconclusive, most of the evidence suggests that they share similar pathogenesis as essential hypertension, with an emphasize on genetic variability. Perhaps in the near future, salt-sensitivity trait can be a determinant for early diagnosis of hypertension, as well as an indicator for personalized treatment approach to achieve optimal blood pressure control in this population.

ACKNOWLEDGEMENT

This research was supported by Fundamental Research Grant Scheme (FRGS) from the Ministry of Higher Education of Malaysia and Malaysia Society of Hypertension.

REFERENCES

[1] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003;289(19):2560-71.
[2] Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2224-60.
[3] Murray CJ, Lopez AD. Measuring the global burden of disease. The New England journal of medicine 2013;369(5):448-57.

[4] WHO. World Health Statistic 2016: Monitoring Health for the SDGs: World Health Organization;2016.
[5] Cohen JD. Hypertension epidemiology and economic burden: refining risk assessment to lower costs. Managed care 2009;18(10):51-8.
[6] WHO. World Health Statistic 2015. 2015.
[7] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. The Lancet 2005;365(9455):217-23.
[8] Intersalt CRG. INTERSALT: an international study of electrolyte excretion and blood pressure. Result for 24hour urinary sodium and potassium excretion. BMJ 1988;297(6644):319-28.
[9] Elliott P, Stamler J, Nichols R, Dyer A, Stamler R, Kesteloot H, et al. INTERSALT Revisited: Further analyses of 24 hour sodium excretion and blood pressure within and across population. BMJ 1996;312:1249-53.
[10] Macnair A. INTERSALT data: Conclusion drawn in paper "revisiting" Intersalt data are of questionable validity. BMJ 1997;315(7106):484-91.
[11] Wood S. Cochrane Salt/Blood-Pressure Message Blasted in the Lancet. Medscape; 2011.
[12] Gray N. Lancet paper blasts Cochrane salt study 2011 [Available from: www.foodnavigator.com/Science/Lancet-paper-blasts-Cochrane-salt-study.
[13] Ritz E. The history of salt-aspects of interest to the nephrologist. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 1996;11:969-75.
[14] Cirillo M, Capasso G, Leo VAD, Santo NGD. A History of Salt. American Journal of Nephrology 1994;14(4-6):426-31.
[15] Dahl LK. Possible role of salt intake in the development of essential hypertension. 1960. Int J Epidemiol 2005;34(5):967-72.
[16] Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiol Rev 2005;85(2):679-715.
[17] de Wardener HE, MacGregor GA. Harmful effects of dietary salt in addition to hypertension. J Hum Hypertens 2002;16(4):213-23.
[18] Cirillo M, Del Giudice L, Bilancio G, Franzese MD, De Santo NG. Low salt diet and treatment of hypertension: an old story. J Nephrol 2009;22 Suppl 14:136-8.
[19] Amiri M, Kelishadi R. Can salt hypothesis explain the trends of mortality from stroke and stomach cancer in western Europe? International Journal of Preventive Medicine 2012;3(6):377-8.
[20] Goldring W, Chasis H, editors. Hypertension and hypertensive disease. New York: Commenwealth FUnd; 1944.
[21] Elliott P. Commentary: Role of salt intake in the development of high blood pressure. International Journal of Epidemiology 2005;34(5):975-8.
[22] Elliott P, Walker LL, Little MP, Blair-West JR, Shade RE, Lee DR, et al. Change in salt intake affects blood pressure of chimpanzees: implications for human populations. Circulation 2007;116(14):1563-8.
[23] Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339:b4567.
[24] He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ 2013;346:f1325.
[25] Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ 2013;346:f1326.
[26] Land MA, Webster J, Christoforou A, Johnson C, Trevena H, Hodgins F, et al. The association of knowledge, attitudes and behaviours related to salt with 24-hour urinary sodium excretion. Int J Behav Nutr Phys Act 2014;11(1):47.
[27] Mattes RD, Donnelly D. Relative contributions of dietary sodium sources. J Am Coll Nutr 1991;10(4):383-93.
[28] Dahl LK, Leitl G, Heine M. Influence of dietary potassium and sodium/potassium molar ratios on the development of salt hypertension. The Journal of experimental medicine 1972;136(2):318-30.
[29] Olesen KH. Interrelations Between Total Exchangeable Sodium, Potassium, Body Water, and Serum Sodium and Potassium Concentrations in Hyponatremic and Normonatremic Heart Disease. Circulation 1967;35(5):895-903.
[30] Warner GF, Dobson EL, Rodgers CE, Johnston ME, Pace N. The Measurement of Total "Sodium Space" and Total Body Sodium in Normal Individuals and in Patients with Cardiac Edema. Circulation 1952;5(6):915-9.
[31] Patel S. Sodium balance-an integrated physiological model and novel approach. Saudi J Kidney Dis Transpl 2009;20(4):560-9.
[32] Blaustein MP. The interrelationship between sodium and calcium fluxes across cell membranes 1974;70:33-82.
[33] Simpson FO. Sodium Intake, Body Sodium, and Sodium Excretion. The Lancet 1988;332(8601):25-9.
[34] Franco V, Oparil S. Salt sensitivity, a determinant of blood pressure, cardiovascular disease and survival. J Am Coll Nutr 2006;25(3 Suppl):247S-55S.

[35] Elliott P. Commentary: Role of salt in the development of high blood pressure. International journal of epidemiology 2005;34: 975-8.
[36] Dahl LK, Heine M, Tassinari L. Role of Genetic Factors in Susceptibility to Experimental Hypertension due to Chronic Excess Salt Ingestion. Nature 1962;194(4827):480-2.
[37] Weinberger MH. Salt Sensitivity of Blood Pressure in Humans. Hypertension 1996;27(3):481-90.
[38] Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. The American Journal of Medicine 1978;64(2):193-8.
[39] Luft FC, Rankin LI, Bloch R, Weyman AE, Willis LR, Murray RH, et al. Cardiovascular and humoral responses to extremes of sodium intake in normal black and white men. Circulation 1979;60(3):697-706.
[40] Sullivan JM. Salt sensitivity. Definition, conception, methodology, and long-term issues. Hypertension 1991;17(1 Suppl): I61-8.
[41] Peters RM, Flack JM. Salt sensitivity and hypertension in african american: implications for cardiovascular disease. Medscape 2000; 15(4).
[42] Campese VM. Salt sensitivity in hypertension. Renal and cardiovascular implications. Hypertension 1994;23(4):531-50.
[43] Weinberger MH, S. FN, E. FS, Weinberger M. Salt sensitivity, pulse pressure and death in normal and hypertension humans. Hypertension 2001;37(2 Pt 2):429-32.
[44] Frohlich ED. The salt conundrum: a hypothesis. Hypertension 2007;50(1):161-6.
[45] Dahl LK, Heine M, Thompson K. Genetic influence of renal homografts on the blood pressure of rats from different strains. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine 1972;140(3):852-6.
[46] Dahl LK, Heine M, Thompson K. Genetic influence of the kidneys on blood pressure. Evidence from chronic renal homografts in rats with opposite predispositions to hypertension. Circulation research 1974;34(1):94-101.
[47] Dahl LK, Heine M. Primary role of renal homografts in setting chronic blood pressure levels in rats. Circulation research 1975;36(6):692-6.
[48] Rodriguez-Iturbe B, Vaziri ND. Salt-sensitive hypertension--update on novel findings. Nephrol Dial Transplant 2007;22(4):992-5.
[49] Guyton A. Blood pressure control--special role of the kidneys and body fluids. Science 1991;252(5014):1813-6.
[50] Bachmann S, Bostanjoglo M, Schmitt R, Ellison DH. Sodium transport-related proteins in the mammalian distal nephron - distribution, ontogeny and functional aspects. Anat Embryol (Berl) 1999;200(5):447-68.
[51] Blaustein MP, Zhang J, Chen L, Hamilton BP. How does salt retention raise blood pressure? Am J Physiol Regul Integr Comp Physiol 2006;290(3): R514-23.
[52] Thomson SC, Bachmann S, Bostanjoglo M, Ecelbarger CA, Peterson OW, Schwartz D, et al. Temporal adjustment of the juxtaglomerular apparatus during sustained inhibition of proximal reabsorption. The Journal of clinical investigation 1999;104(8):1149-58.
[53] Wilcox CS, Welch WJ, Murad F, Gross SS, Taylor G, Levi R, et al. Nitric oxide synthase in macula densa regulates glomerular capillary pressure. Proceedings of the National Academy of Sciences of the United States of America 1992;89(24):11993-7.
[54] Tan DY, Meng S, Manning RD, Jr. Role of neuronal nitric oxide synthase in Dahl salt-sensitive hypertension. Hypertension 1999;33(1 Pt 2):456-61.
[55] Wang X, Chandrasheka K, Wang L, Lai EY, Wei J, Zhang G, et al. Inhibition of Nitric Oxide Synthase 1 Induces Salt-Sensitive Hypertension in Nitric Oxide Synthase 1α Knockout and Wild-Type Mice Hypertension 2016;67:792-9.
[56] Lu Y, Wei J, Stec DE, Roman RJ, Ge Y, Cheng L, et al. Macula Densa Nitric Oxide Synthase 1beta Protects against Salt-Sensitive Hypertension. Journal of the American Society of Nephrology : JASN. 2015.
[57] Lu D, Fu Y, Lopez-Ruiz A, Zhang R, Juncos R, Liu H, et al. Salt-sensitive splice variant of nNOS expressed in the macula densa cells. American journal of physiology Renal physiology 2010;298(6): F1465-71.
[58] Atlas SA. The renin-angiotensin aldosterone system: Pathophysiological role and pharmacologic inhibition. J Manag Care Pharm 2007;13(8):9-20.
[59] Ritz E. Salt and hypertension. Nephrology 2010;15 Suppl 2:49-52.
[60] Thomson SC, Deng A, Wead L, Richter K, Blantz RC, Vallon V. An unexpected role for angiotensin II in the link between dietary salt and proximal reabsorption. The Journal of clinical investigation 2006;116(4):1110-6.
[61] Ando K, Fujita T. Pathophysiology of salt sensitivity hypertension. Annals of Medicine 2012;44(sup1): S119-S26.
[62] Makhanova N, Hagaman J, Kim HS, Smithies O. Salt-sensitive blood pressure in mice with increased expression of aldosterone synthase. Hypertension 2008;51(1):134-40.
[63] Fujita T. Mechanism of salt-sensitive hypertension: focus on adrenal and sympathetic nervous systems. J Am Soc Nephrol 2014;25(6):1148-55.

[64] Nagase M, Matsui H, Shibata S, Gotoda T, Fujita T. Salt-induced nephropathy in obese spontaneously hypertensive rats via paradoxical activation of the mineralocorticoid receptor: role of oxidative stress. Hypertension 2007;50(5):877-83.
[65] DiBona GF. Nervous Kidney: Interaction Between Renal Sympathetic Nerves and the Renin-Angiotensin System in the Control of Renal Function. Hypertension 2000;36(6):1083-8.
[66] Campese VM, Romoff MS, Levitan D, Saglikes Y, Friedler RM, Massry SG. Abnormal relationship between sodium intake and sympathetic nervous system activity in salt-sensitive patients with essential hypertension. Kidney Int 1982;21(2):371-8.
[67] Grisk O. Interactions between the sympathetic nervous system and the kidneys in arterial hypertension. Cardiovascular Research 2004;61(2):238-46.
[68] Sowers J, Zemel M, Zemel P, Beck F, Walsh M, Zawada E. Salt sensitive in blacks: salt intake and natriuresis substances. Hypertension 1988;12(5):485-90.
[69] Gill JR, Jr., Grossman E, Goldstein DS. High urinary dopa and low urinary dopamine-to-dopa ratio in salt-sensitive hypertension. Hypertension 1991;18(5):614-21.
[70] Joossens JV, Geboers J. Salt and hypertension. Preventive medicine 1983;12(1):53-9.
[71] Luft FC, Miller JZ, Grim CE, Fineberg NS, Christian JC, Daugherty SA, et al. Salt sensitivity and resistance of blood pressure. Age and race as factors in physiological responses. Hypertension 1991;17(1 Suppl):I102-8.
[72] Drenjancevic-Peric I, Jelakovic B, Lombard JH, Kunert MP, Kibel A, Gros M. High-salt diet and hypertension: focus on the renin-angiotensin system. Kidney & blood pressure research 2011;34(1):1-11.
[73] Rampal L, Rampal S, Azhar MZ, Rahman AR. Prevalence, awareness, treatment and control of hypertension in Malaysia: a national study of 16,440 subjects Public Health. 2008;122(1):11-8.
[74] Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. Hypertension 1991;18(1):67-71.
[75] Hall WD. A rational approach to the treatment of hypertension in special populations. Am Fam Physician 1999;60(1):156-62.
[76] Satterfield S, Cutler JA, Langford HG, Applegate WB, Borhani NO, Brittain E, et al. Trials of hypertension prevention. Phase I design. Annals of epidemiology 1991;1(5):455-71.
[77] Kumanyika S, Hebert PR, Cutler JA, Lesser VI, Sugars CP, Steffen-Batey L, et al. Feasibility and efficacy of sodium reducton in the Trials of Hypertension Prevention, Phase 1. Hypertension 1993;22(4):502-12.
[78] Klemmer P, Grim CE, Luft FC. Who and what drove Walter Kempner? The rice diet revisited. Hypertension 2014;64(4):684-8.
[79] Sacks FM, Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, et al. A dietary approach to prevent hypertension: a review of the Dietary Approaches to Stop Hypertension (DASH) Study. Clinical cardiology 1999;22(7 Suppl):III6-10.
[80] Svetkey LP, Simons-Morton D, Vollmer WM, Appel LJ, Conlin PR, Ryan DH, et al. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. Archives of internal medicine 1999;159(3):285-93.
[81] Conlin PR, Chow D, Miller ER, Svetkey LP, Lin PH, Harsha DW, et al. The effect of dietary patterns on blood pressure control in hypertensive patients: Results from the dietary approaches to stop hypertension (DASH) trial. American journal of hypertension 2000;13(9):949-55.
[82] Roush GC, Sica DA. Diuretics for Hypertension: A Review and Update. American journal of hypertension 2016;29(10):1130-7.
[83] Ogihara T. Treatment with antihypertensive drugs. Hypertension Research 2009;32(1):33-9.
[84] Yasutake K, Horita N, Umeki Y, Misumi Y, Murata Y, Kajiyama T, et al. Self-management of salt intake: clinical significance of urinary salt excretion estimated using a self-monitoring device. Hypertension research : official journal of the Japanese Society of Hypertension 2016;39(3):127-32.
[85] Grossman E, Verdecchia P, Shamiss A, Angeli F, Reboldi G. Diuretic treatment of hypertension. Diabetes Care 2011;34 Suppl 2(Suppl 2):S313-9.
[86] Pasty B, Smith N, Siscovick D, Koepsell T, Weiss N, Heckbert S, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA 1997;277(9):739-45.
[87] Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289(19):2534-44.
[88] Klungel OH, Heckbert SR, Longstreth WT, Jr., Furberg CD, Kaplan RC, Smith NL, et al. Antihypertensive drug therapies and the risk of ischemic stroke. Archives of internal medicine 2001;161(1):37-43.
[89] Grossman E, Verdecchia P, Shamiss A, Angeli F, Reboldi G. Diuretic treatment of hypertension. Diabetes Care 2011;34 Suppl 2:S313-9.
[90] Weir MR, Hall PS, Behrens MT, Flack JM. Salt and Blood Pressure Responses to Calcium

Antagonism in Hypertensive Patients. Hypertension 1997;30(3):422-7.
[91] Khan JM, Beevers DG. Management of hypertension in ethnic minorities. Heart 2005;91(8):1105-9.
[92] Gibbs CR, Beevers DG, Lip GY. The management of hypertensive disease in black patients. QJM: monthly journal of the Association of Physicians 1999;92(4):187-92.
[93] Brown NJ, Vaughan DE. Angiotensin-Converting Enzyme Inhibitors. Circulation 1998;97(14):1411-20.
[94] Weir MR, Chrysant SG, McCarron DA, Canossa-Terris M, Cohen JD, Gunter PA, et al. Influence of race and dietary salt on the antihypertensive efficacy of an angiotensin-converting enzyme inhibitor or a calcium channel antagonist in salt-sensitive hypertensives. Hypertension 1998;31(5):1088-96.
[95] Fliser D, Nowack R, Wolf G, Ritz E. Differential effects of ACE inhibitors and vasodilators on renal function curve in patients with primary hypertension. Blood pressure 1993;2(4):296-300.
[96] Sweitzer NK. What is an angiotensin converting enzyme inhibitor? Circulation. 2003;108(3):e16-8.
[97] Endo S, Mori T, Yoneki Y, Nakamichi T, Hosoya T, Ogawa S, et al. Blockade of angiotensin II type-1 receptor increases salt sensitivity in Sprague-Dawley rats. Hypertension research: official journal of the Japanese Society of Hypertensio 2009;32(6):513-9.
[98] Ando K, Isshiki M, Takahashi K, effect ONEod, Safety of combination therapy with T, low-dose hydrochlorothiazide Study G. Effect of switching from amlodipine to combination therapy with telmisartan and low-dose hydrochlorothiazide. Hypertension research: official journal of the Japanese Society of Hypertension 2009;32(9):748-52.
[99] Yamamoto E, Kataoka K, Dong YF, Koibuchi N, Toyama K, Sueta D, et al. Calcium channel blockers, more than diuretics, enhance vascular protective effects of angiotensin receptor blockers in salt-loaded hypertensive rats. PloS on. 2012;7(6):e39162.
[100] Imanishi M, Okada N, Konishi Y, Morikawa T, Maeda I, Kitabayashi C, et al. Angiotensin II receptor blockade reduces salt sensitivity of blood pressure through restoration of renal nitric oxide synthesis in patients with diabetic nephropathy. Journal of the renin-angiotensin-aldosterone system : JRAA. 2013;14(1):67-73.