Salt Sensitivity in Hypertension

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INTRODUCTION

Salt and Sodium has been intensely studied for its role in human physiology and impact on human health. In particular, excessive dietary salt consumption over an extended period of time has been associated with Hypertension apart from other adverse health effects. Salt chemically is defined as any combination of an acid and base resulting in formation of an ionic compound (examples KCl, KBr, NaSO4, etc.). Common edible salt is composed of sodium chloride NaCl (table salt) is the ionic combination of the cation (Na+) and anion (Cl-). Salt is found naturally in seawater (around 3%), in mineral deposits (halite) and in natural bodies of water (lakes, streams). Salt can be mined from underground deposits, either by rock salt mining or vacuum evaporation. It can be evaporated from seawater (sea salt, fleur de sel) or other bodies of water. Sodium is necessary for life for osmo-regulation, maintaining "water balance" and nerve transduction and other biological functions. Human body contains about 250 grams of salt (3 or 4 full salt shakers).

The human body has evolved to balance salt intake with need through means such as the renin-angiotensin system. The well-known effect of sodium on blood pressure can be explained by comparing blood to a solution with its salinity changed by ingested salt. Artery walls are analogous to a selectively permeable membrane, and they allow solutes, including sodium and chloride, to pass through (or not), depending on osmosis. When salt is ingested, it is dissolved in the blood as two separate ions :- Na+ and Cl−. The water potential in blood will decrease due to the increase solutes, and blood osmotic pressure will increase. While the kidney reacts to excrete excess sodium and chloride in the body, water retention causes blood pressure to increase.

HISTORY OF SALT

Salt is essential for human life, and saltiness is one of the basic human tastes. The tissues of animals contain larger quantities of salt than do plant tissues. Salt is one of the oldest and most ubiquitous food seasonings, and salting is an important method of food preservation. Salt has been used in foods throughout and before history for more than 8000 years. It has had politically and economically important place in human history. Salt was scarce in most areas until recently and important as a traded commodity also used as currency, in fact the world "salary" comes from salt. The word "salary" comes from the Latin word for salt because the Roman Legions were sometimes paid in salt, which was quite literally worth its weight in gold. In Britain, the suffix "-wich" in a place name means it was once a source of salt, as in Sandwich and Norwich. The Natron Valley was a key region that supported the Egyptian Empireto its north, because it supplied it with a kind of salt that came to be called by its name, natron. There is more salt in animal tissues such as meat, blood and milk, than there is in plant tissues. Nomads who subsist on their flocks and herds do not eat salt with their food, but agriculturalists, feeding mainly on cereals and vegetable matter, need to supplement their diet with salt. With the spread of civilization, salt became one of the world's main trading commodities. Some of the earliest evidence of salt processing dates to around 8,000 years ago, when people living in an area in what is now known as the country of Romania were boiling spring water to extract the salts; a salt-works in China dates to approximately the same period. Salt was prized by the ancient Hebrews, the Greeks, the Romans, the Byzantines, the Hittites and the Egyptians. Salt became an important article of trade and was transported by boat across the Mediterranean Sea, along specially built salt roads, and across the Sahara in camel caravans. The scarcity and universal need for salt has led nations to go to war over salt and use it to raise tax revenues. Salt is also used in religious ceremonies and has other cultural significance.

Salt and Sodium

The terms salt and sodium are often used synonymously, although on a weight basis salt comprises 40% sodium and 60% chloride. Table 1 indicates an overview of different units.8

Sodium is the principal cation in extracellular fluid in the body. In healthy individuals, almost 100% of ingested sodium is absorbed during digestion. Sodium and chloride are the chemical components of common table salt; however, sodium can be found in other forms. Sodium is found naturally in a variety of foods, such as milk, meat and shellfish etc. It is often found in high

Table 1: Comparable amounts of sodium (in mg and mmol) and salt (in g)		
Sodium (mg)	Sodium (mmol)	Salt* (g)
400	17	1
2000	87	5
4000	174	10

*a teaspoon of salt contains approximately 6 g salt

Table 2: Selected scientific reviews/reports on salt and health		
Review / reports	Year	Main recommendation
Scientific Advisory Committee on Nutrition, UK	2003	Reduce the mean population salt intake to 6 g/day
Diet, Nutrition and the Prevention of Chronic Diseases: report of a Joint WHO/FAO Expert Consultation	2003	Salt consumption of <5 g/day while ensuring that the salt is iodized
Institute of Medicine (IOM). Dietary Reference Intakes: Water, Potassium, Sodium Chloride, and Sulfate	2004	Set 3.75 g/day as an adequate intake, and 5.8 g/day as the upper tolerable intake level for most adults
World Health Organization (WHO) Forum on Reducing Salt Intake in Populations	2006	Salt consumption of <5 g/day
Institute of Medicine (IOM). A Population-Based Policy and Systems Change Approach to Prevent and Control Hypertension	2010	Salt consumption of 5.75 g/day or less
American Heart Association (AHA) Presidential Advisory	2011, 2012	Salt consumption of 3.75 g/day or less

amounts in processed foods such as breads, crackers, processed meats, snack foods, condiments

Data from around the world suggest that the population average sodium consumption is well above the minimal physiological needs, and in many countries is above the value recommended by the 2002 Joint World Health Organization/Food and Agriculture Organization of the United Nations (WHO/ FAO) Expert Consultation of 2 g sodium/day (equivalent to 5 g salt/day). Increased sodium consumption is associated with increased blood pressure, whereas lower sodium consumption appears to decrease blood pressure in adults.

SALT AND HUMAN HEALTH

The relationship between dietary salt intake and the development of hypertension has been the subject of continuing debate for decades. Despite abundant epidemiological, experimental, and interventional observations demonstrating an association between salt intake and blood pressure, skepticism still remains regarding how a high salt intake can be mechanistically linked to an increase in blood pressure. This skepticism is partly due to the heterogeneity in the blood pressure responses to increases in salt intake in humans. Our inability to explain why salt raises blood pressure in some individuals described as 'salt sensitive', but not in others, termed as 'salt resistant', has hampered the development of a comprehensive theory as to how a high salt intake causes high blood pressure in salt sensitive subjects. Extensive studies have been conducted to identify the pathophysiological mechanisms responsible for the heterogeneity of responses to increased.

The DASH-Sodium study was a sequel to the original DASH (Dietary Approaches to Stop Hypertension) study. Both studies were designed and conducted by the National Heart, Lung, and Blood Institute in the United States, each involving a large, randomized sample. While the original study was designed to test the effects of several varying nutrients on blood pressure, DASH-Sodium varies only in salt content in the diet. Participants were pre-hypertensive or at stage 1 hypertension, and either ate a DASH-Diet or a diet reflecting an "average American Diet". During the intervention phase, participants ate their assigned diets containing three distinct levels of sodium in random order. Their blood pressure is monitored during the control period, and at all three intervention phases. The study concluded that the effect of a reduced dietary sodium intake alone on blood pressure is substantial, and that the largest decrease in blood pressure occurred in those eating the DASH eating plan at the lowest sodium level (1,500 milligrams per day). However, this study is especially significant because participants in both the control and DASH diet group showed lowered blood pressure with decreased sodium alone. In agreement with studies regarding salt sensitivity, participants of African descent showed high reductions in blood pressure.

Excess Dietary Salt Intake and Health: The Evidence.

Numerous authoritative scientific reviews that have critically examined this association have confirmed the harmful health impact of excess salt consumption, particularly on cardiovascular health, and unequivocally recommended salt reduction (Table 2).

A number of randomized controlled trials (RCTs) have concluded that decreased sodium intake relative to usual or higher intake results in lowered blood pressure in adults with or without hypertension. A review concerning advice to reduce sodium consumption concluded that intensive behaviour-change interventions targeting decreasing sodium WHO| Guideline 6 Sodium intake for adults and children. There is little disagreement that decreased sodium intake decreases blood pressure, but there is some concern that it might also lead to adverse effects in health. Decreased sodium intake results in reduced blood volume and thus activates the renin–angiotensin–aldosterone and sympathetic nervous systems (indicated by increased adrenaline and noradrenaline), which
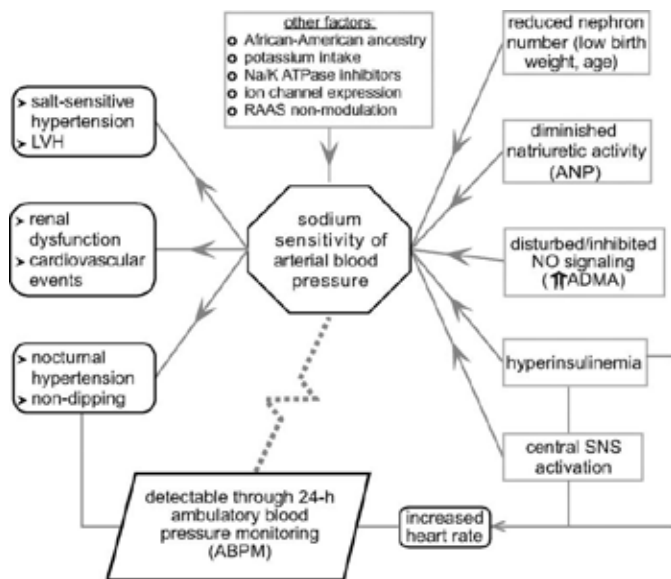
Fig. 1: Causes and consequences of salt sensitivity of blood pressure and their relation to ABPM. ANP- atrial natriuretic peptide; ADMA- asymmetrical dimethylarginine; SNS- sympathetic nervous system; RAAS- renin-angiotensin-aldosterone system; LVH- left ventricular hypertrophy

help to control blood volume. Likewise, a reduction in blood volume without a concurrent reduction in blood lipids can lead to an increased concentration of lipids in the blood. A systematic review reported an increase in renin, aldosterone, adrenaline and noradrenaline, total cholesterol and triglyceride with reduced sodium. However, the changes in blood lipids and catecholamine levels were transient and no longer present after 4 weeks of reduced sodium intake. Although the changes in renin and aldosterone levels persisted with longer term reduced sodium intake, the importance of these changes is uncertain. An increased risk of cardiovascular morbidity and mortality with increased renin or aldosterone level has been reported , but the evidence is not conclusive. Unlike blood pressure, a change in these hormones is not currently recognized as a reliable biomarker for future risk. intake successfully reduced blood pressure in adults with or without hypertension. However, the reductions in sodium intake and in blood pressure were modest, and the authors concluded that environmental changes (e.g. reduction of sodium in processed foods) would facilitate a greater reduction in sodium consumption and, therefore, have a greater impact on blood pressure.

SALT SENSITIVITY

The simplest definition of salt sensitivity of blood pressure (SSBP) states that it is a physiological trait present in rodents and other mammals, including humans, by which the blood pressure (BP) of some members of the population exhibits changes parallel to changes in salt intake. In animals, the trait has been inbred such that the salt-sensitive (SS) ones will sustain increases in BP with salt loading and decreases with salt depletion, whereas the salt resistant (SR) ones will not. In humans, the trait is normally distributed; therefore, the distinction between

SS and SR members of the population has been made by choosing an arbitrary magnitude of the salt-induced change in BP to define the groups. Regardless of possible causation by abnormalities of sodium handling, the SS phenotype is not usually characterized by alterations in salt balance (eg, impaired natriuresis or expanded plasma volume) but rather by a hypertensive response to maintain it. In an unselected population, SSBP is a continuous, normally distributed quantitative trait. As with any other trait with these characteristics, there is the issue of whether population members with the largest and smallest quantities of the trait represent the randomness of its distribution or are qualitatively different from the population at large. The Gaussian distribution of population BP is probably the result of a random mixture of pro-hypertensive and antihypertensive genes and genetic variants in a heterogeneous population interacting with environmental factors (eg, diet), physiological characteristics (eg, aging), and clinical features (eg, renal function). Research on SSBP in humans is more complex than that in animal rodent strains. The reason is that methodological issues such as random error in BP measurements and physiological issues such as the multiple sources for BP variability may confound the assessment of the BP responses to salt loading or salt depletion. Therefore, defining an individual as SS or SR depends on the selection of arbitrarily chosen cut offs for the magnitude of the BP changes. Environmental factors substantially affect whatever the genetic component may be for SSBP in humans. Additionally, despite the unquestionable influence of environmental factors in the determination of SSBP in humans, estimates of its heritability have been as high as 74% in blacks and 50% in Chinese subjects, both higher than those for hypertension. However we do not have evidence base whether the Asian Indian subjects have heritability like the Chinese or African American populations and is now an area we are investigating. An important issue is the clinical significance of the SSBP phenotype. There was increasing understanding that it represents an abnormality. The reasons were that it contradicts the basic physiological tenet that salt balance can be maintained by natriuretic and anti-natriuretic systems independently of BP, it occurs less frequently than salt resistance in normal subjects, and is associated with several forms of human and experimental hypertension.

Mechanisms of salt sensitivity are complex

They may include low birth weight with reduced nephron number, subtle renal injury and inflammation, nonmodulation of the renin-angiotensin-aldosterone axis and ouabain-like activity (Na /K -ATPase inhibition), changes in potassium intake, and expression of ion channels and supporting cellular skeleton, activation of macrophages by hypertonic interstitial environment, changes in nitric oxide signaling and presence of endogenous inhibitors, diminished atrial and other natriuretic peptides, aberrant renal prostanoid production, central activation of the sympathetic nervous system, among other candidates by the hyperinsulinemia

frequently present in lean hypertensive subjects. However, in numerous studies, salt sensitivity with high-salt diet were linked to higher nocturnal blood pressure (or lesser nighttime blood pressure decrease), recognizable only by ambulatory blood pressure monitoring (ABPM) and independently predicting adverse outcome in hypertensive patients.6 Thus, knowledge of a given patient's salt sensitivity is important for diagnostic, prognostic, and therapeutic reasons.

Studies of salt sensitivity in rats were pioneered by Dahl, inspired by ecological and epidemiological studies of the association of salt intake with human hypertension. Dahl et al selected Sprague-Dawley rats with the highest BP response to a high-salt diet (facilitated by triiodothyronine administration) and mated them with equally responsive siblings. After few generations, an SS strain with a consistent hypertensive response to a high-salt diet was created. Contrary to common belief, this was not a pure inbred strain because its descendants were also outbred with other SS Sprague-Dawley rats as a result of breeding problems and small litters. Additionally, Sprague-Dawley rats without a hypertensive response to a high-salt diet were inbred to produce the SR strain. From the creation of these strains and the demonstration that a donor SS kidney transplanted into an SR rat conferred SSBP to the recipient (and vice versa), a major role for a renal abnormality was hypothesized as the factor determining the phenotype. Later, Rapp and Dene developed the fully inbred DS/Jr and DR/Jr strains that have subsequently been used by most researchers. The original SS and subsequent DS/Jr rats developed fulminant hypertension when exposed to a high salt (8%) diet and died by the age of 8 weeks. They had a plethora of vascular lesions, renal fibrosis, and cardiac hypertrophy. Several investigators reported a variety of physiological abnormalities contributing to hypertension in DS/Jr rats, among them differences in cellular ion transport and concentration, enhanced sympathetic activity and blunted baroreflexes, reduced renal medullary blood flow, disturbed balance between vasoconstrictors and vasodilators with a special role for nitric oxide (NO), enhanced oxidative stress, and activated Rac1 GTPase mineralocorticoid receptor interaction.

Research into the possible physiological mechanisms determining SSBP has been driven mostly by a conceptual framework derived from the work of Guyton and co-workers. The major tenet of such framework is that one or many mechanisms that normally regulate the adaptation of the cardiovascular system to a salt load must be impaired in SSBP. This somehow leads to the need for the whole animal to raise BP to excrete the salt load via pressure natriuresis. The result is that an SS animal or human being will be able to maintain a normal salt balance at the expense of developing hypertension, the main feature of SSBP. Obviously, the putative defect can involve a variety of mechanisms. Activation of a natriuretic system required to excrete a salt load (eg, natriuretic peptides, renal eicosanoids) may be impaired, or conversely, lack of physiological suppression of an

anti-natriuretic system in response to a salt load (eg, ineralocorticoid or renal transport activity) might be the culprit. Evidence for a genetic basis of salt sensitivity has come from heritability estimates in family studies. Miller et al examined the change in BP between random-sodium and low sodium diets among white US families and found a higher correlation in monozygotic pairs compared with sibling pairs: 0.72 for systolic BP (SBP), 0.62 for diastolic BP (DBP), and 0.68 for MAP in monozygotic twins compared with 0.50, 0.33, and 0.36, respectively, for siblings. Svetkey et al used an established inpatient protocol253 to examine the change in BP between intravenous sodium loading and furosemide induced volume depletion in black US families and found evidence of heritability, although effects of variable family sizes contributed to variation in estimates. Additional evidence was provided by the description of an association of salt sensitivity with haptoglobin phenotypes. The BP response to a change in salt (sodium chloride) intake is not uniform. Different types of study designs have been used to identify subgroups of the population whose BP response to salt is greater (or lesser) than other subgroup responses. Studies include small, brief challenge studies, feeding trials, and meta-analyses of trials. Factors that might influence the BP response to salt include sex, age, adiposity, race-ethnicity, and clinical conditions (hypertension, diabetes mellitus, and chronic kidney disease). For several factors, evidence is insufficient to make strong conclusions because individual studies were not designed to test the effects of salt reduction simultaneously in a comparator group. For example, a few trials have tested the effects of salt reduction in patients with diabetes mellitus, but none tested the effects concurrently in patients without diabetes mellitus. Additionally, most meta-analyses that aggregate published data across studies rather than analyzing individual-level data are poorly suited to identify subgroups that are SS because of potential residual confounding. In contrast, in some studies, the effects of salt were examined in both sexes, in blacks (versus whites), across the age span in adults, and over a broad range of BPs.

In summary, a strong and consistent body of evidence has documented that on average blacks compared with whites have a greater BP response to a change in salt intake and that this finding is independent of baseline BP level. Likewise, individuals with hypertension have a greater BP response to a change in salt than individuals without hypertension, and older individuals have a greater BP response than younger adults. The effects of salt reduction depend on concurrent diet. The effects of salt on BP are greater in the setting of a low-potassium intake and in the setting of poor-quality diet compared with the DASH diet. A less consistent body of evidence suggests that women might be more SS than men and that overweight individuals are more SS than normal-weight individuals. The effects of salt reduction in Asians and in individuals with diabetes mellitus or chronic kidney disease have been tested in few studies, in which salt reduction lowered BP. However, the absence of comparator

groups precludes strong statements about whether these groups are more SS than corresponding groups without the factor. Current methods for determining SSBP are labor intensive and therefore costly; thus, they are rarely if ever undertaken outside the clinical research arena. Two areas of research seeking easily obtainable surrogate markers for SSBP have developed recently, one based on analysis of BPs and heart rates from ambulatory monitors and the other based on excretion of proximal tubular cells or renal exosomes. A group of Italian researchers hypothesized that characteristics in a 24-hour ABPM would reflect SSBP in individuals on habitual salt intake. Other investigators had measured beat-by-beat BP and pulse rate variability in 34 essential hypertensive subjects studied during 1 week of low- and high salt diets and determined by sophisticated spectral analysis methods that SSBP was associated with lesser baroreflex sensitivity and higher pulse interval power. In other words, pulse rate and SSBP increased in parallel in their SS patients but were unaffected by salt intake in SR individuals. Continued research on hemodynamic characteristics that are surrogates of SSBP such as those conducted with ABPM techniques may conceivably provide a biomarker, particularly with incorporation of predictive variables into multivariate models that achieve high sensitivity and specificity compared with direct measurement of SSBP with currently accepted techniques. Additionally, an easily obtained biomarker from urine samples might be developed from continued research on properties of urine renal tubular cells or exosomes. Emerging novel knowledge about the storage of sodium in tissue compartments and the study of possible differences in such storage between SS and SR animals or humans, coupled with the ability to use magnetic resonance imaging techniques to measure such storage, may also lead to the development of a radiological marker for the SSBP phenotype.

Almost five decades ago, Guyton and Coleman proposed that whenever arterial pressure is elevated, pressure natriuresis enhances the excretion of sodium and water until blood volume is reduced sufficiently to return arterial pressure to control values. According to this hypothesis, hypertension can develop only when something impairs the excretory ability of sodium in the kidney. However, recent studies suggest that nonosmotic salt accumulation in the skin interstitium and the endothelial dysfunction which might be caused by the deterioration of vascular endothelial glycocalyx layer (EGL) and the epithelial sodium channel on the endothelial luminal surface (EnNaC) also play an important role in nonosmotic storage of salt. These new concepts emphasize that sodium homeostasis and salt sensitivity seem to be related not only to the kidney malfunction but also to the endothelial dysfunction. Further investigations will be needed to assess the extent to which changes in the sodium buffering capacity of the skin interstitium and develop the treatment strategy for modulating the endothelial dysfunction.

Thus "Salt sensitivity" is estimated to be present in 51% of the hypertensive and 26% of the normotensive populations. The individual blood pressure response to salt is heterogeneous and possibly related to inherited susceptibility. Although the mechanisms underlying salt sensitivity are complex and not well understood, genetics can help to determine the blood response to salt intake.

Salt Recommendation

Salt reduction is a WHO goal globally now. A modest reduction in salt intake for 4 or more weeks causes significant and, from a population viewpoint, important falls in BP in both hypertensive and normotensive individuals, irrespective of sex and ethnic group. With salt reduction, there is a small physiological increase in plasma renin activity, aldosterone and noradrenaline. This will likely lower population BP and, thereby, reduce cardiovascular disease. WHO recommends a reduction in sodium intake to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults. WHO recommends a reduction to < 2 g/day sodium (5 g/day salt) in adults. WHO recommends a reduction in sodium intake to control blood pressure in children. These recommendations apply to all individuals, with or without hypertension (including pregnant or lactating women), except for individuals with illnesses or taking drug therapy that may lead to hyponatraemia or acute build-up of body water, or require physician-supervised diets (e.g. patients with heart failure and those with type I diabetes).

Available information indicates that most salt in India is added during cooking and/or at the table in contrast to the developed world where processed foods contribute most substantially to overall population salt intake. However, with rapidly increasing urbanization, proliferation of multinational food outlets/fast food centres, increasing availability of prepared foods, and increasing frequency of eating out, processed foods are anticipated to become a major source of salt intake.

Salt Rich Foods in India to be avoided

- Preserved foods like: Pappads, pickles, dried fish etc
- Namkeen bhujiya, dalmoth, mathri, sev, farsan chaat-pakori, french fries
- Convenience foods are high in sodium : instant foods, TV Dinners
- Salted nuts, potato chips, popcorn, salted crackers, biscuits and Crisps.
- Salted butter, and processed cheese
- Frozen foods
- Sea fish, cured meats, sausages, ham, and bacon
- Instant cooked cereals and commercial salad dressings
- Pastries, cakes, and ice creams

TIPS TO REDUCE SALT IN DIET

- For seasoning of foods, herbs, spices, lemon, lime, vinegar or salt-free seasoning blends make a better choice than table salt.

- In rice and other cereal preparations like roti, poori, do not mix salt. Avoid the use of salted rice, salted porridge, and other salted cereal mixes.

- Avoid packaged mixes, canned soups, or broths—they generally have a high sodium content.

- Use fresh vegetables. Avoid the use of canned vegetables as they contain salt preservatives.

- Substitute fruits, salad, and fresh vegetables for salted snack foods.

- Limit the use of foods packed in brine such as pickles, pickled vegetables, and olives.

- Use little or no sauces: avoid tomato ketchup, soy sauce, MSG, mustard sauce, and *chutney.*

- Use fresh poultry, fish and lean meat, rather than the canned, smoked or processed types.

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