Indian Heart Journal xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Review Article

Salt sensitivity and its implication in clinical practice

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ARTICLE INFO

Article history:
Received 21 June 2017
Accepted 10 October 2017
Available online xxx

Keywords:
Hypertension
Salt sensitivity
Patho-physiological mechanisms
Azilsartan

ABSTRACT

Hypertension (HTN) is a complex multi-factorial disease and is considered one of the foremost modifiable risk factors for stroke, heart failure, ischemic heart disease and renal dysfunction. Over the past century, salt and its linkage to HTN and cardiovascular (CV) mortality has been the subject of intense scientific scrutiny. There is now consensus that different individuals have different susceptibilities to blood pressure (BP)-raising effects of salt and this susceptiveness is called as salt sensitivity. Several renal and extra-renal mechanisms are believed to play a role. Blunted activity of the RAAS, adrenal Rac1-MR-Sgk1-NCC/ENaC pathway, renal SNS-GR-WNK4-NCC pathway, defect of membrane ion transportation, inflammation and abnormalities of Na^+/Ca^{2+} exchange have all been implicated as pathophysiological basis for salt sensitive HTN. While salt restriction is definitely beneficial recent observation suggests that treatment with Azilsartan may improve salt sensitivity by selectively reducing renal proximal tubule Na^+/H^+ exchange. This encourages the future potential benefits of recognising and therapeutically addressing the salt sensitive phenotype in humans.

Contents

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https://doi.org/10.1016/j.ihj.2017.10.006

Please cite this article in press as: S. Mishra, et al., Salt sensitivity and its implication in clinical practice, Indian Heart J (2017), https://doi.org/10.1016/j.ihj.2017.10.006

1. Introduction

Hypertension (HTN) has been attributed as one of the foremost modifiable risk factors for stroke, heart failure, ischemic heart disease and renal dysfunction.[1] Data suggests that life expectancy is reduced by approximately 5 years if HTN remains untreated.[2] Effective treatment of HTN has been one of the key achievements in last five decades in the field of Medicine. Noteworthy developments in the antihypertensive therapy have resulted in better control of blood pressure (BP) in majority of the patients with HTN. Nevertheless, despite continued research, HTN continues to be a major public health problem. Moreover, the burden of uncontrolled HTN is also increasing dramatically despite the therapeutic advances. One reason for this paradox is that HTN is a multifactorial disease with various patho-physiologic mechanisms. We undertook this comprehensive review to comprehend salt sensitivity which is one of the major factors responsible for this growing burden and to better understand the strategies required for addressing this. This review is also expected to elucidate the complex patho-physiological mechanisms of salt sensitivity.

2. Dietary salt

Meticulous physiologic regulation of the sodium levels is of critical importance for optimum efficiency of various physiological functions in the body. Dietary salt i.e. sodium chloride is essential for maintaining extracellular fluid volume and serum osmolality.[3] Any changes in the plasma concentration of sodium may be directly detrimental to plasma osmotic pressure, acid-base balance, plasma volume, interstitial fluid volumes, electrical activity of cells and cardiovascular system's response to circulating endogenous pressor agents.[4] Normal human beings can sustain the ill effects of extremely low sodium intake by conserving sodium by way of marked reduction in sodium losses in the urine and sweat. On the other hand, in case of acute or chronic salt challenges, body can quickly excrete very large salt loads without any significant changes in volume homeostasis or BP.[3]

2.1. Dietary salt and common belief

There is a common belief amongst people that too much of salt in diet will lead to increase in BP. But contrary to this belief, not everyone with high salt diet develops HTN. The effects of dietary sodium on BP vary from person to person because of their differential sensitivity to salt. Thus, those who are salt-sensitive are more likely to develop HTN than those who are resistant to salt.[5]

2.2. Dietary salt and HTN controversy

Over the past century, salt has been the subject of intense scientific research in relation to HTN and cardiovascular (CV) mortality. Association of dietary salt and HTN has been an area of continuing controversy since many decades. INTERSALT study which was a standardized, worldwide epidemiologic study of large cohort ($n = 10{,}079$) revealed no significant relationship between 24-h urinary sodium excretion and BP.[6] However, 8 years later, extrapolation of INTERSALT data suggested that reducing salt intake by 1/3rd of the current mean level would reduce BP by an average of 4/2.5 mm Hg in patients with HTN and by 2/1 mm Hg in normotensive people.[7] However, this re-analysis being an extrapolation of data has its own limitations. The fact is that different individuals have different susceptibilities to the BP-raising effects of salt.[8] While BP in the population as a whole is only modestly affected by the changes in sodium intake, some individuals in response to acute or chronic salt depletion or repletion shows large BP changes and are called as "salt sensitive".[3] Weinberger et al. showed that salt-sensitive subjects had a significantly greater increase in systolic ($p < 0.001$) and diastolic ($p < 0.001$) pressure over time than those who were salt resistant.[9]

3. What is salt sensitivity and how much is the burden?

Salt sensitivity of BP is defined as a physiological trait existing in rodents and other mammals, including humans, by which BP of some members of the population shows changes parallel to changes in salt intake.[10] In many individuals, when salt intake increases, the excess amount is excreted by the way of kidney or sweat. However, there are some individuals where this mechanism is faulty and increased salt is retained and manifests as high BP. There is an inter-individual difference in the BP response to changes in dietary sodium chloride intake which could be attributed to salt sensitivity.[11,12] Overall, salt sensitivity appears to be a major public health problem with estimated incidence of 51% in patients with HTN and 26% in normotensive people.[12]

4. Salt sensitivity and predisposing factors

Excess salt intake along with higher salt sensitivity remains one of the key risk factors for the predisposition to essential HTN. However, the BP response to a change in salt intake is not uniform. Variety of physiological, demographic, genetic and even environmental characteristics differentiate between salt sensitive and resistant population.[13] Salt sensitivity appears to be determined by genetic factors, race/ethnicity, age, gender, body mass index and diet. Associated co-morbidities e.g. HTN, diabetes, chronic kidney disease and metabolic syndrome also play a vital role.[3,10] Salt sensitivity is specifically common in older adults, African Americans, and in people with a higher level of BP or other comorbidities.[13]

Several studies have identified subgroups of the population who are salt sensitive. Black race population manifest a higher BP response to change in salt intake than Whites independent of baseline BP.[14] Similarly, data suggests that elderly people and patients with HTN have a greater BP response to a change in salt than young adults and normotensive individuals.[9,15] Furthermore, Weinberger et al. observed that BP responses of both normotensive and hypertensive subjects to salt depletion increased significantly as the age advanced with higher response in patients >30 years of age.[9] They concluded that salt sensitivity was a predictor of subsequent, age-related BP increase. Another finding of this study was that patients with HTN were more salt sensitive than normotensives, a fact that has been confirmed in numerous subsequent studies.

Please cite this article in press as: S. Mishra, et al., Salt sensitivity and its implication in clinical practice, Indian Heart J (2017), https://doi.org/10.1016/j.ihj.2017.10.006