

WORLD CONFERENCE ON CARDIOMETABOLIC  
MEDICINE

# Salt sensitivity and Hypertension (APRIL 27-28 ,MUMBAI)

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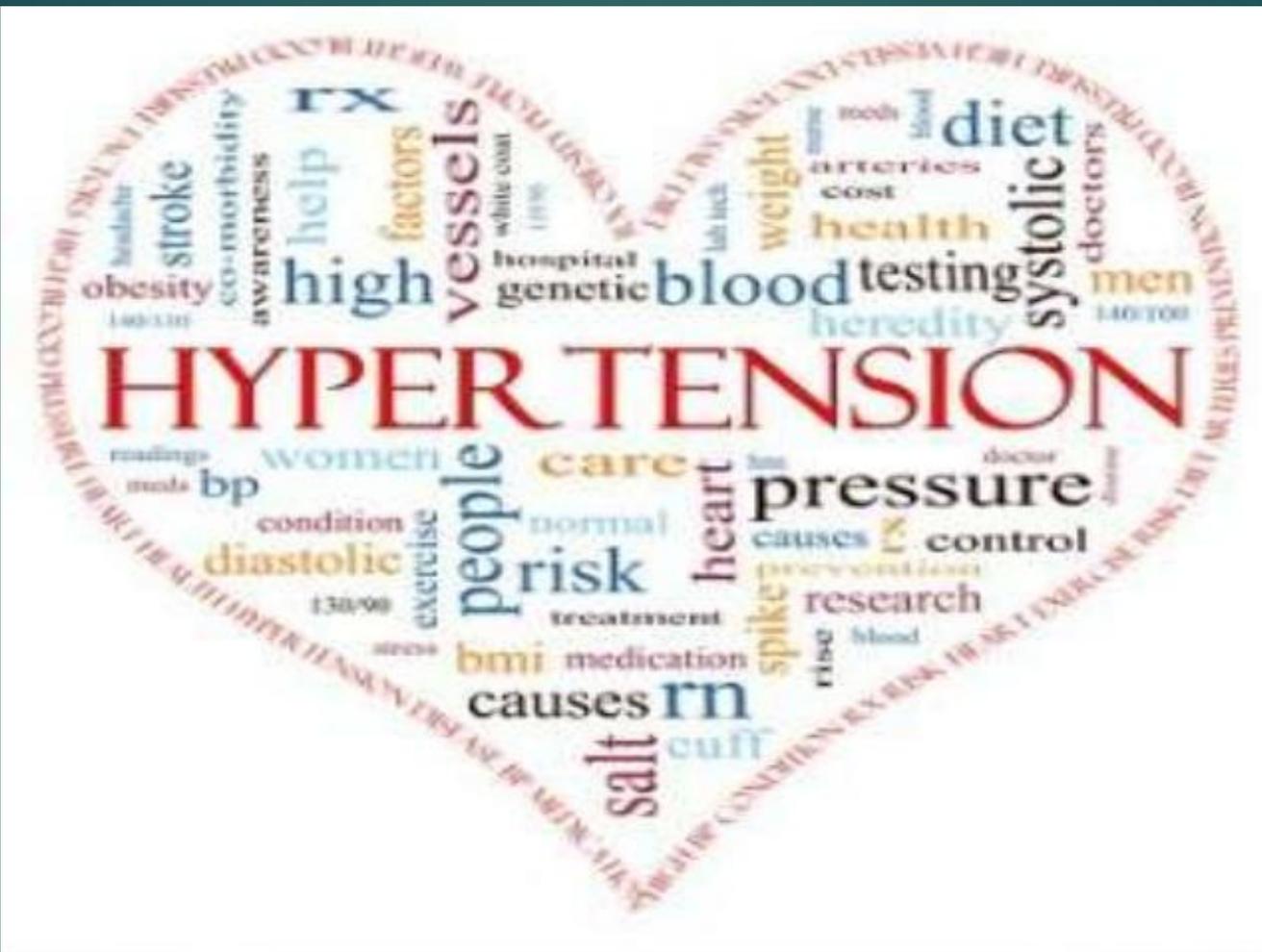
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# Introduction

- ▶ Despite continued research, HTN continues to be a major public health problem in india and the global burdon of HTN is rising
- ▶ Over the past century salt has been the subject of intense scientific reaseach linked to HTN and CV mortality
- ▶ Human body has immense capacity to adjust to the extremse of salt intake , meticulous physiological regulation of Na level is of critical importance for optimal efficacy of body functions.

# Definition

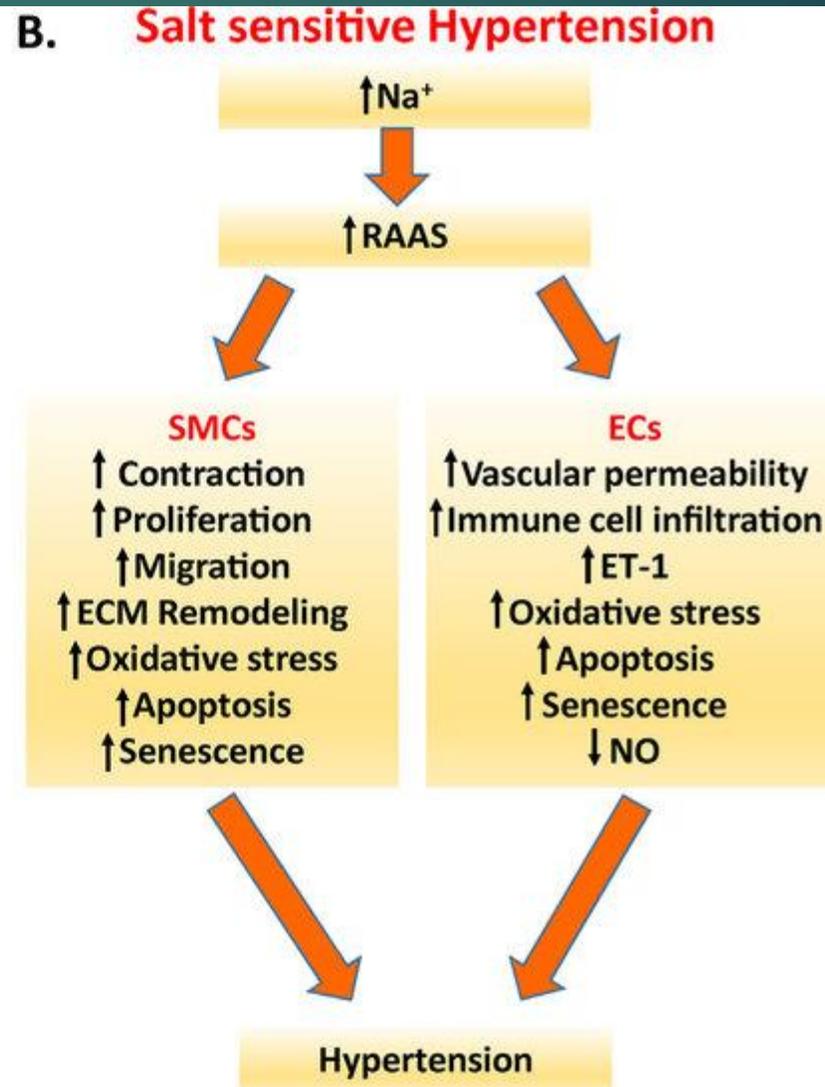
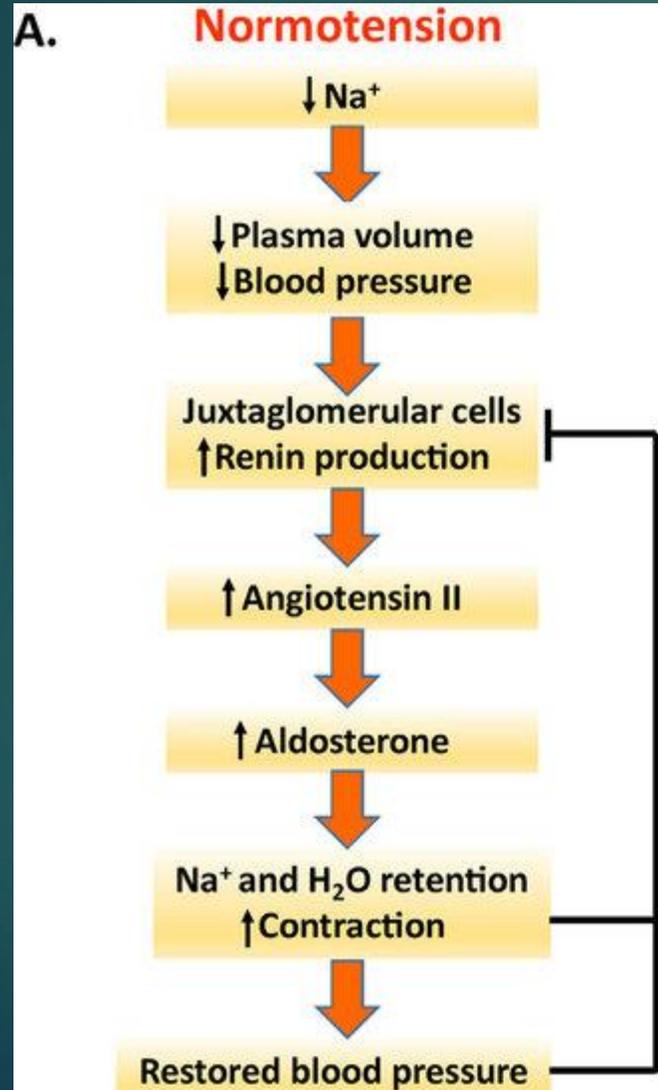
- ▶ A common belief prevails that too much salt in diet will lead to increase in BP. Not everyone with high salt diet may develop HTN . The effects of dietary Na on BP vary from person to person because of their differential SENSITIVITY to salt .
- ▶ Those who are salt sensitive are more likely to develop HTN than those who are resistance to salt.
- ▶ Salt sensitivity of BP is defined as physiological trait in humans by which BP of some persons shows changes parallel to the changes in salt intake. When the mechanism to excrete the excess amount of salt through kidney and sweat is faulty, increase salt is retained and manifest as high BP.
- ▶ Salt sensitivity is determined by genetic factors , race and ethnicity, age, gender, body mass index and diet .Co morbidities- HTN,DM,CKD,MS also tend to play a role
- ▶ Black race, elderly manifest higher BP response . Salt sensitivity was predictor of subsequent age BP rise, patient with HTN were more salt sensitive than normotensive. females obese Asians low potassium intake and poor quality diet compared to DASH

# Demographic variables

- ▶ Demographic affect the relation between salt intake and BP in salt sensitive individual.
- ▶ Screening for salt sensitivity – defined as an increase in sitting DBP of 5mm of hg when the patient change from a low salt (50-80 mmol/day) to a high salt (200 to 250 mmol/day) diet.
- ▶ Total patients screen 1916
- ▶ 624 found salt (%) sensitive .
- ▶ 59% -white , 25%-black , 15%- Hispanic .
- ▶ Age 55 or younger -56%. Men -50%, BMI of 27 or less -31%
- ▶ There were no significant differences in BP change in response to low or high salt diets by race,age, gender, BMI.
- ▶ Salt intake was co related with damage to three target organs ( cardia,renal,cerebrovascular), but the correlation was patially independent of BP\*
- ▶ Study from Japan -156 HTN patients assessed for Na sensitivity and followed an average of 7 years – Na sensitive patients had a two fold increase in CVA.
- ▶ Despite the power of drug treatment of HTN , dietary salt restriction remains important. Recomendation: moderate salt restriction to less than 100 mmol/day(6gm of salt or 2.4 gm of Na), at least for those who are likely to be salt sensitive.
- ▶ \*Chrysant SG et al.Arch Intern Med

Messerli FH. Arch Intern Med 1997

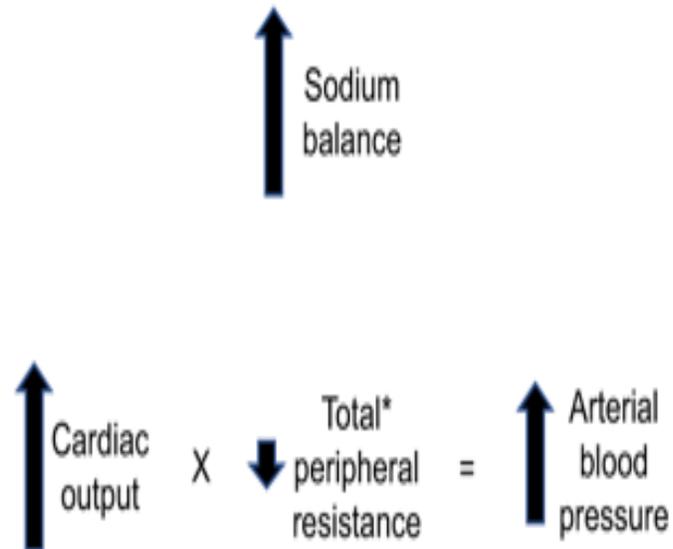
Weinberger MH .Arch Intern Med



## - The Vasodysfunction Theory -

### Salt sensitive subjects

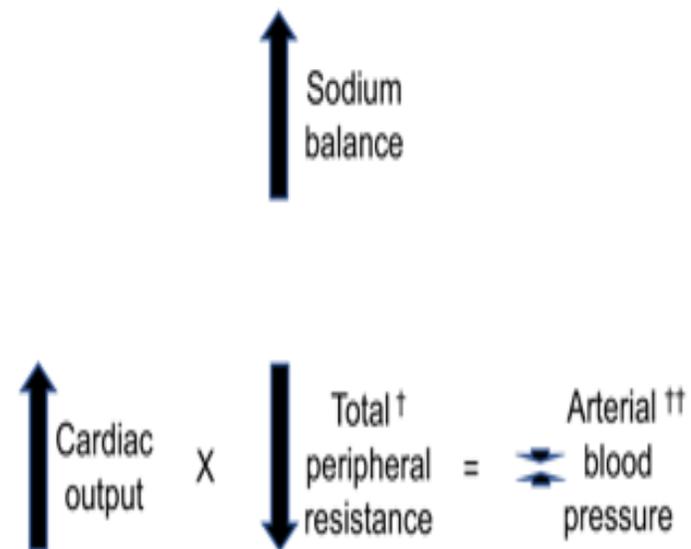
Usual responses to acute salt loading



\* Includes increased renal vascular resistance

### Salt resistant normotensive controls

Usual responses to acute salt loading

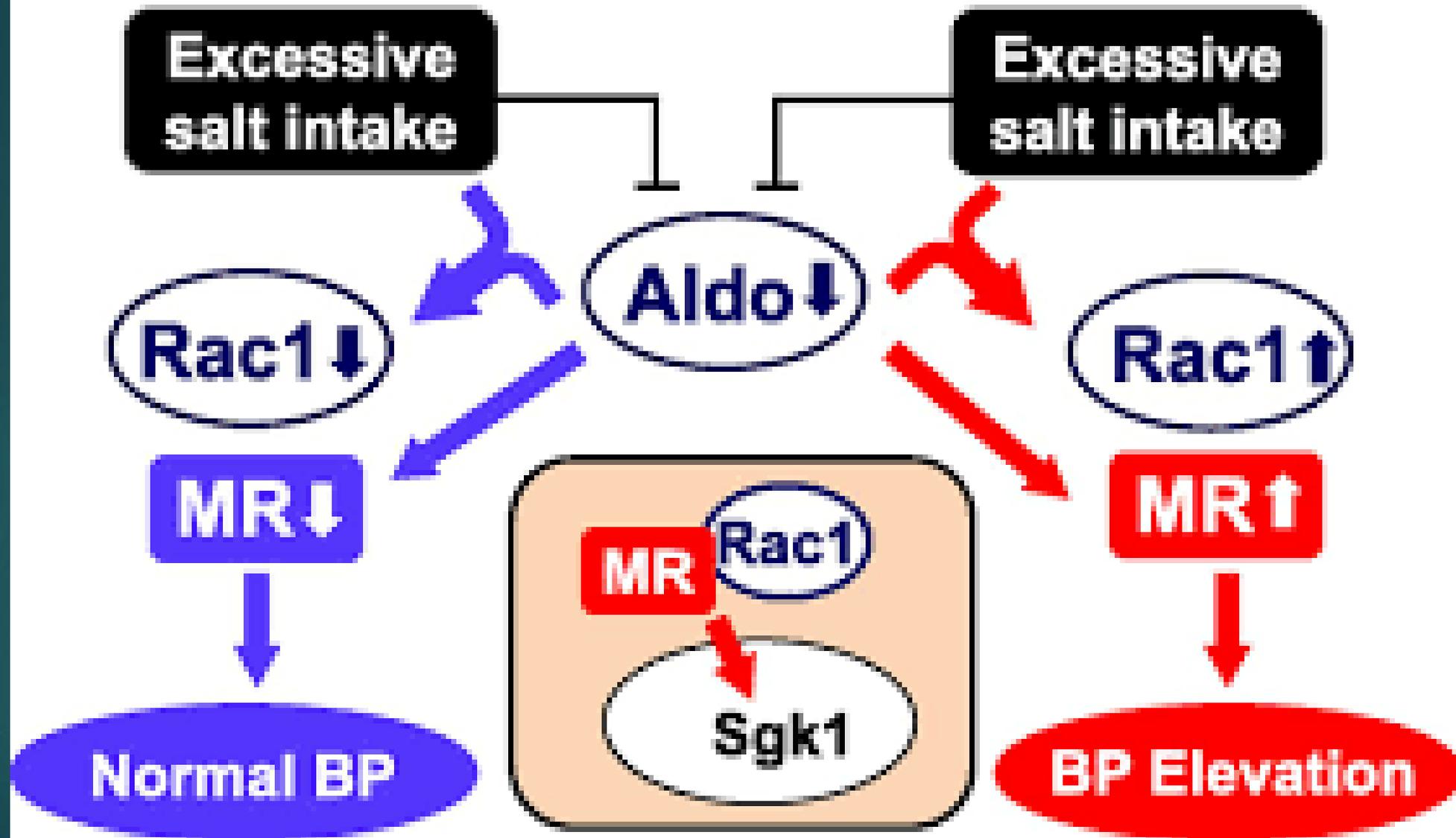


† Includes decreased renal vascular resistance

†† Blood pressure may decrease within the first several days of salt loading

## Salt-resistant

## Salt-sensitive



# The Na factor

- ▶ Normal human being can sustain the ill effects of poor Na intake by conserving Na through marked reduction in Na losses in the urine and sweat.
- ▶ Equally, in case of acute or chronic salt challenges, body can quickly excrete very large salt loads without any significant changes in volume, homeostasis or blood pressure.
- ▶ NOT all hypertensives are salt sensitive and NOT all salt sensitive people are hypertensive.
- ▶ Normotensive salt sensitive individual are at high cardiovascular risk and lower survival rate ,the BP eventually rises later in life with high salt diet.
- ▶ Beyond HTN : Salt sensitivity is an independent risk factor for cardiovascular disease, beyond the detrimental prognosis conferred by HTN alone .

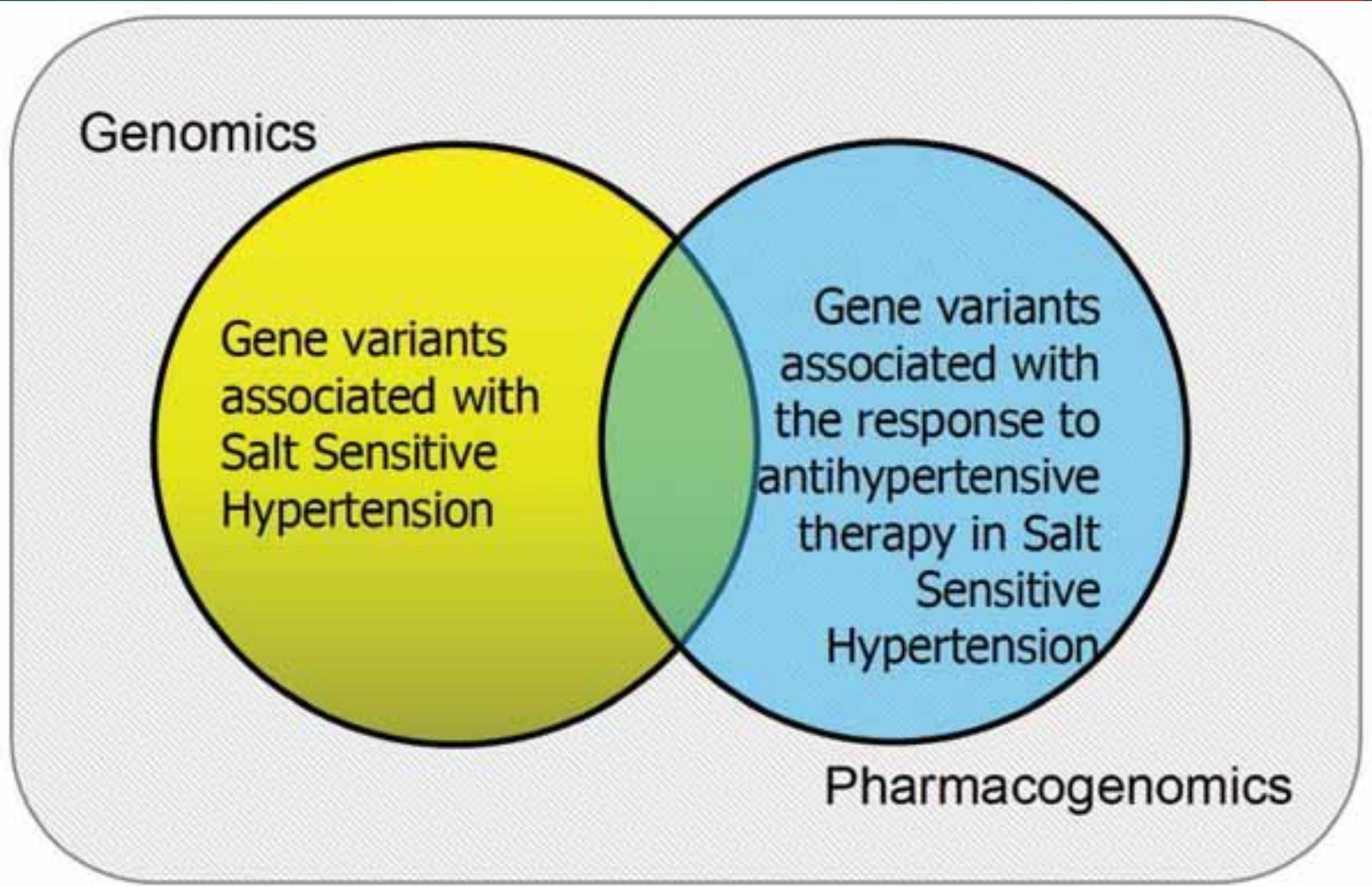


Genomics

Gene variants associated with Salt Sensitive Hypertension

Gene variants associated with the response to antihypertensive therapy in Salt Sensitive Hypertension

Pharmacogenomics



## Salt sensitive hypertension

- Heterogeneous blood pressure (BP) response to increase dietary salt
- Salt sensitive hypertension is a frequent finding in the cohort of essential hypertensive patients (40-45%) and it is associated to CV risk.
- Although salt sensitivity is well established in experimental and human hypertension, the pathophysiological mechanisms leading to such individual susceptibility remain unresolved

# Differentiation and measurement

- ▶ There is no evidence based method for measurement of salt sensitive BP (SSBP) in humans. Different individual have differential susceptibilities to BP raising effects of salt and this susceptibility is called as salt sensitivity
- ▶ Consensus exist on sequential low salt diet and high salt diet protocol to identify an individual as salt sensitive or salt resistant\*.

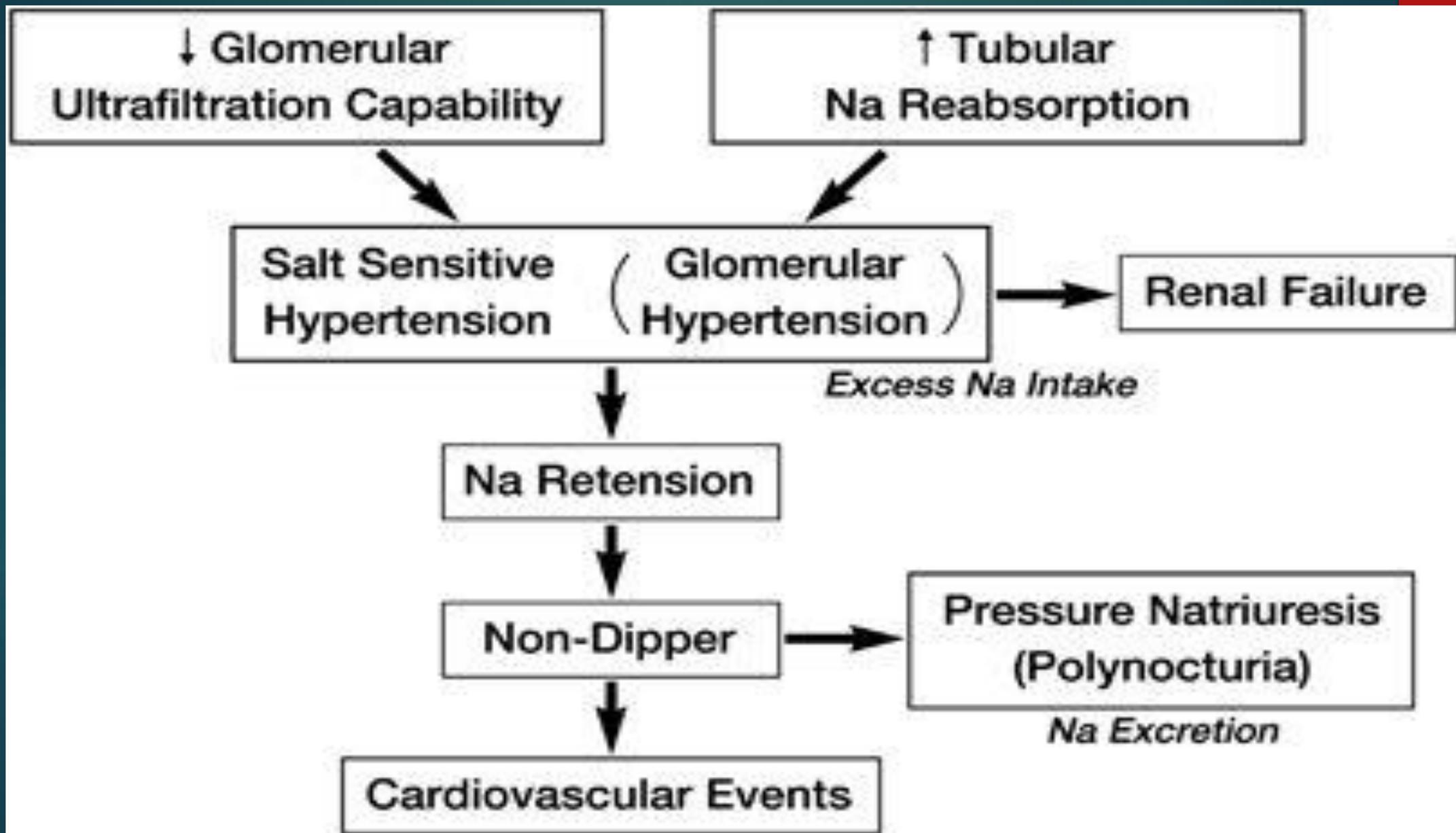
The recommended method is to give low Na diet (600mg of table salt per day) followed by high Na diet (12gm of table salt per day) for 4 days. At the end of high Na period, if the BP increases by at least 5% from base line the person can be labelled as salt sensitive\*\*

- ▶ Technique of salt loading with acute intravenous saline challenges after achieving Na and volume depletion through salt reduction along with diuretic treatment\*\*\* – subjects decrease in MAP > 10mm hg after Na and volume depletion are considered as salt sensitive and those with decrease less than 5 mm hg are salt resistance\*\*\*
- ▶ \*Elijovich F, Weinberger MH et al salt sensitivity of BP scientific statement of AHA Hypertension 2016: 68:e7-e46
- ▶ \*\*Sullivan JM .salt sensitivity definition conception ,methodology ,and long term issues. Hypertension 1991;17:161-168
- ▶ \*\*\*Weinberger MH , miller JZ Luft FC et al .definitions and characteristics of Na sensitivity BP resistance , hypertension 1986;8:1127-134.

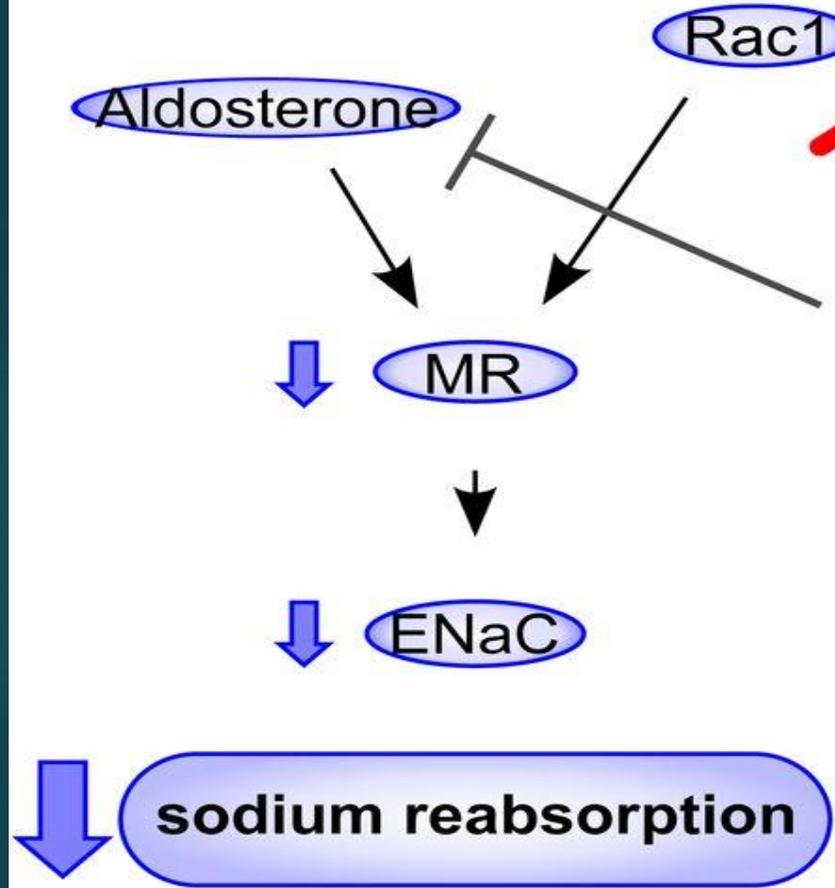
# Mechanism

- ▶ The underlying mechanisms that promote salt sensitivity are complex and range from genetic to environmental influences.
- ▶ The phenotype of salt sensitivity is heterogenous with multiple mechanisms that potentially linked high salt intake to increase in BP.
- ▶ Guyton and Colman hypothesis proposed that HTN can develop only when something impairs the excretory ability of Na in the kidney .
- ▶ Renal and extra renal mechanisms that may play a role:

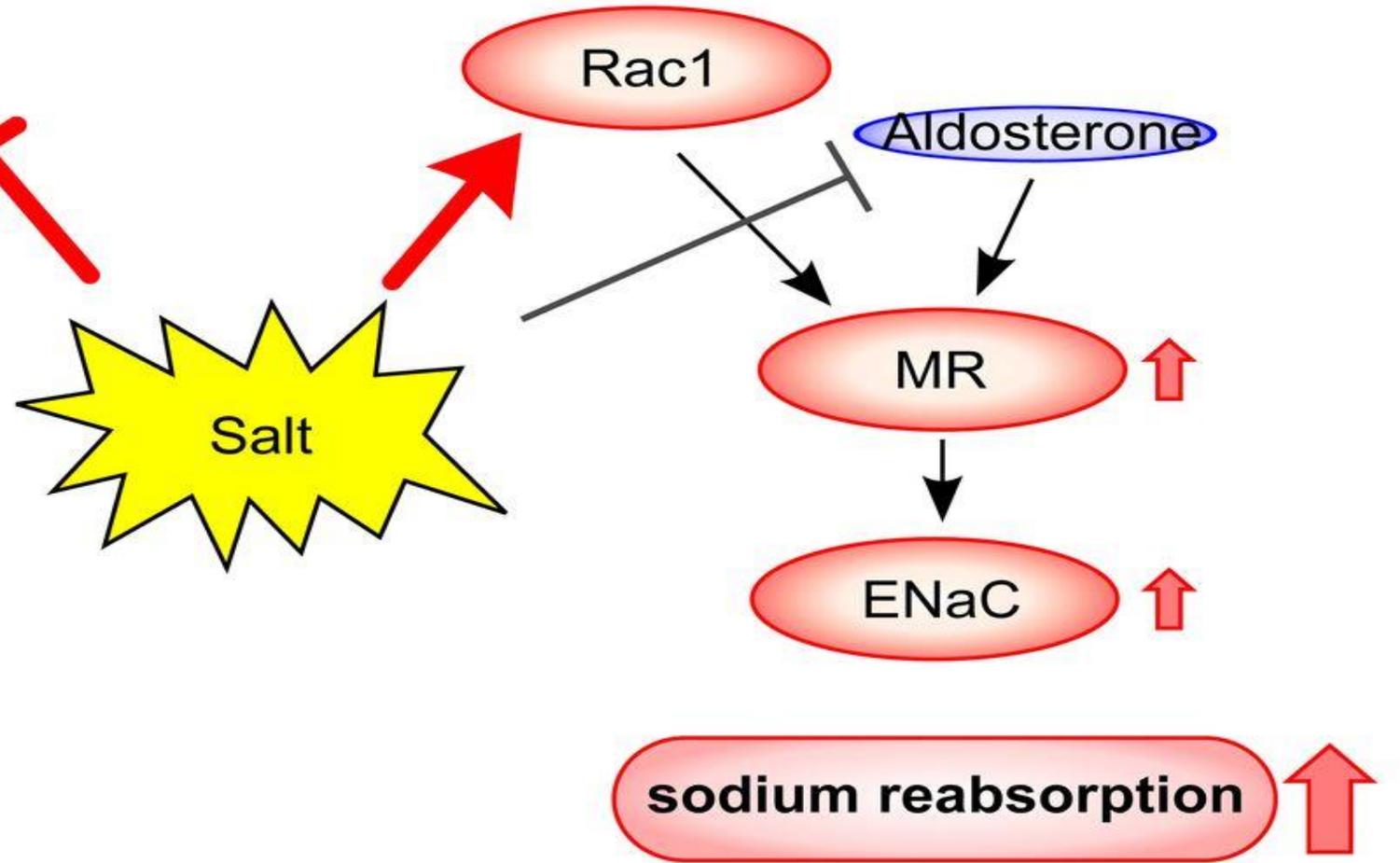
Blunted activity of the RAAS, adrenal Rac1-MR-Sgk1-NCC/ENaC pathway , renal SNS-GR-WNK4-NCC pathway, defect of membrane ion transportation, inflammation and abnormalities of Na<sup>+</sup>, Ca<sup>++</sup> exchange, nuclear mineralocorticoid and glucocorticoids receptors have all been implicated as pathophysiological basis of salt sensitive HTN and salt – induced cardiorenal injury.



## Salt-resistant phenotype



## Salt-sensitive phenotype



→ activation    —| suppression

# Recent studies and paradigm shift

- ▶ Recent studies have added some insights and questions to the classic view of salt sensitivity; two novel pathways have suggested molecular mechanisms of renal handling in salt sensitive hypertension.
- ▶ Non osmotic salt accumulation in the skin interstitium and the *endothelial dysfunction*\* which might be caused by deterioration of vascular endothelial glycocalyx layer (EGL) and the epithelial Na channel on the endothelial luminal surface (EnNaC) may also play an important role in nonosmotic storage of salt .
- ▶ These new concepts emphasize that Na homeostasis and salt sensitivity seem to be related not only to the kidney malfunction but also to the endothelial dysfunction.
- ▶ \* Choy HY1, Park HC1, Ha SK 1 , Electrolyte Blood press .2015 jun;13(1):

## The Recommended Guidelines

- The 2005 Dietary Guidelines for Americans recommends
  - Consume less than 2,300 mg of sodium per day.
  - Except individuals with hypertension, blacks and middle aged and older adults – these groups aim to consume no more than 1,500 mg of sodium per day (and meet the potassium recommendation with food).
- Average American daily intake of sodium is 3,375 mg
- Sodium consumption has increased over the past few decades

## Reducing Salt, Reducing Mortality

- By decreasing the population intake of sodium from 3,500mg/day to 1,500mg/day it's estimated there would be a 30% decrease in hypertension prevalence
- Reducing sodium levels in packaged foods and restaurant foods by half would save about 150,000 American lives per year from fatal heart attacks and strokes



# Salt sensitivity matters

- ▶ On a positive note\* it is conceivable to prevent or delay the subsequent age-related increase in BP, and thus the future development of HTN and thereby reduce the risk of CV events and mortality in salt sensitive subjects .
- ▶ “non-dipper” HTN patients with blunted nocturnal decline in BP are more likely to exhibit salt sensitivity and disturbances in the circadian rhythm of BP.
- ▶ Salt sensitive patients are prone not only CV events but also renal events.
- ▶ More patients with resistance HTN were found to be salt sensitive.
- ▶ Strong relationship between increase salt sensitivity and insulin resistance\*\* leading to metabolic syndrome and CV disease, relevant to india, where the salt consumption is among the highest large population.
- ▶ Salt sensitivity has also been attributed to end organ damage- LVH and proteinuria.

▶ \*Mishra S, Ingole S, Jain R, salt sensitivity and its implication in clinical practice, Indian heart journal .2018, 70:556-564

▶ \*\*Ganda OP, Fonseca VA, salt sensitivity insulin resistance and public health india. Endocr pract 2010.16(6), 940-944.

*THANK YOU*

