Salt-sensitivity

Israeli Society of Hypertension
Kibbutz Hagoshrim
Salt-Sensitivity

• Increased salt intake raises BP, increasing thereby the risk to CVS and renal disease

• Increased salt-intake may have direct effects (unrelated to HTN) on:
  – Stroke
  – LVH
  – Proteinuria
  – Progression of renal disease
  – Obesity
  – Renal stones
  – Osteoporosis
  – Stomach cancer
Salt-sensitive Hypertension
Definition of salt-sensitivity

- An increase in BP in response to increased salt ingestion
Definition of salt-sensitivity

- A decrease in BP when salt intake is reduced
Operational definitions of salt-sensitivity

• Some define salt-sensitivity as a change in pressure (i.e., >3 mm Hg increase or decrease).

• Others define it as a proportional change (i.e., a 10% change in pressure).
Operational definitions of salt-sensitivity

- A variety of protocols have been used to determine salt-sensitivity.
  - Rapid i.v. salt loading followed by furosemide-induced volume depletion
  - Manipulations of the amount of dietary salt intake
Is there such a thing as “Salt-sensitivity” in terms of BP?
Evidence for the existence of salt-sensitivity
In animal models
Experimental models of salt-sensitivity
Experimental models of salt-sensitivity

The Sabra Rat Model

SBH/y and SBN/y
Welcome to the Israeli Rat Genome Center

http://www.irgc.co.il
Experimental models of salt-sensitivity

The Dahl Rat Model
SS and SR
Evidence in animal models
Sabra model

Systolic BP

Weeks on 8% NaCl in chow and 0.1% NaCl in water

mmHg

SBH/y M
SBH/y F
SBN/y M
SBN/y F
Evidence in animal models
Dahl model

[Graph showing systolic blood pressure over time with different groups and statistical notations]
Evidence for the existence of salt-sensitivity in humans
Observational studies

• Habitual ingestion of high levels of dietary salt (NaCl) is associated with increased BP.
• As the aggregate level of salt ingestion increases, so does the prevalence of HTN.
• In populations whose dietary salt intake is low, hypertension is rare, and the trend of rising BP with advancing age does not occur.
Clinical trials

- DASH-sodium study

Are all humans created equal?

Do we all respond similarly to salt-loading?
Population heterogeneity in salt-sensitivity

- In a given population, there is significant heterogeneity among individuals in BP sensitivity to sodium intake
Population heterogeneity in salt-sensitivity

Salt-sensitive individuals

Salt-resistant individuals
Prevalence of salt-sensitive hypertension

Up to 75% of the population may experience BP changes in response to sodium intake
The Salt-Sensitivity Phenotype


- Increasing sodium chloride intake in SS patients leads to volume expansion and HTN
- Increasing sodium intake with another anion (such as citrate) does not lead to HTN
- Increasing chloride intake with another cation (such as ammonium) does not lead to HTN
- NaCl (salt) appears to be the culprit
Variables known to affect Salt-sensitivity

- Demography
- Race
- Social elements
- Renal function
- Hormones
- Dietary habits
Age and salt-sensitivity

• There is a direct, relationship between age and salt-sensitivity.
• Salt-sensitivity usually occurs in mid-life or later (after age 45), but it has also been documented in overweight adolescents.
• Increasing salt-sensitivity is noted in older subjects.
Gender and salt-sensitivity

- Women are usually more salt-sensitive than men.
Body weight and salt-sensitivity

• Salt-sensitive subjects tend to weigh more than salt-resistant subjects.
• Weight reduction in white adolescents eliminates the sensitivity of BP to sodium.

Race and salt sensitivity

- Salt-sensitivity is more prevalent in African Americans than in Caucasians.
- Salt-sensitivity is found in 73% of all African American hypertensive patients.
- Salt-sensitivity is so prevalent that it is considered a "hallmark" of “black hypertension”.

30
Salt-sensitivity and renal insufficiency

• People with renal insufficiency are more likely to be salt-sensitive

• Salt-sensitive subjects are more likely to have altered intrarenal hemodynamics with attenuated hyperfiltration following salt-loading, increased glomerular capillary permeability, microalbuminuria and suppressed circulating renin levels.
Salt-sensitivity and renal insufficiency

- The end result is a shift in the pressure-natriuresis curve to the right, indicating that salt-sensitive persons require higher systemic pressure to effect the level of natriuresis required to maintain steady-state sodium homeostasis.
Sympathetic nervous system and salt-sensitivity

• The sympathetic nervous system may play a role in mediating salt-sensitivity.
• This is based on the findings that many salt-sensitive subjects have higher levels of NE (associated with sodium retention) and decreased levels of dopamine (which promotes sodium excretion).
Salt-sensitivity and diet beyond salt

• In the salt sensitivity – BP relationship, dietary habits beyond salt-intake are also important.
Salt sensitivity and diet beyond salt

• Salt-sensitive subjects excrete more calcium than salt-resistant subjects while on high salt diet.

• Calcium supplementation during normal dietary sodium intake is associated with significantly reduced blood pressure in salt-sensitive and in African American subjects.
Salt-sensitivity and diet beyond salt

• A low level of potassium intake is associated with increased salt intake, sodium retention, and increased blood pressure.

• Subjects with a high potassium intake appear to achieve a state of relative salt-resistance.

• It is important to note that high sodium foods are typically low in potassium
Genetic basis of salt-sensitive hypertension
Why the interest in the genetic basis of salt-sensitivity?

- May help elucidate the pathogenesis of salt-sensitivity
- May provide the basis for genetic intervention (gene therapy?) and prevention of salt-sensitivity
- May help identify biomarkers for salt-sensitivity
What is the contribution of genetics to the Salt-sensitivity phenotype?

\[ \text{Phenotype} = \text{Genotype} + \text{Environment} \]
Heritability of salt-sensitivity

• In a study of BP response to a 12-week sodium-restricted diet in white families, heritability accounted for 64% of the SBP response [Am J Epidemiol 1987; 126:822].

• Using an intravenous sodium-loading and furosemide volume depletion protocol in 20 African-American families, heritability accounted for 26-74% for SBP [Hypertension 1996; 28:854].
Heritability of salt-sensitivity

- In the GenSalt dietary feeding study in 1906 individuals, heritability was 22% for SBP and 33% for DBP [Hypertension 2007; 50:116].

- **Conclusion**: Heritability analyses support unequivocally the contribution of genetic factors to salt-sensitivity.
Salt-sensitivity

- A complex phenotype
- Polygenic and multifactorial
Genetic basis of hypertension

Gene 1: +/-
Gene 2: +/-
Gene 3: +/-

Environment

Susc. Genes

Body Mass

Susc. Genes

HTN

Sex

Age

Diet

Susc. Genes
Genetic basis of hypertension

Gene 1  Gene 2  Gene 3
+/-  +/-  +/-

Susc. Genes  Susc. Genes  Susc. Genes

Environment  Sex  Age

Body Mass  Susc. Genes

SALt
Which susceptibility genes account for salt-susceptibility?

- Salt-sensitivity genes +/-
- Salt-resistance genes +/-
- Salt-resistance and salt sensitivity genes
Necessary interaction with the environment
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<th></th>
<th>Bad genes</th>
<th>Good genes</th>
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<tr>
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<td>Sensitivity genes</td>
<td>No sensitivity genes</td>
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<tr>
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<td>NT</td>
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<td><strong>No salt</strong></td>
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<tr>
<td></td>
<td>No resistance genes</td>
<td>Resistance genes</td>
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<td>Resistance genes</td>
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<td><strong>Salt</strong></td>
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<td><strong>No salt</strong></td>
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</table>
Prevalence of salt-sensitive hypertension

Salt-sensitivity

- Present in 30% of non-hypertensive individuals
- Present in greater than 50% of hypertensive individuals
Which genes are involved in salt-sensitivity?
Whole-genome linkage studies of salt-sensitivity
Animal studies

Animal studies have reported several QTLs in chromosomes 1 and 17 linked to salt sensitivity of BP among spontaneously hypertensive rats or salt-sensitive Sabra hypertension-prone rats.


Human studies

• In the only human genome-wide linkage scan of salt-sensitivity, GenSalt detected strong linkage signals on chromosome 2 for MAP responses to dietary sodium intervention (Unpublished manuscript).

• Follow-up of this linkage signal implicates the novel melatonin receptor 1B gene in BP salt-sensitivity.
Candidate gene studies of salt-sensitivity
icv NaCl → ↑ Dietary salt → ↑ CSF [NaCl] → ↑ Aldosterone synthesis → ↑ MR activation → ↑ ENaC activity → ↑ TEO

Rostral ventral medulla (Fast acute pathway) → ↑ PVN Ang II → ↑ AT1R activity

Catecholaminergic neurons? → ↑ AT1R activity

(Slow chronic pathway)

↑ Preganglionic nerve traffic

↑ ↑ ↑ Sympathetic activity

Salt retention

↑ Tone ↑ BP

Shift in pressure-natriuresis relationship

↑ NCX1.3, ↑ TRPC6, ↑ [Ca²⁺]e↑ (chronic)

↑ Plasma CTS (chronic)

Pituitary EO-releasing factor? ACTH? AVP?

Adrenal

Artery

Renal Na⁺ excretion

Kidney

↓ Medullary NO synthesis (chronic)
<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene</th>
<th>Chr</th>
<th>Physical position (bp)</th>
<th>Associated gene variants</th>
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Notes: 
- rs = Single nucleotide polymorphism (SNP) code.
- vD = Variants of unknown direction.
- NA = Not applicable or not available.
- G1065A = A variant that changes a glycine (G) to an aspartate (D) at position 1065.
- 27bp VNTR = Variable number tandem repeat (VNTR) sequence length variation of 27 base pairs.
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</table>
Systems in which genes have been found to be associated with salt-sensitivity

- RAAS related
- Ion and water channels, transporters, and exchangers (e.g. ENaC)
- Endothelial system (endothelin and its R)
- Intracellular messengers (e.g. GNB3, adducin)
- Sympathetic nervous system
- Natriuretic peptide system
- Kallikrein-kinin system
Genome-wide association studies (GWAS) of salt-sensitivity
Despite the critical role of genome-wide association studies (GWAS) in uncovering novel mechanisms underlying disease susceptibility, none have been conducted so far to examine the salt sensitivity phenotype.
Conclusion as to the genetic basis of salt-susceptibility

- We are still in the early phases of understanding the genetic causes of salt-sensitivity.
Why the interest in the genetic basis of salt-sensitivity?

• May help elucidate the pathogenesis of salt-sensitivity
• May provide the basis for genetic intervention (gene therapy?) and prevention of salt-sensitivity
• May help identify biomarkers for salt-sensitivity
The clinical significance of salt-sensitivity
Clinical application

- Multiple dietary sodium reduction trials, including the DASH-sodium study, indicate that sodium restriction results in reduced SBP and DBP.
- The greatest BP response to dietary sodium interventions is in older, hypertensive subjects.
Salt restriction

• Do all individuals need to be sodium restricted, or only those who are sensitive to salt?

• Can we detect in an effective way salt-sensitivity? Salt-resistance?
Current recommendations

• The U.S. Dietary Guidelines for Americans recommend eating a diet of 2300 mg of sodium a day or lower, with a recommendation of 1500 mg/day in adults who have elevated blood pressure; the 1500 mg/day is the low sodium level tested in the DASH-Sodium study.

• Is this recommendation justified?
Bad Salt

Good Salt