Genes, Diets, & Hypertension

Chou-Long Huang, MD PhD
Relationship between salt intake and hypertension

Dahl, 1960
Sensitivity to Salt-Induced Hypertension

Genetic & Environmental factors

Sensitivity to Salt-Induced Hypertension

Dietary sodium intake
Urine Blood

Epithelial Na Channel (ENaC)

Steroid Hormones:
1. Sex hormones
2. Mineralocorticoids
3. Glucocorticoids

Mineralocorticoid receptor (MR)

11-β-Hydroxysteroid dehydrogenase

Blood volume ↑

Aldosterone

Cortisol

Cortisone

11-βHSD2

Na

MR

Blood

Urine
Defense Mechanisms Against Salt-Induced Hypertension

1. Aldosterone

Na intake $\rightarrow$ Na reabsorption by kidney $\rightarrow$ Aldosterone $\rightarrow$ Circulating volume

2. Pressure-Natriuresis

Na intake $\rightarrow$ Na reabsorption by kidney $\rightarrow$ Blood pressure $\rightarrow$ Circulating volume
Sensitivity to Salt-Induced Hypertension

Genetic & Environmental factors

Sensitive

Resistant

Dietary sodium intake

BP
Genetic Factors (Diseases) That Increase Na Reabsorption

Urine

Blood

ENaC

Na

Liddle's Disease

Cortisone ← Cortisol

11-βHSD2

Cortisol

MR

Aldosterone
Liddle’s Disease

1. Autosomal-dominant disease featured by hypertension and hypokalemia (low blood potassium).

2. Occurs as a result of gain-of-function mutations of ENaC, leading to increased number of ENaC channels at the cell surface.

**Normal**

**Liddle’s Disease**

Hypertension
Patch-Clamp Recording of Ion Channels

Glass Pipette

NaCl

Cell with ENaC

NaCl

NaCl

Suction

Na

Na

pico (10^{-12}) Amp
Liddle’s Disease

Normal

Kidney

ENaC

Na

Blood

Na

Liddle’s Disease

Kidney

ENaC

Na

ENaC

Na

Hypertension

Blood

Na

Na

Na
Cell Membrane Proteins are Endocytosed and Degraded
Clathrin-dependent endocytosis

- AP-2 complex: α-adaptin, β2-adaptin, μ2-chain, σ2-chain
- Formation of clathrin-coated vesicles
- Uncoating
- Fusion
- Early endosomes
Recognition of Proteins for Clathrin-Mediated Endocytosis

1. Intracellular region contains specific amino acid sequence for recognition by AP2 or clathrin

\[ \text{NPXY} \]  
(asparagine-proline-any-tyrosine)

2. Tagging mechanism:
   Ubiquitin (Ub) is a 76 amino acid peptide that can be used to tag proteins destined for endocytosis

Nedd4-2 is a ubiquitin ligase. Nedd4-2 attaches ubiquitin (Ub) molecules to membrane proteins.
Nedd4-2 binds to intracellular region of proteins rich in amino acid proline (P) and tyrosine (Y)

Ubiquitination of membrane proteins leads to their endocytosis and degradation.
Mutations of ENaC in Liddle’s Disease Prevent Ubiquitination
Genetic Factors (Diseases) That Increase Na Reabsorption

- Urine
- Blood

- ENaC
- Na
- Liddle’s Disease
- 11-βHSD2
- Cortisone
- Cortisol
- Cortisone
- Licorice
- Conn’s Disease
- Aldosterone
- AME (Apparent Mineralcorticoid Excess)
Apparent Mineralcorticoid Excess (AME)

1. Autosomal-recessive disease

2. Occurs as result of loss-of-function mutations of $11\beta$HSD2

Liddle’s Disease

Autosomal-dominant Gain-of-function mutation

11-$\beta$HSD2

AMΕ (Apparent Mineralcorticoid Excess)
In general, loss-of-function mutations are inherited as recessive

Exceptions:

1. Haplo-insufficiency (50% of protein function is insufficient)
2. Second-hit phenomena (somatic mutation on top of inherited recessive mutation)
3. Dominant-negative effect (mutant protein antagonizes non-mutant protein function)
Sensitivity to Salt-Induced Hypertension

Genetic & Environmental factors:
- Stress
- Smoke
- Cocaine
- Potassium deficiency

BP

Dietary sodium intake

Sensitive

Resistant
Role of Dietary Potassium in Salt-Sensitive Hypertension

Dietary K Intake

Dietary sodium intake

BP
Dietary Sodium and Potassium Intake in Paleolithic vs Current Nutrition

Late paleolithic

- Sodium (meq) ~20
- Potassium (meq) ~320
- Ratio 1:16

Current

- Sodium (meq) ~150
- Potassium (meq) ~50
- Ratio 3:1

Eaton and Konner, “Paleolithic Nutrition”, NEJM, 1985
Prevalence of Hypertension Inversely Related to Potassium Intake

High Dietary Potassium Intake Suppress Salt-Induced Hypertension

24 B, 14 W healthy normotensive subjects

<table>
<thead>
<tr>
<th>Week</th>
<th>Na (15 meq)</th>
<th>Na (250 meq)</th>
<th>K (30 meq)</th>
<th>K (70 meq or 120 meq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Morris et al., Hypertension, 1999
Genetic Diseases That Increase Na Reabsorption

Gordon’s syndrome: gain-of-function mutation of WNK1 kinase

Liddle’s Disease: gain-of-function mutations of ENaC

AME: loss-of-function mutations of 11-βHSD2
Low potassium intake

![Diagram showing the effect of low potassium intake on blood pressure and sodium transport]

Blood pressure↑

High potassium intake

![Diagram showing the effect of high potassium intake on blood pressure and sodium transport]

Blood pressure↓
Mechanism of Salt-Induced Hypertension

- **Sensitive**
  - Genetic & Environmental factors
  - Stress
  - Smoke
  - Cocaine
  - Potassium deficiency

- **Resistant**

Dietary sodium intake vs. BP