Overview

- Introduction
- Mechanisms
- Diagnosis
- Clinical Relevance
Perspective of Age, Genes, and Blood pressure

- Age and gene-related increases in blood pressure provide a slope of change over time.
- This can be modified with non-pharmacologic or pharmacologic approaches.
- Earlier in life, dietary modification may prevent or delay the development of higher levels of blood pressure.
- Later in life, dietary modification may delay requirement for pharmacologic treatment, or reduce the amount of medication required to reach ideal blood pressure goals.
BP and Salt Sensitivity Increase with Age
Two important considerations

- You cannot change your age
- You cannot change your parents
Will earlier modification of the slope of change of BP alter the risk for cardiovascular disease?
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The kidney is the most important organ that keeps blood pressure normal.
Renal Regulation of Blood Pressure

- Regulation of fluid, electrolyte, and acid base balance
- Regulation of mineral balance
- Synthesis of hormones (e.g., erythropoietin, renin) and vitamins (1,25 dihydroxycholecalciferol)
- Degradation of proteins, including hormones
- Detoxification
- Excretion of waste products of metabolism
• In chronic hypertension, early afferent arteriolar constriction and later vascular smooth muscle hypertrophy (nephrosclerosis) create a tendency toward reduced renal blood flow and GFR.

• In chronic hypertension, a higher BP is required to achieve the same degree of salt and water excretion found in a normotensive (pressure-natriuresis resetting).

Angiotensin II Generation and Effects

Angiotensinogen → Angiotensin I → Angiotensin II

ACE, Renin

Angiotensin II Receptors

AT₁, AT₂

Systemic: Liver

Tissue: Heart, Brain, Kidney, Arteries

“ACE bypass pathways”

Bradykinin, Substance P, Enkephalins, Other Peptides → Inactive Fragments

SNS activation, Arteriolar constriction, Aldosterone release → Free radical generation

Thirst, Vasopressin release, Cardiac and smooth muscle hypertrophy

Essential Hypertension

Proximal tubule and medullary thick ascending limb of Henle - sites of increased sodium reabsorption in essential hypertension


- sites of $D_1$-like receptor inhibition of sodium transport

Dopamine and Renal Function

- Dopamine produced in renal tubules (high nM) from L-DOPA is not converted to norepinephrine.

- Dopamine exerts its autocrine/paracrine function by regulating tubular mechanisms.

- Circulating concentrations of dopamine (pM) are too low to stimulate its own receptors – affinity (nM).

- Dopamine administered to increase blood pressure acts on non-dopaminergic receptors (β and α-adrenergic receptors).
Renal Proximal Tubular Dopamine is Important in Preventing Salt-Sensitive Hypertension


- Renal tubules, unlike neural tissues, do not convert dopamine to norepinephrine.
Dopamine and Renal Function

- Renal tubular effects - modulated by state of sodium balance
- Endogenous dopamine - >50% of sodium excreted under conditions of moderate sodium excess
- Multiple sites of action - proximal tubule and thick ascending limb (major sites of action)
- Inhibits multiple sodium transporters/channels/pump – dopamine is multifunctional

Reactive Oxygen Species in Health and Disease

- Reactive oxygen species – is important in microdomain-specific signaling: $\text{H}_2\text{O}_2 > \text{O}_2^-$
H$_2$O$_2$, a Necessary Evil for Cell Signaling
(Rhee SG. Science. 2006;312:188)
Na-CSF ↑
Ouabain ↓
AngII ↓
HTN
Na-CSF
↓
Ouabain
↓
AngII
↓
Aldo
↓
HTN
SNA
Two Novel Mechanisms: Distal Nephron

- Two novel mechanisms that impair renal Na(+) –excreting function and result in an increase in BP

- Mineralocorticoid receptor (MR) activation in the kidney, which facilitates distal Na(+) reabsorption through epithelial Na(+) channel activation, causes salt-sensitive hypertension. Rac1 activation by salt excess causes MR stimulation

- Renospecific sympathoactivation may cause an increase in BP under considerations of salt excess. Renal beta2 adrenoceptor stimulation in the kidney leads to decreased transcription of the gene encoding WNK4, a negative regulator of Na (+) reabsorption through Na(+) –Cl (-) cotransporter in the distal convoluted tubules, resulting in salt-dependent hypertension

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Salt Sensitivity

- Salt Sensitivity (SS) of blood pressure is an inappropriate increase in blood pressure following high Na\(^+\) intake.
- Salt-Resistant (SR) individuals show an increase in mean arterial pressure (MAP) of 7mmHg or less on both high and low Na\(^+\) diets.
- SS affects 25% of the U.S. adult population and has equal morbidity/mortality (independent of blood pressure) to essential hypertension, yet it is difficult to diagnose without extensive clinical tests.
Prevalence Estimates
(Despite Lack of Agreed Upon Definition)

Hypertensives
66.9M (30.4%)

Salt-sensitive
58M (26.4%)

Hypertensive Non-salt-sensitive
35 million (16%)

Salt-sensitive Non-hypertensive
31M (14%)

Hypertensive and Salt-Sensitive
26M (11.8%)
Hypertensive and Salt-Sensitive

Hypertensives
66.9M (30.4%)  
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Hypertensive Non-salt-sensitive
35 million (16%)  
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- Despite the high incidence of salt-sensitivity it is under-diagnosed
- Current diagnosis of salt-sensitivity requires extensive protocols
  - 2 liters of saline IV followed by diuretic
  - 2 week controlled diet and 24-hour urines
- There is not general agreement regarding the optimal diagnostic protocol
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Innovation:

Renal proximal tubule cells from an individual can provide:

- Instantaneous renal physiology: phenotype of salt handling
- Instantaneous measure of renal toxicity: possibly related to too much salt in the diet

This is the forerunner of personalized medicine!
Cardiovascular Death

Hazard Ratio (95% CI)

1.0
0.8
1.4
2.2
2.6
0
2
4
6
8
10
12

Sodium Excretion (G/day)

Sodium chloride intakes above and below the range of 2.5 to 6.0 grams/day are associated with increased cardiovascular risk (Curr Hypertens Rep. 2012;14:193-201).

Adequate Intake – Upper Limit: 3.8- 5.8 – young adults, 2.08 - <5.8 older adults and elderly (Institute of Medicine, National Academy of Sciences, USA 2005)
Clinical Relevance of Salt Sensitivity

Reducing the daily sodium chloride intake by 3 G, from the estimated sodium intake of 10.4 G in adult men and 7.3 G in adult women “would save 194,000 to 392,000 quality-adjusted life years and $10-24 billion in health costs annually” (N Engl J Med. 2010;362:590-9).
Clinical Relevance of Salt Sensitivity

1. Salt sensitivity is real, but is impossible to quantify prevalence
2. Salt sensitivity increases as we age
3. The idea that lower salt intake increases risk of CVD mortality is based on evidence with significant methodologic flaws
4. There is a need to develop methods to better classify patients in a simple way which can help focus emphasis on dietary modification