Essential Hypertension—
a renal disease?

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Sodium Sensitivity Increases with Age

Major Hypotheses on Renal Etiology of Hypertension

• Genetic: Alterations in Na regulation (Lifton hypothesis)

• Congenital: Low birth weight resulting in low nephron number (Barker-Brenner hypothesis)

• Acquired Renal Injury (Goldblatt hypothesis, and our group)
The syndrome of Liddle-the ENAC mutation
Genetic Polymorphisms are Important, but there is a major Environmental Component

- Most studies suggest genetics accounts for 20-30% of hypertension variation
- Identical twins concordant for BP only 40% of time
- Does not readily explain epidemic rise in BP or rise with age
- In early hypertension sodium handling is often normal and blood volume is low
- Does not explain salt resistant hypertension
Major Hypotheses on Hypertension

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• Acquired: renal microvascular disease (Goldblatt hypothesis)
Barker-Brenner Hypothesis

- Low birth weights are associated with future hypertension (Barker et al, BMJ 1989)
- Low birth weight is associated with low nephron number (Brit J Obst Gynecol 1992)
- Low nephron number is associated with increased risk for future hypertension (Brenner et al Am J Hypertens 1988)
- Nephron number is reduced in essential hypertension patients (NEJM 2003; 348:101-8)
Barker-Brenner Hypothesis

Keller et al, NEJM 2003; 348:101-8
Problems with the Low Nephron Number Hypothesis

• Mechanism not clear--- nephrectomy does not cause hypertension (renal donors)-- appears to require time to develop

• Not evident how it can explain the epidemic increase in hypertension in last century

• Low birth weight only accounts for 20% of hypertension variation
Low birth weight is associated with chronic kidney disease only in men

Figure 2 | Odds ratios of CKD for men by birth weight: results from multivariable logistic regression, adjusted for age; race; education; insurance status; region; self-reported diabetes, hypertension, or cardiovascular disease; family history of kidney disease; and hypertension control.

Figure 3 | Odds ratios of CKD for women by birth weight: results from multivariable logistic regression, adjusted for age; race; education; insurance status; region; self-reported diabetes, hypertension, or cardiovascular disease; family history of kidney disease; and hypertension control.

Major Hypotheses on Hypertension

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Hypertension is Associated with Subtle Renal Injury

- Renal arteriolosclerosis is present in 90-98% of essential hypertension, ischemic tubular injury in 99%
  
  ((Sommers et al AJP 34:685, 1958)

- Arteriolosclerosis in the kidney correlates with BP; in other organs it does not correlate with BP
  
  (Moritz and Oldt AJP 1937; 13:679)

- Degree of arteriolosclerosis can predict the degree of BP elevation
  
  (Tracy R Semin Nephrol 1996; 16:126)
Hypotheses

Could salt-sensitivity be the consequence of acquired renal injury?
Goldblatt’s Hypothesis of Hypertension

“[My view] is that the [renal] arterial and arterial sclerosis are primary, but of unknown origin, and that … the vascular disease… produces disturbances of intrarenal hemodynamics ….that determines hypertension”

Goldblatt H.

Physiol Reviews 27:120-165, 1947
The Rebuttal of Goldblatt

- Renal microvascular disease is absent in 5-10% of biopsied cases of hypertension (Castleman and Smithwick, 1940s)
- Renal microvascular disease is worse with longer duration or more severe hypertension (Perera, 1953)
- Goldblatt had no mechanism for how renal microvascular disease would develop as a primary process
Angiotensin II Induces an Arteriolopathy

Johnson et al, Hypertension, 1992
Subtle Renal Injury Predisposes to Salt-sensitivity

Hypertension 33:1013, 1999
Subtle Renal Injury Predisposes to Salt-sensitivity

Franco et al
JASN
12:2263, 2001
Mycophenolate (MMF) Prevents Angiotensin II-Induced Salt-sensitive Hypertension

Role of the Immune System in the Salt Sensitivity Associated with Tubulointerstitial Disease

Rodriguez-Iturbe B, et al
Mechanism of Renal Vasoconstriction: Leukocytes Expressing Oxidants and Ang II

Rodriguez-Iturbe et al
Kidney Int 59:2222, 2001
Models of Hypertension

Sympathetic Nervous System
Overactivity

Model: phenylephrine infusion

Increased renin, Angiotensin
Model: ang II infusion

Toxins
Model: CSA

Aging
Model: Aging Rat

Microvascular Disease
Interstitial Inflammation

Endothelial Dysfunction
Model: L-NAME

Systemic hypoxia
Model: hypobaric

Metabolic (low K)
Model: hypokalemia

Genetic
Model: SHR, Dahl S

Sodium sensitive Hypertension
The Spontaneously Hypertensive (SHR) Rat

Develops hypertension several weeks after birth

Has a low nephron number

Also has a congenitally small afferent arterioles
Studies in the Spontaneously Hypertensive Rat (SHR)

SHR Hypertensive Rat
Narrow afferent arteriole
Low Nephron Number

WKY Normotensive Rat
Normal afferent arteriole
Normal Nephron Number

F2 Generation

Narrow afferent arteriole
Low Nephron Number

↑BP

Normal BP

Offspring of SHR RATS: BP correlates with Arteriolar Diameter, Not Nephron Number

Kidney Int 2004; 65:582-588

Acta Physiol Scand 2004; 181:397-405
Uric acid and Hypertension

“People who are subject to this high blood pressure ... frequently belong to gouty families, or have themselves suffered from the symptoms of this disease”

Frederick Mahomeded.
Lancet i:400, 1879
The Gout Epidemic

Mean uric acid (mg/dl)

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean Uric Acid (mg/dl)</th>
</tr>
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<tbody>
<tr>
<td>1920</td>
<td>3.5</td>
</tr>
<tr>
<td>1950</td>
<td>5</td>
</tr>
<tr>
<td>1960</td>
<td>5.5</td>
</tr>
<tr>
<td>1970</td>
<td>6</td>
</tr>
<tr>
<td>1980</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Uric Acid: A Product of Purine Metabolism

- Purines
- Xanthine
  - Xanthine oxidase
  - Uric Acid
  - Urate oxidase (Uricase)
  - Allantoin
  - Other mammals

Mutation

Man and Great and Lesser Apes
A Model of Mild Hyperuricemia

Normal Rat
Uric Acid (0.5-1.4 mg/dl)

Hyperuricemic Rat
Uric Acid (1.7-3.0 mg/dl)

Uricase inhibitor
Oxonic acid (OA)

Hypertension 2001;38:1101-6
Chronic Hyperuricemia Increases Blood Pressure

* LSD = 0.125% NaCl, ** p<0.05

Hypertension 2001;38:1101-6
Allopurinol Prevents BP Increase in Hyperuricemic Rats

![Graph showing the effect of different diets on systolic blood pressure over time.]

- Low Salt Diet (LSD)*
- LSD/Oxonic Acid
- LSD/OA/Allopurinol

* LSD = 0.125% NaCl, ** p<0.05

Hypertension 2001;38:1101-6
Hyperuricemia Increases Renin Expression

Mazzali et al  Hypertension 38:1101-1106, 2001
Hyperuricemia Induces Preglomerular Vascular Disease

Mazzali et al, AJP Renal Physiol 282:F991, 2002
Hyperuricemia Induces Salt-sensitivity

Watanabe S et al., Hypertension 2002; 40:355-360

Biopsy: arteriolopathy

Oxonic acid stopped
Serum Uric Acid is Elevated in newly Diagnosed Hypertension in Adolescents

Serum Uric Acid (mg/dl)

Primary Hypertension
N=64
Mean = 6.7 mg/dl

Secondary Hypertension
N=39
Mean = 4.3 mg/dl

White Coat Hypertension
N=22
Mean = 3.5 mg/dl

Controls
N=41
Mean = 3.6 mg/dl

Hypertension 42:247-252, 2003
Lowering Uric Acid Reduces SBP in Adolescents with Hypertension

In Subjects whose Uric acid was reduced to < 5 mg/dl, 86% (19/22) became normotensive versus 3% (1/30) controls

*Feig et al, JAMA. 2008;300(8):924-932*
Sugar Intake Correlates with Obesity Rate

Sugar intake per year:
- 1700: 4 lbs
- 1800: 18 lbs
- 1900: 90 lbs
- 2000: 155 lbs

Sugar and Fructose

• Sugar (sucrose) consists of a disaccharide of glucose and fructose

• Fructose is also present in honey and fruit (especially fruit juices and dried fruits)

• The introduction of high fructose corn syrup (HFCS, which is 55% fructose and 45% glucose) in 1971 has led to a marked increase in total fructose intake in the USA
Fructose Induces Metabolic Syndrome in Animals

Sugar

HFCS

Fructose

Honey, Fruits

Brain

Activates taste centers
Addicting behaviors (dopaminergic and opioid receptors)
Leptin resistance
Neurostimulant

Liver

Fatty liver
Elevated triglycerides
ATP depletion
Inflammation
Uric acid generation

Vasculature

Inflammation
Endothelial dysfunction

Kidney

Renal vasoconstriction
Glomerular hypertension
Renal injury
Renal inflammation

Adipocyte

Oxidative stress
Inflammation
Reduced adiponectin

Metabolic Syndrome

Insulin resistance
Elevated blood pressure
Abdominal obesity
Dyslipidemia
Fatty Liver
Inflammation
Oxidative stress
Endothelial dysfunction
Hyperuricemia

Type II Diabetes

End Rev 2009;30:96-116
Fructose Metabolism

Fructose $\xrightarrow{\text{Glut 5}}$ Fructose $\xrightarrow{\text{Fructokinase}}$ Fructose-1-phosphate $\xrightarrow{\text{AMP deaminase}}$ ADP $\xrightarrow{\text{AMP deaminase}}$ AMP $\xrightarrow{\text{Acyl CoA}}$ Uric acid

$\uparrow$ Acyl CoA $\downarrow$ Phosphate $\uparrow$ AMP deaminase $\downarrow$ Phosphate

Fructose Acutely Increases Serum Uric Acid

Fructose (1 g/kg body wt) increases serum uric acid within 30 minutes

Lancet 1970; 2:1310-1311
Fructose-induced Hyperuricemia causes Systemic and Glomerular Hypertension

Serum Uric acid is Increasing and correlates with the epidemic of Metabolic Syndrome

Choi et al Am J Med 2007;120:442-7

8669 Adults, NHANES III
Proposed Mechanism for Uric Acid–Mediated Hypertension

A Unified Pathway for Essential Hypertension

In absence of arteriolar disease, the increase in systemic and renal perfusion pressure relieves ischemia, causing a parallel shift in Pressure Natriuresis = Salt Resistant HTN.

In presence of arteriolar disease, the increase in systemic and renal perfusion pressure does not completely relieve ischemia, causing a right shift and change in slope of Pressure Natriuresis = Salt Sensitive HTN.

All pathways will be influenced by genetic polymorphisms involved in regulation of endothelial function, RAS, and Na reabsorption.
URIC ACID
As a factor in the causation of disease.

A contribution to the pathology of high arterial tension, headache, epilepsy, mental depression, gout, rheumatism, diabetes, Bright's disease, and other disorders.

By Alexander Haig, M.A., M.D.Oxon., F.R.C.P.

Haig Alexander, 1892
London
JA Churchill Publishers
The Rising Tide of Hypertension

% HTN

10 25.3 28.9 31.3

1939 1975 1990 2000
Arthur Guyton: Hypertension is Due to a Physiological Defect in Sodium Excretion

Hypertension Correlates with Na Intake

MacGregor GA. Hypertension 1985; 7:628-37
The Yanomamo, a No-Salt Culture

Oliver et al, Circulation, 1974
Hyperuricemia Induces Salt-sensitivity

Watanabe S et al., Hypertension 2002; 40:355-360

Biopsy

Hypertension 40:355, 2002

Uric acid dependent
Salt resistant
Renin and NO dependent
No renal structural changes

Uric acid independent
Salt sensitive
Volume dependent
Renal arteriolosclerosis

Hyperuricemia Induces Salt-sensitivity

Hypertension 40:355, 2002
MMF Lowers BP in Human Hypertension

Figure 2. Molecular Mechanisms Implicated in the Retention of Sodium and Loss of Potassium by the Kidneys in Primary Hypertension.

Solid arrows indicate an increase or stimulation, and the broken arrow indicates inhibition. Numbers on the left denote the approximate percentage of reabsorption of filtered sodium in each nephronal segment during normal conditions. Several influences acting on the luminal sodium transporters and the basolateral sodium pump stimulate sodium retention and potassium loss. Promotion of sodium reabsorption by the activated epithelial sodium channel (ENaC) generates a more negative luminal membrane voltage (Vm) in the collecting duct that enhances potassium secretion through the luminal potassium channel and promotes kaliuresis. NHE-3 denotes sodium-hydrogen exchanger type 3, ACE angiotensin-converting enzyme, NKCC2 sodium-potassium2 chloride cotransporter, and NCC sodium-chloride cotransporter. PST 2238 (rostafurox) antagonizes the effect of digitalis-like factor on the sodium pump.
Figure 3. Molecular Pathways Implicated in the Generation of Increased Arterial and Arteriolar Smooth-Muscle Tone by an Excess of Sodium and a Deficit of Potassium in Primary Hypertension.

Solid arrows indicate an increase or stimulation, and broken arrows indicate a decrease or inhibition. The inhibition of the sodium pump and the resulting stimulation of the sodium-calcium exchanger type 1 (NCX1) increase the intracellular concentration of calcium that in turn triggers actin–myosin interaction and stimulation of vascular contraction. Na⁺, denotes intracellular sodium concentration; K⁺, intracellular potassium concentration; Ca²⁺, intracellular calcium concentration; Vm, membrane potential; and RyR,ryanodine-receptor calcium channel. PST 2238 (rostafuroxin) antagonizes the effect of digitalis-like factors on the sodium pump. SEA-0400 is a specific inhibitor of the bidirectional NCX1, preferentially blocking the calcium influx pathway.
Figure 4. Molecular Pathways Implicated in Potassium-Induced, Endothelium-Dependent Vasodilation.

Solid arrows indicate an increase or stimulation, and broken arrows indicate a decrease or inhibition. The stimulation of the sodium pump and the opening of the potassium channels hyperpolarizes the endothelial cell (with membrane potential [Vm] shifting to more negative values). Endothelial-cell hyperpolarization is transmitted to the vascular smooth-muscle cell by means of myoendothelial gap junctions and also by increasing the intracellular calcium concentration ([Ca²⁺]). The latter change activates potassium channels of small (SK3) and intermediate (IK1) conductance localized to the cell membrane, causing the potassium to exit the cells and to accumulate in the myoendothelial intercellular space. This accumulation of potassium adds to vascular smooth-muscle hyperpolarization by activating membrane potassium channels and stimulating the sodium pump. Vascular smooth-muscle hyperpolarization lowers Ca²⁺, resulting in vascular relaxation.
Figure 3. Framework of the mechanisms involved in the fetal origins of kidney disease. Data from Hershkovitz et al,37 Vehaskari and Woods,57 Ojeda et al,63 Hoy et al,71 and Ingelfinger and Schnaper.99 EtOH, alcohol; SA, substance abuse; Vit A, vitamin A; mtDNA, mitochondrial DNA; DM, diabetes mellitus; AKI, acute kidney injury; VUR, vesicoureteral
Hypertension: Relation with Age and Race

![Graph showing the prevalence of hypertension in men by age and race. The graph compares Non-Hispanic Black, Non-Hispanic White, and Mexican-American populations.](image-url)
Low Nephron Rats Generated by Maternal Malnutrition Develop Arteriolar and Interstitial Lesions: MMF blocks the lesions and Hypertension

High Fructose Intake from Added Sugars is associated with Increased Risk of Elevated BP

Adjusted for: age, gender, race/ethnicity, smoking, diabetes, MET category, waist circumference, body mass index, serum glucose, serum uric acid, total, LDL-, and HDL- cholesterol, triglycerides, eGFR- MDRD, 24 hour dietary recall of total kcals, total carbohydrate, sodium, alcohol, and vitamin C intake.
**Effect of Fructose (200 g/d) for 2 weeks on Metabolic syndrome in Men: Menorcan Study**

Perez-Pozo et al Int J Obes in press

<table>
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<tr>
<th>Metabolic Syndrome (NCEP-ATPIII)(%)</th>
<th>Baseline</th>
<th>Change</th>
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<tr>
<td></td>
<td>19%</td>
<td>44%</td>
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<table>
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<tr>
<th>P Value</th>
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<tr>
<td>Triglycerides</td>
<td>136 ± 15</td>
<td>55±20</td>
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<tr>
<td>&lt;0.001</td>
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<tr>
<td>HDL Cholesterol</td>
<td>46.5 ± 1.5</td>
<td>-2.5 ± 0.7</td>
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<tr>
<td>Insulin resistance (HOMA)</td>
<td>1.7 ± 0.2</td>
<td>0.57 ± 0.16</td>
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<tr>
<td>&lt;0.005</td>
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<tr>
<td>Weight (kg)</td>
<td>84.3 ± 2.3</td>
<td>0.6 ± 0.2</td>
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<tr>
<td>&lt;0.003</td>
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<td>BMI (kg/m2)</td>
<td>29.0 ± 0.6</td>
<td>0.2 ± 0.1</td>
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<tr>
<td>&lt;0.003</td>
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<tr>
<td>24 hr Systolic BP (mm Hg)</td>
<td>126±2</td>
<td>7 ± 2</td>
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<tr>
<td>&lt;0.001</td>
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<tr>
<td>24 hr Diastolic BP (mm Hg)</td>
<td>75 ± 2</td>
<td>5 ± 3</td>
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<tr>
<td>&lt;0.001</td>
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<tr>
<td>Uric acid (mg/dl)</td>
<td>5.2 ± 0.2</td>
<td>1.1 ± 0.8</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td></td>
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</table>
Fructose-induced Change in 24 Ambulatory BP in Overweight Men: Effect of Allopurinol

Low Protein (LP) Diet in Pregnancy Results in Low Nephron Number and Salt-sensitivity in the Offspring

Kidney Int 2004; 65:1339-1348
Febuxostat (XO inhibitor) Reduces Fructose-induced Hypertension

Fructose Induces Metabolic Syndrome in Rats

Nakagawa et al, Am J Physiol 2006; 290:F625-631
Birth Weight and Cumulative Incidence of Hypertension in a Finnish Cohort

% HTN

Birth Weight

Hypertension 2000; 36:790-794
Supremacy of the Kidney in Hypertension

Proposed mechanism of fetal programming of hypertension and renal disease