Chapter 11
Antihypertensive drugs
Scopes and Aims of CV pharmacology

was a CV pharmacologist
Scopes and Aims of CV pharmacology

• Classical CV pharmacology
  – Drugs for hypertension, angina pectoris, heart failure, arrhythmia, shock, hyperlipidemia, disorders of coagulation, renal failure, edema related diseases.

• Aims of the CV pharmacology
  – Understand the mechanisms of different types of drugs used for CV diseases
  – Memorize the major applications of each types of the drugs
  – Memorize the major types of drugs for each CV disorders
  – Familiar with the major side effects and toxicities
Antihypertensive drugs

• Four major types
  – Alter sympathetic NS:
    • Centrally acting sympathoplegic drugs
    • Ganglion-blocking agents
    • Adrenergic neuron-blocking agents
    • Adrenoceptor antagonists: beta & alpha blockers
  – Calcium channel blockers
  – Vasodilators
  – Act on angiotensin system:
    • ACEI & receptor blockers
General info of hypertension (HTN)

– Nearly 90% people will develop HTN
  • Causes are not clear for primary HTN
  • Diagnosed by Bp measurement, rather than symptoms at the early stage
  • Many complications:
    – renal failure
    – heart failure
    – coronary disease,
    – stroke
  • CV diseases are pressure related
    – From 115/75 mmHg, each 20/10 mmHg doubles risk
Normal regulation of BP

- BP = CO x PVR
- CO: myocardial contractility & basic filling pressure
  - Ref Fig 11-1 in the book
Normal regulation of BP

- **BP = CO x PVR**
- **CO : myocardial contractility & basic filling pressure**
- **Ref Fig 11-1 in the book**
  - CNS sympathetic nerves
    - *Resistance vessels*
    - *Capacitance vessels*
    - *Cardiac output*
    - *Basic filling pressure via kidney*
      - *Renin angiotensin aldosterone system*
    - *Baroreceptor reflex arc*
  - Local released vasoactive substances (*)
    - *Vasodilator & vasoconstrictive factors*
Normal regulation of BP: some examples

Local released vasoactive substances (*)


Normal regulation of BP
Local released vasoactive substances (*)

• **Protective effects of captopril and enalapril on myocardial ischemia and reperfusion damage of rat.** *J Mol Cell Cardiol.* 1987

• In Langendorffs heart, captopril remarkably preserved force of contraction & coronary flow in segmental infarction deteriorated by angiotensin I.

• Captopril infusion reduced CPK release. This action was abolished by pretreating with indomethacin (?). As a positive control, prostacyclin infusion further reduced CPK release.

• ACEI can protect both myocardial ischemia and reperfusion damage in rat hearts, through reducing production of angiotensin II by ACEI and increased prostacyclin release in the heart.
Normal regulation of BP

Local released vasoactive substances (*)

Myocardial contractile actions of endothelin-1 in rat and rabbit papillary muscles. Role of endocardial endothelium. Circ Res. 1991;69:301
Normal regulation of BP

Local released vasoactive substances (*)

• **Effect of dysfunctional vascular endothelium on myocardial performance in isolated papillary muscles. Circ Res. 1993.**

• **Using an isolated perfused rabbit heart treated with Triton X-100 treatment, then testing coronary flow with Ach and Nitroprusside (question ?)**

• Conclusion: vascular endothelial dysfunction had similar effects on contractile characteristics as endocardial endothelial removal.
Normal regulation of BP

- \( BP = CO \times PVR \)
- \( CO : \) myocardial contractility & basic filling pressure

- *Systematic and local vasoactive substances*
  - NE
  - Angiotensin
  - Nitric Oxide
  - Prostaglandins
Normal regulation of BP (1b)

• Gender difference:

• Food: particularly the salt intake

• Physical exercise

• Conscious control: such as Yuga
  – In situ tests
Normal regulation of BP (1c)

• Gender difference

The frequency distribution of the systolic pressure of 16429 undergraduates

Female (N=6821)
Male (N=9607)
Normal regulation of BP (1d)

- Gender and ethnic differences

Death rate of heart disease in selected population by race and sex: USA 2003
Normal regulation of BP (1e)

- Gender difference

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Male rats or men</th>
<th>Female rats or women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II (low dose)</td>
<td>Increase BP</td>
<td>Decrease BP</td>
</tr>
<tr>
<td>Angiotensin II (high dose)</td>
<td>More increase in BP</td>
<td>Less increase in BP</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>More effective, less side-effect</td>
<td>Less effective, more side-effect</td>
</tr>
<tr>
<td>L-NAME</td>
<td>More increase in BP</td>
<td>Less increase in BP</td>
</tr>
<tr>
<td>Cafeteria diet</td>
<td>hypertensive</td>
<td>Not hypertensive</td>
</tr>
<tr>
<td>Aspirin</td>
<td>More effective in primary prevention of MI</td>
<td>More effective in primary prevention of stroke</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Less reported deaths</td>
<td>More reported deaths</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>More effective</td>
<td>Less effective, more tachycardia</td>
</tr>
</tbody>
</table>
Normal regulation of BP (1e)

• Question

• Why are gender and ethnic differences important to medical doctor when we deal with hypertension?
Major sites of antihypertensive drugs

**brain-heart-vessels-kidney**
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

- Diuretics

- Alter sympathetic NS:
  - Centrally acting sympathoplegic drugs
  - Ganglion-blocking agents
  - Adrenergic neuron-blocking agents
  - Adrenoceptor antagonists: beta & alpha blockers

- Vasodilators

- Act on angiotensin system:
  - ACEI & receptor blockers

- Calcium channel blockers

Figure 11-3 in the book
## Selected antihypertensive drugs

**Table 11-1 in the book**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (h)</th>
<th>Bioavailability (percent)</th>
<th>Suggested Initial Dose</th>
<th>Usual Maintenance Dose Range</th>
<th>Reduction of Dosage Required in Moderate Renal Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>35</td>
<td>65</td>
<td>2.5 mg/d</td>
<td>5.5–10 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Atenolol</td>
<td>6</td>
<td>60</td>
<td>50 mg/d</td>
<td>50–100 mg/d</td>
<td>Yes</td>
</tr>
<tr>
<td>Benazepril</td>
<td>0.6</td>
<td>35</td>
<td>5–10 mg/d</td>
<td>20–40 mg/d</td>
<td>Yes</td>
</tr>
<tr>
<td>Captopril</td>
<td>2.2</td>
<td>65</td>
<td>50–75 mg/d</td>
<td>75–150 mg/d</td>
<td>Yes</td>
</tr>
<tr>
<td>Clonidine</td>
<td>8–12</td>
<td>95</td>
<td>0.2 mg/d</td>
<td>0.2–1.2 mg/d</td>
<td>Yes</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>3.5</td>
<td>40</td>
<td>120–140 mg/d</td>
<td>240–360 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>5 d</td>
<td>3–50</td>
<td>10 mg/d</td>
<td>25–50 mg/d</td>
<td>Possible</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>1.5–3</td>
<td>25</td>
<td>40 mg/d</td>
<td>40–200 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>12</td>
<td>70</td>
<td>25 mg/d</td>
<td>25–50 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>12</td>
<td>25</td>
<td>10 mg/d</td>
<td>10–80 mg/d</td>
<td>Yes</td>
</tr>
<tr>
<td>Losartan</td>
<td>1–2</td>
<td>25</td>
<td>10 mg/d</td>
<td>25–100 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>2</td>
<td>25</td>
<td>1 g/d</td>
<td>1–2 g/d</td>
<td>No</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>3–7</td>
<td>40</td>
<td>50–100 mg/d</td>
<td>200–400 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>6</td>
<td>90</td>
<td>5–10 mg/d</td>
<td>40 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>2</td>
<td>50</td>
<td>30 mg/d</td>
<td>30–60 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Prazosin</td>
<td>3–4</td>
<td>70</td>
<td>3 mg/d</td>
<td>10–30 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3–5</td>
<td>80</td>
<td>80 mg/d</td>
<td>80–480 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Reserpine</td>
<td>24–48</td>
<td>50</td>
<td>0.25 mg/d</td>
<td>0.25 mg/d</td>
<td>No</td>
</tr>
<tr>
<td>Verapamil</td>
<td>4–6</td>
<td>22</td>
<td>180 mg/d</td>
<td>240–480 mg/d</td>
<td>No</td>
</tr>
</tbody>
</table>

1Creatinine clearance ≥ 30 mL/min. Many of these drugs do require dosage adjustment if creatinine clearance falls below 30 mL/min.
### Selected antihypertensive drugs

**Table 11-1 in the book**

<table>
<thead>
<tr>
<th>Drug</th>
<th>T1/2</th>
<th>Bioavailability (%)</th>
<th>Suggested initial dose</th>
<th>Maintenance dose range</th>
<th>↓ dose in renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>atenolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Benazepril</td>
<td>Pro(drug)</td>
<td>0.6 (10h)</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>captopril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>guanethidine</td>
<td>5d</td>
<td>3-50</td>
<td></td>
<td></td>
<td>possible</td>
</tr>
<tr>
<td>clonidine</td>
<td></td>
<td>95</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>lisinopril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>reserpine</td>
<td>1-2d</td>
<td></td>
<td></td>
<td></td>
<td>no</td>
</tr>
</tbody>
</table>
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Diuretics: for mild or moderate essential HTN, can lower 10-15 mmHg;

natriuretic

direct vasodilatory effect
decrease body volume

Dietary sodium restriction is better for prevention
Major sites of antihypertensive drugs

*brain-heart-vessels-kidney*

**Diuretics:** side effects

- **K+ depletion:** exaggerate digitalis toxicity
- Mg++ depletion
  - ↑ uric acid, precipitate gout
  - renal carcinoma risk

1). Dietary sodium restriction
2). lowering dose of diuretics
3). Alternatively use of potassium-sparing diuretics
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Drugs alter sympathetic NS:

1. methyldopa
2. Clonidine
3. Guanethidine
4. Reserpine
5. Propranolol and other beta antagonist
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Drugs alter sympathetic NS:

useful in polytherapy in moderate to severe HTN

effects limited by Na retention and volume expansion

different side effects

CNS: sedation, depression, nightmares

ganglia: inhibition parasympathetic system as well

sympathetic end (NE release): ejection (-), postural hypotension

block postsynaptic receptors: more selective effects
Major sites of antihypertensive drugs

*brain-heart-vessels-kidney*

Drugs alter sympathetic NS:

metyldopa

Enters CNS via Aromatic aa transport;
Converts into alpha-metyldopamine & alpha-methylNE
Partial alpha agonist: initial ↑ BP by stimulating vascular receptor, & then ↓ BP by stimulating CNS alpha-2 receptors
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Methldopa-

\[ \downarrow \text{BP mainly by reducing PVR} \]

Side effects promptly reversal after discontinuation

- overt sedation
- lactation
- positive Comb’s test (10-20%)
Major sites of antihypertensive drugs

*brain-heart-vessels-kidney*

**Clonidine**

**pharmacokinetics**
- low dose rarely cause hypertension, overdose can cause severe HTN
- twice a day, or single transdermal preparation for 7d

**pharmacodynamics**
- $\downarrow$ BP by $\downarrow$ cardiac output and $\downarrow$ PVR (*maintaining renal blood supl*)
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Clonidine side effects

dry mouth & sedation

counterindication: depression; or withdraw it if depression occurs

HTN crisis: stopped gradually & substituted with other antihypertensive drugs
Major sites of antihypertensive drugs

<table>
<thead>
<tr>
<th></th>
<th>Methyldopa</th>
<th>Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic activity</td>
<td>weaker</td>
<td>stronger</td>
</tr>
<tr>
<td>Alpha-2 agonist</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>decrease CO</td>
<td>+/-</td>
<td>yes</td>
</tr>
<tr>
<td>Side effect</td>
<td>+ Comb’s test</td>
<td>HTN crisis</td>
</tr>
</tbody>
</table>
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Question

Why is a drug such as clonidine that can cause hypertension crisis still used as a antihypertensive drug?
Major sites of antihypertensive drugs

Ganglion-blocking agents: historically, 1st generation of antihypertensive drugs;
Mechanism: block postganglia’s N receptor

<table>
<thead>
<tr>
<th>mechanisms</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathoplegia</td>
<td>Orthostatic hypotension, sexual dysfunction</td>
</tr>
<tr>
<td>parasympathoplegia</td>
<td>Constipation, urinary retention, + glaucoma, blurred vision, dry mouth</td>
</tr>
<tr>
<td>Neuromuscular block</td>
<td>Muscle relaxation</td>
</tr>
</tbody>
</table>
Major sites of antihypertensive drugs

Ganglion-blocking agents: historically, 1st generation of antihypertensive drugs;

Question

Why are ganglion-blocking agents not routinely used as antihypertensive drugs now?
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Adrenergic neuron-blocking agents:

Guanethidine
replace NE, gradual depletion of NE store in the nerve ending

Antihypertensive effects
short term: ↓ CO, ↓ capacitance vessels;
long term: ↓ PVR sedation, compensatory Na+, H2O retention

Toxicity
postural hypotension, hypotension after exercise, shock
Effects ↓ by tricyclic antidepressant, may cause severe HTN
in pheochromocytoma, cause HTN crisis
## Major sites of antihypertensive drugs

*brain-heart-vessels-kidney*

### Adrenergic neuron-blocking agents:

<table>
<thead>
<tr>
<th></th>
<th>Guanethidine</th>
<th>Reserpine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>uses</strong></td>
<td>Not routinely used</td>
<td>Mild to moderate HTN</td>
</tr>
<tr>
<td><strong>mechanism</strong></td>
<td>Replace NE</td>
<td>Depletion of amines</td>
</tr>
<tr>
<td><strong>kinetics</strong></td>
<td>No CNS distribution</td>
<td>CNS &amp; nerve ending</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>sympatoetomy</td>
<td>Mental depression, peptic ulcer</td>
</tr>
</tbody>
</table>
Major sites of antihypertensive drugs

*brain-heart-vessels-kidney*

Adrenergic neuron-blocking agents:

<table>
<thead>
<tr>
<th></th>
<th>Guanethidine</th>
<th>Reserpine</th>
</tr>
</thead>
<tbody>
<tr>
<td>mechanism</td>
<td>Replace NE</td>
<td>Depletion of amines</td>
</tr>
</tbody>
</table>


Myocardial catecholamine depletion with reserpine had effects similar to those of propranolol. The effects of phenylephrine and endothelin were modified in a similar manner by propranolol (10^{-5}) M). The presence of nicardipine (3 X 10^{-7} M) decreased the absolute increase in contractility caused by endothelin but did not alter the percent change or shift the dose-response curve of endothelin.
Major sites of antihypertensive drugs

*brain-heart-vessels-kidney*

Adrenoceptor antagonists (1): **the prototype**

**Propranolol**: Nonselective beta-blocker, preventing reflex tachycardia, reduce mortality in heart failure

Effects: $\downarrow$ **CO**, CNS inhibition, $\downarrow$ renin production

Side effects: related to beta blockage at heart, bronchi, vessels, pancreas; **should not be discontinued abruptly as MI reported**
Major sites of antihypertensive drugs

*brain-heart-vessels-kidney*

Adrenoceptor antagonists (2): good for asthma

**Metoprolol**: relatively selective beta-1-blocker, 50-100-fold less potent than propranolol in blocking beta-2 receptor

Property: Less bronchial constriction

Indications: HTN with asthma, diabetes, or peripheral vascular diseases
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Adrenoceptor antagonists (3):

**Beta-1-selective** blockers: nadolol, carteolol, atenolol, betaxolol, & bisoprolol

property: these drugs are excreted to a considerably extent in the urine

Clinical relevance: lowering dose in renal insufficiency
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Adrenoceptor antagonists (4): Partial

Partial agonists: acebutolol, Pindolol, Penbutolol

property: intrinsic activity

Clinical relevance: beneficial to bradyarrhythmias or heart failure pts
Major sites of antihypertensive drugs

*brain-heart-vessels-kidney*

Adrenoceptor antagonists (5): magic example of racemic mixture as a drug

Labetalol: 4 isomers, only 2 of them have effects: used for pheochromocytoma and HTN emergencies

Carvedilol: 2 isomers, S(-) is nonselective beta blockers, both isomers have equal alpha-blocking potency, used for ordinary HTN
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Adrenoceptor antagonists (6): Esmolol, Short T1/2

Property: beta-1-selective, and short T1/2 (9-10 min)

Indications: lowering BP in
  operation
  postoperation,
  HTN emergencies
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Adrenoceptor antagonists (6): Esmolol, Short T1/2
Property: beta-1-selective, and short T1/2 (9-10 min)
Indications: lowering BP in operation, postoperation, & HTN emergencies

Question: why is this short effective drug advantageous in dealing with HTN during operation?
Major sites of antihypertensive drugs (*Lesson2*)

*brain-heart-vessels-kidney*

Adrenoceptor antagonists (7): alpha-1-specific blockers

Prazosin, terazosin, doxazosin (T1/2: 4h, 12h, 22h)

Mechanisms: **block alpha-1; & allow alpha-2 (-) feedback**

Decrease BP mainly via dilating vessels, more effective upright than in supine position

More effective when combined with beta blockers or diuretics
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Adrenoceptor antagonists (8): alpha-1-specific blockers

Phentolamine, Phenoxybenzamine

Administration of 1-3 weeks before surgery for pheochromocytoma
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Adrenoceptor antagonists: important points reviewed

Prototype: propranolol

Relatively beta-1 selective: Metoprolol, good for asthma

Racemic and alpha & beta blockers: labetanol & carvedinol

Partial agonist: Intrinsic acitivity, Pindolol, acetutolol, penbutolol

Beta-1 selective and short T1/2: Esmolol
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Vasodilators:

1. Oral: outpatient
2. Parental: HTN emergencies
3. Calcium channel blockers: for both

Work best in combination with other drugs to oppose the compensatory CV responses
Major sites of antihypertensive drugs

**brain-heart-vessels-kidney**

Vasodilators:
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

Monotherapy vs polypharmacy in HTN

Therapy regimen: One drug, then 2, then 3,...

1. Increase efficiency via different mechanisms
2. Decrease toxicity

Tip: oral vasodilators are least effect when used for monotherapy in HTN.
Major sites of antihypertensive drugs

**brain-heart-vessels-kidney**

**Oral vasodilators:** Hydralazine: relaxing arterioles

First pass effect: bimodal acetylation
Wide dose range 50-300 mg/d

**Toxicities:**
1. Tachycardia and angina
2. Symptoms resembles lupus erythematosus: not associated with renal damage, reversed by discontinuation of drug

Effective in severe HTN in combination therapy
### Major sites of antihypertensive drugs

#### Oral vasodilators: Hydralazine vs minoxidil

<table>
<thead>
<tr>
<th></th>
<th>Hydralazine</th>
<th>Minoxidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>mechanism</td>
<td>Dilate arteriole</td>
<td>Dilate arteriole by opening K channel in muscle membrane</td>
</tr>
<tr>
<td>bioavailability</td>
<td>Low &amp; variable</td>
<td>90%</td>
</tr>
<tr>
<td>effect</td>
<td>high</td>
<td>Very high</td>
</tr>
<tr>
<td>combination</td>
<td>1 or more</td>
<td>B-blocker &amp; loop diuretic</td>
</tr>
<tr>
<td>Topical use</td>
<td></td>
<td>Hair growth</td>
</tr>
</tbody>
</table>
Major sites of antihypertensive drugs

**brain-heart-vessels-kidney**

**Nitroprusside:** Dilates arterial & venous vessels through increased cGMP

Increased CO in HTN with heart failure

Effects disappeared within 10 minutes, light sensitive

**Thiocyanate toxicity**
**Delayed hypothyroidism**

Tips: Sodium thiosulfate and hydroxocobalamin are used for prophylaxis or treatment of cyanide poisoning
Major sites of antihypertensive drugs

brain-heart-vessels-kidney

**Diazoxide:** Dilates arterial vessels, K+ channel opener

Occasionally used to treat HTN emergencies

**Side effects:** extensive hypotension

**Tips:** Diazoxide and Thiozoxide are structurally similar, the former causes salt & water retention, while the latter has been used as diuretics.
## Major sites of antihypertensive drugs

*parenteral vasodilators*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Vascular target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>NO &amp; cGMP</td>
<td>Arterial and venous vessels</td>
</tr>
<tr>
<td>diazoxide</td>
<td>K+ channel opener</td>
<td>A</td>
</tr>
<tr>
<td>fenoldopam</td>
<td>D1 receptor agonist</td>
<td>A</td>
</tr>
<tr>
<td>Verapamil &amp; CCB</td>
<td>CCB</td>
<td>A</td>
</tr>
</tbody>
</table>
Antihypertensive drugs

Inhibitors of angiotensin
Antihypertensive drugs
Inhibitors of angiotensin

• Two major types
  – ACEI: Captopril, .....pril
    • ↓ Angiotensin II, aldosterone
    • ↑ bradykinin, prostacyclin,...

• Effect inhibited by BK antagonist icatibant
• Effect inhibited by indomethacin
• More effective in Angiotensin I augmented heart damage
• Similar effect observed in administration of Illoprost

– Contraindication: pregnancy
  • Severe hypotension
  • Dry couph
Normal regulation of BP
Local released vasoactive substances (*)

- *Protective effects of captopril and enalapril on myocardial ischemia and reperfusion damage of rat. J Mol Cell Cardiol. 1987*

- In Langendorffs heart, captopril remarkably preserved force of contraction & coronary flow in segmental infarction deteriorated by angiotensin I.

- Captopril infusion reduced CPK release. This action was abolished by pretreating with indomethacin (?). As a positive control, prostacyclin infusion further reduced CPK release.

- ACEI can protect both myocardial ischemia and reperfusion damage in rat hearts, through reducing production of angiotensin II by ACEI and increased prostacyclin release in the heart.
Normal regulation of BP (1e)

- **Gender difference**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Male rats or men</th>
<th>Female rats or women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II (low dose)</td>
<td>Increase BP</td>
<td>Decrease BP</td>
</tr>
<tr>
<td>Angiotensin II (high dose)</td>
<td>More increase in BP</td>
<td>Less increase in BP</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>More effective, less sideeffect</td>
<td>Less effective, more sideeffect</td>
</tr>
<tr>
<td>L-NAME</td>
<td>More increase in BP</td>
<td>Less increase in BP</td>
</tr>
<tr>
<td>Cafeteria diet</td>
<td>hypertensive</td>
<td>Not hypertensive</td>
</tr>
<tr>
<td>Aspirin</td>
<td>More effective in primary</td>
<td>More effective in primary</td>
</tr>
<tr>
<td></td>
<td>prevention of MI</td>
<td>prevention of stroke</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Less reported deaths</td>
<td>More reported deaths</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>More effective</td>
<td>Less effective, more tachycardia</td>
</tr>
</tbody>
</table>
Antihypertensive drugs
Inhibitors of angiotensin

• Two major types
  – Ang II receptor blockers: Losartan, .....sartan
    • blocking AT1 receptor
      • Effect inhibited by BK antagonist icatibant
      • Effect inhibited by indomethacin
      • More effective in Angiotensin I augmented heart damage
      • Similar effect observed in administration of Illoprost

  – Contraindication: pregnancy (similar to ACEI but less common)
    • Severe hypotension
    • Dry cough
Clinical pharmacology of antihypertensive agents

• Individualized medicine
  – Same disease, may use different drug
  – Same drug, may use different dosage

• When to start medication
  – Diagnosis of essential HTN: excluding secondary HTN
  – Initial step: non-pharmacologic
    • Sodium restriction
    • Weight reduction
    • Low saturated fat and total fat
    • Physical exercise
    • Small amount of wine (200 ml of 20 proof)
Clinical pharmacology of antihypertensive agents

- **Individualized medicine**
  - Ethnic, gender, age, disease,

- **How to treat HTN**
  - 1 drug first, most of the pts requires 2 or more drugs
  - Concomitant disease
    - Chronic kidney disease: ACEI
    - Angina: beta blocker, CCB
    - Heart failure: diuretics, beta blocker, ACEI, AT1 blocker
    - Benign prostate hyperplasia: alpha-1- blocker
    - Ethnic: AA __diuretics & CCB vs b-blocker __Chinese
Diuretic agents
renal tubule transport mechanisms

Figure 15–1. Tubule transport systems and sites of action of diuretics.
Diuretic agents
basic pharmacology of diuretic agents (1)

- Carbonic anhydrase inhibitor
  - **Discovery history**
    sulfonamide: alkaline diuresis & hyperchloremic metabolic acidosis
  - **Mechanism:** $\uparrow$ NaHCO$_3$ in urine
  - **Major clinical indications**
    - glaucoma: no systematic side effects
    - urinary alkalinization: $\uparrow$ excretion of weak acids
    - acute mountain sickness
  - **Drugs available:** Acetazolamide, dichlorphenamide, methazolamide
Diuretic agents
loop diuretic (2)

• Furosemide and ethacrynic acid

  – Mechanism: ↓ NKCC2,
    • then ↓ NaCl reabsorption at thin ascending limb

  – Major clinical indications (1)
    • acute pulmonary edema
    • other edematous conditions
    • hypercalcemia
Diuretic agents
loop diuretic (2b)

• Furosemide and ethacrynic acid
  – Mechanism: ↓ NKCC2,
    • then ↓ NaCl reabsorption at thin ascending limb
  – Specified clinical indications (2)
    • hyperkalemia (toxicity: hypokelemia)
    • acute renal failure
    • anion overdose
  – Toxicity
    • Ototoxicity: dose related hearing loss
Diuretic agents

Thiazides (3)

• Identified during synthesize more carbonic anhydrase inhibitors

  – Chemistry
    Share an unsubstituted sulfonamide group

  – Mechanism: ↓ NaCl reabsorption by ↓ Na+/Cl- transporter

  – Major clinical indications: a frequently used subgroup

  – Drugs available:
    • table 15-5: thiazide & sulfonamide
Diuretic agents

Thiazides (3b)

– Major clinical indications
  • glaucoma: no systematic side effects
  • urinary alkalinization: ↑ excretion of weak acids
  • acute mountain sickness

– Mechanism: ↑ NaHCO3 in urine

– Drugs available:
  • Acetazolamide, dichlorphenamide, methazolamide
Diuretic agents

Potassium-sparing diuretics (4)

- Chemistry
  Spironolactone, aldosterone antagonist; Eplerennone is a spironolactone analog but with higher selectivity
  Amiloride & triameterene: inhibitor of Na+ influx

- Applications:
  1). Primary or secondary hyperaldosteronism;
  2). Combined used with other diuretics

- Toxicity
  - Hyperkalemia; & Hyperchloremic metabolic acidosis
  - Gynecomastia, impotence, prostatic hyperplasia (effects by inhibiting aldosterone receptor, not with eplerenone)
Diuretic agents
Agents altering water excretion (5a)

- **Osmotic diuretics**: **mannitol**
  Be filtered by the glomerulus, but not reabsorbed

  - **Applications**:
    - 1). ↑ urine volume
    - 2). ↓ intracranial & intraocular pressure

  - **Toxicity**
    - Distributed to extracellular compartment
    - Dehydration
Diuretic agents
Agents altering water excretion (5b)

- **Antidiuretic hormone agonists**
  - Vasopressin and desmopressin: for central diabetes insipidus

- **Antidiuretic hormone antagonists**
  - Conivaptan, lithium, demeclocycline
    For primary or secondary ADH elevation
  - Toxicity
    - Hypernatremia & nephrogenic diabetes insipidus
    - Renal failure
Clinical pharmacology of Diuretic agents

- Common reason: ↓ peripheral or pulmonary edema
  - Heart failure: for pts CO maintained with high filling pressure
  - Kidney disease: loop diuretics are often the best (furosemide)
  - Hepatic cirrhosis: hypoalbuminemia, high aldosterone
    - loop diuretics + aldosterone antagonist

Nonedematous states: 1). HTN, 2). diabetes insipidus
Drugs used for Cardiac Arrhythmias