Tips for Drug Learning

- Learn agents by drug classes
  ie. beta-blockers, Ca++-blockers etc
- Key points:
  - Clinical application
  - Mechanism of action
  - Important drug/drug interactions
    ie. MAOI and tyramine rich foods
  - Adverse drug reactions
    ie. beta-blockers – asthma, Raynaud D.
- Drugs of choice (DOC)
  ie. epinephrine (anaphylaxis)
- Prototype drugs, commonly prescribed
  ie. propranolol, atenolol; captopril, lisinopril
- Do not focus on dosage or trade names
## ANS – Review

1. **Tissues / Organs:**
   - receptors present, tissue / organ response

2. **Transmitters:**
   - NE, Ach, synthesis, storage, release, regulation

3. **Eye:**
   - miosis, mydriasis, cycloplegia, Glaucoma: wide- vs narrow-angle, Horner’s Syndrome

4. **Drugs:**
   - receptor selectivity, mechanism of action

5. **Can predict:**
   - clinical application, side effects, toxicity, treatment of toxicity

6. **General:**
   - learn by drug classes, important adverse reactions, not dosage

### Neurons of the ANS

![Neurons of the ANS](image)
Receptors of the ANS

Adrenoceptors

Alpha
- $\alpha_1$- Vascular smooth muscle
- $\alpha_2$- Nerve terminals

Beta
- $\beta_1$- Cardiac muscle
- $\beta_2$- Bronchial smooth muscle
- $\beta_3$- Fat cells

Dopamine
- D - Renal smooth muscle ($D_1$)

Cholinoceptors

Muscarinic
- $M_1$ - Ganglia cells
- $M_2$ - Cardiac muscle
- $M_3$ - Sweat glands
- $M_4$/$M_5$

Nicotinic
- $N_N^+$ - Ganglia cells
- $N_M^+$ - Neuromuscular junction

Selective agents available

Selective agents available for major groups but not for M-receptor subtypes

ANS – Overview Tissues/Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic NS</th>
<th>Parasympathetic NS</th>
<th>Cardiovascular System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye: Radial m.</td>
<td>Mydriasis $\alpha_1$</td>
<td></td>
<td>Refelexes oppose direct action to correct BP change (not HR change)</td>
</tr>
<tr>
<td>Circular m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciliary m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart: $\beta_1$, $\beta_2$</td>
<td>$\alpha_1$</td>
<td>$M_2$, $M_3$</td>
<td>$\alpha_1$ vasoconstriction $\rightarrow$ $\uparrow$ TPR $\rightarrow$ $\uparrow$ BP</td>
</tr>
<tr>
<td>Vascular muscle</td>
<td>Constrict $\alpha_1$</td>
<td>$M_2$ (NO)</td>
<td>$\beta_2$ vasoconstriction $\rightarrow$ $\uparrow$ TPR $\rightarrow$ $\uparrow$ BP</td>
</tr>
<tr>
<td>Relax $\beta_2$, $D_{term}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial m.</td>
<td>Relax $\beta_2$</td>
<td>$M_2$</td>
<td>(vaso) $\Downarrow$ HR $\rightarrow$ $\downarrow$ CO $\rightarrow$ $\downarrow$ BP</td>
</tr>
<tr>
<td>GI-tract $\downarrow$ motility $\alpha_1$, $\beta_2$</td>
<td>$\uparrow$ motility $M_2$</td>
<td>$M_3$ (NO) relaxation $\rightarrow$ $\downarrow$ TPR $\rightarrow$ $\downarrow$ BP</td>
<td></td>
</tr>
<tr>
<td>Sphincter m.</td>
<td>Contract $\alpha_1$</td>
<td>$M_2$</td>
<td></td>
</tr>
<tr>
<td>Genitourinary m.</td>
<td>Relax $\beta_2$</td>
<td>Contract $M_2$</td>
<td>Cardiovascular Drug Effects</td>
</tr>
<tr>
<td>Penis</td>
<td>Ejaculation $\alpha_1$</td>
<td>Erection M</td>
<td>Norepinephrine $\uparrow$ BP ($\downarrow$, $\downarrow$), $\uparrow$ HR, $\downarrow$ PP</td>
</tr>
<tr>
<td>Uterus</td>
<td>Relax $\beta_2$</td>
<td>NO $\rightarrow$ Nitric oxide</td>
<td>Isoproterenol $\uparrow$ BP ($\downarrow$, $\downarrow$), $\uparrow$ HR, $\downarrow$ TPR</td>
</tr>
<tr>
<td>Pilomotor</td>
<td>Contract $\alpha_1$</td>
<td>2nd Messengers</td>
<td>Epinephrine $\uparrow$ TBP, $\uparrow$ HR, $\uparrow$ TPR</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>$\uparrow$ secretion $M_1$</td>
<td>$\beta_2$, $D_{term}$</td>
<td>$\uparrow$ AMP $\rightarrow$ Mecamylamine $\downarrow$ BP ($\uparrow$, $\downarrow$) HR</td>
</tr>
<tr>
<td>Liver</td>
<td>$\uparrow$ glucose</td>
<td>$\alpha_1$, $M_2$</td>
<td>$\uparrow$P, $\downarrow$Ca$^{2+}$ $\rightarrow$ Propranolol $\uparrow$ BP ($\downarrow$, $\downarrow$), $\downarrow$ HR</td>
</tr>
<tr>
<td>Kidney</td>
<td>$\uparrow$ renin</td>
<td>$\beta_2$</td>
<td>$\downarrow$ AMP $\rightarrow$ Atropine $\uparrow$ BP ($\downarrow$, $\downarrow$), $\downarrow$ HR</td>
</tr>
<tr>
<td>Fat cell</td>
<td>Lipolysis $\beta_2$</td>
<td>$N_1$, $N_m$</td>
<td>$Na^+$, $K^+$ $\rightarrow$ Phenolamine $\downarrow$ BP, $\downarrow$ HR (reflex), $\downarrow$ TPR</td>
</tr>
</tbody>
</table>
Transmitter synthesis and release

ANS Excess / Deficiency

- **Cholinergic excess**: (ie. AchE inhibition or mushrooms) salivation, lacrimation, urination, diarrhea, emesis (slude), miosis, ↓HR, sweating, cycloplegia, (paralysis)
- **Cholinergic deficiency**: (ie. Atropine toxicity) ↓GI motility, mydriasis, cycloplegia, ↓secretions, tachycardia, delirium, hallucinations

- **Sympathetic excess**: (ie. Tyr-MAOI or Pheochromo.) ↑BP, ↑HR, pupil dilation (mydriasis), ↓GI motility
- **Sympathetic deficiency**: (ie. Guanethidine-block) ↓BP, ↓tissue perfusion, pupil constriction (miosis)
Terminology – ANS

i. clammy: → PNS excess, ie. ↑secretion (sweating)

ii. wheezy: → PNS excess, ie. difficulty in breathing (↑bronchial resistance, ↑secretion)

iii. flushed: → PNS deficiency ie. vasodilatation, thermoregulation (atropine toxicity)

iv. cramps: → muscle contraction ie. abdominal (↑PNS)

v. palpitations: → SNS excess ie. hypertension, hypertensive crisis, MAOI-Tyramine or pheochromocytoma

Question 1a

• A 42-old woman who is a biochemist is brought to the emergency department because of a 1-hour history of severe abdominal cramps, nausea, vomiting, sweating, and difficulty in breathing due to bronchospasm and congestion. On physical examination her pulse is 45/min, BP is 85/50 mm Hg and she exhibits generalized muscle weakness. Laboratory studies show no abnormalities. Exposure to which of the following is most likely?
  
  A. atropine
  B. bethanechol
  C. botulinum toxin
  D. isofluorophate
  E. phentolamine
Question 1b
A 42-old woman who is a biochemist is brought to the emergency department because of a 1-hour history of severe abdominal cramps, nausea, vomiting, sweating, and difficulty breathing due to bronchospasm and congestion. On physical examination her pulse is 45/min, BP is 85/50 mm Hg and she exhibits generalized muscle weakness. Laboratory studies show no abnormalities. In addition to pralidoxime, which of the following is the most appropriate pharmacotherapy for this patient?
A. atropine
B. dantrolene
C. epinephrine
D. phentolamine
E. propranolol

Question 2
A 32-year old man is brought to the emergency department because of confusion, wheezing, vomiting and diarrhea for the past 6 hours. He is sweating and salivating profusely. There is generalized muscle weakness. Which of the following substances is the most likely cause of these findings?
A. Mushrooms
B. Heroin
C. Jimson weed (belladonna alkaloids)
D. Parathion
E. Aged cheese/red wine

USMLE Step 1: 2003, 2005
Question 3

A 59-year old man develops excessive sweating and salivation, diarrhea, and bradycardia while being treated with neostigmine for myasthenia gravis. Which of the following is the most appropriate therapy for these symptoms and signs?

A. Atropine  
B. Carbachol  
C. Edrophonium  
D. Epinephrine  
E. Pralidoxime

USMLE Step 1: 2003, 2005

Drugs of Choice

<table>
<thead>
<tr>
<th>Agent</th>
<th>Therapeutic use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Acute hypersensitivity reaction is. bee attack</td>
<td>α-β-agonist, physiologically counters the effects of released histamine (ie. bronchospasm, ↓BP)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Shock is. septic</td>
<td>Pressor agent (α1-receptors) to maintain BP but dilates renal vessels (G1-receptors, NE → renal vasoconstriction)</td>
</tr>
<tr>
<td>Timolol, Latanoprost</td>
<td>Glaucoma</td>
<td>β-blocker, common agent used for chronic glaucoma (↓secretion); PGF2α analogue, ↓outflow, SE red eye, eyelashes, dark pupils</td>
</tr>
<tr>
<td>α-blocker or</td>
<td>Hypertensive crisis is. tyramine effect,</td>
<td>β-blockers (ie. phenoxymethylamine or phentolamine only reduce BP)</td>
</tr>
<tr>
<td>Labetalol, Carvedilol</td>
<td>Phenochromocytoma</td>
<td>Fenoldopam D1a-agonist</td>
</tr>
<tr>
<td>β-Blockers (Propranolol)</td>
<td>A-M β1-selective</td>
<td>Hypertension, angina, arrhythmias, CHF, tremor, migraine, hyperthyroidism, panic stress</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Emergency glaucoma</td>
<td>M-agonist causes ↓outflow</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Reverse atropine toxicity</td>
<td>Reversible AChE inhibitor, can cross CNS</td>
</tr>
<tr>
<td>Pralidoxime</td>
<td>Regenerate AChE enzyme</td>
<td>Need to use before ‘aging’ occurs</td>
</tr>
<tr>
<td>Atropine</td>
<td>Reverse AChE inhibition</td>
<td>Reverse toxic effects of AChE inhibitors ie. neostigmine, physostigmine, or organophosphates</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Malignant hyperthermia</td>
<td>Inhibits calcium release from SR</td>
</tr>
</tbody>
</table>
Anaphylaxis

Epinephrine

- bronchodilation
- vasoconstriction

bronchoconstriction
↑secretions
↓blood pressure

Asthma

Albuterol
Terbutaline,
Metaproterenol
Salmeterol (LABA)

- bronchodilation

β₂-selective agonists

Inhalation vs oral
- less side effects

Ritodrine
- premature labor
Question 4

A 45-year-old man with cardiogenic shock is treated with drug X. This drug increases blood flow through the mesenteric and renal vascular beds, activates alpha1-adrenergic receptors in several other vascular beds, and directly and indirectly stimulates beta1-adrenergic receptors in the myocardium. Drug X increases blood flow through the mesenteric and renal vascular beds by activating which of the following receptors?

A. Alpha-adrenergic  
B. Beta-adrenergic  
C. Dopaminergic  
D. Muscarinic-cholinergic  
E. Serotonergic

Glaucoma

Increased intraocular pressure: Untreated → blindness

Glaucoma:
- Open angle (wide, chronic) – treated with beta-blockers and other agents
  - Closed-angle (narrow-angle) – dilated iris can occlude outflow
    Pilocarpine or surgical removal of part of iris (iridectomy)

Glucoma treatment
1. α-Agonist: ↑Outflow  
2. M-Agonist/AchEI: ↑Outflow  
3. β-Blocker: ↓Secretion  
4. α2-Agonist: ↓Secretion  
5. Prostaglandins (PGF2α): ↑Outflow  
6. Carbonic acid inhibitors: ↓Secretion
### Question 5

The circles represent the size of the pupils of a patient's right and left eyes, both without treatment and with two different treatments. Which of the following is compatible with the findings shown for the left eye?

- **A. Blockade of α-adrenergic rec.**
- **B. Blockade of β-adrenergic rec.**
- **C. Blockade of muscarinic rec.**
- **D. Inhibition of cholinesterase**
- **E. Sympathetic denervation**

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without treatment</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Treatment With TYR</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Treatment With EPI</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Wrong: **C B**

Correct: **A D E**


### Question 6

Which of the following drugs applied topically produces mydriasis without producing cycloplegia?

- **A. Atropine**
- **B. Neostigmine**
- **C. Phentolamine**
- **D. Phenylephrine**
- **E. Pilocarpine**

Parkinson's Disease

- General population 1:1000, over 60 1:75
- Tremor, stiffness, or clumsiness, usually involving one side, difficulty walking, fatigue, depression
- Progressive destruction of the dopaminergic nigrostriatal pathway
- Elevated cholinergic activity

**Treatment:**
- MAO inhibitors:
- Dopamine agonists: bromocriptine, pramipexole
- L-Dopa
- Anticholinergics: benztropine
- Decarboxylase inhibitor: carbidopa
- COMT inhibition

### Parkinsonian Brain: Action of dopamine agonists

Schizophrenia

- Altered perception or expression of reality
- Affects 1% of the population
- Affects men and women equally
- Strong genetic component

- Dopamine (DA) excess theory:
  - Amphetamine exacerbates symptoms and high doses → paranoia, delusions, auditory hallucination. Effects blocked by DA antagonist chlorpromazine.

**Antipsychotic Pharmacotherapy:**
- Typical: chlorpromazine, haloperidol
- Atypical: risperidone, olanzapine, sertindole
Beta-Adrenoceptor Blocking Agents (β-blockers)

(Drugs A-M are β1-selective exp. Labetalol & Carvedilol)

Properties of several beta-receptor blocking drugs

- **Acetamolol**
  - β1
  - Yes
  - Yes
  - Low
  - 3-4 hours
  - 50

- **Atenolol**
  - β1
  - No
  - No
  - Low
  - 6-12 hours
  - 80

- **Betaxolol**
  - β1
  - No
  - Slight
  - Low
  - 14-22 hours
  - 80

- **Bisoprolol**
  - β1
  - No
  - No
  - Low
  - 3-12 hours
  - 80

- **Carvedilol**
  - None
  - Yes
  - No
  - Low
  - 6 hours
  - 85

- **Ceprolol**
  - β2
  - Yes¹
  - No
  - ...
  - 4-5 hours
  - 70

- **Entalolol**
  - β1
  - No
  - No
  - Low
  - 60 minutes
  - ...

- **Labetalol**
  - None
  - Yes¹
  - Yes
  - Moderate
  - 5 hours
  - 30

- **Metoprolol**
  - β1
  - No
  - Yes
  - Moderate
  - 6-12 hours
  - 50

- **Nadolol**
  - None
  - No
  - No
  - Low
  - 14-24 hours
  - 30

- **Penbutolol**
  - None
  - No
  - No
  - Low
  - 12 hours
  - 90

- **Pindolol**
  - None
  - Yes
  - Yes
  - Moderate
  - 3-4 hours
  - 30

- **Propranolol**
  - None
  - No
  - No
  - High
  - 8-9 hours
  - 30

- **Sotalol**
  - None
  - No
  - No
  - Moderate
  - 4-6 hours
  - 50

- **Timolol**
  - None
  - No
  - No
  - Moderate
  - 4-6 hours
  - 50

¹Partial agonist effects at β1 receptors. ²Labetalol also causes α1-selective blockade. ³Bioavailability is dose-dependent.

**Question 7**

The histograms show changes in HR and bronchiolar resistance produced by the administration of epinephrine alone, drug X alone, and epinephrine together with drug X. Drug X is most likely to be?

A. Isoproterenol  
B. Metoprolol  
C. Nadolol  
D. Pindolol  
E. Propranolol
Hypertension (JNC VII – 2003)

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120–139</td>
<td>or 80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>or 90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160</td>
<td>or &gt;100</td>
</tr>
</tbody>
</table>

*Requires three measurements (repeat visits)
BP lowest in the morning → ↑ during the day

<table>
<thead>
<tr>
<th>β-Blockers</th>
<th>α-Blockers</th>
<th>D1a-Agonist</th>
<th>α2-Agonists</th>
<th>Reserpine</th>
<th>Guanethidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontline agents</td>
<td>- Hypertensive crisis, special circumstances</td>
<td>Hypertensive crisis iv, ie. Fenoldopam</td>
<td>Useful, not frontline ie. Clonidine, α-methyl dopa (prodrug)</td>
<td>Resistant hypertension, significant side effects, rarely used</td>
<td>Resistant hypertension, significant side effects, rarely used</td>
</tr>
</tbody>
</table>

β-Blockers: Contraindications/Cautions

- **Supersensitivity:**
  Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol). Gradual withdrawal

- **Asthma:**
  Blockade of pulmonary β2-receptors. β1-selective agents preferred

- **Diabetes:**
  Compensatory hyperglycemic effect of EPI in hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred

- **Raynauds D:** - may induce

- **Caution in Congestive Heart failure:**
  β-blockers can precipitate latent heart failure by removing compensatory increase in sympathetic effects on heart.

  **Note CI:** unstable CHF, depression, significant bradycardia or bronchospasm
Deadly Nightshade

Approx 5,000 per yr

Mainly atropine
Devil’s apple
Stink weed
Devil’s cherries

Datura

Mainly scopolamine & hyoscyamine
Thorn apple
Jimson weed

Myasthenia gravis
Autoimmune disease

1:10,000 (250,000 USA)

- antibodies to NMJ nicotinic receptors leads to degradation
- simplified synaptic folds
- normal nerve terminal and transmitter
- wider synaptic junction

**Diagnosis:** Edrophonium (Tensilon, short acting) is used for diagnosis and determination of maintenance dose

**Treatment:** Neostigmine has direct (stimulates receptor) and indirect actions (inhibition of AchE). No CNS activity.
Acetylcholinesterase & Irreversible Inhibition

DFP, Isoflurophate, Malathion, Parathion

2-PAM
Pralidoxime
No cns action

Aging
30-40 min

Nerve gas
secs / min

Parathion,
Malathion
(prodrugs)
4 – 6 hr

Neuromuscular Junction

Succinylcholine (non-competitive):
- depolarizing (only agent)
- cannot reverse, short-acting, fasciculations
- atypical pseudo-AchE, hyperkalemia (burn or trauma, develops slowly), malignant hyperthermia

Tubocurarine (competitive):
- non-depolarizing
- reversible, long-acting,
- relaxed paralysis (flaccid)
- some ganglia blockade and histamine release
Competitive (nondepolarizing) NMBs - Others

- **Pancuronium**
  - more potent than tubocurarine (x5)
  - reduced histamine release than curare
  - lack of ganglionic blockade

- **Rocuronium**
  - fast onset (1-2min), 30-40min duration, hypersensitivity

- **Atracurium** (~10 isomers)
  - hydrolysis by AchE
  - replaced by cisatracurium, Hoffmann degradation, organ independent

- **Gallamine**
  - also some muscarinic block

- **Mivacurium**
  - fast onset (2-4min), short acting (12-18min), hydrolysis by AchE, some histamine release

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**Hyperkalemia**

- burn & trauma
- usually small ↑K+
- cardiac arrest
- support: dialysis glucose / insulin
Malignant Hyperthermia

- more likely with halothane
- 60% mortality
- ↑Ca++ → ↑ body temp
- tachycardia
- dysrhythmia
- ↑HR, muscle rigidity

Treatment:
- Dantrolene
- drug of choice
- ↓Ca++ release

NMJ Blocking Agents – Other Actions

<table>
<thead>
<tr>
<th>Neostigmine</th>
<th>Ganglia</th>
<th>Muscarinic Receptors</th>
<th>Histamine Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>Stimulates</td>
<td>Stimulates</td>
<td>Slight</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Blocks</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Metacurine</td>
<td>Blocks weakly</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Gallamine</td>
<td>None</td>
<td>Blocks strongly</td>
<td>None</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>None</td>
<td>Blocks weakly</td>
<td>None</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>cisAtracurium</td>
<td>None</td>
<td>None</td>
<td>Minimal</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>None</td>
<td>None</td>
<td>Slight</td>
</tr>
</tbody>
</table>
### Onset, Duration and Elimination of Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Mode of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>1-2</td>
<td>6-8</td>
<td>Hydrolysis by AchE</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Metaocurine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td>Gallamine</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>2-4</td>
<td>30-40</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>cisAtracurium</td>
<td>2-4</td>
<td>30-40</td>
<td>Hoffman</td>
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<tr>
<td>Atracurium</td>
<td>2-4</td>
<td>30-40</td>
<td>Hydrolysis by AchE</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1-2</td>
<td>30-40</td>
<td>Liver</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>2-4</td>
<td>80-100</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>2-4</td>
<td>12-18</td>
<td>Hydrolysis by AChE</td>
</tr>
</tbody>
</table>

### ANS – Cardiovascular Receptors

**Blood Pressure = Cardiac Output X TPR**

**Cardiac Output = Heart rate X Stroke volume**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Response</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha_1</td>
<td>vasoconstriction</td>
<td>↑ TPR ↑ BP</td>
</tr>
<tr>
<td>beta_1</td>
<td>↑ heart rate</td>
<td>↑ CO ↑ BP</td>
</tr>
<tr>
<td>beta_2**</td>
<td>vasodilation</td>
<td>↓ TPR ↓ BP</td>
</tr>
<tr>
<td>M_2 (vagus)</td>
<td>↓ heart rate</td>
<td>↓ CO ↓ BP</td>
</tr>
<tr>
<td>M (vascular)**</td>
<td>vasodilation</td>
<td>↓ TPR ↓ BP</td>
</tr>
</tbody>
</table>

**not innervated**
Cardiovascular – Resting & Reflex Response

<table>
<thead>
<tr>
<th>Resting: BP 120/80 mmHg</th>
<th>HR 70 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tone: BP 60/40 mmHg</td>
<td>HR 75 bpm</td>
</tr>
</tbody>
</table>

vagus (-10 bpm)  beta1 (+5 bpm)

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>After ↑BP</th>
<th>After ↓BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha\textsubscript{1}</td>
<td>++++</td>
<td>o</td>
<td>++++++++</td>
</tr>
<tr>
<td>beta\textsubscript{1}</td>
<td>+</td>
<td>o</td>
<td>+</td>
</tr>
<tr>
<td>beta\textsubscript{2}</td>
<td>+</td>
<td>++</td>
<td>o</td>
</tr>
<tr>
<td>vagus</td>
<td>++</td>
<td>+++</td>
<td>o</td>
</tr>
</tbody>
</table>

note: athletic individual has low HR (high vagal tone)

Cardiovascular Responses

Moderate/high doses:
- NE  ↑BP, ↓HR (reflex)
- EPI  ↑BP, ↑HR
- ISO  ↓BP, ↑HR
- ACH  ↓BP, ↓HR

- Epinephrine reversal (EPI response in presence of α-blocker ie. phentolamine)
- Norepinephrine in presence of atropine (↑BP, ↑HR)
Cardiovascular Actions – Low dose

Key Diagrams

NE, PE, EPI, ISO
α-blocker, β-blocker

http://www2.courses.vcu.edu/ptxed/ptx/

Cardiovascular Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>α (1)</th>
<th>β1</th>
<th>β2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>↑TPR</td>
<td>↑BP</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>↑HR</td>
<td>↑BP</td>
<td></td>
</tr>
<tr>
<td>EPI</td>
<td>↓TPR</td>
<td>↓BP</td>
<td>**</td>
</tr>
<tr>
<td>ISO</td>
<td>↓HR</td>
<td>↓BP</td>
<td>**</td>
</tr>
</tbody>
</table>

Key Diagrams
NE, PE, EPI, ISO
α-blocker, β-blocker

NE + atropine
NE + α-blocker
NE + β-blocker
PE + atropine

EPI + α-blocker
EPI + β-blocker
Cardiovascular Actions – High dose

- **Phenylephrine**
  - α-agonist, PP constant

- **Epinephrine**
  - α-β-agonist, ↑ PP

- **Isoproterenol**
  - β-agonist, ↑ PP

**Epinephrine Reversal**

- **Phentolamine**
  - α-antagonist
  - ↑ PP, ↓ BP, ↑ HR (reflex)

In the presence of phentolamine, epinephrine now causes ↓ BP

---

**Question 8**

A 65-year old woman on holidays is stung by a bee. She goes to the first aid station where she receives an intramuscular injection of epinephrine. A few minutes later she develops a pounding headache, and blood pressure is measured at 250/150 mmHg. Which of the following drugs might the patient have previously taken that could account for this unexpected effect?

A. atropine  
B. clonidine  
C. alpha-methyldopa  
D. prazosin  
E. propranolol
Question 9

A new agent (X) was tested for its cardiovascular actions in three anaesthetized animals.

i. Control animal
   ii. Animal treated with a ganglion blocker
   iii. Animal treated with a muscarinic blocker

Drug X caused a 50 mmHg rise in BP in the control animal, no change in BP in the ganglion blocker treated animal and a 75 mmHg rise in the muscarinic blocker treated animal. Drug X is a drug similar to?

A. Acetylcholine
B. Atropine
C. Mecamylamine
D. Epinephrine
E. Nicotine

Question 10

A new agent (Y) was tested for its cardiovascular actions in three anaesthetized animals.

i. Control animal
   ii. Animal treated with a ganglion blocker
   iii. Animal treated with a muscarinic blocker

Drug Y caused a 40 mmHg fall in BP in the control animal, a 50 mmHg fall in BP in the ganglion blocker treated animal and no change in BP in the muscarinic blocker treated animal. Drug Y is a drug similar to?

A. Acetylcholine
B. Edrophonium
C. Mecamylamine
D. Pralidoxime
E. Nicotine
Question 11

A 60-year old asthmatic man comes in for a check-up and complains that he is having some difficulty in voiding urine. Physical examination indicates that the man has a blood pressure of 160/100 mmHg and a slightly enlarged prostate. Which of the following medications would be useful in treating both the hypertension and the enlarged prostate?

A. prazosin
B. propranolol
C. clonidine
D. atenolol
E. isoproterenol

USMLE Step 1: 1998

Benign Prostrate Hypertrophy (BPH)

Enlarged prostrate leads to difficulty in urination
Alpha-receptor blocker (ie Prazosin) causes prostrate relaxation
Relaxed prostrate improves urination
A 30 yr male has been treated with several autonomic agents for 4 weeks. He is now admitted to the emergency department showing signs of drug toxicity. Which of the following signs would distinguish between an overdose of a ganglionic blocker versus a muscarinic blocker?

A. Mydriasis  
B. Tachycardia  
C. Postural hypotension  
D. Blurred vision  
E. Dry mouth, constipation