ADRENERGIC AGONISTS

- **Course:**
  Integrated Therapeutics 1

- **Lecturer:**
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- **Date:**
  September 16, 2010

- **Materials on:**
  Exam #2

- **Required reading:**
  Katzung, Chapter 9
ADRENERGIC NEUROTRANSMISSION

Pre-Synaptic Neuron

Tyrosine

Tyrosine Hydroxylase

NE = norepinephrine

Synapse

Reuptake

α₂-autoreceptors

MAO

Post-Synaptic Neuron

α-receptors

β-receptors
REGULATION OF ADRENERGIC TRANSMISSION BY PRESYNAPTIC RECEPTORS

- Autoreceptors ($\alpha_2$)
- Heteroreceptors
CATECHOLAMINES AS ADRENERGIC NEUROTRANSMITTERS

Sympathetic Neurotransmitters
TYPES OF ADRENERGIC RECEPTORS

- $\alpha$-AR defined by the following potency
  norepinephrine > epinephrine >> isoproterenol
  - Subtypes of $\alpha$ were originally identified by selective antagonists
    - $\alpha_1$ blocked by prazosin
    - $\alpha_2$ blocked by yohimbine
  - Further subtypes are now known
  - Selective $\alpha_1$ and $\alpha_2$ agonists are now known

Dr. Raymond Ahlquist (1914-1989), suggested that CA act via two principal types of AR, $\alpha$ and $\beta$ (1948)
TYPES OF ADRENERGIC RECEPTORS

• β-AR defined by the following potency
  isoproterenol >> epinephrine > norepinephrine
  – β₁ and β₂ subtypes of β determined by affinity
    • β₁ affinity – epinephrine = norepinephrine
    • β₂ affinity – epinephrine >> norepinephrine
  – β₃-AR subtype has now been described
• Dopamine (D) receptors
  – Distinct from α and β receptors
  – Important in brain, splanchnic and renal vasculature
# TYPES OF ADRENERGIC RECEPTORS

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonist</th>
<th>Antagonist</th>
<th>Effects</th>
<th>Gene on Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$ type</td>
<td>Phenylephrine</td>
<td>Prazosin</td>
<td>↑ IP$_3$, DAG common to all</td>
<td></td>
</tr>
<tr>
<td>$\alpha_{1A}$</td>
<td></td>
<td></td>
<td></td>
<td>C5</td>
</tr>
<tr>
<td>$\alpha_{1B}$</td>
<td></td>
<td></td>
<td></td>
<td>C8</td>
</tr>
<tr>
<td>$\alpha_{1D}$</td>
<td></td>
<td></td>
<td></td>
<td>C20</td>
</tr>
<tr>
<td>$\alpha_2$ type</td>
<td>Clonidine</td>
<td>Yohimbine</td>
<td>↓ cAMP common to all</td>
<td></td>
</tr>
<tr>
<td>$\alpha_{2A}$</td>
<td>Oxymetazoline</td>
<td></td>
<td></td>
<td>C10</td>
</tr>
<tr>
<td>$\alpha_{2B}$</td>
<td></td>
<td></td>
<td></td>
<td>C2</td>
</tr>
<tr>
<td>$\alpha_{2C}$</td>
<td></td>
<td></td>
<td></td>
<td>C4</td>
</tr>
<tr>
<td>$\beta$ type</td>
<td>Isoproterenol</td>
<td>Propranolol</td>
<td>↑ cAMP common to all</td>
<td></td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Dobutamine</td>
<td>Betaxolol</td>
<td></td>
<td>C10</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Albuterol</td>
<td>Butoxamine</td>
<td></td>
<td>C5</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td></td>
<td></td>
<td></td>
<td>C8</td>
</tr>
<tr>
<td>Dopamine type</td>
<td>Dopamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_1$</td>
<td>Fenoldopam</td>
<td></td>
<td>↑ cAMP</td>
<td>C5</td>
</tr>
<tr>
<td>$D_2$</td>
<td>Bromocriptine</td>
<td></td>
<td>↓ cAMP</td>
<td>C11</td>
</tr>
<tr>
<td>$D_3$</td>
<td></td>
<td></td>
<td>↓ cAMP</td>
<td>C3</td>
</tr>
<tr>
<td>$D_4$</td>
<td>Clozapine</td>
<td></td>
<td>↓ cAMP</td>
<td>C11</td>
</tr>
<tr>
<td>$D_5$</td>
<td></td>
<td></td>
<td>↑ cAMP</td>
<td>C4</td>
</tr>
</tbody>
</table>
**SIGNAL TRANSDUCTION BY ADRENOCEPTORS**

\( \alpha_1 \) receptor activation

IP\(_3\) – increase in cytosolic Ca

DAG – activation of PKC

Activation of mitogen-activated kinases (MAPK) and polyphosphoinositol-3-kinase (PI-3 kinase) regulate gene expression, lead to stimulation of cell growth and proliferation
SIGNAL TRANSDUCTION BY ADRENOCEPTORS

**β-receptor activation**
- Accumulation of cAMP
- Activation of protein kinase A (PKA) by cAMP

**α₂-receptor activation**
- Decrease in cAMP levels
- Inhibition of PKA
DOWNREGULATION OF ADRENERGIC TRANSMISSION

- Desensitization of adrenergic receptors
  - GRK, G-protein coupled receptor kinase
DOWNREGULATION OF ADRENERGIC TRANSMISSION

- Receptor internalization and lysosomal degradation
The Sympathetic Nervous System
“fight or flight”

- **EYES**: Dilates pupil: mydriasis
- **SALIVARY GLANDS**: Decreased salivation
- **HEART**: Increases heart rate, speeds up conduction through AV node, increases force of contraction
- **LUNGS**: Relaxation of bronchial smooth muscle
- **GI TRACT**: Decreased motility (relaxes smooth muscle, contracts sphincters)
- **LIVER**: Increased glucose production (stimulates gluconeogenesis and glycogenolysis)
- **ADRENAL MEDULLA**: Releases norepinephrine and epinephrine
- **BLADDER**: Relaxation (urinary retention)
- **PROSTATE GLAND**: Smooth muscle contraction (urinary obstruction)
- **SWEAT GLANDS**: Increased sweating
- **VASCULAR SMOOTH MUSCLE**: Arteries supplying skeletal muscle and liver: relaxation (vasodilation). Most other vessels: contraction (vasoconstriction)
**HEART:**
- Increases heart rate
- Speeds up conduction through AV node
- Increases force of contraction

**LUNGS:**
- Relaxation of bronchial smooth muscle

**LIVER:**
- Increased glucose production
  (stimulates gluconeogenesis and glycogenolysis)

**ADRENAL MEDULLA:**
- Releases norepinephrine and epinephrine
  (via circulating norepinephrine and epinephrine)

**PROSTATE GLAND:**
- Smooth muscle contraction (urinary obstruction)

**SWEAT GLANDS:**
- Increased sweating

**SOME IMPORTANT SYMPATHETIC RECEPTORS**

- **α₂ Receptors:** Inhibit sympathetic n.s.
- **β₁ Receptors:**
  - Increases heart rate
  - Speeds up conduction through AV node
  - Increases force of contraction
  - Increased cardiac output
- **β₂ Receptors:**
  - LUNGS: Relaxation of bronchial smooth muscle
  - LIVER: Increased glucose production
    (stimulates gluconeogenesis and glycogenolysis)
  - ADRENAL MEDULLA: Releases norepinephrine and epinephrine
    (via circulating norepinephrine and epinephrine)
  - PROSTATE GLAND: Smooth muscle contraction (urinary obstruction)
- **α₁ Receptors:**
  - Most other vessels: Contraction (vasoconstriction)

- **M Receptors:**
  - SWEAT GLANDS: Increased sweating

**VASCULAR SMOOTH MUSCLE:**
- Arteries supplying skeletal muscle and liver: Relaxation (vasodilation)
# DISTRIBUTION OF ADRENOCEPTORS

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissue</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Most vascular smooth muscle (innervated)</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Pupillary dilator muscle</td>
<td>Contraction (dilates pupil)</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Contraction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Platelets</td>
<td>Aggregation</td>
</tr>
<tr>
<td></td>
<td>Adrenergic and cholinergic nerve terminals</td>
<td>Inhibition of transmitter release</td>
</tr>
<tr>
<td></td>
<td>Some vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Fat cells</td>
<td>Inhibition of lipolysis</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Heart</td>
<td>Increases force and rate of contraction</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Respiratory, uterine, and vascular smooth muscle</td>
<td>Promotes smooth muscle relaxation</td>
</tr>
<tr>
<td></td>
<td>Human liver</td>
<td>Activates glycogenolysis</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>Fat cells</td>
<td>Activates lipolysis</td>
</tr>
<tr>
<td>$D_1$</td>
<td>Smooth muscle</td>
<td>Dilates renal blood vessels</td>
</tr>
<tr>
<td>$D_2$</td>
<td>Nerve endings</td>
<td>Modulates transmitter release</td>
</tr>
</tbody>
</table>
ORGAN SYSTEM EFFECTS

• Overall effect of adrenergic drugs on organs and tissues is determined by
  – The type of receptor(s) the tissue is expressing
  – Selectivity of the drug for receptor subtypes
  – Intrinsic activity of the drug at receptor
  – Compensatory reflexes
  – Development of tolerance and tachyphylaxis
**DIRECT vs. INDIRECT SYMPATHOMIMETIC DRUGS**

**Pre-Synaptic Neuron**
- Reuptake Blockers
  - Cocaine
  - INDIRECT ACTING

**Synapse**
- MAO
- α-receptors
- β-receptors
- NE
- Reuptake

**Post-Synaptic Neuron**
- Adrenergic Receptor Agonists
  - INDIRECT ACTING
- Direct Acting Releasing agents
  - Amphetamines, Ephedrine
  - INDIRECT ACTING

**Monoamine Oxidase (MAO) Inhibitors**
- Phenelzine
  - INDIRECT ACTING

**NE - Norepinephrine**
**TYPES OF SYMPATHOMIMETIC DRUGS**

- **Direct sympathomimetics**
  - Alpha agonists
    - Phenylephrine
    - Methoxamine
    - Clonidine
  - Mixed alpha and beta agonists
    - Norepinephrine
    - Epinephrine
  - Beta agonists
    - Dobutamine
    - Isoproterenol
    - Terbutaline
    - Albuterol
    - Ritodrine
  - Dopamine agonists
    - Dopamine
    - Fenoldopam

- **Indirect sympathomimetics**
## SELECTIVITY OF ADRENERGIC AGONISTS

<table>
<thead>
<tr>
<th>Relative Receptor Affinities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha agonists</strong></td>
</tr>
<tr>
<td>Phenylephrine, methoxamine</td>
</tr>
<tr>
<td>Clonidine, methylnorepinephrine</td>
</tr>
<tr>
<td><strong>Mixed alpha and beta agonists</strong></td>
</tr>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Epinephrine</td>
</tr>
<tr>
<td><strong>Beta agonists</strong></td>
</tr>
<tr>
<td>Dobutamine$^1$</td>
</tr>
<tr>
<td>Isoproterenol</td>
</tr>
<tr>
<td>Terbutaline, metaproterenol, albuterol, ritodrine</td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Fenoldopam</td>
</tr>
</tbody>
</table>
ORGAN SYSTEMS EFFECTS

• Cardiovascular system
  – Blood vessels
    • $\alpha_1$ causes contraction and increase in vascular resistance
    • $\beta_2$ causes smooth muscle relaxation
    • $D_1$ causes smooth muscle relaxation
    • Significant differences in receptor types found in vascular beds
      – Skin vessels and mucous membranes – mostly $\alpha_1$
      – Splanchnic – mostly $\alpha_1$ and $D_1$
      – Skeletal muscle – $\alpha_1$ and $\beta_2$
      – Renal, cerebral – $D_1$ and $\alpha_1$
ORGAN SYSTEM EFFECTS

• Cardiovascular system
  – Heart – mostly $\beta_1$
    • Increase calcium influx
      – Positive chronotropic – increase pacemaker rate
      – Increase in conduction velocity at AV node
      – Refractory period decreased
      – Positive inotropic effects
    • Presence of normal reflexes – heart rate response may be dominated by reflex response to blood pressure changes
**ORGAN SYSTEM EFFECTS**

Cardiovascular system

- Blood Pressure = Cardiac Output x Vascular Resistance
- **Epinephrine** = agonists at ALL adrenergic receptors; little change in blood pressure
- **Norepinephrine** = low affinity towards beta-2 adrenergic receptors; large increase in blood pressure

**Norepinephrine**

- $\alpha_1$
  - Vasoconstriction = Increased Blood Pressure

**Epinephrine**

- $\beta_1$
  - Increased Cardiac Output = Increased Blood Pressure

- $\beta_2$
  - Vasodilation = Decreased Blood Pressure
ORGAN SYSTEM EFFECTS

Effect of adrenomimetics on heart rate (HR) and blood pressure (BP)
ORGAN SYSTEM EFFECTS

• Cardiovascular system
  – Alpha agonist – phenylephrine
    • Increases peripheral arterial resistance
    • Decreases venous capacitance
    • Increase blood pressure but a reflex decrease in heart rate
    • CO may not change - increase venous return may increase stroke volume
  – Beta agonist – isoproterenol
    • Increases cardiac function and cardiac output
    • Relaxes vascular smooth muscle and decreases blood pressure
ORGAN SYSTEMS EFFECTS

• Eye
  – $\alpha_1$ agonist – contracts pupil dilator muscle - mydriasis

• Respiratory tract
  – $\beta_2$ agonist – bronchodilation
  – $\alpha_1$ agonist – decrease in mucus secretion in the upper respiratory tract – decongestant action – is due to the contraction of vascular smooth muscle
**ORGAN SYSTEMS EFFECTS**

- **Genitourinary system**
  - Human uterus contains both $\alpha$ and $\beta_2$
    - $\beta_2$ – mediates relaxation – useful in pregnancy
  - Bladder base, urethral sphincter and prostate
    - $\alpha_1$ promotes contraction $\rightarrow$ urinary retention
    - $\beta_2$ mediates relaxation
  - Ejaculation – proper $\alpha$ receptor activation
  - Detumescence of erectile tissue – via $\alpha_1$
ORGAN SYSTEM EFFECTS

• Metabolic effects
  – $\beta_3$ activation – fat cells – lipolysis, enhance the release of free fatty acids into plasma
  – $\alpha_2$ in lipocytes – inhibits lipolysis by decreasing intracellular cAMP
  – $\beta_2$ agonists – increase glycogenolysis and gluconeogenesis in the liver

• Endocrine effects
  – $\beta_2$ receptor activation – stimulates insulin secretion
  – $\alpha_2$ agonists – inhibit insulin secretion
  – Stimulation of renin release by $\beta_1$ (inhibited by $\alpha_2$)

• One mechanism by which $\beta$-receptor antagonists are effective for the treatment of hypertension
ORGAN SYSTEM EFFECTS

• Central nervous system
  – Vary significantly with the ability to pass BBB
  – Catecholamines – do not pass
  – Non-catecholamines (such as amphetamine) will pass BBB and have following effects
    • Mild alerting effects
    • Improved attention to boring tasks
    • Insomnia
    • Euphoria
    • Anorexia
    • Psychotic behavior
ALPHA ADRENERGIC AGONISTS

- Phenylephrine – direct acting $\alpha$ agonist
  - $\alpha_1 > \alpha_2 >>>\beta$
    - Not a catechol – not inactivated by COMT – longer duration of action
    - Effective mydriatic and decongestant
    - Can be used to raise blood pressure

- Methoxamine – direct acting $\alpha_1$ selective agonist
  - Similar to phenylephrine
  - Limited use – hypotensive states
ALPHA ADRENERGIC AGONISTS

• Midodrine – direct acting $\alpha_1$ selective agonist
  – Use for disabling chronic orthostatic hypotension
  – Unlabeled use – urinary incontinence

• Xylometazoline and Oxymetazoline – direct acting $\alpha$ agonists
  – Topical decongestants – constrict vessels in nasal mucosa
  – Large dose of oxymetazoline may cause hypotension similar to clonidine because of high $\alpha_{2A}$ affinity
ALPHA ADRENERGIC AGONISTS

- $\alpha_2$ selective agonists $\alpha_2 > \alpha_1 >>>>> \beta$
  - Decrease blood pressure – central effect – decreasing sympathetic outflow
  - Local application may produce vasoconstriction
    - Clonidine
    - Methyldopa
    - Guanfacine – may have less adverse effects than clonidine
    - Guanabenz
    - Dexmedetomidine – indicated for sedation during initial intubation
MIXED ALPHA AND BETA AGONISTS

- **Epinephrine** - $\alpha_1 = \alpha_2 ; \beta_1 = \beta_2$
  - Potent cardiac stimulant
  - Variable effects on the vascular tone
  - Because of significant $\beta_2$ agonist effects causes bronchodilation and vasodilation in certain vascular beds (skeletal muscle)
  - Total peripheral vascular resistance may fall

- **Norepinephrine** - $\alpha_1 = \alpha_2 ; \beta_1 >> \beta_2$
  - Potent cardiac stimulant
  - Potent vasoconstrictor
  - Lacks $\beta_2$ agonist effects – no bronchodilation and vasodilation
  - Increases peripheral vascular resistance and blood pressure
BETA ADRENERGIC AGONISTS

- **Isoproteanol** - $\beta_1 = \beta_2 \gg \gg \alpha$
  - Non-selective beta agonist
  - Potent cardiac stimulant, increases cardiac output
  - Vasodilator, decreases arterial pressure
  - Causes bronchodilation

- **Dobutamine** - $\beta_1 > \beta_2 \gg \gg \alpha$
  - Selective beta-1 agonist
  - Cardiac stimulant
BETA ADRENERGIC AGONISTS

• Ritodrine - $\beta_2 > \beta_1 >>>> \alpha$
  – Selective beta-2 agonist
  – Causes uterine relaxation

• Terbutaline, Albuterol - $\beta_2 > \beta_1 >>>> \alpha$
  – Selective beta-2 agonists
  – Cause bronchodilation
DOPAMINE AGONISTS

- Dopamine $D_1 = D_2 \gg \beta_1 \gg \alpha_1$
  - $D_1$ stimulation causes vasodilation
  - Especially important for renal blood flow
  - Activation of presynaptic $D_2$ – suppresses norepinephrine release
  - Activates $\beta_1$ in heart at higher doses
  - At still higher doses stimulates vascular $\alpha$AR $\rightarrow$ vasoconstriction – at high concentration mimics the actions of mixed AR agonists

- Fenoldopam $D_1 \gg D_2$
  - Causes peripheral vasodilation – used in severe hypertension
TYPES OF SYMPATHOMIMETIC DRUGS

• Direct sympathomimetics
• Indirect sympathomimetics
  – Cocaine: inhibits re-uptake
  – Phenelzine: inhibits MAO
  – Amphetamines: releasing agents, may have weak direct effect
  – Ephedrine: releasing agent AND direct adrenergic receptor agonist
SELECTIVITY OF INDIRECT vs. DIRECT ADRENERGIC AGONISTS DRUGS

- **Indirect-acting Drugs**
  - **Non-selective:** All receptors that respond to NE are affected
- **Direct-acting Drugs** (receptor agonists)
  - **More Selective:** Only receptors that directly bind drugs are affected
  - Some DIRECT-ACTING drugs are NON-SELECTIVE (bind to multiple receptor types – Epinephrine)

**EXAMPLE:**
- **Cocaine:** inhibits NE re-uptake (indirect acting sympathomimetic, non-selective agonist)
- **Phenylephrine:** selective alpha-1 receptor agonist (selective adrenergic receptor agonist)
- **Dobutamine:** selective beta-1 receptor agonist (selective adrenergic receptor agonist)
INDIRECT ADRENERGIC AGONISTS

- Usually more lipophilic compounds (not catecholamines)
- Easily penetrate BBB – have significant central effects – central nervous system stimulants
  - Amphetamine, methamphetamine
    - Marked stimulant effect on mood and alertness
    - Decrease appetite
    - Drugs of abuse
  - Methylphenidate
    - Used in children with attention deficit hyperactivity disorder (ADHD)
    - Similar to amphetamine – has abuse potential
INDIRECT ADRENERGIC AGONISTS

– Ephedrine – releases stored catecholamines with some direct action
  • Plant constituent
  • Non-catechol – long duration of action
  • Nonselective – similar to epinephrine in actions
  • Mild stimulant – enters CNS
  • Clinical use
    – Nasal decongestant
    – Pressor agent
    – Stress incontinence in women
– Pseudoephedrine – indirect action only
  • Nasal decongestant
  • Stress incontinence in woman
INDIRECT ADRENERGIC AGONISTS

– Mephentermine
  • Both direct alpha- and indirect agonist
  • Used in the treatment of hypotension, and shock
  • Central stimulant effects are less severe than with amphetamine

– Cocaine
  • Inhibits transmitter reuptake at adrenergic synapses
  • Peripheral and intense central action
  • Local anesthetic properties
  • Heavily abused drug

– Phenelzine
  • Inhibitor of MAO
  • Increases NE stores in CNS
  • Antidepressant action
INDIRECT ADRENERGIC AGONISTS

– Tyramine
  • a product of tyrosine metabolism that is found in high concentrations of certain types of food
    – Cheese
    – Cured meats
    – Smoked and pickled fish
  • Releases stored NE from presynaptic adrenergic terminals
  • Is metabolized by MAO in liver
  • May lead to marked increase in blood pressure in patients taking MAO inhibitors
CLINICAL PHARMACOLOGY OF ADRENERGIC AGONISTS

Cardiovascular conditions
• To increase blood pressure
  – Hypotensive emergencies – hemorrhagic shock, overdose of antihypertensives, CNS depressants
    • Norepinephrine
    • Phenylephrine
    • Methoxamine
  – Chronic hypotension
    • Ephedrine
    • Midodrine
  – Cardiogenic shock – due to massive acute myocardial infarction
    • Dopamine
    • Dobutamine
Cardiovascular conditions

• Conditions when blood flow is to be reduced
  – Decongestion of mucous membranes
    • Phenylephrine, ephedrine, pseudoephedrine, xylomethazoline, oxymethazoline
  – Hemostasis during surgery
    • Epinephrine
  – Combination with local anesthetics
    • Epinephrine, phenylephrine, norepinephrine


CLINICAL PHARMACOLOGY OF ADRENERGIC AGONISTS
Other cardiovascular conditions

- Heart failure (short-term use of beta-1 agonists)
- Hypertension (alpha-2 agonists)
- Emergency therapy for complete AV block and cardiac arrest
  - Epinephrine
  - Isoproterenol
CLINICAL PHARMACOLOGY OF ADRENERGIC AGONISTS

• Bronchial asthma
  – Beta-2 selective agonists
    • Albuterol
    • Terbutaline
• Anaphylaxis – immediate (type 1) allergic reaction characterized by respiratory and cardiovascular components
  – Respiratory component – bronchospasm and upper airway congestion
  – Cardiovascular component – severe hypotension, cardiac depression
  – Epinephrine – effective at both components
CLINICAL PHARMACOLOGY OF ADRENERGIC AGONISTS

• Ophthalmic applications
  – Examination of retina – induction of mydriasis
    • Phenylephrine
  – Glaucoma
    • Alpha-2 selective agonists (Apraclonidine, brimonidine)

• Genitourinary applications
  – Suppression of premature labor
    • Beta-2 agonists (ritodrine, terbutaline)
  – Stress incontinence
    • Ephedrine
    • Pseudoephedrine
  – Priapism
    • Alpha-1 agonists (phenylephrine) via injection into the penis
Central nervous system conditions

- Narcolepsy – sudden brief sleep attacks
  - Amphetamines
  - Methylphenidate

- ADHD – short attention span, learning problems, and hyperkinetic physical behavior
  - Methylphenidate
  - Modafinil
Central nervous system conditions

- Obesity – central inhibition of appetite and increased energy expenditure
  - Phentermine
  - Ephedrine
- Sedation in general anesthesia and intensive care units
  - Dexmedetomidine
ADVERSE EFFECTS OF ADRENERGIC AGONISTS

- Present extensions of their pharmacologic effects in CVS and CNS
- Cardiovascular adverse effects
  - Elevation in blood pressure
  - Increased cardiac work may precipitate myocardial ischemia and heart failure – special attention should be given to elderly patients and patients with hypertension, coronary artery disease, and chronic heart failure
  - Sinus tachycardia and serious ventricular arrhythmias
  - Direct myocardial damage leading to cardiomyopathy
  - May induce sudden cardiac death
ADVERSE EFFECTS OF ADRENERGIC AGONISTS

• Central nervous system toxicity
  – Most of agonist drugs (catecholamines and other polar drugs that do not cross BBB), do not cause CNS toxicity
  – Amphetamine and amphetamine-like compounds cause
    • Insomnia
    • Anxiety, restlessness
    • Paranoid state
  – Cocaine may cause
    • Convulsions
    • Arrhythmias
    • Hemorrhagic stroke