Adrenergic drugs 1

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Sources

Lippincott Illustrated Reviews: Pharmacology 7th Edition
Katzung ; Basic & Clinical Pharmacology 14th Edition
Bennett & Brown ; Clinical pharmacology 11th edition
Essentials of Medical Pharmacology; Lafi 09

α- Adrenergic Receptors : Molecular Actions

α1 receptor increase IP3, DAG, and intracellular Ca+2

lead to contraction of smooth muscle in;

1. blood vessels,
2. prostate ,
3. eye in glaucoma

α2 receptor inhibit adenylyl cyclase

For persynaptic α2 receptors, lead to decreased calcium influx and decreased release of nor epinephrine .

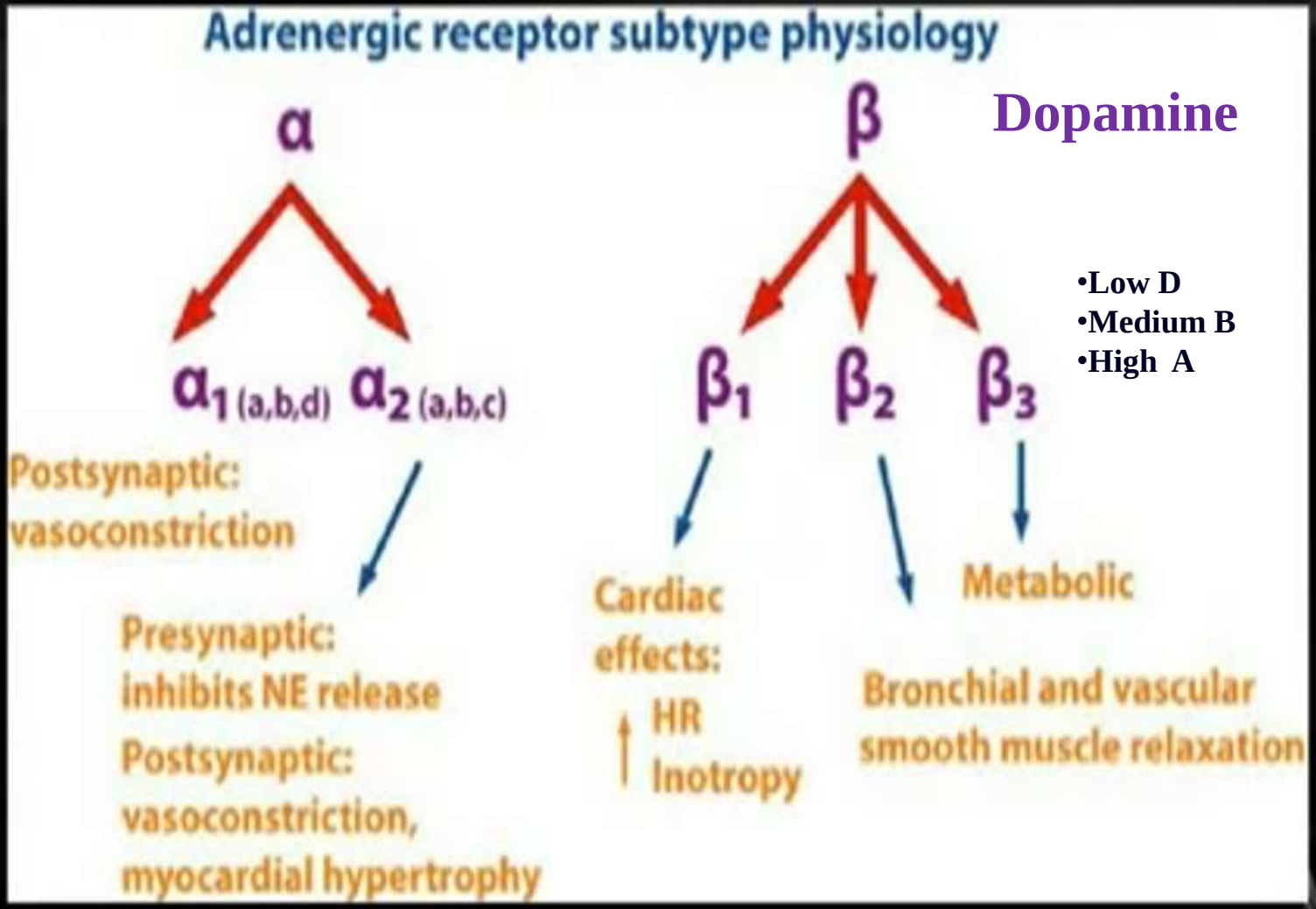
β- Adrenergic Receptors : Molecular Actions

β receptor activate adenylyl cyclase and intracellular cAMP

β1 receptor generally increase cardiac out put,

β2 receptor generally dilate bronchial , uterine and vascular smooth muscle (skeletal blood vessels)

Adrenergic Receptors



Each receptor had

- Physiological function (that may be deranged by disease)
- Agonist drug (and mediator)
- Antagonist drug
- Each of the last two had clinical application

α 1 **Adrenergic receptors**

- Activation causes :
  - Vasoconstriction
  - Mydriasis
  - Contraction of bladder trigone and sphincter (urinary retention)
  - Contraction of capsular smooth muscle prostate

Adrenoreceptor sensitivity

- β-receptors are usually more sensitive to activators than α-receptors

- With drugs that exert both effects,
  - the β responses predominate at low doses :
  - at higher doses , the α responses predominate

Exception is NE , for which α responses predominate at lower doses

α_1-adrenergic Receptor Agonist

Agonist (specific) is phenylephrine
- Used to treat nasal congestion
- A similar drug is methoxamine
- Phenylephrine is also used to raise blood pressure intravenously
- Causes rebound bradycardia

These medications must be given in large central veins to prevent digital necrosis secondary to vasoconstriction

Drug	Action (receptors)	Selected therapeutic uses and important remarks
Non-catecholamines♠ **Phenylephrine**	α_1	Nasal congestion, hypotension
Methoxamine	α_1	Hypotension (during surgery, does not produce cardiac arrhythmias in sensitised heart, i.e. no beta activity) Paroxysmal supraventricular tachycardia

α_1-adrenergic Receptor Antagonists

Antagonists (specific) are prazosin, terazosin, and tamsulosin, doxazosin

- Prazosin used for hypertension
- Terazosin and tamsulosin used for benign prostatic hypertrophy (relaxes prostatic capsular smooth muscle)

Antagonists (nonspecific, i.e., they block α_1 and α_2) are phenoxybenzamine and phentolamine

- Medical management of pheochromocytoma

These meds can cause rebound tachycardia

α_1-adrenergic Receptor Antagonists

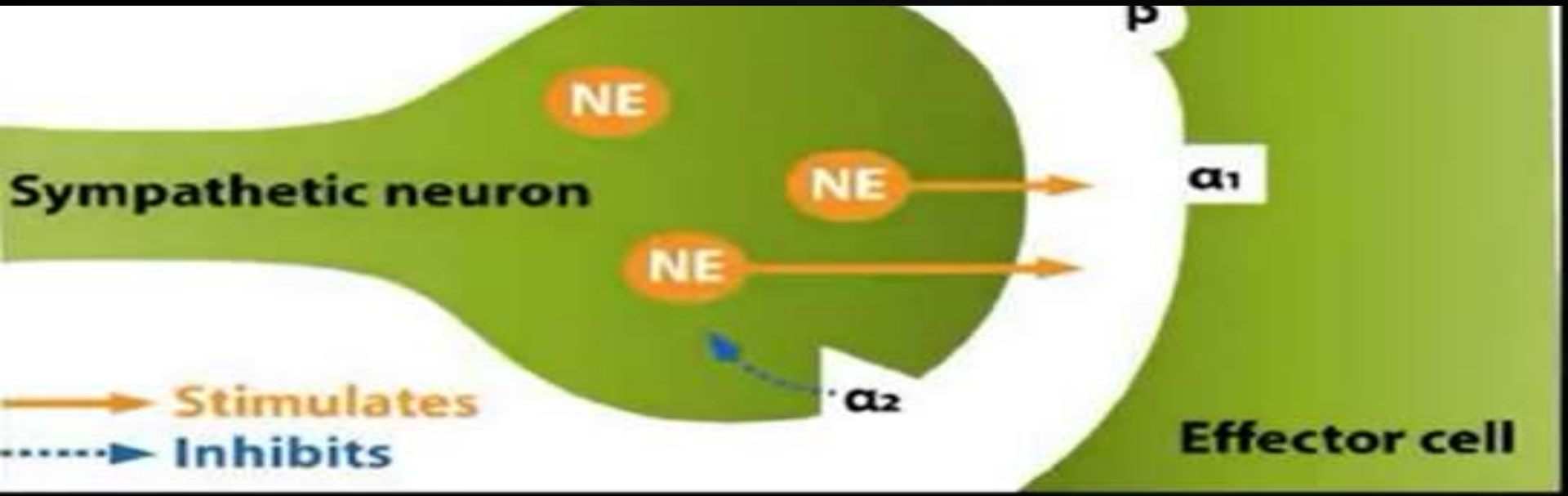
Drug	Action (receptors)	Selected therapeutic uses and important remarks
α-adrenoceptor antagonists		
Phenoxybenzamine	α_1, α_2 (blocking)	Pheochromocytoma, Raynaud's disease (irreversible block)
Phentolamine	α_1, α_2	Diagnosis of pheochromocytoma (competitive block); it induces reflex tachycardia. (by vasodilatation and blocking autoregulatory α_2 receptors)

α_2-adrenergic Receptors

Found at prejunctional nerve terminals

- Activation inhibits neurotransmitter release (presynaptic inhibition)

Also found peripherally where they behave like α_1 receptors



α_2-adrenergic Receptors (cont.)

Agonist is clonidine

- Used to treat hypertension
- A similar drug is guanabenz

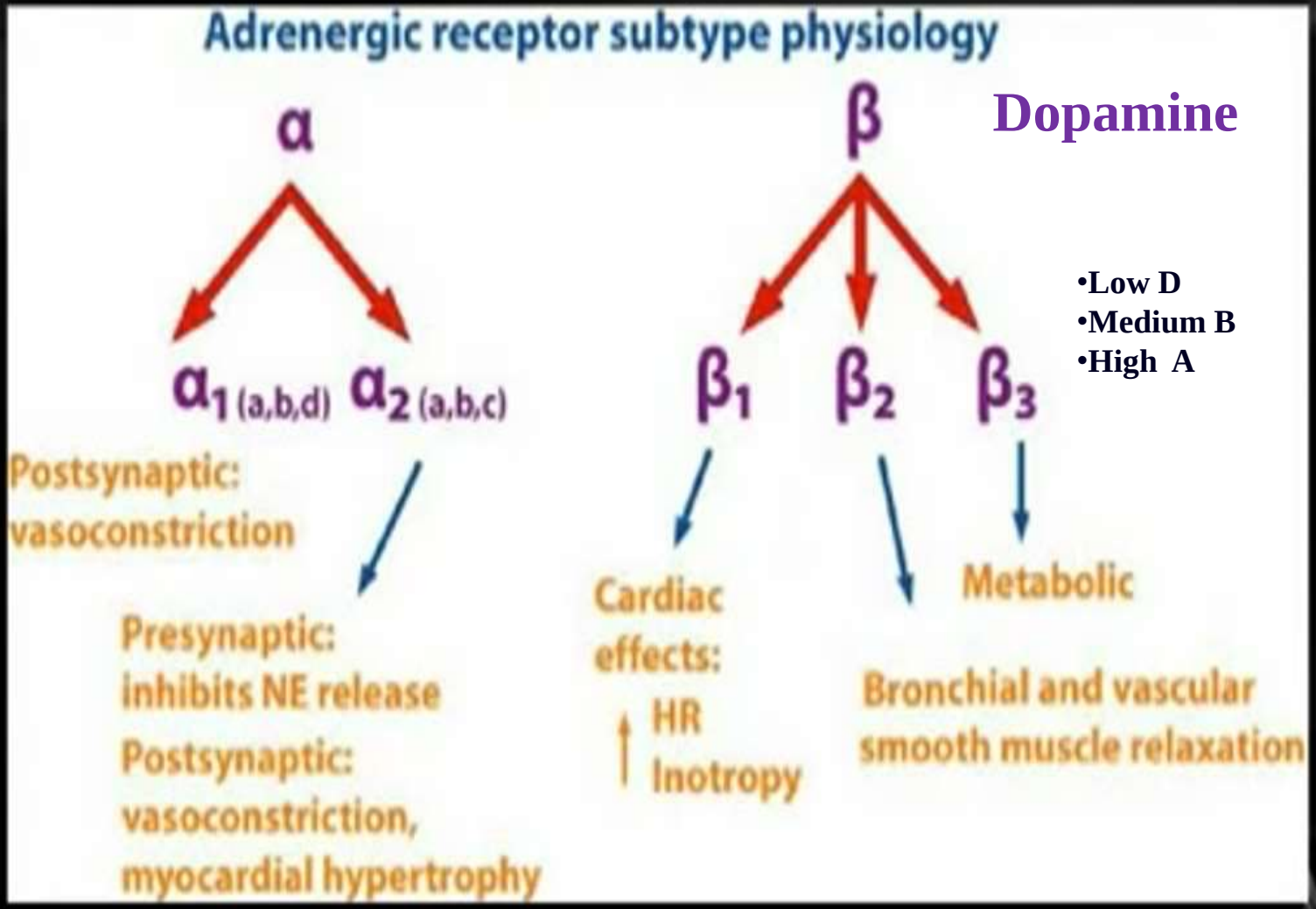
Antagonist (specific) is yohimbine

- Not used clinically

Phenoxybenzamine	α_1, α_2 (blocking)	Pheochromocytoma, Raynaud's disease (irreversible block)
Phentolamine	α_1, α_2	Diagnosis of pheochromocytoma (competitive block); it induces reflex tachycardia. (by vasodilatation and blocking autoregulatory α_2 receptors)

Adrenergic drugs 2

Adrenergic Receptors



β_1-adrenergic Receptors

Activation causes

- Increased heart rate (effect on SA node)
- Increased conduction velocity (effect on AV node)
- Increased force of contraction (positive inotropy; effect on atrial and ventricular muscle)

β_1-adrenergic Receptors (cont.)

Agonist is dobutamine

Used to treat cardiogenic shock and heart failure

Drug	Action (receptors)	Selected therapeutic uses and important remarks
Dopamine DBA	dopaminergic β_1	1decreased renal function 2Congestive heart failure 3Shock,
Dobutamine	β_1	Congestive heart failure

β_1-adrenergic Receptors (cont.)

Antagonists ("β-blockers") are used to treat angina, hypertension, and arrhythmias

- Propranolol (nonspecific; blocks β_1 and β_2)
- Esmolol (specific, β_1 only)
- Metoprolol (specific, β_1 only)

Drug	Action (receptors)	Selected therapeutic uses and important remarks
β-adrenoceptor antagonists[2]		
Acebutolol Atenolol Metoprolol Esmolol (4Minutes)	β_1	Hypertension

Drug	Action (receptors)	Selected therapeutic uses and important remarks
β-adrenoceptor antagonists[2]		
Propranolol	β_1, β_2	Hypertension, migraine, hyperthyroidism, pheochromocytoma, angina pectoris, myocardial infarction
Timolol	β_1, β_2	Glaucoma, hypertension
Pindolol	β_1, β_2	Hypertension

Drug	Action (receptors)	Selected therapeutic uses and important remarks
β-adrenoceptor antagonists[2]		
Labetalol	β_1, β_2, α_1	Pheochromocytoma , Cocaine Over dose (hypertension)
Carvedolol	β_1, β_2, α_1	Angina pectoris, cardiomyopathy, (heart failure, hypertension) Higher ratio of β to α blockade than labetolol

β_2-adrenergic Receptors

Activation causes

- Vasodilation (all vessels)
- Decreased preload
- Muscle tremor
- Glycogenolysis
- Uterine relaxation
- Bronchodilation

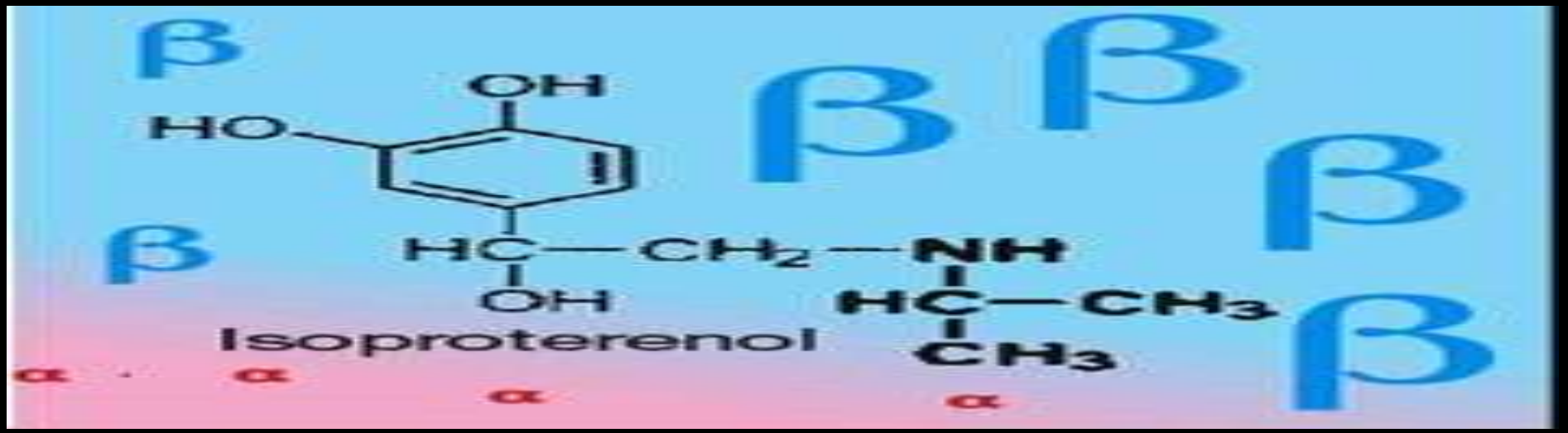
β_2-adrenergic Receptor Agonists

Salbutamol Terbutaline Ritodrine	**β2**	**Asthma (bronchospasm), premature labour (they have short onset and duration of action)**
Salmeterol Formoterol	**β2**	**Asthma (they have slow onset and long duration of action)**

Drug	Action (receptors)	Selected therapeutic uses and important remarks
Catecholamine* Noradrenaline	α_1, α_2, β_1	Shock

Drug	Action (receptors)	Selected therapeutic uses and important remarks
Adrenaline	α_1, α_2, β_1, β_2	Acute asthma, open angle glaucoma, anaphylactic shock, in local anaesthetics to increase duration of action

Drug	Action (receptors)	Selected therapeutic uses and important remarks
Isoprenaline	β_1, β_2	Asthma, severe bradycardia, heart block, sinus bradycardia



Amphetamines: Clinical Uses

Attention-deficit hyperactivity disorder (ADHD)

Methylphenidate

Short-term weight loss

Narcolepsy

Amphetamine	**α, β (CNS)**	**Attention deficit syndrome (in children)**

Ephedrine

Similar effects to amphetamines although not used for ADHD or narcolepsy

Used therapeutically as decongestant

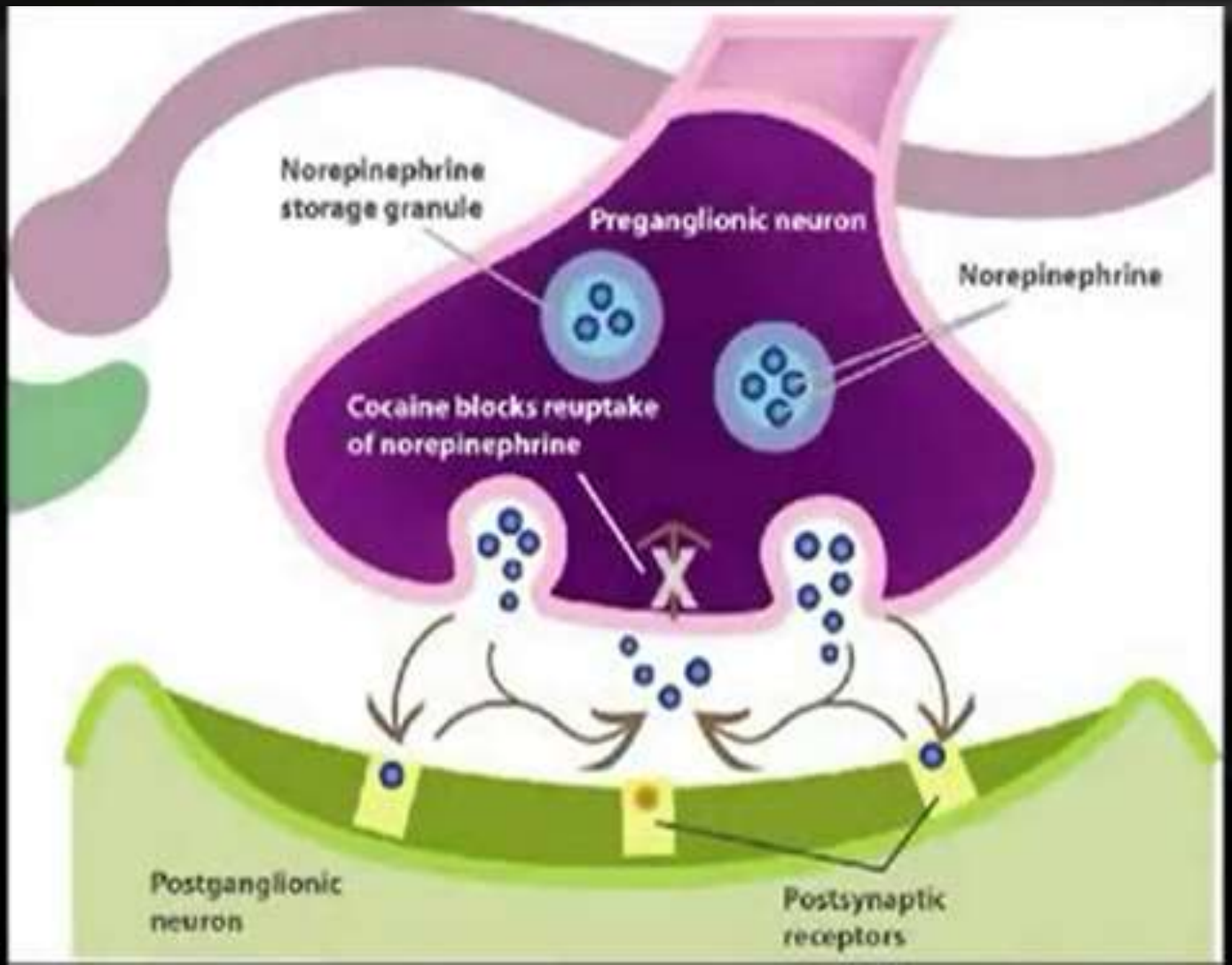
Used in unregulated dietary supplements (e.g., Metabolife®) and herbal preparations such as ephedra and *ma huang* until removed from market by FDA in 2004

- Association with adverse effects including sudden death (e.g., when used by athletes)

Ephedrine	**α_1, α_2, β_1, β_2 (CNS)**	**Nasal congestion, asthma**

Drug	Action (receptors)	Selected therapeutic uses and important remarks
Drugs affecting neurotransmitter release or re-uptake		
Reserpine	Disrupts storage of amines causing depletion of amines	Hypertension (no longer used because of adverse-effects like depression)
Guanethidine	Adrenergic neurone blocking agent	Hypertension (no longer used because of adverse-effects, orthostatic hypotension, male sexual dysfunction
Cocaine	Neuronal amine re-uptake (U_1) blocker	CNS stimulant (drug abuse)

Cocaine


Norepinephrine storage granule
Preganglionic neuron
Norepinephrine
Cocaine blocks reuptake of norepinephrine
X
Postganglionic neuron
Postsynaptic receptors

Dopamine Receptors : Molecular Actions

Complex action at multiple receptors depending on the dose

Activation of D1 causes vasodilation of renal , mesenteric , and coronary vasculature

activate adenylyl cyclase → intracellular cAMP

D1 receptors are also found on the brain / CNS.

D2 receptors are inhibitory have less important role, are responsible for presynaptic feedback inhibition

"Low-dose dopamine"

Activates D_1 receptors.

Increases renal/mesenteric blood flow.

Commonly used in ICU to preserve renal blood flow.

"Medium-dose dopamine"

Increases cardiac output via activation of β_1-adrenoreceptors.

Useful in management of shock states.

Can precipitate arrhythmias

"High-dose dopamine"

Activates α_1-adrenoreceptors

Vasoconstriction

Increases systolic and diastolic blood pressure

Can lead to adverse effects

- Peripheral ischemia
- Possible necrosis and gangrene

Thank you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Home work

Summarize adrenergic receptors in the following mind map

1. **Alpha 1**
    A. **Site**
    B. **Physiological function**
    C. **Agonists**
    D. **Antagonists**
        A. **Selective**
        B. **None selective**
    E. **Clinical uses of drugs for each C&D**
2. **Alpha2**
3. **Beta1**
4. **Beta 2**
5. **D1**
6. **D2**