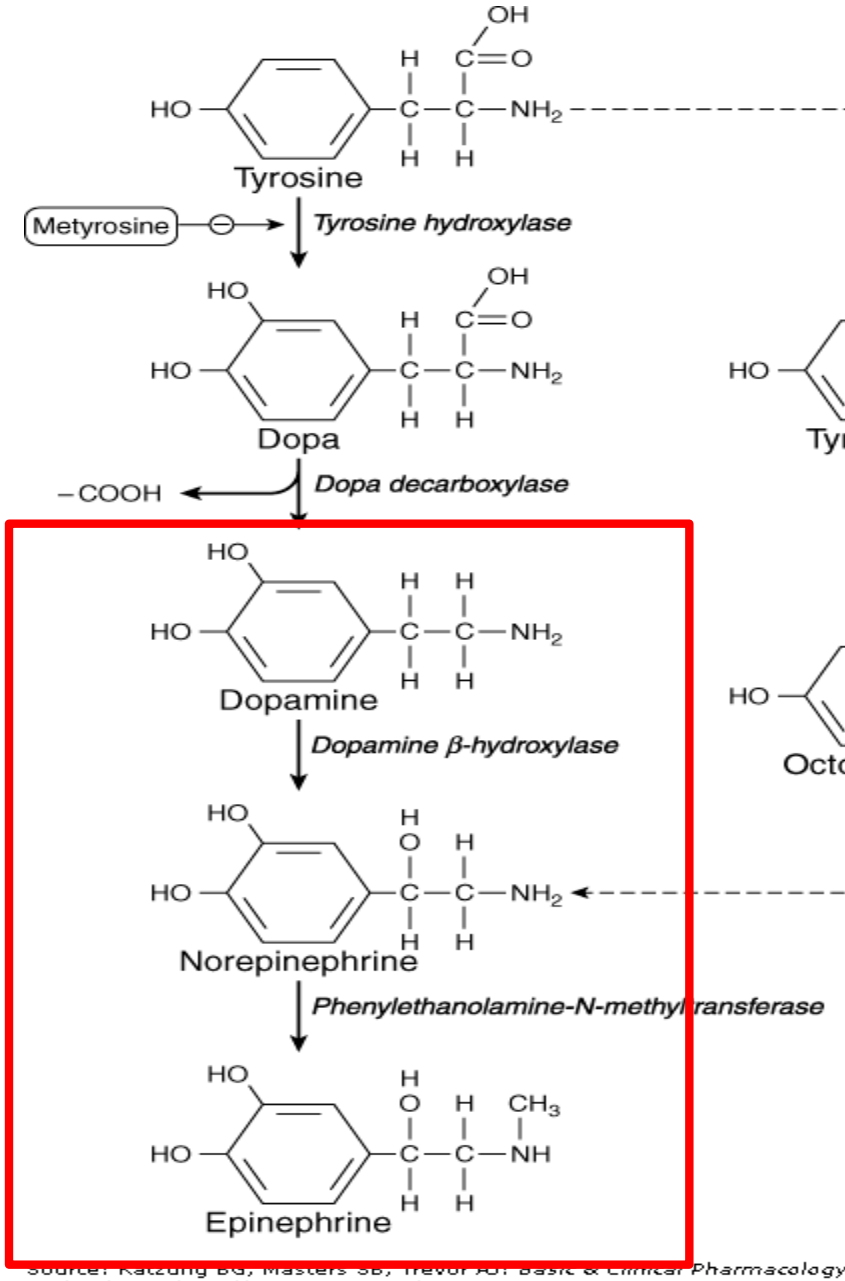
ADRENOCEPTOR AGONISTS & SYMPATHOMIMETIC DRUGS

OVERVIEW

- The sympathetic nervous system is an important regulator of virtually all organ systems

- The ultimate **effects of sympathetic stimulation** are **mediated** by
  - release of **norepinephrine** from **nerve terminals**,
  - which then activates **adrenoceptors (*pre*- or *post*-synaptically)**

- Also, in **response to a variety of stimuli** such as stress, the **adrenal medulla** releases epinephrine, which is transported in the blood to target tissues…….HORMONE
- CATECHOLAMINES…..RECEPTORS



sympathomimetic amines that contain **3,4-*dihydroxy*benzene** group (such as:

epinephrine,
norepinephrine,
isoproterenol,
and dopamine) are called **catecholamines**

Drugs that **mimic** the actions of **epinephrine or norepinephrine** have traditionally been termed **sympathomimetic drugs**

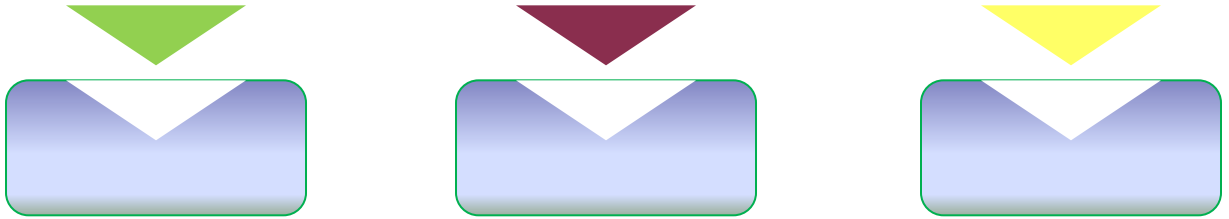
ADRENERGIC RECEPTORS (ADRENOCEPTORS)

- There are **two main groups** of adrenergic receptors, **α** and **β**,
  - with several subtypes.

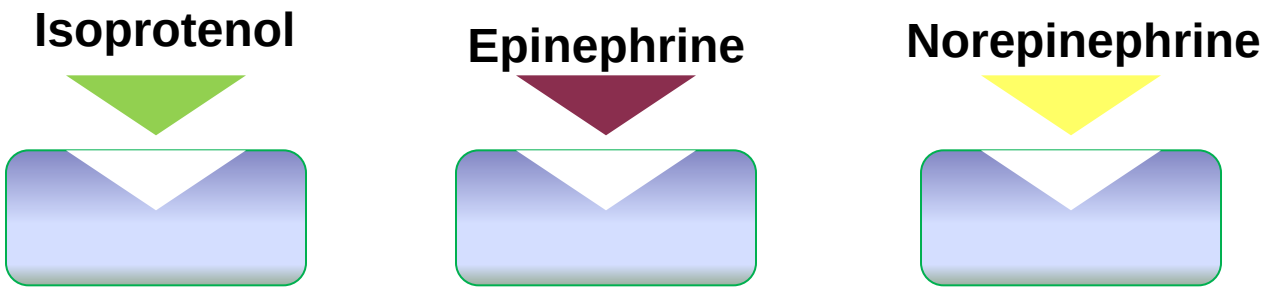
- These were initially **identified on the basis of** their responses to the adrenergic agonists:
  - epinephrine,
  - norepinephrine,
  - and isoproterenol

- **All the adrenoceptors** are G-protein coupled receptors **(GPCRs)**…..G????

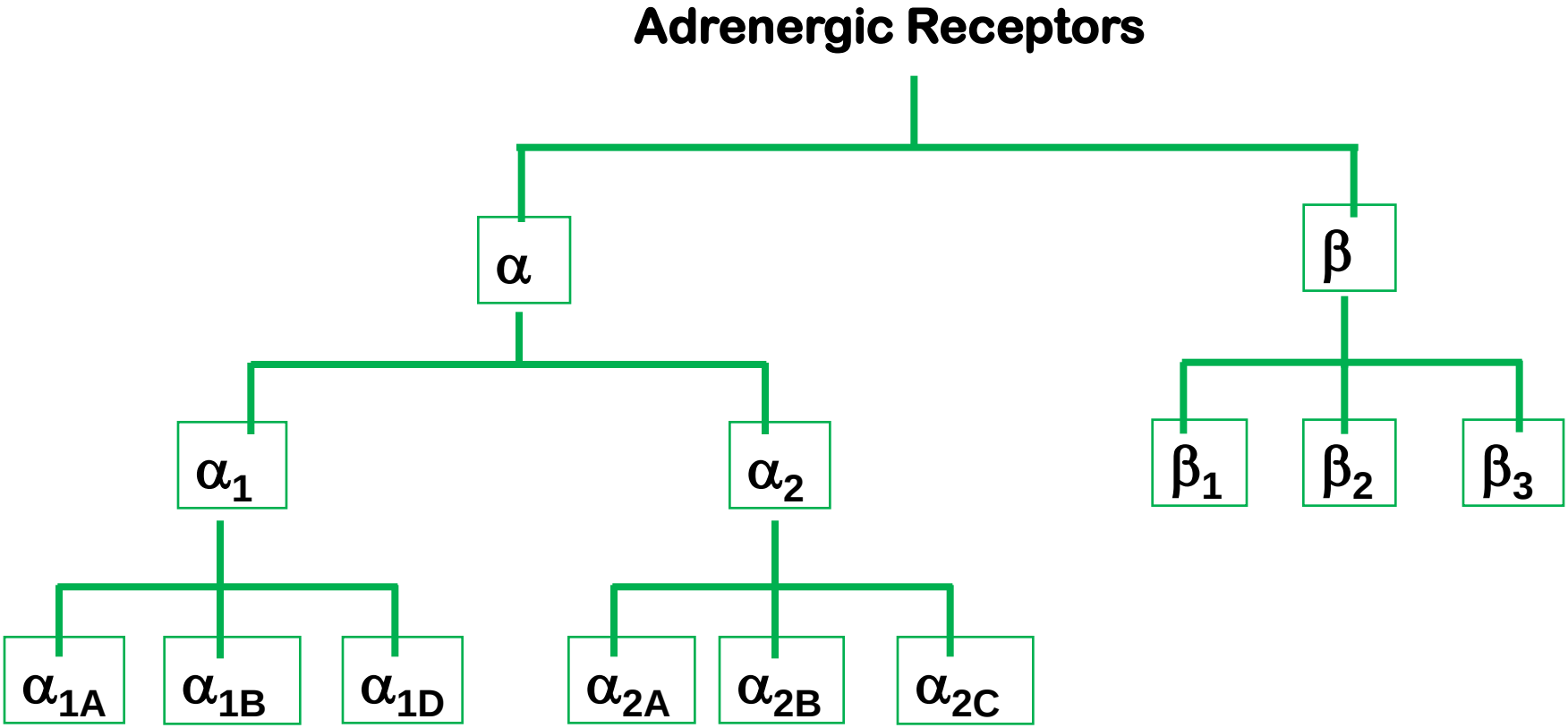
α Adrenoceptors



β Adrenoceptors



- The development of selective antagonists revealed the presence of subtypes of these receptors, which were finally characterized by molecular cloning. These proteins/receptors belong to a multigene family



Necessary for understanding the selectivity of some drugs. ***Tamsulosin*** (selective α_{1A} antagonist), benign prostate hyperplasia, (urinary tract and prostate gland)

Table 9-1 Adrenoceptor Types and Subtypes

Receptor	Agonist	Antagonist	Effects
α_1 type (α_{1A}, α_{1B}, α_{1D})	Phenylephrine	Prazosin	↑ IP3, DAG common to all
α_2 type (α_{2A}, α_{2B}, α_{2C})	Clonidine	Yohimbine	↓ cAMP common to all
β type (β_1, β_2, β_3)	Isoproterenol	Propranolol	↑ cAMP common to all
Dopamine type	Dopamine		
D1-like (D_1, D_5)			↑ cAMP
D2-like (D_2, D_3, D_4)			↓ cAMP

ADRENERGIC RECEPTORS (ADRENOCEPTORS)

ALPHA RECEPTORS

- The **α_1** receptors have a **higher affinity** for **phenylephrine** than do the **α_2** receptors.
- Conversely, **clonidine** is more selective **to α_2** receptors (has less effect on α_1 receptors)
- Both **epinephrine and norepinephrine** have **similar affinity for α and β** receptors

SELECTIVITY

- **Selectivity??** A drug may **preferentially bind** to one **subgroup of receptors** at concentration **too low** to **interact e**xtensively **with other subgroup**! (e.g., important in β receptors)

- ***Selectivity not absolute***…
  - **higher concentration**, the drug interacts **with other subgroups**!! >>>>>>>(**drug are not specific**!)

- The **effect depends also** on the
  - **expression** of the **subtype on a given tissue**

- The **function of specific subtype receptor** is known through development of ***"knockout mice"***

ADRENERGIC RECEPTORS (ADRENOCEPTORS)

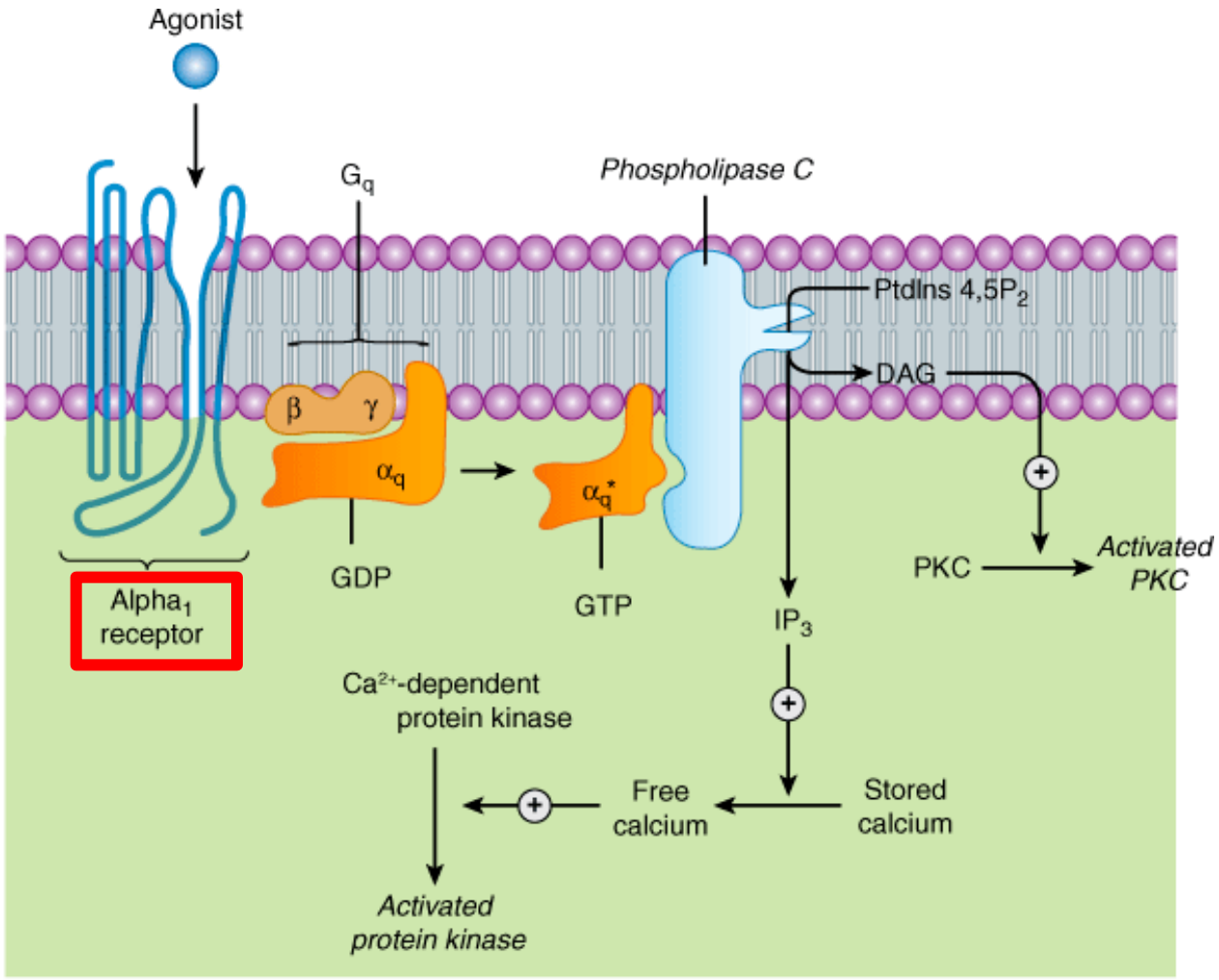
ALPHA RECEPTORS

I. **α_1 Adrenoceptors:**

- These receptors are **present on the postsynaptic membrane of the effector organs**
  - and mediate many of the classic involving **contraction of smooth muscle**

- **Alpha$_1$** receptors are **coupled** via **G_q** proteins to **phospholipase C.**
  - Activation of α_1 receptors result in the generation of inositol-1,4,5-trisphosphate **(IP_3)** and diacylglycerol (**DAG)** from phosphatidylinositol. **IP_3 initiates the release of Ca^{2+} from the endoplasmic reticulum into the cytosol** and the **activation of various calcium-dependent protein kinases**.
  - Activation of these receptors may **also increase influx** of **calcium** across the **cell's plasma membrane**.

- **DAG activates protein kinase C**, which modulates activity of many signaling pathways



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

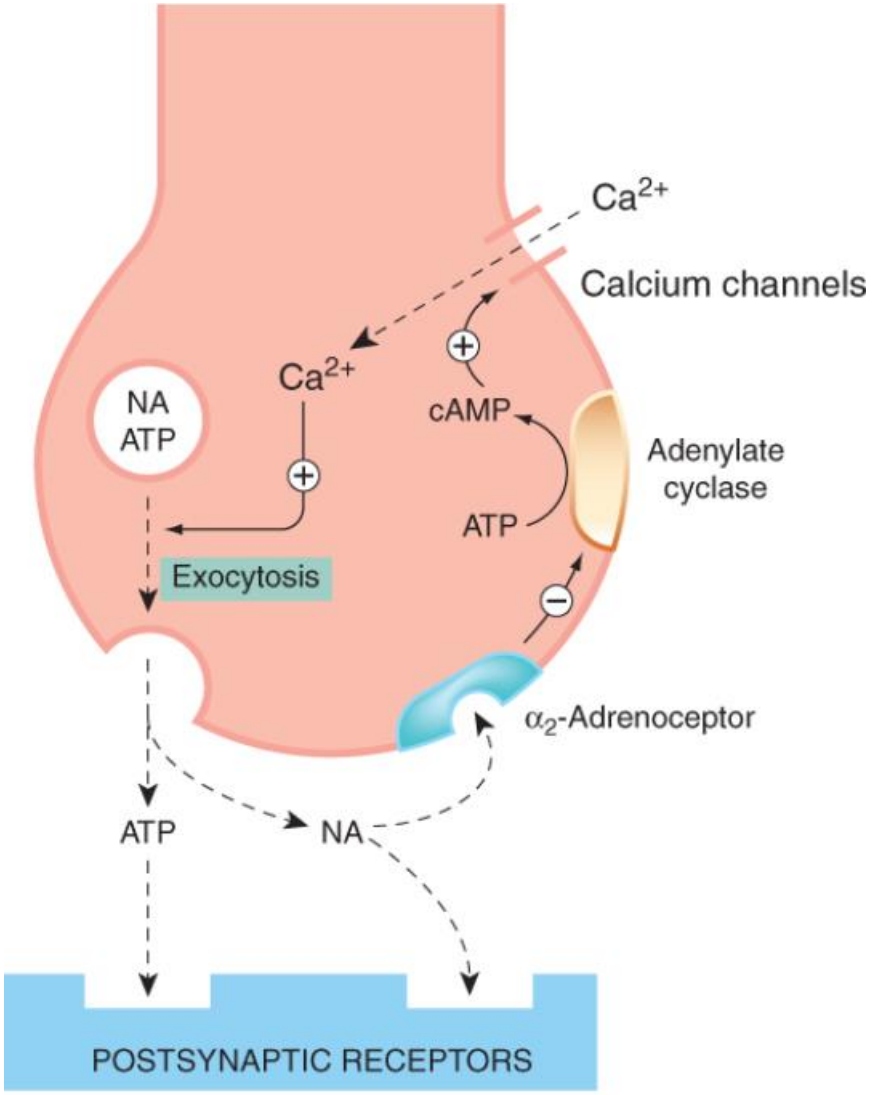
Alpha receptors

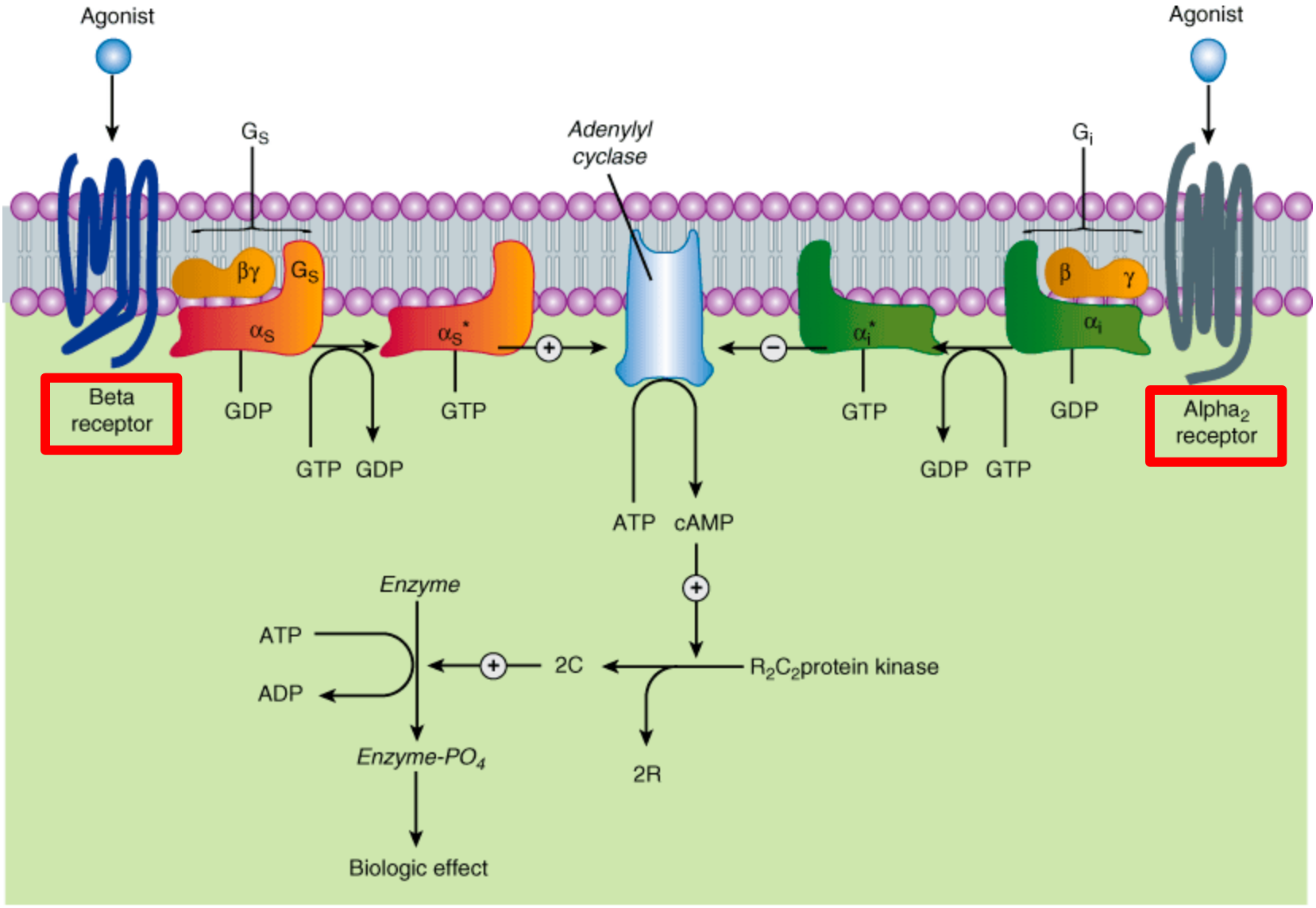
II. α_2 Adrenoceptors:

- These receptors, **located primarily on presynaptic nerve endings** and on other cells, such as the β cell of the pancreas, and on certain vascular smooth muscle cells, **control**
- **adrenergic neuromediator**
  - and **insulin output**, **respectively**

- **Alpha$_2$** receptors are coupled via **G_i** protein to **adenylyl cyclase**.
  - Alpha$_2$ receptors **inhibit adenylyl cyclase** activity and
  - cause intracellular cyclic adenosine monophosphate **(cAMP) levels to decrease**

Feedback control of noradrenaline release





BETA RECEPTORS

- **β_1** Receptors have approximately **equal affinities** for **epinephrine and norepinephrine**,

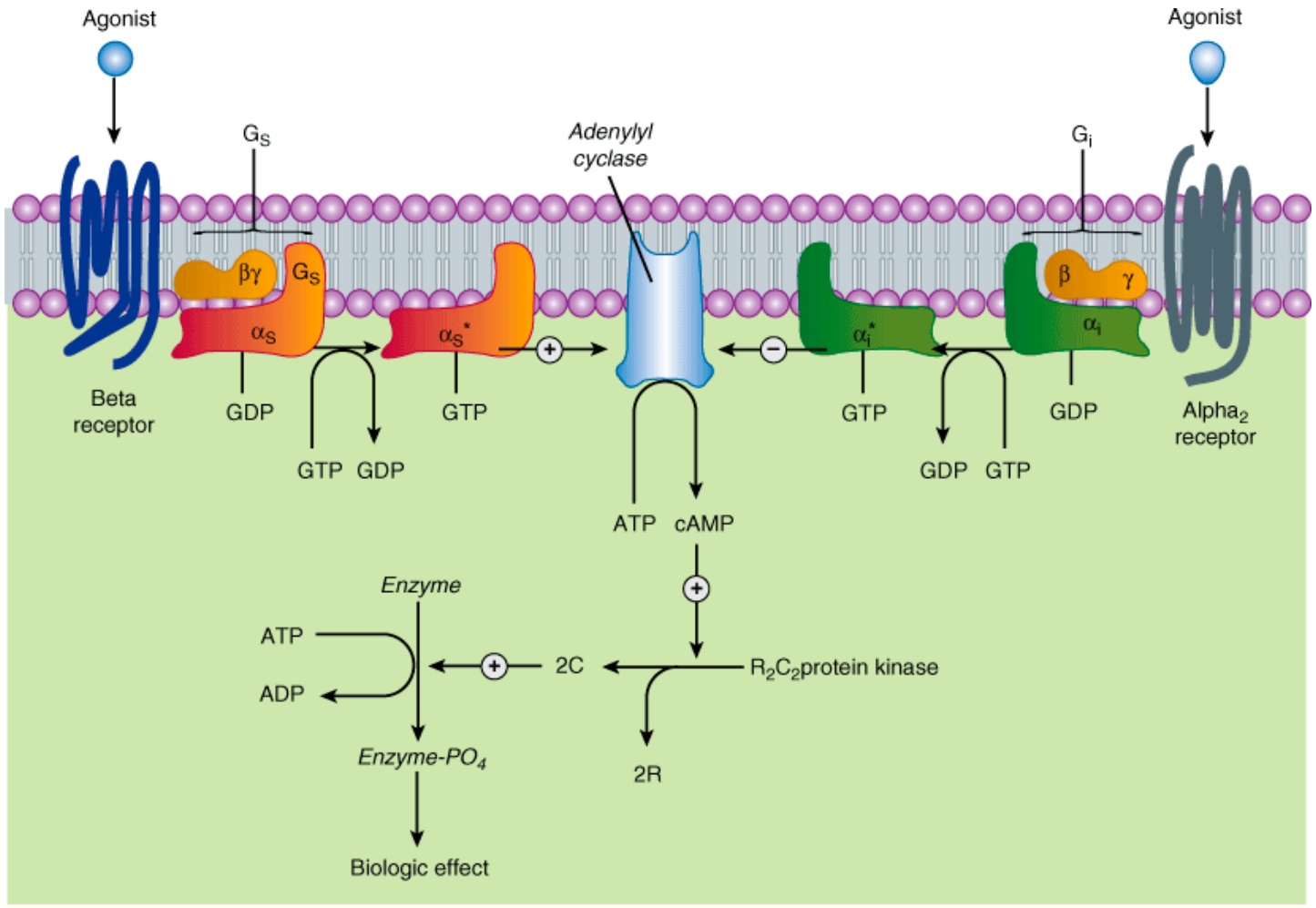
- whereas **β_2** receptors have a **higher affinity** for **epinephrine than** for **norepinephrine**.
  - Thus, **tissues** with a **predominance of β_2** receptors (such as the **vasculature of skeletal muscle**) are particularly **responsive** to the hormonal effects of circulating **epinephrine** released by the adrenal medulla

- **β_3** Receptors may **mediate responses** to **catecholamine at sites with** "atypical" pharmacological characteristics (*e.g.*, **adipose tissue**)

BETA RECEPTORS

All the β-adrenoceptors (β_1, β_2, β_3) are coupled via G proteins to **the G_s family** to **adenylyl cyclase**

….stimulation of **adenylyl cyclase and increased cAMP!**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*,

BETA RECEPTORS

cAMP** is the **major second messenger** of **β-receptor activation!

For example:

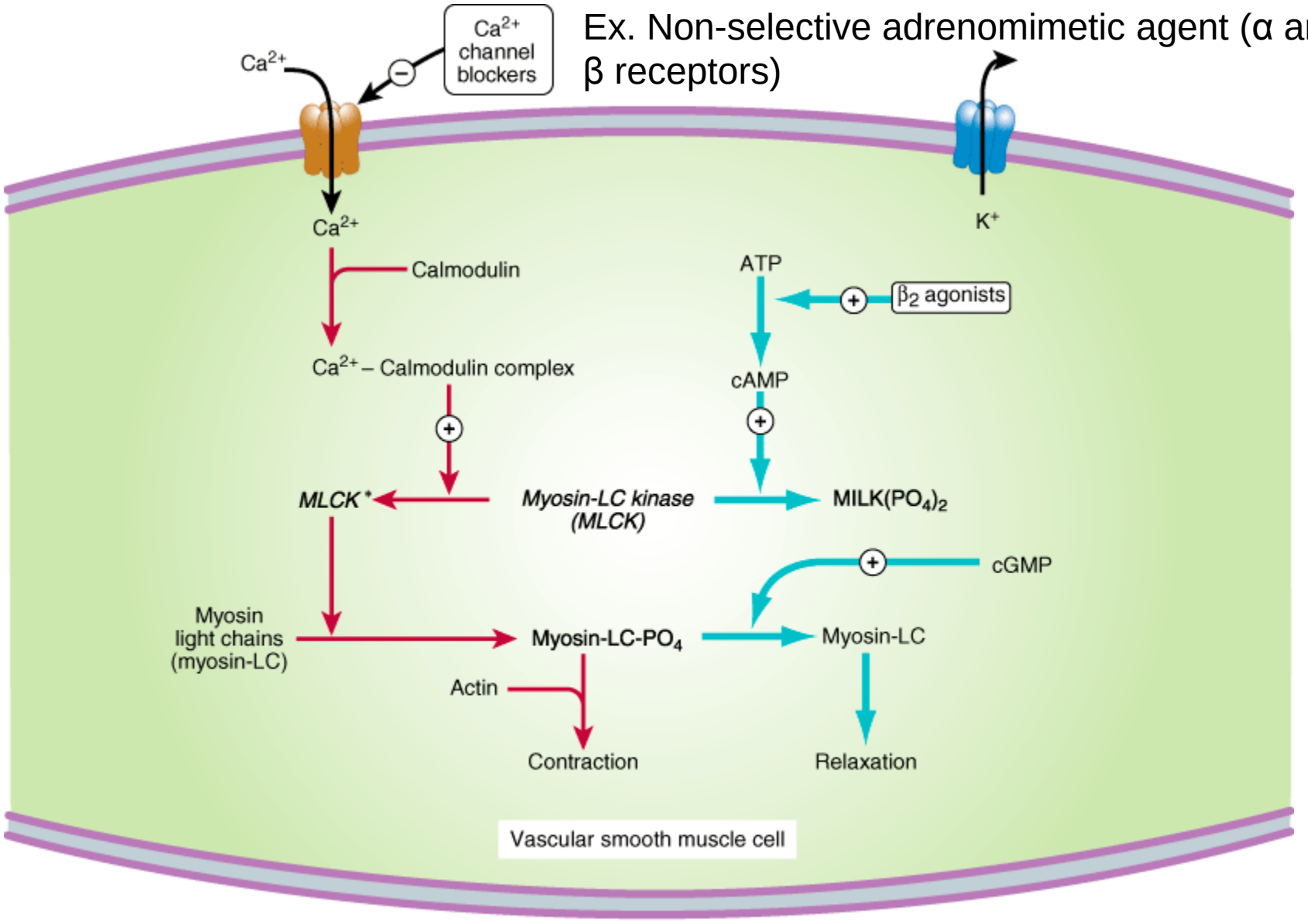
- **In the heart**,
  - increases the **influx of calcium** across the cell membrane and its **sequestration inside the cell**

- cAMP also promotes the **relaxation of smooth muscle**
  - (uncertain mechanism….may involve the **phosphorylation** of **myosin light-chain kinase** to an **inactive form**) (see Figure 12–1)

- **In the liver**, β-receptor-activated cAMP synthesis leads to activation of **glycogen phosphorylase**

Remember interplay between signaling mechanism???

Ex. Non-selective adrenomimetic agent (α and β receptors)



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Dopaminergic receptors

- The endogenous catecholamine "**dopamine**" is imp. In
  - **brain** and
  - in the **splanchnic and renal vasculature**
  - *(5 receptor subtypes)*

- The **D_1-like receptor** is typically associated with the
  - **stimulation of adenylyl cyclase** (for example**, D_1-receptor-induced smooth muscle relaxation** is presumably due to **cAMP accumulation** in the **smooth muscle** of those **vascular beds** in which **dopamine is a vasodilator**)

- **D_2-like receptors** have been found to:
  - inhibit adenylyl cyclase activity,
  - open potassium channels,
  - and decrease calcium influx

ADRENERGIC RECEPTORS (ADRENOCEPTORS)
RECEPTOR REGULATION

- Responses mediated by adrenoceptors are not fixed and static
- **Prolonged exposure** to the **catecholamine**s
  - **reduces** the tissue response **to further stimulation** by **that agent**
- This process has potential clinical significance because it may limit the therapeutic response to sympathomimetic agents

ADRENERGIC RECEPTORS (ADRENOCEPTORS)
RECEPTOR REGULATION

- **Two major categories of desensitization** of responses mediated by **G protein-coupled receptors**:

  - **Homologous desensitization:**
    - refers to **loss** of **responsiveness exclusively** of the **receptors** that have been **exposed** to **repeated or sustained** activation by an **agonist**:

    - **Inability** to **couple** to **G protein**,
      - because the **receptor** has been **phosphorylated** on the **cytoplasmic side** by **G protein-coupled receptor kinase (GRK) family**

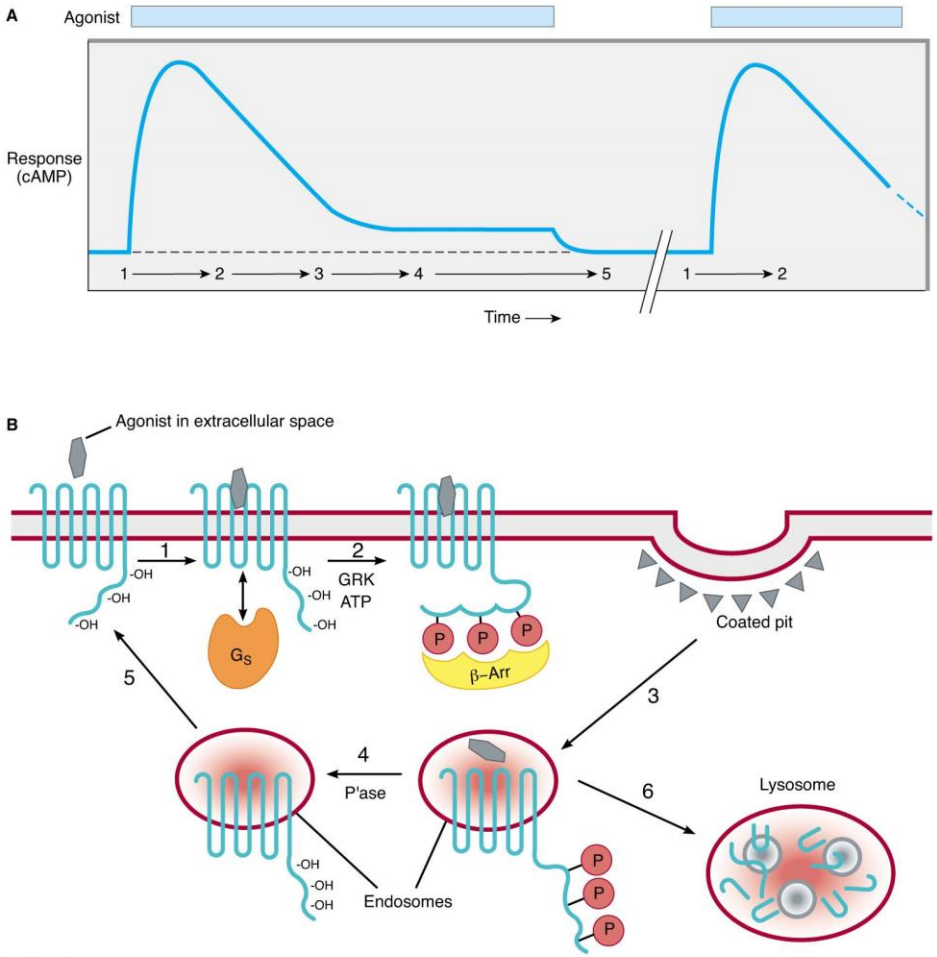


FIGURE 2–12 Rapid desensitization, resensitization, and down-regulation of β adrenoceptors. **A:** Response to a β-adrenoceptor agonist (ordinate) versus time (abscissa). (Numbers refer to the phases of receptor function in B.) Exposure of cells to agonist (indicated by the light-colored bar) produces a cyclic AMP response. A reduced cAMP response is observed in the continued presence of agonist; this "desensitization" typically occurs within a few minutes. If agonist is removed after a short time (typically several to tens of minutes, indicated by broken line on abscissa), cells recover full responsiveness to a subsequent addition of agonist (second light-colored bar). This "resensitization" fails to occur, or occurs incompletely, if cells are exposed to agonist repeatedly or over a more prolonged time period. **B:** Agonist binding to receptors initiates signaling by promoting receptor interaction with G proteins (G_s) located in the cytoplasm (step 1 in the diagram). Agonist-activated receptors are phosphorylated by a G protein-coupled receptor kinase (GRK), preventing receptor interaction with G_s and promoting binding of a different protein, β-arrestin (β-Arr), to the receptor (step 2). The receptor-arrestin complex binds to coated pits, promoting receptor internalization (step 3). Dissociation of agonist from internalized receptors reduces β-Arr binding affinity, allowing dephosphorylation of receptors by a phosphatase (P'ase, step 4) and return of receptors to the plasma membrane (step 5); together, these events result in the efficient resensitization of cellular responsiveness. Repeated or prolonged exposure of cells to agonist favors the delivery of internalized receptors to lysosomes (step 6), promoting receptor down-regulation rather than resensitization.

ADRENERGIC RECEPTORS (ADRENOCEPTORS)
RECEPTOR REGULATION

- **Heterologous desensitization:**
  - refers to the **process** by **which desensitization** of **one receptor** by **its agonists**
    - also results in **desensitization** of **another receptor** that has **not** been **directly activated** by **the agonist in questio**n

- This can be mediated by **second-messenger feedback mechanism:**
  - For example, **β_1-adrenoceptors** stimulate **cAMP accumulation**, which leads to **activation** of **protein kinase A**;
  - which can **phosphorylate** **serine residues** of **intracellular tail of β_2** receptors, resulting in **inhibition of this receptor function**

Sympathomimetic drugs

- Sympathomimetic drugs are classified as:

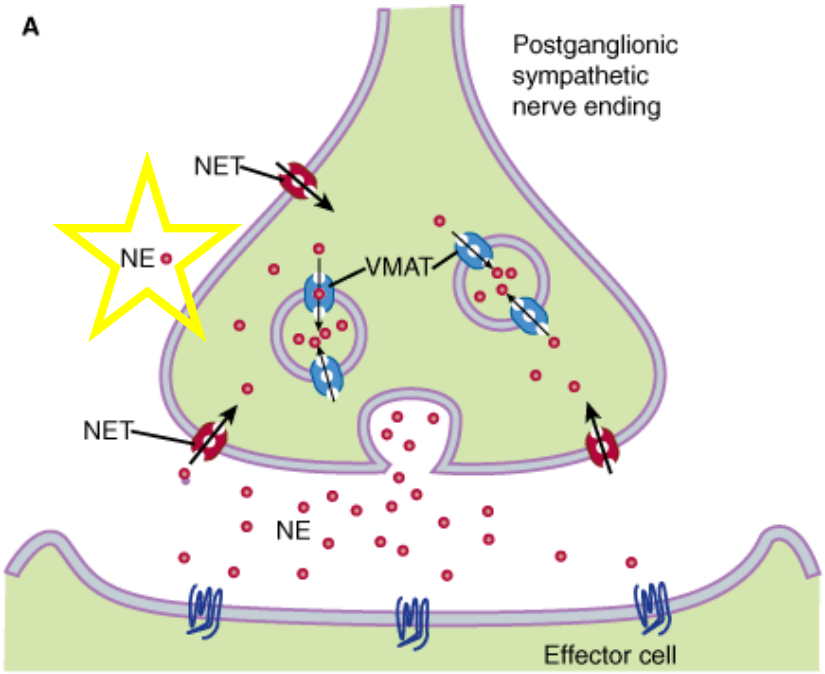
I. **Direct acting sympathomimetics:** act directly on one or more of the adrenergic receptors

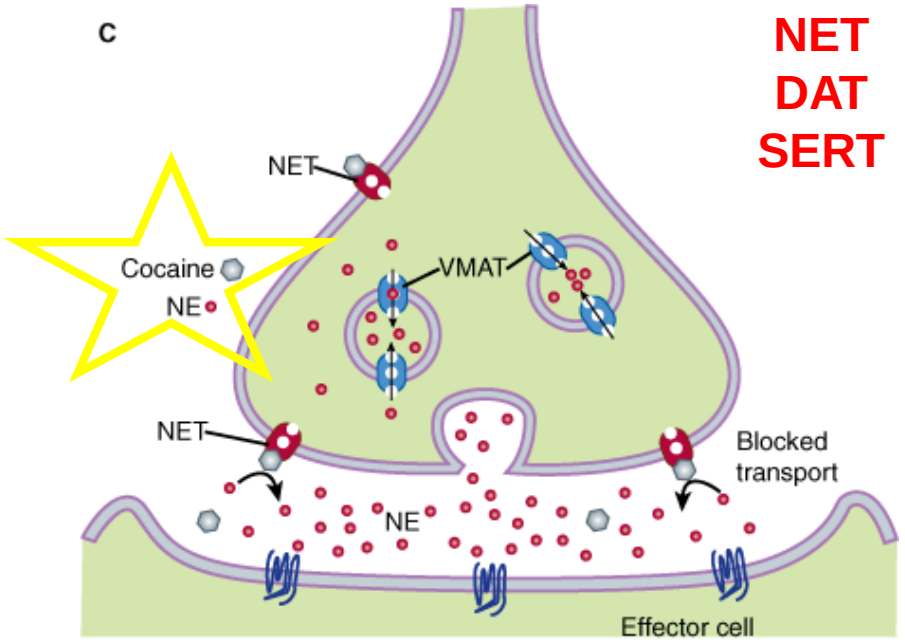
II. **Indirect acting sympathomimetics:** increase the availability of norepinephrine or epinephrine to stimulate adrenergic receptors

1) **Displacement of stored catecholamines** from the adrenergic nerve ending (e.g. tyramine & amphetamine) (**amphetamine-like or 'displacers'**)

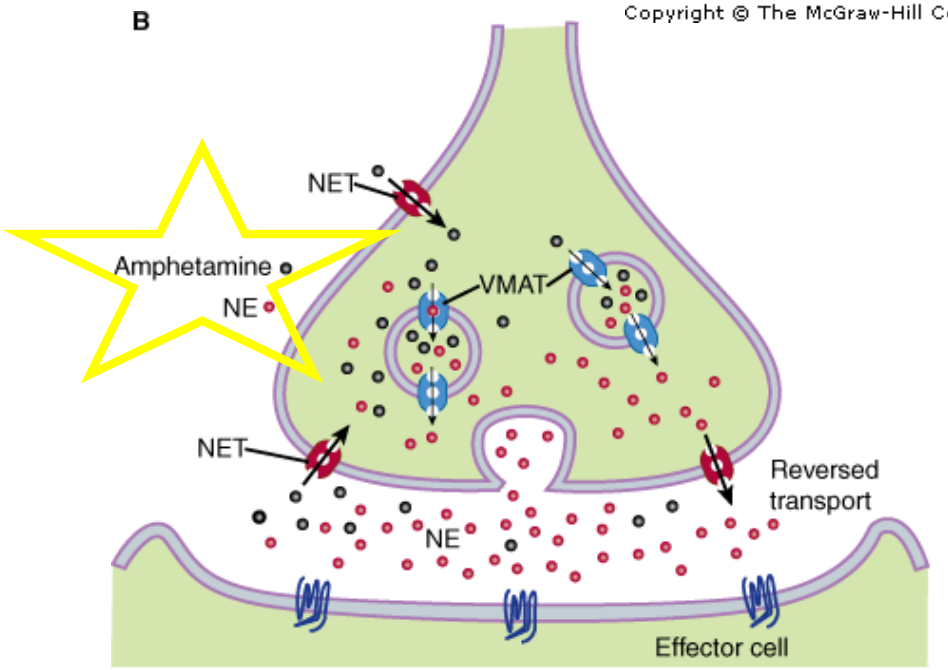
2) **Inhibition of reuptake** of catecholamines already released (e.g. cocaine & tricyclic antidepressants)

3) **Blocking the metabolizing enzymes**, monoamine oxidase (MAO) (*e.g., pargyline*) or catechol-*O*-methyltransferase (COMT) (*e.g., entacapone*)





NET
DAT
SERT



Tyramine
"cheese effect"

SYMPATHOMIMETIC DRUGS (CONT'D)

III. **Mixed acting sympathomimetics:**

- **indirectly induce** the **release** of **norepinephrine** from the presynaptic terminal
- **and directly activate receptors**
- ***(e.g. Ephedrine)***

SYMPATHOMIMETIC DRUGS (CONT'D)

N.B:

The pharmacologic effects of direct agonists depend on:

- the route of administration,
- their relative affinity for adrenoreceptor subtypes,
- and the relative expression of these receptor subtypes in target tissues

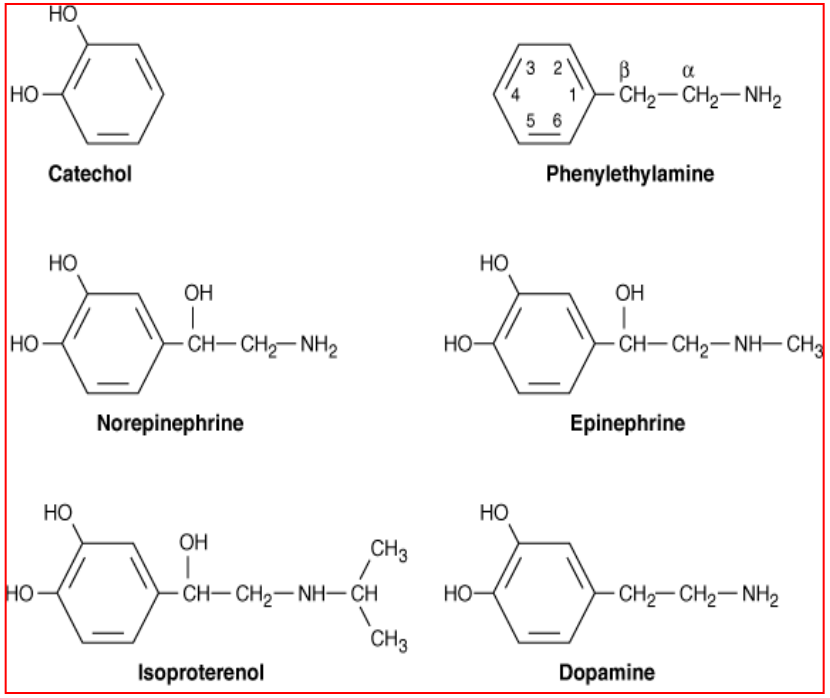
The pharmacologic effects of indirect sympathomimetics are **greater** under conditions of:

- **increased sympathetic activity**
- and **norepinephrine storage and release**

SYMPATHOMIMETIC DRUGS (CONT'D)

- Phenylethylamine may be considered the:
  - **parent compound** from which sympathomimetic drugs are derived
  - This compound consists of a **benzene ring** with **an ethylamine side chain**

- Substitutions may be made on (1) the benzene ring, (2) the terminal amino group, and/or (3) the carbons of the amino chain
- These modifications produce a great variety of compounds **with:**
  - **varying affinities to α and β receptors**,
  - as well as to **influence the intrinsic ability to activate the receptors,**
  - **their pharmacokinetic properties**,
  - and **different abilities to penetrate the CNS**



Maximal α- and β- activity is found with **catecholamines**

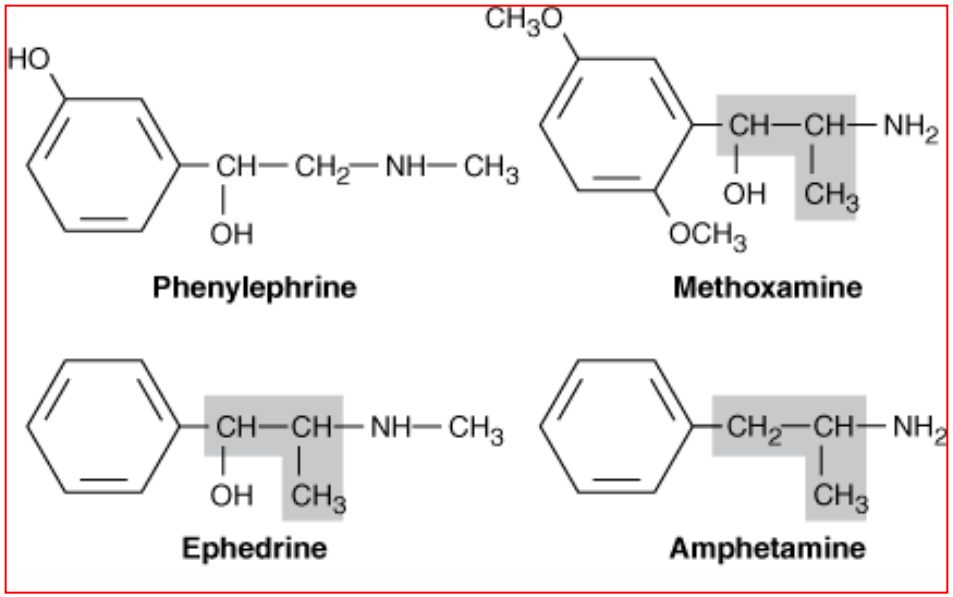
Catecholamines are subject to inactivation by COMT (found in the **gut and liver**)

So…catecholamines are not active orally

Furthermore, absence of ring –OH groups **increase distribution** of the molecule to the **central nervous system**

(**ephedrine and amphetamine** are :

- orally active,
- have a prolonged duration of action,
- and produce central nervous system effects)



Substitutions at the α-carbon block oxidation by monoamine oxidase (MAO) and **prolong the action of** such drugs (p**henylisopropylamine**s) (**alpha methyl compounds**)

α-substitution give indirect activity (displacement)

ORGAN SYSTEM EFFECTS OF SYMPATHOMIMETIC DRUGS

- The **response of any cell or o**rgan to s**ympathomimetics depends on:**
  - the **density** and **proportion** of **α and β adrenergic** receptors;
  - their **relative selectivity** for the **different adrenoceptor** subtype,
  - and its **pharmacological action** on **those receptors**
  - Don't forget compensatory **baroreflex mechanisms** (CV system)

- Adrenergically innervated organs and tissues tend to have a predominance of one type of receptor……tissues such as the **vasculature of skeletal** muscle have predominantly **β_2 receptors**
- ……the **heart** contains **mainly β_1 receptors**

TABLE 9–3 Distribution of adrenoceptor subtypes.

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS adrenoceptors	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibition of transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibition of lipolysis
β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve endings	Modulates transmitter release

TABLE 9–2 Relative receptor affinities.

	Relative Receptor Affinities
Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

[1] See text.

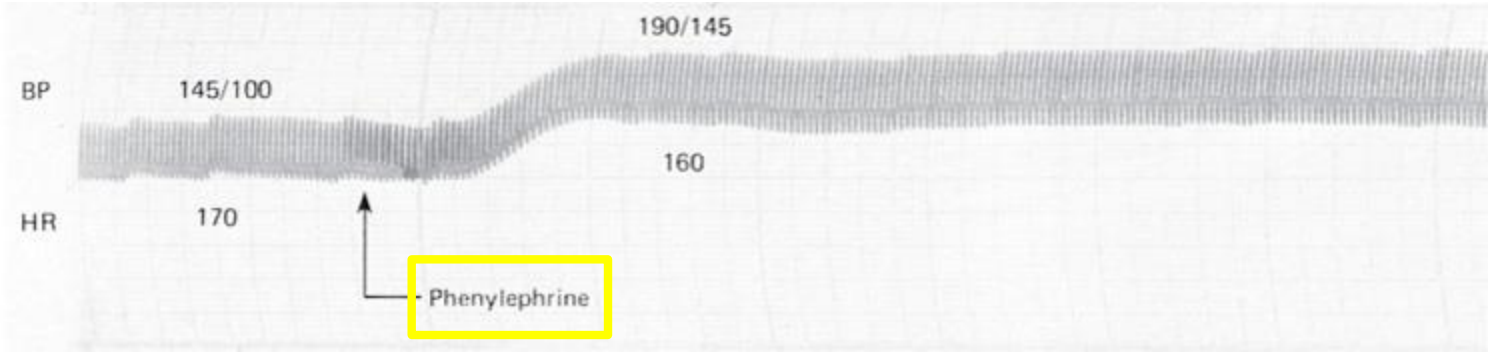
CARDIOVASCULAR SYSTEM

- **Alpha$_1$-Receptor Activation**

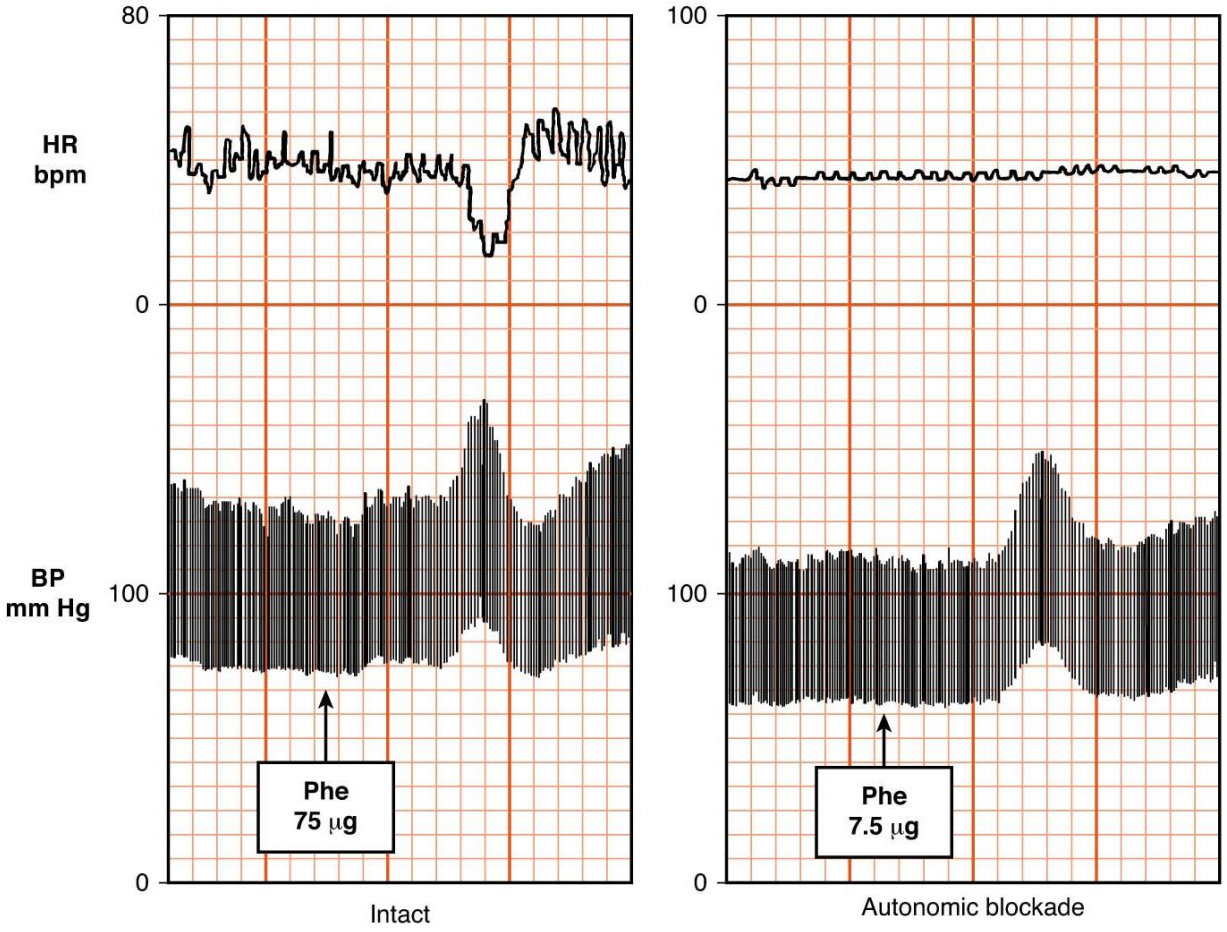
  - Alpha$_1$ receptors expressed in **most vascular beds,** and
    - their activation causes **vasoconstriction**
    - and rise in **peripheral resistance**……**dose-dependent rise in blood pressure**

  - In the presence of **normal cardiovascular reflexes**, the
    - rise in blood pressure elicits a baroreceptor-mediated increase in vagal tone with slowing of the heart rate (bradycardia) (fig. 9-7)

  - **Trimethaphan: ganglion blocker**….bradycardia is no longer observed



- Phenylephrine given as I.V bolus to **a dog**
- **Reflex are blunted** (but not eliminated) in **anesthetized** animal



- Note that the increase in BP is associated with a baroreflex-mediated compensatory decrease in HR
- **Patients** with **impaired autonomic function** (diabetic autonomic neuropathy) may have **exaggerated increases** in **heart rate** or **blood pressure** when taking **sympathomimetics**

CARDIOVASCULAR SYSTEM

- **Alpha$_2$-Receptor Activation**

  - **α_2 adrenoceptors** are present in the **vasculature**,
    - and their **activation** leads to **vasoconstriction**
    - This effect, is observed **only** when **α_2 agonists** are **given locally**, by **rapid I.V injection** or **in very high oral doses**

  - When given ***systemically,*** these **vascular effects** are **obscured** by the **central effects** of **α_2 receptors**,
    - which lead to **inhibition of sympathetic tone** and **blood pressure** (sympatholytic effect)

  - **Clonidine**: used to **treatment (Tx.) Hypertension**

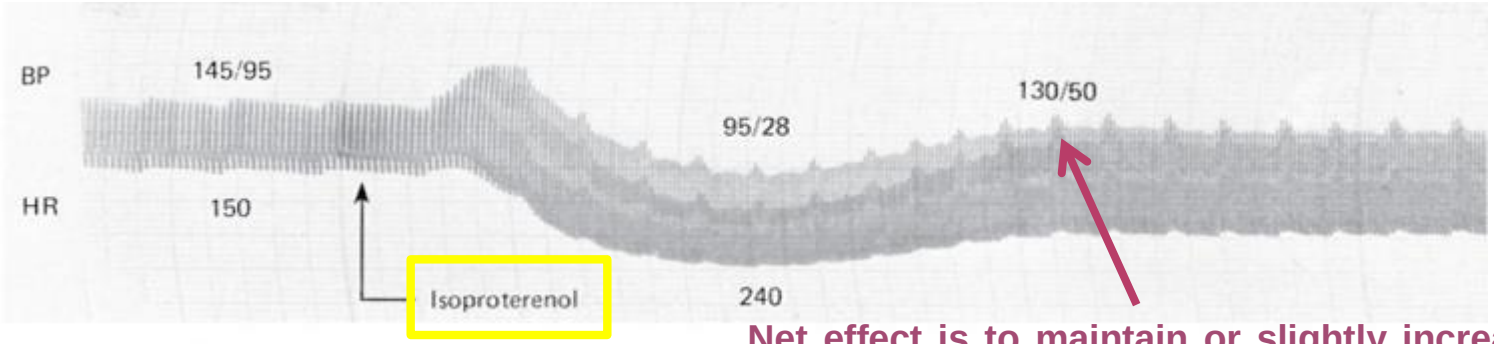
  - Patients with **pure autonomic failure**??

CARDIOVASCULAR SYSTEM

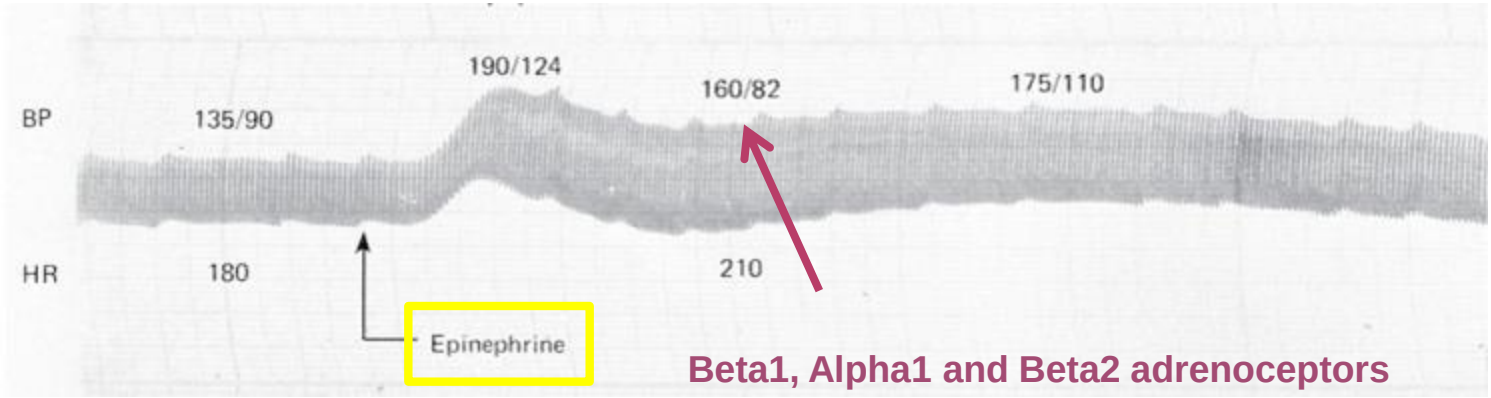
- **Beta-Receptor Activation**
  - **Isoproterenol** activates both **beta1 and beta** 2 adrenoceptor???

  - **Direct effects** on the **heart** are determined largely by **β_1 receptors**.
    - **Positive *chronotropic* *effect*, *inotropic* *effect*** and ***dromotropic* *effect*….increase coronary blood flow**
    - …..resulting in a markedly **increased cardiac output** and cardiac **oxygen consumption**

  - **β_2 receptors activation**, leads to **vasodilation** in certain **vasculature of smooth muscles**
    - **Increase blood flow** in **skeletal muscle** during **exercise**



Net effect is to maintain or slightly increase SYSTOLIC pressure and decrease DYASTOLIC pressure….mean BP decreased



Beta1, Alpha1 and Beta2 adrenoceptors

CARDIOVASCULAR SYSTEM

- **Dopamine receptors??**
- **D1**: **vasodilation** of renal, splanchnic, coronary, cerebral and other resistance vessels
- **D2**: presynaptic receptor (unclear role)
- Dopamine activates **beta1** receptors on the **heart** and…..
- ….. (at higher doses) **alpha r**eceptors on the **vessels**….
- …..at **high doses** **vasoconstriction** (similar to epinephrine)

TABLE 9–4 Cardiovascular responses to sympathomimetic amines.

	Phenylephrine	Epinephrine	Isoproterenol
Vascular resistance (tone)			
Cutaneous, mucous membranes (α)	↑↑	↑↑	0
Skeletal muscle (β_2, α)	↑	↓ or ↑	↓↓
Renal (α, D_1)	↑	↑	↓
Splanchnic (α, β)	↑↑	↓ or ↑[1]	↓
Total peripheral resistance	↑↑↑	↓ or ↑[1]	↓↓
Venous tone (α, β)	↑	↑	↓
Cardiac			
Contractility (β_1)	0 or ↑	↑↑↑	↑↑↑
Heart rate (predominantly β_1)	↓↓ (vagal reflex)	↑ or ↓	↑↑↑
Stroke volume	0, ↓, ↑	↑	↑
Cardiac output	↓	↑	↑↑
Blood pressure			
Mean	↑↑	↑	↓
Diastolic	↑↑	↓ or ↑[1]	↓↓
Systolic	↑↑	↑↑	0 or ↓
Pulse pressure	0	↑↑	↑↑

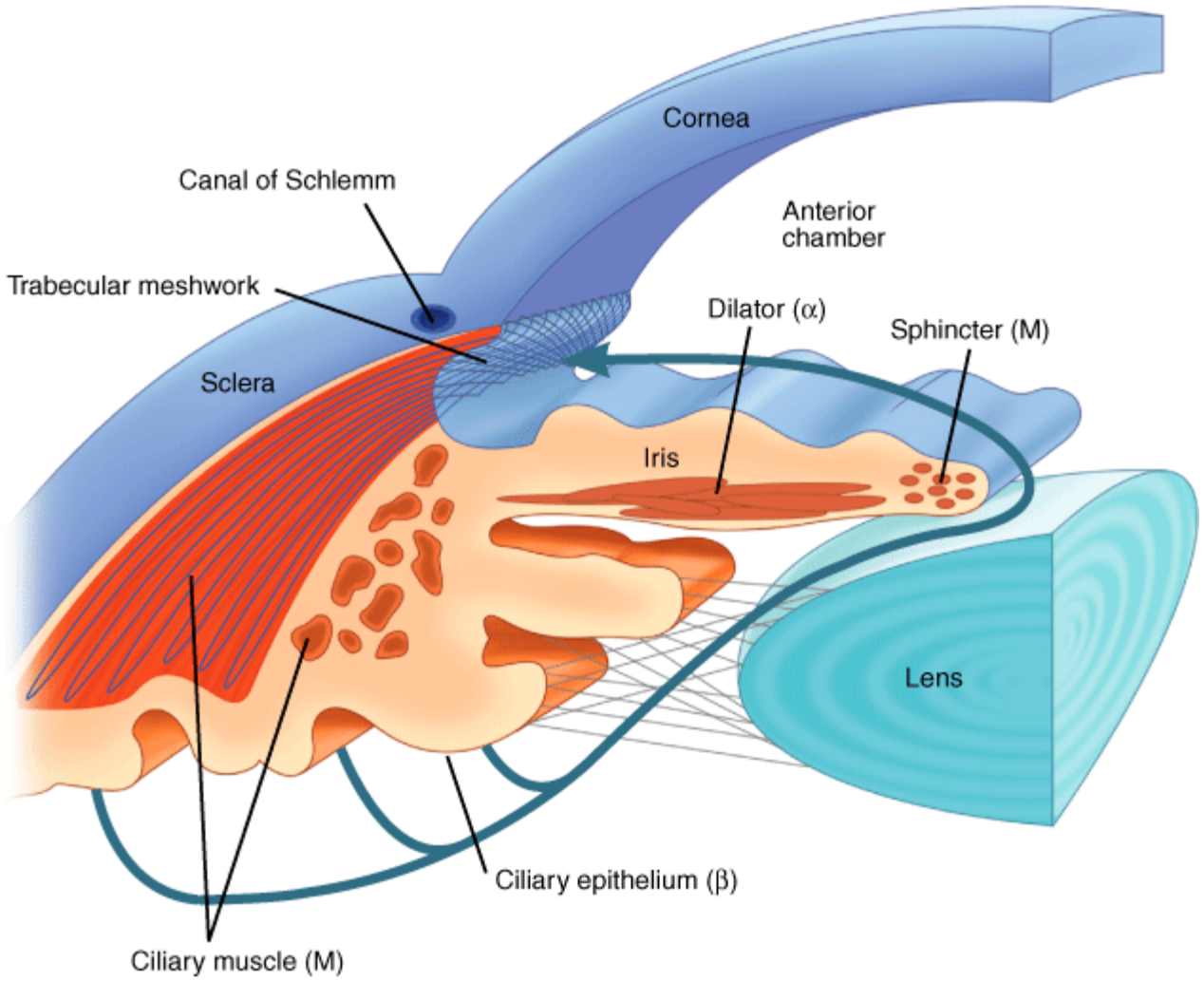
[1]Small doses decrease, large doses increase.

↑ = increase; ↓ = decrease; 0 = no change.

THE EYE……/ …RESPIRATORY SYSTEM

- **The Eye**
- Activation of **α_1 receptors** mediates **contraction** of the **radial** pupillary dilator muscle of the iris and results in **mydriasis**
- **Reduces intraocular pressure** due **to (alpha)**
  - **vasoconstriction** and **increase the outflow of** aqueous humor from the eye
- **β receptors antagonists** reduce the production of aqueous humor (ciliary epithelium)

- **Respiratory system**
- Activation of **β_2 receptors** in **bronchial smooth muscle** leads to:
  - **bronchodilation** and
  - also **inhibits the release** of **allergy mediator** such as h**istamines from mast cells**
  - (albuterol, salmeterol used for treatment (Tx.) of asthma)



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

GENITOURINARY TRACT

- The **bladder base**, **urethral sphincter**, **and prostate** contain **α receptors** that mediate **contraction**……**urinary continence**

- The **specific α_{1A}** receptor subtype seems to be involved in mediating **constriction** of the **bladder base** and **prostate** (urinary retention is a potential ADE of the **α_1** agonist midodrine)

- Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in normal ejaculation.

- **Uterus**: Similar effect on **uterine smooth muscle** (ritodrine) for the **Tx of prematur labor**

EXOCRINE GLANDS

- **Salivary glands:** contain **adrenoceptors** that **regulate** the **secretion of amylase** and **water**

- However, certain sympathomimetic drugs (clonidine) produce symptoms of dry mouth…..mechanism uncertain; (probably CNS effects are responsible, though peripheral effects may contribute)

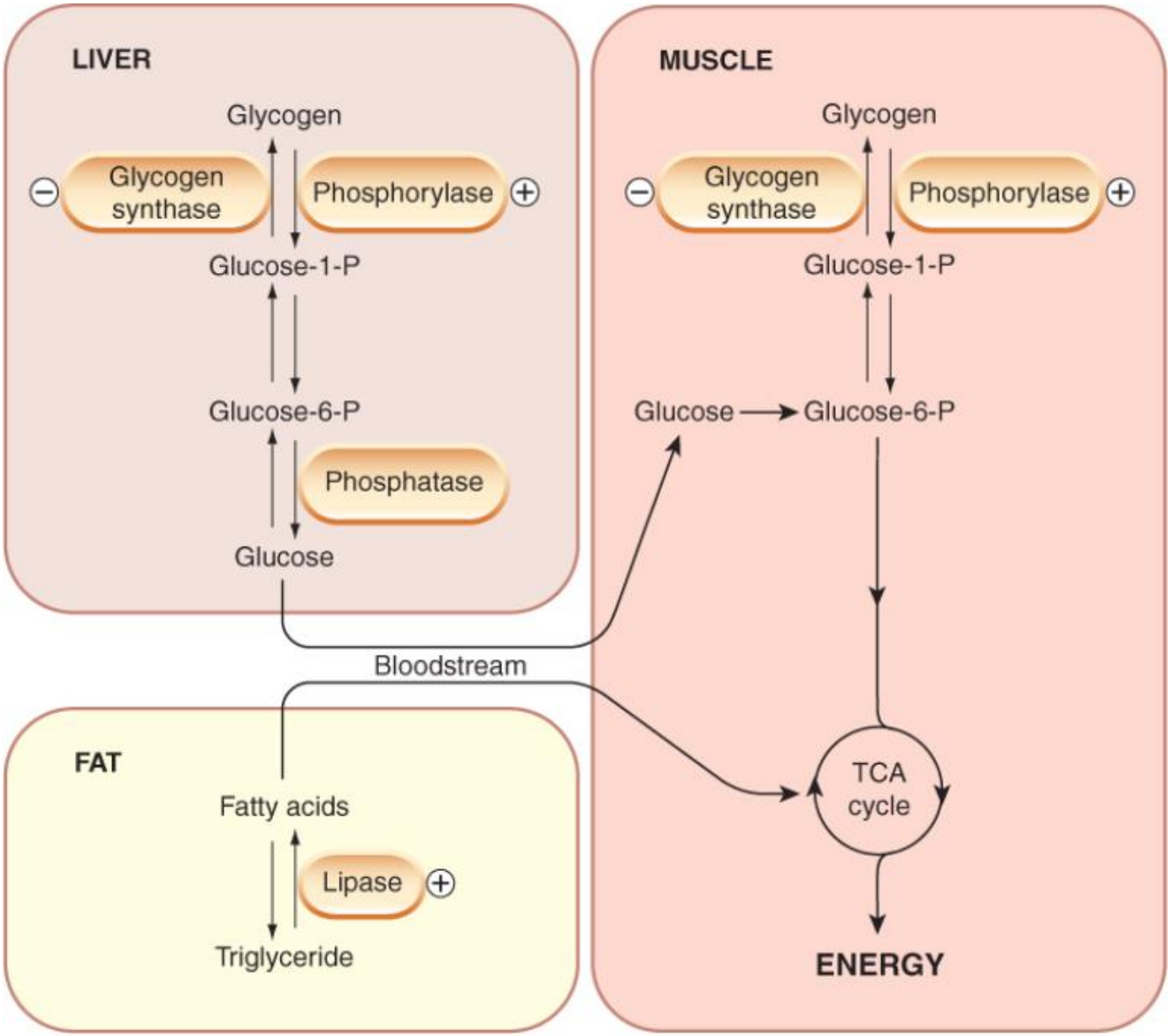
- **Apocrine sweat glands:** contain adrenoceptors and their stimulation **increase sweat production** (nonthermoregulatory glands associated with psychological stress) (**sympathetic adrenergic**)

METABOLISM

- **Catecholamines** encourage the **conversion of energy** stores (***glycogen and fat***) to **freely available fuels** (***glucose and free fatty acids***), and cause an increase in the plasma concentration of these substances

1. Activation of **β_3** receptors in adipocytes **stimulate lipolysis……**enhance release of FFA and glycerol into the blood
2. **α_2** receptors activation **inhibit lipolysis** by decreasing intracellular cAMP

3. **Stimulate glycogenolysis** in the **liver and muscles**, which leads to **increased glucose release into the circulation**……mediated mainly by β receptors



METABOLISM

- Activation of **β_2 receptors promotes K^+ uptake** into cells, particularly skeletal muscles……

- **Stress result in**
  - ……**Fall in plasma K^+** potassium concentration (hypokalemia) **during *stress***

- and ***protect*** *against* ***a rise in plasma potassium during exercise***

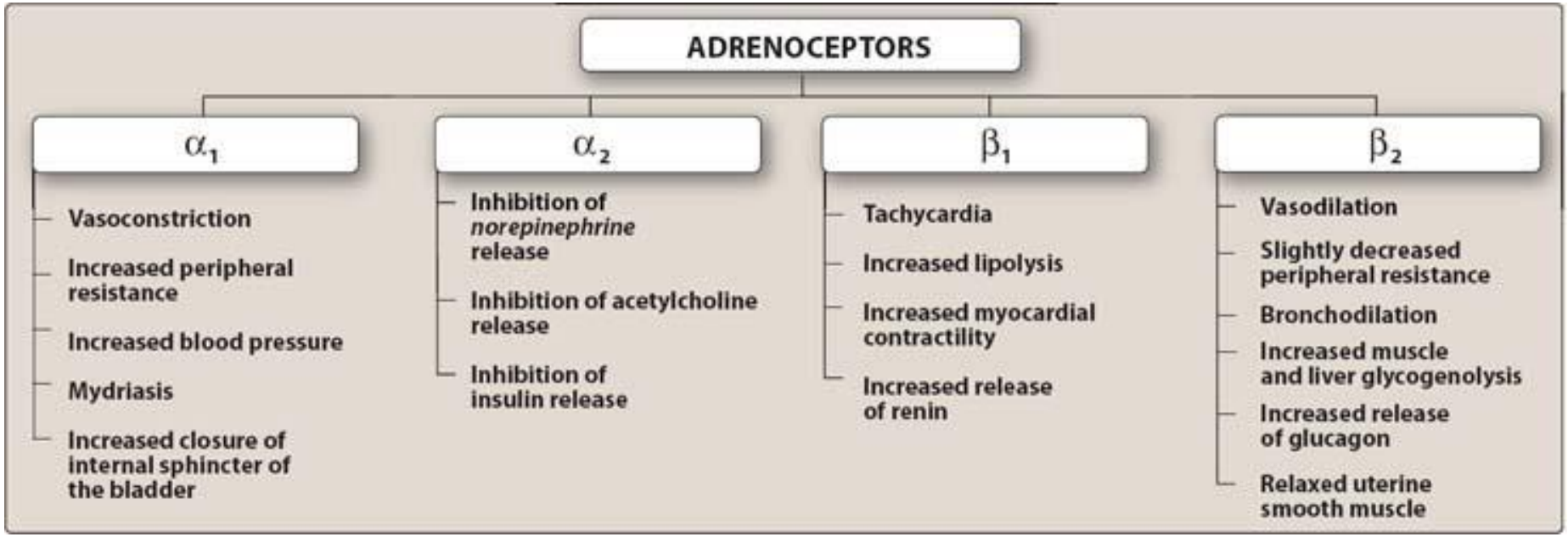
HORMONES SECRETION

- **β receptors** enhance **insulin secretion and renin secretion**….
- ….while……
- **α_2 receptors inhibit insulin secretion and renin secretion**
- **Adrenoceptors** also modulate the secretion of
  - **parathyroid hormone,**
  - **calcitonin,**
  - **thyroxine,**
  - **and gastrin**…….limited physiologic significance

CENTRAL NERVOUS SYSTEM

- The **catecholamines** are almost completely unable to enter the CNS
  - At **highest rates of infusion** effects are noted as **nervousness**
  - **Tremor** and **tachycardia** are **peripheral effect** and are similar to the somatic manifestations of anxiety
- **Noncatecholamines** with **indirect actions** (amphetamines**), readily enter the** CNS….
  - ….their actions vary from **mild alerting**, with **improved attention to boring tasks**;
  - through elevation of mood,
  - insomnia,
  - euphoria,
  - and anorexia;
  - to full-blown psychotic behavior

Major effects mediated by α and β adrenoceptors



THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS

- Selection of a particular sympathomimetic drug depends on:

1. Whether **activation** of **α, β_1, or β_2** receptors is desired
2. The desirable **duration of action**
3. The preferred **route of** administration

DIRECT ACTING ADRENERGIC AGONISTS
ENDOGENOUS CATECHOLAMINE

a. **Epinephrine (adrenaline)**

- **Potent stimulant** of both **α and β adrenoceptors**

- **CV effect: potent vasoconstrictor** and **cardiac stimulant**
  - +ve **inotropic and chronotropic** actions on the heart **(B1**)
  - and **vasoconstriction** induced in many vascular beds **(a1)**
  - Epinephrine also activates **β_2** receptors in some vessels (eg, **skeletal muscle blood vessels**), leading to their **dilation**

- Therefore, the **net effect** is :
  - an **increase** in **systolic blood pressure**,
  - coupled with a slight decrease in **diastolic pressure**

a. **Epinephrine (adrenaline)**

- **Respiratory:**
  - causes **powerful bronchodilation** by acting **directly** on **bronchial smooth muscle** and
  - **inhibiting the release of allergic mediators** such as histamine from mast cells (β_2 action)

- **Hyperglycemia:** epinephrine has a **significant hyperglycemic effect** because of
  - increased glycogenolysis in the liver (β_2 effect),
  - and a decreased release of insulin (α_2 effect)

- **Lipolysis:** epinephrine initiates **lipolysis** through its a**gonist** activity on **the β receptors of adipose tissue**

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
ANAPHYLAXIS

- **Epinephrine (IM)** is the **1ry** Tx **for anaphylaxis** (drug of choice "DOC")
- ??Epinephrine activates α, β_1, and β_2 receptors
- Can **relief anaphylactic shock:**
  - **bronchospasm**,
  - **mucous membrane congestion**,
  - **angioedema**,
  - and **severe hypotension**

- Glucocorticoids and antihistamines useful as 2ry therapy
- "**EpiPen" recommended for patients at risk for:**
  - **insect sting** hypersensitivity,
  - severe **food allergies**,
  - or other types of anaphylaxis

DIRECT ACTING ADRENERGIC AGONISTS
ENDOGENOUS CATECHOLAMINE

b. Norepinephrine (noradrenaline, levarterenol)

- At **therapeutic doses** to human, **stimulate** the **α-adrenergic receptors** (both **α_1 & α_2**) and **the β_1 receptors with similar potency** as **epinephrine**, but has **relatively little effect on β_2 receptors**

- Norepinephrine:
  - **increases peripheral resistance**
  - and both **diastolic and systolic blood pressure**
  - **Compensatory baroreflex activation** tends to **overcome** the **direct positive chronotropic** effects of **norepinephrine**; however, the **positive inotropic** effects on the **heart are maintained**

DIRECT ACTING ADRENERGIC AGONISTS
ENDOGENOUS CATECHOLAMINE

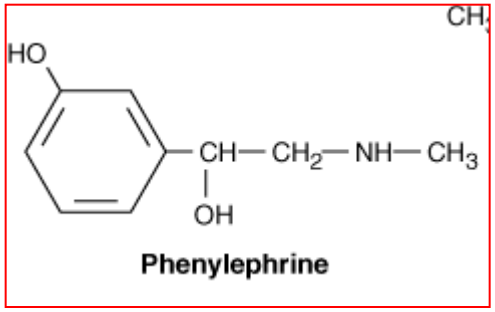
c. Dopamine

- Important **neurotransmitter in the CNS** and is involved in the **reward stimulus relevant to addiction**
- Its **deficiency** in the **basal ganglia** leads to **Parkinson's** disease (treated with levodopa)
- Its i**ncrement** seems to be the cause **of psychosis (Tx dopamine antagonist)**
- Dopamine promotes **vasodilation** via activation of **D_1 receptors.**
- The activation of presynaptic **D_2 receptors** s**uppresses norepinephrine** release

DIRECT ACTING ADRENERGIC AGONISTS
DIRECT ACTING SYMPATHOMIMETICS

d. Phenylphrine

- **Direct-acting and synthetic α_1** receptors **agonist**
- **Not a catechol** derivative and, therefore, **not** a **substrate for COMT** (longer duration of action)
- It is a **vasoconstrictor** that raises **both systolic and diastolic** blood pressures
- Has **no effect** on **the heart** itself but rather **induces reflex bradycardia** when given **parenterally**



Phenylephrine

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS

- **Phenylephrine** is an effective :
  - **mydriatic agent** frequently used to facilitate **examination of the retina**
  - Topically on the **nasal mucous membrane** as a **decongestant** for minor **allergic** hyperemia and **itching of the conjunctival membranes**
- **N.B: Nasal blood vessels are rich in α receptors…..**vasoconstriction

Tetrahydrozoline used also to **induce mydriasis**

…..both drugs do not cause cycloplegia

DIRECT ACTING ADRENERGIC AGONISTS
DIRECT ACTING SYMPATHOMIMETICS

Xylometazoline and oxymetazoline

- Both are **direct-acting α-adrenoceptor** agonists
- These drugs have been used as **topical decongestants** because of their ability to promote constriction of the nasal mucosa (available as **over-the-counter** nasal spray products)

- When taken **in large doses**, **oxymetazoline** may cause **hypotension** (**α_{2A} receptors**)

DIRECT ACTING ADRENERGIC AGONISTS
DIRECT ACTING SYMPATHOMIMETICS

Midodrine

- It is a **prodrug** that is enzymatically hydrolyzed to **DesGly**Midodrine……**selective α_1-receptor agonist**

- **USE:** primarily indicated for the **treatment** of **orthostatic hypotension,**
  - typically due to **impaired autonomic nervous** system function

- **Effective** when the **patient is standing**, but may **cause HTN** when the subject is **supine**…..can be minimized by
  - **avoiding dosing prior** to **bedtime**
  - and **elevating the head of the bed**

DIRECT ACTING ADRENERGIC AGONISTS
DIRECT ACTING SYMPATHOMIMETICS

c. **Methoxamine**

- **α_1 receptors agonist**
- It may cause a prolonged increase in blood pressure due to vasoconstriction;
- it also causes a vagally mediated bradycardia

- **USE:** clinical applications are rare….overcome **hypotensive states** during surgery involving **halothane anesthetics** (parenterally)

DIRECT ACTING ADRENERGIC AGONISTS
DIRECT ACTING SYMPATHOMIMETICS

d. Alpha$_2$-selective agonists

"Clonidine, Methyldopa, Guanfacine, Guanabenz"

- **Primarily** used for the treatment of **systemic hypertension**
  - due to their ability to **decrease blood pressure** through actions in the **central nervous system**

- Apraclonidine and brimonidine (**α_2-selective agonists**)
  - **lower intraocular pressure** and are **approved** for use in **glaucoma** (used more than non-selective alpha agonist).

- Tizanidine (α_2 agonist) that is used as a muscle relaxant

DIRECT ACTING ADRENERGIC AGONISTS
DIRECT ACTING SYMPATHOMIMETICS

f. Isoproterenol (isoprenaline)

- Direct acting synthetic **catecholamine** that predominantly **stimulates β adrenoceptors**. **Little effect** on **α-receptors**

- Produces **intense stimulation** of the **heart** to increase its **rate and force of contraction**.....**increases cardiac output** **(β_1 effect)**

- **Dilates** the **arterioles of skeletal muscle** (**β_2 effect**), resulting in **decreased peripheral resistance**

- Net effect: **marked fall** in **diastolic** and a **lesser decrease** or **a slight increase in systolic pressure**

- **Rarely used therapeutically**.....used to stimulate the heart in emergency situations.....

- Advantage……increase cardiac output with less reflex tachycardia (no vasodilation effect)

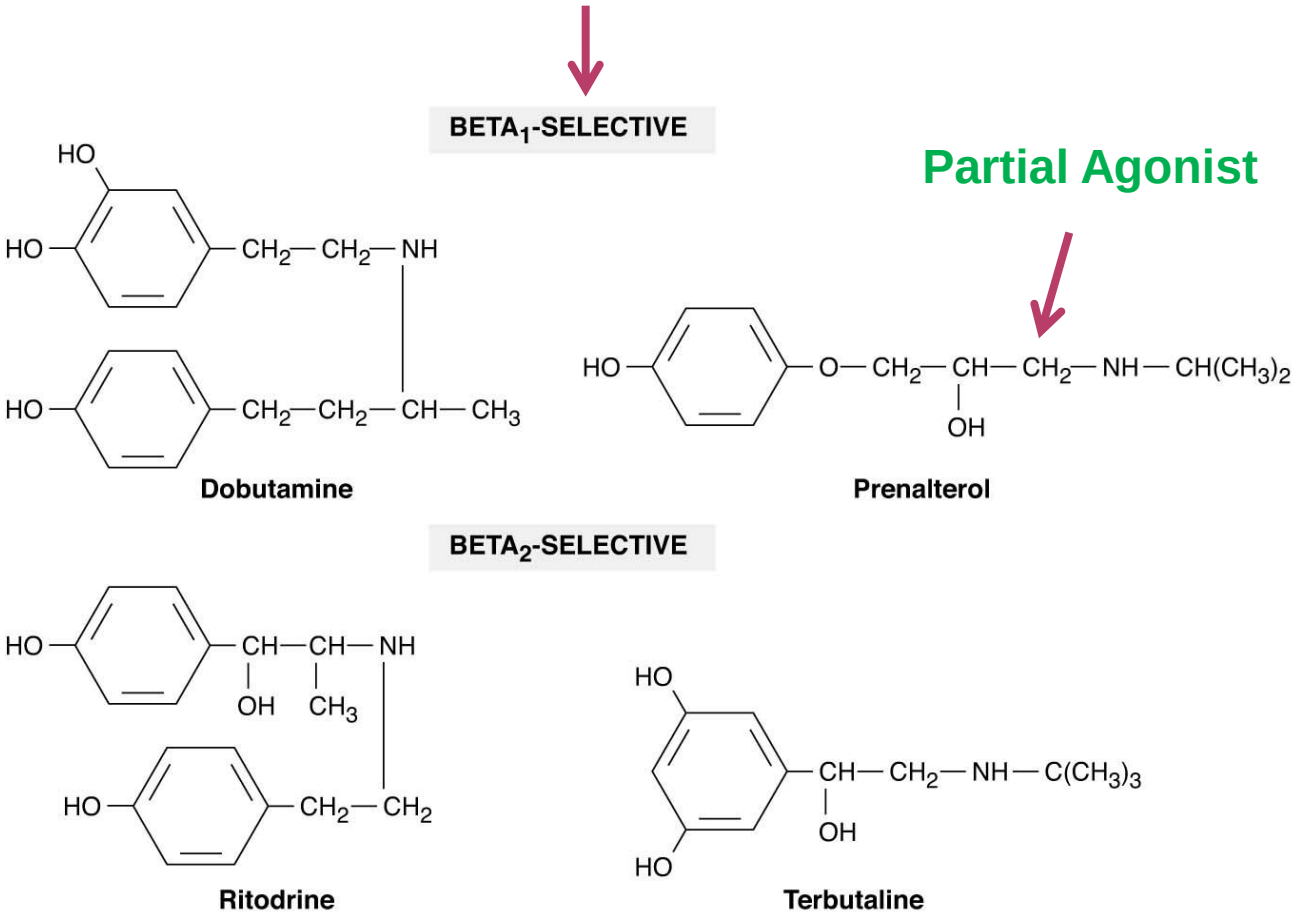


FIGURE 9–8 Examples of β_1- and β_2-selective agonists.

g. Beta-selective agonists

- **β_1-selective agents:** ***dobutamine*** & *prenalterol (partial agonist)*

- **Clinical preparations** of **dobutamine** are a **racemic mixture of (–) and (+)** isomers,
  - (+) isomer…….potent β_1 agonist and α_1 antagonist
  - (–) isomer…..potent α_1 agonist (cause **significant vasoconstriction when given alone**)

  - The **resultant CV effects** of dobutamine reflect this **complex** pharmacology:
    - **Increases cardiac output** (**positive inotropic action**)
    - with little change in HR,
    - and **peripheral resistance does not decrease significantly**
    - **Does not significantly elevate O2 demands** of the **myocardium** — advantage over other sympathomimetic drugs

g. **Beta-selective agonists**

- **β_2-selective agents:**
  - These agents are used primarily as **bronchodilator** and their use have achieved an important place in the **treatment of asthma (reliever)**

  - **Short-acting (inhalers):**
    - "albuterol (salbutamol), metaproterenol, terbutaline".
    - ..effective for **Tx** of **acute symptoms.**

  - **Long-acting(inhalers):**
    - "salmeterol, formeterol"..... combined with corticosteroid used as prophylaxis

- Nonselective drugs (epinephrine), β-selective agents (isoproterenol), are available

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
GENITOURINARY APPLICATIONS

- **Beta-selective agonists**

- ***Ritodrine (B2-selective)*** used clinically to achieve **uterine relaxatio**n in **premature labor** (arrest premature labor)

- **"Terbutaline"** have been used to **suppress premature labor**

  The goal is to **defer labor** long enough to ensure adequate **maturation of the fetus**.

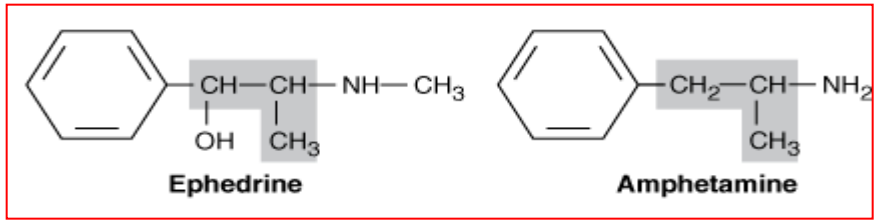
  This may **afford time** to **administer corticosteroid drugs**, which **decrease** the incidence of **neonatal respiratory distress syndrome (IRDS)**

MIXED-ACTING SYMPATHOMIMETICS

- **EPHEDRINE**
  - 1st **orally active** sympathomimetic (**non-chatecol**)
  - Relatively **long duration** of action
  - Can **enter the CNS** with **mild stimulant** effect

- **PSEUDOEPHEDRINE**
  - **One of the four ephedrine enantiomers**
  - Was available as **OTC component** of many **decongestant mixtures**
  - Used as a **precursor** in the **illicit manufacture** of **methamphetamine** (restrictions on its sale)

- **GENITOURINARY APPLICATION**: "Ephedrine or pseudoephedrine" is occasionally useful in the treatment of **stress incontinence**



INDIRECT ACTING ADRENERGIC AGONISTS

A. AMPHETAMINE-LIKE OR DISPLACERS

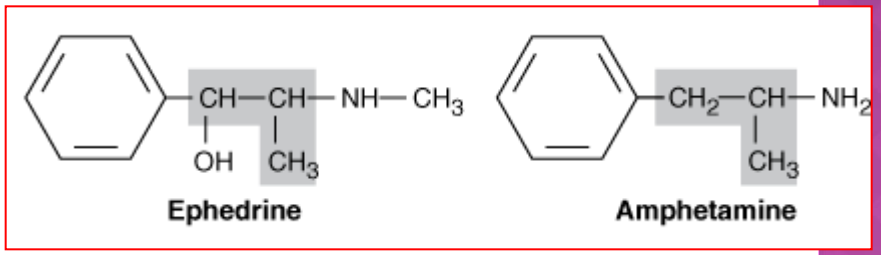
1. **Amphetamine:**

- It is a racemic mixture of **phenylisopropylamine** (D-isomer is more potent than L-isomer)

- Amphetamine's actions are mediated through the **release of norepinephrine and,** to some extent**, dopamine**

- Amphetamine and other phenylisoproylamines are widely **abused** as **CNS stimulants** (orally active)

- **Legitimate indications include:**
  - narcolepsy,
  - attention deficit disorder
  - and weight reduction



INDIRECT ACTING ADRENERGIC AGONISTS
A. AMPHETAMINE-LIKE OR DISPLACERS

2. **Methamphetamine:**

- **Very similar to amphetamine** with an even **higher ratio of central to peripheral actions.**

- In **the brain**, methamphetamine:
  - **releases dopamine** and other biogenic amines,
  - and **inhibits MAO**

3. **Phenmetrazine:**

- It is a **variant phenylisopropylamine** with **amphetamine-like effects.**
  - It has been promoted as an **anorexiant**
  - and is also a **popular drug of abuse**

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
CNS APPLICATIONS

- **Obesity:**
- an encouraging **initial appetite-suppressing effect** of these agents may be observed in **obese humans**,
- but there is **no evidence** that **long-term improvement in weight control** can be achieved with **amphetamines alone**…..
- intensive dietary and psychological counseling and support is needed

INDIRECT ACTING ADRENERGIC AGONISTS

A. AMPHETAMINE-LIKE OR DISPLACERS

4. **Methylphenidate:**

- Amphetamine variant whose major pharmacologic effects and abuse potential are **similar to** those of **amphetamine**

- It is a **mild CNS stimulant**
  - with **more prominent effe**cts on **mental t**han on **motor activities**

- **CNS application: <u>attention-deficit hyperactivity disorder (ADHD).</u>**
- Some patients respond well to low doses of methylphenidate or to clonidine.

- **<u>Extended-release</u>** formulations may
  - **<u>simplify dosing</u>** regimens
  - and **<u>increase adherence</u>** to therapy, especially in **<u>school-age children</u>**

INDIRECT ACTING ADRENERGIC AGONISTS
A. AMPHETAMINE-LIKE OR DISPLACERS

5. **Modafinil:** a new amphetamine substitute

- It is a **psychostimulant** that **differs from amphetamine**
  - in structure,
  - neurochemical profile,
  - and behavioral effects

- **Mech of action not fully known**
  - **Inhibits both NET and DAT**,
  - and **increases interstitial concentrations:**
    - not only of **norepinephrine and dopamine**, but also **serotonin and glutamate**
    - while **decreasing GABA levels**

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
CNS APPLICATIONS

- All amphetamine-like and displacer have:
  - a mood-elevating (**euphoriant**) **effect**,
  - **alerting**, & **sleep-deferring action**
  - that is manifested by **improved attention to repetitive tasks**

- **Modafinil** is ***approved*** for use in **NARCOLEPSY** (chronic sleep disorder)

- **MODAFINIL** is claimed to have **fewer disadvantages** than **amphetamine i**n this condition
  - ……LESS excessive mood changes,
  - LESS insomnia
  - and LESS abuse potential

TYRAMINE

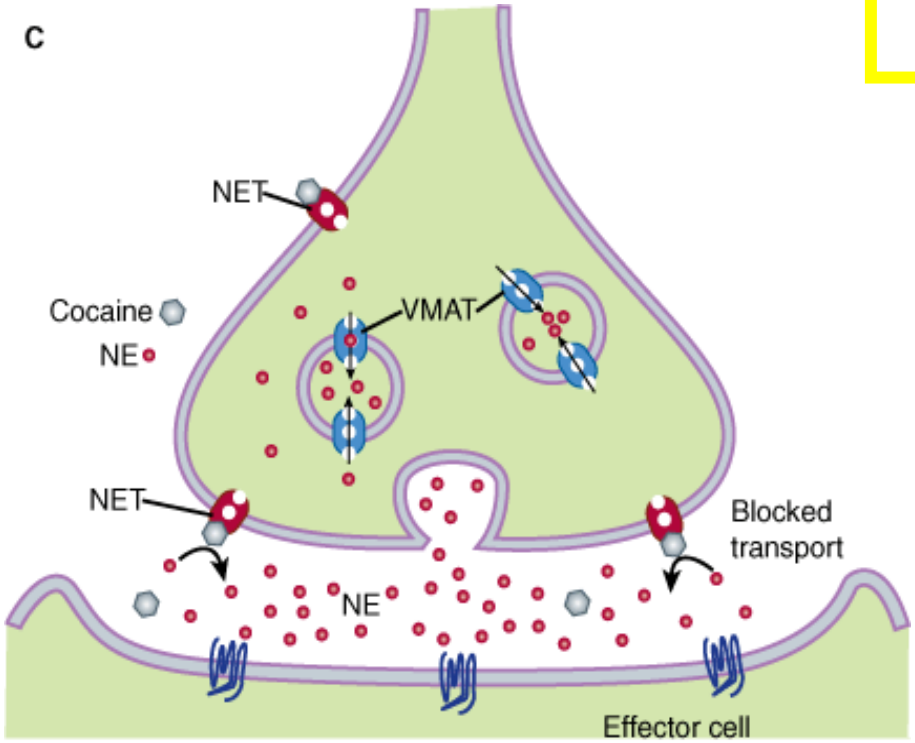
- It is by-product of tyrosine metabolism in the body and is also found in high concentrations in some fermented foods such as cheese (table 9-5)
- Tyramine's spectrum of action is similar to that of norepinephrine
- Inactive orally……readily metabolized by MAO in the liver
- If the patient is taking **MAOI "inhibitors"** (MAO-A), BE CAREFUL!.....can precipitate **serious vasopressor effects**

INDIRECT ACTING ADRENERGIC AGONISTS
B. CATECHOLAMINE REUPTAKE INHIBITORS

1. **Atomoxetine & reboxetine**

- They are **selective inhibitors** of the **NET**
- **Surprisingly** it has **little cardiovascular effect**
  - because it has a **clonidine-like effect** in the **central nervous** system to **decrease sympathetic outflow**
-
- while at the same time **potentiating** the **effects of norepinephrine in the periphery**

NET
DAT
SERT



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

INDIRECT ACTING ADRENERGIC AGONISTS

B. CATECHOLAMINE REUPTAKE INHIBITORS

2. **Sibutramine:** is a **serotonin and norepinephrine reuptake inhibitor**
   - and is the **only appetite suppressant approved** by the **FDA** for **long-term treatment of obesity**

3. **Duloxetine:** is also a widely used **antidepressant** with
   - **serotonin and norepinephrine reuptake inhibitory effects**

COCAINE:

- **Local anesthetic** with **peripheral** **indirect sympathomimetic action**

- Enters the CNS and produces a **shorter lasting** but **more intense amphetamine-like** effect through
  - **inhibiting dopamine reuptake** into neurons in the "**pleasure centers"** of the **brain**

- **+** can be **smoked**, **snorted** into the nose, or **injected** for rapid onset of effect…..have made it a **heavily abused drug**

- *INTERESTING….*that dopamine-transporter knockout mice still self-administer cocaine, suggesting that cocaine may have additional pharmacologic targets

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
CARDIOVASCULAR APPLICATIONS

- **Condition in which :**
  - **an increase in cardiac output and blood flow to the tissue is desired**
  - **(severe hypotension, cardiac shock, heart failure)**

- **β agonist** may be useful in this situation because they:
  - **increase cardiac contractility**
  - and **reduce diastolic pressure by β2 effect**

- Dobutamine and dopamine are used (**dopamine is DOC)**

- **Isoproterenol and epinephrine** have been used:
  - in the temporary **emergency management** of complete **heart block** and **cardiac arrest**
  - (electronic pacemaker are safer and more effective)

- **Shock: Acute cardiovascular syndrome** that results in:
  - a **critical reduction** in **perfusion** of **vital tissues**,
  - **altered mental state**,
  - **hypotension**
  - and **oliguria**

- **Usually due to**:
  - **hypovolemia**,
  - **cardiac insufficiency**,
  - and **altered vascular resistance**

- **Treatment**:
  - **volume replacement**
  - and treatment of the **underlying disease** are the mainstays of the treatment
  - **Adrenergic receptor agonists** may be used……:
  - **β receptor agonists** increase **heart rate and force** of contraction, **α receptor** agonists increase **peripheral vascular resistance**, and **dopamine (DOC) promotes dilation of renal and splanchnic vascular beds, in addition to activating α and β receptors**

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
CARDIOVASCULAR APPLICATIONS

- **Condition in which a DECREASE in blood flow or increase in blood pressure is desired**

- **Decrease blood flow:**

- **α1 agonist** are **useful** in situation in which **vasoconstriction is appropriate**
  - Such as decongestant effect (phenylephrine)

- **α agonist** are often **mixed** with **local anesthetic** to:
  - **reduce** the **loss of anasthetic** from the **area of injection** into the **circulation** (epinephrine is DOC)

THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
CARDIOVASCULAR APPLICATIONS

- **Increase blood pressure**
- spinal shock (NE) in which **maintenance of blood pressure** may help in **maintain perfusion to brain, heart, & liver (we need increase in blood pressure)**
- **Shock due to MI** is
  - usually made **worse** by vasoconstriction

- **Chronic orthostatic hypotension**: On standing, gravitational forces induce venous pooling, resulting in decreased venous return
  - Increasing peripheral resistance is one of the strategies to treat chronic orthostatic hypotension
  - **Midodrin**e, an orally **active α_1 agonist**, is frequently used for this indication

APPLICATION OF BASIC PHARMACOLOGY TO CLINICAL PROBLEM

Horner's syndrome

- **is a condition (usually unilateral**) that results **from**
  - **interruption** of the **sympathetic nerves** to **the face**
  - (caused by either **preganglionic** or **postganglionic lesion**, **such as a tumor**)

- **Symptoms include:**
  - vasodilation,
  - ptosis,
  - miosis,
  - and loss of sweating on the side affected.

HORNER'S SYNDROME

- **Sympathomimetics** administered as **ophthalmic drops**
  - are also useful in **localizing** the **lesion** in **Horner's syndrome**

- If the **lesion is *postganglionic***,
  - **indirectly** acting **sympathomimetics** (eg, **cocaine, amphetam**ine) will **not dilate** the abnormally **constricted pupil**
    - because **catecholamines** have **been lost from** the **nerve endings** in the **iris**
  - But **phenylephrine** will **dilate** the pupil (**acts directly** on **the α** receptors on the **smooth muscle of the iris)**

- If the **lesion is *preganglionic***,
  - it will show a **normal response to both drugs**,
  - since the **postganglionic fibers** and their **catecholamine stores** remain **intact** in this situation

Horner's syndrome