Sympathomimetics

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Adrenoceptor Agonists

ADRENERGIC RECEPTORS

alpha-1- phospholipase C (IP3, DAG, calcium)

alpha-2 - inhibitory G-protein (Gi). activates potassium channels , inhibits calcium channels

- **beta-1 - stimulatory G-protein**

cAMP dependent P-kinases leads to Phosphry. Of Ca++ ch

- **beta-2 - stimulatory G-protein. cAMP dependent p-kinase phosphorlates (inactivate) MLC-kinase for contraction in s.muscles**

- **beta-3 - stimulatory G-protein**

Table 6–3
Characteristics of Subtypes of Adrenergic Receptors[1]

RECEPTOR	AGONISTS	ANTAGONISTS	TISSUE	RESPONSES
α_1[2]	Epi ≥ NE >> Iso Phenylephrine	Prazosin	Vascular smooth muscle	Contraction
			Genitourinary smooth muscle	Contraction
			Liver[3]	Glycogenolysis; gluconeogenesis
			Intestinal smooth muscle	Hyperpolarization and relaxation
			Heart	Increased contractile force; arrhythmias
α_2[2]	Epi ≥ NE >> Iso Clonidine	Yohimbine	Pancreatic islets (β cells)	Decreased insulin secretion
			Platelets	Aggregation
			Nerve terminals	Decreased release of NE
			Vascular smooth muscle	Contraction
β_1	Iso > Epi=NE Dobutamine	Metoprolol CGP 20712A	Heart	Increased force and rate of contraction and AV nodal conduction velocity
			Juxtaglomerular cells	Increased renin secretion
β_2	Iso > Epi >> NE Terbutaline	ICI 118551	Smooth muscle (vascular, bronchial, gastrointestinal, and genito-	Relaxation

			Platelets	Aggregation
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β_2	Iso > Epi >> NE Terbutaline	ICI 118551	Smooth muscle (vascular, bronchial, gastrointestinal, and genitourinary)	Relaxation
			Skeletal muscle	Glycogenolysis; uptake of K^+
			Liver[3]	Glycogenolysis; gluconeogenesis
β_3[4]	Iso=NE > Epi BRL 37344	ICI 118551 CGP 20712A	Adipose tissue	Lipolysis

[1] This table provides examples of drugs that act on adrenergic receptors and of the location of subtypes of adrenergic receptors. *Abbreviations*: epinephrine (Epi); norepinephrine (NE); isoproterenol (Iso).

[2] At least three subtypes each of α_1- and α_2-adrenergic receptors are known, but distinctions in their mechanism of action and tissue location have not been clearly defined.

[3] In some species (*e.g.*, rat), metabolic responses in the liver are mediated by α_1-adrenergic receptors, whereas in others (*e.g.*, dog) β_2-adrenergic receptors are predominantly involved. Both types of receptors appear to contribute to responses in human beings.

[4] Metabolic responses in adipocytes and certain other tissues with atypical pharmacological characteristics may be mediated by this subtype of receptor. Most β-adrenergic receptor antagonists (including propranolol) do not block these responses.

Direct-Acting Adrenoceptor Agonists

Catecholamines

- Dobutamine
- Dopamine
- Epinephrine
- Isoproterenol
- Norepinephrine

Noncatecholamines

- Albuterol
- Apraclonidine†
- Clonidine
- Oxymetazoline
- Phenylephrine

Direct-Acting Adrenoceptor Agonists

A. Catecholamines

- Dobutamine
- Dopamine
- Epinephrine
- Isoproterenol
- Norepinephrine

Direct-Acting Adrenoceptor Agonists

B. Noncatecholamines

- Albuterol (VENTOLIN)
- Apraclonidine
- Clonidine
- Midodrine
- Oxymetazoline
- Phenylephrine
- Ritodrine

(II) Indirect-Acting Adrenoceptor Agonists

- Amphetamine
- Cocaine

(III) Mixed-Acting Adrenoceptor Agonists

- Ephedrine
- Pseudoephedrine

Indirect-Acting Adrenoceptor Agonists

three different mechanisms:

(1) Displacement of stored catecholamines from the adrenergic nerve ending. Amphetamine and related drugs are substrates for the transporter, which transports the drugs into the presynaptic neuron where they inhibit the storage of norepinephrine by synaptic vesicles, leading to reverse transport of norepinephrine into the synapse by the catecholamine transporter or

(2) Inhibition of reuptake of catecholamines already released, Cocaine & TCAs binds to and competitively inhibits the catecholamine transporter located in the presynaptic nerve terminal

Indirect-Acting Adrenoceptor Agonists

(3) Another group of drugs act by inhibiting the breakdown of norepinephrine by COMT or MAO. C**atechol-<*O*-methyltransferase inhibitors** and **monoamine oxidase inhibitors** primarily exert their effects on the central nervous system.

ADRENERGIC RECEPTORS

Table 6–4
Adrenergic Receptors and Their Effector Systems

ADRENERGIC RECEPTOR	G PROTEIN	EXAMPLES OF SOME BIOCHEMICAL EFFECTORS
β_1	G_s	↑ adenylyl cyclase, ↑ L-type Ca^{2+} channels
β_2	G_s	↑ adenylyl cyclase
β_3	G_s	↑ adenylyl cyclase
α_1 Subtypes	G_q	↑ phospholipase C
	G_q	↑ phospholipase D
	G_q, G_i/G_o	↑ phospholipase A_2
	G_q	? ↑ Ca^{2+} channels
α_2 Subtypes	$G_{i\ 1, 2, \text{ or } 3}$	↓ adenylyl cyclase
	G_i ($\beta\gamma$ subunits)	↑ K^+ channels
	G_o	↓ Ca^{2+} channels (L- and N-type)
	$?G_{i/o}$	↑ PLC, PLA_2

Adrenoceptors

- classified as **α-adrenoceptors and β-adrenoceptors**

α-Adrenoceptors:

- The **α_1- adrenoceptors are primarily located in smooth muscle at sympathetic neuroeffector junctions,** but these receptors are also found in exocrine glands and the central nervous system.
- The α_1-adrenoceptors mediate contraction of vascular smooth muscle, the iris dilator muscle, and smooth muscle in the lower urinary tract (bladder, urethra, and prostate)

Adrenoceptor

- The α_2-adrenoceptors are widely distributed in presynaptic neurons, various tissues, and blood platelets
- The α_2-adrenoceptors located on sympathetic postganglionic neurons serve as **autoreceptors whose activation leads** to feedback inhibition of norepinephrine release from nerve terminals.
- The α_2-receptors are also found in blood platelets and in ocular, adipose, intestinal, hepatic, renal, and endocrine tissue.

Adrenoceptor

- In blood platelets, α_2-receptors mediate platelet aggregation.
- The α_2 in ciliary epithelium decrease aqueous secretion
- In the pancreas, α_2-receptors mediate the inhibition of insulin secretion that occurs when the sympathetic nervous system is activated.

TABLE 7.5 Selected Sympathomimetics

DRUG	PRIMARY RECEPTOR SUBTYPE	CLINICAL USE
albuterol (Proventil, Ventilin, Provax)	$beta_2$	to treat asthma
dobutamine (Dobutrex)	$beta_1$	to stimulate the heart
dopamine (Intropin)	$alpha_1$ and $beta_1$	to treat shock
epinephrine (Adrenalin, Primatene, Bronkaid)	alpha and beta	to treat asthma, cardiac arrest
isoproterenol (Isuprel)	$beta_1$ and $beta_2$	to treat asthma, dysrhythmias, heart failure
metaproterenol (Alupent)	$beta_2$	to treat asthma
metaraminol (Aramine)	$alpha_1$ and $beta_1$	to treat shock
norepinephrine (Levarterenol, Levophed)	$alpha_1$ and $beta_1$	to treat shock
oxymetazoline (Afrin)	alpha	to treat nasal congestion
Pr phenylephrine (Neo-Synephrine)	alpha	to treat nasal congestion
pseudoephedrine (Sudafed, Afrin, and others)	alpha and beta	to treat nasal congestion
ritodrine (Yutopar)	$beta_2$	to slow uterine contractions
salmeterol (Serevent)	$beta_2$	to treat nasal congestion
terbutaline (Brethine and others)	$beta_2$	to treat asthma

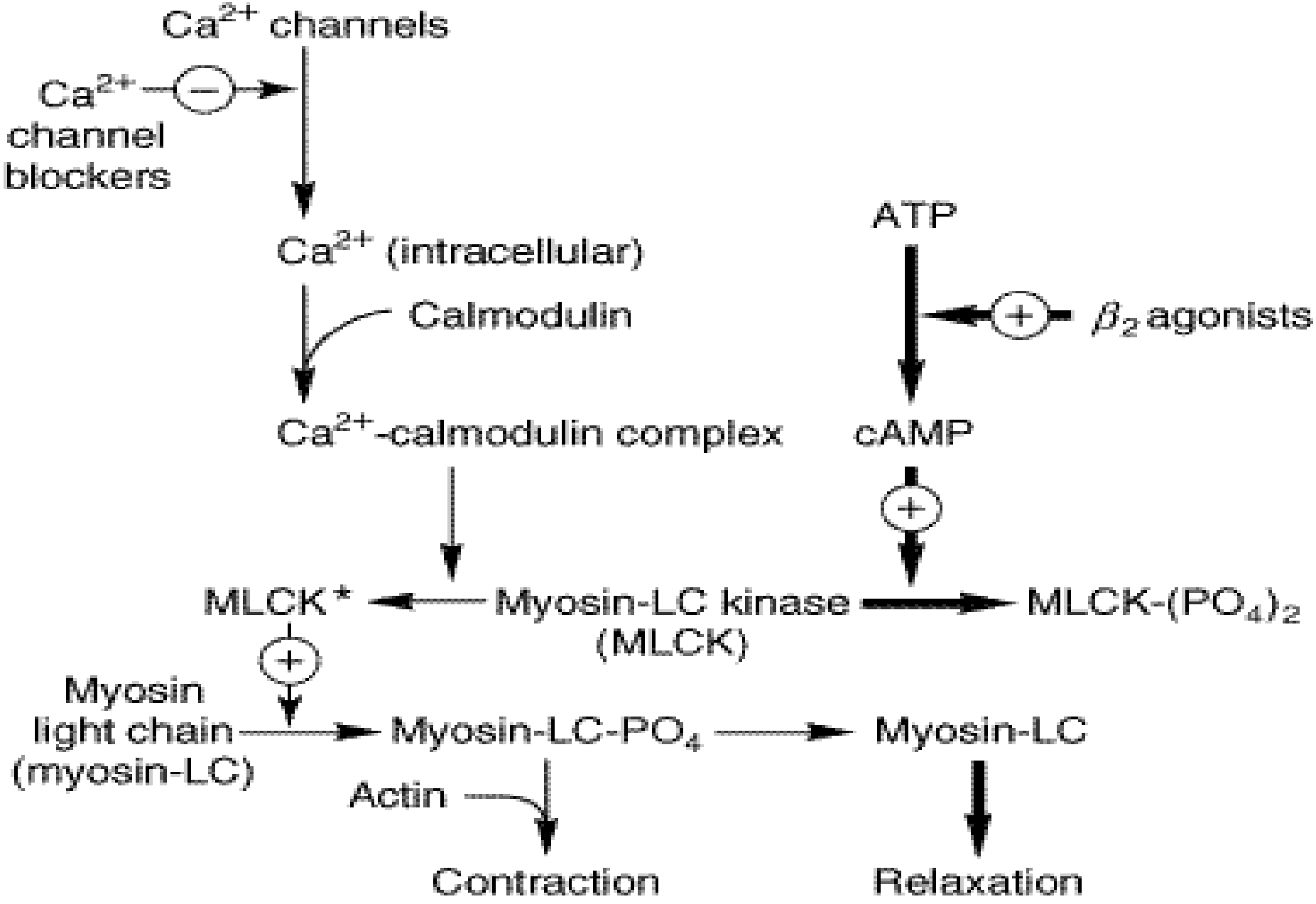
TABLE 9.1 Responses to Adrenergic and Cholinergic Nerve Stimulation

Organ or Tissue Function	Predominant Adrenoceptor Type	Adrenergic Response	Cholinergic Response[a]
Heart[b]			
Rate (chronotropic effect)	β_1	Increase	Decrease
Contractile force (inotropic effect)	β_1	Increase	None
Conduction velocity (dromotropic effect)	β_1	Increase	Decrease
Eye			
Pupil size	α_1	Constriction of radial muscle causing dilation (mydriasis)	Contraction of circular muscle (miosis)
Accommodation		No innervation	Contraction of ciliary muscle producing accommodation for near vision
Bronchial smooth muscle	β_2	Relaxation	Contraction
Blood vessels (arteries and arterioles)[c]			
Cutaneous	α_1	Constriction	No innervation[e]
Visceral	α_1	Constriction	No innervation[e]
Pulmonary	α_1	Constriction	No innervation[e]
Skeletal muscle	α_1, β_2	Constriction[d]	No innervation[e]
Coronary	α_1, β	Constriction, dilation[f]	No innervation[e]
Cerebral	α_1	Constriction	
Veins	α_1	Constriction	No innervation
Gastrointestinal tract (tone, motility, and secretory activity)	α_2, β_2	Decrease[g]	Increase
Sphincters	α	Contraction	Relaxation
Splenic capsule	α_1	Contraction	No innervation
Urinary bladder			
Detrusor muscle	β	Relaxation	Contraction
Trigone-sphincter muscle	α_1	Contraction	Relaxation
Uterus	α_1, β_2	Contraction-relaxation[h]	Contraction-relaxation
Glycogenolysis			
Skeletal muscle	β_2	Increase	None
Liver	α_1, β_2	Increase	None
Lipolysis	β_1	Increase	None
Renin secretion	β_1	Increase	None
Insulin secretion	α_2	Decrease	Increase

β-Adrenoceptors

- Activation of β_1-adrenoceptors produces cardiac stimulation, leading to a positive chronotropic effect (increased heart rate), a positive inotropic effect (increased contractility), and a positive dromotropic effect (increased cardiac impulse conduction velocity).
- Activation of β_1 receptors also increases renin secretion from renal juxtaglomerular cells.
- β2- receptors are stimulatory at some sites and inhibitory at certain sites

- The β_2-adrenoceptors mediate relaxation of bronchial, uterine, and vascular smooth muscle
- In skeletal muscle, β_2-receptors cause contraction.
- In the liver, they mediate glycogenolysis, which increases the glucose concentration in the blood.


Ca^{2+} channels
Ca^{2+} channel blockers
Ca^{2+} (intracellular)
Calmodulin
Ca^{2+}-calmodulin complex
ATP
β_2 agonists
cAMP
MLCK*
Myosin-LC kinase (MLCK)
MLCK-$(PO_4)_2$
Myosin light chain (myosin-LC)
Myosin-LC-PO_4
Myosin-LC
Actin
Contraction
Relaxation

Mechanisms of Smooth Muscle Relaxation

1. Increasing cGMP

- cGMP facilitates the dephosphorylation of myosin light chains, preventing the interaction of myosin with actin.
- Nitric oxide is an effective activator of soluble guanylyl cyclase and acts mainly through this mechanism.
- Important molecular donors of nitric oxide include nitroprusside and the organic nitrates used in angina.

Mechanisms of Smooth Muscle Relaxation

2. Decreasing intracellular Ca2+

- Calcium channel blockers cause vasodilation because they reduce intracellular Ca2+, a major modulator of the activation of myosin light chain kinase. (Beta blockers and calcium channel blockers reduce Ca2+*influx in cardiac muscle,* thereby reducing rate, contractility, and oxygen requirement unless reversed by compensatory responses.)

Mechanisms of Smooth Muscle Relaxation

3. Stabilizing or preventing depolarization of the vascular smooth muscle cell membrane:

- The membrane potential of excitable cells is stabilized by increasing potassium permeability. Potassium channel openers, such as minoxidil sulfate
- Antihypertensive Agents) increase the permeability of K+ channels, probably ATP-dependent K+chan
- Certain newer agents under investigation for use in angina (eg, nicorandil) may act, in part, by this mechanism.

Mechanisms of Smooth Muscle Relaxation

4. Increasing cAMP in the vascular cells

- An increase in cAMP increases the rate of inactivation of myosin light chain kinase, the enzyme responsible for triggering the interaction of actin with myosin in these cells.
- This appears to be the mechanism of vasodilation caused by 2-agonists, drugs that are *not used in angina.*

Mechanisms of Smooth Muscle Relaxation

- Beta2 agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle by accelerating the inactivation of MLCK (heavy arrows) and by facilitating the expulsion of calcium from the cell

β-Adrenoceptors

- β_2- enhance secretions of the ciliary epithelium
- Activation of β3-adrenoceptors produces lipolysis, a process in which the hydrolysis of triglycerides in adipose tissue leads to the release of fatty acids into the circulation.
- Selective β_3-adrenoceptor agonists has Lipolytic effect , so would be useful in the treatment of obesity.
- In GI smooth muscle, both α_2 & β_2 mediate the inhibitory effects i.e. relaxation

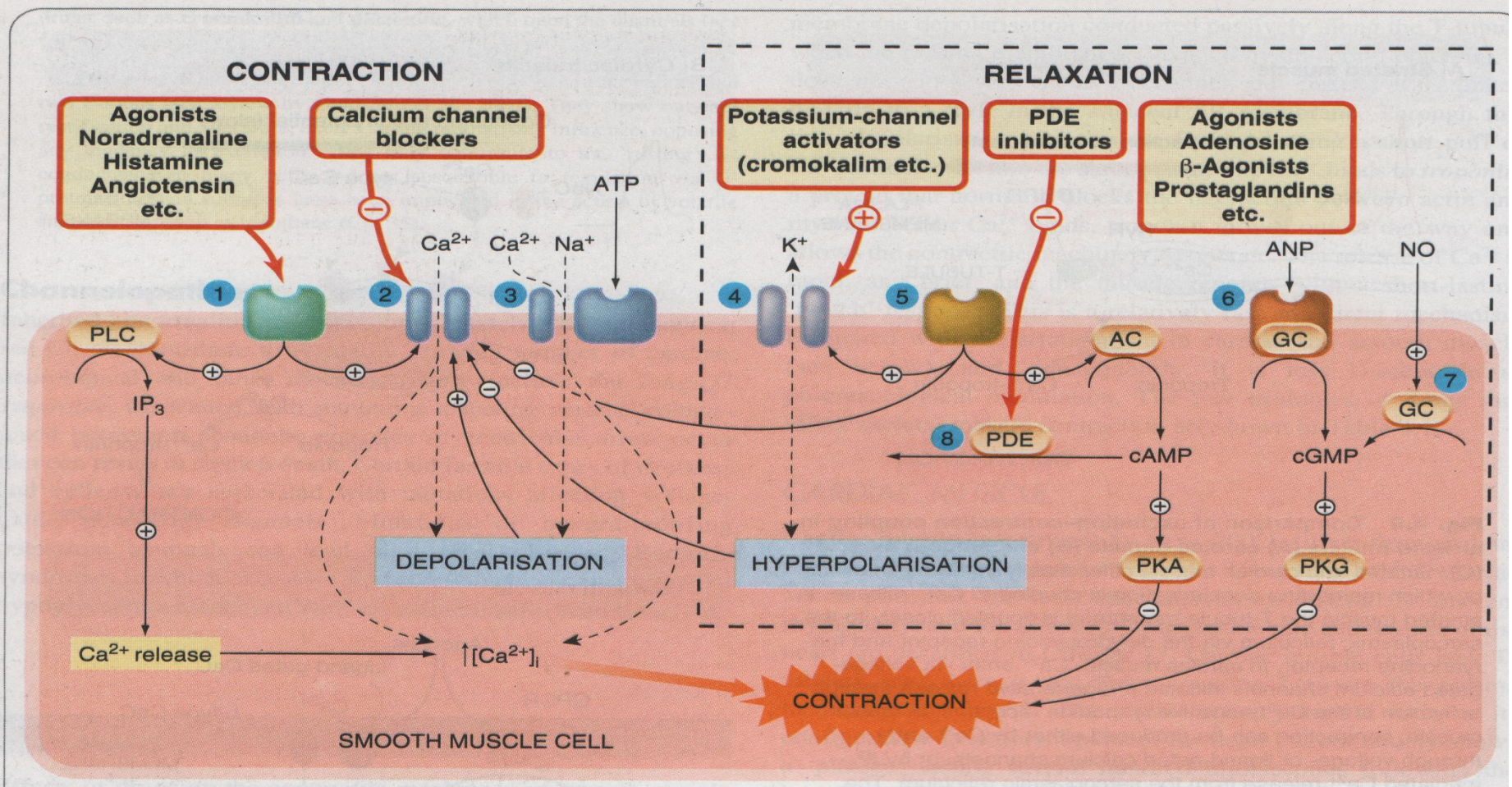
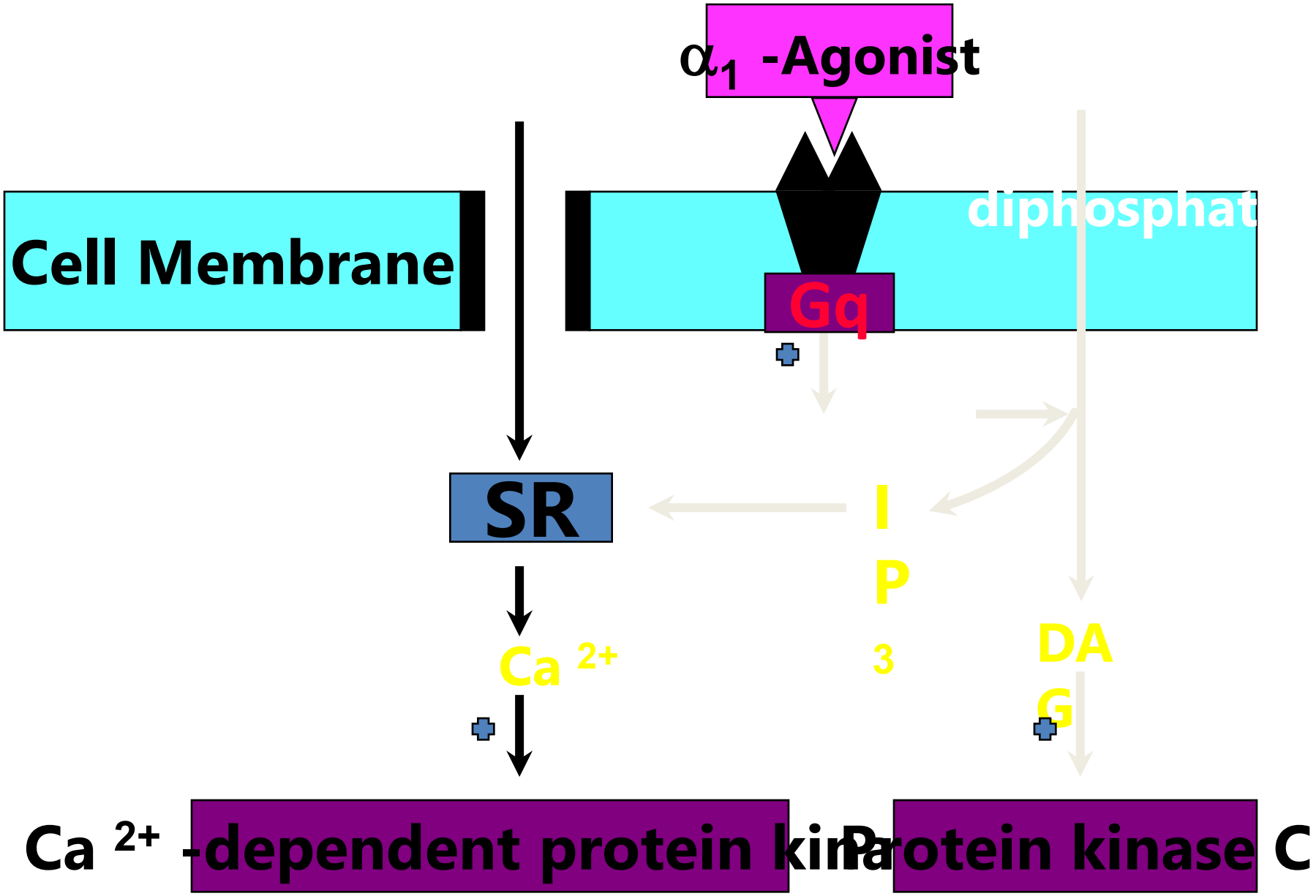


Fig. 4.10 Mechanisms controlling smooth muscle contraction and relaxation. 1. G-protein coupled receptors for excitatory agonists, mainly regulating inositol trisphosphate formation and calcium channel function. 2. Voltage-gated calcium channels. 3. Ligand-gated cation channels (P_{2X} receptor for ATP is the main example). 4. Potassium channels. 5. G-protein-coupled receptors for inhibitory agonists, mainly regulating cAMP formation, potassium and calcium channel function. 6. Receptor for atrial natriuretic peptide (ANP), coupled directly to guanylate cyclase (GC). 7. Soluble guanylate cyclase, activated by nitric oxide (NO). 8. Phosphodiesterase (PDE) is the main route of inactivation of cAMP and cGMP. (AC, adenylate cyclase; PKA, protein kinase A; PKG, protein kinase G; PLC, phospholipase C.)

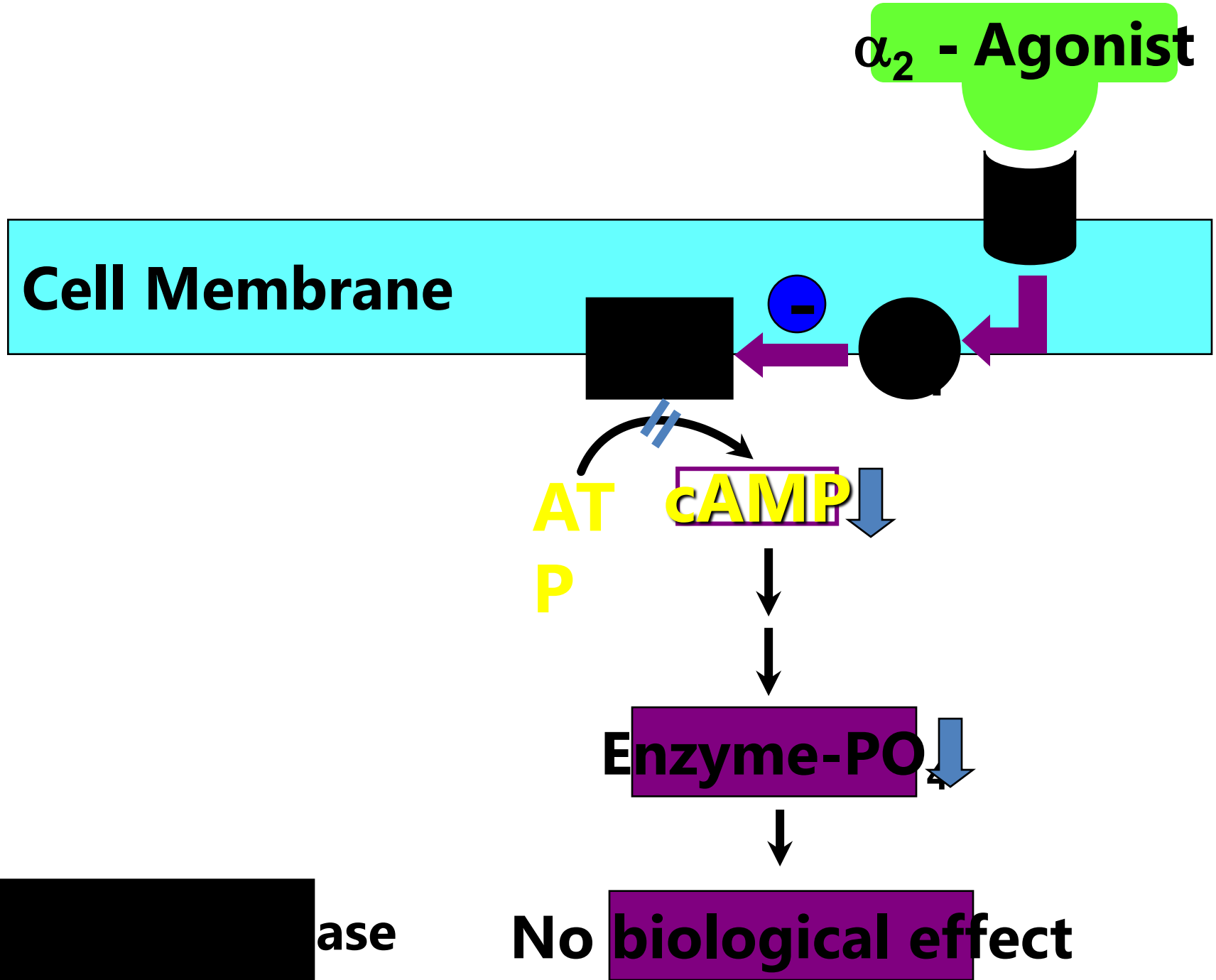
Signal Transduction

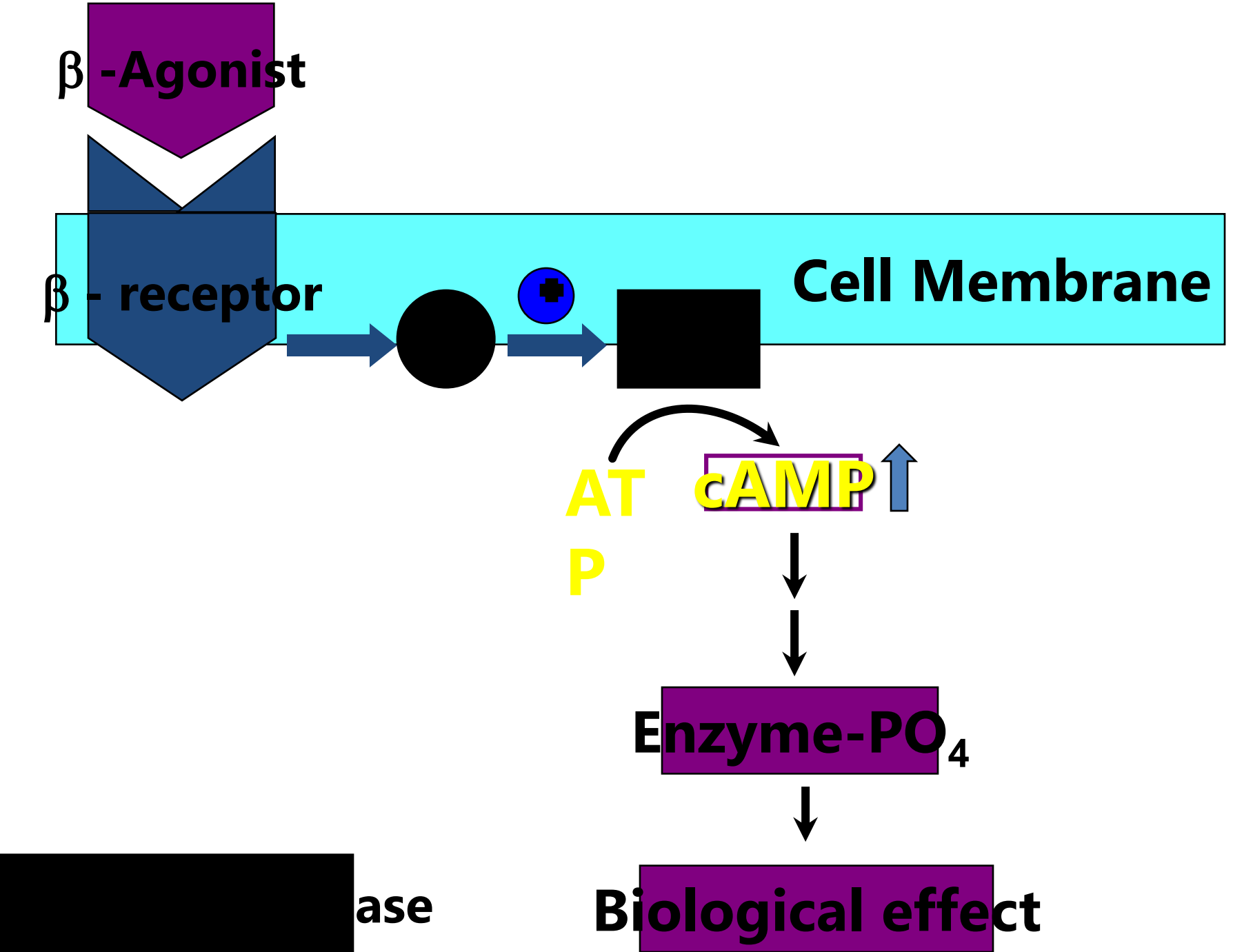
- Activation of α_1-adrenoceptors is coupled with activation of **phospholipase C, which catalyzes** the release of **inositol triphosphate (IP3) from membrane phospholipids.**
- **In smooth muscle, IP3** stimulates the release of calcium from the sarcoplasmic reticulum, and this leads to muscle contraction. This is the mechanism by which adrenoceptor agonists cause vasoconstriction and increase blood pressure. In exocrine glands, formation of IP3 leads to calcium release and gland secretion.


α1 -Agonist
Cell Membrane
diphosphat
Gq
SR
I
P
3
Ca 2+
DA
G
Ca 2+ -dependent protein kin
Protein kinase C

Signal Transduction

- Activation of α_2-adrenoceptors leads to inhibition of adenylyl cyclase and a decrease in the levels of cyclic adenosine monophosphate (cAMP) in sympathetic neurons an other tissues.
- This is the mechanism responsible for a decrease in aqueous humor secretion and for other effects of α2-adrenoceptor agonists
- Activation of β-adrenoceptors receptors leads to stimulation of adenylyl cyclase and an increase in the levels of cAMP in cardiac tissue and smooth muscle. Cyclic AMP activates protein kinase A, which phosphorylates other proteins and enzymes.


α_2 - Agonist
Cell Membrane
AT
P
cAMP
Enzyme-PO
ase
No biological effect


β -Agonist
β - receptor
Cell Membrane
AT
P
cAMP
Enzyme-PO4
ase
Biological effect

Signal Transduction

- The cellular response depends on the specific proteins that are phosphorylated in each tissue.
- In cardiac tissue, calcium channels are phosphorylated, thereby augmenting calcium influx and cardiac contractility.
- In smooth muscle, cAMP produces muscle relaxation via effects on multiple targets, including potassium channels, calcium channels, and myosin light chain kinase

DIRECT-ACTING ADRENOCEPTOR AGONISTS

Catecholamines:

- The naturally occurring catecholamines include norepinephrine, an endogenous sympathetic neurotransmitter; epinephrine, the principal hormone of the adrenal medulla; and dopamine, the precursor to norepinephrine and epinephrine.
- Synthetic catecholamines include isoproterenol and dobutamine.

MECHANISMS AND EFFECTS

- Epinephrine is a potent agonist at all α- and β-adrenoceptors.
- Norepinephrine differs from epinephrine only in that it has greater affinity for β1-adrenoceptors than for β2-adrenoceptors.
- Because of this difference, norepinephrine constricts all blood vessels, whereas epinephrine constricts some blood vessels but dilates others.
- Isoproterenol is considered to be a selective β1- and β2-adrenoceptor agonist because it has little affinity for α-receptors.
- Dobutamine primarily stimulates β1-receptors but has minor stimulatory effects on β2- and α-receptors.

Pharmacological Effects

CARDIOVASCULAR EFFECTS:

- Direct effects on the heart are determined largely by β1 receptors, although β2 and to a lesser extent α1 receptors are also involved.
- Beta-receptor activation results in increased calcium influx in cardiac cells leading to positive chronotropic effect).
- Conduction velocity in the atrioventricular node is increased
- Intrinsic contractility is increased (positive inotropic effect)
- Activation of α1 produces vasoconstriction and increases peripheral resistance, which, in turn, increases the systolic and diastolic blood pressure.

(2) RESPIRATORY TRACT EFFECTS

- Epinephrine and isoproterenol are potent bronchodilators.
- Although they have been used in the treatment of asthma, more selective β2-adrenoceptor agonists are usually used for this purpose today.

ADVERSE EFFECTS:

- Catecholamines can cause excessive vasoconstriction, leading to tissue ischemia and necrosis.
- Excessive doses of catecholamines can reduce blood flow to vital organs, such as the kidneys, or cause excessive cardiac stimulation that leads to tachycardia and other cardiac arrhythmias
- The β-adrenoceptor agonists can cause hyperglycemia secondary to glycogenolysis, and this is usually undesirable in patients with diabetes.

Clinical Pharmacology of Sympathomimetics Drugs

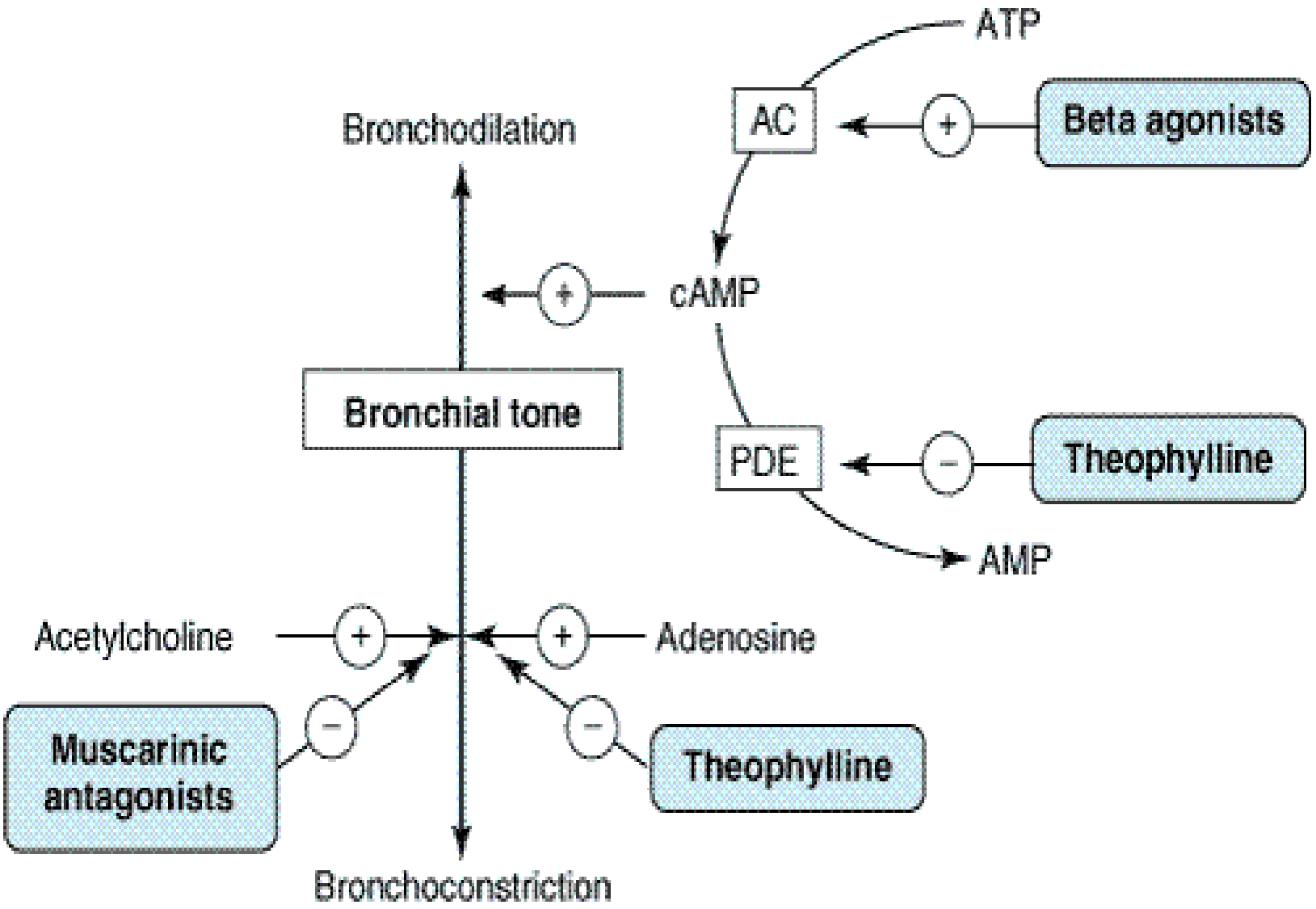
Cardiovascular Applications

- Sympathomimetic drugs may be used in a hypotensive emergency to preserve cerebral and coronary blood flow. Such situations might arise in severe hemorrhage, spinal cord injury, or overdoses of antihypertensive or central nervous system depressant medications.
- Conditions in which blood flow is to be Reduced e.g. achieving hemostasis in surgery, for reducing diffusion of local anesthetics away from the site of administration, and for reducing mucous membrane congestion

  - Epinephrine is usually applied topically in nasal packs (for epistaxis) or in a gingival string (for gingivectomy).

Clinical Pharmacology of Sympathomimetics Drugs

- **Cardiac Applications:**Catecholamines such as isoproterenol and epinephrine have been utilized in the temporary emergency management of complete heart block and cardiac arrest.
- **Pulmonary Applications:**One of the most important uses of sympathomimetic drugs is in the therapy of bronchial asthma.
- **Anaphylaxis:** Epinephrine is the agent of choice because of extensive experimental and clinical experience with the drug in anaphylaxis and because epinephrine activates, 1, and 2 receptors, all of which may be important in reversing the pathophysiologic processes underlying anaphylaxis.


ATP
AC
Beta agonists
Bronchodilation
cAMP
Bronchial tone
PDE
Theophylline
AMP
Acetylcholine
Adenosine
Muscarinic antagonists
Theophylline
Bronchoconstriction

Clinical Pharmacology of Sympathomimetics Drugs

Ophthalmic Applications:

-Phenylephrine is an effective mydriatic agent frequently used to facilitate examination of the retina.

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

-Apraclonidine and brimonidine are α_2-selective agonists that also lower intraocular pressure and are approved for use in glaucoma.

Genitourinary Applications: As noted above, β_2-selective agents relax the pregnant uterus. **Ritodrine, terbutaline, and similar** drugs have been used to suppress premature labor. The goal is to defer labor long enough to ensure adequate maturation of the fetus.

Clinical Pharmacology of Sympathomimetics Drugs

Central Nervous System Applications

- The amphetamines have a mood-elevating (euphoriant) effect; this effect is the basis for the widespread abuse of this drug
- The amphetamines also have an alerting, sleep-deferring action. A therapeutic application of this effect is in the treatment of narcolepsy.
- CNS-active sympathomimetics used in the attention-deficit hyperactivity disorder (ADHD) of children
- Appetite-suppressing effect of these agents, in obese humans

Clinical Pharmacology of Sympathomimetics Drugs

Additional Therapeutic Uses:

- Clonidine is in the treatment of hypertension, the drug has been found to have efficacy in the treatment of diarrhea in

  diabetics with autonomic neuropathy, perhaps due to its ability to enhance salt and water absorption from the intestines.
- In addition, clonidine has efficacy in diminishing craving for narcotics and alcohol during withdrawal and may facilitate cessation of cigarette smoking.
- Clonidine has also been used to diminish menopausal hot flushes

Drug Treatment of Shock

- Shock is a condition in which the circulation to vital organs is profoundly reduced as a result of inadequate blood volume **(hypovolemic shock), inadequate cardiac function (cardiogenic shock), or inadequate** vasomotor tone **(neurogenic shock and septic shock).**
- **Septic shock is associated with massive** vasodilation secondary to the production of toxins by pathogenic microorganisms.

- **Anaphylactic shock, resulting from severe immediate hypersensitivity reactions, is usually manifested by** hypotension and difficult breathing.

Drug Treatment of Shock

- Catecholamine drugs that increase blood pressure **(vasopressors) are used in treating shock** when the organ function is impaired because mean arterial blood pressure is less than 60 mm Hg.
- **Hypovolemia should be corrected by intravenous fluid administration before the use of** vasopressors because vasopressors will not be effective if hypovolemia is present.
- In cases of cardiogenic shock, mechanical devices (e.g., the intra-aortic balloon pump) are often used in conjunction with vasopressor drugs in the treatment of this condition.

Drug Treatment of Shock

- Dopamine is used to treat **septic or cardiogenic shock when patients remain hypotensive** despite adequate fluid administration.
- Norepinephrine, which is a potent vasoconstrictor, is used to treat septic shock and is often given to persons with cardiogenic shock when the response to dopamine is inadequate or is accompanied by marked tachycardia.
- In cases of **anaphylaxis, epinephrine is the treatment of choice**
- Dobutamine is a cardiac stimulant (inotropic agent) that also produces vasodilation. It is used as a **cardiac stimulant during heart surgery and in the short-term management of acute heart failure and cardiogenic shock**

Noncatecholamines

- These drugs do not contain a catechol moiety, and they are not substrates for COMT.
- Some of the noncatecholamines are also resistant to degradation by MAO.
- For this reason, noncatecholamines are effective after oral administration and have a longer duration of action than do the catecholamines.

Beta-2 Agonists

- Albuterol, ritodrine, and terbutaline are selective β_2-adrenoceptor agonists that can be administered orally, parenterally, or by inhalation.
- To reduce their systemic absorption and adverse effects, albuterol and the related agonists are usually administered by inhalation in the treatment of asthma.
- The duration of action of these agonists is about 4 to 6 hours after inhalation or oral administration and is about 2 to 3 hours after intravenous administration.
- The β_2-adrenoceptor agonists act by causing smooth muscle relaxation, these drugs are helpful in the treatment of **asthma and other obstructive** lung diseases because they produce bronchodilation.

Beta-2 Agonists

- **Ritodrine is specifically used in the** treatment of **preterm labor,**
- Several other β_2-adrenoceptor agonists have been introduced to treat asthma, including fenoterol, formoterol, pirbuterol, and salmeterol.
- The adverse effects of selective β_2-adrenoceptor agonists include tachycardia, muscle tremor, and nervousness caused by activation of β2-adrenoceptors in the heart, skeletal muscle, and central nervous system.

Indirect Acting Adrenoceptor Agonists

Amphetamine and Tyramine

- Amphetamine and related compounds have high lipid solubility and indirectly increase synaptic concentrations of norepinephrine in the central and peripheral nervous systems
- Amphetamine produces vasoconstriction, cardiac stimulation, increased blood pressure, and central nervous system stimulation
- Tyramine is a naturally occurring amine found in a number of foods, including bananas. Cheese etc.
- Under normal conditions, tyramine is rapidly degraded by MAO in the gut and liver.

Indirect Acting Adrenoceptor Agonists

- In patients receiving MAO inhibitors, however, tyramine can be absorbed from foods in a quantity that is high enough to exert sympathomimetic effect and increase blood pressure.

Indirect Acting Adrenoceptor Agonists

Cocaine:

- Cocaine, a naturally occurring alkaloid, acts as a local anesthetic and also stimulates the sympathetic nervous system by blocking the neuronal reuptake of norepinephrine at both peripheral and central synapses.
- The sympathomimetics effects of cocaine are similar to those of amphetamine. Cocaine produces both vasoconstriction and cardiac stimulation and thereby elevates blood pressure.
- When the drug is used as a local anesthetic, its vasoconstrictive effect serves to retard its absorption into the systemic circulation, and this prolongs its duration of action.

Indirect Acting Adrenoceptor Agonists

- The vasoconstrictive effect, however, can also cause ischemia and necrosis of the nasal mucosa in people who abuse cocaine.
- The sympathomimetic effects of cocaine also appear to be responsible for the severe hypertension and cardiac damage that may occur in people who abuse cocaine.

MIXED-ACTING ADRENOCEPTOR AGONISTS

Ephedrine and Pseudoephedrine:

- Ephedrine is a naturally occurring compound obtained from plants of the genus *Ephedra*
- *Ephedrine is well absorbed from the gut and has sufficient lipid solubility to* enter the central nervous system.
- Relatively resistant to metabolism by MAO and COMT, ephedrine's duration of action is several hours.
- **Pseudoephedrine, an isomer of ephedrine, has** been used as a nasal decongestant in the treatment of colds and allergies.

MIXED-ACTING ADRENOCEPTOR AGONISTS

- Ephedrine and related drugs activate both α- and β-adrenoceptors by direct and indirect mechanisms.
- Via the activation of α_1-adrenoceptors, these drugs produce vasoconstriction. Which make them useful as **nasal decongestants in the treatment of viral and allergic rhinitis.**
- Via the action of β-adrenoceptors, the drugs produce bronchodilation.
- The adverse effects of ephedrine and pseudoephedrine include tachycardia caused by β1- receptor stimulation, increased blood pressure, and urinary retention.

MIXED-ACTING ADRENOCEPTOR AGONISTS

- Urinary retention is caused by stimulation of the sphincter muscle of the bladder.
- These drugs also cause central nervous system stimulation and can produce insomnia.
- Dietary supplements containing *Ephedra have* been widely used as appetite suppressants as an aid to losing weight.
- The U.S. Food and Drug Administration has banned the sale of such products because fatalities caused by hypertension and excessive cardiovascular stimulation have occurred following the use of these preparations

SUMMARY OF IMPORTANT POINTS

- Activation of α_1-adrenoceptors mediates smooth muscle contraction, leading to vasoconstriction, dilation of the pupils, and contraction of the bladder sphincter muscle.
- Activation of α_2-adrenoceptors inhibits the release of norepinephrine from sympathetic neurons, decreases the secretion of aqueous humor, and decreases the secretion of insulin.
- Activation of β_1-adrenoceptors produces cardiac stimulation and increases the secretion of renin, whereas activation of β_2- adrenoceptors mediates smooth muscle relaxation.

SUMMARY OF IMPORTANT POINTS

- The catecholamines include norepinephrine, epinephrine, isoproterenol, dopamine, and dobutamine. These drugs are rapidly metabolized, must be administered parentally, and are used primarily to treat cardiac disorders and various types of shock.
- In addition to activating adrenoceptors, dopamine activates D1- receptors and thereby increases renal blood flow.
- Noncatecholamines (e.g., phenylephrine and albuterol) are resistant to degradation by COMT.
- Phenylephrine activates α-adrenoceptors and causes vasoconstriction.
- Albuterol activates β_2-adrenoceptors and produces bronchodilation.

SUMMARY OF IMPORTANT POINTS

- Imidazoline compounds are agents that activate both α-adrenoceptors and imidazoline receptors.
- Examples include oxymetazoline, a topical decongestant; clonidine, an antihypertensive agent; and apraclonidine, an agent used to treat glaucoma.
- The indirect-acting adrenoceptor agonists increase the synaptic concentration of norepinephrine. Amphetamine causes reverse transport of norepinephrine by the catecholamine transporter, whereas cocaine blocks the reuptake of norepinephrine by the catecholamine transporter.
- Mixed-acting agonists, such as pseudoephedrine, have both direct and indirect actions. Pseudoephedrine is used as a nasal decongestant.

- Thank you