Cholinergic Antagonists

- Also called :

✓ Cholinergic Blocker

✓ Parasympatholytics

✓ Anticholinergic drugs

- Bind to cholinoceptors, but they

  do not trigger the usual receptor-mediated intracellular effects

- Fall into :

1. Muscarinic Antagonists
2. Nicotinic Antagonist *(clinically irrelevant)*
3. Neuromuscular - Blocking Agents *(Skeletal muscle relaxants)*

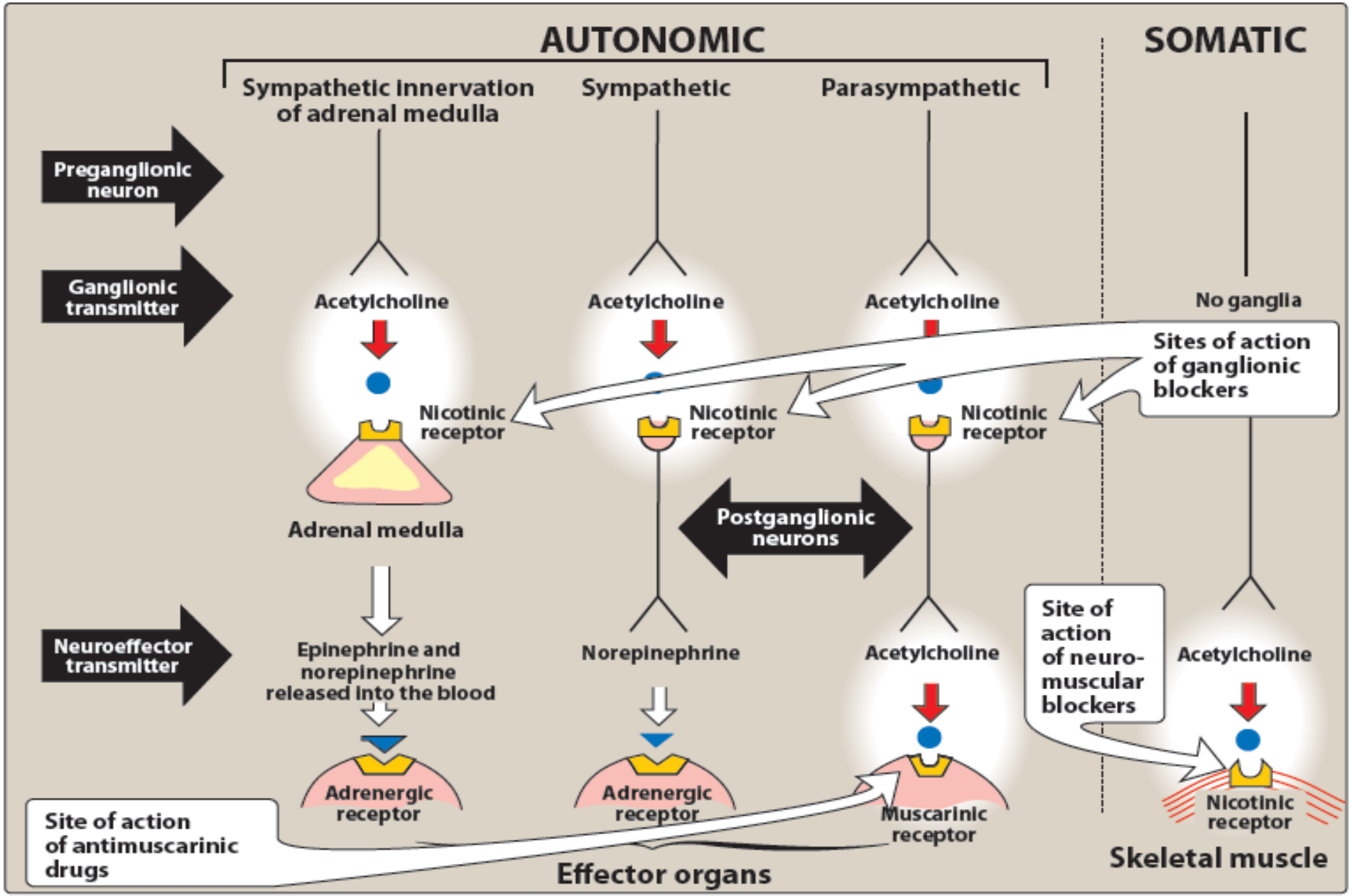


Figure 5.2
Sites of actions of cholinergic antagonists.

ANTIMUSCARINIC AGENTS

❖ **Atropine**

✓ Tertiary amine *Belladona* Alkaloid

✓ Competitive Antagonist to Ach on the muscarinic receptor

✓ Acts both centrally and peripherally

✓ Its general actions last about 4 hours

✓ Topical eye application renders it effective for days

✓ Mostly effective in bronchial tissues

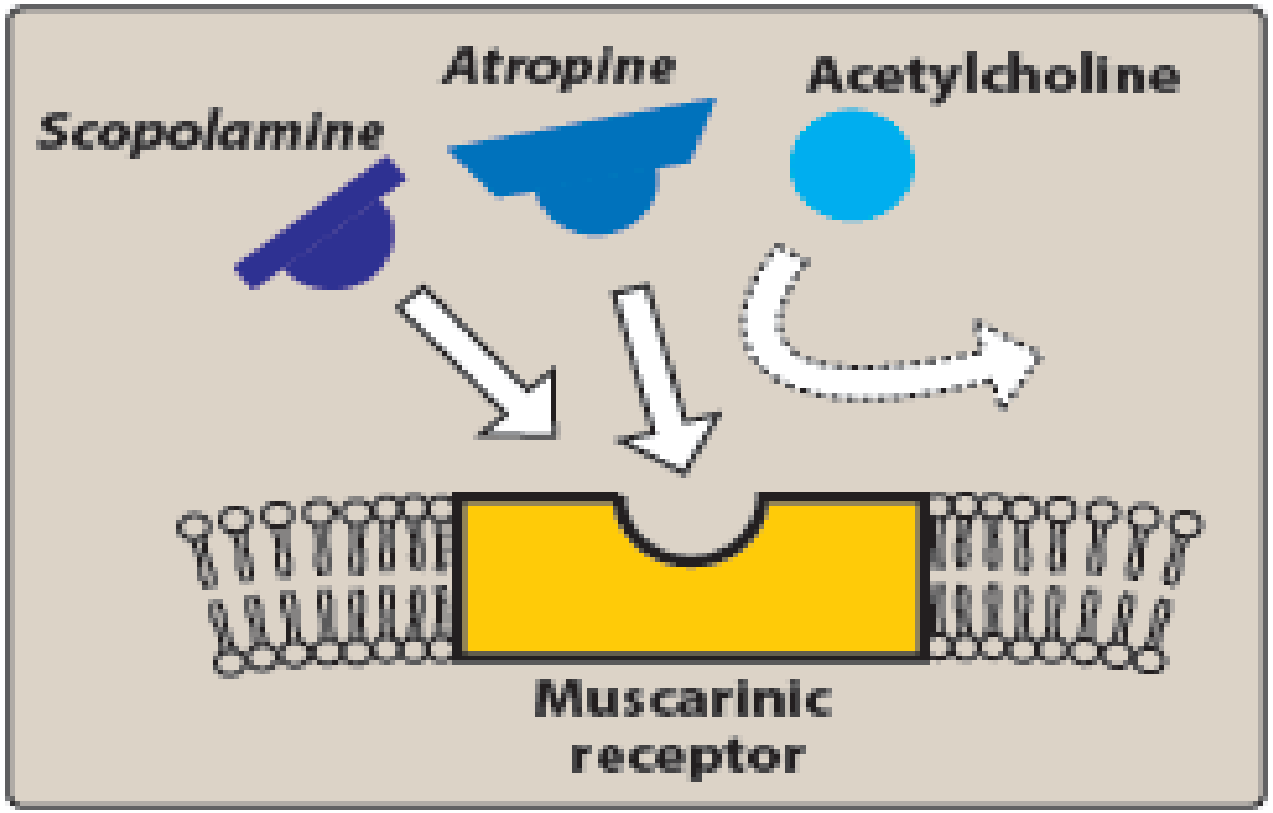


Figure 5.3
Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor.

Atropine Actions

- persistent mydriasis
- caution in glucoma

The most potent antispasmodic

- Decrease bladder contraction
- Inhibit secretion of saliva and sweat

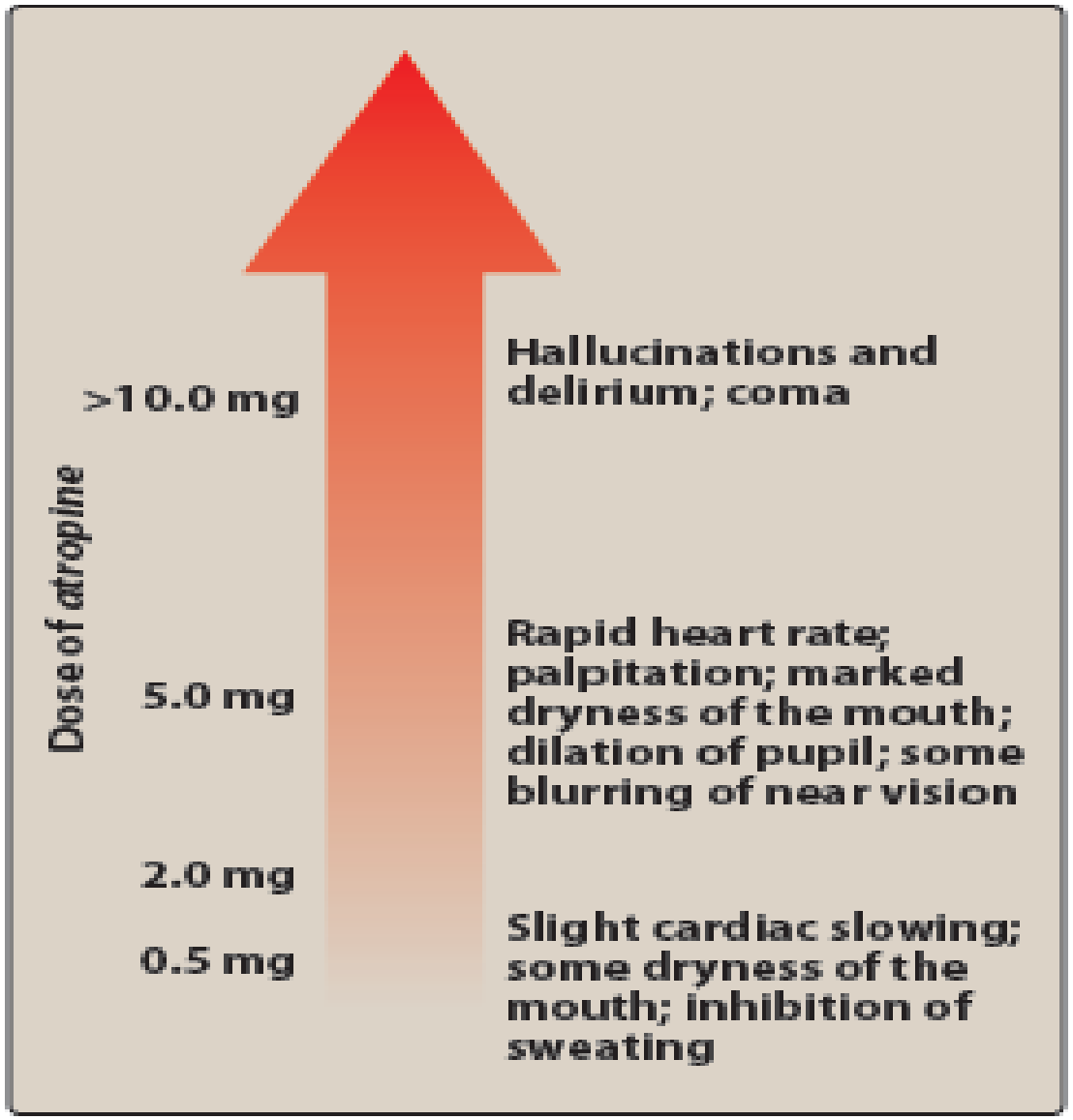


Figure 5.4
Dose-dependent effects of *atropine*.

Atropine Actions

- Cardiovascular :

- At low doses : Bradycardia

- At higher doses: Tachycardia

- Arterial blood pressure is unaffected

- Atropine is the Antidot for cholinergic agonist

- treatment of overdoses of cholinesterase inhibitor as insecticides

- some types of mushroom poisoning

Adverse effects

- Dry mouth
- Blurred vision
- Urinary retention
- Constipation
- CNS related : restlessnes , hallucnations,,,
- exacerbate glucoma
- increase body temperature

Scopolamine

- ✓ another tertiary amine plant alkaloid
- ✓ *scopolamine has greater action on the CNS*
- ✓*Scopolamine is one of the most effective anti–motion sickness* drugs available
- ✓ In contrast to *atropine, scopolamine* produces sedation.

- ✓it is much more effective prophylactically than for treating motion sickness once it occurs.
- ✓ administered as patches

Ipratropium and tiotropium

- ❑ Quaternary derivatives of *atropine*
- ❑ *Inhaled products*
- ❑ Approved as bronchodilators for maintenance treatment of
  - COPD
  - Chronic bronchitis
  - Emphysema

- *Tiotropium is administered once daily, a major*

  advantage over *ipratropium, which requires dosing up to four times* daily.

Muscarinic blockers

Trihexyphenidyl *Benztropine*	● Treatment of Parkinson disease
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	● Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	● To treat spastic disorders of the GI and lower urinary tract ● To treat organophosphate poisoning ● To suppress respiratory secretions prior to surgery
Scopolamine	● In obstetrics, with *morphine* to produce amnesia and sedation ● To prevent motion sickness
Ipratropium	● Treatment of COPD

Ganglionic blockers

Nicotine	● None

GANGLIONIC BLOCKERS

- Nicotine :

  - A component of cigarette smoke

  - It is without therapeutic benefit and is deleterious to health.

  - depolarizes autonomic ganglia, causing stimualtion (increase release of NTs) and then paralysis of all ganglia

- Nicotin has complex stimulatory action
- Effects include :
  - Increase BP & HR
  - Loss of apetite
  - Sexual Arousal
  - Mood modulation

NEUROMUSCULAR-BLOCKING DRUGS

- Block choliergic transmission between motor nerve endings and cholinergic receptors in the skeletal muscles on the endplate NMJ
- They include :

❖ **Nondepolarizing (competitive) blockers**

❖ **Depolarizing agents**

Nondepolarizing (competitive) blockers

- *Curare : a toxin used to primarily to paralyse animals*
- *Pancuronium (long acting)*
- *Atracurium and vecuronium(intermediate acting)*

- binds to nicotinic recptors at NMJ and inhibit Ach binding.
- Inhibits muscle contraction
- Its action can be reverse (competively) by increasing Ach dose or using AchE inhibitors
- High doses lead to furhter irreversible blockade

- Paralysis starts with muscles of the face and eyes
- Then subsequently spreads to fingers, neck trunck
- Finally the diaphragm becomes paralyzed

- These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle.

- NM blockers are adminstered IV.
- Poor penetration of cells , BBB
- Poorly metabolized agents
- *pancuronium* is excreted unchanged in urine.

❖ S/E : hyperkalemia,IOP,

Drug interactions

- AchE inhibitors
- Aminoglycosides
- CCB

Depolarizing agents

- Act as Ach , but with longer duration of action due to more resistance to AchE
- Succinylcholine is the only depolarizing agent is used.

- The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic

  receptors, which results in depolarization of the receptor **(Phase I).** (fasciculations).

- Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses.
- **With time**, continuous depolarization gives way to **gradual repolarization** as the sodium channel closes or is blocked. This causes a resistance to depolarization **(Phase II)** and flaccid paralysis.

- the respiratory muscles are paralyzed last
- Normally, the duration of action of ***Succinylcholine*** *is extremely* short, because this drug is rapidly broken down by plasma pseudocholinesterase.
- Because of its rapid onset and short duration of action, *succinylcholine is useful when rapid endotracheal intubation is required*

- *Succinylcholine is injected intravenously*
- sometimes given by continuous infusion to maintain a longer duration of effect. Drug effects rapidly disappear upon discontinuation

Adverse effects

- Hyperthermia
- Apnea (in genetically suseptable patients)
- Hyperkalemia

Adrenergic Agonists

Adrenergic Agonists

❑ Neurotransmission at adrenergic neurons

- **N**orepinephrine is the neurotransmitter instead of acetylcholine

- The process involves :

1.Synthesis

2. Storage

3.Release

4.receptor binding

5. removal of the neurotransmitter from the synaptic gap

1. Synthesis of norepinephrine

- Tyrosine entry to the adrenergic neuron via Na+ dependent carrier
- Tyrosine hydoxylation ** RLS
- DOPA decarboxyation
- Dopamine hydroxylation(inside the vesicles)

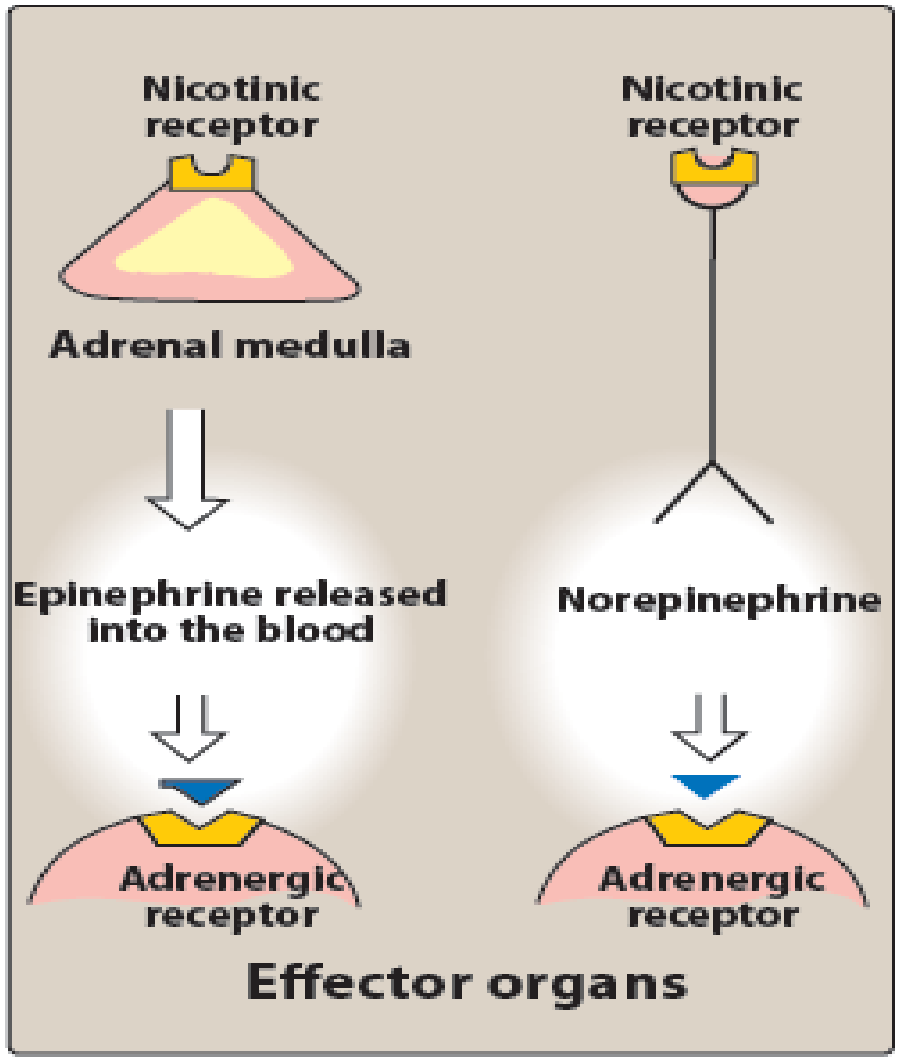


Figure 6.2
Sites of actions of adrenergic agonists.

2.Storage of norepinephrine in vesicles

- *Dopamine is then transported* into synaptic vesicles by an amine transporter system that is also involved in the reuptake of preformed norepinephrine.
- This carrier system is blocked by *reserpine*
- *Dopamine is hydroxylated* to form norepinephrine by the enzyme, dopamine b-hydroxylase
- Stored in the vesicle untill released

- • In the adrenal medulla, norepinephrine is methylated to yield epinephrine, which is stored in chromaffin cells along with norepinephrine.

3.Release of norepinephrine

- Ca+2 influx to the cytoplasm
- Vesicles fuse with the cell membrane
- Expelling of its content

4. Binding to receptors

- Norepinephrine binds to postsynaptic receptors
- Elicit cascade of events including secondary messengers.
  - cyclic adenosine monophosphate cAMP
  - phosphatidylinositol cycle
- “Norepinephrine also binds to presynaptic

receptors that modulate the release of the neurotransmitter”

5. Removal of norepinephrine

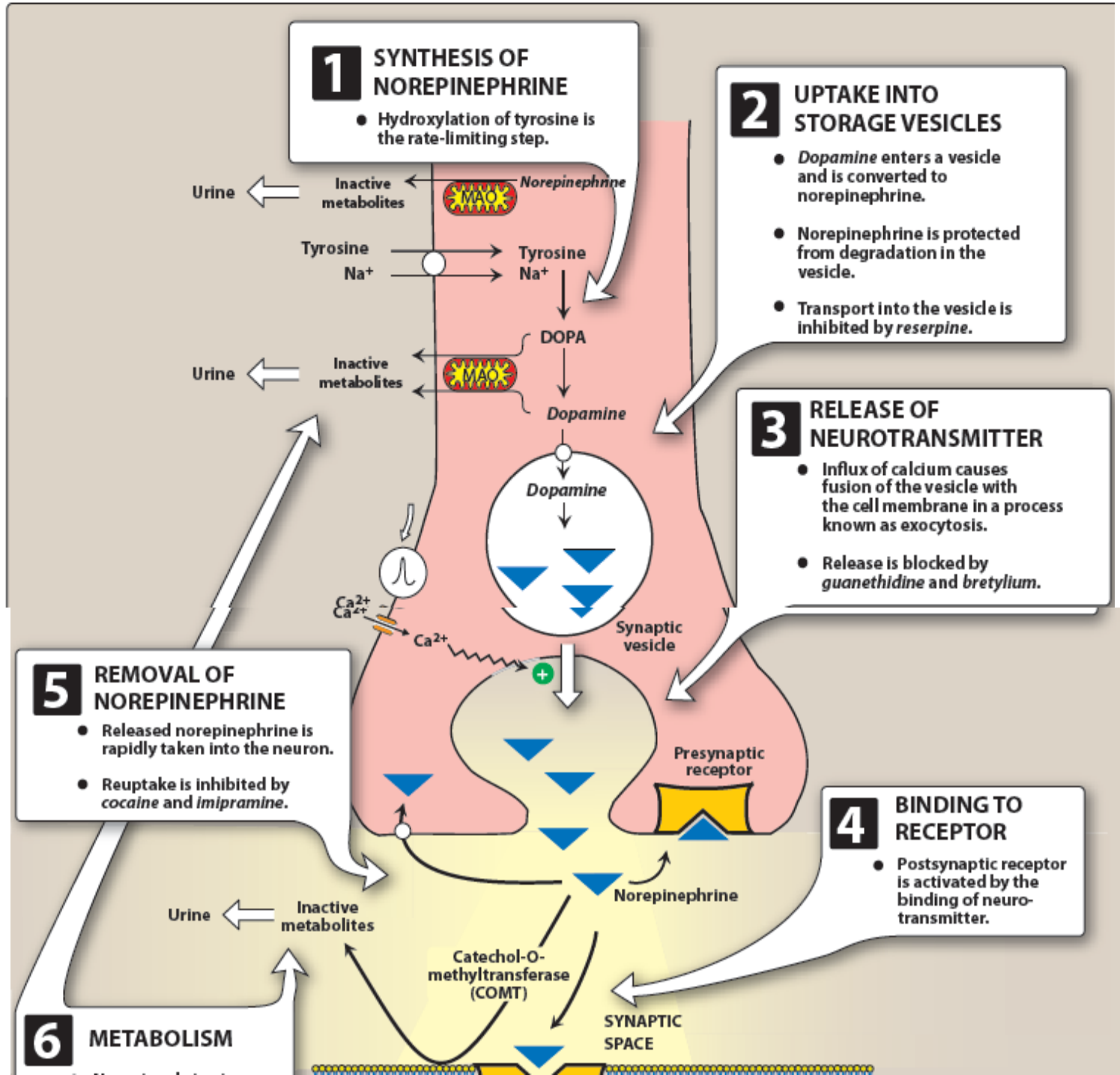
Possible removal mechanisms:

- Diffuse out of the synaptic space and enter the general circulation
- Metabolism to O-methylated derivatives by postsynaptic cell membrane–associated catechol O-methyltransferase **(COMT)** in the synaptic space
- Be recaptured by an uptake system that pumps the norepinephrine back into the neuron

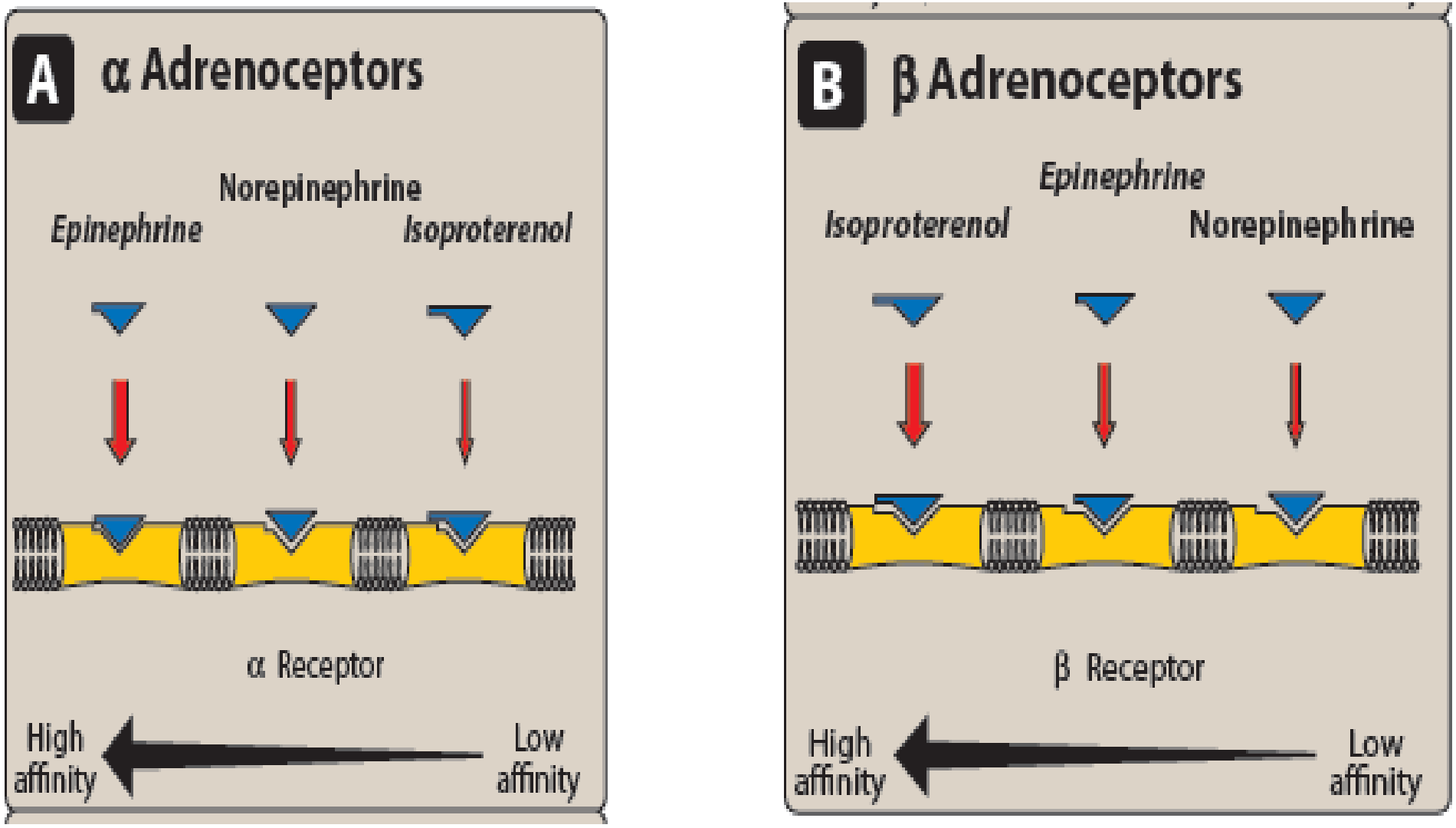
When NE reenters Adrenergic neurons

- can be oxidized by monoamine oxidase **(MAO)** present in neuronal mitochondria.

- The inactive products of norepinephrine metabolism are excreted in urine as vanillylmandelic acid, metanephrine, and normetanephrine.


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
Urine
Inactive metabolites
MAO
Norepinephrine
Tyrosine
Na+
Tyrosine
Na+
DOPA
Urine
Inactive metabolites
MAO
Dopamine
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
Release is blocked by guanethidine and bretylium.
Dopamine
Ca2+
Ca2+
Ca2+
Synaptic vesicle
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by cocaine and imipramine.
Presynaptic receptor
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
Norepinephrine
Urine
Inactive metabolites
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE
6 METABOLISM

Adrenergic receptors (adrenoceptors)

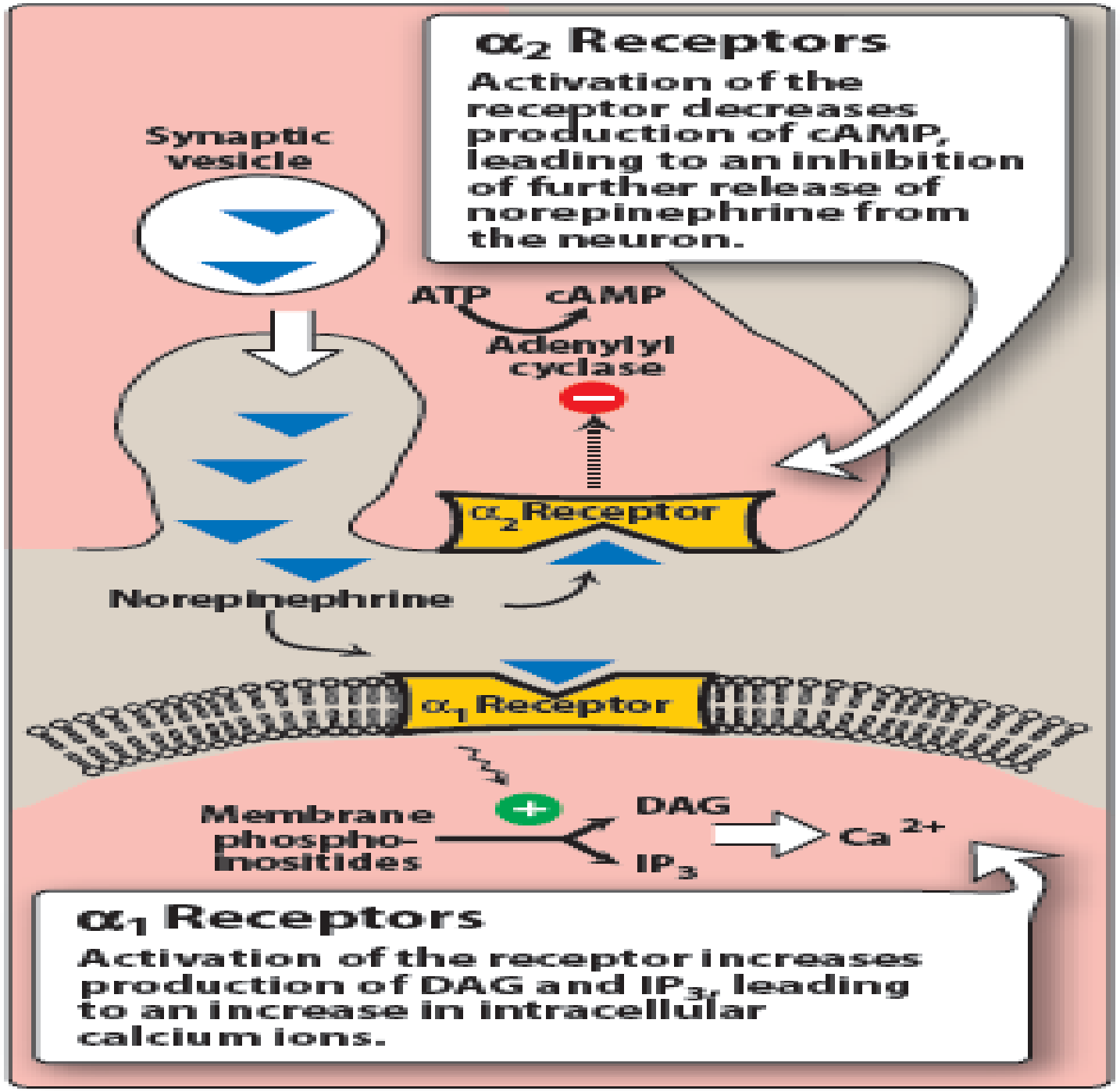


Adrenergic receptors (adrenoceptors)

α Receptors

- α 1 :
  - postsynaptic effector organs
  - contraction of smooth muscles
  - Activation increases IP3 and DAG and Calcium release from the ER to cytplasm

- α 2 :
  - located presynaptically
  - Beta cell of the pancreas and on certain vascular smooth muscle cells, control adrenergic neuromediator and insulin output,
  - feedback inhibition on NE
  - fall in the levels of intracellular cAMP.


α2 Receptors
Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron.
Synaptic vesicle
ATP
cAMP
Adenylyl cyclase
α2 Receptor
Norepinephrine
α1 Receptor
Membrane phospho-inositides
DAG
IP3
Ca 2+
α1 Receptors
Activation of the receptor increases production of DAG and IP3, leading to an increase in intracellular calcium ions.

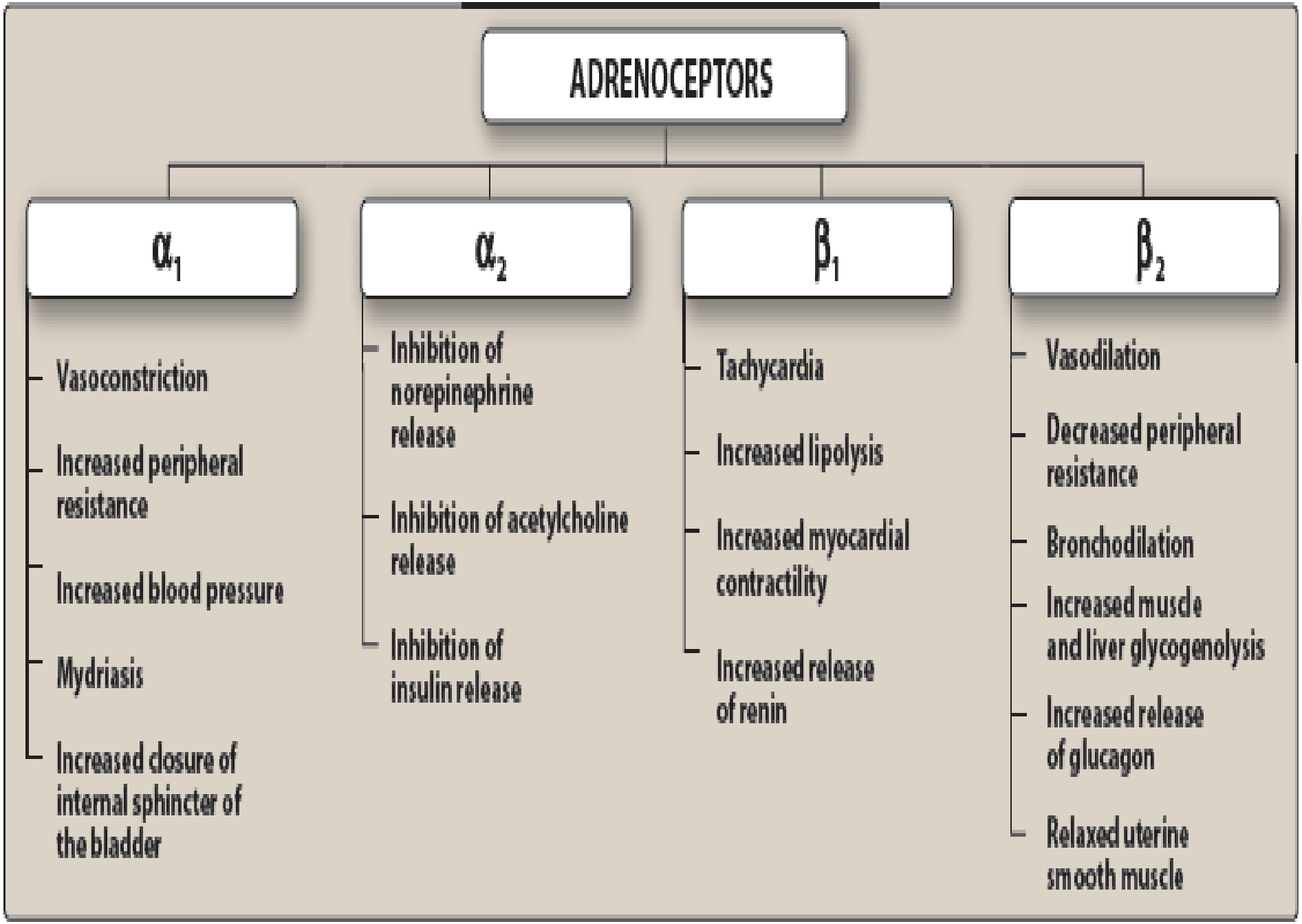
- The α1 and α2 receptors are further dividedinto α1A, α1B, α1C, and α1D and into α2A, α2B, and α2C. This extended classification is necessary for understanding the selectivity of some drugs.
- For example***, tamsulosin*** *is a* ***selective α1A*** **antagonist** that is used to treat **benign prostate hyperplasia**. The drug is clinically useful because it targets α1A receptors found primarily in the urinary tract and prostate gland.

β Receptors

- Strong response to **isoproterenol** rather than to epinephrine
- The β-adrenoceptors can be subdivided into three major subgroups

- **β1 (heart, kidney)**
- **β2 (lung, blood vessels)**
- **β3 (AD)**

Binding of a neurotransmitter at any of the three β receptors results in increased concentrations of cAMP within the cell


ADRENOCEPTORS
α1
Vasoconstriction
Increased peripheral resistance
Increased blood pressure
Mydriasis
Increased closure of internal sphincter of the bladder
α2
Inhibition of norepinephrine release
Inhibition of acetylcholine release
Inhibition of insulin release
β1
Tachycardia
Increased lipolysis
Increased myocardial contractility
Increased release of renin
β2
Vasodilation
Decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle