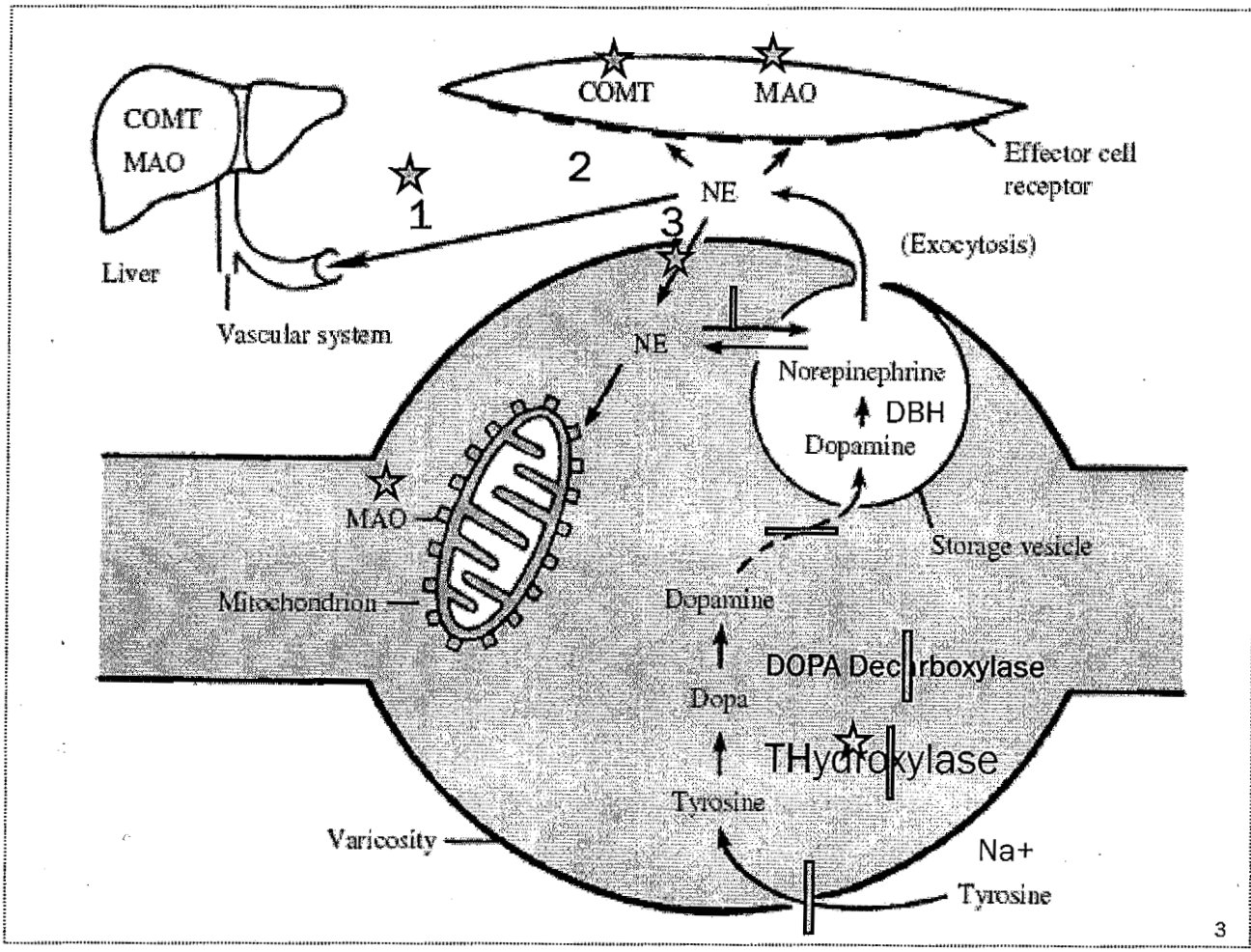
3rd-stage Pharmacy - number 28

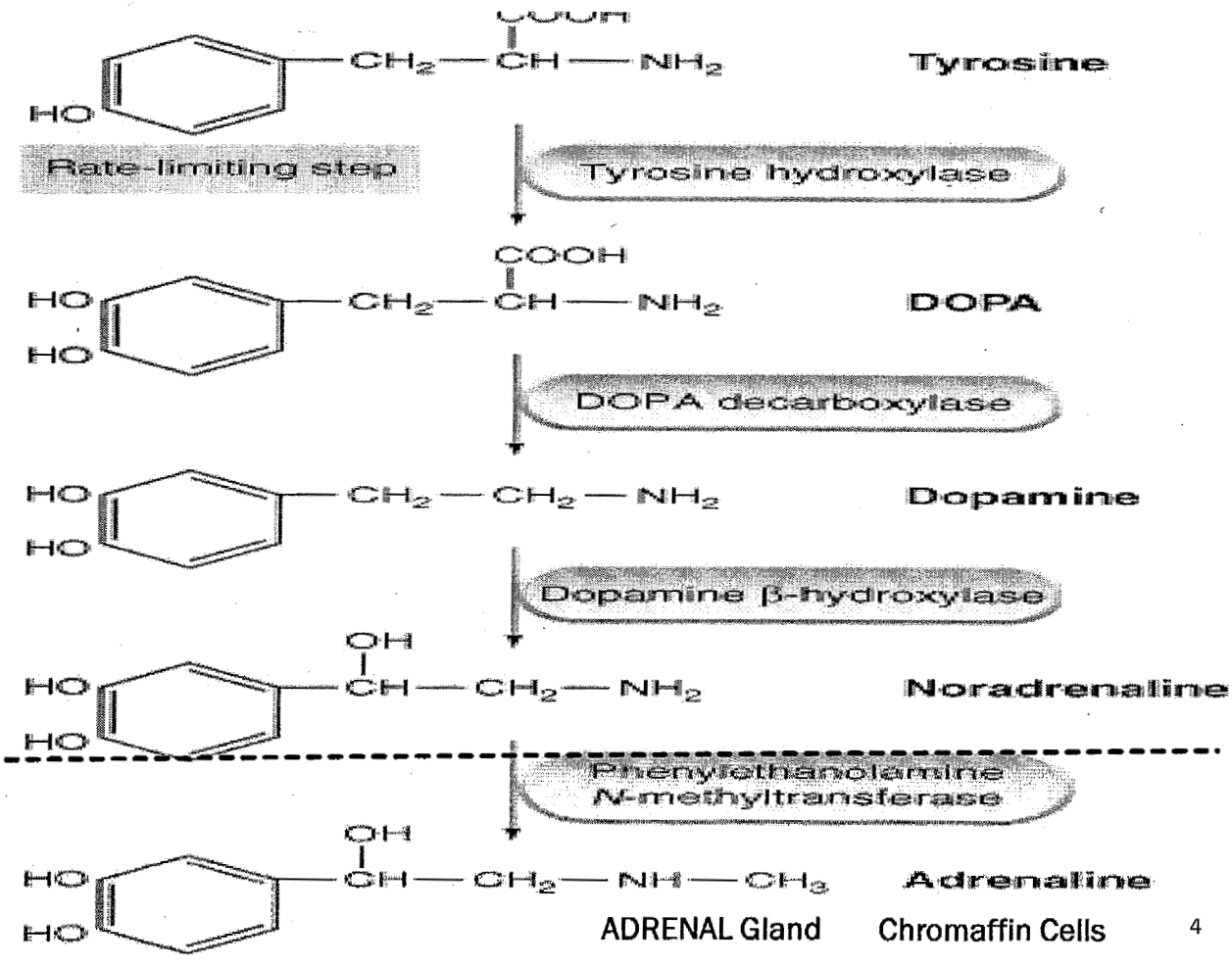
ADRENERGIC DRUGS

Dr. Zheen A. Mutabchi

Adrenergic neurons release NE as a neurotransmitter.

These neurons are found in the CNS & Sympathetic N.S.





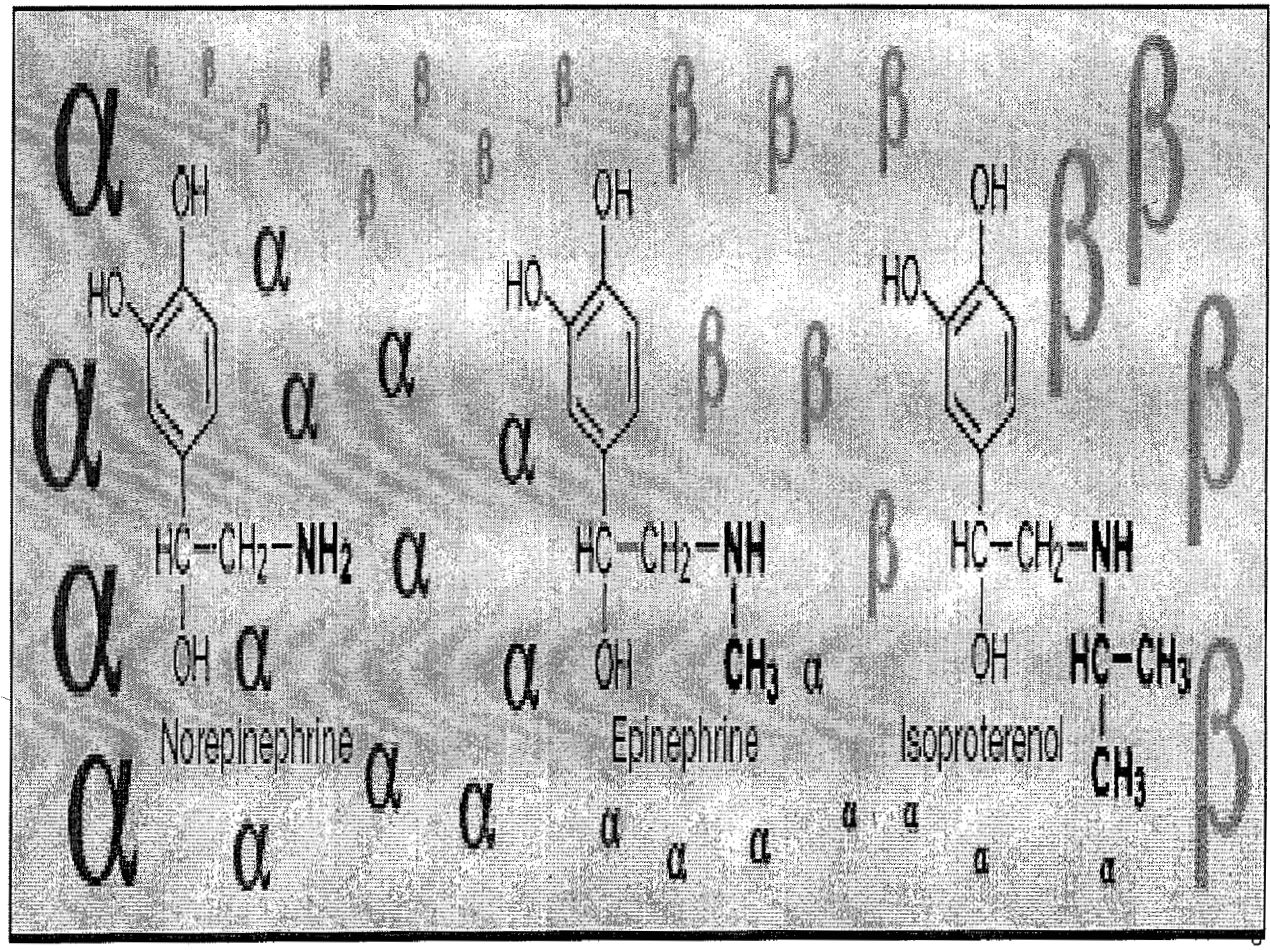
ADRENAL Gland Chromaffin Cells

Classification of adrenoceptors

Main pharmacological classification into **α**- and **β**-subtypes, based originally on order of potency among agonists, later on selective antagonists.

There are **two** main **α- adrenoceptor** subtypes (α_1 and α_2, each divided into **4** further subtypes) and **three β- adrenoceptor** subtypes (β_1, β_2, β_3).

All belong to the superfamily of **G-protein-coupled receptors.**



Adrenoceptor Sensitivity

Beta receptors are usually more sensitive to activators than αlpha receptors with drugs that exert both effects.

The beta responses are dominant at low doses, at higher doses, the alpha responses will predominate.

- NE Activates B1 compared to B2 AT LOW DOSE.
- NE $\alpha 1 = \alpha 2$, $ß_1 >> ß_2$
- Phenylephrine, methoxamine $\alpha_1 > \alpha_2 >>>>$ B.
- Clonidine, methylnorepinephrine

  $\alpha_2 > \alpha_1 >>>>>$ B
- EP $\alpha 1 = \alpha 2$, B1 = B2.
- ISOPROTERINOL B1=B2>> >> α
- DOBUTAMIN B1 > B2 > > > α .

×Second messengers:

+α_1-adrenoceptors activate phospholipase C, thus producing inositol trisphosphate and diacylglycerol as second messengers

+$\alpha 2$-adrenoceptors inhibit adenylate cyclase and thus decrease cAMP formation.

+all types of **β-adrenoceptor** stimulate adenylate cyclase.

× The main effects of receptor activation are:

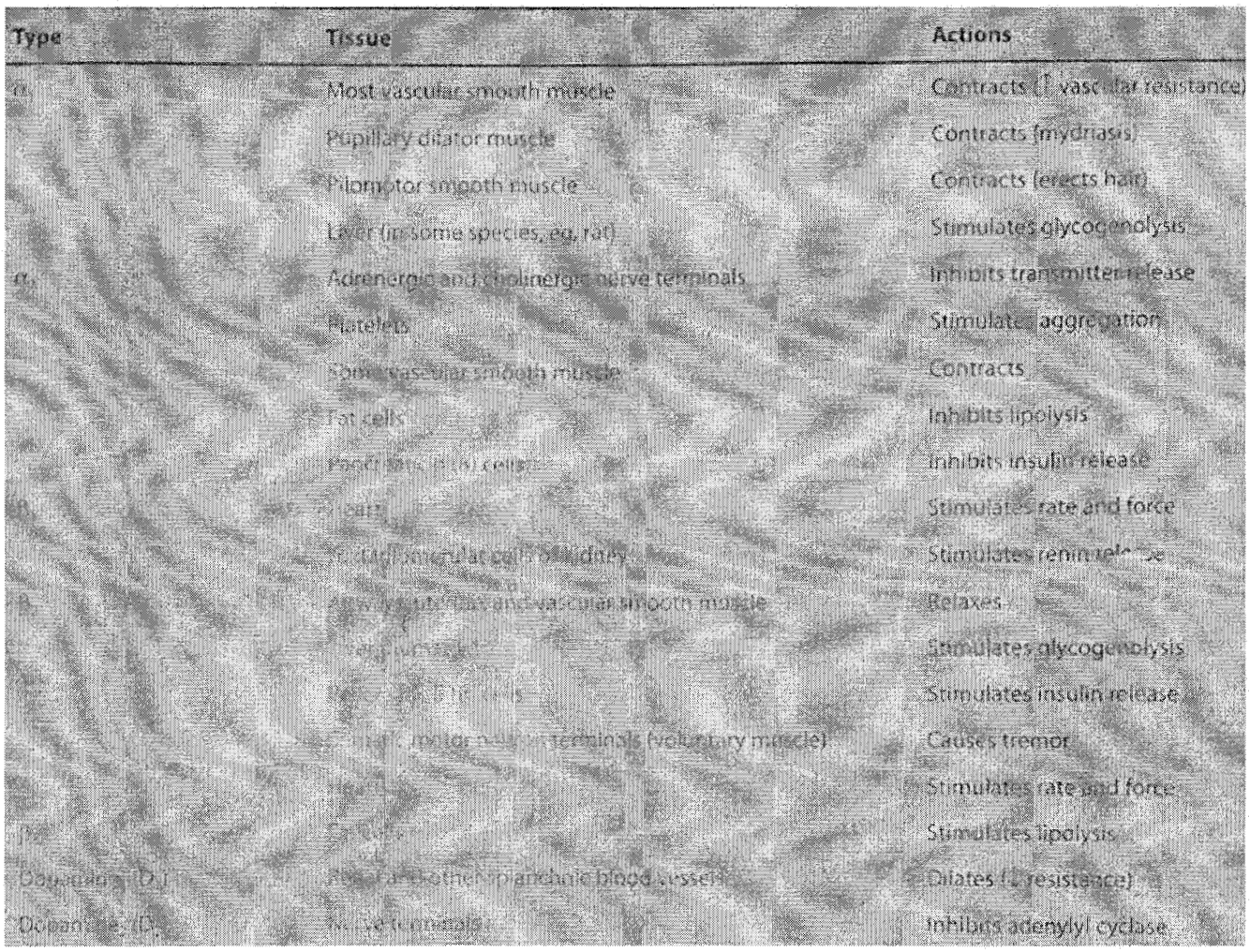
+α_1-adrenoceptors: vasoconstriction, salivary secretion and hepatic glycogenolysis

+α_2-adrenoceptors: inhibition of transmitter release (including noradrenaline and acetylcholine release from autonomic nerves), platelet aggregation, contraction of vascular smooth muscle, **inhibition of insulin release** & inhibition of Lipolysis.

+β_1-adrenoceptors: increased cardiac rate and force

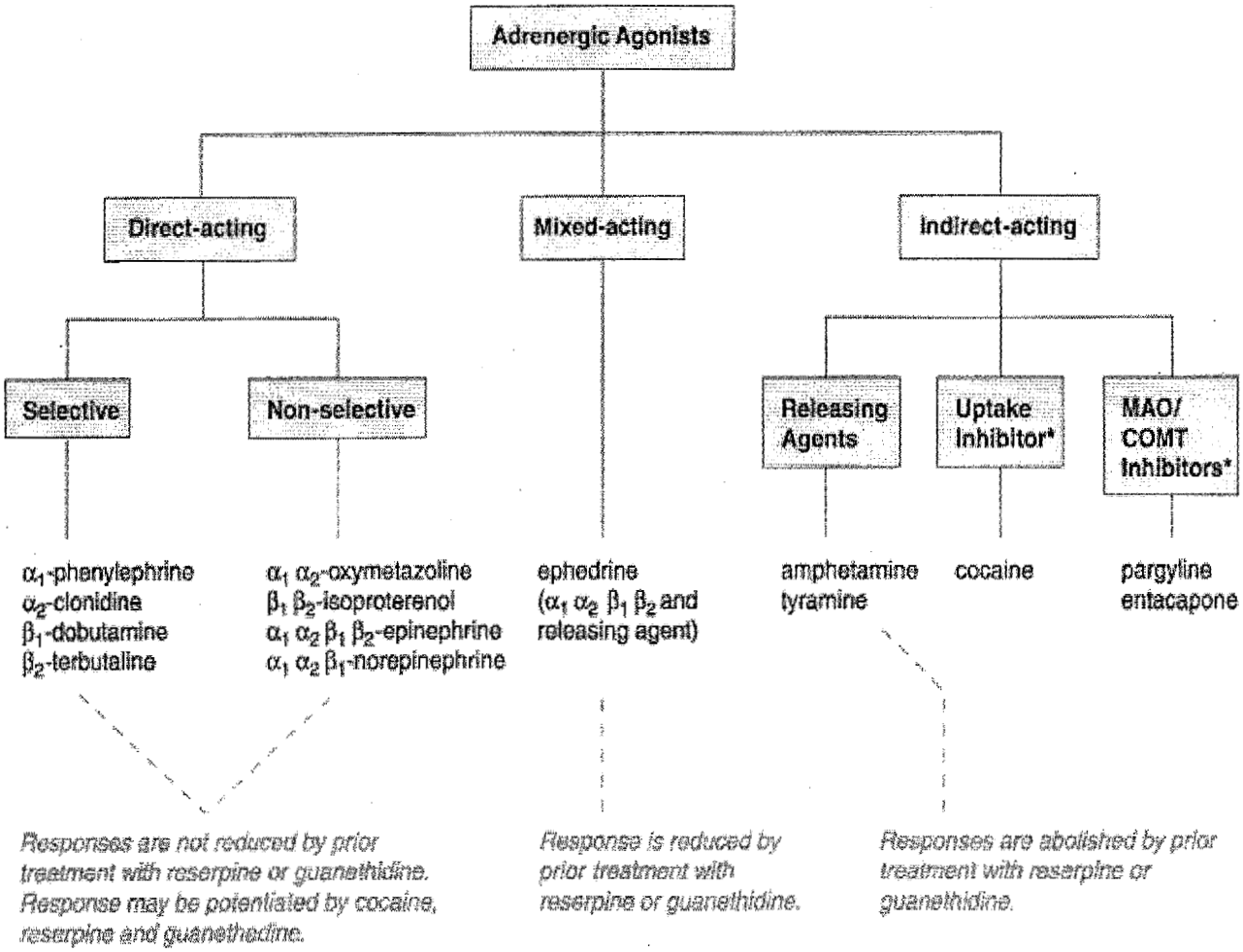
+β_2-adrenoceptors: bronchodilatation, vasodilatation, relaxation of visceral smooth muscle, muscle tremor & hepatic glycogenolysis and **GLUCAGON** secretion.

+β_3-adrenoceptors: **lipolysis** of triglycerides.



Type	Tissue	Actions
α	Most vascular smooth muscle	Contracts (↑ vascular resistance)
	Pupillary dilator muscle	Contracts (mydriasis)
	Pilomotor smooth muscle	Contracts (erects hair)
	Liver (in some species, eg, rat)	Stimulates glycogenolysis
α_2	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Platelets	Stimulates aggregation
	Some vascular smooth muscle	Contracts
	Fat cells	Inhibits lipolysis
	Pancreatic β cells	Inhibits insulin release
β	Heart	Stimulates rate and force
	Juxtaglomerular cells of kidney	Stimulates renin release
β_2	Bronchial and vascular smooth muscle	Relaxes
	Liver	Stimulates glycogenolysis
	Pancreatic β cells	Stimulates insulin release
	Motor nerve terminals (voluntary muscle)	Causes tremor
	Heart	Stimulates rate and force
	Fat cells	Stimulates lipolysis
Dopamine (D_1)	Renal and other splanchnic blood vessels	Dilates (↓ resistance)
Dopamine (D_2)	Nerve terminals	Inhibits adenylyl cyclase

Adrenergic Agonists



DIRECT ACTING AGONISTS

EPINEPHRINE.

NOREPINEPHRINE.

ISOPROTERINOL.

DOPAMINE.

DOBUTAMINE.

PHENYLEPHRINE.

METHOXAMINE.

SALBUTAMOL

CLONIDINE

METAPROTERINOL

ALBUTEROL

TERBUTALINE

SALMETEROL

FORMETEROL

INDIRECT ACTING AGONISTS

Drugs that facilitate NE release

Drugs that block NE uptake

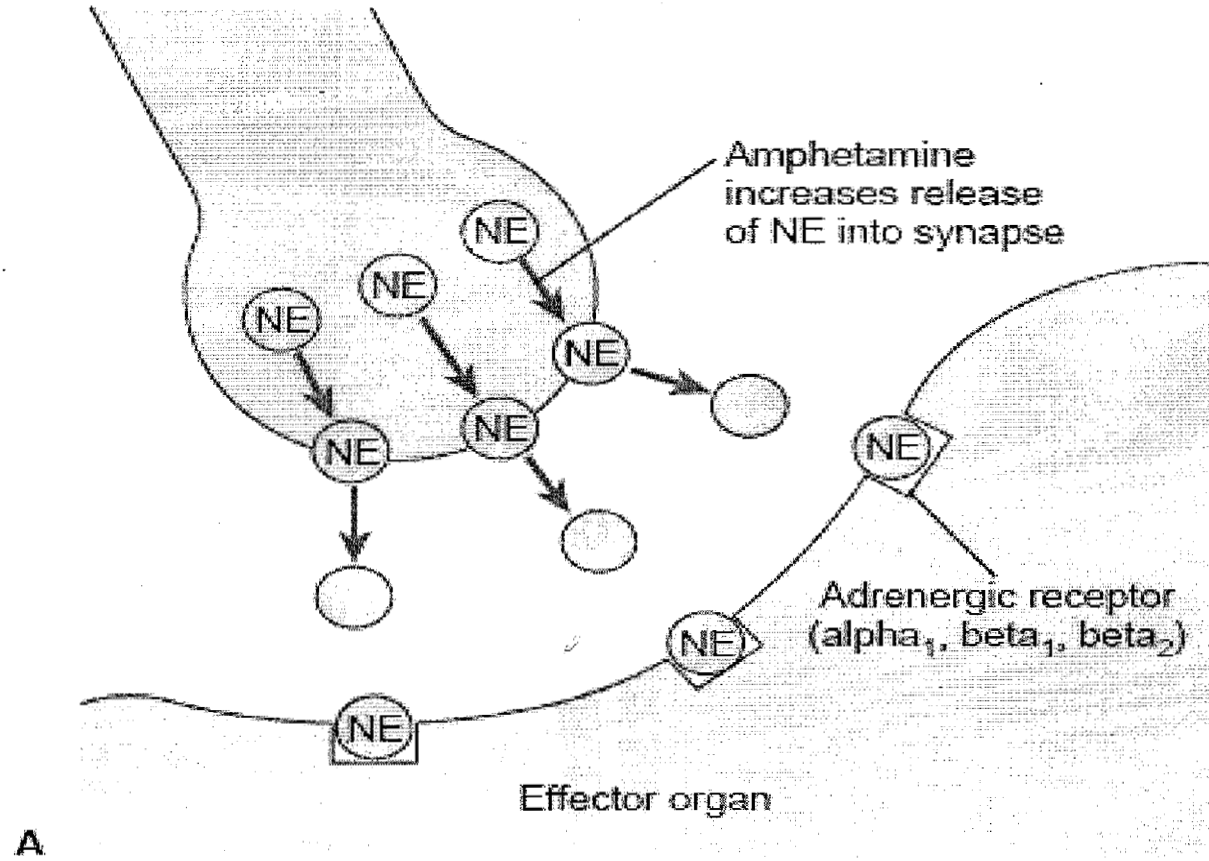
AMPHETAMINE TYRAMINE

MIXED ACTION

EPHEDRINE

METARAMINOL

INDIRECT ACTING AGONISTS



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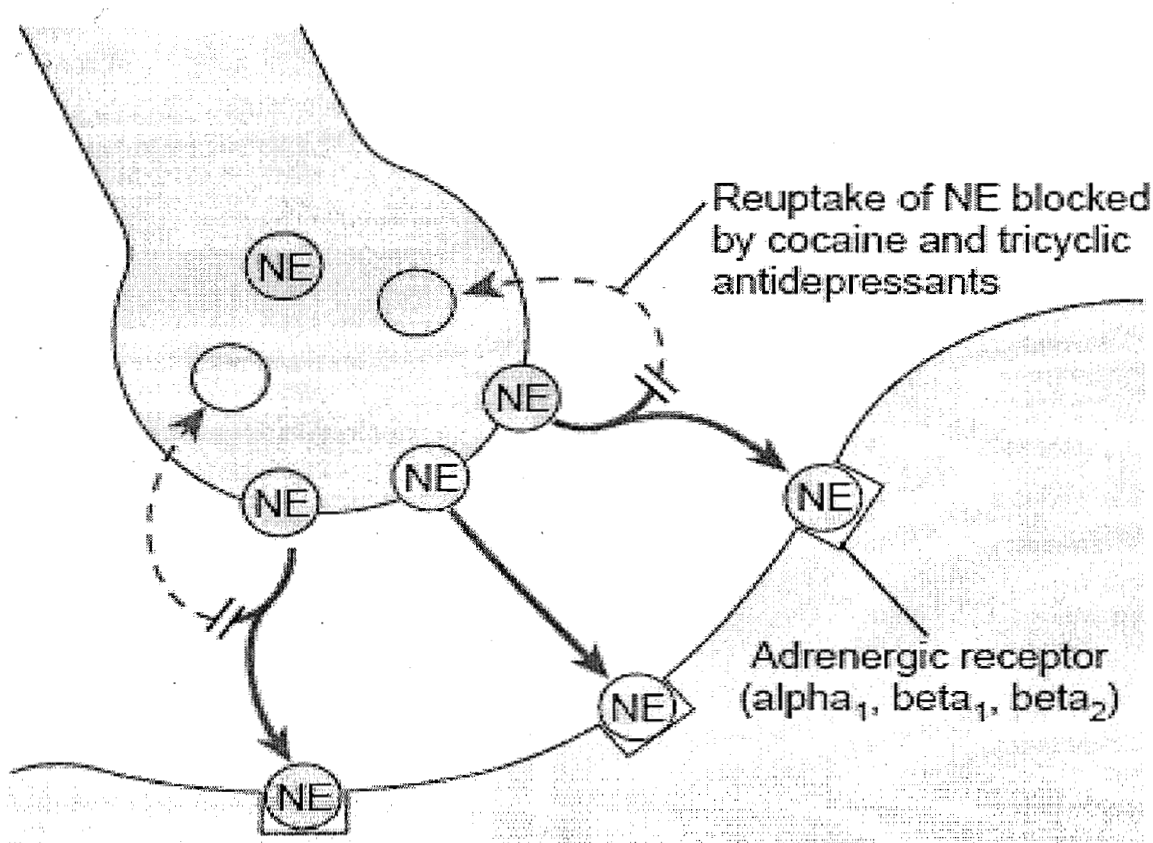


B

AMPHETAMINE

Facilitates NA release

It also inhibits MAO

ACTIONS

- CNS stimulant effects: euphoria

Increased alertness, decreased fatigue,

depressed appetite, insomnia.

High dose result in convulsion.

- Sympathetic N.S.

NE release.

THERAPEUTIC USES

1. *Attention Deficit Hyperactivity Disorder ADHD*

   Increased alertness .....????
   reduce the hyperkinesia

   ATOMOXETINE

2. *Narcolepsy*

PHARMACOKINETICS

- Well absorbed after oral administration.
- Metabolized in liver.
- Excreted in the urine.
- Alkalinization of urine reduces its excretion. .....?

ADVERSE EFFECTS

- Addiction.
- Tolerance.
- Drug-seeking behavior.
- G.I.S Effects: N.V.D. & Abdominal cramps.
- C.V Effects: palpitation, arrhythmias, hypertension, anginal pain, circulatory collapse.
- Central effects :insomnia, irritability, weakness, dizziness, tremor, & hyperactive refluxes.

CONTRAINDICATIONS

- HYPERTENSION.
- HYPERTHYROIDISM.
- CARDIOVASCULAR DISEASE.

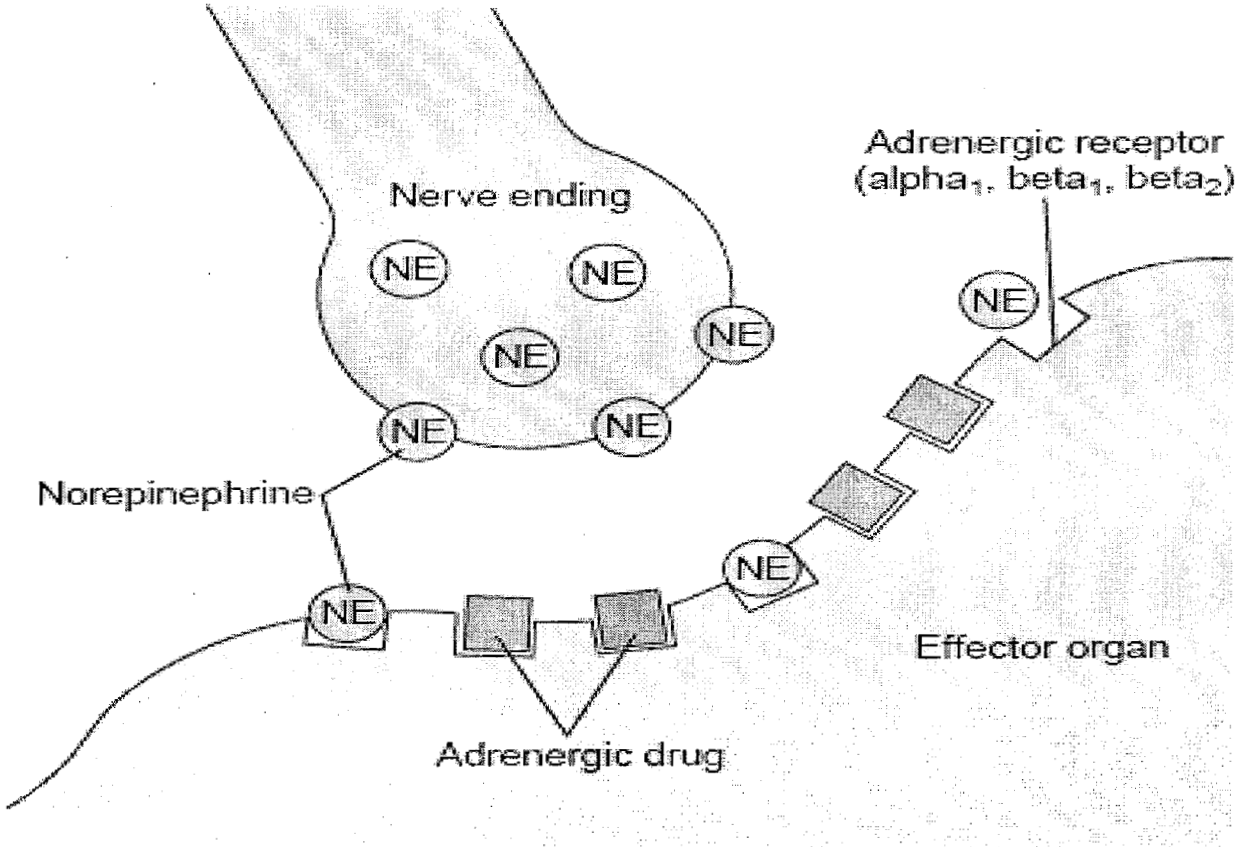
TREATMENT OF OVERDOSE

- CHLORPROMAZINE & HALOPERIDOL

TYRAMINE

- Normal byproduct of tyrosine metabolism.
- Has no clinical indication.
- Present in certain foods and beverages.
- rapidly metabolized by MAO type A in GIT and liver.
- Metabolized (oxidized) by MonoAminoOxidase (MAO) .

DIRECT ACTING ADRENERGIC AGONISTS



α1	G_q	↑ DAG , IP_3..... ↑ Calcium
α2	G_i	↓Adenylylcyclase..... ↓cAMP
B_1,B_2, D_1	G_s	↑Adenylylcyclase..... ↑cAMP

α1 Agonists

- Given systemically, they increase mean blood pressure (BP) via vasoconstriction, with minimal effects on pulse pressure (PP). The increase in BP elicits a reflex bradycardia. Cardiac output (CO) may be decreased but can be offset by an increase in venous return, which may increase stroke volume (SV).

Drugs

- Phenylephrine (α1): decongestant-mydriasis without cycloplegia.

- Methoxamine (α1): use in paroxysmal atrial tachycardia-elicits vagal reflex.

α2 Agonists

- Stimulate prejunctional receptors in the CNS to decrease vasomotor outflow and decrease mean BP.

  Primary use is in mild-to-moderate HTN.

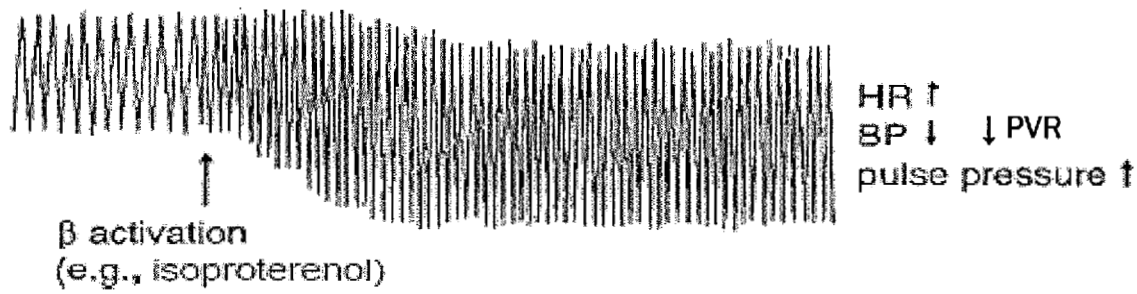
- **Clonidine**: initial increase in BP (some α1 activity) followed by decrease in BP .

abrupt discontinuation causes rebound HTN.

- **α-Methyldopa**: a pro-drug forming a-methyl NE.

ß - ADRENERGIC AGONISTS

- Agents that activate both ß1 and ß2 receptors cause a decrease in (PVR), a decrease in mean BP, and an increase in HR. Diastolic pressure falls more than systolic pressure, so pulse pressure (PP) increases.



- **Isoproterenol** (ß I = ß 2): bronchospasm, heart block, and bradyarrhythmias.

May cause flushing, angina, and arrhythmias.

- Dobutamine (ß I>ß 2): ↑ HR, **and CO (positive inotropy and chronotropy).**

No change in PVR, GFR, or renal blood flow (RBF).
use in acute congestive heart failure (CHF)

S/E tachyphylaxis .

Selective ß2 Agonists

Salmeterol, albuterol, metaproterenol, and **terbutaline** use in asthma.

- **Ritodrine** use in premature labor.

- Selective ß2 Agonists resulting in :
- TOLERANCE.
- TREMOR.
- TACHYARRHYTHMIA.

NOREPINEPHRINE

- Norepinephrine (NE) has little effect on ß 2 receptors. It increases PVR and both diastolic and systolic BP. Positive inotropic action of NE causes a small to moderate increase in pulse pressure(PP). Compensatory vagal reflexes tend to overcome the direct positive chronotropic effects of NE (reflex bradycardia may ensue), but the positive inotropic effects are maintained.

EPINIPHRINE A 1 = A 2 ,B1 = B2

- Epinephrine increases HR, systolic BP, and PP. Its effects on diastolic blood pressure depend on dose. **At moderate to high doses, alpha activation predominates, leading to increases in PVR, diastolic pressure, and mean BP.**

  At **Very low doses**, beta activation predominates, resulting in a decrease in PVR and diastolic pressure, although mean BP may not decrease significantly.

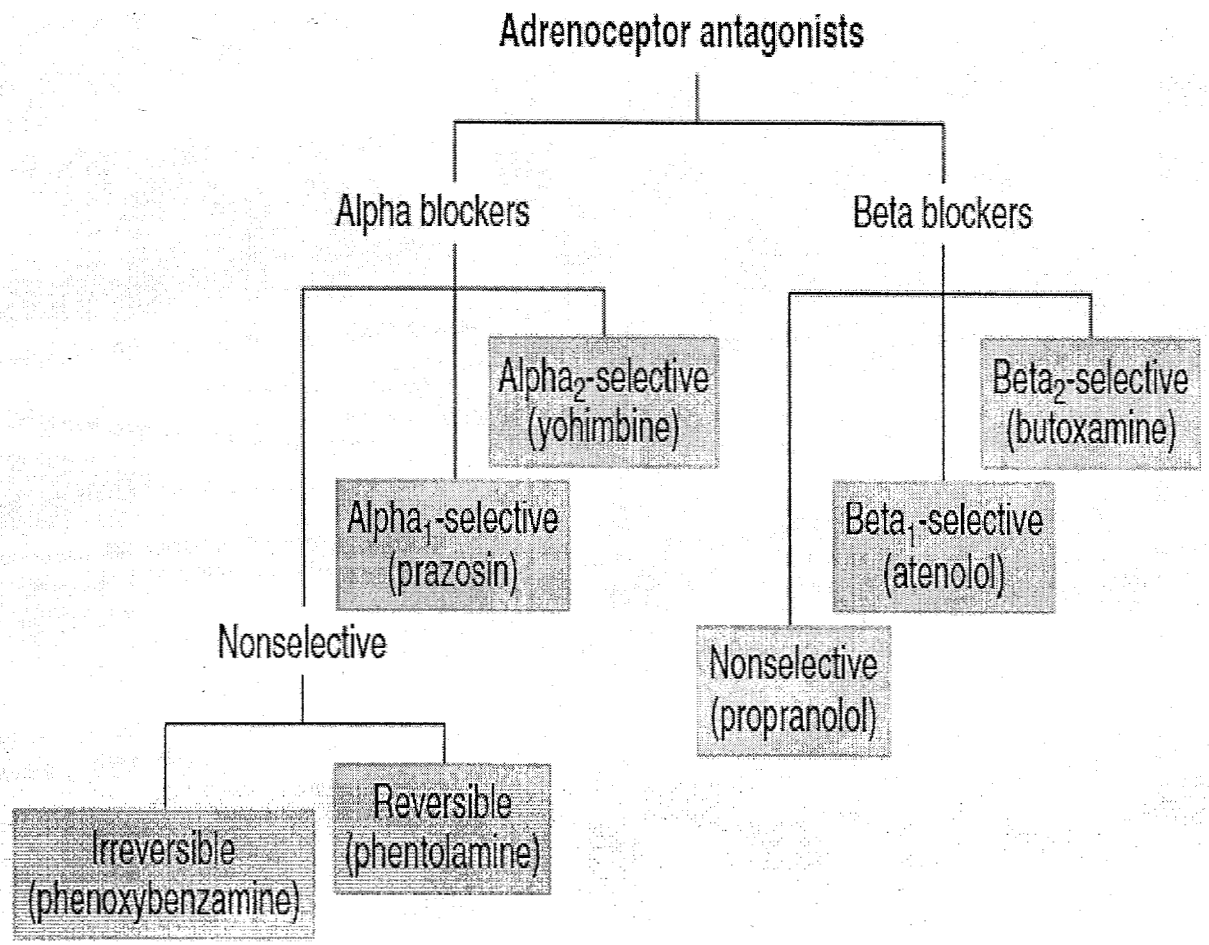
CLINICAL USES OF SYMPATHOMIMETICS

- ANAPHYLAXIS
- CNS
- EYE ..... glaucoma
- BRONCHI ..... bronchial tree relaxation
- CVS ..... cardiac arrest
- G.U. Tract .....relaxation of uterus
- With local anesthetics.
- Selective B_3 agonist can be used in OBESITY

A selective β3 agonist, **Mirabegron**, is used to treat overactive bladder; β3 agonists promote lipolysis and have potential in the treatment of obesity.

ADRENERGIC BLOCKERS

Dr. Zheen A. Mutabchi



ALPHA BLOCKERS

1. Irreversible, long acting:

   PHENOXYBENZAMINE it is slightly α1 selective.

2. Reversible ,Shorter acting:

   Phentolamine nonselective

   Tolazoline slightly α 2 selective

3. α 1 selective Tamsulosin, Prazosin, Alfuzocin, Indoramine, Urapidil, terazosin, doxazosin

4. α 2 selective Yohimbine rauwolscine

ACTION

CVS effects ..... Reflux tachycardia

increased C.O.

Epinephrine reversal

EP α 1 = α 2 , B1 = B2

×EPINEPHRINE REVERSAL

The fall in blood pressure produced by epinephrine when given following blockage of α-adrenergic receptors by an appropriate drug such as Phenoxybenzamine; the vasodilation reflects the ability of epinephrine to activate β-adrenergic receptors that, in vascular smooth muscle, are inhibitory; in the absence of α-receptor blockade, the β-receptor activation by epinephrine is masked by its predominant action on vascular α-receptors, which causes vasoconstriction.

SELECTIVITY OF ALPHA BLOCKERS

DRUG	AFFINITY
Prazosin, Doxazosin, Terazosin	$\alpha_1 >>>> \alpha_2$
Phenoxybenzamine	$\alpha_1 > \alpha_2$
Phentolamine	$\alpha_1 = \alpha_2$
Rauwolscine, Yohimbine, Tolazoline	$\alpha_2 > \alpha_1$

PHENOXYBENZAMINE

- Nitrogen mustard related drug.
- Irreversible nonselective covalent bond with the α 1 and α 2 receptors.
- **Pheochromocytoma:** Chronic management

  Prior to surgery to prevent hypertensive crisis resulted from tissue removal

  Raynaud disease, SEROTONIN RELEASING CARCINOID TUMOR.

- Result in increase in GI tract motility and secretions, and glycogen synthesis.

7

ADVERSE EFFECTS

- Postural hypotension.
- N.V.
- Nasal stuffiness.
- Inhibition of ejaculation.
- Decreased coronary perfusion.....anginal pain

PHENTOLAMINE

- Competitive blocker.
- DOA 4 hrs after single administration
- Epinephrine reversal .
- Postural hypotension.
- Useful in treatment of pheochromocytoma.
- With papaverine in erectile dysfunction(ED).

TAMSULOSIN, PRAZOSIN, TERAZOSIN, & DOXAZOSIN

- Selective Competitive blocker of α 1 .

- Decrease PVR & Decrease BP .
- Hypertension & BPH.
- Hypertensive Emergencies.

Tamsulosin has higher affinity for α_{1A} & α_{1D} subtypes.

ADVERSE EFFECTS

- Dizziness. Drowsiness. Headache. .
- Nasal congestion.
- **ORTHOSTATIC HYPOTENSION.**
- **Na & Water retention (Prazosin)**

GENERAL EFFECTS OF ALPHA BLOCKERS

- Block of alpha1 reduces PR & causes pooling of blood in the capacitance ,by this venous return & C.O. are reduced which results in reduction in B.P.
- Marked hypotension occurs on standing (dizziness & syncope) .
- Reflux tachycardia occurs due to fall in arterial pressure & ↑ NE release by alpha 2 blocking. Rare in alpha 1 blockers(selective).

GENERAL EFFECTS OF ALPHA BLOCKERS

- Miosis & nasal stuffiness.
- Hypotension causes ↓renal blood flow ...↓ GFR ..... Sodium & water retention.... ↑ blood volume.
- Tone of the smooth muscle in bladder trigone, sphincter, & prostate is ↓.
- Impotence & impaired ejaculation due to blocking of the alpha receptors on vas deferens.

BETABLOCKERS

	Selectivity	Partial Agonist Activity	Local Anesthetic Action	Lipid Solubility	Elimination Half-Life
Acebutolol	β_1	Yes	Yes	Low	3–4 hours
Atenolol	β_1	No	No	Low	6–9 hours
Betaxolol	β_1	No	Slight	Low	14–22 hours
Bisoprolol	β_1	No	No	Low	9–12 hours
Carteolol	None	Yes	No	Low	6 hours
Carvedilol[1]	None	No	No	No data	6–8 hours
Celiprolol	β_1	Yes[2]	No	No data	4–5 hours
Esmolol	β_1	No	No	Low	10 minutes
Labetalol[1]	None	Yes[3]	Yes	Moderate	5 hours
Metoprolol	β_1	No	Yes	Moderate	3–4 hours
Nadolol	None	No	No	Low	14–24 hours
Penbutolol	None	Yes	No	High	5 hours
Pindolol	None	Yes	Yes	Moderate	3–4 hours
Propranolol	None	No	Yes	High	3.5–6 hours
Sotalol	None	No	No	Low	12 hours
Timolol	None	No	No	Moderate	4–5 hours

CARDIOSELECTIVITY

- × Less bronchoconstriction.
- × Less interference with CHO metabolism & less inhibition of glycogenolysis. Safer in diabetics.
- × Less deleterious effect on lipid profile.
- × Lower incidence of cold hand & feet, & less chance to ppt. Raynaud phenomena.
- × Less liable to impair exercise capacity.
- × Ineffective in suppressing essential tremor.

ISA

- Bradycardia & depression of contractility at rest are not prominent.
- **Withdrawal** is less likely to exacerbate hypertension or angina.
- Plasma lipid profile is not/ less worsened.
- Not effective in migraine prophylaxis.
- Less suitable for secondary prophylaxis of MI.

Application	Drugs	Effect
Hypertension	Propranolol, metoprolol, timolol, others	Reduced cardiac output, reduced renin secretion
Angina pectoris	Propranolol, nadolol, others	Reduced cardiac rate and force
Arrhythmia prophylaxis after myocardial infarction	Propranolol, metoprolol, timolol	Reduced automaticity of all cardiac pacemakers
Supraventricular tachycardias	Propranolol, esmolol, acebutolol	Slowed AV conduction velocity
Hypertrophic cardiomyopathy	Propranolol	Slowed rate of cardiac contraction
Congestive heart failure	Carvedilol, labetalol, others	Mechanism not understood
Migraine	Propranolol	Prophylactic; mechanism uncertain
Familial tremor, other types of tremor, "stage fright"	Propranolol	Reduced β_2 alteration of neuromuscular transmission; possible CNS effects
Thyroid storm, thyrotoxicosis	Propranolol	Reduced cardiac rate and arrhythmogenesis; other mechanisms may be involved
Glaucoma[1]	Timolol, others	Reduced secretion of aqueous humor

ADVERSE EFFECTS

- BRONCHOCONSTRICTION.
- ARRHYTHMIAS.
- SEXUAL IMPAREMENT.
- DISTURBANCE IN (CHO) METABOLISM.

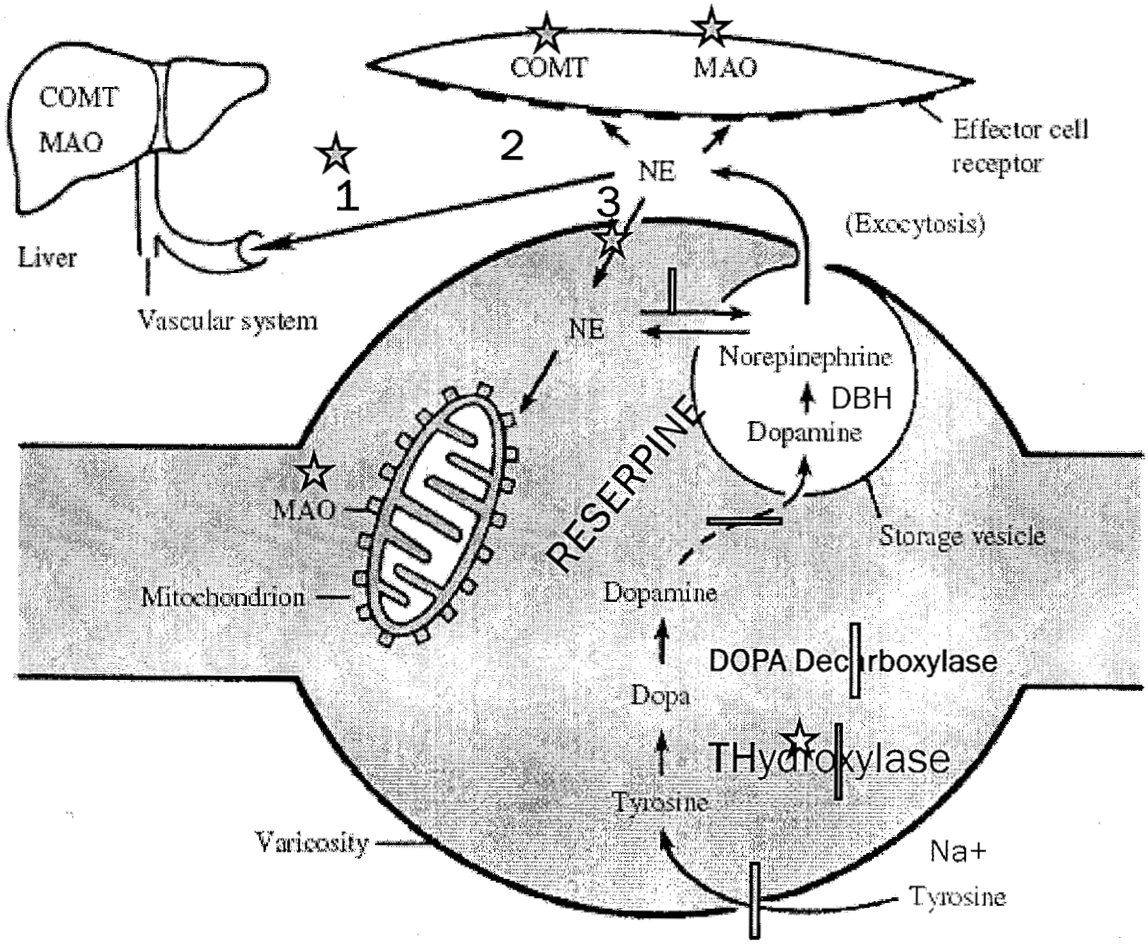
SYMPATHETIC NERVOUS SYSTEM DEPRESSANTS

- Adrenergic Neuron Blockers - Guanethidine, Bretylium
- Synthesis Inhibitors -Metyrosine
- Catecholamine Depleting Drugs -Reserpine
- Centrally Acting Drugs -Alpha methyldopa
  -Clonidine

The primary use of most of these drugs is the treatment of essential hypertension

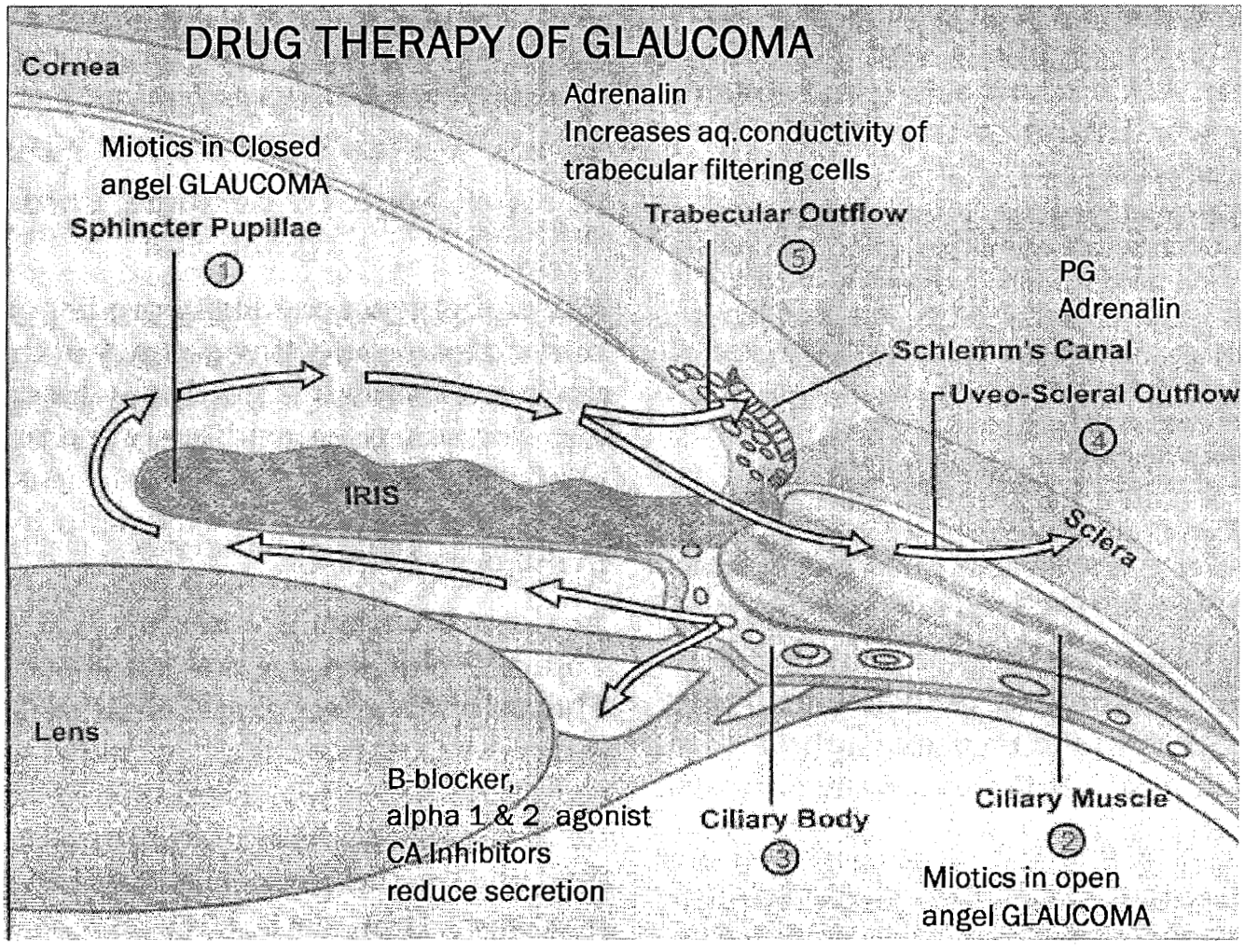
RESERPINE

- PLANT ALKALOID.
- BLOCKS THE Mg++/ATP DEPENDENT TRANSPORT OF BIOGENIC AMINES(5HT,DOPAMINE& NE).
- HAS SLOW OOA, LONG DOA.
- RESERVED FOR HYPERTENSIVE CASES FAILED TO BE TREATED BY OTHER DRUGS.



METYROSINE

- alpha-methyl tyrosine.
- competitive inhibitor of tyrosine hydroxylase, the rate-limiting step in the synthesis of NA.
- tissue levels of NA decline after Metyrosine because of continued metabolism without sufficient new synthesis.
- adverse effects are typical of sympathetic nervous system depression, esp. **sedation**.



Group, Drugs	Mechanism
holinomimetics Pilocarpine, carbachol, physostigmine, echothiophate	Ciliary muscle contraction, opening of trabecular meshwork; increased outflow
lpha agonists, nonselective Epinephrine, dipivefrin	Increased outflow, probably via the uveoscleral veins
lpha$_2$-selective Apraclonidine, brimonidine	Decreased aqueous secretion
eta-blockers Timolol, betaxolol, carteolol, levobunolol, metipranolol	Decreased aqueous secretion from the ciliary epithelium
iuretics Acetazolamide, dorzolamide	Decreased secretion due to lack of HCO_3^- ion
rostaglandin $PGF_{2\alpha}$ Latanoprost	Increased outflow

TOPICAL B-BLOCKERS vs. Miotics

No change in pupil size.

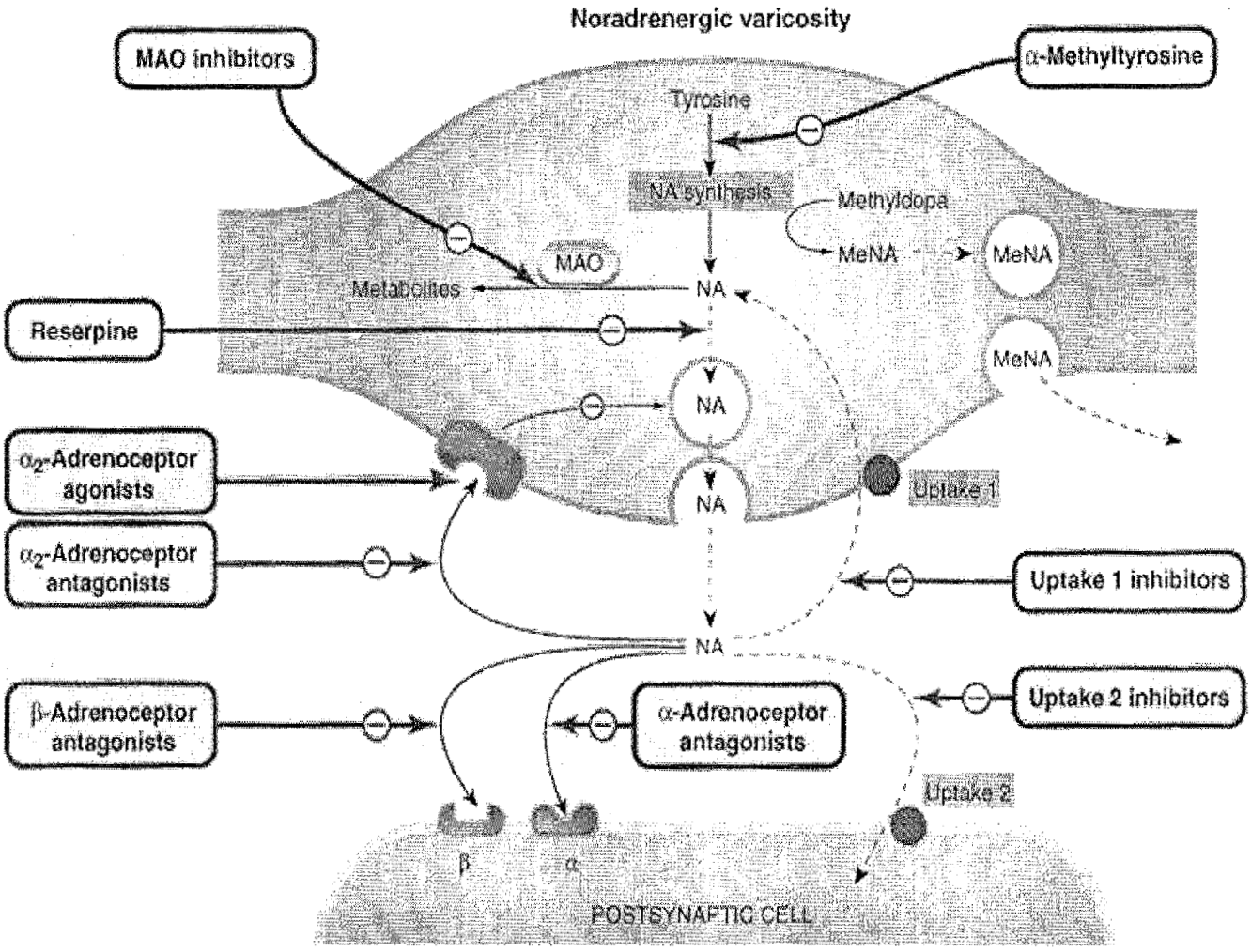
No diminution of vision in dim light & in patient with cataract.

No induce myopia (young patient).

No headache /brow pain due to persistent spasm of iris and ciliary muscles.

No fluctuations in i.o.t. as with pilocarpine.

More convenient (twice or once application is sufficient)



280. Of the many types of adrenergic receptors found throughout the body, which is most likely responsible for the cardiac stimulation that is observed following an intravenous injection of epinephrine?

a. α1-adrenergic receptors
b. α2-adrenergic receptors
c. β1-adrenergic receptors
d. β2-adrenergic receptors
e. β3-adrenergic receptors

281. The enzyme that is inhibited by echothiophate iodide is

a. Tyrosine hydroxylase
b. Acetylcholinesterase (AChE)
c. Catechol-*O-methyltransferase (COMT)*
d. Monoamine oxidase (MAO)
e. Carbonic anhydrase

282. Applied to the skin in a transdermal patch (transdermal therapeutic delivery system), this drug is used to prevent or reduce the occurrence of nausea and vomiting that are associated with motion sickness.

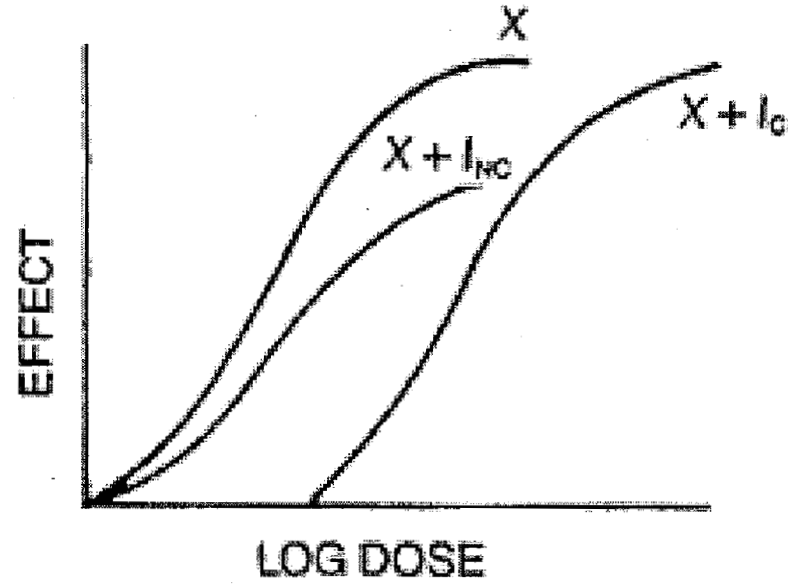
a. Diphenhydramine
b. Chlorpromazine
c. Ondansetron
d. Dimenhydrinate
e. Scopolamine

283. The nonselective β-adrenergic blocking agent that is also a competitive antagonist at α1-adrenoceptors is

a. Timolol
b. Nadolol
c. Pindolol
d. Acebutolol
e. Labetalol

✖ 284. The contractile effect of various doses of norepinephrine (NE) (*X*) alone on vascular smooth muscle is represented in the figure below. When combined with an antagonist (*IC or INC), a shift in the dose response* curve occurs. The curve labeled ***X + INC*** *would most likely occur from* treatment with NE in the presence of

a. Terazosin
b. Phentolamine
c. Labetalol
d. Phenoxybenzamine
e. Prazosin



285. The reversible cholinesterase inhibitor indicated in the treatment of Alzheimer's disease is

a. Tacrine

b. Edrophonium

c. Neostigmine

d. Pyridostigmine

e. Ambinonium

× Match the descriptions of use with the appropriate drug.

a. Pilocarpine

b. Methylphenidate

c. Propranolol

d. Ritodrine

e. Phenoxybenzamine

×330. Used in pheochromocytoma

×331. Used in thyroid storm

×332. Used in glaucoma