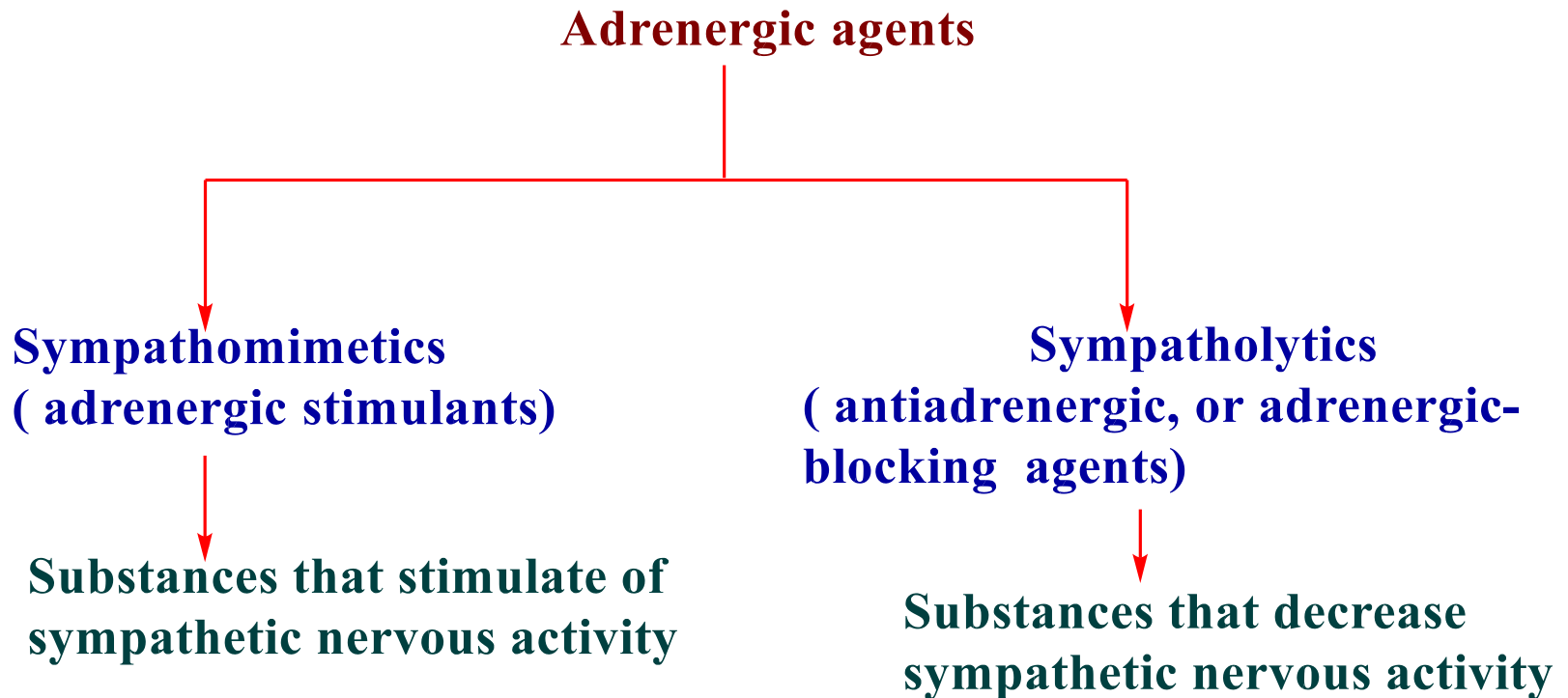# Adrenergic Agents

Adrenergic drugs: - are chemical agents that exert their principal pharmacological and therapeutic effects by either enhancing or reducing the activity of the various components of the sympathetic division of the autonomic nervous system.

Adrenergic agents

Sympathomimetics (adrenergic stimulants)

Substances that stimulate of sympathetic nervous activity

Sympatholytics (antiadrenergic, or adrenergic-blocking agents)

Substances that decrease sympathetic nervous activity

Adrenergic agent

act on

adrenergic receptors
(adrenoceptors, ARs)

effect the life cycle of adrenergic
neurotransmitters(NTs)

Norepinephrine
(NE, noradrenaline)

Epinephrine
(E, adrenaline)

Dopamine
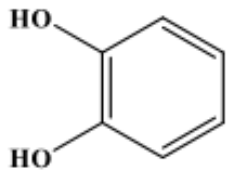(DA)

Vital functions that modulates by NTs, includes-:

1- The rate and force of cardiac contraction. Constriction.
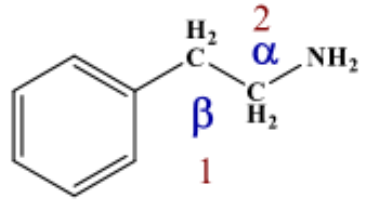
2- Dilation of blood vessels and bronchioles.

-3 The release of insulin.
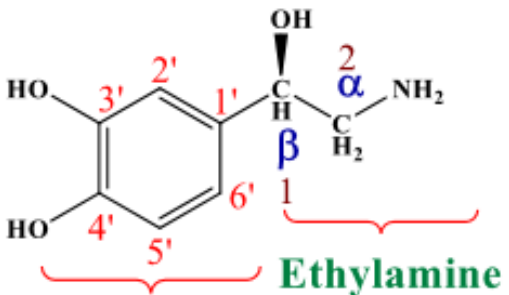
4- The breakdown of fat.

Structure and Physicochemical properties of adrenergic neurotransmitters
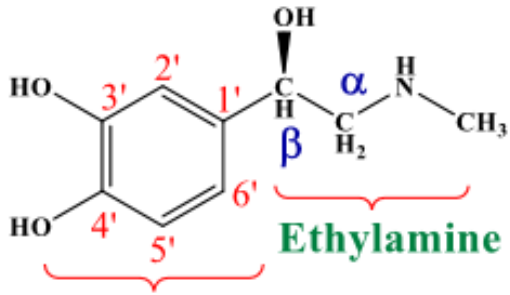

Catechol

β-phenylethylamine

Catechol / Ethylamine

Catecholamine

Noepinephrine (NE)

Catechol / Ethylamine

Catecholamine

Epinephrine (E)
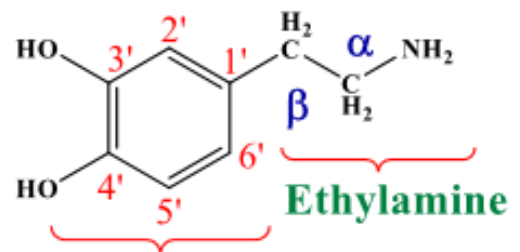
Catechol / Ethylamine

Catecholamine

Dopamine (DA)

pKa= 8.7 for phenolic hydroxyl group

pKa= 9.9 for aliphatic amine group

physiological pH

Epinephrine (E)
2°amine, containe 3 OH group
log p=- 0.63 (polar and soluble in water)

Cationic form
log D at pH 7= -2.75
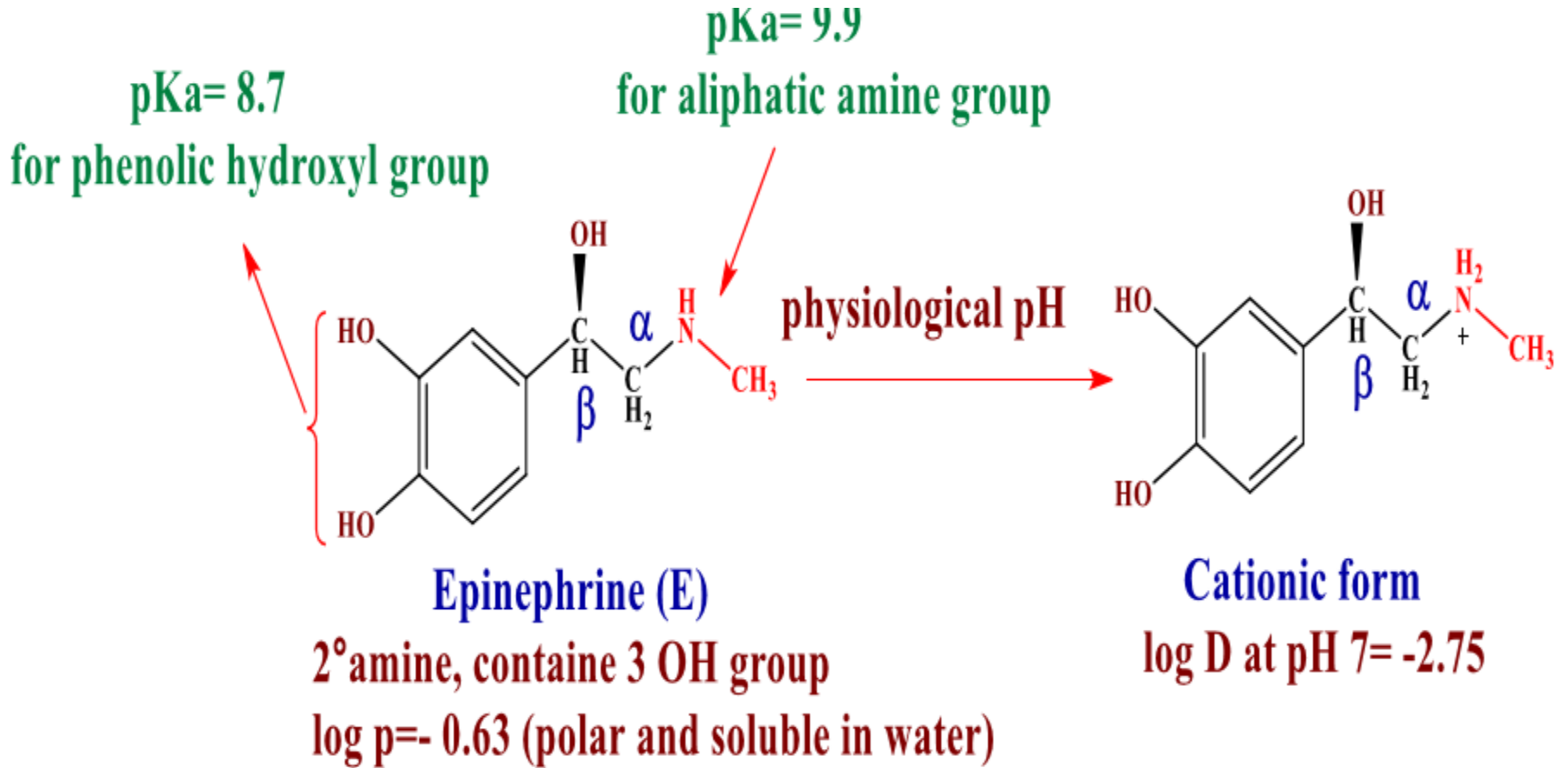
E has poor absorption and poor central nervous system (CNS) penetration.
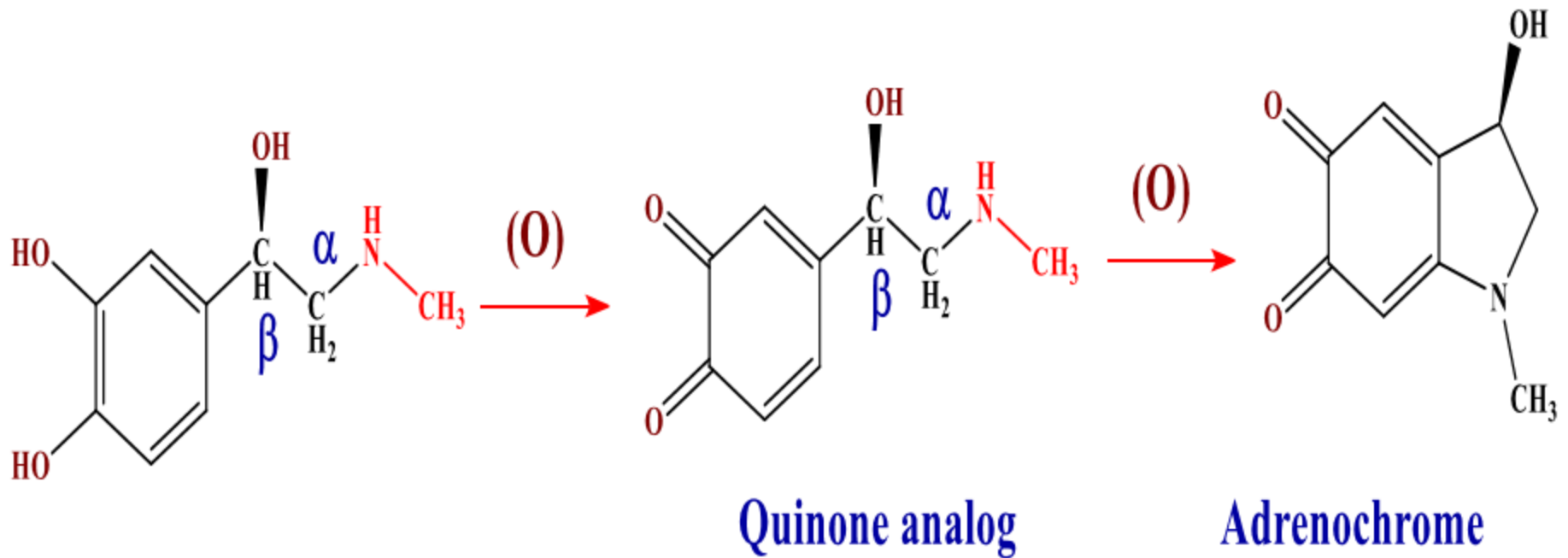
Oxidation of epinephrine
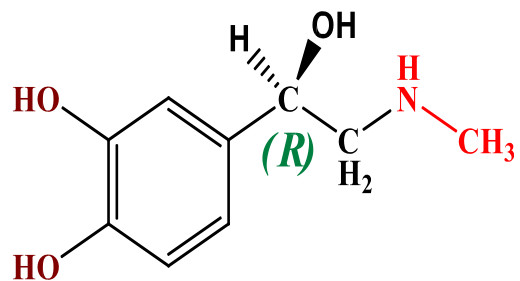
(R) isomer of Epinephrine
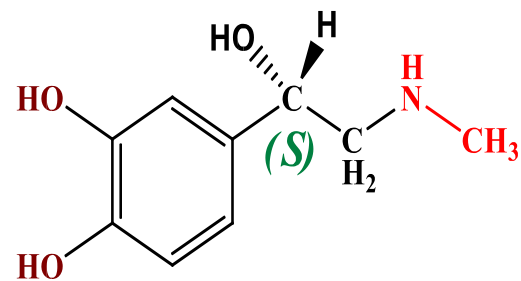
(S) isomer of Epinephrine
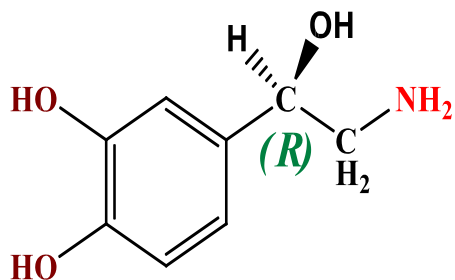
(R) isomer of Norepinephrine
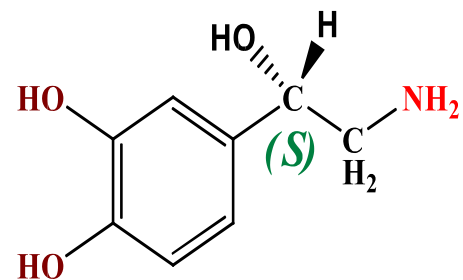
(S) isomer of Norepinephrine

Biosynthesis :

CAs → are widely distributed in mammals

in neuroendocrine cells

in a state of constant flux

levels   physiological functions

are regulating at many sites

yet they maintain a remarkable constant level in tissues.

They are continuously being synthesized,
released, and metabolized

Biosynthesis-:

The biosynthesis involves a sequence of enzymatic reaction

α-methyl-p-tyrosine, α-methyl-3-iodotyrosine, and α-methyl-5-hydroxy tryptophan. In general,α-methyl analogs are more potent than the unmethylated analogs.

Metyrosine(Demser)
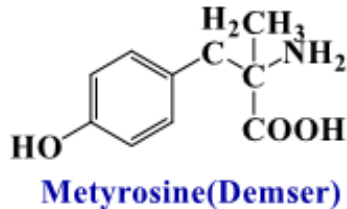
(An α-methyl analog of tyrosine and an inhibitor of TH)

Carbidopa

L-Tyrosine
normally present in the circulation and transport actively into the adrenergic neuron

Tyrosine Hydroxylase

L-Dihydroxyphenylalanine (L-Dopa)

L-aromatic Aminoacid Decarboxylase(AADC)

Dopamine

Dopamine-β-Hydroxylase (DβH)

where it is 3-hydroxylated by tyrosine hydroxylase (TH, tyrosine-3-monooxygenase). TH is stereospecific and requires molecular O_2, Fe^{2+}, and a tetrahydropteridine cofactor. TH hydroxylation is the rate-limiting step in the biosynthesis of NE. This enzyme plays a key role in the regulation of CA biosynthesis and is, therefore, the logical biological target of some drugs.

Phenylethanolamine N-methyltransferase (PENMT)

Epinephrine

Norepinephrine

Biosynthesis of the catecholamines dopamine, norepinephrine and epinephrine

Important Notes:

1- Most of the agents in this category act as competitive inhibitors of TH. α-Methyl-p-tyrosine (metyrosine, Demser, Fig.) and its methyl ester have been the TH inhibitors most widely used to demonstrate the effects of exercise, stress, and various drugs on the turnover of CAs and to lower NE formation in patients with pheochromocytoma and malignant hypertension.

2-TH is a specific phenotypic marker of CA-producing cells in the CNS and peripheral nervous system (PNS). The activity of TH is carefully controlled. For example, adrenergic nerve stimulation leads to activation of a protein kinase that phosphorylates TH, thereby increasing its activity. In addition, through end-product inhibition, NE markedly reduces TH activity. The basis of this feedback inhibition is believed to be a competition between the CA product and the pterin cofactor.

3-In simplest term, parkinsonism can be characterized as a DA deficiency in the brain. Thus, increasing brain levels of DA should ameliorate the symptoms. Unfortunately, direct parenteral DA administration is useless because the compound does not penetrate the blood-brain barrier (BBB). However, oral dosing with L-DOPA (levodopa, Dopar) could act as a prodrug because it entered the brain (on a specific carrier) and then was decarboxylated to DA there. LDOPA is effective and decrease tremor and rigidity.

4-Unfortunately, many adverse systemic effects were the result of the high doses needed to achieve the desired results. The main reason is the relatively higher concentration of AADC in peripheral system than in the brain. Inhibition of peripheral AADC activity by coadministration of at peripheral decarboxylase inhibitor such as carbidopa (charged at physiological pH), can markedly increase the proportion of levodopa that crosses the BBB.

5-The third step in CA biosynthesis is side-chain β-hydroxylation of DA to give NE. DA formed in the cytoplasm of the neuron is actively transported into storage vesicles by a 12-helix membrane–spanning proton antiporter called the vesicular monoamine transporter (VMAT) and is then hydroxylated stereospecifically at the β -carbon to NE inside the vesicle by dopamine β -hydroxylase (DBH, dopamine β -monooxygenase).

6-The NE formed is stored in the vesicles until depolarization of the neuron initiates the process of vesicle fusion with the plasma membrane and extrusion of NE into the synaptic cleft.

7-DBH has rather low substrate specificity and acts in vitro on various substrates besides DA, hydroxylating almost any phenylethylamine to its corresponding phenylethanolamine (e.g., tyramine to octopamine, α-methyldopamine to α-methylnorepinephrine).

8-The last step in CA biosynthesis is the N-methylation of NE to give E in the adrenal medulla. The reaction is catalyzed by the enzyme phenylethanolamine-N-methyltransferase (PNMT).

9-PNMT is a cytosolic enzyme and the methyl donor S-adenosyl methionine (SAM) is required for the N-methylation of NE. The adrenal medullary enzyme has rather low substrate specificity and transfers methyl groups to the nitrogen atom on various β-phenylethanolamines. The reaction occurs in the cell cytoplasm, and the E formed is transported into the storage granules of the chromaffin cells. Although PNMT is mostly found in the adrenal medulla, low levels of activity exist in heart and mammalian brain. Regulation of this enzyme in the brain has not been extensively studied, but glucocorticoids are known to regulate the activity of PNMT in the adrenal gland.

Storage, Release, Uptake, and Metabolism
Storage and Release

storage
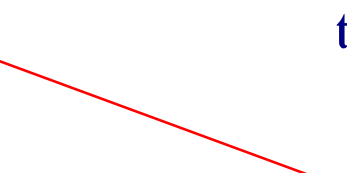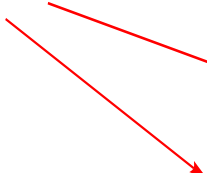
↓

large percentage of the NE present

↓ is located

synaptic vesicles (granules) → concentration in the vesicles maintained also by the vesicular monoamine transporter(VMAT).
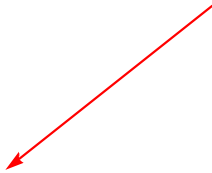
sympathetic nerve endings   chromaffin cells.   CNS

Following its biosynthesis and storage in granules, the entrance of Ca2+ into these cells results in the extrusion of NE by exocytosis of the granules. Ca2+-triggered secretion involves interaction of highly conserved molecular scaffolding proteins leading to docking of granules at the plasma membrane and then NE is released from sympathetic nerve endings into the synaptic cleft, where it interacts with specific presynaptic and postsynaptic adrenoceptors, on the effector cell, triggering a biochemical cascade that results in a physiologic response by the effector cell.

Indirectly acting and mixed sympathomimetics (e.g., tyramine, amphetamines, and ephedrine) are capable of releasing stored transmitter from noradrenergic nerve endings by a calcium-independent process. These drugs are poor agonists (some are inactive) at adrenoceptors, but they are excellent substrates for VMAT. They are avidly taken up into noradrenergic nerve endings by NE reuptake transporter (NET) responsible for NE reuptake into the nerve terminal. In the nerve ending, they are then transported by VMAT into the vesicles, displacing NE, which is subsequently expelled into the synaptic space by reverse transport via NET. Their action does not require vesicle exocytosis.

Uptake. Once NE has exerted its effect at adrenergic receptors, there must be mechanisms for removing the NE from the synapse and terminating its action at the receptors. These mechanisms include:

(a) reuptake of NE into the presynaptic neuron (recycling, major mechanism) by NET and into extraneuronal tissues,
(b) conversion of NE to an inactive metabolite, and
(c) diffusion of the NE away from the synapse.

The first two of these mechanisms require specific transport proteins or enzymes, and therefore are targets for pharmacologic intervention. By far, the most important of these mechanisms is recycling the NE. This process is termed uptake-1 and involves a Na+/Cl—dependent transmembrane (TM) NET that has a high affinity for NE. This reuptake system also transports certain amines other than NE into the nerve terminal, and can be blocked by such drugs as cocaine and some of the tricyclic antidepressants

Similar transporters, dopamine transporter (DAT) and serotonin transporter (SERT) are responsible for the reuptake of DA and 5-HT (serotonin), respectively, into the neurons that release these transmitters. Some of the NE that reenters the sympathetic neuron is transported from the cytoplasm into the storage granules carried out by an H+ dependent TM VMAT. There, it is held in a stable complex with adenotriphosphate (ATP) and proteins until sympathetic nerve activity or some other stimulus causes it to be released into the synaptic cleft.

Certain drugs, such as reserpine, block this transport, preventing the refilling of synaptic vesicles with NE and eventually cause nerve terminals to become depleted of their NE stores. By this mechanism, reserpine inhibits neurotransmission at adrenergic synapses.

In addition to the neuronal uptake of NE, there exists an extraneuronal uptake process, called uptake-2 with relatively low affinity for NE. Although its physiological significance is unknown, it may play a role in the disposition of circulating CAs, because CAs that are taken up into extraneuronal tissues are metabolized quite rapidly.

Adrenergic neuron

Effector cells

Inhibition of NE release

α2

Storage vesicle

DA → DA → NE →

NE
NE NE NE
NE

Recycling

NE

MAO

Uptake 1

DA

L-Dopa

Tyrosine

NE
NE
NE
NE

ARs

3',4'-Dihydroxyphenylglycolaldehyde

Tyrosine

Diffusion and metabolism

Model of the life cycle of NE

Na$^+$/ Cl$^-$dependent transmembrane
transporter (NET)
DAT, SERT....etc

Metabolism

major mammalian enzymes

monoamine oxidase (MAO)   **catechol-O- methyltransferase (COMT)**

Both E and NE are orally inactive and have short durations of actions because of their-:

- **High hydrophilicity.**
- **Ionization.**
- **Extensive first-pass metabolic deactivation by COMT and MAO.**

3,4-Dihydroxyphenyl-glycolaldehyde

MAO

Norepinephrine: R = H
Epinephrine: R = CH$_3$

1) MAO
2) Aldehyde Dehydrogenase

3,4-Dihydroxymandelic Acid

Aldehyde Reductase
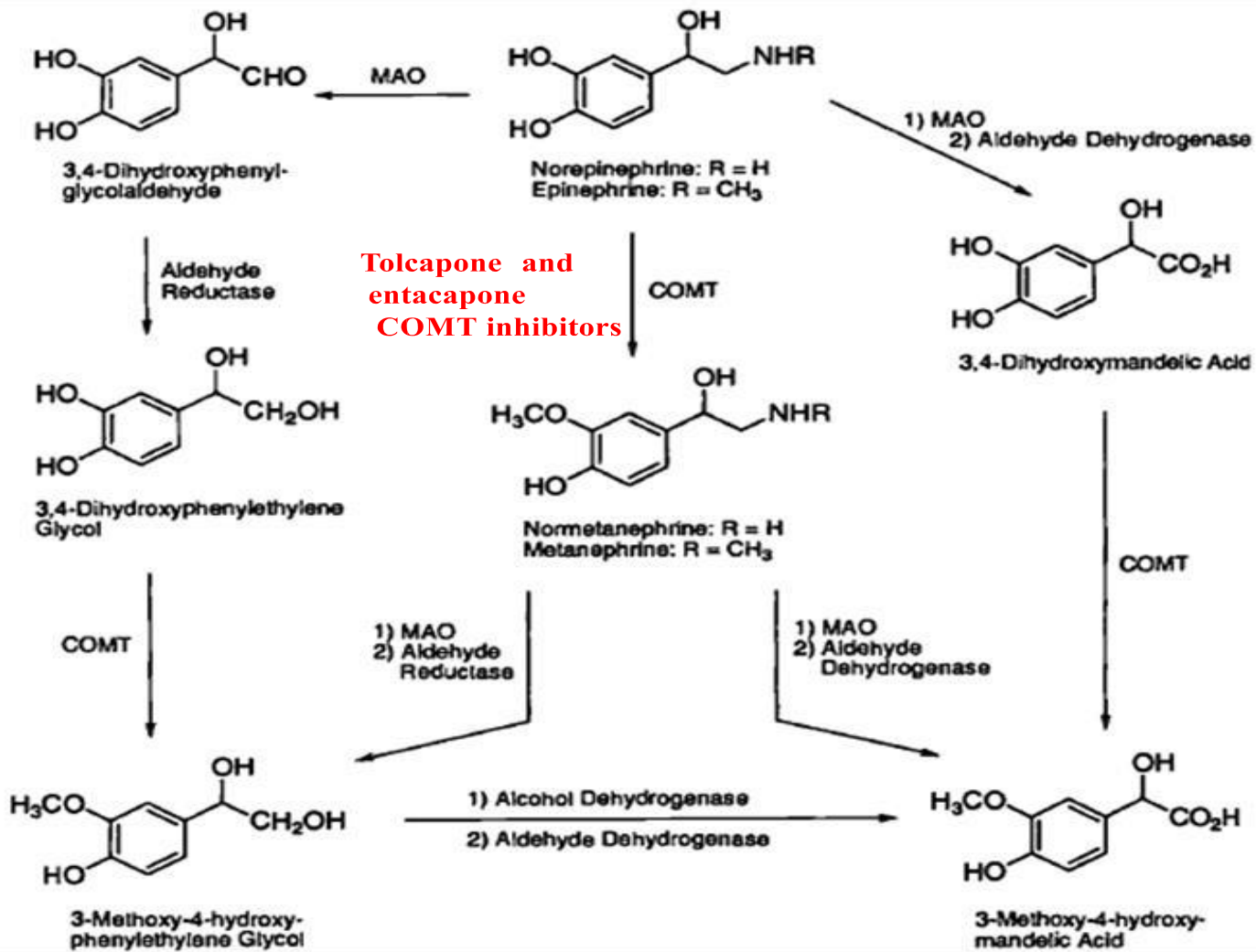
Tolcapone and entacapone COMT inhibitors

COMT

3,4-Dihydroxyphenylethylene Glycol

Normetanephrine: R = H
Metanephrine: R = CH$_3$

COMT

1) MAO
2) Aldehyde Reductase

1) MAO
2) Aldehyde Dehydrogenase

COMT

COMT

3-Methoxy-4-hydroxy-phenylethylene Glycol

1) Alcohol Dehydrogenase
2) Aldehyde Dehydrogenase

3-Methoxy-4-hydroxy-mandelic Acid

Vanillylmandelic acid major end product (VMA)

sulfate conjugates   **glucuronide conjugates**

Urine

TABLE 16.2 Comparison of MAO and COMT

	MAO	COMT
Location in Neurons	In neuronal mitochondria metabolism of intraneuronal CAs	Not in sympathetic neuron metabolism of extraneuronal CAs
Reaction	Deaminate CAs to aldehydes	O-methylate CAs to 3′-OMe-CAs
Substrates	Compounds with a terminal aliphatic amino group (primary or N-methyl-amino groups) preference:	Catechol-containing molecules
	MAO-A MOA-B	
	NE and 5-HT DA β-phenylethylamine benzylamine	DA, E, NE, ISO, etc.

The lack of substrate specificity of COMT and MAO is manifested in the metabolism of NE and E, shown in Figure. Not only do both MAO and COMT use NE and E as substrates, but each also acts on the metabolites produced by the other.

Drugs that are catechols are subject to metabolism by COMT, whereas drugs with unsubstituted or secondary N-methyl-amino amino groups are often substrates for MAO. The first enzyme of importance in the metabolism of CAs in the adrenergic neurons of human brain and peripheral tissues is MAO.

MAOs oxidatively deaminate CAs to their corresponding aldehydes, which are rapidly oxidized to the corresponding acid by the enzyme aldehyde dehydrogenase (AD). In some circumstances, the aldehyde is reduced to the glycol by aldehyde reductase (AR).

For example, NE is deaminated oxidatively by MAO to give 3,4-dihydroxyphenylglycolaldehyde (DOPGA), which then is reduced by AR to 3,4-dihydroxyphenylethylene glycol. It is primarily this glycol metabolite that is released into the circulation, where it undergoes methylation by the COMT that it encounters in nonneuronal tissues.

The product of methylation, 3-methoxy-4-hydroxyphenylethylene glycol, is oxidized by alcohol dehydrogenase and AD to give 3-methoxy-4-hydroxymandelic acid. This metabolite commonly is referred to as vanillylmandelic acid (VMA), and is the major end product of several pathways of NE metabolism. An estimate of CA turnover can be obtained from laboratory analysis of total metabolites (sometimes referred to as VMA and metanephrines) in 24-hour urine sample.

In the oxidative deamination of NE and E at extraneuronal sites such as the liver, the aldehyde formed is oxidized usually by AD to give 3,4-dihydroxymandelic acid (DOMA). MAO inhibitors (MAOIs) prevent MAO-catalyzed deamination of NE, DA, and 5-HT following their reuptake into the nerve terminal from the synaptic cleft. As a result, higher concentration of the NTs will be stored in the vesicles and become available for release from the presynaptic terminals on demand. Antidepressants such as phenelzine (Nardil), isocarboxazid (Marplan), and tranylcypromine (Parnate) are MAOIs.

There are two types of MAOs, and these exhibit different substrate selectivity. MAO-B primarily metabolizes DA and thus MAO-B inhibitors would tend to preserve brain DA and be effective by themselves and/or potentiate levodopa.

Selegiline (Eldepryl) is a specific type MAO-B inhibitor and does extend the duration and increase the efficacy of levodopa. The drug is promising, probably as an adjunct to levodopa or in levodopa refractory patients. The understanding of CAs metabolism can be important in the management of certain drug therapies and may even aid in diagnosis. For example, changes resulting from drugs may indicate the success of a treatment. The cerebrospinal fluid (CSF) levels of methylhydroxyphenylglycoaldehyde (MOPEG) are indicative of NE levels. Just as they can be related to the intensity of depression, the degree of improvement expected with antidepressants can be monitored in the weeks it may take before the clinical symptoms improve.

A CSF level of homovanillic acid (HVA, the major metabolite of brain DA, which is a counterpart of end metabolite of NE) is understandably low in parkinsonism. The second enzyme of importance in the metabolism of CAs is COMT that O-methylates 3-OH group of CAs and renders them inactive. Methylation by COMT occurs almost exclusively on the meta-OH group of the catechol, regardless of whether the catechol is NE, E, or one of the metabolic products.

For example, the action of COMT on NE and E gives normetanephrine and metanephrine, respectively. A converging pattern of the metabolism of NE and E in which 3-methoxy-4-hydroxymandelic acid (VMA) and 3-methoxy-4-hydroxyphenylethylene glycol are common end products thus occurs, regardless of whether the first metabolic step is oxidation by MAO or O-methylation by COMT.

In patients with tumors of chromaffin tissue that secrete these amines (a rare cause of high blood pressure), the urinary excretion of VMA is markedly increased and is used as a diagnostic test for this condition. Under normal circumstances, VMA is the principal urinary metabolite of NE, although substantial amounts of 3methoxy-4-hydroxyphenylethylene glycol are excreted along with varying quantities of other metabolites, both in the free form and as sulfate or glucuronide conjugates.

Endogenous E is excreted primarily as metanephrine and VMA. These pathways of metabolism are also important to drugs that are structural analogs of NE. Tolcapone (Tasmar) and entacapone (Comtan) are COMT inhibitors presently available. CAs released from either noradrenergic nerve terminals or the adrenal medulla are recognized by and bind to specific receptor molecules on the plasma membrane of the neuroeffector cells. These receptor ligand interactions produce a physiological response.

Many cells possess these receptors, and the binding of an agonist will generally cause the organism to respond in a fight-or-flight manner. For instance, the heart rate will increase and the pupils will dilate, energy will be mobilized, and blood flow will be diverted from other organs to skeletal muscle.

Adrenergic receptor subtypes

There are two types of adrenergic receptors

-1α- adrenergic receptor (α1 and α(2

-2β − adrenergic receptor (β1, β2, and β(3

they all belong to the guanine nucleotide (G)- regulatory proteins
)G-protein)-coupled receptors(GPCR.(

ADs	Organ or tissue	Effect of activation	Physiological effect	Drugs	Therapeutic uses
α_1	Blood vessels Skin	vasoconstriction	Increase blood pressure	α_1-agonist	Shock hypotension
α_1	Mucosa membrane	vasoconstriction	Nasal congestion	α_1-agonist	Nasal congestion
		Vasodilators	hypotension	α_1-Antagonist	Hypertension
α_2	CNS	Relax vascular smooth muscle. Decrease NE release	Decrease blood pressure	α_{-1} agonist(clonidine(	Hypertension
α_1	uterus	contraction			
β_1	Heart muscle	Muscle contraction	Increase heart rate and force	β_1-Antagonist	Hypertension Angina, Cardiac arrhythmias
β_1	Kidney	Increase rennin secretion			
β_2	Bronchial smooth muscle	Smooth muscle relaxant	Dilates and open airways	β_2- agonist	Asthma
β_2	uterus	Smooth muscle relaxation		β_2- agonist	Uterine contractions
β_3	brown adipose tissue	stimulation of lipolysis			