ADRENERGIC NEURONS INHIBITORS

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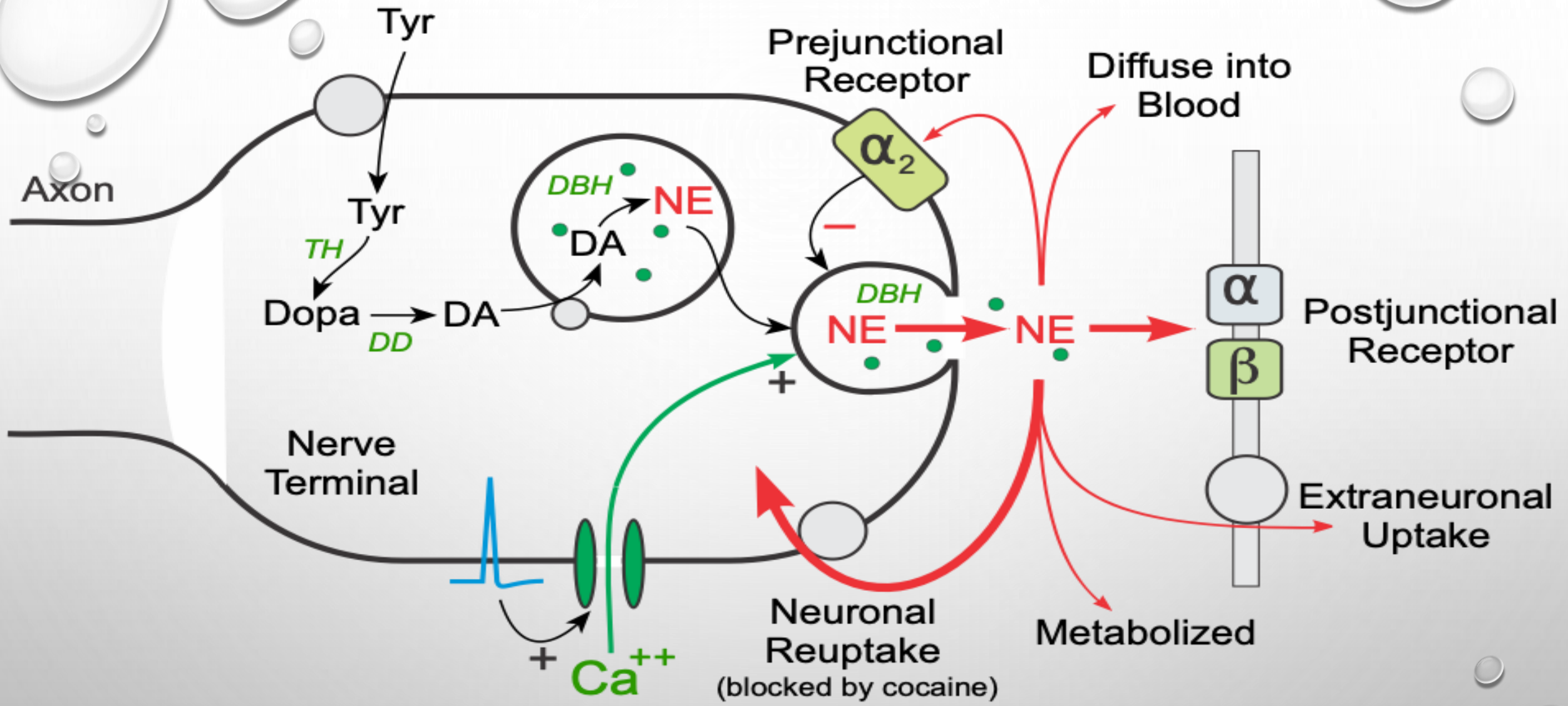


Tyr, tyrosine; *TH*, tyrosine hydroxylase; *DD*, DOPA decarboxylase; *DA*, dopamine; *DBH*, dopamine β-hydroxylase; *NE*, norepinephrine

I-Synthesis, storage, release and termination of the action of catecholamines

(I) Synthesis:

1- It occurs in the sympathetic nerve endings.

2-**Tyrosine** is actively transported from extracellular fluid to sympathetic endings by Na^+ dependent carrier.

3- In the cytoplasm:

• Tyrosine is hydroxylated to **DOPA** by tyrosine hydroxylase and this is the ***rate limiting step*** in the synthesis of catecholamines

• DOPA is decarboxylated to **dopamine** by dopa decarboxylase; dopa decarboxylase is non-specific enzyme as it can also convert α-methyldopa to α-methyldopamine.

4- **Dopamine** is transported into the vesicle by a carrier. The same carrier can transport NE and several other amines into these vesicles.

5- Inside the vesicles dopamine is hydroxylated to **NE**.

6- In the **adrenal medulla** and certain areas of the brain NE is methylated to **EP** by N-methytransferase.

(II) Storage:

-NE is stored in specific granules at the nerve endings.

III) Release:

1- Release of the transmitter occurs when the action potential opens voltage-sensitive Ca^{++} channels leading to increase in the intracellular Ca^{++} which cause fusion of the vesicles with the surface membrane (exocytosis) resulting in expulsion of NE, cotransmitters (as ATP and certain peptides) and dopamine hydroxylase

-The released **NE** acts on the adrenoceptors on the post-synaptic membrane causing change in ionic conductance.

(IV) Termination of the action of the released catecholamines:

-It occurs by 2 mechanisms:

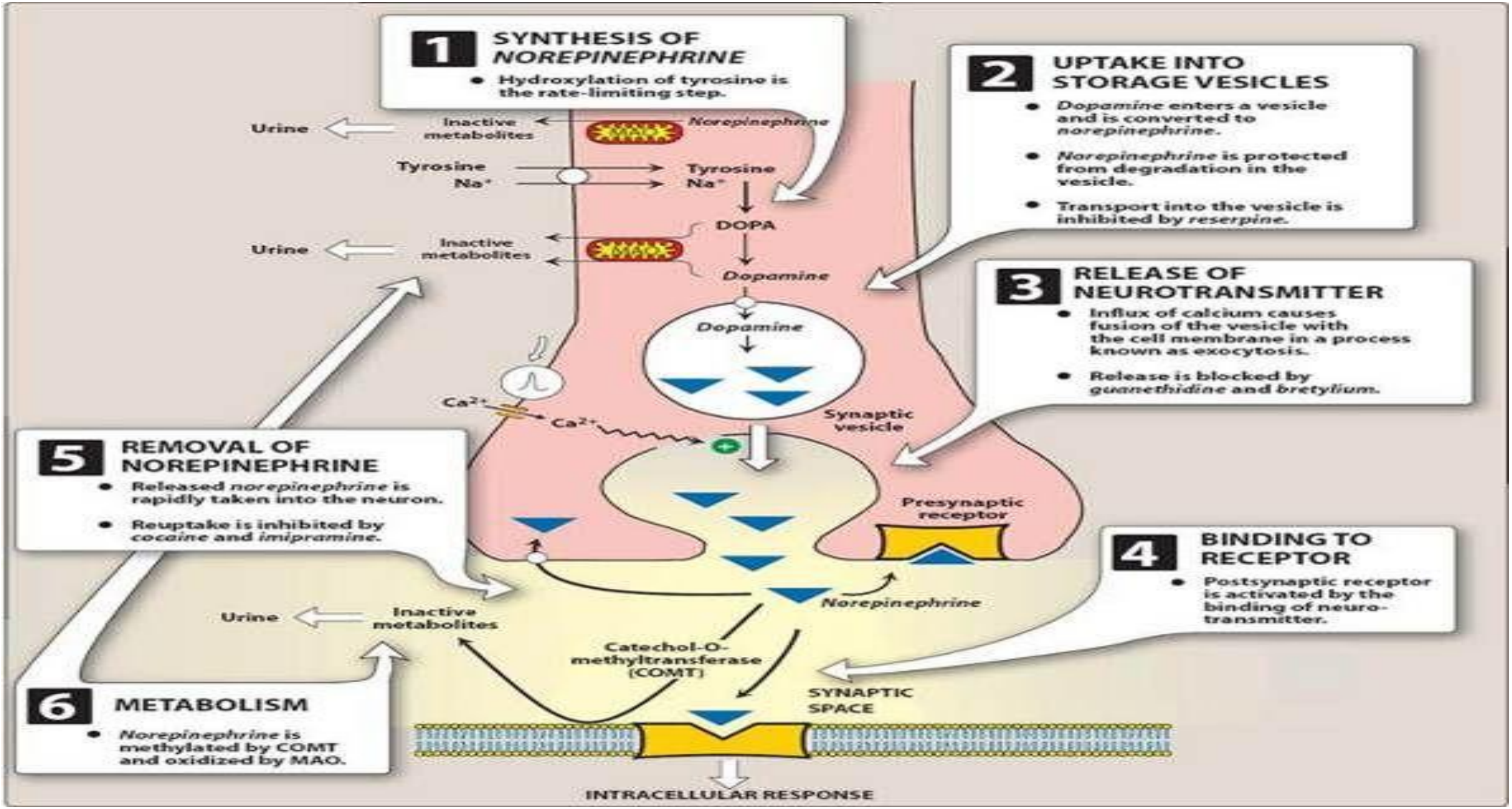
a) **Active reuptake** which is ***the most important*** mechanism and includes:

-Uptake 1 into the sympathetic nerve terminal which is ***the most important***

-Uptake 2 into post-junctional cells (***less important***) to be metabolism by **COMT**.

b) **Enzymatic metabolism** by **MAO** and **COMT**:

-Both MAO and COMT are widely distributed throughout the body including the brain with highest concentration in ***liver and kidney.*** However, **little or no COMT is found in adrenergic neurons.**


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
Urine
Inactive metabolites
Norepinephrine
Tyrosine
Na+
Tyrosine
Na+
DOPA
Urine
Inactive metabolites
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+
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)
6 METABOLISM
Norepinephrine is methylated by COMT and oxidized by MAO.
SYNAPTIC SPACE
INTRACELLULAR RESPONSE

- these drugs reduce adrenergic neurotransmission by affecting the synthesis, storage, release, or reuptake of norepinephrine (NE) in sympathetic neurons.
- they are mainly used for hypertension, psychiatric disorders, or experimental research.

1. Drugs that inhibit NE synthesis

these drugs block the enzymes involved in NE production, reducing adrenergic transmission.

Drug	Mechanism of Action	Effects	Clinical Use
Metyrosine (α-Methyltyrosine)	Inhibits Tyrosine Hydroxylase (TH), the rate-limiting enzyme in NE synthesis	↓ NE, ↓ dopamine (DA), ↓ epinephrine (E); hypotension, sedation	Pheochromocytoma (to lower catecholamines)
Carbidopa	Inhibits DOPA decarboxylase, preventing conversion of L-DOPA to dopamine (DA)	↓ DA, ↓ NE; does not cross BBB	Used with Levodopa in Parkinson's disease
Methyldopa	Converted to α-methyl-NE, a false neurotransmitter that replaces NE and activates α2-receptors (CNS inhibition)	↓ Sympathetic output, hypotension, sedation	Hypertension in pregnancy

2. Drugs that inhibit NE storage

these drugs deplete ne from vesicles by interfering with vesicular monoamine transporter (VMAT-2), leading to decreased adrenergic transmission.

Drug	Mechanism of Action	Effects	Clinical Use
Reserpine	Irreversibly inhibits VMAT-2, preventing storage of NE, DA, and serotonin in vesicles	Depletes catecholamines → hypotension, bradycardia, depression and suicide	Hypertension (obsolete), Huntington's disease (low dose)
Tetrabenazine	Reversible VMAT-2 inhibitor, reducing DA & NE storage	↓ DA & NE → sedation, movement suppression	Huntington's disease, tardive dyskinesia
Deutetrabenazine	Similar to tetrabenazine but longer-lasting	Less frequent dosing than tetrabenazine	Huntington's disease, tardive dyskinesia

3. Drugs that inhibit NE release

these drugs block exocytotic NE release, leading to sympathetic inhibition.

Drug	Mechanism of Action	Effects	Clinical Use
Guanethidine	Taken up by NET (norepinephrine transporter) → replaces NE in vesicles and blocks release	Profound hypotension, bradycardia and can cross blood brain barrier	Severe hypertension (obsolete)
Guanadrel	Similar to guanethidine but shorter-acting	Less severe hypotension than guanethidine, can not cross blood brain barrier	Hypertension (obsolete)
Bretylium	Blocks NE release by inhibiting vesicle fusion	Initial NE release (hypertension) → then inhibition (hypotension)	Antiarrhythmic (ventricular arrhythmias)
Clonidine	α2-agonist → inhibits NE release via presynaptic α2-autoreceptors	Lowers BP, causes sedation, bradycardia	Hypertension, opioid withdrawal, ADHD
Methyldopa	Converted to α-methyl-NE, which activates α2-receptors to inhibit NE release	Sympathetic suppression → hypotension, sedation	Hypertension in pregnancy
Dexmedetomidine	Central α2-agonist, potent NE release inhibitor	Sedation, bradycardia, hypotension	ICU sedation, anesthesia adjunct

4. Drugs that inhibit NE reuptake (NET inhibitors) (indirect sympatholytics)

these drugs block norepinephrine transporter (net), preventing reuptake and leading to either inhibition (depletion over time) or initial excitation.

Drug	Mechanism of Action	Effects	Clinical Use
Cocaine	Blocks NET, DAT, and SERT, preventing catecholamine reuptake	Initially increases NE (hypertension) → then depletes stores (crash)	Local anesthetic (rare), drug of abuse
Tricyclic Antidepressants (TCAs) (e.g., Amitriptyline, Imipramine)	Inhibit NET and SERT, increasing synaptic NE and serotonin	Antidepressant effect, hypotension (long-term)	Depression, chronic pain, migraine prevention
Atomoxetine	Selective NET inhibitor	↑ NE in CNS, but peripheral NE depletion	ADHD (non-stimulant therapy)

5. Enzyme inhibitors that reduce NE breakdown

these drugs inhibit catecholamine-degrading enzymes, leading to either increased ne (MAO-A inhibitors) or reduced ne metabolites (MAO-B inhibitors).

Drug	Enzyme Inhibition	Effects	Clinical Use
MAO-A Inhibitors (Phenelzine, Tranylcypromine)	Inhibits MAO-A, reducing breakdown of NE, DA, serotonin	↑ NE, hypertension risk with tyramine	Depression (last-line therapy)
MAO-B Inhibitors (Selegiline, Rasagiline)	Inhibits MAO-B, sparing dopamine more than NE	Used in Parkinson’s disease	Parkinson’s disease

Clinical uses of adrenergic neuron blockers

Condition	Drug Used	Mechanism
Pheochromocytoma	Metyrosine	Inhibits NE synthesis
Hypertension (historical use)	Reserpine, Guanethidine	Inhibits NE storage/release
Huntington's disease, Tardive dyskinesia	Tetrabenazine	Depletes dopamine & NE
Ventricular arrhythmias	Bretylium	Blocks NE release (antiarrhythmic effect)

Side effects of adrenergic neuron blockers

Category	Common Side Effects
Inhibitors of NE Synthesis	Sedation, depression, orthostatic hypotension
VMAT Inhibitors	Depression (Reserpine), Parkinsonism (Tetrabenazine)
NE Release Inhibitors	Severe hypotension, diarrhea, fluid retention
NET Inhibitors	Hypertension (Cocaine), cardiac arrhythmias (TCAs)


Thank
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