(indirect and mixed) SYMPATHOMIMETIC

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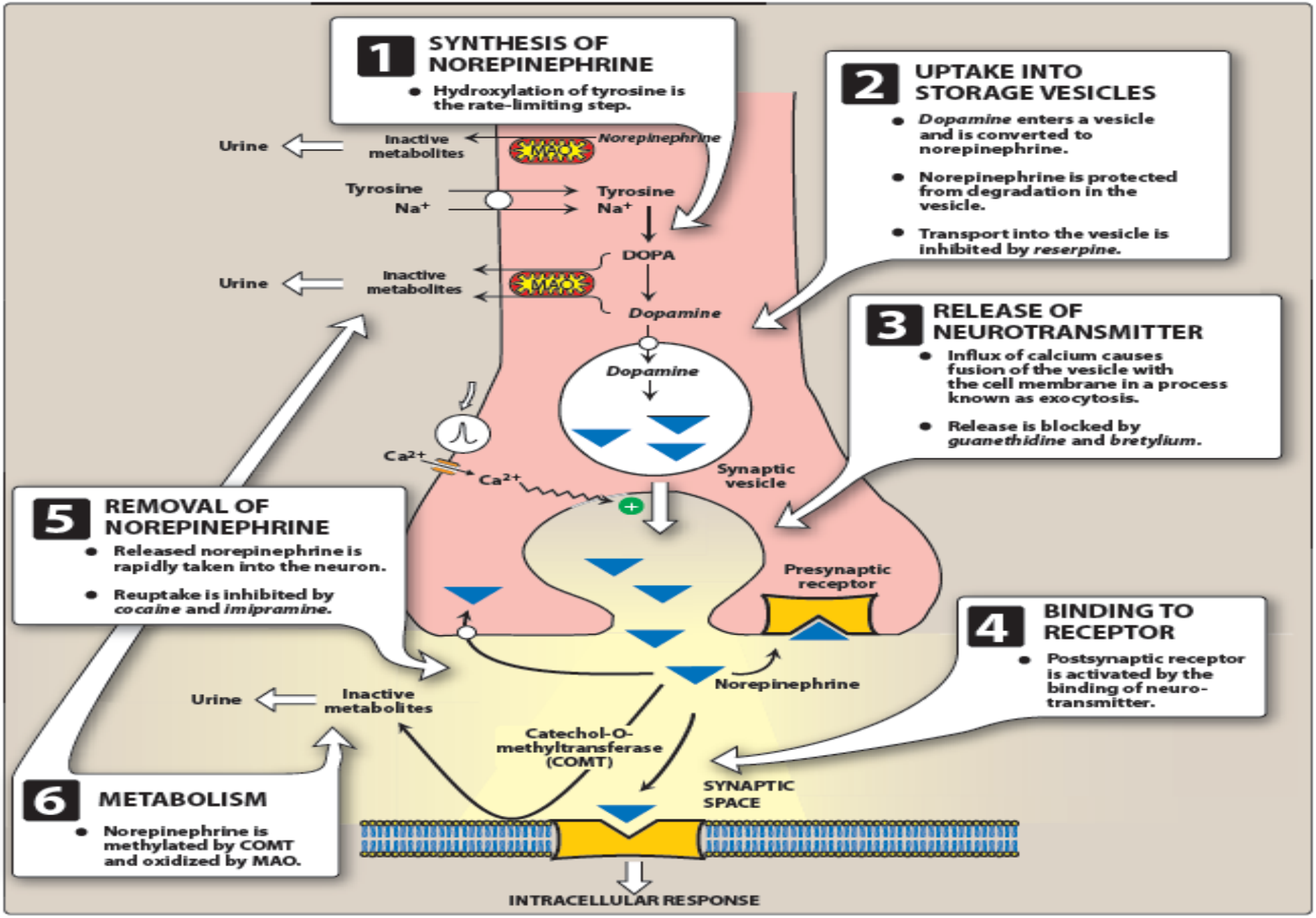

Synthesis, release & fate of NE in adrenergic neurons

INDIRECT-ACTING SYMPATHOMIMETIC

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A. Drugs that release the stored catecholamine transmitters:

- **Amphetamine**
- **Tyramine**

B. Catecholamine reuptake inhibitors:

- **Atomoxetine**
- **Cocaine**

INDIRECT-ACTING SYMPATHOMIMETIC

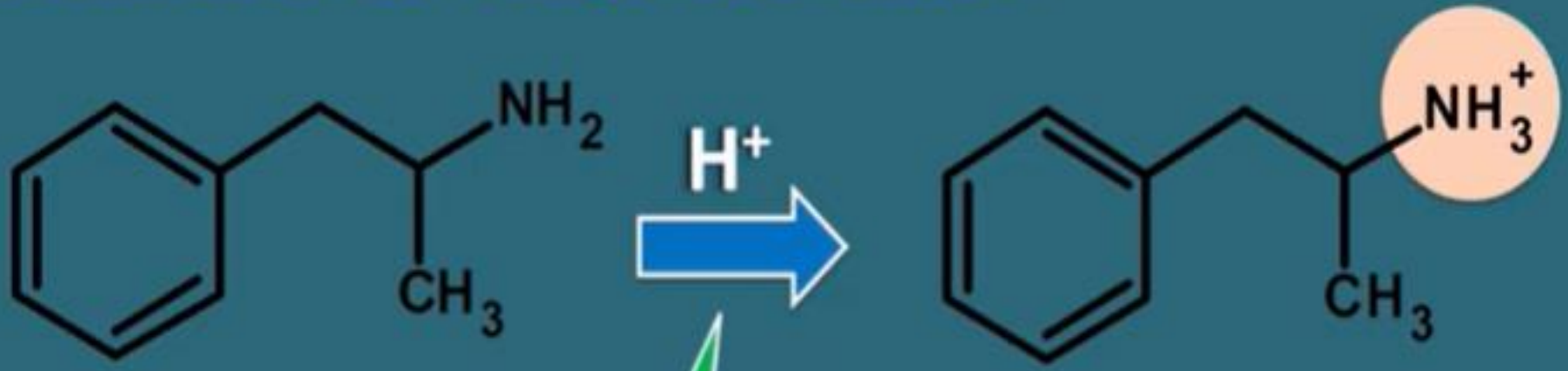
AMPHETAMINE

Pharmacokinetics:

- **Routs:** orally and can be given parenterally.
- **Metabolism:** It is poor substrate to MAO and COMT, so it has long duration of action.
- **Distributed:** all over the body and passes BBB.
- **Excreted:** in urine.
- Acidification of urine by ammonium chloride increases its excretion

EXCRETION OF AMPHETAMINE

Ionization of Amphetamine :



AMPHETAMINE

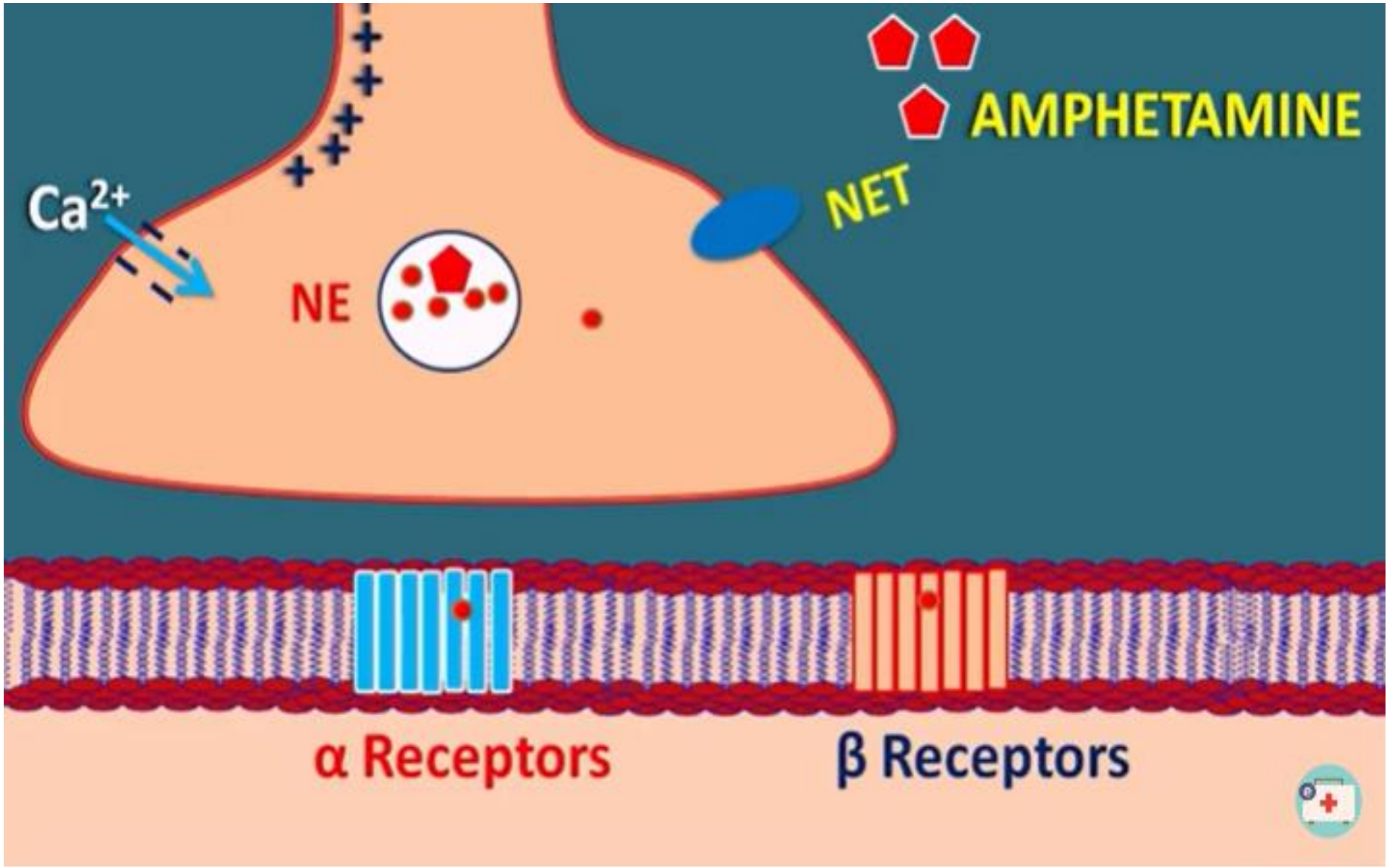
Ionized

(Less absorbed)

(More excreted)

Acidifying agents

MECHANISM OF ACTION



Pharmacological actions:

1) It stimulates cerebral cortex, reticular activating system, midbrain and spinal cord.

2) Also it has analeptic and anti-fatigue actions.

- These effects are manifested as euphoria, increased mental activity, alertness and wakefulness.

3) It decreases appetite (anorexiogenic).

4) It produces sympathomimetic action with little effect on bronchi.

5) Tolerance: occurs to anorexiogenic and psychic effects.

6) Addiction (dependence): on prolonged use.

Therapeutic uses:

1) Narcolepsy.

2) Obesity.

3) Attention-deficit hyperkinetic disorder (ADHD).

Adverse effects:

1) CVS:

- Palpitations, hypertension, arrhythmias.

2) CNS:

i. Anxiety, anorexia, insomnia, hallucination and convulsions.

ii. Dependence.

iii. Psychosis and coma.

AMPHETAMINE DERIVATIVES

➢ Methamphetamine:

More CNS effects with less peripheral actions.

➢Modafinil:

- It acts on α, serotonin (5-HT) and glutamate receptors in CNS.
- It is used in narcolepsy and ADHD.

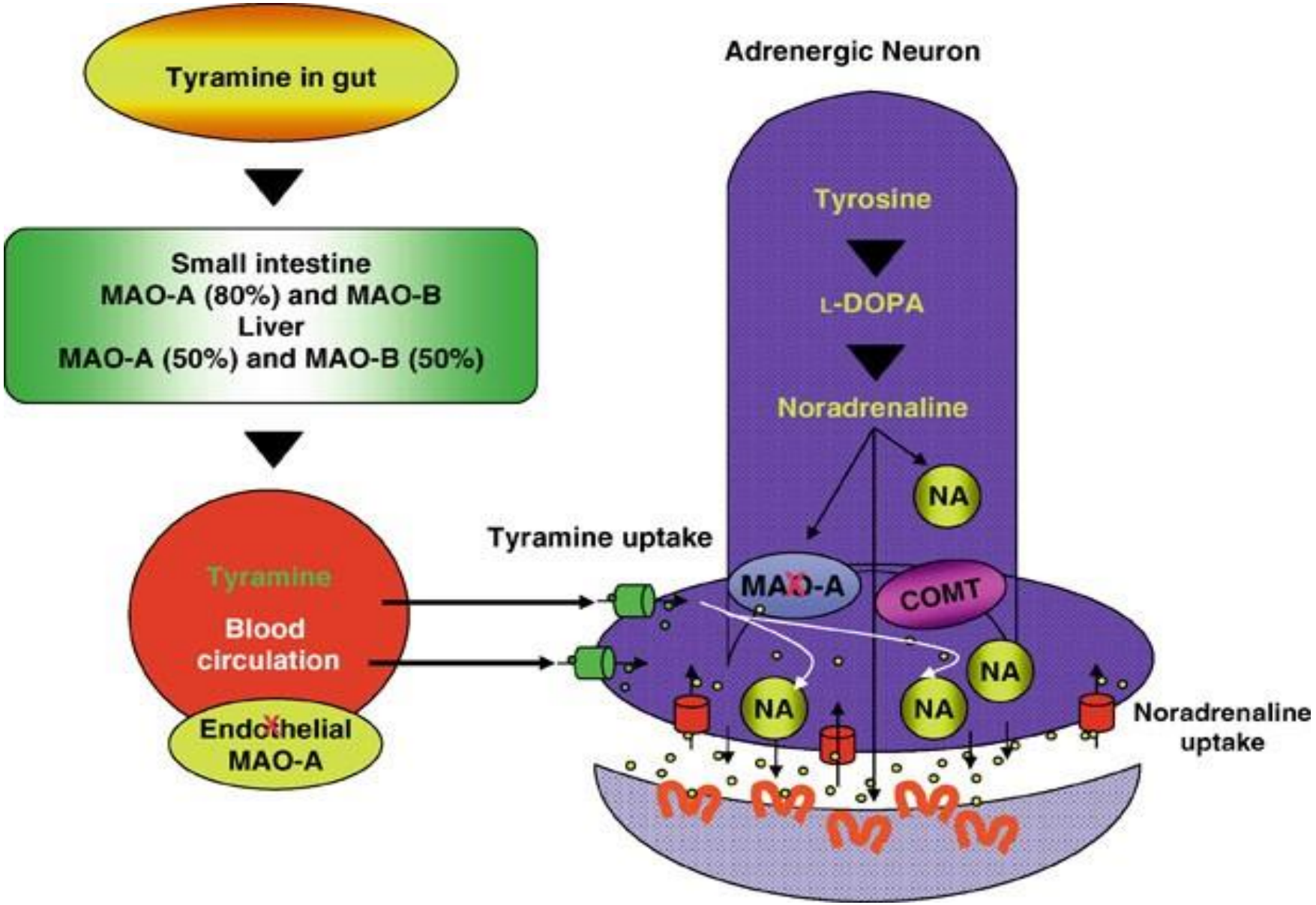
➢Methylphenidate

- used in ADHD.

TYRAMINE

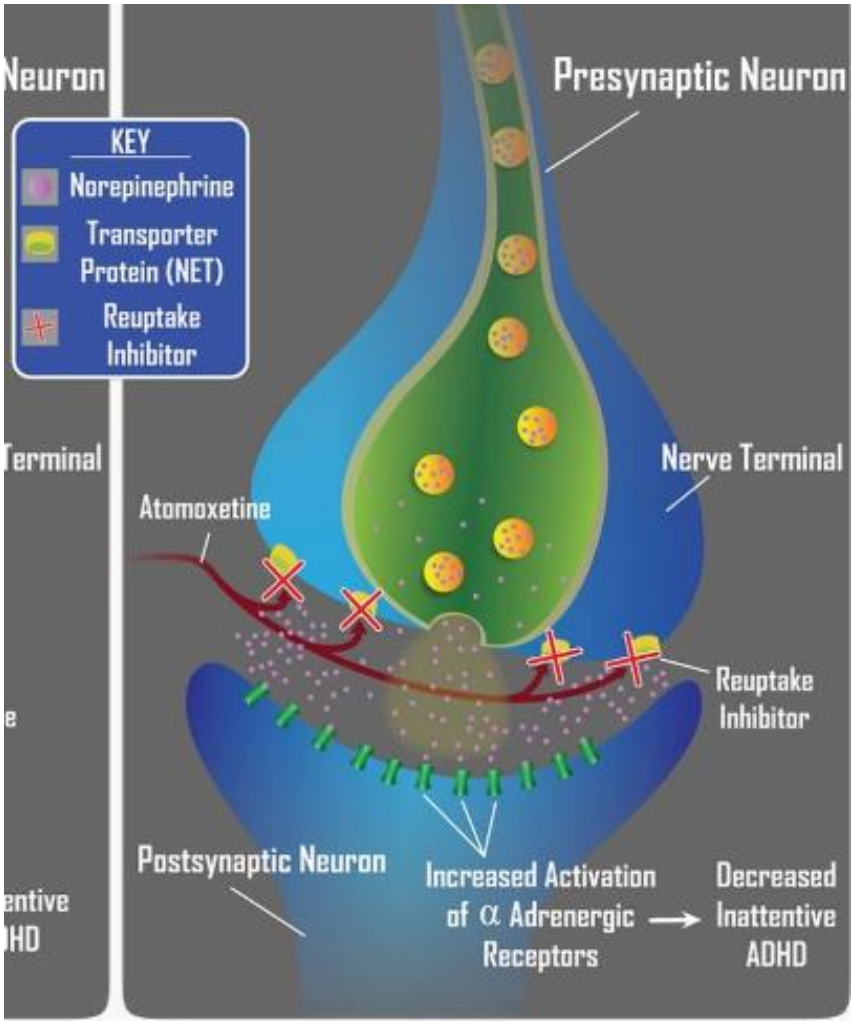
- It is a normal byproduct of tyrosine metabolism in the body and is also found in high concentrations in some fermented foods (such as cheese), chicken liver, chocolate, and smoked fish.

- It is inactivated by MAO in the liver and intestine when taken orally.
- If administered parenterally, it produces an indirect sympathomimetic action.
- In patients treated with non-selective MAO inhibitors, effect of tyramine is exaggerated, leading to severe hypertension (cheese reaction).


Tyramine in gut
Small intestine
MAO-A (80%) and MAO-B
Liver
MAO-A (50%) and MAO-B (50%)
Tyramine
Blood circulation
Endothelial MAO-A
Adrenergic Neuron
Tyrosine
L-DOPA
Noradrenaline
NA
Tyramine uptake
MAO-A
COMT
NA
NA
NA
Noradrenaline uptake

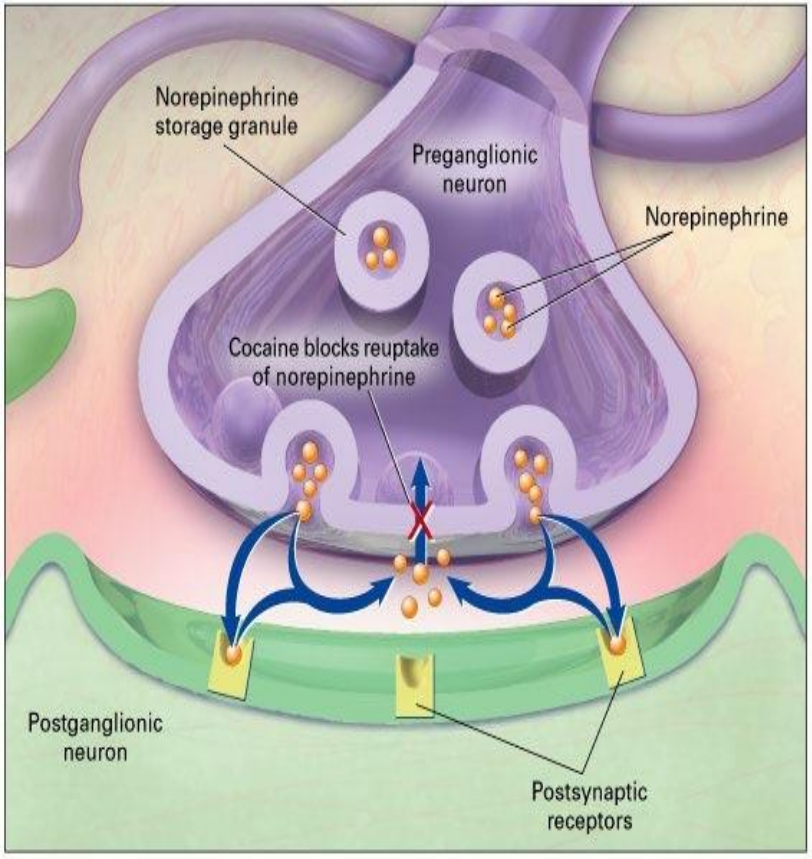
ATOMOXETINE

- It is a selective inhibitor of the norepinephrine reuptake transporter.
- It is used in the treatment of ADHD.



COCAINE

- It is a local anesthetic with a peripheral sympathomimetic action due to inhibition of both:
  i. Neuronal uptake [uptake-1] of catecholamines
  ii. MAO
- It penetrates CNS and produces amphetamine-like psychological effects.



MIXED-ACTING SYMPATHOMIMETIC

Ephedrine

Ephedrine

Pharmacokinetics:

- **As amphetamine**

mechanism of actions .

It is a mixed sympathomimetic. It acts mainly indirectly; its actions are slower in onset and have longer duration.

activates α_1, β_1 and β_2-adrenoceptors

Pharmacological Actions

A- Local actions

1) Produces VC of blood vessels.
2) In the eye, it produces active mydriasis.
3) It is decongestant to nasal mucosa; however, it causes rebound congestion.

B-Systemic actions

1) CNS:

-Stimulates cerebral cortex → insomnia, anxiety, tremors and convulsions.

In contrast, it causes sedation in ADHD

- **Heart:** Stimulates all cardiac properties.
- **Blood vessels**: VC of skin and mucous membrane Bl.Vs.
- **Bronchi:** Bronchodilatation (β_2), and VC of mucous membrane Bl.Vs.

4) GIT and urinary bladder:

- Contraction of sphincters (α_1)
- Relaxation of walls (β_2)

5) Skeletal muscles:

- Stimulant more than epinephrine

Therapeutic uses:

1) Analeptic in toxicity with CNS depressants.
2) Attention-Deficit Hyperkinetic Disorder (ADHD).
3) Nasal decongestant (pseudoephedrine is better).
4) For reversal of hypotension from spinal or epidural anaesthesia (by I.V ephedrine).

Adverse effects:

1) **CNS stimulation:** insomnia, tremors, anxiety, convulsions and vomiting (CTZ).
2) **CVS:** tachycardia, palpitation, angina, arrhythmia, hypertension.
3) **Urine retention** (in old age with senile enlargement of prostate).
4) **Tolerance and tachyphylaxis.**


Thank you!