Sympatholytic & adrenergic blockers
α-receptor Antagonists

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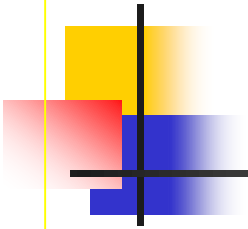
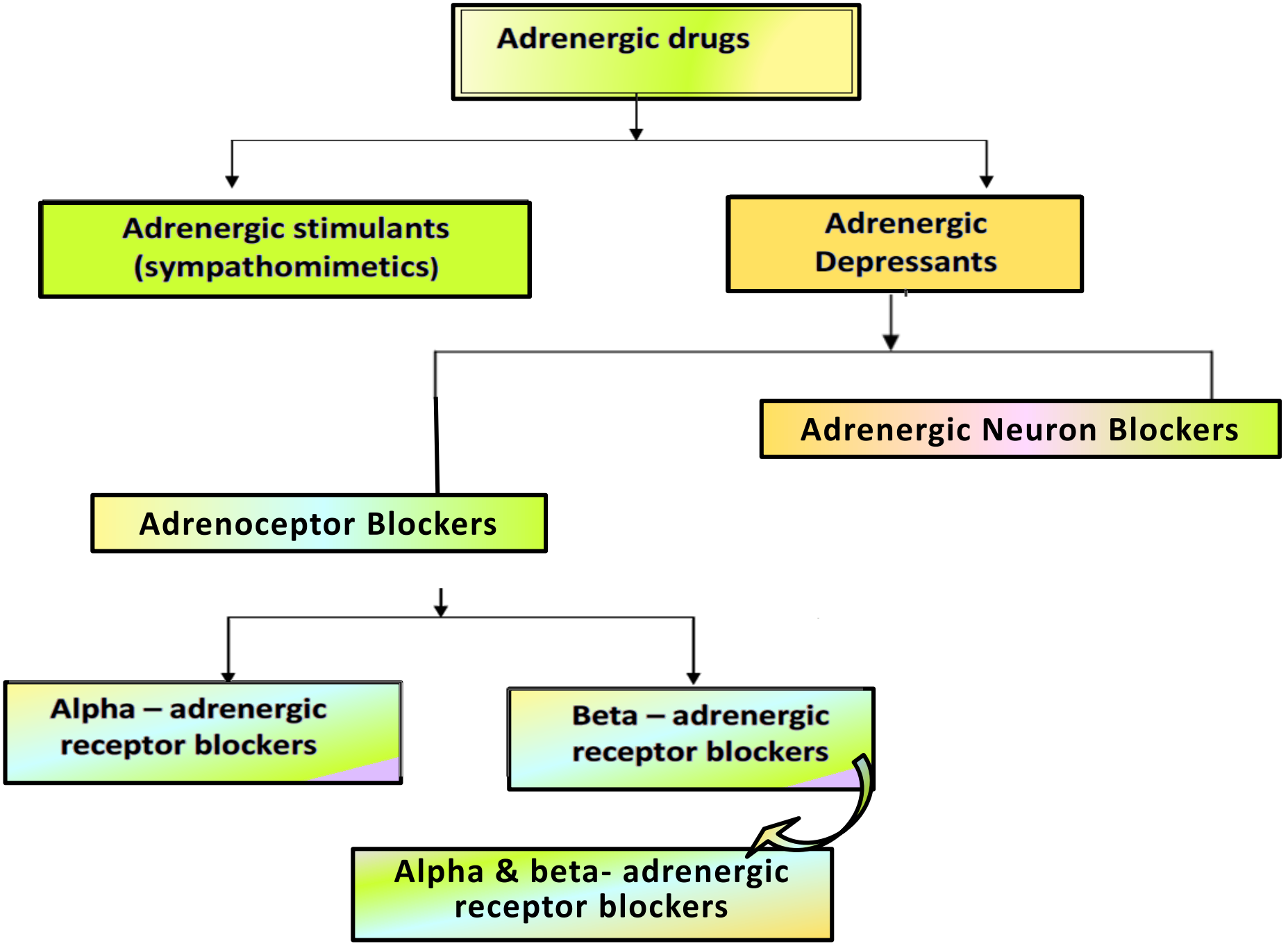
By the end of this lecture, the student should be able to

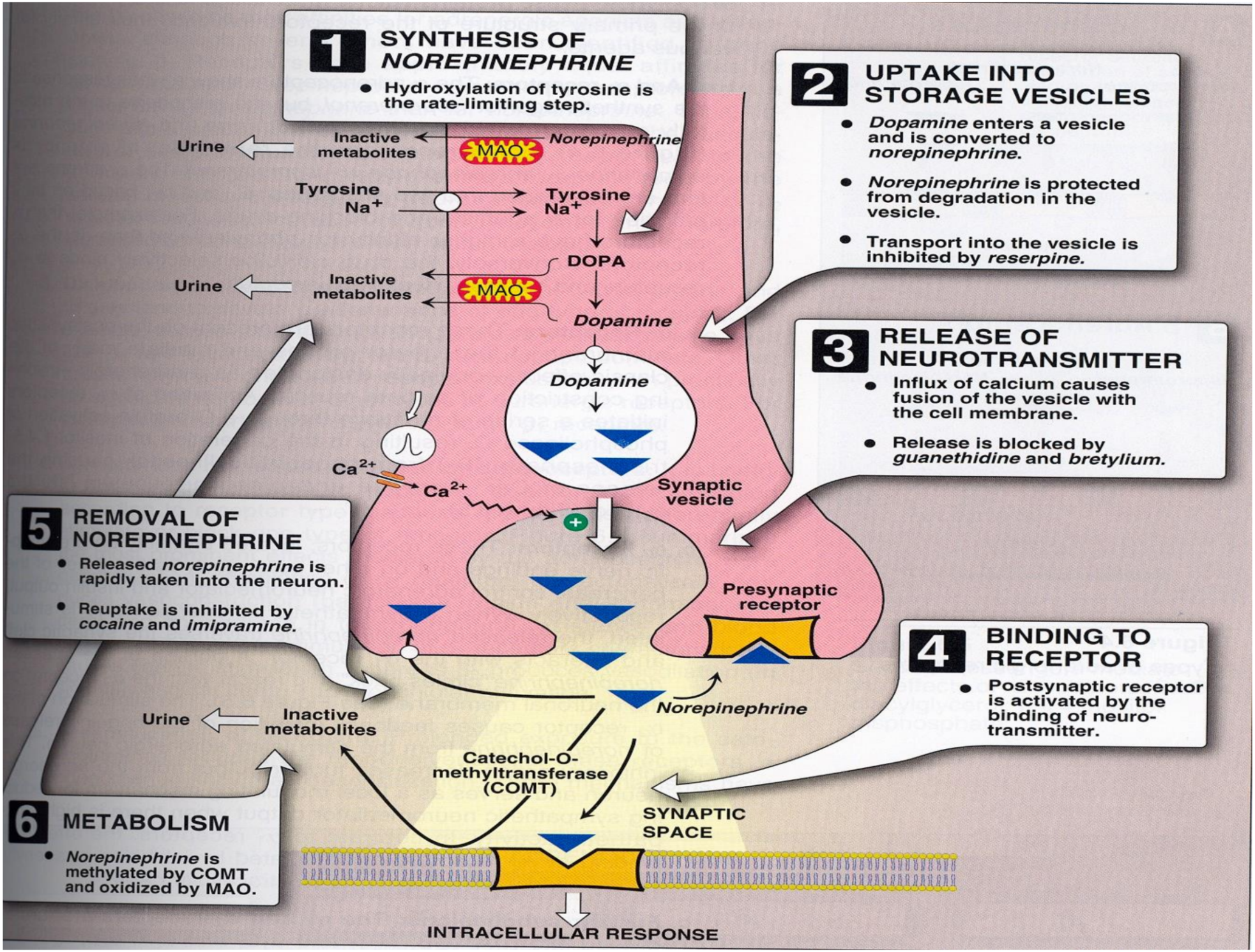


- **Outline the mechanisms of action of adrenergic neuron blockers**
- **Classify α-receptor blockers into selective & non- selective**
- **Know the pharmacokinetic aspects & pharmacodynamic effects of α adrenergic blockers.**
- **Identify the specific uses of non selective and selective α -adrenergic blockers.**


Adrenergic drugs
Adrenergic stimulants (sympathomimetics)
Adrenergic Depressants
Adrenergic Neuron Blockers
Adrenoceptor Blockers
Alpha – adrenergic receptor blockers
Beta – adrenergic receptor blockers
Alpha & beta- adrenergic receptor blockers

Classification of sympatholytics

- *Adrenergic neuron blockers*
- *Adrenergic receptor blockers*


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
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.
Release is blocked by guanethidine and bretylium.
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by cocaine and imipramine.
6 METABOLISM
Norepinephrine is methylated by COMT and oxidized by MAO.
Urine
Inactive metabolites
MAO
Norepinephrine
Tyrosine
Na+
DOPA
Dopamine
Ca2+
Synaptic vesicle
Presynaptic receptor
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE
INTRACELLULAR RESPONSE

Classification of sympatholytics

➢ *Adrenergic neuron blockers*

- **Formation of False Transmitters**

  e.g. α-Methyl dopa

- **Depletion of storage sites**

  e.g. reserpine

- **Inhibition of release & enhance uptake**

  e.g. guanethidine

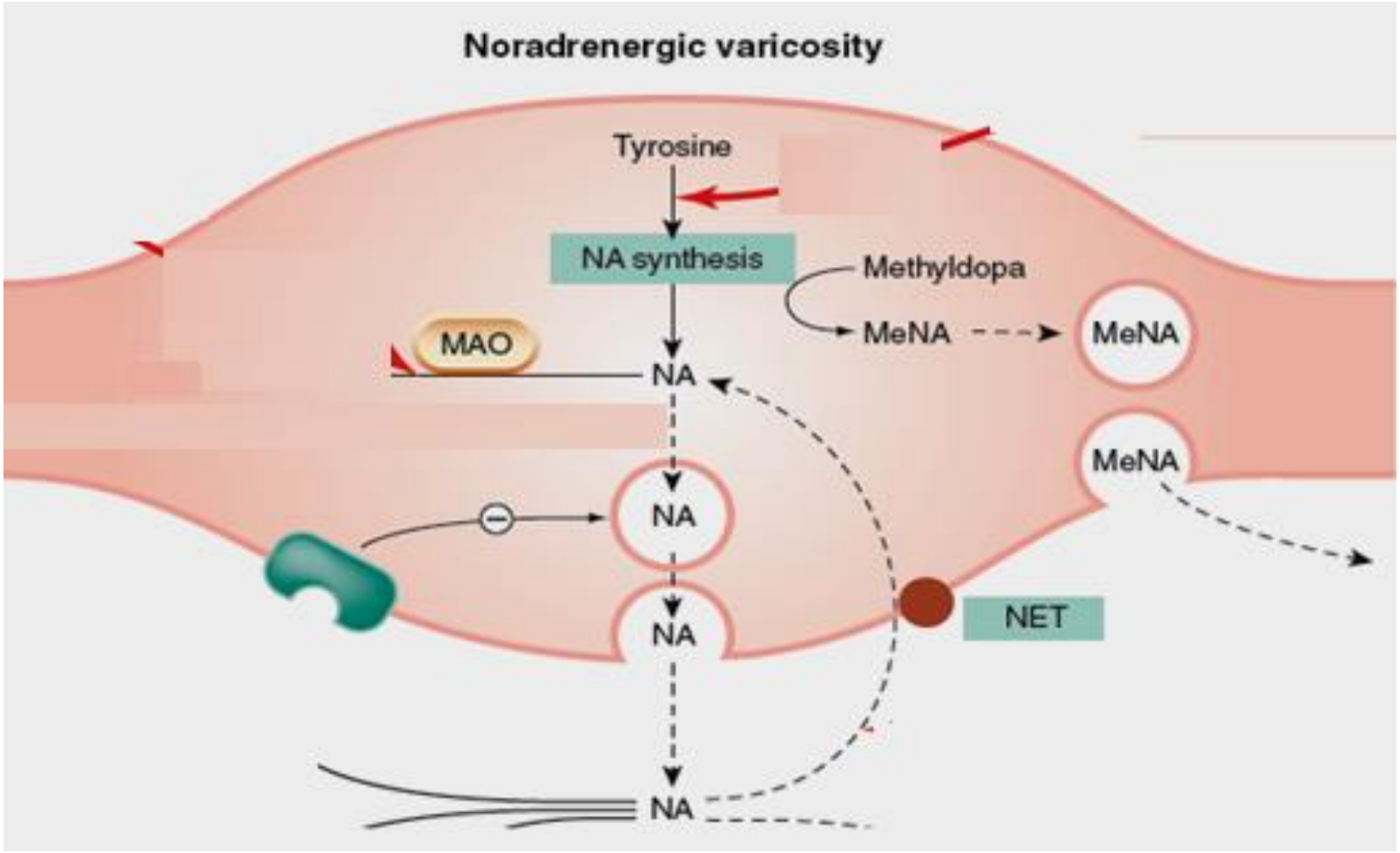
- **Stimulation of presynaptic α_2 receptors**

  e.g. Clonidine and α-Methyl dopa

MECHANISMS OF ADRENERGIC BLOCKERS

Formation of False Transmitters

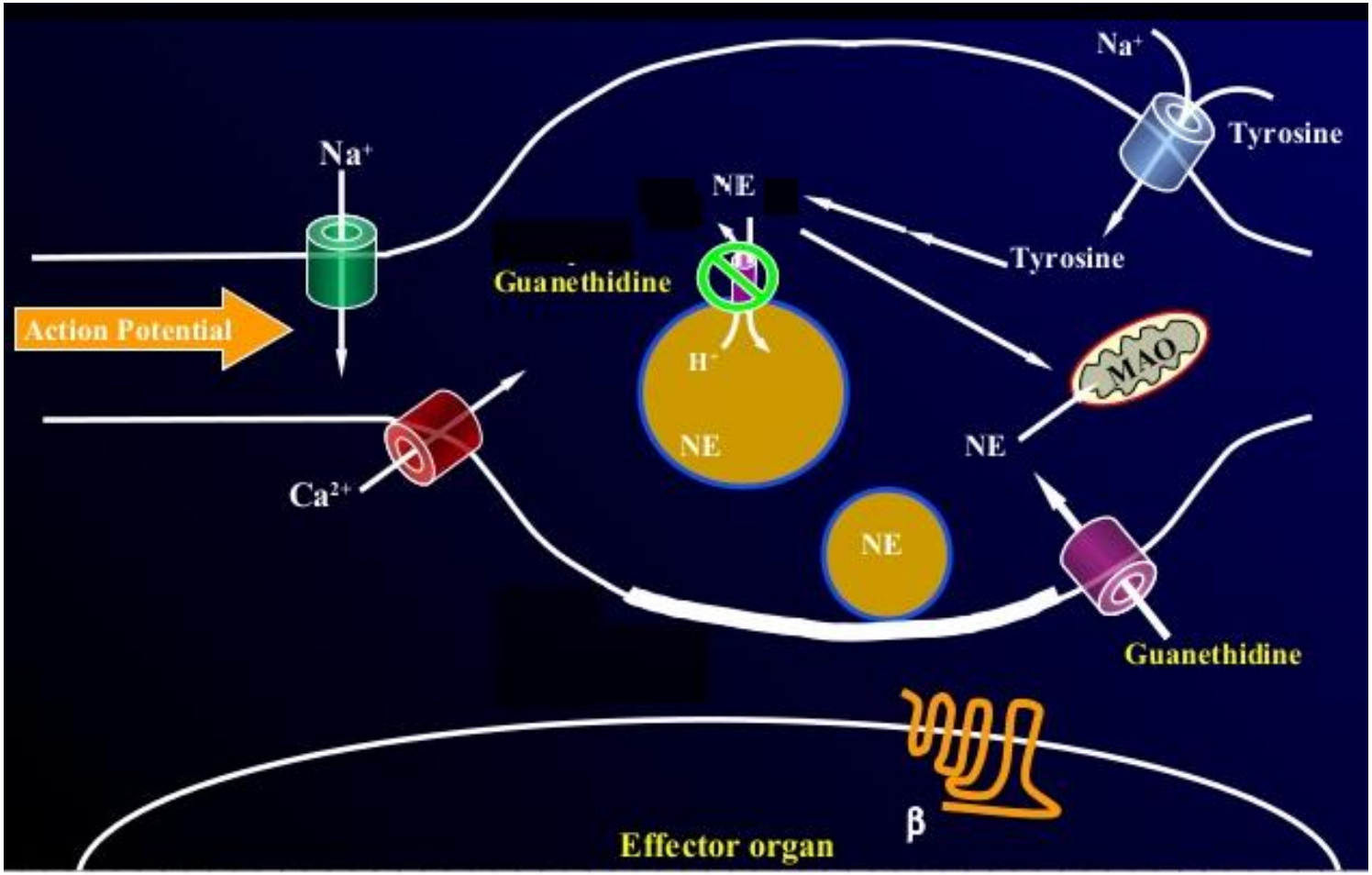
α-Methyl dopa



MECHANISMS OF ADRENERGIC BLOCKERS

- **Inhibition of release and enhance reuptake**

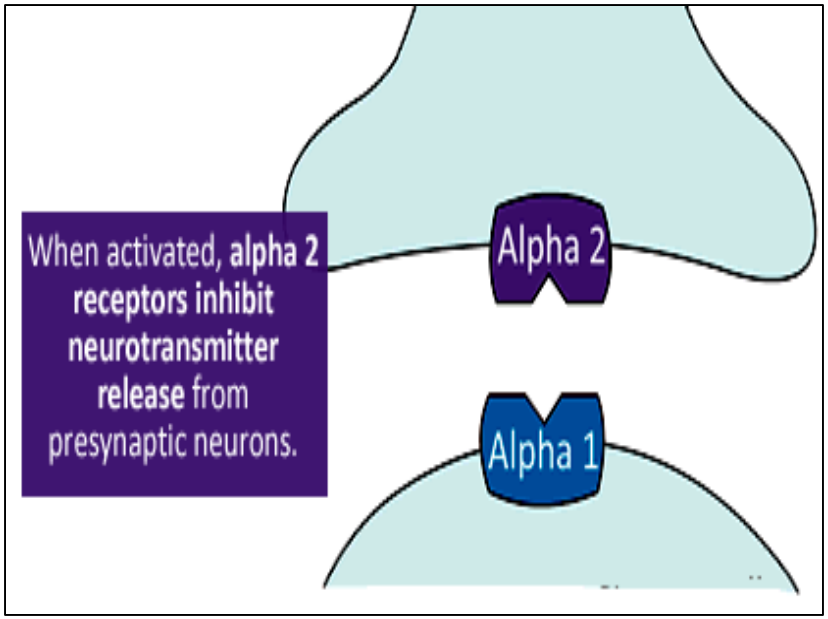
Guanethidine

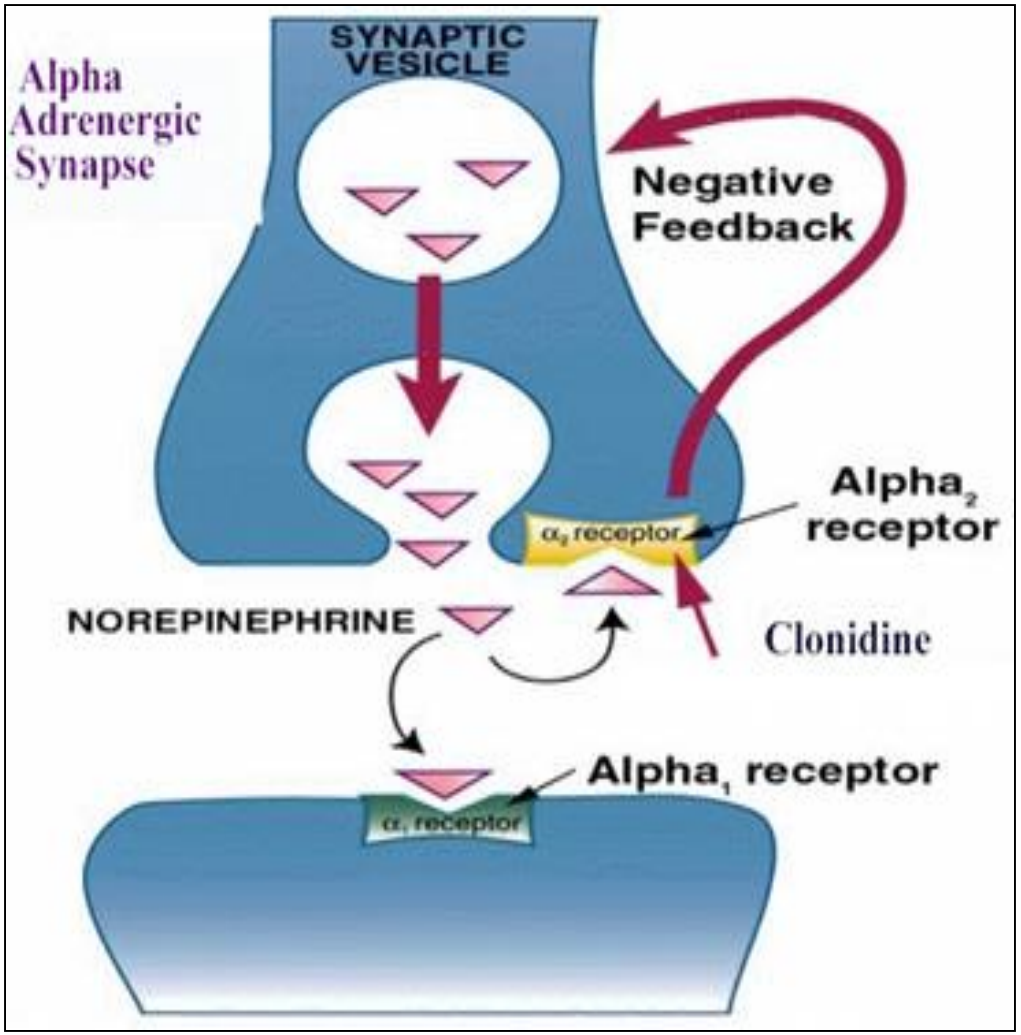


MECHANISMS OF ADRENERGIC BLOCKERS

Stimulation of presynaptic α_2 receptors

Clonidine and α-Methyldopa

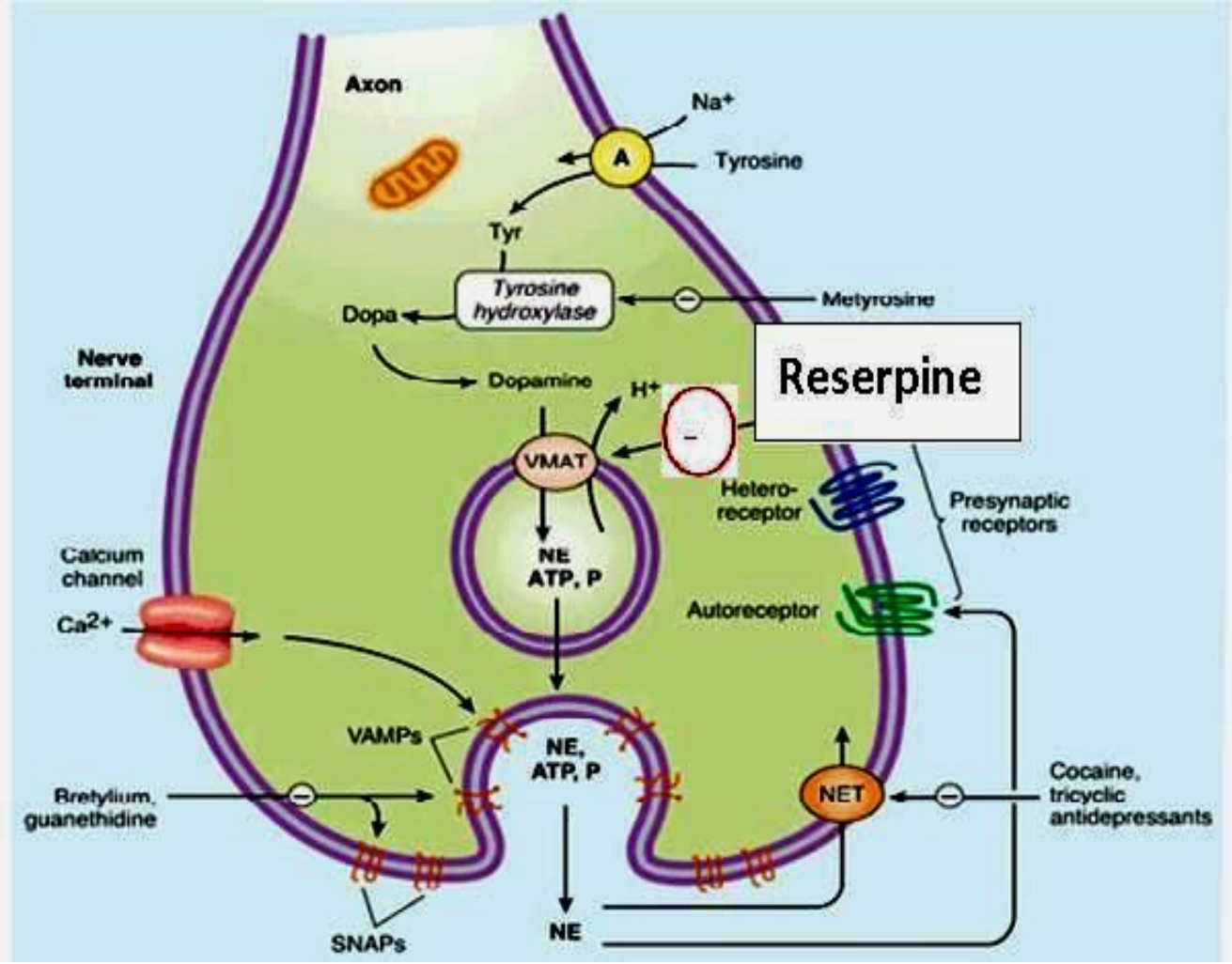




MECHANISMS OF ADRENERGIC BLOCKERS

Interferes with NA storage = Depletion of storage sites

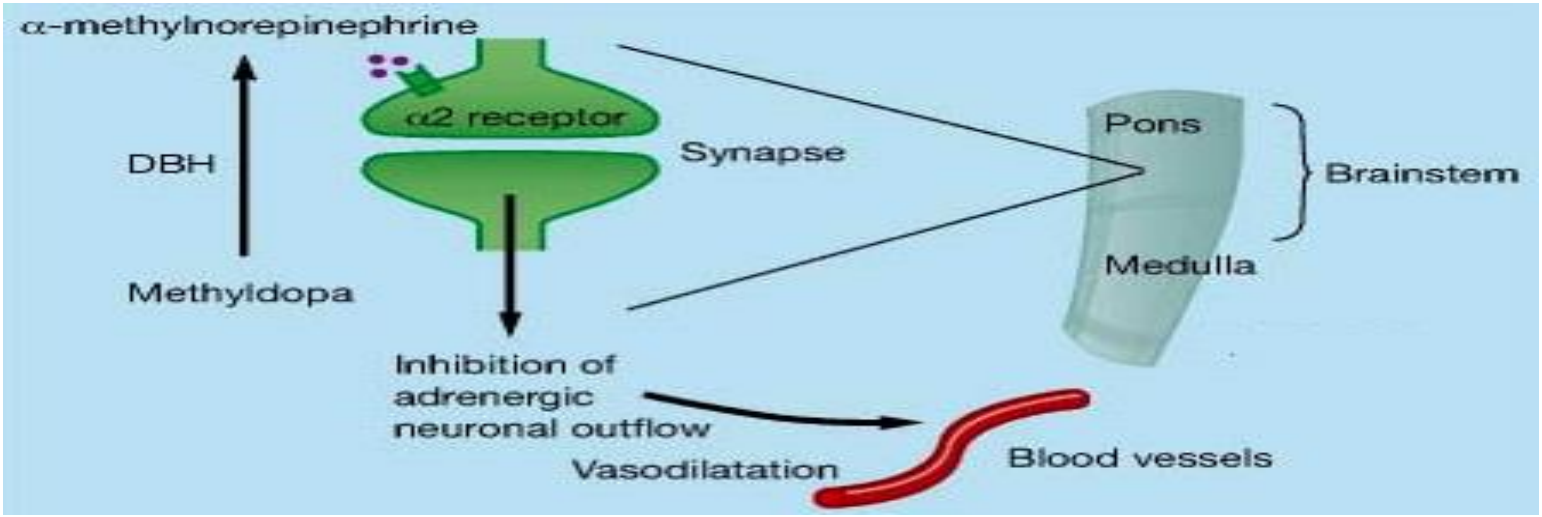
RESERPINE



MECHANISMS OF ADRENERGIC BLOCKERS

α-Methyl dopa

- Forms false transmitter that is released instead of NE
- Acts as central α_2 receptor agonist to inhibit NE release
- Drug of choice in
- Treatment of hypertension in pregnancy (gestational hypertension & pre-eclampsia).



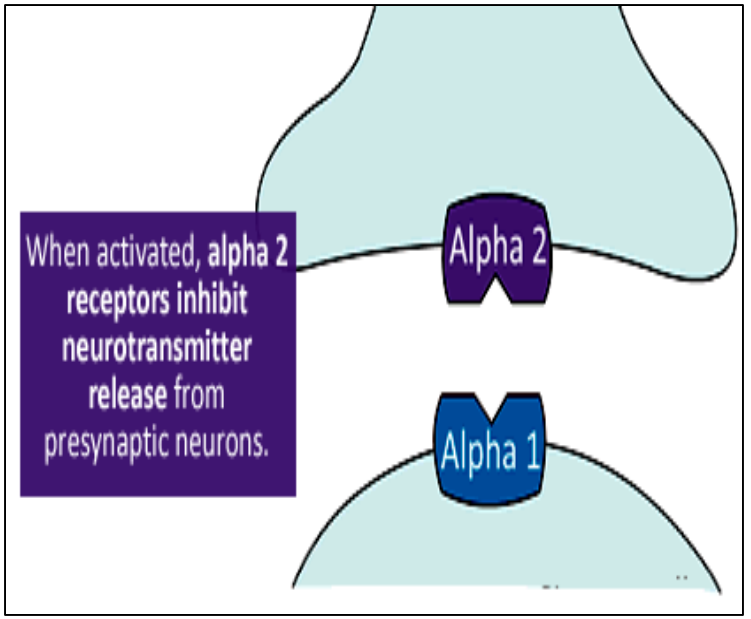
Classification of sympatholytics

Clonidine

- Acts as central α_2 receptor agonist to inhibit NE release
- suppresses sympathetic outflow activity from the brain.
- Little used as antihypertensive agent due to rebound hypertension upon abrupt withdrawal.

Apraclonidine

- is used in open angle glaucoma as eye drops.
- acts by decreasing aqueous humor formation.



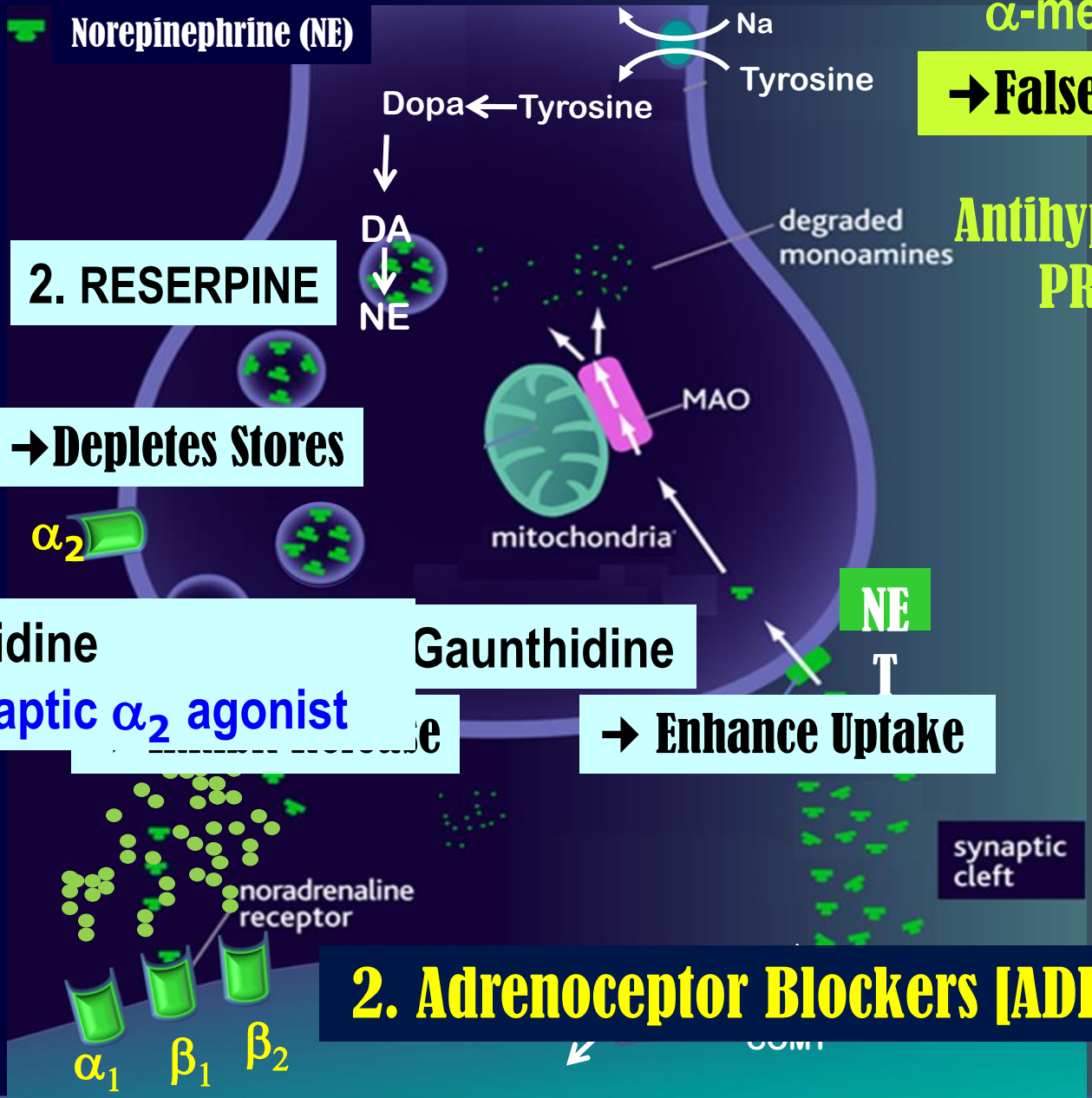
1. Adrenergic Neuron Blockers [SYMPATHOLYTICS]

1. METHYLDOPA

α-methyl tyrosine

→ False Transmitters

→ Antihypertensive in PREGNANCY



2. RESERPINE

→ Depletes Stores

3. Gaunthidine

→ Enhance Uptake

4. Clonidine

Presynaptic α_2 agonist

2. Adrenoceptor Blockers [ADRENOLYTICS]

Adrenergic receptor blockers

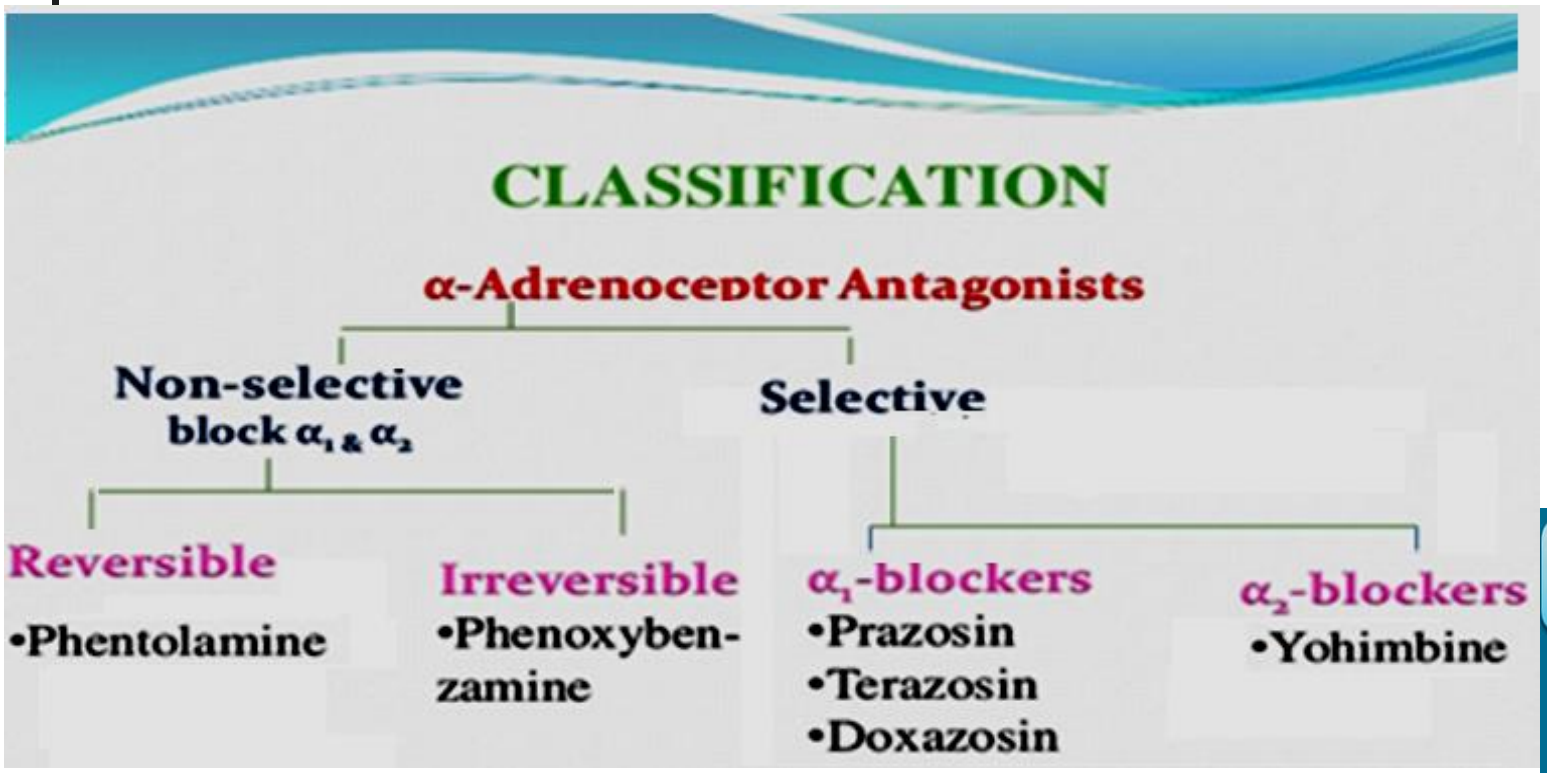
Include

- **α-receptor antagonists**
- **β-receptor antagonists**

Classification of α-receptor Antagonists

- **Non-selective antagonists e.g. phenoxybenzamine & phentolamine.**
- **α_1-selective antagonists e.g. prazosin, doxazosin.**
- **α_{1A}-selective antagonists e.g. Tamsulosin**
- **α_2-selective antagonists e.g. yohimbine**

Classification of α-receptor Antagonists



Non-Selective α- Adrenoceptor Antagonists

Phenoxybenzamine:

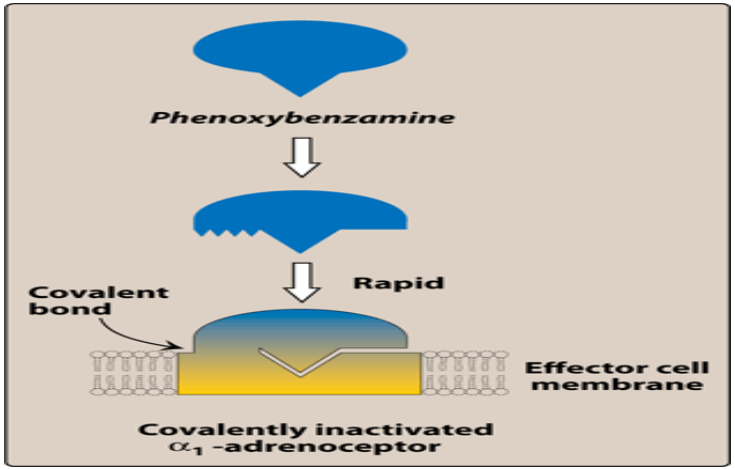
Irreversible block of both α_1 and α_2 receptors

Long-acting (24 hrs)

Phentolamine:

reversible blocking of α_1 & α_2 receptors.

Short acting (4 hrs).



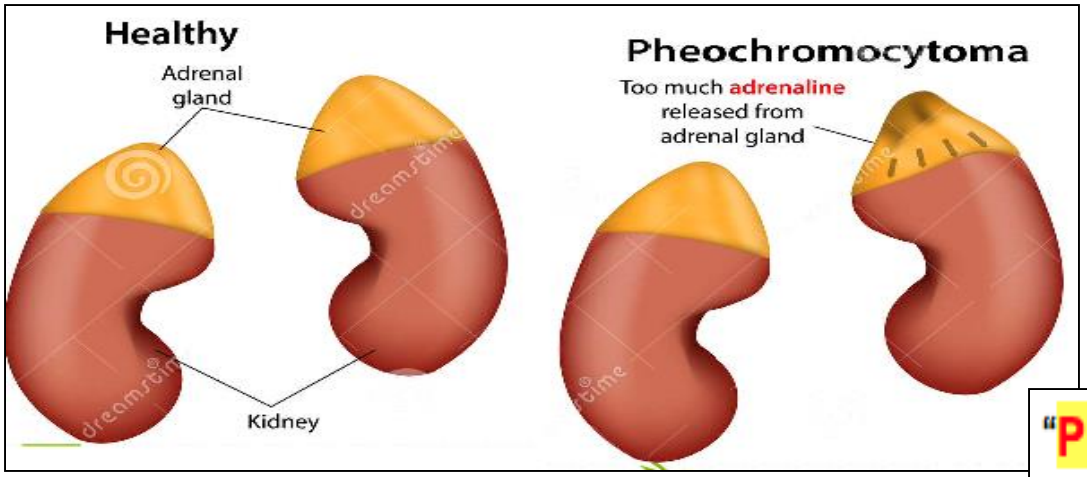
Pharmacological actions

Both drugs cause:

1) **Decrease peripheral vascular resistance**
2) **Postural hypotension.**
3) **Reflex tachycardia.**
4) **Reflex tachycardia due to the fall in B.P, mediated by baroreceptor reflex and due to block α_2 in heart.**

Therapeutic Uses:

Pheochromocytoma: Should be given before surgical removal to protect against hypertensive crisis.



"PHEochromocytoma"

- Palpitations
- Headache
- Episodic sweating (diaphoresis)

Contraindicated:

Both drugs can precipitate arrhythmias and angina and are contra-indicated in patients with decreased coronary perfusion.

Adverse Effects of non-Selective α- Adrenoceptor Antagonists :

- **Postural hypotension**
- **Tachycardia**
- **Headache**
- **Nasal stuffiness or congestion**
- **Vertigo & drowsiness**
- **Male sexual dysfunction (inhibits ejaculation).**

Selective α1- Antagonists

Prazosin, Doxazosin, Terazosin

Prazosin (short half-life)

Doxazosin, terazosin (long half life)

Selective α1- Antagonists

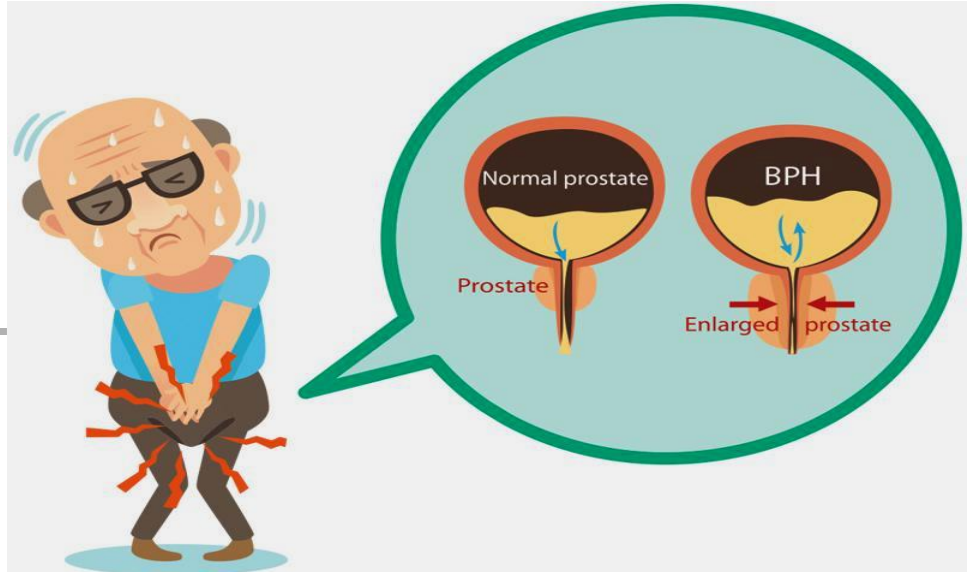
Pharmacological effects of α_1–antagonists:

- **Vasodilatation due to relaxation of arterial and venous smooth muscles**
- **Fall in arterial pressure**
- **less reflex tachycardia than with non-selective α blockers**

Selective α1- Antagonists

First dose of α_1 receptor blocker may produce an orthostatic hypotensive response that can result in syncope (fainting).

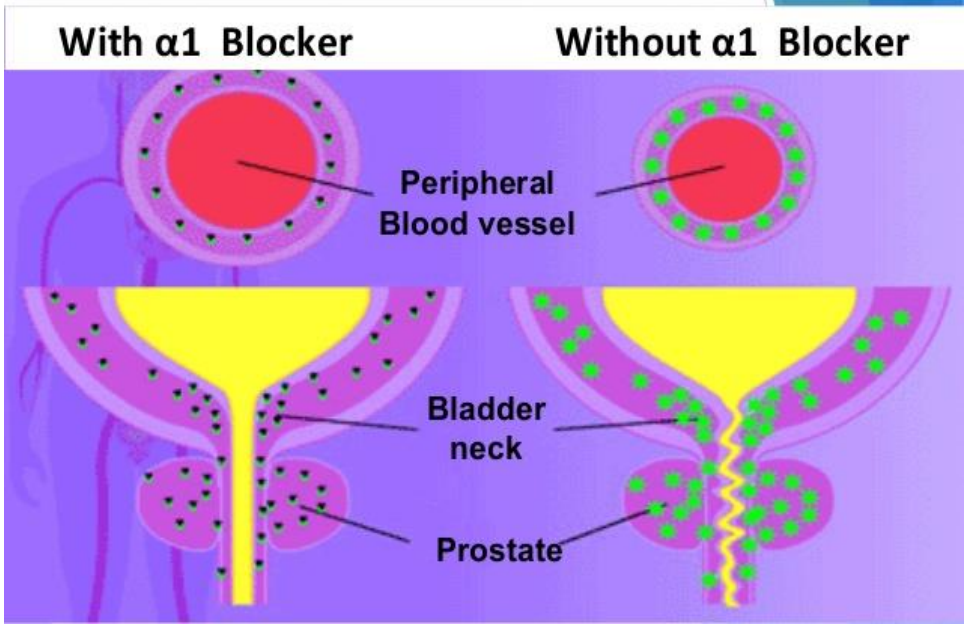
Therapeutic Uses:



- **Urinary obstruction of benign prostatic hypertrophy (BPH).**

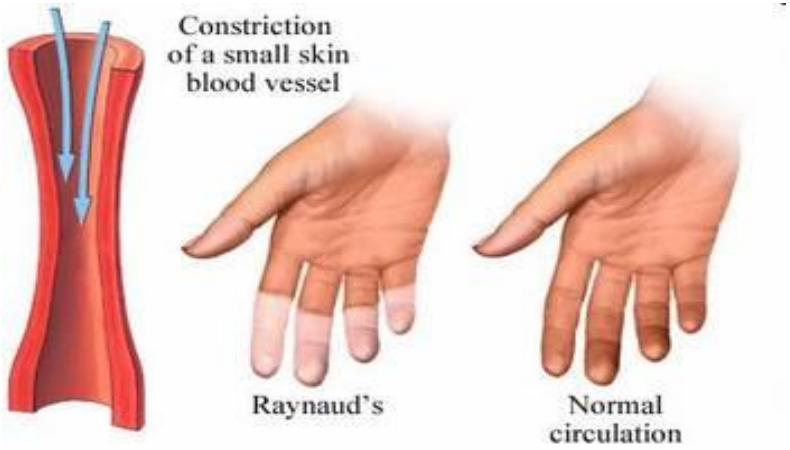
- **Treatment of essential hypertension with prostate enlargement.**

PRAZOSIN



Therapeutic Uses:

- **Reynaud's disease (vasospasm): causes fingers and toes to feel numb and cold in response to cold temperature.**



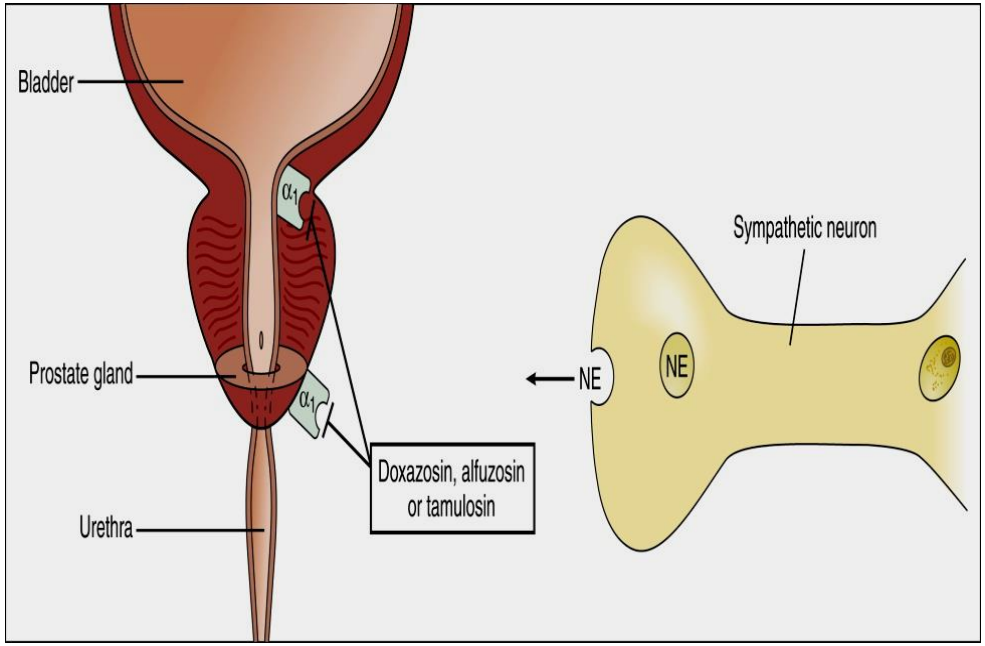
Selective α_{1A}–antagonists
Tamsulosin

- **Is a selective α_{1A} antagonist (Uroselective).**
- **α_{1A} receptors present in prostate**
- **Causes relaxation of smooth muscles of bladder neck & prostate →improve urine flow.**
- **Has minimal effect on blood pressure.**
- **Is used in the treatment of benign prostatic hypertrophy (BPH).**

Selective α_{1A} antagonist Tamsulosin

Tamsulosin

Relaxation of bladder neck can improve urine flow



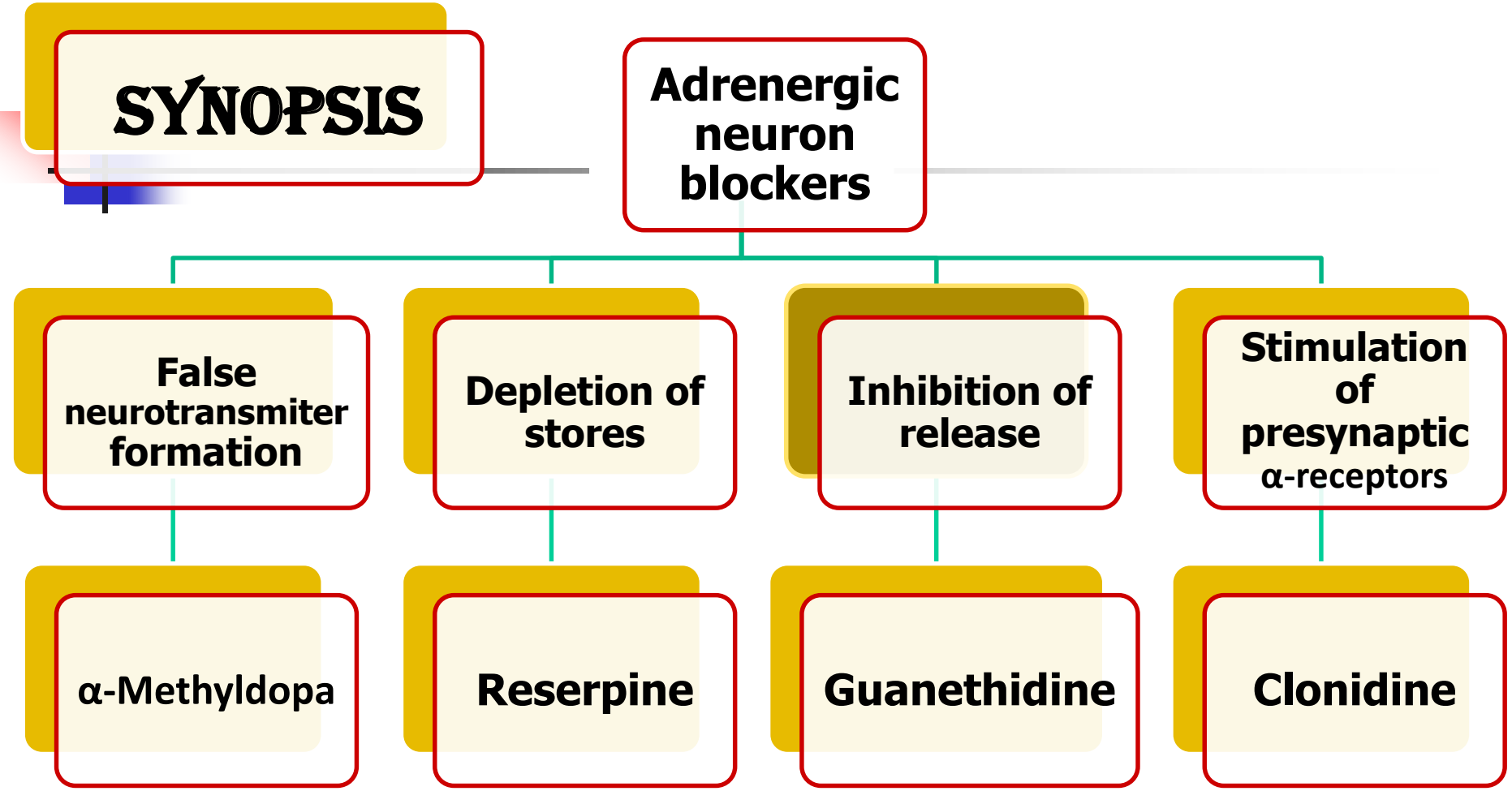
Adverse effects of α1A- Antagonists

as before with non selective but to a lesser degree

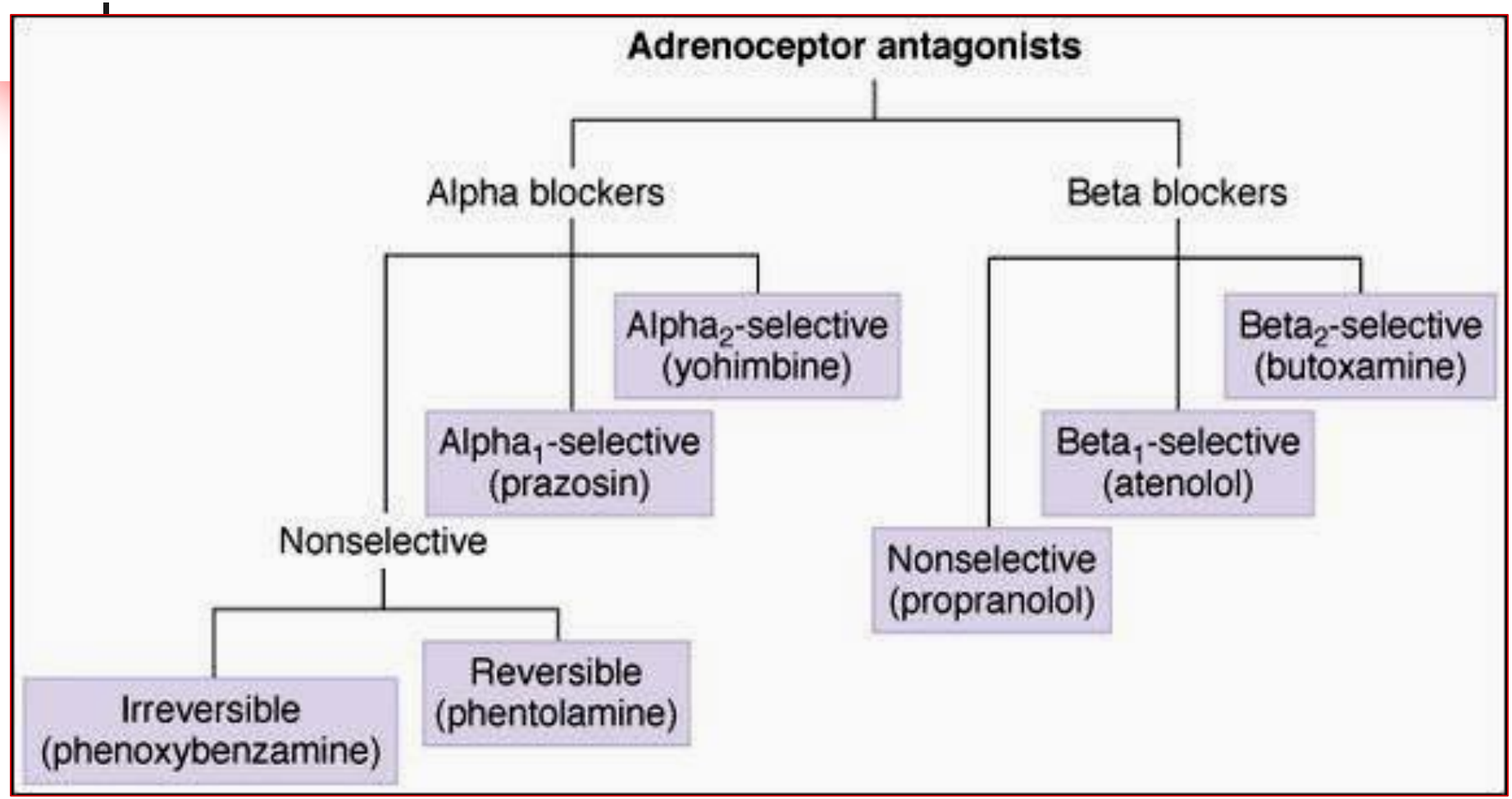
α_2-selective antagonists

- **e.g. yohimbine**
- **Increase nitric oxide released in the corpus cavernosum thus producing vasodilator action and contributing to the erectile process.**
- **Used as aphrodisiac in the treatment of erectile dysfunction.**

SYNOPSIS


Adrenergic neuron blockers
False neurotransmiter formation
Depletion of stores
Inhibition of release
Stimulation of presynaptic α-receptors
α-Methyldopa
Reserpine
Guanethidine
Clonidine

SUMMARY


Adrenoceptor antagonists
Alpha blockers
Beta blockers
Alpha2-selective (yohimbine)
Alpha1-selective (prazosin)
Nonselective
Irreversible (phenoxybenzamine)
Reversible (phentolamine)
Beta2-selective (butoxamine)
Beta1-selective (atenolol)
Nonselective (propranolol)