

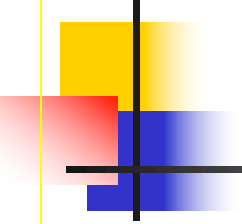


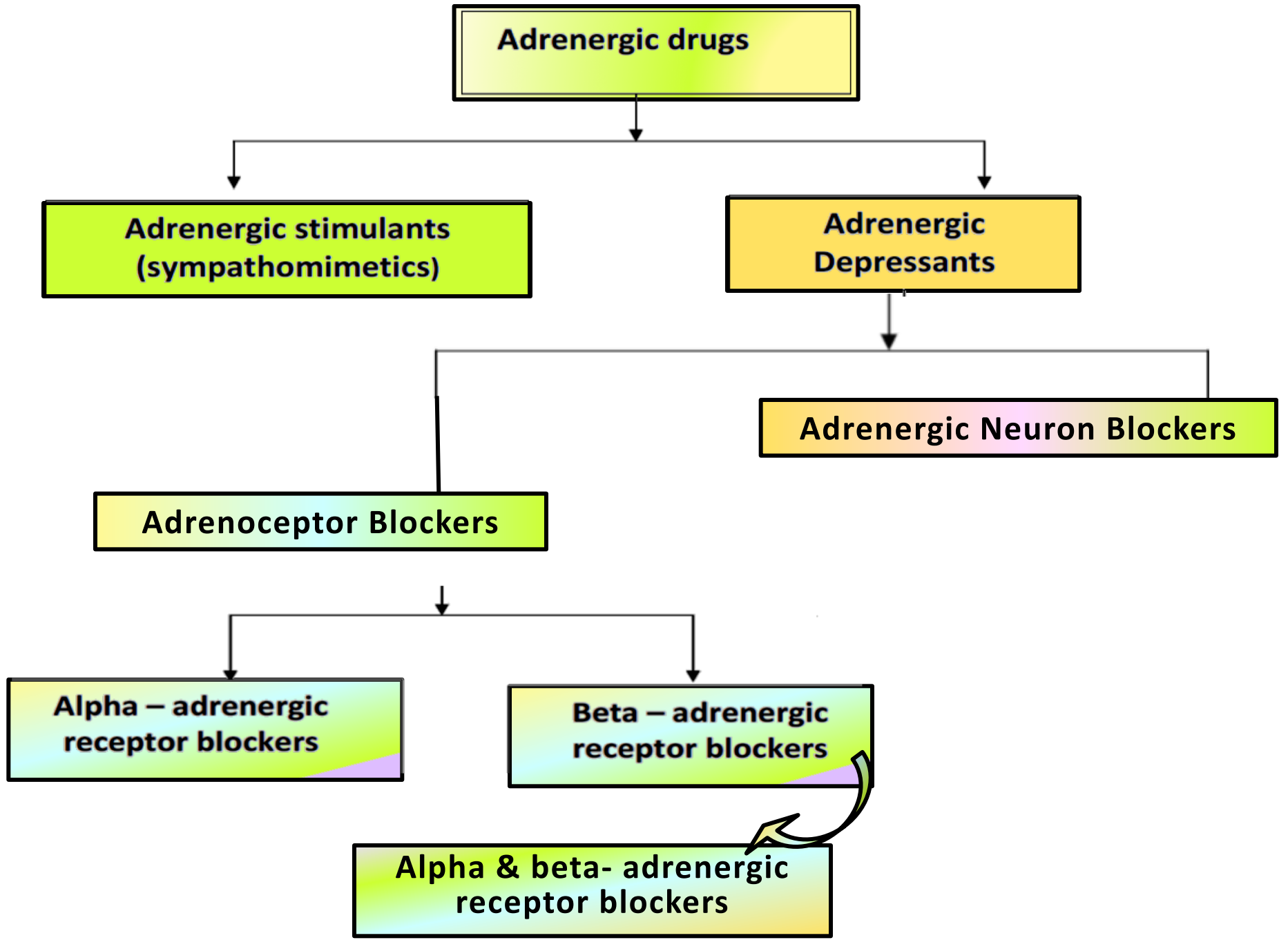
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*Sympatholytic & adrenergic blockers*  
 *$\alpha$ -receptor Antagonists*

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Pharmacology Unit  
College of Medicine

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

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

# 4 BINDING TO RECEPTOR

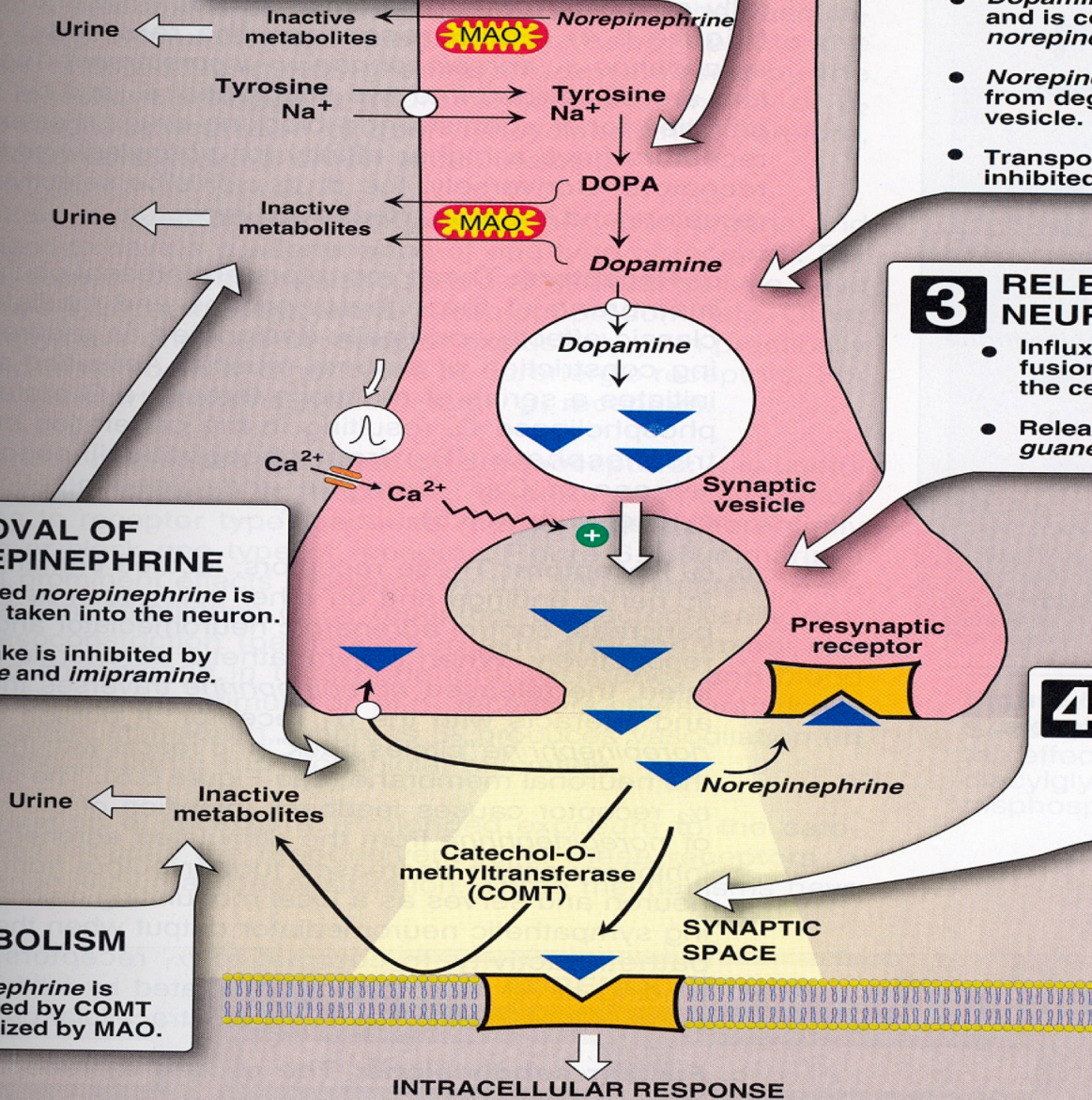
- Postsynaptic receptor is activated by the binding of neurotransmitter.

# 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.



# *Classification of sympatholytics*

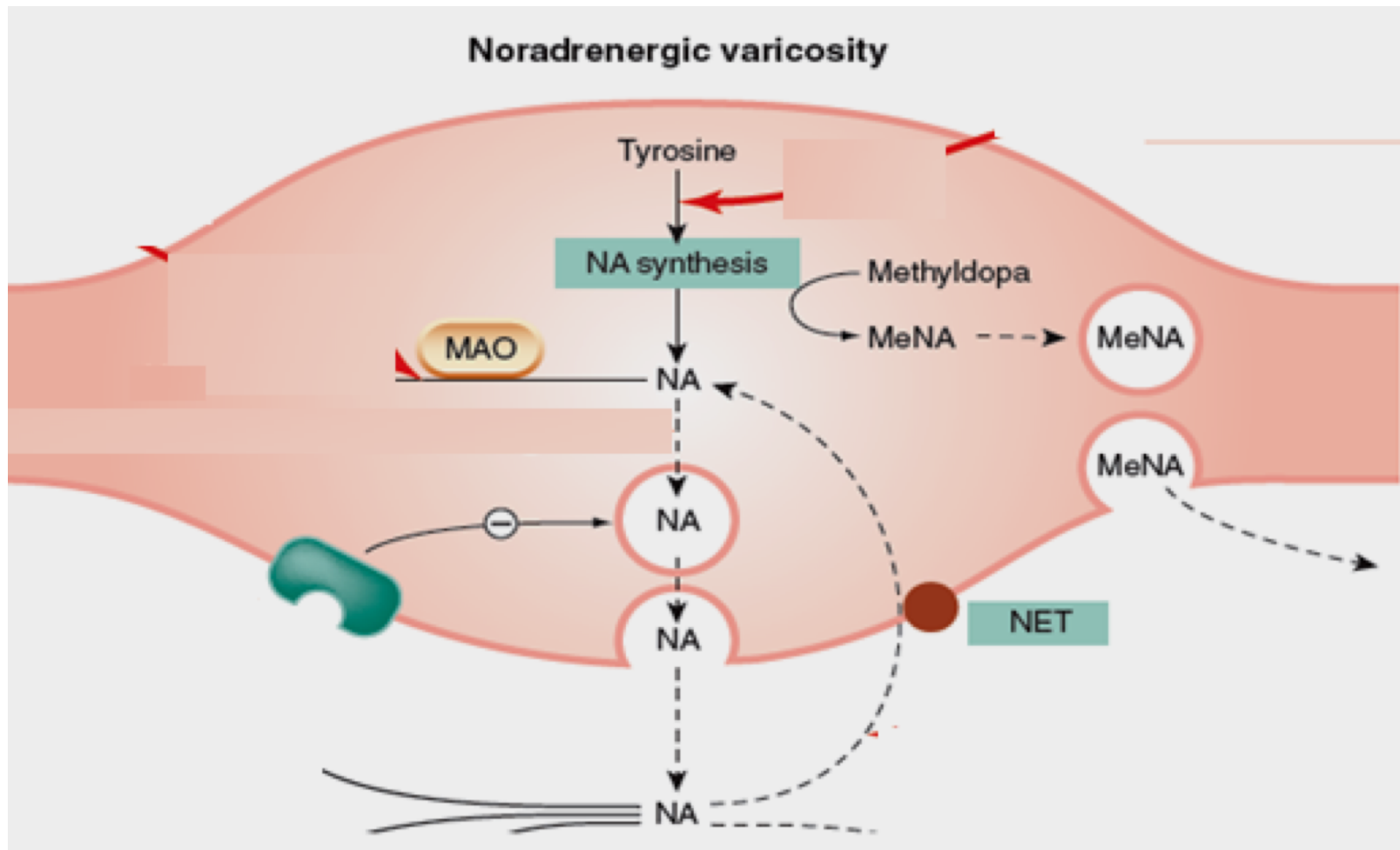
## ➤ *Adrenergic neuron blockers*

- **Formation of False Transmitters**  
**e.g.  $\alpha$ -Methyl dopa**
- **Depletion of storage sites**  
**e.g. reserpine**
- **Inhibition of release & enhance uptake**  
**e.g. guanethidine**
- **Stimulation of presynaptic  $\alpha_2$  receptors**  
**e.g. Clonidine and  $\alpha$ -Methyl dopa**

# MECHANISMS OF ADRENERGIC BLOCKERS

## Formation of False Transmitters

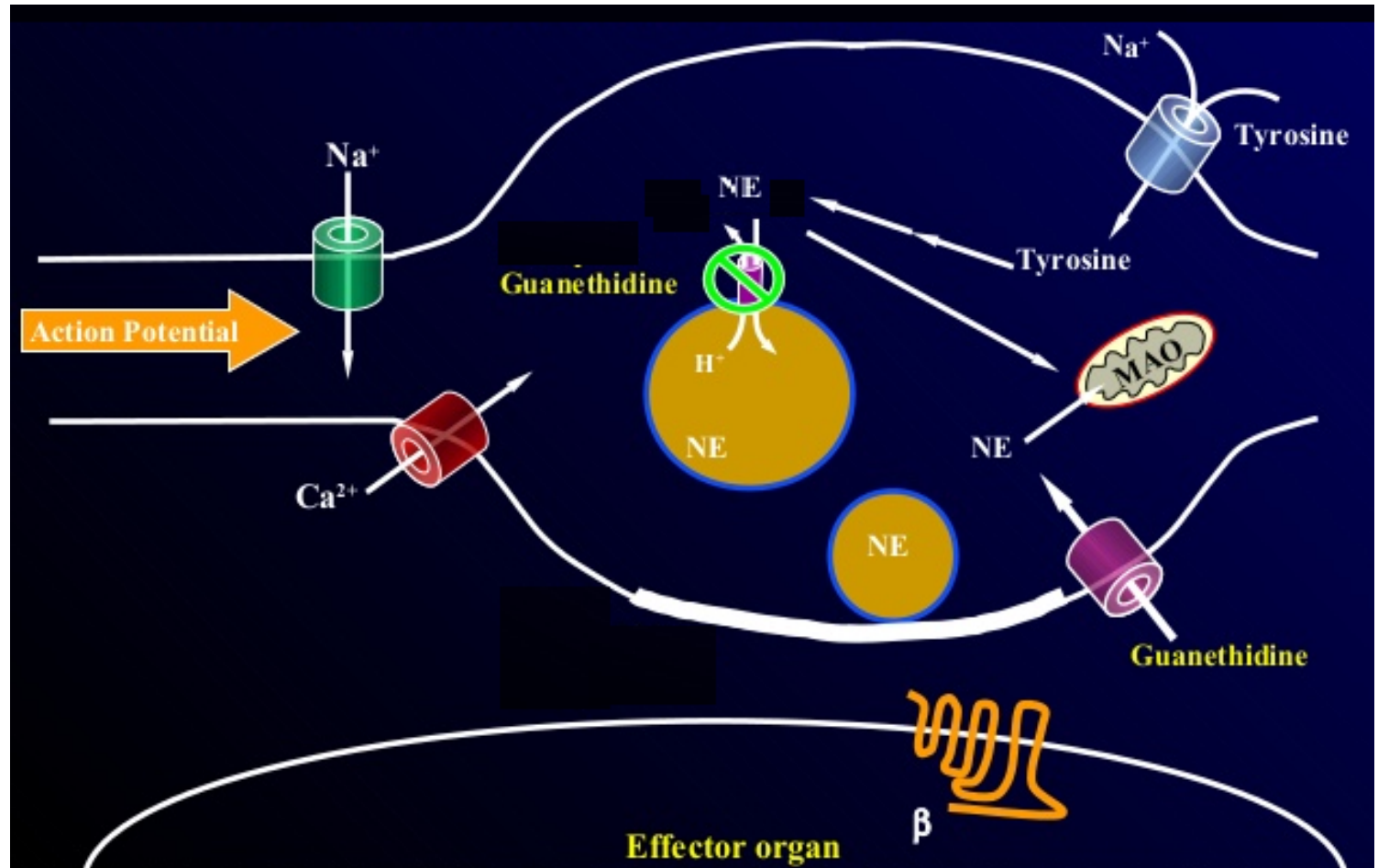
## $\alpha$ -Methyl dopa



# MECHANISMS OF ADRENERGIC BLOCKERS

- Inhibition of release and enhance reuptake

## Guanethidine



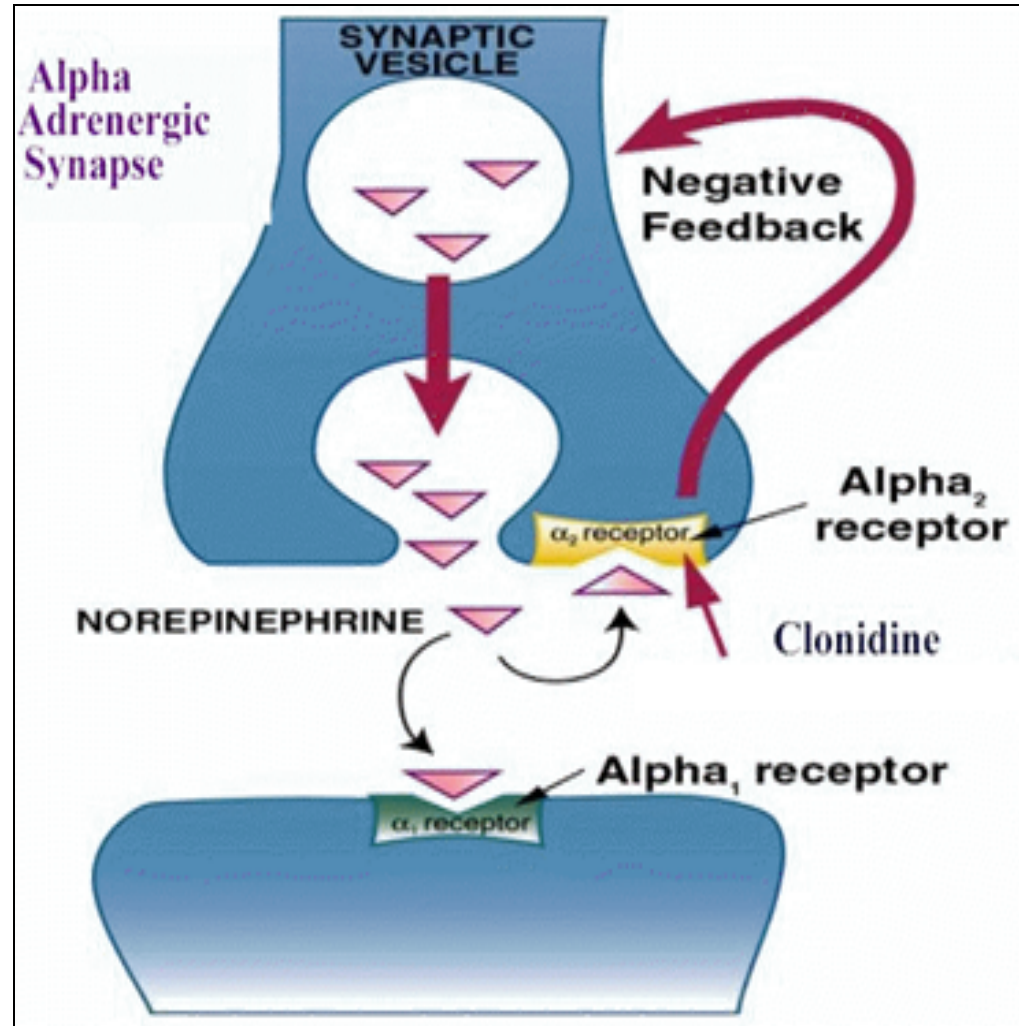
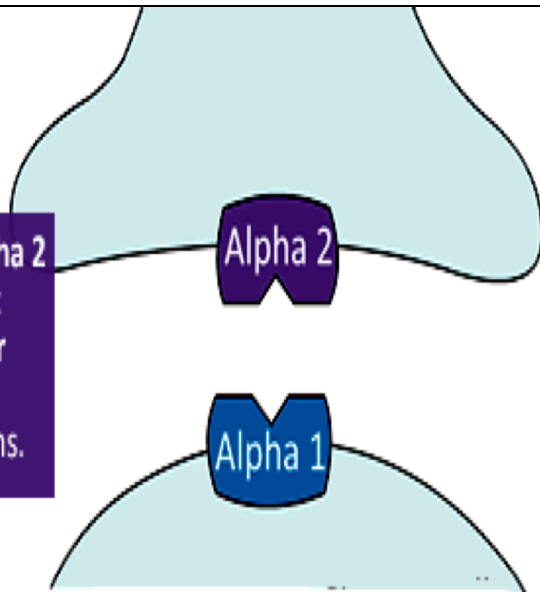


# MECHANISMS OF ADRENERGIC BLOCKERS

## Stimulation of presynaptic $\alpha_2$ receptors

Clonidine and  
 $\alpha$ -Methyldopa

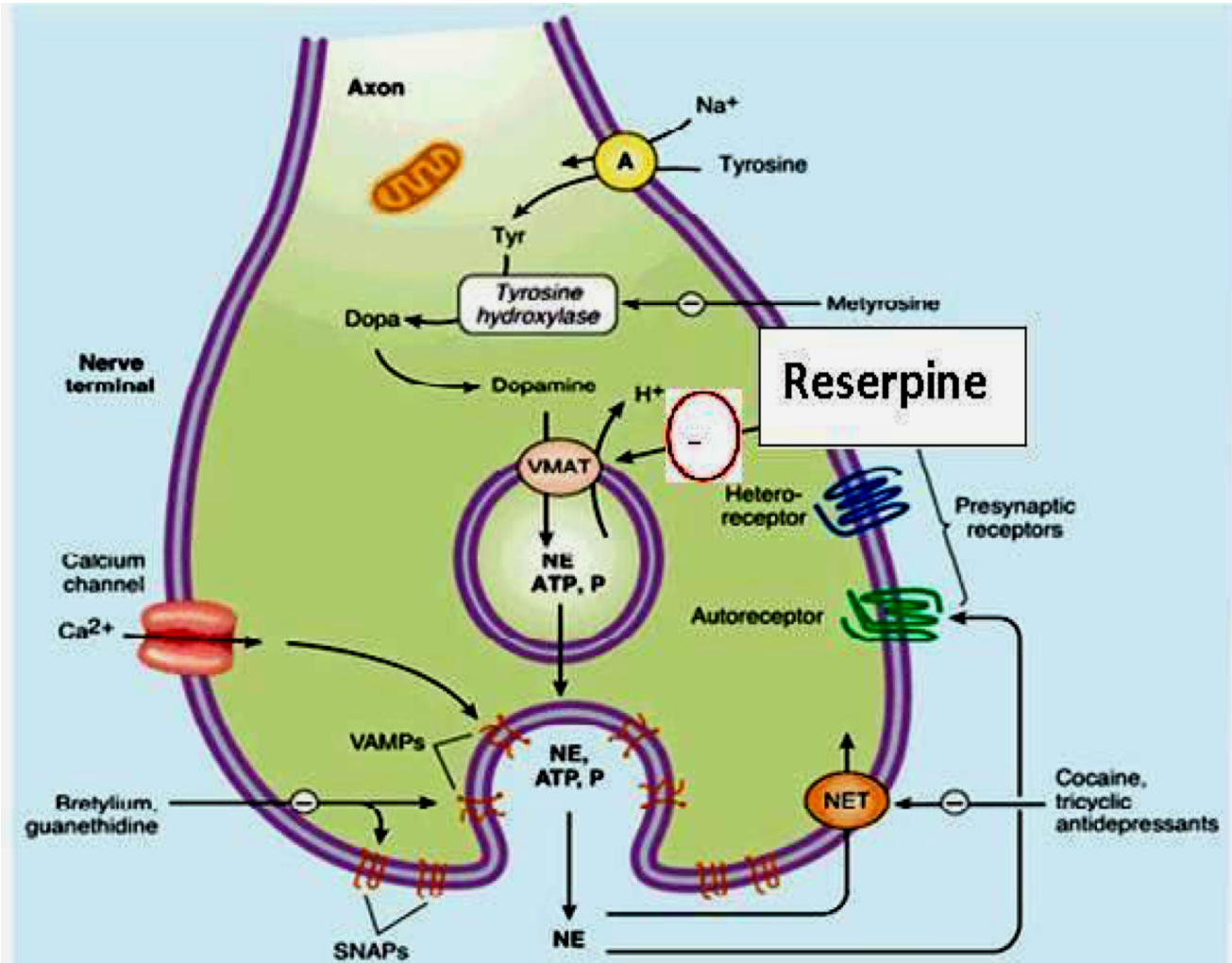
When activated, alpha 2 receptors inhibit neurotransmitter release from presynaptic neurons.



# MECHANISMS OF ADRENERGIC BLOCKERS

Interferes with NA storage = Depletion of storage sites

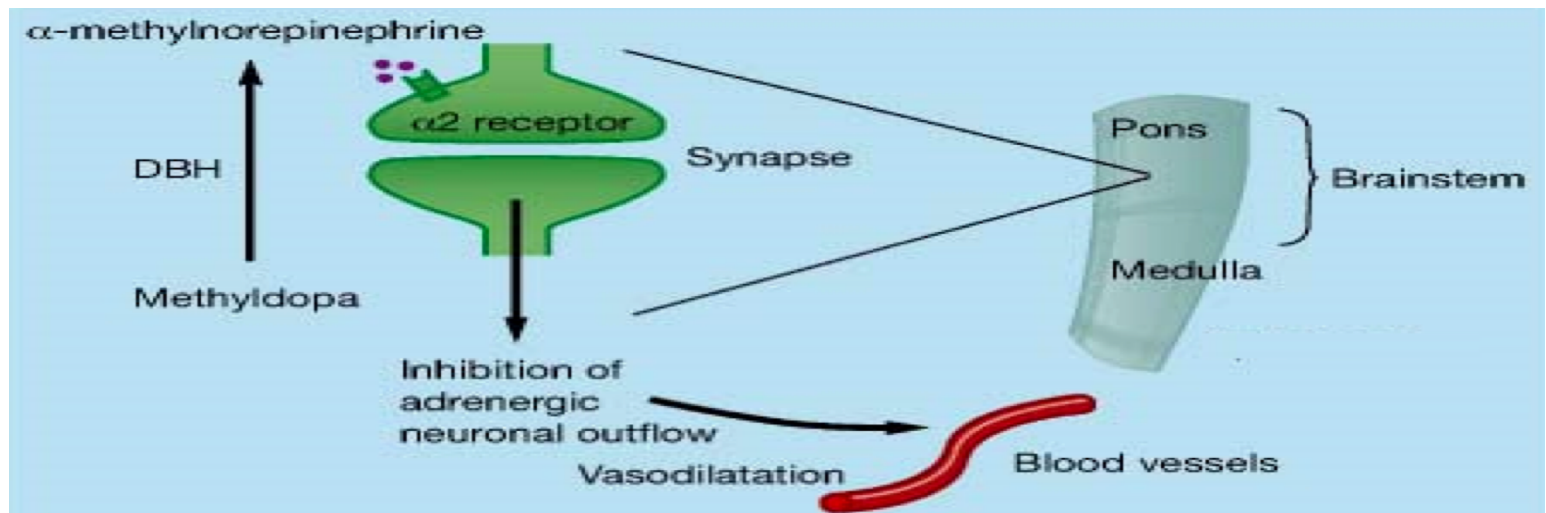
## RESERPINE



# *Adrenergic neuron blockers*

## **$\alpha$ -Methyl dopa**

- Forms false transmitter that is released instead of NE
- Acts as **central**  $\alpha_2$  receptor **agonist** to inhibit NE release
- Drug of choice in
- Treatment of hypertension in pregnancy ( gestational hypertension & pre-eclampsia ).



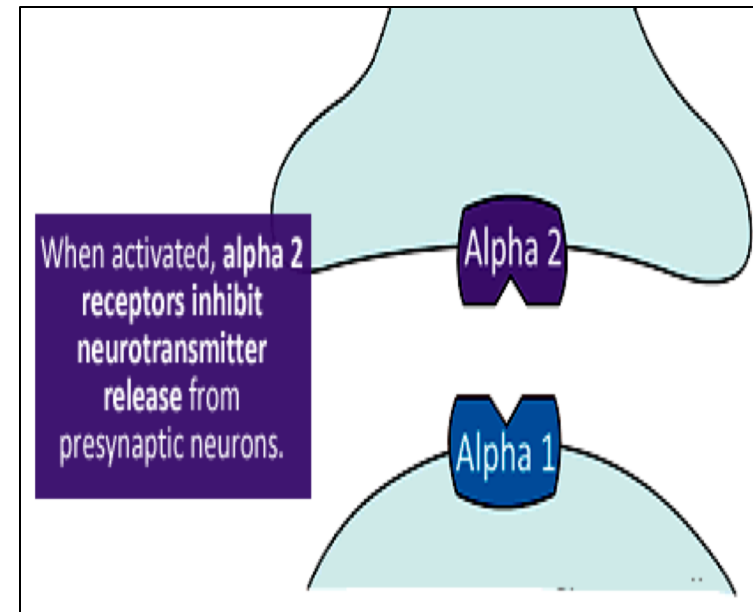
# *Classification of sympatholytics*

## Clonidine

- Acts as **central**  $\alpha_2$  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.



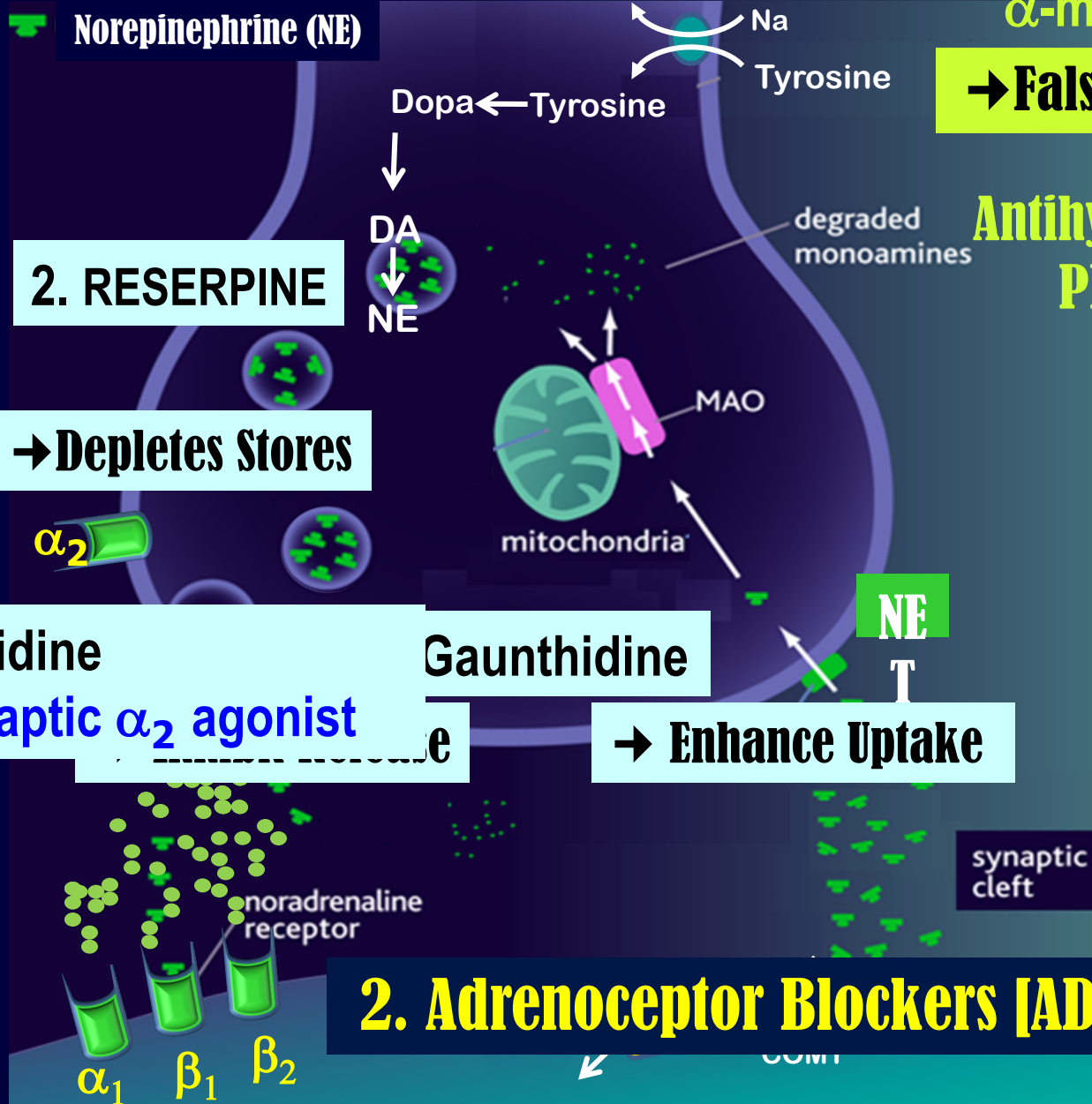
# 1. Adrenergic Neuron Blockers [SYMPATHOLYTICS]

## 1. METHYLDOPA

$\alpha$ -methyl tyrosine

→ False Transmitters

Antihypertensive in PREGNANCY



## 2. RESERPINE

→ Depletes Stores

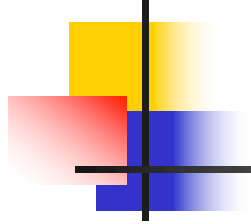
4. Clonidine  
Presynaptic  $\alpha_2$  agonist

Gaunthidine

→ Enhance Uptake

# 2. Adrenoceptor Blockers [ADRENOLYTICS]

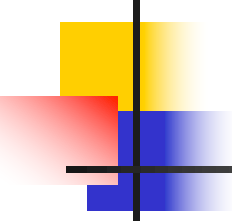
# *Adrenergic receptor blockers*



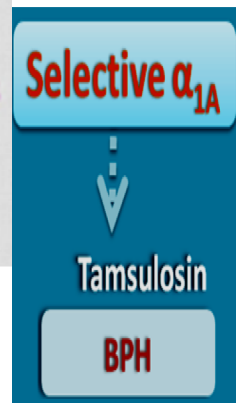
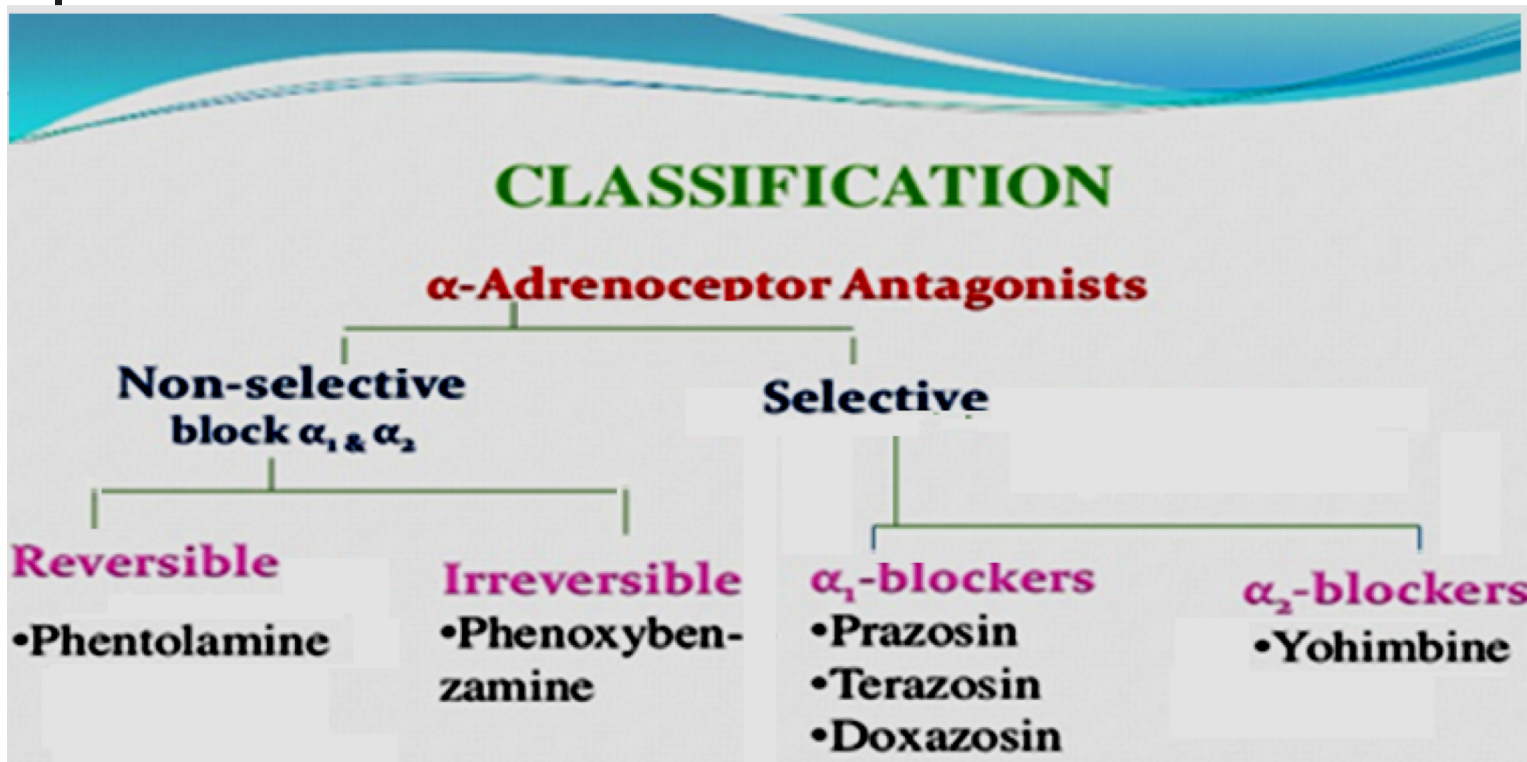
## **Include**

- **$\alpha$ -receptor antagonists**
- **$\beta$ -receptor antagonists**

## *Classification of $\alpha$ -receptor Antagonists*

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- 
- **Non-selective antagonists** e.g. phenoxybenzamine & phentolamine.
  - **$\alpha_1$ -selective antagonists** e.g. prazosin, doxazosin.
  - **$\alpha_{1A}$ -selective antagonists** e.g. Tamsulosin
  - **$\alpha_2$ -selective antagonists** e.g. yohimbine

# Classification of $\alpha$ -receptor Antagonists





# *Non-Selective $\alpha$ -Adrenoceptor Antagonists*

## Phenoxybenzamine:

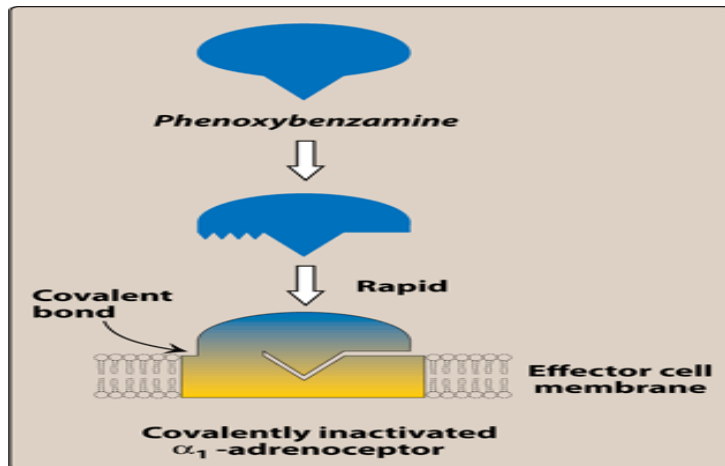
**Irreversible** block of both  $\alpha_1$  and  $\alpha_2$  receptors

**Long-acting (24 hrs)**

## Phentolamine:

**reversible** blocking of  $\alpha_1$  &  $\alpha_2$  receptors.

**Short acting (4 hrs).**



# Pharmacological actions



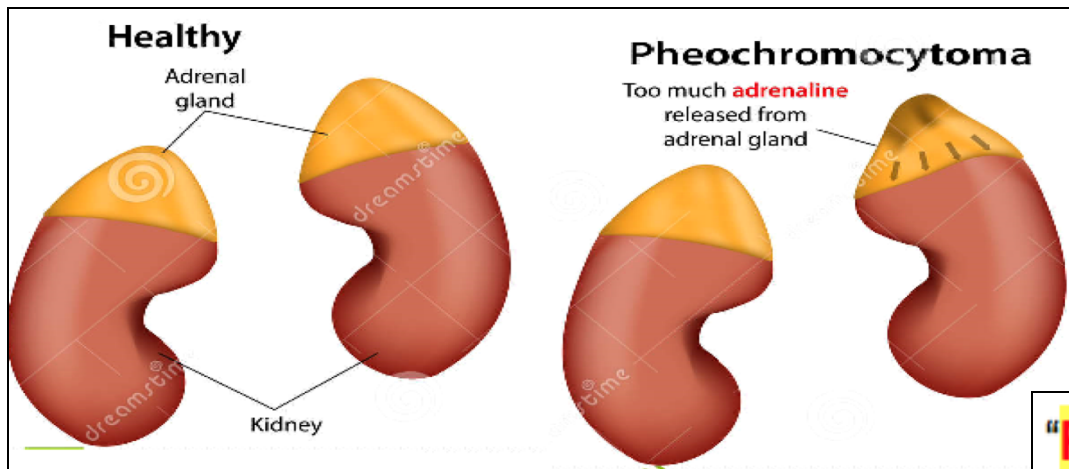
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**Both drugs cause:**

- 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  $\alpha_2$  in heart.

# Therapeutic Uses:

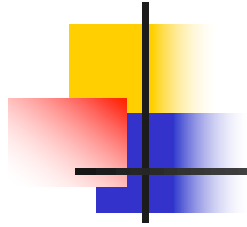
**Pheochromocytoma:** Should be given before surgical removal to protect against hypertensive crisis.



## "PHEochromocytoma"

- **P**alpitations
- **H**eadache
- **E**pisodic sweating (diaphoresis)

## Contraindicated:



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

# *Adverse Effects of non-Selective $\alpha$ -Adrenoceptor*

## *Antagonists :*

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

# *Selective $\alpha_1$ -Antagonists*



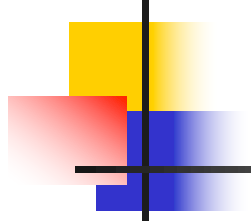
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**Prazosin, Doxazosin, Terazosin**

**Prazosin (short half-life)**

**Doxazosin, terazosin (long half life)**

# *Selective $\alpha_1$ -Antagonists*



## **Pharmacological effects of $\alpha_1$ -antagonists:**

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

# *Selective $\alpha_1$ -Antagonists*

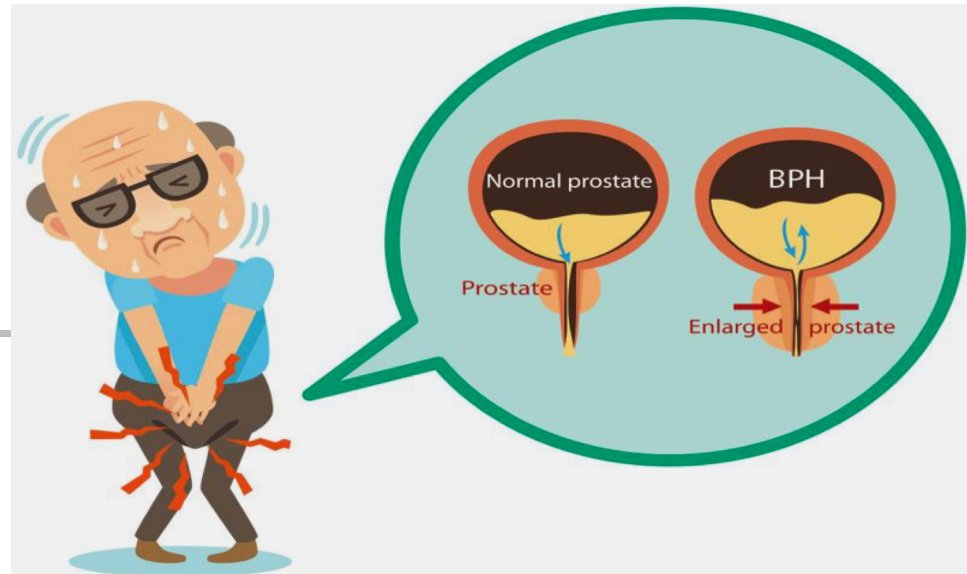


First dose of  $\alpha_1$  receptor blocker may produce an orthostatic hypotensive response that can result in syncope (fainting).

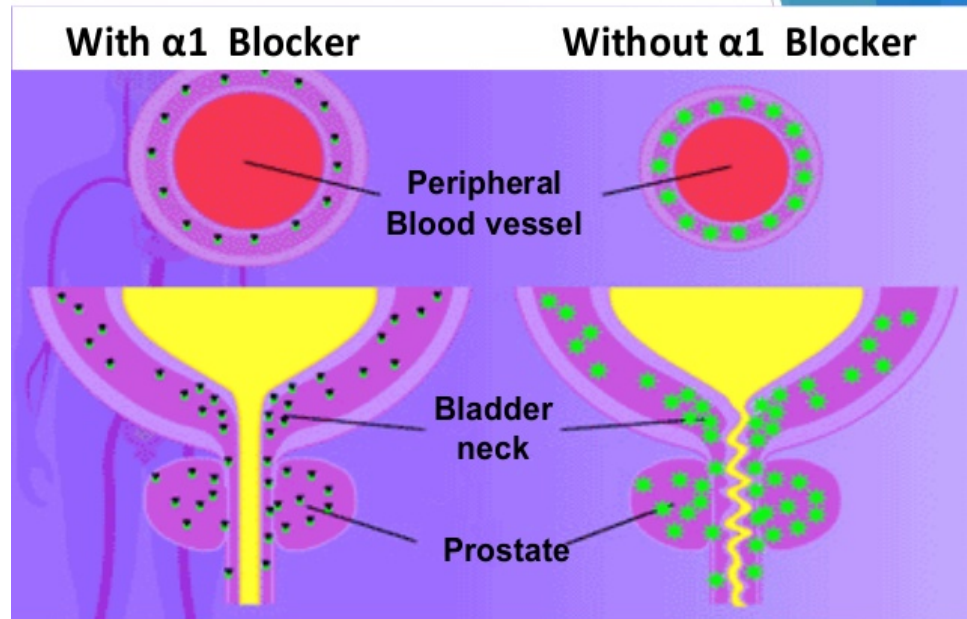


# Therapeutic Uses:

- Urinary obstruction of benign prostatic hypertrophy (BPH).
- Treatment of essential hypertension with prostate enlargement.

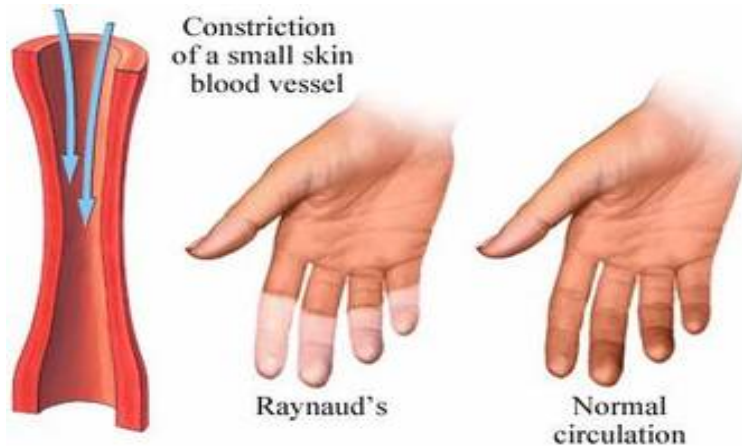


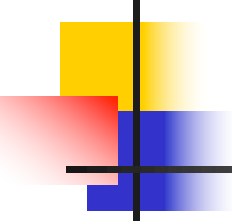
PRAZOSIN



# Therapeutic Uses:

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





# Selective $\alpha_{1A}$ -antagonists

## Tamsulosin

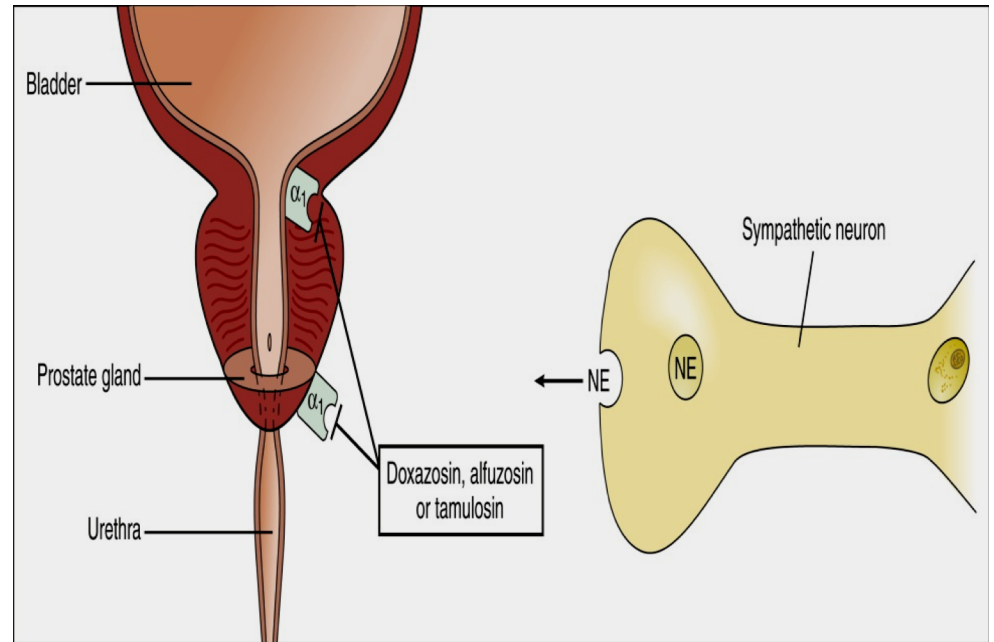
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- ❖ Is a selective  $\alpha_{1A}$  antagonist (Uroselective).
- ❖  $\alpha_{1A}$  receptors present in prostate
- ❖ Causes relaxation of smooth muscles of bladder neck & prostate → improve urine flow.
- ❖ Has minimal effect on blood pressure.
- ❖ Is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

# Selective $\alpha_{1A}$ antagonist Tamsulosin

## *Tamsulosin*

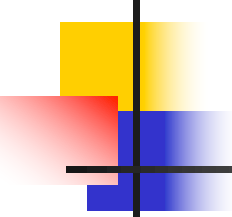
**Relaxation of  
bladder neck can  
improve urine flow**



## *Adverse effects of $\alpha_{1A}$ -Antagonists*

**as before with non selective but to a lesser degree**

## $\alpha_2$ -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 neurotransmitter formation

$\alpha$ -Methyldopa

Depletion of stores

Reserpine

Inhibition of release

Guanethidine

Stimulation of presynaptic  $\alpha$ -receptors

Clonidine

# SUMMARY

