

# **ADRENERGIC RECEPTOR ANTAGONISTS**

- 1) Block the interaction of adrenergic agents (i.e., NE, Epi) with their receptors.**
- 2) Most are competitive antagonists, except phenoxybenzamine that binds  $\alpha$  receptor covalently**
- 3) Some antagonists act selectively on  $\alpha$  or  $\beta$  receptors**

# **$\alpha$ -ADRENERGIC RECEPTOR ANTAGONISTS: EFFECTS**

## **$\alpha$ 1 Antagonists:**

**BLOOD VESSELS:** inhibit vasoconstriction  $\rightarrow$   $\downarrow$  BP  $\downarrow$ TPR

- \* Depend on the status of the system, i.e. more marked in supine
- \* Baroreflex may increase HR and CO ( $\downarrow$  MAP  $\rightarrow$   $\downarrow$  Vagus/NE release  $\rightarrow$   $\beta$ 1 effect)
- \* Block effects of sympathomimetic drugs, i.e. Epi reversal: vasodepressor effect
- \* Side effects: orthostatic hypotension, tachycardia (reflex), nasal stuffiness, myosis

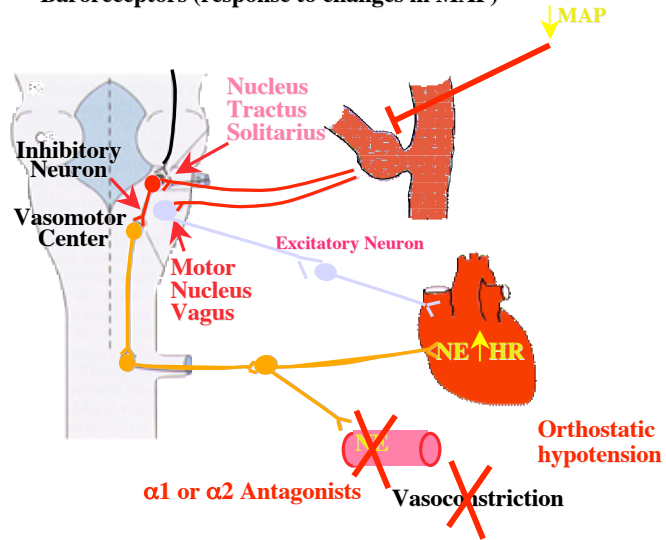
## **$\alpha$ 2 Antagonists (Yohimbine):**

**Effects on CNS and Nerve Endings  $\rightarrow$  regulate cardiovascular effects:**

- \* Can potentiate release of NE by blocking the receptor on nerve endings
- \* Increase in NE  $\rightarrow$  activates  $\alpha$ 1 and  $\beta$ 1  $\rightarrow$  increase in BP

# Cardiovascular Effects of Catecholamines

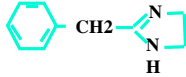
Baroreceptors (response to changes in MAP)



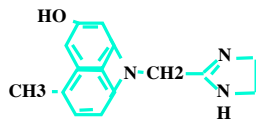
# $\alpha$ -ADRENERGIC RECEPTOR ANTAGONISTS: EFFECTS

There are 3 groups of  $\alpha$  Adrenergic Antagonists:

## Imidazoline Derivatives



**Tolazoline** (rarely used)

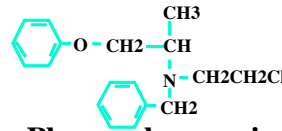


**Phentolamina (Regitine)**  
( $\alpha_1 = \alpha_2 > 5HT$ )

Uses: Pheochr., Hypert.  
Crisis, Amphetamine OD

Side Eff: increase HR, Sexual Dysf.

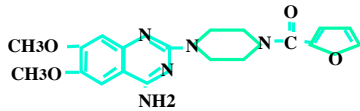
## $\beta$ -Haloalkylamine Derivatives



**Phenoxybenzamine**  
Blocks  $\alpha_1 = \alpha_2 > 5HT, Ach$   
receptors irreversibly  
Used in Pheochr.

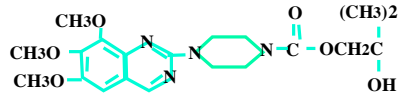
# **$\alpha$ -ADRENERGIC RECEPTOR ANTAGONISTS: DRUGS**

## **Piperazynil Quinazoline Derivatives**



**Prazosin (Minipress)**  
( $\alpha_1 \gg \alpha_2$ )

- \*  $\downarrow$  vascular resistance  $\downarrow$  Preload
- \* CNS  $\downarrow$  sympathetic outflow  
and  $\downarrow$  Baroreflex  $\rightarrow$  HR unchanged
- \* Side effects: syncope and postural hypot.
- \* Indications: Hypertension, CHF ( $\downarrow$  pre  
and  $\downarrow$  afterload =  $\downarrow$  lung congestion), Benign  
Prostate hyperplasia. Half-life 3hr.



**Trimazosin**  
Similar to Prazosin

**Others:**  
Terazosin  
(Half-life 9-12hr)  
and  
Doxazosin  
(Half-life 22hr.)

# **$\beta$ - ADRENERGIC RECEPTOR ANTAGONISTS: EFFECTS**

- \*They are important in the treatment of hypertension, arrhythmias, and ischemic heart disease
- \* Propranolol is the prototype (blocks  $\beta$ 1 and  $\beta$ 2)
- \* They can be distinguished by properties such as:
  - ♥ Relative affinity for  $\beta$ 1 and  $\beta$ 2 receptors (i.e. metoprolol  $\beta$ 1 $\gg$  $\beta$ 2)
  - ♥ Intrinsic sympathomimetic activity, ISA (i.e. pindolol, acebutolol)
  - ♥ Induction of vasodilation (celiprolol blocks  $\beta$ 1 and activates  $\beta$ 2)
  - ♥ Membrane Stabilizing Activity, MSA, Quinidine-like (higher doses)
  - ♥ Cross BBB
- \*  $\beta$ -Blockers have little effect on normal heart, but block effects of exercise and stress

# **$\beta$ - ADRENERGIC RECEPTOR ANTAGONISTS: EFFECTS**

**CARDIOVASCULAR SYSTEM** (most effects are modest when stimulation is low):

**Lower BP:** \*  $\downarrow$  HR  $\downarrow$  Contratility =  $\downarrow$  CO

\* Increase in TPR (reflex)

\* Block  $\beta_2$  presynap  $\rightarrow$   $\alpha_2$  presynap  $\rightarrow$   $\downarrow$  NE

\* Some  $\beta$ -Blockers produce vasodilation by:

-blocking  $\alpha$  receptors, i.e. labetalol/carvedilol

- $\beta_2$  agonist effect, celiprolol

-independent mechanisms

**Anti-Arrhythmic:** \* Increase PR interval  $\rightarrow$  Refract. Period AV node

\*  $\downarrow$  Sinus Rate,  $\downarrow$  Depolarization of ectopic pacemakers

$\downarrow$  Slow conductivity in atria and AV node

**Reduce ischemia:** \*  $\downarrow$  O<sub>2</sub> consumption  $\rightarrow$  increase cardiac efficiency

**Side Effects:** \* Asthma; Hypoglycemia; block increase HR during exercise

# **$\beta$ - ADRENERGIC RECEPTOR ANTAGONISTS: EFFECTS**

## **PULMONARY SYSTEM (effect modest in normal persons):**

- \* COPD and ASTHMA patients can develop severe bronchoconstriction

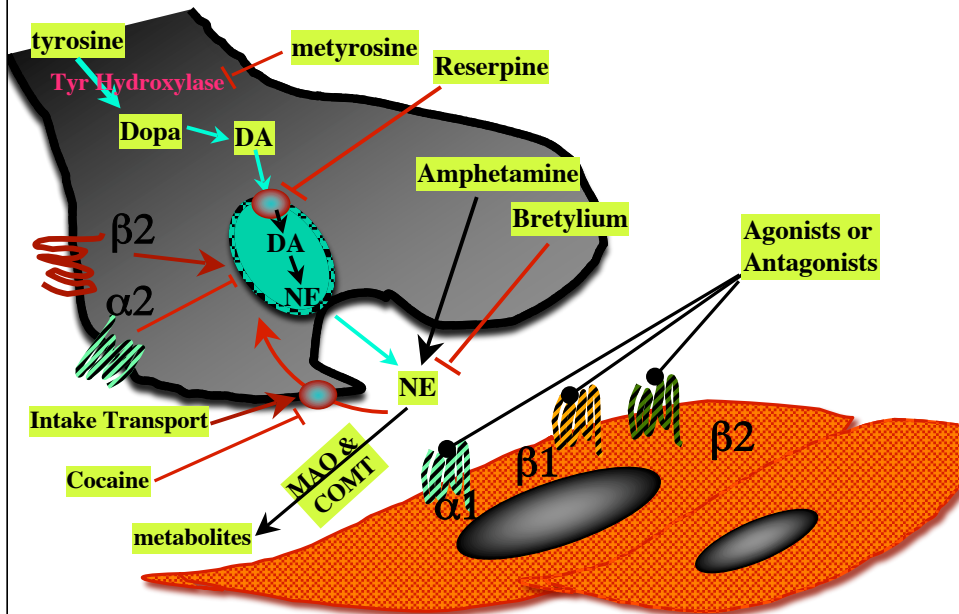
## **METABOLIC EFFECTS:**

- \* Carbohydrates: Inhibit glycogenolysis ( $\beta_2$ ), caution in labile diabetes, but rarely affect insulin secretion
- \* Lipids: May cause modest increase in TG and decrease in HDL
- \* Propranolol blocks renin release

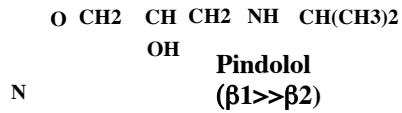
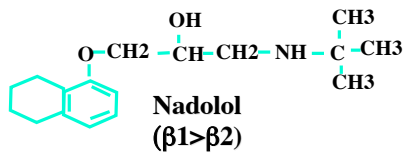
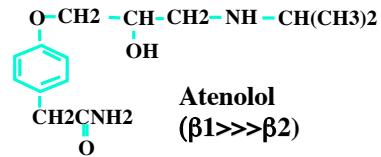
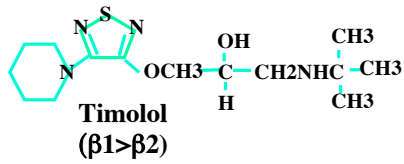
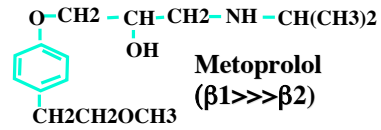
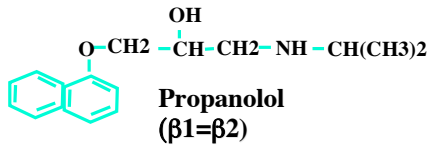
## **CNS:**

- \* Decrease release of NE from presynaptic terminals resulting in an increase in the  $\alpha_2$  effect. Sedation.

# ADRENERGIC NEUROTRANSMISSION



# $\beta$ - ADRENERGIC RECEPTOR ANTAGONISTS



# $\beta$ - ADRENERGIC RECEPTOR ANTAGONISTS

Agent	Selectivity	ISA	MSA	lipo.Sol	T1/2 (availability)
Propranolol	$\beta_1=\beta_2$	-	++	+++	3-6h (30%)
Nadolol	$\beta_1=\beta_2$	-	-	+	12-24h (35%)
Pindolol	$\beta_1=\beta_2$	++	++	++	3-4h (90%)
Labetalol	$\beta_1=\beta_2$	+	+	+	5h (30%)
Carteolol	$\beta_1=\beta_2$	+	-	±	6h (85%)
Carvedilol	$\beta_1=\beta_2$	-	-	N/A	6-8h (30%)
Penbutolo	$\beta_1=\beta_2$	+	-	+++	5h (>90%)
Sotalol	$\beta_1=\beta_2$	-	-	+	12h (90%)
Metoprolol	$\beta_1 \gg \beta_2$	-	++	++	3-4h (50%)
Atenolol	$\beta_1 \gg \beta_2$	-	-	+	6-9h (40%)
Acetobutolol	$\beta_1 \gg \beta_2$	+	+	+	3-4h (50%)
Betaxolol	$\beta_1 \gg \beta_2$	-	±	+	14-22h (90%)
Bisoprolol	$\beta_1 \gg \beta_2$	-	-	±	9-12h (80%)
Celiprolol	$\beta_1 \gg \beta_2$	+	-	N/A	4-5h (70%)
Esmolol	$\beta_1 \gg \beta_2$	-	-	±	10 min (0%)
Timolol	$\beta_1 \gg \beta_2$	-	-	++	4-5h (50%)

# **$\beta$ - ADRENERGIC RECEPTOR ANTAGONISTS**

**Adverse effects due to  $\beta$ -receptor blockade:**

**Bronchoconstriction, Exacerbate heart failure, Bradycardia, worsen peripheral vasc. disease, CNS (fatigue, insomnia).**

**May precipitate and/or block recognition of hypoglycemia and delay recovery from insulin-induced hypoglycemia.**

# **$\beta$ - ADRENERGIC RECEPTOR ANTAGONISTS**

## **Therapeutic Uses:**

- 1) Hypertension**
- 2) Angina (reduce cardiac work)**
- 3) Supraventricular and Ventricular Arrhythmias**
- 4) MI**
- 5) Hypertrophic Obstructive Mycardiopathy**
- 6) Other: hyperthyroidism, migraine (prophylaxis), panic, glaucoma.**