Adrenomimetic Drugs

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α- Adrenergic Receptors

They are sub divided into

1. α-1 Adrenergic receptors:

present on smooth muscle, all blood vessels (causing constriction) and the muscles that cause dilation of pupil of eye.

2. α-2 Adrenergic receptors:

They are mainly presynaptic are found at adrenergic and cholinergic nerve terminals.

Also, postsynaptic are found in the blood vessels and in the CNS.

β-Adrenergic Receptors

Divided into:

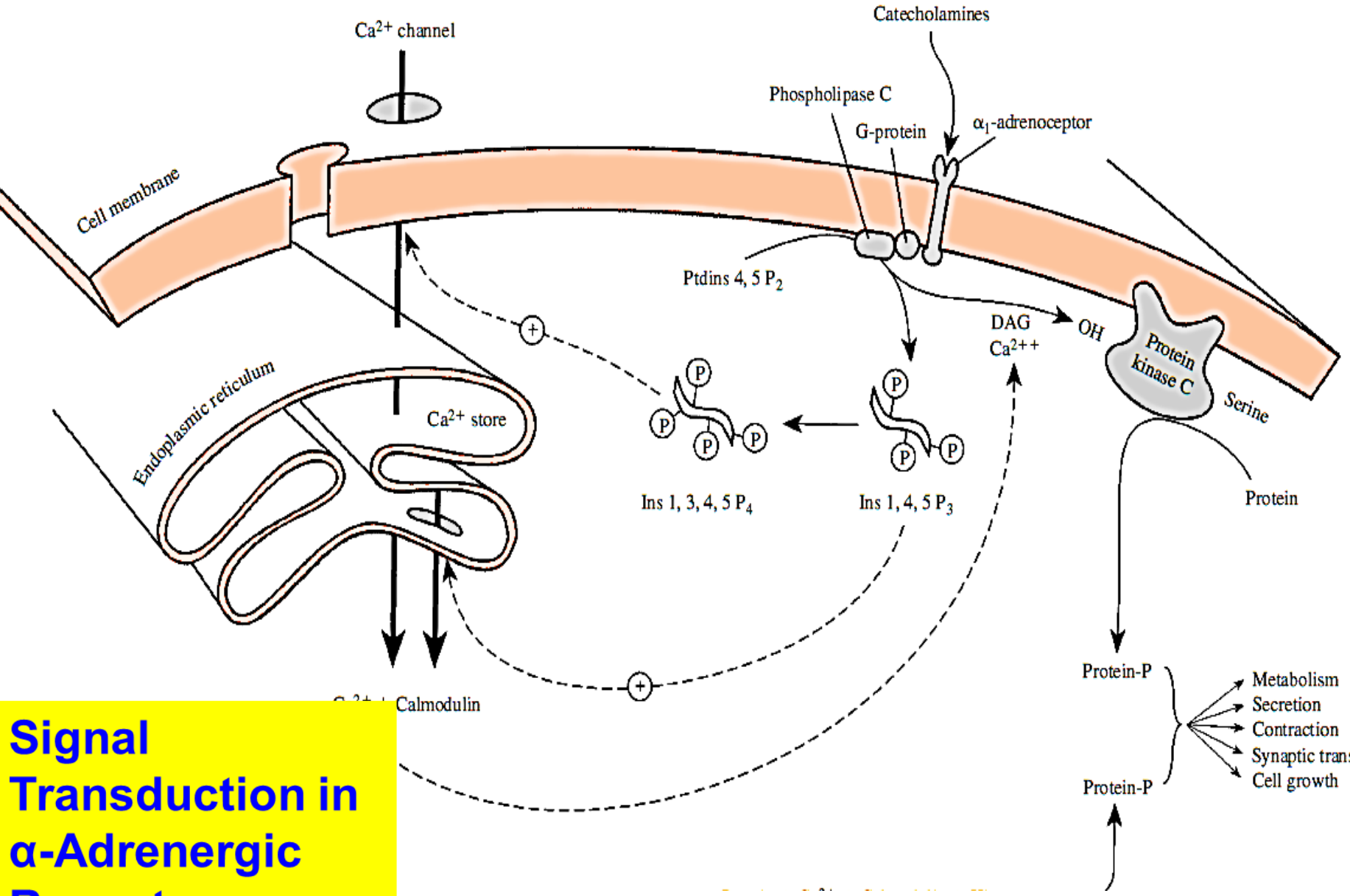
1.β1 adrenergic receptors: on heart (some β2 also) increases rate and force of contraction.

2.β2 adrenergic receptors: present on smooth muscle, some blood vessels (in skeletal muscles), bronchial smooth muscles, skeletal muscles and liver

3.β3 adrenergic receptors: present in adipose tissue

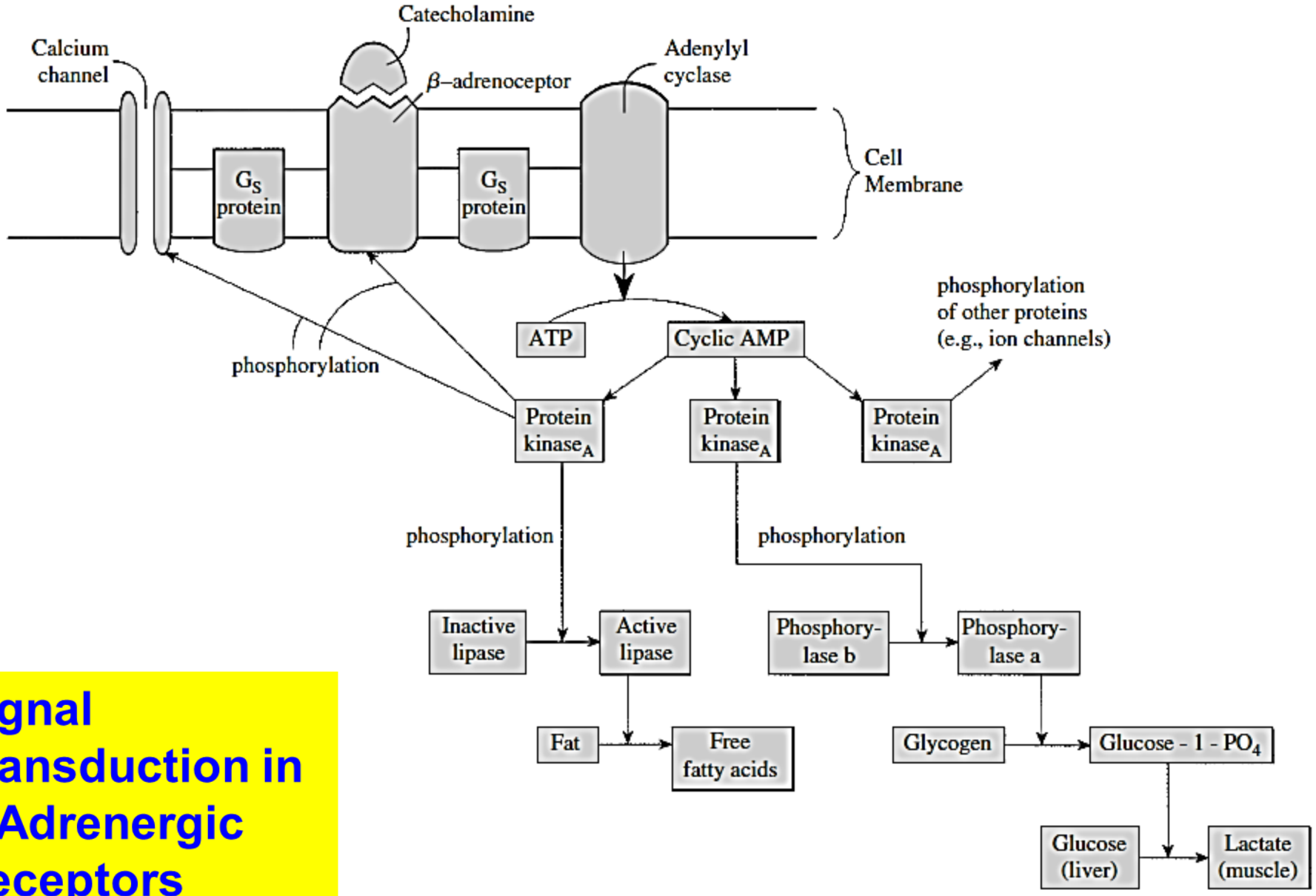
What adrenoceptors "generally" do

Effector organ	Receptor	Response
Heart		
Sinoatrial node	β	Tachycardia
Atrioventricular node	β	Increase in conduction rate and shortening of functional refractory period
Atria and ventricles	β	Increased contractility
Blood vessels		
To skeletal muscle	α and β	Contraction or relaxation
To skin	α	Contraction
Bronchial muscle	β	Relaxation
Gastrointestinal smooth muscle		
To stomach	β	Decreased motility
To intestine	α and β	Decreased motility
Gastrointestinal sphincters		
To stomach	α	Contraction
To intestine	α	Contraction
Urinary bladder		
Detrusor	β	Relaxation
Trigone and sphincter	α	Contraction
Eye		
Radial muscle, iris	α	Contraction (mydriasis)
Ciliary muscle	β	Relaxation



Signal Transduction in α-Adrenergic Receptors

Signal Transduction in β-Adrenergic Receptors



Adrenergic Signal Transduction

Alpha-1 (similar to M1,M3,M5): Gq → PLC → IP_3 → PKC → Ca

Alpha-2 (similar to M2,M4): Gi → inhibit adenylyl cyclase

Beta-1 and -2 : Gs → stimulate adenylyl cyclase

Sympathomimetics

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS neurons	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Some vascular smooth muscle	Contraction

β_1	Heart, juxtaglomerular cells	Increases force and rate of contraction; increases renin release
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Bladder	Relaxes detrusor muscle
	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve endings	Modulates transmitter release

Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

Catecholamine Effects

Cardiovascular system:

Blood vessels:

- **Catecholamines are important in the regulation of peripheral vascular resistance and venous capacitance.**
- **Skin and splanchnic vessels have predominantly α-receptors → constriction.**
- **Skeletal muscle blood vessels have predominantly β-receptors → dilation.**
- **Dopamine D1 receptors promote vasodilation of renal resistance vessels (arterioles).**
- **Vasoconstriction reduces blood flow, while vasodilation increases blood flow.**

Catecholamine Effects

Cardiovascular system:

Heart:

- **Effects on the heart are predominantly mediated through β1 receptors.**
- **Increase pacemaker activity → increase heart rate = "positive chronotropic effect".**
- **Conduction velocity in the atrioventricular (AV) node is increased "positive dromotropic effect".**
- **AV node refractory period is decreased.**

Catecholamine Effects

Cardiovascular system:

B. Heart:

Myocardial contractility is increased = “positive inotropic effect”.

Sympathomimetic that stimulate β1-receptors in the heart, increase cardiac output and thus, systolic blood pressure.

Cardiac output is also increased by an increase in venous return to the heart.

Catecholamine Effects

Cardiovascular system:

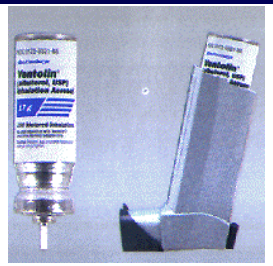
Blood Pressure :

- **Diastolic blood pressure is related to systemic vascular resistance and is increased by vasoconstrictors and reduced by vasodilators.**

- **α-agonists increase peripheral arterial resistance → rise in diastolic blood pressure.**

- **β2-agonists decrease peripheral vascular resistance and thus diastolic blood pressure.**

Autonomic Control of Smooth Muscle



Bronchial smooth muscle has beta-2 adrenoceptors

Be careful with nonselective beta agonists!

"Because the excessive cardiac stimulation produces cardiac arrhythmias and enhanced myocardial oxygen consumption, there is no rationale for using non-beta-2 selective agonists in the treatment of asthma."

Relax G.I. smooth muscle
- **alpha and beta effects**
- **reduce motility**
- **may contract sphincters**

Relax uterine smooth muscle
- **beta-2 agonists delay premature labor**

Relax detrusor muscle (β); contracts sphincter (α)
- **urinary retention**

Contract radial muscle (α)-- mydriasis

Effects on endocrine function

Metabolic effects: stress / ”fight or flight”

- **Lipolysis (β3)**
- **Glycogenolysis (β2)**
- **Increased metabolic rate (β)**
- **Decreased insulin secretion (α2)**
- **Renin release (β1)**

Epinephrine

- Stimulates all adrenoceptors (α1, α2, β1, β2).
- Very potent vasoconstrictor and cardiac stimulant.
- Positive inotropic and chronotropic actions on the heart (β1).

Vasoconstrictor in many vascular beds (α1), and vasodilator in skeletal muscle blood vessels (β2) → increase blood flow during exercise.

Norepinephrine

Similar to epinephrine except it has no significant effect on β2 receptors.

D1 Agonists

Dopamine

- Activates D1 receptors and produce vasodilation, which is specially clinically important in renal vascular bed → increase renal blood flow.
- Activates β1 receptors in the heart.
- At high concentration, it activates vascular α receptors leading to vasoconstriction including the renal vascular bed.

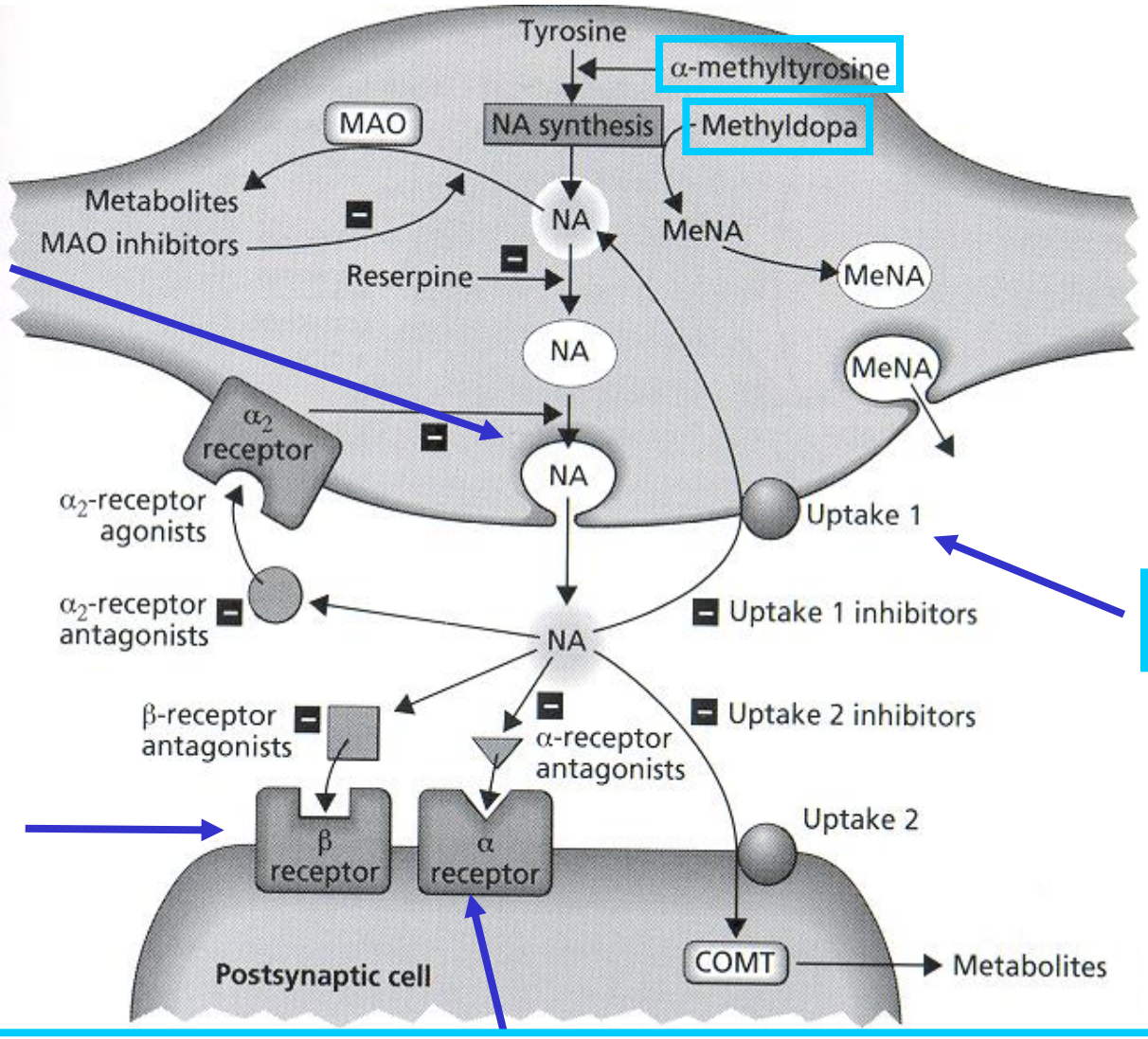
•Fenoldopam

- Is a selective D1 receptor agonist causing peripheral vasodilation.
- Very useful intravenously in treating severe hypertension

Adrenergic Pharmacology

NE release
+ amphetamine
+ ephedrine
- guanethidine
- reserpine

β-AR
+ isoproterenol
+ dobutamine
+ terbutaline
+ albuterol
- propranolol
- metoprolol



- cocaine

α-AR: +phenylephrine, +methoxamine, +clonidine
- phenoxybenzamine, - phentolamine, - prazosin

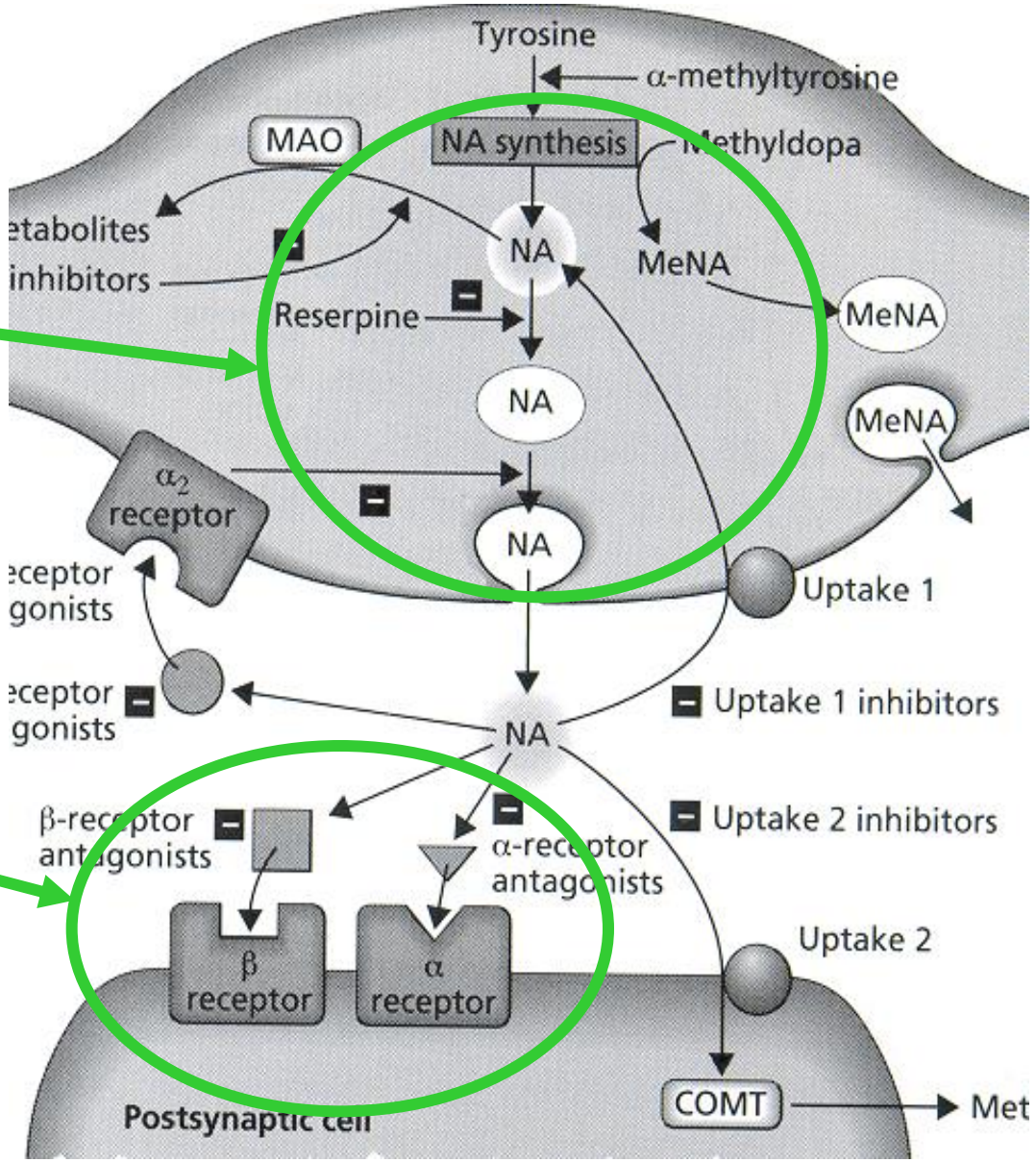
Adrenergic Agents: a dual strategy

2) **Indirect Effect**: nerve terminal

enhance / inhibit NE release

1) **Direct Effect**: adrenoceptors

mimic / antagonize effect of NE (Adrenomimetics / blockers)



Adrenomimetic Amines

"mimic" the effect of NE

Direct selective adrenergic agonists:

stimulate alpha or beta adrenoceptors

alpha-1:	**phenylephrine**
	methoxamine
alpha-2:	**clonidine**
beta-1:	**dobutamine**
beta-2:	**terbutaline**
	albuterol

Alpha-1 Adrenergic Agonists

PHENYLEPHRINE

- Alpha-1 adrenergic agonist
- Weak beta effects
- Not a substrate for COMT
- Primary use: vasoconstrictor
- Treat hypotensive states
  - *shock, spinal anesthesia*
- Nasal decongestant (Neosynephrine)
  - *rhinitis medicamentosa or rebound*
- Mydriasis

Alpha-1 Adrenergic Agonists

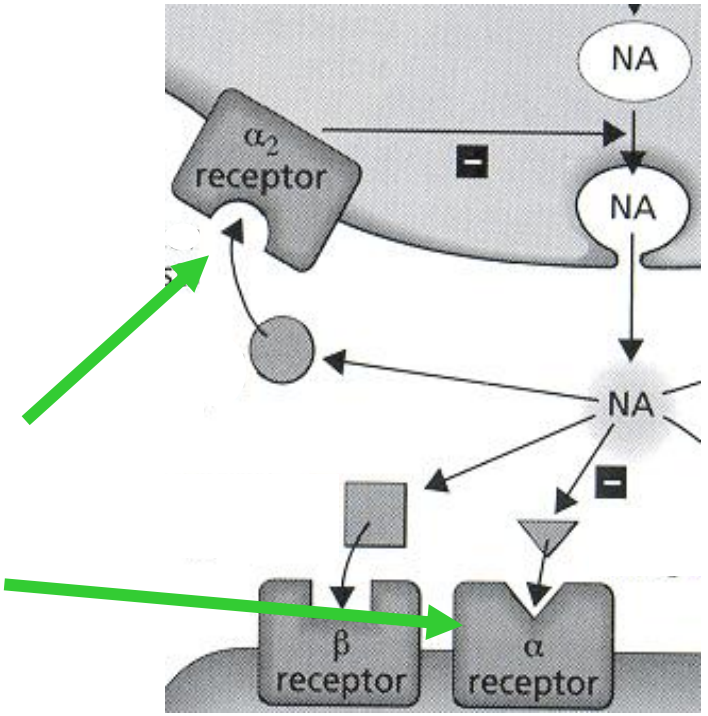
METHOXAMINE

- Alpha-1 adrenergic agonist
- Does not stimulate beta adrenoceptors
- Primary use: vasoconstrictor
- Treat hypotensive states
  - *shock, spinal anesthesia*
- Not metabolized by COMT or MAO

Alpha-2 Adrenergic Agonists

CLONIDINE

- Alpha-2 adrenergic agonist
- Direct vasoconstrictor
- Indirect antihypertensive agent
  - *central suppression*
- Rebound hypertension



Beta-1 Adrenergic Agonist

DOBUTAMINE

- **"Beta-1" adrenergic agonist**
- **Stimulates beta-2 and alpha adrenoceptors**
- **Inotropic agent**
- ***Vasodilation predominates***
  - ***preserves renal and G.I. blood flow***
  - ***heart failure***
- ***Tolerance may develop***

Beta-2 Adrenergic Agonists

TERBUTALINE and ALBUTEROL

- Selective beta-2 agonists (normal doses)
- Primary use: *broncodilator*
- Reduced risk of cardiac stimulation
- May inhibit mast cell secretion
- Not metabolized by COMT or MAO
  - *long duration of action than ISO*
- Inhalation helps limit side effects

Indirect Adrenergic Agonists

AMPHETAMINE

- Enhances NE release (exact mechanism)
- Action similar to NE
- Powerful CNS stimulant
  - *Less fatigue, increased alertness*
  - *Better physical performance*
- Appetite suppression
- Dependency and tolerance

Mixed-Acting Adrenergic Agonist

EPHEDRINE

- Indirect: induces NE release
- Direct: stimulates α and β adrenoceptors
- Bronchodilation due to beta effects
  - *replaced by beta-2 agonists*
- Urinary incontinence
- CNS stimulation
- Appetite suppression
  - *more effective combined with caffeine*
  - *herbal preparation: Ma huang*

Beta-3 Adrenergic Agonist

Vibegron: a selective beta-3 adrenergic receptor agonist in the detrusor muscle.

- ➢ Used for the treatment of overactive bladder.

- Side effects:
- Headache
- Urinary tract infection
- Common cold
- Diarrhea, nausea
- Upper respiratory tract infection.

Mirabegron: Similar uses and side effects