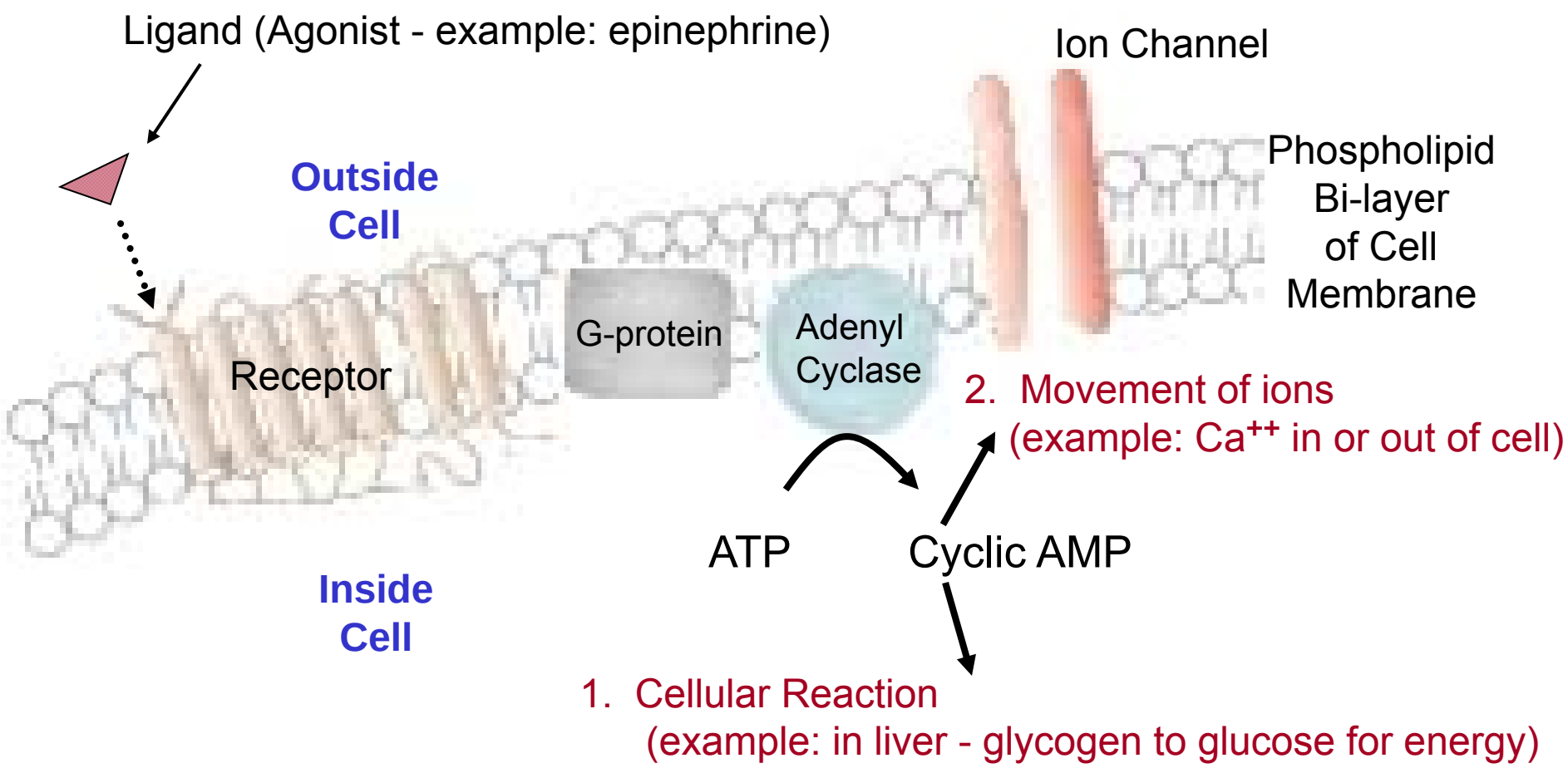
Pharmacology for Clinical Exercise Physiologists

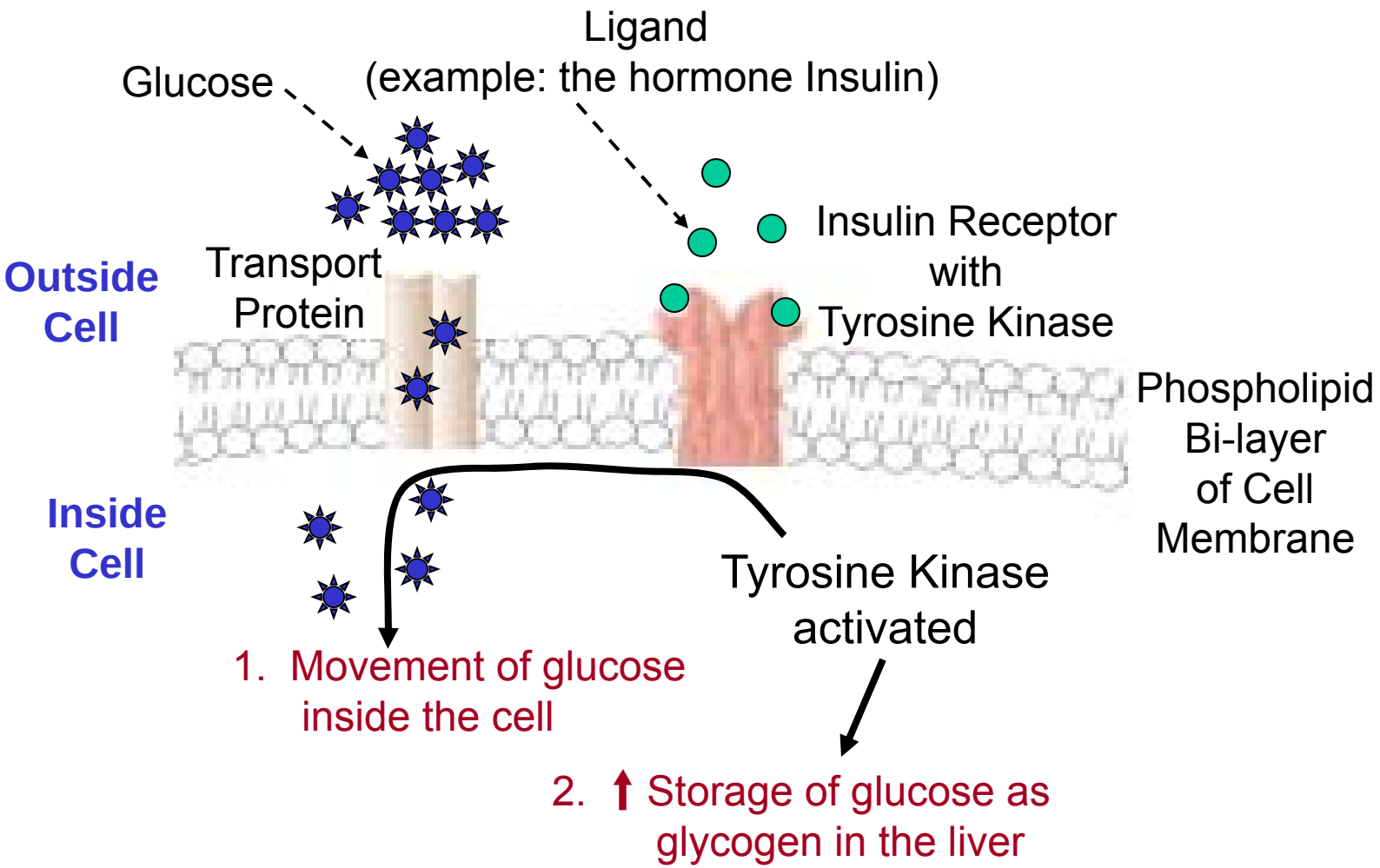
- **Drug development** - about 1 out of 1000 substances tested is approved
  - **Pre-clinical testing**
    - Experiments on isolated cells, cell cultures, or intact organs
      - determine mechanisms of action
    - Animal experiments to determine:
      - toxicity, genotoxicity (mutagenicity), carcinogenicity, teratogenicity
      - pharmacokinetics: what the body does to a drug
        - rates and methods of absorption, distribution, metabolism, elimination
  - **Clinical trials** – pharmacodynamics: what the drug does to the body
    - Phase I - studies on **healthy subjects** to determine:
      - pharmacokinetics, dose-response relationships, side effects
    - Phase II - studies on **selected patients having the target disease**
      - effectiveness, pharmacokinetics, dose-response relationships, side effects
    - Phase III - studies on **larger groups of patients** - FDA approval determined
      - effectiveness, pharmacokinetics, dose-response relationships, side effects
      - comparisons made with other standard treatments
    - Phase IV - post-licensing studies to **determine risk / benefit ratio**

Selected Drug Mechanisms

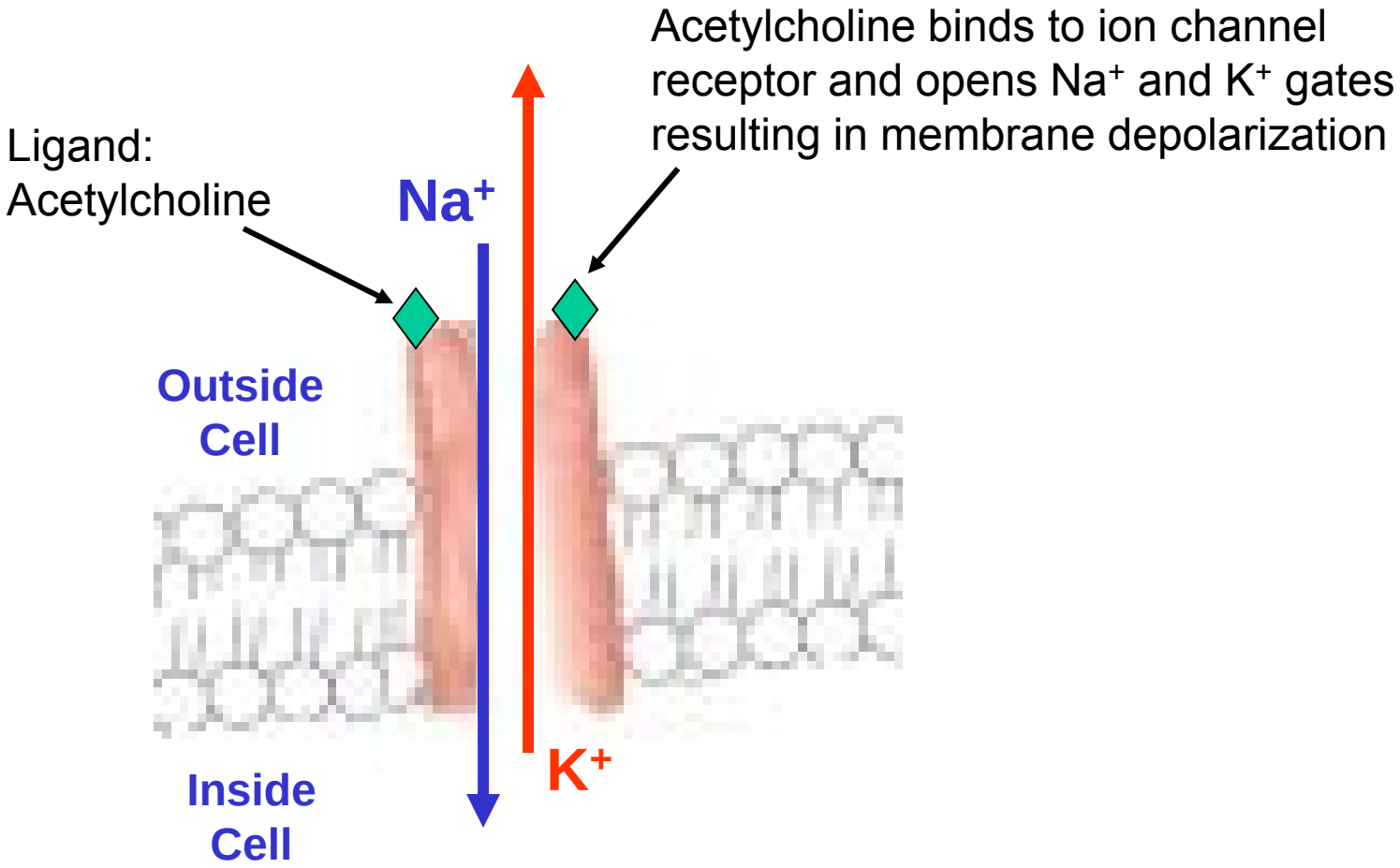
- **Activation or prevention of activation of receptors on the surface of individual target cells.**
  - **G-protein receptors**



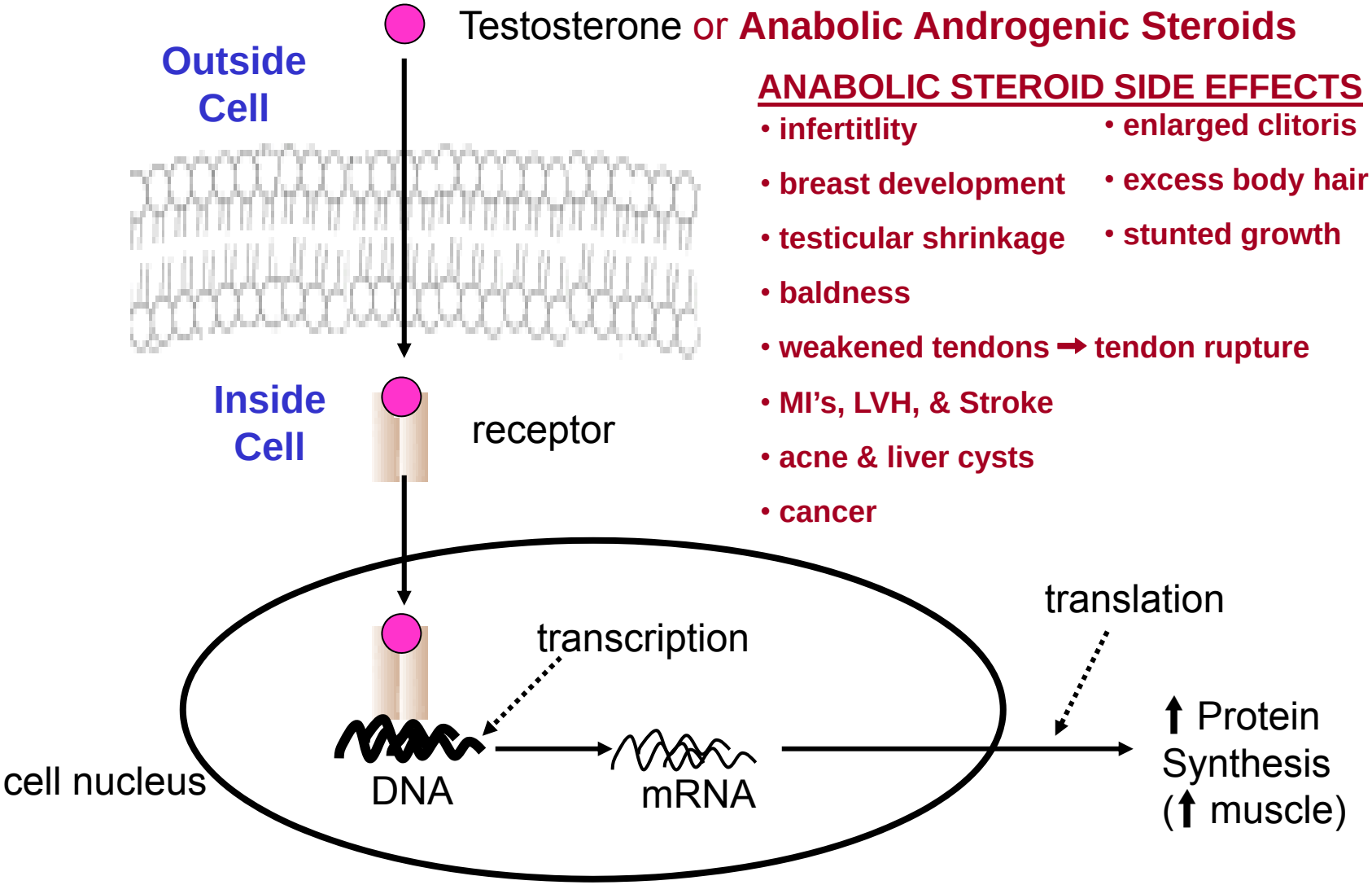
- **Activation or prevention of activation of receptors on the surface of individual target cells (continued).**
  - **Ligand regulated enzyme (tyrosine kinase) receptors**
    - best example: Insulin receptors



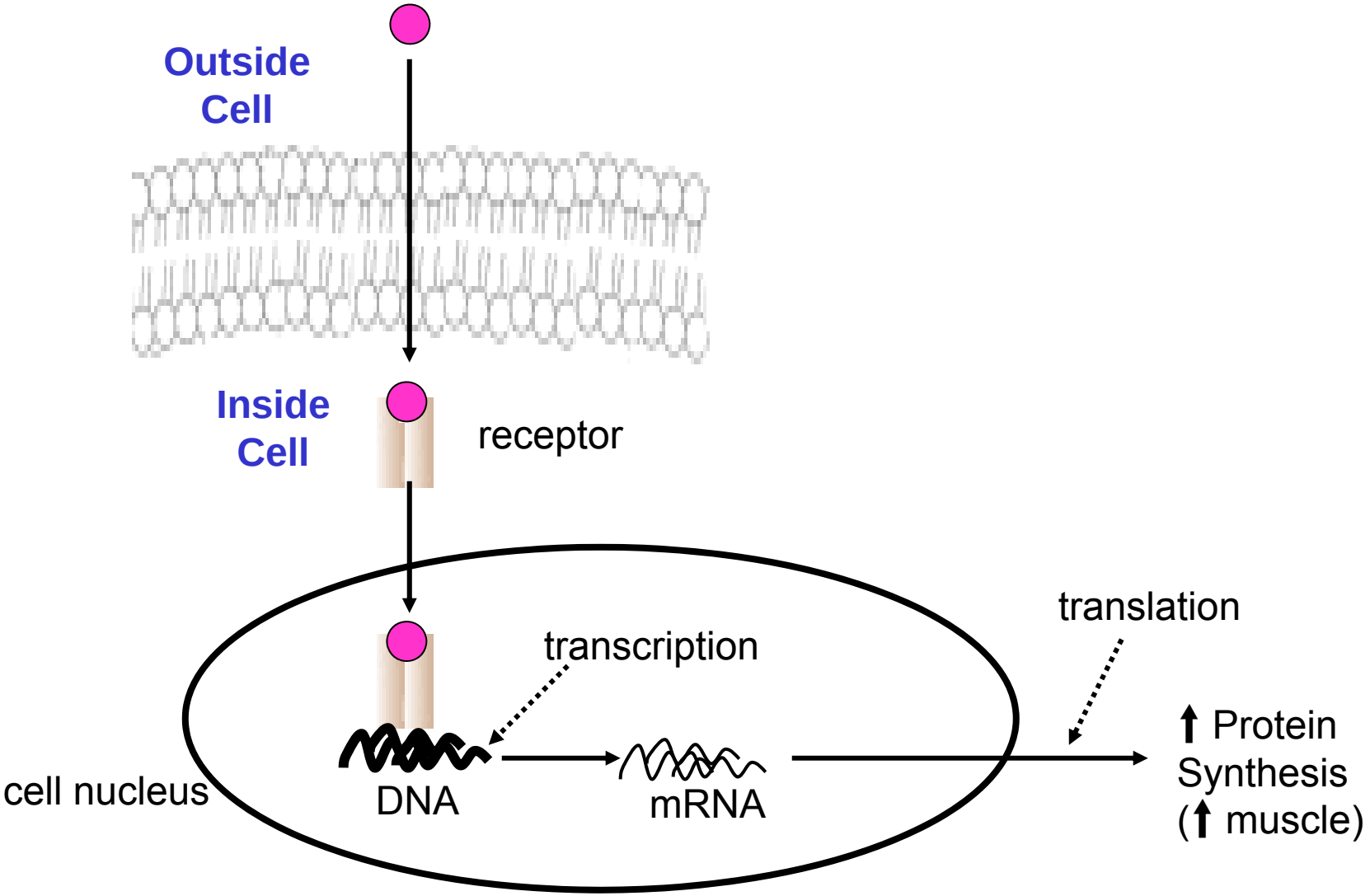
- **Activation or prevention of activation of receptors on the surface of individual target cells (continued).**
  - **Ligand gated ion channel**
    - Example: motor end plate of muscle



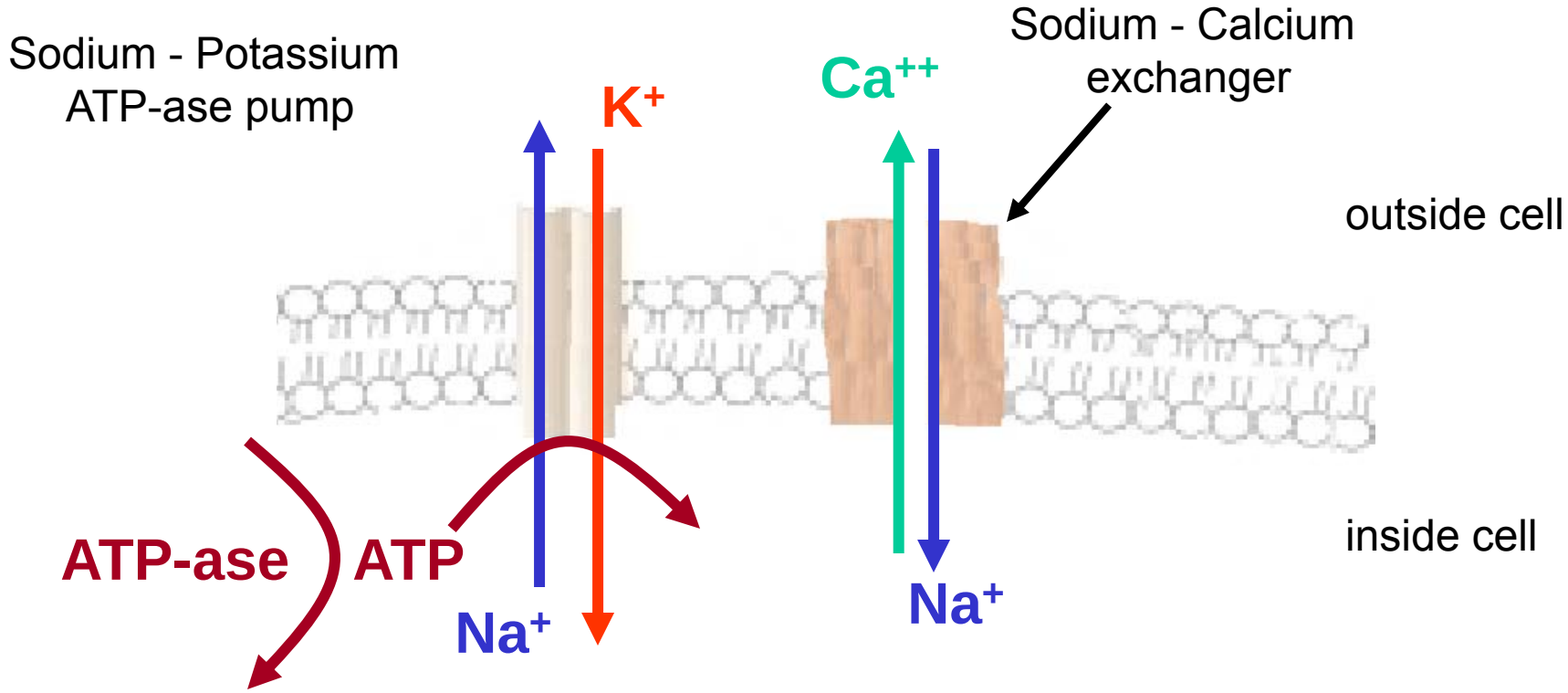
- **Interference with metabolic processes**
  - **Protein synthesis regulating receptor**
    - Examples: Testosterone



- **Interference with metabolic processes**
  - **Protein synthesis regulating receptor**
    - Examples: Thyroxine (T4) and Triiodothyronine (T3)



- **Alteration of Transport Protein Function**
  - **Ion exchanger proteins**
    - Example: Na^+ K^+ ATP-ase pump



Ca^{++} extrusion is passively linked to Na^+ extrusion from repolarizing cells. This process involves active transport and requires energy

Bio-transformation & Metabolism of Drugs

The LIVER is the chief organ for drug metabolism because:

- The blood flow through the liver is high (half of $\dot{Q}$)
- Hepatocytes contain numerous metabolic enzymes
    - Elevation of these enzymes may indicate disease or liver strain
        - **AST, ALT, GGT (labeled differently on some printouts)**

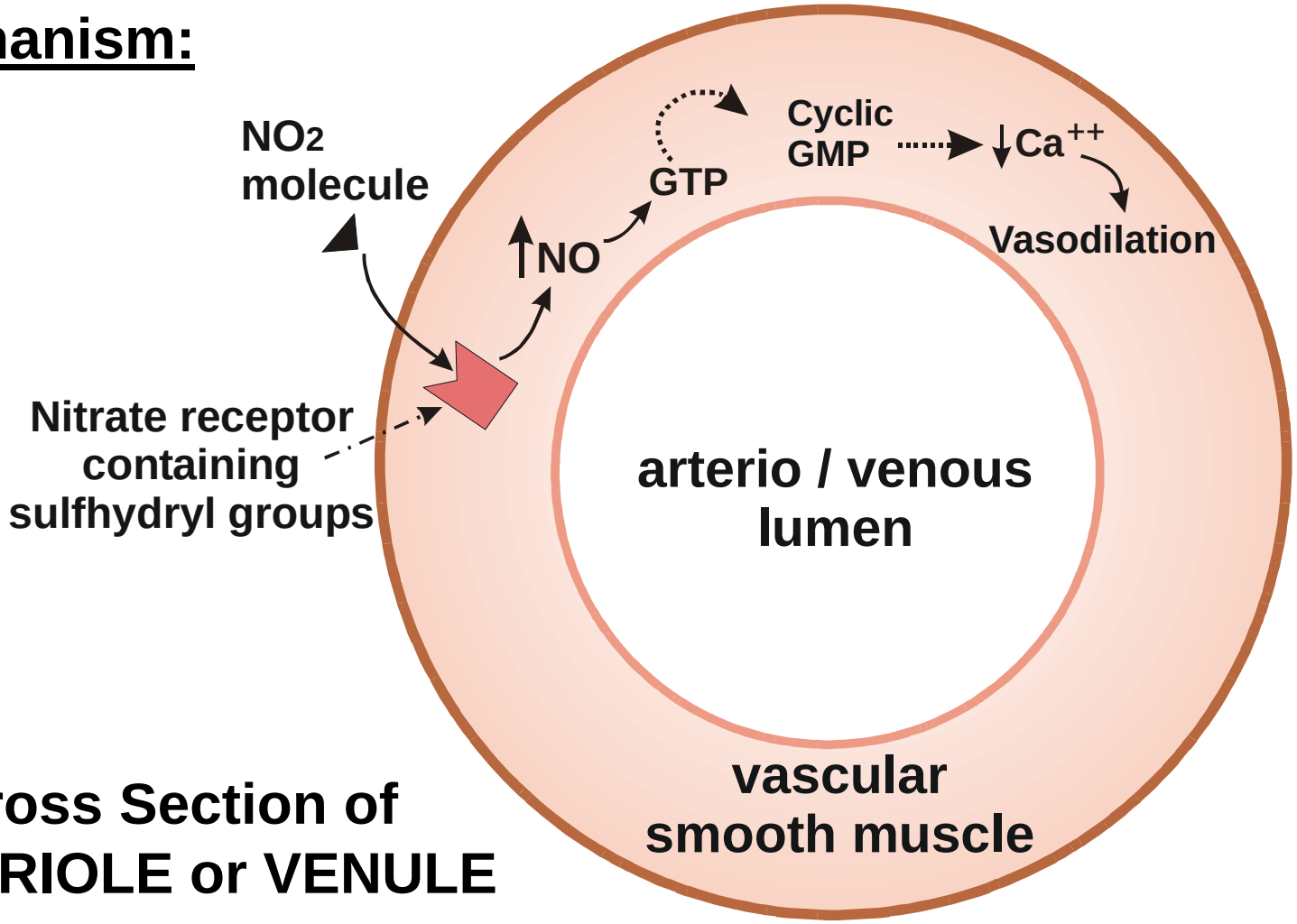
The KIDNEY is the chief excretory pathway for most drugs becasue:

- Size of pores in glomerular capillaries allow for filtration of substances with molecular weights of < 5000 into the urine
        - Most drugs & associated metabolites fall into this category
- Proximal tubule contains active transport systems that can be used for transporting substances into the urine
- Elevation of **BUN** or **CREATININE** in blood may indicate kidney problems
- Some elderly cannot take needed drugs because of ↓ kidney & liver function

Nitrates (NO_2) - anti-anginal medication

Nitrates provide exogenous source of Endothelial Derived Relaxation Factor (EDRF) now known to be Nitrous Oxide (NO)

Mechanism:



Cross Section of ARTERIOLE or VENULE

Nitrates

TRIDIL ISORDIL SORBITRATE DILATRATE CARDILATE ISMO MONOKET

Indications

- angina (stable angina management)
- ↓ coronary artery spasm

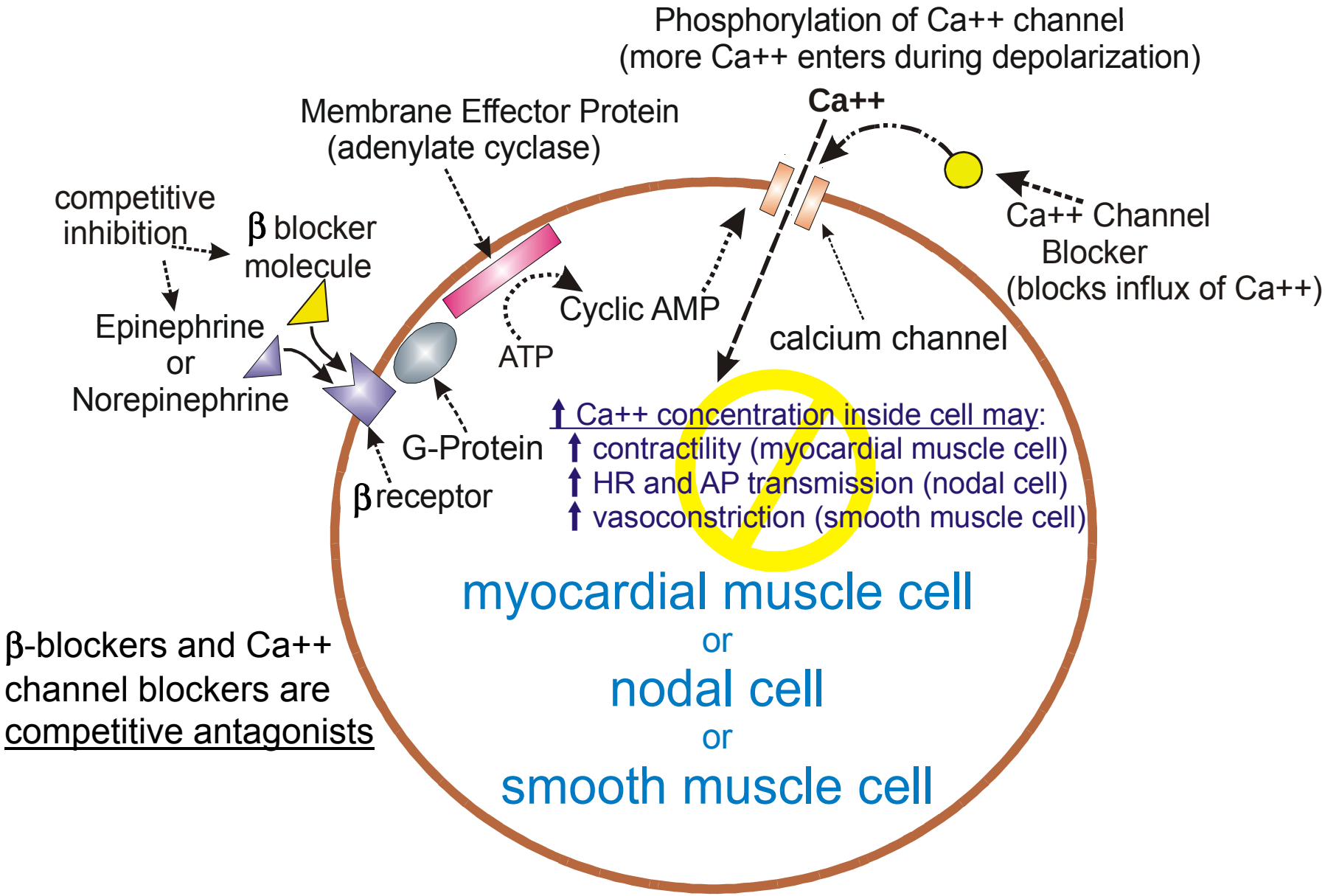
Effects

- venous & arterial vasodilator
- ↓ preload
- ↓ afterload
- ↑ myocardial O2 supply
- ↓ myocardial O2 demand
- ↓ BP
- ↑ HR (via baroreceptor)
- ↑ exercise angina threshold

Adverse Reactions

- dizziness & syncope (↓↓ BP)
- orthostatic hypotension
- tolerance can be built up which means that, over time, more of the drug must be used to achieve the desired effect

β - blocker and Calcium Channel Blocker Mechanisms



β-blockers and Ca++ channel blockers are <u>competitive antagonists</u>

β-blockers

INDEROL, VISKIN, BLOCADREN, CORGARD, COREG Carvedolol, BYSTOLIC

Indications:

- angina
- hypertension (not a 1st line drug for hypertension)
- ventricular & supraventricular arrhythmias
- congestive heart failure & cardiomyopathies
- treatment of MI's

Effects

- ↓ HR & contractility → ↓ $\dot{Q}$ → ↓ BP
- ↑ O_2 supply + ↓ O_2 demand
- ↑ exercise angina threshold
- ↓ functional capacity
- ↓ susceptibility to ventr. arrhyth.

Adverse Reactions

- lethargy (↓ functional capacity)
- ↓ signs of hypoglycemia in diabetics
- ↓ cold tolerance
- depression
- vivid & bizarre dreams

Notes: Some β-blockers are <u>cardioselective</u>, meaning they have greater affinity for β1 (heart) receptors:

BREVIBLOC Esmolol, LOPRESSOR TOPROL-XL Metaprolol

Notes: β blockers are also considered Class II antiarrhythmic agents

Calcium Channel Blockers

CALAN (Verapamil), CARDAZEM (Diltiazem), PROCARDIA (Nifedipine), CARDENE (Nicardipine), NIMOTOP, NORVASC, PLENDIL, VASCOR, SULAR

Indications:

- **hypertension (1st line drug for hypertension)**
- **PSVT , atrial fibrillation & flutter**
- **angina**
- **coronary artery spasm**

Effects

- **↓ HR & contractility → ↓ $\dot{Q}$ → ↓ BP**
- **↑ O_2 supply + ↓ O_2 demand**
- **↑ exercise angina threshold**
- **↓ arterial vasoconstriction → ↓ BP**
- **↓ PSVT**
- **↓ atrio-ventricular conduction rate**
- **↓ coronary artery spasm**
  - **drug of choice for variant angina**

Adverse Reactions

- **headaches**
- **flushing**
- **↓ cold tolerance**
- **depression**
- **vivid & bizarre dreams**

Notes: Nifedipine and Nicardipine may ↑ HR

Notes: Calcium Channel Blockers are Class IV antiarrhythmic agents

Diuretics

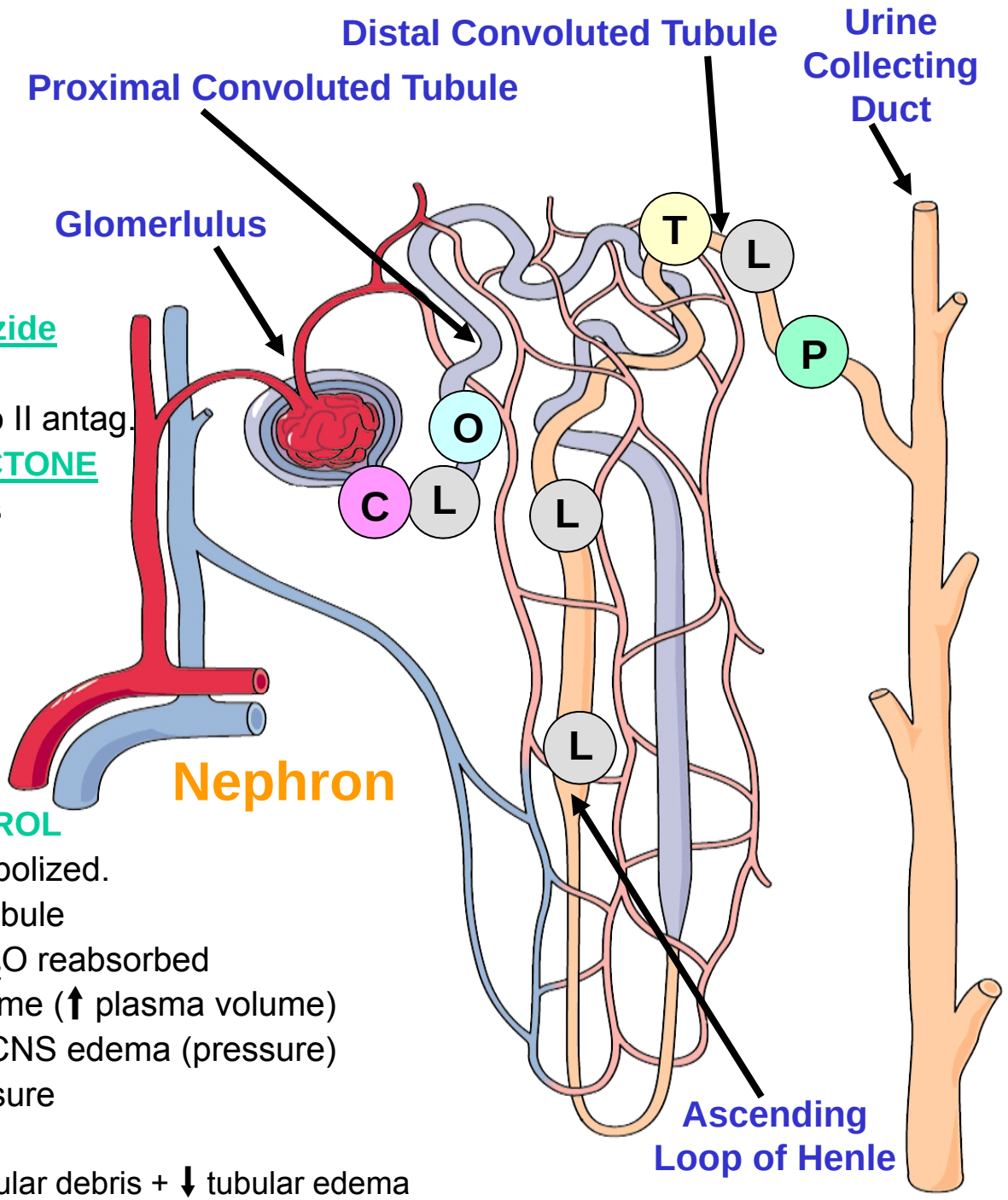
L - **Loop diuretics** **Furosemide LASIX**
- Block reabsorption of Na^+ & Cl^-
- Fast acting - edema removal
- Used to treat CHF

T - **Thiazide diuretics** **Hydrochlorothiazide**
- Block reabsorption of Na^+ & Cl^-
- Combined with ACE inhib. & Angio II antag.

P - **K^+ sparring** **Spironolactone ALDACTONE**
- Some are aldosterone antagonists
- Others are thiazides
- All have antikaliuretic properties

C - **Carbonic anhydrase inhibitors**
- ↓ HCO_3 resorption → mild ↓ H_2O
- Primarily used to treat glaucoma
- ↓↓ production of aqueous humor

O - **Osmotic diuretics** **Mannitol OSMITROL**
- 6-C sugar alcohol that is not metabolized.
- Filtered through glomerulus into tubule
- ↑ osmolarity of tubular fluid →↓ H_2O reabsorbed
- ↑ plasma osmolarity → ↓ ICF volume (↑ plasma volume)
- Primarily used to ↓ intracranial & CNS edema (pressure)
- Can be used to ↓ intraocular pressure
- Can be used to treat renal failure
  - ↑ fluid flow rate flushes out cellular debris + ↓ tubular edema

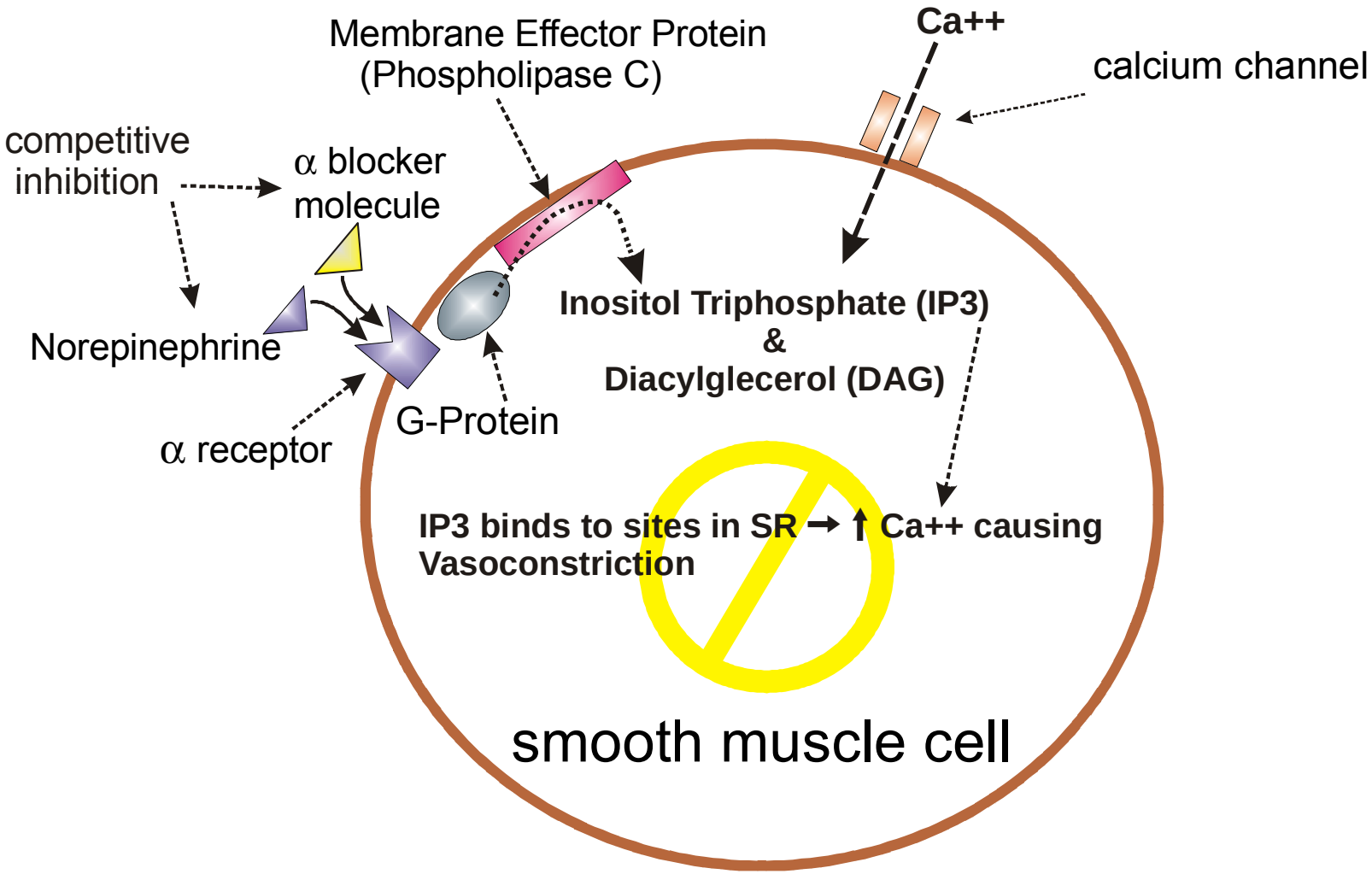


Diuretic Mechanisms – cont.

- **Caffine**:
  - competitive inhibitor of adenosine in the brain
    - → ↓ constriction of glomerular arterioles → ↑ renal blood flow → ↑ GFR
    - → ↑ dopamine level in the brain → ↑ stimulation → ↓ drowsiness
  - ↑ serotonin levels → positive mood changes

α Blockers

- **FLOMAX, DETROL LA, VESICARE, SANCTURA, HYTRIN, CARDURA**
- ↓ vasoconstriction → ↓ TPR → ↓ blood pressure
- Relaxation of selected sphincters (also used to treat urinary symptoms in BPH)



Peripheral Vasodilators

↓ Total Peripheral Resistance (TPR) → ↓ Blood Pressure

HYDRALAZINE

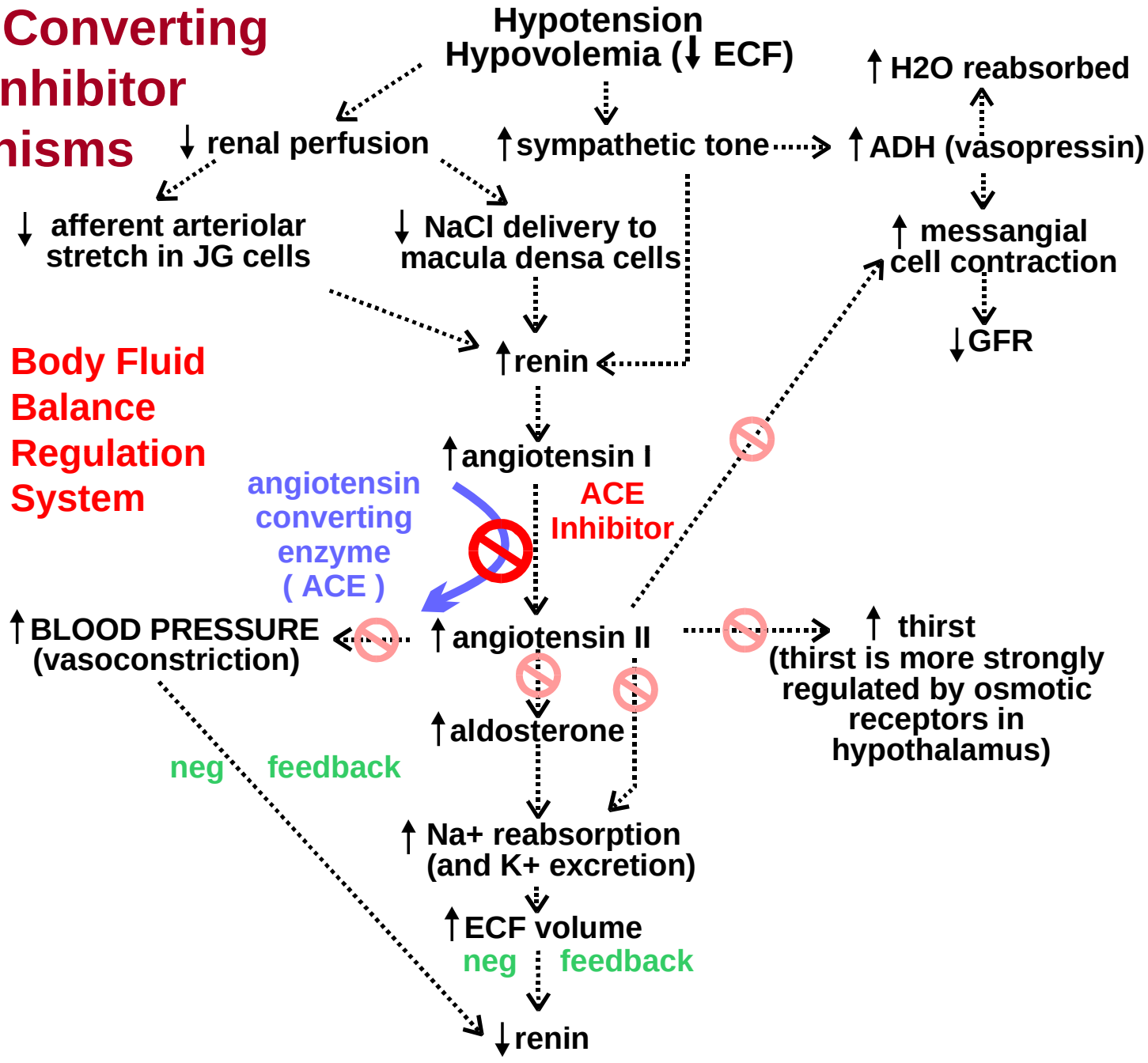
- Interferes with calcium influx into peripheral smooth muscle
- ↓ contractile state of peripheral arterial smooth muscle → vasodilation → ↓ BP

MINOXIDIL

- Hyperpolarizes peripheral smooth muscle cells via the opening of K^+ channels
  - Cell membrane potential moved away from the zone that results in opening of Ca^{++} channels → Ca^{++} kept out of cell → vasodilation → ↓ BP

- **Notes**:
  - In CHF, reducing TPR results in a reduction in afterload → ↑ $\dot{Q}$
  - Be aware of side effects:
    - Reflex tachycardia → angina
    - Orthostatic and post exercise hypotension

Angiotensin Converting Enzyme Inhibitor Mechanisms



Drugs Affecting the Renin-Angiotensin System

1. Angiotensin Converting Enzyme Inhibitors

VASOTEC CAPOTEN ZESTRIL ACCUPRIL MONOPRIL LOTENSIN LISINOPRIL

Indications:

- Hypertension (1st line drug for hypertension – along with Ca^{++} blockers)
- Congestive heart failure

Effects:

- ↓ blood (plasma) volume
- ↓ vasoconstriction
- ↓ preload & afterload
- ↑ cardiac effciency & ↓ edema
  - drug of choice in CHF patients

Adverse effects:

- cough
- hypotension

3. Renin Blockers (new)

Blocks action of Renin's role in making Angiotensin I TEKTURNA

2. Angiotensin II Antagonists COZAAR BENICAR DIOVAN

Competitive antagonist of Angiotensin II:

- ↓ aldosterone production and ↓ angiotensin II mediated vasoconstriction

Antiadrenergic Drugs

Inhibition of Central Adrenergic Outflow → ↓ Blood Pressure

SERPASIL (Reserpine), CATAPRESS, TENEX, ALDOMET

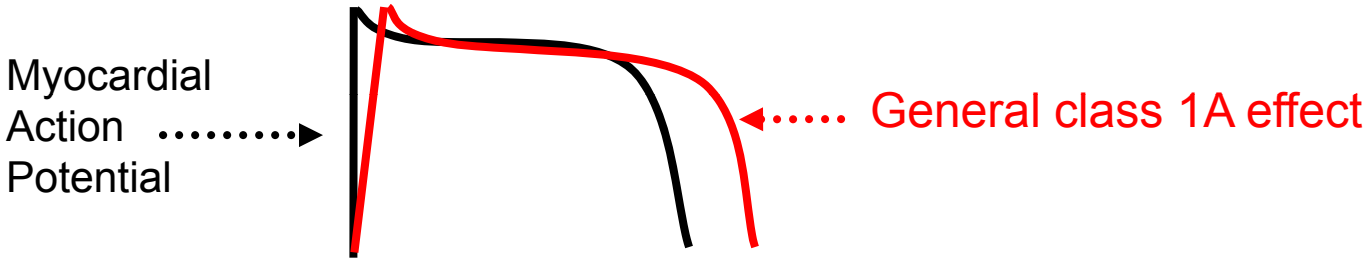
- Binds to central inhibitory α_2 receptors → ↓ sympathetic outflow:
  - ↓ TPR → ↓ BP
  - ↓ HR → ↓ BP

- Side Effects
  - Dry mouth
  - Sedation and weakness (orthostatic & post exercise hypotension)
  - Sexual dysfunction

Antiarrhythmic Drugs

Class IA antiarrhythmic agents NORPACE Disopyramide, PRONESTYL Procainamide

- Lengthens refractory period, ⬇ automaticity, slows overall conduction via:
  - Inhibition of the fast sodium channels
  - Prolongation of the action potential by inhibiting the repolarizing K^+ current



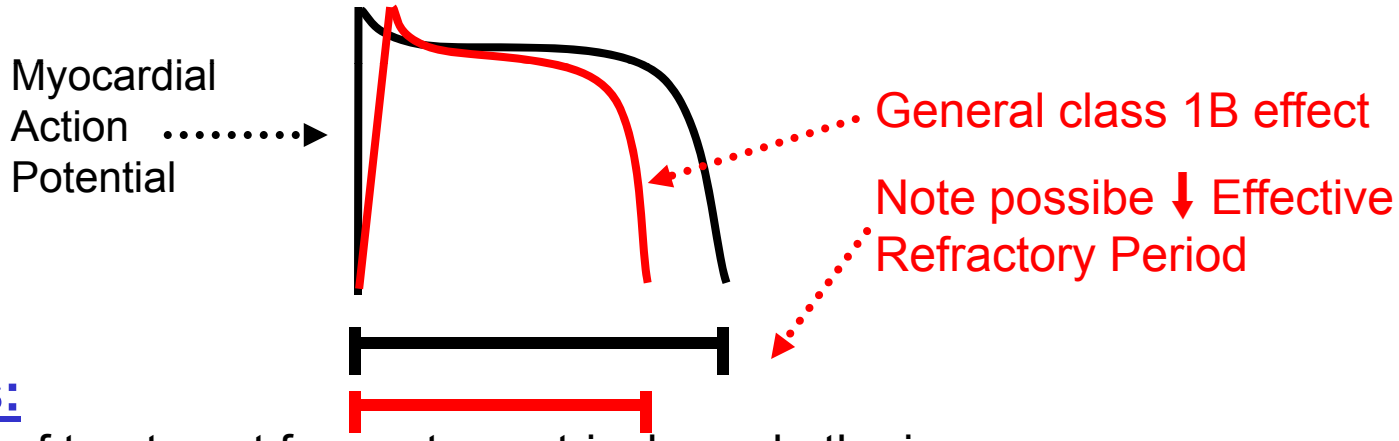
- **Indications:**
  - Treatment and prevention of recurrent ventricular tachycardia
  - Treatment of supraventricular arrhythmias and supraventricular tachycardias
    - Conversion of atrial fibrillation and atrial flutter to sinus rhythm
    - Prevention of PSVT
- **Precautions & side effects: nausea, diarrhea, vomiting**
- **Pro-arrhythmic effects**, ⬆ QRS & QT-interval ➡ ⬆ Torsades de Pointes risk
- SA blocks, ⬇ TPR ➡ orthostatic & post ex. hypotension, ⬆ HR, ⬇ contractility

Antiarrhythmic Drugs

Class IB antiarrhythmic agents **Lidocaine, TONOCARD Tocainide, Mexilititne**

Depresses automaticity and reduces the incidence of ventricular ectopic beats via:

- Inhibition of fast sodium channels → ↓ action potential duration
  - Works especially well in hyperkalemic (ischemic) myocardium & during MI



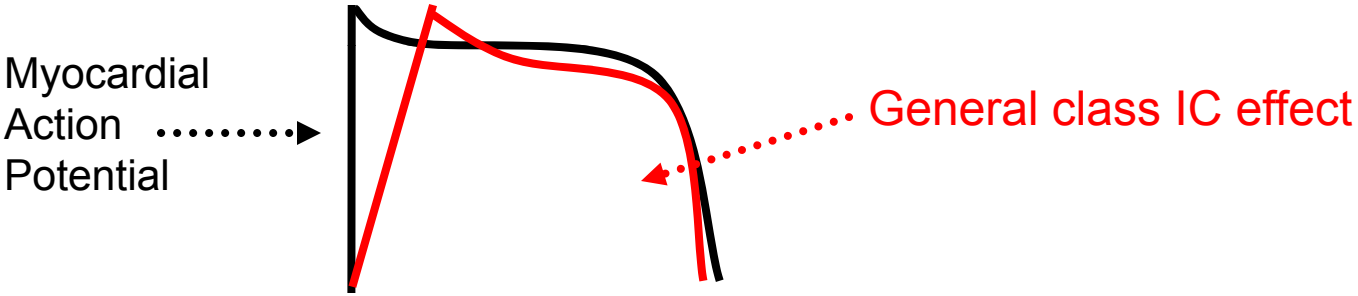
- **Indications:**
  - First line of treatment for acute ventricular arrhythmias
  - Also used in ventricular arrhythmias associated with cardiac surgery
- **Precautions & side effects:**
  - **Pro-arrhythmic effects**, limb tingling or burning (paresthesia), nausea, tremors

Antiarrhythmic Drugs

Class IC antiarrhythmic agents **RHYTHMOL Propafenone, TAMBICOR flecainide**

Depresses automaticity in ectopic beats via:

- Marked inhibition of the fast sodium channels
- **RHYTHMOL** has mild β - blocking and calcium channel blocking properties



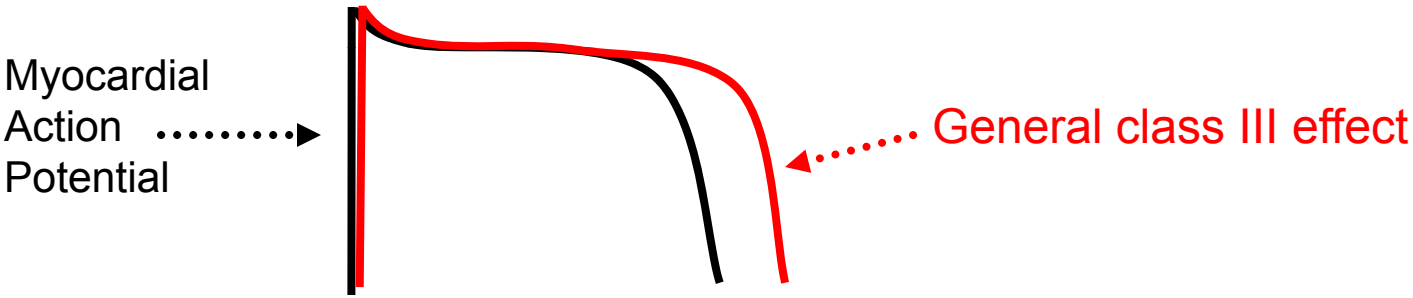
- **Indications:**
  - Treat ventricular tachyarrhythmias that are resistant to first line treatment
  - May be used to treat supraventricular arrhythmias (atrial fibrillation, PSVT)
- **Precautions & side effects:**
  - ↑ in PR, QRS intervals
  - **Substantial pro-arrhythmia tendencies** **ENKAID (Encainide)** is no longer used

Antiarrhythmic Drugs

Class III antiarrhythmic agents **CORDARONE Amiodarone, BETAPACE Sotolol, CORVERT Ibutilide, TYKOSIN Dofetilide**

Depresses automaticity in ectopic beats via:

- Inhibition of the potassium channels ➞ delayed repolarization
- **Sotolol** has β - blocking properties



- **Indications:**
  - Emergency Use: treatment of choice for shock resistant V-Fib
  - Used to treat and prevent atrial fibrillation, esepicially after cardiac surgery
- **Precautions & side effects:**
  - Pulmonary fibrosis and decreased pulmonary function
  - Not recommended for long term use

Antiarrhythmic Drugs

New Drug (2009) with properties of all Vaughn-Williams Classifications
MULTAQ Dromedarone

- Blocks sodium channels
- Blocks beta1-adrenergic receptors
- Alters adenyl cyclase generation (ie, negative inotropic effects)
- Blocks potassium channels ➞ prolongs cardiac repolarization.

- **Indications:**
  - Atrial Fibrillation and Atrial Flutter
  - Substantially reduces the likelihood of hospitalization in AF patients
- **Precautions & side effects:**
  - Known to cause death in heart failure patients **(black box warning)**
  - Not recommended for patients with 2nd or 3rd degree heart block

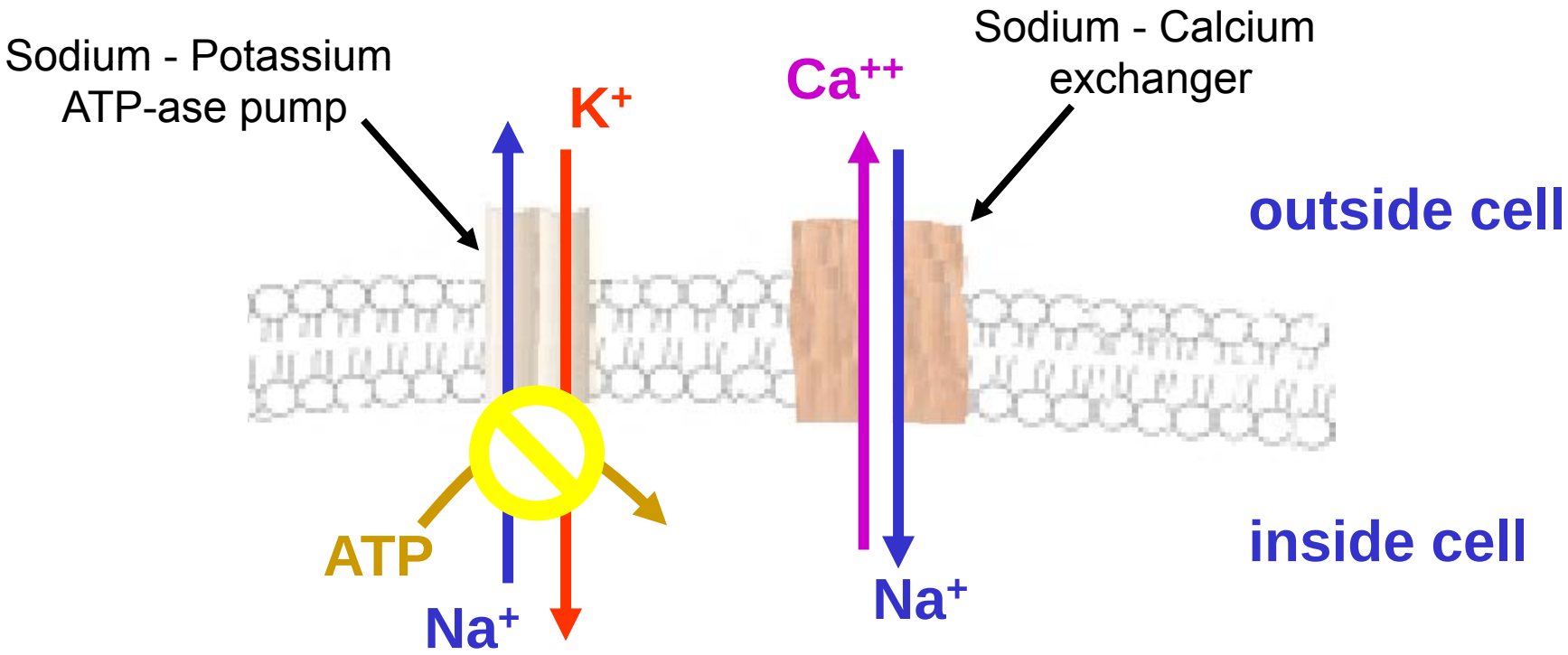
DIGITALIS DIGOXIN, LANOXIN

Poisons the Na^+ K^+ ATP-ase pump → ↑ $[Na^+]$ inside cell

- ↑ $[Na^+]$ inside cell → ↓ activity of exchanger → ↑ Ca^{++} inside cell
- ↑ Ca^{++} inside cell → ↑ myocardial contractility

Vagul stimulation → ↓ SA and AV activity → anti-arrhythmia effect

- Digitalis: Class 5 antiarrhythmic along with **ADENOSINE, ATROPINE**



Ca^{++} extrusion is passively linked to Na^+ extrusion from repolarizing cells. This process involves active transport and requires energy

Anti-platelet Drugs: Thienopyridines

PLAVIX (Clopidogril) TICLID (Ticlopidine)

- **Inhibits platelet aggregation (stops platelets from sticking together)**
- **Irreversibly blocks ADP receptors on platelet → no fibrin crosslinking**
  - ↓ platelet aggregation → ↓ clot formation (↓ atherothrombolic events)
  - Often used in conjunction with Aspirin
  - Often used after CABG surgery, angioplasty / stent placement
- **Indications:**
  - Helps prevent MI's, Strokes, TIA's
  - used to prevent clots in valvular heart disease or during various surgeries
- **Precautions & side effects:**
  - Major side effects: ↑ Gastrointestinal and other bleeding, ↓ neutrophil number
    - ↑ time for coagulation to take place → ↑ bleeding or bruising from trauma
      - use NSAID's with caution
  - FDA has issued updated warnings:
    - ↑ risk for heart problems & ↓ effectiveness in those with poor metabolism

Anti-platelet Drugs: Phosphodiesterase (PDE) Inhibitors

PERSANTINE (Dipyridamole) AGGRENOX (Dipyridamole + Aspirin)

- **Inhibits Phosphodiesterase → ↓ breakdown of C-AMP + ↑ Adenosine**
  - **↑ Cyclic-AMP in the platelet → ↓ platelet aggregation**
  - **↑ adenosine → relaxation of arterial smooth muscle → vasodilation**
    - Can be used as a coronary vasodilator in nuclear stress testing scenarios

- **Indications:**
  - Used as an adjunct to other anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement
  - **AGGRENOX** is used prophylactically to help prevent Strokes and TIA's

- **Precautions & side effects:**
  - Use cautiously in CAD patients (may cause chest pain), hepatic patients (Liver failure) and hypotensive patients (vasodilation may ↓ TPR → ↓↓↓ BP)

VIAGRA (Sildenafil), CIALIS (tadalafil), LEVITRA (vardenafil): PDE5 Inhibitors

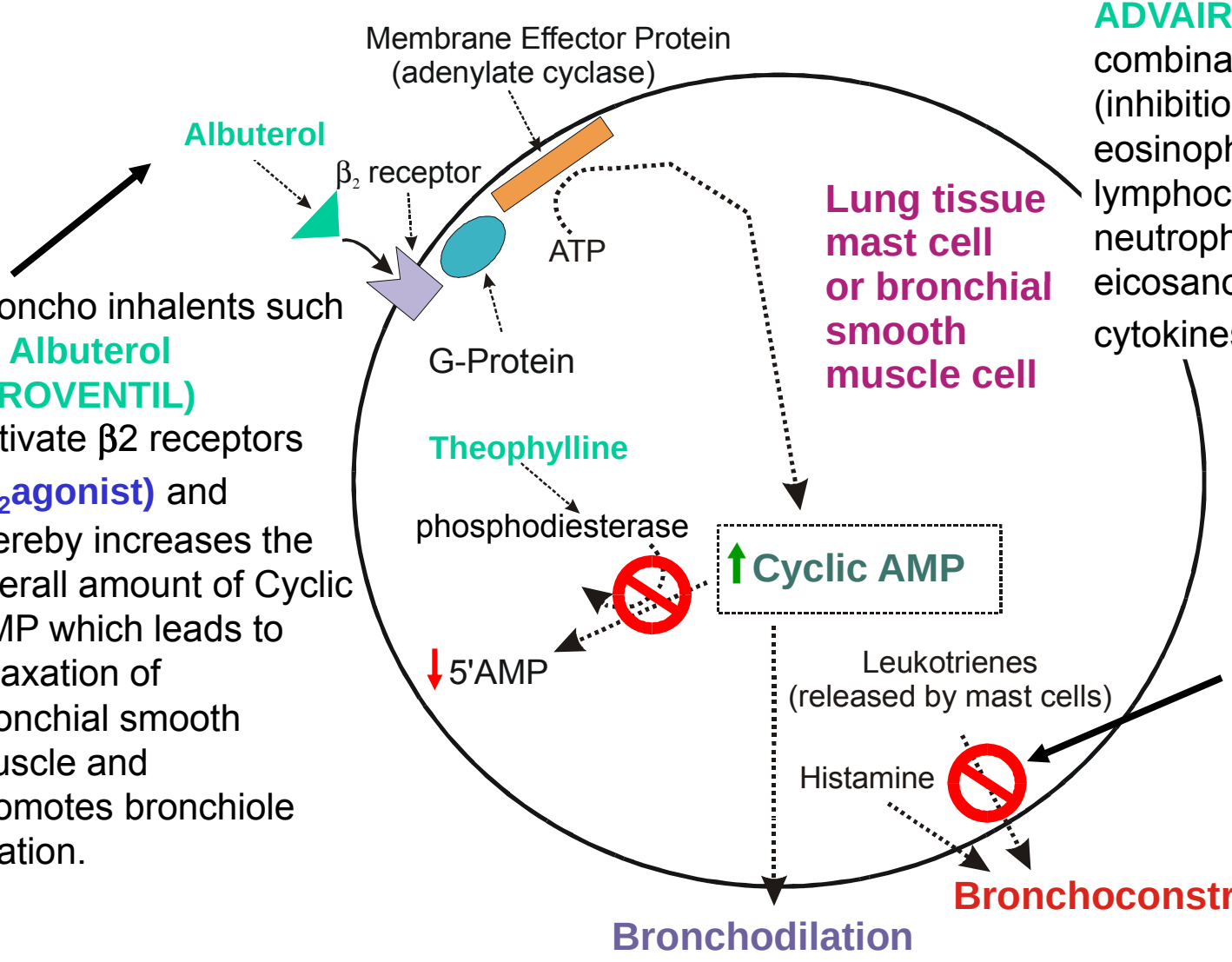
- ↓ PDE5 → ↑ Cylic-GMP → ↑ vascular smooth muscle relaxation in corpus cavernosum
  - vasodilation and ↑ blood flow to penis → better erection

Common drugs which are not used to directly affect cardiovascular function

- Bronchodilators and other COPD drugs
- Gastrointestinal medications
- Antilipemic (anti-cholesterol) drugs
- Tranquilizers
- Antidepressants
- Hypothyroid medications
- Cold & Flu Medications
- Alcohol & Nicotine
- Drugs that fight anemia as a side effect of chemotherapy
- Drug that fight breast and colon cancer

Bronchodilators

Methylzanthine drugs like **Theophylline (THEODUR)** **inhibit a form of the enzyme phosphodiesterase** which, in turn, results in an increase in Cyclic AMP (less Cyclic AMP converted to 5-AMP). The increase in Cyclic AMP promotes bronchodilation.



Broncho inhalents such as **Albuterol (PROVENTIL)** activate β2 receptors **($\beta_2$agonist)** and thereby increases the overall amount of Cyclic AMP which leads to relaxation of bronchial smooth muscle and promotes bronchiole dilation.

ADVAIR SYMBICORT – combination of **corticosteroid** (inhibition of mast cells, eosinophils, basophils, lymphocytes, macrophages, neutrophils histamine, eicosanoids, leukotrienes, and cytokines) plus a **β_2 agonist**

Montelukast drugs **(SINGULAIR, ACCOLATE)** **prevent the binding of leukotrienes to their receptors**, thereby preventing a bronchoconstriction response

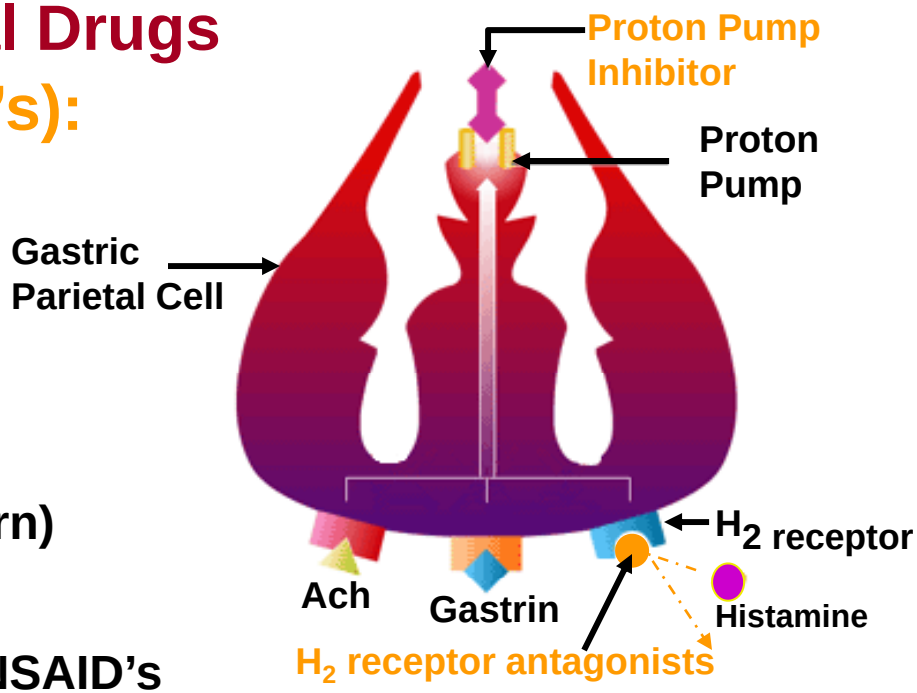
Gastrointestinal Drugs

1. Proton Pump Inhibitors (PPI's):

NEXIUM esomeprazole

PRILOSEC omeprazole

PROTONIX pantoprazole



Indications:

- Healing of Erosive Esophagitis
- Gastrointestinal Reflux Disease (Heartburn)
- Treatment & prevention of ulcers
  - Sometimes given to patients taking NSAID's

Effects:

- Inhibition of H+/ K+- ATPase
  - ↓ gastric HCL secretion

Adverse effects (rare):

- Diarrhea
- Feeling "sick"
- Constipation
- Abdominal pain
- Headaches
- "Wind"

2. Histamine H_2 receptor antagonists: ZANTAC ranitidine

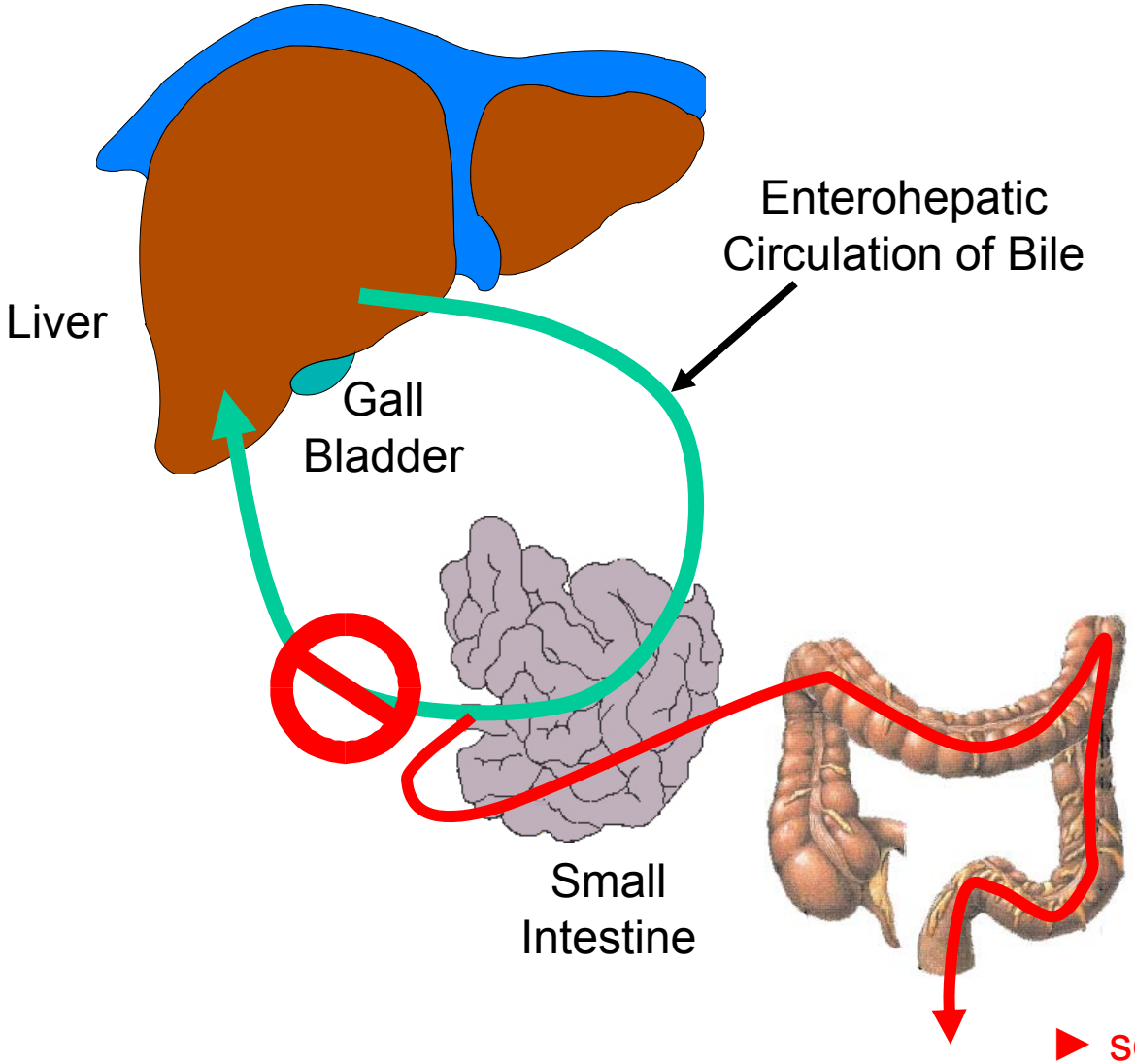
Effects:

- Inhibition of Gastric HCL secretion by competitive antagonism of Histamine
- Indications and Adverse effects are very similar to PPI's

Antilipemic Drugs

Bile Acid Binding Resins

QUESTRAN



Bile acids are created in the liver using cholesterol and are secreted into the small intestine to aid in digestion. They are reabsorbed in the distal end and are taken back to the liver in the portal circulation.

Bile acid binding resins prevent the reabsorption of bile acids, causing them to be eliminated via the large bowel. This forces the liver to remove cholesterol from the circulation (via an upregulation of LDL-C receptors) in order to make more bile, causing a decreases systemic cholesterol levels.

Side effects:

* constipation
  dyspepsia
  gas
  bloating

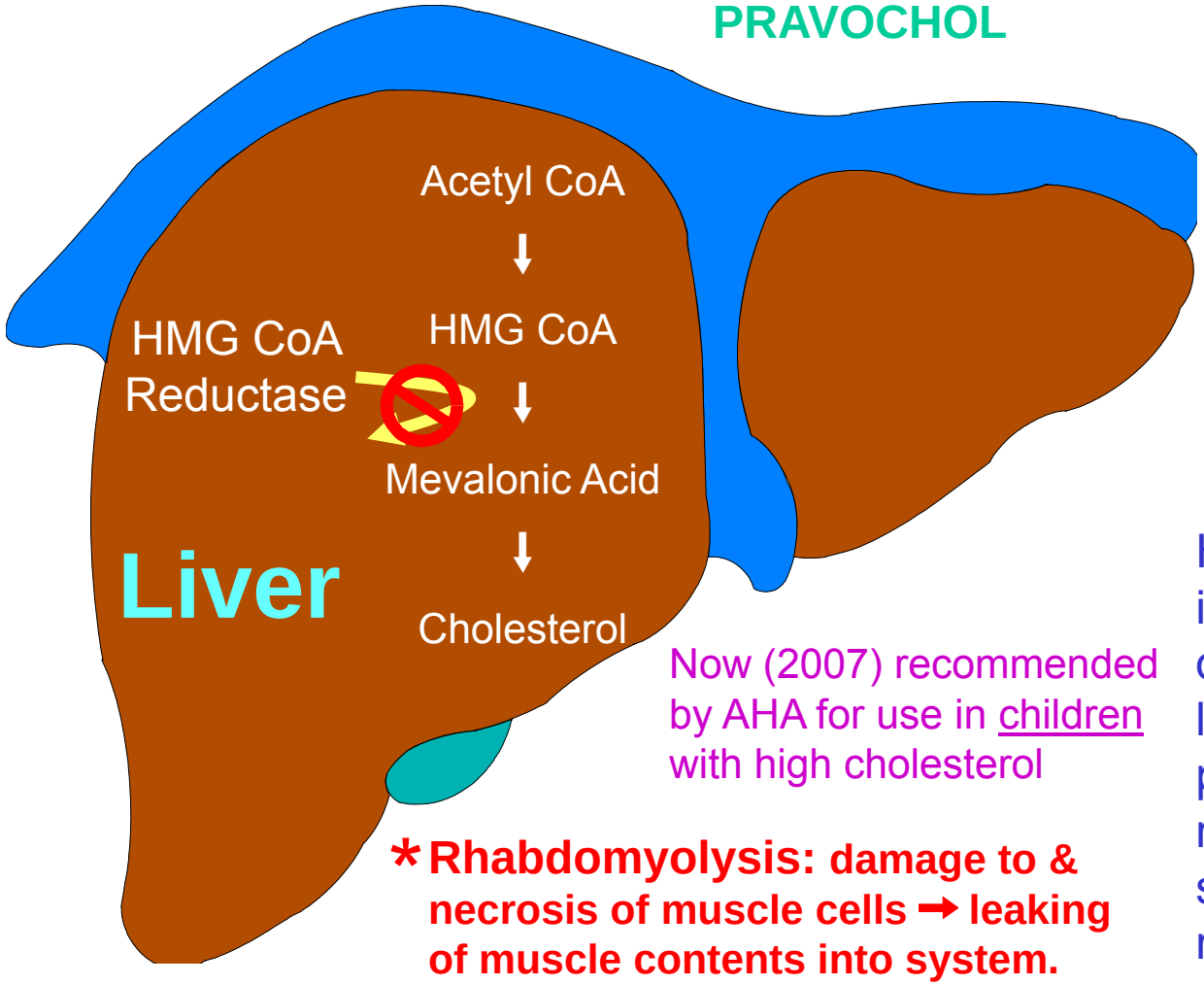
► sometimes used to treat diarrhea

Antilipemic Drugs

(most widly prescribed antilipemic)

HMG CoA reductase inhibitors (Statins)

LIPITOR ZOCOR CRESTOR PRAVOCHOL



Now (2007) recommended by AHA for use in children with high cholesterol

***Rhabdomyolysis:** damage to & necrosis of muscle cells ➡ leaking of muscle contents into system. Myoglobin may block kidney glomeruli ➡ kidney failure*

Side effects: (usually mild)
variety of GI problems
⬆ liver enzymes myalgia
***Rhabdomyolysis**

Recent studies through 2007 suggest statin drugs may ⬇ BP, ⬇ risk of: colon, lung, & prostate cancer, diabetes, Alzheimer's, COPD, CHF hospitalizations, osteoporosis, and community pneumonia.

LIPITOR
#1 selling drug in 2005
$12.9 billion for Pfizer

HMG CoA reductase inhibitors inhibit the rate limiting enzyme of cholesterol synthesis in the liver. Although cholesterol production is only slightly reduced, lipid clearance is significantly enhanced via up-regulation of LDL-receptors.
1 in 6 could benefit (better lipid profile) from taking a statin.

Antilipemic Drugs

Combination of intestinal absorptive drugs and statins
VYTORIN (2007 best selling drug), (ZETIA (Ezetimibe) plus ZOCOR (Simvastatin)

- **ZETIA inhibits sterol transporter in small intestine → ↓ cholesterol absorption**
- **ZOCOR is an HMG CoA reductase inhibitor → ↓ cholesterol synthesis**

Fibric Acid Derivatives **LOPID (gemfibrozil)**

- ↑ lipoprotein lipase activity → ↑ breakdown of VLDL-C → ↓ LDL-C
- ↑ transfer of TG from VLDL-C and Chylomicrons to tissues & HDL-C → ↓ TG
- Drug of choice for hypertriglyceridemia and genetic TG disorders

Nicotinic Acid **NIACIN** - high doses necessary - available without a RX

- ↓ flux a fatty acids from adipose tissue to liver → ↓ VLDL-C → ↓ LDL-C + ↑ HDL-C
- Side effects are common: flushing, rashes, itching, GI disturbances
- Seldom used due to ineffectiveness and side effects

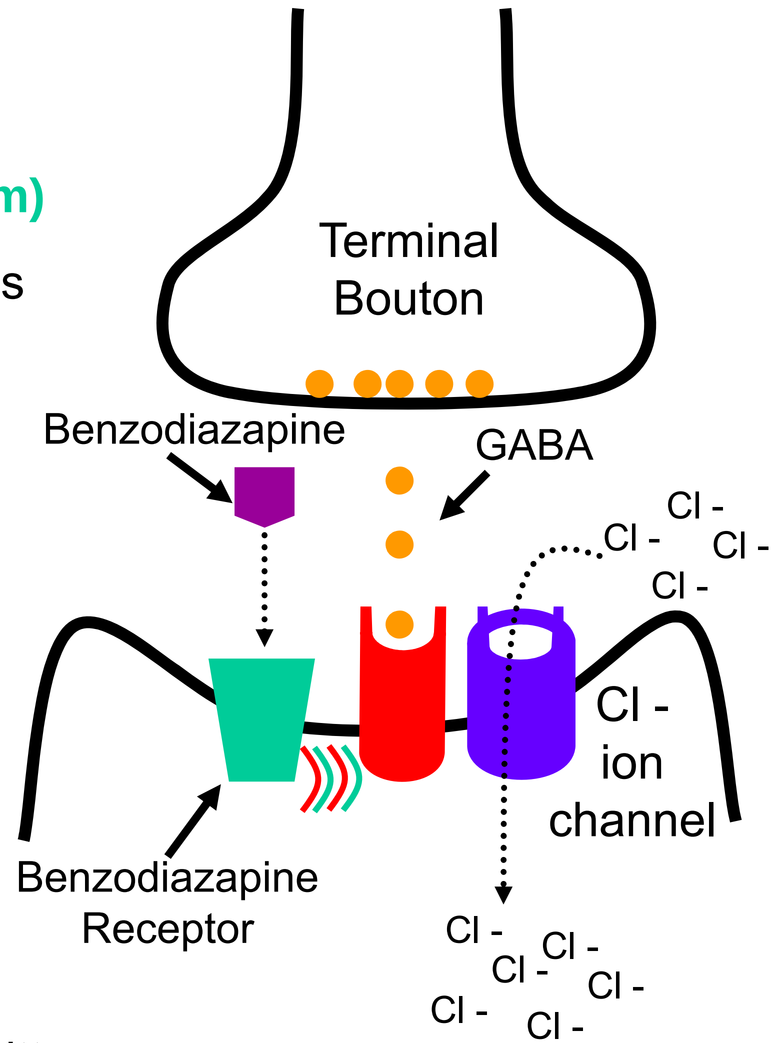
Anxiolytic Drugs

<u>**Benzodiazapines**</u>: minor tranquilizers

ATIVAN (Lorazapam), VALLIUM (Diazapam),

XANAX (Alprazolam), Rohypnol (Flunitrazepam)

- augments the activity of GABA inhibitory neurons
    - more Cl - ➞ hyperpolarization of neuron
    - "short circuits" depolarization of neurons
- has an anxiolytic effect (⬇ anxiety)
- may ⬇ HR and BP simply by ⬇ anxiety
    - often given to acute MI patients
- Side effects: drowsiness, ataxia, dependence



<u>**Azapriones**</u>: **BUSPAR (Buspirone)**

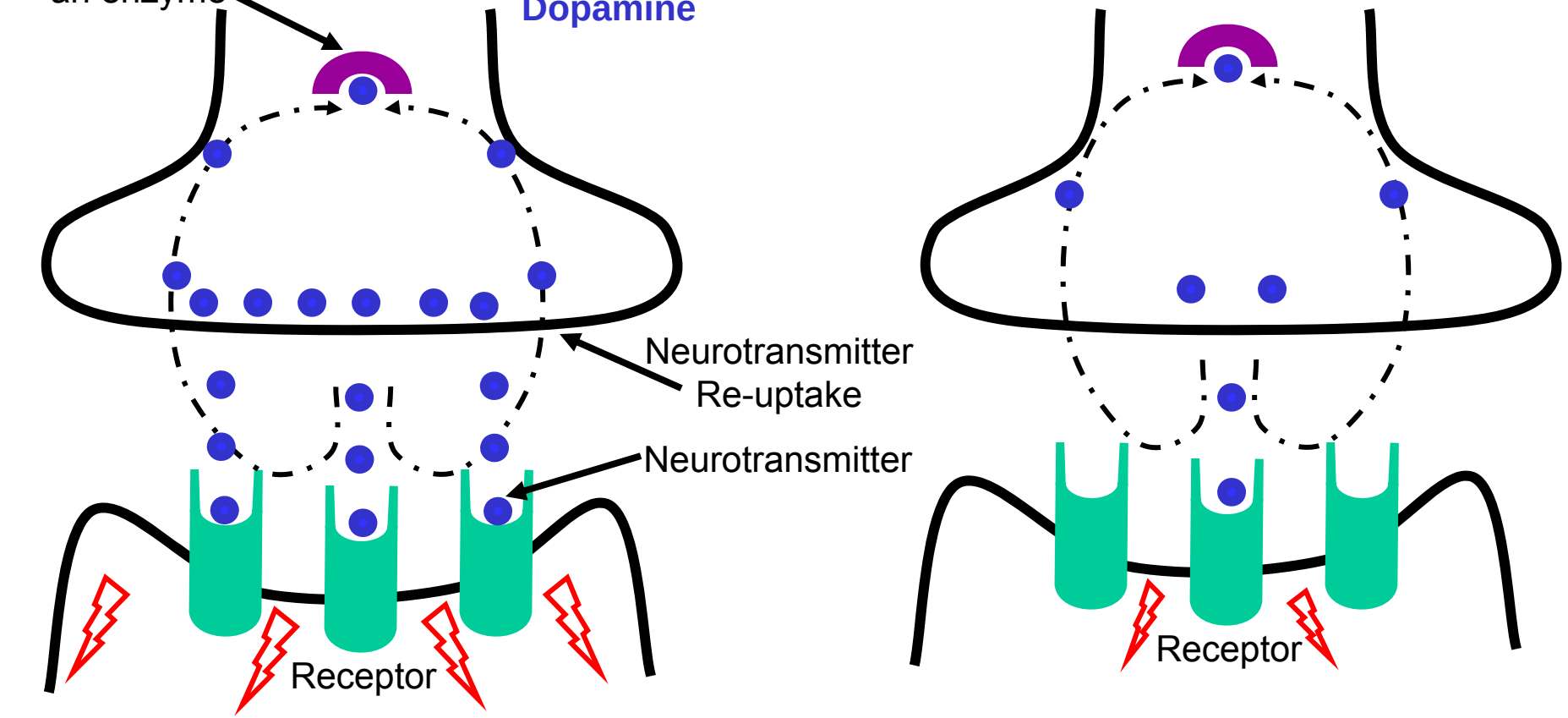
- ⬇ firing of neurons using 5-HT as a neurotransmitter
    - no significant side effects

Depression

In **normal brain activity**, neurotransmitters are constantly being released, re-absorbed, and then broken down using an enzyme

In **depression**, fewer neurotransmitters are being released which leads to a reduction in stimulation of target brain cells

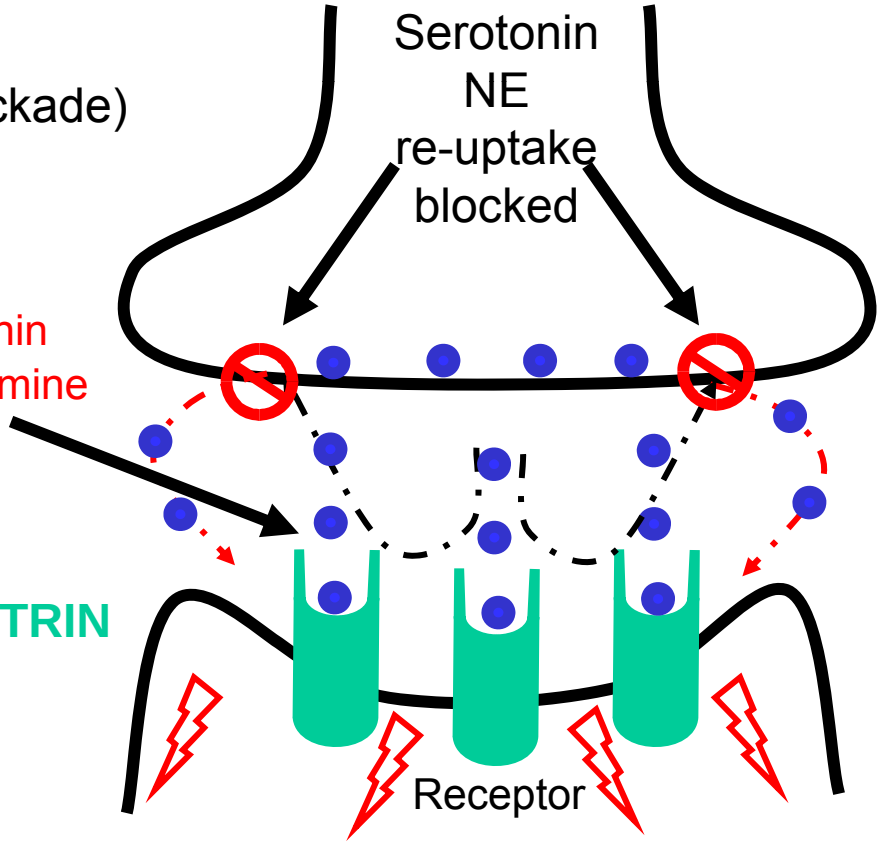
Neurotransmitters:
5-hydroxytryptamine (5-HT) (Serotonin)
Norepinephrine (NE)
Dopamine



Antidepressants

Tricyclic Agents: **ELAVIL TOFRANIL PAMELOR ABILIFY**

- block the re-uptake of serotonin and NE (some block dopamine as well)
  - ↑ serotonin and NE → ↑ excitation & stimulation
- all TCA's may also partially block histamine, muscarinic, α1, and α2 receptors
- Side Effects:
  - dry mouth, constipation (muscarinic blockade)
  - postural hypotension (α1 blockade)
  - sedation (histamine blockade)
  - loss of libido, anorgasmia
- Contraindications
  - recent MI or SA block
    - ↑ risk of conduction problems



Heterocyclic Agents: **DESYREL WELLBUTRIN ZYBAN**

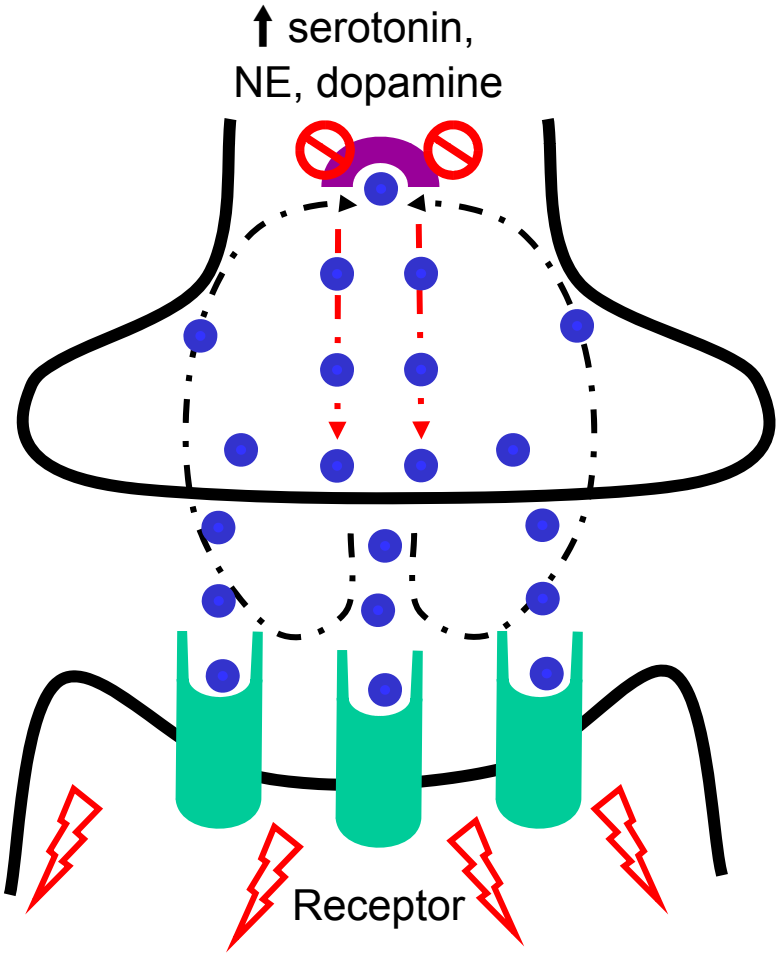
- similar to tricyclics
  - block different neurotransmitters to variable degrees

Antidepressants

Monoamine Oxidase Inhibitors (MAOI's):

NARDIL PARNATE

- block the action of MAO → ↓ breakdown of NE, dopamine, & 5-HT
- A form of MAO resides in the GI tract and breaks down the protein tyramine (MAOI drugs would negate this breakdown → tyramine enters the circulation)
  - If tyramine enters the circulation, a hypertension crisis may ensue
  - people who take MAOI's must avoid foods rich in tyramine
    - cheese, chicken liver, beer, chianti wine
  - because of this danger MAOI inhibitors are usually the last drug to be tried

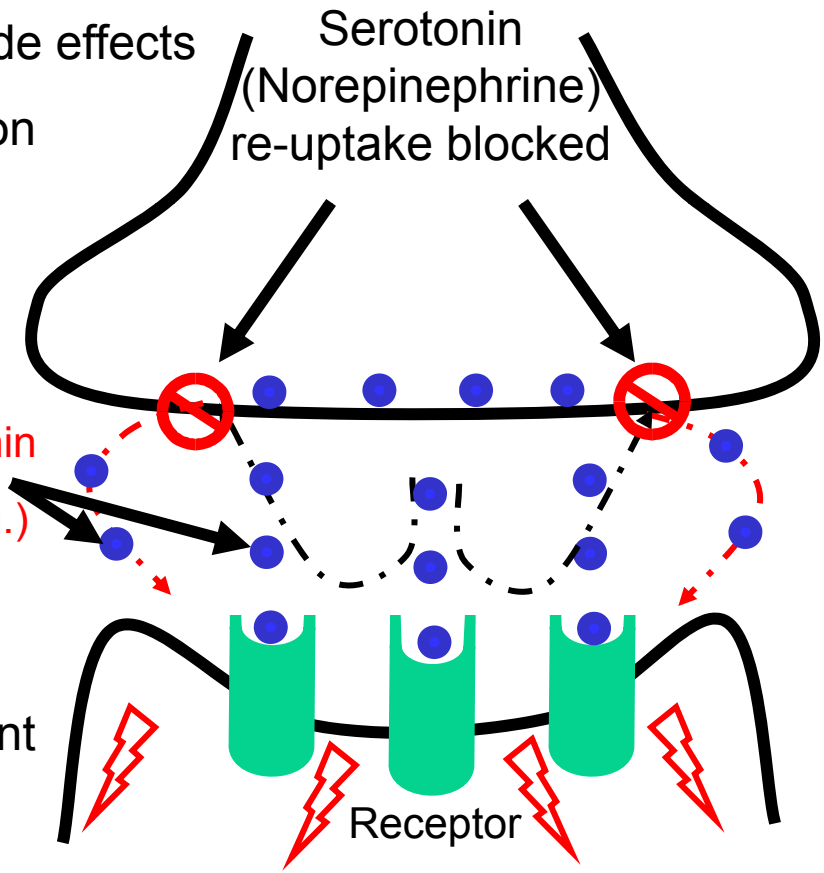


Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRI's):

PROZAC ZOLOFT PAXIL CELEXA

- Inhibits the re-uptake of serotonin in the synaptic cleft
- Similar to TCA drugs but without the really bad side effects
    - first line drug to be used to combat depression
- Side Effects: anxiety, agitation, insomnia



- **Selective Serotonin – Norepinephrine Re-uptake Inhibitors (SSNRI's)**

EFFEXOR

CYMBALTA (2nd leading drug sold in US: 2007)

- may also bloc dopamine reuptake to a small extent

Thyroid Medications

- **Hypothyroidism:** autoimmune destruction of thyroid (myxedema) → ↓ T3 & T4
  - Although 90% of the secreted thyroid hormone is T4, T3 is 10 X more potent
  - T4 is converted to T3 in the liver, kidney, and other tissues
  - **T3 is the active hormone**
  - In the blood, T4 & T3 are partially bound to proteins:
    - thyroxine binding globulin, transthyretin, and albumin
  - Only a very small fraction of the circulating hormone unbound and active:
    - T4 has .03% unbound (free) and T3 has .3% unbound (free)
    - Thyroid hormones regulate metabolism
- **Hypothyroid medications** (replaces lost endogenous thyroid hormone T4)
  - **SYNTHROID, LEVOTHROID levothyroxin**
- **Adverse Reactions**
  - Resting & Exercise HR and BP may be higher than normal
    - In CAD angina patients, Ischemia may ↑ due to ↑ myocardial demand
  - An increased incidence of arrhythmias has been reported in some people

Drugs Used to Decrease Incidence of Infection Caused by Neutropenia due to Chemotherapy

NEULASTA Pegfilgrastim, NUPOGEN Filgrastim
(Granulocyte Colony Stimulating Factor)

Indications:

- **Reduce the incidence of infection due to Neutropenia**
  - **Neutropenia (reduction in neutrophil number) caused by chemotherapy for myeloid cancers (cancers of granulocytes, monocytes, and platelets)**

Effects

- **Stimulates hematopoietic cells**
  - **↑ Neutrophil number & function**

Adverse Reactions

- **Spleen enlargement or rupture**
- **Allergic reactions**
  - **Wheezing, dizziness, ↓ BP**

New Drug Used to Treat Breast Cancer

HERCEPTIN Trastuzumab

Indications:

- Breast cancer that over-expresses HER2 protein receptors
  - HER2: Human Epidermal growth factor Receptor 2
  - 25% of breast cancers are HER2 positive
  - HER2 is a very aggressive form of breast cancer
    - Less likely to respond to treatment
    - More likely to return

Effects

- Inhibition of tumors expressing HER2 proteins
  - Tags HER2 cells for body defenses
  - Restricts substances that tells HER2 cells to divide

Adverse Reactions

- Cardiomyopathy
  - Left ventricular failure
- Infusion reactions
  - Pulmonary problems, anaphylaxis
- Exacerbation of neutropenia
  - From chemotherapy

Notes: this drug has a black box warnings from the FDA

New Drug Used to Treat Colon Cancer

AVASTIN Bevacizumab

Indications:

- Metastic cancer of the colon or rectum
- Non - squamous non small cell lung cancer
- HER2 negative breast cancer

Effects

- Binds to and inhibits biologic activity in human vascular endotheleum.
  - Inhibits vascular growth factors resulting in a reduction of the cancer's blood supply (inhibits angiogenesis)

Adverse Reactions

- Gastrointestinal perforations
- Incision healing complications
  - Wound dehiscence – spontaneous opening of suture lines
- Pulmonary Hemorrhage
  - From chemotherapy

Notes: this drug has a black box warnings from the FDA

New Drugs Used to Treat Diabetes

ACTOSE Pioglitazone Hydrochloride

Indications:

- Type II Diabetes

Effects

- Decreases insulin resistance in the periphery and in the Liver

Adverse Reactions

- Exacerbation of CHF
- May ↓ Hematocrit and Hb
- May cause edema

LANTUS Pioglitazone Hydrochloride (human insulin analog)

Indications:

- Adult & Pediatric Type I Diabetes
- Adult Type II Diabetes requiring control of hyperglycemia

Effects

- Facilitates glucose uptake like insulin

Adverse Reactions

- Hypoglycemia
- Allergic Reactions

AVANDIA Rosiglitazone Maleate

Effects

- agonist (activator) for peroxisome proliferator- activated receptor-gamma PPAR-γ which results in increased insulin sensitivity

Indications:

- Type II Diabetes

Adverse Reactions

- Exacerbation of CHF
- May cause ischic events & MI
- May cause edema

Cold & Flu Medications

- **Histamine receptor blockers (antihistamines):**
  - H1 blockers are divided into 2 groups
    - short acting (less than 12 hour half life)

      CHLORTRIMETON (chlorpheniramine), TYLENOL COLD, THERAFLU

      CLARITIN (Loratadine)
    - long acting (more than 12 hour half life)

      SELDANE (terfenadine), CLARITIN
  - Short term antihistamines have chemical structures similar to CNS depressants
    - sedation (drowsiness) is a prominent common side effect
  - Long acting antihistamines take longer to accumulate in CNS ➞ less sedation
  - Indications: colds, flu, allergic rhinitis, upper respiratory infections

Cold & Flu Medications

- **Sympathomimetic amines (decongestants):**

  NEO-SYNEPHRINE, SUDAFED (pseudophedrine), AFRIN

- These drugs act on the α1 receptors in the nasal mucosa
  - α1 activation → ↑ vasoconstriction (↓ fluid to mucosa) → ↓ secretions
  - Rebound vasodilation after drug wears off → habit forming vicious circle
  - HR and BP may be increased

- **Combination Drugs**
  - **ACTIFED** - pseudoephedrine (decongestant) + Tripolidine (antihistamine)
  - **CLARITIN-D** – pseudoephedrine (deongestant) + Loratadeine (antihistamine)

Alcohol & Nicotine

- **Alcohol:**
  - CNS depressent
  - May be associated with elevation of both HR and BP
- **Nicotine**
  - Elevation of HR and BP have been found in tobacco users
  - Causes vasoconstriction
  - May precipitate various tachycardias