# 20.201 Mechanisms of Drug Action

## Lecture #20: Omeprazole Case Study

November 7, 2005

# Review of Lecture #19

- Covered the concepts of PBPK's
- Constructed a PBPK model based on cisplatin

# Today

- Brief lecture on receptors and drug-receptor interactions
- Begin omeprazole case study

## *Drug-receptor interactions*

- ***Pharmacodynamics*** - Quantitative relationship between drug binding to a receptor and the pharmacological effect

- ***Definition of a receptor*** - Cellular macromolecule that specifically (chemically) recognizes a ligand and carries out a function in response to ligand binding.

  Limitations: Fat cells are not receptors for lipophilic drugs: no specific function follows

- Receptors provide means to "amplify" drug
  ~ Example: 70 μg sufentanil causes respiratory arrest
  ~ 1 billionth the mass of 70 kg adult

- **Types of receptors**
  - Trans membrane ion channels: conduct ions across membrane in response to ligand binding, voltage gradient or second messenger; e.g., $H^+/K^+$-ATP'ase
  - Transmembrane linked to intracellular G protein; e.g., adrenergic receptors
  - Transmembrane with enzymatic cytosolic domain; e.g., receptor tyrosine kinases
  - Intracellular: cytoplasm or nucleus; e.g., DNA, estrogen receptor

- Drugs not acting through "receptors"
  - ethanol (?)
  - general anesthetics
  - antacids
  - osmotic diuretics

## Types of receptors

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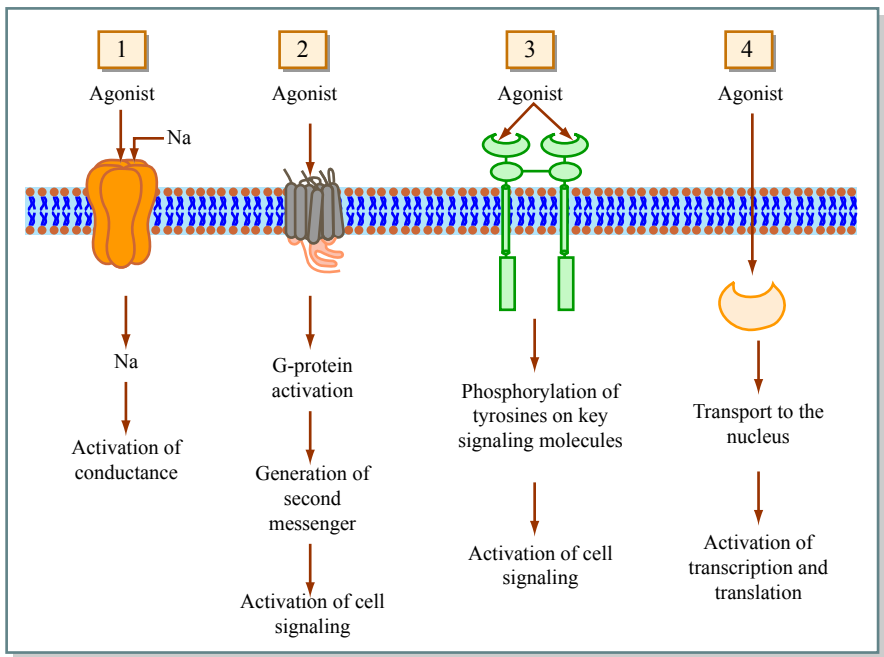



Figure by MIT OCW.

## *Characteristics of a Receptor*

- ***Specificity***
  - Receptor interacts with one type of ligand or a structurally related family of ligands
  - Competition between related ligands
  - Example: glucose transporter binds D-glucose specifically

| ***Substrate*** | $K_m$ |
|---|---|
| L-Glucose | >3000 |
| Galactose | 30 |
| Mannose | 20 |
| D-Glucose | 1.5 |

- ***Affinity***
  - Energetics of ligand receptor interactions
  - Energetics of binding determine specificity

- ***Intrinsic activity***
  - A measure of the ability of a bound drug to activate the receptor
  - Distinguishes agonist from antagonist

- ***Saturability***
  - Finite number of binding sites on a receptor, along with specificity of interactions, implies that binding sites can become fully occupied with ligand molecules
  - Additional ligand leads to non-specific binding

## *Types of Chemical Bonds in Ligand-Receptor Interactions*

- Affinity and Specificity based on chemical bonds
- Covalent binding of omeprazole occurs only after non-covalent, specific interaction with $H^+/K^+$-ATPase
- Ionic bonds ⮙ initial attraction
- Cation-π interactions, hydrogen bonds ⮙ improved binding, some specificity
- Van der Waals forces, hydrophobic interactions ⮙ most specificity

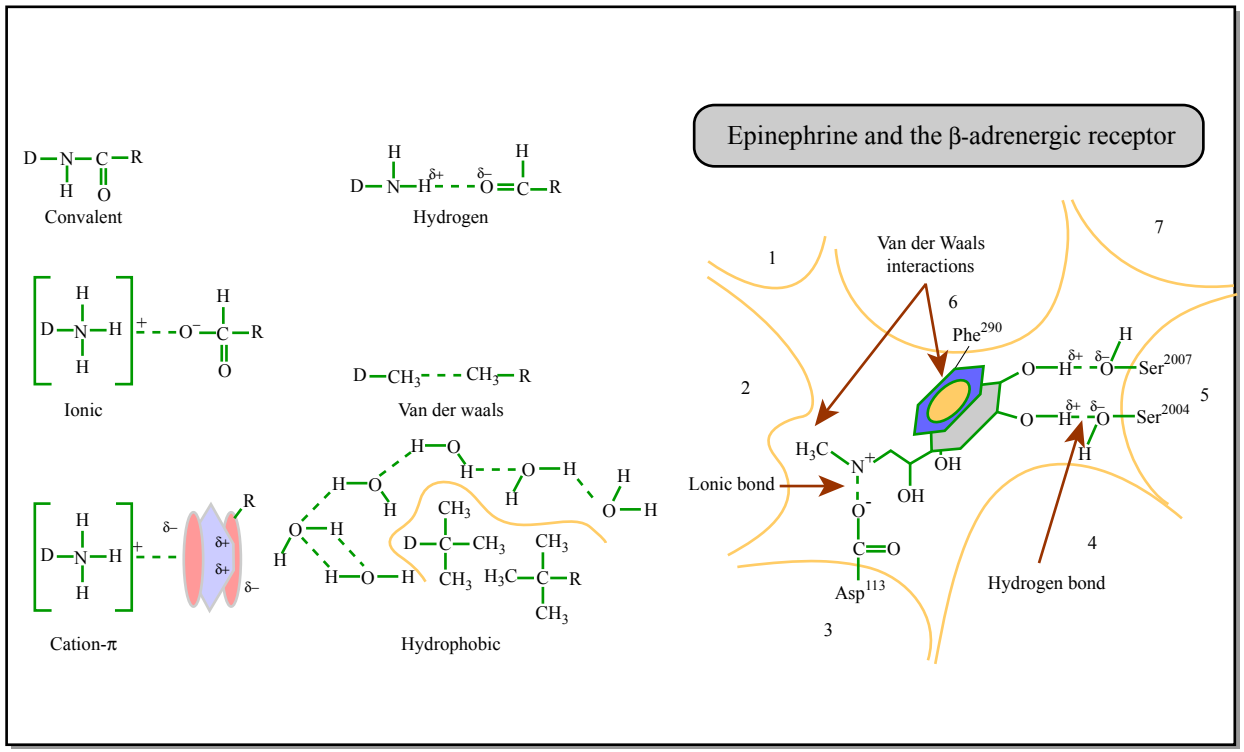



Figure by MIT OCW.

# *Quantitation of Ligand-Receptor Interactions*

• Consider interaction of drug (X) with receptor ( R) single binding site
• Equivalent to multiple non-interacting binding sites on a single receptor molecule

$$K_a = \frac{1}{K_d} = \frac{[RX]}{[R][X]}$$

• Association constant; not acidity
• [R] = unoccupied receptor
• [X] = free (unbound) drug concentration

$$\Delta G_f^\circ = -RT\ln(K_a)$$

• R = gas constant; T = temperature
• -$\Delta$G = tight binding

• Define "saturation fraction" = r
• average number of ligands bound per receptor molecule (Langmuir isotherm)

$$r = \frac{[X]_{bound}}{[R]_{total}} = \frac{[RX]}{[R]_{free} + [RX]}$$

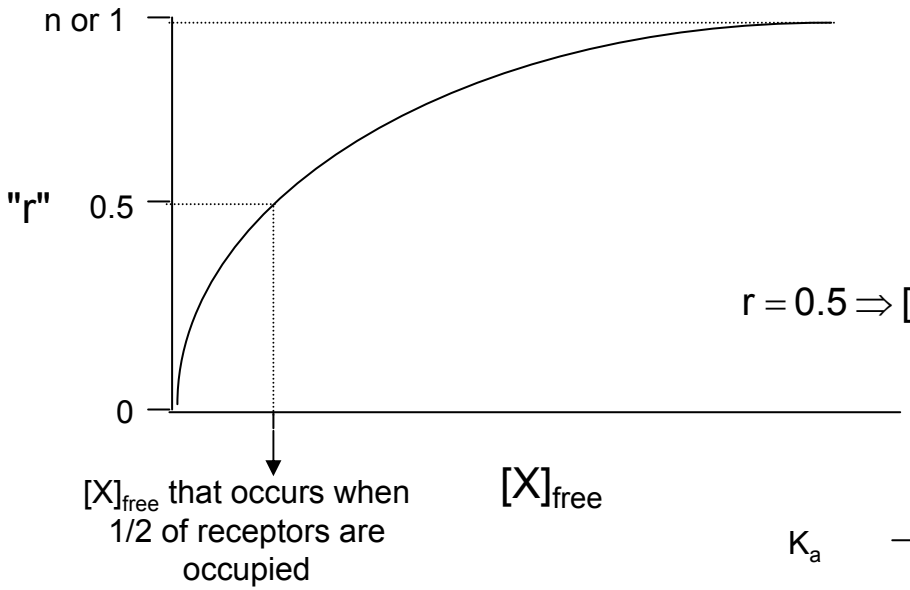
$$K_a = \frac{[RX]}{[R]_{free}[X]_{free}} \Rightarrow r = \frac{K_a[R]_{free}[X]_{free}}{[R]_{free} + (K_a[R]_{free}[X]_{free})} = \frac{K_a[X]_{free}}{1 + [X]_{free}}$$

•For receptor with "n" binding sites:

$$r = \frac{nK_a[X]_{free}}{1 + [X]_{free}}$$

# *Quantitation of Ligand-Receptor Interactions*

- Binding isotherm: increase ligand concentration and measure bound and free (at constant temp)
- Nonlinear regression to fit the data and determine $K_a$



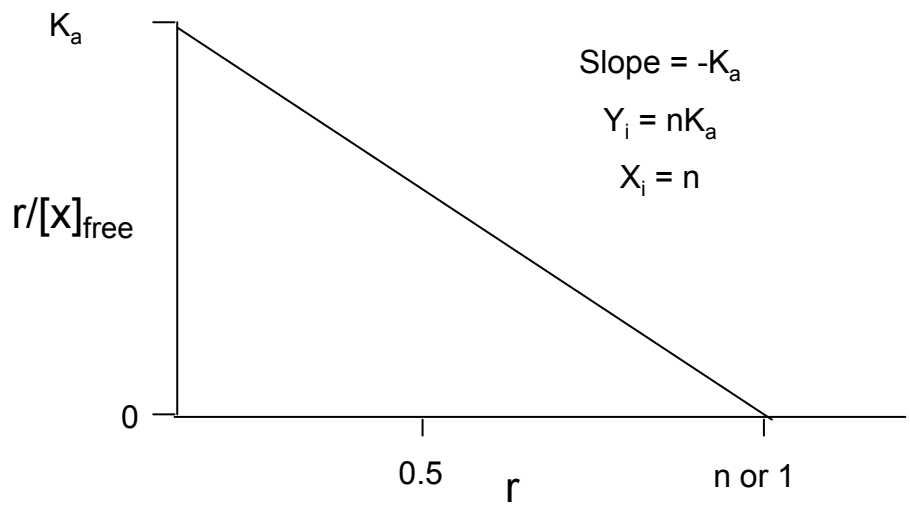

$$r = \frac{nK_a[X]_{free}}{1+[X]_{free}}$$

$$r = 0.5 = \frac{K_a[X]_{free}}{1+[X]_{free}}$$

$$r = 0.5 \Rightarrow [R]_{free} = [RX] \Rightarrow K_a = \frac{1}{[X]_{free}} \text{ and } \frac{1}{K_a} = [X]_{free1/2}$$

- More useful presentation of binding data
- "Scatchard plot": $r/[X]_{free}$ versus r

$$r = \frac{nK_a[X]_{free}}{1+[X]_{free}} \Rightarrow \frac{r}{[X]_{free}} = nK_a - K_a r$$



## *Agonists and Antagonists*

- ***Agonist***
  - Ligand that binds to receptor and stabilizes an "active state" of the receptor
  - "Active state" is defined as the functionally activated form (e.g., open ion channel, activated tyrosine kinase)
  - Endogenous ligands are generally agonists: neurotransmitters

- ***Antagonist***
  - A ligand that binds to the receptor with affinity/specificity but does not have intrinsic activity
  - Inhibits the action of an agonist but has not activity in the absence of agonist
  - ***Receptor antagonist*****:** binds to the active site or an allosteric site *reversibly* or *irreversibly*
  - ***Non-receptor antagonist*****:** binds to molecule downstream in activation pathway, or acts in a pathway that opposes the agonist pathway
    - ~ *Chemical antagonist*: protamine binds to and inhibits heparin, an anticoagulant
    - ~ *Physiological antagonist*: β-adrenergic receptor agonists block the tachycardia caused by hyperthyroidism (though thyroid hormone acts by a different receptor)

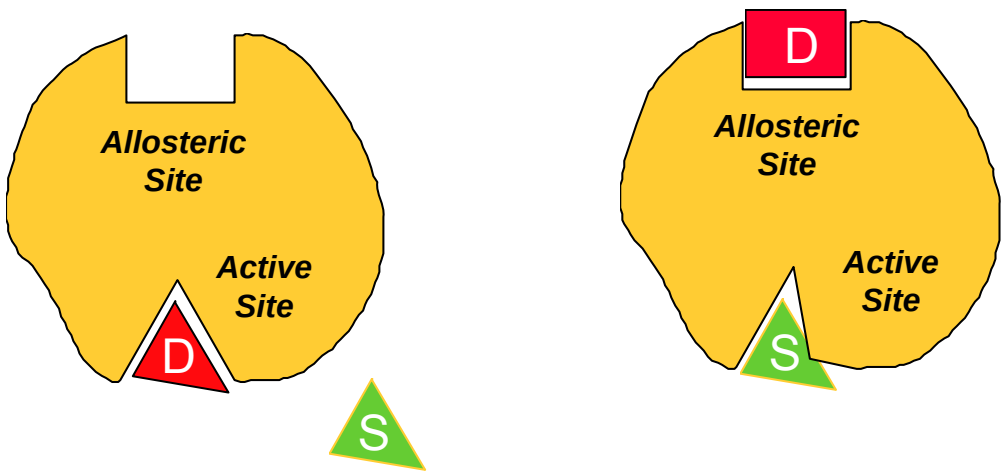
# *Agonists*

- Ligand that binds to receptor and stabilizes an "active state" of the receptor
- "Active state" represents conformational change caused by agonist binding
- Binding can occur at the active site or at another region of the receptor (exerts allosteric effects)
- The kinetics of drug binding and receptor activation are distinct

$$D + R \underset{k_{off}}{\overset{k_{on}}{\leftrightarrows}} DR \underset{k_{\beta}}{\overset{k_{\alpha}}{\leftrightarrows}} DR^*$$

***Potency*** ***Efficacy***

- ***Potency*** related to drug binding affinity (i.e., association constant)
- ***Efficacy*** related to the rate and extent of receptor activation AFTER drug binding

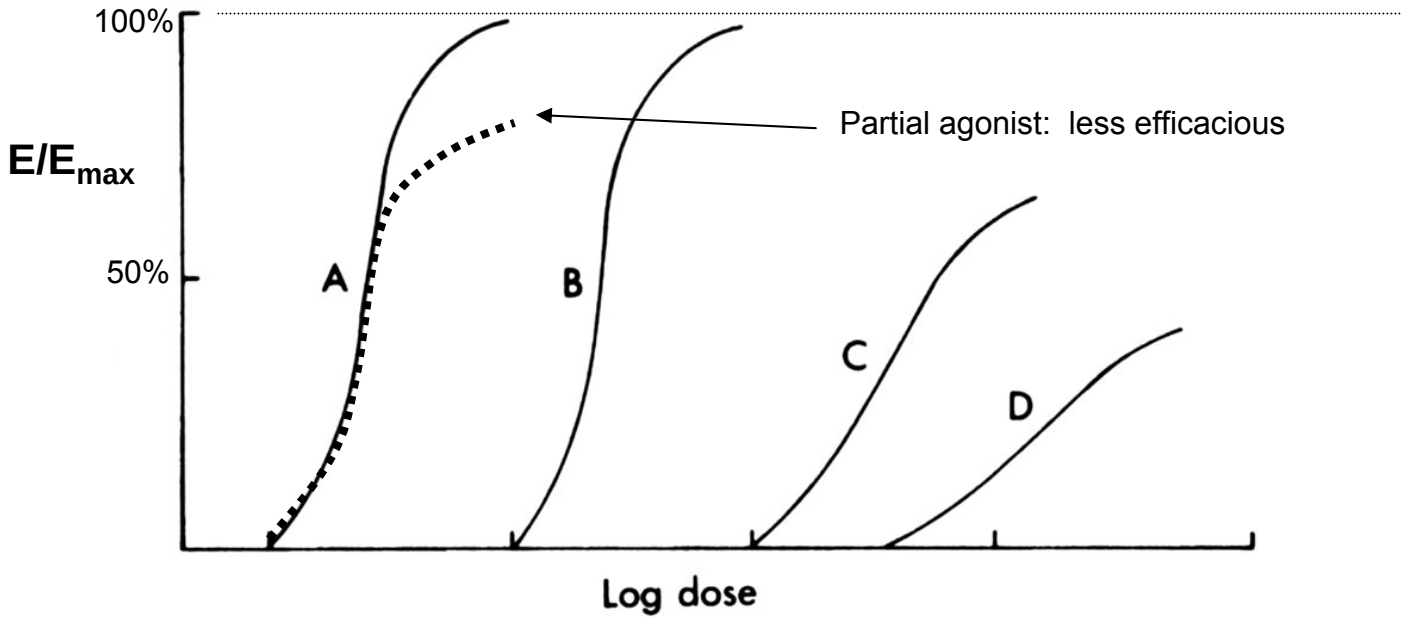


$$D + R \underset{k_{off}}{\overset{k_{on}}{\leftrightarrows}} DR \underset{k_{\beta}}{\overset{k_{\alpha}}{\leftrightarrows}} DR^*$$

***Potency*** ***Efficacy***

## *Agonists*

- ***Potency*** related to drug binding affinity (i.e., association constant)
- ***Efficacy*** related to the rate and extent of receptor activation AFTER drug binding
- ***Partial agonist***: sub-maximal response when drug binds to receptor; judged relative to the most efficacious drug in class



## *Irreversible Antagonists*

- ***Irreversible Antagonist = Noncompetitive Antagonist***
  - Drug binds to receptor at active or allosteric site with extremely high affinity or by covalent bonds
  - Example: omeprazole
  - Antagonist action terminates when receptor degraded

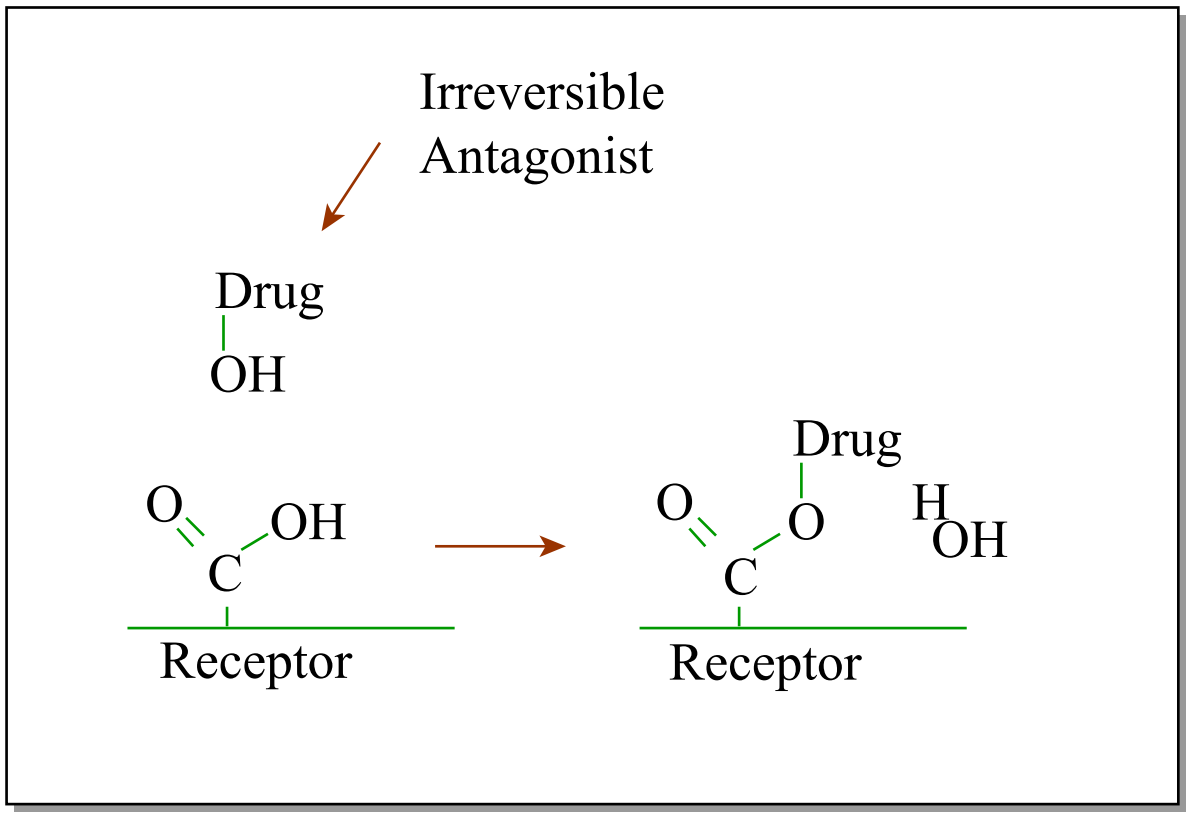



Figure by MIT OCW.

# Gastric anatomy

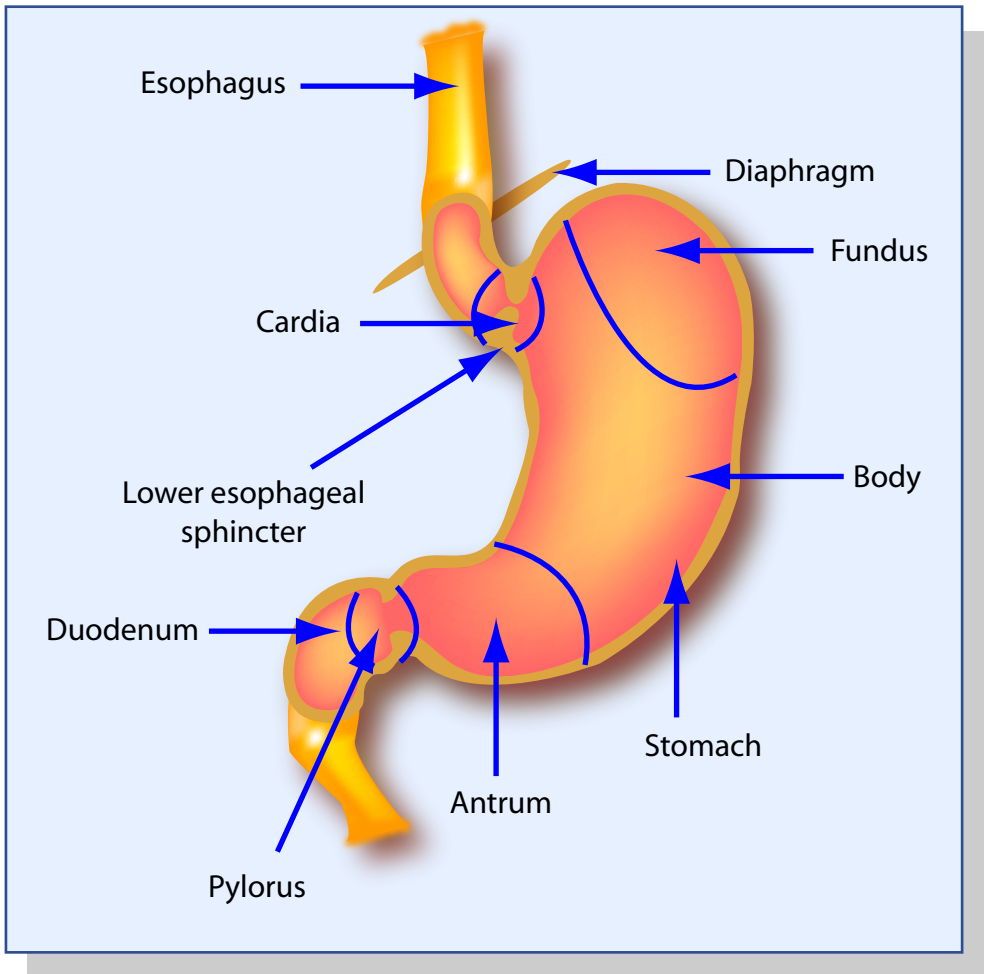



Figure by MIT OCW.

# Gastric anatomy and physiology

**Gastric Gland Structure**

**Gastric Pit**

**Gastric Gland**

## Generic Stomach Gland

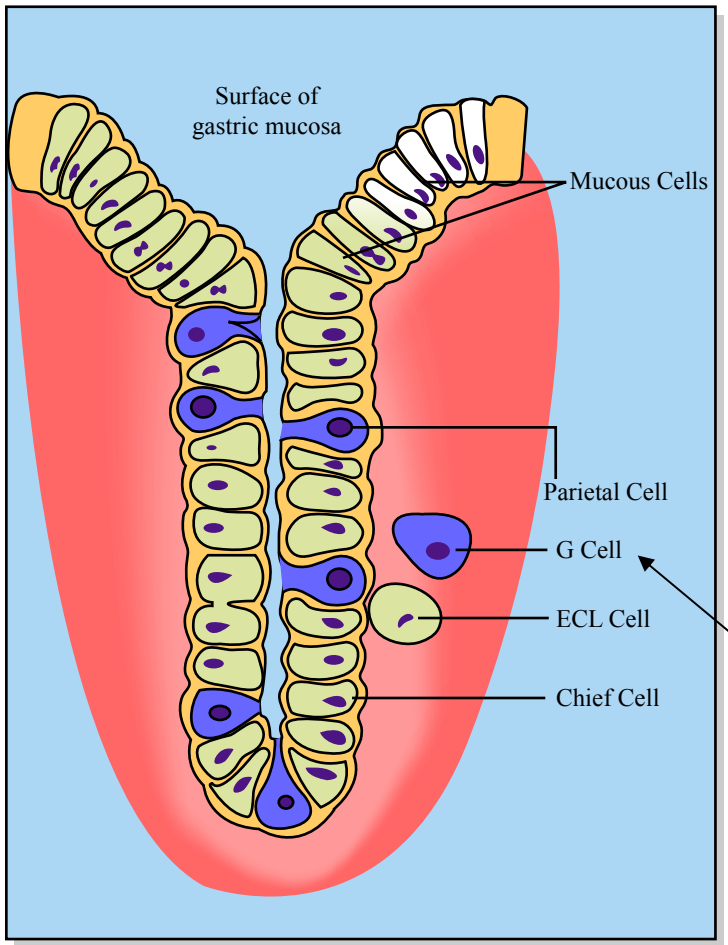



Figure by MIT OCW.

- 2 glandular elements in the stomach
  - ~ Gastric (oxyntic) gland
  - ~ Pyloric (antral) gland

- **Gastric gland** - body and fundus
  - ~ Oxyntic (parietal) cells
    - -HCl
    - - Intrinsic factor (B12 absorption)
  - ~ Peptic (chief) cells - pepsinogen
  - ~ ECL cells (enterochromafin-like): histamine
  - ~ Mucous secreting cells

- **Pyloric gland** - antrum
  - ~ Shallower pit
  - ~ Gastrin (G) cells - gastrin
  - ~ Peptic cells - pepsinogen (minor)
  - ~ ECL cells (enterochromafin-like): histamine
  - ~ Mucous secreting cells

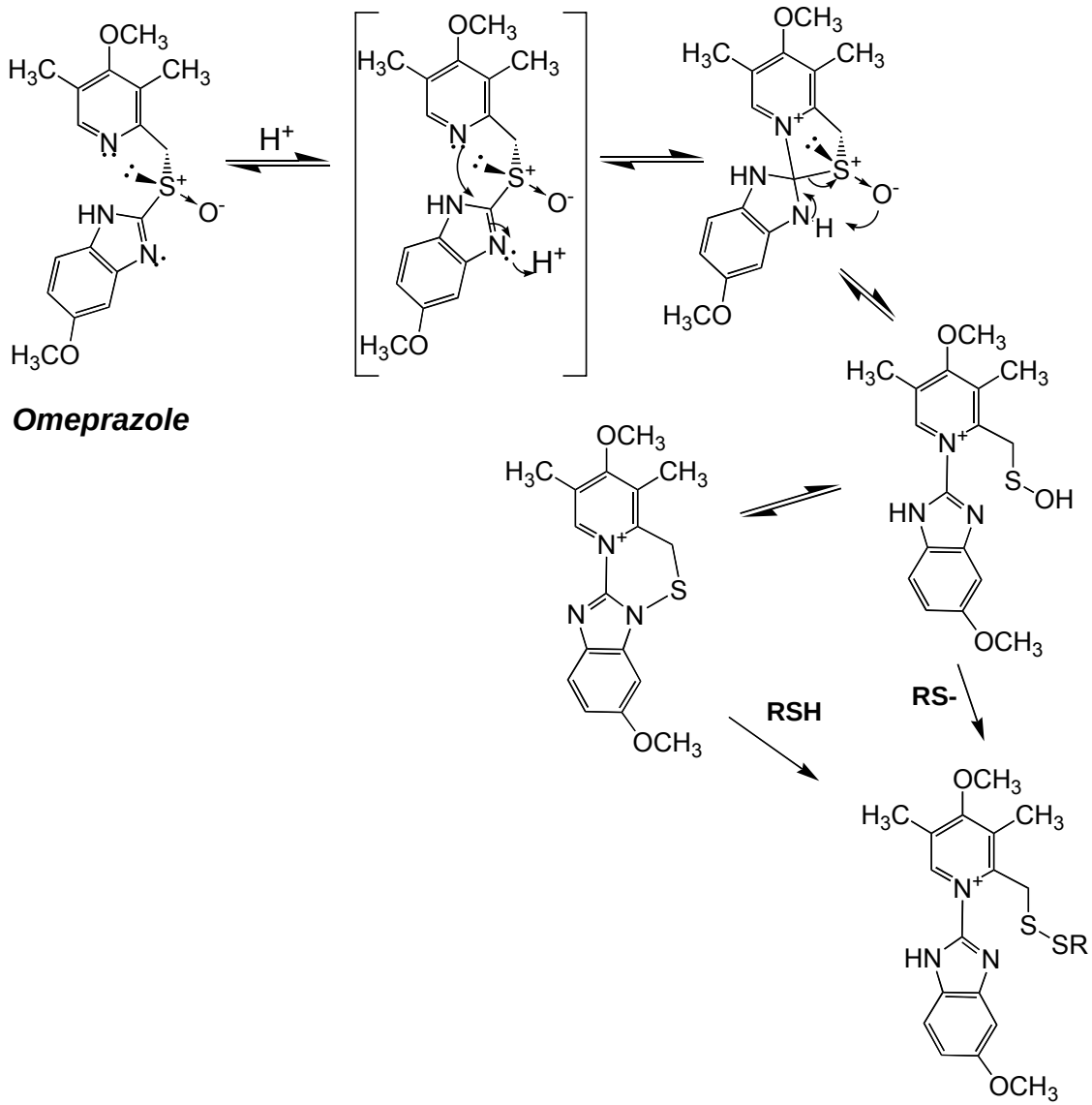
# *Gastric physiology*

Images of Acetylcholine Pathways, Gastrin Pathways, Histamine Pathways removed due to copyright restrictions.

***Acid Secretion Pathways***

http://hopkins-gi.org/multimedia/database/intro_247_Parietal.swf

# *Mechanism of action of omeprazole et al.*




***Omeprazole***