Option D:
Medicinal Chemistry

D.3 & D.4

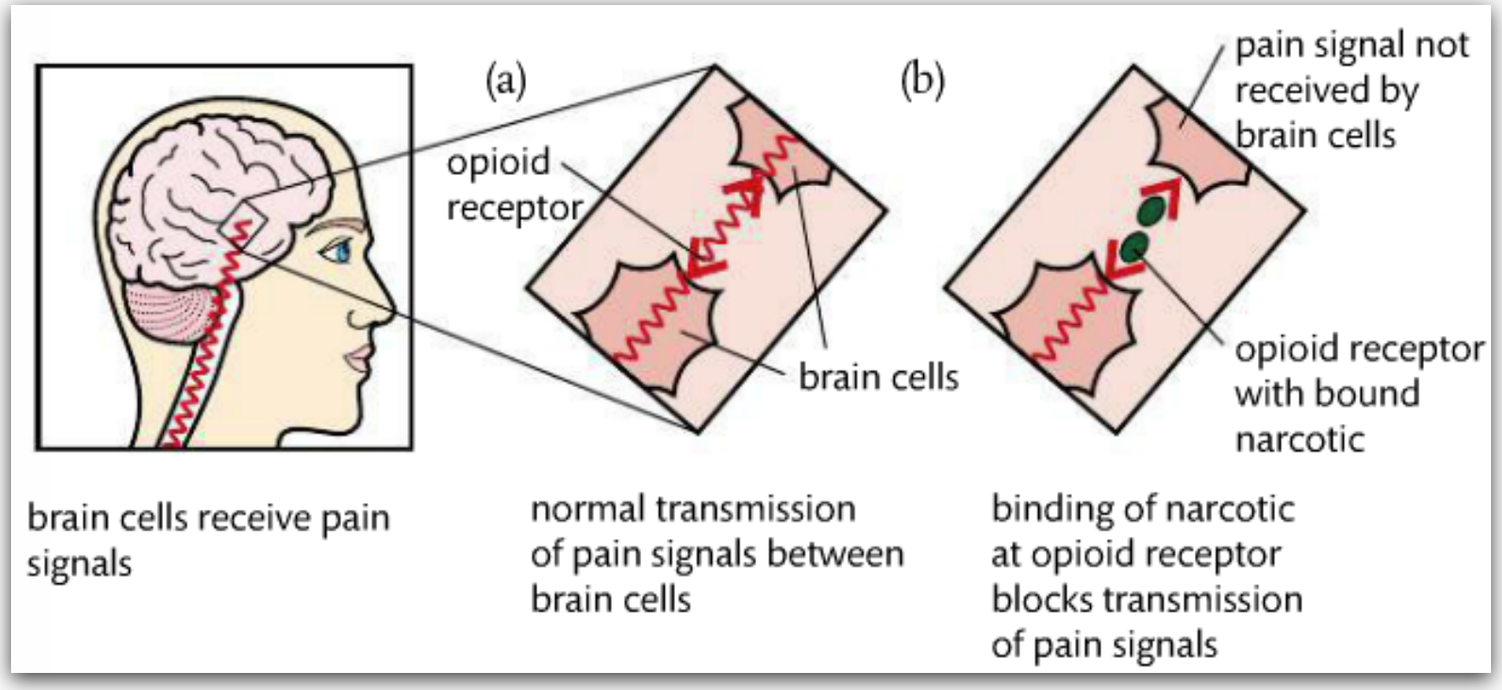
D.3 Opiates

- Strong analgesic
- prevents transmission of pain in the brain, rather than at the source
- natural, derived from opium
- discovered 5000 years ago in Mesopotamia, and responsible for more wars and legislative changes than any other chemical substance

D.3 Opiates

How they work:

- opiates bind to opioid receptors - blocks the transmission of impulses between brain cells that would signal pain
- interfere with the perception of pain, without depressing the central nervous system



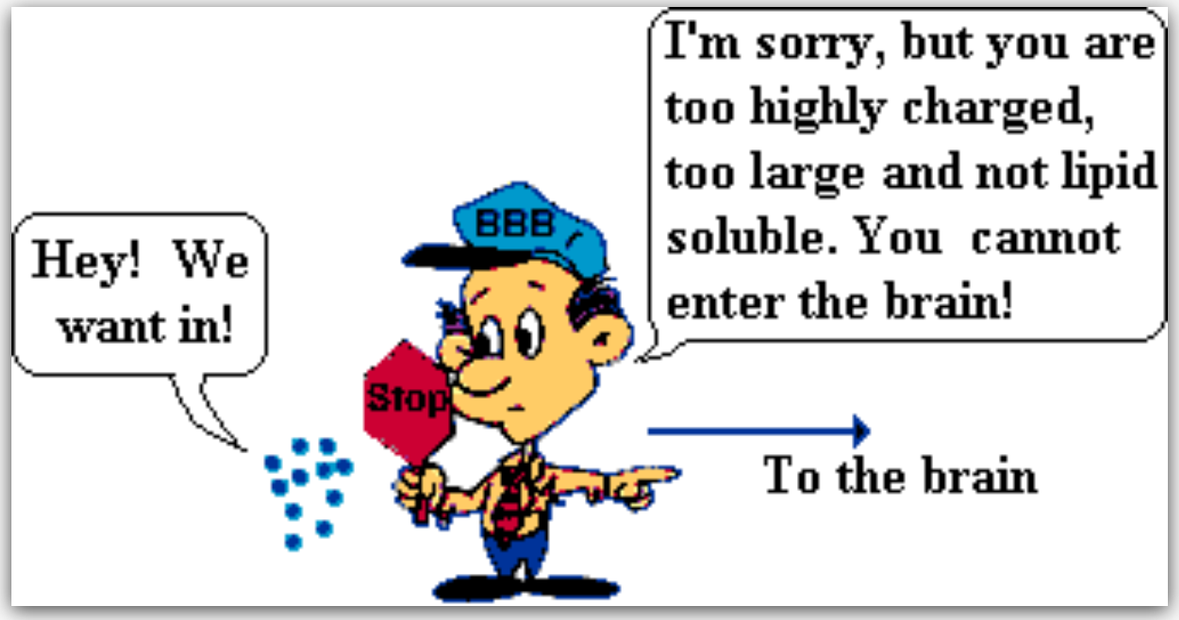
D.3 Opiates

More intro…

- can cause changes in mood or behavior
  - called narcotics…
- most effective painkillers for severe pain
- because of side effects and potential for dependance, opiates must be monitored through medical supervision

Getting into the brain

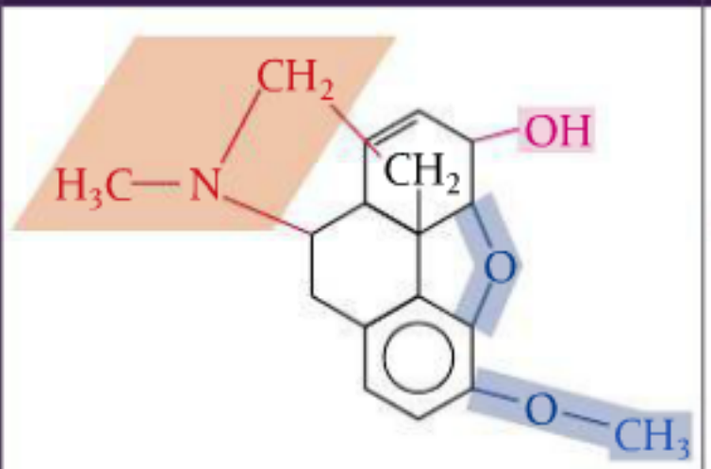
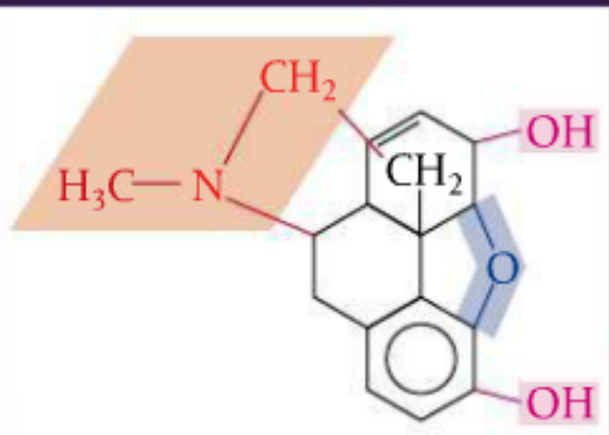
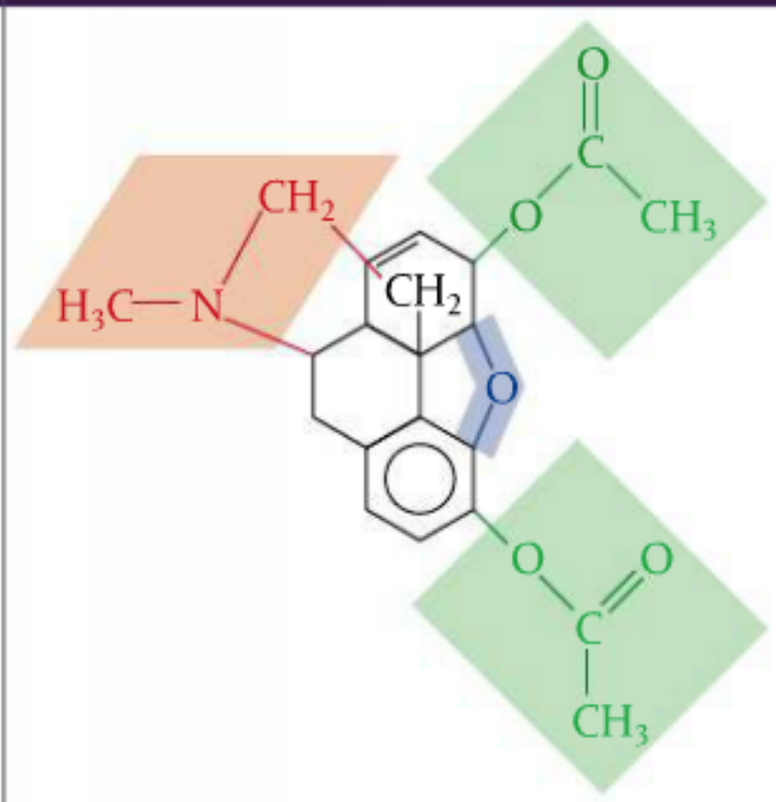
- Must cross the blood-brain barrier as the opiates target the brain
- BBB is a hydrophobic membrane made of mainly lipids
  - non-polar environment not often crossed by polar molecules



- must be aqueous soluble in blood and lipid soluble in the brain
- solubilities of drugs depend upon their structure

D.3 Opiates

Opium derivative - morphine (will make codeine + diamorphine)

	Codeine	Morphine	Diamorphine (heroin)
structure			

D.3 Opiates

Morphine

- obtained from 10% raw opium
- Therapeutic uses
  - pain management (such as severe cancer)
  - can be habit forming - must be regulated by a medical professional
- intravenous injection has 6x the bioavailability than if taken orally

D.3 Opiates

Codeine

- obtained from 0.5% raw opium, but usually prepared from morphine (semi-synthetic drug)
- prepped with a non-narcotic such as aspirin (2nd stage of pain management ladder)

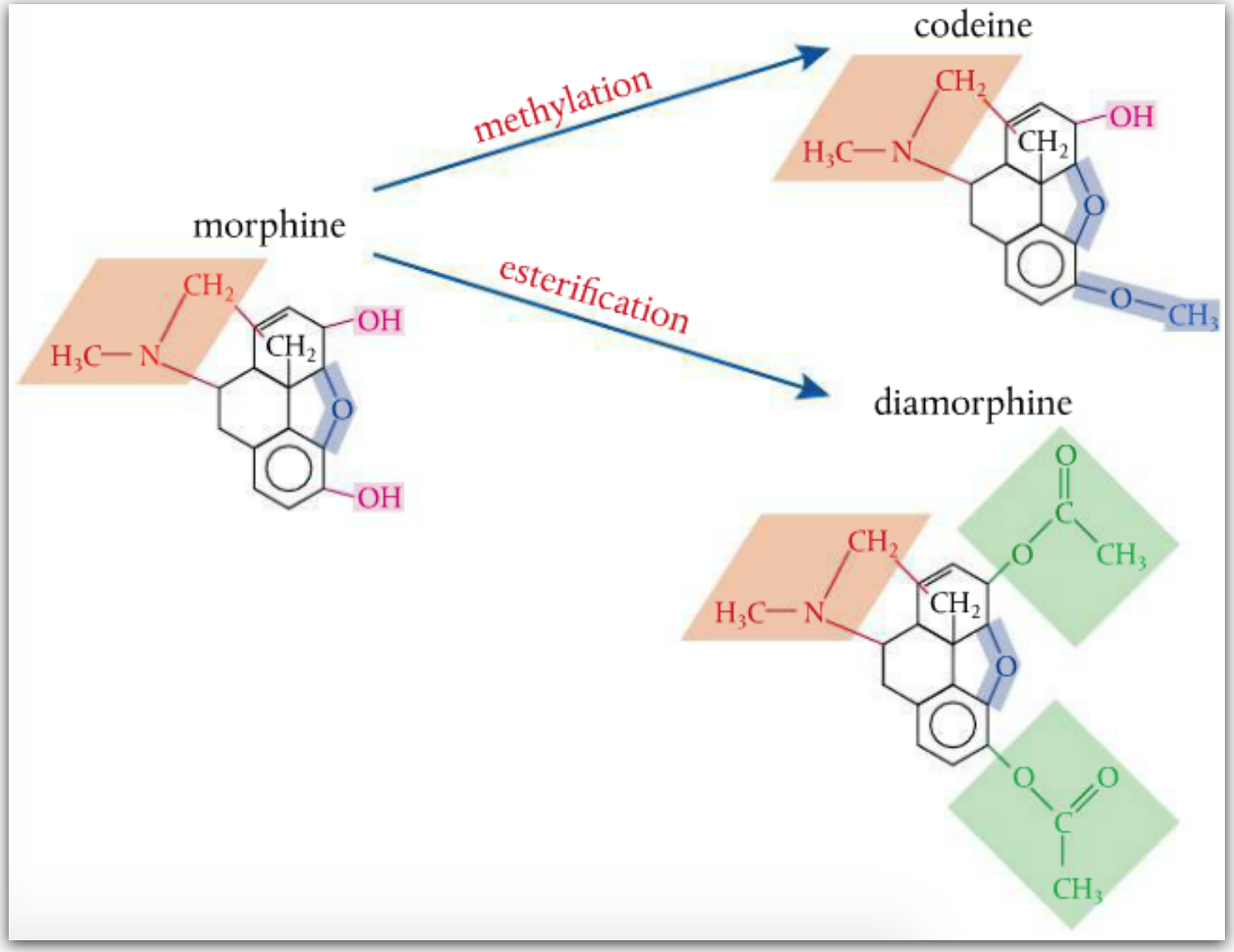
D.3 Opiates

diamorphine (heroin)

- found in opium - usually obtained by a reaction of morphine
- used medically in few countries
- most rapidly acting and abused narcotic
- produces euphoric effects, but very high potential for addiction and increasing tolerance
- dependance leads to withdrawal

D.3 Opiates

Reactions of Opiates



D.3 Opiates

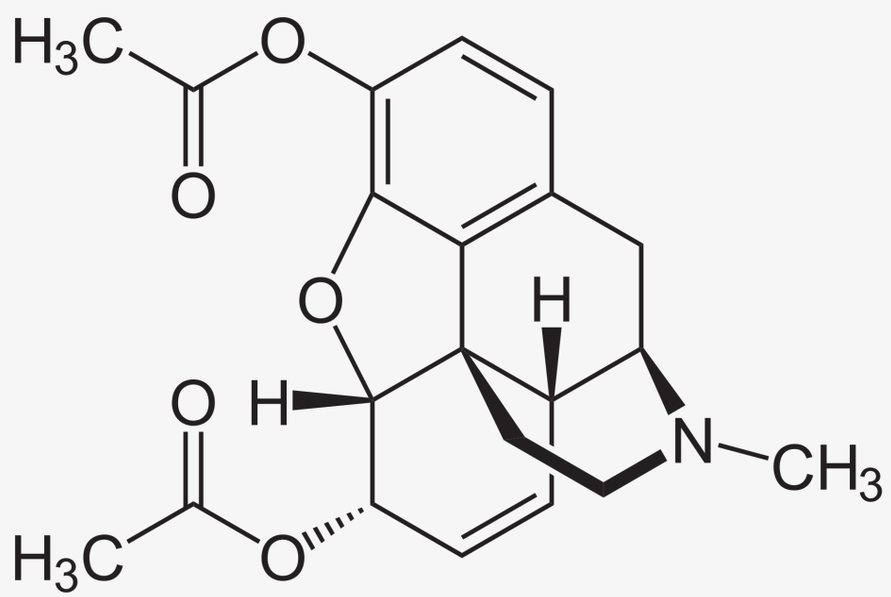
Properties

- Codeine
- Morphine
- Diamorphine

- increasing strength of analgesics
- increasing narcotic effects
- increasing side effects

D.3 Opiates

diamorphine (heroin)

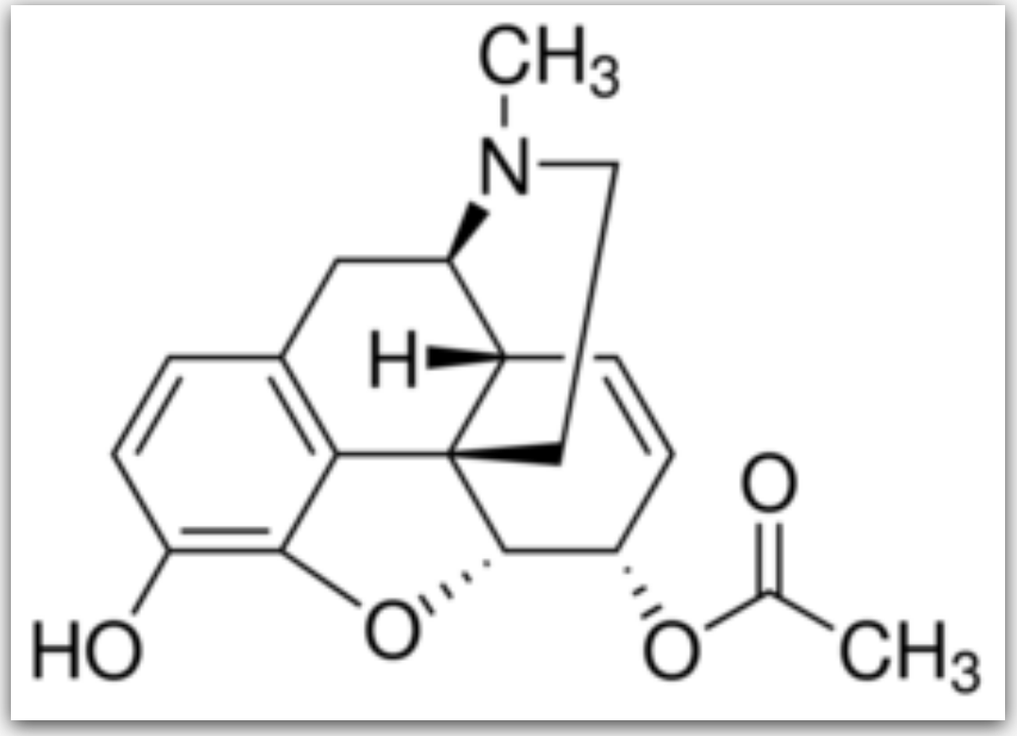


- reaches brain cells faster and in higher concentration
- more active by a factor of 2
- must undergo metabolic change before it can be active - ester links are broken
- products of change are basically morphine
- structure of diamorphine is "packaged" morphine - so it can reach target (brain) more efficiently

D.3 Opiates

6-acetylmorphine

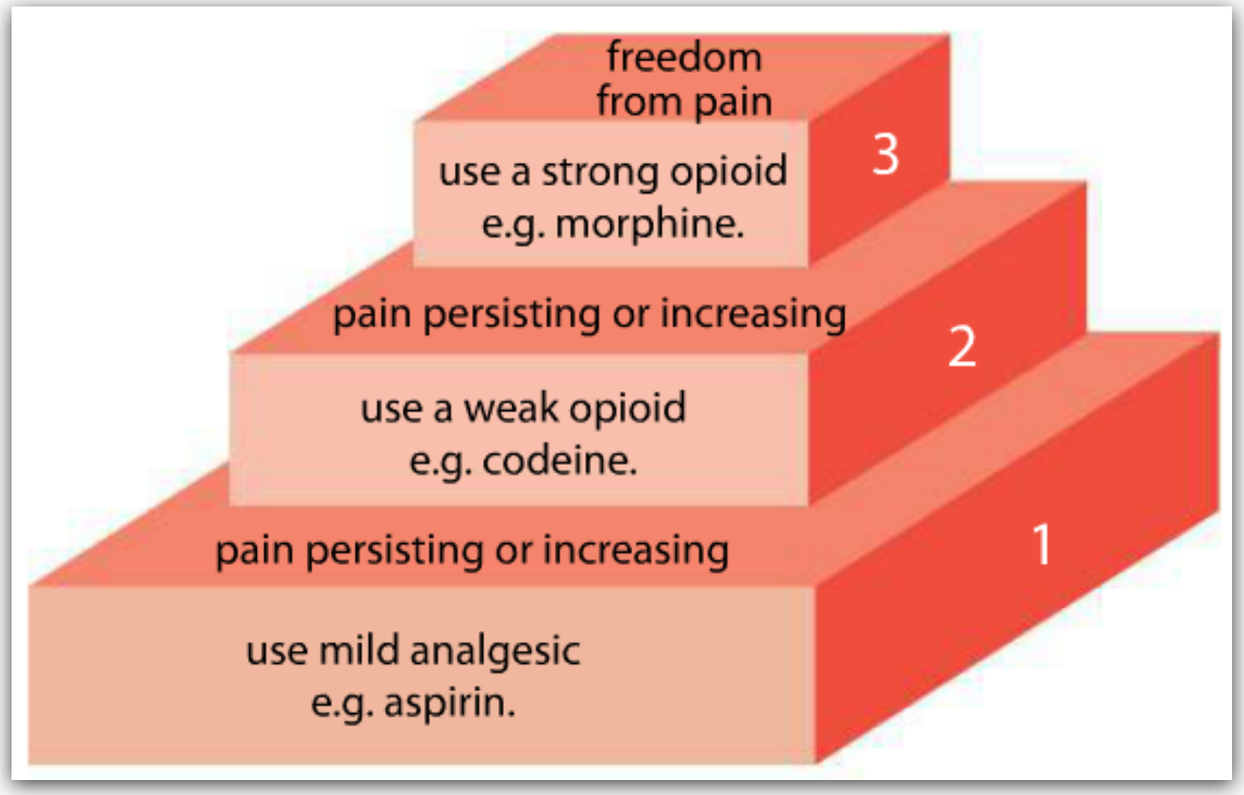
- derivative of morphine
- has only one of the ester linkages
- more potent than heroin as it doesn't need to undergo the hydrolysis reaction in order to interact with the brain
- extremely dangerous when taken in pure form



D.3 Opiates

Advantages and Disadvantages to Strong Analgesics

- WHO (World Health Organization) three step 'analgesic ladder'
- intravenous morphine is the most widely used in cases of severe pain
- In the UK and some European countries, diamorphine (heroin) can be legally prescribed (highly controlled)



D.3 Opiates

Side Effects

- constipation
- suppression of cough reflex
- constricted pupils
- narcotic effects

- mixture of kaolin and morphine is used to treat diarrhea
  - reduces muscle contractions and slows the passage of "matter"
  - not a pain killer in this use

D.3 Opiates

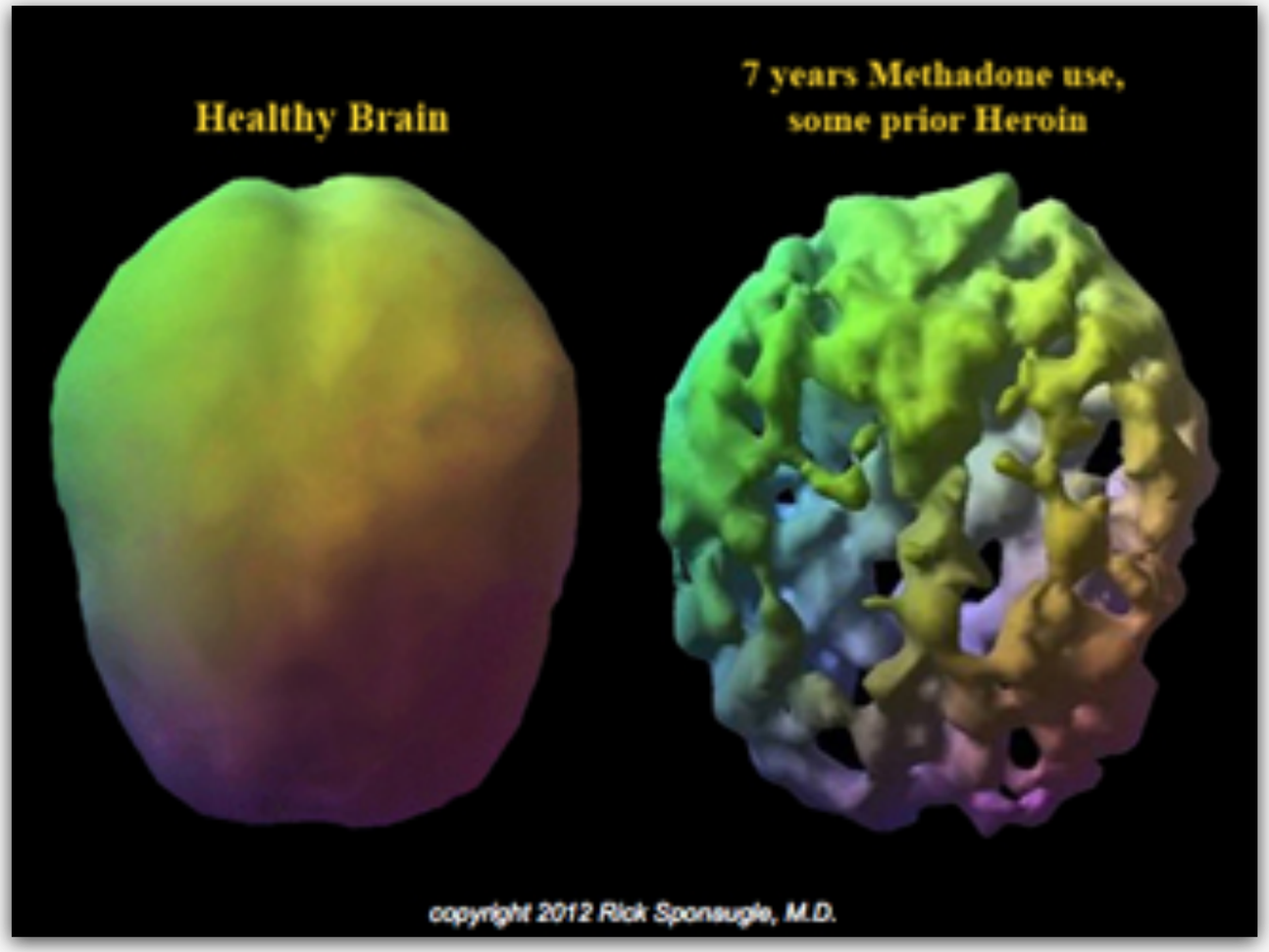
Narcotic Effects

- narcotic - (greek) - numbness or stupor
- depress brain function, induces sleep, addictive
- short term
  - euphoric, feels lessening tension
  - quickly dependant with increasing tolerance
- long term
  - addiction, high cost leads to crime/social issues
  - injected drug - HIV + Hepatitis from unclean needles

D.3 Opiates

Addiction Treatment

- **Methadone** - taken orally, longer duration of action
- can reduce craving, and prevent withdrawal
- controversial, but effective treatment
- reduces death rate of heroin addicts



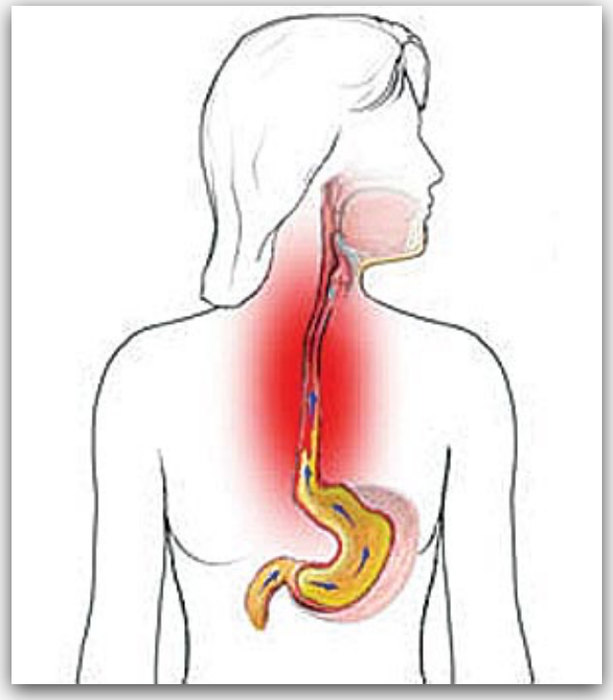
D.4 pH Regulation of the Stomach

- body systems have strict regulation of pH throughout
- stomach is unique with HCl being produced by **perital cells** in lining of stomach wall (pH approx 1-2)
- acid not only kills bacteria ingested with food, but provides optimal environment for digestive enzymes

D.4 pH Regulation of the Stomach

Excess acidity in the stomach is harmful

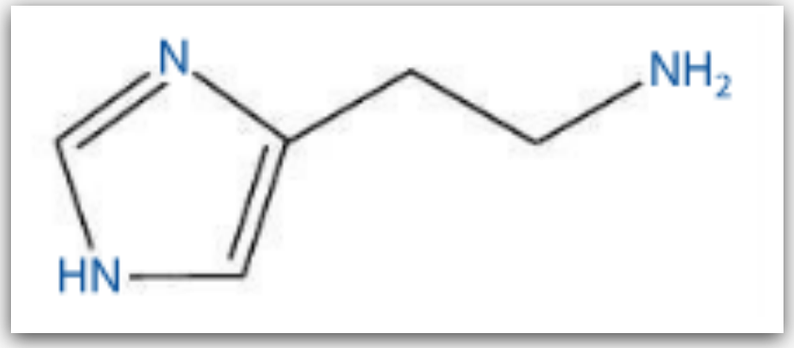
- Excess alcohol, smoking, caffeine, stress and some anti-inflammatory drugs — can cause excess acidity
- lead to the following:
  - acid indigestion - discomfort from too much acid
  - heartburn - acid rising into the esophugus (acid reflux)
  - ulceration - damage to the lining of the gut wall, loss of tissue and inflammation
  - **dyspepsia** - refers to feelings of pain and discomfort in the upper abdomen (indigestion and heartburn)

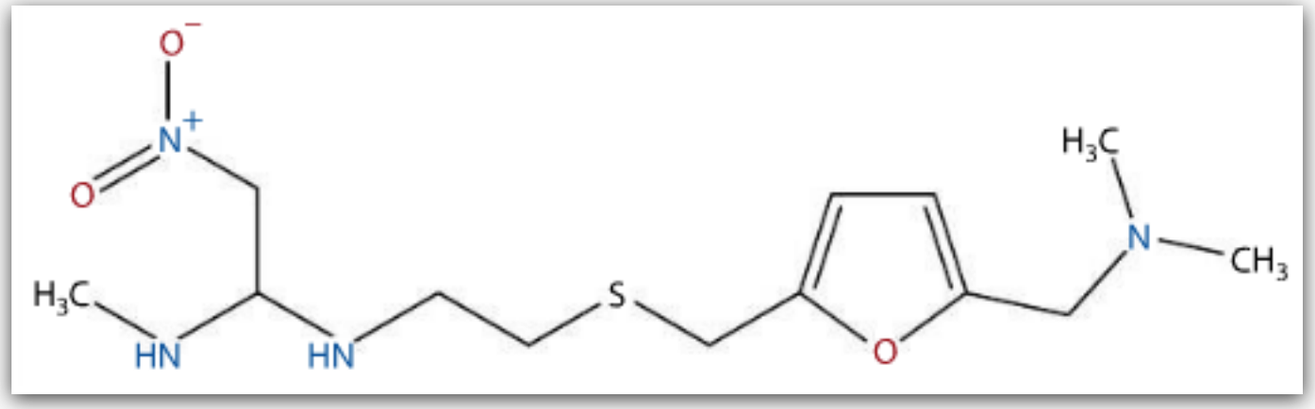


D.4 pH Regulation of the Stomach

Some drugs work to prevent excess stomach acid

- The hormone histamine stimulates the stomach to stimulate the production of stomach acid - they interact at receptors known as H_2 (not hydrogen gas…)
- Rantidine (Zantac) - **H_2-receptor antagonist**
  - competes with histamine @ the H_2 receptors
  - available as an OTC drug - but higher doses require a prescription





D.4 pH Regulation of the Stomach

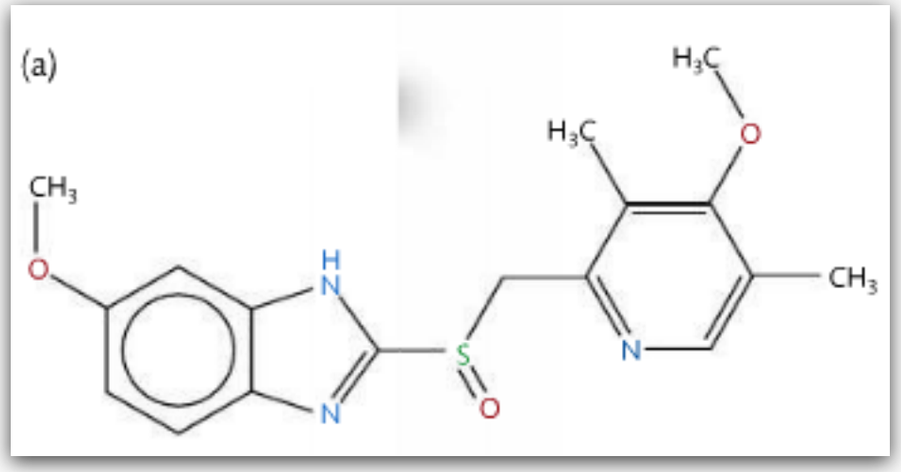
Proton Pump Inhibitors

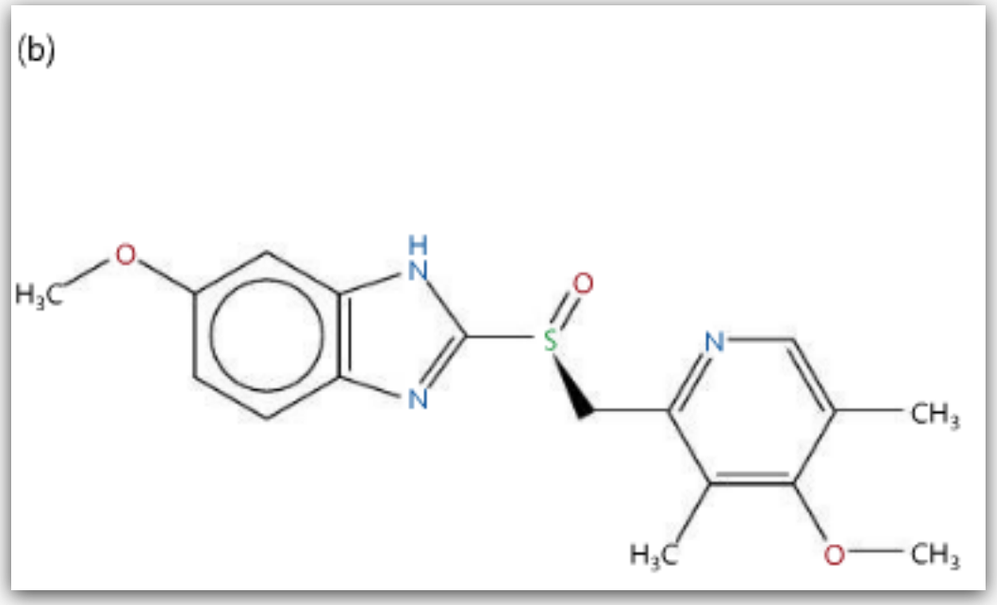
- In the last step of gastric acid secretion, H^+ ions are pumped into the stomach as K^+ ions are pumped in the opposite direction to prevent charge buildup
- Requires energy (against concentration gradient)
  - Hydrolysis of ATP (energy carrier) using the enzyme ATPase (embedded in cell membrane)
  - AKA **H^+/K^+ ATPase** or a gastric proton pump

D.4 pH Regulation of the Stomach

Proton Pump Inhibitors

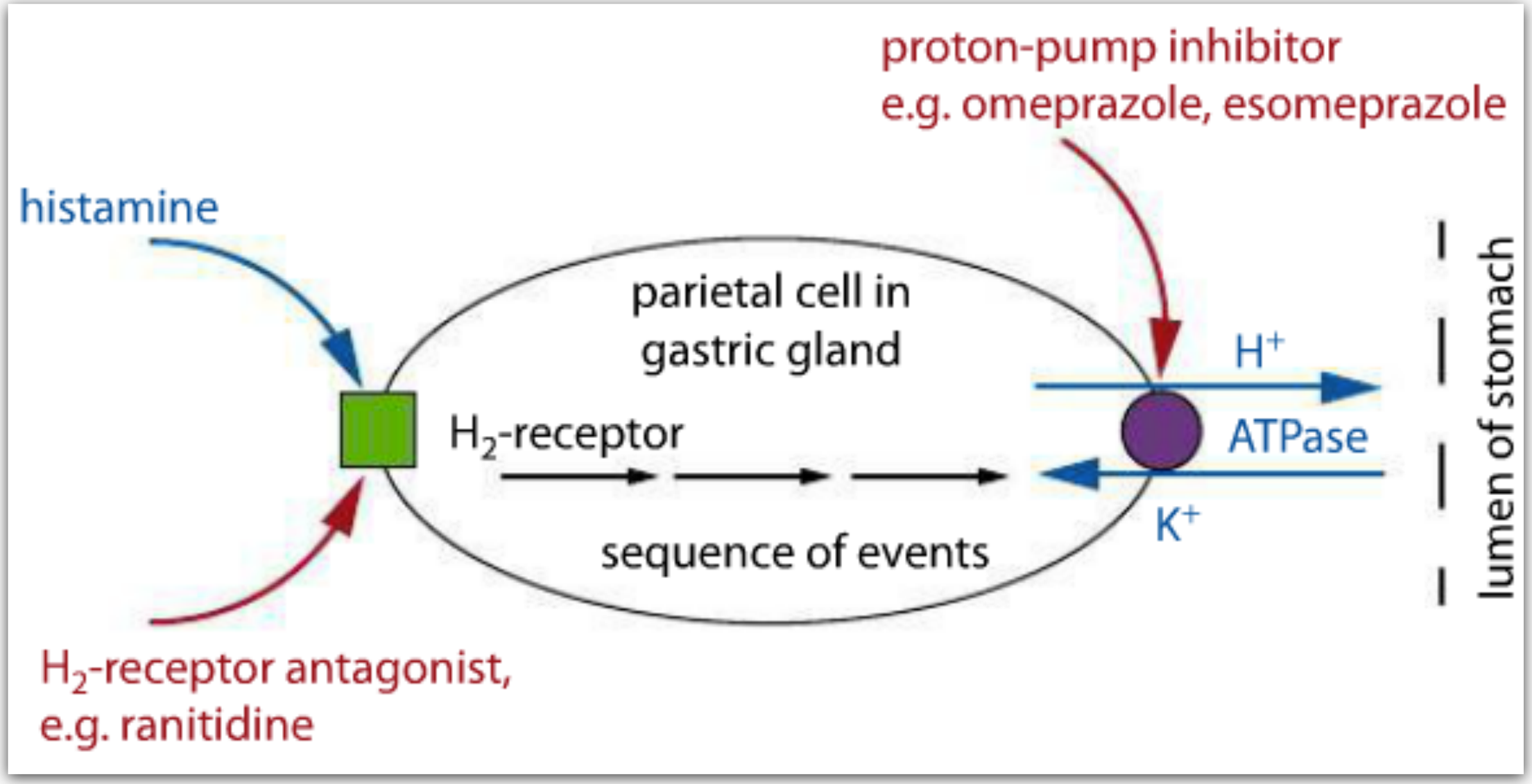
- First proton pump inhibitor - **omeprazole** (Prilosec)
  - followed by release of **esomeprazole** (Nexium) when the patent expired for Prilosec (in 2001)





D.4 pH Regulation of the Stomach

Summary



D.4 pH Regulation of the Stomach

Antacids

- drugs that help combat stomach acid
- weak bases that neutralizing the HCl
- do not fix any stomach damage, but reduce the level of acid to allow the stomach time to heal
- ex. $Ca(OH)_2$, $Mg(OH)_2$, $Al(OH)_3$
- $Ca(OH)_{2(aq)} + HCl_{(aq)} \rightarrow CaCl_{2(aq)} + 2H_2O_{(l)}$

D.4 pH Regulation of the Stomach

Effects of Mg/Al combo antacids

- Mg salts - faster acting
  - laxative effect
- Al salts - slower acting but last longer
  - causes constipation
  - linked (but not proven to cause) to Alzheimer's
- Carbonates ($NaHCO_3$) - create CO_2 - cause bloating
  - $NaHCO_{3(aq)} + HCl_{(aq)} \rightarrow NaCl_{(aq)} + H_2O_{(l)} + CO_{2(g)}$

D.4 pH Regulation of the Stomach

pH and Buffering

- body system is complex and requires specific pHs to work properly
- buffers prevent major fluctuations of pH

How buffers work

- 2 main types of buffers
  - acidic - maintain the pH at a value less than 7
  - basic - maintain the pH at a value more than 7
- Mixture of 2 solutions
  - each contain a conjugate acid-base pair

Determining pH of a Buffer Solution

- Consider an acidic buffer made of generic weak acid HA and its salt MA
  - $HA \Leftrightarrow H^+ + A^-$
  - $MA \rightarrow M^+ + A^-$
- We will make 2 approximations in order to help calculations
  - dissociation of HA is small $\therefore [HA]_{initial} = [HA]_{equilibrium}$
  - the salt will fully dissociate $\therefore [MA]_{initial} = [A^-]_{equilibrium}$

Henderson-Hasselbalch

- $K_a = [H^+][A^-] / [HA]$
- $\therefore [H^+] = K_a \cdot [HA] / [A^-]$
  - These equations are known as the Henderson-Hasselbalch Equations.
- Values must be in equilibrium concentrations
- we know: $[HA]_{initial} = [HA]_{equilibrium}$ & $[A^-]_{equilibrium} = [MA]_{initial}$

Buffer & pH

- $\therefore [H^+] = K_a \cdot [HA]_{initial} / [MA]_{initial}$
- usually shown as:
  - $[H^+] = K_a \cdot [acid] / [salt]$
  - negative log of both sides
    - $pH = pK_a + \log_{10} ([salt] / [acid])$
- for a base - $[OH^-] = K_b \cdot [base] / [salt]$
  - $pOH = pK_b + \log_{10} ([salt] / [base])$

Example

- Calculate the pH of a buffer solution at 298K, prepared by mixing 25cm^3 of 0.10 mol dm^{-3} ethanoic acid, CH_3COOH, with 25cm^3 of 0.10 mol dm^{-3} sodium ethanoate, Na^+ CH_3COO^-.

  - K_a of CH_3COOH = 1.8 x 10^{-5} at 298K.

- In a buffer -

  - when [acid] = [salt], pH = pK_a

  - when [base] = [salt], pOH = pK_b

Example

- How would you create a buffer solution with a pH 3.75 starting with methanoic acid, HCOOH?

Example

- How much 0.10 mol dm^{-3} butanoic acid solution and solid potassium butanoate should be used to make 1.00 dm^3 of pH 5.00 buffer solution? State the assumptions made in the calculation.

In summary...

- The pH of a buffer depends on
  - the pK_a (or pK_b) of its acid or base (Table 21)
  - the ratio of initial concentrations of acid and salt (or base and salt) used in preparation