Pharmacokinetics

by the end of this lecture you should be able to

- explain how drugs move through animals
- decide on an appropriate route of administration for a drug

pharmacokinetics

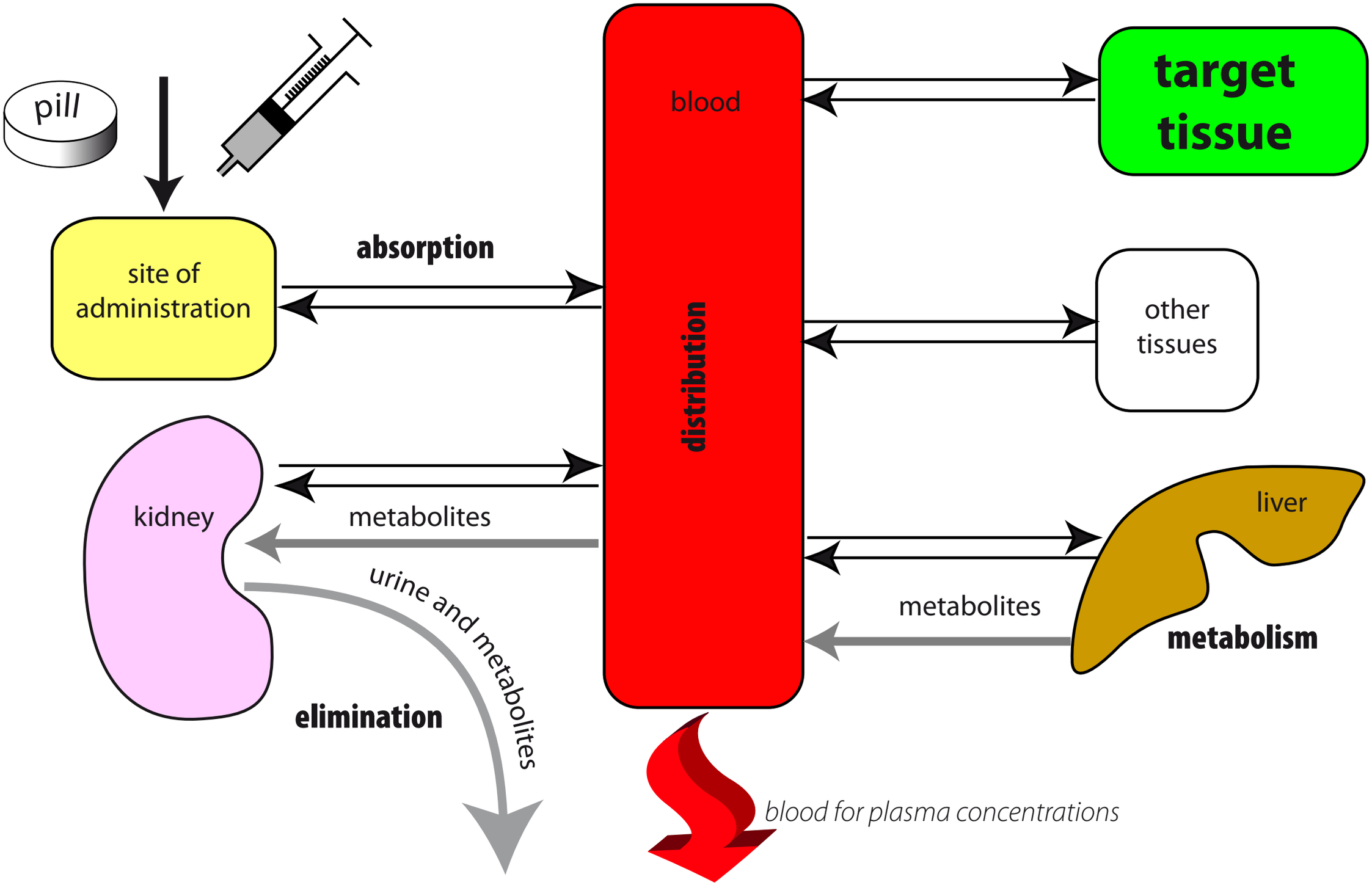
- What the animal does to the drug
- Movement of the drug through the body

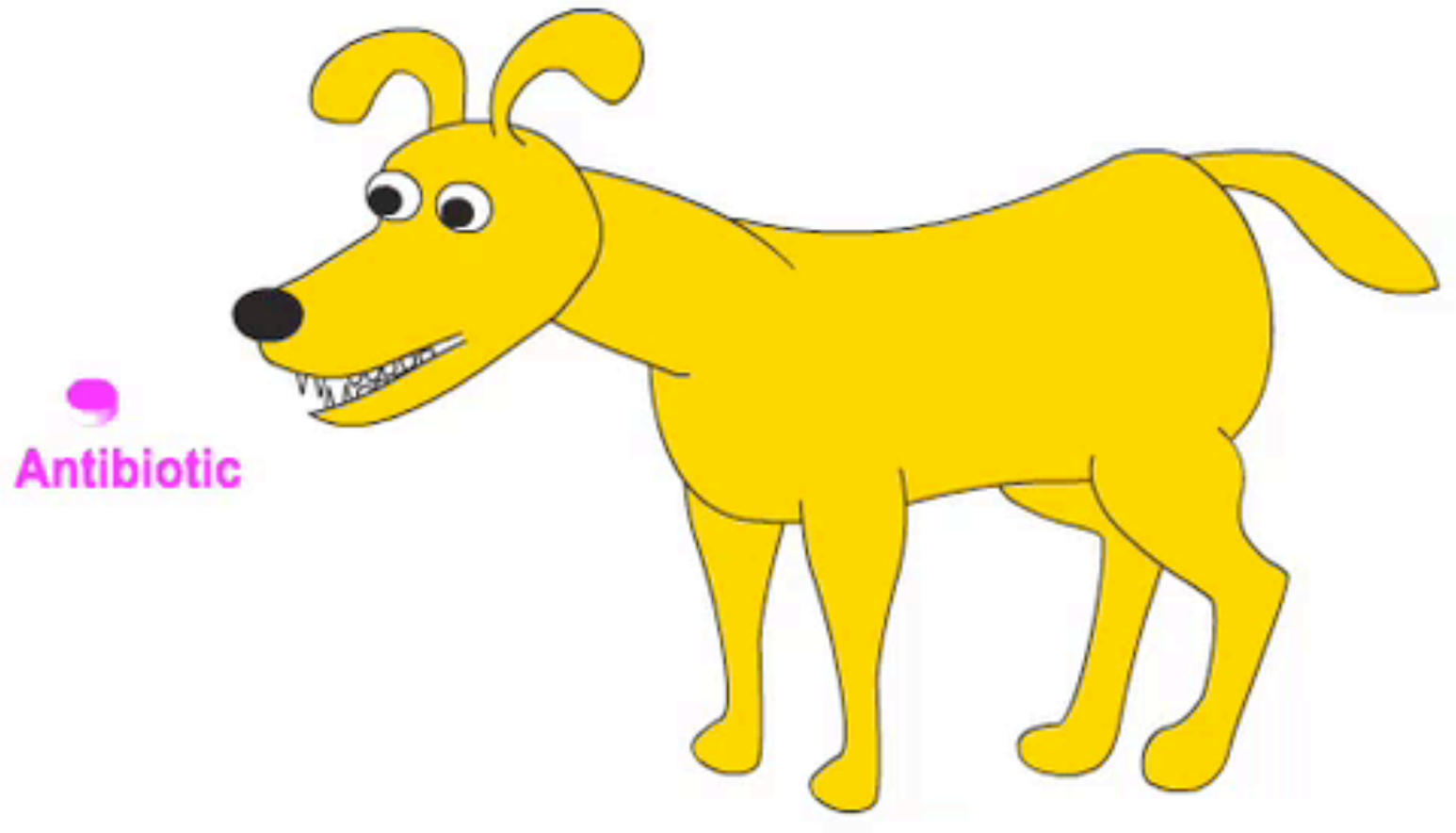

How would you get an antibiotic to here?

pharmacokinetics

- absorption
- distribution
- metabolism
- elimination

pharmacokinetics




Antibiotic

basic assumptions

- drugs must cross membranes to get to target
- actions are proportional to plasma concentrations
- not always true!

routes of administration

- enteral
  - via the gut
- parenteral
  - by injection
- other

routes of administration

- enteral
  - oral (po = *per os*)
  - sublingual
  - rectal

routes of administration

- parenteral
  - intravenous (iv)
  - intramuscular (im)
    - nb muscle becomes meat in food animals!
  - subcutaneous (sc or SQ)
  - intraperitoneal (ip)

iv injection

im injection

routes of administration

- parenteral
  - intravenous (iv)
  - intramuscular (im)
    - nb muscle becomes meat in food animals!
  - subcutaneous (sc or SQ)
  - intraperitoneal (ip)

routes of administration

- inhalation
- topical
  - onto skin
  - intramammary
  - intrauterine
  - onto cornea
- transdermal
- nasal
- epidural / intrathecal


How would you get an antibiotic to here?

absorption

- dissolution
- movement out of site of administration
- movement into blood vessels

dissolution

- most drugs must dissolve in water and oil
- ionisation important
  - pH important

dissolution

- main factors
  - pills
    - coatings
    - disintegrants
    - vehicle
  - all
    - solute
      - gastric juice
      - rumen contents
      - interstitial fluid

injection formulation

- solutions in water
  - rapid onset of action
- suspensions of insoluble salts
  - slower release
  - mixtures of salts can be used
  - not iv
- solutions in oil
  - slow release
  - not iv

injection formulation

- complexes with soluble carriers
  - cyclodextrins
  - polyvinyl pyrrolidine (PVP)
  - propylene glycol
- used to get lipid soluble drugs into aqueous solution

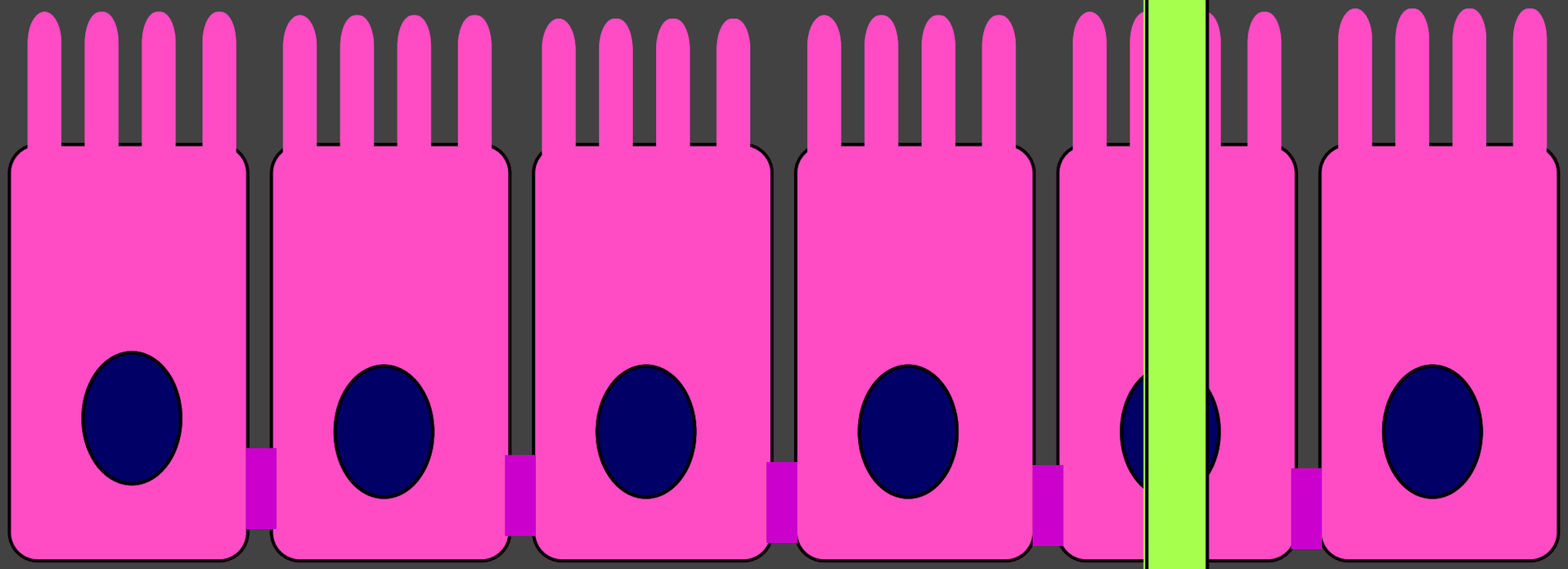
drug delivery devices

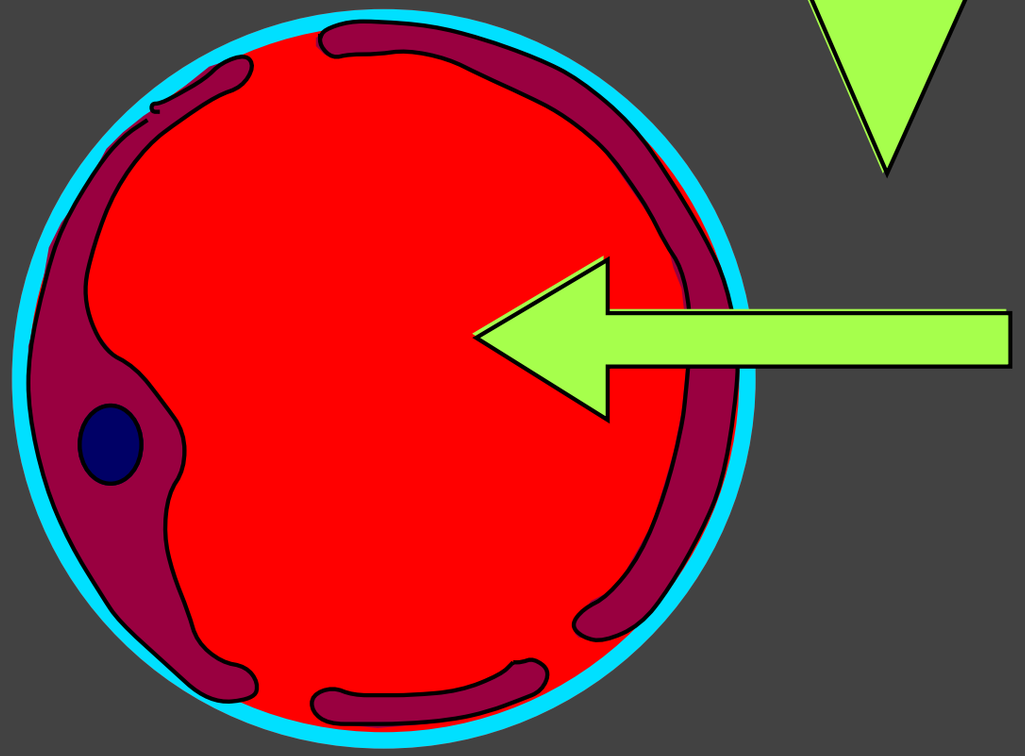
- "solution" in silicone rubber
  - very slow release
- osmotic pumps
  - predictable slow release
- mechanical pumps
  - variable rates of delivery
  - can be computer controlled ± feedback

barriers to absorption

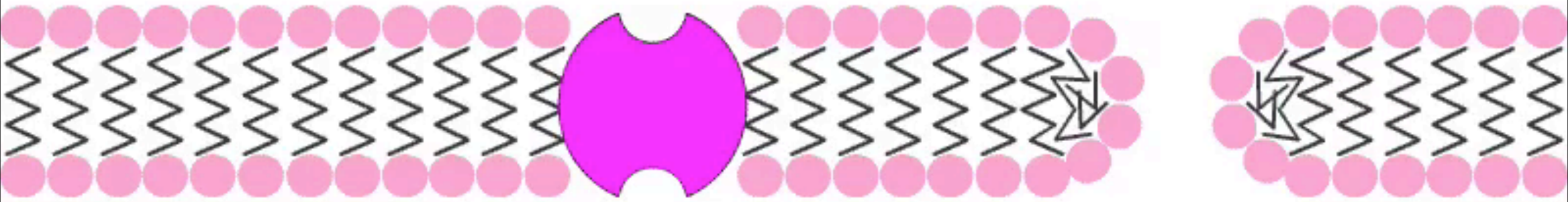
- after iv administration
  - none
- after oral administration
  - gastric mucosa
  - endothelium
- after im or sc administration
  - endothelium

drug





drug



diffusion across
lipid membranes

ATP

carrier mediated
transport

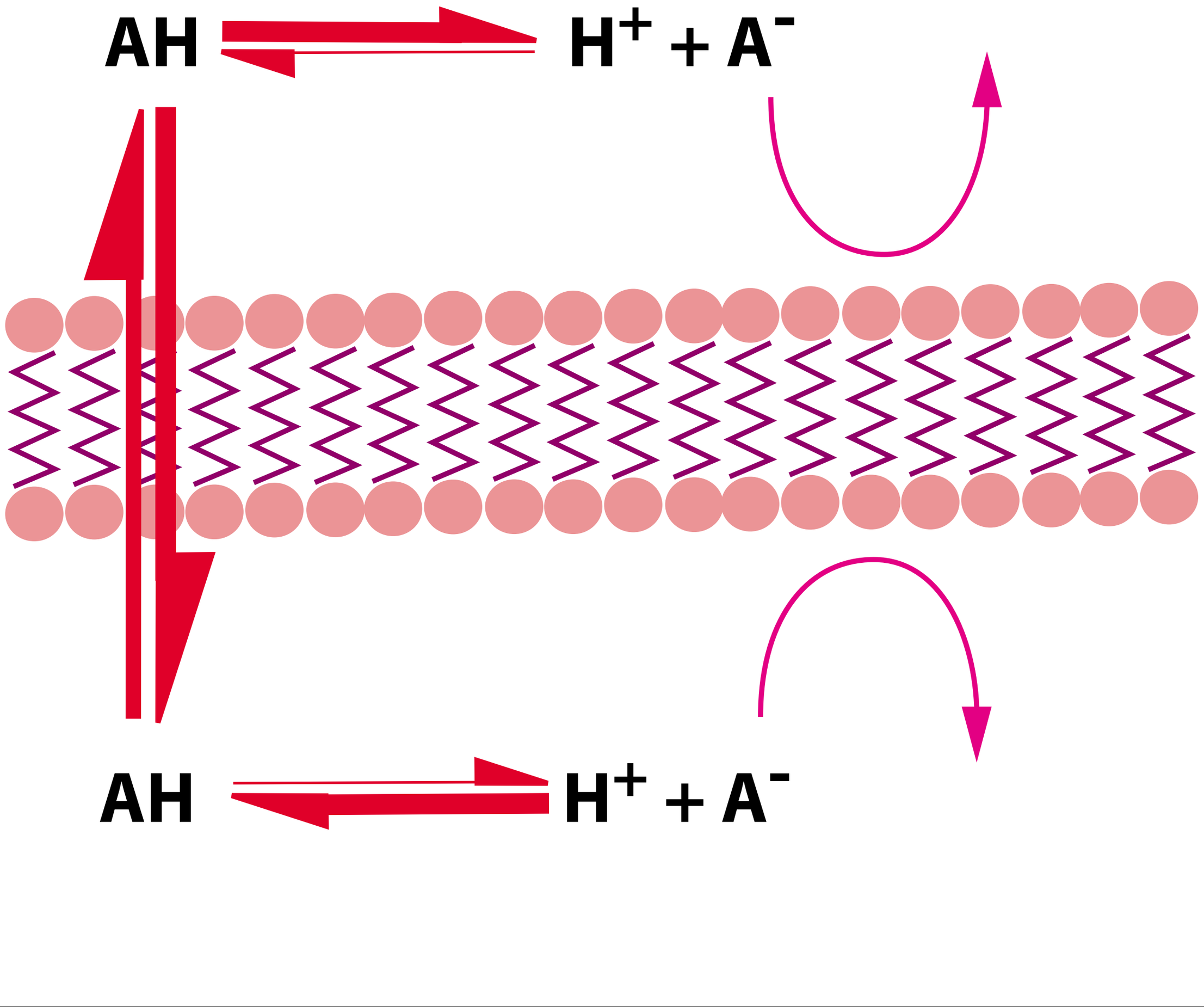
diffusion through
aqueous channel

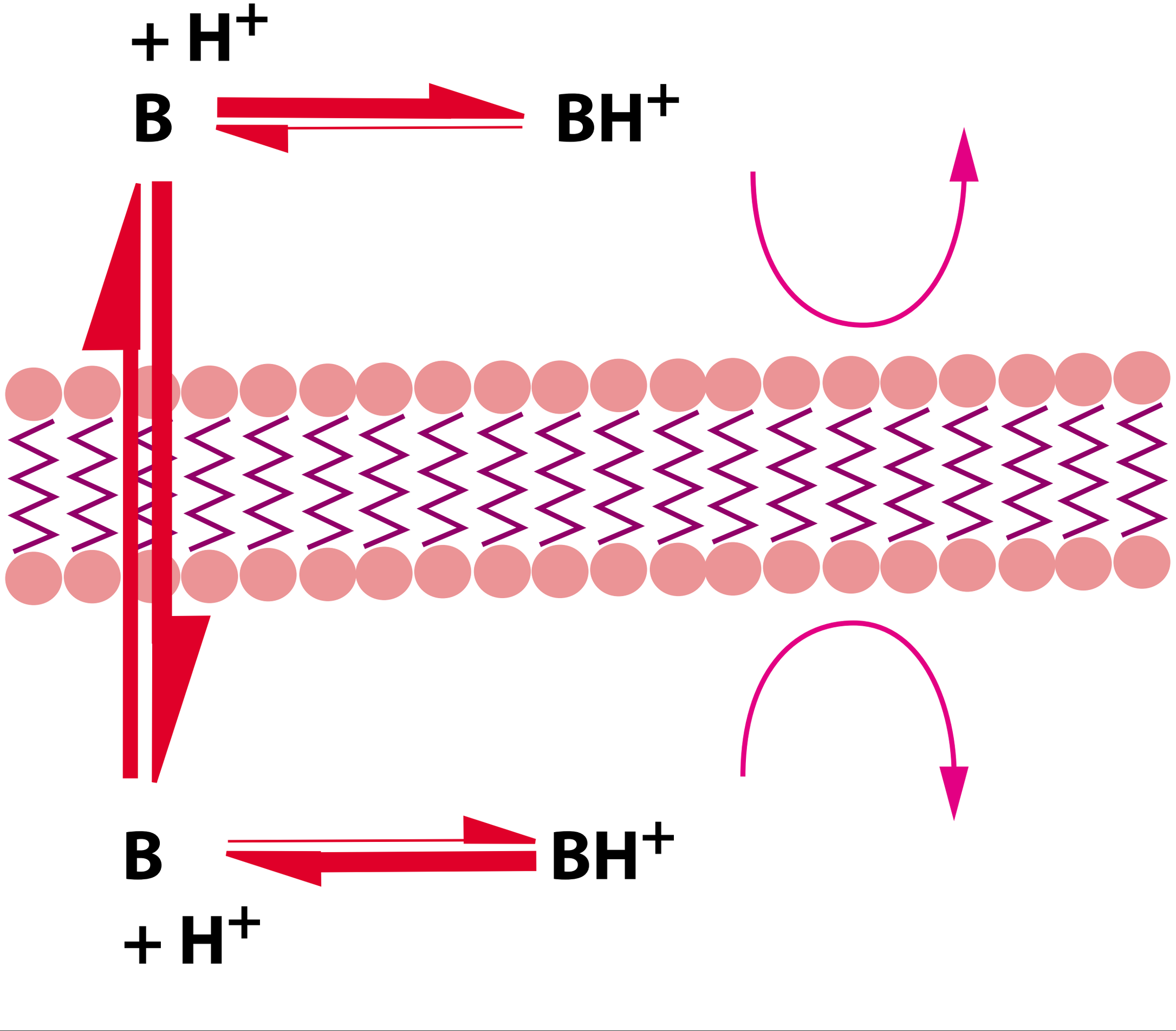
effects of pH

- most drugs are either weak bases or weak acids
- ionised forms are not lipid soluble

$$HA \rightleftharpoons H^+ + A^-$$

$$BH^+ \rightleftharpoons H^+ + B$$


AH
H+ + A-
AH
H+ + A-


+ H+
B
BH+
B
BH+
+ H+

Henderson Hasselbach equation

for acids $pH = pK_a + \log \frac{A}{AH}$

for bases $pH = pK_a + \log \frac{B}{BH^+}$

ie, when $pH = pK_a$, the drug is 50% ionised

effects of pH

- when pH < pKa, more protonated drug exists (AH & BH^+)
- when pH > pKa, more unprotonated drug exists (A^- & B)

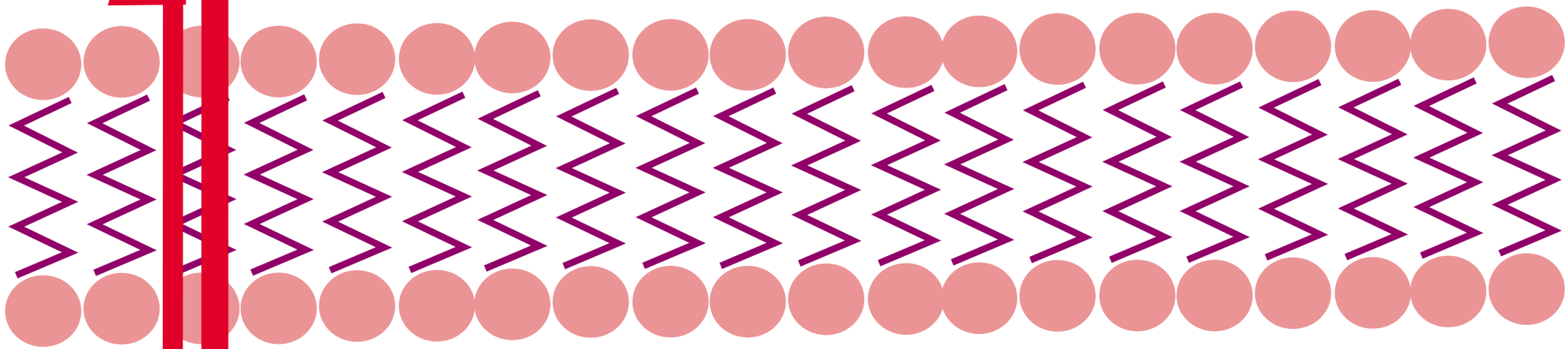
effects of pH

- bases are ionised in acid solutions
- acids are ionised in alkaline solutions

[1] [1000]

$AH \rightleftharpoons H^+ + A^-$

plasma pH 7.4



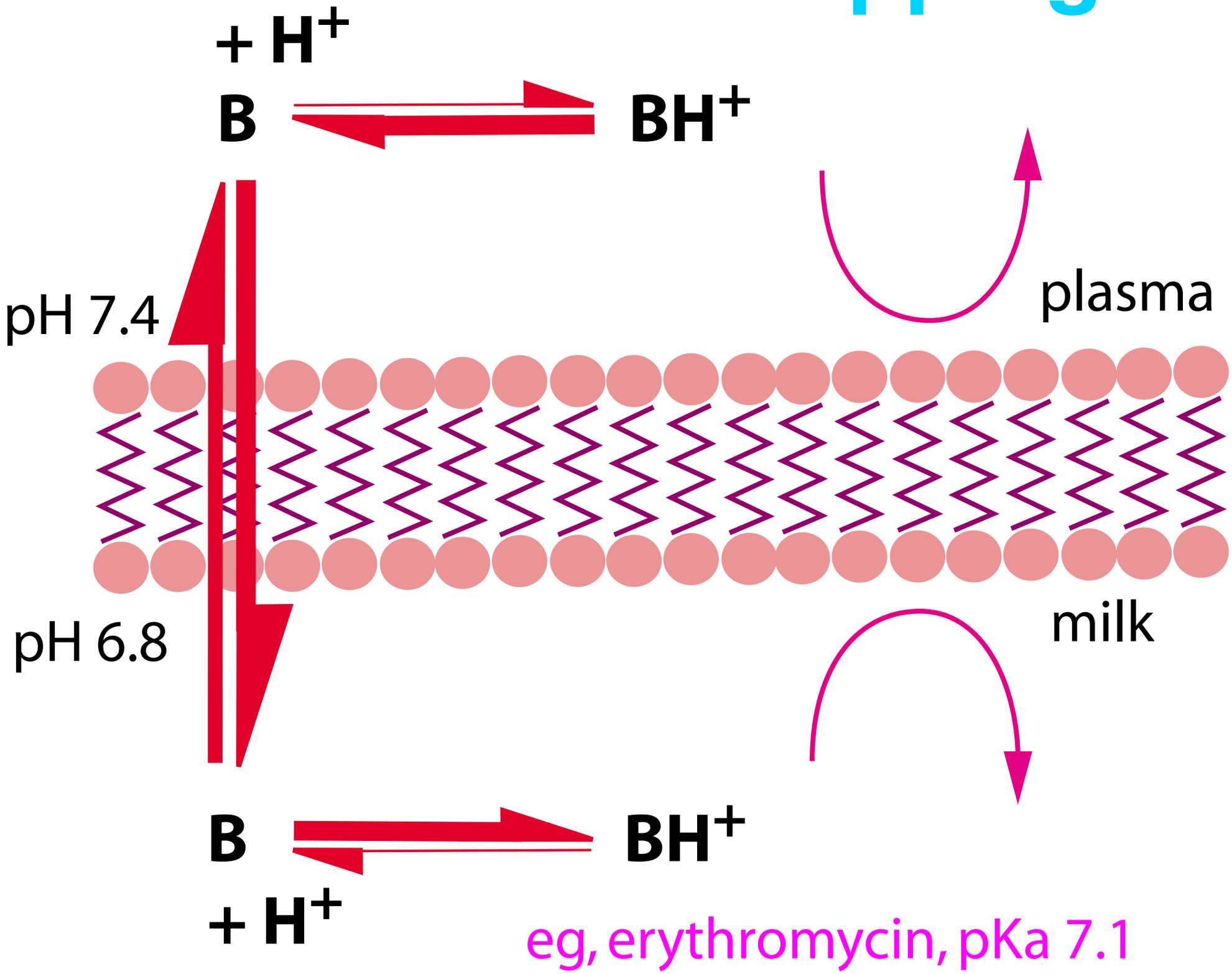
gastric juice pH 1.4

$AH \rightleftharpoons H^+ + A^-$

[1] [0.001]

eg, aspirin - weak acid, pKa 4.4

ion trapping



other factors influencing oral absorption

- **blood flow**
  - reduced in shock
- **surface area**
  - intestine > stomach
- **contact time**
  - reduced in vomiting & diarrhoea
- **food**
  - drugs may bind to food
- **carrier mediated transport**
  - both ways

other factors influencing parenteral absorption

- blood flow
  - im - medium speed
    - exercise
    - intra-fat rather than im!
  - sc - slow and variable
    - ambient temperature
- pH
- inflammation
- formulation

iv "absorption"

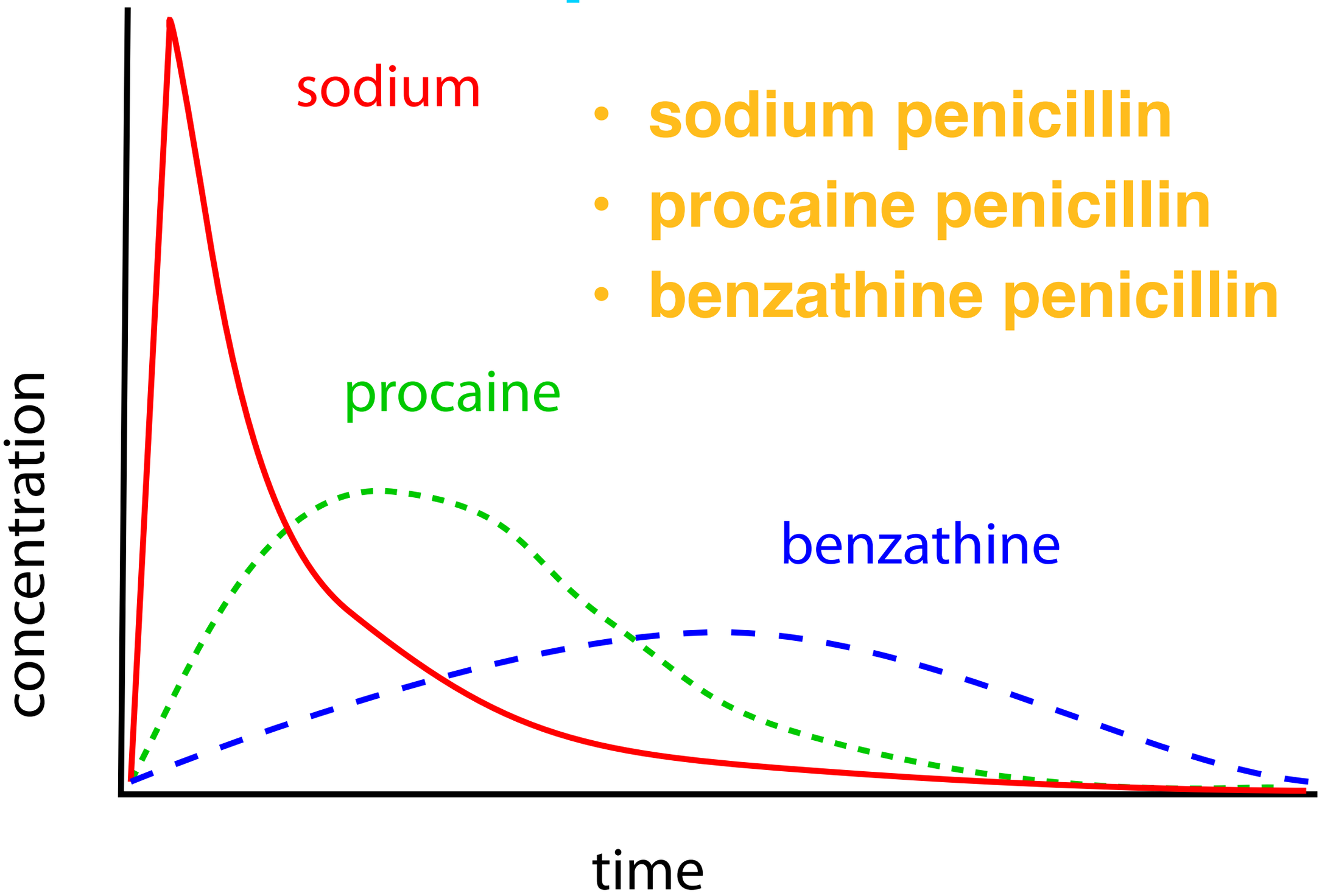
- absorption is bypassed by iv injection
- rate of injection = rate of absorption
- if rate of absorption is critical to the patient, iv infusion can be used

alterations in rate of absorption can have clinical effects

- antibiotics
- sedatives

penicillin

- **sodium penicillin**
- **procaine penicillin**
- **benzathine penicillin**



penicillin

- **sodium penicillin**
- **procaine penicillin**
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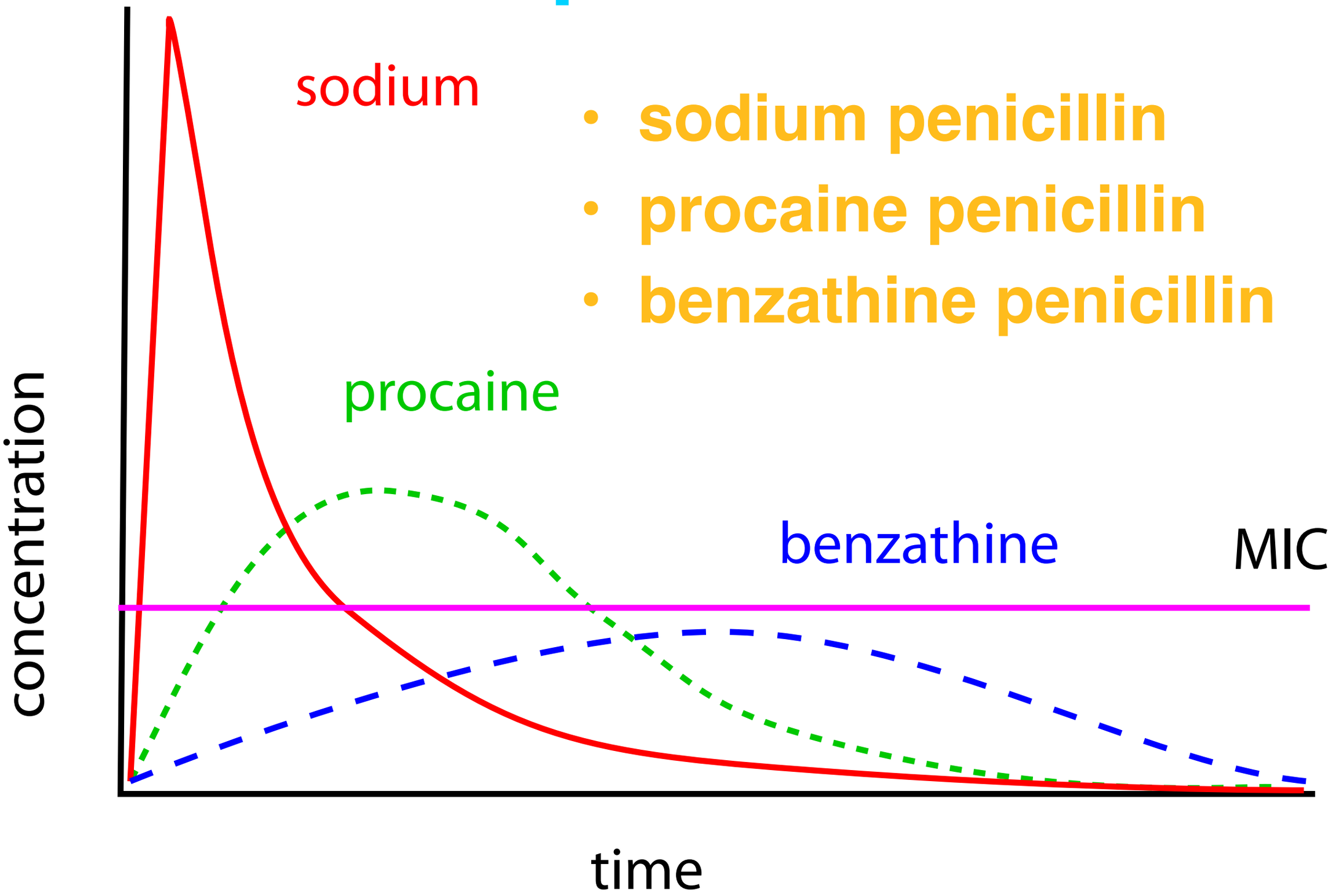


How would you get an antibiotic to here?

absorption

- most drugs must be absorbed to act
- iv administration bypasses absorption
- absorption depends on lipid solubility and ionisation
- drugs are often formulated to provide delayed absorption