Pharmacokinetics: Absorption
(pH Partition hypothesis & other aspects of drug absorption)

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The pH Partition Hypothesis

- ✓ Most drugs are weak organic acids or bases and exist in solution as both non-ionized and ionized forms.

$$HA \leftrightarrow A^- + H^+, \quad \text{where } K_a = \frac{[A^-]\,[H^+]}{HA}$$

$$BH^+ \leftrightarrow B + H^+, \quad \text{where } K_a = \frac{[B]\,[H^+]}{[BH^+]}$$

- ✓ **Non-ionized form:** Lipid-soluble & diffusible.
- ✓ **Ionized form:** Relatively lipid insoluble and poorly diffusible.

The pH Partition Hypothesis contd...

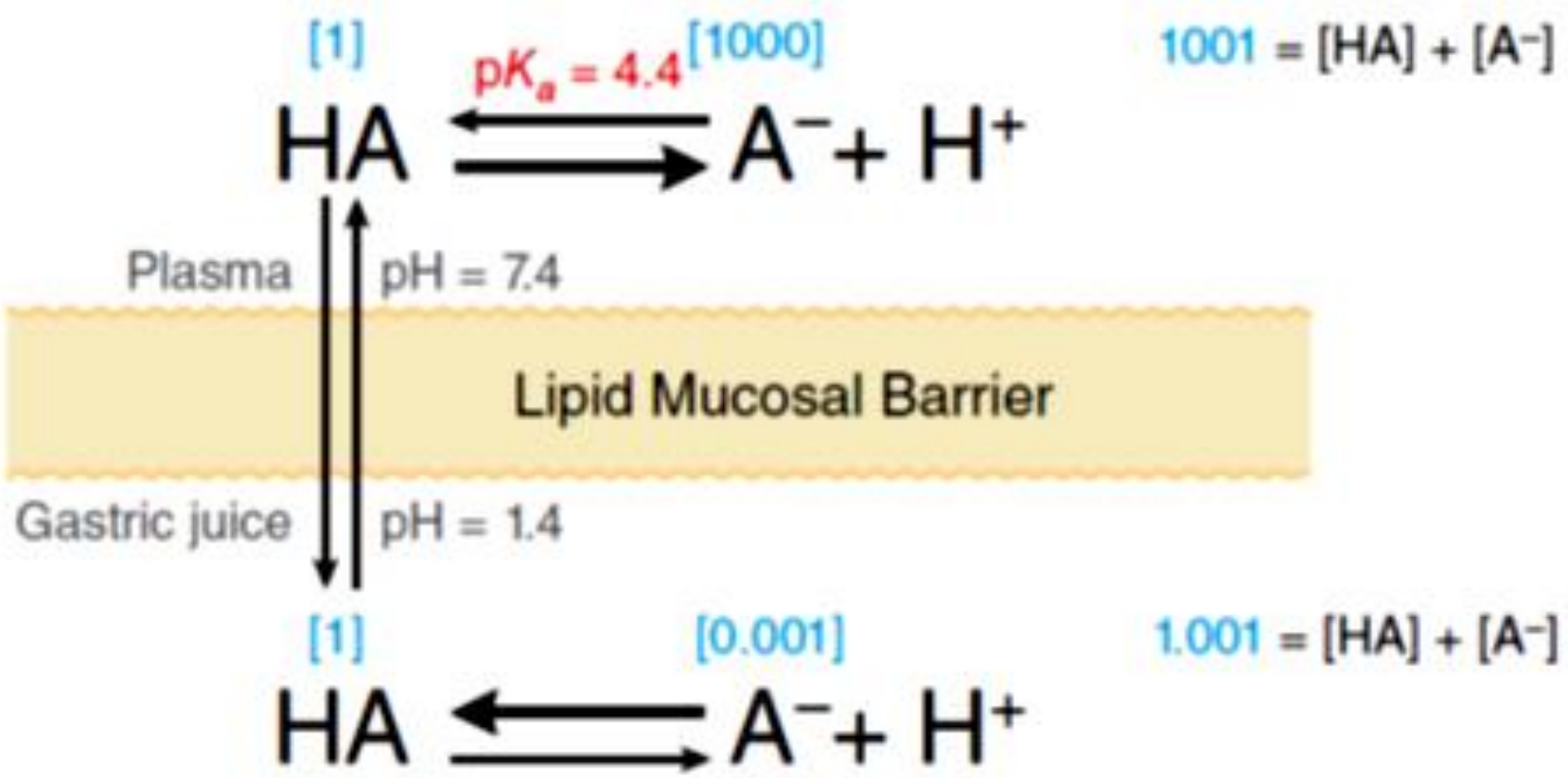
- ✓ Among the common ionizable groups are carboxylic acids (—COOH) and amino ($—NH_3$) groups.

$$—COOH \leftrightarrow —COO^- + H^+$$

$$—NH_4^+ \leftrightarrow —NH_3 + H^+$$

- ✓ The transmembrane distribution of a weak electrolyte is influenced by its pKa and the pH gradient across the membrane.

Influence of pH on distribution of weak acid



Source: Goodman & Gilman's The Pharmacological Basis of Therapeutics (13th Edn.)

The pH Partition Hypothesis contd...

- ✓ The ratio of non-ionized to ionized drug at any pH may be calculated from the **Henderson-Hasselbalch equation**:

$$log \frac{[protonated\ form]}{[unprotonated\ form]} = \mathrm{pKa} - \mathrm{pH}$$

- ✓ Protonated form (HA or BH^+) and unprotonated form (A^- or B)

$$HA \leftrightarrow A^- + H^+ \qquad BH^+ \leftrightarrow B + H^+$$

The pH Partition Hypothesis contd...

- ✓ The pKa is the pH at which half the drug (weak acid or base electrolyte) is in its ionized form.
- ✓ 1 scale change in pH will cause 10 fold change in ionization.

Implications of pH and pKa considerations

- ✓ Acidic drugs, e.g. aspirin (pKa 3.5) are largely unionized at gastric pH and are absorbed from stomach, while bases, e.g. atropine (pKa 10) are largely ionized and are absorbed only when they reach the intestines.
- ✓ **Ion Trapping:** At steady state, an acidic drug will accumulate on the more basic side of the membrane and a basic drug on the more acidic side. This phenomenon, known as ion trapping, is an important process in drug distribution with potential therapeutic benefit.

Implications of pH and pKa considerations contd…

- ✓ Basic drugs attain higher concentration intracellularly (pH 7.0 versus 7.4 of plasma).

- ✓ Acidic drugs are ionized more in alkaline urine – do not back diffuse in the kidney tubules and are excreted faster. Accordingly, basic drugs are excreted faster if urine is acidified.

Bioavailability

- ✓ It refers to the rate and extent of absorption of a drug from dosage form.
- ✓ It is a measure of the fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form.

Bioavailability contd...

- ✓ Bioavailability of drug injected i.v. is 100%, but is frequently lower after oral ingestion because –
  - (a) the drug may not be completely absorbed.
  - (b) the absorbed drug may undergo first pass metabolism in intestinal wall/ liver or be excreted in bile.
- ✓ Formula:-

$$\text{Bioavailability (F)} = \frac{AUC_{oral}}{AUC_{IV}}$$

Bioequivalence

- ✓ Two drug products are considered to be bioequivalent when the rates and extents of absorption of active ingredient in the two products are statistically equivalent to each other according to predetermined criteria under controlled test conditions.

- ✓ Bioequivalence assessment relies on the concept that pharmaceutically equivalent drug products provide essentially equivalent plasma concentration profiles, in terms of rate and extent of absorption, will produce the same pharmacologic response (therapeutic effect).


Thank You