Pharmacology and Pharmacokinetics class for epfl master students, spring 2025

Detailed objectives of the part by Stephan Kellenberger

→The aim of this class is to learn mechanisms and concepts of pharmacology, not to learn by heart the small details of the class!

At the end of the course, the student is expected to be able:

1. Pharmacodynamics

- to describe the principles of the interaction between ligands and their receptors and to describe the relative importance of different forces in this
- to describe the methods that are used to measure binding at the equilibrium and the kinetics of association and dissociation; including competition binding assays
- to describe the forces and mechanisms that govern ligand association and dissociation, including typical values of association and dissociation rate constants
- to define and explain the terms "drug", "receptor", "occupancy" "efficacy", "potency", "desensitization" and "therapeutic index"
- to describe the models/hypotheses about the coupling between ligand binding and response
- to describe how the effect of a drug depends on different parameters, that are characteristics of the tissue (Number of receptors, transducer function) or of the ligand-receptor pair (the dissociation or equilibrium constant of the binding (Kd or Ka), and the intrinsic efficacy)
- Quantitative description: to calculate, and to draw qualitatively the following types of graphs and to determine and define the parameters indicated in ():
    - a concentration-binding and concentration-effect curve (Kd, EC50)
    - time course of association and dissociation of a drug (t1/2 or k)
    - inhibition by a competitive or a non-competitive antagonist, using a graph of occupancy as a function of the agonist or of the antagonist concentration (K_B, K_i, IC50 [qualitatively])
- to define and explain the terms "agonist", "antagonist", "inverse agonist", "full agonist", "partial agonist" and to cite an example for each
- to explain different types of antagonism
- to describe the function of (allosteric) modulators, as discussed for the case of benzodiazepines
- to be able to describe the effects of agonists, antagonists and inverse agonists on receptors with constitutive activity, by using the two-state model
- to be able to analyze an article on pharmacology and to determine for example whether an observed effect is clinically relevant (based on provided information on drug concentrations reached clinically)

2. Drug targets

- to list the main classes of drug targets, indicating their relative importance as drug targets
- to describe the drug target discussed in class, the classes of drugs acting on them; describe the mode of action and the most important pharmacological effects.

2.1. Receptors

- to describe the principles of G-protein-coupled receptor signaling, including the G protein cycle, the function of the most important downstream targets (adenylate cyclase, PLC), and G protein-independent signaling
- to describe the main functions of adrenergic receptors, and the principal way by which drugs can interact with the adrenergic system (i.e. ways of interaction with receptors, ways of interaction with ligand formation, transport and degradation)
- to describe the 4 steps in pain sensation, describe examples of proteins (receptors, channels) involved in the different steps.
- to describe the term "peripheral sensitization" in the context of pain sensation
- to describe the mode of action of opioid receptor drugs and of non-steroidal anti-inflammatory drugs (NSAIDs) and to list their most important pharmacological effects

$GABA_A$ receptors:

- To describe the mechanisms by which ligands of the benzodiazepine site affect $GABA_A$ receptor function
- To describe the rationale for the search for subunit-specific functions of $GABA_A$ receptors, the strategies used, and the possible advantages of subunit-specific ligands.
- Describe the binding sites, mode of action, and effects of the two drug classes "neurosteroids" and "anesthetics" acting on $GABA_A$ receptors

- to describe the activation mechanism of kinase-linked transmembrane receptors, and illustrate this with an example
- to describe type I and type II diabetes, the long-term risks of diabetes, and the pharmacological strategies used in diabetes
- to describe the different functional units of nuclear receptors, their mode of action and the main differences between class I and class II receptors; and to name and describe examples for each of the two receptor classes
- to describe how some nuclear receptors control the metabolism and/or elimination of drugs

2.2. Enzymes

- to describe the mode of action of inhibitors of the folate synthesis and of the dihydrofolate reductase
- to describe the mode of action and uses of ACE inhibitors; to discuss the effect of drugs acting on other targets of the same signaling pathway (Renin inhibitors, AT1 receptor inhibitors)
- to explain why tyrosine kinases are important drug targets in some cancers, to describe how imatinib inhibits the BCR-ABL kinase, and strategies to cope with resistance to imatinib

2.3. Protein therapeutics

- to mention examples of protein therapeutics that replace a protein or augment an existing pathway
- to describe the pharmacological effects of GLP-1 receptor agonists, their mechanism of action, their pharmacokinetics and the structural organization of these molecules
- to describe the mechanisms by which monoclonal antibodies affect their targets (there are 3 different ways)
- to describe the principle of bi-specific antibodies
- to describe the types of monoclonal antibodies and similar agents used (as discussed for the treatment of rheumatoid arthritis)
- to describe the basic differences between small molecule and protein-based drugs
- to describe the challenges of therapies with monoclonal antibodies, the risks and the advantages

2.4. Gene therapy

- to cite examples of target proteins and/or diseases for gene therapy
- to describe an example of an RNA-based therapeutic approach that is in clinical development or approved for clinical use (including the physiological context)
- to describe the mechanism of action of antisense oligonucleotides, of siRNAs and splice-switching oligonucleotides
- to describe the main challenges in gene therapy of monogenic disorders
- to discuss the possible problems due to vector insertion in the genome
- to explain which approaches in gene therapy of monogenic disorders are most promising and describe an example of successful gene therapy that is in clinical trial or approved for the clinic
- to describe the principle of CAR T-cell therapy
- to describe the principles of targeted genome editing

3. Context for chemotherapy and general topics

- to cite different principles of selective targeting by anti-cancer and anti-infective drugs (unique drug target/ selective inhibition of similar targets/common targets) and illustrate it with examples
- to describe the mechanisms of development of resistance of pathogens or cancer cells to drugs, and illustrate it with examples

- to describe the terms “therapeutic index”, “ED50” and “TD50”
- to discuss the context in which drug toxicity most often occurs (overdose / drug-drug or drug-herb interactions)
- to explain the risks of a prolonged QT interval, and to cite other factors that contribute to the risk of torsades de pointes.

4. Drug discovery and development

- to provide an overview of drug development, including the pre-clinical and clinical phases, and postmarketing surveillance;
- to describe the aims of preclinical development
- to describe the characteristics of the three clinical phases in drug development
- to describe an example of a historical event with a major disfunction in drug development
- to name organizations that can approve drugs for the market (FDA, EMA, Swissmedic), describe the most important activities of such organizations
- to explain why the postmarketing surveillance is important

If you have questions, don’t hesitate to ask me
Stephan.Kellenberger@unil.ch 021 692 5422