Fundamental Relationships in Toxicology

M1 – Methods in Toxicology

Dose \leftrightarrow \text{Response}
1. General principles of drug action

- Affinity, Efficacy, Potency of drugs
- Dose-response-curves
- Types of agonists/antagonists
- Therapeutic index

2. Targets of drugs

- Receptors, enzymes, ion-channels, transporters
Affinity vs. Efficacy

- **Affinity**: ability of the toxicant to bind to its receptor
- **Efficacy**: ability of a toxicant to evoke a cellular response

- **Agonist**: high affinity and intrinsic activity/efficacy
- **Antagonist**: certain affinity but no intrinsic activity/efficacy
Dose-response-curve

occupancy/affinity:

\( K_d \): concentration, at which 50% of receptors are occupied

response/potency:

\( EC_{50} \): concentration, that causes 50% of the maximal effect

https://accesspharmacy.mhmedical.com/content.aspx?sectionid=95700976&bookid=1568
Potency and Efficacy

- **Potency**: refers to the amount of drug needed to produce a given effect → EC$_{50}$
- **Efficacy**: determines the maximum effect that a drug can produce regardless of dose → E$_{max}$

Source: http://tmedweb.tulane.edu/pharmwiki/doku.php/basic_principles_of_pharm
Types of Agonists

- **Full agonist**: activate the receptor with a maximum response (e.g. morphine)

- **Partial agonist**: have only partial efficacy at the receptor relative to a full agonist (e.g. buprenorphine)

- **Neutral Antagonist**: intrinsic/basal level of activity in absence of any ligand

- **Inverse agonist**: decreases the activity below basal level (e.g. rimonabant)
Types of Antagonists

- **Competitive antagonist:**
  bind to receptor at the same binding site as the agonist but without activating it
  
  \[
  \text{EC}_{50} \uparrow \\
  \text{E}_{\text{max}} = \text{const.}
  \]

- **Non-competitive antagonists:**
  1. bind irreversibly to the same site as the agonist
  2. allosteric modulation: bind to a different site as the agonist → change in the binding affinity of the ligand (enhanced or decreased)

http://tmedweb.tulane.edu/pharmwiki/doku.php/basic_principles_of_pharm
IC\textsubscript{50} value: concentration of antagonist, that is required for 50% inhibition of receptor or enzyme

Partial agonists as antagonists

Clinical relevance

- Full agonist + partial agonist → partial agonist acts as an antagonist: decrease in receptor activation

- Clinically used to treat opiate dependence (milder effects + lower abuse potential) → ceiling effect

Therapeutic Index

- **Toxic response curve:** $TD_{50} =$ dose producing death in 50% of cases

- **Therapeutic Index:** measure of drug safety

$$TI = \frac{Median \ toxic \ dose}{Median \ effective \ dose} = \frac{TD_{50}}{ED_{50}}$$

High TI = “safe” drug
Example: Penicillin

Low TI = risky drug
Example: cardiac glycosides

http://tmedweb.tulane.edu/pharmwiki/doku.php/basic_principles_of_pharm
Targets for drugs/toxicants

- **Receptors**
  - [Image](https://medcraveonline.com/JSR-T-JSRT-02-00065)

- **Enzymes**
  - [Image](http://www.ncbi.nlm.nih.gov/pubmed/25679644)

- **Ion channels**
  - [Image](http://pharmrev.aspetjournals.org/content/57/4/387)

- **Transporters**
  - [Image](https://courses.washington.edu/conj/bess/transport/su mmary/NaKpump.png)
Receptors

- Cell membrane
  - Channel linked receptors
  - G-protein-coupled receptors
- Intracellular
  - Kinase-linked receptors
  - Nuclear receptors
Channel linked receptors

- coupled directly to an ion channel
- crucially important for synaptic transmission in the CNS
- e.g. nicotinic Ach-receptor
- toxin: α-Bungarotoxin

\[
\text{IC}_{50} = 0.23 \text{ pmol}
\]

http://jpet.aspetjournals.org/content/296/2/260

http://www.tomhsiung.com/wordpress/2014/12/ligand-and-voltage-gated-channels-receptors/

http://www.hongkongsnakeid.com/many-banded-krait
- site of action of about 45% of drugs
- coupled to intracellular effector mechanism via G-proteins → enzyme activation or opening of ion channel
- e.g. muscarinic Ach-receptor
- ligand: atropine

[Diagram of G-protein coupled receptors and competitive antagonist]

https://www2.courses.vcu.edu/ptxed/m2/powerpoint/download/Damaj%20DR%20Curves.PDF

Kinase-linked receptors

- linked directly to an intracellular protein kinase that triggers a cascade of phosphorylation reactions
- receptor for cytokines, growth factors and hormones
- e.g. growth factor receptor
- ligand: dasatinib

Dasatinib is more potent in terms of IL-10 production

http://www.biochemj.org/content/465/2/271.figures-only

https://www.nature.com/articles/nbt.3028
- intracellular receptors
- act as transcription factors that promote or inhibit synthesis of new proteins
- e.g. oestrogen receptor
- Ligand: tamoxifen

\[ K_{d}(4\text{-OH-TAM}) << K_{d}(\text{TAM}) \]
30 to 100 times greater affinity of 4-OH-TAM

https://www.quora.com/Are-nuclear-receptors-attached-to-DNA-or-to-the-nuclear-membrane
### Enzymes

- site of action of about 30% of drugs
- inhibition of the active site may be competitive or long lasting and irreversible
- e.g. acetylcholinesterase
- toxicant: organophosphates

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**Malathion-oxon: lowest IC$_{50}$ → highest potency**

[Diagram showing inhibition of AChE by pesticides](https://www.researchgate.net/figure/The-concentration-dependent-inhibition-of-rat-brain-AChE-by-the-OP-pesticides_fig4_8369600)

[Chemical structure of Malathion-oxon](http://www.u-helmich.de/bio/lexikon/A/acetylcholinesterase.html)
Ion channels

- ion channels that are activated by changes in the electrical membrane potential near the channel
- found in excitable tissues along the axons and synapses
- e.g. voltage gated sodium channel
- toxin: aconitine

LD for humans: 0.028mg/kg orally → 2.24mg for a 80kg person

Aconitum napellus

https://www.chemistryworld.com/podcasts/aconitine/1017356.article

Transporters

- specialized proteins that carry ions or molecules across the cell membrane
- transport may be passive or active
- e.g. Na\(^+\)/K\(^+\)-ATPase
- drug: cardiac glycoside

Digitalis purpurea

https://link.springer.com/referenceworkentry/10.1007%2F978-3-642-22144-6_159

TI (digoxin) ≈ 2:1
Thank you for your attention!