Neuromuscular Junction - Pharmacology

1. Some pharmacological principles, illustrated by ACh at the NMJ
2. Targets for drug action at the NMJ
3. Drugs affecting ACh Receptors (activation) - competitive and depolarising block
4. Drugs affecting ACh Esterase (inactivation)
5. Drugs affecting synthesis, storage and release of ACh

Reading
Rang et al. Pharmacology

General Principle of Pharmacology: 1
Most drugs are effective because they bind to proteins:
- Enzymes
- Carriers
- Ion channels
- Receptors

General Principle of Pharmacology: 2
Drugs are useful as:
- Experimental tools
- Clinical treatments

General Principle of Pharmacology: 3
The concept of the receptor, and most kinds of receptors, have been identified by the selective effects of specific drugs

General Principle of Pharmacology: 4
Drug assays are based on:
- Ligand binding (~affinity, $K_D$)
- Biological response (~efficacy, EC50)

General Principle of Pharmacology: 5
When “doing drugs” a good pharmacologist needs to know:
- Target specificity/Ligand specificity
- Agonist/Antagonist
- Dose/Response
- Affinity ($K_D$)/Efficacy (EC50/IC50)
- Competitive/Non-competitive
- Clinical/Non-clinical uses
- Side-effects
The biological responses normally measured in skeletal muscle are:

- muscle contraction (twitch/tetanus);
- transmitter release (EPCs/EPPs);
- receptor/ion channel response (nAChR channels)

**Acetylcholine**

\[
\text{CH}_3 - \text{C} = \text{O} - \text{CH}_2 - \text{CH}_2 - \text{N}^+ \text{CH}_3
\]

Quaternary nitrogen

**The "nicotinic" ACh Receptor**

**Testing drugs on ACh receptors**

- Iontophoresis
- Bath application
- Patch clamp

**Ligand Binding**

\(\alpha\)-bungarotoxin
General scheme for Agonist-Receptor Interaction (illustrated by ACh binding to its Receptors)

\[ \text{ACh} + \text{R} \xrightarrow{\text{bound}} \text{ACh-R} \xrightarrow{\text{activated}} \text{ACh-R}^* \]

“desensitized”

\[ K_0 = \frac{[\text{ACh}][\text{R}]}{[\text{ACh-R}]} = \sim 80 \, \mu\text{M} \]

Ligand-gated (eg AChR)  Voltage-gated (e.g. NaV)

V-gated Ion-channel Pharmacology

<table>
<thead>
<tr>
<th>Channel</th>
<th>Antagonist/blocker</th>
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<tbody>
<tr>
<td>Na channels</td>
<td>tetrodotoxin (TTX)</td>
</tr>
<tr>
<td></td>
<td>saxitoxin (STX)</td>
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<tr>
<td></td>
<td>µ-conotoxin</td>
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<td></td>
<td>lignocaine</td>
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<tr>
<td>K channels</td>
<td>Cs⁺</td>
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<tr>
<td></td>
<td>tetraethylammonium (TEA)</td>
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<tr>
<td></td>
<td>4-aminopyridine (4-AP)</td>
</tr>
<tr>
<td>Ca channels</td>
<td>Ca²⁺, Mg²⁺</td>
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<tr>
<td></td>
<td>α-conotoxin</td>
</tr>
<tr>
<td>N-type</td>
<td>ω-agatoxin</td>
</tr>
<tr>
<td>L-type</td>
<td>dihydropyridines (DHP)</td>
</tr>
</tbody>
</table>

\[ \text{Drugs that stimulate ACh Receptors (agonists)} \]

- Acetylcholine
- Carbachol
- Decamethonium
- Suxamethonium (I)
- Suxamethonium (II)
Drugs that block ACh Receptors (antagonists)

- Atropine
- d-Tubocurarine

Example: d-tubocurarine

Example: α-bungarotoxin

ACh antagonists that are used clinically

- Suxamethonium
  - Not broken down by AChE (nmj)
  - Broken down by BuChE (blood plasma)
  - Short lasting
  - Not counteracted by cholinesterase inhibitor
  - Used clinically for brief muscle relaxation
  - "Depolarising blocker"
Other targets in neuromuscular pharmacology:

- Synthesis
- Storage
- Release
- Action
- Inactivation

Drugs that block ACh esterase:

- Anticholinesterase
- Edrophonium
Drugs that inhibit transmitter synthesis/storage

- Choline uptake
- Vesicle filling

Drugs that inhibit transmitter release

- Ca²⁺ channel blockers
- Botulinum toxins + 'SNARE' blockers

EPPs in μ-conotoxin/d-tubocurarine

EPP in low Ca/high Mg

K channel blockers and some toxins enhance transmitter release

Targets of drug action at the neuromuscular junction
Summary
1. Drugs with effects on neuromuscular synapses may be tested in many ways: bioassay of muscle contractions, electrophoresis during intracellular recording, or patch-clamp recording from single receptors and channels.
2. Every step in the cycle of ACh synthesis, storage, release, activation and inactivation is a potential target for drug action at the NMJ.
3. Drugs affecting storage and release:
   - 4-AP, TEA, latrotoxin, botulinum toxin, agatoxin
   - hemicholinium, vesamicol
4. Drugs that block ACh Esterase:
   - edrophonium, prostigmine, neostigmine, sarin
5. Drugs affecting ACh Receptors:
   - carbachol, decamethonium, suxamethonium
   - tubocurarine, α-bungarotoxin, atracurium
6. Clinical uses of drugs acting at the NMJ:
   - muscle relaxants as adjunct to anaesthesia in surgery
   - treatment of neuromuscular disease