Neuromuscular Junction - Pharmacology

1. Principles and methods for studying ACh pharmacology at the NMJ
2. Targets for drug action at the NMJ
3. Drugs affecting ACh Receptors (activation)
4. Drugs affecting ACh Esterase (inactivation)
5. Drugs affecting ACh release
6. Drugs affecting ACh synthesis and storage.

Drugs acting at the NMJ are useful as:
- Experimental tools
- Clinical treatments

When “doing drugs” a good pharmacologist needs to know:
- Target specificity/Ligand specificity
- Agonist/Antagonist
- Dose/Response
- Efficacy (EC50/IC50)/Affinity (Kd)
- Competitive/Non-competitive
- Clinical/Non-clinical uses
- Side-effects
Drug assays at the NMJ are based on:

- Biological response (→ efficacy, EC50)
- Ligand binding (→ affinity, \( K_D \))

Specificity and dose-response of antagonists

Ligand binding visualised:

- \( \alpha \)-bungarotoxin

But normally measured chemically (e.g. radioactively-labelled ligand):
3. Drugs affecting ACh Receptors (activation)
General scheme for Agonist-Receptor Interaction (illustrated by ACh binding to its Receptors)

$$ACh + R \rightleftharpoons ACh-R \rightleftharpoons ACh-R^*$$

- Bound
- Activated
- Desensitized

$$K_d = \frac{[ACh][R]}{[ACh-R]} = \approx 80 \mu M$$

The nicotinic ACh Receptor at NMJ

Stereospecificity of skew ("gauche") configuration of ACh/receptor binding. (View as "magic eye" stereo pair.)

nACh Receptor Pharmacology - Neuromuscular Junction

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Antagonist/blocker</th>
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<tbody>
<tr>
<td>nicotine</td>
<td>d-tubocurarine (curare)</td>
</tr>
<tr>
<td>acetylcholine</td>
<td>α-bungarotoxin</td>
</tr>
<tr>
<td>carbachol</td>
<td>atracurium</td>
</tr>
<tr>
<td>decamethonium</td>
<td>pancuronium</td>
</tr>
<tr>
<td>suxamethonium (I)</td>
<td>suxamethonium (II)</td>
</tr>
</tbody>
</table>
Reversible competitive antagonism of the ACh receptor. 1

Drugs that block ACh Receptors (antagonists)

Example: d-tubocurarine

Example: α-bungarotoxin

Irreversible competitive antagonism of ACh Receptor
Dual effect of suxamethonium (succinyl choline)

1. Depolarisation

2a. Sodium inactivation (depolarising block)

2b. Desensitization of AChR (depolarising block)

Non-competitive antagonists of the nicotinic ACh receptor

Phencyclidine (PCP, "angel dust")

Methyl violet 10B (hexamethyl violet; crystal violet)

4. Drugs affecting ACh Esterase (inactivation)
Drugs that block ACh esterase

<table>
<thead>
<tr>
<th>CH₃</th>
<th>CH₂</th>
<th>O</th>
<th>CH₂</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂C—N⁺⁻—CH₂—CH₂—O—C—CH₂</td>
<td>Acetylcholine</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Drugs that inhibit transmitter release

- Botulinum toxins + "SNARE" blockers
- P/Q Ca²⁺ channel blockers
- ω-agatoxin/ω-conotoxin

K channel blockers and some toxins enhance transmitter release

Before

During

After

Countering the depression of ACh release by low Ca²⁺ or high Mg²⁺ using 4-AP

6. Drugs affecting synthesis and storage
1. Every step in the ACh cycle - synthesis, storage release, activation and inactivation - is a potential target for drug action at the NMJ.
2. Clinical uses of drugs acting at the NMJ:
   - Muscle relaxants as an adjunct to anaesthesia in surgery
   - Treatment of neuromuscular disease
3. Drugs affecting ACh Receptors:
   - Carbachol, decamethonium, suxamethonium (agonists)
   - Tubocurarine, α-bungarotoxin, atracurium (antagonists)
4. Drugs that block ACh Esterase:
   - Edrophonium, prostigmine, neostigmine, sarin
5. Drugs affecting release:
   - TEA, 4-AP, α-latrotoxin (agonists)
   - Botulinum toxin, ω-agatoxin (antagonists)
6. Drugs that block uptake, storage and synthesis:
   - Hemicholinium-3, vesamicol, AF64A

Summary