Pharm-05A4 Outline the mechanism of action of drugs that inhibit cholinergic transmission at the neuromuscular junction giving examples.

**Background**

Cholinergic transmission at the NMJ involves the following steps:

1. synthesis of acetylcholine from acetyl-CoA and choline catalysed by choline acetyltransferase (ChAT)
2. ACh packaged into vesicles and stored in axon terminus
3. nerve action potential arrives at axon terminus $\rightarrow$ Ca$^{2+}$ influx $\rightarrow$ release of ACh-containing vesicles into synaptic cleft
4. ACh binds to post-synaptic nAChR receptors $\rightarrow$ depolarises post-synaptic membrane
5. ACh binds to pre-synaptic nAChR receptors $\rightarrow$ enhance ACh release $\rightarrow$ positive feedback
6. Acetylcholinesterases in the NMJ degrades ACh $\rightarrow$ terminate actions of ACh

Drugs can disrupt each of the above steps thereby inhibiting cholinergic transmission

**Depolarising NMB**

Suxamethonium is a depolarising NMB

*Chemical structure:* dimer of ACh with C–C linkage

*Phase I (depolarising) block mechanism:* 2 molecules of sux binds the 2 alpha subunits of nAChR $\rightarrow$ activation and channel opening $\rightarrow$ depolarisation $\rightarrow$ sux is not metabolised by NMJ AChE $\rightarrow$ remains bound to nAChR $\rightarrow$ nAChR remains open & in inactive state $\rightarrow$ forms small zone of depolarisation/inactivation around synapse $\rightarrow$ blocks further depolarisation $\rightarrow$ muscle relaxation

($\sim$ 20% post-synaptic nAChR occupancy required to achieve depolarising block)

Sux exerts pre-junctional action $\rightarrow$ retrograde conduction up motor neuron $\rightarrow$ triggers axon to depolarise entire motor unit $\rightarrow$ fasciculation observed prior to onset of depolarising block

*Phase II (desensitisation) block mechanism:* exact mechanism uncertain.

After sux has been present for a period of time $\rightarrow$ motor end plates loses sensitivity to ACh/sux $\rightarrow$ depolarisation cannot occur

Desensitisation continues (for several minutes) even after drug is no longer present

**Non-Depolarising NMB**

Two groups divided based on chemical structure:

1. aminosteroids – rocuronium, vecuronium
2. benzylisoquinolinium – atracurium, cisatracurium, mivacurium

*Non-depolarising block mechanism:* ND-NMB acts as competitive antagonist $\rightarrow$ competes with ACh for nAChR binding $\rightarrow$ blocks cholinergic transmission $\rightarrow$ muscle relaxation
ND-NMB also inhibits pre-synaptic ACh receptors → prevents enhancement of ACh release → fade with repeated stimulation

**Disrupts ACh synthesis**

Hemicholinium blocks reuptake of choline into nerve terminal by high-affinity choline transporter at presynapse → disrupts ACh synthesis

When neuron is affected by hemicholinium, ACh synthesis relies on choline transported from the soma

Affects both nicotinic and muscarinic pharmacology

**Disrupts ACh release**

Many drugs can affect ACh release from presynaptic terminal

1. botulinum toxin: endocytosed into presynaptic nerve terminal → cleaves docking proteins (e.g. SNARE) → prevents docking of vesicles containing ACh → ↓ release of ACh vesicles
2. aminoglycosides (e.g. gentamicin): blocks pre-synaptic Ca²⁺ channels → ↓ release of ACh vesicles
3. high dose Mg: competitive inhibition of pre-synaptic Ca²⁺ channels → ↓ release of ACh vesicles
4. volatile anaesthetics: block pre-synaptic ACh receptors → ↓ positive feedback → ↓ACh release

**Reduces efficacy of ACh at post-synaptic AChR**

1. high dose local anaesthetics: blocks post-synaptic Na⁺ channels → stabilises post-synaptic membrane
2. lithium: stabilises post-synaptic membrane

**Examiner’s comments** - 59% pass rate

The main points expected for a pass were:
- **depolarising neuromuscular blocking agents**: eg sux, mechanism of action
- **non depolarising blocking agents**: eg cisatracurium, mechanism of action
- example and mechanise of action of at least one other mechanism inhibiting cholinergic transmission at the NMJ, such as: deficiency blockade: drugs inhibiting ACh synthesis or release; desensitisation blockade: drugs inhibiting ACh efficacy at the post junctional receptor; phase 2 blockade; channel blockade.

Extra marks were awarded for a full answer incorporating all of the above mechanisms with examples of drugs that have these effects.

Common mistakes included drawing a diagram of a normal motor end plate, including a lengthy discussion of the normal physiology of excitation-contraction coupling, without incorporating relevance to the question of the mechanisms of drug action inhibiting cholinergic transmission. Also, many candidates discussed mechanisms of
action of drugs inhibiting cholinergic transmission, but did not provide examples. Finally, many candidates did not explain how suxamethonium-induced post junctional receptor opening inhibited cholinergic transmission.