Pharmacological Inhibition of skeletal muscle activity

By actions at different anatomical/physiological sites, such as

CNS – by general anaesthetics

Spinal cord - by acting on spinal motor control mechanisms

Motor nerves – via local anaesthetic action - including toxins (TTX - tetrodotoxin)

At the motor nerve ending – botulinum toxin

At the neuromuscular junction – nicotinic skeletal muscle receptor antagonists (neuromuscular blocking drugs)

Miscellaneous mechanisms
The NMJ
Nerve endings spread along muscle

Nerve

Muscle

A nerve ending

Acetylcholine is released from nerve ending

Antibody

Surface of muscle fibre

Neuromuscular junction (gap between nerve and muscle)

Receptor on surface of muscle fibre

Some receptors are stimulated by acetylcholine

Some receptors are blocked or damaged by antibodies
Nicotinic Cholinergic Transmission

Nicotinic receptor sites are found at:
Post junctional membrane on the neuromuscular endplate where they exist on a 1:1 relationship with AChE
   On the skeletal muscle spindle (afferent physiological receptor in skeletal muscle-extrafusal fibres)
   At the ganglion of the sympathetic, parasympathetic and enteric ANS
   Within CNS at various synaptic sites - both pre and post synaptic

Functionally there are two peripheral types of nicotinic receptors: skeletal muscle and ganglionic (with at least two different CNS types).
The basic theme for NACHR nicotinic receptors is a ligand-gated ion channel where the neurotransmitter is ACh whose binding opens the channel. NACHR receptors are generally "protected" by adjacent AChE molecules. In the neuromuscular junction ACh released from the nerve generally only has a single binding to the receptor before it is hydrolyzed by acetylcholinesterase into choline and acetate.
**Ganglionic nicotinic receptors**

**Agonists:** ACh, CCh, nicotine (after which the receptor is named), lobeline and DMPP

All "agonize" receptor **but** high and continuous occupancy desensitizes the receptor to the action of further ACh – this results in so-called desensitizing block. Nicotine first activates receptor, and then blocks. This type of block also occurs in the skeletal muscle receptor.

**Antagonists (ganglion blockers):** Hexamethonium (C6), trimethaphan
Skeletal muscle nicotinic receptors

**Agonists:**
ACh, CCh, succinylcholine ('2 ACh molecules back to back’ as an ester condensed from the dicarboxylic acid [succinic acid] and two acetates). Succinylcholine "agonizes" the NACHr receptor, but when present at high enough concentrations to produce high and continuous occupancy of the receptors, succinylcholine desensitizes the receptors to ACh resulting in a depolarizing block (may be followed by a desensitizing block.)
\[
(\text{CH}_3)_3\text{N}-\text{CH}_2-\text{CH}_2-\text{O}^{-}\text{C}^-\text{CH}_3
\]

ACETYLCOLINE

\[
(\text{CH}_3)_3\text{N}-\text{CH}_2-\text{CH}_2-\text{O}^{-}\text{C}^-\text{CH}_2-\text{CH}_2-\text{C}^-\text{O}^-\text{CH}_2-\text{CH}_2-\text{N}\left(\text{CH}_3\right)_3
\]

SUCCINYLCHOLINE

\[
(\text{CH}_3)_3\text{N}-\left(\text{CH}_2\right)_{10}-\text{N}\left(\text{CH}_3\right)_3
\]

DECAETHANETHIUM
Non depolarizing neuromuscular blockers

The original neuromuscular blocking drug, d-tubocurarine, was isolated from curare a South American dart poison. Classic experiments with curare in the 1800s led to the identification of its neuromuscular site of action. However, decades passed before it was used to produce neuromuscular block in medicine. Only in the last decades have the newer “curare” drugs been invented, primarily, because d-tubocurarine does not have an “ideal” pharmacological profile since it releases histamine, and can lower blood pressure via ganglion blockade.

Other curare-like drugs can be regarded as being steroid, or iso-quinoline derivatives, i.e. d-tubocurarine. All have charged nitrogens at physiological pH values therefore are poorly absorbed orally (hence the relative safety of curare when used as an arrow poison to kill animals for food).
Steroid derivatives: end in ‘curonium’ as in Pancuronium, Vecuronium, and Rocuronium.

All are similar in actions and pharmacology, except that Rocuronium and Vecuronium are shorter acting. Pancuronium, the oldest of such drugs, has more side effects.

Isoquinolone derivatives: end in ‘curium’ as in Atacurium, Mivacurium and Doxacurium.

Mivacurium short acting and broken down by plasma esterases.

Uses: intravenous to produce neuromuscular blockade to aid surgery – rarely in any other conditions.
Botulinus toxin (botox)

Botulinum toxin produces skeletal muscle neuromuscular blockade indirectly by depleting cholinergic nerves (motor axons) of ACh. Once depleted it takes months for the nerve ending to recover its normal levels of ACh. Botulinus toxin (botox) given locally to produce local skeletal muscle blockade used therapeutically where botulinus toxin is injected locally to block inappropriate muscle contractions in various motor and muscle diseases (e.g. strabismus). Non therapeutic use of botulinus toxin as “botox” is more familiar where it is used cosmetically to remove the lines of worry, age, too much sun, and tobacco.

Toxic protein produced by spoiled canned food (by the anaerobe - Clostridium botulinum). Death occurs because respiratory muscle paralysis – treatment is artificial ventilation until Ach repopulates cholinergic nerve endings - takes weeks to months.