# NeuroMuscular Blocking Agents (NMBA)

## Use
- Render patients unable to move or breathe during surgery conducted under general anesthesia for patients requiring intubation for airway management
- Facilitate endotracheal intubation, maintain paralysis during surgery, sustain paralysis for mechanically ventilated patients in ICU

## MOA: altering transmission at neuromuscular junction
- **Presynaptically:** \( - \)ACh synthesis, \( - \)ACh release
- **Postsynaptically:** persistently \( + \) ACh receptors leading to hyperpolarization, competitively block ACh

## Botulinum toxin
- Not an NMBA, acts presynaptically
- **MOA:** prevents vesicle docking by cleaving SNAP-25 protein \( \rightarrow \) prevents release of ACh
- **Effects:** local neuromuscular blockade \( \rightarrow \) ↓ activity of individual muscles or muscle groups

## NMBAs: Overview
- Act postsynaptically
- Highly polar: can’t cross BBB, administered parenterally
- Prior to giving NMBA, patient must be sedated and ventilated

## The only depolarizing NMBA: succinylcholine (SCh)
- **Structure:** small, resembles ACh, acts like an agonist
- **MOA:** binds to nicotinic receptor \( \rightarrow \) opens channel like ACh does \( \rightarrow \) membrane depolarization \( \rightarrow \) \( + \) muscle contractions \( \rightarrow \) resists AChase degradation \( \rightarrow \) depolarization blockade & paralysis
- **Two phases of SCh blockade**
  - **Phase I:** depolarization block
    - Membrane depolarization \( \rightarrow \) transient fasiculations \( \rightarrow \) flaccid paralysis
    - Desired effect
  - **Phase II:** desensitization to ACh despite restored membrane potential
    - Continuous infusion \( \rightarrow \) altered postjunctional membrane \( \rightarrow \) membrane desensitized \( \rightarrow \) resists depolarization \( \rightarrow \) repolarization \( \rightarrow \) membrane resists effects of ACh
    - Undesired effect
- Resistant to breakdown by true AChase found in NMJ, but broken down by plasma pseudocholinesterases
- **P’kinetics:** quickest onset (30-60 sec), rapid breakdown, short duration of action (5-8 mins)
- **SE:** fasiculations (chest, abdomen), pain, ↑intracranial/intraocular/intracranial pressure, bradycardia (kids), tachyphylaxis (adults), hyperkalemia (leading to arrhythmias or cardiac arrest), malignant hyperthermia, myalgias, anaphylaxis
  - **Malignant hyperthermia:** pharmacogenetic hypermetabolic state of skeletal muscle induced in susceptible individuals by inhalational anesthetics and/or succinylcholine
    - **MOA:** acute massive Ca2+ release \( \rightarrow \) uncontrolled muscle metabolism \( \rightarrow \) lactic acid, CO2, heat
    - **Triggering agents:** SCh, inhalational anesthetic agents
    - **Clinical signs:** ↑ET CO2, body rigidity, ↑HR, acidosis, ↑temp
    - **Treatment:** dantrolene, ice packs, restore acid-base balance
### Non-depolarizing NMBAs

- **Structure:** resemble ACh
- **MOA:** reversibly bind to postsynaptic terminal → hyperpolarization → prevent ACh from depolarizing muscle
  - Muscle paralysis occurs when 80% of receptors are blocked
  - Does not block direct stimulation of muscle
- **Classes of depolarizing NMBAs**
  - **Isoquinolines:** atracurium, cisatracurium
    - Metabolism: non-enzymatic inactivation by ester hydrolysis (Hofmann elimination)
    - Breakdown product: laudanosine → CNS excitation (atracurium > cisatracurium)
    - Atracurium: release histamine from mast cells → bronchospasm, tachycardia, hypotension
  - **Aminosteroid derivatives:** pancuronium, vecuronium, rocuronium
    - Rocuronium: rapid onset (1-2 min)
    - Pancuronium: longest duration of action (60-90 min)
      - Active metabolite: 3-hydroxypancuronium
      - Long t½ is problem, especially with renal or hepatic insufficiency patients
      - Vagolytic effect: ↑HR by 10bpm
- **Active metabolites:** pancuronium, vecuronium
- **Drug interactions:** volatile anesthetics, aminoglycosides, corticosteroids, local anesthetics

### Reversing neuromuscular blockade

- **Cholinesterase inhibitors**
  - MOA: ↑ACh levels at synaptic cleft
  - Onset of action: 5-7 mins
  - Muscarinic SE
  - Agents: edrophonium, neostigmine, pyridostigmine
    - Edrophonium has quicker onset but less effective
  - Parasympatholytic agents (atropine, glycopyrrolate) competitivemuscarinic effects of cholinesterase inhibitors
  - Cannot reverse SCh blockade

Intubation (propofol) → induction (SCh, rocuronium) → maintenance (inhaled anesthetic or non-depolarizing NMBA) → emergence/recovery (turn off inhaled anesthetic or revere NMBA with neostigmine or glycopyrrolate)

### 1. Facilitate endotracheal intubation

- Need rapid acting agents: succinylcholine & rocuronium
- Indicated of patients at risk of aspiration: pregnant, diabetic, history of GI reflux, morbidly obese
- Succinylcholine
  - Only depolarizing NMBA
  - Onset: 30-60 sec
  - Duration: 5-8 min
  - Metabolism: plasma pseudocholinesterase
  - Advantages: produce intense paralysis rapidly, reliable, predictable, wears off quickly
  - Disadvantages: SE, malignant hyperthermia trigger, phase II blockade possible
- Rocuronium

### 2. Paralysis Maintenance

- Only nondepolarizing NMBAs used
- Onset & duration of action
  - Short: rocuronium (60-90 sec onset, 30-40 min duration)
  - Intermediate: atracurium, cisastracurium, vecuronium (2-3 min onset, 30-40 min duration)
  - Long: pancuronim (>3 min onset, >60 min duration)
- Elimination
• Hepatic: rocuronium, vecuronium
• Renal: rocuronium, pancuronium
• Hofmann elimination: atracurium, cisatracurium

• Monitoring NMBAs: peripheral nerve stimulator
  o Train of four nerve stimulation: 4 short bursts → how many twitches?
    ▪ 0 → intubation dose
    ▪ 1-2: maintenance dose
    ▪ 3-4: end of surgery, time to admin reversal agent

3. Reversal of neuromuscular blockade
• Agents: neostigmine, edrophoium, pyridostigmine
• Recovery process: occurs first at larynx then last at adductor pollicis (thumb)
• SE: ↓HR, ↓BP, N&V, salivation
• Anticholinergic agents (atropine, glycopyrrolate): always used in combination with anticholinesterase to block muscarinic effects since we only really want to block nicotinic receptors