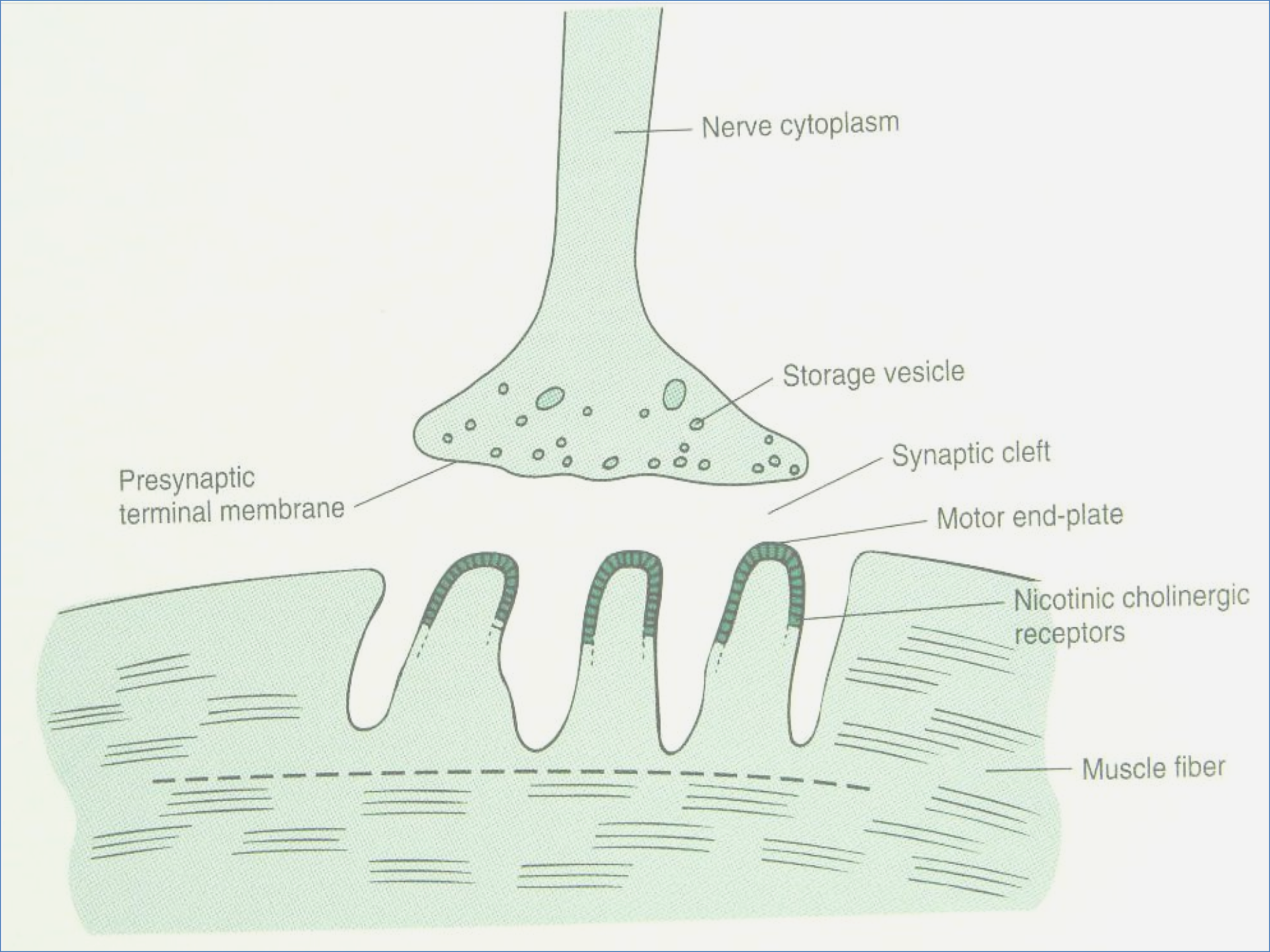
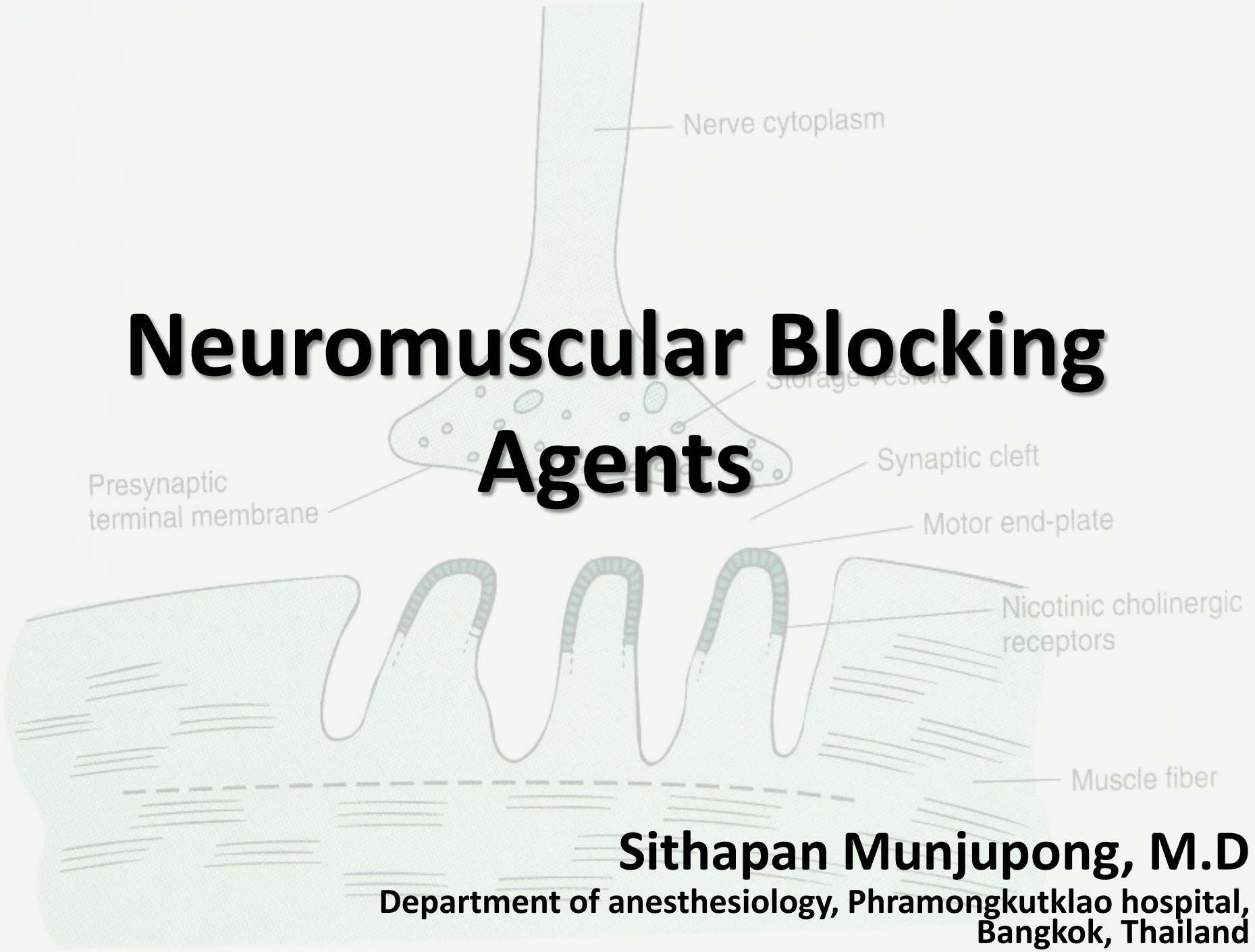

Nerve cytoplasm
Storage vesicle
Synaptic cleft
Presynaptic
terminal membrane
Motor end-plate
Nicotinic cholinergic
receptors
Muscle fiber



Neuromuscular Blocking Agents

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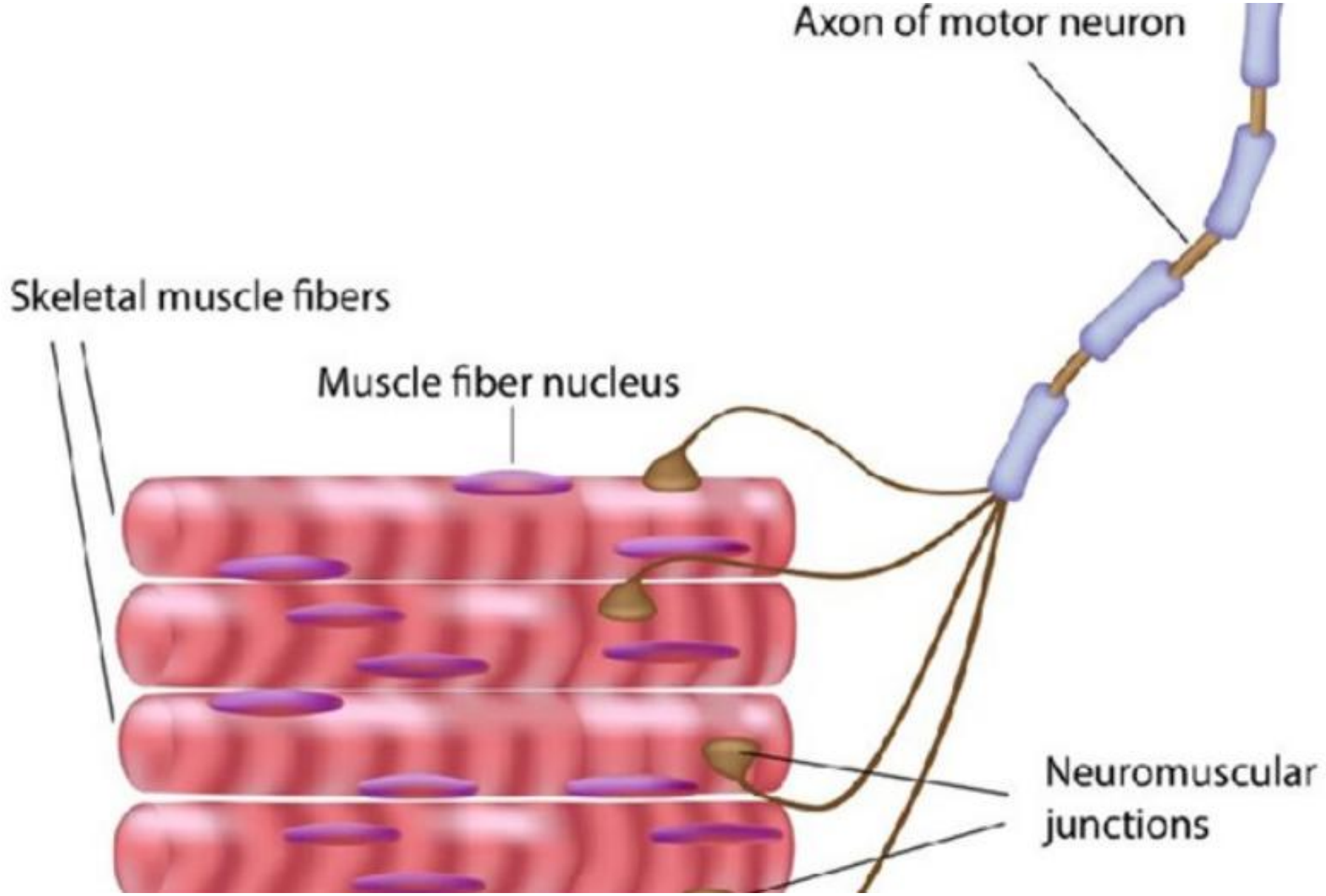
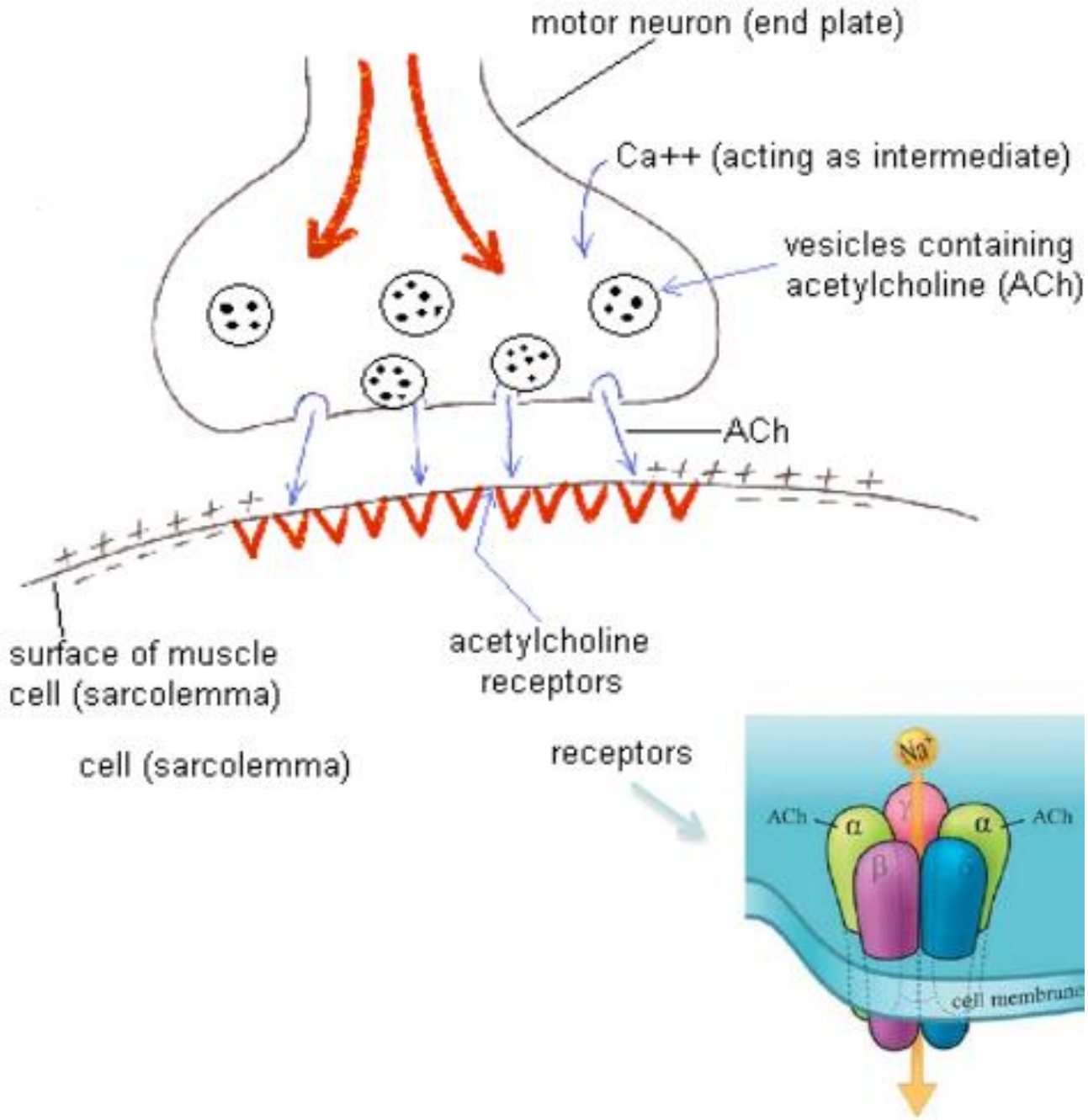
Objective

- Classification of NMBA
- Mechanism of action
- Clinical application
- Adverse effects

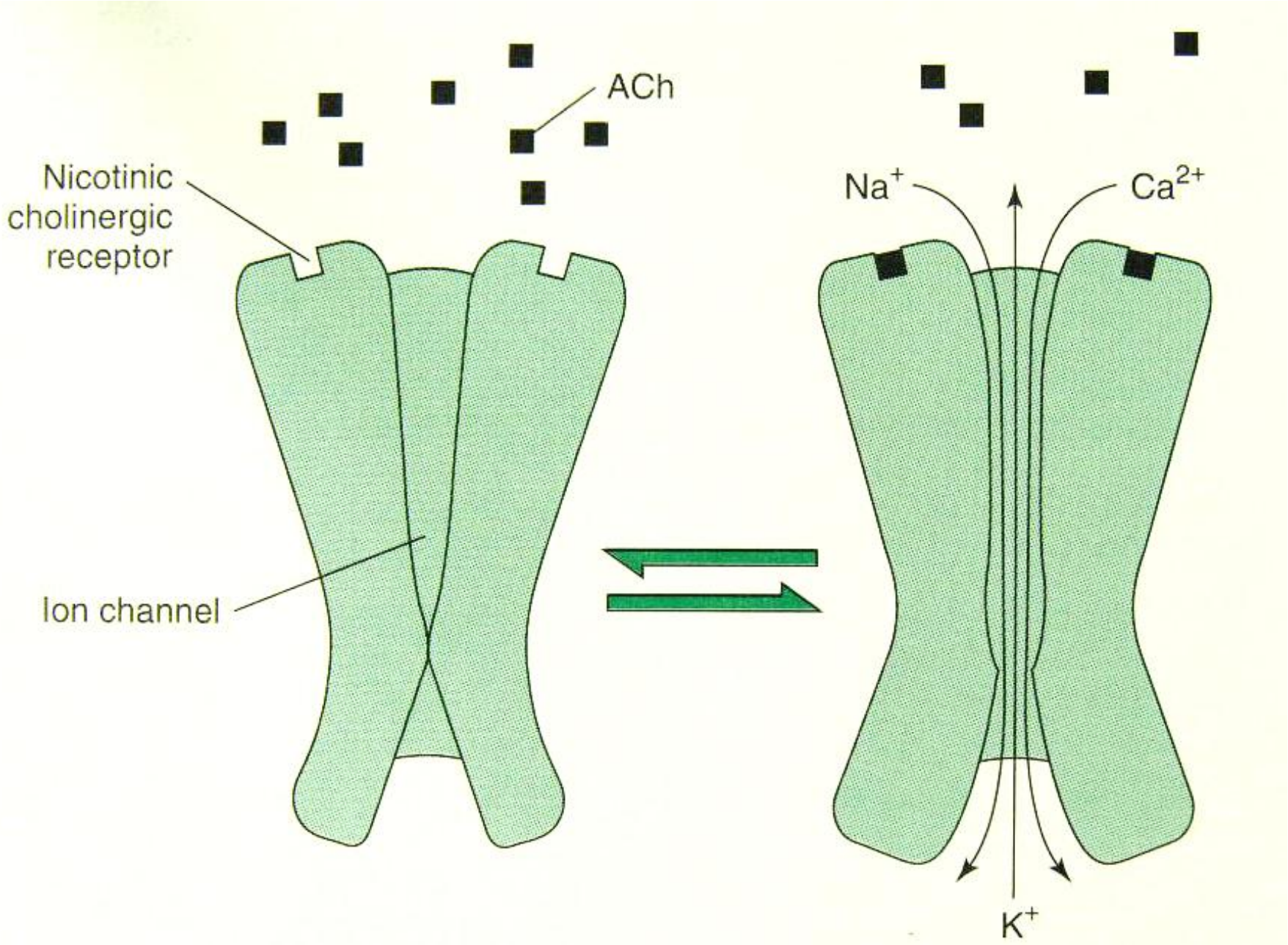
How do you move your body?

Innervation of Skeletal Muscle





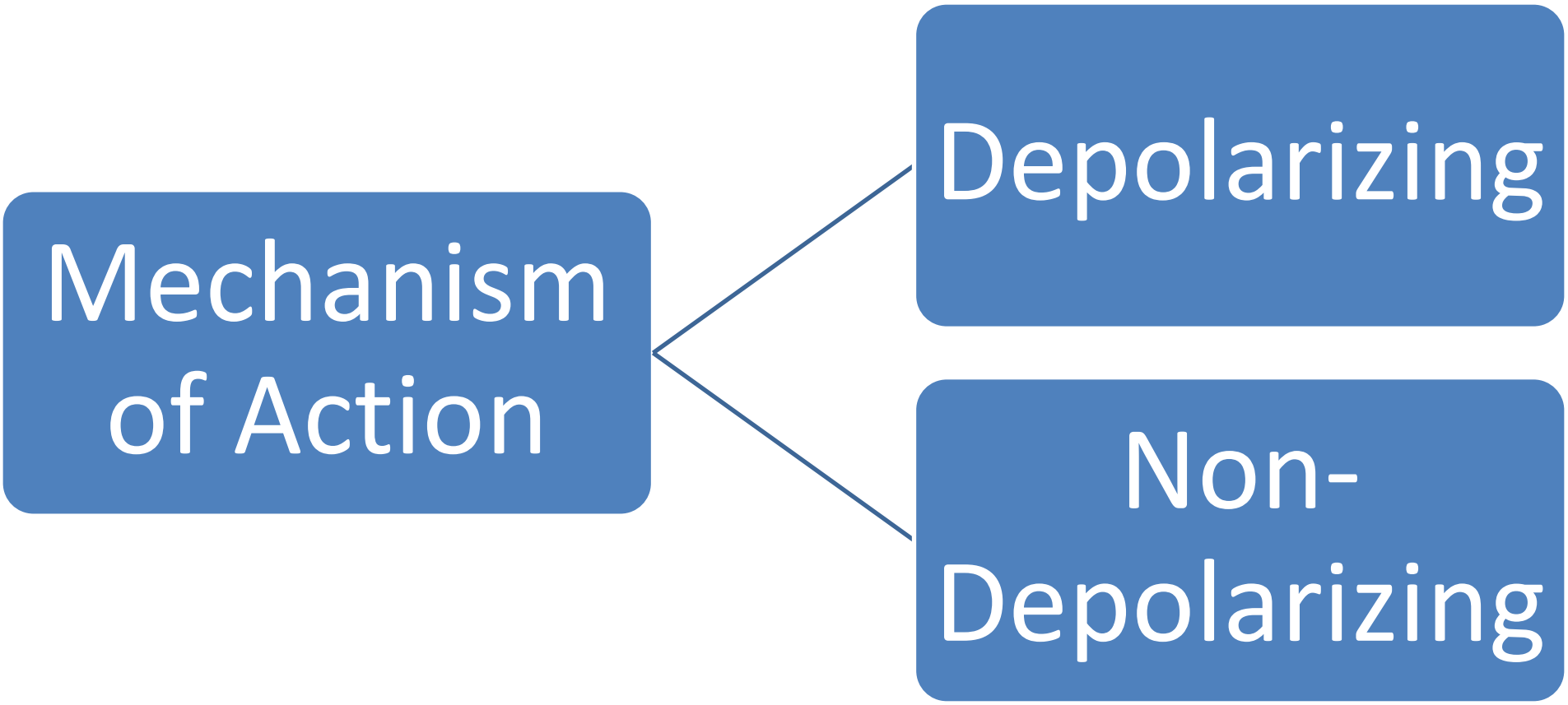
Alpha subunit
Nicotinic receptor

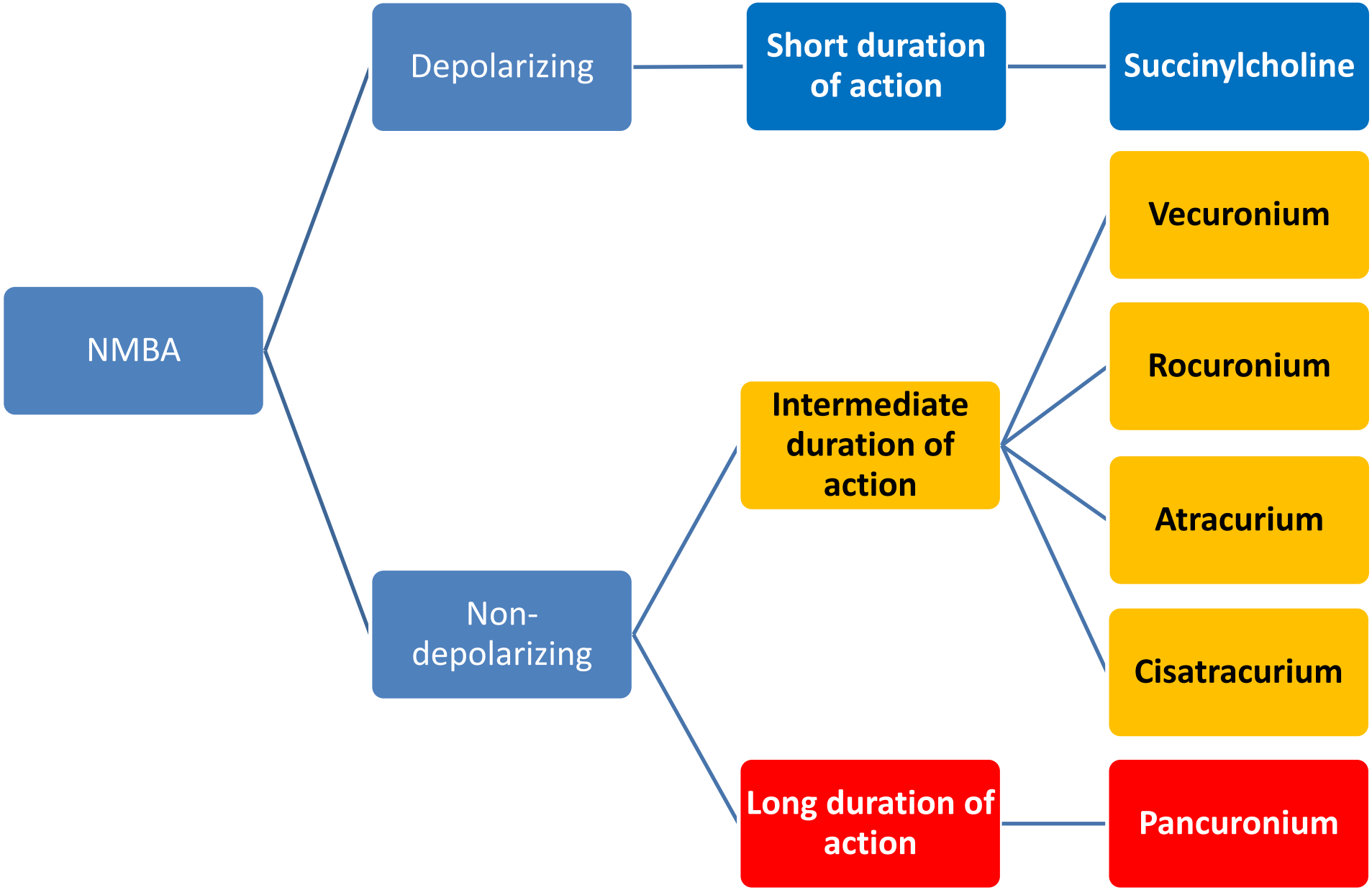


Binding of Ach to receptors on muscle end-plate

Ideal muscle relaxant drug

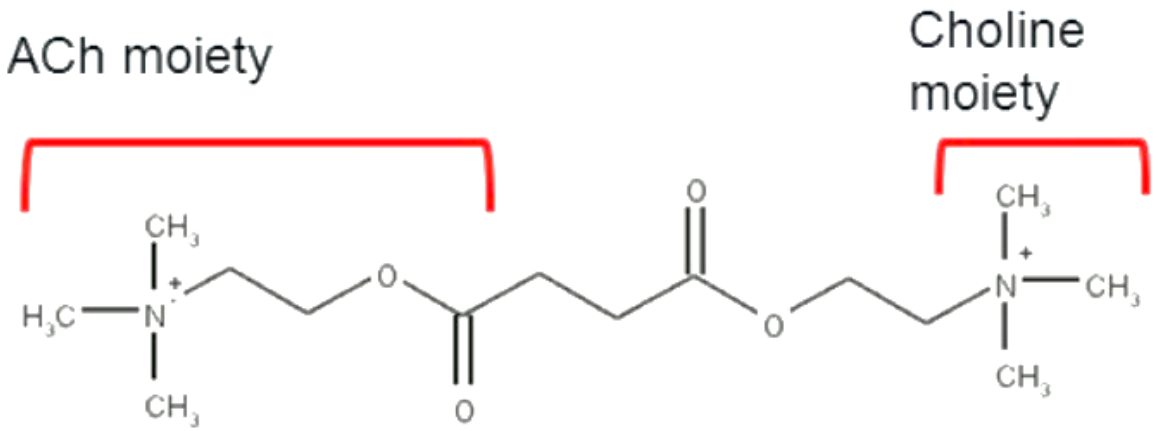
- Rapid onset
- Intermediate duration
- Rapid recovery
- No accumulation
- No cardiovascular side effect
- No histamine release
- No active metabolite


Mechanism of Action
Depolarizing
Non-Depolarizing

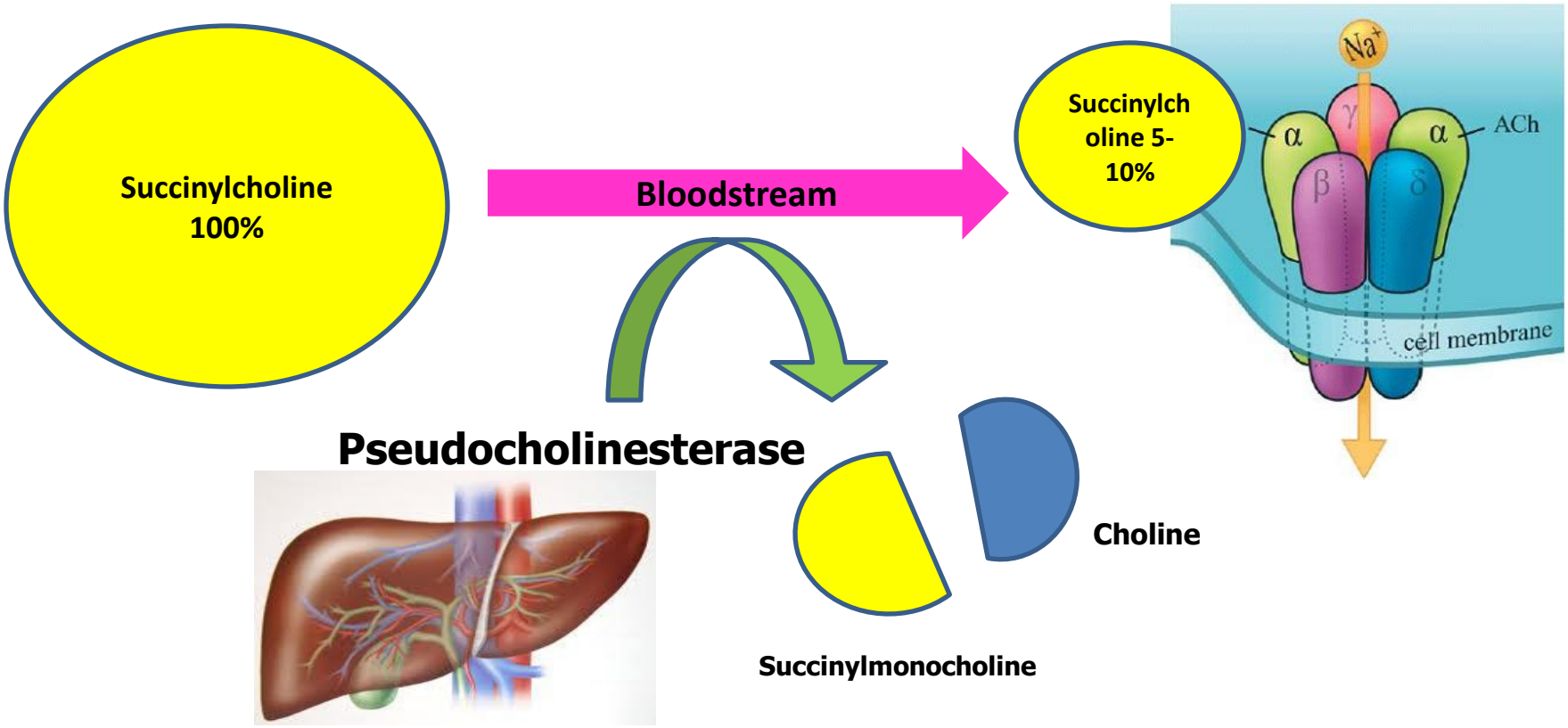

NMBA
Depolarizing
Short duration of action
Succinylcholine
Non-depolarizing
Intermediate duration of action
Vecuronium
Rocuronium
Atracurium
Cisatracurium
Long duration of action
Pancuronium

Depolarizing NMBA: Mechanism of Action

- **Succinylcholine**
  - Analogue of Acetylcholine
  - Two ACh molecules joined by methyl groups
  - Agonizes nACh Receptor



Anesth Analg. 2006;105:151-5.
Anesth Analg. 2006;102:438-42.



Hydrolysed by pseudocholinesterase or plasma cholinesterase

Not degraded by Acetylcholinesterase

Depolarizing NMBA: Succinylcholine

- **Intubating Dose**: 1.5 mg/kg : for RSI
  - Dose based on total body weight (TBW)
- **Rapid Onset**: 45-60 sec
- **Short acting**: Duration 6-10 min depending on dose

Naguib M, Samarkandi AH, Emad El-Din M, et al. The dose of succinylcholine required for excellent endotracheal intubating conditions. Anesth Analg. 2006;105:151-5.

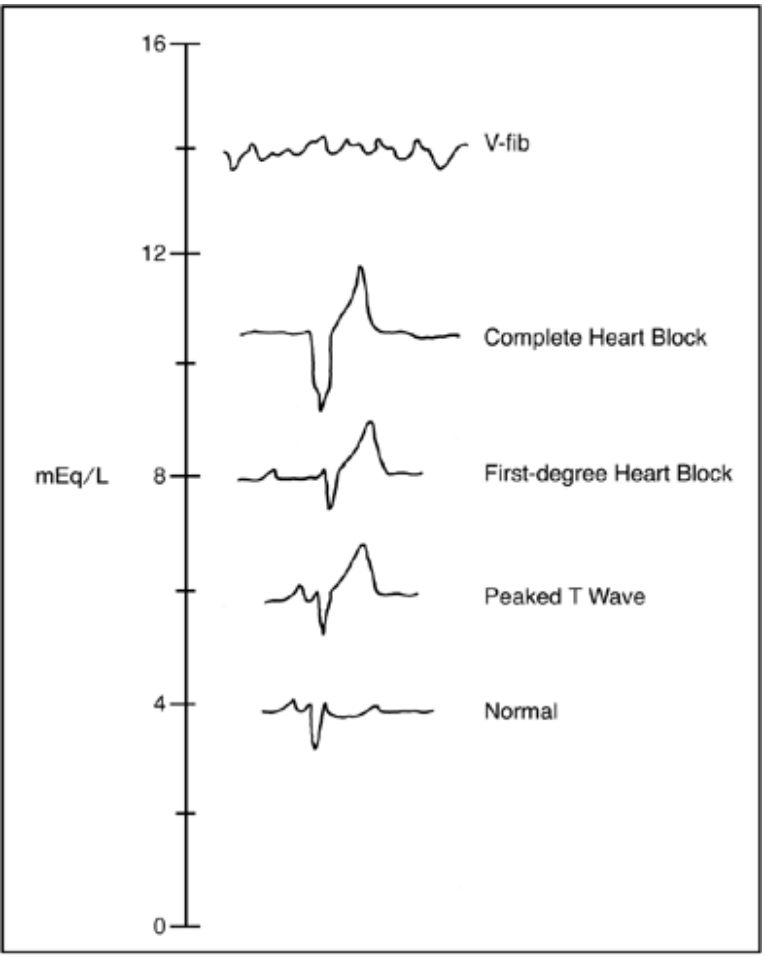
Lemmens HJ, Brodsky JB. The dose of succinylcholine in morbid obesity. Anesth Analg. 2006;102:438-42.

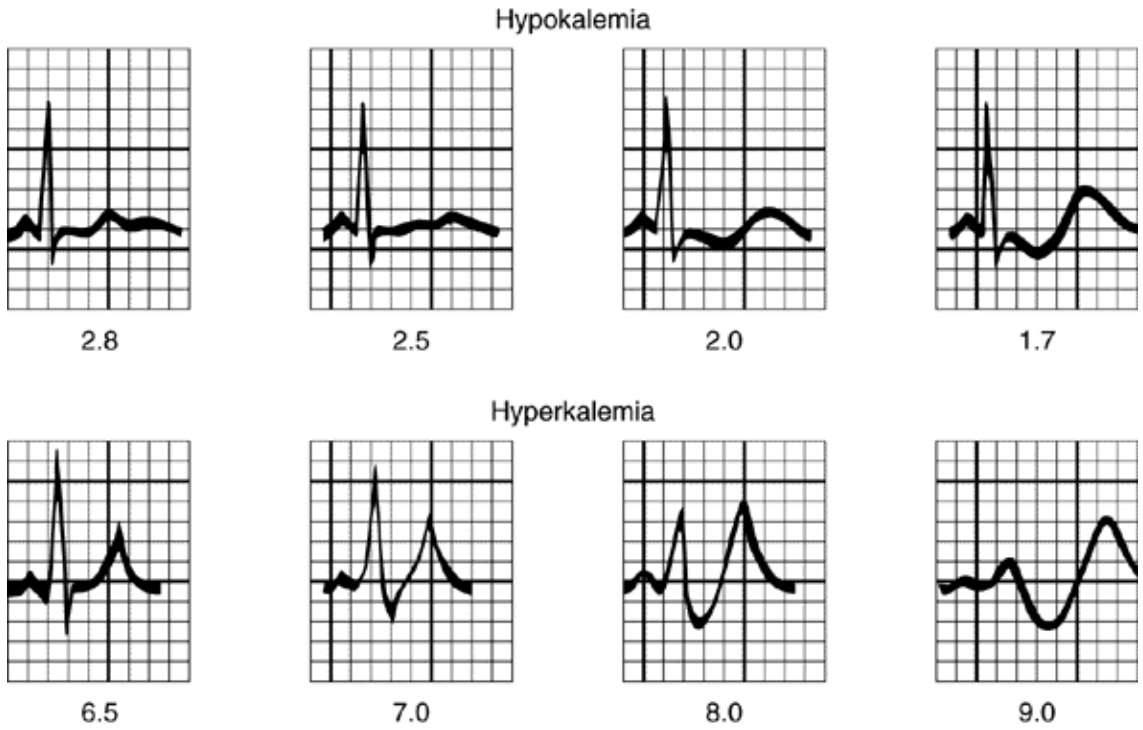
Avoids succinylcholine

- **Extrajunctional nAChRs** (exaggerated hyperkalemic response)
  - **Neuromuscular diseases**
    - Spinal cord injury(after first 24 hr,peak 7-10 day,persisted upto 6 mo)
    - Muscular dystrophies,Guillain-Barré syndrome
    - Multiple sclerosis
  - **Burns** (24h after burn → 2 years after burned skin healed)
  - **ICU patients**
    - Upregulation of nAChRs induced by immobilization (>24h)
  - **Severe hypovolemia and metabolic acidosis**
- **ICP, IOP**
- **MH associated conditions** (triggering agents)
- **Cardiac arrhythmias** (bradycardia after repeated dose)

Can Anaesth Soc J. 1986; 33: 195-208.
Anesthesiology. 2003;99:220-3.
Eur J Anaesthesiol. 2001;18:632-52.
Anaesthesia. 2000;55:144-152.

- Decreased amplitude and broadening of the T waves
- Prominent U waves
- ST segment depression and
- T and U wave fusion, which is seen in severe hypokalemia





•50% of patients with potassium levels greater than 6.5 mEq/L will not manifest any electrocardiographic changes.
•The ECG changes due to **mild potassium elevations (K = 5.5 – 7.0 mEq)** include tall, peaked, narrow-based T waves and fascicular blocks (LAFB and LPFB).
•**Moderate hyperkalemia (K = 7.5 – 10.0 mEq)** is associated with first-degree AV block and diminished P wave amplitude.

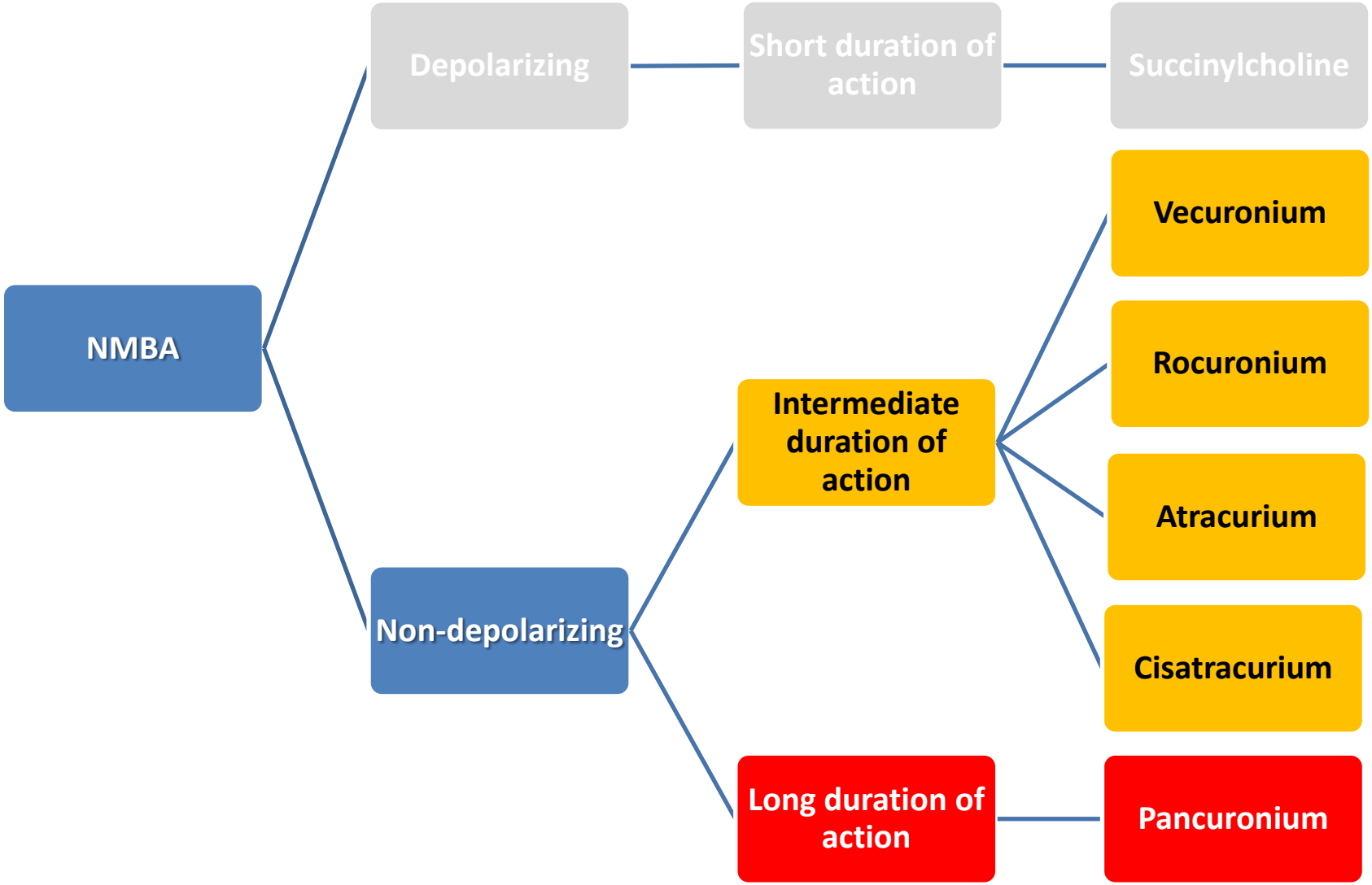
The ECG manifestations of progressive hyperkalemia. (Adapted from Burch GE, Winsor T. A primer of electrocardiography. Philadelphia: Lea & Febiger, 1966:143.)

Contraindications

- Conditions with upregulated Ach receptors
- History malignant hyperthermia
- Open globe (anterior chamber): causes transient ↑ IOP
- **Normokalemic renal failure is NOT a contraindication**

Anesth Analg. 2006;105:151-5.
Anesth Analg. 2006;102:438-42.

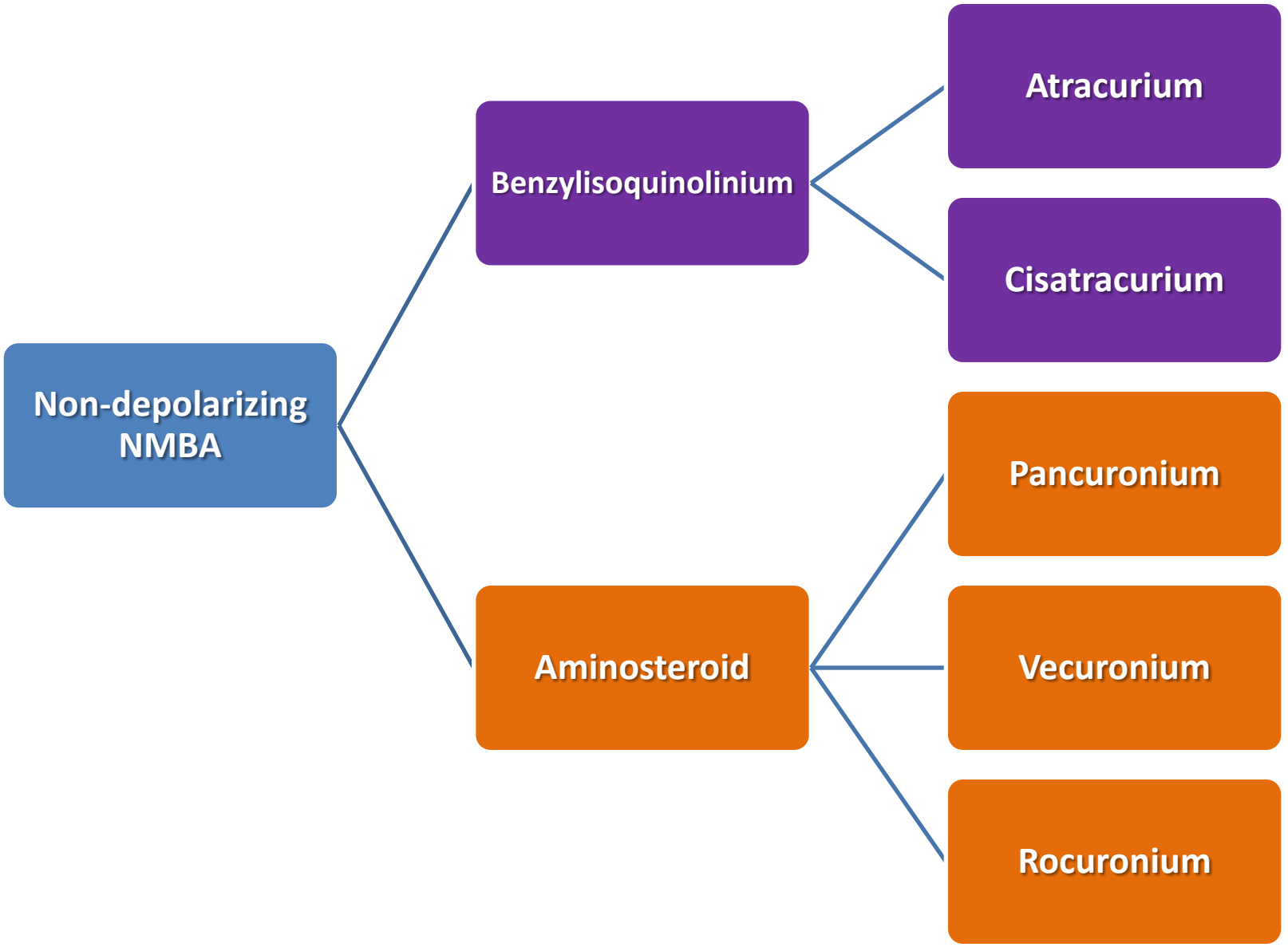
Neuromuscular Blocking Agents



Murrell MT, Savarese JJ. New vistas in neuromuscular blockers. In: Kaye AD, Kaye AM, Urman RD. editors. Essentials of pharmacology for anesthesia, pain medicine, and critical care. New York: Springer-Verlag;2015.

Nondepolarizing Muscle Relaxants

- What is the mechanism of action?
  - Act as competitive antagonist
    - Competitive inhibition of nicotinic Ach receptor (nAChR)
  - Excessive concentration causing channel blockade
  - Act at presynaptic sites, prevent Ach release



Contin Educ Anaesth Crit Care Pain. 2004;4:2-7.

Long-Acting Pancuronium

- Long-acting
  - Onset: 3-5 mins
  - Duration: 60-90 mins
- Elimination
  - Mainly by kidney (85%)
  - By liver (15%)
- Adverse Effects
  - tachycardia (vagolytic effect)
  - No histamine release

Anesth Analg. 1989;69:752-5.

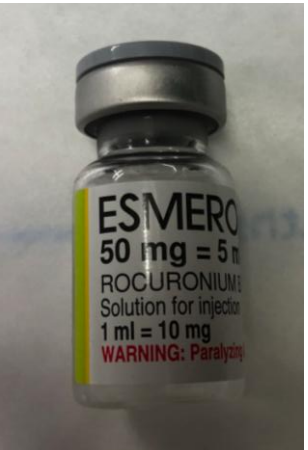
Intermediate-acting Vecuronium

- Intermediate-acting
  - Analogue of pancuronium
  - Onset: 3-5 mins
  - Duration: 20-30 mins
- Elimination
  - Primarily by liver(60%)
  - Slightly by kidney(40%)
  - Prolonged in hepatic failure
  - **Less renal effect than pancuronium**
- Adverse Effects
  - **Less vagal blockade**
  - No histamine release

Anesth Analg. 1989;69:752-5.

Intermediate-acting Rocuronium

- Intermediate-acting
  - Analogue of vecuronium
  - Rapid onset 1-2 minutes
  - Duration 20-35 minutes
- Dose
  - Intubating: 0.6 mg/kg
  - **RSI: 1-1.2 mg/kg**



- Elimination
  - Prolonged in hepatic failure
  - No significant renal excretion
- Adverse Effects
  - Minimal vagal blockade
  - No histamine release

Anesth Analg. 1989;69:752-5.

Intermediate-acting Atracurium

- Isomer of atracurium
- Intermediate-acting
  - Onset: 3-5 mins
  - Duration: 25-35 mins
- Dose
  - Intubating: 0.4-0.5 mg/kg

- Elimination
  - **No hepatic elimination**
  - **No renal excretion**
  - Dependent on Hoffman elimination(pH, temp)
- Adverse Effects
  - No vagal blockade
  - **Histamine release**

Anesth Analg. 1989;69:752-5.

Intermediate-acting Cisatracurium

- Intermediate-acting
  - Onset: 3-5 mins
  - Duration: 20-25 mins
- Dose
  - Intubating: 0.1-0.2 mg/kg

- Elimination
  - No hepatic elimination
  - No renal excretion
  - Dependent on Hoffman elimination and ester hydrolysis
- Adverse Effects
  - No vagal blockade
  - No histamine release **(in the clinical dose range)**

Anesth Analg. 1989;69:752-5.

Agent	ED95 (mg/kg)	Intubating Dose (mg/kg)	Onset (min)	Duration to 25% recovery (min)	Intra-op Mainenance	Metabolism / Excretion
Succinylcholine	0.3	1	1-1.5 min	6-8 min	Rarely done	plasma cholin-esterase
Rocuronium	0.3	0.6	1.5-2	30-40	0.1 -0.2 mg/kg prn	>70% Liver
		RSI 1.2	1	>60		Bile + Urine
Vecuronium	0.05	0.1 -0.2	3-4	35-45	0.01 -0.02 mg/kg prn	50% Liver / Bile + Urine*
Cisatracurium	0.05	0.15-0.2	5-7	35-45	0.3 mg/kg q20min prn	Hoffman elimination

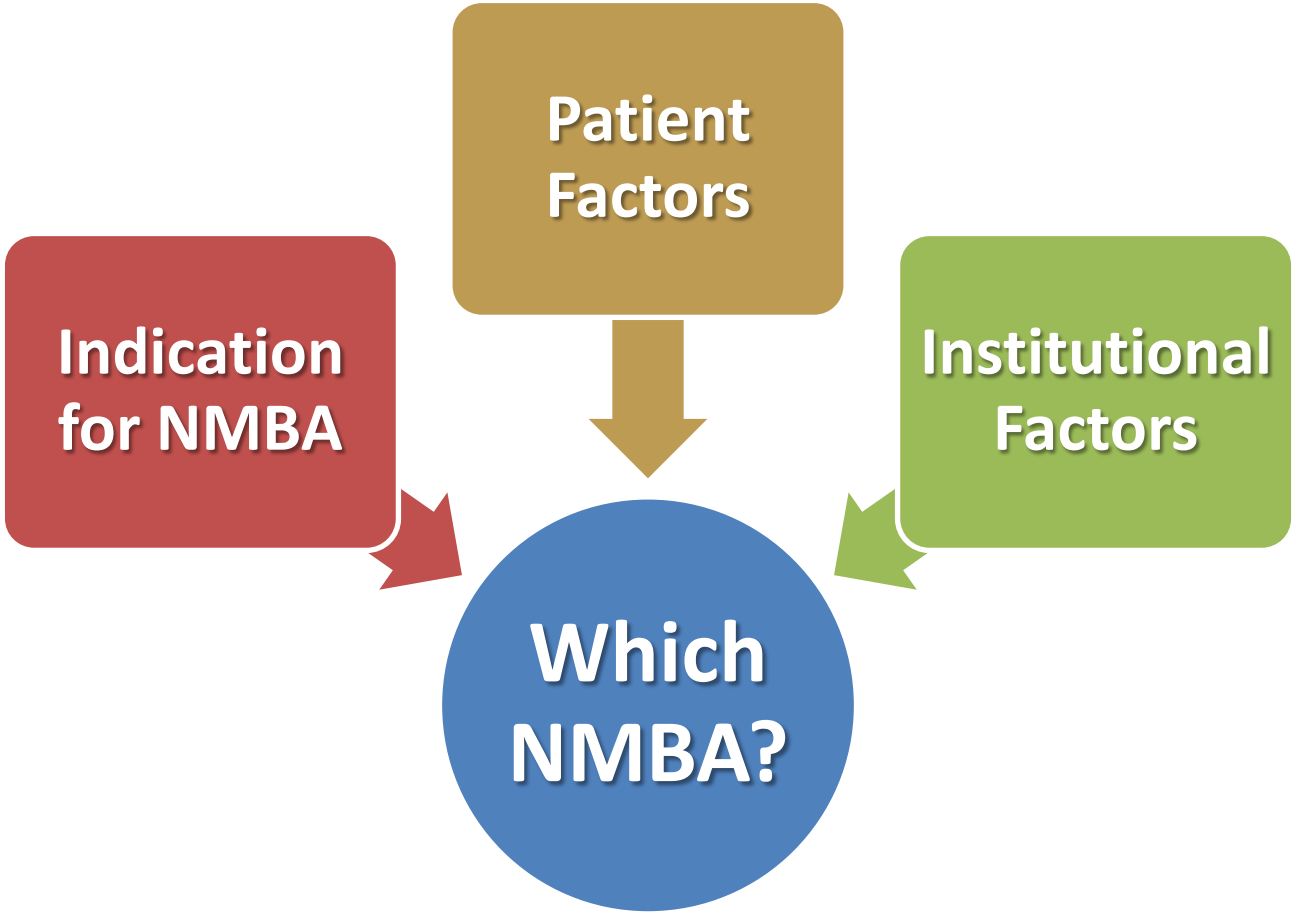
*Vecuronium's 3-OH metabolite (80% potency) accumulates in renal failure. Rocuronium however does not have any active metabolites

**Recovery of neuromuscular function takes place as plasma concentrations decline, and the greater part of this decrease initially occurs primarily because of distribution after initial drug administration. After a large or repeated dose, recovery relies more on elimination

**Rocuronium has lower molar potency (requires a larger mg/kg dose) and in effect has faster onset (i.e. it equilibrates faster from plasma to the neuromuscular junction)

Anesth Analg. 1989;69:752-5.

Choosing an NMBA



Clinical test of postoperative neuromuscular recovery

Unreliable signs	Reliable signs
Sustained eye opening	Sustained head lift for 5 second
Protrusion of the tongue	Sustained leg lift for 5 second
Arm lift to opposite shoulder	Sustained hand gift for 5 second
Normal tidal volume	Sustained “tongue depressor test”
Normal or near normal vital capacity	Maximum inspiratory p>40-50 cmH2O
Maximum inspiratory pressure >/= 40-5-cmH_20	

Mogensen JV. Neuromuscular monitoring. In Miller RD : Basics of Anesthesia 5th edition. Philadelphia, Churchill Livingstone, 2005;1551-1569.

Ideal muscle relaxant drug

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- Intermediate duration
- Rapid recovery
- No accumulation
- No cardiovascular side effect
- No histamine release
- No active metabolite