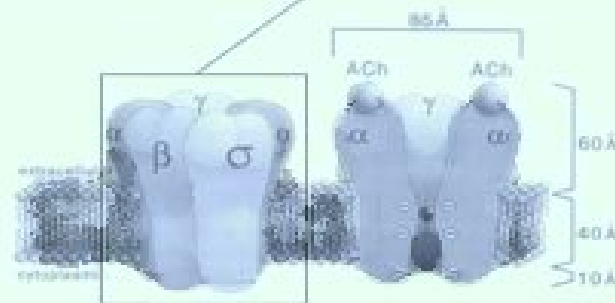
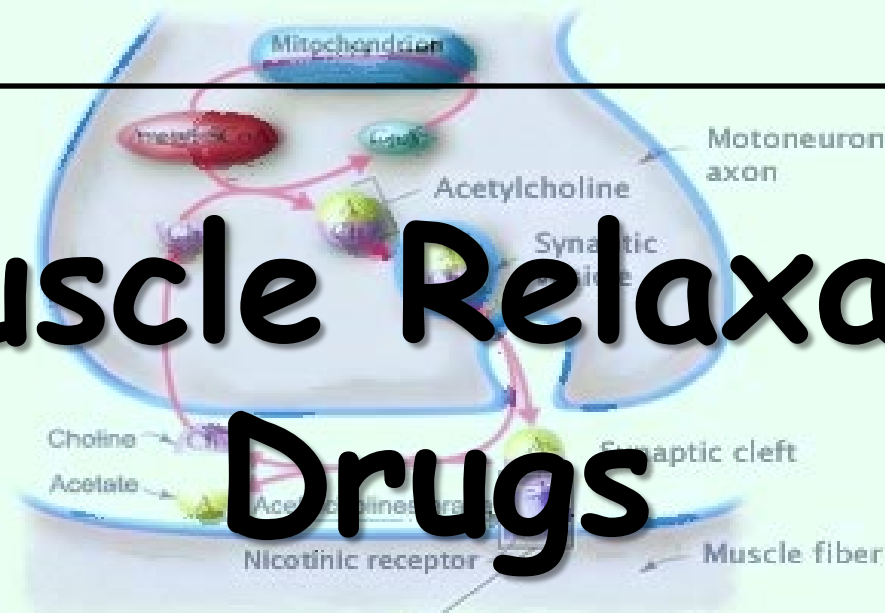
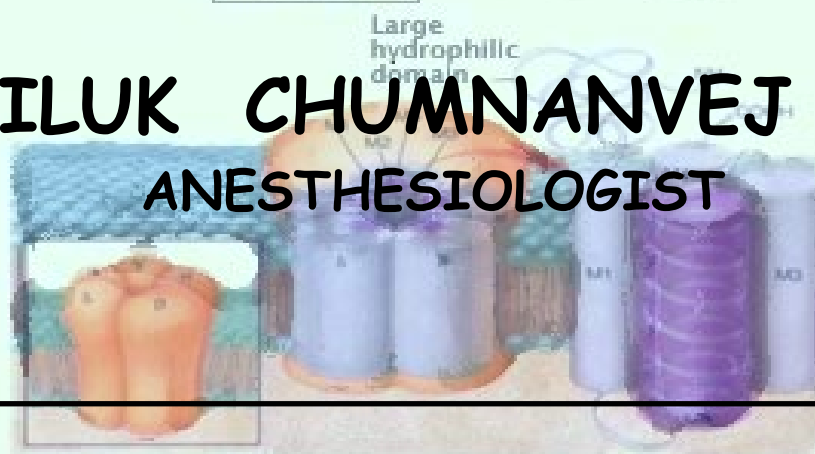


# Muscle Relaxant Drugs



SIRILUK CHUMNANVEJ MD.  
ANESTHESIOLOGIST



# Ideal muscle relaxant

- Rapid onset

- Duration (20-30 min)

- Rapid recovery

- No accumulation

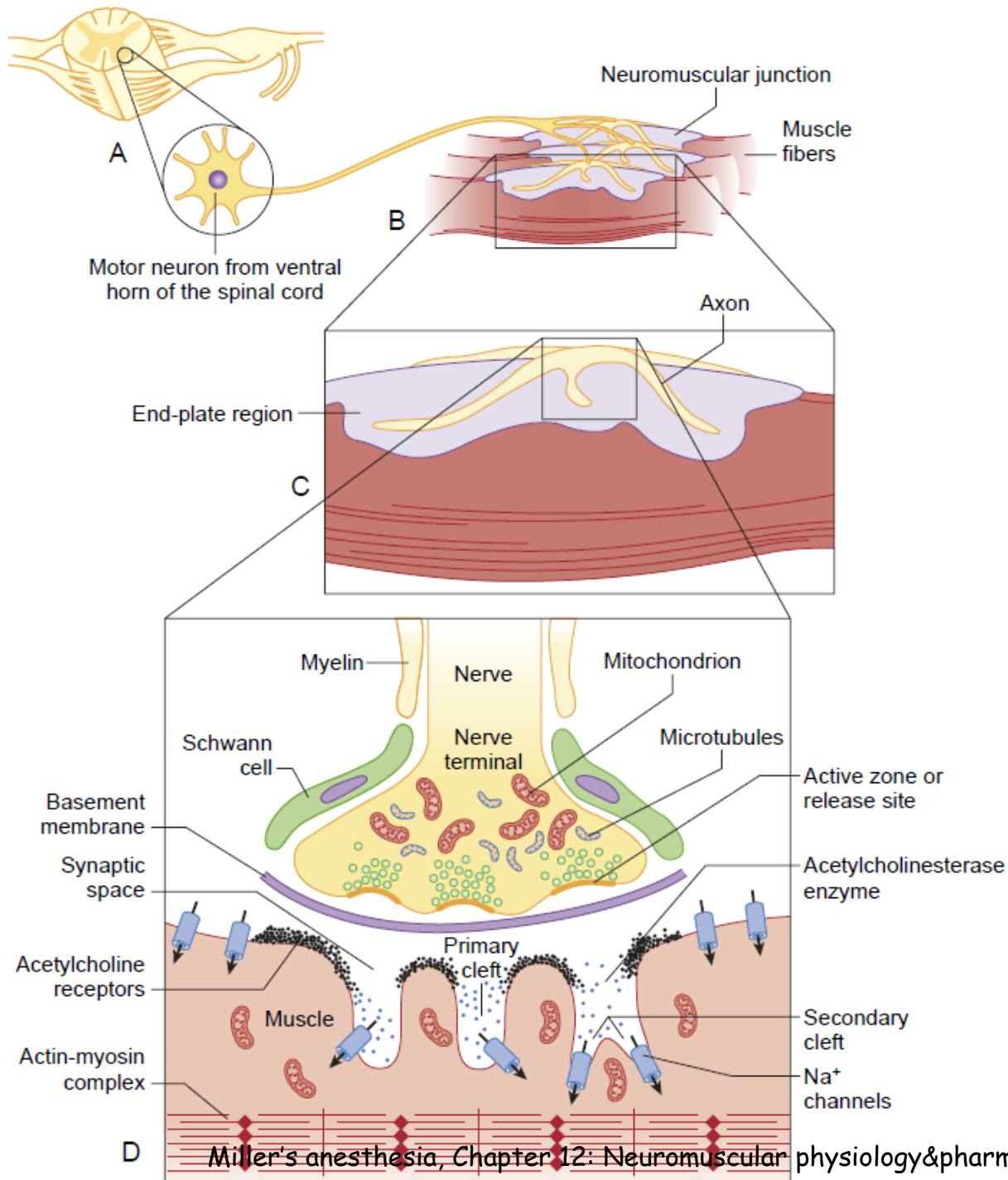
- No side effect(cardiovascular)

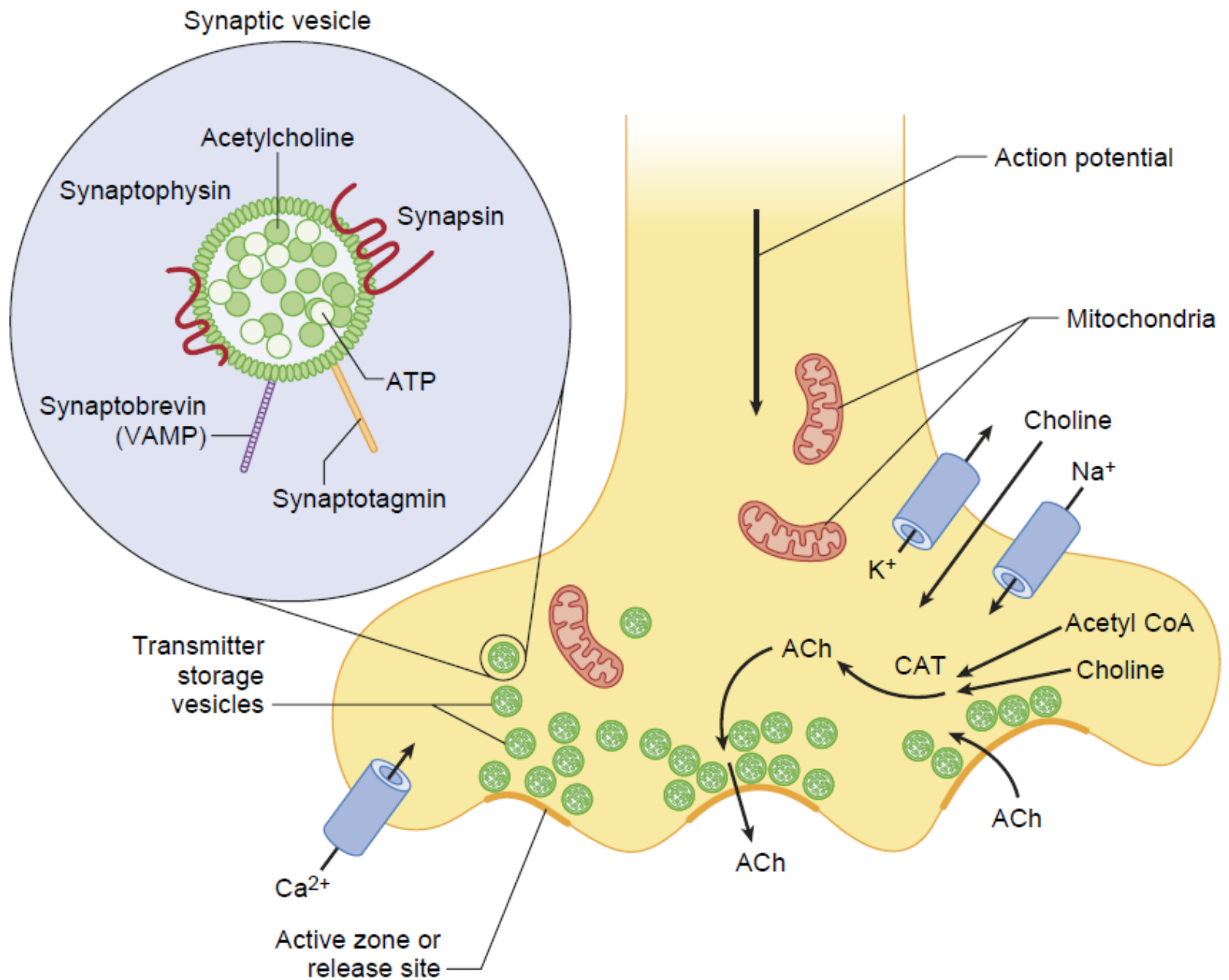
- No histamine release

- High potency

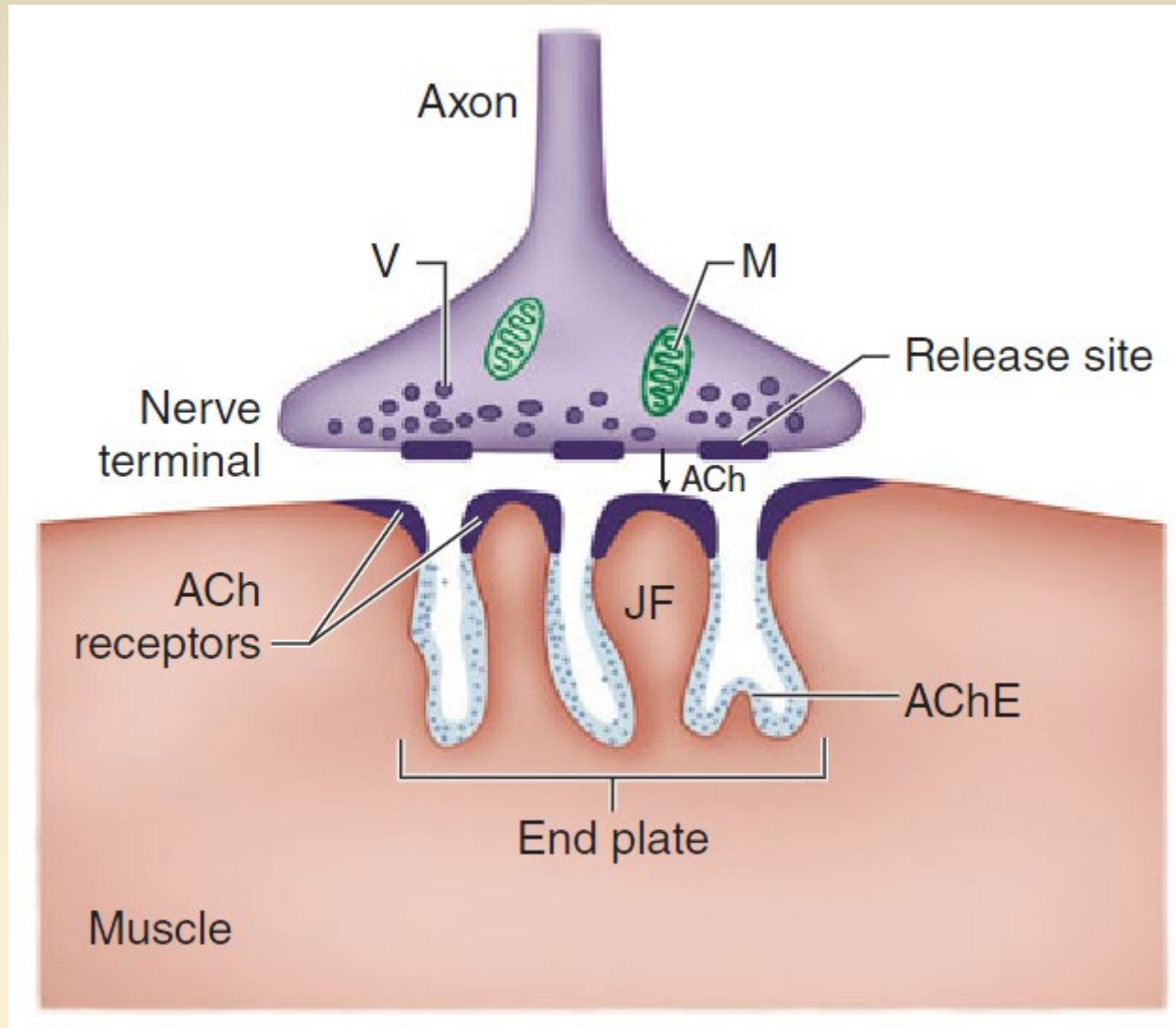
- No active metabolite

- Can reversed by cholinesterase inhibitor

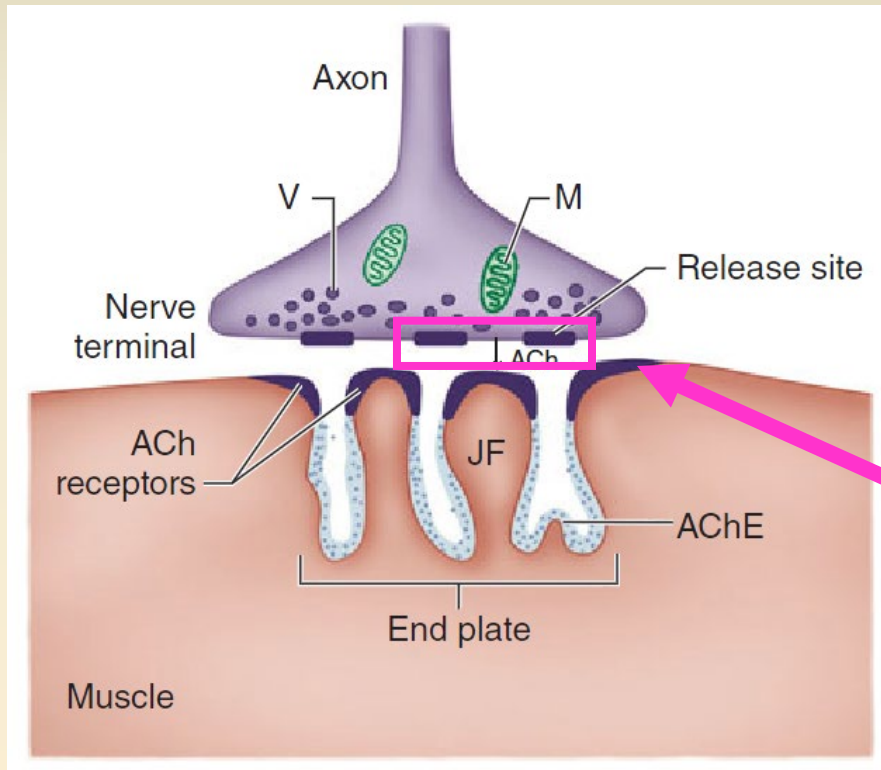




# Neuromuscular junction



# Neuromuscular junction

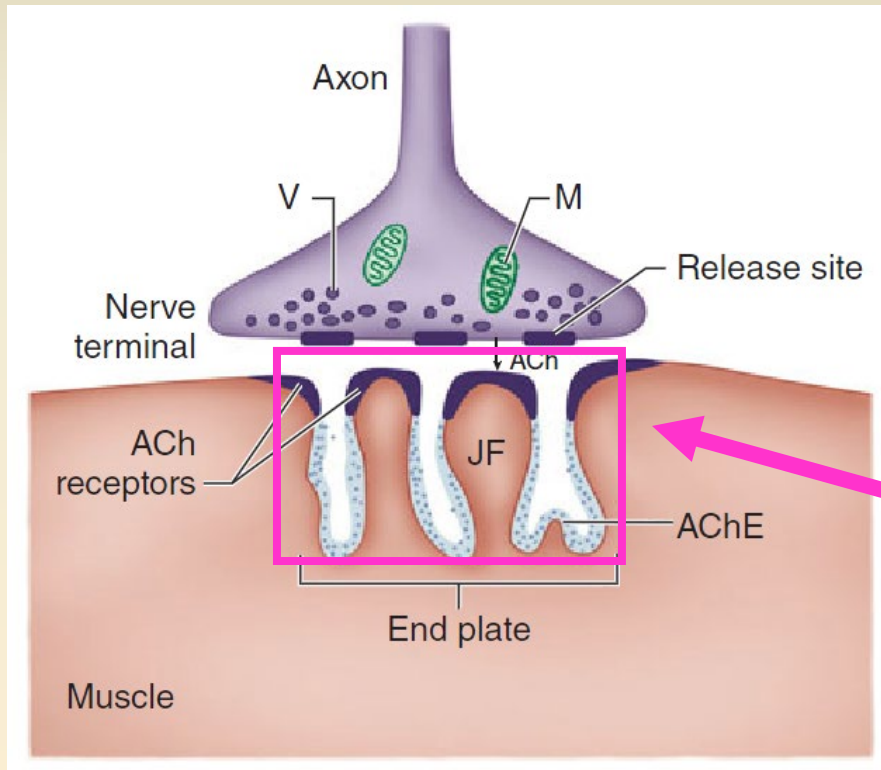


## Nicotinic receptor

3 ชนิด

1.Pre synaptic  
nicotinic receptor

# Neuromuscular junction

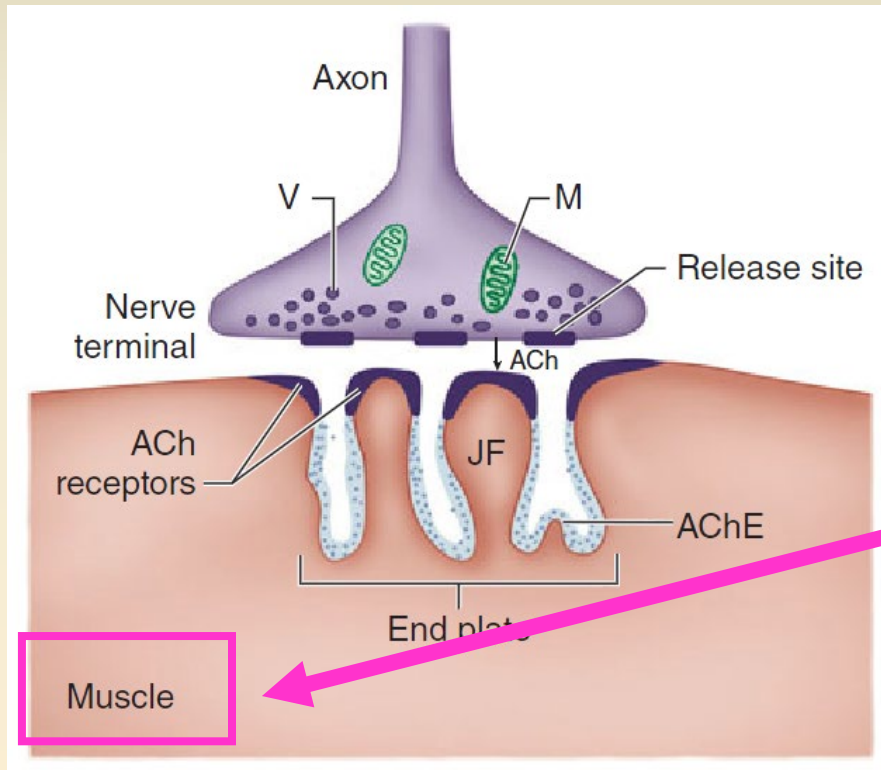


## Nicotinic receptor

3 ชนิด

2. Post synaptic  
nicotinic receptor

# Neuromuscular junction



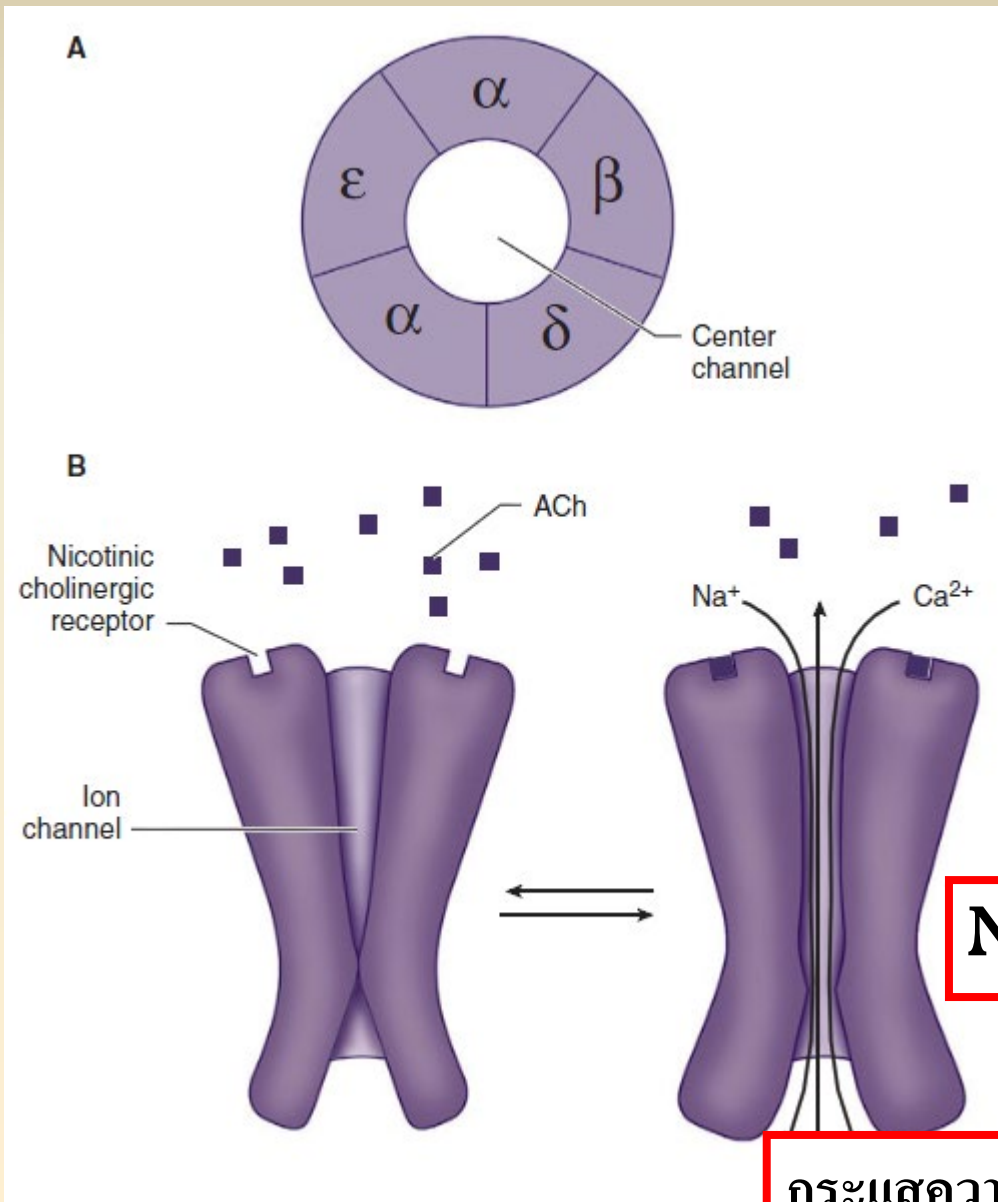
## Nicotinic receptor

3 ชนิด

3. Extra junctional  
nicotinic receptor



# Neuromuscular junction



## Nicotinic receptor

5 subunits

$2\alpha$

$\beta$

$\gamma$

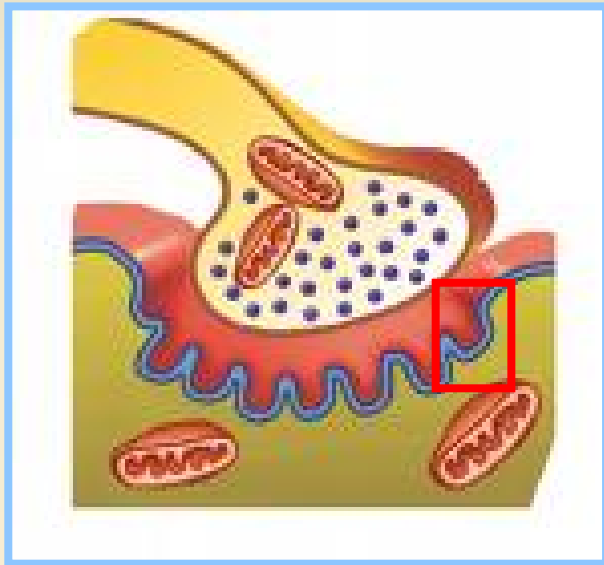
$\delta$

Acetylcholine

Na , Ca เข้า cell และ K ออก cell

กระแสวนต่างศักย์เปลี่ยนแปลงที่ Membrane

# Neuromuscular junction



< 1 mv



~90 mv

## Nicotinic receptor



5 subunits

2 $\alpha$

$\beta$

$\gamma$

$\delta$

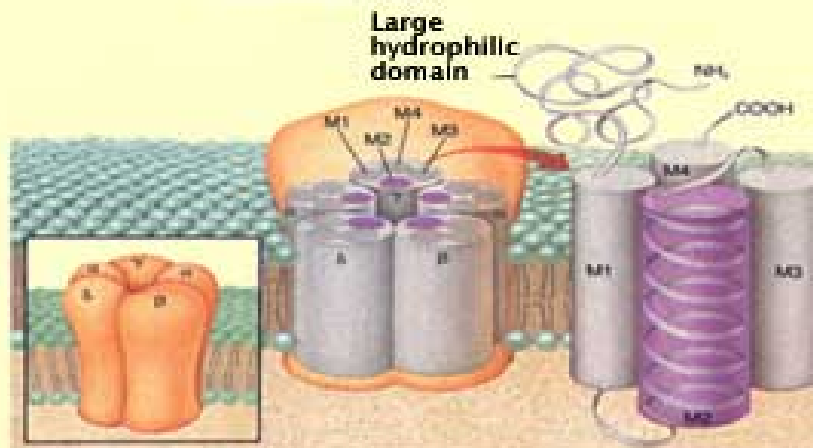
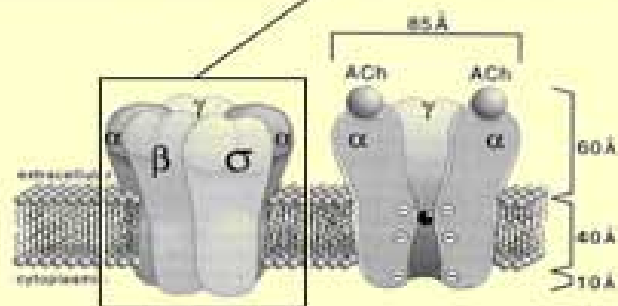
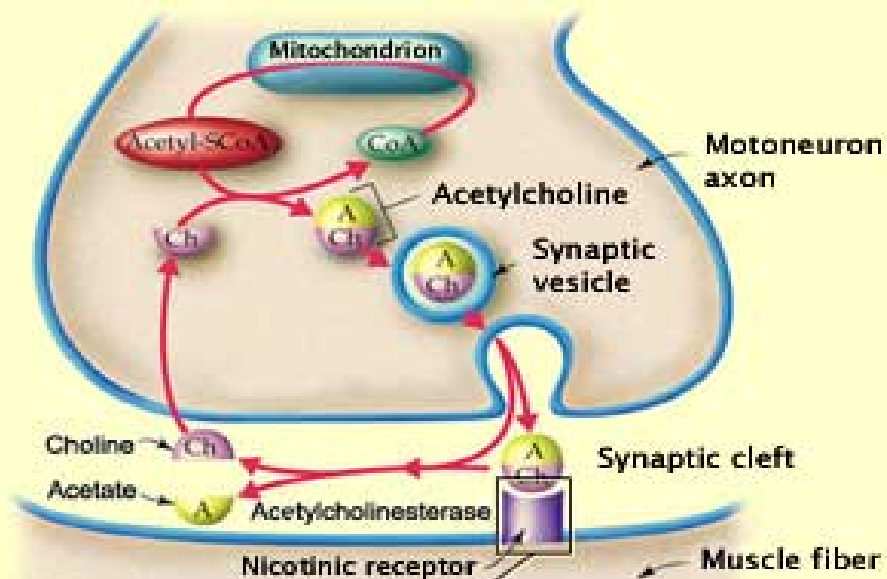
Na , Ca เข้า cell และ K ออก cell

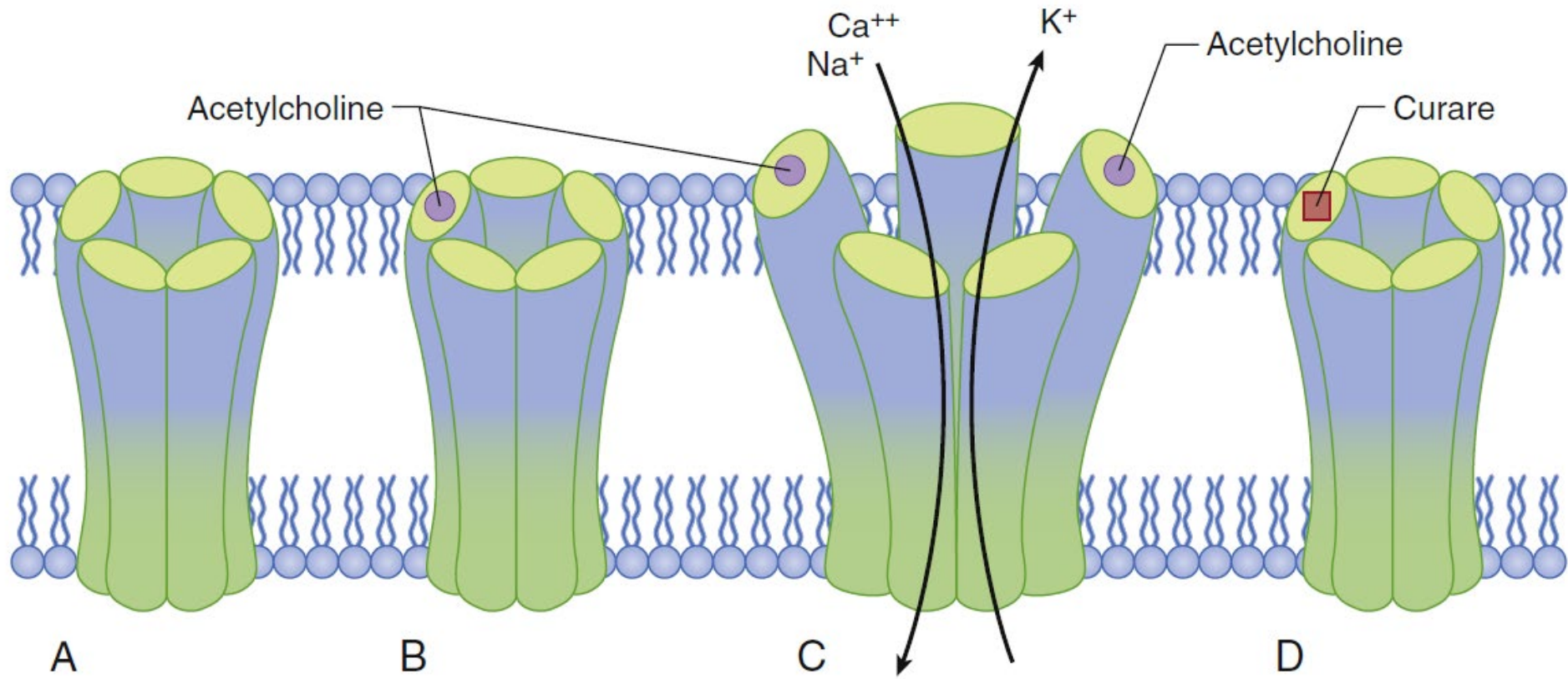


กระแสความต่างศักย์เปลี่ยนแปลงที่ Membrane



Depolarization





-Ion channel inactivate-

-Ion channel -Open-

-Ion channel Antagonist-

VDO : Neuromuscular junction



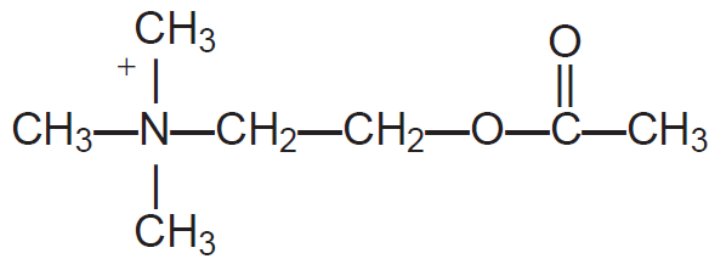
# NMBA

Muscle relaxant แบ่งเป็น

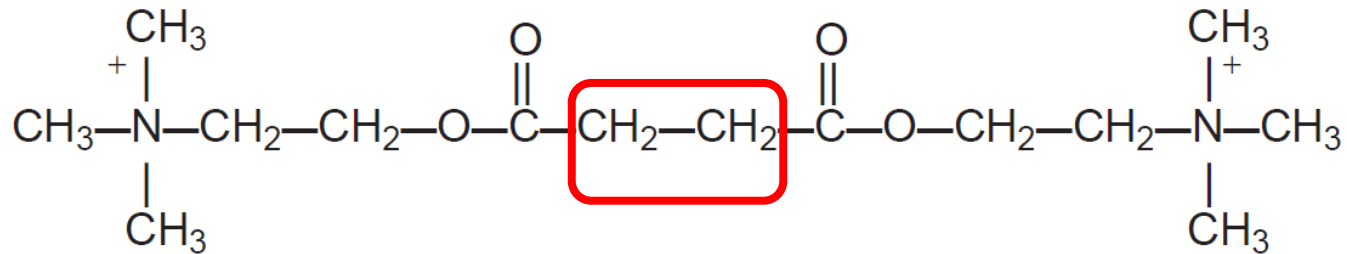
1. Depolarizing NMBA
2. Non-depolarizing NMBA:
  - Steroidal compounds
  - Benzyloquinolinium compounds
3. Others

# MECHANISM OF ACTION

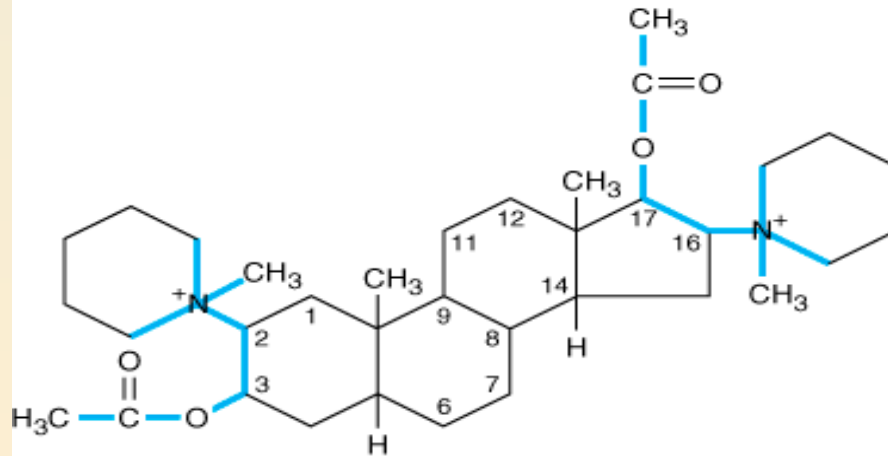
Depolarizing	Nondepolarizing
Short-acting Succinylcholine	Short-acting Gantacurium <sup>1</sup> Intermediate-acting Atracurium Cisatracurium Vecuronium Rocuronium Long-acting Pancuronium



Acetylcholine



Succinylcholine



Pancuronium

Quaternary ammonium compounds

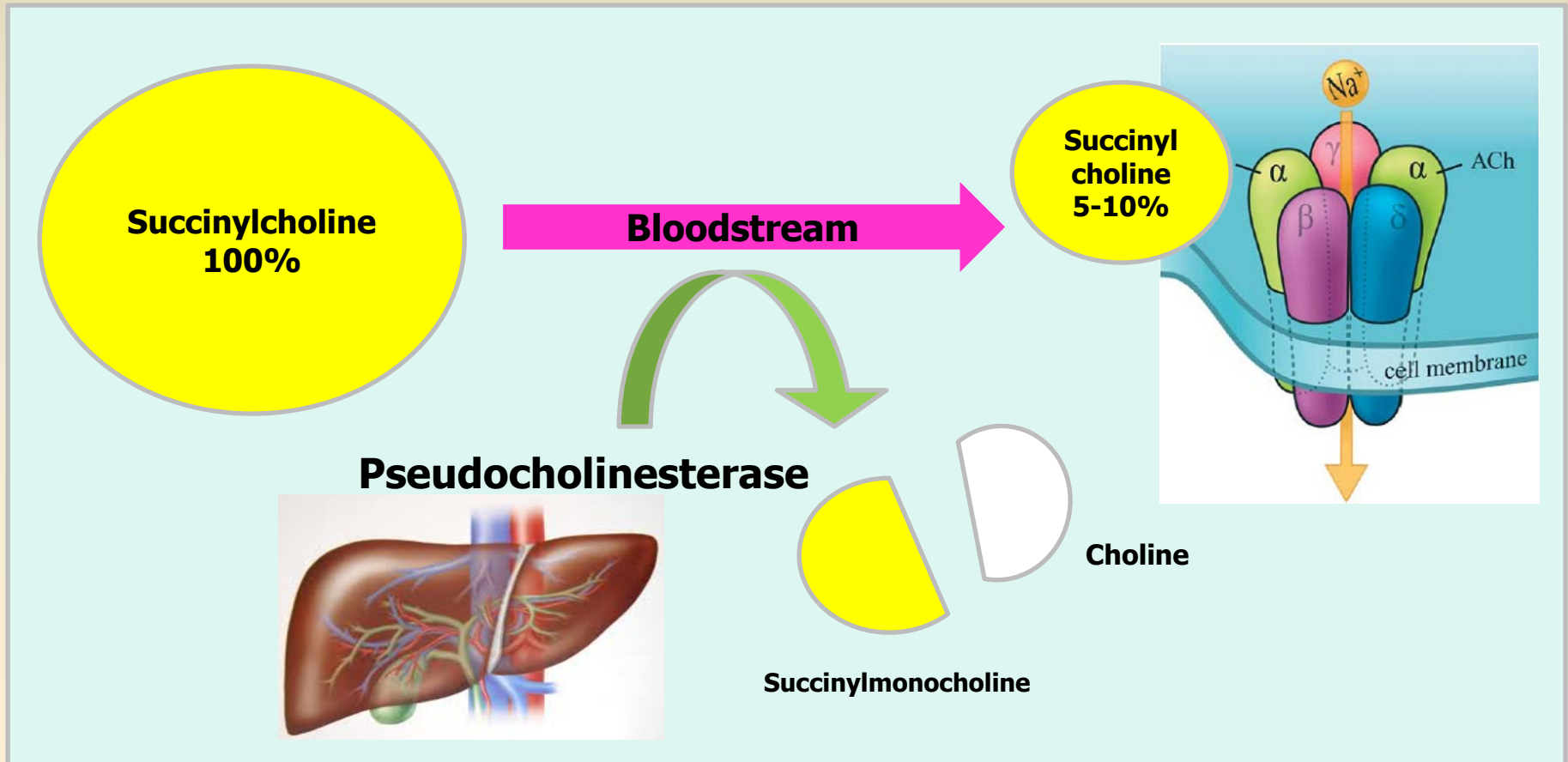


# 1. Depolarizing NMBA

## Succinylcholine (Suxamethonium)

- ❑ **Only** available depolarizing neuromuscular blocker
- ❑ Rapid onset & ultrashort duration → rapid hydrolysis by **butyrylcholinesterase** (*plasma or pseudocholinesterase*) → succinylmonocholine & choline
- ❑ Succinylmonocholine (much weaker than succinylcholine) and is metabolized much more slowly to succinic acid & choline
- ❑ **Not hydrolysis by acetylcholinesterase**

# Normal population



Drug	Duration	Metabolism (%)	ELIMINATION		Metabolites
			Kidney (%)	Liver (%)	
Succinylcholine	Ultrashort	Butyrylcholinesterase (98%-99%)	<2%	None	Monoester (succinyl monocholine) and choline; the monoester is metabolized much more slowly than succinylcholine

# Succinylcholine (Suxamethonium)

- ❑ neuromuscular blocker of *choice for RSI*
- ❑ 1.0 mg/kg of succinylcholine → recommended to facilitate endotracheal intubation at 60 seconds

## Phase II block

- After prolonged exposure to SCh *7-10 mg/kg iv*
- Change character & resembles a nondepolarizing block

# Avoids succinylcholine

- **Extrajunctional nAChRs** (exaggerated hyper  $K^+$  response)
  - **Neuromuscular diseases**
    - Spinal cord injury
    - Multiple sclerosis
    - Muscular dystrophies
    - Guillain-Barré syndrome
    - CVA (weakness)
  - **Burns** (24-48 h after burn → 2 years after burned skin healed)
  - **ICU patients**
    - Upregulation of nAChRs induced by immobilization (>24h)
  - **Severe hypovolemia & metabolic acidosis**
- **ICP, IOP**
- **MH associated conditions** (triggering agents)
- **Cardiac arrhythmias** (bradycardia after repeated dose)

# Adverse Side Effects of Succinylcholine

Cardiac dysrhythmias

Sinus bradycardia

Junctional rhythm

Sinus arrest

Fasciculations

Hyperkalemia

Myalgia

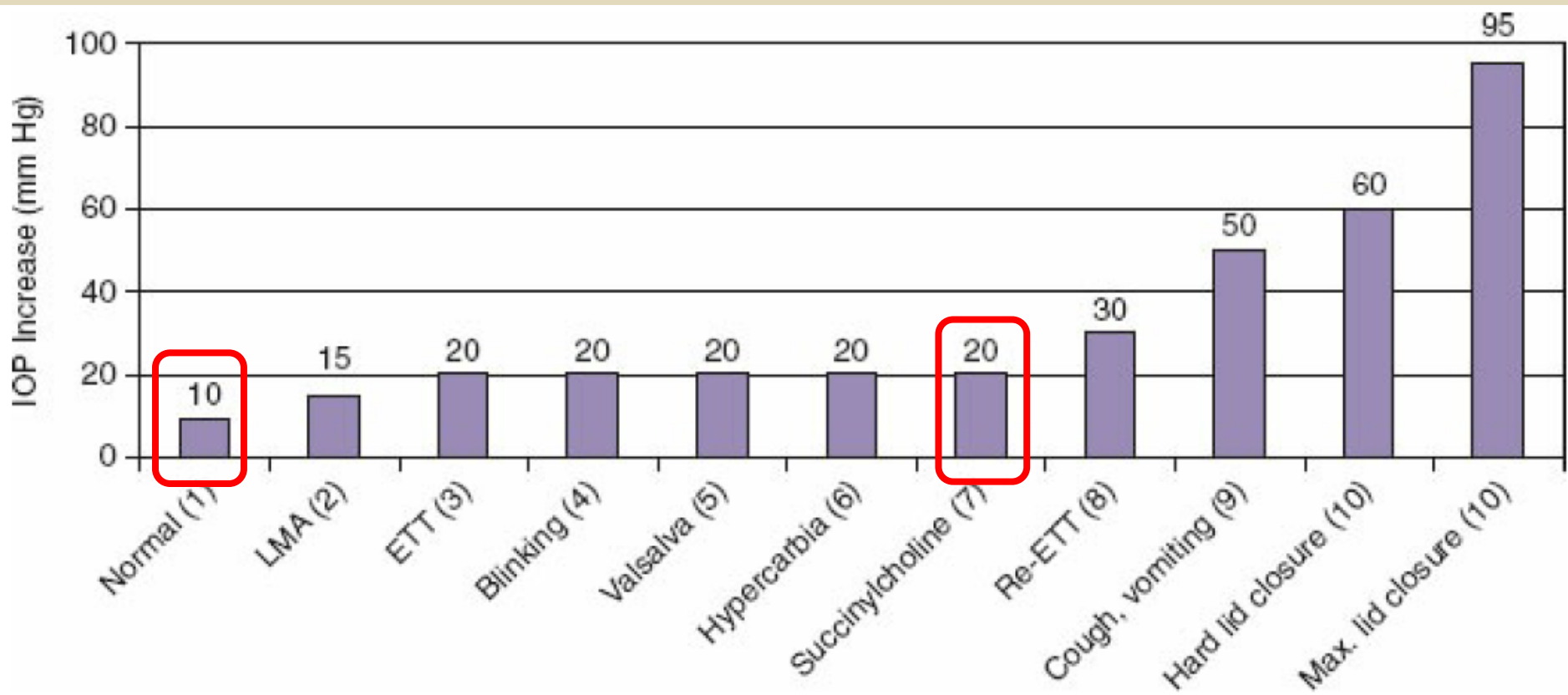
Myoglobinuria

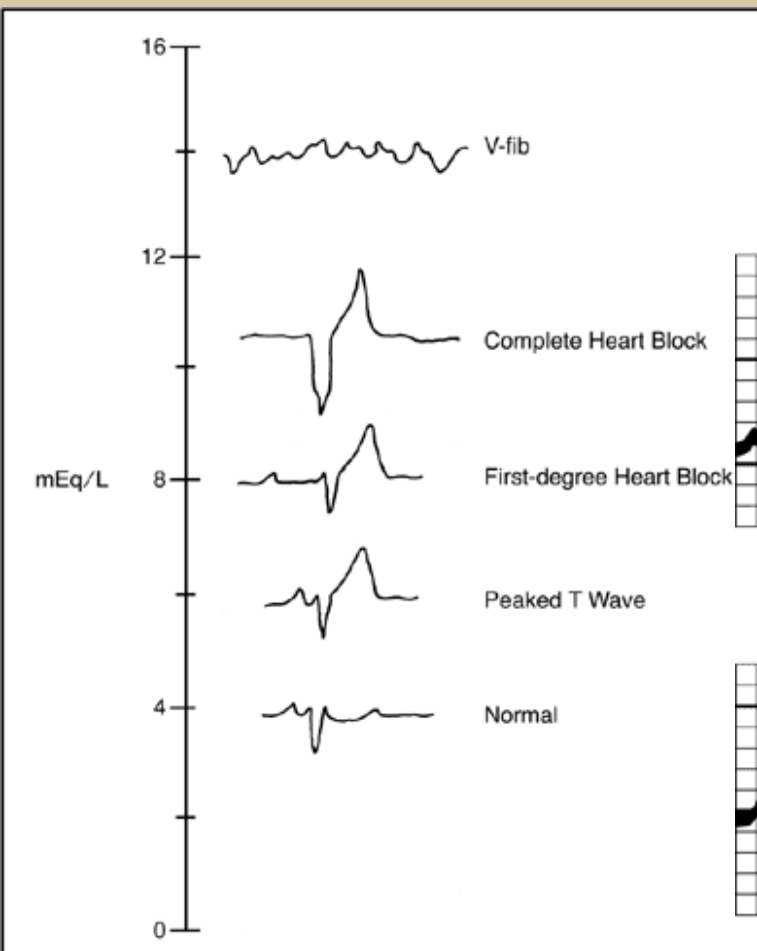
Increased intraocular pressure

Increased intragastric pressure

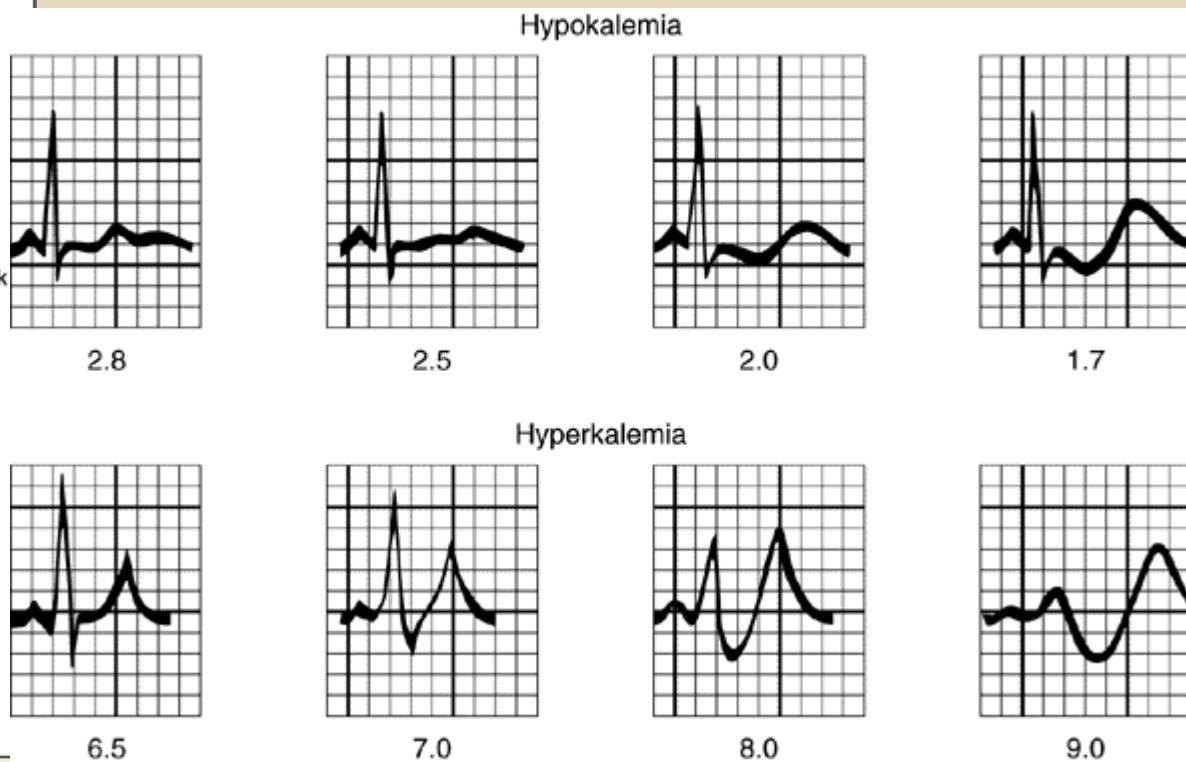
Trismus

## Mean increase in intraocular pressure (IOP) from baseline





- 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.



# Dibucaine number

## 1. What are they?

- Acetylcholinesterase
- Pseudocholinesterase
- Plasma cholinesterase
- Butyrylcholinesterase
- Atypical pseudocholinesterase

## 2. What are dibucaine and dibucaine number?

## 3. Who are impacted?

## 4. Is it only genetic causes?

## 5. What drugs are impacted?

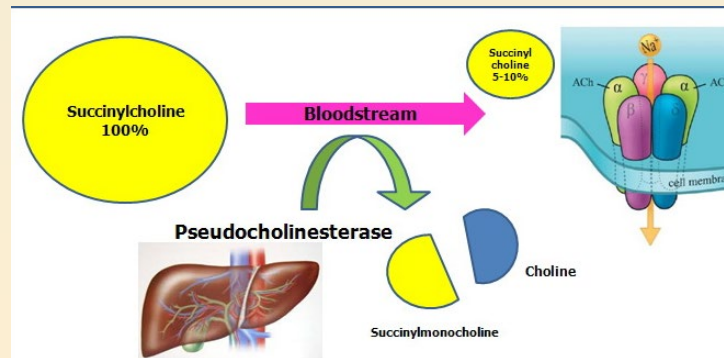
## 6. How to interpretation of dibucaine number?

# 1. What are they?

- **Acetylcholinesterase; RBC (or erythrocyte) cholinesterase**
  - Breakdown acetylcholine → choline + acetate
  - Acetylcholinesterase is found in nerve tissue and red blood cells
- **Pseudocholinesterase; Plasma cholinesterase; Butyrylcholinesterase**
  - Pseudocholinesterase is found primarily in the liver
  - Degrade succinylcholine, mivacurium, amino ester LA
- **Atypical pseudocholinesterase**
  - Abnormal function of pseudocholinesterase

## 2. Dibucaine

- Amino amide local anesthetic agent
- Inhibiting plasma cholinesterase enzyme (80%)
- Dibucaine Number test\*
- Dibucaine Number
  - % of cholinesterase activity in serum that inhibited by dibucaine
  - Normal 80



\*Kalow W, Genest K. A method for the detection of atypical forms of human serum cholinesterase: determination of dibucaine numbers. Can J. Biochem 1957;35:339-46.

# 3. Who are impacted?

- Hindu Arya Vysya community, India
- Inherited causes
  - $E_1$  locus; long arm chromosome 3
    - 96% normal genotype =  $E_uE_u$  (Wild type homozygous)
    - 4% Heterozygous and Homozygous atypical cholinesterase fashion =  $E_a, E_f, E_s$

# Interpretation of Dibucaine Number

Type of Butyrylcholinesterase	Genotype	Incidence	Dibucaine Number*	Response to Succinylcholine or Mivacurium
Homozygous typical	$E_1^u E_1^u$	Normal	70-80	Normal
Heterozygous atypical	$E_1^u E_1^a$	1/480	50-60	Lengthened by 50%-100%
Homozygous atypical	$E_1^a E_1^a$	1/3200	20-30	Prolonged to 4-8 h

Variants of Plasma Cholinesterase	Duration of Succinylcholine-Induced Neuromuscular Blockade (min)
Homozygous, typical (usual, U)	5-10
Heterozygous	20
Homozygous, atypical (A)	60-180

# 4. Is it only genetic causes?

- **Acquired causes**

- Severe liver disease, malnutrition
- Renal failure with hemodialysis, uremia
- Pregnant, Infants
- Tuberculosis infection
- **5. Drugs**

- Oral contraceptive drugs
- Anticholinesterase drugs (treated MG)
- Cyclophosphamide

## 2. Non-depolarizing NMBD

CLINICAL DURATION				
	Long-acting (>50 min)	Intermediate-acting (20-50 min)	Short-acting (10-20 min)	Ultrashort-acting (<10 min)
Steroidal compounds	Pancuronium	Vecuronium Rocuronium		
Benzyisoquinolinium compounds	<i>d</i> -Tubocurarine	Atracurium Cisatracurium	Mivacurium	
Asymmetric mixed-onium fumarates		CW 002		Gantacurium

# Pharmacology of nondepolarizing muscle relaxants

Relaxant	Chemical Structure <sup>1</sup>	Metabolism	Primary Excretion	Onset <sup>2</sup>	Duration <sup>3</sup>	Histamine Release <sup>4</sup>	Vagal Blockade <sup>5</sup>
Atracurium	B	+++	Insignificant	++	++	+	0
Cisatracurium	B	+++	Insignificant	++	++	0	0
Pancuronium	S	+	Renal	++	+++	0	++
Vecuronium	S	+	Biliary	++	++	0	0
Rocuronium	S	Insignificant	Biliary	+++	++	0	+
Gantacurium	C	+++	Insignificant	+++	+	+	0



# Non-depolarizing NMBD

Can be classified according to

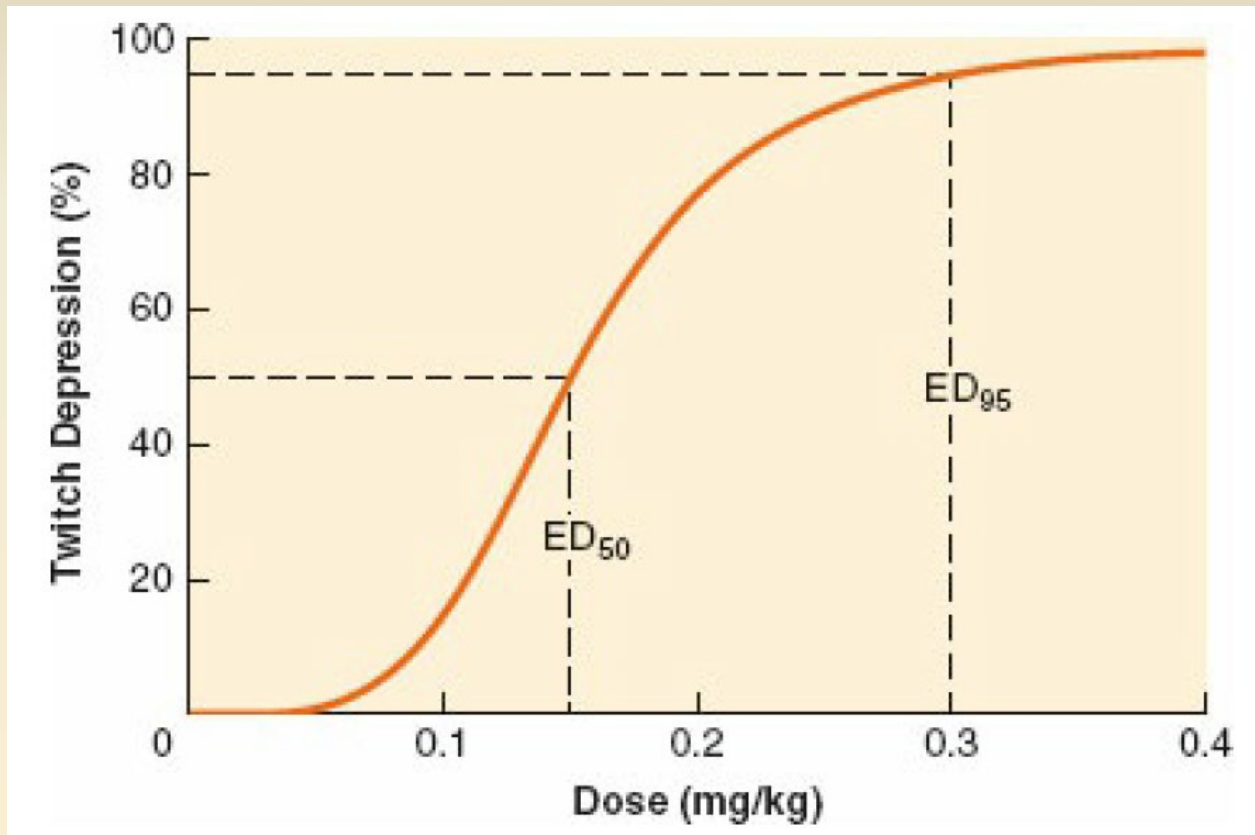
- Chemical class

1. steroidal
2. benzyliisoquinolinium
3. other compounds

- Onset or duration of action

1. long-acting drugs
2. intermediate-acting drugs
3. short-acting drugs

# Dose-response relationship



# Clinical characteristics of NDMR

Drug	ED <sub>95</sub> for Adductor Pollicis During Nitrous Oxide/Oxygen/Intravenous Anesthesia (mg/kg)	Intubation Dose (mg/kg)	Onset of Action for Intubating Dose (min)	Duration of Intubating Dose (min)	Maintenance Dosing by Boluses (mg/kg)	Maintenance Dosing by Infusion (µg/kg/min)
Succinylcholine	0.5	1.0	0.5	5–10	0.15	2–15 mg/min
Gantacurium <sup>1</sup>	0.19	0.2	1–2	4–10	N/A	—
Rocuronium	0.3	0.8	1.5	35–75	0.15	9–12
Mivacurium <sup>2</sup>	0.08	0.2	2.5–3.0	15–20	0.05	4–15
Atracurium	0.2	0.5	2.5–3.0	30–45	0.1	5–12
Cisatracurium	0.05	0.2	2.0–3.0	40–75	0.02	1–2
Vecuronium	0.05	0.12	2.0–3.0	45–90	0.01	1–2
Pancuronium	0.07	0.12	2.0–3.0	60–120	0.01	—
Pipecuronium <sup>2</sup>	0.05	0.1	2.0–3.0	80–120	0.01	—
Doxacurium <sup>2</sup>	0.025	0.07	4.0–5.0	90–150	0.05	—

# Non-depolarizing NMBD

## *Steroidal groups*

### ○ Pancuronium

- presence of 2 acetyl ester groups on the A & D rings of the steroidal molecule
- potent neuromuscular blocking drug
- **vagolytic** property
- **butyrylcholinesterase-inhibiting** property

# Non-depolarizing NMBD

## *Steroidal groups*

### ○ Vecuronium

- N-demethylated derivative of pancuronium
- minor molecular modification relative to pancuronium :
  1. slight change in potency
  2. marked **reduction in vagolytic** properties
  3. molecular instability in solution(explains in part the shorter duration than pancuronium)
  4. **increased lipid solubility**(greater biliary elimination than pancuronium)

# Non-depolarizing NMBD

## *Steroidal groups*

### ○ Rocuronium

- lacks the acetyl ester that is found in the steroid nucleus of pancuronium & vecuronium in the A ring
- *Fast-onset* compound
- stable solution (At room temperature, rocuronium is stable for only 60 days, whereas pancuronium is stable for 6 months)

# Non-depolarizing NMBD *Benzylisoquinolinium Compounds*

- **Atracurium**

isoquinolinium nitrogens connected by a diester-containing hydrocarbon chain.:

**Hofmann elimination reaction** ( pH- and temperature-dependent reaction in which higher pH and temperature favor )

**Ester hydrolysis**

# Non-depolarizing NMBD *Benzylisoquinolinium Compounds*

## ○ Cisatracurium

- 1R *cis*-1'R *cis* isomer of atracurium
- **potency** of neuromuscular blocking activity > **50%** of atracurium
- metabolized by **Hofmann elimination**
- **no histamine release** in the clinical dose range



# Non-depolarizing NMBD

## ***Benzylisoquinolinium Compounds***

- **Mivacurium**

- metabolized by **butyrylcholinesterase** at 70% to 88% the rate of succinylcholine → a monoester, a dicarboxylic acid

- **Doxacurium**

- bisquaternary benzylisoquinolinium diester of succinic acid
  - The interonium chain is shorter than that of either atracurium or mivacurium.

Drug	Duration	Metabolism (%)	ELIMINATION		Metabolites
			Kidney (%)	Liver (%)	
Mivacurium	Short	Butyrylcholinesterase (95%-99%)	<5%	None	Monoester and quaternary alcohol; the metabolites are inactive and most likely are not metabolized any further
(Metabolites eliminated in urine and bile)					
Atracurium	Intermediate	Hofmann elimination and nonspecific ester hydrolysis (60%-90%)	10%-40%	None	Laudanosine, acrylates, alcohols, and acids; although laudanosine has CNS-stimulating properties, the clinical relevance of this effect is negligible
(Metabolites eliminated in urine and bile)					
Cisatracurium	Intermediate	Hofmann elimination (77%?)	Renal clearance is 16% of total		Laudanosine and acrylates; ester hydrolysis of the quaternary monoacrylate occurs secondarily; because of the greater potency of cisatracurium, laudanosine quantities produced by Hofmann elimination are 5-10 times lower than in the case of atracurium, thus making this a nonissue in practice

Drug	Duration	Metabolism (%)	ELIMINATION		Metabolites
			Kidney (%)	Liver (%)	
Vecuronium	Intermediate	Liver (30%-40%)	40%-50%	50%-60% ≈60%	The 3-OH metabolite accumulates, particularly in renal failure; it has ≈80% the potency of vecuronium and may be responsible for delayed recovery in ICU patients
			(Metabolites excreted in urine and bile) ≈40%		
Rocuronium	Intermediate	None	10%-25%	>70%	None
Pancuronium	Long	Liver (10%-20%)	85%	15%	The 3-OH metabolite may accumulate, particularly in renal failure; it is approximately two thirds as potent as the parent compound
<i>d</i> -Tubocurarine	Long	None	80% (?)	20%	None

# Comparative Pharmacology of NMBDs

Drug	ED <sub>95</sub> (mg/kg)	Onset to Maximum Twitch Depression (min)	Duration to Return to ≥25% <sup>a</sup>	Intubating Dose (mg/kg)	Continuous Infusion (mg/kg/ min)	Renal Excretion (% Unchanged)	Hepatic Degrada- tion (%)	Biliary Excretion (% Un- changed)	Hydrolysis in Plasma
Pancuro- nium	0.07	3-5	60-90	0.1		80	10	5-10	No
Vecuro- nium	0.05	3-5	20-35	0.08-0.1	1	15-25	20-30	40-75	No
Rocuro- nium	0.3	1-2	20-35	0.6-1.2		10-25	10-20	50-70	No
Atracu- rium	0.2	3-5	20-35	0.4-0.5	6-8	NS	NS	NA	Enzymatic, spontane- ous
Cisatracu- rium	0.05	3-5	20-35	0.1	1-1.5	NS	NS	NS	Spontane- ous
Mivacu- rium	0.08	2-3	12-20	0.25	5-6	NS	NS	NS	Enzymatic

# Interactions Among Nondepolarizing Neuromuscular Blocking Drugs

Additive interaction & Synergistic interaction

use of two different nondepolarizing NMBDs → 3 half-lives are required for a clinical changeover

# Interactions Between Succinylcholine & Nondepolarizing Neuromuscular Blocking Drugs

depends on the order of administration and the doses used

- Small doses of nondepolarizing NMBDs administered before succinylcholine  
→ increased dose of succinylcholine

## Effect of muscle relaxant

	Cardiac muscarinic receptor
Succinylcholine	Stimulation
Pancuronium	Blockade
Vecuronium	None
Rocuronium	None
Atracurium	None
Cisatracurium	None

Structure like Ach

# Non ~depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Volatile anesthetic

Aminoglycoside ATB

Local anesthetic

Cardiac antiarrhythmic

Diuretic : Furosemide

Magnesium

Cyclosporin , Lithium

Ganglionic blocking



↑ Duration



# Non -depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Volatile anesthetic

Aminoglycoside ATB

Local anesthetic

Cardiac antiarrhythmic

Diuretic : Furosemide

Magnesium

Cyclosporin , Lithium

Ganglionic blocking



↓ Tone of skeletal muscle

Desflurane > sevoflurane > isoflurane  
> halothane > nitrous oxide

# Non -depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Volatile anesthetic

Aminoglycoside ATB

Local anesthetic

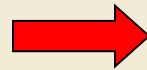
Cardiac antiarrhythmic

Diuretic : Furosemide

Magnesium

Cyclosporin , Lithium

Ganglionic blocking



↓ Ach จาก Pre-junctional  
nicotinic receptor

# Non ~depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Volatile anesthetic

Aminoglycoside ATB

Local anesthetic

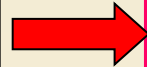
Cardiac antiarrhythmic

Diuretic : Furosemide

Magnesium

Cyclosporin , Lithium

Ganglionic blocking



↓ Ach จาก Pre-junctional  
nicotinic receptor

# Non -depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Volatile anesthetic

Aminoglycoside ATB

Local anesthetic

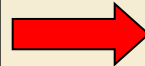
Cardiac antiarrhythmic

Diuretic : Furosemide

Magnesium

Cyclosporin , Lithium

Ganglionic blocking



↓ Ach จาก Pre-junctional  
nicotinic receptor



Quinidine

# Non -depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Volatile anesthetic

Aminoglycoside ATB

Local anesthetic

Cardiac antiarrhythmic

Diuretic : Furosemide

Magnesium

Cyclosporin , Lithium

Ganglionic blocking



↓ Ach จาก Pre-junctional  
nicotinic receptor



Low dose 1 mg/kg

dose



High dose

↑ cAMP

↑ Ach

## Non ~depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Hypothermia
Hypokalemia
Thermal burn
Paresis & Hemiplegia
Female

# Non ~depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Hypothermia
Hypokalemia
Thermal burn
Paresis & Hemiplegia
Female



การขับออกของยา ↓

# Non ~depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Hypothermia
Hypokalemia
Thermal burn
Paresis & Hemiplegia
Female



Ach ↓



# Non ~depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Hypothermia
Hypokalemia
Thermal burn
Paresis & Hemiplegia
Female



↓ Affinity ต่อยาหย้อนกล้ามเนื้อ



ใช้ยามากขึ้น

# Non ~depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Hypothermia
Hypokalemia
Thermal burn
Paresis & Hemiplegia
Female



↑ Extra-junctional  
nicotinic receptor



ใช้ยามากขึ้น

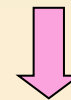
# Non ~depolarizing muscle relaxant

ปัจจัยที่มีผลต่อการออกฤทธิ์ของยา

Hypothermia
Hypokalemia
Thermal burn
Paresis & Hemiplegia
Female



Muscle mass น้อยกว่า



ใช้ยาน้อยลง

# Conditions Associated With Upregulation & Downregulation of Acetylcholine Receptors

nAChR Upregulation	nAChR Downregulation
Spinal cord injury	Myasthenia gravis
Stroke	Anticholinesterase poisoning
Burns	Organophosphate poisoning
Prolonged immobility	
Prolonged exposure to neuromuscular blockers	
Multiple sclerosis	
Guillain-Barré syndrome	

# Drugs known to decrease pseudocholinesterase activity

Drug	Description
Echothiophate	Organophosphate use for glaucoma
Neostigmine Pyridostigmine	Cholinesterase inhibitors
Phenelzine	Monoamine oxidase inhibitor
Cyclophosphamide	Antineoplastic agent
Metoclopramide	Antiemetic/prokinetic agent
Esmolol	$\beta$ -Blocker
Pancuronium	Nondepolarizing muscle relaxant
Oral contraceptives	Various agents

# Additional considerations in special populations

Pediatric	Succinylcholine – should not be used routinely Nondepolarizing agents – faster onset Vecuronium – long-acting in neonates
Elderly	Decreased clearance – prolonged duration, except with cisatracurium
Obese	Dosage 20% more than lean body weight; onset unchanged Prolonged duration, except with cisatracurium
Hepatic disease	Increased volume of distribution Pancuronium and vecuronium – prolonged elimination due to hepatic metabolism and biliary excretion Cisatracurium – unchanged Pseudocholinesterase decreased; prolonged action may be seen with succinylcholine in severe disease
Renal failure	Vecuronium – prolonged Rocuronium – relatively unchanged Cisatracurium – safest alternative
Critically ill	Myopathy, polyneuropathy, nicotinic acetylcholine receptor up-regulation

# Recommendations for the Use of Neuromuscular Blockers in the Intensive Care Unit

Avoid the use of neuromuscular blockers by

- Maximal use of analgesics and sedatives

- Manipulation of ventilatory parameters and modes

Minimize the dose of neuromuscular blocker

- Use a peripheral nerve stimulator with train-of-four monitoring

- Do not administer for more than 2 days continuously

- Administer by bolus rather than infusion

- Administer only when required and to achieve a well-defined goal

- Continually allow recovery from paralysis

- Consider alternative therapies

# References

- Edward G. Morgan, Chapter 11: Neuromuscular Blocking Agents, Clinical Anesthesiology, 5<sup>th</sup> ed. 2013.
- Miller's anesthesia, Chapter 12: Neuromuscular physiology & pharmacology, 9<sup>th</sup> ed. 2020.
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