Muscle Relaxants

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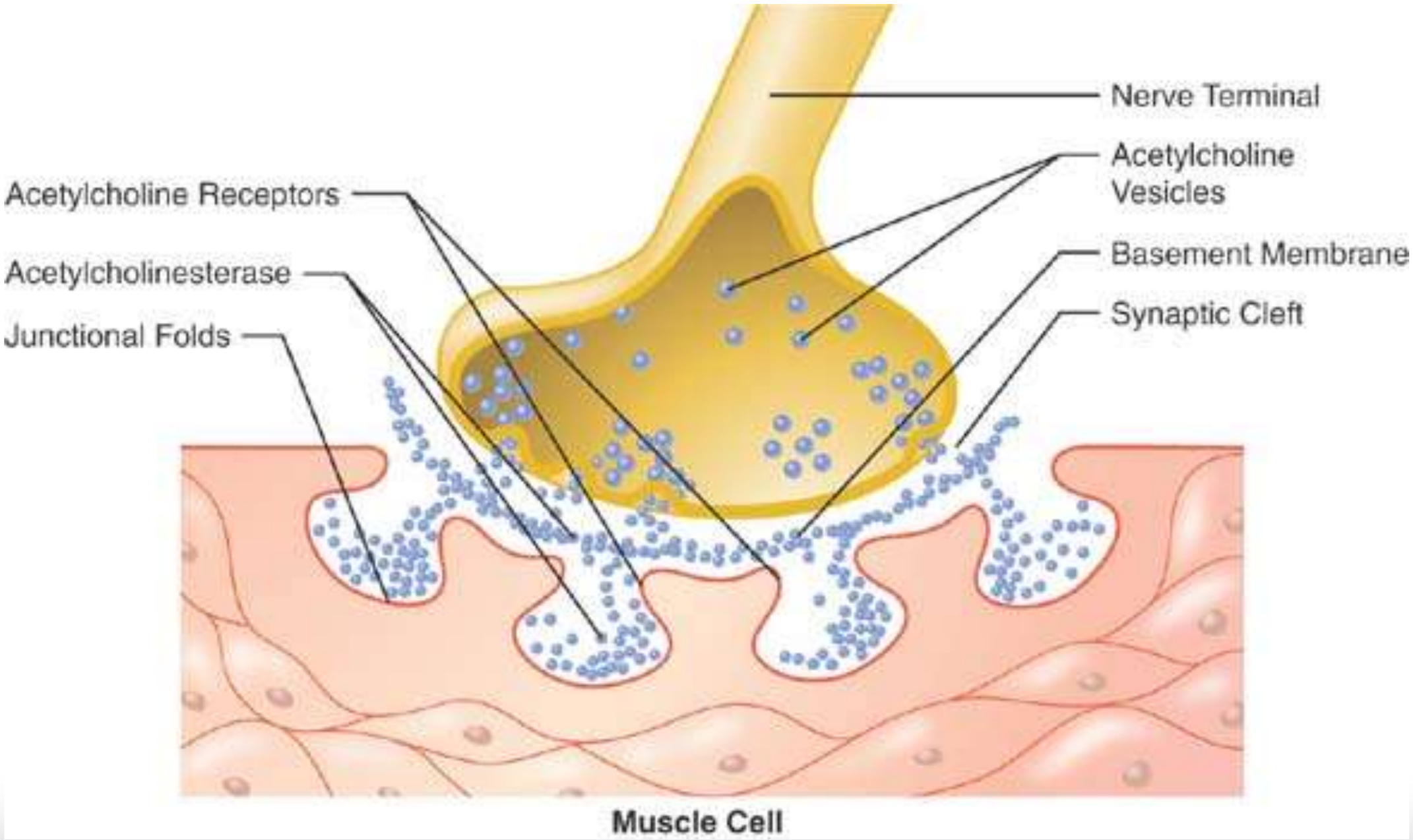
Physiology

- The cell bodies of motor neurons supplying skeletal muscle lie in the spinal cord
- Receive and integrate information from CNS
- Information is carried to distant site via axon
- The terminal portion of the Axon is the synapse
  - Produces and releases Ach

Physiology

- The synapse is separated from the endplate of muscle fibers by a narrow gap, called the synaptic cleft
- The nicotinic acetylcholine receptors are concentrated on the endplate

NMJ


Nerve Terminal
Acetylcholine Vesicles
Acetylcholine Receptors
Basement Membrane
Acetylcholinesterase
Synaptic Cleft
Junctional Folds
Muscle Cell

Nerve Stimulation

- Under resting conditions, the electrical potential of the inside of a nerve cell is negative with respect to the outside (-90 mV)
- If this potential is made less negative, Na channels open and allow Na to enter the cell
- The next segment of the membrane is depolarized and an Action Potential (AP) propagates

Calcium

- AP triggers opening of Ca channels, allowing Ca ions to penetrate the cell
- The entry of Ca facilitates release of the neurotransmitter at the nerve terminal

Release of Ach

- Each vesicle contains 5k to 10K molecules
- When an AP reaches the nerve terminal, appx 200-400 quanta are released unloading 1-4 mil Ach molecules into the synaptic cleft
- Calcium is required for vesicle fusion and release

Neuromuscular Blocking Agents

- Interact with the Ach receptor
  - Depolarizing the endplate (depolarizing agents)
  - Competing w/ Ach for binding sites (nondepolarizing agents)

Depolarizing Drugs: Succinylcholine

- Among drugs that depolarize the endplate, only succinylcholine is still used clinically
- Succinylcholine remains popular because it is the only ultra rapid onset/ultra short duration neuromuscular blocking drug currently available.

Succinylcholine

- Depolarizes postsynaptic and extra junctional receptors
- When the receptor is in contact with any agonist, including acetylcholine, for a prolonged time it ceases to respond to the agonist.
- This desensitization process does not occur with acetylcholine because of its rapid breakdown (<1 msec).

Succinylcholine

- Succinylcholine remains at the endplate for much longer, so desensitization develops after a brief period of activation.
- Within 1 minute after succinylcholine injection and before paralysis is manifest, some disorganized muscular activity is frequently observed.
- This phenomenon is called **fasciculation**.

- Small doses of nondepolarizing drugs are effective in reducing the incidence of fasciculations
- In some muscles, like the masseter and to a lesser extent the adductor pollicis, a sustained increase in tension that may last for several minutes can be observed.
- The mechanism of action of this tension change is uncertain but is most likely mediated by acetylcholine receptors because it is blocked by large amounts of nondepolarizing drugs

Characteristics of Depolarizing Blockade

- After injection of succinylcholine, single-twitch height is decreased.
- The response to high-frequency stimulation is sustained
- Minimal train-of-four and tetanic fade is observed.

Characteristics of Depolarizing Blockade

- The block is antagonized by nondepolarizing agents so that the ED_{95} is increased by a factor of two if a small dose of nondepolarizing drug is given before
- Succinylcholine blockade is potentiated by inhibitors of acetyl cholinesterase, such as neostigmine and edrophonium.

Phase II Block

- Train-of-four and tetanic fade become apparent.
    - After administration of 7 to 10 mg/kg, or 30 to 60 minutes of exposure to succinylcholine
- Neostigmine or edrophonium can antagonize this block
- The onset of phase II block coincides with tachyphylaxis, as more succinylcholine is required for the same effect.

Pharmacology of Succinylcholine

- Rapidly hydrolyzed by plasma cholinesterase (AKA pseudocholinesterase)
- Because of the rapid disappearance of succinylcholine from plasma (elimination half-life of <1 minute), the maximum effect is reached quickly

Pharmacology of Succinylcholine

- ED_{95} at the adductor pollicis muscle is 0.30 to 0.35 mg/kg with opioid–nitrous oxide anesthesia
- These values are doubled if a defasciculating dose of NDNMB is given
- The time until full recovery is dose-dependent and reaches 10 to 12 minutes after a dose of 1 mg/kg

Side Effects

- Sinus bradycardia with nodal or ventricular escape beats (or both) may occur, especially in children
- Asystole has been described after a second dose of succinylcholine in both pediatric and adult patients
- These effects can be attenuated with atropine or glycopyrrolate
- Succinylcholine increases catecholamine release, and tachycardia is seen frequently.

Fasciculations

- The prevalence of fasciculations is high (60 to 90%) after the rapid injection of succinylcholine, especially in muscular adults
- a small dose of a nondepolarizing neuromuscular blocking drug given 3 to 5 minutes before succinylcholine is effective in preventing fasciculations
- In one study, rocuronium, 0.03 mg/kg, decreased the incidence of fasciculations from 90 to 10%

- Other drugs, such as diazepam, lidocaine, fentanyl, calcium, vitamin C, magnesium, and dantrolene, have all been used to prevent fasciculations.
- The results are no better than with nondepolarizing relaxants and they may have undesirable effects of their own

Muscle Pains

- Generalized aches and pains are common 24 to 48 hours after succinylcholine administration
- More common in young, ambulatory patients
- The methods that have been shown effective to prevent fasciculations usually prevent muscle pains
- Lidocaine (1 to 1.5 mg/kg), especially in conjunction with precurarization, has also been shown to be of value

Intragastric Pressure

- Succinylcholine increases intragastric pressure, and this effect is blocked by precurarization
- Causes even greater increases in lower esophageal sphincter pressure
  - does not appear to increase the risk of aspiration of gastric contents unless the lower esophageal sphincter is incompetent.

Intraocular Pressure

- Intraocular pressure increases by 5 to 15 mm Hg after injection of succinylcholine
- Precurarization with a nondepolarizing blocker has little or no effect on this increase

Open Eye Injuries

- Inadequate anesthesia, elevated systemic BP, and insufficient NMB during DL and tracheal intubation might increase IOP more than succinylcholine
- there is little evidence that the use of succinylcholine has led to blindness or extrusion of eye content (Vachon CA, Warner DO, Bacon DR: Succinylcholine and the open globe. Tracing the teaching. Anesthesiology 2003; 99: 220)

Intracranial Pressure

- Succinylcholine may increase intracranial pressure, and this response is probably diminished by precurarization
  - (Minton MD, Grosslight K, Stirt JA, Bedford RF: Increases in intracranial pressure from succinylcholine: prevention by prior nondepolarizing blockade. Anesthesiology 1986; 65: 165)
- DL and tracheal intubation with inadequate anesthesia or muscle relaxation are likely to increase ICP even more than succinylcholine.

Hyperkalemia

- Serum potassium increases by approximately 0.5 mEq/L after injection of succinylcholine.
- Not prevented completely by precurarization.
- Subjects with pre-existing hyperkalemia, such as patients in renal failure, do **not** have a greater increase in potassium levels, but the absolute level might reach the toxic range

Hyperkalemia

- Severe hyperkalemia → to cardiac arrest, has been described in
  - patients after major denervation injuries
  - spinal cord transection
  - peripheral denervation
  - stroke
  - trauma
  - extensive burns, and prolonged immobility
- May be related to potassium loss via a proliferation of **extrajunctional receptors**

Hyperkalemia

- Reported with myotonia and muscle dystrophies, and cardiac arrests have been reported in children before the diagnosis of the disease was made.
- Severe hyperkalemia after succinylcholine resulting in cardiac arrest has also been observed in acidotic hypovolemic patients

Abnormal Plasma Cholinesterase

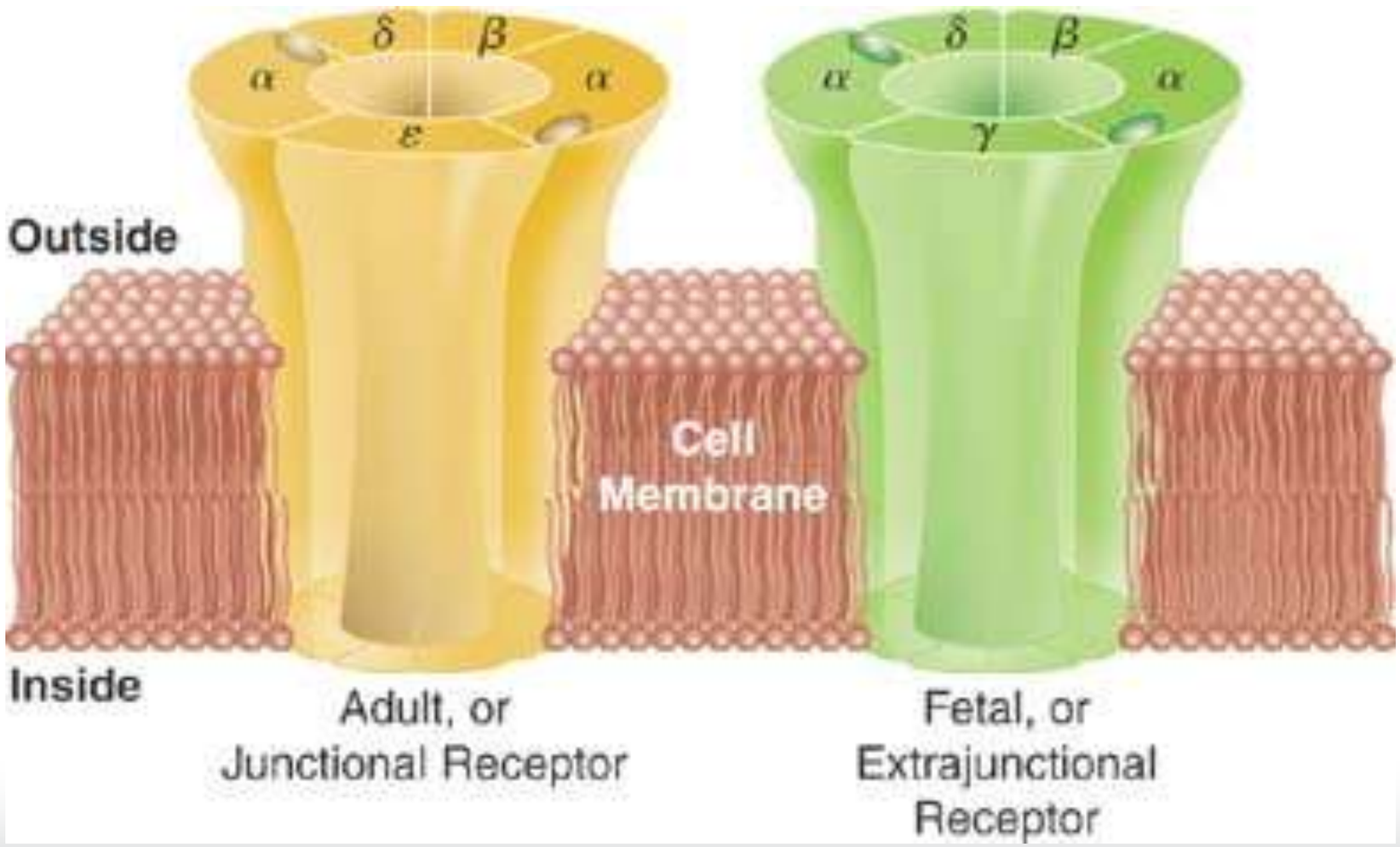
- Homozygous for the condition (approximately 1:2,000 individuals) → prolonged paralysis (3 to 6 hours) after usual doses of succinylcholine (1 to 1.5 mg/kg)
- Heterozygous patients (1:30 cases) → duration of action is only slightly prolonged compared with normal individuals

Dibucaine Number

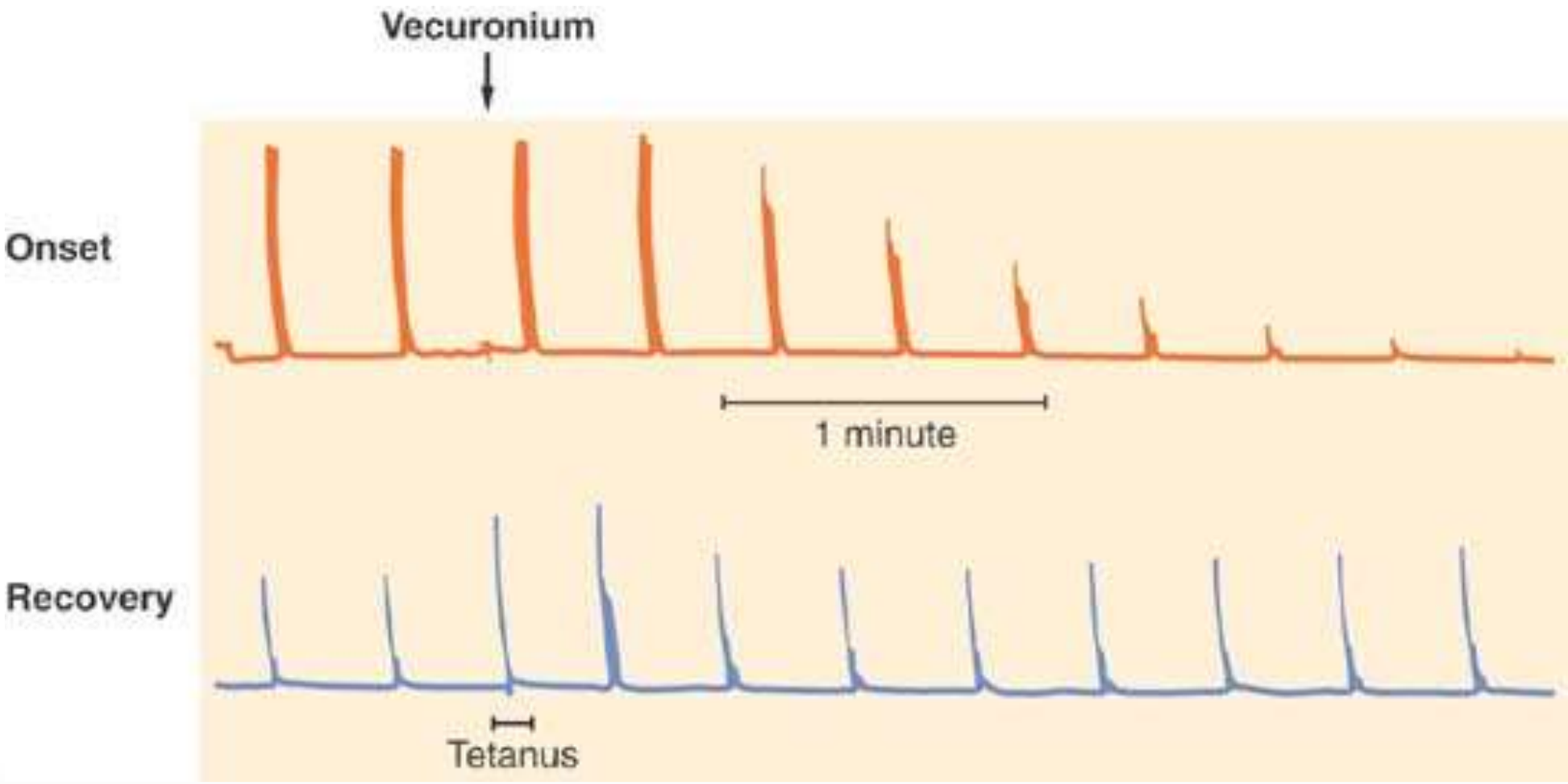
- A laboratory assay to characterize plasma cholinesterase activity
  - Normal Plasma cholinesterase is 80% inhibited in vitro by LA dibucaine
  - Homozygous atypical plasma cholinesterase is 20% inhibited
  - 30 – 60 in heterozygous atypical

Nondepolarizing NMB

- Bind to the postsynaptic receptor in a competitive fashion, by binding to one of the α subunits of the receptor



- The fade observed in response to high-frequency stimulation (>0.1 Hz) is characteristic of nondepolarizing blockade



Pharmacokinetics

- Elimination half-life of neuromuscular blocking agents does not always correlate with duration of action.
  - termination of action sometimes depends on redistribution instead of elimination

General Principles

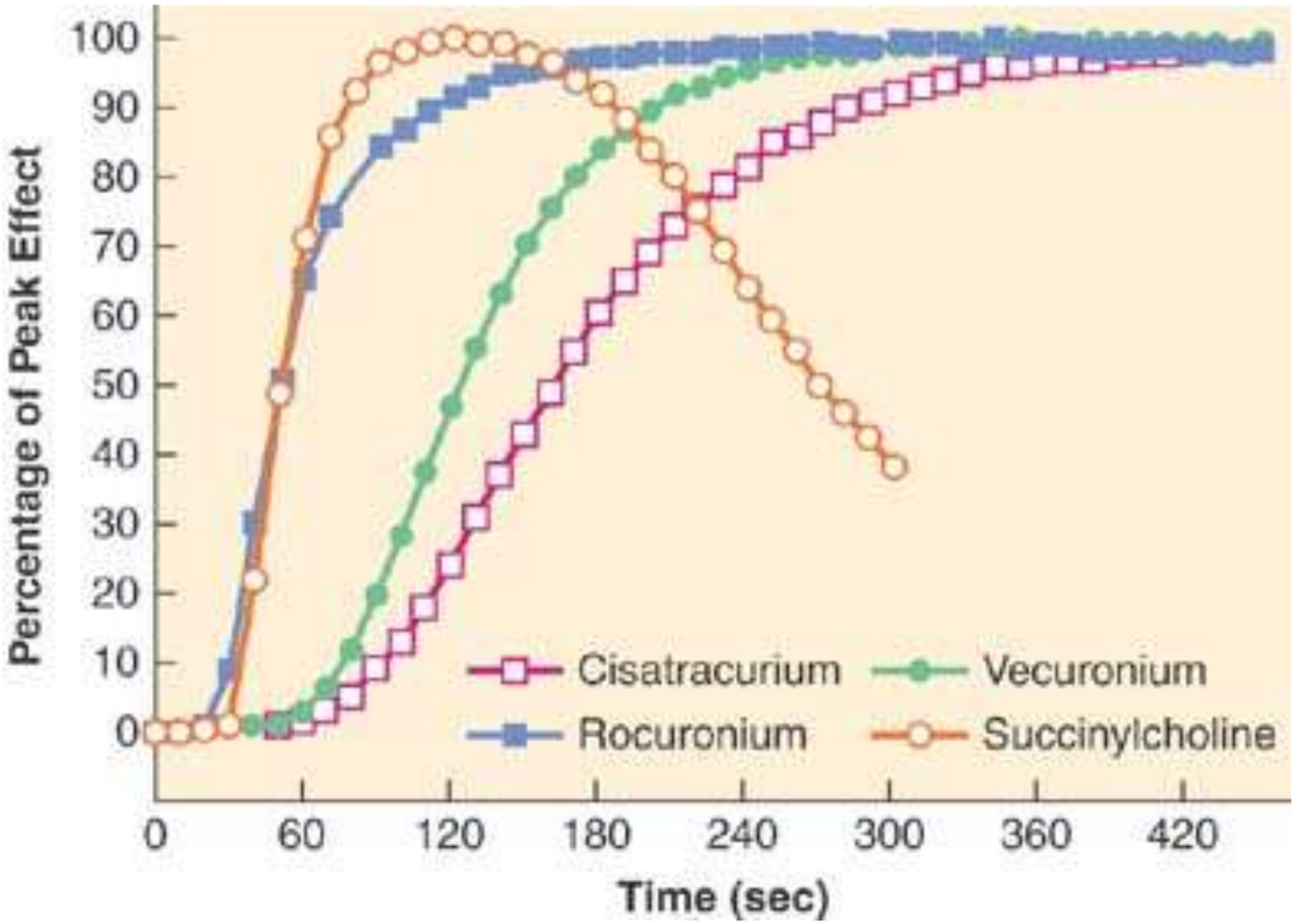
- Long-duration drugs all have a long (1 to 2 hours) elimination half-life and depend on liver and/or kidney function for termination of action
- Intermediate-duration drugs either have an intermediate elimination half-life (atracurium and cisatracurium) or they have long elimination half-lives (1 to 2 hours) but depend on redistribution rather than elimination for termination of effect (vecuronium and rocuronium

General Principles

- Short-duration drugs have either short elimination half-lives (the active isomers of mivacurium) or long elimination half-life but extensive redistribution (rapacuronium)
- Ultrashort-duration drugs have a very short elimination half-life (succinylcholine).

- Onset time of neuromuscular blocking drugs is determined by the time required for drug concentrations at the site of action to reach a critical level.
- Onset time (2 to 7 minutes) is longer than time to peak plasma concentrations (<1 minute).
  - reflects the time required for drug transfer between plasma and neuromuscular junction

- Potent drugs have a slower onset of action than less potent agents.



Cisatracurium

- Because cisatracurium (4 min) is a potent drug, its onset time is longer than that of atracurium and longer still than that of rocuronium (1.7 min).
- There is no need to adjust dosage in the elderly, children, or infants, when compared with young adults.
- In obese individuals, the dose of cisatracurium should be calculated on the basis of ideal body weight.
- Devoid of histamine-releasing properties even at high doses ($8 \times ED_{95}$)

Pancuronium

- The ED_{95} of pancuronium is 0.07 mg/kg
- The duration of action is long, being 1.5 to 2 hours after a 0.15 mg/kg dose
- Clearance is decreased in renal and hepatic failure

Cardiovascular Effects of Pancuronium

- Increases in heart rate, blood pressure, and cardiac output, particularly after large doses (2 × ED_{95})
  - vagolytic effect at the postganglionic nerve terminal
  - sympathomimetic effect as a result of blocking of muscarinic receptors
  - increase in catecholamine release
- Pancuronium does not release histamine.

Rocuronium

- An aminosteroid compound with structural similarity with vecuronium and pancuronium
- Plasma concentrations of rocuronium decrease rapidly after bolus injection because of hepatic uptake
  - the duration of action of the drug is determined chiefly by redistribution
- Most of the drug is excreted unchanged in the urine, bile, or feces

Rocuronium

- ED_{95} → 0.3 mg/kg
- With equipotent doses, rocuronium onset at the adductor pollicis muscle is much faster than that of cisatracurium, atracurium, and vecuronium
  - the onset of action of rocuronium is more rapid at the diaphragm and adductor laryngeal muscles than at the adductor pollicis muscle
  - Recovery is faster at the diaphragm and larynx than at the adductor pollicis muscle.

Cardiovascular Effects of Roc

- No hemodynamic changes after doses of up to 4 × ED_{95}
- No increases in plasma histamine concentrations
- Anaphylactic reactions have been described, and a French study indicated that these events occurred more frequently with rocuronium than with other neuromuscular blocking agents
  - It is possible that overdiagnosis has played a role in the relatively high incidence of rocuronium anaphylaxis reported

Rocuronium

- In the United States, the incidence of anaphylactic reactions to rocuronium and vecuronium may be as low as 1:1,000,000 .
- Bhananker SM, O'Donnell JT, Salemi JR, et al: The risk of anaphylactic reactions to rocuronium in the United States is comparable to that of vecuronium: an analysis of food and drug administration reporting of adverse events. Anesth Analg 2005; 101: 819

Rocuronium

- Rocuronium and thiopental do not mix. They form a precipitate when they are in the same intravenous line. If thiopental is used for induction of anesthesia, the line must be flushed carefully before rocuronium is given.

Vecuronium

- An intermediate-duration aminosteroid neuromuscular relaxant without cardiovascular effects
- ED_{95} is 0.04 to 0.05 mg/kg
- Undergoes spontaneous deacetylation to produce metabolites

Vecuronium

- 3-OH vecuronium, about 60% of the activity of vecuronium, is excreted by the kidney and may be responsible, in part, for prolonged paralysis in patients in the ICU
- Duration of action of vecuronium, like that of rocuronium, is governed by redistribution, not by elimination

Cardiovascular Effects of Vec

- No cardiovascular effects with clinical doses
- Does not induce histamine release
- Allergic reactions have been described, but no more frequently than after the use of other neuromuscular blocking drugs

THANK YOU

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