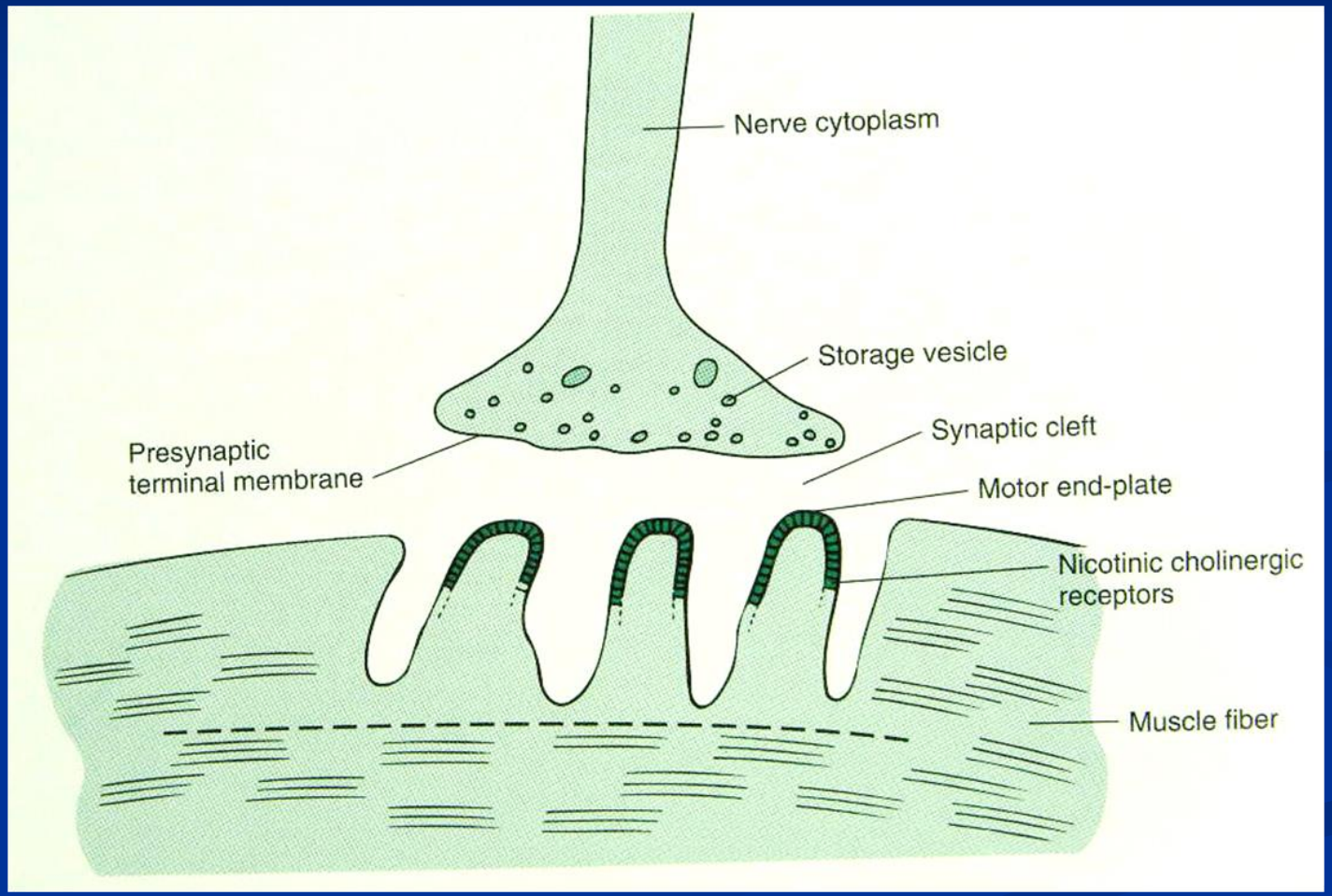
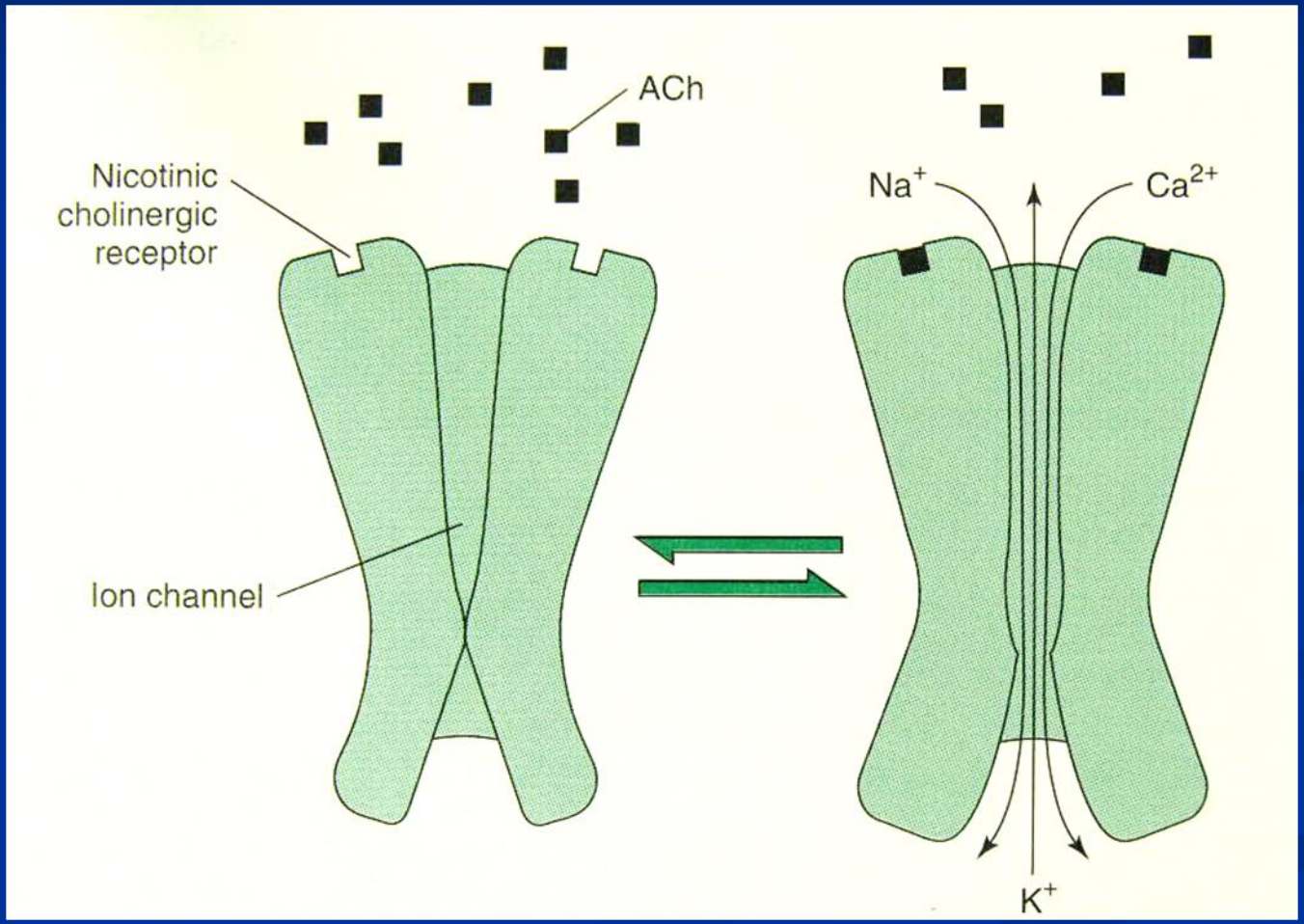
Neuromuscular blockers (muscle relaxants)


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


ACh
Nicotinic
cholinergic
receptor
Ion channel
Na^+
Ca^{2+}
K^+

Acetylcholine

- Acetylcholine is released from motor neurons in discrete quanta
- Causes "all-or-none" rapid opening of Na+/K+ channels (duration 1 msec)
- Development of miniature end-plate potentials (mEPP)
- Generate muscle action potential resulting in muscle contraction
- ACh is rapidly hydrolyzed by acetylcholinesterase; no rebinding to receptor occurs unless AChE inhibitor is present

Muscle relaxant

- Muscle relaxation could be achieved by:

1. Blocking NM nicotinic receptors

Nondepolarizing muscle relaxants:

D-Tubocurarine (Curare) (prototype)

Atracurium

Mivacurium

Pancuronium

Gallamine

Vecuronium

Recuronium

Muscle relaxant

2. Desensitization of NM nicotinic receptors

Depolarizing muscle relaxants:

Succinylcholine (Suxamethonium)

3. Directly acting muscle relaxants (antispasticity agents):

Baclofen

Benzodiazepines (Diazepam=Valium®)

Dantrolene sodium

Muscle relaxant

4. Centrally acting skeletal muscle relaxants

Carisoprodol

Chlorzoxazone

Cyclobenzaprine

Methocarbamol

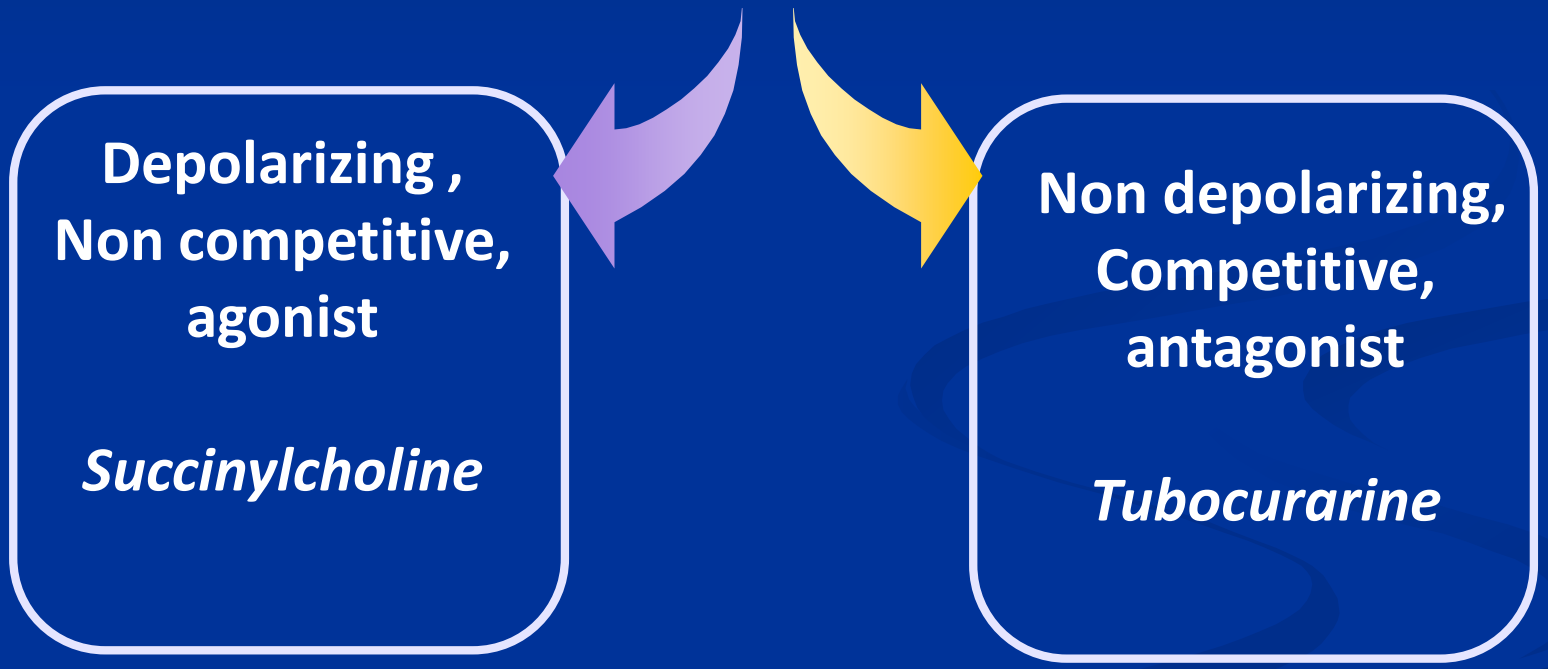
Orphenadrine

Muscle relaxant

- **General clinical uses to muscle relaxants**

- Provide muscle relaxation before major surgeries (↓ dose of general anaesthetic)
- Provide muscle relaxation before intubation e.g. endotracheal intubation...
- Prevent fractures and bone dislocation during electroconvulsive therapy
- Spinal spasticity and spasticity associated with multiple sclerosis
- Spasticity of malignant hyperthermia

Classification of Neuromuscular Blockers According to Mechanism of Action



Classification of Neuromuscular Blockers According Duration of Action

Ultra-Short	Short	Intermediate	Long
Succinylcholine	Mivacurium		
Rapacuronium			
		Vecuronium	Pancuronium
		Atracurium	
	Cis-atracurium	Rocuronium	

Different agents differ in OOA; DOA and fate of metabolism

Nondepolarizing muscle relaxants

Reversible competitive antagonists to Ach nicotinic receptors at NM junction

- In small doses they act predominantly at the nicotinic receptor site to block ACh
- At higher dose they can block prejunctional Na^+ channels thereby decreasing ACh release

Because of their competitive nature, their effects could be reversed by antiCHE's

Have no effects on muscarinic receptors

Nondepolarizing muscle relaxants

Do not enter CNS (quaternary ammonium; charged molecules)

Given IV; OOA 3-4 min → flaccid paralysis

1st muscles to be affected head & neck muscles, then limb muscles and finally respiratory muscles; recovery occurs in reverse

Nondepolarizing muscle relaxants

- **Clinical uses to nondepolarizing muscle relaxants**

- Preanaesthetic medications
- Prevention of bone fractures and dislocations that could be associated with electroconvulsive therapy
- Control of spasm of tetanus

- **Side effects and drug-drug interactions to nondepolarizing muscle relaxants:**

- Histamine release by mast cells → ↓ BP, skin rashes, & bronchospasm (newer drugs e.g. Pancuronium)
- Partial block to symp. ganglia → ↓ BP

Nondepolarizing muscle relaxants

- Newborn and children are more sensitive to their effects due to lower No. of Ach receptors (need lower doses)

- Aminoglycosides and macrolide antibiotics increase their effects

Nondepolarizing muscle relaxants are mainly metabolized by liver and kidney (Pancuronium)

Mivacurium is metabolized by plasma cholinesterase

- Most widely used nondepolarizing muscle relaxants:

Pancuronium

More potent than curare, does not release histamine; does not block symp. ganglia and has longer OOA & DOA

Vecuronium

Similar to Pancuronium

Rapacuronium

Has rapid OOA (1.5 min) and short DOA (20 min), good for short procedures, releases histamine

Depolarizing muscle relaxants

- Act as strong Ach agonists

- Muscle relaxation is achieved through 2 steps:

1. Phase I or depolarization block

An initial depolarization of end plate producing muscle action potential and fasciculation Maintained depolarization leads to Na^+ channel inactivation and hence action potential cannot be generated

Depolarizing muscle relaxants

2. Phase II or desensitization block

In continued presence of the depolarizing agent, the membrane becomes repolarized, Na^+ channel inactivation will be reversed and membrane excitability is restored. But neuromuscular blockade continues due to desensitization of Ach receptors (Succinycholine is not metabolized like acetylcholine so it continues to occupy the Ach receptors to "desensitize" the end-plate)

Succinylcholine (Suxamethonium)

Succinylcholine is two acetylcholine molecules linked end-to-end

Depolarizing muscle relaxant (produce sustained contractions) given IV, good for minor procedures because has short DOA

Metabolized by plasma cholinesterase

Has no effects on autonomic ganglia or on muscarinic receptors

It does not enter CNS

It releases histamine

Succinylcholine (Suxamethonium)

- Actions of Succinylcholine are not reversed by antiCHE's and may actually prolong the block
- Actions of Succinylcholine could be prolonged in:

- Pts with liver disease (plasma cholinesterase is synthesized in liver)
- Individuals with genetic defects leading to a decrease in plasma cholinesterase or presence of atypical enzyme with decreased affinity to Succinylcholine

Succinylcholine (Suxamethonium)

- **Succinylcholine side effects:**

- Prolonged apnea
- Fasciculation that could lead to myoglobinuria and postoperative pain
- Hyperkalemia → cardiac arrhythmias
- Increased intraocular pressure due to contraction of extra ocular muscles
- Malignant hyperthermia

Directly acting muscle relaxants (spasmolytics):

- **Diazepam**

Acts at $GABA_A$ receptors in the CNS

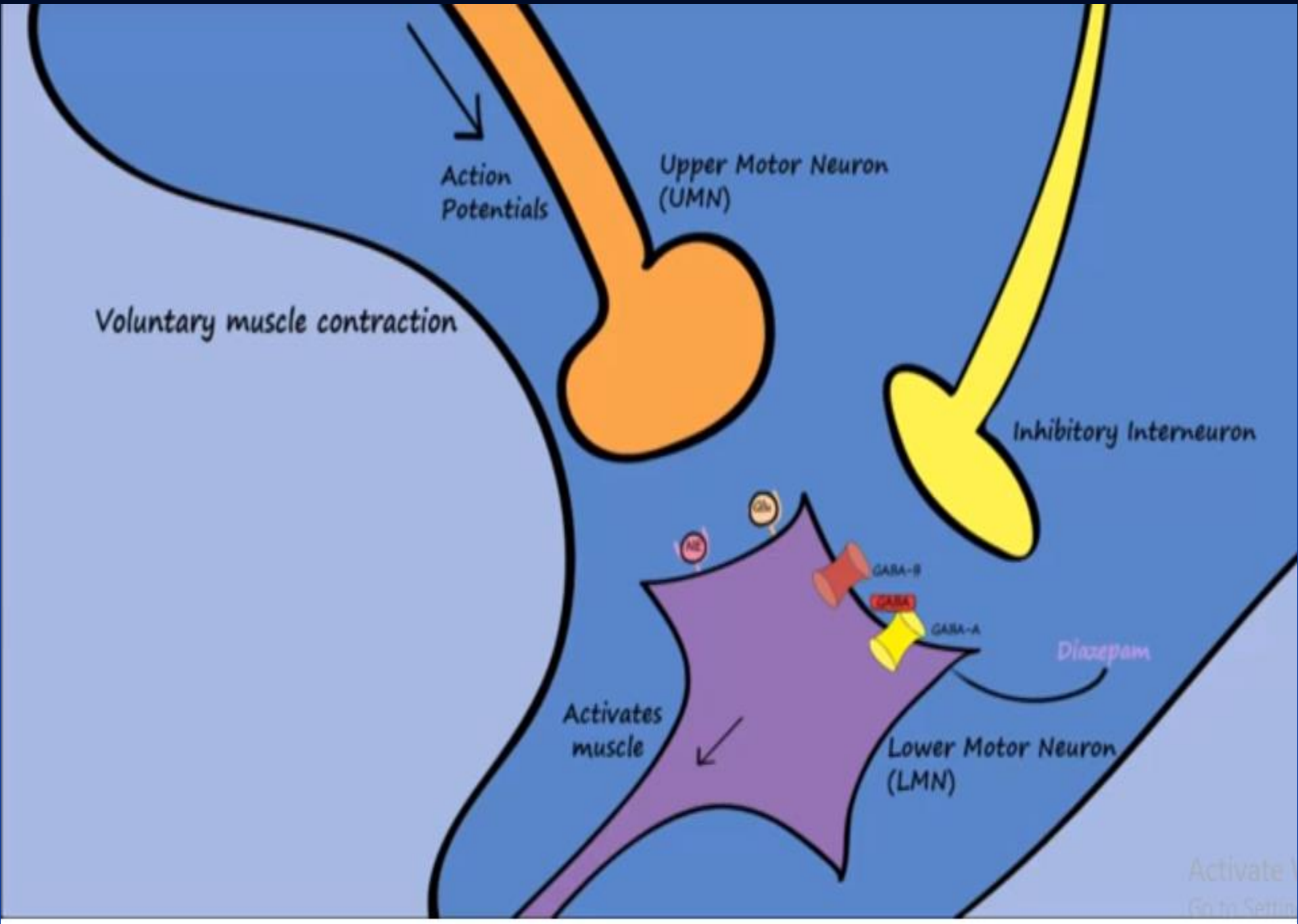
Leads to sedation & addiction

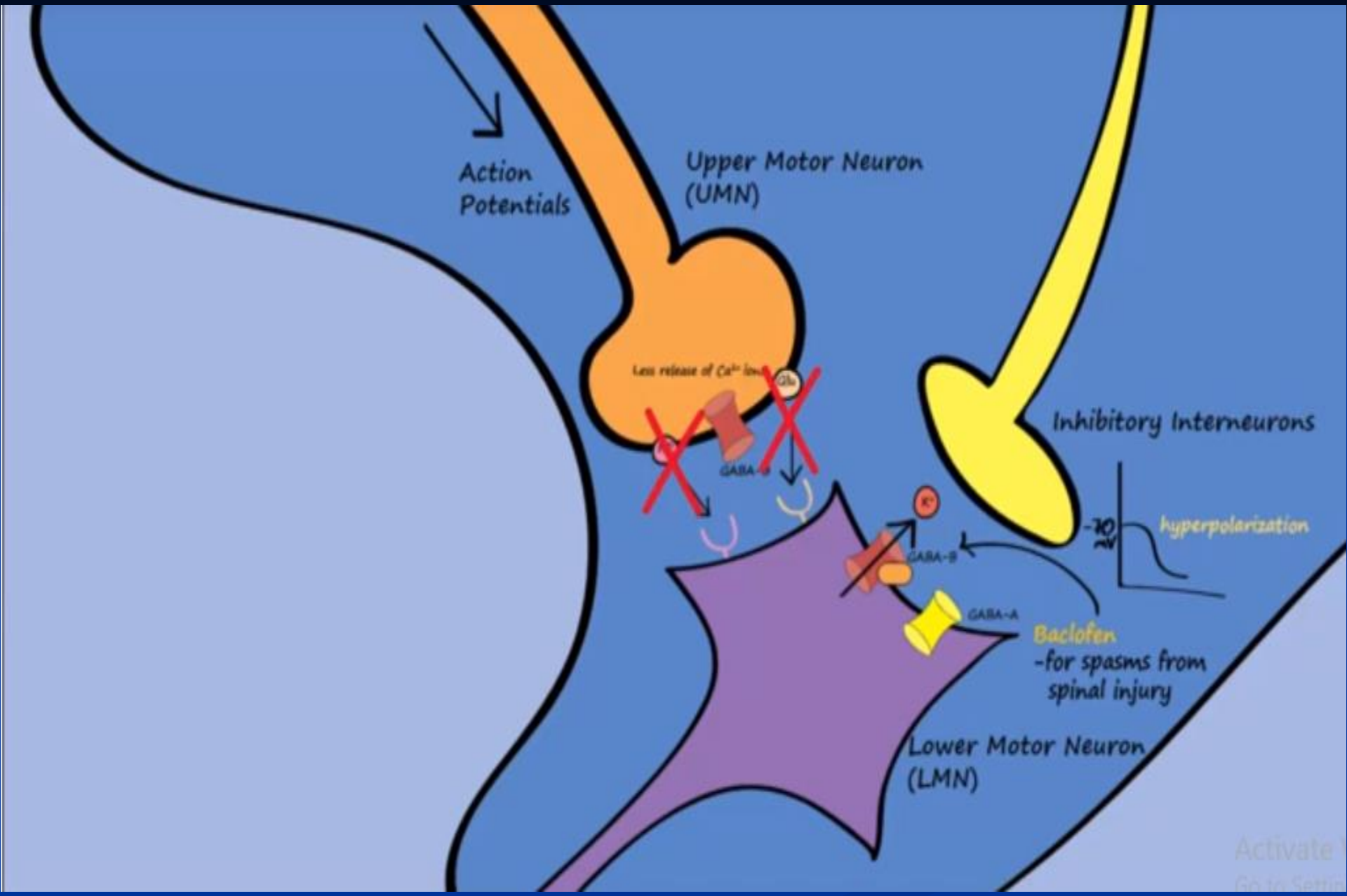
Relieves muscle spasm

- **Baclofen**

Orally effective; drug of choice for treating spinal spasticity and spasticity of multiple sclerosis

Acts at $GABA_B$ receptors, resulting in hyperpolarization and presynaptic inhibition through reducing calcium influx


Action Potentials
Upper Motor Neuron (UMN)
Voluntary muscle contraction
Inhibitory Interneuron
GABA-B
GABA
GABA-A
Diazepam
Activates muscle
Lower Motor Neuron (LMN)


Action Potentials
Upper Motor Neuron (UMN)
Less release of Ca2+ ions
Glu
GABA-B
Inhibitory Interneurons
K+
GABA-B
-70 mV
hyperpolarization
GABA-A
Baclofen
-for spasms from spinal injury
Lower Motor Neuron (LMN)

Baclofen

Less sedative, but can cause drowsiness

Can be given intrathecally

Can reduce craving in alcoholics and in migraine

Tezanidine

- α2 adrenergic receptor agonist
- Congener of clonidine
- Results in presynaptic inhibition of motor neurons
- Has 1/10-1/50th potency as clonidine in lowering blood pressure
-Effective in treating spasms, cramping, and tightness of muscles caused by multiple sclerosis
- Given orally
- It is also prescribed for migrainous headaches, as a sleeping aid, and as an anticonvulsant
- Side Effects: Drowsiness, hypotension, dry mouth

Dantroline sodium

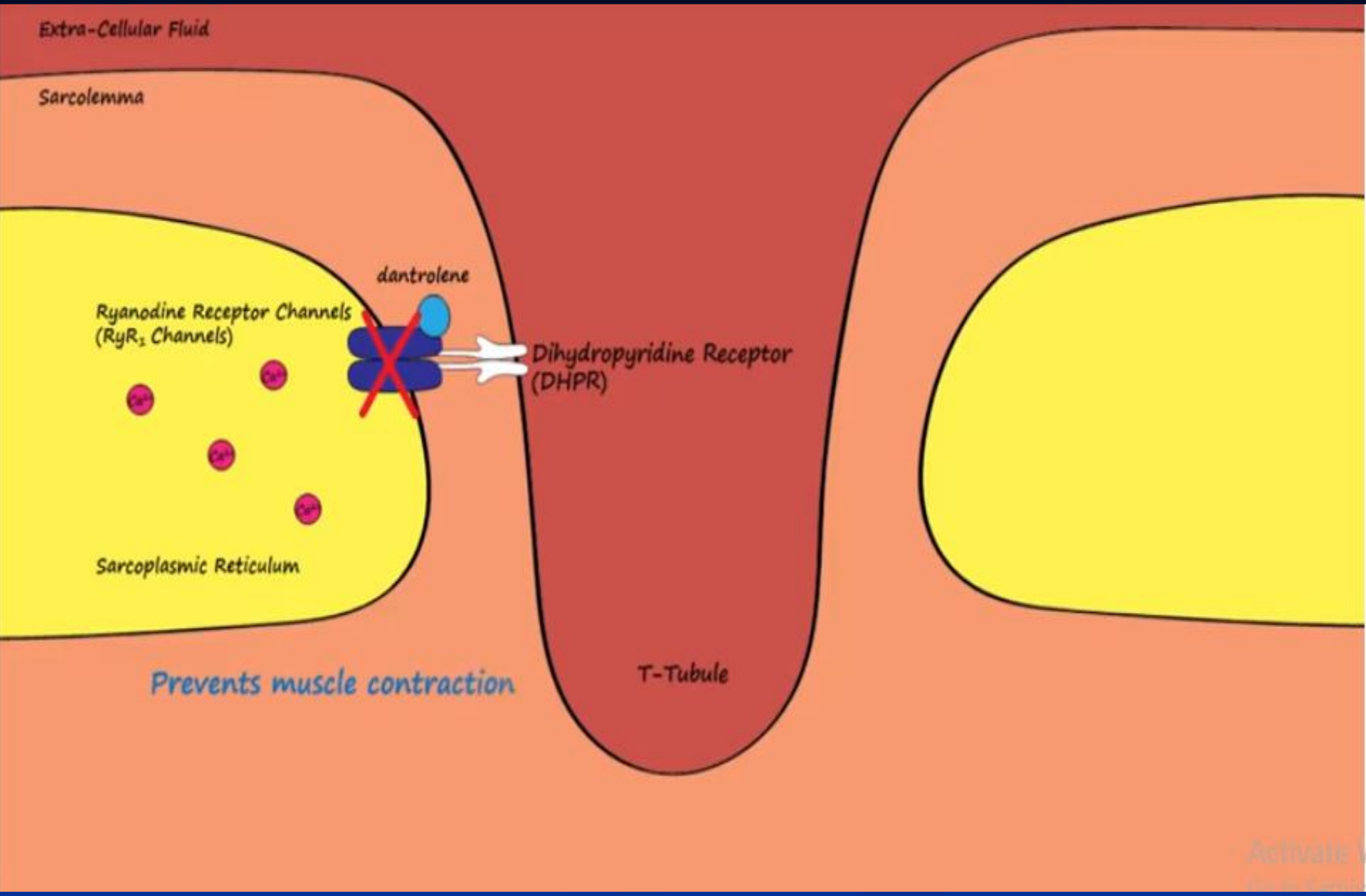
Interferes with excitation-contraction coupling

Reduces release of Ca^{++} from the sarcoplasmic reticulum and thus blocks contraction

Uses: Cerebral palsy, multiple sclerosis and malignant hyperthermia

Given orally and IV

Side Effects: Muscle weakness, sedation, rare hepatitis


Extra-Cellular Fluid
Sarcolemma
dantrolene
Ryanodine Receptor Channels
(RyR1 Channels)
Dihydropyridine Receptor
(DHPR)
Sarcoplasmic Reticulum
T-Tubule
Prevents muscle contraction

Centrally acting muscle relaxants

e.g. Carisoprodol...

Block pain sensations between the nerves and the brain

Depress spinal polysynaptic reflexes

Effective in muscle spasm associated with injuries

Have no over advantage above analgesic antiinflammatory agents

Have mild sedative & antianxiety properties

Combined with other analgesics (e.g. Aspirin) and with caffeine