SKELETAL MUSCLE RELAXANTS

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Where to use

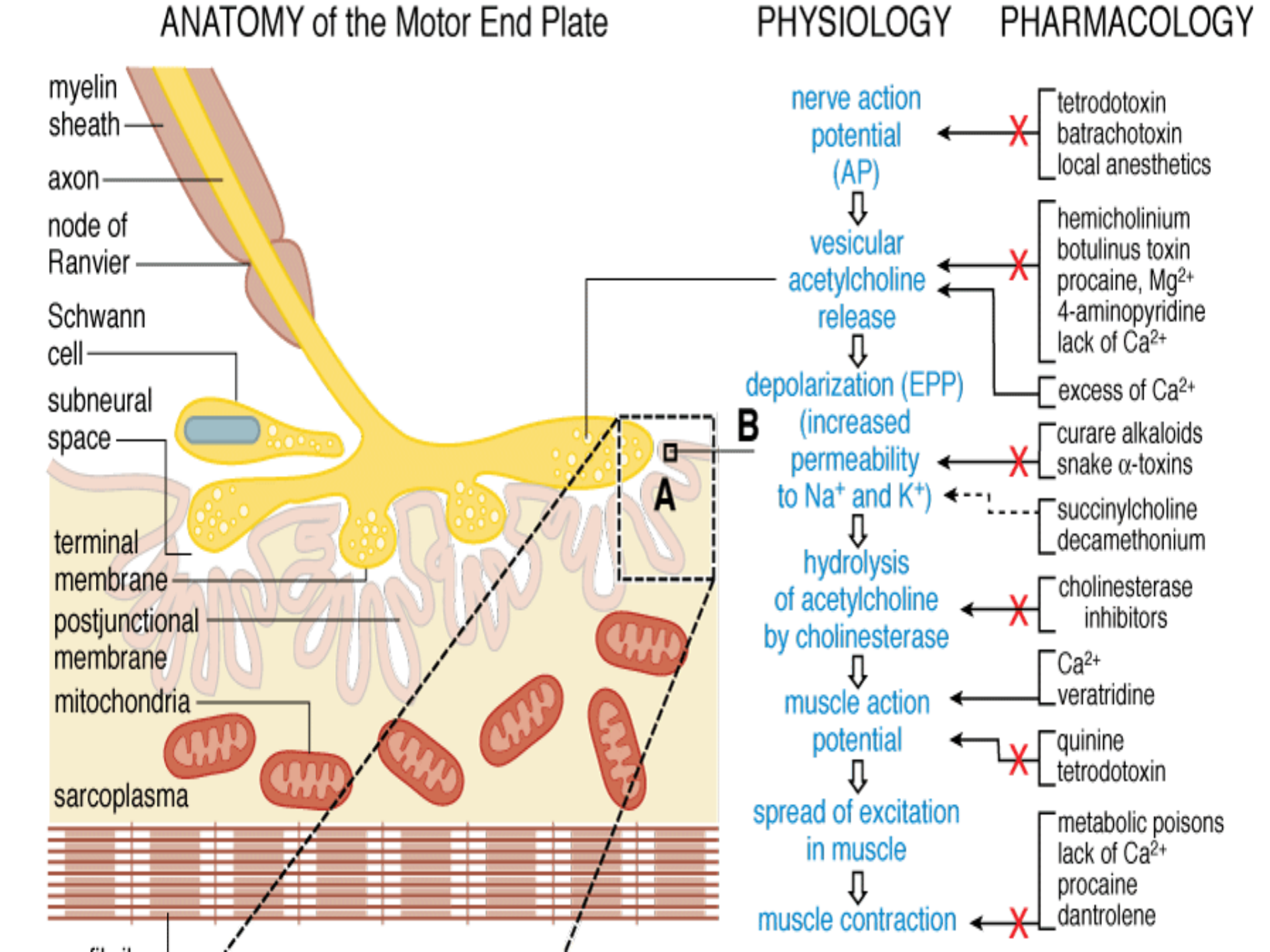
As adjuvant in surgical anaesthesia to obtained relaxation of skeletal muscle

- Relaxation of skeletal muscle to make operative manipulations easy.
- Endotracheal intubation.
- Counteract laryngospasm during barbiturate anaesthesia.
- Require lighter level of anaesthesia.
- Shorten post-anaesthesia recovery period.

- Cerebral palsy
- Multiple sclerosis
- Amyotrophic lateral sclerosis
- Spinal injuries
- Trigeminal neuralgia
- Malignant hyperthermia

Muscle spasm of local origin

- Spondylitis
- Sprains
- lumbago


ANATOMY of the Motor End Plate
PHYSIOLOGY
PHARMACOLOGY
myelin sheath
axon
node of Ranvier
Schwann cell
subneural space
terminal membrane
postjunctional membrane
mitochondria
sarcoplasma
A
B
nerve action potential (AP)
vesicular acetylcholine release
depolarization (EPP) (increased permeability to Na+ and K+)
hydrolysis of acetylcholine by cholinesterase
muscle action potential
spread of excitation in muscle
muscle contraction
tetrodotoxin
batrachotoxin
local anesthetics
hemicholinium
botulinus toxin
procaine, Mg2+
4-aminopyridine
lack of Ca2+
excess of Ca2+
curare alkaloids
snake α-toxins
succinylcholine
decamethonium
cholinesterase inhibitors
Ca2+
veratridine
quinine
tetrodotoxin
metabolic poisons
lack of Ca2+
procaine
dantrolene

Classification on basis of site of action and mechanism of action

A) Peripherally Acting

Acts at N-M junction fall into two catagories :

i- Non depolarizing (Competitive blockers)- prevent access of Ach at Nm rec of motor end plate- prevent depolarization

a). Long acting

- Pancuronuium, Doxacurium, Pipecuronium

b). Intermediate acting

- Vecuronium, Atracurium, Rocuronium

c). Short acting

- Mivacurium, Rapacuronium

ii-Depolarizing:

Act as agonists at acetylcholine receptors.

B) Centrally acting (spasmolytic drugs)

Selective action in the cerebrospinal axis.

- Carisoprodol, Chlorzoxazone, Chlormezanone, Methocarbamol
- Diazepam, Clonazepam (act through $GABA_A$ receptors)
- Baclofen (GABA $_B$ receptors)
- Tizanidine (central α_2 agonist)

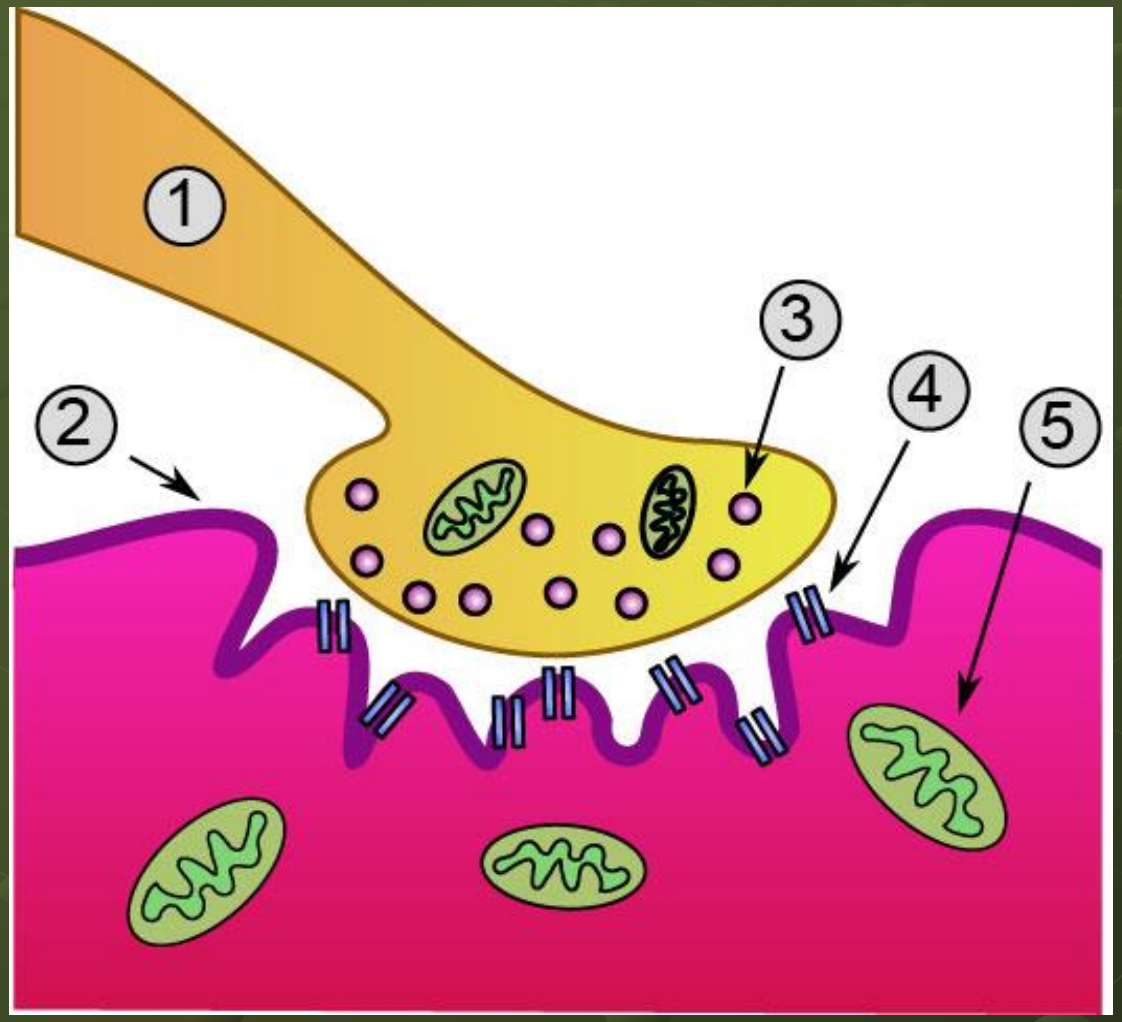
C) Directing acting (spasmolytic drugs)

- Dantroline (act directly by interfering release of calcium from sarcoplasmic reticulum)

Mechanism of Sk. muscle contraction

- Initiation of impulse
- Release of acetylcholine
- Activation of nicotinic receptor at motor end plate
- Opening of ion channel, passage of Na^+ , depolarization of end plate
- Muscle contraction.

NEUROMUSCULAR JUNCTION



- 1: Cholinergic motor neurone
- 2: motor end-plate
- 3: vesicles
- 4: N_MR

Mechanism of action
(non depolarizing agents)

a) At low doses:

- These drugs combine with nicotinic receptors and prevent acetylcholine binding. As they compete with acetylcholine for receptor binding they are called competitive blockers.
- Thus prevent depolarization at end-plate.
- Hence inhibit muscle contraction, relaxation of skeletal muscle occurs.

- Their action can be overcome by increasing conc. of acetylcholine in the synaptic gap (by ihibition of acetyle choline estrase enzyme, e.g.: Neostigmine ,physostigmine)

- Anaesthetist can apply this strategy to shorten the duration of blockage or overcome the over dosage.

At high doses

- These drugs block ion channels of the end plate.
- Leads to further weakening of the transmission and reduces the ability of Ach-esterase inhibitors to reverse the action.

ACTIONS

- All the muscles are not equally sensitive to blockade.
- Small and rapidly contracting muscles are paralyzed first.
- Respiratory muscles are last to be affected and first to recover.

Pharmacokinetics:

- Administered intravenously (not absorbed orally as they remain ionized at physiological pH).
- Cross blood brain barrier poorly (they are poorly lipid soluble)
- They have limited volume of distribution as they are highly ionized.

- Drugs excreted by kidney

  -Longer duration of action (35-100min)
- Drugs eliminated by liver

  -Intermediate duration of action (25-50min)
- Drugs inactivated spontaneously in plasma (Hoffmann elimination)

  -Intermediate duration of action (25-50min)
- Drugs inactivated by plasma cholinesterase

  -Shorter duration of action (15-20min)

- Atracurium is degraded spontaneously in plasma by ester hydrolysis
- it releases histamine and can produce a fall in blood pressure ,flushing and bronchoconstriction.
- Its metabolite can provoke seizures.
- Cisatracurium with similar pharmacokinetics is more safer.

Drug interactions

- Choline esterase inhibitors such as neostigmine, pyridostimine and edrophonium reduces or overcome their activity but with high doses they can cause depolarizing block due to elevated acetylcholine concentration at the end plate.

- Halothane, aminoglycosides , calcium channel blockers synergize their effect.

Unwanted effects

- Fall in arterial pressure- chiefly a result to ganglion block , may also be due to histamine release .
- Bronchospasm due to histamine release from mast cells (especially with tubocurarine ,mivacurium ,and atracurium).
- Pancuronium block muscarinic receptors also, particularly in heart which may results tachycardia.
- Hypoxia and respiratory paralysis.

DEPOLARIZING AGENTS

DRUG- Succinylcholine

Mechanism of action:

- act like acetylcholine but persist at the synapse at high concentration and for longer duration and constantly stimulate the receptor.
- First, opening of the Na+ channel occurs resulting in depolarization, this leads to transient twitching of the muscle, continued binding of drugs make the receptor incapable to transmit the impulses, paralysis occurs.
- The continued depolarization makes the receptor incapable of transmitting further impulses.

- **Therapeutic uses:**
- When rapid endotracheal intubations is required.
- Bronchoscopy
- laryngoscopy
- Electroconvulsive shock therapy.

- **Pharmacokinetics:**
- Administered intravenously.

- Due to rapid inactivation by plasma cholinestrase, given by continued infusion.

Succinylcholine (cont)

- It causes paralysis of skeletal muscle.
- Sequence of paralysis may be different from that of non depolarizing drugs but respiratory muscles are paralyzed last.
- Produces a transient twitching of skeletal muscle before causing block.
- It causes maintained depolarization at the end plate, which leads to a loss of electrical excitability.
- It has shorter duration of action (5-10 min).

- It stimulate ganglion (sympathetic and para sympathetic both).
- In low dose it produces negative ionotropic and chronotropic effect
- In high dose it produces positive ionotropic and chronotropic effect.

- It act like acetylcholine but diffuse slowly to the end plate and remain there for long enough that the depolarization causes loss of electrical excitability

- If cholinestrase is inhibited ,it is possible for circulating acetylcholine to reach a level sufficient to cause depolarization block.

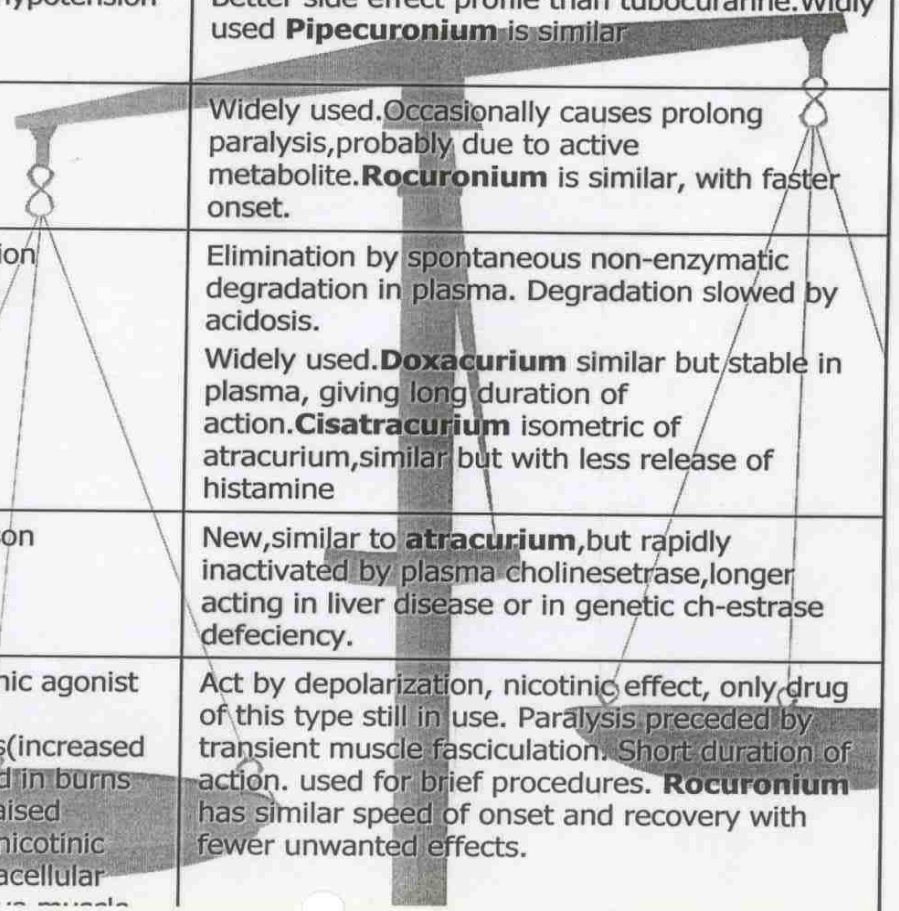
- ***Unwanted effects:***
- Bradycardia (preventable by atropine).
- Hyperkalemia in patients with trauma or burns.
- this may cause arrhythmia or even cardiac arrest.
- Increase intraocular pressure due to contracture of extra ocular muscles .
- increase intragastric pressure which may lead to emesis and aspiration of gastric content.

- **Malignant hyperthermia:** rare inherited condition probably caused by a mutation of Ca^{++} release channel of sarcoplasmic reticulum, which results muscle spasm and dramatic rise in body temperature. (This **is treated by cooling the body and administration of Dantrolene)**

- **Prolonged paralysis:** due to factors which reduce the activity of plasma cholinesterase
  - genetic variants as abnormal cholinesterase, its severe deficiency.
  - anti -cholinesterase drugs
  - neonates
  - liver disease

Characteristics of neuromuscular-blocking drugs

Drug	Speed of onset	Duration of action	Main side -effects	Notes (additional)
Tubocurarine	Slow (5 min)	Long (1-2hrs)	Hypotension (ganglionic block plus histamine release) Broncohoconstriction	Plant alkaloid,rarely used. **Alcuronium** is semi - synthetic with similar properrties but few side effects
Gallamine	Slow	long	Tachycardia (muscarinic antagonist)	100% renal excretion, avoided in renal failure. Rarely used
Pancuronium	Intermediate (2-3 min)	long	Tachycrdia mild,no hypotension	Better side effect profile than tubocurarine.Widly used **Pipecuronium** is similar
Vecuronium	Intermediate	Intermediate (30-40 min)	Few side effects	Widely used.Occasionally causes prolong paralysis,probably due to active metabolite.**Rocuronium** is similar, with faster onset.
Atracurium	Intermediate	Intermediate (20-30 min)	Transient hypotension (histamine release)	Elimination by spontaneous non-enzymatic degradation in plasma. Degradation slowed by acidosis. Widely used.**Doxacurium** similar but stable in plasma, giving long duration of action.**Cisatracurium** isometric of atracurium,similar but with less release of histamine
Mivacurium	Fast (2 min)	Short (15 min)	Transient hypotensison (histamine release)	New,similar to **atracurium**,but rapidly inactivated by plasma cholinesetrase,longer acting in liver disease or in genetic ch-estrase defeciency.
Suxamethonium	Fast	Short (10 min)	Bradycardia(muscarinic agonist effect) Cardiac dysrhythmias(increased plasma k+ conc.avoid in burns and severe trauma.raised intraocular pressure,nicotinic agonist effect on extacellular	Act by depolarization, nicotinic effect, only drug of this type still in use. Paralysis preceded by transient muscle fasciculation. Short duration of action. used for brief procedures. **Rocuronium** has similar speed of onset and recovery with fewer unwanted effects.



Some properties of neuromuscular blockers

Drug	Elimination	**Approximate potency relative to Tubocurarine**
Atracurium	spontaneous	1.5
Doxacurium	kidney	6
Mivacurium	Plasma cholinesterase	4
Metocurine	Kidney 40%	4
Tubocurarine	Kidney 40%	1
Panacurium	Kidney 80%	6
Rocuronium	Liver 70-80%,kidney	0.8
vecuronium	Liver 75-90%,kidney	6
pipecuronium	Kidney ,liver	6
Rapacuronium	liver	0.4

Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous[1]	6.6	20–35	1.5
Cisatracurium	Mostly spontaneous	5–6	25–44	1.5
Doxacurium	Kidney	2.7	>35	6
Metocurine	Kidney (40%)	1.2	>35	4
Mivacurium	Plasma ChE[2]	70–95	10–20	4
Tubocurarine	Kidney (40%)	2.3–2.4	>35	1
Steroid derivatives				
Pancuronium	Kidney (80%)	1.7–1.8	>35	6
Pipecuronium	Kidney (60%) and liver	2.5–3.0	>35	6
Rapacuronium[3]	Liver	6–11	10–20	0.4
Rocuronium	Liver (75–90%) and kidney	2.9	20–35	0.8
Vecuronium	Liver (75–90%) and kidney	3–5.3	20–35	6

Depolarizing agent

Centrally acting muscle relaxants
(Spasmolytic Drugs)

- Mephenesin group-

  Carisoprodol, Chlorzoxazone, Chlormezanone, Methocarbamol
- Diazepam, Clonazepam (act through $GABA_A$ receptors)
- Baclofen (GABA $_B$ receptors)
- Tizanidine (central α_2 agonist)

- Mechanisms underlying spasticity involve
- - stretch reflex arc itself
- -also higher centers in the CNS (ie, upper motor neuron lesion), with damage to descending pathways in the spinal cord resulting in hyperexcitability of the alpha motoneurons in the cord.

- Pharmacologic therapy
- - ameliorate some of the symptoms of spasticity by modifying the stretch reflex arc
- -or by interfering directly with skeletal muscle (ie, excitation-contraction coupling).

Baclofen

- It acts through GABA- B receptors

- It causes hyper polarization by increased K^+ conductance, reducing calcium influx and reduces excitatory transmitter in brain as well as spinal cord
- It also reduces pain by inhibitory substance P. in spinal cord

- It is less sedative

- It is rapidly and completely absorbed orally

- It has a half life of 3- 4 hours

- It may increases seizures in epileptics

- It is also useful to prevent migraine.

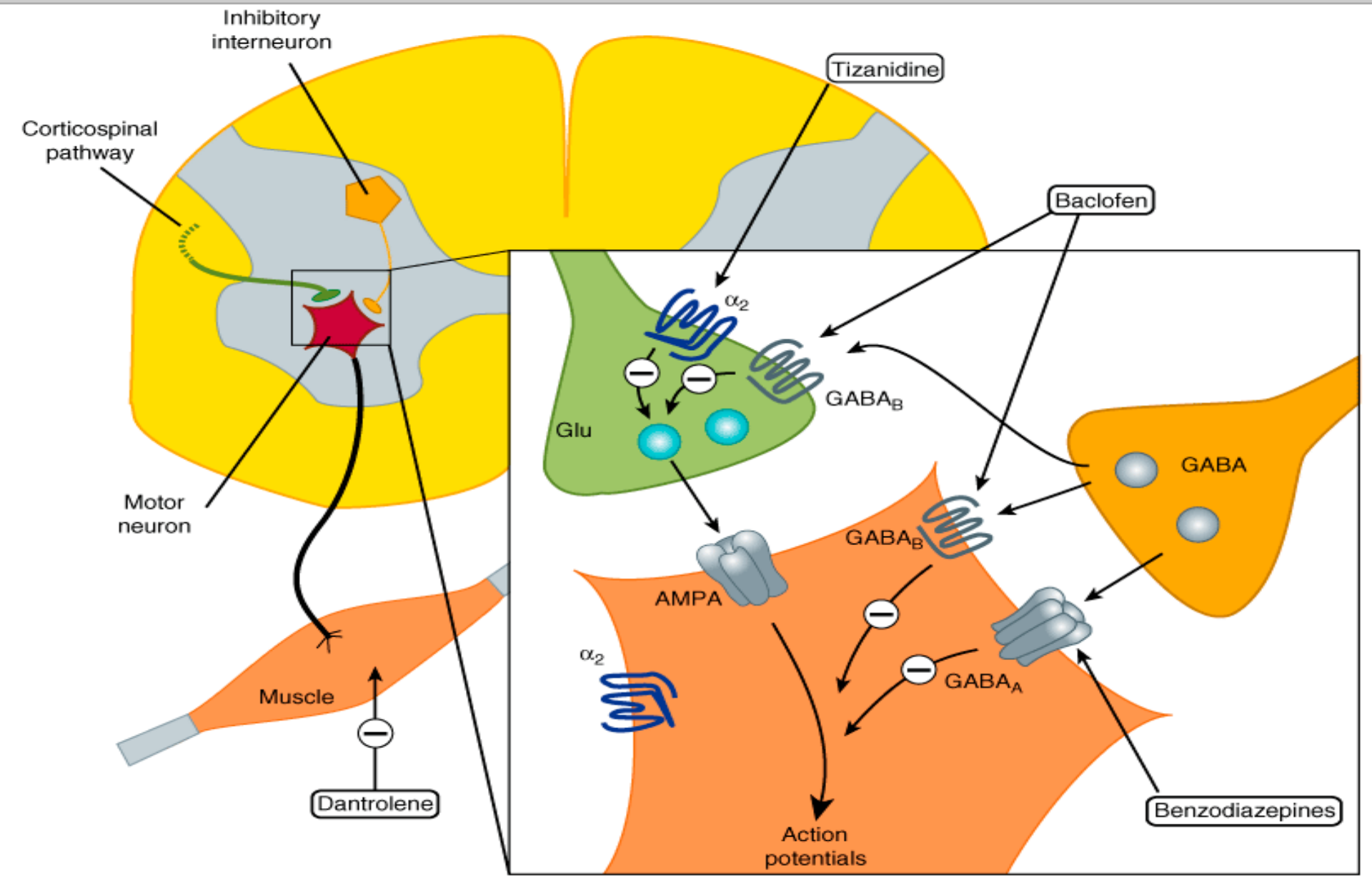
Tizanidine

- Tizanidine has significant **(α_2),** - adrenoceptor agonist effects
- tizanidine reinforces both presynaptic and postsynaptic inhibition in the cord.
- It also inhibits nociceptive transmission in the spinal dorsal horn.

Dantrolene

- **It acts directly**
- It reduces skeletal muscle strength by interfering with excitation-contraction coupling into the muscle fiber, by inhibiting the release of activator calcium from the sarcoplasmic stores.
- It is very useful in the treatment of malignant hyperthermia caused by depolarizing relaxants.
- This drug can be administered orally as well as intravenously. Oral absorption is only one third.
- Half life of the drug is 8-9 hours.

Sites of spasmolytic action of tizanidine (α_2), benzodiazepines ($GABA_A$), and baclofen ($GABA_B$) in the spinal cord. Tizanidine may also have a postsynaptic inhibitory effect. Dantrolene acts on the sarcoplasmic reticulum in skeletal muscle. Glu, glutamatergic neuron.



Thank you