

Skeletal Muscle Relaxants

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In this article, we will study the important pharmacological aspects of skeletal muscle relaxants such as classification, pharmacokinetics, mechanism of action, clinical uses, drug interactions, adverse effects, and toxicity.



Definitions

Skeletal muscle relaxants: drugs indicated during surgery/intubation to induce muscle relaxation/paralysis and for painful conditions due to muscle spasticity.

Depolarizing relaxants: relaxation of muscles achieved by persistent depolarization of the receptors at the end plate of skeletal muscle fibers (**succinylcholine**).

Non-depolarizing relaxants: relaxation of muscles achieved by antagonistic action on the nicotinic receptors at the end plate of skeletal muscle fibers (**rocuronium**).

Spasmolytics: relieve the painful conditions that arouse due to muscle contractions (**dantrolene**).

Classification of Skeletal Muscle Relaxants

Neuromuscular Blockers		Spasmolytics	
Depolarizing	Non-depolarizing	Acute use	Chronic Use

Succinylcholine	Short-acting <ul style="list-style-type: none"> • Rocuronium Intermediate-acting <ul style="list-style-type: none"> • Pancuronium • Pipecuronium Long-acting <ul style="list-style-type: none"> • Tubocurarine 	Cyclobenzaprine	Actions via CNS <ul style="list-style-type: none"> • Baclofen • Diazepam • Tizanidine Actions at muscle <ul style="list-style-type: none"> • Dantrolene
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Mechanism of Action of Skeletal Muscle Relaxants

In order to understand the mechanism of action of **skeletal muscle relaxants**, it is important to first understand how the skeletal muscle contracts.

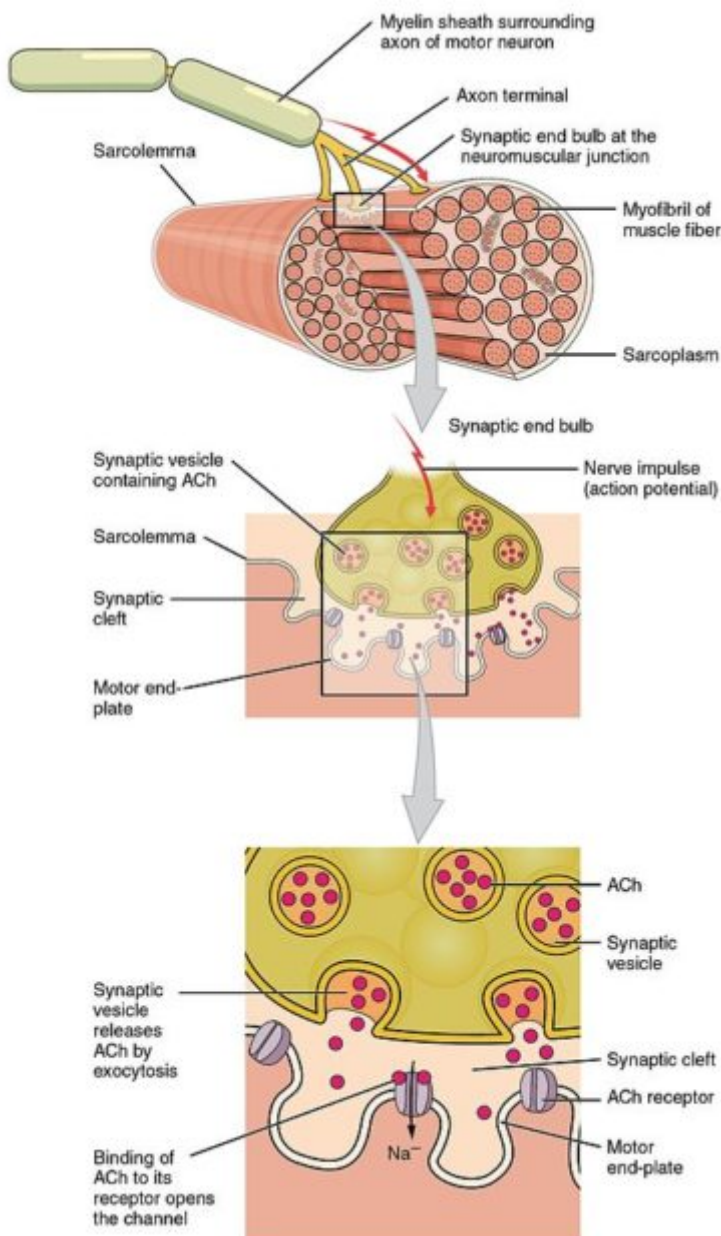


Image: "Motor end plate and Innervation" by OpenStax - <https://cnx.org/contents/FPtK1zmh@8.25:fEI3C8Ot@10/Preface>. License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Muscle contraction is mediated by signals from the **motor axons** of the nervous system. At the neuromuscular junction, **acetylcholine** is released from presynaptic terminal and binds to the **nicotinic receptors** on the motor end plate to generate an **end-plate potential (EPP)**.

Important: end-plate potential (EPP) is produced due to the influx of Na^+ ions.

The end-plate potential initiates the process of muscle contraction by depolarization of muscle fibers.

Always remember: Muscle relaxants act at the **motor neuron end plate** (please see the illustration).

Muscle relaxation can be medically induced by blocking the transmission at the level of the end plate. It is used during **surgery, intubation** and **mechanical ventilation**. Drugs used for this purpose are **amines** and are similar in structure to **ACh** in order to interact with nicotinic receptors. There are of two types: **non-depolarizing and depolarizing**.

Non-depolarizing neuromuscular blockers are **antagonists** of nicotinic receptors and **do not** cause depolarization of the skeletal muscle. These drugs are also called **competitive blockers** because they compete with ACh for binding at neuromuscular junctions.

A typical member of this group of the neuromuscular blocking agent is **tubocurarine**. The action of these drugs can be surpassed with agents that have a higher affinity for nicotinic receptors or by increasing the levels of **agonists (ACh)** at the end plate (by the usage of **cholinesterase inhibitors**).

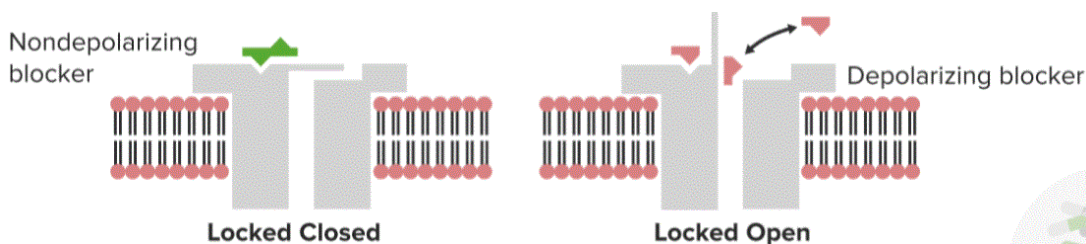
Depolarizing neuromuscular blockers are **agonists of the nicotinic receptors**. There is only one drug used clinically for the purpose of muscle relaxation that acts through depolarization of skeletal muscle – **succinylcholine**. It causes persistent depolarization of the muscle.

After the muscle is depolarized, contraction is impossible. Because of the initial depolarization, **fasciculations** can be seen at the beginning of succinylcholine administration.

The process of depolarization by succinylcholine occurs in two phases:

Phase 1 starts with the opening of **sodium channels** attached with the nicotinic receptors resulting in depolarization of receptor. This causes transient twitching of the muscle.

Phase 2 includes continuous binding of the depolarizing agent to the receptor, which makes it incapable of transmitting impulses. When this continues, gradual repolarization of the **sodium channel** takes place thus blocking it and resulting in resistance to depolarization and flaccid paralysis.



“Action of Skeletal Muscle Relaxants” Image created by Lecturio

Muscle relaxation can be induced by agents called **spasmolytics**, which act on the central nervous system. Spasmolytics made for chronic use (baclofen, diazepam, and

tizanidine) are active in the [spinal cord](#) and they work at the level of primary spinal motor neuron.

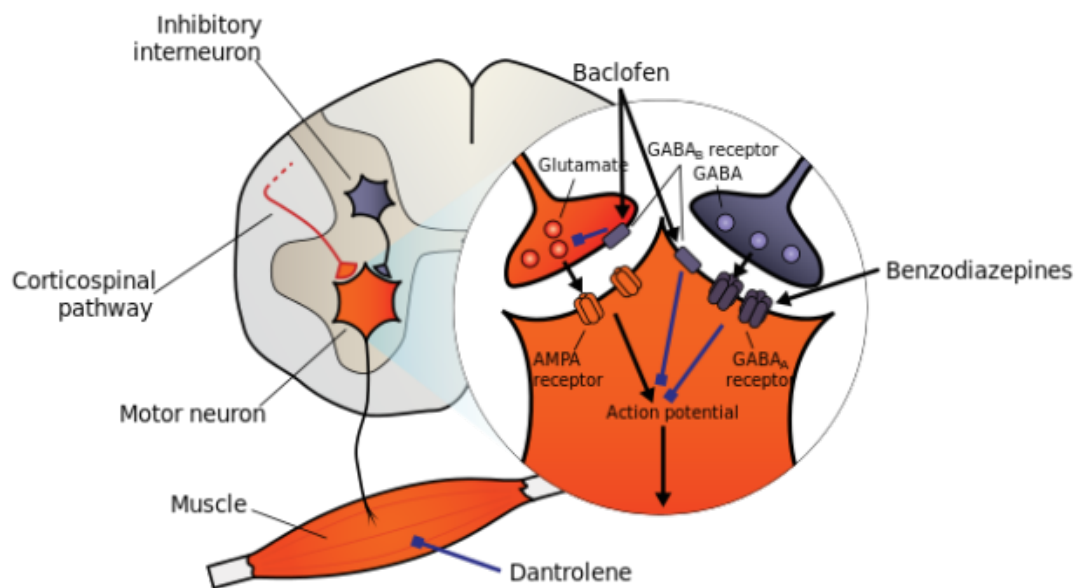


Image: "The action of muscle relaxants, spasmolytics etc. Black lines ending in arrow heads represent chemicals or actions that enhance the target of the lines. Blue lines ending in squares represent chemicals or actions that inhibit the target of the line." by Bill Connolly - Own work. License: [CC BY-SA 3.0](#)

Baclofen is **GABA_B agonist** and it causes hyperpolarization of the membrane.

Diazepam interacts with **GABA_A receptors** and facilitates inhibition.

Tizanidine has α_2 agonist function. It is indicated in spasticity caused by neurological disorders such as [multiple sclerosis](#) and **spinal cord injury**.

Dantrolene acts on the **ryanodine receptor (RyR1) channel**. Dantrolene is relatively selective for skeletal muscle as **cardiac and smooth muscles** are almost unaffected by this drug. It is also used in the treatment of **malignant hyperthermia** - a state caused by a sudden and massive release of calcium from skeletal muscle. This disorder is extremely rare but usually caused by general anesthesia. It is administered via IV route (1 mg/kg repeated as required).

Agents used for acute muscle relaxation are usually administered when a muscle is injured. **Cyclobenzaprime** is a prototype of this group. The mechanism of action of this drug is not fully understood, but it is believed that it **disturbs the maintenance of skeletal muscle tone**. It can be administered orally.

Pharmacology of Neuromuscular Blocking Agents

Non-depolarizing neuromuscular blocking agents are always given **parenterally**. Their polarity insures they do not cross the **blood-brain barrier**. This is why they have to be used after the administration of **sedatives** in general anesthesia protocols.

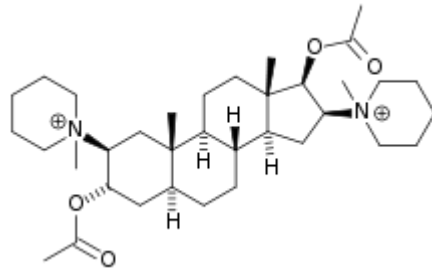


Image: "Structural formula of pancuronium" by Ayacop. License: [Public Domain](#)

They can be metabolized by **plasma cholinesterase**, in [liver](#) or [kidney](#). Typically, those eliminated by kidneys have the longest effect on muscles. Examples of these drugs are **metocurine, pancuronium, pipecuronium, and tubocurarine**. Their effect usually lasts for less than 35 minutes.

Mivacurium is metabolized by plasma cholinesterase, which ensures a shorter period of action (10-20 min). As patients with [renal failure](#) have lower levels of plasma cholinesterase, this drug will be active for longer periods of time in these patients.

Vecuronium (half life of 3.3-9 min) is mostly excreted from the body through the bile/feces. It has a shorter duration of action (20-35 min). It is a drug of choice for patients with **cardiovascular diseases**.

Atracurium has dual metabolism (via kidney and liver). It is metabolized in the liver, but it also breaks down spontaneously, forming several different products. One of these metabolites is **laudanosine** (crosses BBB) and is known to cause seizures. For this reason, **cisatracurium** (a cis-isomer of atracurium) is used more often, as its breakdown produces less amount of laudanosine. Both of these are drugs of choice for patients with renal or hepatic impairments.

Of **depolarizing neuromuscular blocking agents**, the only agent that is used clinically is **succinylcholine**. This drug is metabolized both in plasma and in the liver. Injection of succinylcholine IV results in redistribution of the drug and **hydrolysis by pseudochoolinesterase** in liver and plasmas resulting in a short duration of action. The continuous infusion will produce a longer duration of action. It is the **most commonly used muscle relaxant** during endotracheal intubation.

Important: off-label use of **succinylcholine** is to reduce the intensity of muscle contractions of **electroconvulsive therapy (ECT)**.

Succinylcholine can interact with inhaled anesthetics and cause **malignant hyperthermia**. **Contraction of jaw muscles** is the first sign seen in this condition.

Pharmacology of Spasmolytics

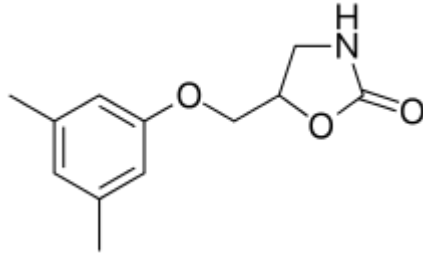


Image: "Structural diagram of metaxalone" by Fvasconcellos - Own work. License: [Public Domain](#)

Spasmolytics for acute use

Prototype drug for this group is **cyclobenzaprine**. It is administered orally and has both **sedative and antimuscarinic** mechanism of action. Other drugs used in the relaxation of muscle spasm caused by muscle injury are **metaxalone**, **methocarbamol**, and **orphenadrine**. If spasm is caused by disorders such as cerebral palsy or injury of the motoneuron, none of these medications will be effective in the treatment.

Spasmolytics for chronic use

These agents are not similar to **ACh both** in structure and in the effect. Members of this group have different mechanisms of action and are suitable for the treatment of chronic conditions that cause excessive **muscle tonus**.

Important: some of the muscle relaxants are also used in the management of back pain mostly in combination with **NSAIDs**.

Diazepam is a member of the benzodiazepine family; **baclofen** is a GABA agonist, **tizanidine** is a similar agent to clonidine, and **dantrolene** is the only agent in this group that **acts peripherally** (a **direct-acting** muscle relaxant). These drugs can be given orally.

Baclofen can also be given **intrathecally**. **Botulinum toxin** can also be used if severe spasm is causing pain or reduces function (contractions of **orbicularis oculi**). Drugs like **gabapentin** and **pregabalin**, usually used as antiseizure medications, have been shown to be effective in patients suffering from **multiple sclerosis**.

Adverse Effects and Toxicity of Skeletal Muscle Relaxants

Neuromuscular blocking agents

Neuromuscular blocking agents are administered to cause **skeletal muscle paralysis/relaxation** and make **surgical procedures/intubation** possible.

A common side effect of **succinylcholine** is muscle pain because it works by tiring out/depolarizing muscles; the pain can vary from mild pain to serious muscle damage.

During muscle contraction at the beginning of succinylcholine administration, **regurgitation** leading to **asphyxiation** is possible. Succinylcholine may also cause **hyperkalemia**.

Other side-effects of succinylcholine:

Excessive salivation, hypertension, tachycardia, bradycardia, ventricular arrhythmias and **cardiac arrest** (due to profound hyperkalemia).

The action of muscle relaxant is potentiated by **inhaled anesthetics**. **Isoflurane** is especially known for this interaction. Specific interaction of succinylcholine is **malignant hyperthermia**. **Trismus** in any patient undergoing general anesthesia should be an alarming sign, as it can be the first sign of development of **malignant hyperthermia**.

Patients with **myasthenia gravis** and older patients are more responsive to neuromuscular blocking agents, and **burn victims** and patients with **upper motor neuron damage** are less responsive to neuromuscular blockade.

Non-depolarizing muscle relaxants such as **tubocurarine** and **mivacurium** cause histamine release. Side-effects are mostly related to histamine release (**erythema** of neck and torso) and mild/non-threatening in nature. **Anaphylactic reactions** are rare with muscle relaxants.

Pancuronium, alcuronium, and rocuronium have **direct vagolytic actions**.

Adverse Effects of Spasmolytics

Spasmolytic	Effect
Diazepam	Sedation, hypotension, ataxia, respiratory depression
Baclofen	Drowsiness, slurred speech, hypotension, constipation, urinary retention
Tizanidine	Asthenia, drowsiness, hypotension, dry mouth
Dantrolene	Drowsiness, dizziness, weakness, general malaise, fatigue, diarrhea
Cyclobenzaprine	Drowsiness, dizziness, headache, dry mouth

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[Treatment of acute low back pain](#) via uptodate.com

[Use of neuromuscular blocking medications in critically ill patients](#) via uptodate.com

[Dantrium](#) via fda.gov

[Cyclobenzaprine \(Rx\)](#) via medscape.com

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