Neuromuscular Physiology

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Skeletal muscle: Motor unit

A typical skeletal muscle receives innervation from ~100 somatic motor neurons.

The whole assembly of muscle fibers innervated by the axon from one motor neuron is called a motor unit.

When that axon fires, all of those myofibers (with one each motor end plate) are going to fire simultaneously and maximally.

The amount of **force generated in an anatomic muscle is dependent on how many motor units in it are "recruited" into use** (hundreds/thousands of motor units in any given muscle).

Not all of them are "in use" at any given time; if the task requires little force, only a few may be "recruited" by the brain, and as these fatigue, they are **shifted smoothly out of service and new motor units switched into use**, to maintain the **steady level of contraction** that muscle has to have.
Motor neuron axon – skeletal muscle synapse: Neuromuscular junction / motor end plate

- motor neuron (spinal cord) → one axon → branches into axon processes near the point of contact with the target muscle
- **one axon process** innervate a **separate muscular fiber** through **terminal arborizations**, a small *tree-like patch* of unmyelinated nerve processes, ending into bulb-shaped terminals called boutons; Schwann cells intimately associate with the nerve terminal to form a cap over the face of the nerve membrane
Synaptic transmission at the neuromuscular junction - motor end plate

- presynaptic boutons contain **Ach vesicles**: 6000-10000 ACh molec./vesicle = quantum → **quantum release** into the synaptic cleft.

- within a few sec. **after each AP**, "**coated pits**" appear in the presynaptic membrane, caused by **clathrin** = contractile proteins in the nerve ending; within ~ 20 sec. the proteins contract and cause the pits to break away to the interior of the membrane, thus forming new vesicles.
- bouton reloads its discharged synaptic vesicles by resynthesizing ACh and transport it into the **vesicles** through an **ACh-H⁺ exchanger**, working on a **vacuolar H⁺-pump** expense.

![Scanning electron micrograph showing termination of a single axon on a skeletal muscle cell.](image)

**AChE** = acetylcholinesterase, in the synaptic cleft
- synaptic cleft: ~50 nm wide, filled with a meshwork of proteins and proteoglycans that are part of the extracellular matrix.

- muscle basement membrane with a synaptic basal lamina:
  - contains proteins (e.g., collagen, laminin, agrin) that mediate adhesion of the neuromuscular junction and play important roles in synapse development and regeneration.
  - contains a high concentration of acetylcholinesterase (AChE), which ultimately terminates synaptic transmission by rapidly hydrolyzing free ACh to choline and acetate.

- the postsynaptic membrane of the skeletal muscle fiber lying directly under the nerve terminal is characterized by extensive invaginations / infoldings = postjunctional folds (increase surface area of postsynaptic muscle plasma membrane)
- postsynaptic nicotinic AChRs (ionotrophic) \( \rightarrow \) end-plate potential (EPP) = excitatory postsynaptic potential (EPSP).
Neuromuscular Junction: Nerve – Muscle Synapse

Collagen, laminin, agrin

AchE (~6,000 – 10,000 Ach molec.)
Neuromuscular Junction

AP spreads over the presynaptic terminal → voltage-gated Ca channels open → calcium influx → ACh vesicles draw to the presynaptic membrane → vesicles fuse with the presynaptic membrane and empty Ach into the synaptic space by the process of exocytosis.

Ach is removed rapidly (few msec) by:
1. *acetylcholinesterase*, attached mainly to the spongy layer of fine connective tissue in the synaptic space
2. diffusion out of the synaptic space (a smaller amount)

*ACh nicotinic receptors* in the muscle fiber membrane are ion channels, with a diameter ~0.65 nm → allow positive ions (Na⁺, K⁺) to move easily. Cl⁻ repelled by the negative charge of the channel pore

Na⁺ influx creates a local positive potential change of 50-75 mV inside the muscle fiber membrane = *end plate potential (EPP)*, that initiates a regenerating AP that spreads along the muscle membrane and causes muscle contraction.
End plate potentials (EPPs)

Curara, a drug that blocks the gating of ACh on the nicotinic receptors by competing for the ACh receptor sites.

Botulinum toxins are bacterial poisons that decrease the quantity of ACh release by the nerve terminals by blocking the fusion of synaptic vesicles.

A, Weakened end plate potential recorded in a curarized muscle, too weak to elicit an AP

B, Normal end plate potential eliciting a muscle action potential.

C, Weakened end plate potential caused by botulinum toxin that decreases end plate release of acetylcholine, again too weak to elicit a muscle action potential.
Excess capacity of a neuromuscular junction

$>10^4$ available vesicles, together with the ability to synthesize ACh and to package it into new vesicles, allows the neuromuscular junction to maintain a high rate of successful transmission without significant loss of function as a result of presynaptic depletion of vesicles or ACh.

Safety factor for transmission at the neuromuscular junction.

**Fatigue of the junction**

- one impulse at the neuromuscular junction causes about 3x as much EPP as that required to stimulate the muscle fiber $\rightarrow$ **safety factor** of the neuromuscular junction

- stimulation of the nerve fiber at rates $>100$ times / sec. for several minutes often diminishes the number of ACh vesicles so much that impulses fail to pass into the muscle fiber $\rightarrow$ **fatigue** of the neuromuscular junction at the most exhausting levels of muscle activity

-under normal functioning conditions, fatigue of the neuromuscular junction occurs rarely
Acetylcholine receptor of skeletal muscle is the best studied transmitter-gated ion channel of the chemical synapse

- ionotropic ligand-gated channel
- classified as a nonselective cation channel (as it is permeable not just to Na+, but also to Ca2+, K+, Cs+, Li+)
- its opening leads to a large influx of Na+ $\rightarrow$ membrane depolarization $\rightarrow$ muscle contraction
Each subunit of an ACh receptor is composed of 4 transmembrane regions, M1, M2, M3, M4, with extramembrane sequences above and below.
Three conformations of the acetylcholine receptor

Binding of 2 ACh molecules opens the ligand-gated Na channel.

Channel remains open until the ACh is hydrolyzed. Alternatively, if ACh is not hydrolyzed within 1 msec., the channel inactivates (desensitizes) i.e. it closes despite the presence of ACh.
Synaptic modulation at the neuromuscular junction

Synaptic facilitation
- short-lived enhancement of the EPP in response to a brief increase in the frequency of nerve stimulation
- transient increase in the mean number of quanta per nerve stimulus

Synaptic potentiation (or post-tetanic potentiation)
- long-lived and pronounced increase in transmitter release that occurs after a long period of high-frequency nerve stimulation;
- can last for minutes after the conditioning stimulus;
- may be caused by a period of intense nerve firing, which increases [Ca2+]i in the presynaptic terminal and thus increases the probability of exocytosis.

Synaptic depression
- transient decrease in the efficiency of transmitter release → a reduction in the EPP in response to a period of frequent nerve stimulation.
- may result from temporary depletion of transmitter-loaded vesicles from the presynaptic terminal - a reduction in the number of available quanta.
Many of the proteins that are involved in synaptic transmission at the mammalian neuromuscular junction are the targets of naturally occurring or synthetic drugs. The antagonists are shown as minus signs highlighted in red. The agonists are shown as plus signs highlighted in green.
Drugs that enhance or block transmission at the neuromuscular junction

Drugs that stimulate the muscle fiber by ACETYLCHOLINE-LIKE ACTION.
- methacholine, carbachol, and nicotine - these Ach agonists are not destroyed by cholinesterase or are destroyed so slowly that their action often persists for many minutes to several hours.
- they cause localized areas of depolarization of motor end plate → every time the muscle fiber recovers from a previous contraction, these depolarized areas, by virtue of leaking ions, initiate a new AP → muscle spasm.

Drugs that stimulate the neuromuscular junction by INACTIVATING ACETYLCHOLINESTERASE
- neostigmine, physostigmine, pyridostigmine and diisopropyl fluorophosphate → inactivate AChE → with each successive AP, additional ACh accumulates and stimulates the muscle fiber repetitively → muscle spasm caused by minimum stimulation (it also can cause death due to laryngeal spasm).
Neostigmine and physostigmine combine with AChE to reversible inactivate the AChE for up to several hours.
Pyridostigmine is used in myasthenia gravis treatment.
Diisopropyl fluorophosphate (powerful "nerve" gas poison) inactivates AChE for weeks, which makes this a particularly lethal poison.

Drugs that inhibit the postsynaptic transmission at the neuromuscular junction.
- curariform drugs can prevent passage of impulses from the nerve ending into the muscle, by competing for the ACh receptor sites. For instance, D-tubocurarine blocks the action of ACh on the muscle fiber ACh receptors, thus preventing sufficient increase in permeability of the muscle membrane channels to initiate an action potential.
Myasthenia gravis = muscle weakness (from the Greek mys and asthenia)

-acquired autoimmune disorder in which the spontaneous production of anti-Ach receptors (AchR) antibodies results in progressive loss of muscle AChRs and degeneration of postjunctional folds. The most common target of these antibodies is a region of the AChR α subunit called MIR (main immunogenic region).

-clinical: fatigue and weakness of skeletal muscle; severe cases - paralysis of the respiratory muscles → death

-treatment:
1) reduce the potency of the immunological attack (immunosuppressants - corticosteroids or plasmapheresis - removal of antibodies from the patient's serum)

2) enhance cholinergic activity within the synapse: AChE inhibitors - pyridostigmine; dosage of these drugs must be carefully monitored to prevent overexposure of the remaining AChRs to Ach → overstimulation of the postsynaptic receptors, prolonged depolarization of the postsynaptic membrane, inactivation of neighboring Na+ channels, and thus synaptic blockade.

3) Some patients with myasthenia gravis have a thymus gland tumor → removal of the thymoma leads to clinical improvement in nearly 75% of the cases.
# NMJ vs. CNS

<table>
<thead>
<tr>
<th>NMJ</th>
<th>CNS synapses</th>
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<tbody>
<tr>
<td>one muscle fiber receives input from only one axon at most</td>
<td>cell receives input from many axons of different cells (convergence)</td>
</tr>
<tr>
<td>one motor neuron axon innervates a small number of muscle fibers</td>
<td>one cell may project to a large number of target neurons (divergence)</td>
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<tr>
<td>area of synaptic contact is huge</td>
<td>smaller area of synaptic contact</td>
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<tr>
<td>muscle fiber fires once in response to one AP in motor neuron</td>
<td>rarely AP released in postsynaptic cell consecutive to one presynaptic AP (fewer vesicles released, many other influences are operative, etc.)</td>
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<tr>
<td>transmitter is excitatory at NMJ (striated mammalian muscle fibers)</td>
<td>transmitter may be excitatory, inhibitory, or modulatory</td>
</tr>
<tr>
<td>acetylcholine (Ach) is the transmitter</td>
<td>many substances in addition to Ach serve as transmitters</td>
</tr>
<tr>
<td>Nicotinic Ach receptor is part of channel (ionotropic receptor)</td>
<td>Ionotropic or metabotropic postsynaptic receptors</td>
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The smallest contractile unit of skeletal muscle is **muscle fiber cell** or **myofiber**, a multinucleated, elongated cell. Single muscle fibers are surrounded by a sheath called the **endomysium**. Beneath the endomysium surrounding each muscle fiber is **sarcolemma**, the plasma membrane of the muscle cell.

A bundle of linearly aligned muscle fibers forms a **fascicle** enveloped by a sheath called the **perimysium**.

Bundles of fascicles form a **muscle**, covered by **epimysium** (extend towards tendons).

An individual skeletal muscle cell contains a densely arranged parallel array of cylindrical elements called **myofibrils** - an end-to-end chain of regular repeating units - or **sarcomeres** - that consist of smaller interdigitating filaments = myofilaments (actin and myosin).
Muscle Action Potential

Resting membrane potential:
  ~ -80 to -90 millivolts in skeletal fibers-the same as in large myelinated nerve fibers.

Duration of AP:
  1 to 5 msec. in skeletal muscle - about 5x longer than in large myelinated nerves.

Velocity of conduction:
  3 to 5 m/sec-about 1/13 the velocity of conduction in the large myelinated nerve fibers that excite skeletal muscle.
Spread of the Action Potential to the Interior of the Muscle Fiber by Way of "Transverse Tubules"

- The skeletal muscle fiber is so large that AP spreading along its surface membrane cause almost no current flow deep within the fiber.
- APs are transmitted along *transverse tubules* (T tubules) that penetrate all the way through the muscle fiber from one side of the fiber to the other → current penetrate deeply into the muscle fiber to the vicinity of the separate myofibrils to cause maximum muscle contraction
- The T tubule action potentials cause release of calcium ions inside the muscle fiber in the immediate vicinity of the myofibrils, and these calcium ions then cause contraction - *excitation-contraction* coupling
Mechanism of Muscle Contraction

An AP travels along a motor nerve to its endings on muscle fibers → Ach released.

Ach acts on a local area of the muscle fiber membrane to open multiple “ACh-gated” channels – Ach nicotinic receptor. → large quantities of Na+ diffuse to the interior of the muscle fiber membrane → initiates an AP at the postsynaptic membrane.

AP depolarizes the muscle membrane, and flows through the T tubes to the center of the muscle fiber → causes the sarcoplasmic reticulum (SR) to release large quantities of Ca$^{2+}$ stored within SR (Ca$^{2+}$ bound in SR by calreticulin and calsequestrin).

Ca$^{2+}$ initiate attractive forces between the actin and myosin filaments (generated by interaction of the cross-bridges from the myosin filaments with the actin filaments), causing them to slide alongside each other, which is the contractile process. Energy (ATP) is needed for the contractile process to proceed.

After a fraction of a second, Ca$^{2+}$ are pumped back into SR by a Ca$^{2+}$-membrane pump, and they remain stored until a new muscle AP comes along; this removal of Ca$^{2+}$ from the myofibrils causes the muscle contraction to cease (relaxation) and is an active process (ATP consume).
Excitation-Contraction Coupling

1. Acetylcholine (ACh) is released from the axon terminal of a motor neuron and binds to receptors in the motor end plate. This binding elicits an end-plate potential, which triggers an action potential in the muscle cell.

2. Action potential propagates along the sarcolemma and down T tubules.

3. The action potential triggers Ca\(^{2+}\) release from SR.

4. Ca\(^{2+}\) binds to troponin, exposing myosin-binding sites.

5. Crossbridge cycle begins (muscle fiber contracts).

6. Ca\(^{2+}\) is actively transported back into lumen of SR following the action potential.

7. Tropomyosin blocks myosin-binding sites (muscle fiber relaxes).
Excitation-Contraction Coupling

When an AP spreads over a muscle fiber membrane, a potential change also spreads along the T tubules to the deep interior of the muscle fiber.

A tetrad of four L-type Ca$^{2+}$ channels on the T tubules faces a single Ca$^{2+}$-release channel of the SR, so that each L-type Ca$^{2+}$ channel interacts with the foot of one of the four subunits of the Ca$^{2+}$-release channel. Half of the Ca$^{2+}$-release channels lack associations with L-type Ca$^{2+}$ channels. DHP, dihydropyridine.
Muscular contraction mechanism

Signal transmission

1. Motor neuron
2. Presynaptic terminal
3. Endplate - Nicotinic receptor $\rightarrow$ Na influx $\rightarrow$ EPP $\rightarrow$ AP

Muscle Contraction

1. AP $\rightarrow$ sarcolemma $\rightarrow$ T tubules intimately associated with SR (TRIAD)
2. T tubules $\rightarrow$ Voltage gated Ca$^{2+}$ channels open $\rightarrow$ TETRAD with Ca-releasing channels in SR membrane
3. SR releases Ca$^{2+}$ $\rightarrow$ Ca$^{2+}$ increase in the sarcoplasm
Muscular contraction mechanism

4. Calcium binds to troponin C
5. Tropomyosin is deflected
6. Active sites of actin exposed
7. ATP attaches to myosin head
8. ATP is hydrolyzed (ADP & P)
9. Myosin head is phosphorylated & tilts
10. Myosin head binds to actin (cross bridge)
11. Myosin head dephosphorylates (head moves) & ADP released (power stroke)
12. Muscle relaxation - Calcium pumped into SR (active mechanism)
Muscle cell must regenerate the ATP needed for muscle contraction

- each round of the cross-bridge cycle consumes ATP.
- cellular store of ATP is sufficient to allow only a few seconds of continuous maximal contraction \( \rightarrow \) muscle cell must resynthesize ATP from ADP at a rate comparable to the rate of ATP consumption
Specialized energy stores in the muscle cell:

The high-energy phosphate bond of **phosphocreatine** (its content in skeletal muscle is adequate to replenish the ATP pool several times, but it is still inadequate to sustain the energy needs of contracting muscle for more than 10 seconds):

**creatine kinase** transfers the high-energy phosphate of phosphocreatine to ADP $\rightarrow$ ATP

**Glycogen** - more abundant energy source within skeletal muscle $\rightarrow$ degradation to pyruvate is rapid and liberates energy that the cell invests in phosphorylating ADP to yield ATP (**anaerobic metabolism**). Pyruvate is further metabolized along with other foodstuffs by **oxidative metabolism**, which during the long term is the primary mechanism for the regeneration of ATP.

The rate of ATP generation by oxidative metabolism is limited by the rate of oxygen delivery to the muscle.

The pathway of muscle glycogen ensures that energy stores are sufficient to sustain muscle activity for nearly a minute even when oxygen is unavailable.
**Single muscle twitch** – an electrical excitation gives rise to a single, sudden contraction lasting for a fraction of a second.

**Phases of muscle twitch**

1. **Lag/delay Phase**
   - from AP in motor neuron

2. **Contraction Phase**
   - crossbridge -> power stroke

3. **Relaxation Phase**
   - calcium pumped into SR

4. **Mechanical signal**
   - measured as tension
Stimulus vs contraction

- all or none response
- subthreshold stimulus -> no response
- Threshold -> AP -> contraction
- increase Ca++ = increase force

Stimulus frequency

- ↑ freq of AP = ↑ freq of contractions
- tetanus
  - calcium not pumped back...

Frequency summation of skeletal muscle twitches.
Length-tension diagram for a single fully contracted sarcomere, showing maximum strength of contraction when the sarcomere is 2.0 to 2.2 µm in length.

At the upper right are the relative positions of the actin and myosin filaments at different sarcomere lengths from point A to point D.
Effect of muscle length on force of contraction in the whole intact muscle.

When the muscle is at its normal resting length, which is at a sarcomere length of about 2 µm, it contracts upon activation with the approximate maximum force of contraction. The increase in tension that occurs during contraction = active tension; it decreases as the muscle is stretched beyond its normal length - that is, to a sarcomere length > 2.2 µm.

Note that the whole muscle has a large amount of connective tissue in it; also, the sarcomeres in different parts of the muscle do not always contract the same amount.
Efficiency of muscle contraction.

The efficiency of an engine: % energy input that is converted into work instead of heat.

Low efficiency of muscle contraction: less than 25 % input energy to muscle (the chemical energy in nutrients) can be converted into work, the remainder becoming heat.

Maximum efficiency of contraction is developed when the velocity of contraction is about 30 % of maximum.
Isometric Versus Isotonic Contraction

Muscle contraction is **-isotonic** when it does shorten but the tension on the muscle remains constant throughout the contraction (the muscle shortens against a fixed load).

**-isometric** when the muscle does not shorten during contraction (the muscle contracts against a force transducer without decreasing the muscle length);
Characteristics of isometric twitches recorded from different muscles.

Durations of contraction are adapted to the functions of the respective muscles:
- **ocular movements** must be extremely rapid to maintain fixation of the eyes on specific objects to provide accuracy of vision
- **gastrocnemius muscle** must contract moderately rapidly to provide sufficient velocity of limb movement for running and jumping
- **soleus muscle** is concerned principally with slow contraction for continual, long-term support of the body against gravity.

Duration of isometric contractions for different types of skeletal muscles, showing a **latent period** between the AP (depolarization) and muscle contraction.
The muscle fibers in each motor unit are not all clustered in the muscle but overlap other motor units in microbundles of 3 to 15 fibers.

This interdigitation allows the separate motor units to contract in support of one another rather than entirely as individual segments.
Muscle contractions of different force - Force Summation.

*Summation* = adding together of individual twitch contractions to increase the intensity of overall muscle contraction.

Occurs:
1. by increasing the number of motor units contracting simultaneously, which is called *multiple fiber summation*,
2. by increasing the frequency of contraction, which is called *frequency summation* and can lead to *tetanization*.

![Diagram showing muscle contractions and summations](image-url)
Multiple Fiber Summation

When the CNS sends a weak signal to contract a muscle, the smaller motor units of the muscle may be stimulated in preference to the larger motor units.

The *size principle*: as the strength of the signal increases, larger and larger motor units begin to be excited as well (with the largest motor units - 50 times the contractile force of the smallest units)
→ allows the gradations of muscle force during weak contraction to occur in small steps, whereas the steps become progressively greater when large amounts of force are required.
The cause of this size principle is that the smaller motor units are driven by small motor nerve fibers, and the *small motoneurons in the spinal cord are more excitable than the larger ones*, so naturally they are excited first.

The different motor units are driven *asynchronously* by the spinal cord, so contraction alternates among motor units one after the other, thus providing *smooth contraction* even at low frequencies of nerve signals.
Frequency Summation and Tetanization

-as the frequency increases, there comes a point where each new contraction occurs before the preceding one is over → one contraction is added partially to the previous one, so the total strength of contraction rises progressively with increasing frequency.

-when the frequency reaches a critical level, the successive contractions eventually become so rapid that they fuse together and the whole muscle contraction appears to be completely smooth and continuous = tetanization.

At a slightly higher frequency, the strength of contraction reaches its maximum, so any additional increase in frequency beyond that point has no further effect in increasing contractile force (calcium ions are maintained in the muscle sarcoplasm, even between APs, so that full contractile state is sustained without allowing any relaxation between APs).
Maximum Strength of Contraction.

The maximum strength of tetanic contraction of a muscle operating at a normal muscle length averages between 3 and 4 kilograms per square centimeter of muscle, or 50 pounds per square inch. Because a quadriceps muscle can have up to 16 square inches of muscle belly, as much as 800 pounds of tension may be applied to the patellar tendon. Thus, one can readily understand how it is possible for muscles to pull their tendons out of their insertions in bone.

Changes in Muscle Strength at the Onset of Contraction—The Staircase Effect (Treppe).

When a muscle begins to contract after a long period of rest, its initial strength of contraction may be as little as one-half its strength 10 to 50 muscle twitches later. That is, the strength of contraction increases to a plateau, a phenomenon called the staircase effect, or treppe.

Although all the possible causes of the staircase effect are not known, it is believed to be caused primarily by increasing calcium ions in the cytosol because of the release of more and more ions from the sarcoplasmic reticulum with each successive muscle action potential and failure of the sarcoplasm to recapture the ions immediately.
Fast Versus Slow Muscle Fibers

Muscles that react rapidly (e.g. anterior tibialis) are composed mainly of “fast” fibers with only small numbers of the slow variety. Conversely, muscles such as soleus that respond slowly but with prolonged contraction are composed mainly of “slow” fibers (red fibers). Slow- and fast-twitch fibers represent the extremes of a continuum of muscle fiber characteristics, each whole muscle is composed of fibers of each twitch type.
Slow Fibers (Type 1, Red muscle)

- Smaller fibers.
- Also innervated by smaller nerve fibers.
- More extensive blood vessel system and capillaries to supply extra amounts of oxygen.
- Greatly increased no. of mitochondria to support high levels of oxidative metabolism
- Fibers contain large amounts of myoglobin, an iron-containing protein similar to hemoglobin in red blood cells. Myoglobin combines with oxygen and stores it until needed; this also greatly speeds oxygen transport to the mitochondria. The myoglobin gives the slow muscle a reddish appearance and the name red muscle.
- Oxidative metabolism is slow but efficient, making these fibers resistant to fatigue.

Fast Fibers (Type II, White muscle)

- Large fibers for great strength of contraction.
- Extensive sarcoplasmic reticulum for rapid release of calcium ions to initiate contraction.
- Large amounts of glycolytic enzymes for rapid release of energy by the glycolytic process (up to lactate) \( \rightarrow \) more easily fatigable.
- Less extensive blood supply because oxidative metabolism is of secondary importance.
- Fewer mitochondria, also because oxidative metabolism is secondary.
  A deficit of red myoglobin in fast muscle gives it the name white muscle.
Fatigued muscle produces less force and has a reduced velocity of shortening.

Muscle fatigue - inability to maintain a desired power output - resulting from muscle contraction against a load - with a decline in both force and velocity of shortening that results from:
- reduction in the number of active cross-bridges
- reduction of the force produced per cross-bridge.

As fatigue develops, the production of force usually declines earlier and to a greater extent than shortening velocity.

Other characteristics of fatigued skeletal muscle are lower rates of both force production and relaxation, owing to impaired release and reuptake of Ca\(^{2+}\) from the sarcoplasmic reticulum (SR). As a result, fast movements become difficult or impossible, and athletic performance suffers accordingly.

Fatigue may serve an important protective role in allowing contractions at reduced rates and lower forces while preventing extreme changes in cell composition that could cause damage.

Muscle fatigue is reversible with rest, which contrasts with muscle damage or weakness, in which even muscles that are well rested are compromised in their ability to develop force.
Factors contributing to fatigue

Changes in the CNS produce central fatigue: altered input from muscle sensory nerve fibers, reduced excitatory input to motor control centers of the brain and spinal cord, and altered excitability of α and γ motor neurons.

Impaired excitability and impaired Ca$^{2+}$ release can produce peripheral fatigue. Fatigue can result from ATP depletion, lactic acid accumulation, and glycogen depletion.
• **Integrating sensory information** at all levels of the nervous system causes appropriate **motor responses**

• **Special neuronal circuits of the spinal cord** make possible any purposeful muscle movement (e.g. the circuits for the walking movements are in the spinal cord, and the brain simply sends *command* signals to the spinal cord to set into motion the walking process).

• The spinal cord gray matter is the integrative area for the **spinal cord reflexes**.

• Peripheral sensory fibers and corticospinal fibers are connected with the interneurons and anterior motor neurons of the spinal cord.
**Stretch reflex**

*Monosynaptic pathway* that allows a reflex signal to return with the shortest possible time delay back to the muscle after excitation of the spindle.
1 - **sensory transducer** in the periphery (a Pacinian corpuscle or other tactile sensor in the skin).

2 - the pseudounipolar **sensory neuron** in the circuit, with the soma located in a **craniospinal ganglion** (a dorsal root ganglion, or a cranial nerve).

3 - an **interconnector neuron**, whose soma is found in the CNS.

4 - **motor neuron** whose soma is in the ventral horn of the spinal cord send an axon to the muscle effector and terminates at a motor end plate on a myofiber to initiate contraction.

5 - the **effector organ** will always be skeletal muscle in the case of somatic reflex arc.

This loop is **completely independent**; it's not necessary to have CNS involvement beyond the "relay" at the interconnector neuron.
**Flexor Reflex and the Withdrawal Reflexes**

*Flexor reflex /nociceptive or pain reflex.*
- any type of cutaneous sensory stimulus from a limb is likely to cause the flexor muscles of the limb to contract, thereby withdrawing the limb from the stimulating object.
- elicited most powerfully by stimulation of pain endings, such as by a pinprick, heat, or a wound.

- Stimulus $\rightarrow$ interneuron pool $\rightarrow$ info to motor neuron through:
  1. diverging circuits to spread the reflex to the necessary muscles for withdrawal OR 2. circuits to inhibit the antagonist muscles (*reciprocal inhibition circuits*), and 3. circuits to cause *afterdischarge* that hold the irritated part away from the stimulus for 0.1 - 3 seconds after!ir5the!irradiation is over (depends on stimulus intensity).

Flexor reflex, crossed extensor reflex, and reciprocal inhibition
Peripheral sensory fibers:
- continuous feedback of sensory information from each muscle to the spinal cord, indicating the functional status of each muscle at each instant (length, instantaneous tension, change in its length or tension)

-muscle sensory receptors:
  (1) *muscle spindles* distributed throughout the belly of the muscle, inform about muscle length or rate of change of length; they emit sensory nerve impulses continuously: stretching muscle spindles increases the rate of firing (positive signals) – stretch reflex, whereas shortening the spindle decreases the rate of firing (negative signals for unstretched muscles).

  (2) *Golgi tendon organs* located in the muscle tendons, transmit information about tendon tension or rate of change of tension; stimulated by increased tension in the connecting muscle → signals transmitted to the spinal cord → one inhibitory interneuron that inhibits the anterior motor neuron → inhibitory reflex of the respective muscle (negative feedback mechanism to prevent development of too much tension on the muscle).
Anterior Motor Neurons:

- several thousand neurons, 50 -100 % larger than most of the others, located in the spinal cord anterior horns
- their axons leave the cord by way of the anterior roots and directly innervate the skeletal muscle fibers.
- are of two types:
  - alpha motor neurons → large type A alpha (Aα) motor nerve fibers (14 μm in diameter) → branch many times after they enter the muscle and innervate one motor unit in the large skeletal muscle fibers.
  - gamma motor neurons → smaller, less numerous then alfa (50%) → smaller type A gamma (Aγ) motor nerve fibers (5 μm in diameter) → intrafusal fibers in the middle of the muscle spindle, helps control basic muscle "tone"
Interneurons:
- present in all areas of the cord gray matter-in the dorsal, anterior horns, and intermediate areas between them.
- are about 30x as numerous as the anterior motor neurons.
- small and highly excitable, often exhibiting spontaneous activity and capable of firing as rapidly as 1500 times /second.
- they have many interconnections with one another, and many of them also synapse directly with the anterior motor neurons.
- the interconnections among the interneurons and anterior motor neurons are responsible for most of the integrative functions of the spinal cord neuronal circuits (diverging, converging, repetitive-discharge)

- only a few incoming sensory signals from the spinal nerves or signals from the brain terminate directly on the anterior motor neurons. Instead, almost all these signals are transmitted first through interneurons, where they are appropriately processed.
- the corticospinal tract from the brain terminates almost entirely on spinal interneurons, where the signals from this tract are combined with signals from other spinal tracts or spinal nerves before finally converging on the anterior motor neurons to control muscle function.
Renshaw cell inhibitory system

**Recurrent inhibition**: the output of a neuron, neuron A, conducts along its axon and out one axon collateral to excite an *interneuron that inhibits another neuron* of the same type as neuron A, in this case neuron B.

The inhibitory interneuron receives collateral branches from the proximal part of the motor neuron axon → transmit inhibitory signals to the surrounding motor neurons → stimulation of each motor neuron tends to inhibit adjacent motor neurons = *lateral inhibition* → allow signals transmission focused in the desired direction, while suppressing the tendency for signals to spread laterally.

Renshaw cells utilize the neurotransmitter **glycine** as an inhibitory substance that synapses on the alpha motor neurons.

- *Strychnine* specifically acts on these cell's ability to control alpha motor neuron firing by binding to the glycine receptors on the motor neuron. This antagonistic poison will predispose someone to tetanic contractions, and can prove fatal if the diaphragm is involved.
- Toxin of *Clostridium tetani*, a spore-forming anaerobic bacterium that lives in the soil, travels to the spinal cord where it inhibits the release of glycine from Renshaw cells → alpha motor neurons become hyperactive, and muscles constantly contract.