General Mechanism of Cardiac Muscle Contraction

Cardiac muscle contraction occurs via excitation-contraction coupling (ECC), utilizing a mechanism called calcium-induced calcium release (CICR). ECC is the process of converting an electrical stimulus (AP) into a mechanism response (muscle contraction). CICR involves the conduction of Ca ions into the cardiomyocyte, leading to the further release of ions into the cytoplasm. Ca prolongs the period of cardiac muscle cell depolarization before repolarization begins. Contraction of cardiac muscle occurs due to the binding of the myosin head to ATP, which pulls actin filaments to the center of the sarcomere, the mechanical force of contraction.

Cardiac muscle contraction initiation and execution occur in the following steps.

1. An AP, induced by the pacemaker cells in the sinoatrial (SA) and atrioventricular (AV) nodes, is conducted to contractile cardiomyocytes through gap junctions.
2. As the AP travels between sarcomeres, it activates the Ca channels in the T tubules, leading to an influx of Ca ions into the cardiomyocyte.
3. Ca in the cytoplasm then binds to cardiac troponin C, which moves the troponin complex away from the actin-binding site. Removal of the troponin complex frees actin, which becomes bound by myosin and initiates contraction.
4. Intracellular Ca is then removed by the SR, dropping the concentration of intracellular Ca. This decrease in intracellular Ca concentration returns the troponin complex to its inhibiting position on the active site of actin, ending contraction as the actin filaments return to their initial position, relaxing the muscle.

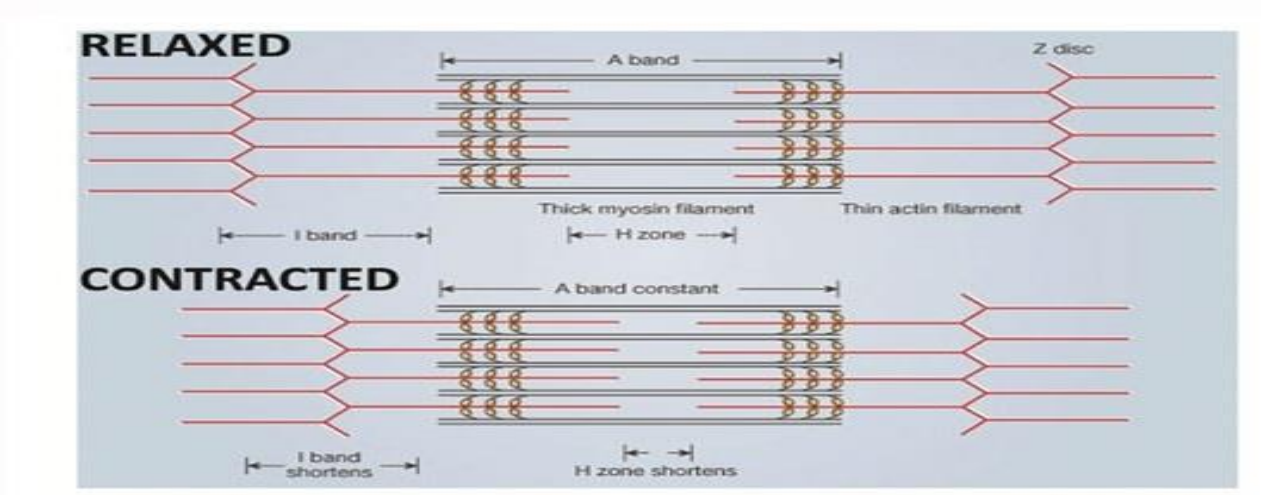
General Mechanism of Smooth Muscle Contraction

The contraction of smooth muscle is not regulated by the binding of Ca to the troponin complex, as is seen in cardiac and skeletal muscle contraction. Smooth muscle instead utilizes calmodulin, an intracellular second messenger which binds calcium.

Smooth muscle contraction initiation and execution occur in the following steps.

1. Intracellular Ca concentration increases when calcium enters the cell and is released from the SR.
2. Calcium binds to calmodulin.
3. Ca-calmodulin activates myosin light chain kinase (MLCK).

4. MLCK phosphorylates myosin head light chains and increases myosin ATPase activity.
5. Active myosin cross-bridges slide along actin and create muscle tension.
6. Smooth muscle relaxation occurs as free Ca in the cytosol decreases when Ca is pumped out of the cell or back into the SR.
7. Ca unbinds from calmodulin.
8. Myosin phosphatase removes phosphate from myosin, decreasing myosin ATPase activity and muscle tension.



Neuromuscular junction

neuromuscular junction, also called **myoneural junction**, site of chemical communication between a nerve fibre and a muscle cell. The neuromuscular junction is analogous to the synapse between two neurons. A nerve fibre divides into many terminal branches; each terminal ends on a region of muscle fibre called the end plate. Embedded in the end plate are thousands of receptors, which are long protein molecules that form channels through the membrane. Upon stimulation by a nerve impulse, the terminal releases the chemical neurotransmitter acetylcholine from synaptic vesicles. Acetylcholine then binds to the receptors, the channels open, and sodium ions flow into the end plate. This initiates the end-plate potential, the electrical event that leads to contraction of the muscle fibre.

1. The neuromuscular junction is a highly specialized synapse formed between a motor neuron and a muscle fiber.
2. These junctions convert the electrical impulses generated by the motor neuron into electrical activity in the muscle fibers.

3. Once the action potential enters a motor neuron, calcium enters the presynaptic terminal to stimulate the release of the neurotransmitters.
4. The neurotransmitters then cross the synaptic cleft and bind to their specific receptors present on the surface of the muscle fiber.
5. This initiates the muscle action potential that results in the muscle contraction or relaxation.

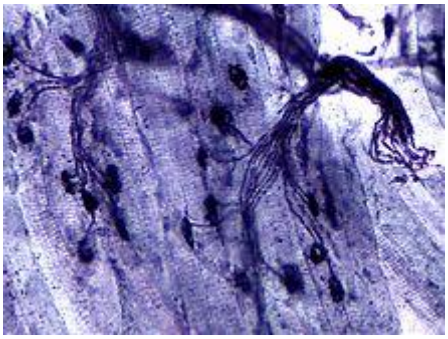
A **neuromuscular junction** (or **myoneural junction**) is a chemical synapse between a motor neuron and a muscle fiber.[1]

It allows the motor neuron to transmit a signal to the muscle fiber, causing muscle contraction.

Muscles require innervation to function—and even just to maintain muscle tone, avoiding atrophy. In the **neuromuscular system** nerves from the central nervous system and the peripheral nervous system are linked and work together with muscles.[2] Synaptic transmission at the neuromuscular junction begins when an action potential reaches the presynaptic terminal of a motor neuron, which activates voltage-gated calcium channels to allow calcium ions to enter the neuron. Calcium ions bind to sensor proteins (synaptotagmins) on synaptic vesicles, triggering vesicle fusion with the cell membrane and subsequent neurotransmitter release from the motor neuron into the synaptic cleft. In vertebrates, motor neurons release acetylcholine (ACh), a small molecule neurotransmitter, which diffuses across the synaptic cleft and binds to nicotinic acetylcholine receptors (nAChRs) on the cell membrane of the muscle fiber, also known as the sarcolemma. nAChRs are ionotropic receptors, meaning they serve as ligand-gated ion channels. The binding of ACh to the receptor can depolarize the muscle fiber, causing a cascade that eventually results in muscle contraction.

Neuromuscular junction diseases can be of genetic and autoimmune origin. Genetic disorders, such as Congenital myasthenic syndrome, can arise from mutated structural proteins that comprise the neuromuscular junction, whereas autoimmune diseases, such as myasthenia gravis, occur when antibodies are produced against nicotinic acetylcholine receptors on the sarcolemma.

Structure and function[edit]



Motor Endplate

Quantal transmission

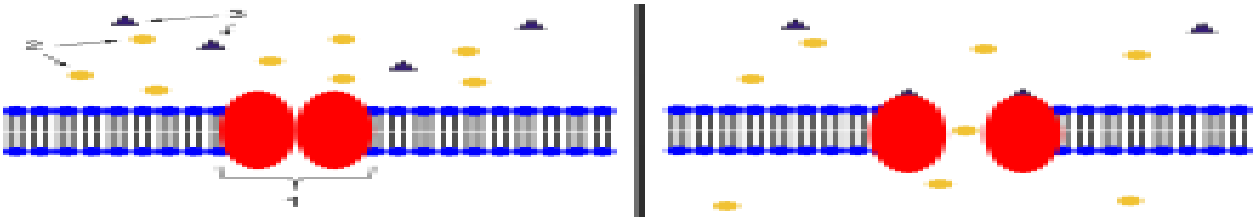
At the **neuromuscular junction** presynaptic motor axons terminate 30 nanometers from the cell membrane or sarcolemma of a muscle fiber. The sarcolemma at the junction has invaginations called postjunctional folds, which increase its surface area facing the synaptic cleft.[3] These postjunctional folds form the motor endplate, which is studded with nicotinic acetylcholine receptors (nAChRs) at a density of 10,000 receptors/micrometer^2.[4] The presynaptic axons terminate in bulges called terminal boutons (or presynaptic terminals) that project toward the postjunctional folds of the sarcolemma. In the frog each motor nerve terminal contains about 300,000 vesicles, with an average diameter of 0.05 micrometers. The vesicles contain acetylcholine. Some of these vesicles are gathered into groups of fifty, positioned at active zones close to the nerve membrane. Active zones are about 1 micrometer apart. The 30 nanometer cleft between nerve ending and endplate contains a meshwork of acetylcholinesterase (AChE) at a density of 2,600 enzyme molecules/micrometer^2, held in place by the structural proteins dystrophin and rapsyn. Also present is the receptor tyrosine kinase protein MuSK, a signaling protein involved in the development of the neuromuscular junction, which is also held in place by rapsyn.

About once every second in a resting junction randomly one of the synaptic vesicles fuses with the presynaptic neuron's cell membrane in a process mediated by SNARE proteins. Fusion results in the emptying of the vesicle's contents of 7000–10,000 acetylcholine molecules into the synaptic cleft, a process known as exocytosis.[5] Consequently, exocytosis releases acetylcholine in packets that are called quanta. The acetylcholine quantum diffuses through the acetylcholinesterase meshwork, where the high local transmitter concentration occupies all of the binding sites on the enzyme in its path. The acetylcholine that reaches the endplate activates ~2,000 acetylcholine receptors, opening their ion channels which permits sodium ions to move into the endplate producing a depolarization of ~0.5 mV known as a miniature endplate potential (MEPP). By the time the acetylcholine is released from the receptors the acetylcholinesterase has destroyed its

bound ACh, which takes about ~0.16 ms, and hence is available to destroy the ACh released from the receptors.

When the motor nerve is stimulated there is a delay of only 0.5 to 0.8 msec between the arrival of the nerve impulse in the motor nerve terminals and the first response of the endplate [6] The arrival of the motor nerve action potential at the presynaptic neuron terminal opens voltage-dependent calcium channels and Ca^{2+} ions flow from the extracellular fluid into the presynaptic neuron's cytosol. This influx of Ca^{2+} causes several hundred neurotransmitter-containing vesicles to fuse with the presynaptic neuron's cell membrane through SNARE proteins to release their acetylcholine quanta by exocytosis. The endplate depolarization by the released acetylcholine is called an endplate potential (EPP). The EPP is accomplished when ACh binds the nicotinic acetylcholine receptors (nAChR) at the motor end plate, and causes an influx of sodium ions. This influx of sodium ions generates the EPP (depolarization), and triggers an action potential that travels along the sarcolemma and into the muscle fiber via the T-tubules (transverse tubules) by means of voltage-gated sodium channels. The conduction of action potentials along the T-tubules stimulates the opening of voltage-gated Ca^{2+} channels which are mechanically coupled to Ca^{2+} release channels in the sarcoplasmic reticulum. The Ca^{2+} then diffuses out of the sarcoplasmic reticulum to the myofibrils so it can stimulate contraction. The endplate potential is thus responsible for setting up an action potential in the muscle fiber which triggers muscle contraction. The transmission from nerve to muscle is so rapid because each quantum of acetylcholine reaches the endplate in millimolar concentrations, high enough to combine with a receptor with a low affinity, which then swiftly releases the bound transmitter.

Acetylcholine receptors



1. Ion channel linked receptor
2. Ions
3. Ligand (such as acetylcholine)

When ligands bind to the receptor, the ion channel portion of the receptor opens, allowing ions to pass across the cell membrane.

Acetylcholine is a neurotransmitter synthesized from dietary choline and acetyl-CoA (ACoA), and is involved in the stimulation of muscle tissue in vertebrates as well as

in some invertebrate animals. In vertebrates, the acetylcholine receptor subtype that is found at the neuromuscular junction of skeletal muscles is the nicotinic acetylcholine receptor (nAChR), which is a ligand-gated ion channel. Each subunit of this receptor has a characteristic "cys-loop", which is composed of a cysteine residue followed by 13 amino acid residues and another cysteine residue. The two cysteine residues form a disulfide linkage which results in the "cys-loop" receptor that is capable of binding acetylcholine and other ligands. These cys-loop receptors are found only in eukaryotes, but prokaryotes possess ACh receptors with similar properties.[4] Not all species use a cholinergic neuromuscular junction; e.g. crayfish and fruit flies have a glutamatergic neuromuscular junction.[3]

AChRs at the skeletal neuromuscular junction form heteropentamers composed of two α, one β, one ε, and one δ subunits.[9] When a single ACh ligand binds to one of the α subunits of the ACh receptor it induces a conformational change at the interface with the second AChR α subunit. This conformational change results in the increased affinity of the second α subunit for a second ACh ligand. AChRs, therefore, exhibit a sigmoidal dissociation curve due to this cooperative binding.[4] The presence of the inactive, intermediate receptor structure with a single-bound ligand keeps ACh in the synapse that might otherwise be lost by cholinesterase hydrolysis or diffusion. The persistence of these ACh ligands in the synapse can cause a prolonged post-synaptic response