17.3 Control of muscle contraction

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When the action potential conducting along the nerve reaches the synapse adhered to muscle cells, the voltage-dependent Ca^{2+} channel distributed in the synaptic membrane open, allowing Ca^{2+} to flow into the synapse. This Ca^{2+} then activates the fusion of synaptic vesicles, which triggers the secretion of neurotransmitters. Acetylcholine is secreted from excitatory synapses binding to the skeletal muscle. When acetylcholine binds to the acetylcholine receptor present in the muscle cell membrane, Na^{+} flows into the muscle cell (**Figure 17-8**). As a result, the membrane potential rises, and this rise is detected by the voltage-dependent Ca^{2+} channel distributed throughout the transverse tubules. This potential is relayed to the Ca^{2+} channel present in the sarcoplasmic reticulum. Subsequently, the Ca^{2+} channel of the sarcoplasmic reticulum opens, allowing large amounts of Ca^{2+} accumulated in the sarcoplasmic reticulum to flow into the cytoplasm. The rise in the Ca^{2+} concentration serves to trigger the contraction of muscle cells (**Figure 17-9**). When the Ca^{2+} flowing into the cytoplasm is uptaken into the sarcoplasmic reticulum by its Ca^{2+} pump, the concentration inside the cytoplasm is lowered once again.

Muscle contraction dependent on Ca^{2+} concentration is controlled by tropomyosin binding to actin filaments and three types of troponin (troponin C, I, and T). Of these, troponin C is a calcium-binding protein. In the normal state, the Ca^{2+} concentration in the cytoplasm is maintained at low levels below 1×10^{-7} M. As Ca^{2+} will not bind to troponin C in this state, the myosin binding site present in actin will be covered by regulatory proteins. For this reason, the myosin head is unable to bind to the actin filament, which means that muscle contraction cannot occur. However, when Ca^{2+} flows out from the sarcoplasmic reticulum and the Ca^{2+} concentration in the cytoplasm rises to around 1×10^{-5} M, Ca^{2+} binds to troponin C and changes its structure. As a result, the myosin-binding site is exposed, allowing actin and myosin to bind, thus causing muscle contraction (**Figure 17-9B**).

This contraction motion by myosin and actin is also carried out by smooth muscles and general cells, during which Ca^{2+} also controls contraction. However, troponin is not present in these cells. Instead, the Ca^{2+}-binding protein **calmodulin** and the regulatory protein caldesmon serve to regulate muscle contraction by sensing the rise in the intracellular Ca^{2+} concentration like in the case of troponin. When calmodulin binds to Ca^{2+}, an enzyme called myosin light chain kinase is activated to phosphorylate the myosin light chain and trigger actin and myosin contraction.

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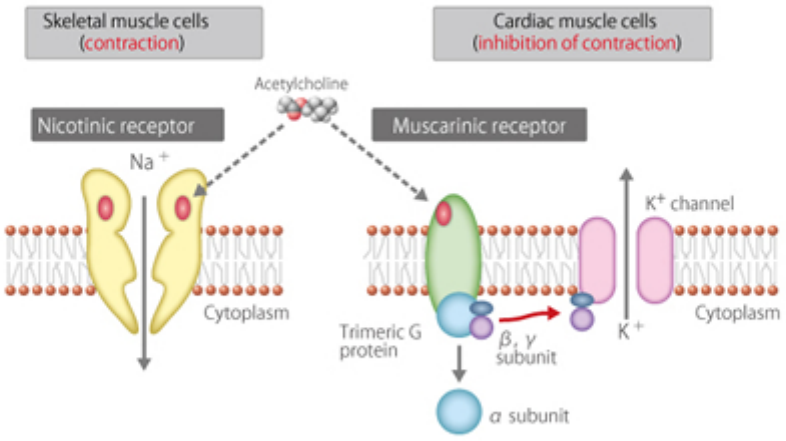
Acetylcholine receptor and its function

Acetylcholine is secreted from the synapses of nerve cells that function to trigger the contraction of skeletal muscle cells. Acetylcholine then binds to the acetylcholine receptor called the nicotinic receptor distributed in the muscle cell membrane. The nicotinic receptor is an ion channel that primarily allows Na^{+} to pass. When acetylcholine binds to this receptor, the channel opens, and Na+ ions enters the cell. As a result, the membrane potential of the muscle cell increases, causing the muscle to contract. In addition, acetylcholine is also secreted from the synapse formed between neurons regulating heartbeat and cardiac muscle cells. However, in cardiomyocytes, acetylcholine serves to inhibit muscle contraction. There are two types of acetylcholine receptors: nicotinic and muscarinic receptors (**Column Figure 17-5**). The acetylcholine receptors present in skeletal muscles are nicotinic receptors, while the acetylcholine receptors found in cardiac muscle cells are muscarinic receptors. These muscarinic receptors are made up of seven-transmembrane proteins (proteins that span the membrane seven times: see **Selection 1 of Chapter 15**) and work together with G-proteins to transmit external information into cells. When acetylcholine binds to muscarinic receptors, the K^{+} channel opens, mediated by the G-protein, and lowers the membrane potential. As a result, the muscle contraction of the heart is inhibited. The autonomic nerves that regulate heartbeat consist of parasympathetic nerves and sympathetic nerves. The former inhibits the beat of cardiac muscle cells (see **Chapter 5**), while the latter does the reverse and promotes heartbeat. Another neurotransmitter secreted from the synapse of sympathetic nerves is adrenaline. The receptor of adrenaline increases cAMP inside the cardiac muscle cell, thereby promoting heartbeat.



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Column Figure 17-5 Two types of acetylcholine receptors

The neurotransmitter acetylcholine exhibits opposite actions in skeletal muscle cells and cardiac muscle cells because the acetylcholine receptors and ion channels activated by acetylcholine action differ between the two.

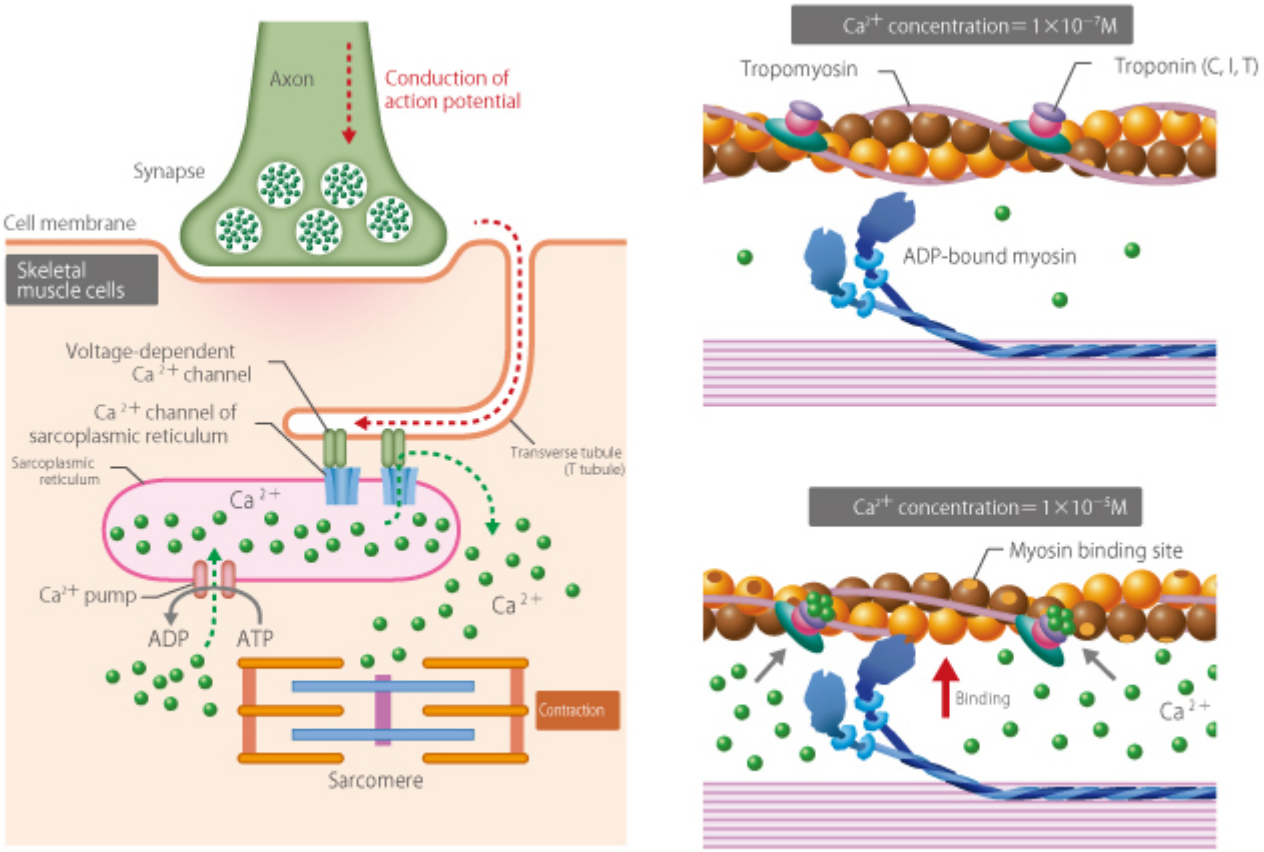

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Figure 17-9 Regulation of skeletal muscle contraction by Ca^{2+}

A) Transmission of excitation from nerve cells triggers changes in the membrane potential of skeletal muscle cell membrane via synapses. The changes are transmitted into cells by transverse tubules, which are cell membranes that elongate into the cell like a tube and adhere to the intracellular sarcoplasmic reticulum. Voltage-dependent Ca^{2+} channels distributed in the transverse tubules bind to Ca^{2+} channels distributed in the sarcoplasmic reticulum to transmit information from the cell membrane to the sarcoplasmic reticulum, triggering the release of Ca^{2+} from the sarcoplasmic reticulum. B) Once increased Ca^{2+} concentration reaches a specific value in the cell, Ca^{2+} binds to troponin C, resulting in the change in the three-dimensional structure of troponin and tropomyosin. This exposes the myosin binding site on the actin filament covered by the tropomyosin, to which myosin binds to allow muscles to contract.

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Elucidating the mechanism behind muscle contraction

Around 1930, muscle contraction was proposed as a phenomenon triggered by chemical reactions. Gradually, it was brought to light that the energy used for muscle contraction is ATP, and the hydrolysis of ATP by myosin provides the energy needed for muscle contraction. At the same time, the structural background of muscle contraction was also being studied intensively, which led to the discovery that muscle contraction is carried out by actin and myosin. Further more, with the evolution of microscopes and X-ray analytical techniques to observe cellular microstructures, in the 1950s it was discovered that the muscle cell contractile apparatus is made up of thick actin filaments and thin myosin filaments, which together form the sarcomere structure. Many studies in this area were conducted from the 1960s to 1970s, leading to the formation of the currently accepted model of muscle contraction carried out by actin and myosin. Then, in the 1990s, with the development of such techniques as X-ray crystallography and cryo-electron microscopy, the structure of myosin, as well as the mechanism of myosin-actin binding at the myosin head, was identified. Importantly, this lead to the clarification of the mechanism of ATP binding and how ATP hydrolysis altered the structure of myosin. These research findings have facilitated understanding on the molecular-level mechanism of contraction by actin and myosin.