Muscle physiology and contraction

Carolyn A Greig
David A Jones

Abstract

Skeletal muscle has important metabolic functions but the focus of this article is to examine its ability to generate mechanical force. Adult skeletal muscle fibres are each innervated by a single branch of the axon arising from an α-motoneuron in the spinal cord. The α-motoneuron and all the fibres it innervates constitute a motor unit, and this is the functional unit of the muscle. α-Motoneurons differ in size and excitability and it is the recruitment of these cell bodies in the spinal cord that determines which fibres within the muscle are active during a movement. Correct functioning of the neuromuscular junction is clearly critical for muscle action and it is a site at which many drugs affecting muscle have their action. Here we describe also the mechanism by which skeletal muscle generates force following activation, a process known as excitation–contraction coupling and examine the contractile properties of muscle as well as describing muscle weakness and fatigue and the assessment of muscle performance in health and disease.

Keywords Excitation–contraction coupling; muscle contraction; muscle fatigue; muscle performance; muscle weakness; neuromuscular junction

> 'All man can do is to move things, and his muscular contraction is his sole means thereto.' C.S. Sherrington, The Gifford Lectures, Edinburgh 1937–8

The control of muscle contraction

Problems with muscle function may not appear to be as dramatic as failures of the vital organs such as heart, lungs, brain, and kidney, but ultimately our mobility and independent lifestyle, not to mention the ability to breathe, cough, speak and swallow, all depend on the proper function of voluntary, or skeletal, muscle. In addition, weakness and fatigue, or at least the perceptions of these problems, constrain our physical activity, mobility and quality of life.

Skeletal muscles work under the close control of the nervous system with afferent feedback from a host of receptors in muscle spindles, tendon organs, joints and skin, modulating activity both at the spinal and higher levels. These aspects of motor control are beyond the scope of this chapter but we will deal briefly with the role of spinal motoneurons before concentrating on the function of the neuromuscular junction, the release of intracellular calcium that activates the contractile proteins and then the generation of force and movement. The chapter concludes with an overview of muscle disorders and methods of testing muscle function.

Carolyn A Greig *PhD is a Senior Lecturer in Nutrition and Ageing, MRC-ARUK Centre for Musculoskeletal Ageing, The University of Birmingham, UK. Conflicts of interest: none declared.*

David A Jones *PhD is Emeritus Professor of Muscle Physiology at the School of Healthcare Science, Neuromuscular and Skeletal Ageing Research Group, Manchester Metropolitan University, Manchester, UK. Conflicts of interest: none declared.*

Spinal motor neurons

Adult skeletal muscle fibres are each innervated by a single branch of the axon arising from an α-motoneuron in the spinal cord. The α-motoneuron and all the muscle fibres it innervates constitute a motor unit, and this is the functional unit of the muscle. α-Motoneurons differ in size and excitability and it is the recruitment of these cell bodies in the spinal cord that determines which fibres within the muscle are active during a movement. Small motor neurons, which are more readily activated, innervate relatively small numbers of muscle fibres while larger less excitable neurons have a greater number of axonal branches and thus control larger motor units. As a consequence of their different excitabilities the small motor units tend to be recruited early and frequently for activities such as walking and maintaining posture since these activities involve small forces while the large motor units are only involved when rapid or large contractions are required. The muscle fibres innervated by these different types of motor neurons have different contractile and metabolic characteristics, the small units being slow contracting, with a high oxidative capacity and fatigue resistance. The large units tend to be fast, predominantly glycolytic and fatigue rapidly.

As with all neurons, whether or not an α-motoneuron fires depends on the extent of excitatory and inhibitory inputs and depending on which way the balance is tipped the muscle contraction may be inhibited or it may go into a cramp or spasm. Afferent signals coming from damaged or inflamed joints can lead to inhibition leading to weakness (arthrogenic weakness). Conversely, tetany, an uncontrolled muscle contraction due to tetanus toxin, is the result of the toxin preventing the release of γ-aminobutyric acid (GABA) which is an inhibitory neurotransmitter in the spinal cord. With muscle cramps and spasms it is not clear whether there is increased excitation or reduced inhibition, nor why this occurs, but generally the condition can be cured or at least ameliorated by increasing inhibition. In the case of cramp the contraction can be relieved by stretching the muscle and activating inhibitory Golgi tendon organs, or by rubbing or cooling the skin. Muscle spasm can be treated with GABA agonists such as *baclofen* and *diazepam*. These are sometimes described as muscle relaxants although this is slightly misleading since they do not work directly on muscle.

When the axons from the motoneurons enter the target muscle they branch and generally make contact with their muscle fibre about halfway along their length, this being the 'motor point' at which the muscle can most easily be stimulated by an external electrical stimulus. The contact between the motor axon and the muscle fibre is the neuromuscular junction, there being just one junction per fibre in mature muscle.

The neuromuscular junction and post-synaptic membrane

At the neuromuscular junction the axon swells and flattens along the muscle fibre membrane, while the underlying muscle plasma

membrane (sarcolemma) is thrown into complex folds or clefts (Figure 1). The post-synaptic muscle fibre membrane contains acetylcholine (ACh) receptors which are situated at the crests of the folds. Cholinesterase, the enzyme which hydrolyses acetylcholine, is synthesized by the muscle fibre and is secreted into the synaptic cleft where it binds to the basement membrane which fills the cleft. In the pre-synaptic terminal acetylcholine is stored in vesicles, together with adenosine triphosphate (ATP) and the peptide hormone calcitonin gene-related peptide (CGRP). Action potentials, arriving at the axon terminal open voltage-sensitive calcium channels and the influx of calcium causes the synaptic vesicles to fuse with specific binding sites on the pre-synaptic nerve membrane and release their contents into the synaptic cleft. The release is, therefore, dependent on the presence of external calcium and release is depressed by high magnesium concentrations.

Release of ACh from the pre-synaptic membrane is inhibited by botulinum toxin A which prevents the vesicle binding to the surface membrane the result being a flaccid paralysis of muscle. The toxin, said to be the most potent poison known, is used at very low concentrations in a variety of conditions where local muscle activity needs to be inhibited, such as where there is spasticity and in strabismus. Botox is currently best known as a cosmetic treatment for wrinkles where it paralyses muscles just beneath the skin. Interestingly, tetanus toxin, which has the opposite effect, sending the muscle into an uncontrolled spasm, works by a very similar mechanism but acts not on the neuromuscular junction but by inhibiting the release of GABA from synapses that have an inhibitory action on motoneurons in the spinal cord.

Binding of ACh to the post-synaptic receptor causes a depolarization of the muscle fibre membrane by opening Na^+ channels. If sufficient ACh receptors are activated the depolarization summates and initiates an action potential that can then spread over the surface of the muscle fibre. ACh does not survive very long in the synaptic cleft as it is rapidly hydrolysed by the enzyme choline esterase. The free choline is then transported back into the axon and resynthesized into ACh.

The uptake of choline into the pre-synaptic terminal can be blocked with *hemicholium* leading to a gradual paralysis as the ACh stored in the pre-synaptic terminal becomes exhausted with repeated stimulation. The action of cholinesterase, hydrolysing ACh, is inhibited by *eserine* and *neostigmine*. These anti-cholinesterase drugs potentiate neuromuscular junction transmission by prolonging the lifetime of ACh within the synaptic cleft thus increasing the chance of its binding to an ACh receptor and depolarizing the muscle membrane. Anti-cholinesterases are used as an antidote to *curare* and some of the nerve gas poisons which also inactivate the ACh receptors. Cholinesterase inhibitors are also used in the management of myasthenia, an autoimmune disease where antibodies against the acetylcholine receptors block transmission. *Curare* was the first drug used in surgery as a muscle relaxant as it specifically binds to ACh receptors. Unlike *curare*, *succinylcholine* and *pancuronium*, which are also used as muscle relaxants, cause the post-synaptic membrane to become depolarized so that the membrane passes into an in-excitable refractory state.

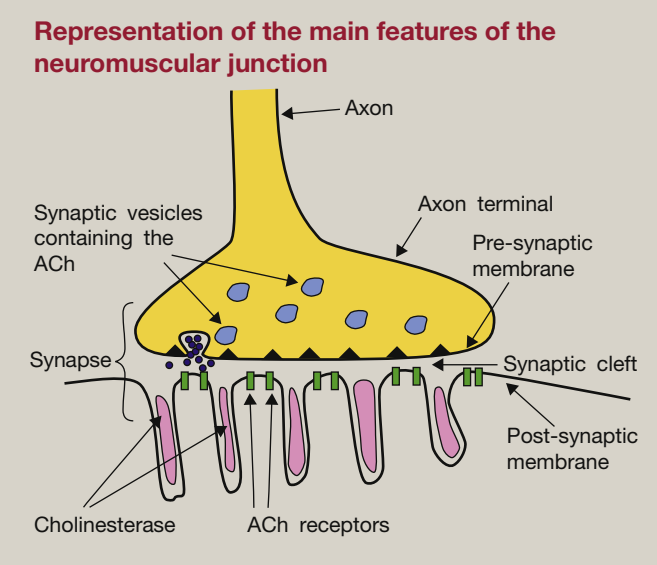

Figure 1 Note the release of acetylcholine (ACh) from a synaptic vesicle that has fused with the pre-synaptic membrane. This will diffuse across the synaptic cleft and bind to the ACh receptors before being hydrolysed by cholinesterase and the choline transported back into the axon terminal.

Electrical activity of muscle

Being an excitable tissue, muscle depends on gradients of K^+ across the surface membrane to maintain the resting membrane potential, and Na^+ to generate the action potential in exactly the same way as nervous tissue. Action potentials initiated at the neuromuscular junction propagate along the length of the fibre and the T tubules, which are an extension of the surface membrane, penetrating into the interior of the muscle fibre. As the action potential spreads into the interior of the fibre the T tubular membrane is depolarized at a time when the surface membrane is repolarizing and this difference in potential could lead to the development of local circuits and repetitive firing (myotonia). However, muscle fibres have a high chloride conductance which makes the muscle membrane more difficult to stimulate than the membrane of a nerve cell and thus reduces the chances of repetitive firing. In some clinical conditions (e.g. myotonia congenita), the chloride conductance is reduced leading to repetitive firing and slow relaxation of muscle.

Excitation–contraction coupling

The calcium that is required to activate the contractile proteins is stored in a complex bag-like structure, the sarcoplasmic reticulum (SR), which envelops the contractile filaments and also makes contact with the T tubules. As a wave of depolarization passes down the T tubules (Figure 2) there is an interaction with the SR, which results in the release of calcium that initiates the interaction of actin and myosin and muscle contraction. This process is known as excitation–contraction coupling (EC coupling).

Structure of the triad: where the T tubules meet the SR the two membranes are opposed to one another and because there is usually one portion of SR membrane on each side of the T tubule, the structure, when seen under the electron microscope is known

