Skeletal muscle contraction: effects of muscular dystrophy

Give an overview of the processes that lead to skeletal muscle contraction (50%). Discuss how these processes are disturbed by muscular dystrophies and discuss one particular dystrophy in detail (50%).

Muscle contraction is when a tension is made from an action potential to cause a movement in of the muscle, this requires interactions between actin filaments and myosin. The Skeletal muscles contract in a sliding filament model: Firstly an action potential that comes from the CNS reaches an alpha motor neuron. This then transmits an action potential down its axon. The action potential then spreads by activating the sodium dependent channels near to the synaptic cleft along the axon. The action potential them reaches the motor neuron terminal and so causes a calcium ion influx through the calcium dependent channels.

The influx of the Ca2+ causes exocitosis of the vesicles containing acetylcholine so it fuses with the plasma membrane and releases acetylcholine into the extracellular space. The acetylcholine then diffuses across the synapse and binds to the nicotinic receptors on the motor end of the muscle cell. When the nicotinic receptor is activated, the sodium/potassium channels open and cause sodium ions to enter in a surge and potassium ions go out. The overall charge on the muscle fibre becomes positive due to the difference in potential (voltage) from sodium in the muscle fibre and potassium outside the muscle fibre. This causes an action potential. As the action potential spreads across the muscle fibre it becomes depolarized.

The depolarization of the muscle fibre activates the voltage dependent calcium channels in the T tubule membrane. The Sarcoplasmic reticulum then releases calcium due to the activated calcium release channels. The calcium then binds to the troponin C which is on the actin containing thin filaments of the myofibrils. This causes the troponin to modulate the tropomyosin. Normally the tropomyosin blocks the myosin binding sites on the thin filament but, the calcium binding to the troponin C causes unblocking of the binding sites.

Myosin can then bind to the newly uncovered binding sites on the thin filament. They are bound to the actin in the strong binding state. When the ATP binds the myosin it allows the release of actin becomes a weaker binding state. The myosin then hydrolyzes the ATP and uses the energy to move into the correct conformation. Calcium is actively pumped back into the sarcoplasmic reticulum and when calcium is no longer present on the thin filament, the tropomyosin changes conformation back to its previous state so it blocks the binding sites again. The myosin stops binding to the thin filament, and the contractions stop.

There are many types of dystrophies that can affect the processes involved in skeletal muscle contraction. One such dystrophy is the becker muscular dystrophy is a less severe variant of Duchenne muscular dystrophy and is caused by the production of a partially functional form of dystrophin.

Another dystrophy is the congenital muscular dystrophy which includes several disorders with a range of symptoms. Muscle degeneration can be severe as problems may be restricted to skeletal muscle, or muscle

degeneration could be paired with the effects on the brain and other organ systems. There are a number of the forms of the congenital muscular dystrophies that are caused by defects in proteins and are thought to have some link to the dystrophin glycoprotein complex. Some types of congenital muscular dystrophy show severe brain malformations.

Emery-Dreifuss Muscular Dystrophy is one that people normally show signs of in childhood and the early teenage years. Clinical signs can include weakness and wasting of the muscles, this can start in the distal limb muscles and progress to the limb-girdle muscles. Most of the patients usually also suffer from arrhythmias or cardiac conduction defects. If they’re left untreated, there is an increase in the risk of stroke and possible death.

Facioscapulohumeral muscular dystrophy is a dystrophy that at first affects the muscles in the face, shoulders, and upper arms as they become weaker. The Symptoms are shown in the teenage years and some people who are affected can become severely disabled. The pattern of inheritance is autosomal dominant, but the underlying genetic defect is inadequately understood.

The Limb-girdle muscular dystrophy shows a similar distribution of muscle weakness, affecting both the upper arms and legs. Many forms of this dystrophy have been identified through varying patterns of inheritance. In the autosomal recessive pattern of inheritance, an person would have two copies of the defective gene, one from each parent. The recessive ones are more common than the dominant forms and can usually have childhood or teenage onset. The dominant genes usually show adult onset. There are

some of the recessive forms that have been linked to defects in proteins that make up the dystrophin-glycoprotein complex.

Myotonic muscular dystrophy is the most common adult form of muscular dystrophy. It is known for muscle wasting and weakness. Myotonic dystrophy varies in seriousness and affects many body systems in addition to skeletal muscles, which include the heart, gastrointestinal tract and the endocrine organs. Myotonic dystrophy follows an autosomal dominant pattern of inheritance. While the exact mechanism of action is not known, the molecular change could interfere with the production of vital muscle proteins.

One particular dystrophy known as the Duchenne muscular dystrophy, is a neuromuscular disorder. It’s an inherited disorder with an incidence of 1 in 3300 live male births.

Duchenne muscular dystrophy is a devastating inherited neuromuscular disorder with an incidence of 1: 3, 300 live male births.

In patients with Duchenne muscular dystrophy, muscle biopsy characteristically demonstrates necrotic or degenerating muscle fibres, often observed in clusters.

Such necrotic fibres are surrounded by macrophages and CD4+ lymphocytes.

In the early stages of the disease, one also finds small immature centrally nucleated fibres which represent muscle regeneration from myoblasts. This indicates that there is balance between necrotic and regenerative processes.

Later, the regenerative capacity of the muscles appears to be exhausted and muscle fibres are gradually replaced by connective and adipose tissue

The gene responsible for this defect codes for the protein dystrophin.

It is the absence of dystrophin that leads to Duchenne muscular dystrophy. However, the comprehensive understanding as to how the absence of this protein leads to muscular degeneration is still not fully understood.

Dystrophin is found in the vicinity of many other proteins and these all form a large complex.

The best studied roles for the dystrophin-associated complex involves structural stabilization of the sarcolemma.

Mutations of other dystrophin-associated protein complex components also cause muscular dystrophy (see later) by disassembling the complex and compromising the linkage between the extracellular matrix of the fibres to the cytoskeleton.

The various pathophysiologic hypotheses for Duchenne muscular dystrophy include:

(i) mechanical hypothesis;

(ii) impaired calcium hypothesis;

Much old data had indicated that there appeared to be an excessive fragility of the muscle fibres in this disease.

The discovery of the dystrophin-associated protein complex scaffolding supported the view that the absence of one of these proteins could compromise the muscle membrane integrity of the fibres.

This could particular be so after sustained contractions, as the ability to sustain contraction with forced lengthening appears to be dramatically reduced in Duchenne muscular dystrophy.

The absence of dystrophin results in a striking alteration in membrane structure related to delocalization of the dystrophin-associated proteins from the membrane. The dystrophin-associated complex together with additional proteins (e. g. vinculin, desmin, spectrin) normally form rib-like lattices on the cytoplasmic faces of the sarcolemma (these regions are called costameres): these anchor the cytoskeleton to the extracellular matrix.

Costameres act as mechanical couplers to distribute contractile forces generated in the sarcomere laterally through the sarcolemma to the basal lamina and thereby maintain uniform sarcomere length along the fibre.

Absence of dystrophin, leads to the loss of the dystrophin-associated protein complex and disruption of the costameric lattice, and it is this that is thought to underlie membrane fragility.

Evidence for membrane fragility in patients is shown by cytoplasmic accumulation of proteins that are not normally present in muscle fibres, such as albumin and immunoglobulins. This indicates that the permeability of the muscle membrane has increased.

Other research would appear to indicate that exercise could provoke greater damage in dystrophin-deficient muscles than in controls.

These ideas clearly have some bearing on the possible management of the disease because whilst physical therapy appears to improve or stabilize muscle functions, too much exercise could lead to further muscle damage.

There is documentation of calcium accumulation and of hypercontracted fibres in muscle biopsies of Duchenne muscular dystrophy patients.

In dystrophin-deficient membrane there is an increased flux of calcium which appears to occur through a voltage-independent mechanosensitive calcium channel.

However, measurements of the basal [Ca2+]i are normal and this could suggests that there may be only abnormal calcium concentrations at localized submembranous compartments.

If mechanical stress induces microlesions in the muscle fibres then this could lead to high influx of extracellular calcium and this could overide the cells capacity to maintain a physiological cytosolic concentration of calcium.

Clearly, higher [Ca2+]i can lead to the activation of proteases (e. g. calpains) and this can lead to further damage and even lead to apoptosis and cell death.

Muscles of patients with Duchenne muscular dystrophy exhibit inflammatory changes.

It would seem that selective chemokine up-regulation may be a key determinant in the inflammatory response. However, no studies have provided any direct insights into the mechanisms implicated in cell death.

Nevertheless, corticosteroids, which have potent anti-inflammatory effects, are the most common used drugs in Duchenne muscular dystrophy.

e. g. prednisolone treated patients experience significant delay in the disease progression, they are able to move about freely for longer and there is prevention of curvature of the spine.