Topics Covered

Z-disc streaming
Contraction of Skeletal Muscle
Control of Force of Contraction
Muscle Fatigue

Module 1 Review
Numerous Early Lesions in a Single Myofiber
Single Myofiber Containing a Large Lesion Arising From the Confluence of Adjacent Small Lesions
Small Lesion Involves Adjacent Sarcomeres in Several Myofibrils
Two Narrow Lesions Involve Several Sarcomeres Between Adjacent Z discs

Z Disc Streaming

common reaction in a wide number of myopathies and denervation atrophy.
lesion must exceed three or more adjacent myofibrils and three or more continuous sarcomeres to be termed z disc streaming.
z disc streaming is frequently associated with a decrease in mitochondrial density within the myofiber although it can occur without mitochondrial loss.
z disc streaming associated with mitochondrial loss is more commonly observed in Type I than Type II myofibers.

z disc streaming associated with calcium effects.
in vivo experimental models (chronic anti-cholinesterase or ACh analogues) result in an accumulation of calcium in the NMJ area due to prolonged ACh receptor activation.
calcium accumulation results in dilation of the SR membranes, mitochondrial damage and z disc streaming.
also associated with mechanically-induced damage to the sarcolemma and consequent Ca²⁺ influx (delta lesions).
**Z Disc Streaming**

*in vitro* experimental models utilizing isolated myofibers can be used to probe the mechanism of z disc streaming.

isolated myofibers can be stimulated with the ACh analogue, carbamylcholine.

removal of calcium and addition of the protease inhibitor, leupeptin, from the extra-cellular fluid during prolonged stimulation protects from z disc streaming supports the concept that z disc streaming is calcium dependent and involves the activation of a calcium dependent protease.

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**Tethering of Z-discs In Striated Skeletal Muscle**

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**Types of Muscle Contraction**

Isometric – no change in muscle length

Dynamic – change in muscle length

- Concentric -- shortening
- Eccentric--lengthening

Isotonic Contraction
- constant force production

Isokinetic Contraction
- constant angular velocity
**Time Course of Contractile Event in Skeletal Muscle**

- **Static**
  - Isometric (same length)
  - Isotonic (constant force)

- **Dynamic**
  - Concentric (shortening)
  - Eccentric (lengthening)
  - Isokinetic (constant angular velocity)

- (a) Muscle contracts and shortens, movement
- (b) Muscle contracts but does not shorten, no movement
Duration of Isometric Contractions for Different Types of Mammalian Muscles.

- Fine movement
- Very Fast Twitch
- Fast Twitch
- Slow Twitch
- Type I
- Type II

Stimulus Strength vs Force Production

Force-Frequency Relationship
**Frequency Summation and Tetanization.**

![Frequency Summation and Tetanization](image)

**Length-tension diagram for a single sarcomere showing maximum strength of contraction.**

![Length-tension diagram for a single sarcomere](image)

**Length-Tension Diagram for Multiple Sarcomeres Showing Maximum Strength of Contraction.**

![Length-Tension Diagram for Multiple Sarcomeres](image)
Control of Force of Contraction

Number of motor units recruited
Types of motor units recruited
- Type I
- Type IIA
- Type IIB
Frequency of motor unit firing

Motor Unit Properties

Definition of a motor unit
- one motor neuron and all of the muscle fibers it innervates

Size principle
- upon stimulation, small motor units contract first followed by larger and larger motor units

All or None Principle
- upon activation of a motor unit, all of the muscle fibers in the unit contract fully

Skeletal Muscle Fatigue

Fatigue - “a transient decrease in working capacity that results from previous physical activity.”

Fatigue defined in this fashion can be due to dysfunction of a number of different physiological systems.
- cardiovascular - pulmonary - endocrine - neuromuscular

Neuromuscular Fatigue - “a transient decrease in muscular performance usually seen as a failure to maintain or develop a certain expected force or power.”
Skeletal Muscle Fatigue

Peripheral (Contractile) Fatigue is Predominant

Causes of Peripheral (Contractile) Fatigue

Two main hypotheses historically

Accumulation of Metabolites

- lactate production
  - consequent accumulation of H+ ions (lowering pH levels), inorganic phosphate (Pi) and ammonia

Measurement of differences in the blood of particular metabolites is not the most accurate or informative approach as local muscle concentrations are much more physiologically relevant.

Depletion of Energy Stores

- depletion of glycogen, blood glucose, ATP and CP

The processes available for ATP re-synthesis (the ultimate energy supply for muscle contraction) are CP degradation, anaerobic glycolysis, and oxidative phosphorylation of CHO or fat.

Maximal rates of ATP synthesis by these 4 processes are 11, 5, 2 and 1 mmol ATP/sec respectively.
Skeletal Muscle Fatigue

appears that elements of both the Accumulation and Depletion Hypotheses play a role in peripheral muscle fatigue
decreased AP amplitude along T-tubule membranes leading to a reduction in DHP receptor activation and consequent SR Ca2+ release via the RyR1 channel.
decreased actin-myosin cross-bridge cycling due to:
- H+ ion inhibition of Ca2+.
- decreased SR re-uptake of Ca2+ by SR Ca ATPase due to excess H+ inhibiting electrochemical gradient across SR membrane or reduced ATP concentrations available for pump activity.
- lack of ATP required to dissociate actin from myosin

increased inorganic phosphate (Pi) accumulation
- decreases actin-myosin binding
reduced rate of ATP utilization in the muscle.
- protective effect to try and preserve cellular homeostasis

Peripheral neuromuscular fatigue is a combination of effects involving both the accumulation of metabolites and depletion of energy stores.

Central fatigue processes appear to be more important in prolonged and low intensity activities.

Central versus Peripheral Causes of Fatigue
**Skeletal Muscle Fatigue**

Central Mediated Effects
- Decreased number of active motor units in the fatigued muscle
- Decreased motor unit firing frequency

“Setchenov Phenomenon”
- During muscle fatigue, feedback of nerve impulses from the fatigued muscles impinges on a part of the reticular formation and causes an inhibition of voluntary effort. Diverting activity, on the other hand, produces an increased inflow of impulses from non-fatigued parts of the body to the facilitatory part of the reticular formation, thus shifting the balance between inhibition and facilitation in a facilitatory direction.

**The Neurotrophic Hypothesis**

Target-derived factors guide axonal growth towards appropriate postsynaptic targets

**Target Cell**

Target-derived factors are transported retrogradely and modulate gene expression in the pre-synaptic cell.

*In neuronal growth and regeneration, nerve growth factor (NGF) is the major trophic signaling factor.*
The Neurotrophic Hypothesis

Removing targets induces more developmental neuronal loss, while addition of extra targets inhibits developmental neuronal cell death.

Levi-Montalcini, Hamburger, and Cohen earned the Nobel Prize for these experiments and the discovery of NGF.

Review of Module One
Areas Covered

- muscle structure (major components of the muscle)
- myofiber structure (major components within a myofiber)
- NMJ structure and function (including blockade)
- E-C coupling (including receptors/channels involved)
- molecular basis of muscle contraction
- myofiber types (functional and biochemical characteristics)
- calcium homeostasis within the myofiber
- contraction of skeletal muscle
- neuromuscular fatigue