TOPIC X: SKELETAL MUSCLE PHYSIOLOGY

Learning Outcomes: Upon completion of Topic X (10), you should be able to

a) Describe the major characteristics and functions of skeletal muscle.
b) Define the sliding filament mechanism of skeletal muscle fibre contraction.
c) Describe the sequence of events involved in contraction of a skeletal muscle, including events at the neuromuscular junction, excitation-contraction coupling and cross bridge cycling.
d) Describe the sequence of events involved in skeletal muscle fibre relaxation.
e) Describe the molecular events leading to rigor mortis.
f) Describe the effects of the following on the neuromuscular junction: myasthenia gravis, curare poisoning, botulism, nicotine and black widow spider venom.
g) Define the following terms: tension, contraction, twitch and motor unit.
h) Interpret a graph of a twitch contraction of a muscle fibre with respect to the duration of the latent, contraction and relaxation periods, and describe the events that occur in each period.
i) Interpret a graph of tension versus stimulation frequency of a muscle fibre, and explain the physiological basis for the phenomena of summation, incomplete tetanus and complete tetanus.
j) Interpret a graph of the length-tension relationship in a muscle fibre and describe the anatomical basis for that relationship.
k) Describe the effect of muscle fibre size on tension development.
l) Compare fast versus slow twitch muscle fibres.
m) Explain the effect on tension development in a whole muscle of the number of fibres (motor units) contracting, the number of fibres per motor unit and the size of the whole muscle.
n) Define muscle tone.
o) Compare and contrast isotonic and isometric contraction.
p) Describe the sources of ATP (e.g. glycolysis, aerobic respiration, creatine phosphate) that muscle fibres use for muscle contraction. Explain when during exercise (short term or long term) that these ATP sources are used.
q) Explain the factors that are believed to contribute to skeletal muscle fatigue.
r) Explain excess post-exercise oxygen consumption and the factors that contribute to it.

A) Skeletal Muscles

- Muscle Characteristics:
    1) excitable - respond to stimuli by producing action potentials
    2) contractile - can shorten, thicken

3) extensible - stretch when pulled
4) elastic - return to original shape after contraction or extension.

- Muscle Functions:
  1) movement – e.g. walking, breathing
  2) posture, facial expression
  3) heat production → 37°C
  4) protection of viscera - body wall

B) Neuromuscular Junction:

- each muscle fibre (cell) innervated by only 1 neuron.
- axon of motor neuron branches to innervate several muscle fibres
  - 1 neuron → ~150 fibres within the same whole muscle
- a single motor neuron + ALL the muscle fibres it innervates = a motor unit
- Structure:
  - presynaptic cell (neuron) with ACh (nt) in vesicles
  - postsynaptic cell (muscle) membrane (sarcolemma) - specialized region with ACh receptors (= motor end plate)
  - two membranes separated by synaptic cleft.
- Function (steps):
  1) AP reaches axon terminal and synaptic end bulb of neuron.
  2) Ca^{++} enters via voltage gates → causes exocytosis of ACh
  3) ACh binds to ACh receptors on motor end plate
  4) chemical gates open and Na^{+} enters → End Plate Potential (EPP = a depolarizing GP)
  5) EPP causes opening of Na^{+} voltage gates on adjacent sarcolemma → AP (AP has same properties/channels as on a neuron) – propagates along sarcolemma

Insert MyFigures Topic X #1 EPP to AP at motor end plate

§ NOTE:
- 1 AP (neuron) → 1 EPP → 1 AP (always!)
- i.e. always a critical stimulus because:
  a) lots of ACh released
  b) motor end plate has many receptors

∴ to inhibit skel. musc., must inhibit motor neuron

(See MyFigures Topic III # 9 (excitatory pathway) & #10 (inhibitory pathway))

C) Molecular Basis of Skeletal Muscle Contraction:

- In a relaxed muscle:
  - tropomyosin covers myosin binding sites on the actin
  - the myosin head is activated

- Myosin Head Activation:

$$\underset{\text{(on myosin head)}}{ATP} \longrightarrow \underset{\text{(still on myosin head) = ACTIVATED}}{ADP} + \underset{}{Pi} + \underset{\text{(stored in myosin head)}}{Energy}$$

- once binding sites on actin are exposed, myosin binds

- Steps:

1) Excitation of muscle fibre (electrical event)

a) Sarcolemma depolarized - EPP → AP

b) AP propagates down T-tubules to deep within fibre

Insert MyFigures Topic X #2 T-tubule

2) Excitation-contraction Coupling (electrical to mechanical event)

c) AP in T-tubules cause release of Ca^{++} (coupling agent) from terminal cisternae of sarcoplasmic reticulum (SR) via mechanically gated channels

Insert MyFigures Topic X #3 Mechanism of Ca^{++} release from SR

Note that Fig. 10.7 in the text says that the voltage-sensitive protein on the sarcolemma (cell membrane) of the T-Tubule is a voltage-gated channel. This is not true!!!! It is not a channel. It is physically connected to the Ca^{++} channel on the SR, and changes shape when the AP passes it (hence it is voltage-sensitive protein, NOT a voltage gated channel). The change in shape of the voltage-sensitive protein causes the SR Ca^{++} channel to change shape by physically moving a part of the channel, thus opening it, and allowing the Ca^{++} in the SR to enter the cytosol.

d) Ca^{++} binds to troponin

e) Troponin-tropomyosin complex moves, exposing myosin binding sites on actin

3) Contraction (mechanical event) = Sliding Filament Mechanism

f) Activated myosin heads attach to binding sites on actin (cross bridge formation)

g) Energy stored in myosin head is released - myosin head pivots (=POWER STROKE), ADP + P_i are released. Actin slides over myosin toward centre of sarcomere (M line).

h) ATP attaches to myosin head, causing its release from actin+ unpivot = RECOVERY STROKE.

i) Myosin head reactivates (ATP → ADP + P_i)

j) If Ca^{++} in cytosol remains high, these steps repeat

- cycle repeats many times to shorten the sarcomere

Sliding Filament Mechanism:

1) Sarcomeres shorten

- H zone, I band shorten

- A band = same length

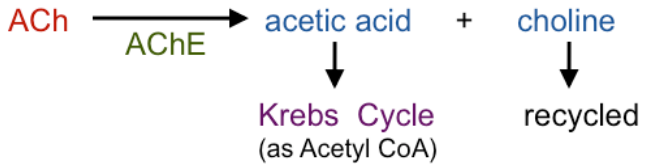
2) Myofibrils shorten ∴ muscle shortens

3) Thin (actin) and thick (myosin) myofilaments remain the same length

D) <u>Relaxation:</u>

- Steps:

1) ACh broken down by AChE on motor end plate (facing cleft)



2) SR actively takes up Ca^{++} (Ca^{++}-ATPase)

3) ATP binds to and releases myosin heads

4) Tropomyosin moves back to cover myosin binding sites on actin.

- <u>ATP necessary for</u>:

1) cross bridge release (ATP <u>not</u> broken down)

2) activation of myosin (ATP → ADP + P_i) + power stroke

3) pump Ca^{++} into SR

4) fibre Na^+/K^+-ATPase activity

E) <u>Clinical Applications:</u>

1) Rigor Mortis: ("stiffness of death")

- myosin heads still activated even after death ∴ can bind to actin
- ATP production gradually stops (no O_2)

∴ a) intracellular Ca^{++} ↑ from ECF, SR (there is leakage) → binding sites exposed (cross bridges form)

b) myosin heads cannot be released from actin (no new ATP produced) → muscle remains contracted

- starts ~ 3 hrs after death, max at about 12h
- gradually subsides over days as cells break down

2) Extracellular Ca^{++}

- stabilizes Na^+ voltage gates (keeps them closed in the <u>absence</u> of APs) ∴ if extracellular Ca^{++} low (pregnancy, lactation) – gates open & Na^+ enters fibre → cramps (contractions)

3) Conditions/Substances resulting in flaccid paralysis:
    a) Myasthenia gravis - ↓ in ACh receptors (autoimmune)
        - use AChE inhibitors (↑ binding to remaining receptors)
    b) Curare Poisoning
        - prevents ACh from binding to receptors
        - was used in surgery
    c)) Botulism
        - improper canning - *Clostridium botulinum*
        - prevents exocytosis of ACh
        - used to control uncontrolled blinking, crossed eyes
        - cosmetic - Botox (wrinkles, sweating)
4) Substances resulting in muscle contractions:
    a) Nicotine
      - binds to receptors + mimics ACh effect
      - muscle spasms
    b) Black Widow Spider Venom
        - massive release of ACh - stops breathing

NOTE:
- effects that stim ACh receptors are initial
- longer term → may depress firing due to receptor desensitization

F) <u>Muscle Tension:</u>

= force exerted by a muscle or muscle fibre
→ determined by # of cross bridges formed

- in a fibre, affected by:

1) <u>Frequency of stimulation:</u>
    a) Single stimulus - produces a twitch (not normally occurring in skel. muscles)
    twitch = weak contraction and relaxation

Insert MyFigures Topic X #4 Muscle Myogram

i) 1 stimulus → 1 AP (lasts 1-2 msec)
ii) latent period (~ 2 msec)
    - processes associated with excitation and excitation-contraction coupling
iii) contraction period (10-100 msec) - ↑ tension
    - cross bridge formation + sliding filaments
    - much Ca^{++} released from SR on stimulation, but taken back rapidly by SR Ca^{++}-ATPase, so not all myosin heads attach – does not reach max. possible tension
iv) relaxation - ↓tension

- Ca^{++} pumped into SR; ATP releases myosin; etc.

b) 2nd stim. arrives before complete relaxation from 1st
- muscle AP over BUT uptake of Ca^{++} by SR not complete (fibre relaxing)
- 2nd stimulus causes release of more Ca^{++}, adding to that already in cytosol → more myosin heads can attach
- produces 2nd contraction with ↑ tension = wave summation (contraction has no refractory period)

c) Rapid sequence of stimuli
- tension increases further (↑ Ca^{++} availability → wave summation)
- <u>partial</u> relaxation between contractions produces quivering = <u>incomplete tetanus</u>

d) High frequency of stimuli
- no relaxation between contractions i.e. sustained contraction = <u>complete tetanus</u>
- highest tension (3-4x twitch) - all troponin saturated with Ca^{++}+ fibre warm (ATP synthesis → heat) → works faster
- occurs normally in body

2) <u>Fibre Length:</u>

a) <u>Resting</u> fibre length is <u>optimum</u>
- max. # of cross bridges formed upon stimulation ∴ <u>max. tension</u>

b) ⇓tension if shorter or longer when stimulated
- shorter → thin filaments overlap + interfere with cross bridge formation ∴ fewer cross bridges form ∴ ↓ tension (min. length = 70% of optimal)
- stretched → not all myosin heads near actin binding sites ∴ fewer cross bridges form ∴ ↓ tension (max. length = 130% optimal)

3) <u>Size of fibre:</u>
- thicker = more myofibrils/fibre
- thicker = more tension
- ↑ with e.g. exercise, ♂ = testosterone

4) <u>Fatigue</u>
- muscle does not contract well
- reduced max tension

- Fibre types in a muscle differ:

1) Fast – contract/relax rapidly - white (little myoglobin)
2) Slow - contract, relax slowly - red (more myoglobin) e.g. postural muscles

- In a whole muscle, tension affected by:
    1) Number of fibres contracting:
        - more active motor units = ↑ tension
          → small motor units recruited first, then larger ones added when more tension needed
    2) # fibres /motor unit:
        - more fibres/unit = ↑ tension
            - 1 neuron → 10 fibres (weak) vs 1000 fibres (strong)
    3) Muscle size:
        - larger = more fibres
            e.g. biceps brachii vs risorius
        - larger = more myofibrils
            e.g. body builder's biceps brachii vs unfit person's
    4) Fatigue

G) Muscle Tone:

- low level of tension in a few fibres that develops as different groups of motor units are alternately stimulated over time
- gives firmness to muscle

H) Whole Muscle Contraction:

- types:
    1) Isotonic:
        - muscle changes length
        - e.g. flexion at the elbow – tension > weight of forearm
        - tension (relatively constant) exceeds the resistance of the load lifted
        - uses ATP

    2) Isometric:
        - muscle length constant
        - tension less than required to move load
        - tension increases – cross bridges form but no shortening
        - uses ATP

- Example: lift a book
    muscle = biceps brachii
        - isotonic to lift
        - isometric to hold

I) <u>Muscle Metabolism:</u>

- energy for contraction:
  1) <u>During resting conditions:</u>
     a) fatty acids used to produce ATP (<u>aerobic</u>)
     b) storage of:
        i) glycogen
        ii) creatine phosphate (C~P)
            ATP + Creatine ⇒ ADP + C~P
        iii) little ATP

  2) <u>During short term</u> exercise (i.e. < 1 minute) e.g. sprinting
     - primarily anaerobic
        a) use available ATP
        b) creatine phosphate used to produce ATP (lasts ~ 15sec.)
            C~P + ADP ⇒ATP + creatine

        c) muscle glycogen → glucose → pyruvic acid → anaerobic pathway → lactic acid (lasts ~ 30 sec.)

  3) <u>Long term exercise (1 min. to hours)</u>
     - ATP - from <u>aerobic</u> pathway
     - glucose (from liver)
     - fatty acids - used more as exercise continues
     - O_2 sources: blood hemoglobin + muscle myoglobin
     - but sometimes anaerobic (discussed under fatigue)

J) <u>Muscle Fatigue:</u>

- types:
  1) <u>Physiological Fatigue</u>
     - inability to maintain tension- not completely understood
     - fatigue ↓ ATP use ∴ protective (if too little, cross bridges can't release)
     - due to
        a) depletion of energy supplies e.g. glycogen
        b) build-up of end products
            - H^+ from lactic acid - muscle contraction compresses blood vessels - ↓ O_2 to muscle ∴ anaerobic for periods, even in long term exercise

            - P_i (from ATP → ADP + P_i) → binds to Ca^{++}
                - less Ca^{++} binds to troponin
                - slows release of P_i from myosin ∴ slows cross bridge release from actin

c) failure of APs →

- ↑ [K^+] in small space of T-tubules during rapid stimuli → disturbs MP, stops Ca^{++} release from SR
- long term: neuron runs out of ACh → not usual in healthy person

2) Psychological Fatigue:

- failure of CNS to send commands to muscles → probably due to lactic acid

K) Muscles and EPOC:

EPOC = Excess post-exercise O_2 consumption

- recovery O_2 consumption (deep rapid breathing)

O_2 used to:

1) replenish stores of glycogen, C~ P, O_2 on Hb/myoglobin
2) convert lactic acid to:
   - pyruvic acid → Krebs
   - glucose in liver

Also ↑ in body temp from exercise = ↑ O_2 demand (faster chemical reactions)