Skeletal Muscle Plasticity

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Medical Doctor Degree

MEDICINE & SCIENCE IN SPORTS & EXERCISE®

Noninvasive Evaluation of Skeletal Muscle Oxidative Metabolism after Heart Transplant

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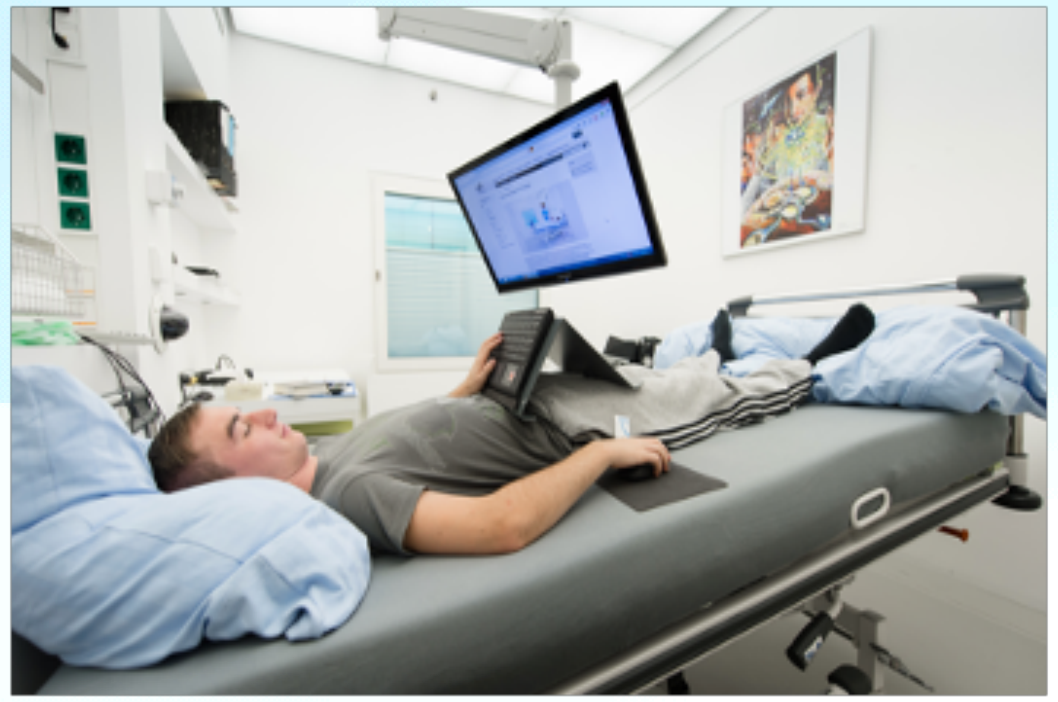
Specialization in Sports Medicine



J Appl Physiol 109: 101–111, 2010.

Role of skeletal muscles impairment and brain oxygenation in limiting oxidative metabolism during exercise after bed rest

Simone Porcelli,[1,2] Mauro Marzorati,[1] Francesca Lanfranconi,[3] Paola Vago,[3] Rado Pišot,[4] and Bruno Grassi[5]

PhD in Human Physiology

J Appl Physiol 121: 699–708, 2016.

Home-based aerobic exercise training improves skeletal muscle oxidative metabolism in patients with metabolic myopathies

Simone Porcelli,[1,3] Mauro Marzorati,[1] Lucia Morandi,[2] and Bruno Grassi[1,3]

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Outline

- **INTRODUCTION**
  - Structural characteristics of skeletal muscle
  - Excitation-contraction coupling and force production
- **EFFECTS OF ENDURANCE AND RESISTANCE TRAINING ON MUSCLE STRUCTURE AND FUNCTION**
- **MUSCLE PLASTICITY IN HEALTHY AGING**

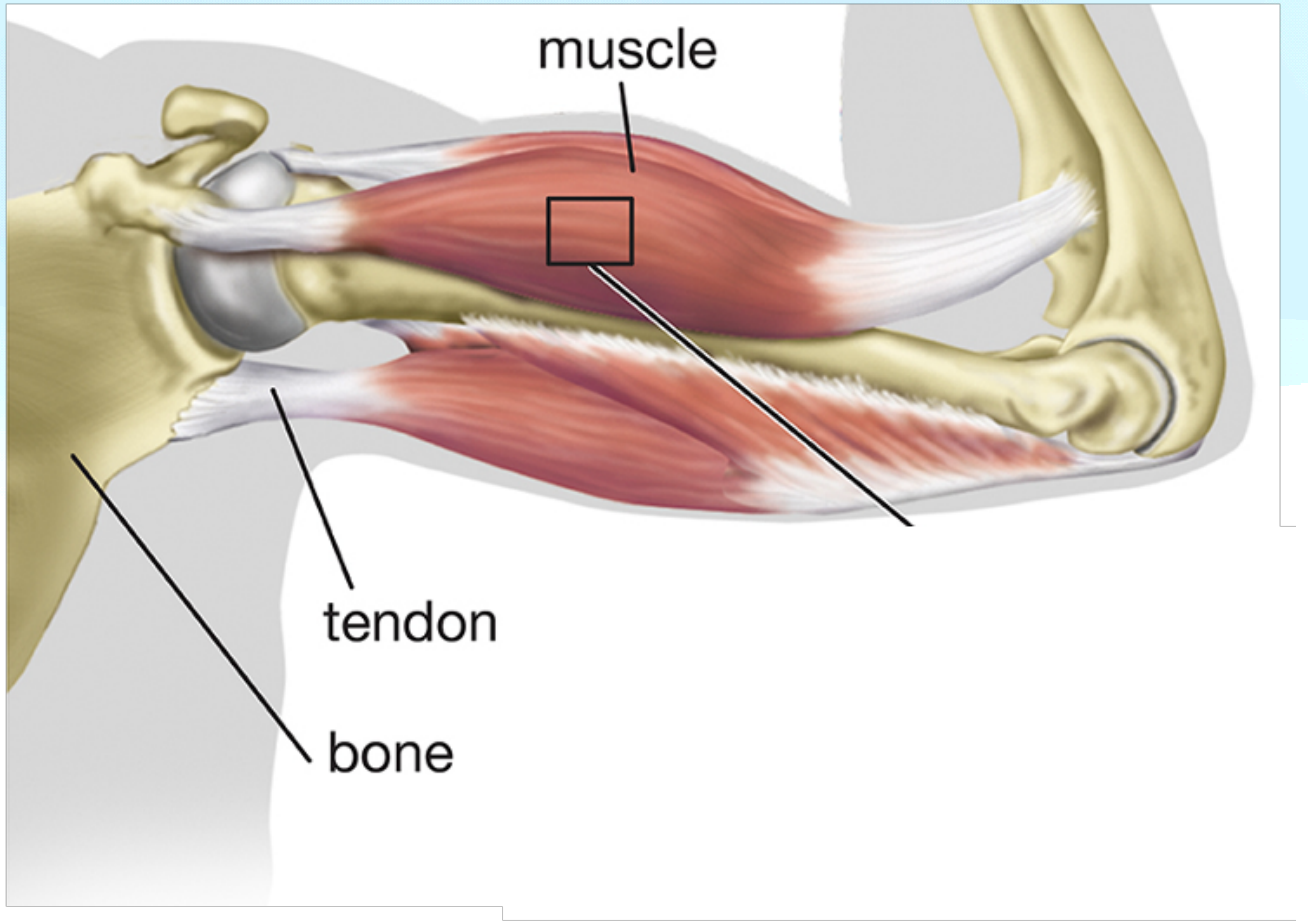
INTRODUCTION

40% lean body mass

15-20 kg in a man of 70 kg body weight

It is responsible for supporting and moving the skeleton

Energy expenditure
Glicemic control
Protein storage
Heat and thermoregulation
Endocrin organ



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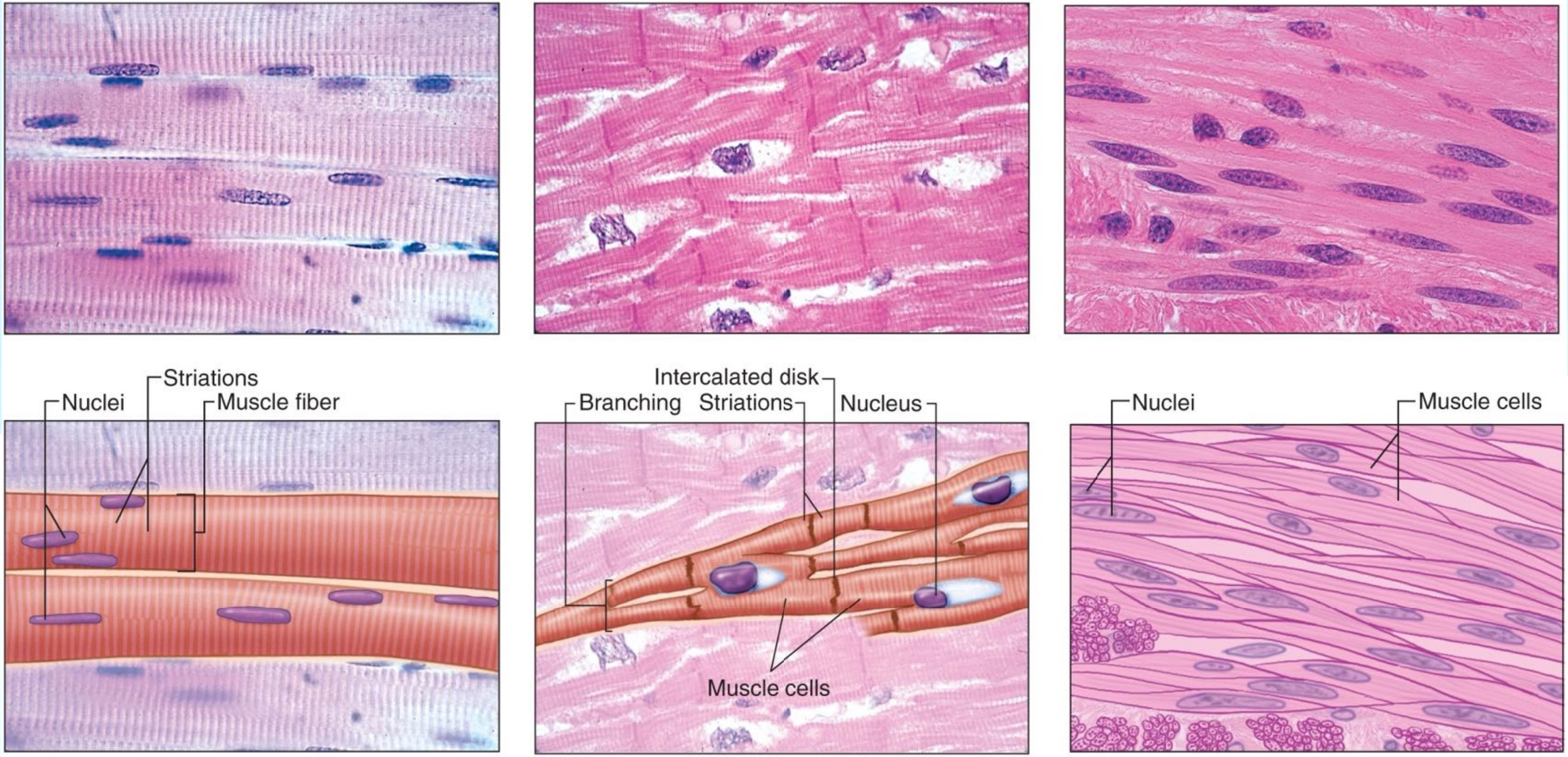

(a) Skeletal muscle **(b)** Cardiac muscle **(c)** Smooth muscle

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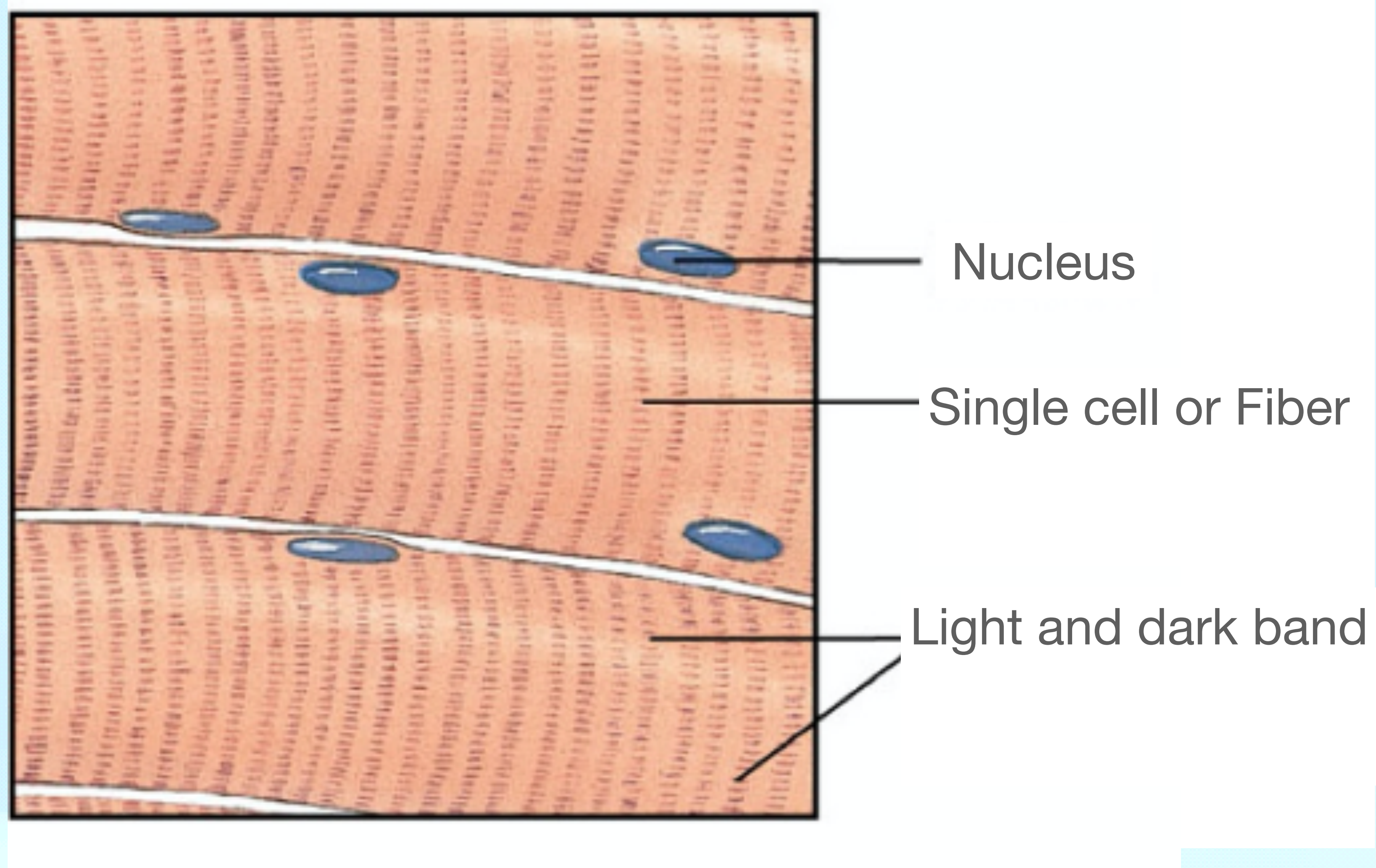
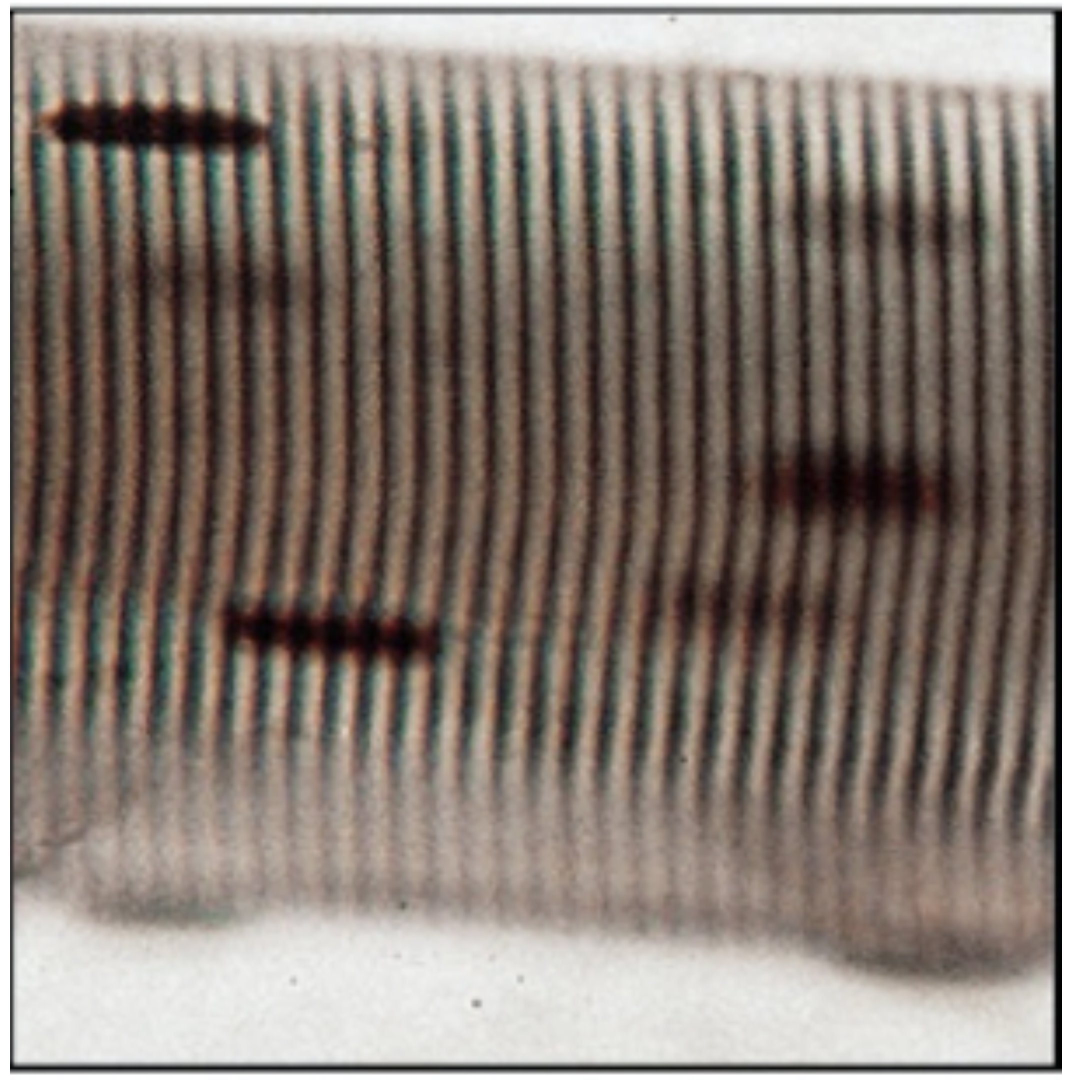
- Striated
- Multinucleated
- 10-100 μm diameter
- Differentiation completed at birth and after birth they continue to increase in size (hypertrophy) not in number (hyperplasia)
- If damaged they cannot be repaired





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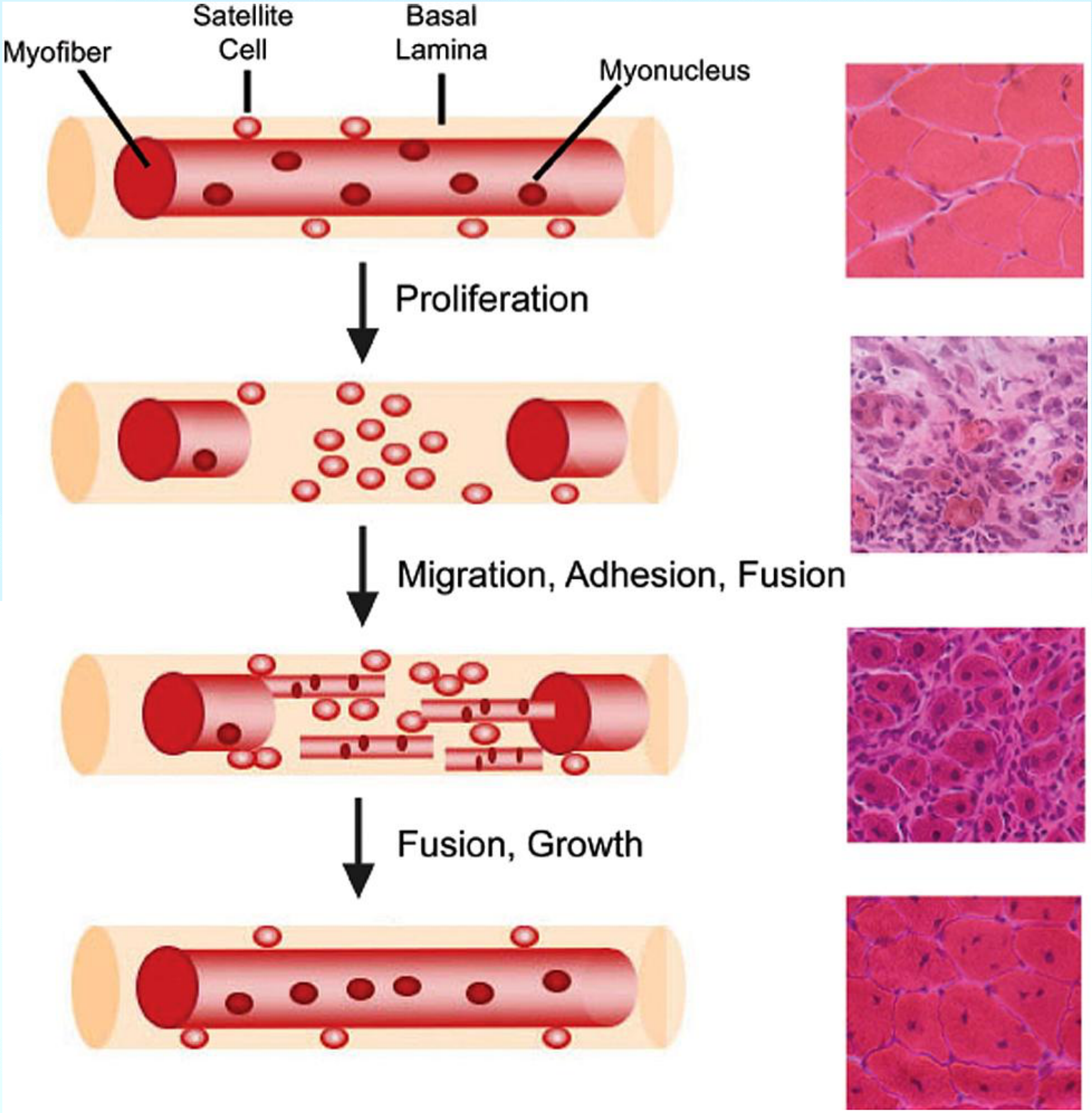
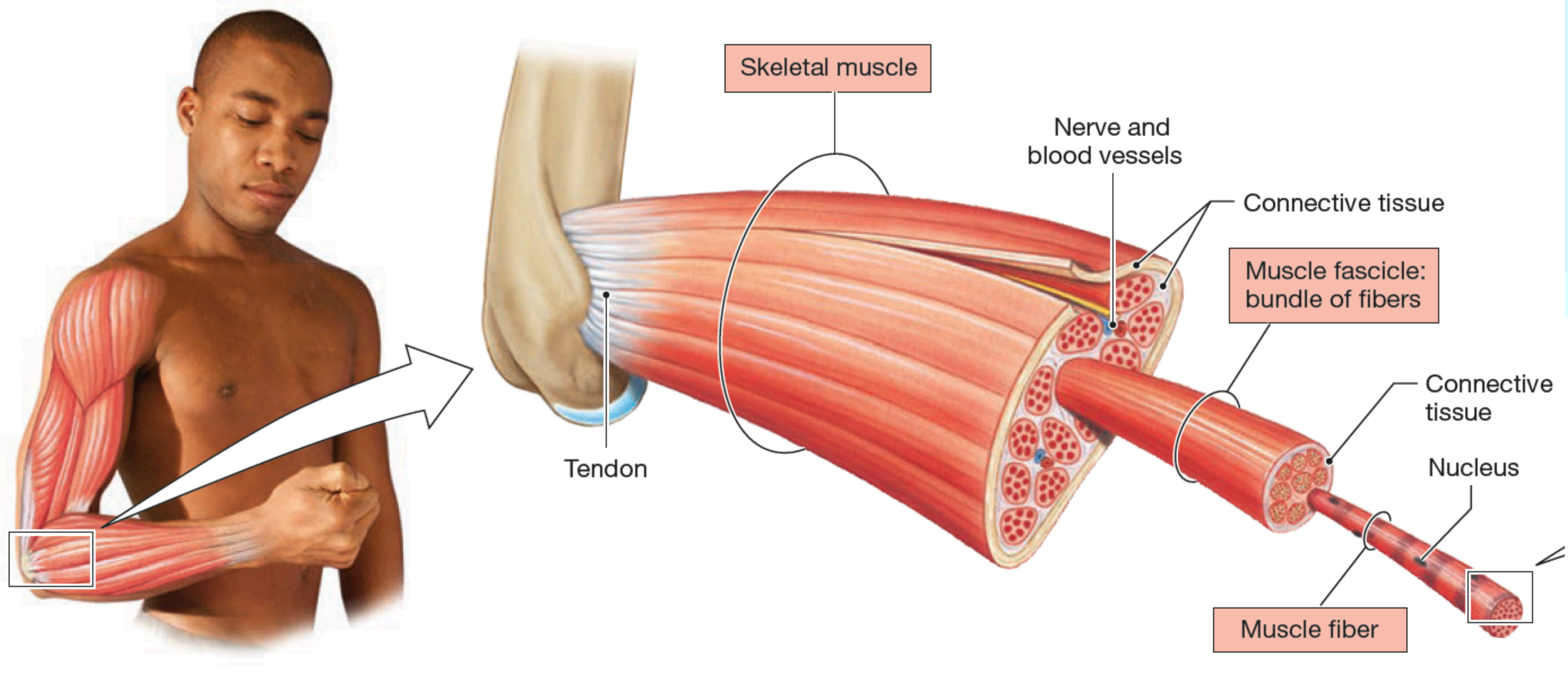
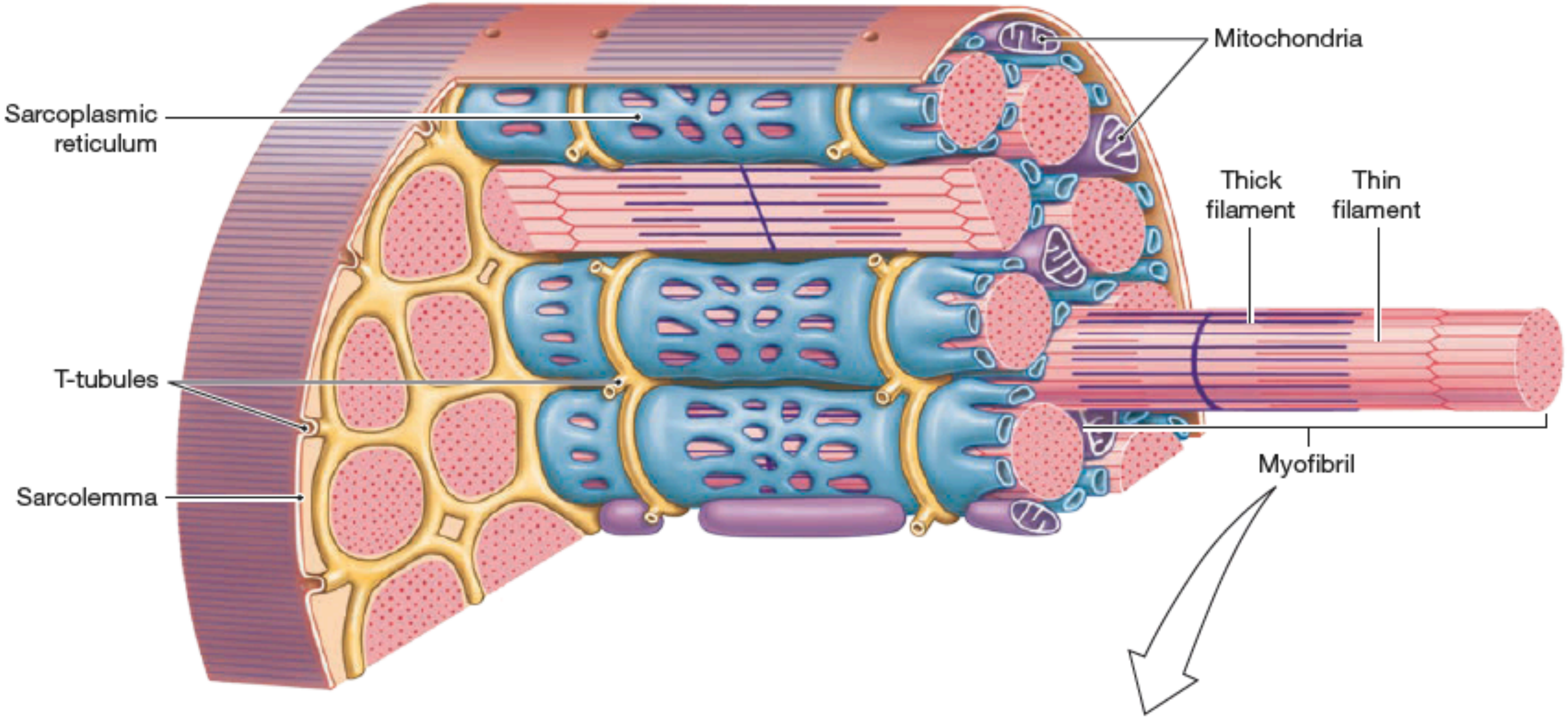


Skeletal muscle fibers are surrounded by satellite cells that are undifferentiated stem cells, normally quiescent, that in response to injury became active, proliferate and differentiate in mononucleated cells (myoblats) that can fuse with damaged fibers to repair them

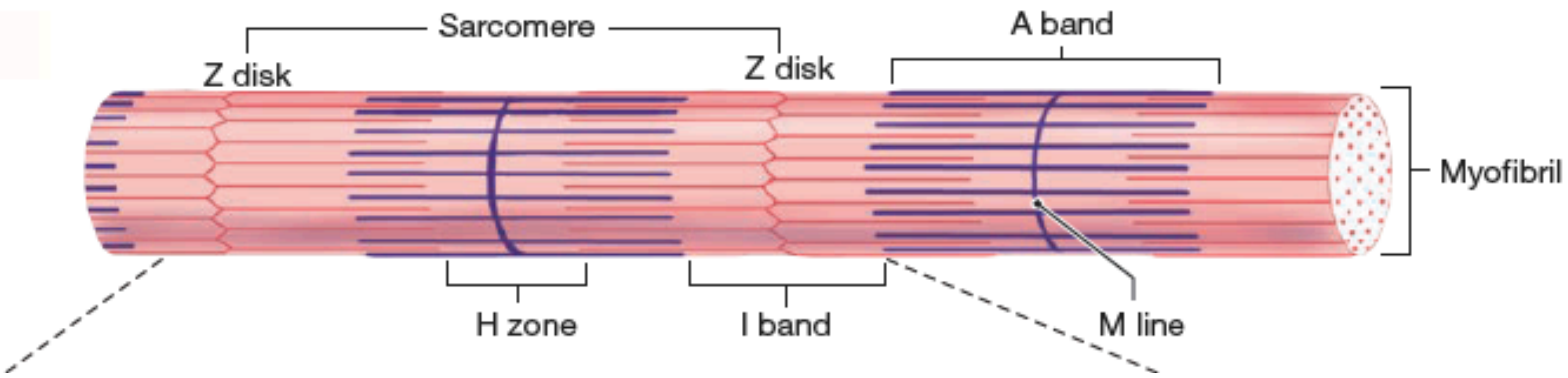
Structural characteristics of skeletal muscle



(b) Structure of a Skeletal Muscle Fiber



(c) Myofibril



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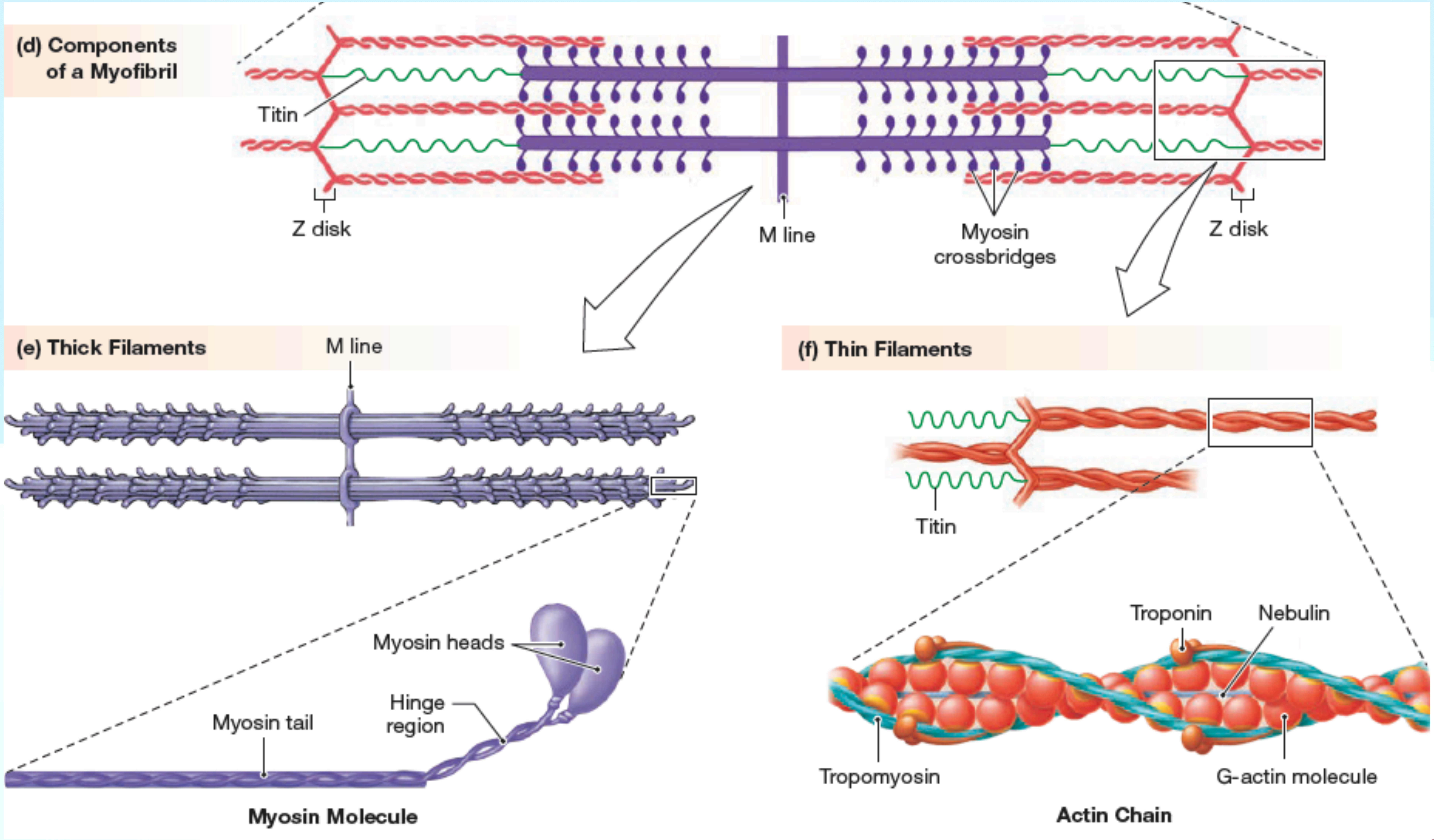
Sarcomere: the smallest functional unit of skeletal muscle tissue



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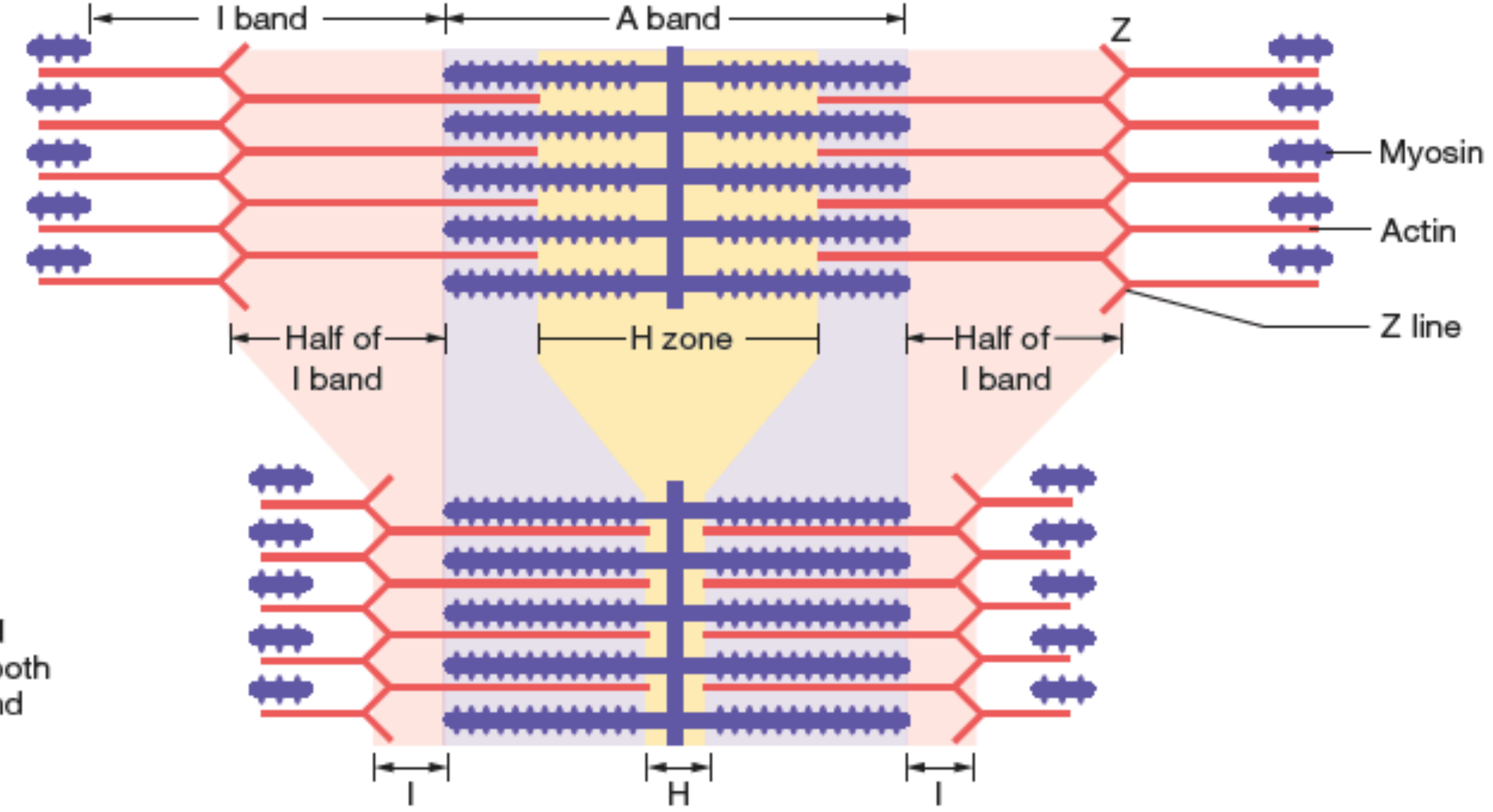
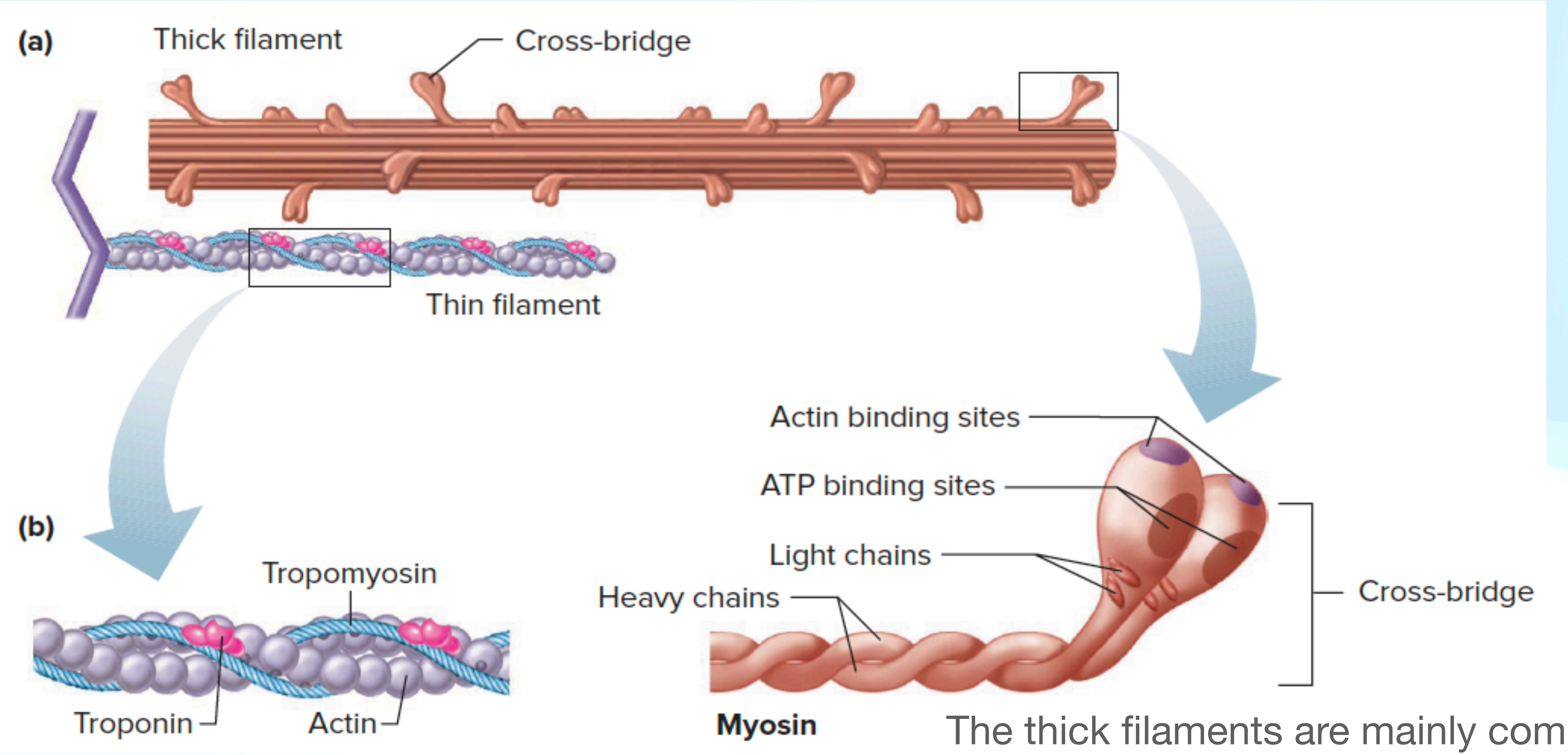
As contraction takes place, actin and myosin do not change length but instead slide past one another.

(d) Muscle Relaxed

Sarcomere shortens with contraction.

(e) Muscle Contracted
H zone and I band both shorten, while A band remains constant.





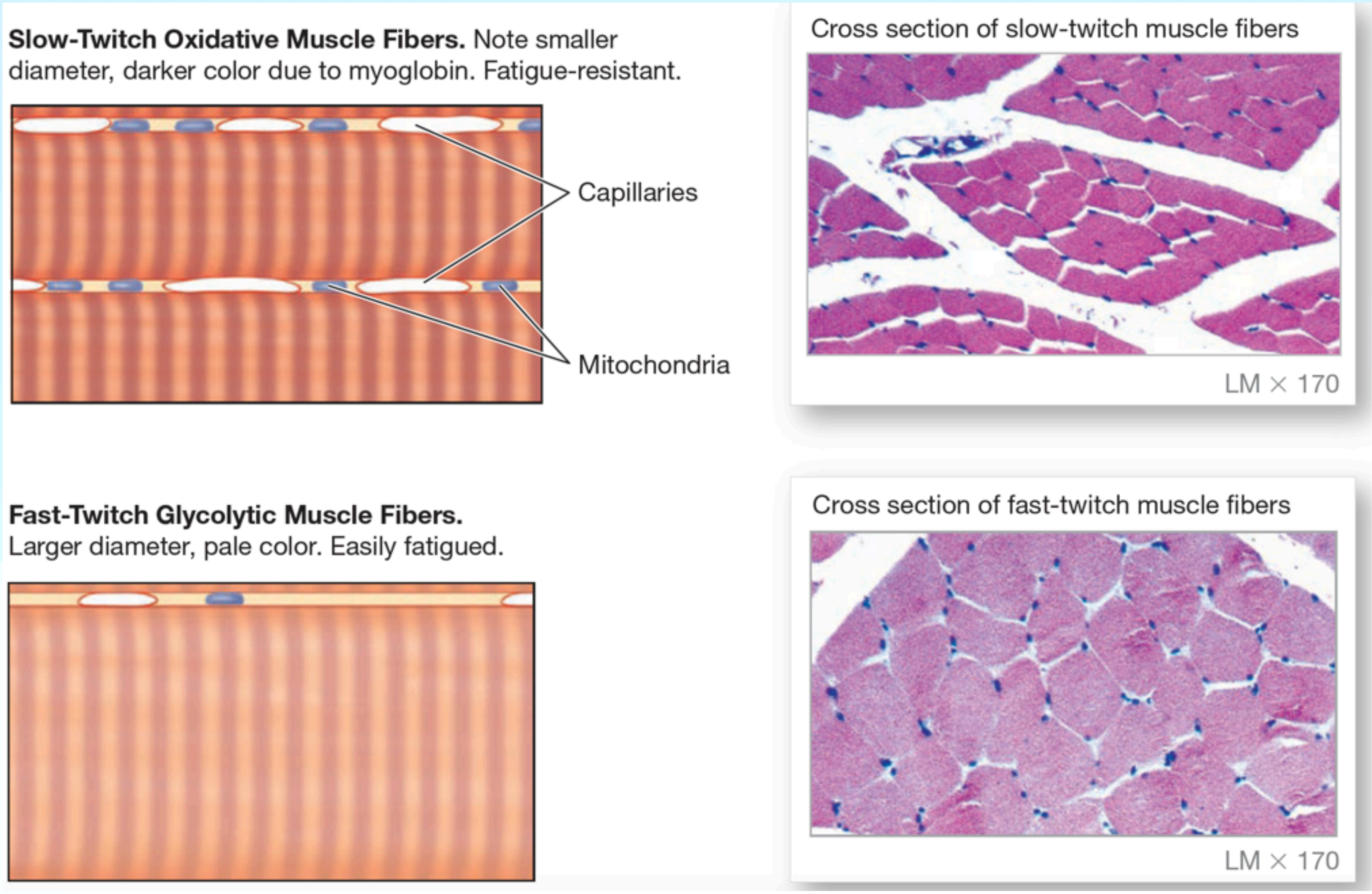
The thin filaments are principally composed of the globular protein **actin**, containing a binding site for myosin. Two other proteins—**troponin** and **tropomyosin**—are present and have important functions in regulating contraction.

The thick filaments are mainly composed by **myosin**, a protein actins as an enzyme able to hydrolyze ATP and release energy for the contraction

Myosin molecules are oriented in opposite directions, the tails are directed towards the center of the sarcomere. Whereas the heads extend out to the thick filaments forming the cross bridges.


Sarcoplasmic reticulum
Myofibrils
Cytosol
Plasma membrane
Transverse tubules
Opening of transverse tubule to extracellular fluid
Terminal cisternae
Mitochondrion

The current classification of muscle fiber types depends on the **isoform of myosin** expressed in the fiber



The currently accepted muscle fiber types in humans include **slow-twitch fibers** (also called ST or type I), **fast-twitch oxidative-glycolytic fibers** (FOG or type IIA), and **fast-twitch glycolytic fibers** (FG or type IIB/IIX).

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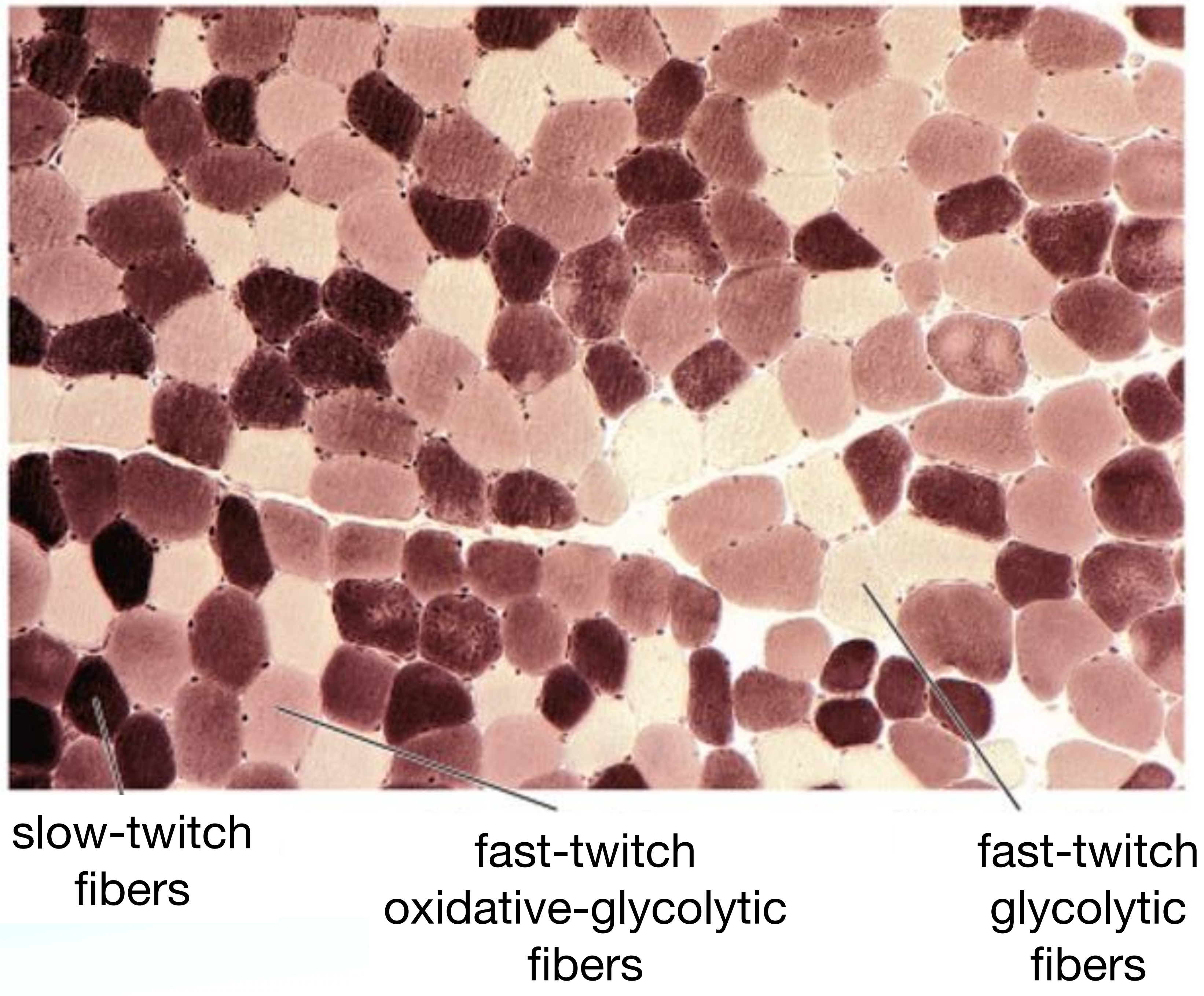
- **Slow-oxidative fibers** combine low myosin ATPase activity with high oxidative capacity
- **Fast-oxidative-glycolytic fibers** combine high myosin ATPase activity with high oxidative capacity and intermediate glycolytic capacity
- **Fast-glycolytic fibers** combine high myosin ATPase activity with high glycolytic capacity



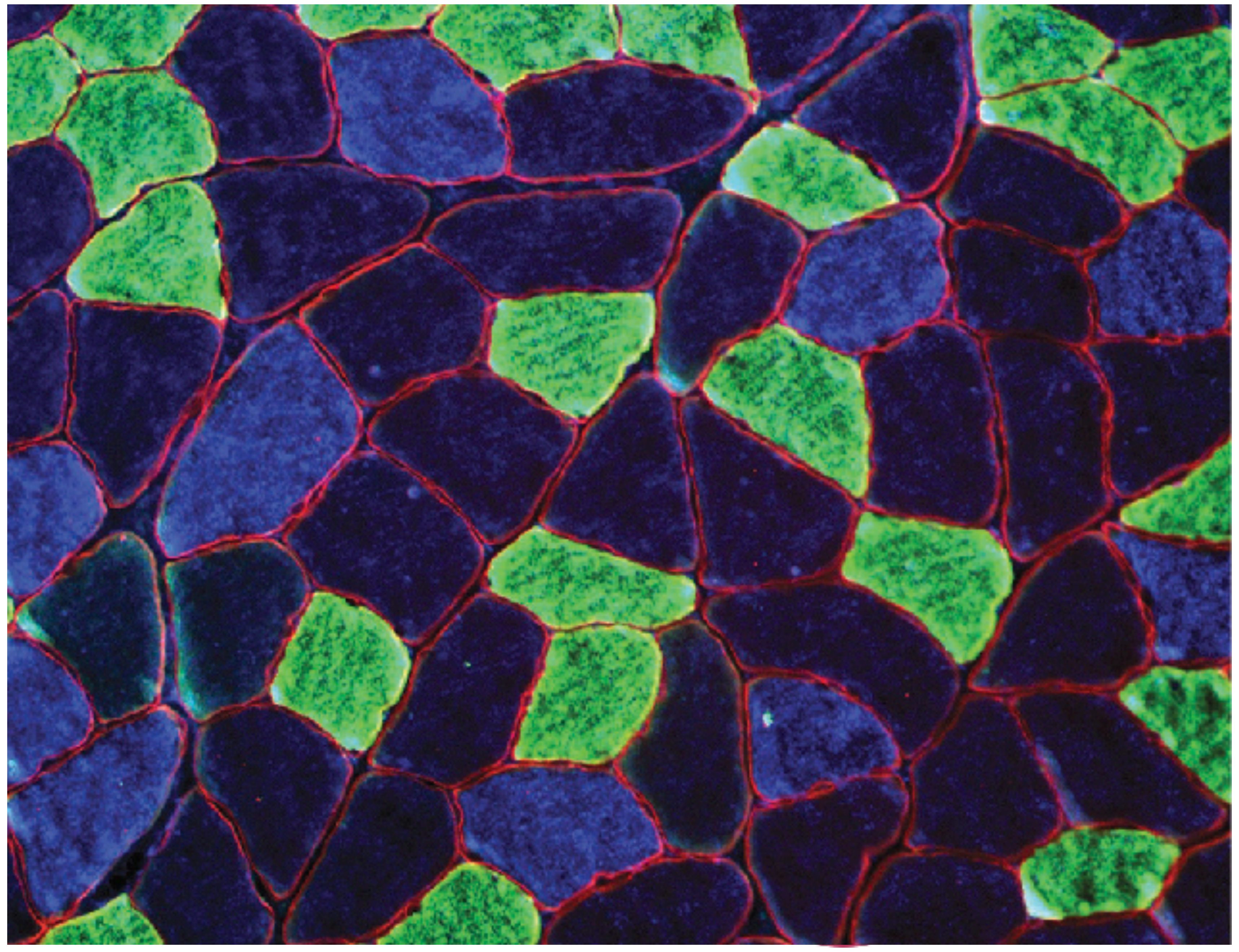
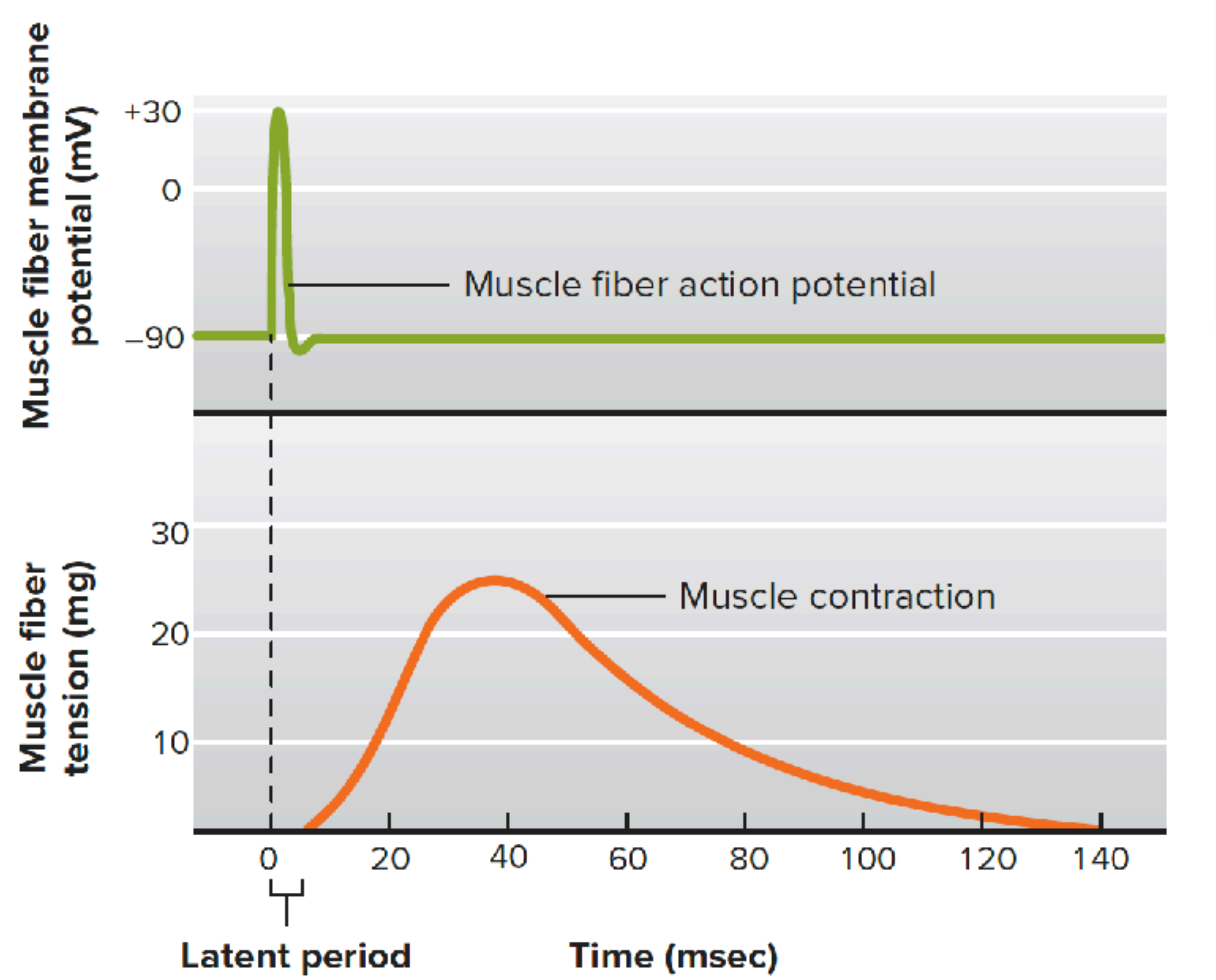


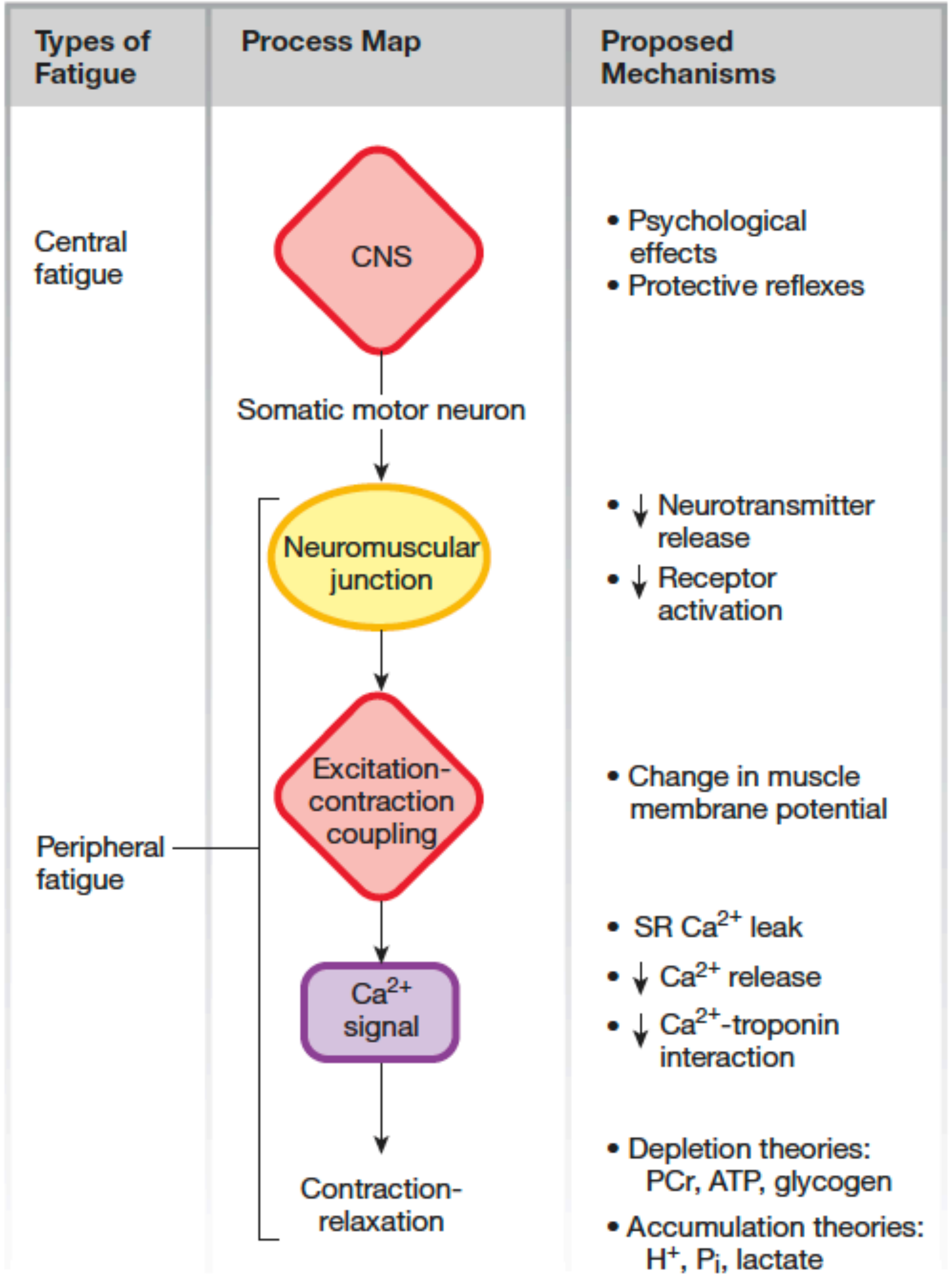
TABLE 9.3 Characteristics of the Three Types of Skeletal Muscle Fibers

	Slow-Oxidative Fibers (Type 1)	Fast-Oxidative-Glycolytic Fibers (Type 2A)	Fast-Glycolytic Fibers (Type 2X)*
Primary source of ATP production	Oxidative phosphorylation	Oxidative phosphorylation	Glycolysis
Mitochondria	Many	Intermediate	Few
Capillaries	Many	Many	Few
Myoglobin content	High (red muscle)	High (red muscle)	Low (white muscle)
Glycolytic enzyme activity	Low	Intermediate	High
Glycogen content	Low	Intermediate	High
Rate of fatigue	Slow	Intermediate	Fast
Myosin-ATPase activity	Low	Intermediate	High
Contraction velocity	Slow	Fast	Fastest
Fiber diameter	Small	Large	Large
Size of motor neuron innervating fiber	Small	Intermediate	Large

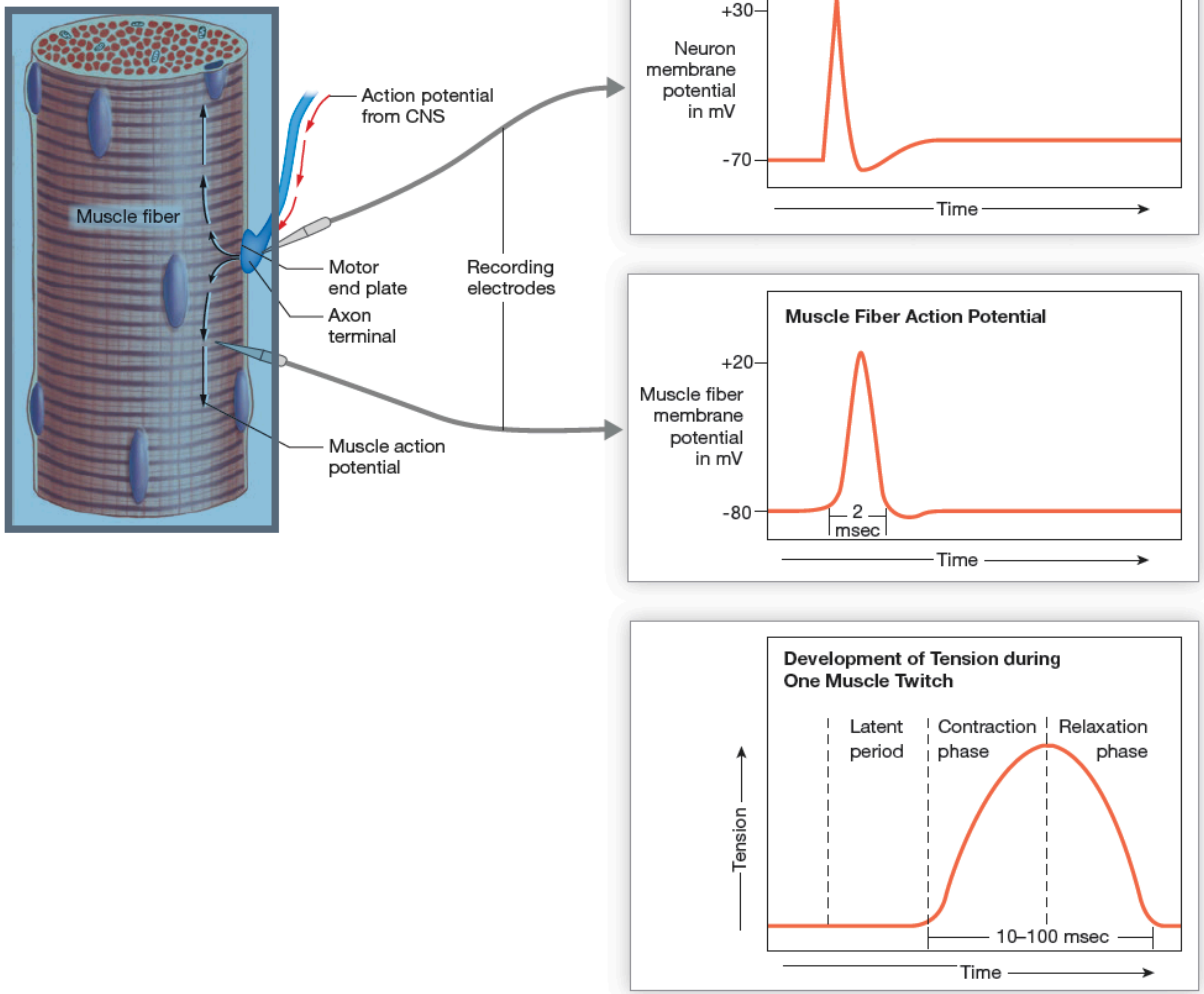
Excitation-contraction coupling and force production

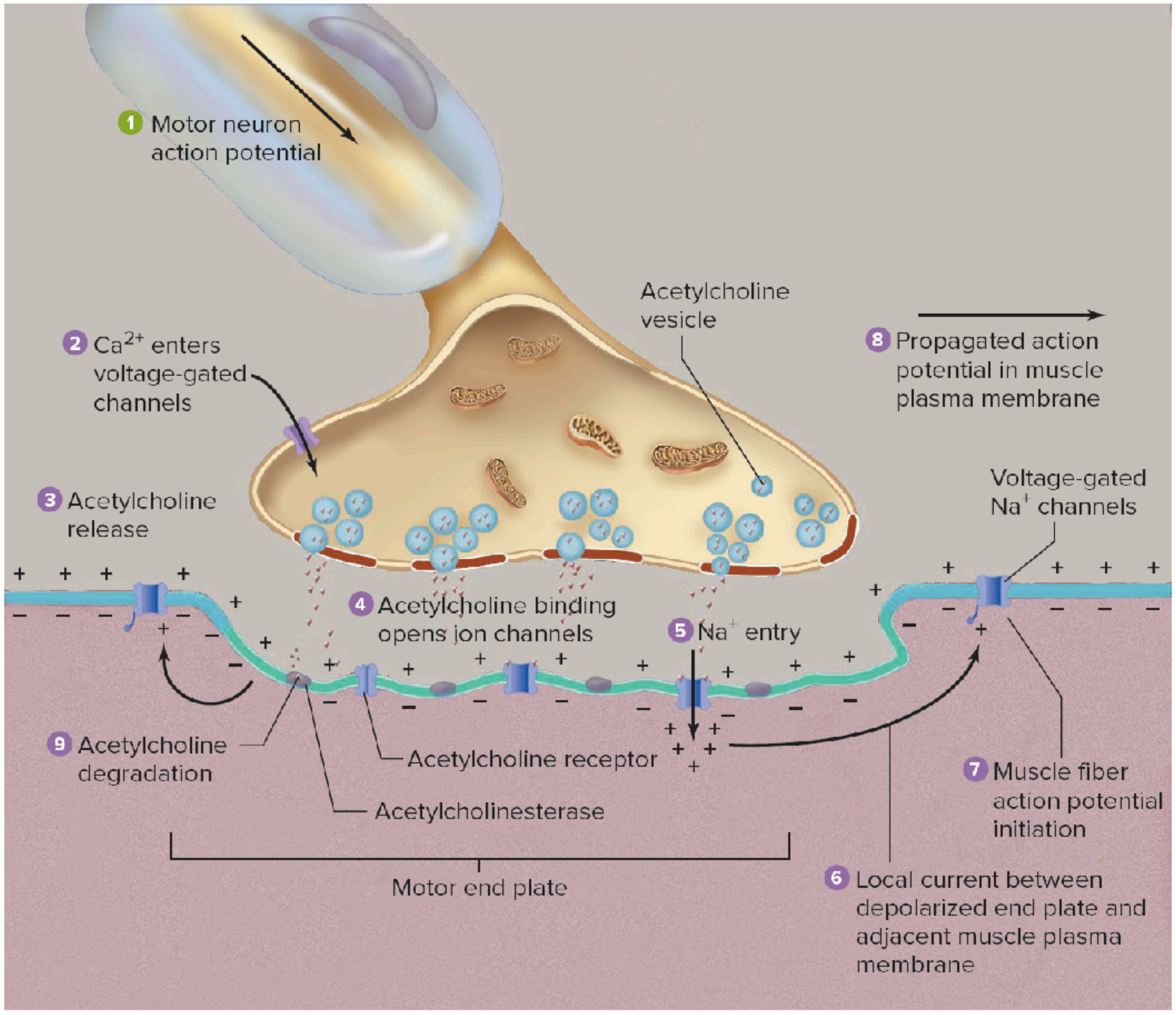
Sequence of events
by which an action potential in the
plasma membrane activates
the force-generating mechanisms.





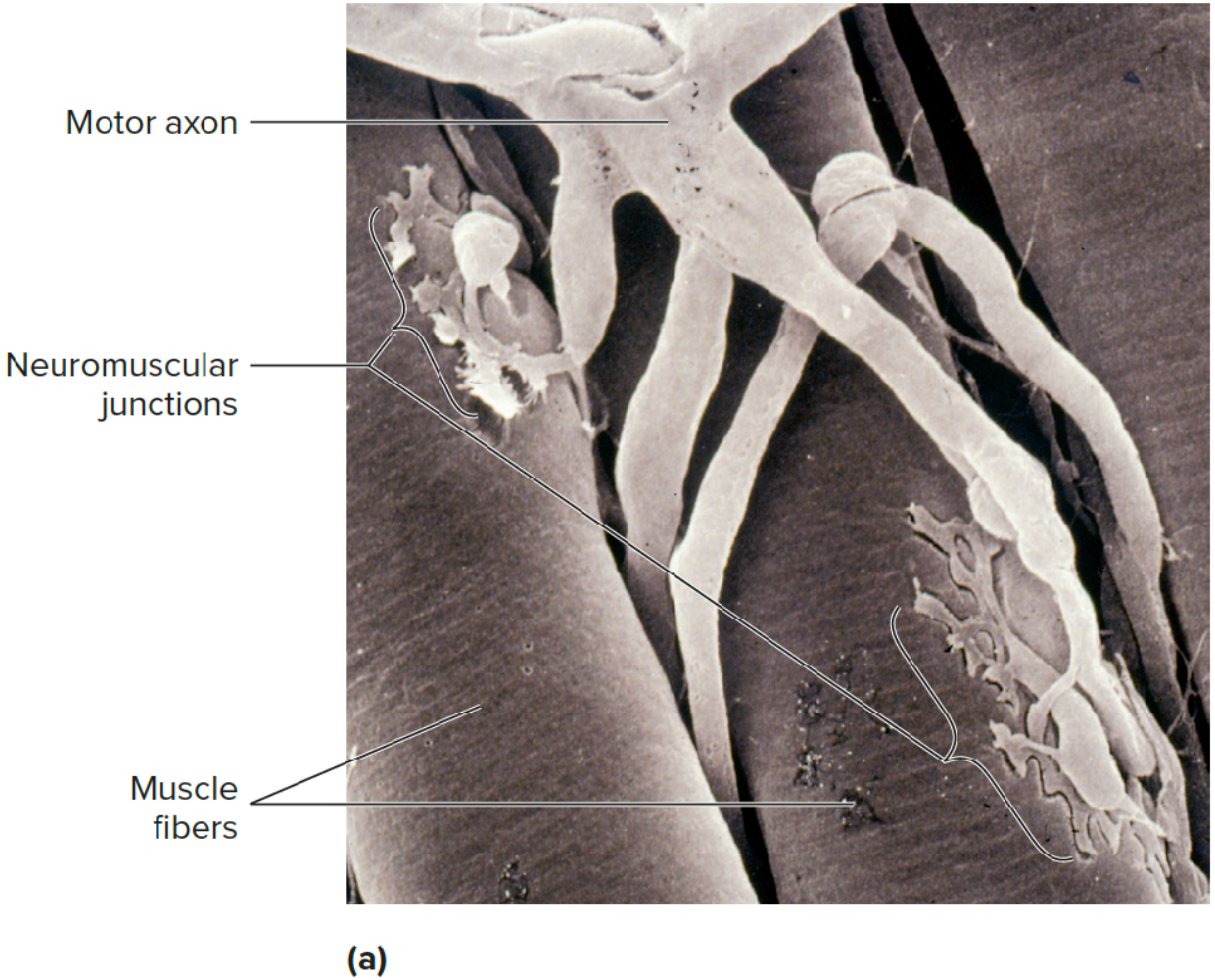
Action potentials in the axon terminal (top graph) and in the muscle fiber (middle graph) are followed by a muscle twitch (bottom graph).

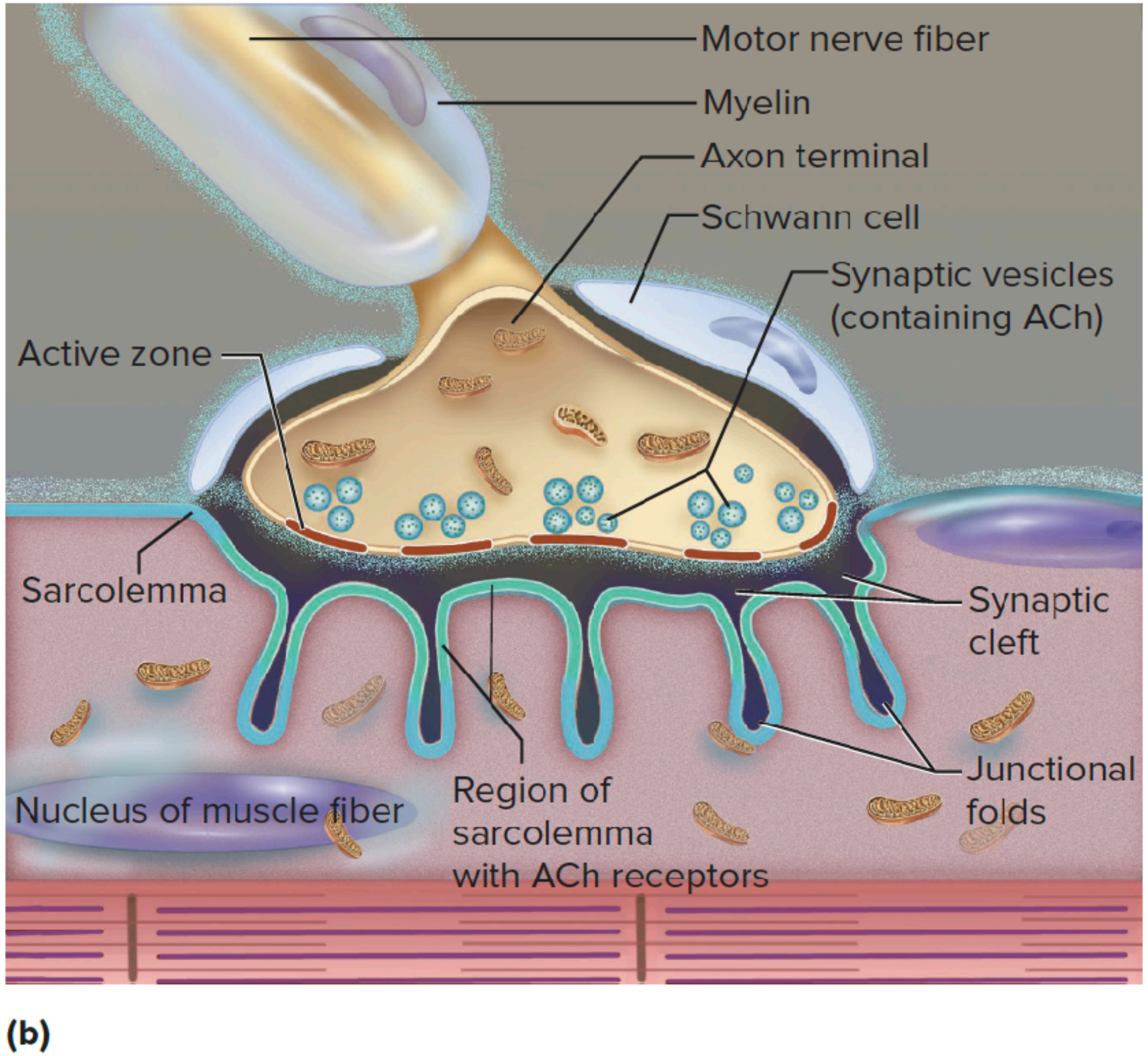




Neuromuscular junction

a synaptic junction between a motor neuron and a muscle fiber in which the neurotransmitter Ach is released and by which the action potential is propagated from motor neuron to muscle fiber





Upon reaching a muscle, the axon of a motor neuron divides into many branches, each branch forming a single synapse with a muscle fiber.

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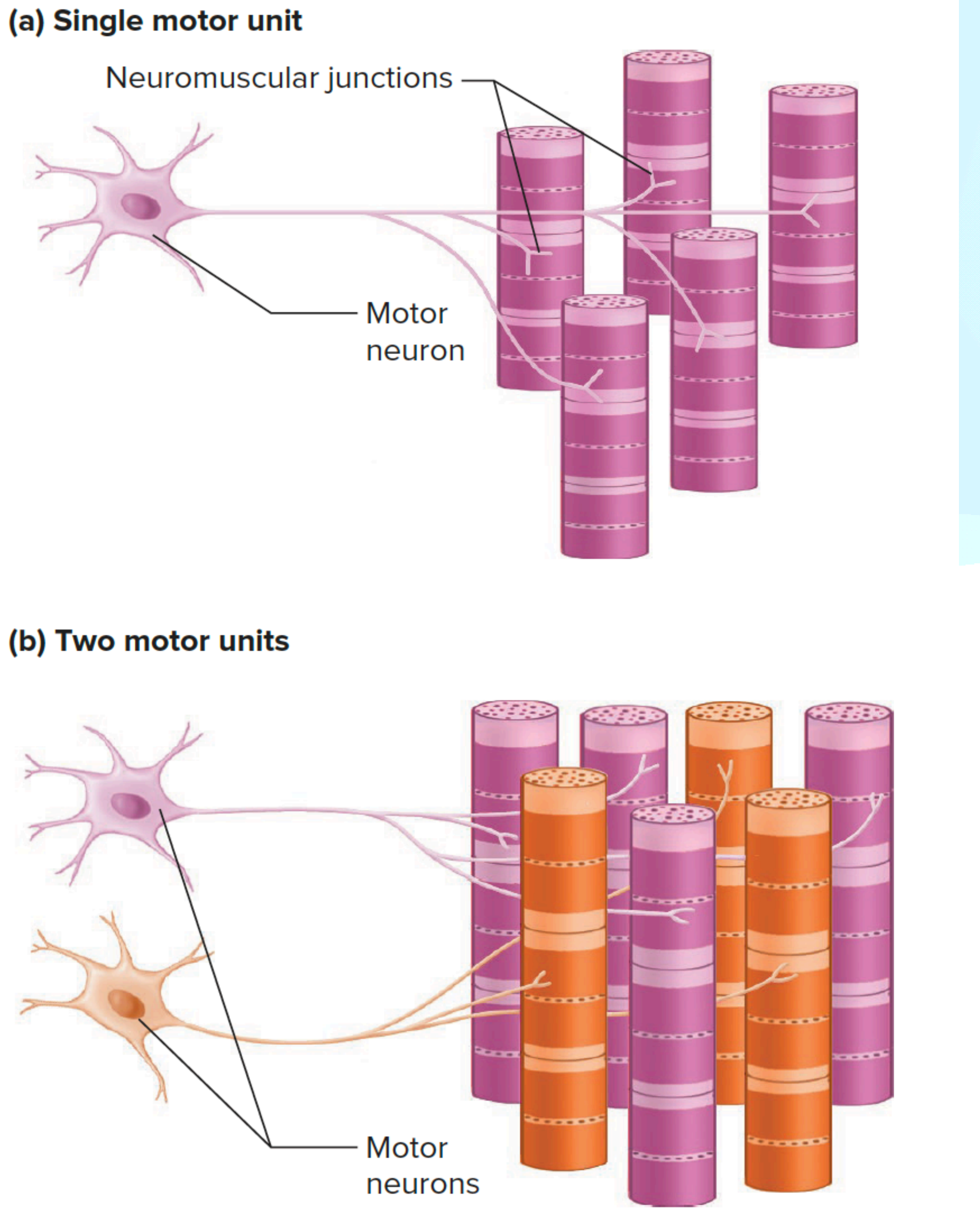
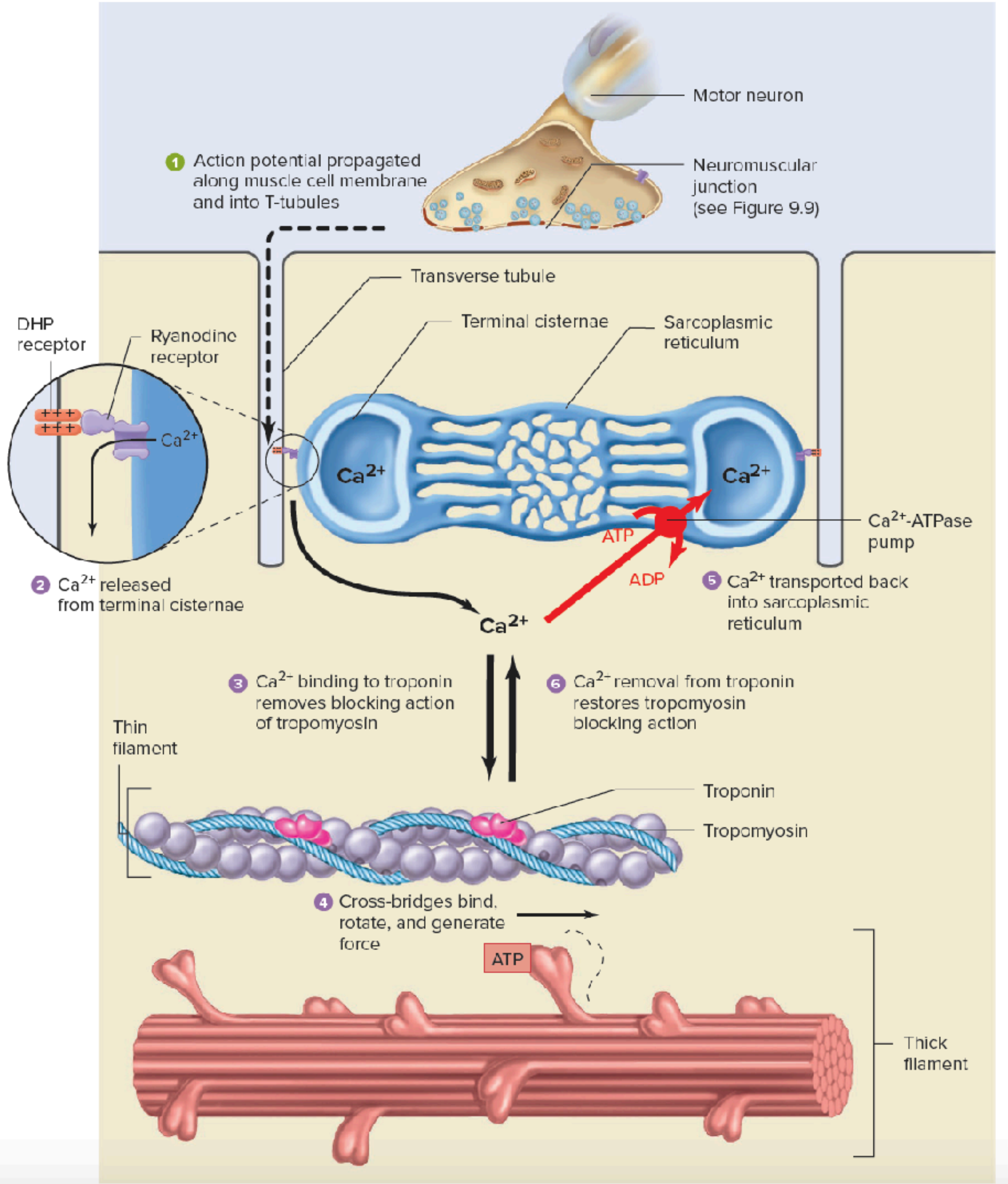
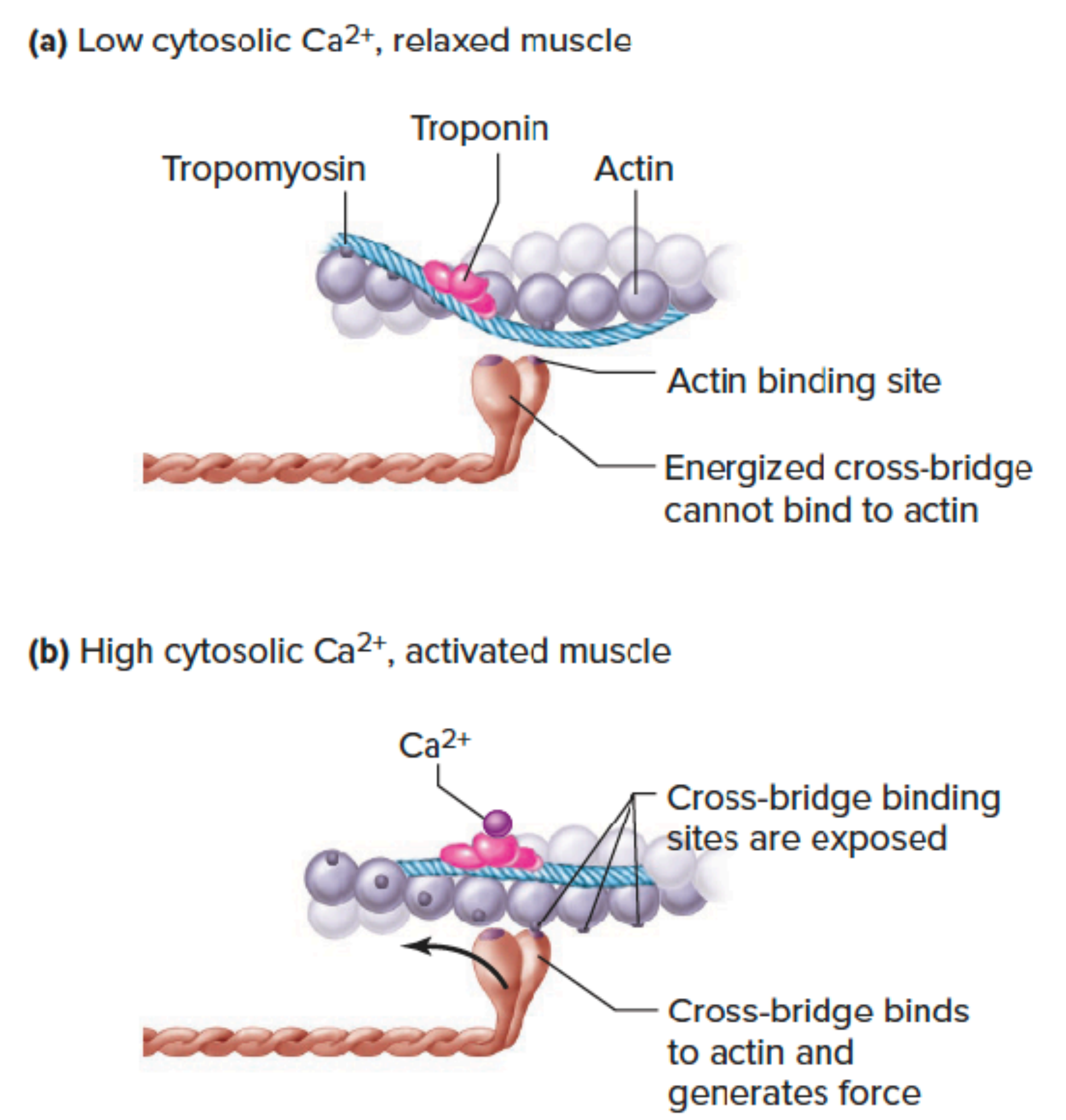
A single motor neuron innervates many muscle fibers, but each muscle fiber is controlled by a branch from only one motor neuron. Together, a motor neuron and the muscle fibers it innervates are called a **motor unit**.

The muscle fibers in a single motor unit are located in one muscle, but they are distributed throughout the muscle and are not necessarily adjacent to each other. When an action potential occurs in a motor neuron, **all the muscle fibers in its motor unit are stimulated to contract**.







Electrical events control changes in cytosolic Ca2+ concentration, modulating muscle contraction

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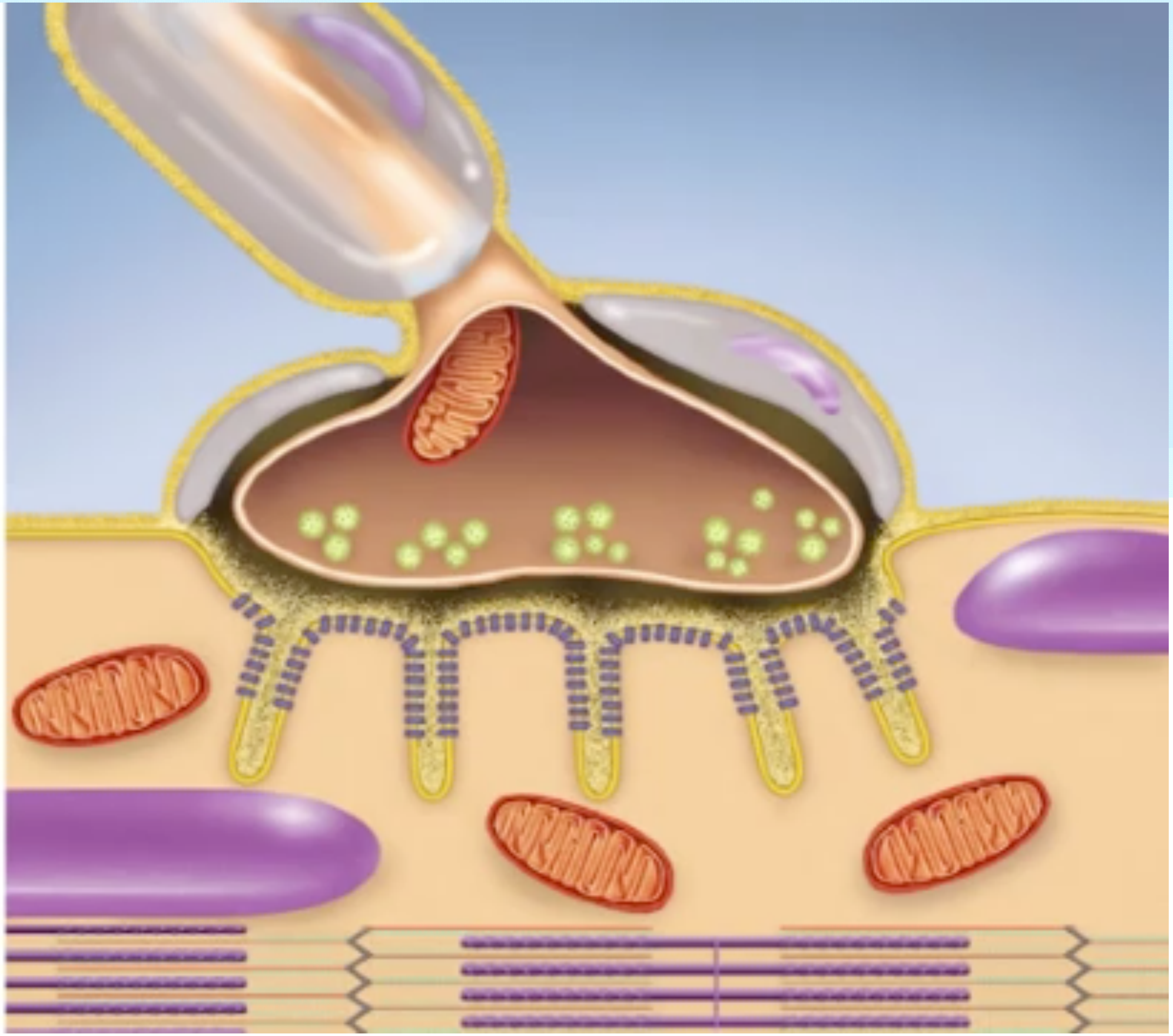

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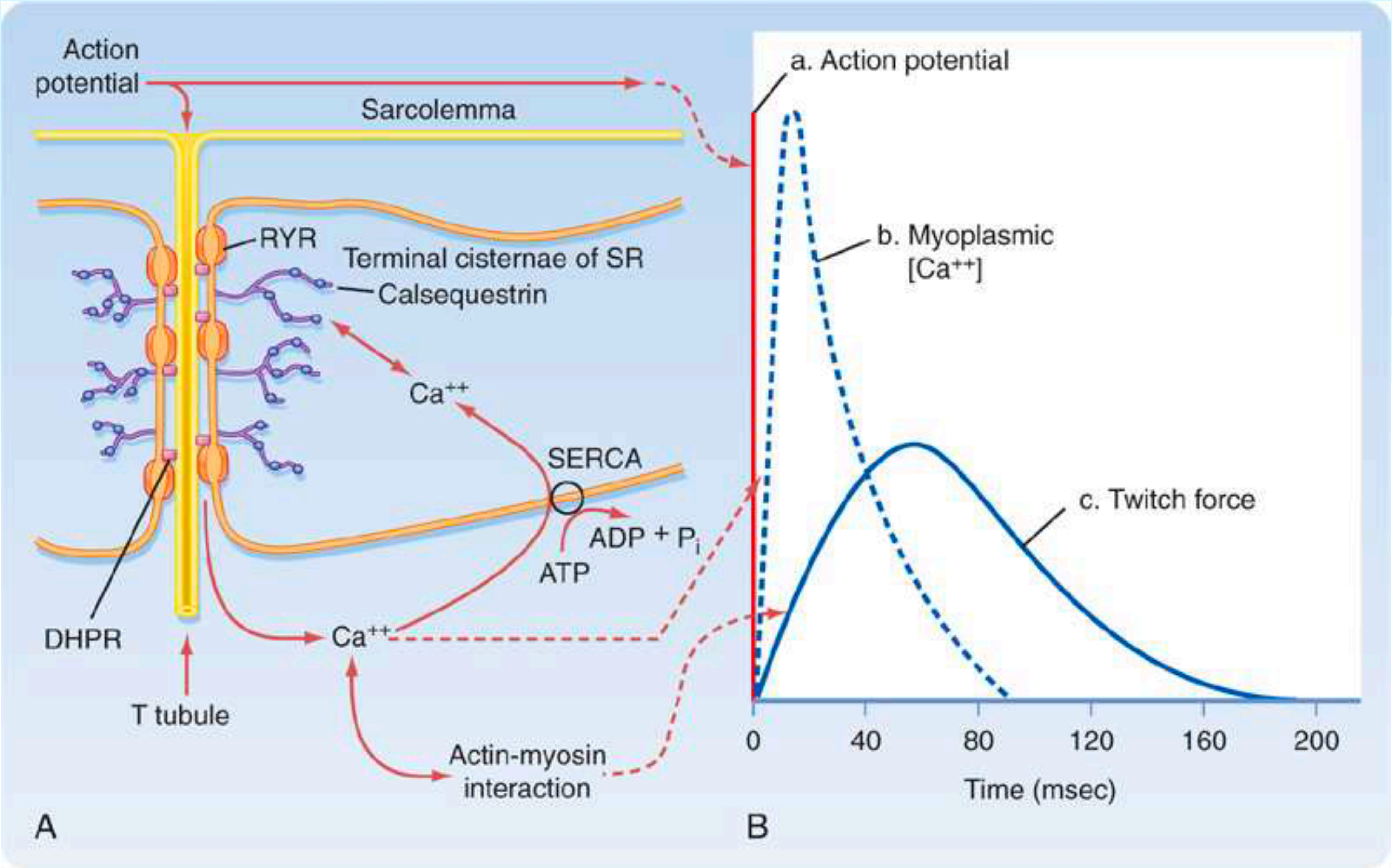
Stimulation of a skeletal muscle fiber initiates an action potential in the muscle that travels down the T tubule and induces release of Ca2+ from the terminal cisternae of the SR .

The rise in intracellular [Ca2+] causes muscle contraction.

As Ca2+ is pumped back into the SR by Ca2+-ATPase (SERCA), relaxation occurs.



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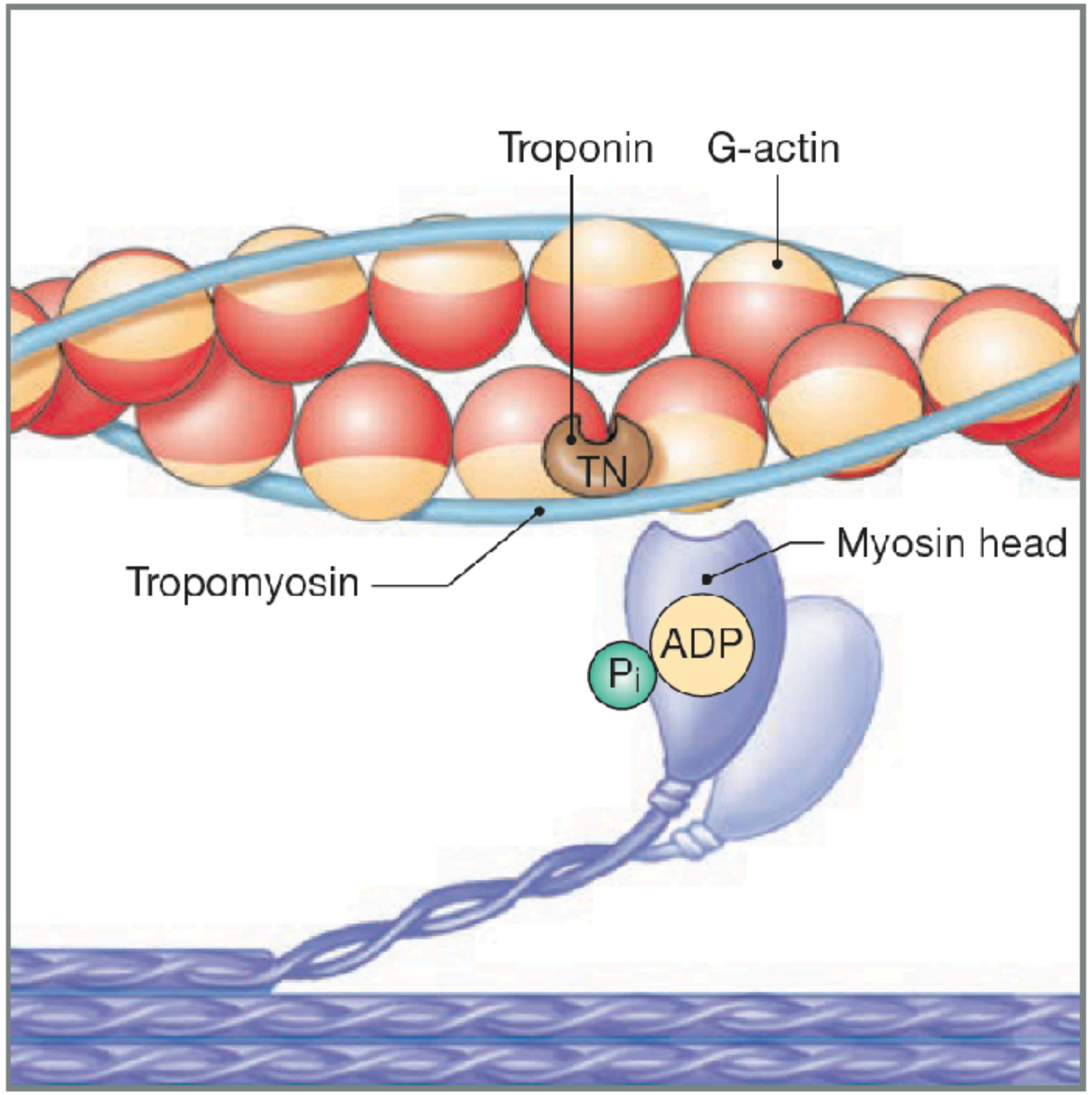
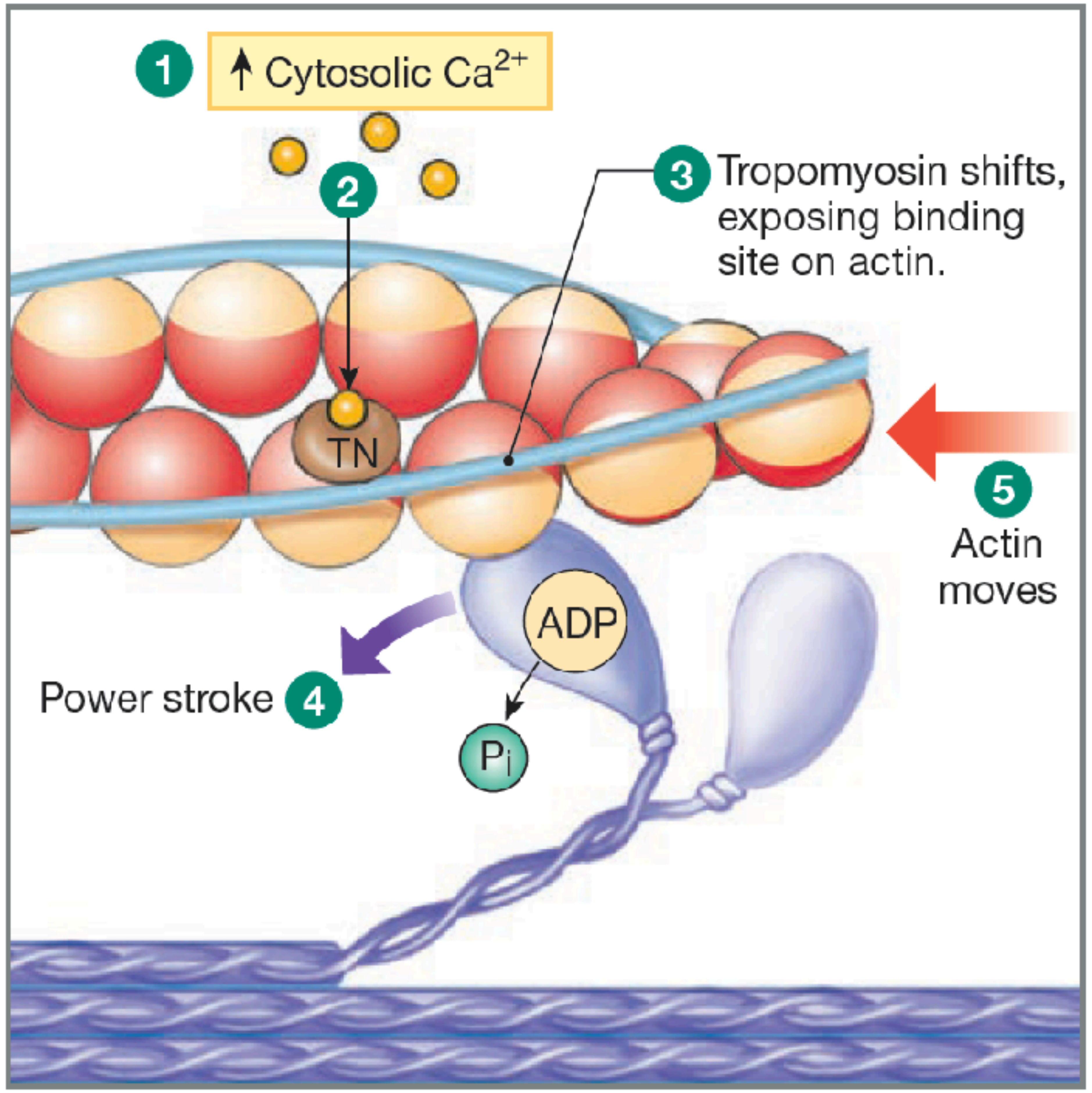
(a) Relaxed state.
Myosin head cocked. Tropomyosin partially blocks binding site on actin. Myosin is weakly bound to actin.



(b) Initation of contraction.
A calcium signal initiates contraction.



1. Ca^{2+} levels increase in cytosol.
2. Ca^{2+} binds to troponin (TN).
3. Troponin-Ca^{2+} complex pulls tropomyosin away from actin's myosin-binding site.
4. Myosin binds strongly to actin and completes power stroke.
5. Actin filament moves.

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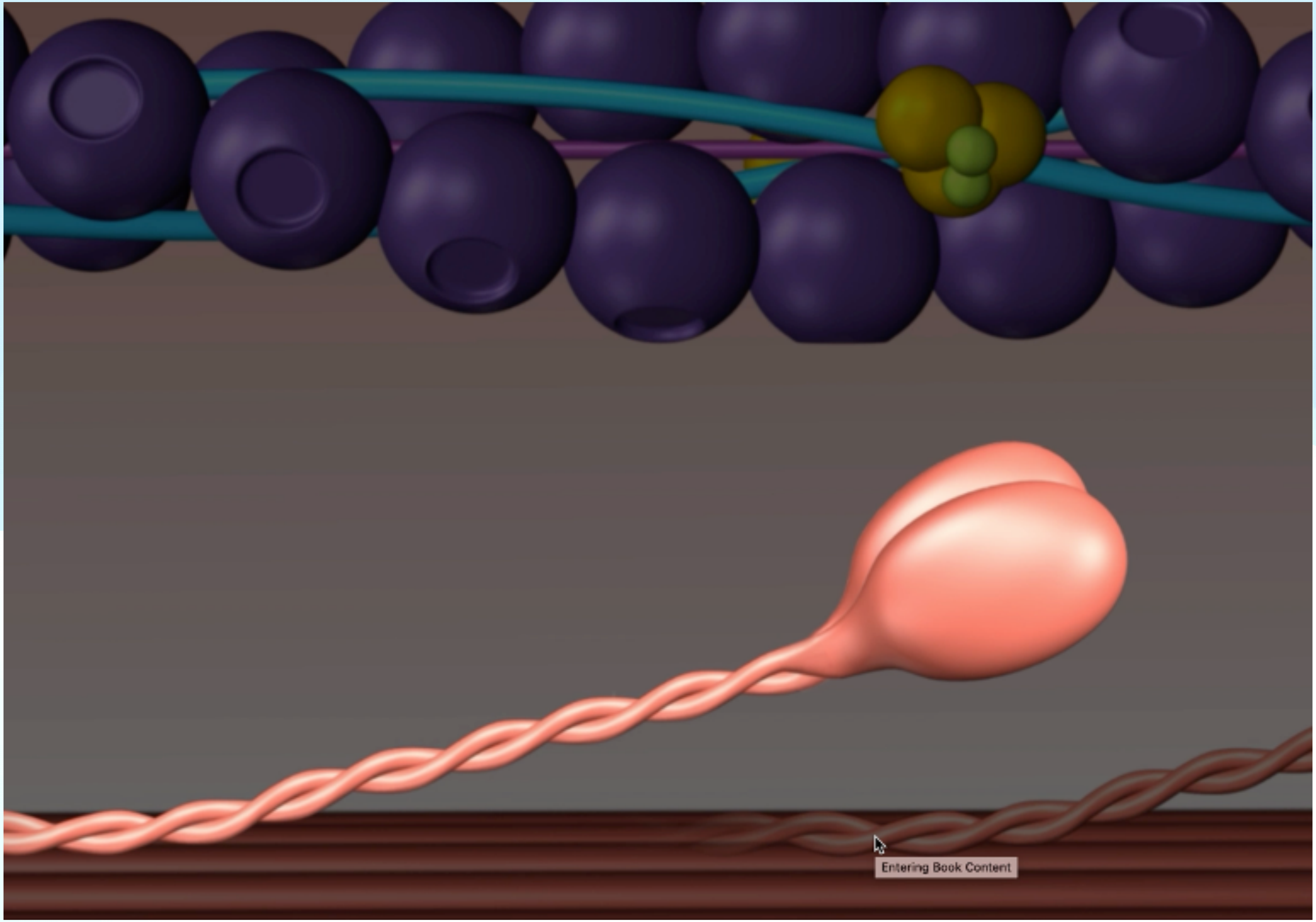

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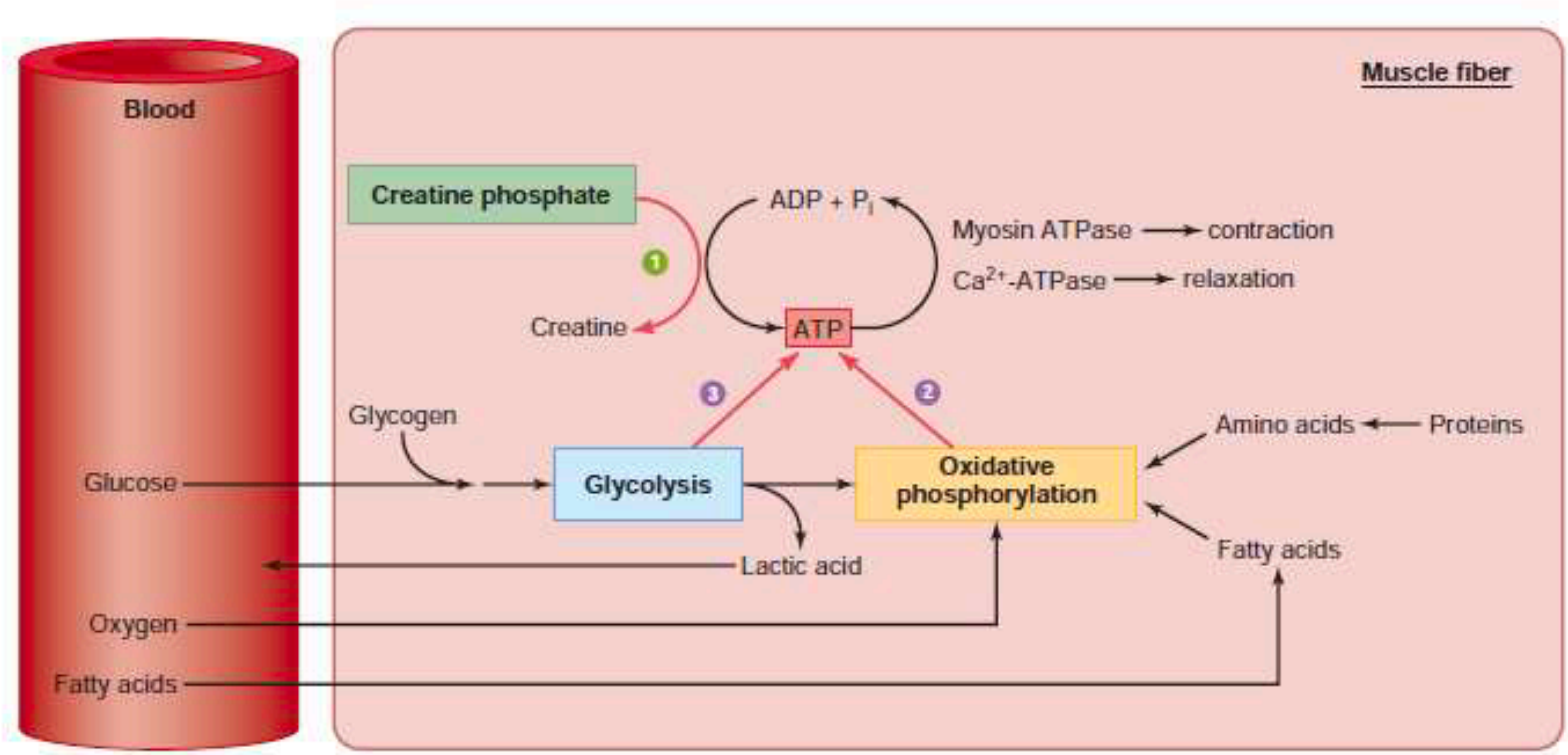
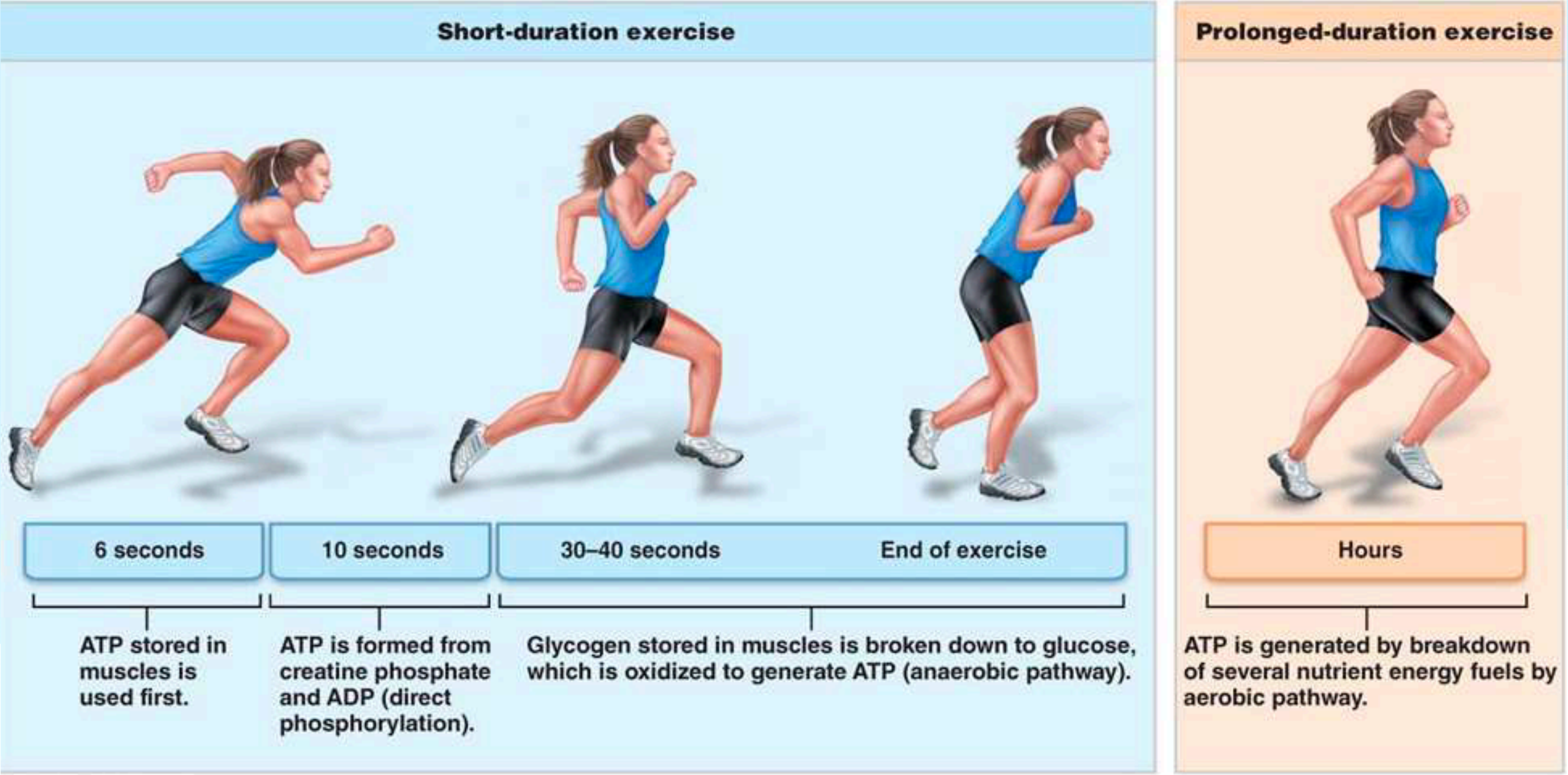
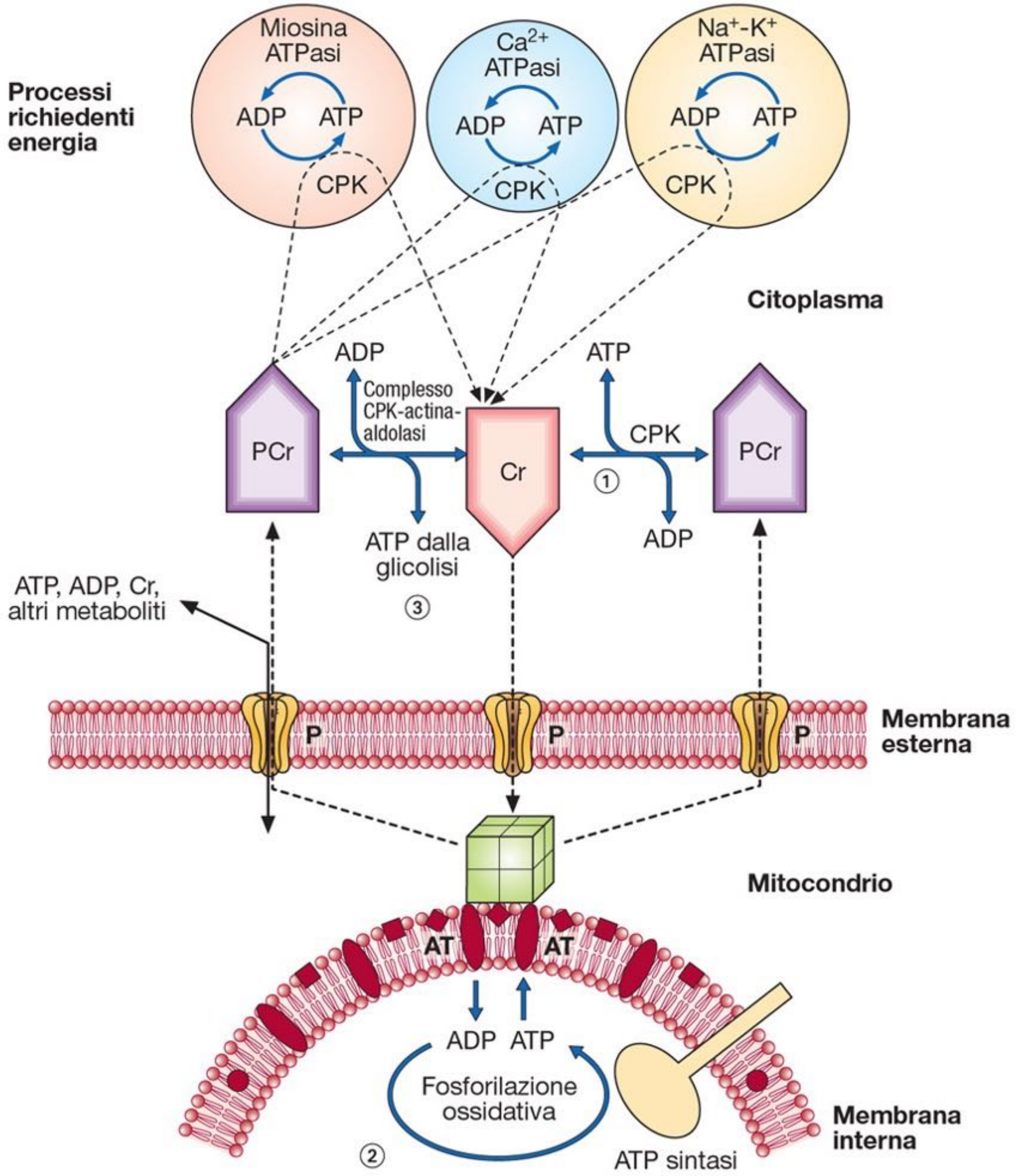

Blood
Muscle fiber
Creatine phosphate
1
Creatine
ADP + Pi
ATP
Myosin ATPase → contraction
Ca2+-ATPase → relaxation
3
2
Glycogen
Glucose
Glycolysis
Oxidative phosphorylation
Amino acids
Proteins
Lactic acid
Fatty acids
Oxygen
Fatty acids



The phosphorylation of ADP by CP provides a very rapid means of forming ATP but the ATP production is very small

Most of the ATP is formed by oxidative phosphorylation is used in long duration muscular activity at moderate levels of intensity

The oxidative pathway produces great quantities of ATP (36 molecules) but can produce ATP very slowly



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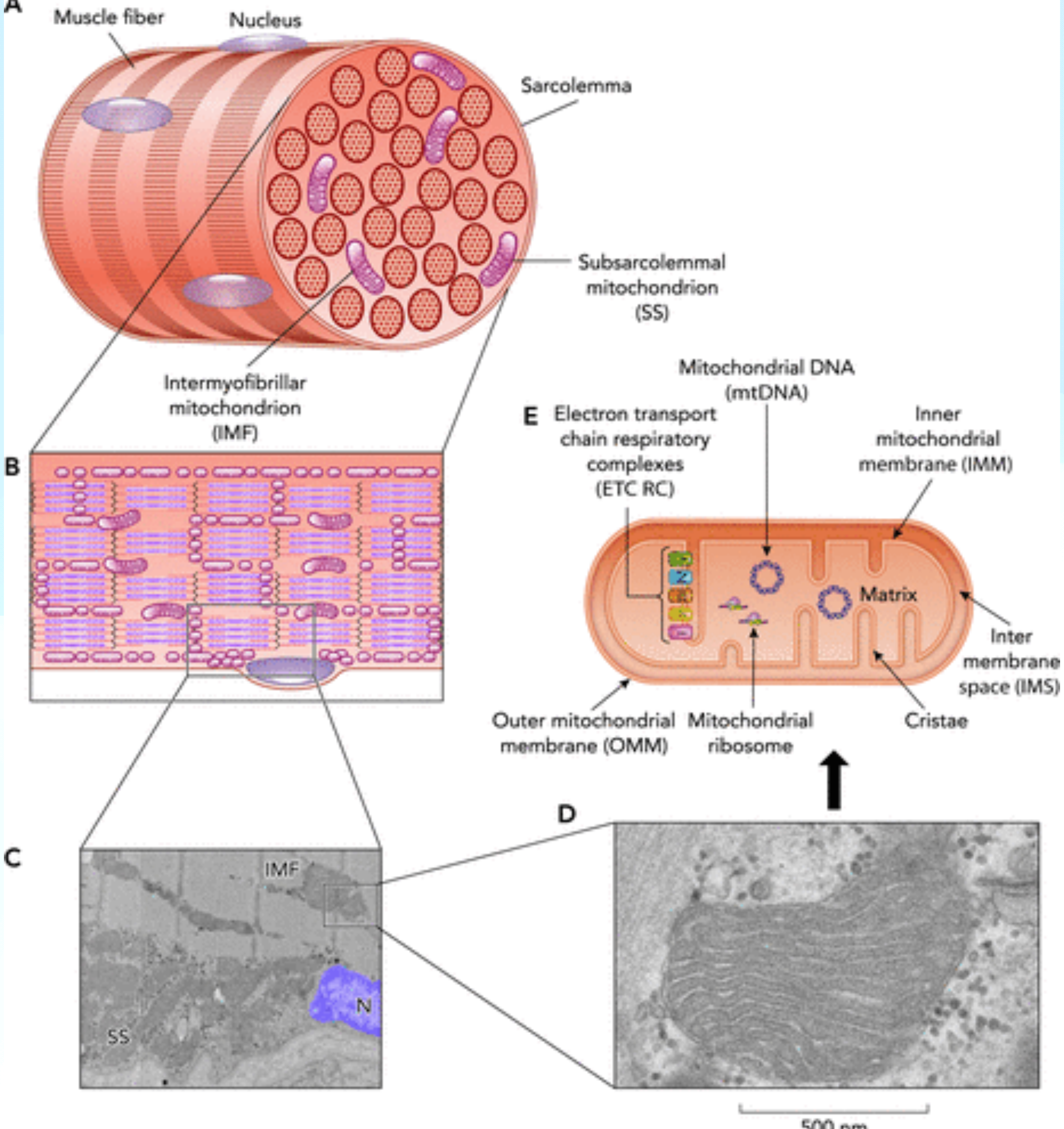

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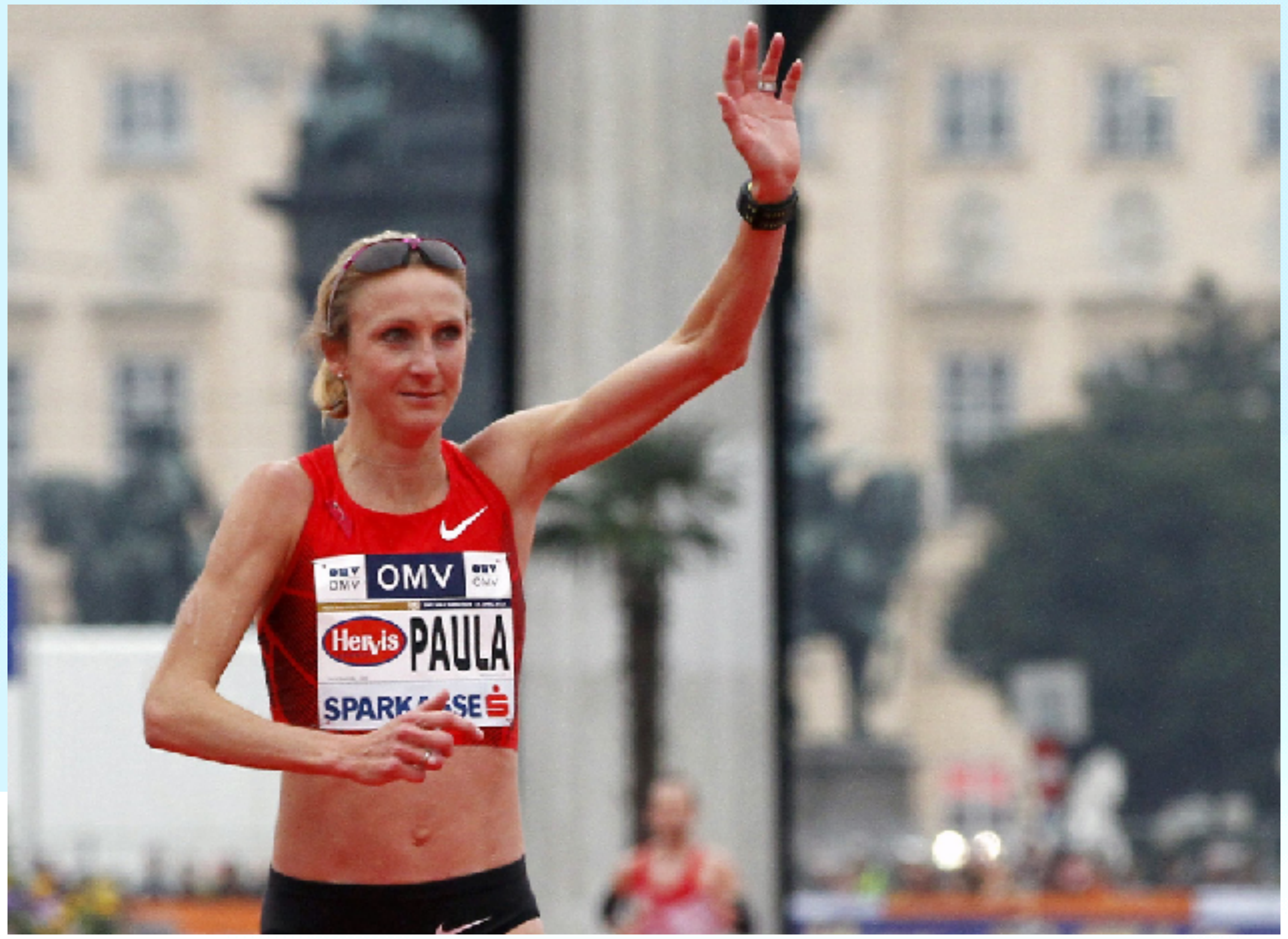
EFFECTS OF ENDURANCE AND RESISTANCE TRAINING ON MUSCLE STRUCTURE AND FUNCTION



Muscle function and phenotype is related to the specific mode of muscle activation an individual engages in. Repetitive stressful use of muscle tissue (**exercise training**) leads to characteristic muscle structural and functional modifications resulting in an improved mechanical performance for the particular mode that the muscle has been stressed. Classically, we distinguish between **endurance training** (low load-high repetitive stimulus) and **strength training** (high load-low repetitive).

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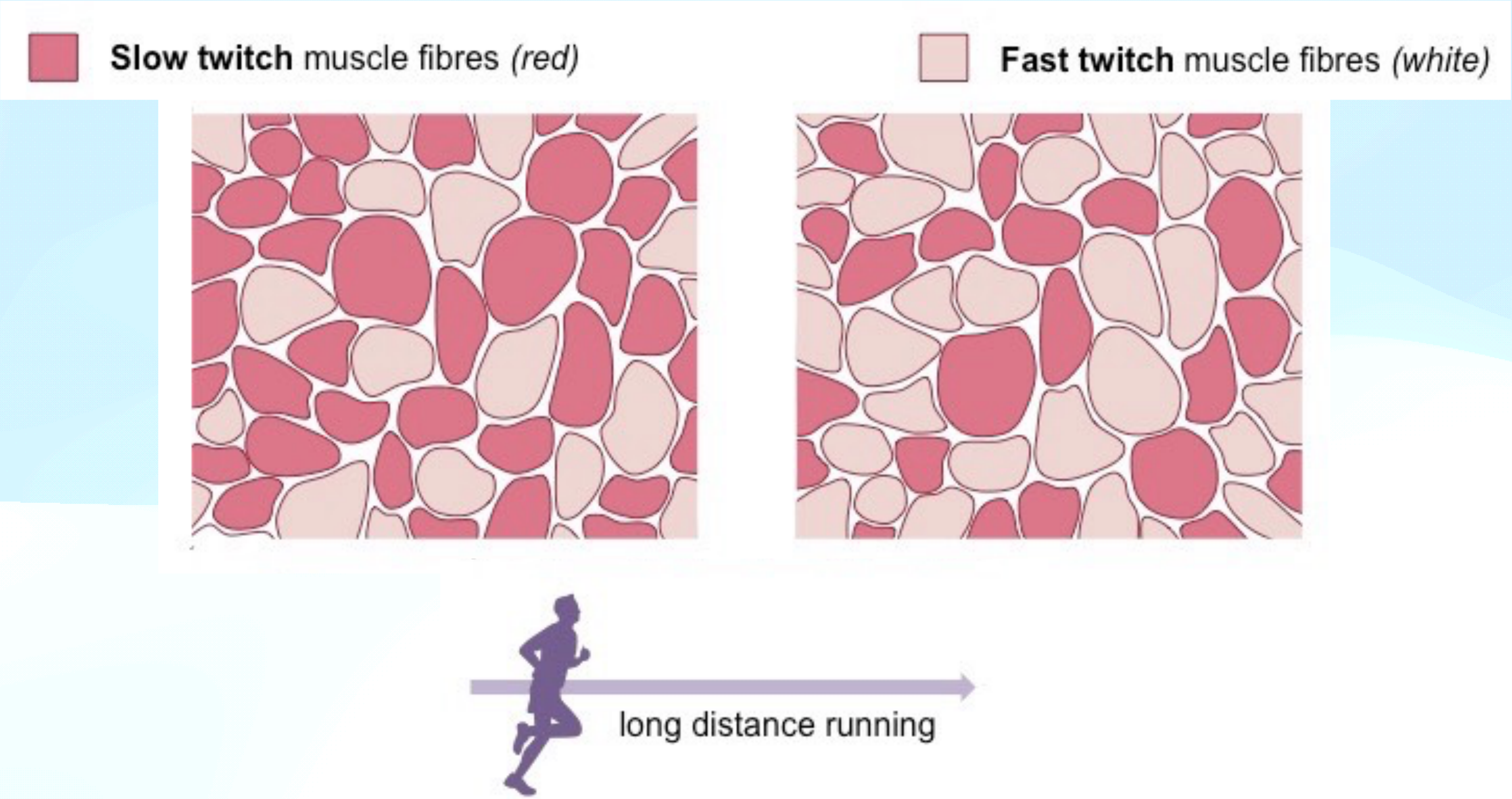
Muscle plasticity in response to endurance training



In muscle tissue, we find the contractile phenotype to drift toward an increased expression of slower myosin phenotypes sometimes associated with a fiber-type shift. Fiber cross-sectional area is little affected by endurance-type exercise

Muscle plasticity in response to endurance training

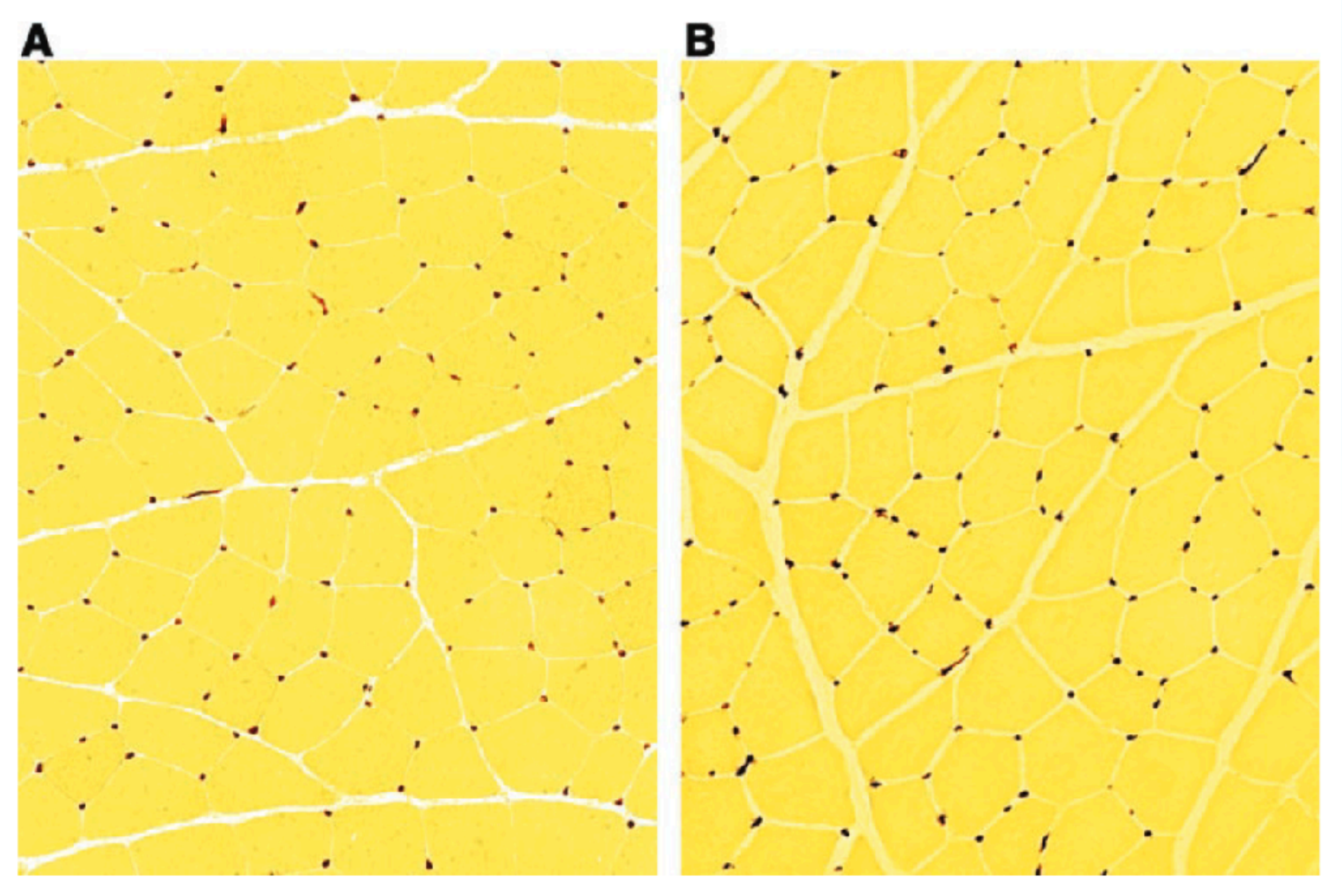


Fig. 2. Angiogenesis increases capillarity in the superficial gastrocnemius muscle of the rat following endurance-type exercise training (*B*) compared with cage-sedentary control (*A*). Capillaries were stained for alkaline phosphatase activity and counterstained with metanil yellow and appear as dark brown circles or lines. Muscle fibers are stained yellow.

Muscle capillarity is enhanced to match the increased demand for oxygen flux by muscle mitochondria.

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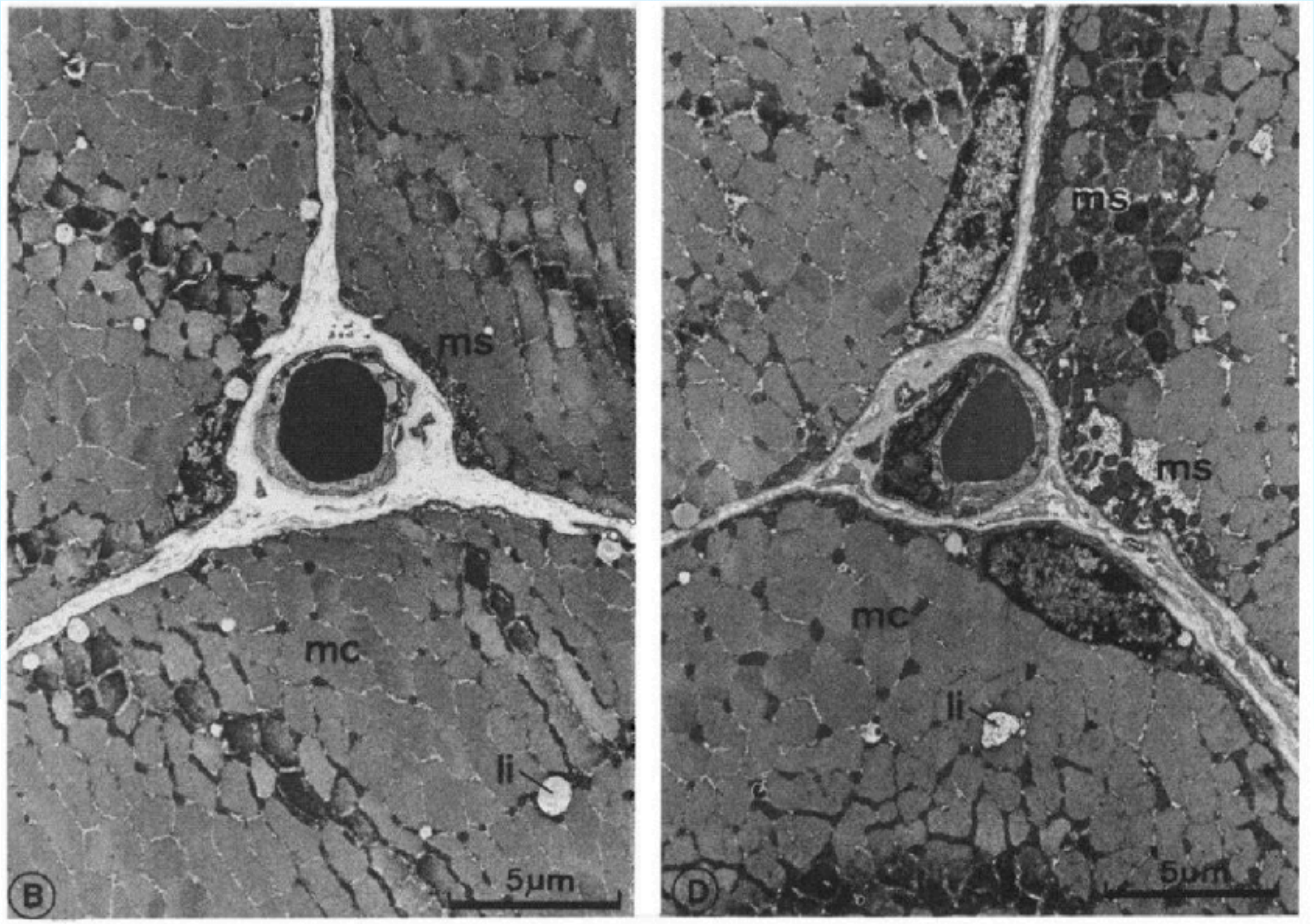
Muscle plasticity in response to endurance training



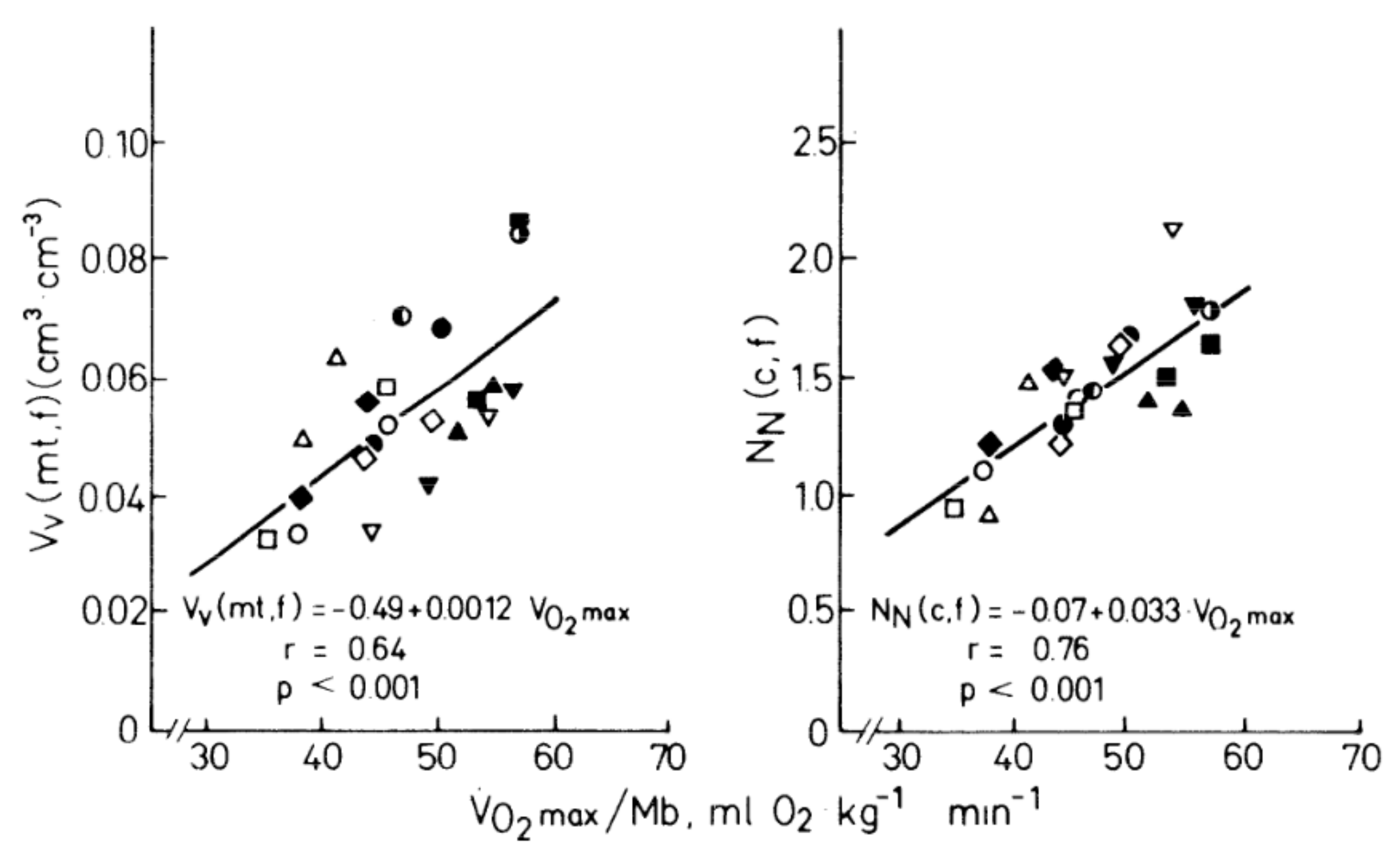


FIG. 5. Relation of volume density of mitochondria, $V_V(mt,f)$, and capillary-to-fiber ratio, $N_N(c,f)$, to mass-specific rate of maximal O_2 consumption, $\dot{V}O_{2\,max}/M_b$ (*symbols*, see Fig. 4).

The muscle mitochondrial compartment can rapidly be expanded with endurance-type exercise in particular when subjectswere previously untrained. Gains in mitochondrial volume of >30% have been realized in periods of 6 weeks.

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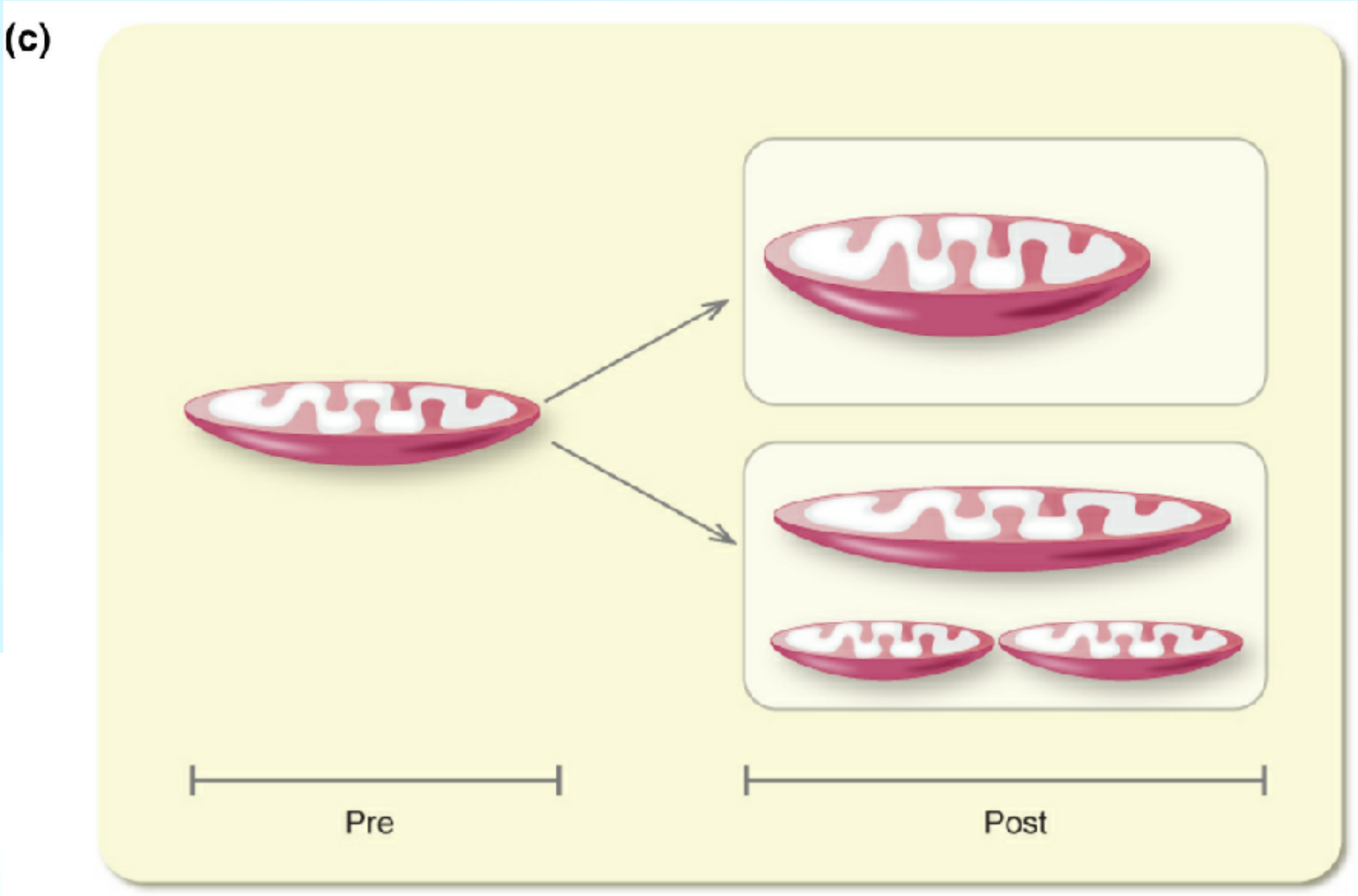
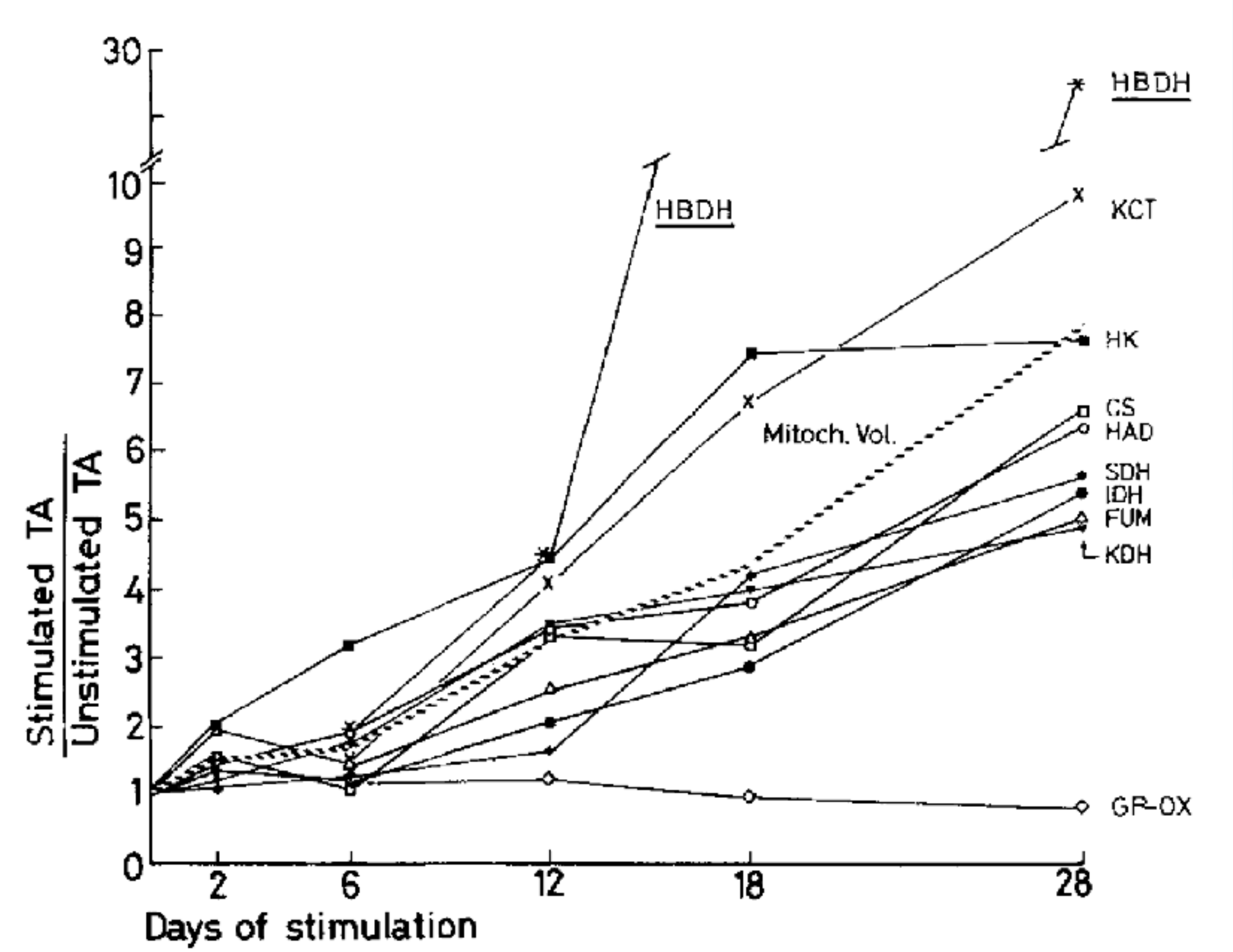
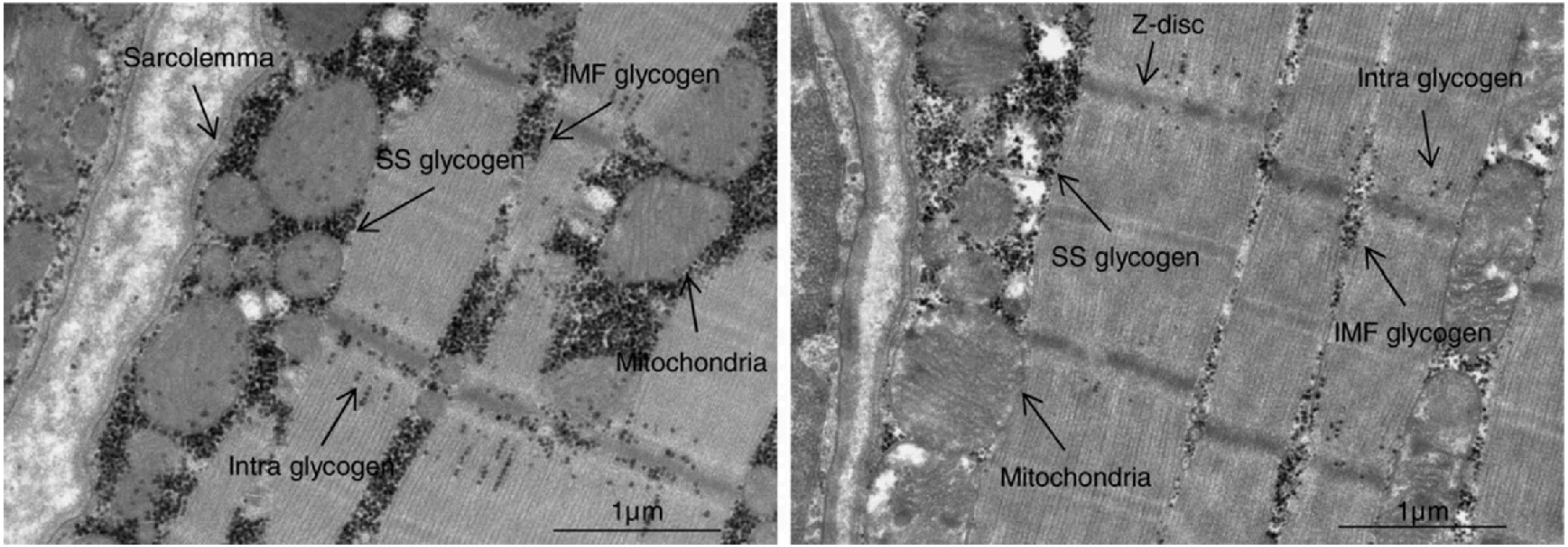
Muscle plasticity in response to endurance training





Changes of mitochondrial volume density are generally paralleled by similar increases in enzymes of the Krebs cycle and oxidative phosphorylation such as SDH (succinate dehydrogenase), C (citrate synthase), and Cytox (cytochrome c oxidase)

Muscle plasticity in response to endurance training



Endurance training further leads to a shift in metabolism toward a higher reliance on lipids as substrates as well as an increase in IMCL (intramyocellular lipid) and carbohydrate stores

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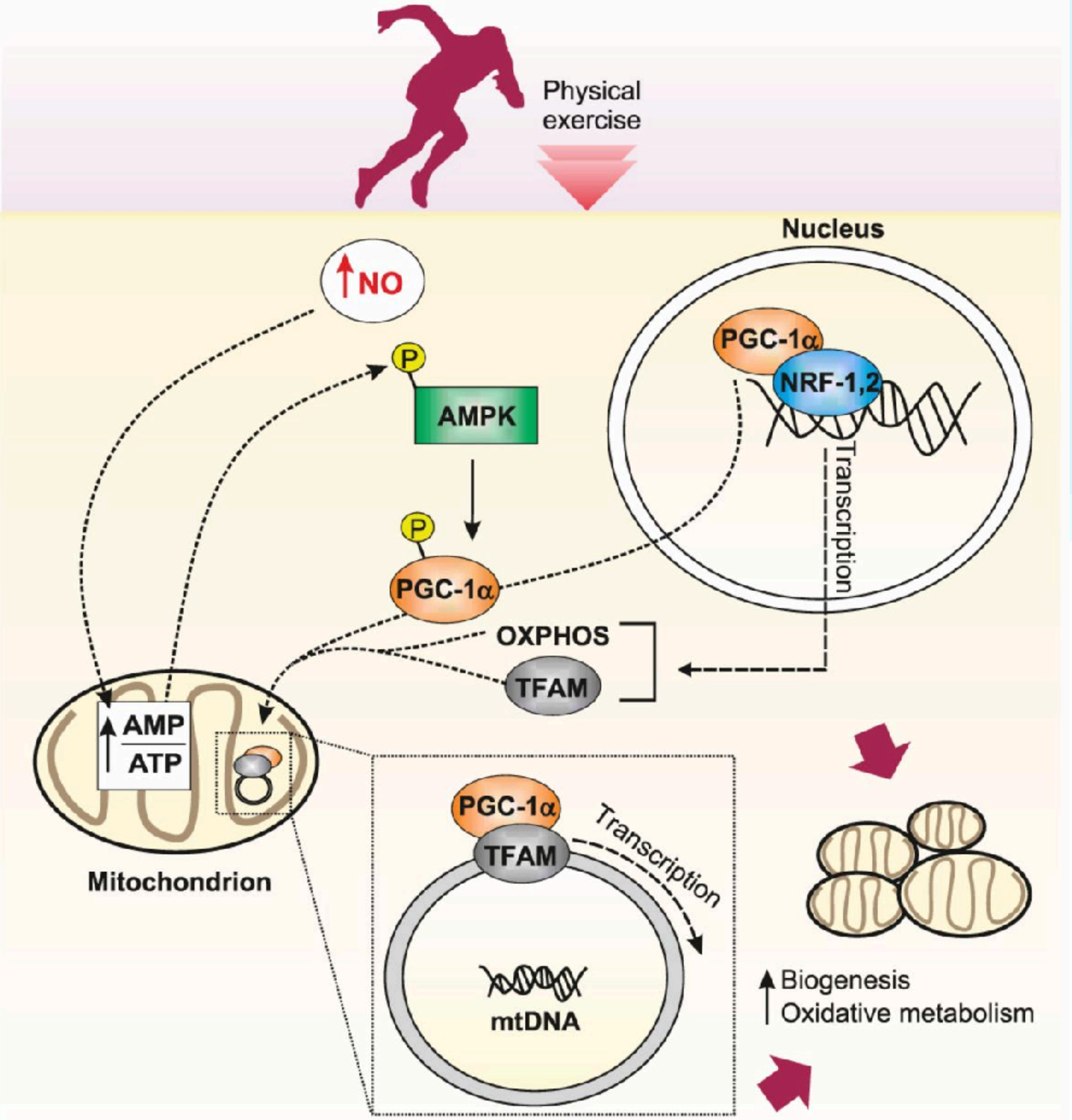
Endurance stimulus results in a coordinated transcriptional upregulation of a multitude of genes involved in accretion of specific muscle proteins.

It is highly likely that exercise-associated Ca2+ signaling as well as an altered skeletal muscle energy status, sensed by the AMPK system are the major input determinants to the signaling network in humans. ROS/redox signaling as well as hypoxia sensing may serve to modify and fine tune the generic muscle endurance response according to environmental cues and intensities.

PGC-1α can be seen as an integrator of muscle tissue phenotype in response to activity, hormonal and nutritional cues.



Muscle plasticity in response to resistance training

Classic strength training protocols impact predominantly on muscle and muscle fiber cross-sectional area, although significant strength gains can be obtained (in particular at the beginning of training episodes) with modifications of the neuromuscular control

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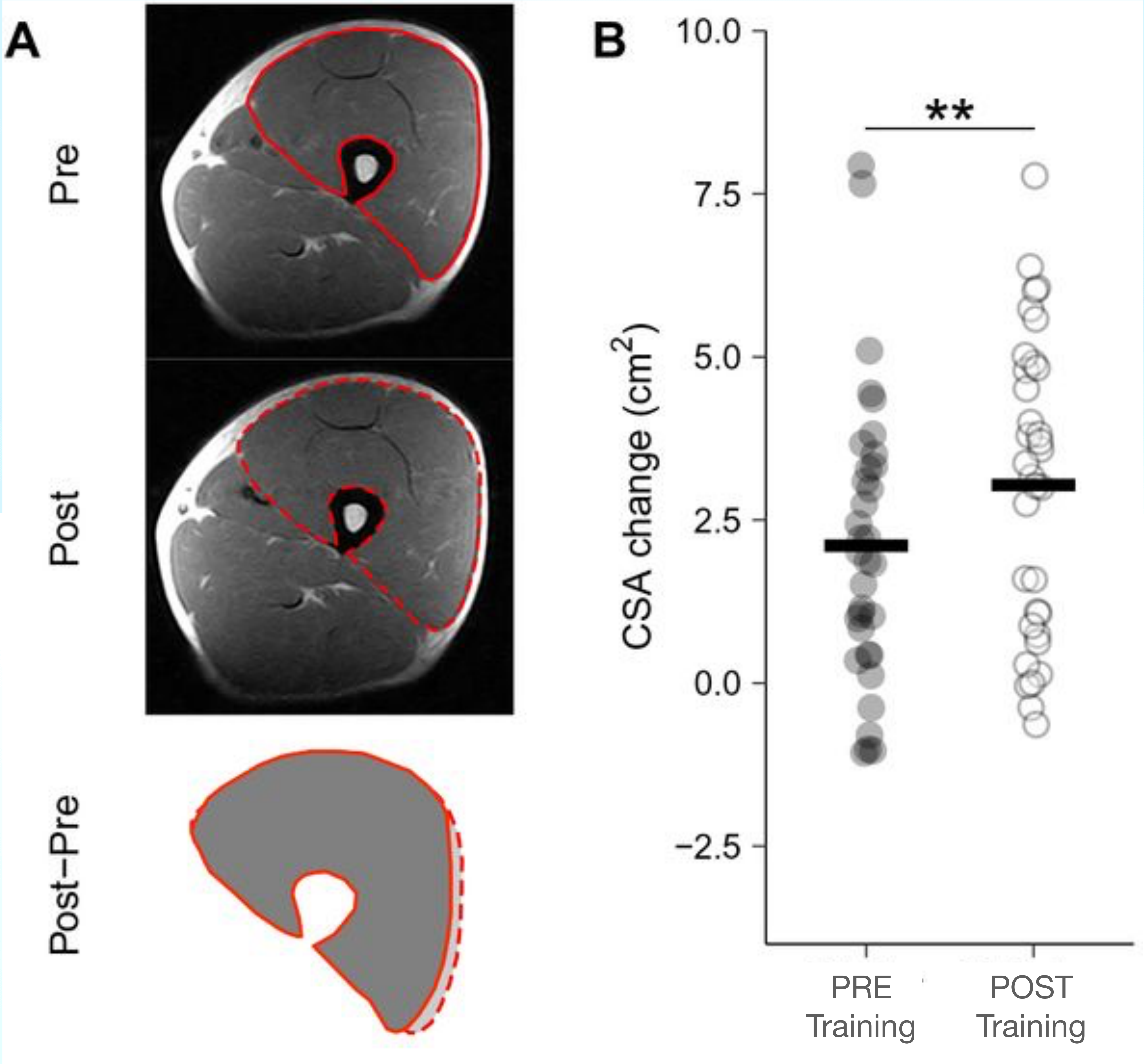
Muscle plasticity in response to resistance training



Strength training induces an increase in muscle cross-sectional area.
The gain in muscle cross-sectional area is mainly due to an increase in the number of myofibrils, whereby the fast fiber types (type IIA and type IIX) are mostly responsible for the net increase in muscle size in humans.

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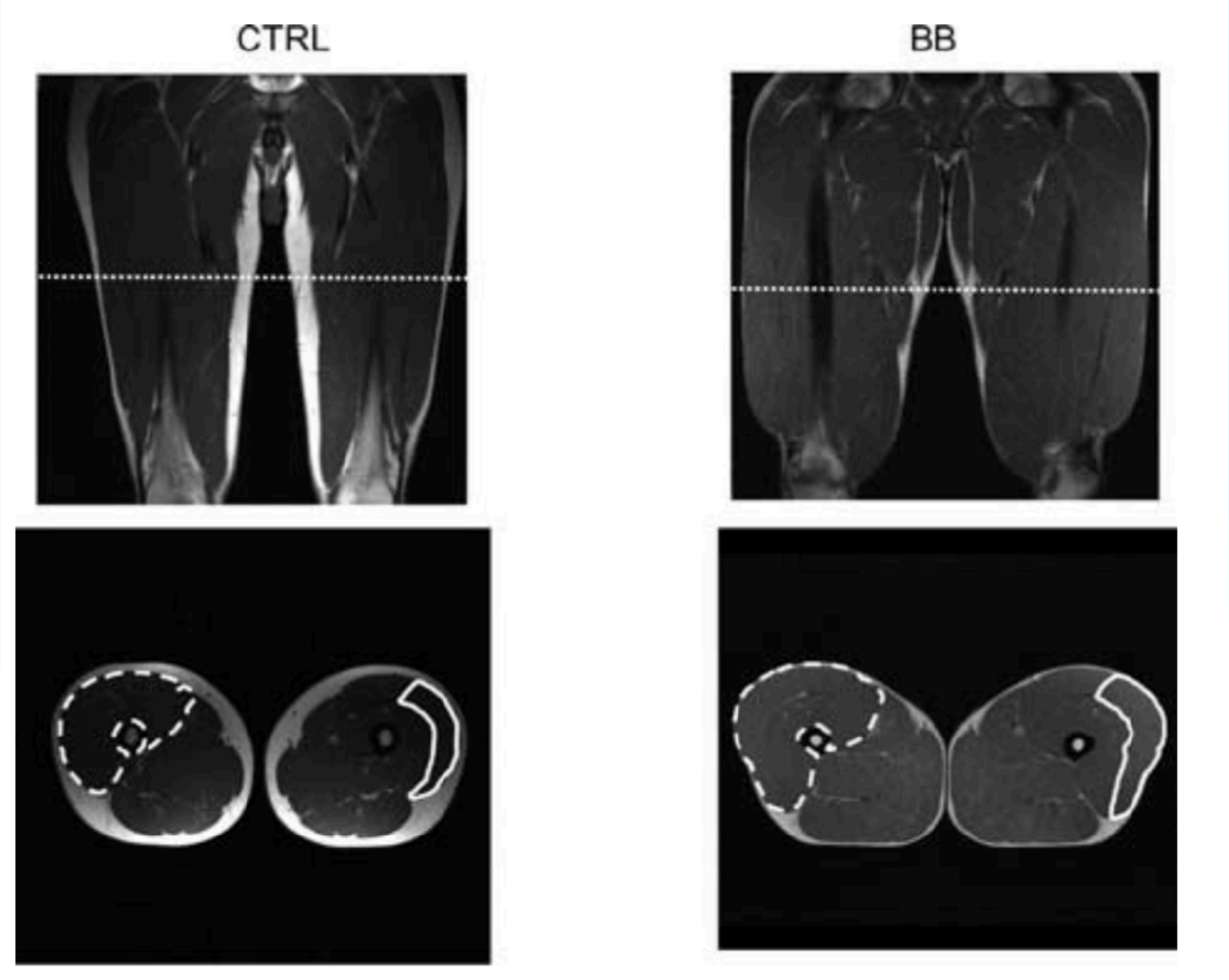

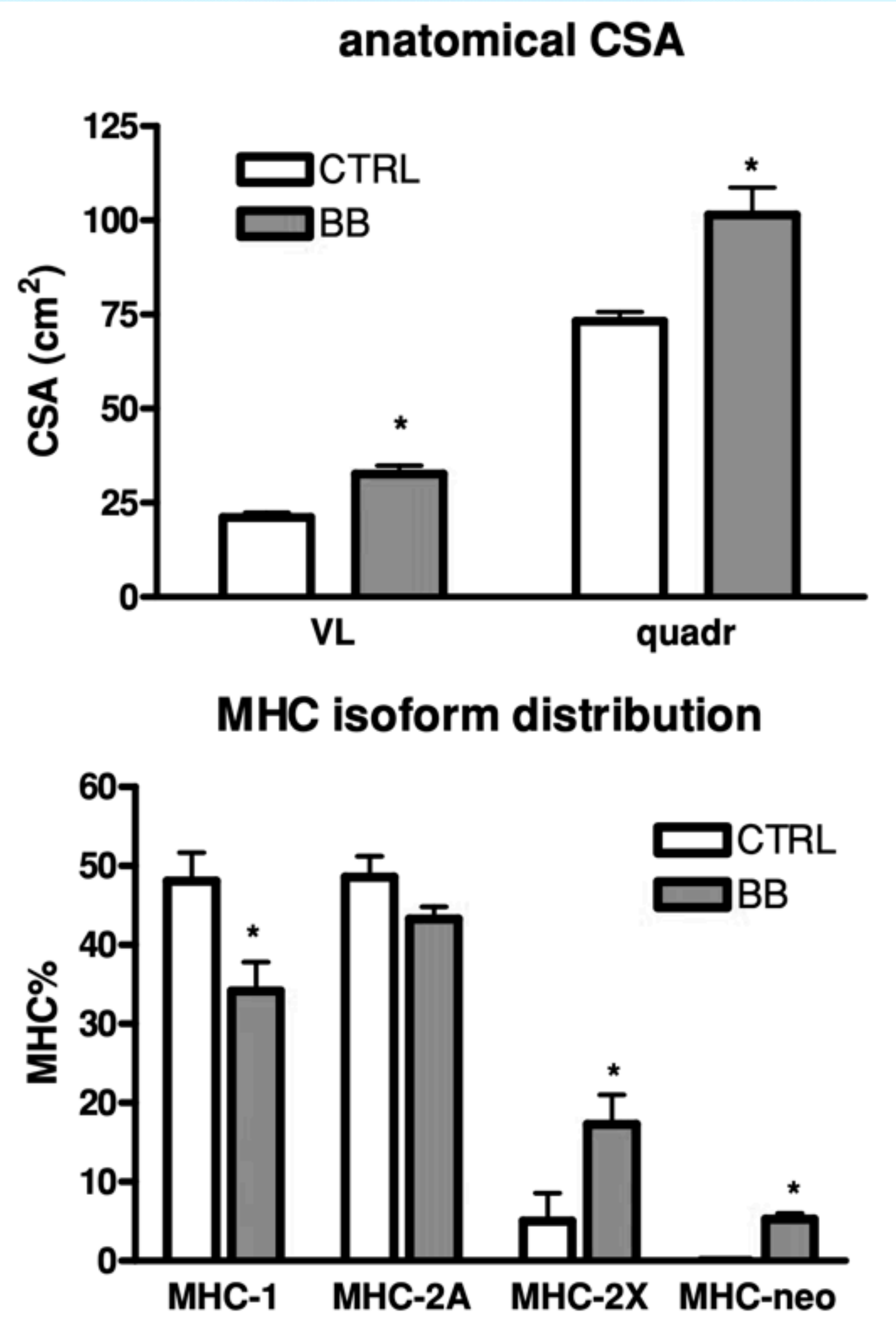

Myosin heavy chain expression can be modified by strength training, however, the extent and direction of observed changes seem to depend from the particularities of the exercise protocol.

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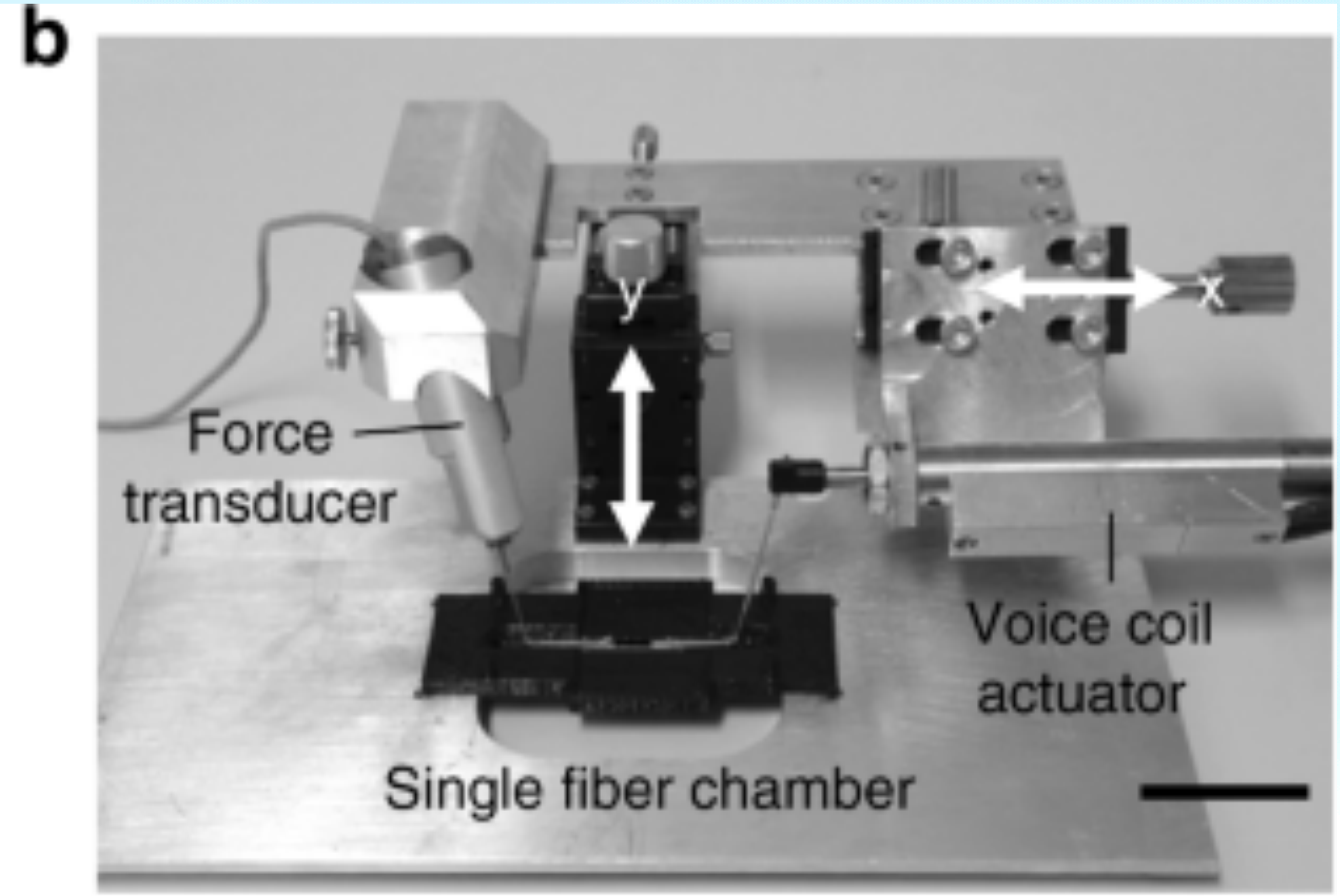

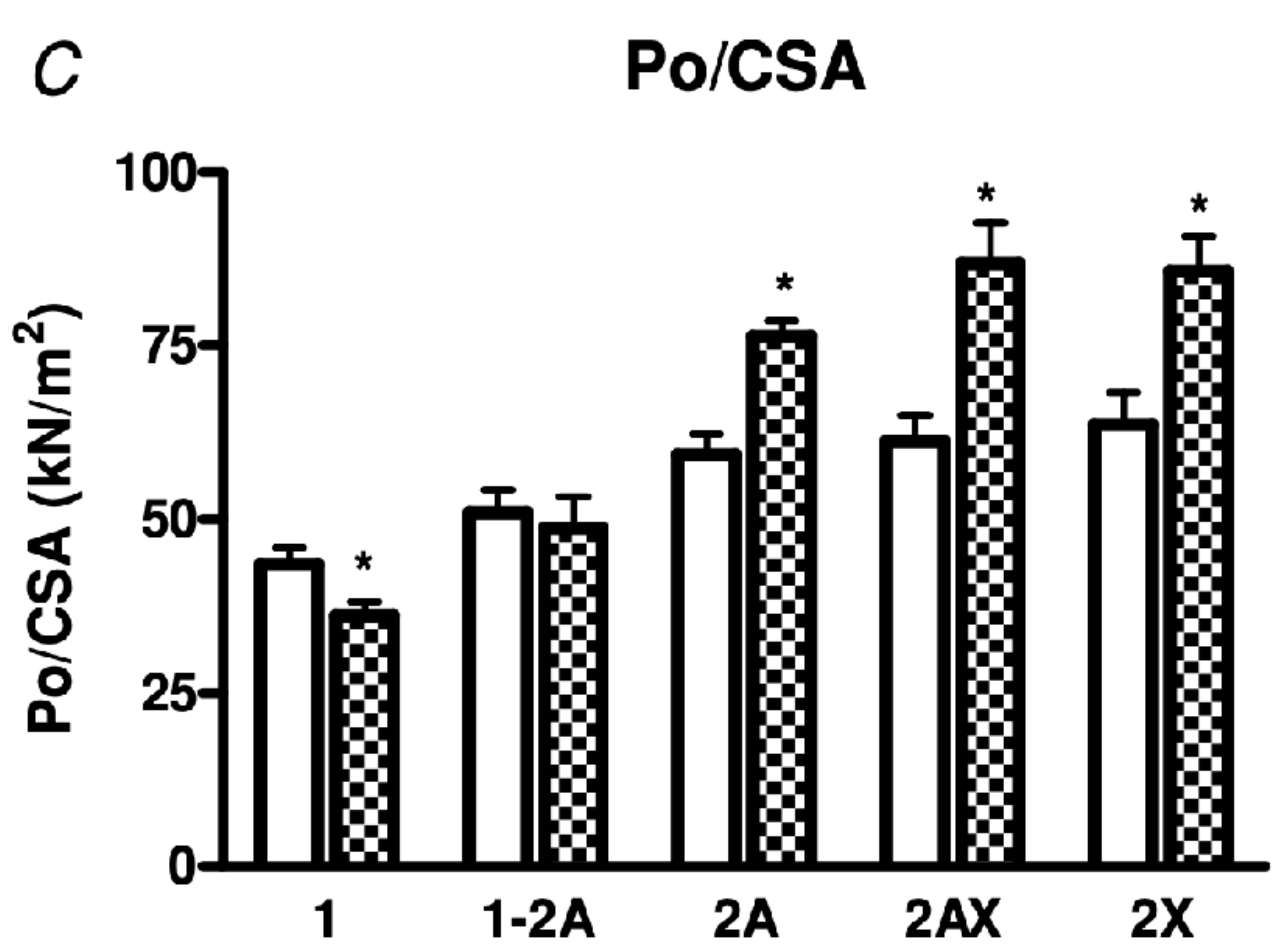

Fast fibres and especially the fastest 2X fibres do not only show a very significant (+76%) preferential hypertrophy, but they develop significantly higher specific force than corresponding fibre types of controls

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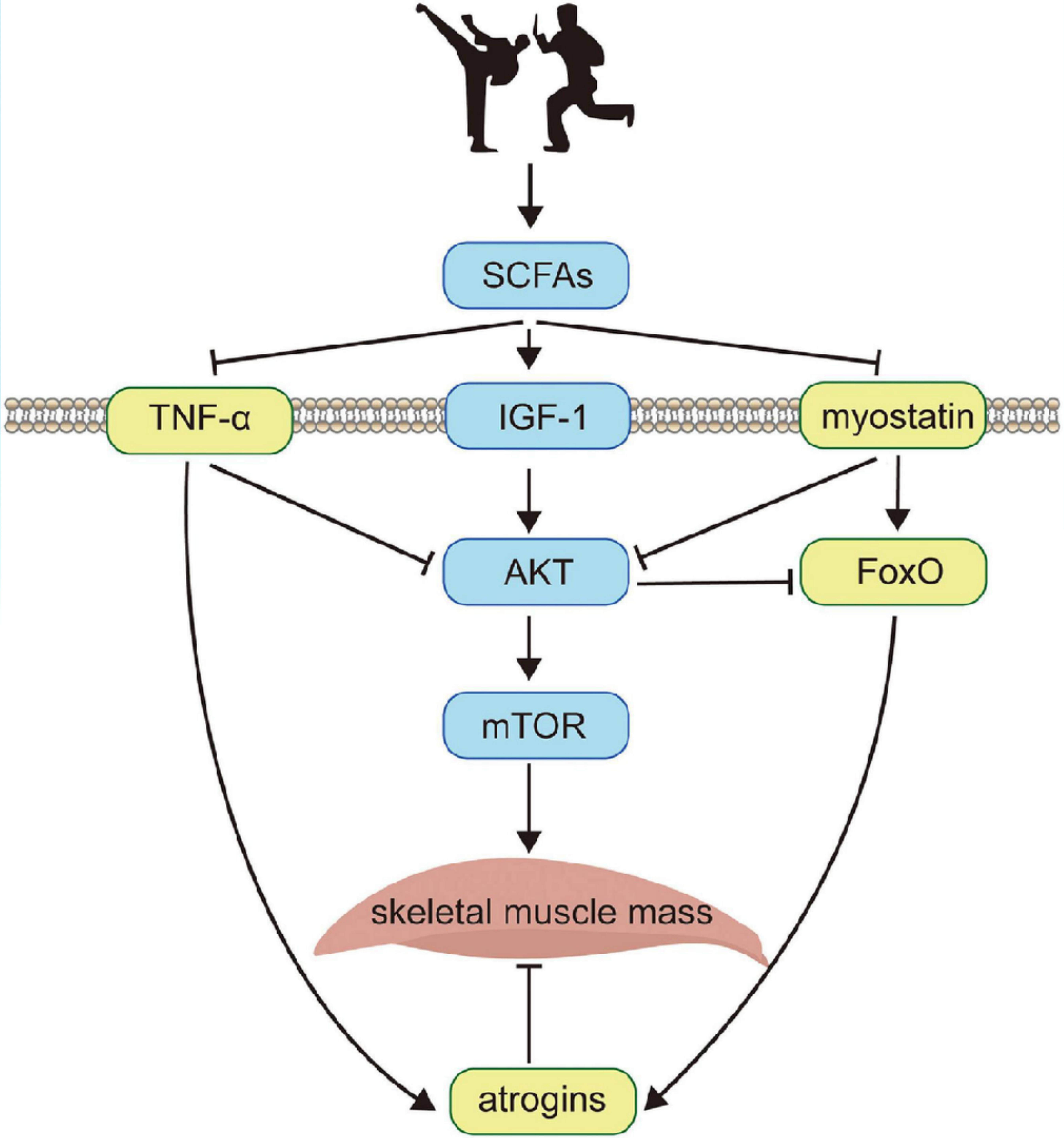
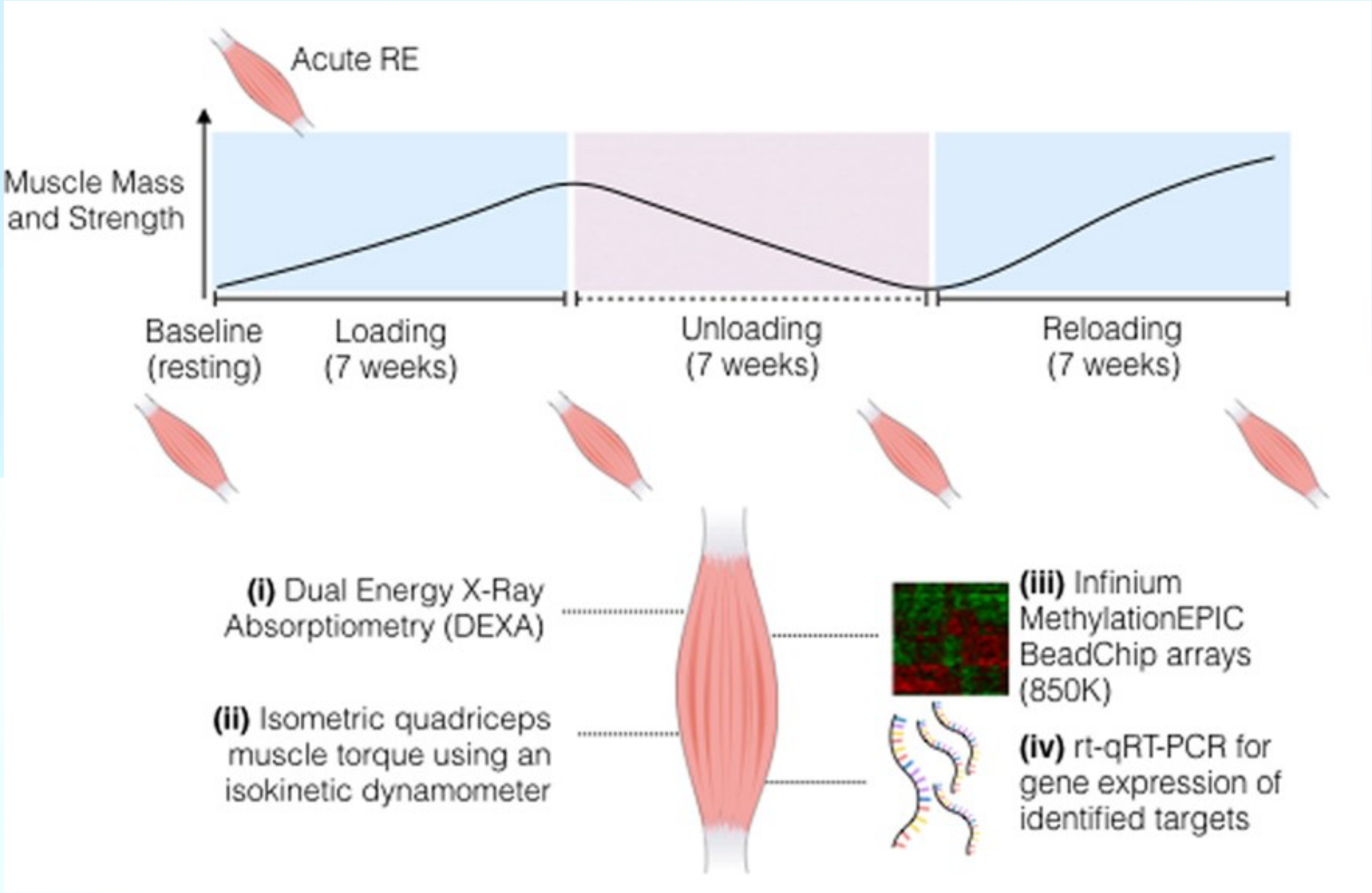
mTOR is considered to be a key integrator of multiple positive and negative stimuli affecting skeletal muscle mass



Muscle “memory”



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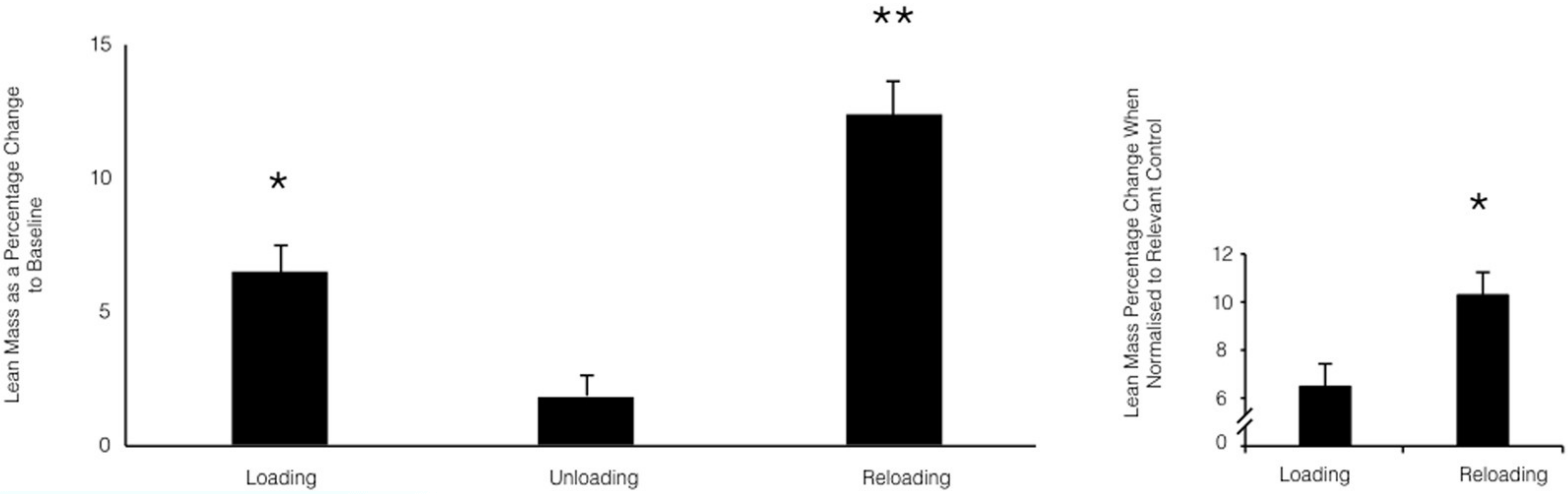

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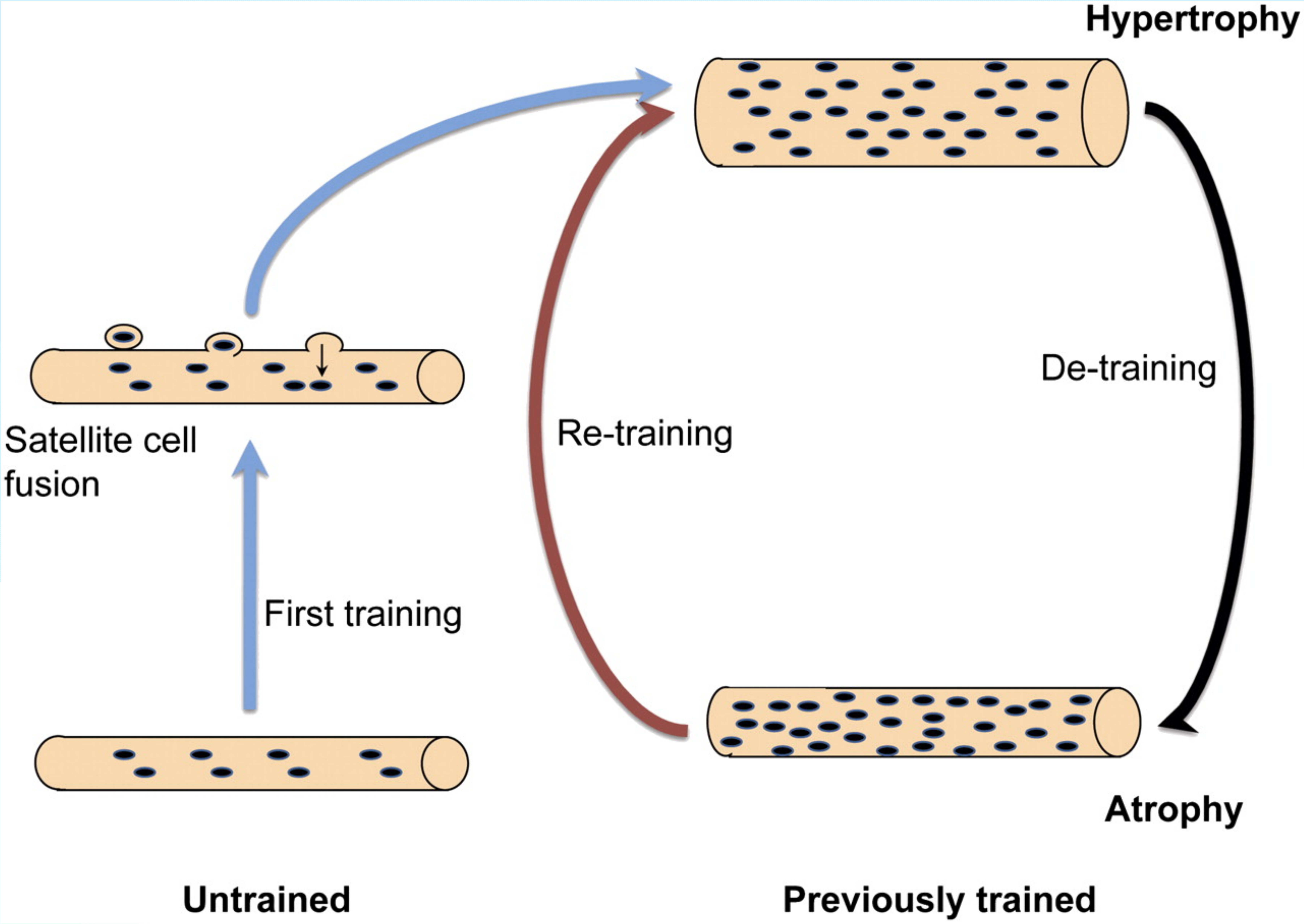
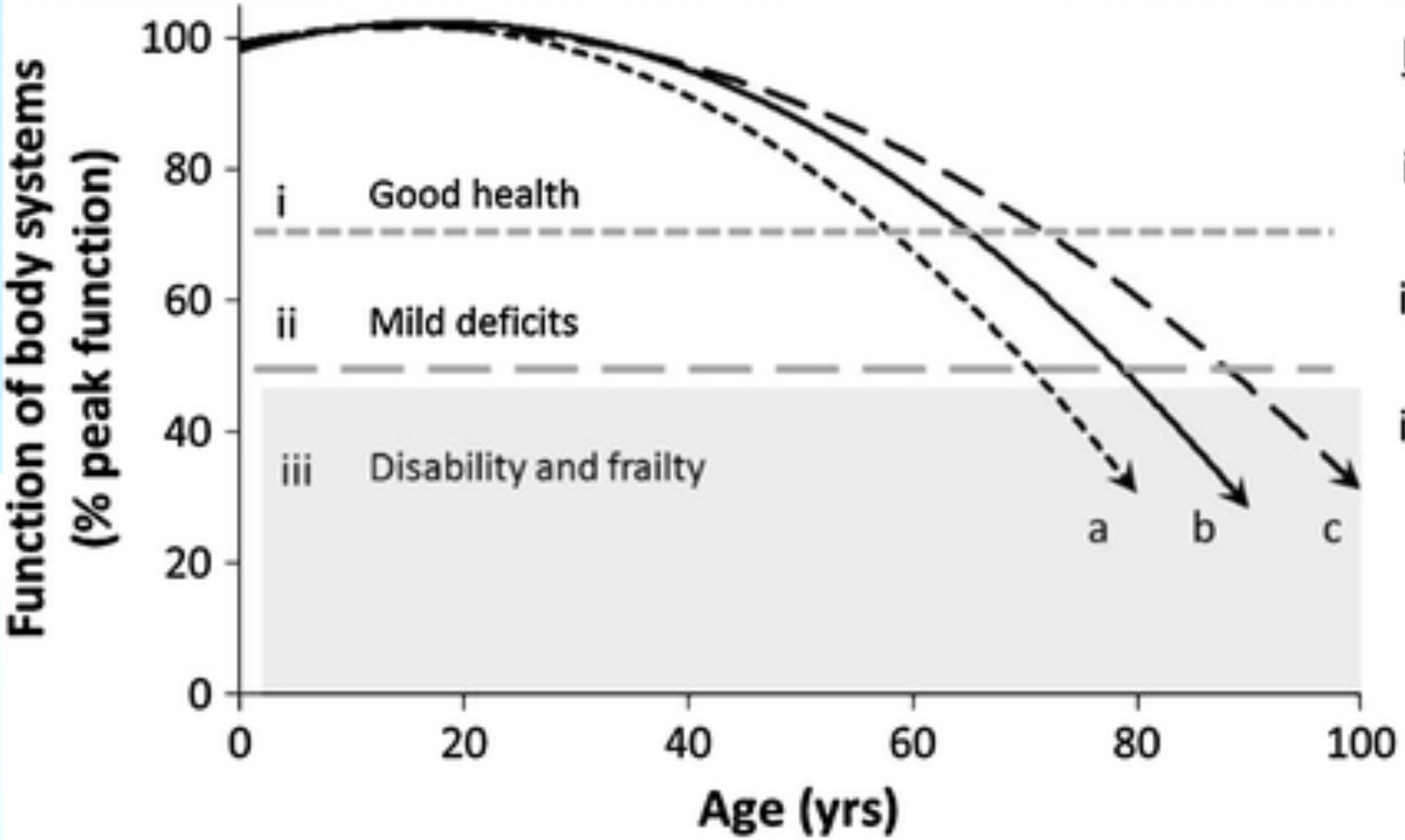

Hypertrophy
Satellite cell fusion
First training
Re-training
De-training
Atrophy
Untrained
Previously trained

MUSCLE PLASTICITY IN HEALTHY AGING



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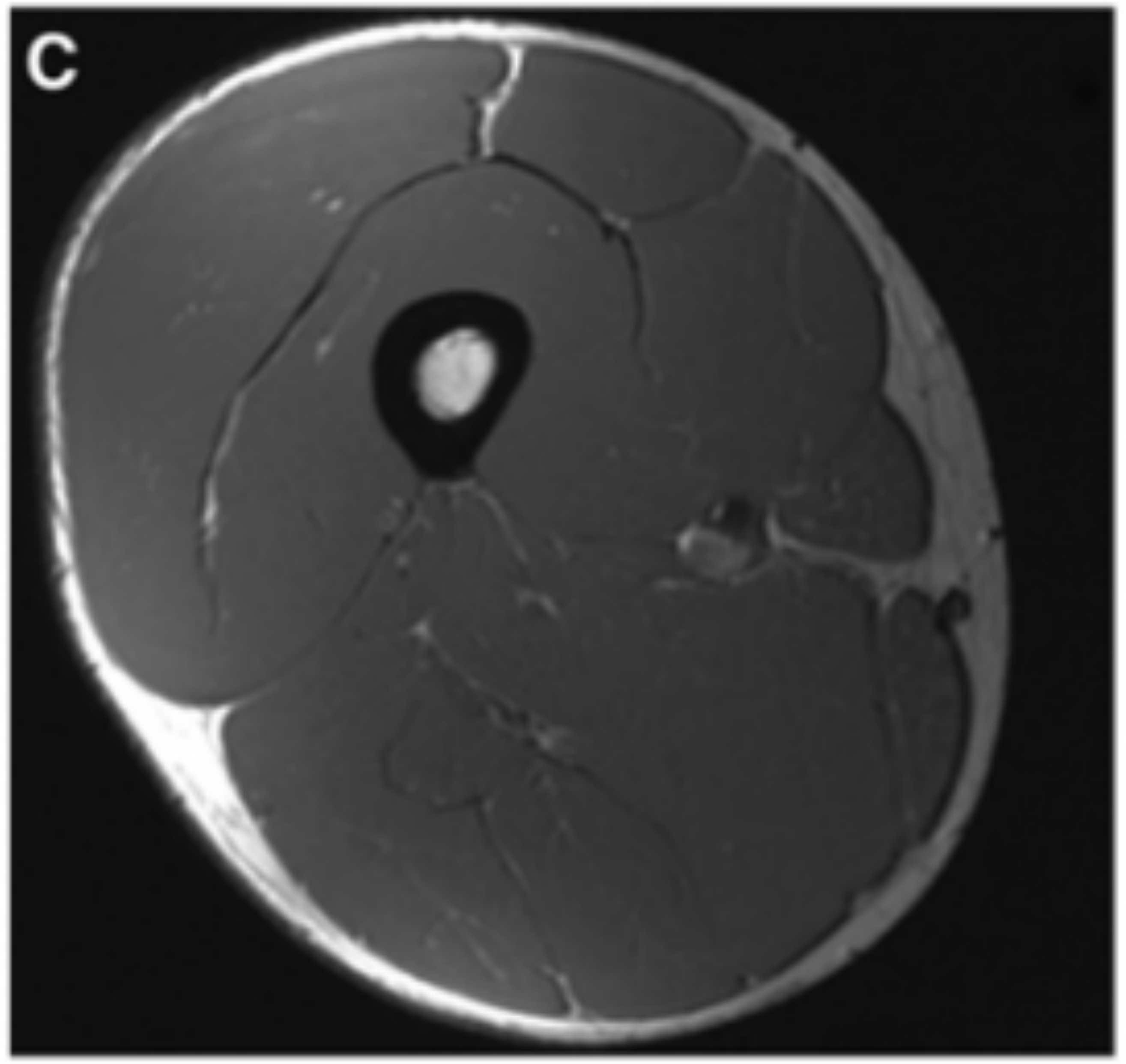
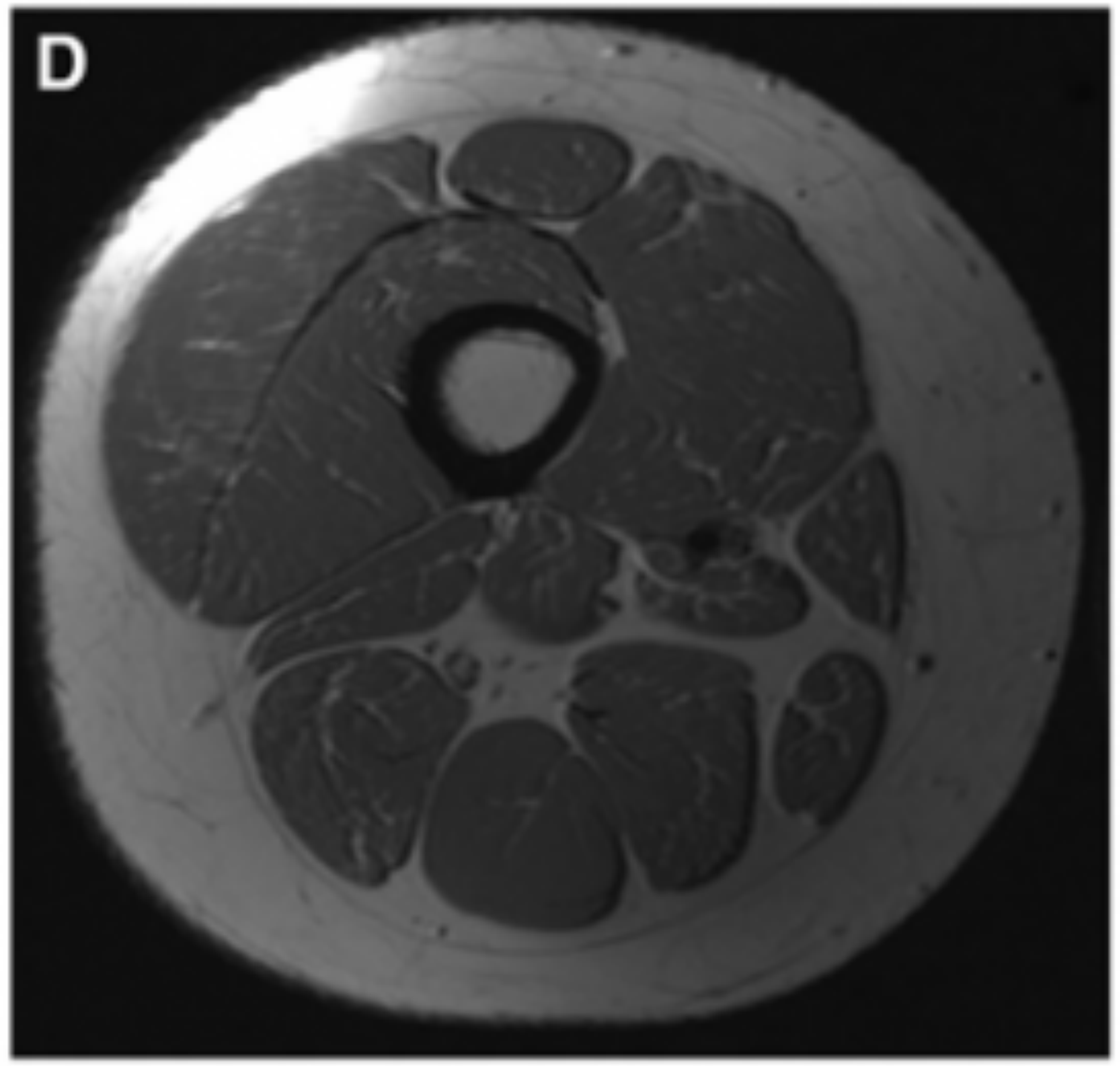
Younger

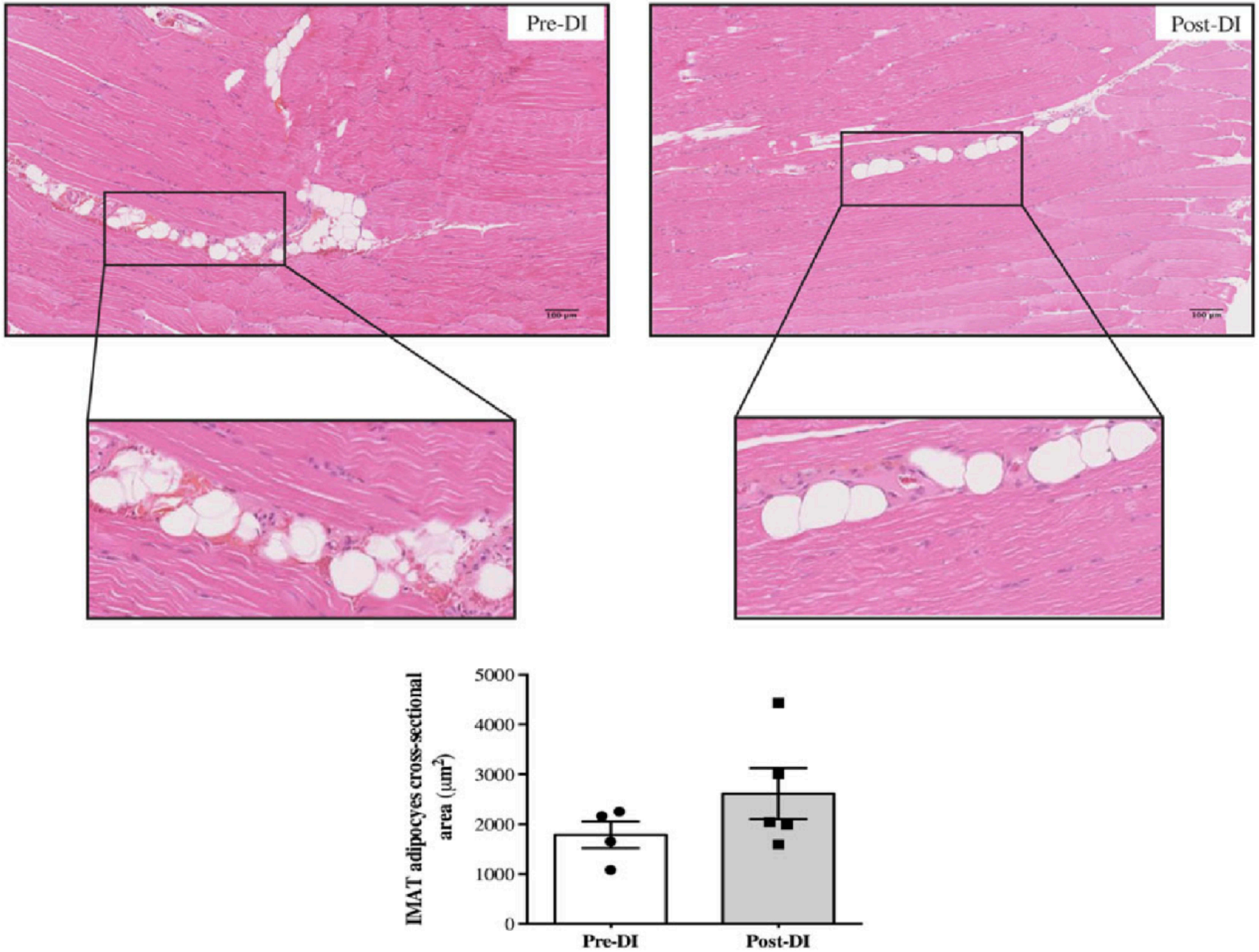


Male – 24 yrs
Body mass – 76kg
Fat mass – 10kg
Fat free mass - 57kg

Older



Male – 66 yrs
Body mass – 81kg
Fat mass – 57kg
Fat free mass – 13kg
Average daily steps = 3141



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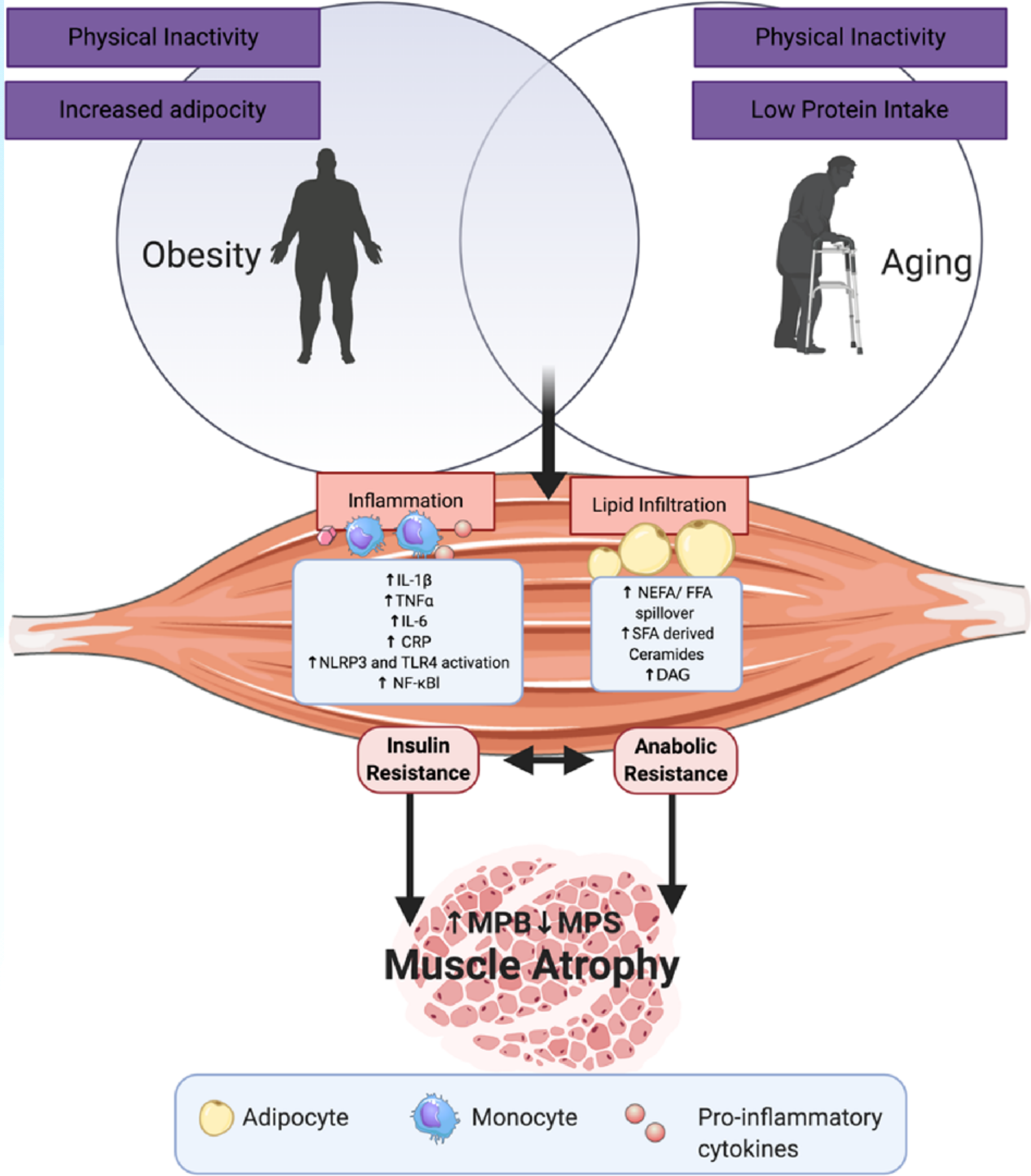

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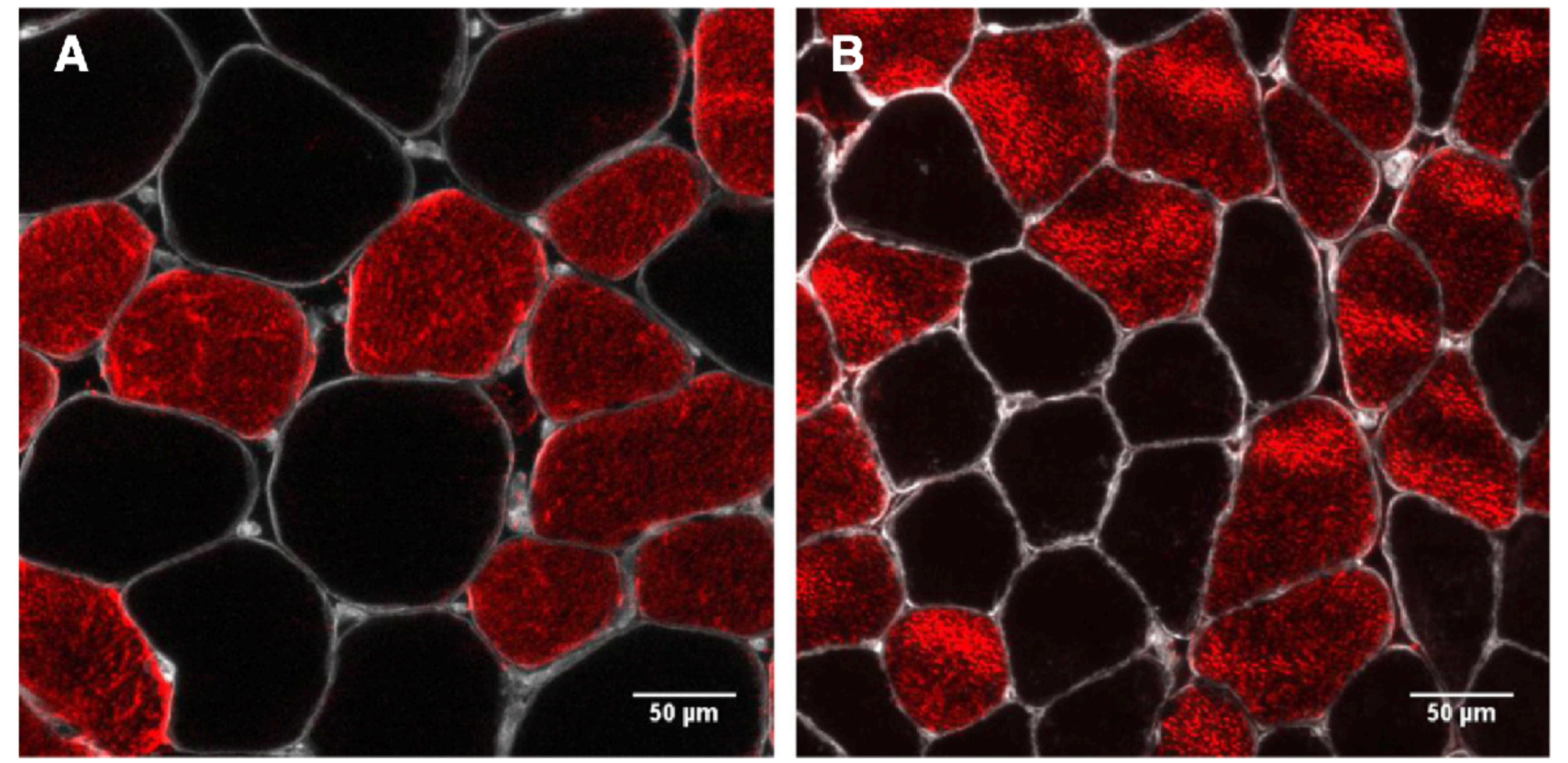
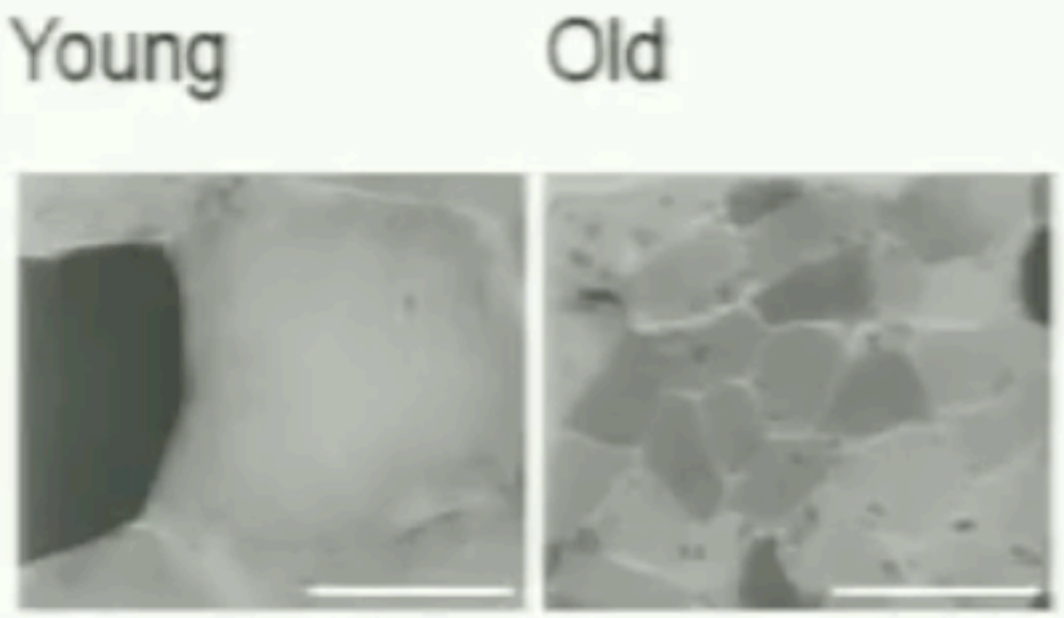


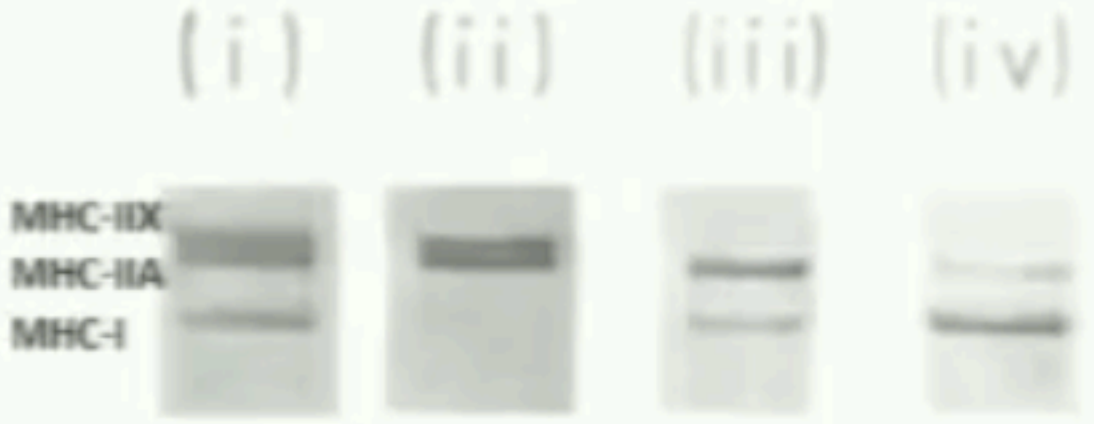
In the elderly subjects type II muscle fiber size is the main factor responsible for changes in muscle mass

In general, <u>most</u> older peoples muscles look different….

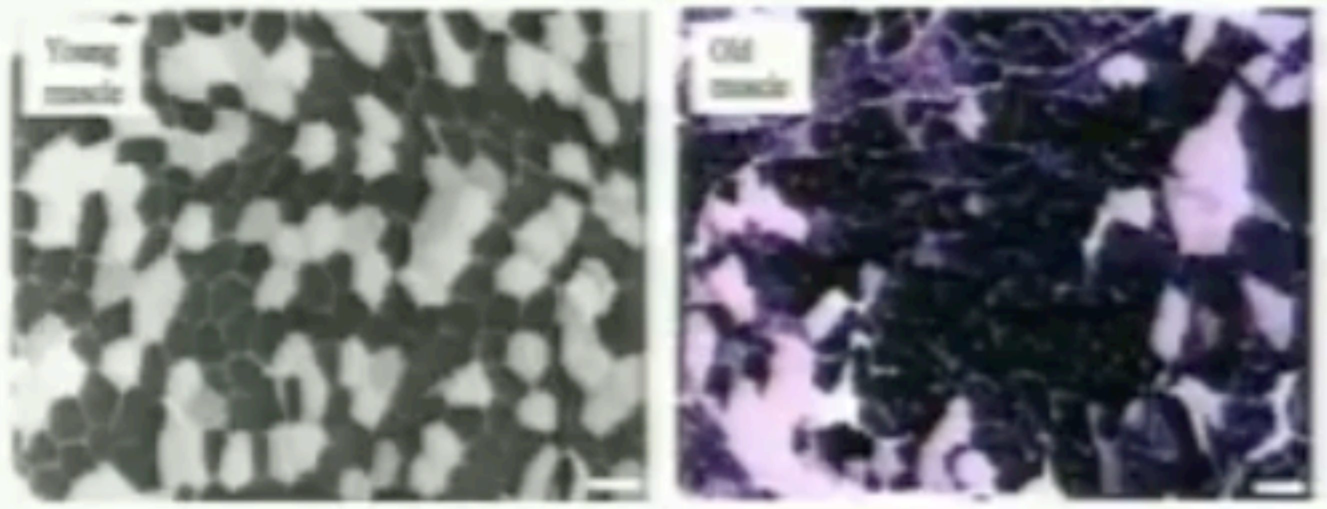
- ↓ type II fibre area
  - Decreased MHC-II expression



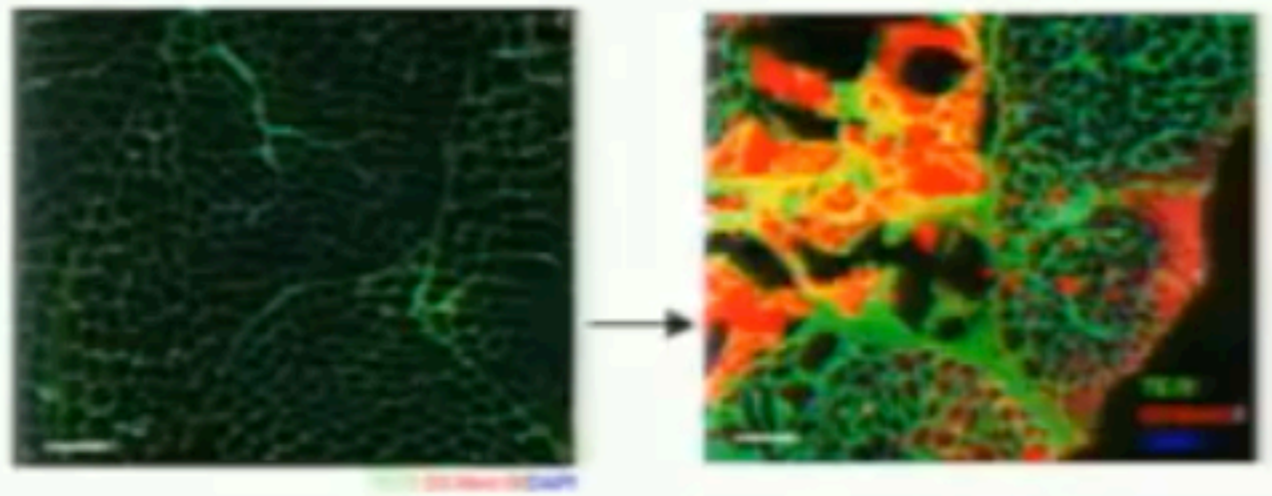
- ↑ # hybrid fibres
  - (co-expressing MHC isoforms)



- Fibre type grouping
  - evidence of collateral sprouting



- Fat & connective tissue infiltration
  - Altered metabolic regulation



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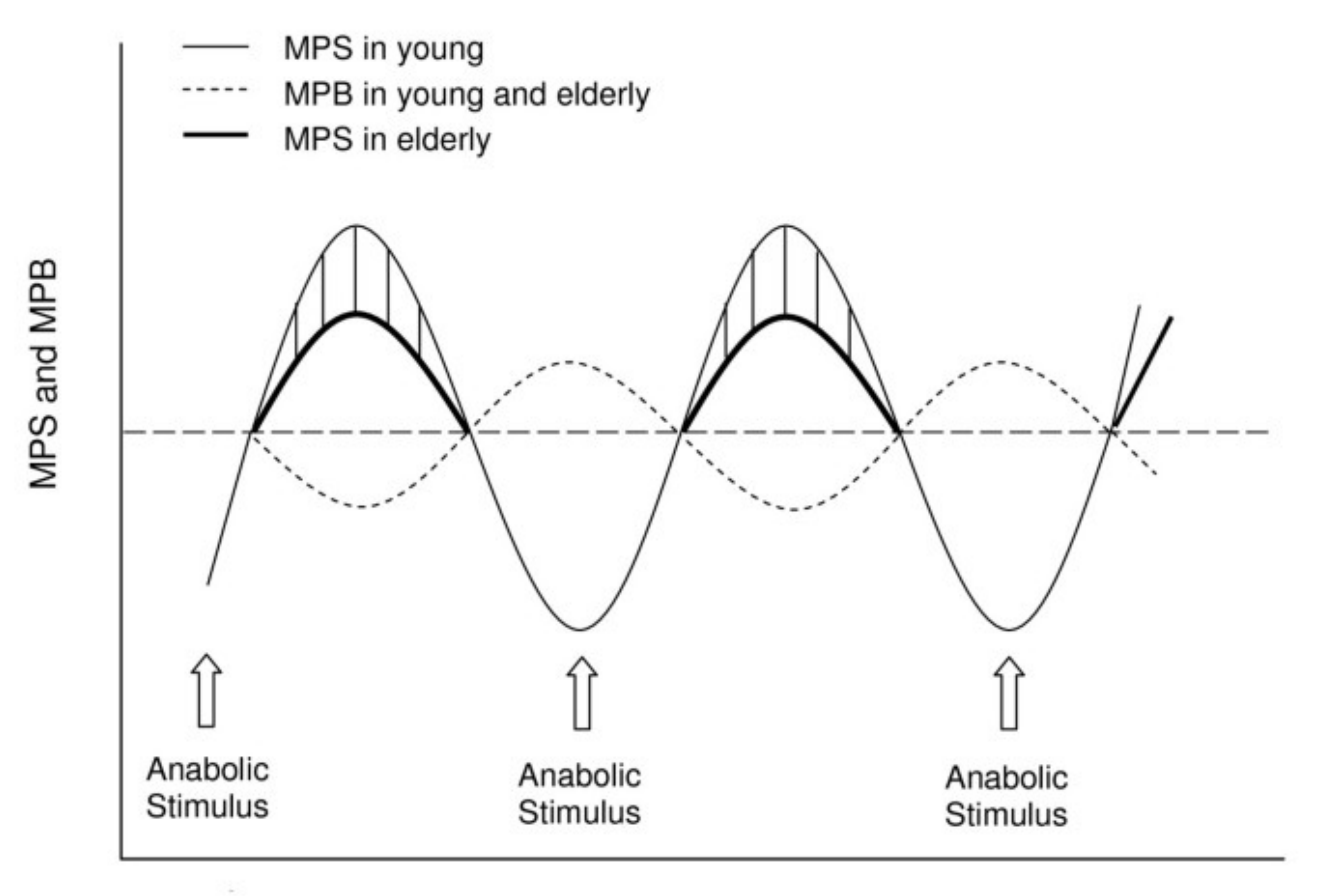

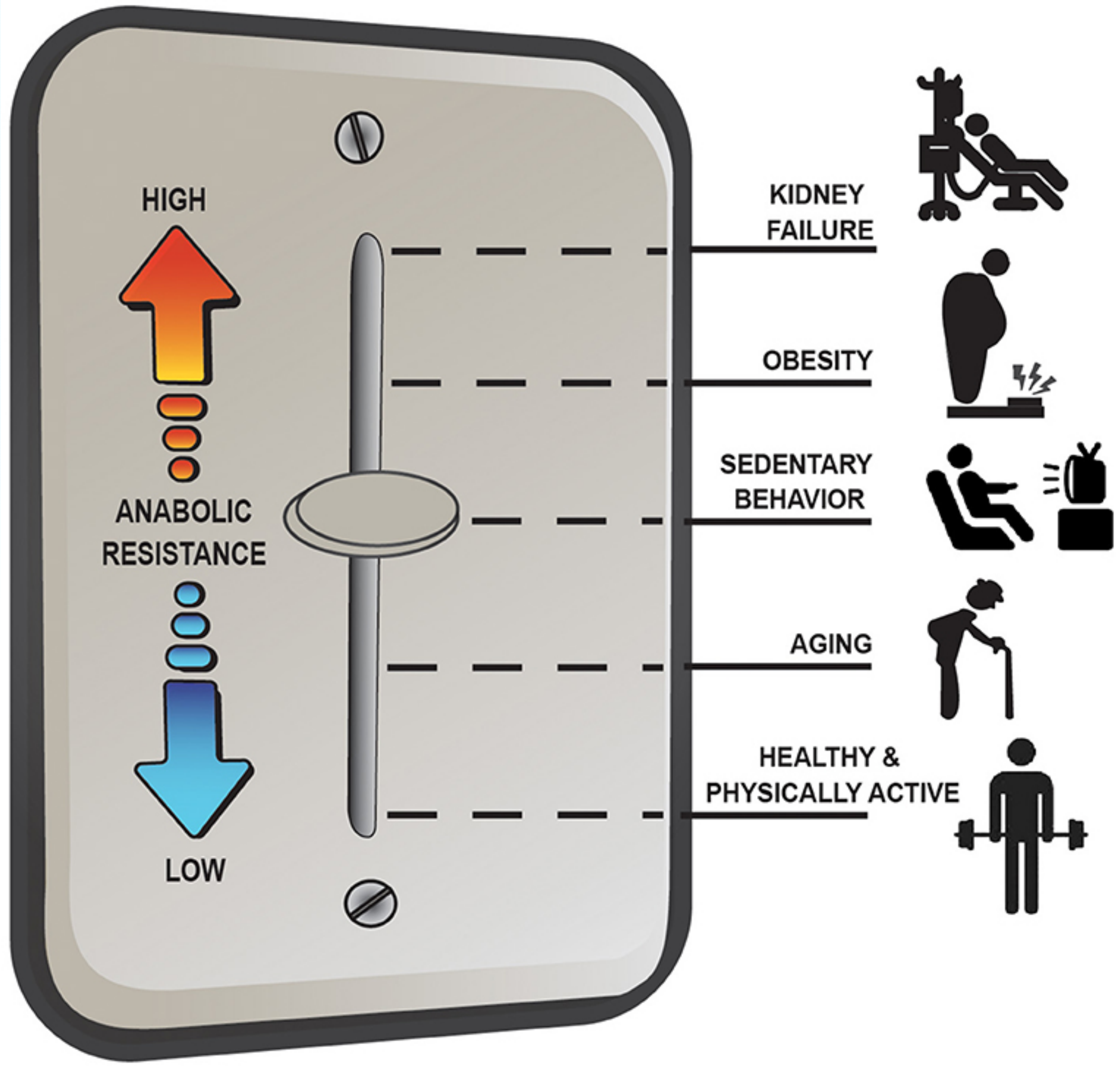

Aging has been associated with a reduced muscle protein synthetic response to protein intake, termed "**anabolic resistance**"

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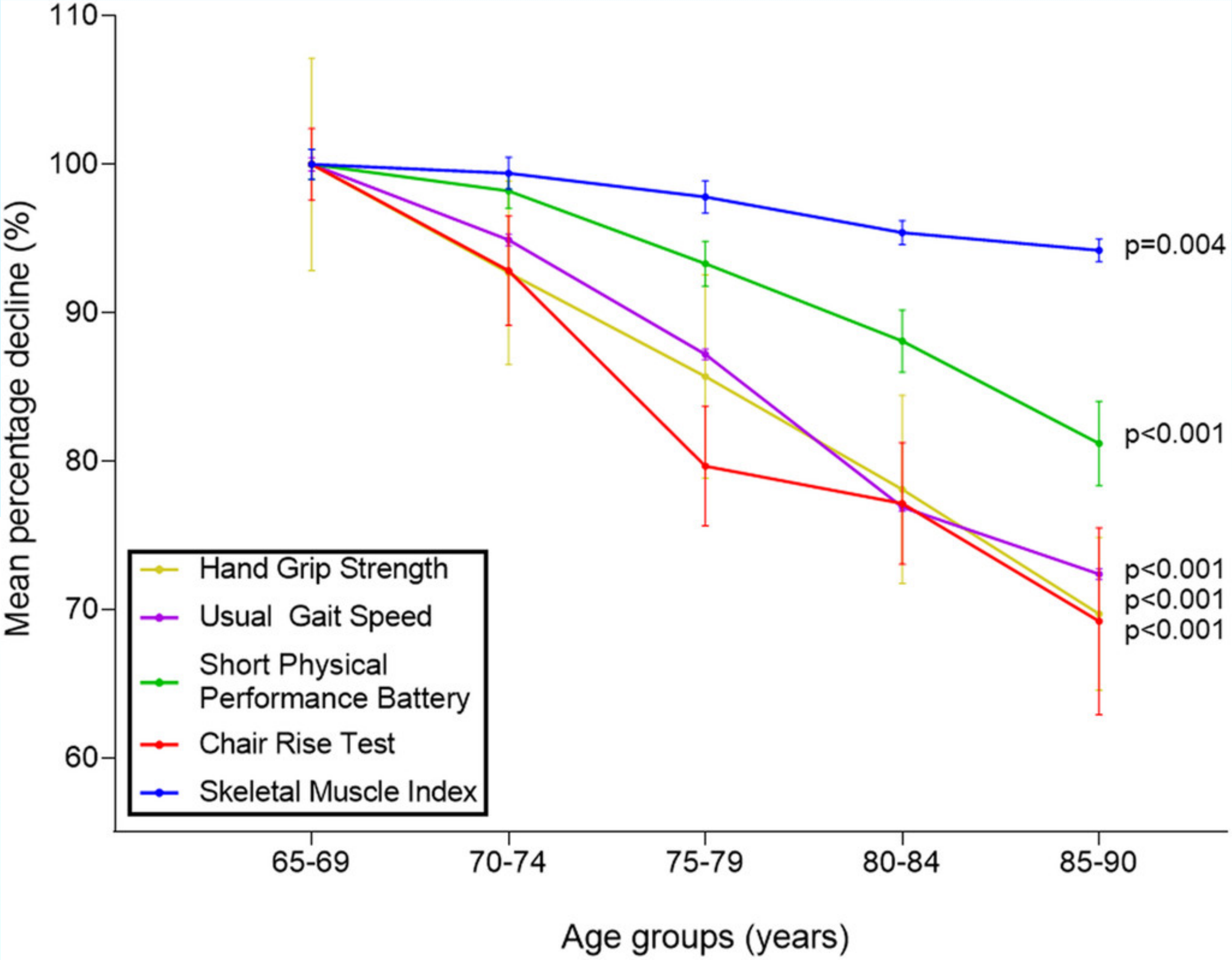

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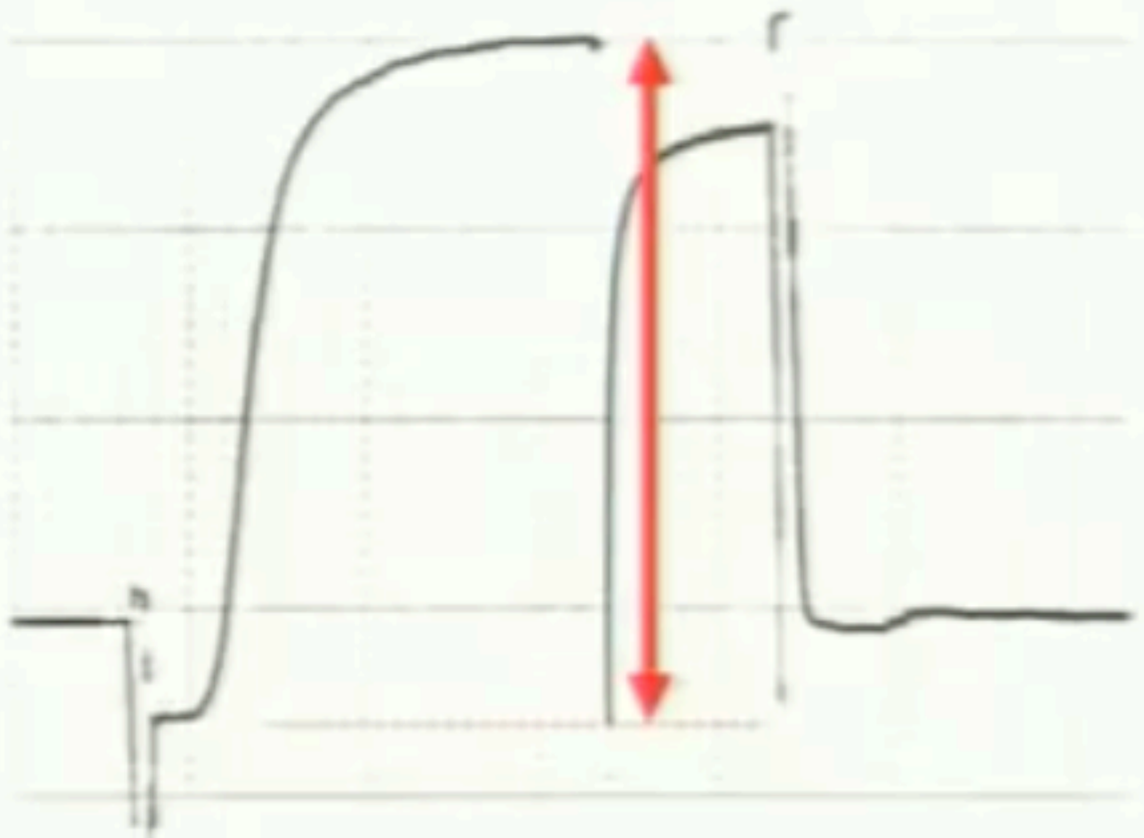
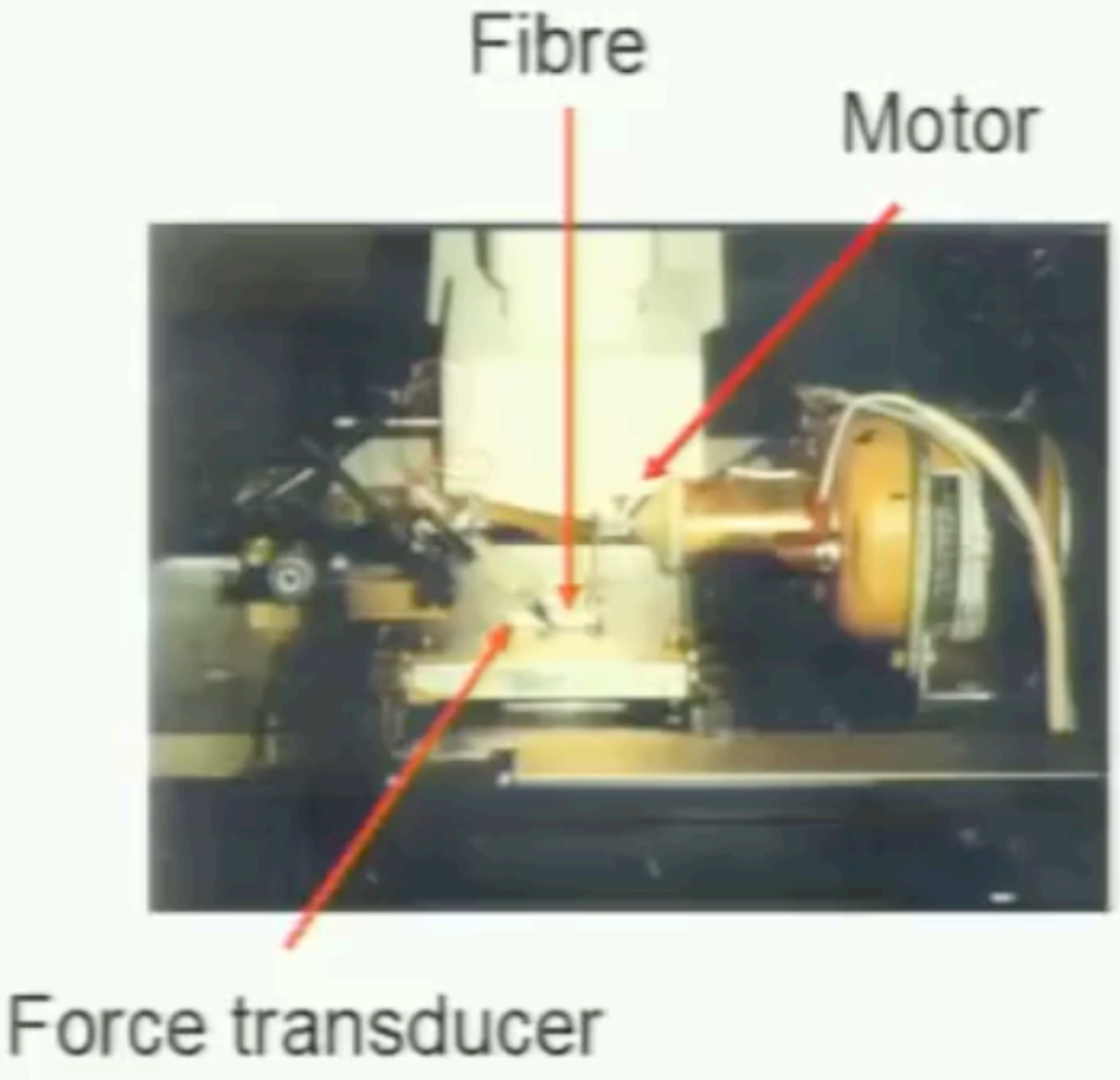
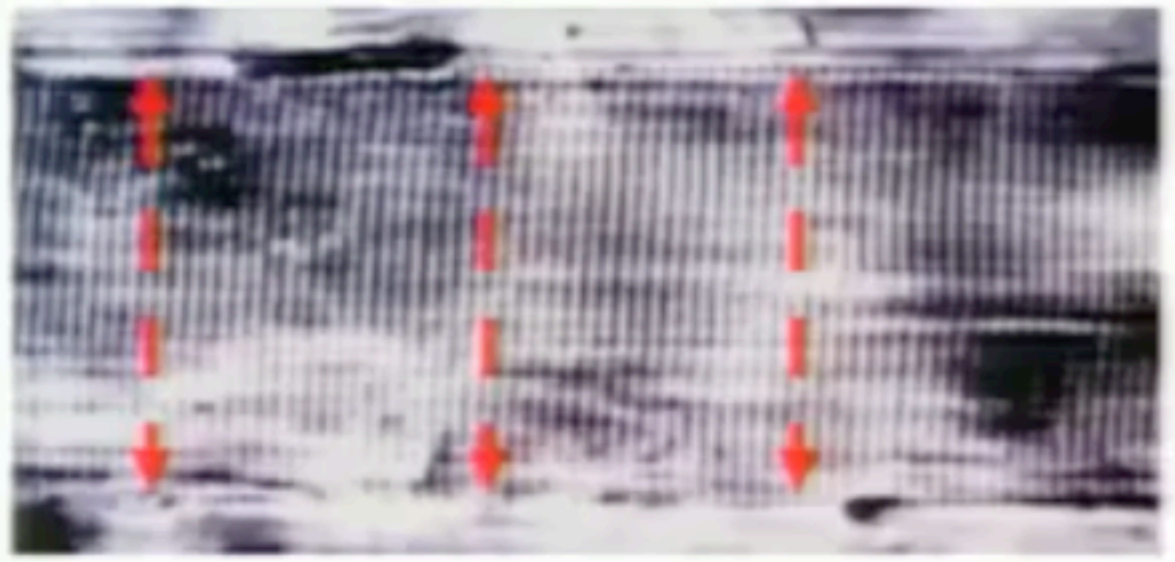
Isometric force in human skinned fibres



Isometric force at max Ca^{2+} activation

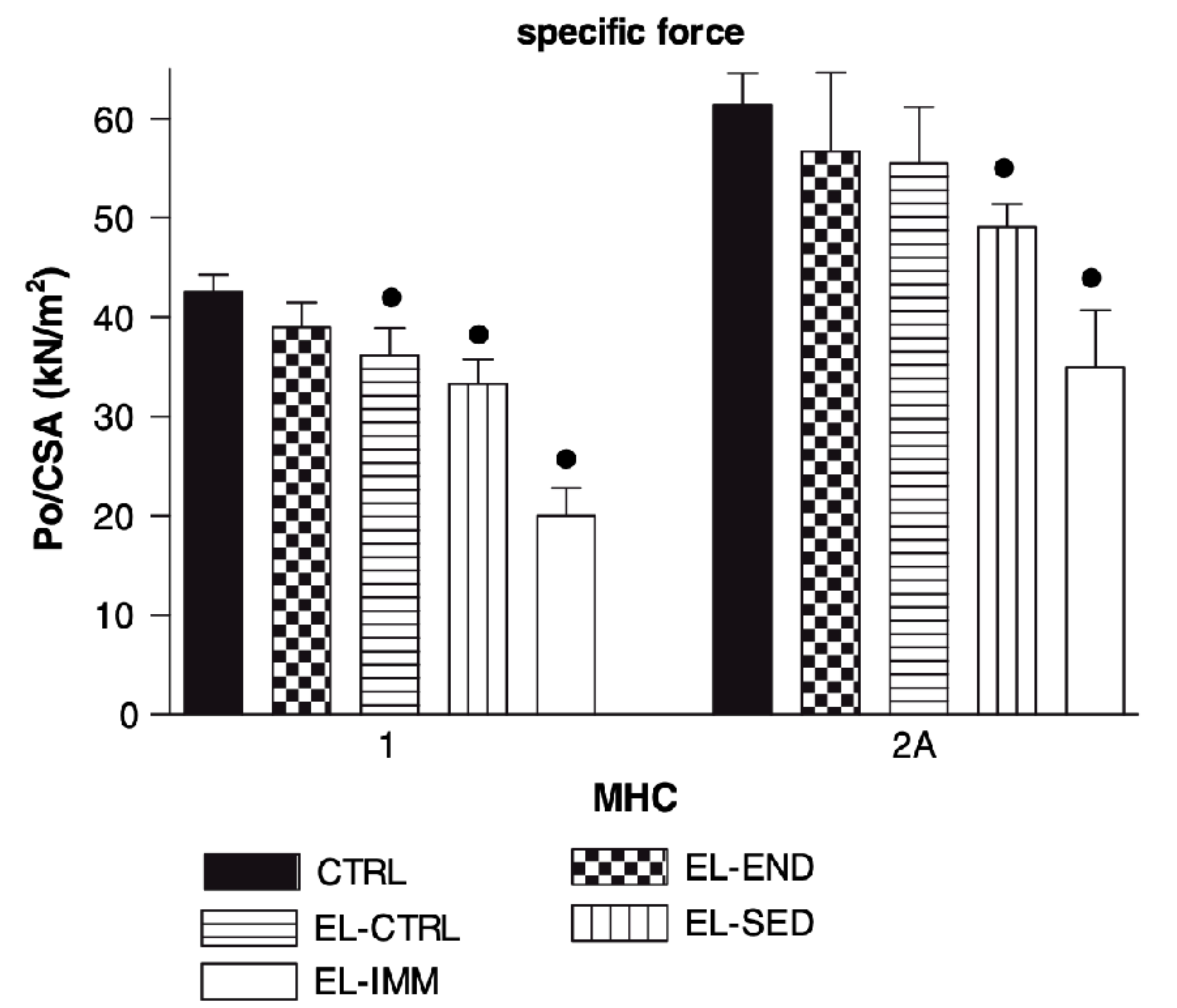




Measurement of fibre diameter for calculation of CSA

Aging or disuse?

A relation exists between the activity levels of elderly subjects and the age-related deterioration of specific force of their muscle. In general, force loss is more evident in elderly sedentary subjects and progressively less evident in more active subjects up to elderly endurance trained subjects whose muscle may have almost normal force.



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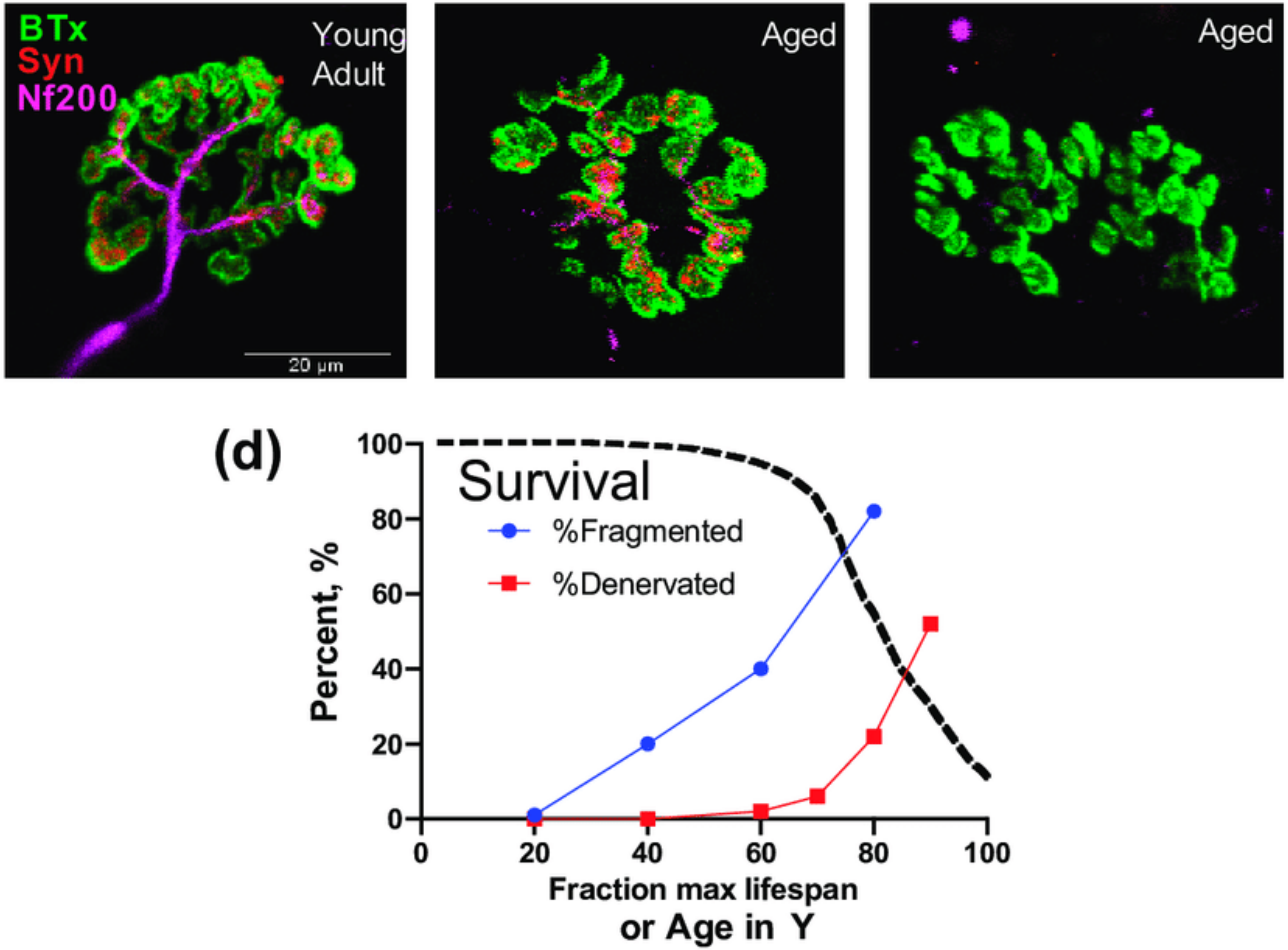
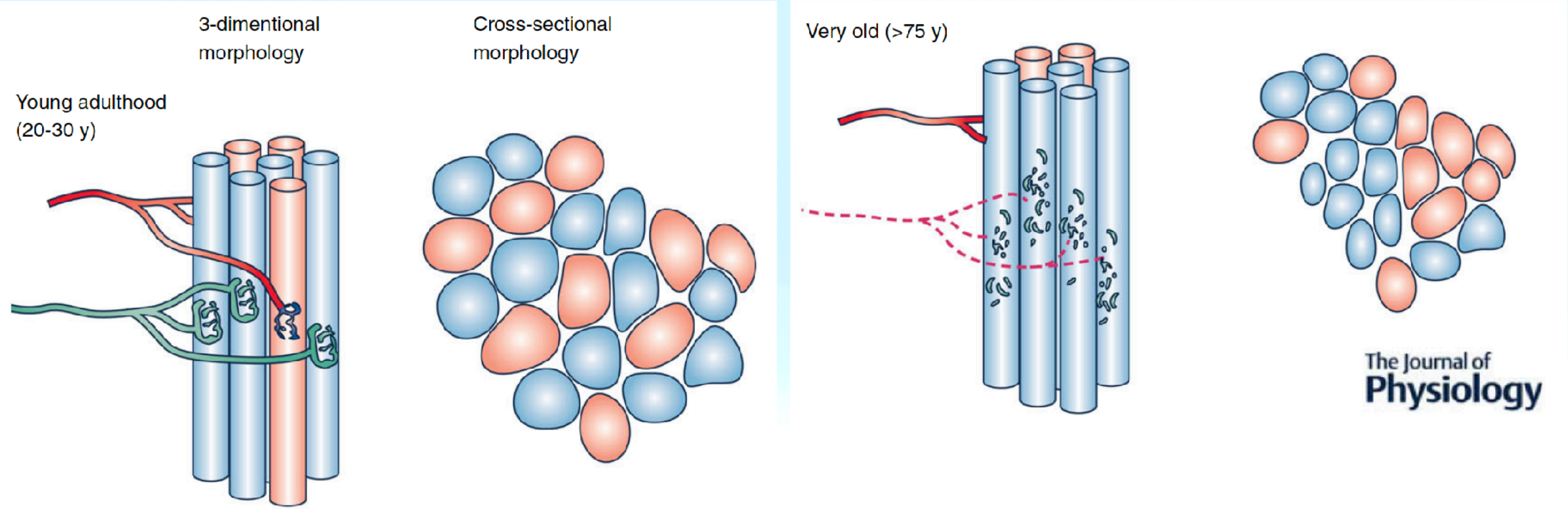
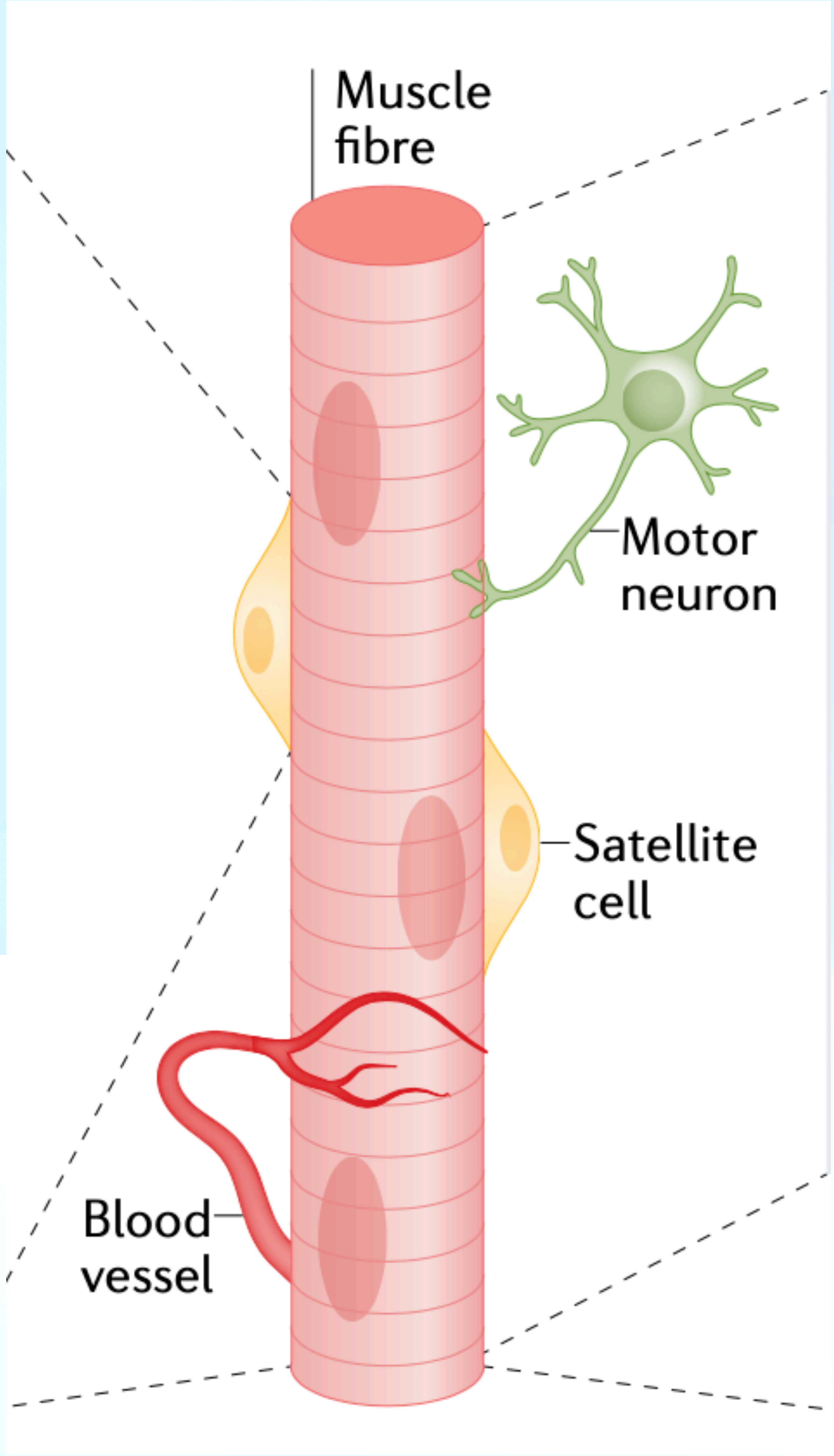
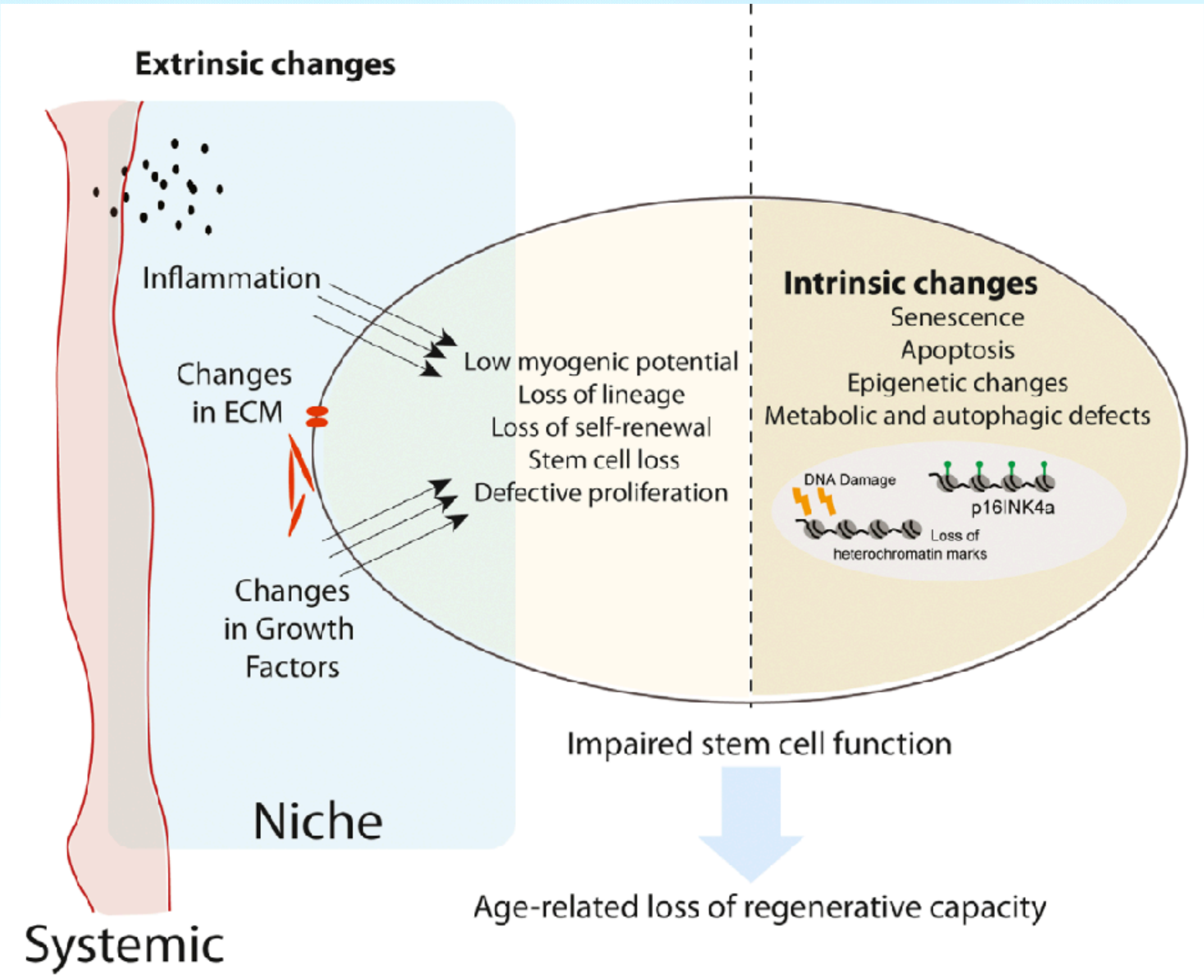

BTx
Syn
Nf200
Young
Adult
20 μm
Aged
Aged
(d)
Survival
%Fragmented
%Denervated
Percent, %
Fraction max lifespan
or Age in Y
0
20
40
60
80
100

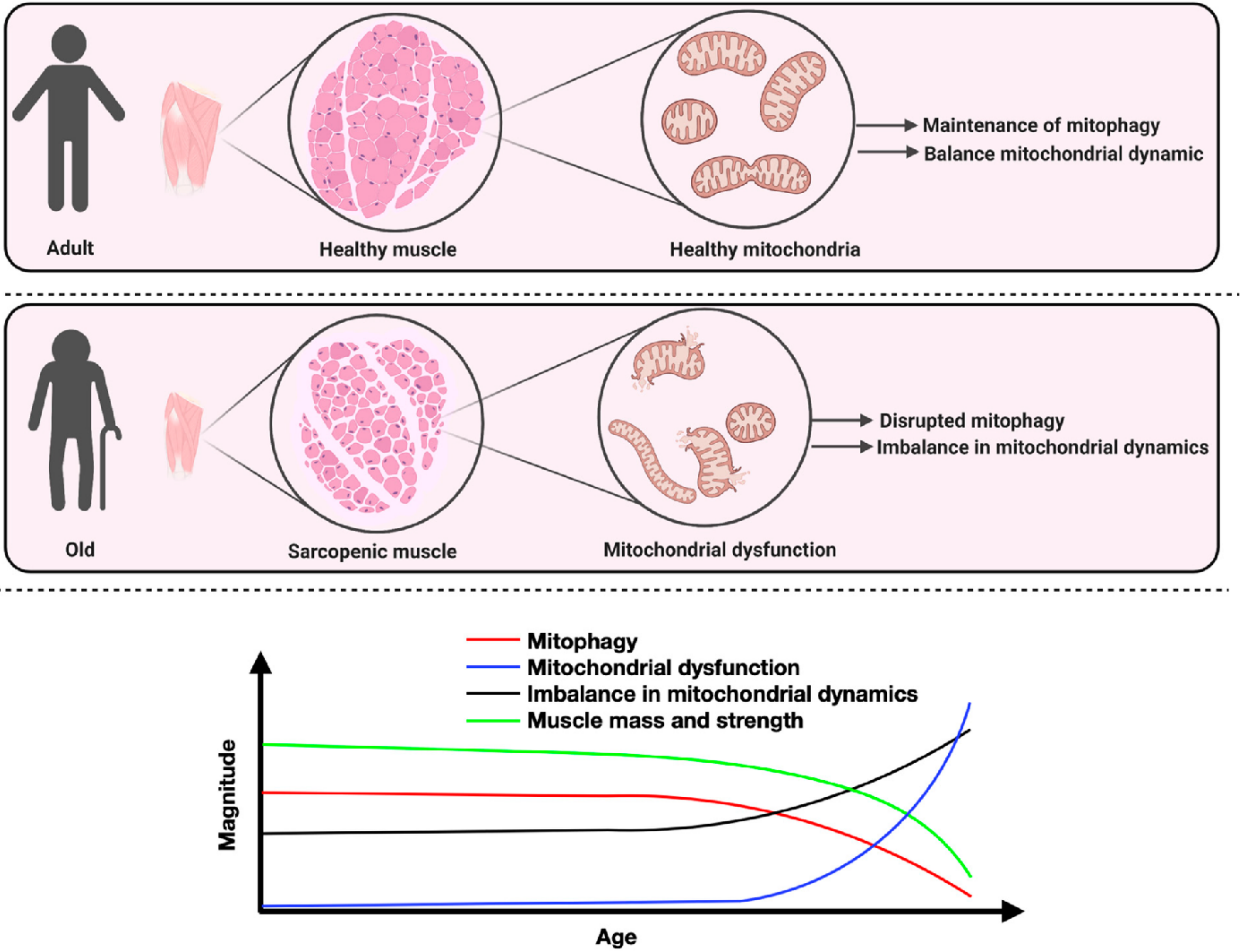


Young adulthood is characterized by an intermingling of fibres belonging to different motor units. This yields a mosaic distribution of fibre types when muscle fibres are viewed in cross-section. Adulthood to old age is characterized by repeating cycles of denervation–-reinnervation that result in axonal degeneration and/or motor neuron death leading to grouped fibre atrophy when viewed in cross-section.





Changes in niche-derived and systemic signaling molecules, along with intrinsic changes in the satellite cell, contribute to the functional impairments of aged muscle stem cells and the consequent defects in regenerative capacity of the aged skeletal muscle.



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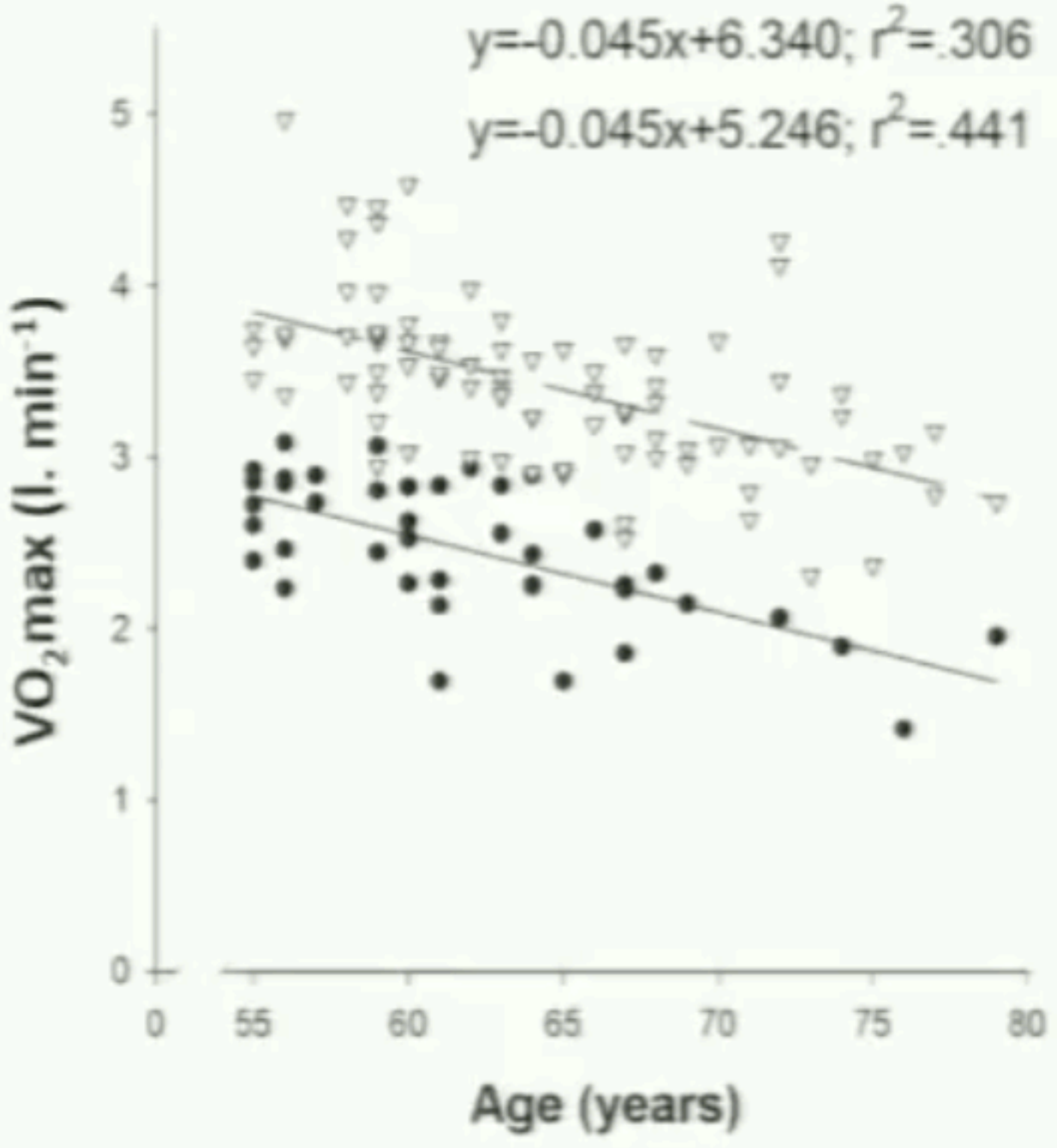
Maximal Oxygen uptake ($\dot{V}O_2max$)



Females ● Males ∇

Pollock et al. (2015)

J Physiol

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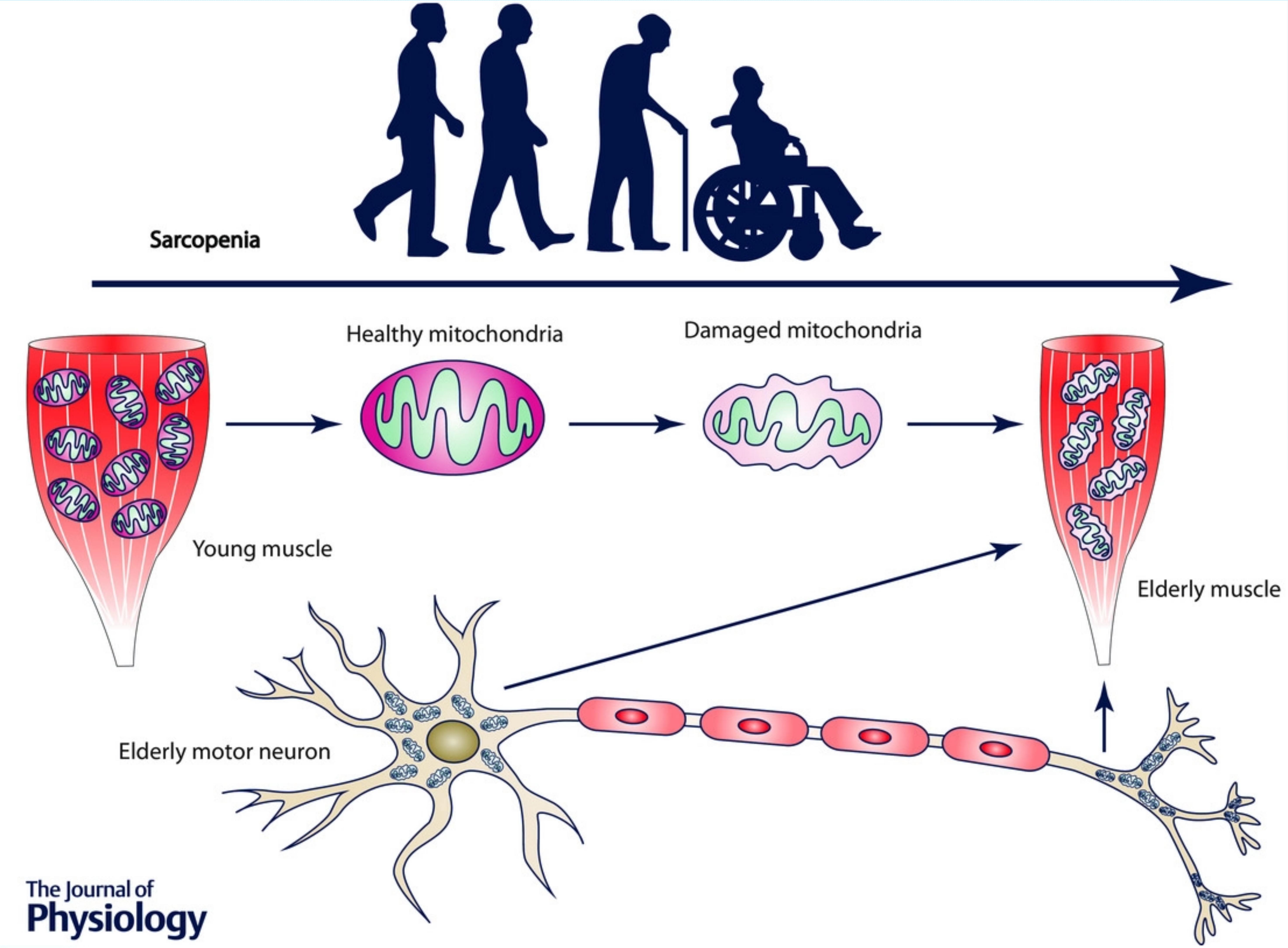
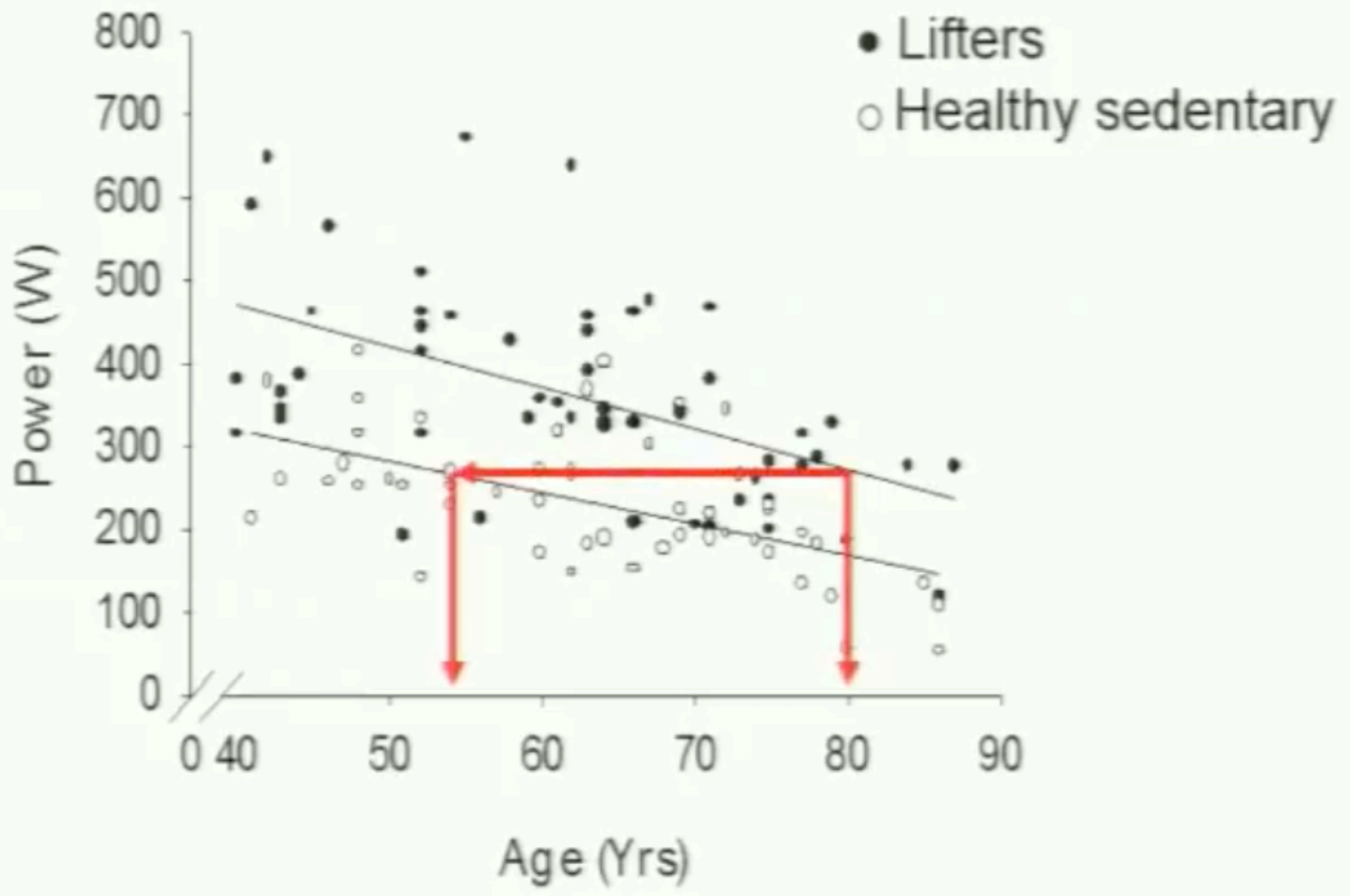

Sarcopenia
Healthy mitochondria
Damaged mitochondria
Young muscle
Elderly muscle
Elderly motor neuron
The Journal of
Physiology

Factors associated with sarcopenia..

- Changes in circulating “anabolic” hormones
  - (↓ e.g. GH/IGF-I, Testosterone, etc)
- Metabolic dysregulation
  - (↑ reactive O_2 species)
- Inflammation (“inflamageing”)
  - (↑ degradation)
- “Anabolic resistance” to feeding and exercise
  - (↓ protein synthesis)
- ↓ regeneration from exercise induced damage
  - (compromised satellite cell behaviour)

Lifters ~35% more powerful



Pearson *et al.* (2001)

Med Sci Sport. Ex.

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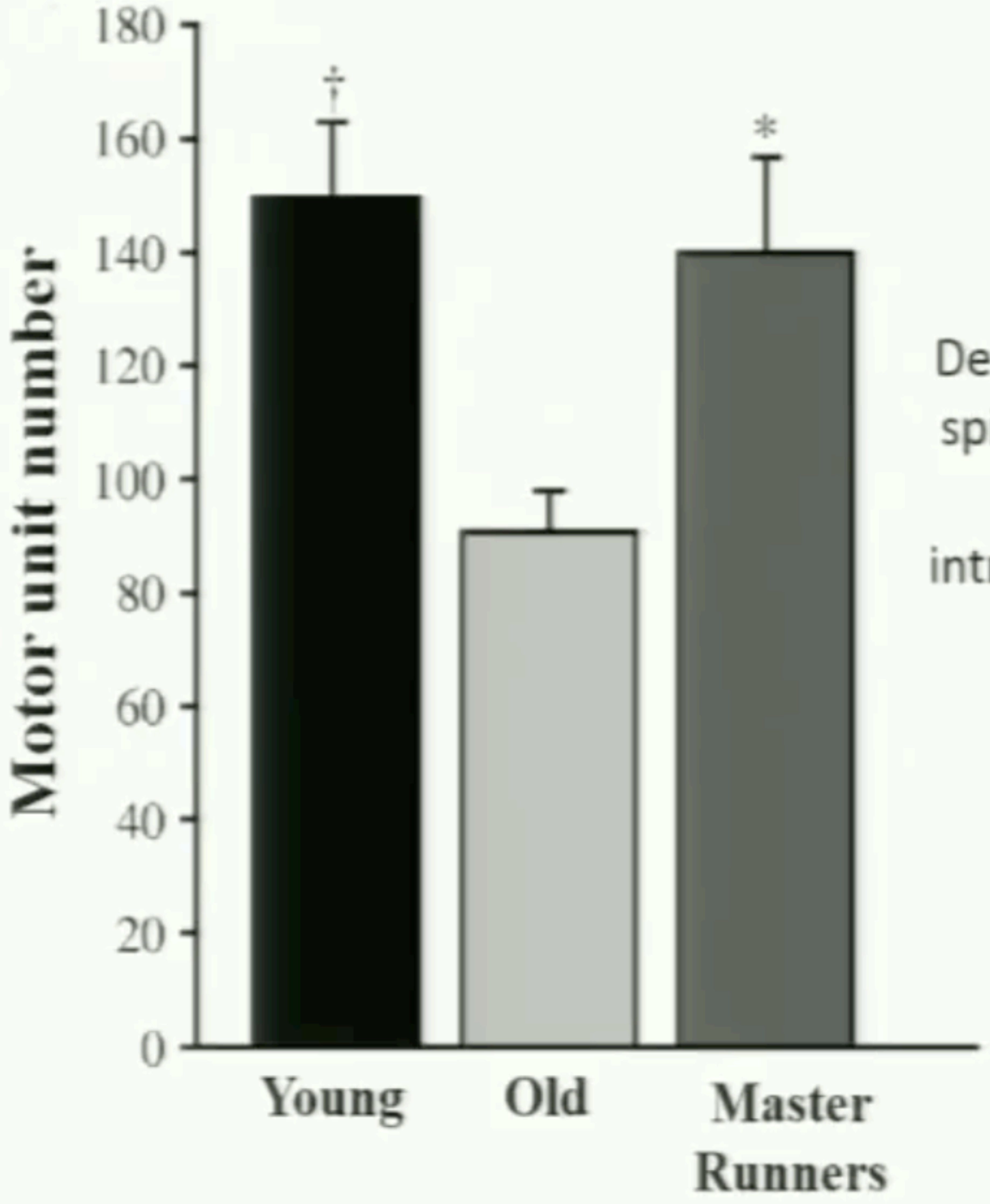
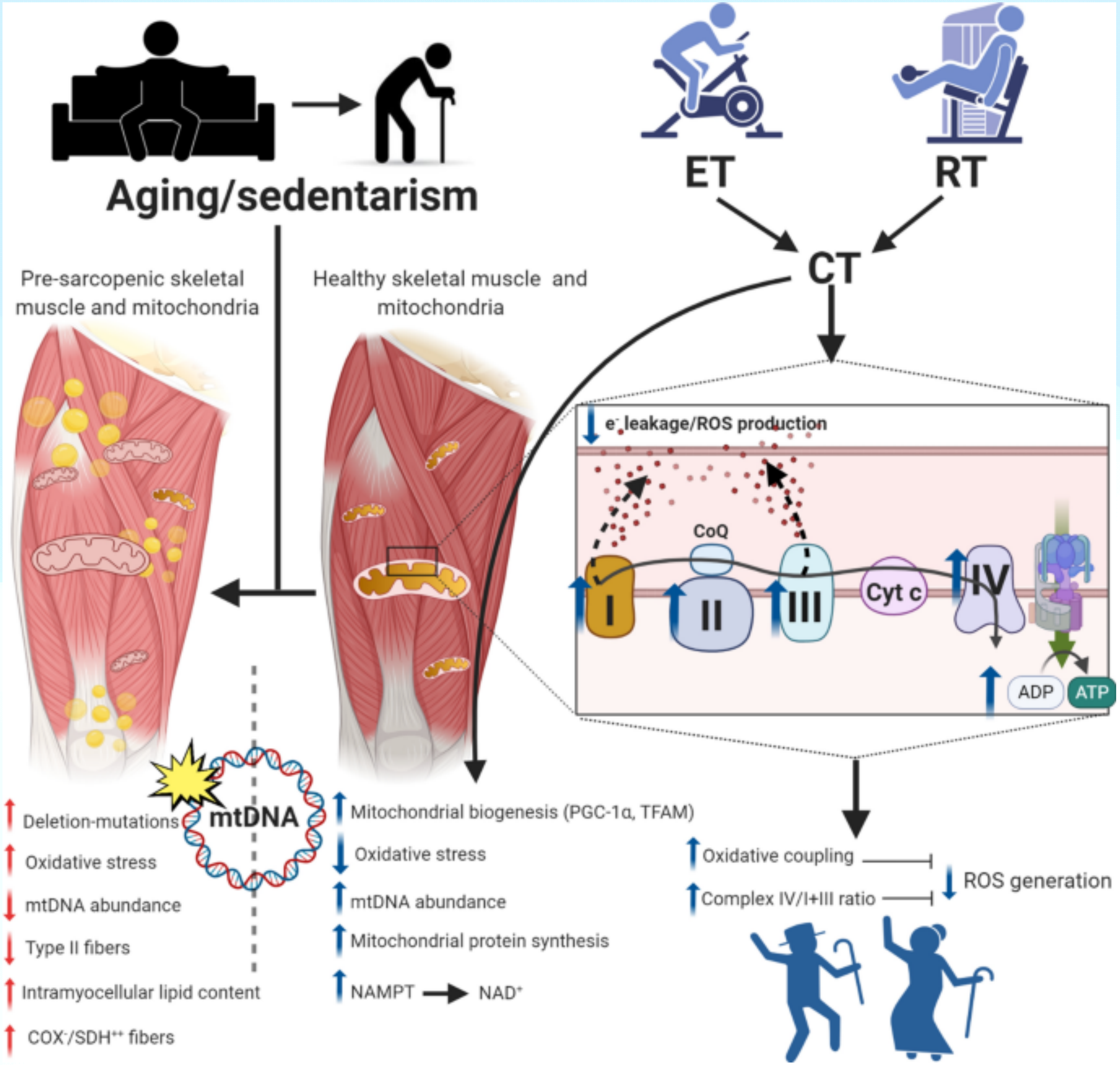
No motor unit loss in the tibialis anterior of master runners (aged 65 years)



Decomposition-enhanced spike-triggered averaging from surface and intramuscular EMG during dorsiflexion at 25% of MVC

Porter *et al.* (2010)



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Muscle plasticity in aging

- Sedentary aging results in a loss of muscle function, mass and quality
- Skeletal muscle is extremely sensitive to mechanical and metabolic signals
- It is difficult to tease out the effects of aging per se from the effects of long term inactivity
- Exercisers provide a model of inherent human aging free from the contaminants of inactivity
- Elderly exercisers have different muscle physiology from sedentary - with morphology and function

Take home message

Skeletal muscle shows an enormous plasticity to adapt to stimuli such as contractile activity (endurance exercise, electrical stimulation, denervation), loading conditions (resistance training, microgravity), substrate supply (nutritional interventions) or environmental factors (hypoxia).

Adaptations occur in both muscle fibres (myofibrils, mitochondria) and associated structures (motoneurons and capillaries), inducing alterations in regulatory mechanisms (neuronal, endocrine and intracellular signalling), contractile properties and metabolic capacities.

Several signalling pathways involving cytoplasmic protein kinases and nuclear-encoded transcription factors are recognized as potential master regulators

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