BONE EMBRYOLOGY AND PHYSIOLOGY

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Pattern formation

- General body plan laid down in embryo.
- Regional separation, patterns for organs, appendages, etc. are established in stages.
- Define cells in the region.
- Establish signaling centers to provide positional information (relative positions of cells).
- Differentiation of cells in response to cues.

Genetic mediators

- Paracrine signaling molecules
- Secreted into intercellular space.
- Diffuse to nearby cells
- Four major families:
- Fibroblast Growth Factor (FGF)
- Hedgehog (SHH) proteins
- Wingless family (WNT)
- Transforming Growth Factor-β (TGF-β)

Genetic mediators

- Transcription factors
- Control genetic expression in cell
- Many families of transcription factors:
- Homeobox: HOX, PAX, EMX, MSX
- High-mobility group (HMG): SOX family
- T-box family: TBX

SOX family

- SOX9 is a transcription factor expressed by proliferating but not hypertrophic chondrocytes that is essential for differentiation of precursor cells into chondrocytes.
- SRY, the sex-determining region of Y, regulate SOX9 expression in genital ridges.
- Increase in male; decrease in female.
- SOX9 regulates chondrogenesis and COL2A1.
- Mutation causes camptomelic dysplasia.
- Short limbs, sex-reversal of XY fetuses.

SOX family

- Hirschsprung's disease is neural crest defect.
- Enteric neurons not develop properly.
- Colon hypomotility, severe constipation.
- 4:1 males.
- SOX10 one of several genes that causes similar phenotype.

Hedgehog family

- Sonic hedgehog (SHH).
- Produced at base of limbs in zone of polarizing activity:
- Left-right axis.
- Neural tube, somites, limbs.
- Defects disrupt midline brain development.
- Holoprosencephaly is severe form.
- Severe mental retardation and early death.
- A complex interaction involving parathyroid hormone-related peptide and the Indian hedgehog (IHH) genes is critical for the development and regulation of the cartilage growth plate.

RUNX2

- RUNX2 is a transcription factor involved in chondrocyte and osteoblast differentiation.
- It is expressed in early hypertrophic chondrocytes and immature mesenchymal cells and controls terminal chondrocyte and osteoblast differentiation, respectively.

Transcription factors

- The WNT signaling pathway is a critical regulator of skeletal development and mass, working in part through the stimulation of RUNX-2 gene expression.
- The pathway includes a number of regulatory factors that can interact with growth factors involved in skeletal development, such as β-catenin and BMP-2.
- The WNT pathway is also a major regulator of joint remodeling, and TNF-α induction of DKK-1 results in the joint erosion typical of rheumatoid arthritis

Transcription factors

- Deletion of the one osteoblast-specific transcription factor called RUNX-2 or CBFA-1, results in the development of a complete cartilaginous skeleton, but no transformation to bone.
- Die at birth because their soft ribcage cannot support respiration.
- Heterozygous deletion of one RUNX-2 gene results in cleidocranial dysplasia.
- There is at least one other transcription factor, probably acting downstream of RUNX-2 called osterix that is also required for full differentiation of osteoblast.

Transcription factors

- Activation of WNT signaling through its co-receptors LRP-5 and 6 may increase bone mass not only by enhancing bone formation but also by inhibiting bone resorption
- Increase in the production of osteoprotegerin
- Inhibit adipogenesis
- Marrow stromal cell precursors are more likely to differentiate into osteoblasts.
- The WNT/β-catenin pathway is in turn down regulated by sclerostin.

Transcription factors

- Skeletal development also requires the formation of blood vessels in the bone and vascular endothelial growth factor (VEGF) signaling is probably critical for the conversion of a vascular cartilage to highly vascular bone.

FGFR3

- Moderate increase in FGFR3 activity inhibits chondrocyte growth.
- Most common abnormality is achondroplasia.
- Disproportionately short stature (short limbs).
- Macrocephaly.
- Autosomal dominant
- 80% of sporadic cases involve mutation in paternal allele
- Milder form is hypochondroplasia.
- Most severe is thanatophoric dysplasia.
- Lethal.
- Very short limbs.
- Highly activated receptor.

Extracellular matrix proteins

- Secreted proteins that form scaffold for tissues:
- Collagens, fibrillins, elastins, laminins, fibronectins, tenascins
- Fibrillin–1 and elastin coordinate microfibril assembly in extracellular matrix.
- Laminin important in anchoring cells to extracellular matrix.
- Integrins are the link between extracellular matrix and cytoskeleton.
- Glycosyltransferases bind glycosyl residues on the extracellular matrix.

Systemic hormonal mediators

- Growth hormone (GH)
- Secreted by the anterior pituitary.
- It acts on resting chondrocytes to induce and maintain proliferation.
- Thyroid hormone (T3)
- Secreted by the thyroid gland
- Acts on proliferating chondrocytes to induce hypertrophy.

Paracrine hormonal mediators

- Indian hedgehog (Ihh)
- Locally secreted regulator (paracrine), made by prehypertrophic chondrocytes
- Coordinates chondrocyte proliferation and differentiation and osteoblast proliferation.
- Parathyroid hormone related protein (PTHrP)
- Local factor, expressed by perichondrial stromal cells and early proliferating chondrocytes that activates the PTH receptor and maintains proliferation of chondrocytes.

Paracrine hormonal mediators

- Wnt is a family of secreted factors that are expressed at highest levels in the proliferating zone and bind to the receptors
- Frizzled and LRP5/6
- Activate β-catenin signaling.
- They can promote both proliferation and maturation of chondrocytes.

Hormonal effects

- Fibroblast growth factors (FGFs) are secreted by a variety of mesenchymal cells.
- FGF (most notably FGF3) acts on hypertrophic chondrocytes to inhibit proliferation and promote differentiation.
- Bone morphogenic proteins (BMPs) are members of the TGF-β family.
- They are expressed at various stages of chondrocyte development in the growth plate and have diverse effects on chondrocyte proliferation and hypertophy.

Table 26-3 Subtypes of Osteogenesis Imperfecta

Subtype	Collagen Defect	Inheritance	Major Clinical Features	Prognosis
I	Decreased synthesis of pro-α1(1) chain Abnormal pro-α1(1) or pro-α2(1) chains	Autosomal dominant	Postnatal fractures, blue sclera Normal stature Skeletal fragility Dentinogenesis imperfecta Hearing impairment Joint laxity Blue sclerae	Compatible with survival
II	Abnormally short pro-α1(1) chain Unstable triple helix Abnormal or insufficient pro-α2(1)	Most autosomal recessive Some autosomal dominant New mutations	Death in utero or within days of birth Skeletal deformity with excessive fragility and multiple fractures Blue sclera	Perinatal lethal
III	Altered structure of pro-peptides of pro-α2(1) Impaired formation of triple helix	Autosomal dominant (75%) Autosomal recessive (25%)	Compatible with survival Growth retardation Multiple fractures Progressive kyphoscoliosis Blue sclera at birth that become white Hearing impairment Dentinogenesis imperfecta	Progressive, deforming
IV	Short pro-α2(1) chain Unstable triple helix	Autosomal dominant	Postnatal fractures, normal sclerae Moderate skeletal fragility Short stature Sometimes dentinogenesis imperfecta	Compatible with survival

OI, Osteogenesis imperfecta.

Axis specification

- Vertebrate body plan has three axes:
- Anterior/posterior, dorsal/ventral, left/right
- Anterior/posterior is first to form. Derives from growth of primitive streak.
- Patterning along the axis is due to HOX genes.
- Four clusters of similar genes
- Expressed in specific spatial and temporal patterns.
- Similar rules for each cluster.
- Respond to retinoic acid.

Homeotic transformation

- HOX genes are expressed from anterior boundary rearward in embryo.
- Combination of expressed genes determines position.
- Missing gene means segment identity wrong.
- Segment transforms, called homeotic transformation.

Dorsal-ventral axis

- WNT-7 is produced at apical ectodermal ridge
- Necessary for proper organization along dorsal-ventral axis.
- Noggin and chordin are dorsalizing signals.
- BMP4 is ventralizing signal.
- Noggin and chordin bind BMP4, prevent binding to receptor.
- Antagonistic pattern common in development.

Left-right axis

- Laterality defects can be random (situs ambiguus) or reversed (situs inversus), and involve one or many organs.
- Asymmetric SHH from notochord causes left side expression of primitive node (TGF-β).
- Rightward looping of heart tube results.
- Mutation in dynein, the motor protein for cilia.

Left-right asymmetry

- Zinc-finger protein of the cerebellum (ZIC3).
- GLI transcription factor family on X chromosome.
- GLI family regulated by forming complex with protein similar to dynein.
- Randomization defects; males affected.
- Heterozygote females, left-right reversal.
- More common in conjoined than normal twins.
- Right side twin randomized, inadequate signaling from left-side twin?

Anterior-posterior limb

- Anterior defects in Holt-Oram syndrome.
- Thumb, radius defects most common.
- T-box gene (TBX5) mutated.
- Posterior defects in ulnar-mammary syndrome.
- Posterior digits, ulna most affected.
- TBX3 mutated, closely linked to TBX5.

Limb development

- Second only to heart defects in frequency in newborns.
- FGF8 is inductive signal.
- Produced at apical ectodermal ridge.
- Stimulates mitosis of underlying mesoderm, providing for lengthening of limbs.
- Can induce entire limb program.
- Signal mediated by FGF10 expression in mesoderm.
- WNT2b and WNT8c maintain FGF10 expression.

Limb growth signals

- Proximal/distal growth stimulated by FGF2, FGF4 and FGF8.
- Stimulate proliferation of mesodermal cells in progress zone.
- The zone of proliferating activity uses SHH to maintain the apical ectodermal ridge.
- Also used in dorsal/ventral and left/right axis.
- Also signals positional information along the proximal/distal axis.

Fourth week

- The ventral and medial parts of the somite dissociate and shift position and are known as the sclerotome.
- Cells of the sclerotome surround the neural tube and notochord and migrate laterally to form limb precursors.
- The remaining part of the somite gives rise to a dermomyotome.

Bone formation and growth

- Bone first appears as condensations of mesenchyme cells that form bone models.
- (1) Bone develops from mesenchyme (intramembranous ossification).
- Responsible for the development of flat bones.
- Bones of the cranium, for example, are formed by osteoblasts directly from a fibrous layer of tissue that is derived from mesenchyme, without a cartilage anlagen.

Bone formation and growth

- Because bone is made only by osteoblasts, the enlargement of bones is achieved by the deposition of new bone on a preexisting surface.
- This mechanism of appositional growth is instrumental in bone development and modeling.

Bone formation and growth

- (2) Bone principally develops from cartilage (endochondral ossification).
- At 8th week, cartilage is removed by osteoclasts forming the medullary canal
- The mid-shaft periosteoum concurrently generates osteoblasts that deposit the beginnings of the cortex (primary ossification center).

Bone formation and growth

- A similar sequence of events occurs in the epiphysis.
- Cartilage is removed and bone deposited in a centrifugal fashion (secondary ossification center).
- The entrapped cartilage anlage between the two centers becomes the growth plate.
- Those chondrocytes are responsible for longitudinal growth.
- The remnant struts become the primary trabeculae.

Bone formation and growth

- The chondrocytes within the growth plate undergo sequential proliferation, hypertrophy and apoptosis.
- In the region of apoptosis the matrix mineralizes and is invaded by capillaries, providing the nutrients for osteoblasts to be activated and synthesize osteoid.
- Although the calcified cartilage matrix is resorbed, remnant struts persist and act as scaffolding for the deposition of bone on their surfaces.
- These structures are known as primary spongiosa and are the first bony trabeculae

Ossification

- By the 5th week chondrification centers appear; the first bone models are present.
- By the end of the 6th week the entire limb is cartilaginous.
- Ossification begins at the end of the embryonic period (week 8).
- By week 12, primary centers are present in nearly all bones of the limb; myoblasts are aggregating.
- The clavicles are the first to begin to ossify; then, femurs.

Ossification

- Secondary centers are present around the knees before birth.
- At birth the shafts of the long bones are largely ossified.
- Epiphyses are still cartilage.
- Secondary ossification centers appear in the epiphyses during the first few years.

Muscle

- Somatic layer of lateral plate mesoderm will form the sternum and limb bones.
- Neural crest will form many of the bones of the skull.
- Head somitomeres form the cranial vault and base of skull.
- The skeletal muscle arises from somites and somitomeres in the head.

Muscle

- Lateral segments of the myotome:
- Cervical region: scalenes, geniohyoid, prevertebral muslces.
- Thoracic region: intercostals, transversus thoracis.
- Abdominal region: obliques.
- Lumbar region: quadratus lumborum.
- Sacral region: pelvic diaphragm.
- Ventral Segments of the myotome:
- infrahyoid muscles and the rectus abdominis.

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Vertebral column

- Still in the fourth week, the caudal caudal portion of each sclerotome proliferates and proceeds to the cranial half of the inferior sclerotome.
- By incorporation of intersegmental tissue, the newly formed vertebral body becomes intersegmental.
- The myotomes and nerves remain segmental.
- The notochord regresses, but persists and enlarges in the region of the intervertebral disc and forms the nucleus pulposus
- Mesenchyme forms the annulus fibrosus.

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Early limb development

- Somites stimulate the somatic layer of lateral plate mesoderm to evaginate.
- The somatic layer of lateral plate mesoderm forms a core of mesenchyme covered by surface ectoderm.
- The earliest sign of limb development are the limb buds.
- Buds appear “low” on the embryo because of the large developing head.
- The upper limb bud (cervical, thoracic) appears by day 26; the lower limb bud (lumbar, sacral), by day 28.

Early limb development

- The apex of each limb bud thickens to form a multilayered apical ectodermal ridge (AER).
- The AER has an inductive effect of the underlying mesenchyme (proliferation).
- The AER causes adjacent cells to remain undifferentiated.
- The AER is essential for proximal-distal axis.
- Mesenchymal cells aggregate at the posterior margin of the limb bud to form a zone of polarizing activity (ZPA).
- The ZPA is responsible for patterning of the anterior-posterior axis.

Early limb development

- The distal ends of the limb buds flatten into paddle like plates, called hand and foot plates and by the end of the 6th week, the mesenchyme in the hand plate has condensed to form digital rays (finger buds).
- By the end of the 7th week, the mesenchyme in the foot plate has condensed to form digital rays (toe buds).
- At the tip of each ray the apical ectodermal ridge induces bone formation. Loss of connective tissue between rays leads to separation of digits.
- Upper limbs rotate medially 90°; lower limbs, laterally 90° to reach anatomical position.

Joints

- Joints begin to develop during the 6th week and are near their adult form by the 8th embryonic week.
- Synovial joints develop from interzonal mesenchyme between the developing bones:
- Peripherally forms capsule and ligaments;
- Centrally it disappears (cavity).
- Forms the synovial membrane
- As a result of joint movements (in utero), the mesenchyme disappears from the articular cartilage.

Limbs

- Motor axons from the spinal cord each the dorsal and ventral muscle masses during the 5th week.
- Upper limb: C5 through T2.
- Lower limb: L2 though S2.
- Motor axons grow out first.
- The sensory axons use the motor axons as a guide to their target.
- Peripheral processes extend from posterior root ganglion neurons and use motor axons as a guide to their target.

Limbs

- As limbs elongate the cutaneous distribution migrates along the limbs; there is overlap between dermatomes.
- The limb buds are initially supplied by dorsal intersegmental arteries, that arise from the dorsal aorta.
- The primordial vascular pattern consists of primary axial arteries and its branches.
- The axial artery drains into a marginal sinus; becomes peripheral vein.

Bone matrix

- Bone matrix is the extracellular component of bone.
- 35% osteoid
- Type I collagen principally
- Osteopontin (also called osteocalcin) is unique to bone.
- It is produced by osteoblasts and plays a role in bone formation and mineralization and in calcium homeostasis
- Hardness of bone related to hydroxyapatite
- Repository for 95% of calcium and 85% of phosphorous

Table 26-1 Proteins of Bone Matrix

Osteoblast-Derived Proteins
Type I collagen
Calcium-binding proteins
Osteonectin, bone sialoprotein
Cell adhesion proteins
Osteopontin, fibronectin, thrombospondin
Cytokines
IL-1, IL-6, RANKL
Enzymes
Collagenase, alkaline phosphatase
Growth factors
IGF-1, TGF-β, PDGF
Proteins involved in mineralization
Osteocalcin
Proteins Concentrated from Serum
Albumin
β_2-microglobulin

IGF, linsulin-like growth factor; *TGF*, transforming growth factor; *PDGF*, platelet-derived growth factor; *IL*, interleukin; *RANKL*, receptor activator of nuclear factor-κB ligand.

Bone formation

- Woven bone is produced rapidly, such as during fetal development or fracture repair,
- The haphazard arrangement of collagen fibers imparts less structural integrity than the parallel collagen fibers in slowly produced lamellar bone.
- In an adult, the presence of woven bone is always abnormal.
- A cross-section of a typical long bone shows a dense outer cortex and a central medulla composed of bony trabeculae separated by marrow.

Bone formation

- Osteoblasts, located on the surface of the matrix, synthesize, transport and assemble the matrix and regulate its mineralization.
- Osteocytes are interconnected by an intricate network of dendritic cytoplasmic processes through tunnels (canaliculi).
- Osteocytes help to control calcium and phosphate levels in the microenvironment
- Osteocytes detect mechanical forces and translate them into biologic activity (mechanotransduction).

Bone resportion

- Osteoclasts are specialized multinucleated macrophages derived from circulating monocytes that are responsible for bone resorption).
- By means of cell surface integrins, osteoclasts attach to bone matrix and create a sealed extracellular trench (resorption pit).
- Secretion of acid and neutral proteases (predominantly matrix metalloproteases, [MMPs]) into the pit results in dissolution of the inorganic and organic components of bone.

Types of collagen

Type	Tissue
I Low carbohydrate; <10 hydroxylysines per chain; two types of polypeptides	Bone, skin, tendon, scar, cardiac valves, intestinal wall, uterine wall
II 10% carbohydrate; >20 hydroxylysines per chain	Cartilage, vitreous
III Low carbohydrate; glycine and hydroxyproline rich; contains cysteine	Blood vessels, intestinal wall, uterine wall, scar
IV 15% carbohydrate; >40 hydroxylysines per chain; 3-hydroxyproline rich; little arginine, alanine; contains cysteine	Basement membrane, lens capsule
V 15% carbohydrate; glycine and hydroxyproline rich	Cell surfaces
VI Cysteine and tyrosine rich	Aortic intima, placenta, kidney

Tropocollagen

- Fundamental unit.
- Rigid, triple-helical rod.
- 3 left-handed α-chains intertwined in a triple right-handed helix.
- Wider pitch than α-helix to accommodate bulky proline and hydroxyproline residues.
- R-, amino, and carbonyl groups on the outside of the helix.
- Hydrogen bonding stabilizes.

Tropocollagen

- High proline, hydroxyproline, glycine, and hydroxylysine content.
- Glycine every 3rd amino acid in repeating sequence (Gly–X–Y).
- Xs are Proline; Ys are Hydroxyproline.
- Some Ys are Hydroxylysine.

Biosynthesis

Intracellular processes

- Synthesized with signal peptide in the endoplasmic reticulum and labeled for export..
- Cleavage of signal peptide.
- Hydroxylation of some proline and lysine (requires α-ketoglutarate, Oxygen and vitamin C).
- Glycosylation of some hydroxylysine residues.
- Triple right handed helix formed.
- Stabilized by intermolecular Hydrogen bonds.
- Abnormal α-keratin in patients with breast and colon cancer (diffuse rings)

Biosynthesis

Extracellular processes

- Extension peptides removed.
- Tropocollagen molecules assembled into fibers.
- Covalent cross linkages formed between allysine and between allysine and lysine residues. Cross-linking stabilizes fibers.
- Lysyl amino oxidase key step in cross-linkage.
- Requires Cu^{2+} to function.
- Aldehyde derivatives form.
- Aldol condensation of lysines cross-link in collagen or formation of Schiff base and lysinoleucine cross-link in elastin or collagen.

Biosynthesis

- Stabilizing hydrogen bonds form between hydroxyprolines in tropocollagen units.
- Menkes' syndrome is a neurodegenerative disorder due to lack of Cu^{2+}.

Extracellular matrix proteins

- Fibrillin–1 and elastin coordinate microfibril assembly in extracellular matrix.
- Fibrillin-1 mutations in Marfan syndrome.
- Elastin mutations in supravalvular aortic stenosis.
- Both show abnormal heart and large blood vessels.
- Laminin important in anchoring cells to extracellular matrix.
- LAMC2 mutations in junctional epidermolysis bullosa.
- Epithelial layers do not attach.

Elastin

- Synthesized by fibroblasts.
- Major protein component of elastic fibers.
- Prevalent in lung, arterial walls, skin, ligaments.
- Encoded by one gene, but differential processing produces several variants.
- Tropoelastin monomers (70 kD) synthesized as proelastin precursors
- Rich in small, non-polar amino acids and in lysine.
- Cross-linkage of (3) lysines produces desmosines.

Fibrillin

- Secreted by fibroblasts. Glycoprotein.
- Major component of microfibrils that provide a scaffold for elastin.
- Genes present on chromosomes 5 and 15.
- Marfan Syndrome.
- Structures of the suspensory ligament of the eye, periosteum, and media of the aorta are affected.
- Characterized by arachnodactyly, long limbs, joint laxity, dilatation of the aorta (and dissecting aneurysm), ectopia lentis.
- Autosomal dominant
- Mutations in fibrillin-1 gene on chromosome 15.

Fibrinonectin

- Large multi-adhesive glycoprotein. Major component of extracellular matrix.
- Complex molecule with several binding domains: collagen, heparin, fibrin, cell receptor (as integrin).
- Also present in plasma in soluble form.
- Important role in cell adhesion and cell migration. Plays key role in would healing.
- Malignant cells appear to be deficient in surface-bound fibronectin.

Laminin

- Large cross-shaped glycoprotein composed of 3 polypeptides. 12 different types of laminin.
- Abundant protein in basal lamina, second only to type IV collagen. Attaches the other components of the basal lamina to the overlying cells. Laminin receptors also are integrins.
- Cross-like structure. Foot of A chain binds to heparan sulfate; B1 arm binds to type IV collagen. Junction of A, B1, B2 chains bind to cell surface. α-helical coil about A chain below junction; binds to axons.

Laminin

- Junctional epidermolysis bullosa is associated with a defect in laminin 5 or 6; blistering of skin and mucous membranes is seen.
- A form of muscular dystrophy is associated with a defect in laminin 2, linking the cell membrane with the exoskeleton.

Proteoglycans (mucopolysaccharides)

- Glycosaminoglycans
- Major component of the ground substance.
- Unbranched, linear polymers.
- Disaccharides repeat. Alternating amino-sugars.
- Negatively charged (polyanion).
- Extended conformation to minimize repulsive forces.
- Bind water forming gel-like matrix.
- Acts as sieve.

Proteoglycans

- Aggrecan core protein attaches to hyaluronate.
- Chondroiton sulfate and keratan sulfate extend from core.
- Brush-like configuration.
- Syndecan
- An integral transmembrane protein associated with actin cytoskeleton inside the cell and fibronectin outside the cell.
- Chondroiton sulfate and heparan sulfate attach outside the cell.

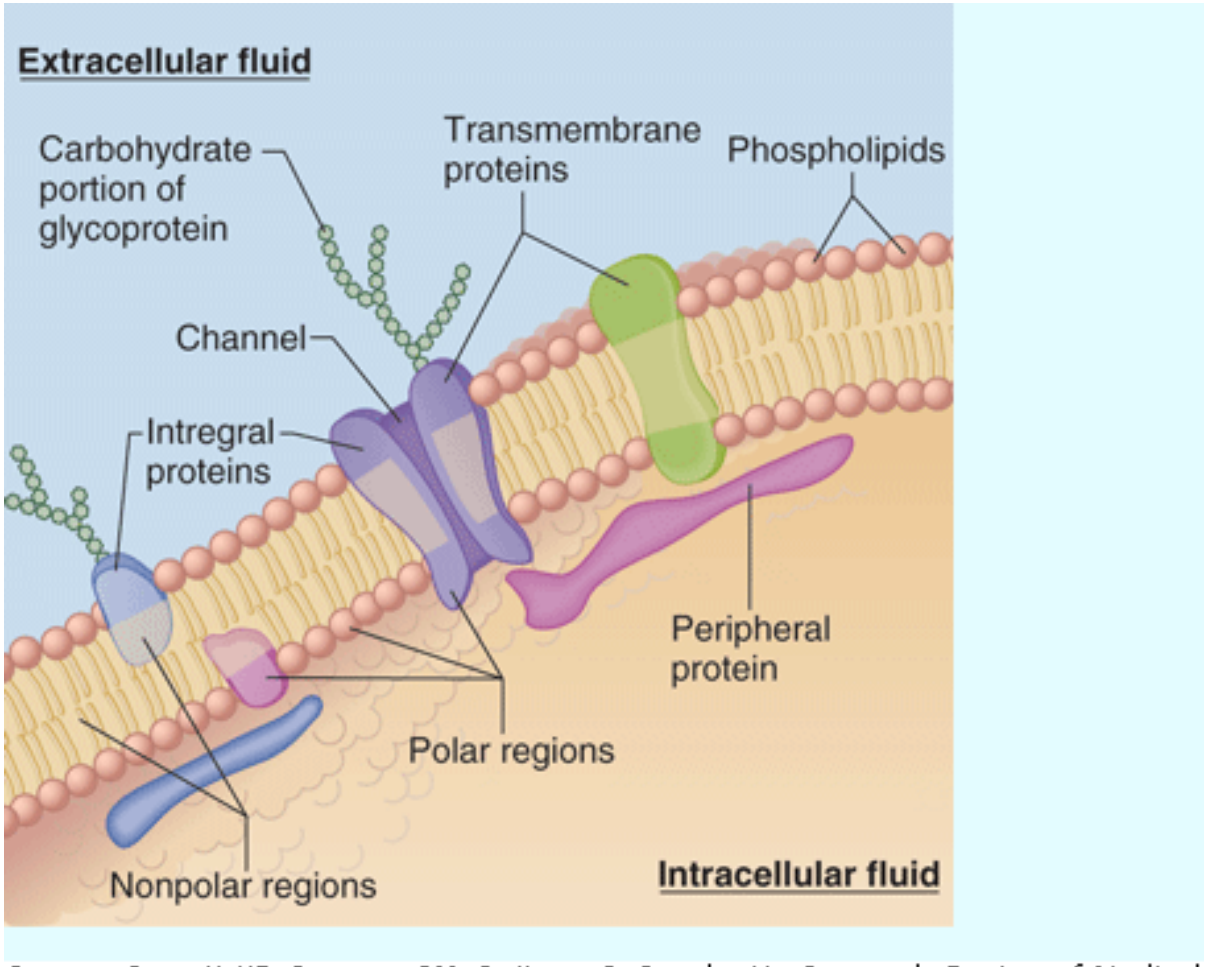
Glycosoaminoglycans

- Hyaluronic acid facilitates cell migration, makes possible cartilage compressibility.
- Non-sulfated.
- Chondroiton sulfate makes possible cartilage compressibility.
- Keratan sulfate I plays a role in corneal transparency.
- Dermatan sulfate plays a role in corneal transparency and has a structural role in the sclera.

Glycosoaminoglycans

- Heparan sulfate
- Determines the charge selectiveness of the renal glomerulus
- Function as receptor in plasma membranes with a role in cell adhesion and cell-cell interactions
- Are components of synaptic and other vesicles
- Acts as an anticoagulant.

Cell membrane

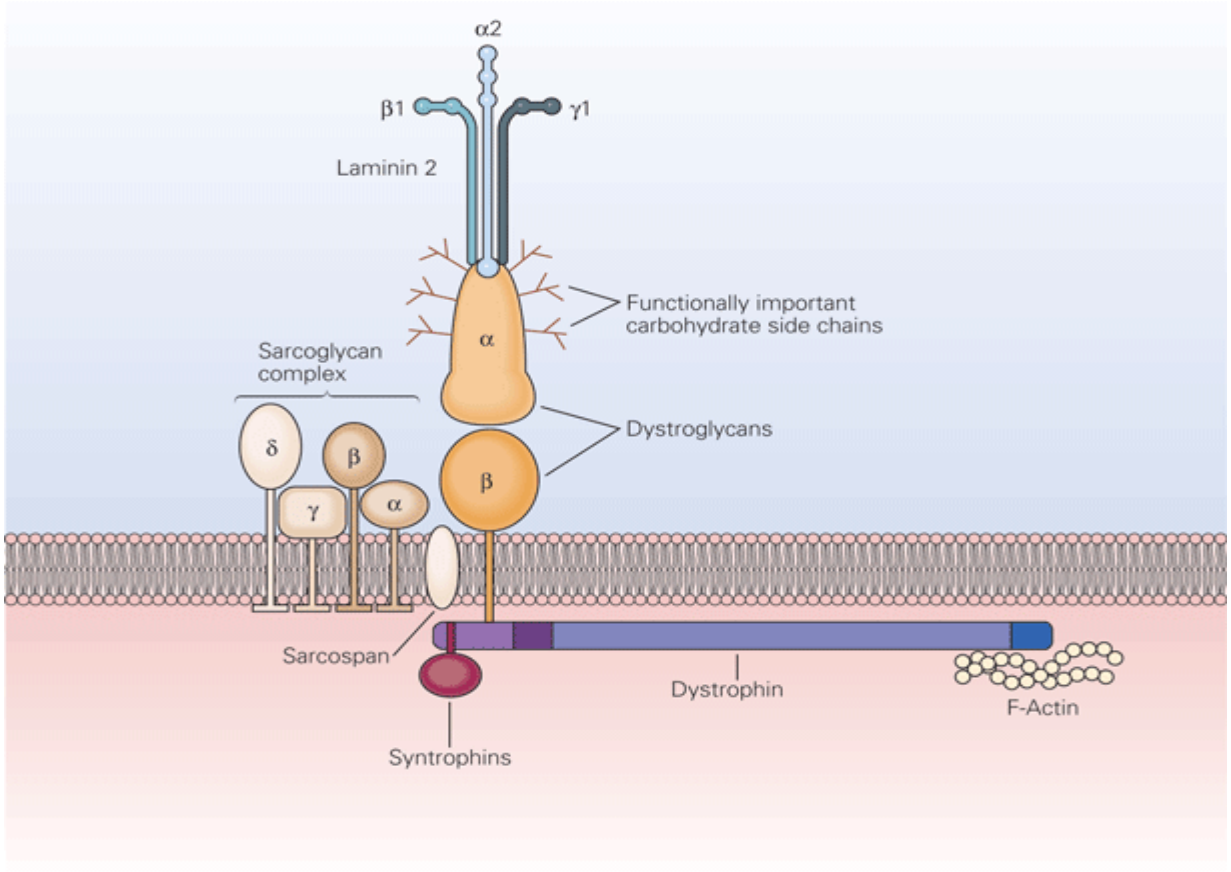


Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Reproduced with permission from Widmaier EP, Raff H, Strang K: *Vander's Human Physiology: The Mechanisms of Body Function*, 11th ed. McGraw-Hill, 2008.)

Fig. 2-2 Accessed 07/01/2010

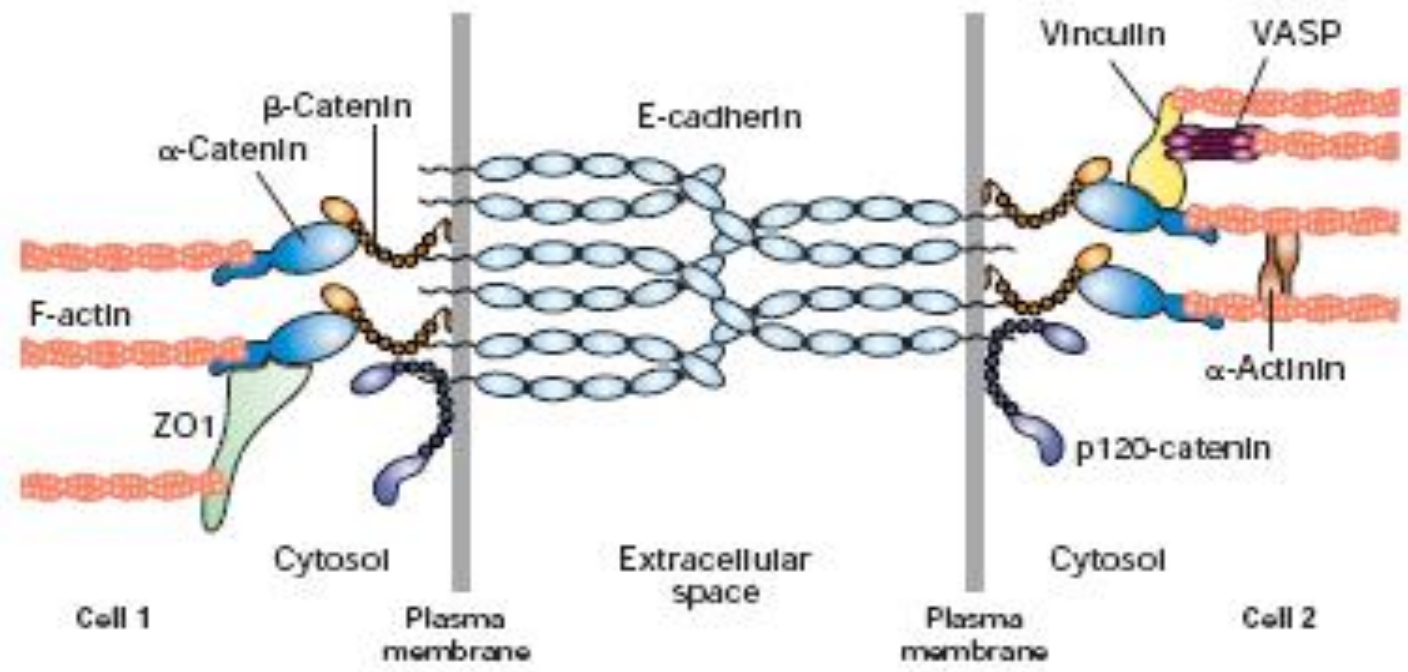
Dystrophin-glycoprotein complex



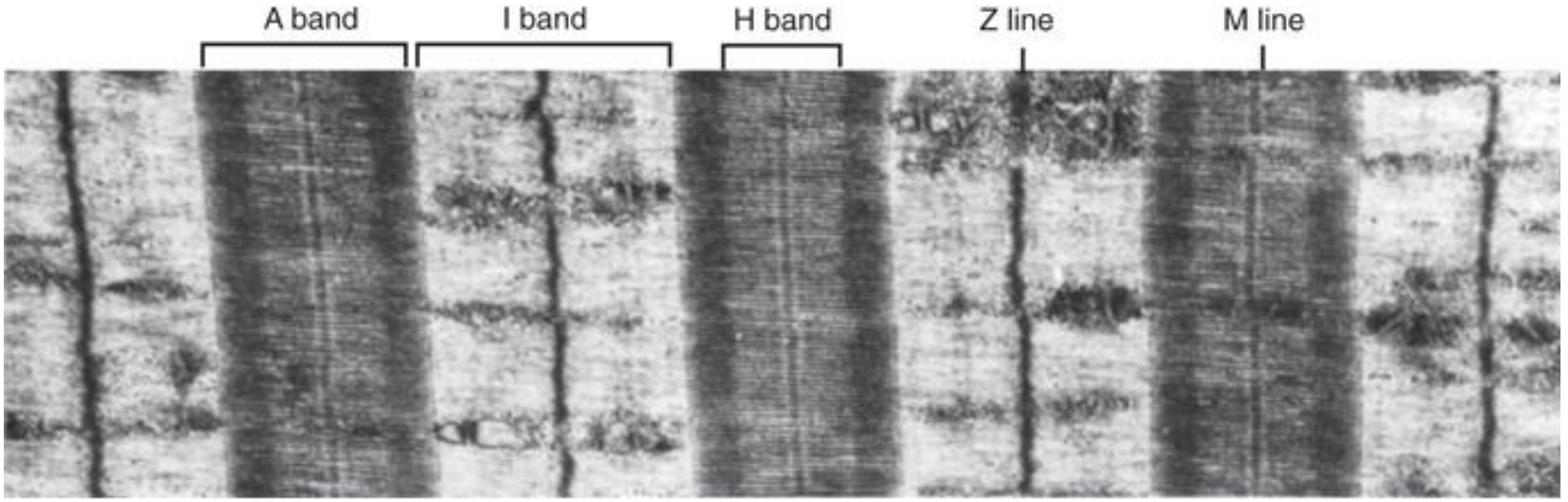
(Reproduced with permission from Kandel ER, Scwartz JH, Jessell TM [editors]: *Principles of Neural Science*, 4th ed. McGraw-Hill, 2000.)

Fig. 5-4 accessed 07/01/2010

Adherens junction architecture



Sarcomere



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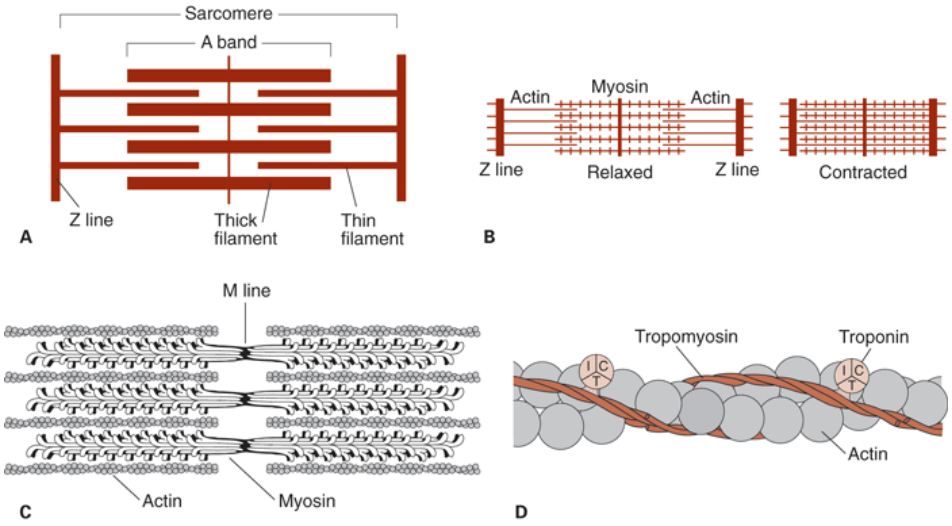
Electron micrograph of human gastrocnemius muscle. x 13,500).
(Courtesy of Walker SM, Schrodt GR.)
Fig. 5-2 Accessed 07/01/2010

Sarcomere



Note that myosin thick filaments reverse polarity at the M line in the middle of the sarcomere, allowing for contraction.

C and D are modified with permision from Kandel ER, Schwartz JH, Jessell TM [editors]: *Principles of Neural Science*, 4th ed. McGraw-Hill, 2000.
Fig. 5-3 Accesssed 07/01/2010

- A) Arrangement of thin (actin) and thick (myosin) filaments in skeletal muscle B) Sliding of actin on myosin during contraction so that Z lines move closer together. C) Detail of relation of myosin to actin in an individual sarcomere, the functional unit of the muscle. D) Diagrammatic representation of the arrangement of actin, tropomyosin, and troponin of the thin filaments in relation to a myosin thick filament. The globular heads of myosin interact with the thin filaments to create the contraction.

Sarcomere characteristics

Landmarks	Description
A band	Dark bands at the center of the sarcomere, composed of myosin filaments; potential for cross-bridge formation (both thin and thick filaments found)
I band	Light bands adjacent to A bands; composed of actin filaments and Z lines; width decreases with contraction.
Z line	Dark. At the center of I bands, marking the boundaries of a single sarcomere
H zone	At the center of the A band; no cross-bridging
M line	Dark. At the center of the H zone; adjacent myosin filaments linked together here

Muscle fiber types

	Type I	**Type II**
Action	Sustained force	Sudden movements
Strength	Weight bearing	Purposeful motion
Lipids	Abundant	Scant
Glycogen	Scant	Abundant
Ultrastructure	Many mitochondria Wide Z-band	Few mitochondria Narrow Z-band
Physiology	Slow twitch Slow oxidative metabolism	Fast twitch Fast oxidative metabolism (IIa) as well as Fast glycolitic metabolism (IIb)

Types I and IIa fibers rely principally on fatty acids as an energy source. Spare glucose. Type IIb fibers rely on glucose from glycogen breakdown.

Energy

- Creatine is synthesized from glycine and arginine in the kidney and S-adenosyl methionine in the liver.
- Synthesis originates in the kidney and terminates in the liver.
- Creatine is then available to brain, heart, and skeletal muscle.
- There it is phosphorylated and used as an energy source.
- Creatine phosphate undergoes spontaneous cyclization to creatinine (with removal of the phosphate group).

Fuel

- Fuel initially used during exercise is principally glycogen.
- Within 30 minutes amino acids and glucose contribute to the fuel supply; at 60 minutes very little glycogen is used as fuel.
- ATP levels do not fall more than 20% before the onset of fatigue.

Muscle types

Skeletal muscle	Cardiac muscle	Smooth muscle
Striated muscle	Striated muscle in syncytium	Non-striated muscle in syncytium
Small T-tubules and abundant sarcoplasmic reticulum	Large T-tubules and abundant sarcoplasmic reticulum	Rudimentary T-tubules and scant sarcoplasmic reticulum
Few hormone receptors	α,β receptors (among others) on membrane surface	α,β receptors (among others) on membrane surface
Nerve impulse initiates contraction	Intrinsic rhythmicity	Nerve impulses (autonomic), hormones initiate contraction
Extracellular Ca2+ concentration not important for contraction	Extracellular Ca2+ concentration important for contraction	Extracellular Ca2+ concentration important for contraction
Troponin system binds Ca^{2+}	Troponin system binds Ca^{2+}	Lacks troponin; Calmodulin binds Ca^{2+}

Skeletal muscle in the fed state

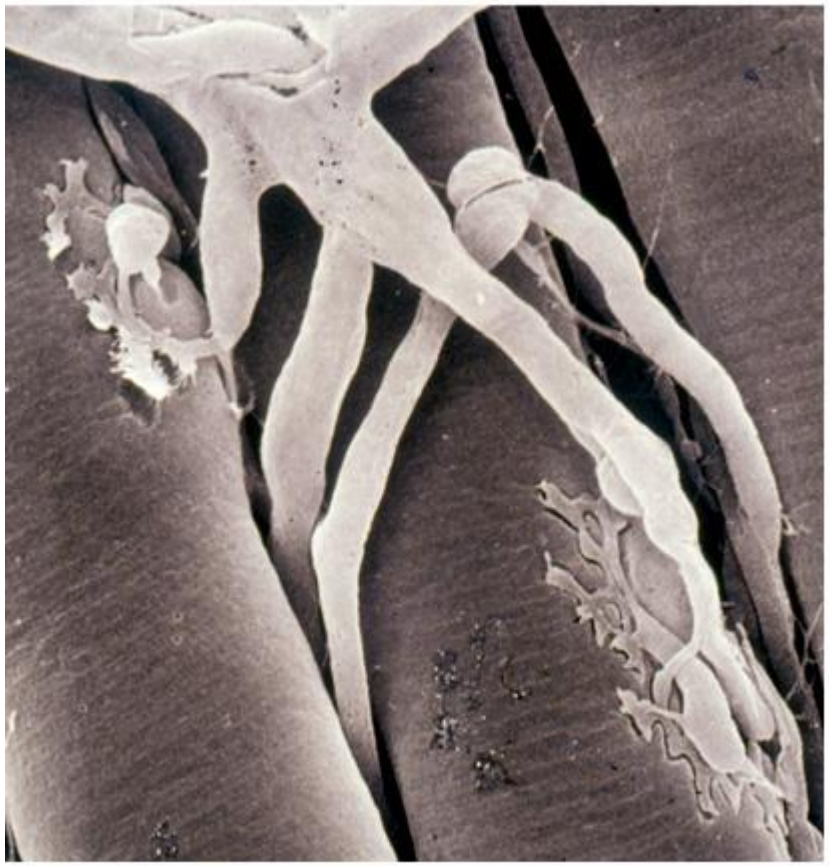
- Glucose transport increases as insulin increases Glut 4 in membrane.
- Glycogen synthesis increases as insulin activates glycogen synthetase; insulin inactivates glycogen phosphorylase.
- If glucose available there is no requirement for glycogen.
- Glycolysis necessary for ATP production.
- Insulin decreases circulating level of fatty acids through inhibition of hormone-sensitive lipase in adipose tissue.
- Protein synthesis increases (particularly branched chain amino acids.)

Skeletal muscle in starvation

- Glucose reserved for brain and red blood cell. (As glucose uptake low, insulin low as well).
- Muscle uses fatty acids and ketone bodies.
- Glucagon does not activate glycogen phosphorylase in muscle.
- Muscle provides amino acid Carbon skeletons for liver to make glucose (gluconeogenesis).
- Stimulated by cortisol.
- Breakdown diminishes after 2 days as ketones provide major fuel source.
- Amino acids largely released as alanine and glutamine.

Neuromuscular junction

(a)



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

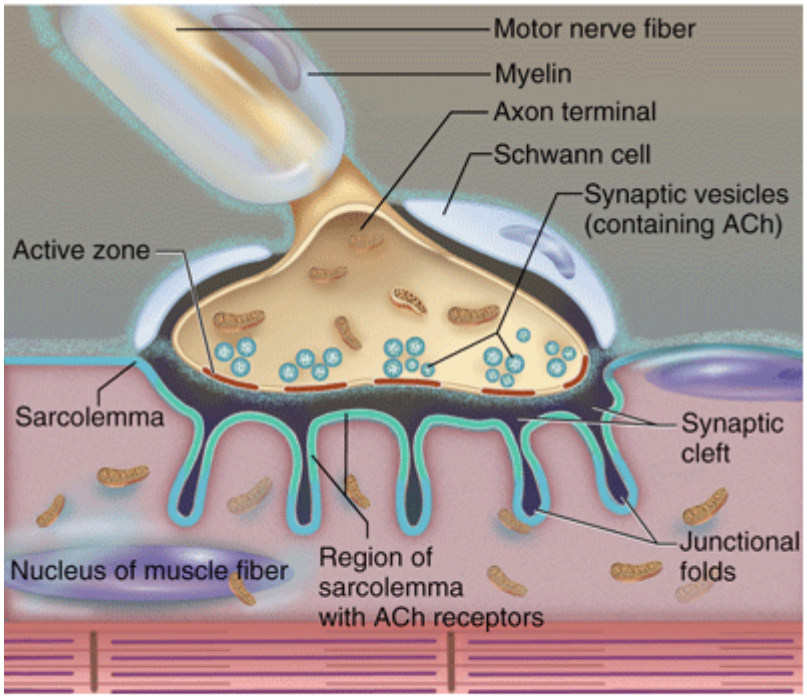
The neuromuscular junction. (a) Scanning electron micrograph showing branching of motor axons with terminals embedded in grooves in the muscle fiber's surface.

(From Widmaier EP, Raff H, Strang KT: Vanders Human Physiology. McGraw-Hill, 2008.)

Fig. 6-13 Accessed 07/01/2010

Neuromuscular junction

(b)



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(b) Structure of a neuromuscular junction.

(From Widmaier EP, Raff H, Strang KT: Vanders Human Physiology. McGraw-Hill, 2008.)

Fig. 6-13 Accessed 07/01/2010

Skeletal muscle action

- Myofibrils are functional components of contraction.
- T-tubules allow action potential to propagate deep into cytoplasm.
- Increase in intracellular Ca^{2+} from sarcoplasmic reticulum triggers excitation-contraction coupling among intracellular contractile proteins.
- The protein complex is known as a sarcomere; repeating units of sarcomeres comprise myofibrils within a single multinculeate myocyte.
- Dantrolene blocks release of Ca^{2+} from the sarcoplasmic reticulum.

Skeletal muscle action

- Troponin binds to Ca^{2+} released, inducing a conformational change that consequently moves tropomyosin from the myosin-binding site on actin, permitting actin to bind myosin light chains, creating cross-bridges.
- Myosin then pivots (conformational change), causing the heavy chain to slide along the actin filament (twitch).
- Blood flow to skeletal muscle is little unchanged between 50-200 mmHg over the long term. In the acute situation (exercise), blood flow may rise 30% between 50-200 mmHg.

Malignant hyperthermia

- Mutation in RYR1 gene at 19q13.2
- Ca2+ release channel opens more easily and remains open longer, flooding cell with Ca2+.
- Elevated intracellular Ca2+ stimulates sustained muscle contraction (rigidity) while also accelerating glycogen breakdown and glycolysis (excess heat produced).
- Dantrolene as treatment.

Contraction

- Isometric contraction sustains the position of a joint without producing movement.
- The muscle changes length in an isotonic contraction.
- In a concentric contraction, the muscle shortens. In an eccentric contraction, the muscle lengthens.

Isometric contraction

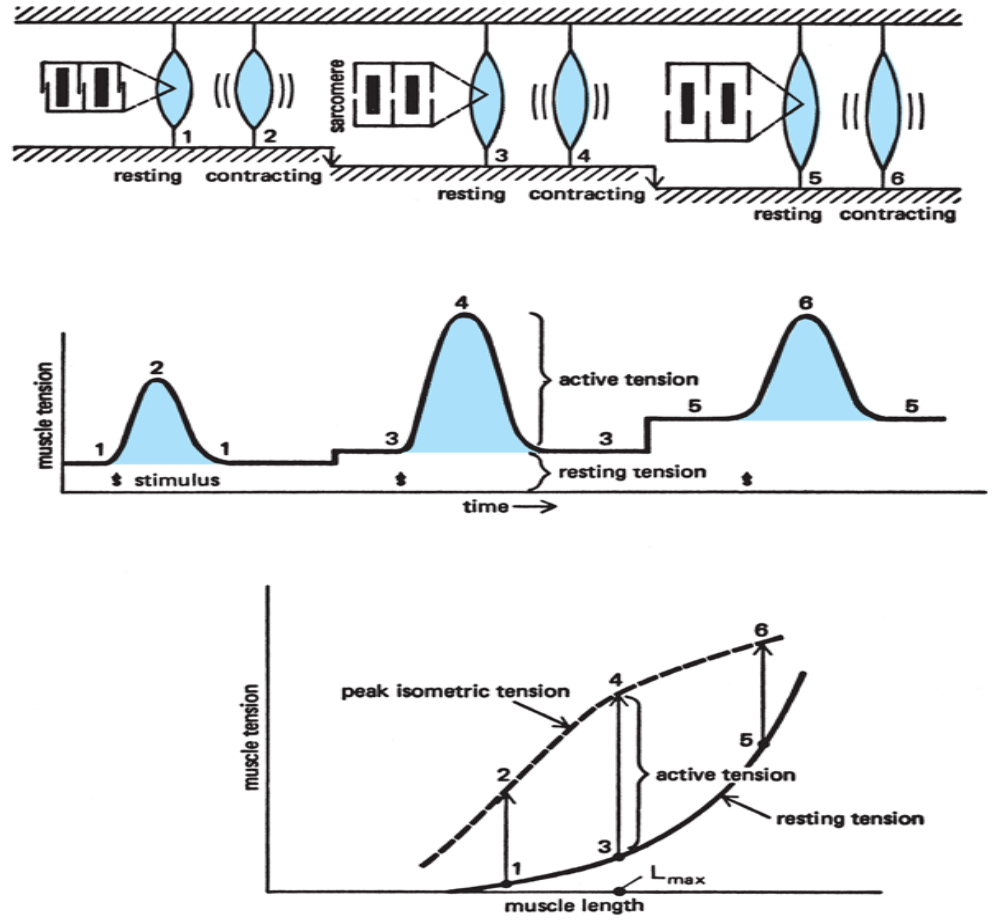


Fig. 2-8 Accessed 03/01/2010

Isometric contractions and the effect of muscle length on resting tension and active tension development.

the active tension developed by muscle during the course of an isometric contraction depends very much on the muscle length at which the contraction occurs

Isotonic contraction

Because of the different loading arrangement, the afterloaded muscle must increase its total tension to 3 g before it can shorten. This initial tension will be developed isometrically and can be represented as going from point 1 to point 4 on the length-tension diagram. Once the muscle generates enough tension to equal the total load, its tension output is fixed at 3 g and it will now shorten isotonically because its contractile potential still exceeds its tension output.

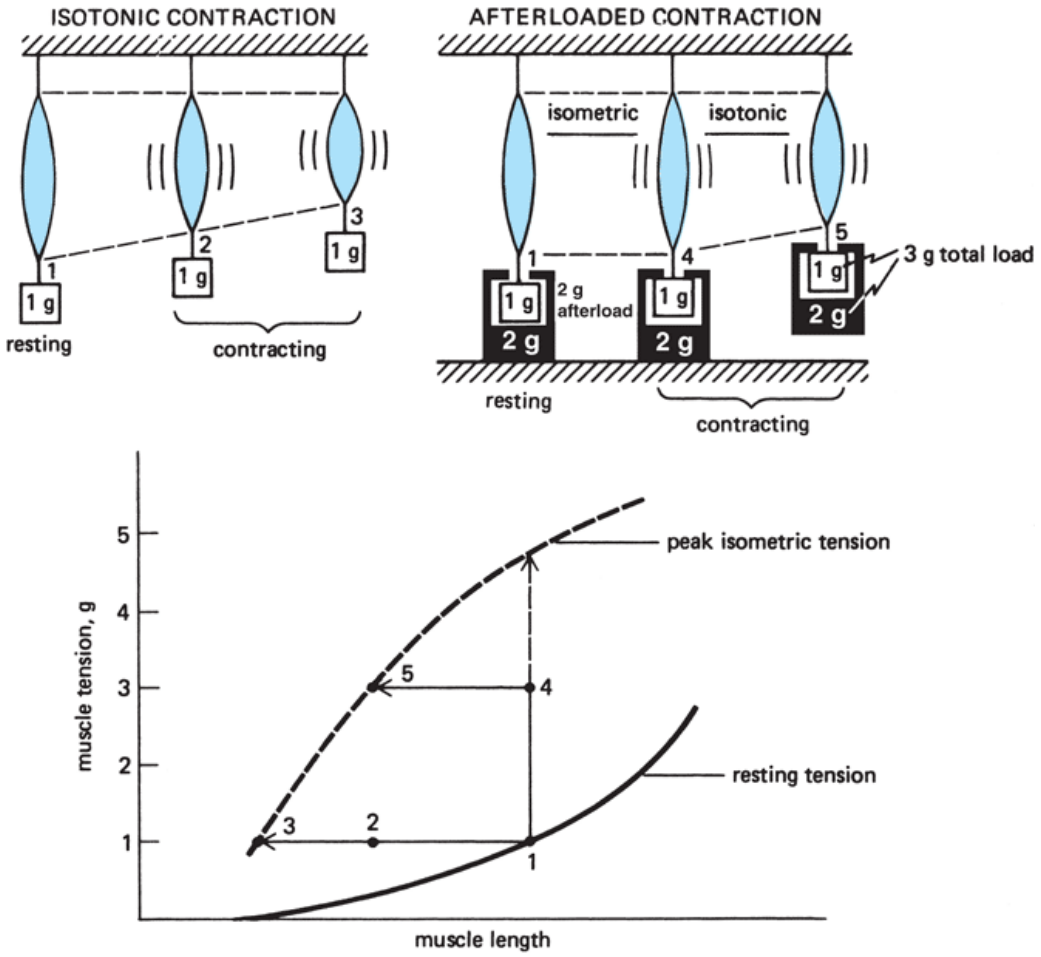


Fig. 2-9 Accessed 03/01/2010

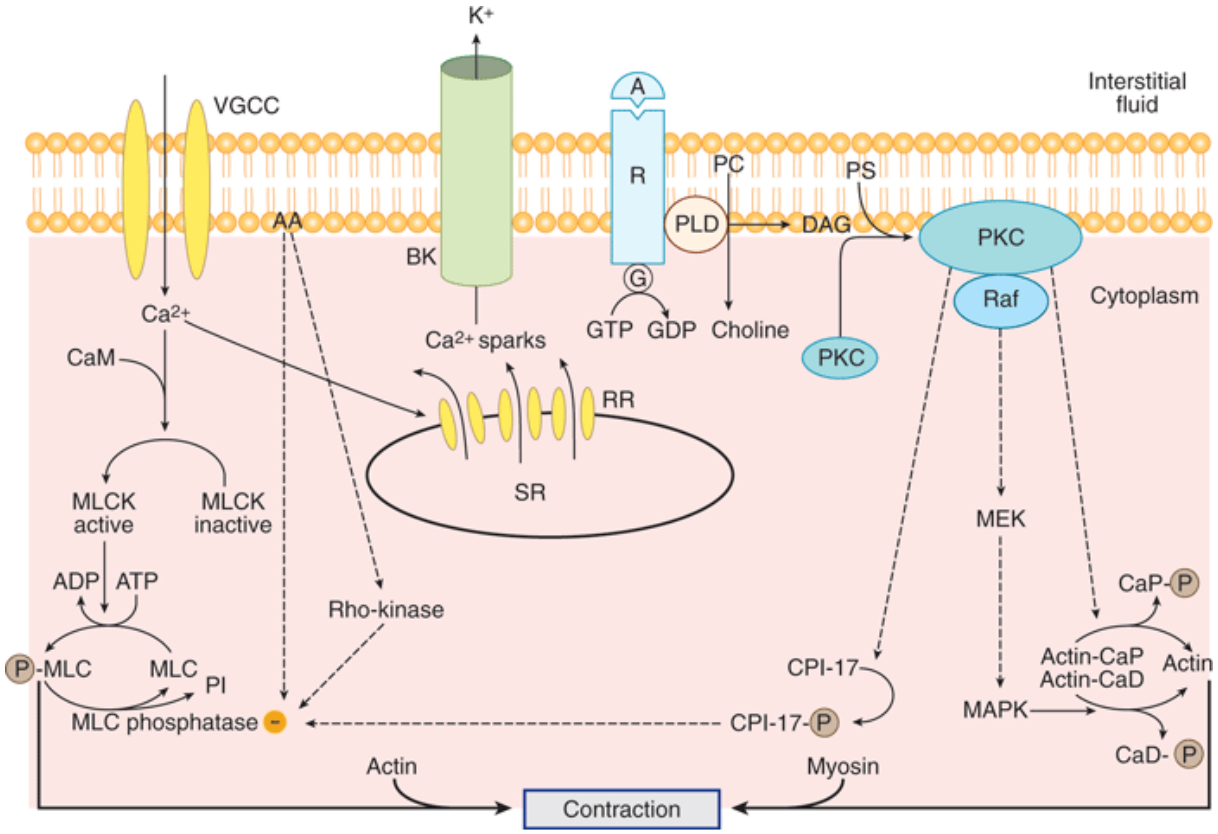
Isotonic contraction

- In any isotonic contraction, shortening must cease when the muscle's tension-producing potential is decreased sufficiently by the length change to be equal to the load on the muscle.
- Therefore, the after-loaded muscle shortens less than the non-after-loaded muscle even though both muscles began contracting at the same initial length.

Smooth muscle action

- Smooth muscle does not have myofilaments organized into sarcomeres
- Iinnervation is via the autonomic nervous system, not the somatic nervous system
- Lacks troponin.
- Calmodulin, not troponin, binds Ca^{2+} and activates myosin light chain kinase which then phosphorylates myosin.
- Activated myosin can then bind and release actin repeatedly.
- However, when Ca^{2+} concentration falls and myosin is dephosphorylated, the dephosphorylated form can still interact with actin via latch bridges, maintaining tone.

Smooth muscle contraction



(Modified from Khahl R: Mechanisms of vascular smooth muscle contraction. Council for High Blood Pressure Newsletter, Spring 2001.) Fig. 32-16 Accessed 07/01/2010

A, agonist; AA, arachidonic acid; BK, Ca^{+}-activated K^{+} channel; G, heterotrimeric G protein; MLC, myosin light chain; MLCK, myosin light chain kinase; PLD, phospholipase D; R, receptor; SF, sarcoplasmic reticulum; VGCC, voltage-gated Ca^{2+} channel; RR, ryanodine receptors.