1. CELLS, NERVES, AND MUSCLES

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CELL MEMBRANE COMPOSITION AND TRANSPORT

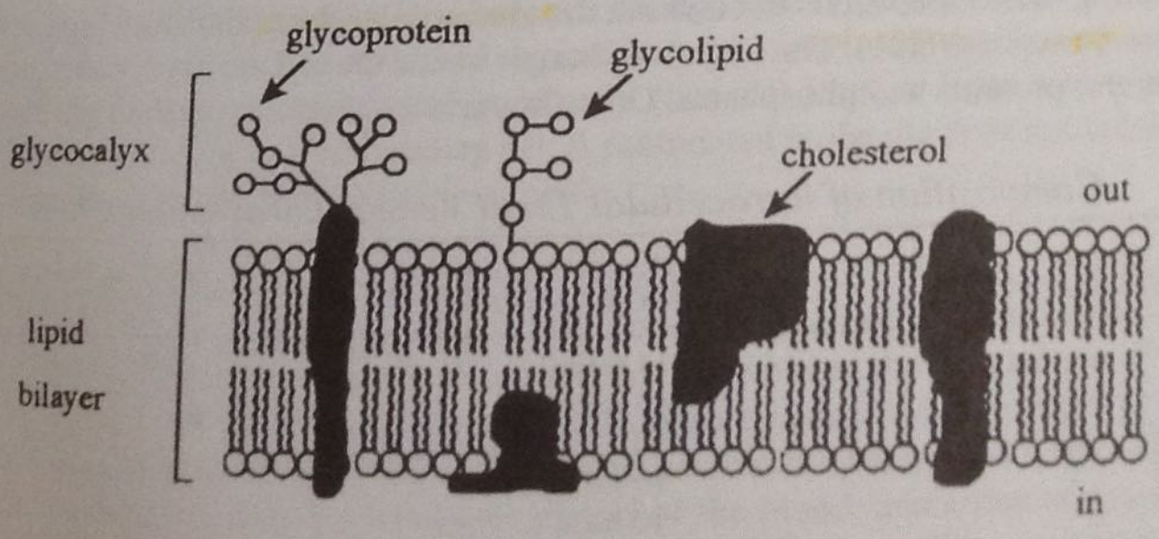
1. What are the main components of the cell membrane?

The **lipids** are amphipathic, or two-sided. They have a phosphorylated glycerol backbone with two hydrophobic fatty acid tails attached by ester bonds. The fatty acid tail of each phospholipid molecule is repelled by water but mutually attracted to other fatty acid tails. Hence, the tails face the inside of the membrane and form the membrane core. Each lipid also contains a phospholipid head, which faces outward because it is polar and attracted to the surrounding water.

The **proteins** float in the lipid bilayer. Substances that cannot pass directly through the lipid bilayer move through protein channels or use carrier proteins for facilitated transport across the membrane. Other proteins involved in cell signaling are located on the inner or outer surface of the membrane, such as receptor molecules for neurotransmitters or transducing proteins, which link receptors to cytoplasmic proteins and enzymes.

Cholesterol is interspersed between the phospholipids of mammalian cell membranes. The steroid structure of cholesterol does not permit it to span the membrane. Cholesterol acts to reduce membrane fluidity at physiologic temperatures but increases fluidity at lower temperatures to maintain normal membrane function. The lipid and protein composition of the membrane varies greatly between different cell types.

Carbohydrates bind to external sites of membrane protein and lipid molecules to form glycoproteins and glycolipids. The resulting carbohydrate layer on the outer membrane surface is called the **glycocalyx**. The glycocalyx, which is negatively charged, performs several important functions. It binds extracellular Ca^{2+} to stabilize membrane structures and acts as an attachment matrix for other cells (see figure).



Lipid and protein components of the cell membrane.

2. What is another name for the cell membrane?

Plasma membrane.

3. At what cellular site are membrane lipids and proteins synthesized?

The **endoplasmic reticulum (ER)** of the cell is the site of synthesis. Lipids are synthesized within the ER, whereas proteins are synthesized on the surface of the ER by the interaction of messenger RNA with ribosomes. The Golgi apparatus processes the ER products for final translocation to the plasma membrane.

4. How does the membrane contribute to cell homeostasis?

The main function of the plasma membrane is to maintain cell homeostasis by closely controlling the internal milieu of the cell cytoplasm. The phospholipid bilayer acts as a barrier to insulate the cell cytoplasm from immediate changes in the outside environment and provides a lipid suspension within which membrane proteins can move to enact critical changes in cell function. Normal membrane fluidity is required for cell function and growth and for optimal function of the transport, carrier, and signaling proteins.

5. Where are membrane proteins located?

Proteins may be located at the internal or external surfaces of the cell membrane or span across the entire lipid bilayer.

6. What are the functions of membrane proteins?

- To transport hydrophilic, large polar substances and ions across the membrane
- To act as signaling or transducing sites to conduct messages across the cell membrane (several proteins may interact to process one signal across the membrane)

7. Does the plasma membrane of different kinds of cells express the same types of proteins?

The population profile of membrane proteins varies tremendously among different kinds of cells and is "tailor made" for each cell's function. For example, neurons rely on membrane Na^+ channels for cell excitation and the release of neurotransmitters, whereas smooth muscle cells do not require Na^+ for cell excitation and contraction. Nerve cell membranes are densely populated with Na^+ channels, whereas Na^+ channels are not found in the plasma membrane of smooth muscle cells.

8. How does the composition of the intracellular and extracellular fluid differ?

The extracellular fluid contains high concentrations of sodium (Na^+) and chloride (Cl^-). Hence, from an evolutionary perspective, mammalian cells continue to be surrounded by a solution resembling dilute sea water. In contrast, the intracellular fluid contains a high concentration of the cation, potassium (K^+). The negative charges inside the cell are mainly attributable to negatively charged proteins and phosphates. Other important substances, such as glucose and Ca^{2+},

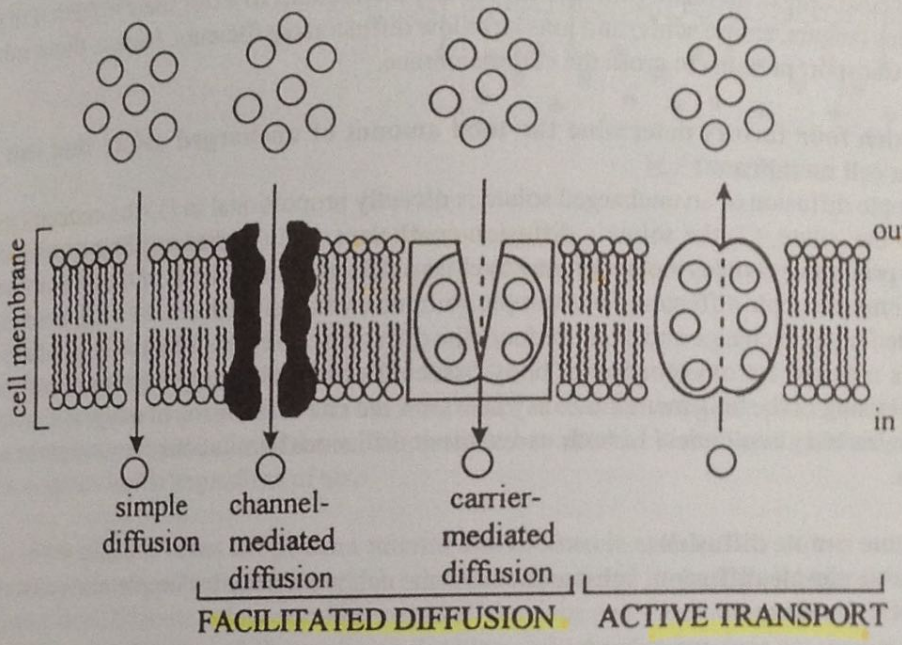
Composition of Intracellular Fluid Versus Extracellular Fluid

CONSTITUENT	INTRACELLULAR CONCENTRATION	EXTRACELLULAR CONCENTRATION
Na^+	14 mEq/L	140 mEq/L
K^+	140 mEq/L	4 mEq/L
Ca^{2+}	10^{-7} M (ionized)	2.5 mEq/L
Cl^-	10 mEq/L	110 mEq/L
HCO_3^-	10 mEq/L	20 mEq/L
Glucose	100 mg/dL	≈ 10 mEq/L
Osmolarity	295 mOsm/L	295 mOsm/L
pH	≈ 7.1	7.4

also are differentially distributed across the plasma membrane. Knowing the intracellular and extracellular concentrations of ions and other critical substances is essential for predicting in which direction these substances will cross the membrane when transport systems are activated.

9. How do lipophilic (lipid-soluble) and hydrophilic (water-soluble) substances cross the cell membrane?

Uncharged lipophilic substances can cross the plasma membrane by simply passing through its lipid core. Important examples of these substances are the gases oxygen and carbon dioxide, which can readily cross all cell membranes. Some small polar substances, including water, also can easily move across the lipid bilayer through intermolecular pores. Hydrophilic substances or large polar molecules, which are not lipid-soluble and are repelled by the lipid core of the membrane, must interact with a specialized carrier protein or channel protein to cross the cell membrane. Lipid-insoluble substances, which require special transport proteins to permeate the membrane, include glucose and amino acids (large polar substances) and all species of ions (Na^+, K^+, $Cl-$, HCO_3^-).



Mechanisms for the movement of substances across the cell membrane.

10. Can the lipid solubility of a single substance change under physiologic conditions?

The lipid solubility of many substances depends on their environment. For example, many molecules can exist in either a protonated (positively charged) form or in an unprotonated (uncharged) form, depending on the surrounding pH. A protonated molecule does not cross the membrane as readily as a neutral, unprotonated molecule.

11. Discuss how lipid solubility is used in drug therapy.

The principle governing lipid solubility is used to advantage in treatments to reduce blood levels of phenobarbital during barbiturate overdose. For example, at the normal blood pH of 7.4, phenobarbital molecules are half-protonated and half-unprotonated. Only the unprotonated form readily crosses membranes from the blood to the urine for removal from the body. Administration of sodium bicarbonate, however, increases the pH of the blood, and some of the protonated phenobarbital molecules lose their proton to the alkaline environment. The resulting increase in unprotonated, membrane-permeable phenobarbital molecules enhances the passing of this drug from the blood to the urine to lower systemic drug levels.

12. List the three main processes by which substances cross cell membranes.

1. Simple diffusion
2. Facilitated diffusion (also called carrier-mediated diffusion)
3. Active transport

13. Define diffusion.

The random motion by which a molecule crosses the cell membrane down its electrochemical gradient.

14. What is a diffusion coefficient?

A diffusion coefficient is a measure of the rate at which a solute can cross a membrane having an area of 1 cm and a thickness of 1 cm, when the concentration difference across the membrane is 1 mol/L. Uncharged, lipophilic substances (oxygen, carbon dioxide) and small polar molecules (water) have high diffusion coefficients because they can quickly cross the cell membrane. Many drugs, such as general anesthetic agents, also are lipophilic and have high diffusion coefficients. These drugs can readily diffuse across cell membranes to exert their effects. Large polar molecules (sugars, amino acids) and ions have low diffusion coefficients. Hence, these substances require transport proteins to cross the cell membrane.

15. Which four factors determine the total amount of uncharged solute that can diffuse across a cell membrane?

Simple diffusion of an uncharged solute is **directly** proportional to (1) the concentration gradient of the solute, (2) the solute's diffusion coefficient, and (3) the membrane area and is **inversely** proportional to (4) the membrane thickness. Changes in the level of these four factors can greatly impact simple diffusion. For example, pulmonary fibrosis reduces the lung membrane area available for gas exchange and hence reduces the diffusion of oxygen from the lung into the blood, which is required for oxygenation of body tissues. During pulmonary infections, inflammation and thickening of the lung membrane may also slow the rate of diffusion of oxygen from the lungs to the pulmonary capillaries. In both cases, these diffusional limitations may result in systemic hypoxia.

16. Define simple diffusion.

During **simple diffusion,** substances cross the cell membrane by simple movement through intermolecular spaces.

17. What are the properties of simple diffusion?

- Diffusion occurs down an electrochemical gradient.
- Diffusion is not rate-limiting but represents a linear function of the concentration gradient.
- The diffusion process is not saturable.
- No energy is required.

18. Define facilitated diffusion.

During **facilitated diffusion,** substances cross the membrane by contacting a transport protein. Large polar molecules are transported by **carrier proteins,** whereas charged ions are transported by **channel proteins**.

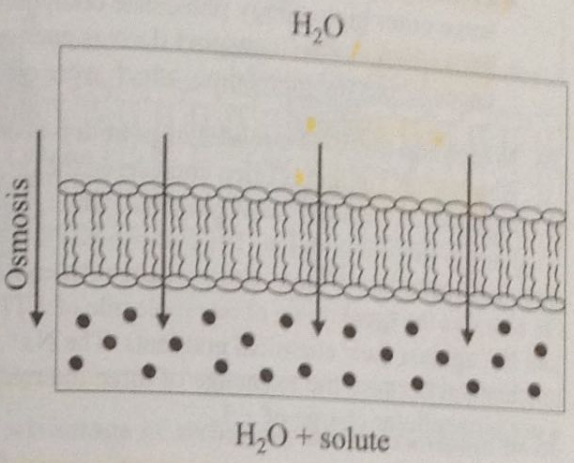
19. What are the properties of facilitated diffusion?

- Diffusion occurs down an electrochemical gradient.
- The substance binds to a transport carrier protein, which undergoes a reversible, conformational change to transport the substance across the membrane.*
- The diffusion process is rate-limiting and saturable because it depends on the availability of a finite number of carrier or channel proteins.*
- No energy is required.

* Property is different from simple diffusion.

20. What is osmosis?

Water is a small, polar molecule, which can easily diffuse across cell membranes through intermolecular spaces. This simple diffusion of water down its concentration gradient is called **osmosis**. Osmosis occurs from an area of low solute concentration (where the water concentration is high) to an area of high solute concentration (where the water concentration is low) and results in the displacement of volume. Hence, osmosis provides a mechanism whereby the cells can regulate their volume.



Diffusion of water across a membrane down its concentration gradient

21. What is osmotic pressure?

The pressure exerted by particles in solution, which provides a concentration gradient for the diffusion of water.

22. How is osmotic pressure determined?

Osmotic pressure is proportional to the number of solute particles per unit volume of fluid and is not determined by the size of the solute particles because the kinetic energy of single solute particles is quite similar regardless of size.

23. How does glucose cross the plasma membrane of muscle cells?

Glucose is a large, polar molecule, which is more concentrated in the extracellular fluid than in the cell cytoplasm. Glucose is transported into the cell down its concentration gradient by facilitated diffusion. Thus, the diffusion of glucose is rate-limiting and saturable but does not require energy.

24. How does insulin enhance the diffusion of glucose across muscle cell membranes?

Insulin, a product of the pancreas, increases the rate of facilitated transport of glucose into muscle cells. Some evidence suggests that this occurs when insulin binds to its receptors on the cell membrane and speeds the translocation of glucose transport proteins from the cytoplasm to the cell membrane. The increased membrane density of glucose transport proteins permits greater glucose entry into the cells.

25. Why is there glucose in the urine in diabetes mellitus?

Glucose in the bloodstream is filtered by the kidney into the urine. Normal levels of glucose in the filtrate can be completely reabsorbed back into the bloodstream by facilitated diffusion in the renal tubules. Thus, no glucose is normally detected in the urine. In diabetes mellitus, blood glucose levels are high, and more glucose is filtered into the urine. The abnormally high levels of glucose in the filtrate saturate the transport proteins in the kidney that are responsible for tubular reabsorption, and a residual level of glucose is detected in urine samples as a hallmark sign of diabetes mellitus.

26. What is active transport?

The movement of substances across the cell membrane **against** an electrochemical gradient.

27. List the characteristics of active transport.

- Substances are moved against their electrochemical gradient.
- The exchange of substances requires a transport protein.
- The process is rate-limiting and saturable.
- The breakdown of adenosine triphosphate (ATP) is required to provide energy.

28. What are the two types of active transport?

- **Primary active transport** requires energy directly derived from the breakdown of ATP or some other high-energy phosphate compound.
- **Secondary active transport** derives energy secondarily from ionic concentration differences across the membrane, which were originally created by primary active transport.

29. Which ion pump is a model of primary active transport?

The Na^+, K^+ pump is often considered the prototype of active transport. The Na^+, K^+ pump is composed of two α-subunit proteins, which constitute the primary transport protein, and two ancillary β-subunit proteins. The cytoplasmic side of the α-subunit binds one ATP molecule and three intracellular Na^+ ions and exchanges them for two external K^+ ions. A single exchange cycle requires the breakdown of one molecule of ATP because energy is required to pump both Na^+ and K^+ against their chemical gradients. The Na^+, K^+ pump is called an **electrogenic** exchange mechanism because the exchange of three internal Na^+ ions for two external K^+ ions generates a net intracellular charge of −1.

30. What are two forms of secondary active transport?

- **Cotransport** occurs when two substances are transported unidirectionally across the cell membrane by the same energy-driven transport protein.
- **Countertransport** refers to the coupled exchange by a transport protein of two substances in opposite directions across the cell membrane.

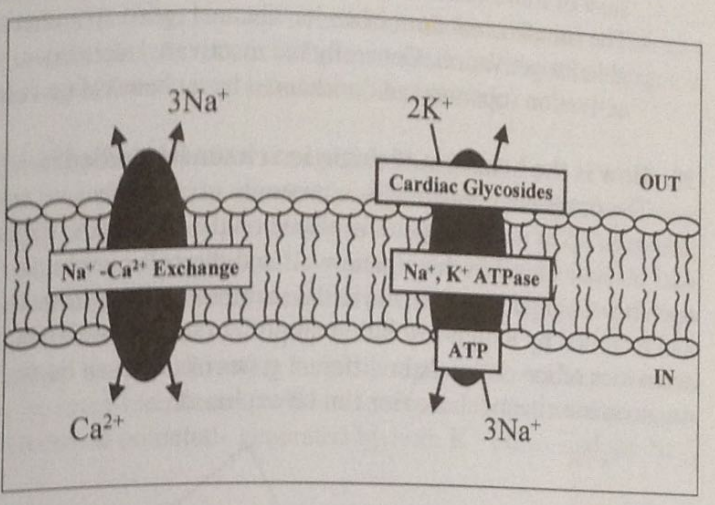
31. Why is cotransport important in the absorption of sugars and amino acids in the gastrointestinal tract?

This secondary active transport mechanism takes advantage of the Na^+ gradient established by the ATP-driven Na^+, K^+ pump, which maintains a high Na^+ concentration (140 mEq/L) in the extracellular fluid and a low Na^+ concentration (14 mEq/L) intracellularly. Because Na^+ concentration is higher outside the cell, the membrane transport protein involved in the cotransport process has a high possibility of binding extracellular Na^+ to its outer face. The subsequent cobinding of either a sugar or an amino acid to the outer face of the same transport protein initiates a conformational change, which provides the outer protein surface accessibility to the inside of the membrane. Hence Na^+ is cotransported with a sugar or amino acid molecule into the epithelial cells. This form of secondary active transport is important for the absorption of sugars and amino acids during digestion.

32. Discuss two examples of countertransport in mammalian cells.

1. The **sodium-hydrogen exchanger** takes advantage of the electrochemical gradient for Na^+ that is established by the ATP-driven Na^+, K^+ pump to transport H^+ out of the cell by secondary active transport. In this process, the binding of extracellular Na^+ and intracellular H^+ to the opposite faces of the transport protein results in a conformational change in protein structure whereby the sidedness of the protein is reversed in the membrane. The subsequent transport of Na^+ into the cell and extrusion of H^+ act as a buffering mechanism to prevent intracellular acidification.
2. The **sodium-calcium exchanger** also takes advantage of the electrochemical gradient for Na^+ established by the ATP-driven Na^+, K^+ pump. This exchanger transports Ca^{2+} out of the cell by secondary active transport. Although the Na^+, Ca^{2+} exchanger, similar to other transport proteins, can transport substrates in either direction across the cell membrane, Na^+ ions are present in tenfold higher concentration at the outside surface of the cell membrane. Hence extracellular Na^+ ions usually bind to the external face of the transport protein. The cobinding of Ca^{2+} to the cytosolic face of the same transport protein results in a conformational change in protein sidedness within the membrane, resulting in the exchange of extracellular Na^+ for intracellular Ca^{2+} (see figure). The sto-

chiometry of the Na^+, Ca^{2+} exchanger is unclear in some tissues but may involve the exchange of extracellular Na^+ for intracellular Ca^{2+} on a 2-for-1 basis (electrically neutral) or a 3-to-1 basis (electrogenic). Regardless, the subsequent decrease in the intracellular concentration of Ca^{2+} will inhibit Ca^{2+}-dependent excitation processes, such as neurotransmitter release and muscle contraction.



Coexpression of the Na^+, K^+ pump and the Na^+ and Ca^{2+} counter-transporter in the cardiac cell membrane.

33. How do digitalis glycoside drugs take advantage of secondary active transport to increase the force of contraction of the heart?

Digitalis glycosides are therapeutic agents used to increase the force of contraction of the failing heart. These drugs bind to the external face of the α-subunit of the Na^+, K^+ pump to inhibit its activity. As a consequence of blocking active Na^+ extrusion from the cell, the intracellular concentration of Na^+ rises. This build-up of Na^+ at the inside surface of the cell membrane indirectly affects Ca^{2+} transport because it reduces the electrochemical gradient for Na^+ and thereby also reduces the activity of the Na^+, Ca^{2+} countertransporter. The subsequent buildup of Ca^{2+} in the cell cytoplasm provides an increased supply of intracellular Ca^{2+} to activate the contractile proteins in cardiac muscle cells, thereby enhancing the force of contraction of the heart.

THE ELECTRICAL PROPERTIES OF CELLS

34. What is an ion channel?

Ion channels are specialized proteins in the membrane that provide a passageway through which charged ions can cross the cell membrane down their electrochemical gradient. The resulting ionic current, generated by the movement of charged ions through membrane channels, is sometimes regarded as a form of facilitated diffusion because it involves a transport protein (see figure in question 9).

35. What is the general structure of ion channels?

Most ion channels are multiunit protein structures, similar to the carrier proteins in the membrane. The channel pore is composed of amino acid sequences called **α-subunits,** which are arranged around a central shaft that spans the membrane. Other regulatory subunits (β, δ, γ) influence the gating behavior of the pore-forming α-subunits and may regulate their level of expression in the membrane. The pores of most ion channels have a **selectivity filter,** which makes the channel selectively conduct only one type of ion. Hence, sodium channels preferentially conduct Na^+ ions over other ion species, whereas potassium channels primarily conduct K^+ ions and reject other ion species.

36. How does an ion channel differ from a pore?

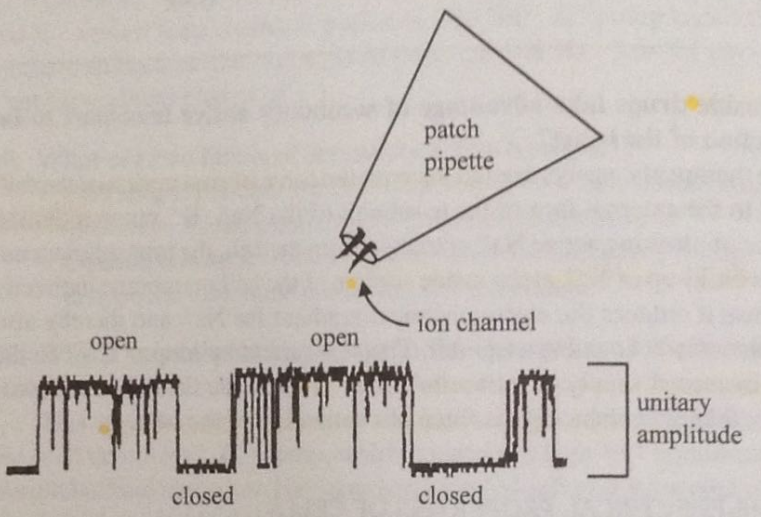
Membrane pores are openings in the membrane between lipid molecules that permit simple diffusion. **Ion channels** are gated pathways that can exist in open or closed states to regulate the rate of ion flux across the membrane. Ions can traverse channels only when in the open state.

37. What are the three main conformational states of an ion channel?

- The **resting state** of an ion channel refers to a channel that is closed but is available for opening if challenged by a chemical or voltage stimulus.
- The **activated state** of an ion channel refers to a channel that is open and permits the passage of ionic current.
- The **inactivated state** of an ion channel refers to a channel that is closed and is not available for activation. Generally the inactivated state occurs immediately after the successful activation (opening) of the channel by a chemical or voltage stimulus.

38. How is the behavior of single ion channels studied?

The patch-clamp method is commonly used to measure current through single ion channels. The open tip of a glass pipette is placed on the membrane surface of a cell, and a high-resistance seal is made between the pipette wall and the cell membrane. Ionic currents resulting from the opening of single ion channels in the membrane patch formed within the pipette tip are detected and recorded by a high-resolution amplifier (see figure). Using this method, the functional characteristics of ion channels in different types of cells can be studied, and the action of therapeutic drugs on ion channel behavior can be explored.



The patch-clamp technique for measuring current through single ion channels.

39. Which factors determine the total amount of ionic current that can be generated across a cell membrane?

The total amount of ionic current (**I**) that crosses a membrane is described by the equation:

$$\mathbf{I = n \times i \times p}$$

where **n** = the number of channels in the membrane, **i** = the amplitude of unitary current through a single channel, and **p** = the probability that a single channel is in the open state.

40. Discuss some types of ion channels and how they participate in cell function.

Ligand-gated ion channels, also called **chemical-gated ion channels,** are channels that are closely associated with a membrane receptor. Binding of a chemical messenger to the receptor causes a conformational change in the channel, which causes it to shift from the resting state to the open state. Ligand-gated channels often are **nonselective** ion channels, which conduct more than one type of similarly charged ion species in the open state. For example, the binding of acetylcholine to its postjunctional receptor on the skeletal muscle membrane activates a ligand-gated ion channel, which permits the passage of Na^+ into and K^+ out of the muscle cell at physiologic levels of membrane potential.

Voltage-gated ion channels are opened by changes in cell membrane potential. Changes in the electrical field surrounding the channel protein trigger the movement of positively charged amino acids in the α-subunits, which form the ion-conducting shaft of the channel. As a result of

this conformational change, the channel is converted to its open state. Most ion-selective channels inherently involved in cell excitability, such as Na^+, K^+, and Ca^{2+} channels, represent voltage-gated ion channels.

41. What is resting membrane potential?

The difference in electrical potential (voltage) between the inside and outside membrane surfaces under resting (unstimulated) conditions. At rest, cells have an excess of negative charges at the inside surface of the membrane and show a negative membrane potential.

42. Why does the resting membrane potential show a negative charge?

1. The resting cell membrane is preferentially permeable to K^+ ions. For example, most mammalian cell membranes are 20–100 times more permeable to K^+ than to Na^+, Ca^{2+}, or other ion species. Because the K^+ concentration inside the cell is much higher than the outside concentration, K^+ moves out of the cell through K^+ channels and leaves an excess of negative charges at the cytoplasmic side of the cell membrane.

2. The electrogenic Na^+, K^+ pump is active at resting membrane potentials and acts as a second force to generate negativity at the inner membrane surface. Hence, the resting membrane potential is the sum of the negative electrical potentials generated by both K^+ efflux and the Na^+, K^+ pump.

43. What are the relative contributions of K^+ efflux and the Na^+, K^+ pump to resting membrane potential?

In mammalian cells, K^+ efflux primarily generates the electrical potential generated across the cell membrane. Resting membrane potential varies between –50 mV and –90 mV in different types of mammalian cells, and the contribution of the Na^+, K^+ pump to this potential is estimated at about 5–20% of the total voltage.

44. What is an equilibrium potential?

The equilibrium potential for an ion is the membrane potential that would exist if the cell membrane suddenly became selectively and completely permeable only to that ion species. Under these conditions, the distribution of the ion across the membrane would be at equilibrium (equal rates of influx and efflux).

45. How is equilibrium potential predicted?

$$\textbf{Nernst equation: } V = \frac{RT}{FZ} \ln \frac{C_o}{C_i}$$

where V = the equilibrium potential in volts, R = the gas constant (2 cal/mol/°K), T = the absolute temperature (°K), F = Faraday's constant (9.65×10^4 coulombs/mole), Z = the valence of the ion, ln = logarithm to the base e, C_o and C_i = the outside and inside concentrations of a positively charged ion. The numerator and denominator of the C_o/C_i ratio are reversed to calculate the equilibrium potential for an ion that is negatively charged.

46. What are the predicted values for the K^+ and Na^+ equilibrium potentials for a mammalian cell using the Nernst equation?

By replacing the constants with their numerical values and converting from the natural log to the base 10 log, the following equation predicts the equilibrium potential (in millivolts) for K^+:

$$E_K = -60 \log \frac{[K_i]}{[K_o]} = -60 \log \frac{[140]}{[4]} \approx -90 \text{ mV}$$

By using the same approach, the following equation predicts the equilibrium potential (in millivolts) for Na^+:

$$E_{Na} = -60 \log \frac{[Na_i]}{[Na_o]} = -60 \log \frac{[14]}{[140]} \approx +60 \text{ mV}$$

47. What do the equilibrium potentials for K^+ and Na^+ reveal about the ionic basis of the resting membrane potential in nerve cells?

The resting membrane potential in nerve cells ranges between −80 mV and −90 mV, near the K^+ equilibrium potential. Because the membrane potential of these cells approaches the K^+ equilibrium potential, their plasma membrane must be highly and selectively permeable to K^+ rather than to Na^+ under resting conditions.

48. What is the Goldmann constant-field equation?

The final level of membrane potential depends on the concentrations of K^+, Na^+, Cl^-, and other ions across the membrane and on the relative permeability of the membrane to each of these ions. The Goldmann constant-field equation can be used to predict the contribution of different ion permeabilities to resting membrane potential:

$$V = \frac{RT}{F} \ln \frac{P_{K+}[K_o^+] + P_{Na+}[Na_o^+] + P_{Cl-}[Cl_i^-] + P_x[X]}{P_{K+}[K_i^+] + P_{Na+}[Na_i^+] + P_{Cl-}[Cl_o^-] + P_x[X]}$$

where **V** = membrane potential, **R** = gas constant, **T** = absolute temperature, **F** = Faraday constant, P_x = permeability of the membrane to x, and [x] = concentration of ion x on the inside or the outside of the cell membrane.

49. Which definitions are commonly used to describe changes in membrane potential?

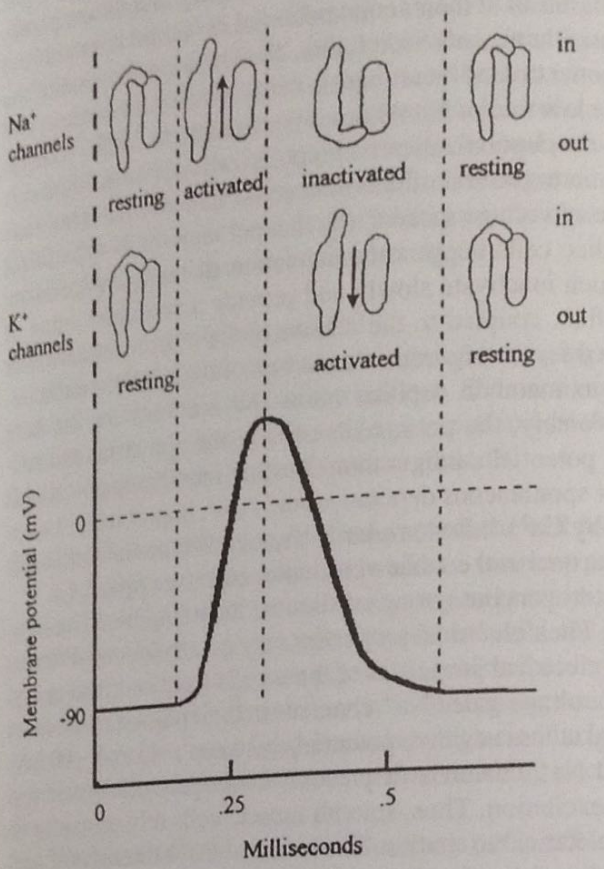
- **Firing threshold:** the level of membrane potential at which sufficient depolarization has occurred to initiate an action potential
- **Depolarization:** the cell membrane potential becomes less polarized (e.g., moves toward 0 mV from a more negative potential level)
- **Repolarization:** the cell membrane potential becomes polarized again (e.g., moves away from 0 mV to a more negative membrane potential)
- **Hyperpolarization:** the cell membrane potential becomes more polarized (negative) than the original resting membrane potential level

50. What is the ionic basis for the action potential in nerve cells?

An **action potential** is the series of membrane potential changes that follow a suprathreshold stimulus and results in cell excitation. The following series of events characterizes the action potential in neurons.

- An excitatory stimulus induces the nerve cell to reach the firing threshold for the initiation of an action potential.
- The initial change in membrane potential causes a conformational change in the Na^+ channel protein, which converts it from its resting to its activated state. As the Na^+ channels open, Na^+ begins to rush into the cell down its electrochemical gradient. This influx of positively charged Na^+ on the inside surface of the cell membrane depolarizes the cell further, and more Na^+ channels open. This chain of events has a snowball effect, and the action potential is now **all or none** and runs its full course regardless of other cell changes. Membrane permeability to Na^+ may increase several thousand-fold during the early stages of the action potential, owing to the almost simultaneous activation of a dense population of Na^+ channels in the plasma membrane of the nerve cell.
- As the cell depolarizes further, voltage-dependent K^+ channels open more and K^+ begins to flow through the cell membrane from inside to outside down its electrochemical gradient. Concurrently the Na^+ channels are inactivated by the sustained depolarization. The slowing of Na^+ influx and the exit of the positively charged K^+ ions begin to repolarize the cell and return it to its original level of resting membrane potential. In many cells, this repolarization process temporarily exceeds the original level of resting membrane potential, resulting in cell hyperpolarization. Increases in membrane K^+ permeability may exceed thirtyfold during the latter stages of the action potential and for a short period thereafter.

- After the cell returns to its original level of resting membrane potential, the Na^+ and K^+ channels return to their resting state.



The conformational changes in voltage-gated Na^+ and K^+ channels, which underlie the action potential in nerve cells.

51. Why do voltage-gated Na^+ channels activate before voltage-gated K^+ channels in response to a depolarizing stimulus?

Na^+ channels are more **voltage-sensitive** than K^+ channels (i.e., they are activated at more negative membrane potentials). Just a small depolarization from a resting membrane potential level of −70 or −90 mV is adequate to activate Na^+ channels, which open rapidly to permit Na^+ influx into the cell and induce cell depolarization. Larger changes in membrane potential consistent with further cell excitation are required to activate the less voltage-sensitive K^+ channels, so increases in membrane K^+ permeability are observed later.

52. Why do action potentials of nerve, cardiac, and smooth muscle cells differ?

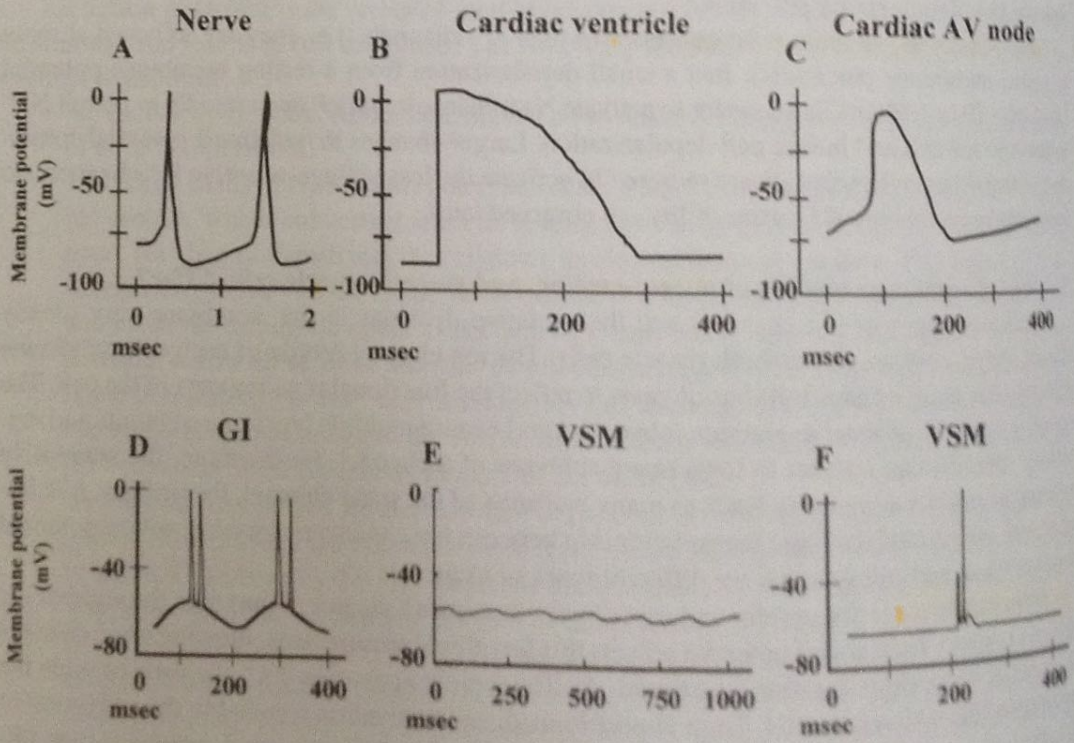
Different types of ion channels and their relative densities in the membrane vary greatly among nerve, cardiac, and smooth muscle cells. The ion channel profile of each cell membrane probably has evolved over millions of years to reflect the functional requirements of the cell. The complexity of ion channel expression is tremendous because multiple types of α-subunits and regulatory subunits can interact to form many subtypes of a channel. Furthermore, the alternative splicing of mRNA sometimes leads to many isoforms of the same channel. Regardless, it is important to understand the basic interrelationship between ion channel expression, action potential configuration, and cell function for different types of tissues.

Nerve cells must fire rapidly and repetitively to transmit electrical impulses throughout the nervous system. Their action potential reflects this functional requirement, showing rapid changes in potential and a short duration (see figure, *A*). The rapidly activating Na^+ channels provide the upstroke of the action potential. Their almost immediate inactivation coupled to the activation of K^+ channels accounts for the rapid course of repolarization. Voltage-gated, neuronal-type (**N-type**) Ca^{2+} channels also are activated during the action potential, and the resulting Ca^{2+} influx

provides the signal for neurotransmitter release. The N-type Ca^{2+} channels show rapid inactivation, which permits the duration of the action potential in neurons to remain short.

Cardiac muscle cells of the ventricular myocardium also show a resting membrane potential between −80 mV and −90 mV. The duration of their action potential is several hundred-fold longer than the length of the action potential in neurons (see figure, *B*). The long duration of the cardiac action potential reflects the functional task of these muscle cells, which is to contract and relax the cardiac ventricles at a relatively slow rate of 60–90 times per minute. Notably, voltage-gated Na^+ and K^+ channels contribute to the depolarization and repolarization phases of the cardiac action potential, similar to their role in excitation of neuronal cells. The plasma membrane of cardiac cells expresses a different type of voltage-gated Ca^{2+} channel than the N-type found in neuronal cells. Depolarization of cardiac cells triggers the activation of voltage-dependent, long-lasting (**L-type**) Ca^{2+} channels, which inactivate slowly and provide a sustained influx of Ca^{2+} into the muscle cell. This Ca^{2+} influx, coupled to the release of Ca^{2+} from intracellular stores, provides the activator Ca^{2+} required for the vigorous contraction of the cardiac ventricles. The sustained influx of Ca^{2+} also acts to maintain depolarization and accounts for the long **plateau phase** of the action potential. Notably, the pacemaker cells in the sinoatrial and atrioventricular node have a different action potential configuration. Resting membrane potential is less negative in these cells, and they show spontaneous depolarization. Also, importantly, the upstroke of the action potential is mediated by Ca^{2+} influx primarily through L-type Ca^{2+} channels rather than by Na^+ influx as occurs in neuronal and cardiac ventricular cells (see figure, *C*).

Smooth muscle cells populate a heterogeneous group of tissues, including blood vessels, bladder, uterus, and gastrointestinal tract. Their electrical properties vary greatly among different tissues. What generally distinguishes the electrical properties of these cells from neuronal or cardiac ventricular cells is (1) the absence of voltage-gated Na^+ channels in their plasma membranes and (2) the setting of their resting potential at less negative potentials between −45 and −60 mV. In this range of potentials, voltage-gated Na^+ channels (if present) are largely inactivated and hence not available to participate in cell excitation. Thus, smooth muscle cells rely primarily on voltage-gated, L-type Ca^{2+} channels for electrical excitation. The influx of Ca^{2+} through voltage-gated Ca^{2+} channels is responsible for the upstroke of action potentials in smooth muscle cells and



Cells from different types of tissue show different action potential configurations.

provides Ca^{2+} for muscle contraction. These action potentials may be sustained or show a spiking configuration as may occur in gastrointestinal (GI) smooth muscle cells (see figure, *D*). In addition, many smooth muscle cells do not show action potentials but rely on graded changes in membrane potential to provide activator Ca^{2+} (see figure, *E*). The excitability patterns of different kinds of smooth muscle cells reflect their functional role in the body. Some gastrointestinal smooth muscle cells that participate in rhythmic contraction designed to support peristalsis show rhythmic Ca^{2+}-dependent action potentials. Vascular smooth muscle cells, which require a continual influx of Ca^{2+} to maintain arterial tone and prevent rapid changes in blood pressure, generally show a relatively constant level of resting membrane potential coupled to voltage-gated Ca^{2+} influx. However, even under these circumstances, a sudden excitatory stimulus may trigger a Ca^{2+}-dependent action potential (see figure, *F*).

53. What is a refractory period?

The period of time after an action potential during which another action potential **cannot** be initiated is called the **refractory period**. The continued inactivation of the voltage-gated Na^+ channels after the firing of an action potential makes them unavailable for opening and provides the physiologic basis for the refractory period.

54. How does a refractory period protect the cell from overexcitation?

A refractory period is required to allow a recovery period between action potentials in the same cell and thereby protect the cell from extremely rapid, repetitive stimulation, which would compromise its function. For example, in neuronal cells, the refractory period protects the cell from the hyperrepetitive firing of action potentials, which could trigger chaos within the nervous system and result in pathologies such as seizures. In the cardiac ventricular cell, the refractory period also prevents rapid, repetitive action potentials, which could trigger a rapid heart rate (tachycardia) or disorganized cell-to-cell conduction patterns resulting in cardiac arrhythmias and death.

55. What are the two types of refractory periods?

1. The **absolute refractory period** begins when the Na^+ channels are inactivated during the action potential and lasts until the Na^+ channels begin to return to their resting state after restoration of the resting membrane potential. During this period, a second action potential cannot be initiated regardless of the strength of the stimulus.

2. The **relative refractory period** refers to the time period immediately after an action potential, when a second action potential can be triggered if a suprathreshold stimulus is applied. During this period, some of the Na^+ channels have returned to their resting state and are available for activation. The relative refractory period always follows the absolute refractory period in the course of an action potential.

NERVES AND NEUROTRANSMISSION

56. What are the three main anatomic regions of a motor neuron?

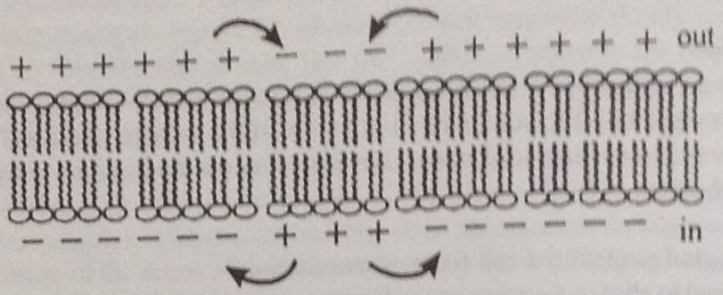
1. The **soma** is the main cell body of the neuron, which acts as a processing center for the nerve fiber.

2. The **dendrites** are antenna-like processes that project out from the soma and increase the cell surface area for the reception of signals from other neurons, which they subsequently transmit to the cell body. The plasma membrane of the dendrites is densely populated with ligand-gated receptors to provide high-affinity binding sites for chemical transmitters released by surrounding neurons.

3. The **axon** is a larger projection that transmits action potentials away from the soma. The axon originates at the axon hillock (a bulge in the soma) and ends in a nerve terminal. This terminal contains vesicles filled with chemical neurotransmitters, which can be released when an action potential is propagated down the axon. Hence the axon ultimately provides an electrochemical connection to other neurons.

57. How is an action potential propagated along a nerve axon?

An action potential initiated at one site in the nerve plasma membrane is propagated throughout the rest of the nerve fiber by a self-perpetuating process (see figure). This process involves the local flow of current (positive charge) from depolarized sites on the inside surface of the cell membrane to adjacent, normally polarized membrane sites available for activation. Hence the original action potential does not propagate along the nerve fiber but rather results in the sequential generation of identical action potentials, which propagate unidirectionally away from the site of the original action potential. The refractory period that follows the action potential along the axon prevents the backward flow of current toward the initial excitation site and acts to restrict the frequency of action potential transmission.



Propagation of an action potential along a membrane by the local flow of current.

58. What is saltatory conduction?

The axons of some nerves are populated by cells called **oligodendrocytes** (in the brain and spinal cord) or **Schwann's cells** (in peripheral nerves). The plasma membrane of oligodendrocytes and Schwann's cells contains a high density of a lipid called **myelin,** and the thick layering of the plasma membranes of these cells at periodic sites along the nerve axon forms myelin blocks, which insulate the underlying nerve cell membrane from excitatory stimuli. Between the myelin blocks are the **nodes of Ranvier,** which are myelin-free sites where the cell membrane remains exposed to the extracellular fluid and is densely populated with voltage-gated Na^+ channels to promote action potential generation. **Saltatory conduction** refers to the unidirectional jumping of depolarization from one node of Ranvier to the neighboring node, which provides a rapid propagation of nerve impulses for long distances.

59. Which two factors are the main determinants of the velocity of action potential propagation?

1. **Myelination** increases the speed of action potential propagation along the axon. The nodes of Ranvier provide a sequence of highly efficient sites to transmit the nerve impulse as it jumps between nodes. Myelination can enhance the velocity of action potential propagation by as much as fiftyfold. The requirement of myelin for normal motor function is revealed by the motor deficits observed in patients with **multiple sclerosis,** a demyelinating disease of the central nervous system of possible autoimmune origin.

2. The **diameter** of nerve fibers also positively influences the velocity of action potential propagation. Large myelinated nerve fibers, such as those innervating skeletal muscle, show the highest conduction velocity. Small, unmyelinated nerve fibers, such as the sympathetic postganglionic fibers, show a low speed of impulse propagation.

60. How are chemical messages transmitted between nerve cells?

Nerve synapses represent the communicating structure between the axon terminal of one nerve (the **presynaptic neuron**) and the dendrites or cell body of a second, target nerve (the **postsynaptic neuron**). The space between the two adjacent nerves that must be spanned to permit the continuation of the nerve signal is called the **synaptic cleft**. When a nerve impulse is propagated to the axon terminal of the transmitting nerve, the influx of Ca^{2+} through voltage-gated Ca^{2+} channels in the plasma membrane of the presynaptic nerve terminal triggers the release of chemical neurotransmitters from vesicles stored in the axon terminal. These neurotransmitters diffuse

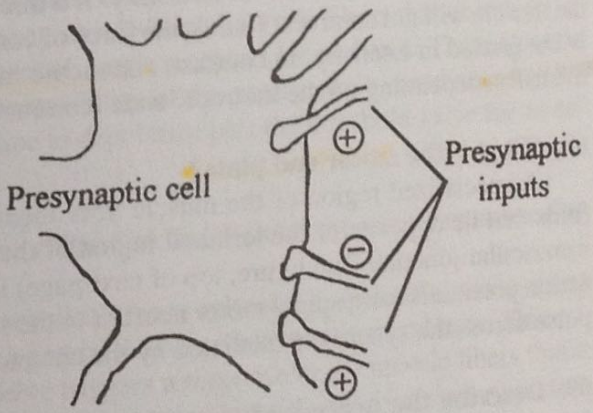
across the synaptic cleft and bind to specific high-affinity receptors on the plasma membrane of the postsynaptic neuron. If the chemical signal is adequate, the activation of these ligand-operated receptors initiates intracellular signals that alter the electrical and functional properties of the postsynaptic neuron.

61. Which four factors determine the concentration of neurotransmitter in the synaptic cleft?

- The amount of neurotransmitter released by the presynaptic nerve terminal
- The passive diffusion of the transmitter down its concentration gradient from the synaptic cleft to adjacent areas of extracellular fluid
- The active uptake of neurotransmitter by transport proteins in the plasma membrane of the surrounding neurons
- The breakdown of neurotransmitter molecules by enzymes located in the presynaptic cleft or in the plasma membranes of the presynaptic or postsynaptic neurons

62. How do the chemical neurotransmitters from different presynaptic neurons interact to regulate the level of excitability of the postsynaptic neuron?

Presynaptic neurons can release neurotransmitters that either promote or inhibit excitation of the postsynaptic neuron (see figure). Neurotransmitters released from excitatory presynaptic neurons produce a small, local, nonpropagated depolarization of the postsynaptic neuron, which is called an **excitatory postsynaptic potential** (EPSP). Because the amplitude of this depolarization is rarely sufficient to bring the membrane potential to the threshold required for the initiation of an action potential, the additive effect of multiple EPSPs is generally required to initiate an action potential at the postsynaptic membrane. Conversely, neurotransmitters released from inhibitory presynaptic neurons induce a small, local, nonpropagated hyperpolarization when they bind to their receptors on the plasma membrane of the postsynaptic neuron. This local hyperpolarization is called an **inhibitory postsynaptic potential** (IPSP). The algebraic summation of these graded changes in potential determines whether the membrane potential of the postsynaptic nerve cell depolarizes sufficiently to reach its firing threshold and initiate an action potential.



Excitatory and inhibitory presynaptic neurons influence the excitability of the postsynaptic neuron.

63. What is the difference between temporal and spatial summation?

Temporal summation refers to the additive effect of sequential multiple EPSPs or IPSPs **originating from a single presynaptic neuron** on the membrane potential of the postsynaptic neuron. For example, the repetitive firing of a single excitatory presynaptic neuron may result in summated EPSPs, which may depolarize the membrane potential to its firing threshold for action potential generation. Because an EPSP results in only a small increment of membrane depolarization that is not sufficient to inactivate voltage-gated Na^+ channels, a refractory period does not occur. This permits multiple EPSPs to exert a summating, depolarizing effect on the membrane potential of the postsynaptic neuron.

Spatial summation refers to the additive effect of multiple EPSPs or IPSPs simultaneously **originating from different presynaptic neurons** on the membrane potential of the postsynaptic

neuron (i.e., the neurotransmitter signals have different geographic origins). Under physiologic conditions, spatial and temporal summation act concurrently to regulate the membrane potential of the postsynaptic neuron.

NEUROMUSCULAR TRANSMISSION

64. How do nerves regulate muscle function?

- In **skeletal muscle,** motor nerves initiate muscle contraction.
- In **cardiac muscle,** sympathetic and parasympathetic nerves modulate the performance of the muscle, even though cardiac muscle contraction is spontaneous and independent of nerve activity.
- In **smooth muscle,** nerves may either initiate contractile activity or modulate the amount of contractile force in the muscle. For example, norepinephrine from adrenergic nerve terminals can increase the level of active tone in a blood vessel above the resting levels of tone that exist as a result of intrinsic excitability of the muscle cells.

65. What is a motor unit?

A motor unit consists of the alpha motor neuron and all the skeletal muscle fibers that it innervates.

66. What is the innervation ratio?

The number of muscle fibers innervated by each alpha motor neuron. If few fibers are innervated by the neuron (low innervation ratio), fine motor control is possible, but the overall strength of contraction is less. If the innervation ratio is high, more powerful contractions are possible, but the movements are less precise. Contraction of motor units with low and high innervation ratios is integrated in the central nervous system.

67. What is the "all or none law" for skeletal muscle?

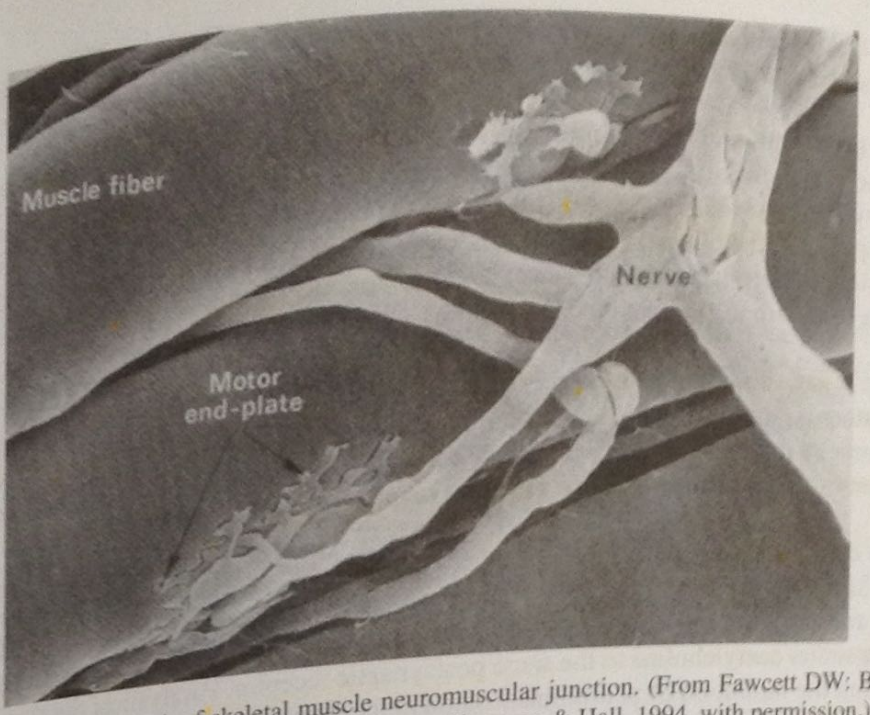
The all or none law states that when any skeletal muscle fiber is stimulated to threshold, it will contract to the maximum of its ability. If a threshold stimulus is not delivered to the muscle, the muscle will not contract. That is, the force of contraction in an individual skeletal muscle fiber is not graded in intensity. In contrast, contractile force of cardiac muscle fibers can be graded in intensity, depending on the inotropic state (contractility) of the heart.

68. What is the motor end plate?

A specialized region of the muscle fiber membrane with receptors at the top of junctional folds that lie opposite of the terminal region of the presynaptic motor neuron. The skeletal neuromuscular junction (see figure, top of next page) is an excitatory synapse that serves to transfer action potentials from spinal motor neurons to the skeletal muscle fibers. Transmission of the impulse across the synapse is mediated by the chemical transmitter acetylcholine.

69. Describe the process of synaptic transmission at the skeletal muscle neuromuscular junction.

Action potentials in the presynaptic motor neurons release acetylcholine, which is packaged in synaptic vesicles that fuse to the presynaptic membrane and release their contents via exocytosis. The exocytosis of the synaptic vesicles requires Ca^{2+} ions that enter the cell through voltage-gated Ca^{2+} channels that are opened in response to the depolarization of the presynaptic membrane during the action potential. Acetylcholine diffuses across the neuromuscular junction and binds to nicotinic receptors on the plasma membrane of the muscle cell. The binding of the transmitter to the receptor leads to an increase in the permeability of the postsynaptic membrane to both Na^+ and K^+ ions, producing a depolarization that triggers a propagated action potential in the skeletal muscle fiber and a subsequent contraction of the muscle cell.



Scanning electron micrograph of skeletal muscle neuromuscular junction. (From Fawcett DW: Bloom and Fawcett's Textbook of Physiology, 12th ed. New York, Chapman & Hall, 1994, with permission.)

70. What is unusual about the nicotinic acetylcholine receptor on the skeletal muscle cell?

The nicotinic acetylcholine receptor in skeletal muscle is an integral part of the ion channel in the postsynaptic membrane that is responsible for the end plate potential. Binding of acetylcholine molecules to the receptor-channel complex leads to opening of the channel, resulting in the motor end plate potential.

71. What is a motor end plate potential and what causes it?

The local depolarization of the end plate region of skeletal muscle fibers that occurs in response to acetylcholine binding to the nicotinic cholinergic receptors located on it. The motor end plate potential is caused by increases in the permeability of the postsynaptic membrane to Na^+ and K^+ ions, causing the postsynaptic membrane to depolarize past the threshold value for an action potential in the skeletal muscle.

72. What is the safety factor for transmitter release at the skeletal muscle neuromuscular junction?

The safety factor refers to the fact that acetylcholine is released in quantities many times greater than those required to produce an action potential at the postsynaptic membrane. This ensures that each action potential in the motor nerve triggers a response in the muscle fibers that it innervates. The large safety factor for transmission at the skeletal muscle neuromuscular junction is in contrast to many excitatory interneurons in the central nervous system, where neurotransmitters cause a subthreshold depolarization that needs to be summated (added together) to produce an action potential in the postsynaptic neuron.

73. What is quantal release of neurotransmitter?

The release of neurotransmitter molecules in discrete packages or quanta. An individual quantum corresponds to a synaptic vesicle in the presynaptic neuron.

74. What is a miniature end plate potential?

A small, nonpropagated change in membrane potential that occurs spontaneously on the motor end plates of the skeletal muscle neuromuscular junction. Miniature end plate potentials

(MEPPs) are due to the spontaneous release of individual quanta of the neurotransmitter acetylcholine and the subsequent binding of acetylcholine to receptors on the postsynaptic membrane.

75. How is the action of acetylcholine terminated at the synapse?

The acetylcholine released into the synaptic cleft is rapidly hydrolyzed to acetate and choline by the enzyme **acetylcholinesterase**. This terminates the action of the transmitter on the postsynaptic receptors. Anticholinesterases, such as those found in classic nerve gases, lead to a prolonged action of acetylcholine and subsequently a prolonged contraction of the skeletal muscle cell owing to failure to eliminate the transmitter.

76. What is myasthenia gravis, and how is it related to neuromuscular transmission?

Myasthenia gravis is a neuromuscular disorder that leads to muscle weakness. It is caused by an autoimmune response to the person's own acetylcholine receptors, leading to a reduction in the number of functional receptors in the postsynaptic membrane.

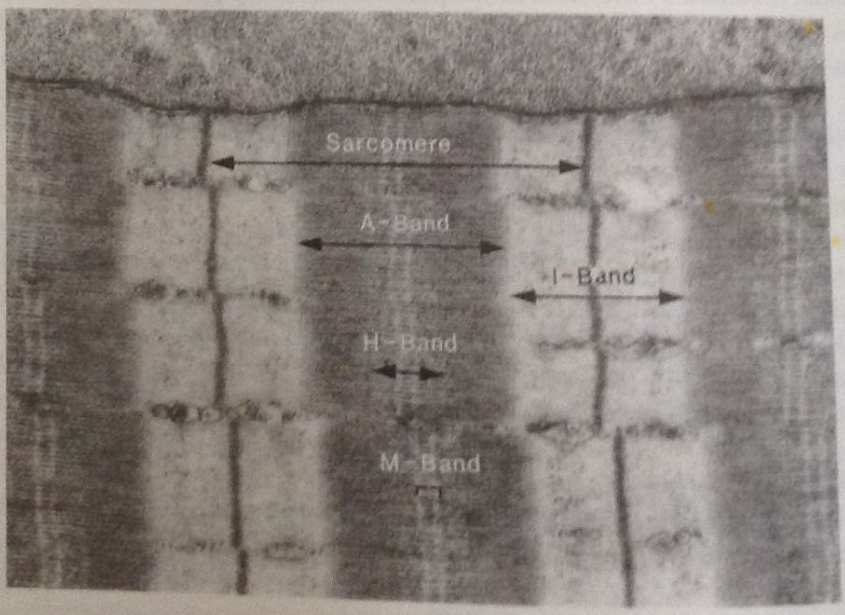
77. How does curare work?

The South American arrow poison curare contains *d*-tubocurarine, a compound that binds to nicotinic receptors at the skeletal muscle neuromuscular junction, inhibiting the binding of the neurotransmitter acetylcholine to the same postsynaptic receptor. Paralysis of the skeletal muscle results from the inhibition of neurotransmission at the junction.

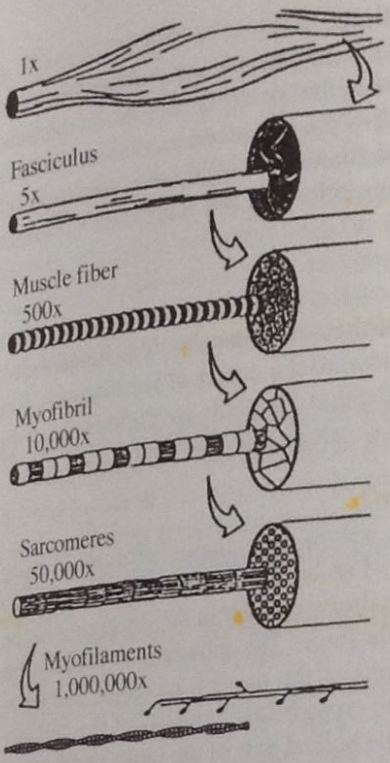
MUSCLE STRUCTURE, CONTRACTILE PROTEINS, AND CROSS-BRIDGE CYCLING

78. Why are skeletal muscle and cardiac muscle called striated muscle? Why is smooth muscle not classified as striated muscle?

Skeletal muscle and cardiac muscle are called striated muscle because of the striations (stripes) in the cells; these striations are absent in smooth muscle cells. The striations in skeletal and cardiac muscle are formed by the orderly arrangement of the thick and thin contractile filaments, which produce alternating areas of light and dark bands, giving the muscle its striated appearance. In contrast, smooth muscle cells do not have a sarcomeric structure, and there is no orderly overlap of thick and thin filaments to cause striations in the muscle cell (see figures).



Electron micrograph of an individual sarcomere of skeletal muscle showing the characteristic banding patterns of striated muscle. (From Fawcett DW: Bloom and Fawcett's Textbook of Histology, 12th ed. New York, Chapman & Hall, 1994, with permission.)



Hierarchical arrangement of structural components of skeletal muscle from the whole muscle through the contractile filament level. (From Rhoades RA, Tanner GA: Medical Physiology. Boston, Little, Brown, 1995, with permission.)

79. What is the hierarchical arrangement of the structural components of skeletal muscle?

The individual skeletal muscle cells are known as **muscle fibers**. Skeletal muscle fibers (and cardiac muscle cells) contain bundles of myofibrils that are composed of many individual **sarcomeres** arranged in series. The sarcomere is the fundamental contractile unit of striated muscle and consists of overlapping thick and thin filaments that produce a characteristic pattern of light and dark bands (see electron micrograph in question 78). The individual fibers are surrounded by a connective tissue layer known as the **endomysium,** which connects the individual fibers to parallel muscle cells. Groups of skeletal muscle fibers make up a **fasciculus,** which is surrounded by a connective tissue layer called the **perimysium**. Bundles of fasciculi make up the muscle itself. The fasciculi, with their associated blood vessels and nerves, are held together by another connective tissue layer, the **epimysium**. The fasciculi, which run the length of the muscle, are surrounded by yet another connective tissue layer, called the **fascia.** The fascia is a strong and dense layer of connective tissue that covers the entire muscle. In addition to separating muscles from each other, the fascia permits frictionless motion and also extends beyond the muscle to become the **tendon**.

80. What are the components of an individual sarcomere?

An individual sarcomere is bordered by two structures known as the **Z-lines** or Z-disks, which serve as the point of attachment for the thin filaments. The thin filaments are attached to the Z-lines by α-actinin, which is a major component of isolated Z-disks. The **I (isotropic) band** is a light band composed of thin filaments only, whereas the **A (anisotropic) band** is a dark band that corresponds to the region of overlap between the thick and thin filaments. As seen in the electron micrograph in question 78, the Z-lines bisect the I band and indicate the borders of the individual sarcomeres. The **H zone** (H-band) corresponds to the center region of the thick filament, which contains the tails but not the heads, of the myosin molecules. Thus, no cross-bridges can be formed in the H zone. A darkly staining **M-line** (M band) in the center of the sarcomere contains proteins that link the thick filaments together to maintain their position. The thick and thin filaments themselves are composed of a collection of individual proteins. Myosin is the primary component of the thick filament, and actin, tropomyosin, and troponin are the major components of the thin filament (see electron micrograph in question 78).

81. What is the sliding filament mechanism of contraction?

This refers to the generation of contractile force by the interaction of thick and thin filaments, causing them to slide between each other. The sliding filament theory explains how the thick and thin filaments move in relation to each other, in order to allow the sarcomeres to shorten. During contraction, the cycling of the cross-bridges causes the thin filaments to slide over the thick filaments; this decreases the distance between adjacent Z lines, allowing the sarcomere to shorten and the muscle to develop force.

82. What is the composition of the thick filament?

The thick filaments are composed of an aggregation of myosin molecules. The myosin molecules are arranged with the tails of the molecules facing toward the center of the filament. This causes the active force to be directionally oriented so that the thin filaments are pulled toward the center of the filament, causing active force generation and shortening of the muscle.

83. What are the biochemical characteristics of myosin?

Myosin is a large protein (470 kD) consisting of six polypeptide chains arranged in pairs. Two of these chains are myosin heavy chains consisting of an α-helical portion and a globular head portion. The globular head portion of the molecule hydrolyzes ATP in the presence of actin and interacts with the thin filaments to generate contractile force. The interactions between the thick and thin filaments are possible because of projections of the myosin molecule known as **cross-bridges**, which extend toward the thin filament. The cross-bridge consists of the globular head of the molecule and part of the α-helical structure. The helical part of the molecule contains two hinges. One of these is located next to the thick filament, and the other is located next to the globular head of the myosin molecule. The hinge near the body of the thick filament allows the cross-bridge to extend toward the active sites on the thin filament, and the hinge near the head of the molecule allows the head to rotate to produce the **power stroke** that generates contractile force. Pairs of cross-bridges are arranged on the opposite sides of the thick filament with a 120° rotation from one set of cross-bridges to another, allowing cross-bridges to reach thin filaments on different sides of the thick filament. Myosin also has two types of polypeptide light chains associated with the globular head of the molecule. These are wrapped around the neck of the molecule, below the myosin head, and appear to stiffen the neck region. One of these chains is called the **essential light chain** and may be important for the ATPase activity of the molecule. The other light chain is known as the **regulatory light chain**. In smooth muscle, phosphorylation of the regulatory light chains allows the myosin molecule to begin ATP hydrolysis, resulting in cross-bridge cycling and the generation of active contractile force.

84. What are the components of the thin filaments?

- **F-actin:** The thin filaments of striated muscle consist of two strands of fibrous actin (F-actin) molecules that are intertwined in a double helical arrangement like two strands of beads. The F-actin is composed of a string of individual globular (G) actin monomers (molecular weight of approximately 42–45 kD) that are arranged in series like a string of beads and contain active sites where the myosin cross-bridges bind and where contractile force is produced by a ratchetlike mechanism involving rotation of the attached myosin head (the **power stroke**).
- **Tropomyosin and troponin: Tropomyosin** is a fibrous protein 38–39 nm in length that has a molecular weight of approximately 50 kD. **Troponin** is a globular protein composed of three different subunits: (1) **troponin C** (18 kD), which binds Ca^{2+} ions; (2) **troponin I** (22 kD), which binds to troponin T and actin; and (3) **troponin T** (22 kD), which binds to the C terminal end of tropomyosin and links troponin I and troponin C to tropomyosin. Troponin molecules are attached to the tropomyosin strands at intervals corresponding to every seven actin monomers. A tropomyosin strand with its associated troponin molecules lies within each of the two grooves of the double helix that is formed by the intertwined F-actin molecules.

85. What is the role of tropomyosin and troponin in muscle contraction?

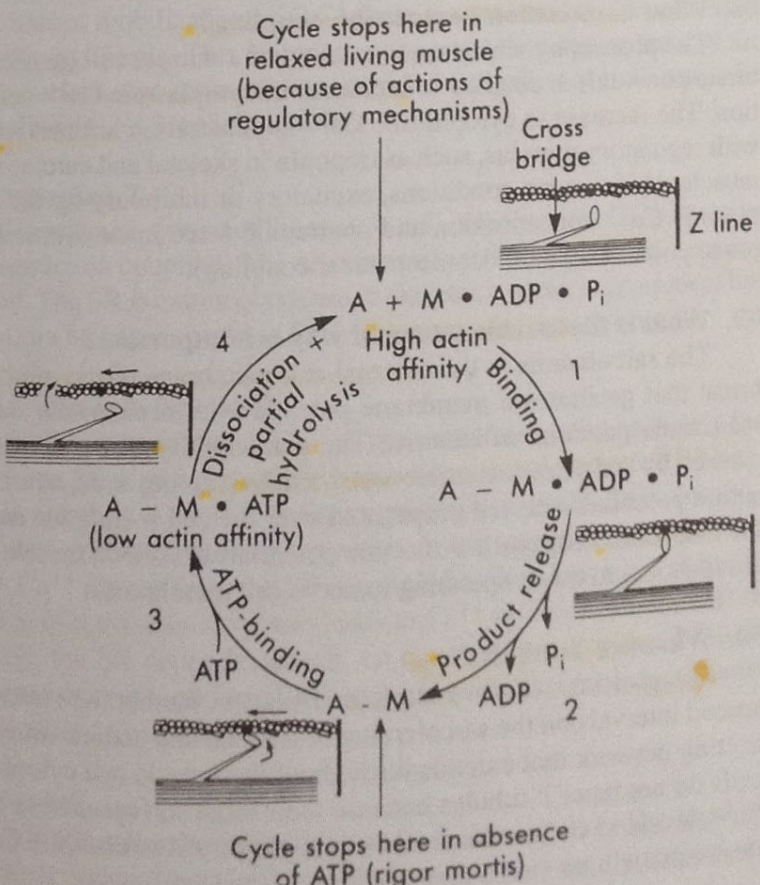
In striated muscle, the tropomyosin strands mask the active sites on the thin filament. This prevents contraction by blocking the interaction between the myosin cross-bridges and the actin monomers. When cytoplasmic Ca^{2+} levels increase during excitation-contraction coupling, the Ca^{2+} ions bind to troponin C. This changes the force of attraction between the troponin subunits and causes the troponin-tropomyosin complex to move farther down into the groove of the actin filament, exposing the active sites on the thin filament. This allows the myosin cross-bridges to gain access to the active sites, and cross-bridge cycling begins, causing muscle contraction. In smooth muscle (which lacks troponin), the tropomyosin may have a structural function, helping to maintain the integrity of the thin filaments.

86. What are the three major roles of ATP in muscle function?

1. ATP provides energy for the generation of contractile force, when it is hydrolyzed by the globular heads of the myosin molecule. The hydrolysis of ATP provides stored energy that is transformed into contractile force by the conformational change in the myosin head (power stroke) that occurs spontaneously right after the myosin head binds to the active site on the thin filament.

2. ATP binds to the head of the myosin molecule, reducing the affinity of the cross-bridge for the active site. This binding of ATP to the myosin head is essential for muscle relaxation to occur. In the absence of ATP, the myosin cross-bridges cannot release from the thin filament, and rigor complexes are formed. These complexes are responsible for the rigor mortis that occurs when ATP stores are exhausted after death.

3. ATP also provides energy for active transport of ions by various transport proteins that maintain normal ionic gradients across the cell, pump Ca^{2+} back into the sarcoplasmic reticulum, or pump Ca^{2+} out of the cell (in smooth muscle).



Steps in cross-bridge cycling during the development of contractile force in striated muscle. (From Berne RM, Levy MN: Physiology, 3rd ed. St. Louis, Mosby, 1993, with permission.)

87. What steps are involved in cross-bridge cycling?

The cross-bridge cycling process that generates contractile force in muscle is a ratchet-like mechanism that depends on the cyclic attachment and release of myosin heads at the active sites on the thin filament. The energy for cross-bridge cycling is derived from the hydrolysis of ATP by the myosin head, which acts as an ATPase when it can interact with active sites on the thin filaments. After the ATP is hydrolyzed by the myosin molecule, the ADP and P_i that result from the hydrolysis remain bound to the myosin head. At this point, the myosin head is in its higher energy state, because it has undergone a conformational change in which it stores the energy derived from hydrolysis of the ATP molecule as potential energy that will be released in the next power stroke. This myosin-ADP-P_i conformation of the molecule's head has a high affinity for actin, causing the head to bind to an active site on the thin filament at the first opportunity.

In the presence of elevated Ca^{2+} levels in the cytoplasm, the cross bridges can interact with the active sites on the thin filament. Right after the myosin head on the cross-bridge combines with the active site on the thin filament, the ADP and P_i are released from the myosin head and the power stroke occurs as a result of a spontaneous change in the conformation of the myosin head to the lower energy state. The net result of this conformational change is that the energy that was stored in the myosin head as a result of ATP hydrolysis is converted to mechanical energy that pulls the thin filament toward the center of the sarcomere via the ratchet mechanism.

After the power stroke is completed, myosin has a high affinity for ATP, which binds to the head portion of the molecule. Binding of ATP to the myosin head reduces the affinity of the cross-bridge for actin, causing it to release its attachment to the active site on the thin filament. The ATP is then hydrolyzed by the myosin head, causing the molecular conformation of the globular head to return to the higher energy conformation for the next cycle. The ADP and P_i formed from the hydrolysis of the ATP molecule remain bound to the head, and the cycle repeats as long as the active sites on the thin filament are exposed to allow cross-bridge attachment (see figure in question 86).

EXCITATION-CONTRACTION COUPLING

88. What is excitation-contraction coupling?

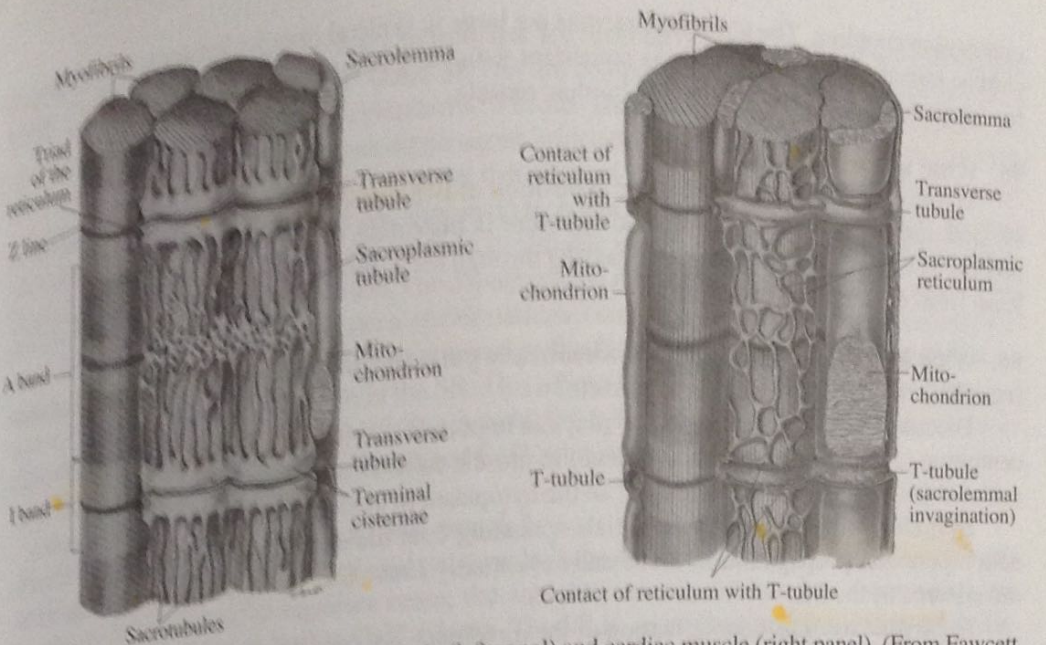
The process by which the excitation of a muscle cell (generally involving changes in membrane potential) is coupled to increases in cytoplasmic Ca^{2+} concentration and muscle contraction. The increase in cytoplasmic Ca^{2+} concentration initiates muscle contraction by interacting with regulatory proteins, such as troponin in skeletal and cardiac muscle or calmodulin in smooth muscle. Under some conditions, excitatory or inhibitory agents also can cause changes in cytoplasmic Ca^{2+} concentration and contractile force in smooth muscle without a change in membrane potential (pharmacomechanical coupling).

89. What is the sarcolemma and why is it important?

The sarcolemma is the external cell membrane of the muscle fiber. It is an excitable membrane that generates a membrane potential via mechanisms similar to those giving rise to the membrane potential in neurons. The permeability of the sarcolemma in skeletal muscle is increased by the neurotransmitter acetylcholine acting at the neuromuscular junction. This leads to action potentials that are propagated over the cell membrane and into the center of the fiber via the T-tubules. Propagation of action potentials in skeletal muscle cells occurs via mechanisms that are identical to those operating in nerve cell membranes.

90. What are T-tubules?

Invaginations of the muscle cell plasma membrane (sarcolemma) that occur at regularly spaced intervals on the sarcolemma of skeletal and cardiac muscle. These form a dense interconnecting network that extends throughout the muscle cell cytoplasm (see figure). Smooth muscle cells do not have T-tubules because their large surface area-to-volume ratio allows intracellular Ca^{2+} levels to be increased easily via influx of extracellular Ca^{2+} and by release of Ca^{2+} ions from intracellular stores (sarcoplasmic reticulum).



Transverse (T) tubule system from skeletal muscle (left panel) and cardiac muscle (right panel). (From Fawcett DW: Bloom and Fawcett's Textbook of Histology, 9th ed. New York, Chapman & Hall, 1994, with permission.)

91. Why are T-tubules important?

The T-tubule is contiguous with the extracellular fluid and contains voltage-gated Na^+ channels, as indicated by the presence of tetrodotoxin binding sites. The T-tubule system allows action potentials that are conducted over the sarcolemma to be conducted deep into the muscle fiber, providing rapid and coordinated excitation of the muscle cell. Excitation of the T-tubule system by the action potential is coupled to Ca^{2+} release from the terminal cisterna of the sarcoplasmic reticulum to allow a rapid, coordinated mobilization of Ca^{2+} from internal stores. This results in a coordinated contraction of all the myofibrils. This is important because the large volume of the skeletal muscle cell relative to its surface area makes the coordinated activation of the contractile filaments by the influx of extracellular Ca^{2+} ions impossible.

92. What is the sarcoplasmic reticulum?

A highly specialized internal membrane system of the muscle cell, which stores Ca^{2+} ions that are released during excitation contraction coupling. The sarcoplasmic reticulum (SR) is not contiguous with the extracellular fluid. The SR is extremely dense in skeletal muscle, is prominent but less dense in cardiac muscle, and can be either sparse or fairly prominent in smooth muscle.

93. How does the sarcoplasmic reticulum function?

After excitation of the muscle fiber is terminated, Ca^{2+} is actively transported back into the SR by a calcium ATPase. This allows large numbers of Ca^{2+} ions to be stored in the SR. The accumulation of Ca^{2+} in the SR is aided by a protein (**calsequestrin**) that binds Ca^{2+} loosely, thereby reducing the electrochemical gradient opposing the action of the sarcoplasmic reticulum Ca^{2+} ATPase. In striated muscle, Ca^{2+} release from the SR is coupled to depolarization of the T-tubule membrane so that excitation of the T-tubule system leads to Ca^{2+} release from the SR. In skeletal muscle, Ca^{2+} release from the SR depends entirely on depolarization of the T-tubule membrane. In cardiac muscle, increases in cytoplasmic Ca^{2+} ions cause the rapid release of more Ca^{2+} ions from the SR (calcium-induced Ca^{2+} release).

94. What are the terminal cisternae?

The specialized sac-like ends of the sarcoplasmic reticulum in skeletal and cardiac muscle. The terminal cisternae are the storage sites for the Ca^{2+} ions that are released during excitation-

contraction coupling. The terminal cisternae are large in skeletal muscle, but are less extensive in cardiac muscle. This arrangement is consistent with the greater role of extracellular Ca^{2+} influx for regulating the contractile force in cardiac muscle.

95. What is a triad?

The structure formed by the close apposition of two terminal cisternae against a T-tubule in skeletal and cardiac muscle. The triad structure is important in the electromechanical coupling process in which the action potential passing through the T-tubule eventually leads to calcium release from the terminal cisternae.

96. What is the relationship among membrane potential, intracellular Ca^{2+} levels, and contractile force in various kinds of muscle?

The membrane potential generally plays an important role in regulating cytoplasmic Ca^{2+} concentration (and therefore contractile force) in muscle cells. Depolarization of the membrane is associated with increased levels of Ca^{2+} in the cytoplasm of skeletal, cardiac, and smooth muscle.

In **skeletal muscle,** action potentials spreading over the sarcolemma in a process similar to action potential propagation in nerve cells eventually cause Ca^{2+} to be released from the terminal cisterna of the SR.

In **cardiac muscle,** depolarization of the membrane not only causes the release of Ca^{2+} from the SR, but also leads to some influx of Ca^{2+} ions from the extracellular fluid. Influx of extracellular Ca^{2+} ions not only contributes to the development of contractile force, but also leads to the release of Ca^{2+} from the SR (calcium-induced Ca^{2+} release).

In **both skeletal and cardiac muscle,** cytoplasmic Ca^{2+} levels reach a peak value rapidly after release from the SR, preceding peak force development. As the Ca^{2+} ions are bound to troponin C, free Ca^{2+} in the cytoplasm falls, while contractile force increases. Peak force develops when all the regulatory sites on troponin are saturated, and the elastic elements in series and in parallel with the contractile filaments are drawn tight by the activity of the contractile filaments. After excitation of the muscle is terminated, Ca^{2+} diffuses off of the regulatory subunit of troponin and is removed from the cytoplasm by active pumping into the SR by the Ca^{2+} ATPase. In cardiac muscle, Ca^{2+} is also extruded from the cell via the Na^+, Ca^{2+} exchanger, which is a secondary active transport mechanism.

In **smooth muscle,** depolarization of the membrane opens voltage-gated Ca^{2+} channels, leading to the influx of extracellular Ca^{2+} ions. This triggers contraction by binding to calmodulin, which, in turn, activates myosin light chain kinase. Binding of excitatory substances, such as some neurotransmitters or hormones, to their receptors on the cell membrane also causes Ca^{2+} release from the SR of smooth muscle. This release of Ca^{2+} from the SR is triggered by inositol triphosphate, a second messenger compound that is is formed by the hydrolysis of membrane lipids by phospholipase C. Phospholipase C is an enzyme that is activated by the binding of the excitatory substance to its receptor on the cell membrane. Increases in cytoplasmic Ca^{2+} levels, in turn, lead to activation of myosin light chain kinase, phosphorylation of the regulatory light chains of the myosin molecule, and cross-bridge cycling. Hyperpolarization of the smooth muscle membrane closes voltage-gated Ca^{2+} channels, resulting in smooth muscle relaxation. Many smooth muscle cells exhibit graded changes in membrane potential that are not associated with action potentials. Some types of smooth muscle (e.g., intestinal smooth muscle and portal vein smooth muscle) exhibit spontaneous action potentials, which are usually associated with spontaneous contractions of the muscle. These action potentials are due to Ca^{2+} ions and are eliminated by Ca^{2+} channel blockers or Ca^{2+} free solution. Under some conditions, contractile force in smooth muscle can also change without a change in membrane potential. A change in smooth muscle contractile force without a change in membrane potential is known as **pharmacomechanical coupling**.

97. What conveys the signal between the sarcolemma, T-tubule, and sarcoplasmic reticulum to release Ca^{2+} during excitation contraction coupling in striated muscle?

The release of Ca^{2+} from the SR of striated muscle during excitation-contraction coupling is due to interactions between the T-tubules and the terminal cisternae of the SR. The T-tubule con-

tains dihydropyridine-sensitive voltage sensors that are lined up opposite from the specialized feet on the terminal cisternae of the SR. These SR feet are composed of four identical subunits with a membrane spanning domain and a cytoplasmic domain. The SR feet also are called **ryanodine** receptors because they bind this pharmacologic agent, which causes release of Ca^{2+} from the SR. The ryanodine receptor is part of the Ca^{2+} channel that releases Ca^{2+} from the SR. In skeletal muscle, the opening of Ca^{2+} channels in the SR appears to be controlled by an electrical coupling between the T-tubules and the foot proteins, where the key variable in the signaling process is the electrical potential across the T-tubule membrane. The depolarization that occurs as the action potential passes down the T-tubule is proposed to cause a conformational change in foot proteins of the terminal cisternae. This conformational change is transmitted to the foot proteins via the dihydropyridine receptors and opens the Ca^{2+} channels in the SR. This allows Ca^{2+} ions to enter the cytoplasm down a large electrochemical gradient. In cardiac muscle, the influx of extracellular Ca^{2+} also leads to rapid Ca^{2+} release from the SR (Ca^{2+}-induced Ca^{2+} release).

98. What stops contraction of skeletal muscle?

The signal to stop contraction of skeletal muscle is the cessation of nerve impulses in the motor neuron. When the nerve impulses cease, the signal to release calcium ions from membrane stores is removed, stopping further Ca^{2+} release. The SR re-sequesters any free calcium remaining in the cytoplasm via an active transport mechanism that requires ATP (SR calcium pump). When calcium is removed from the cytoplasm, Ca^{2+} ions bound to troponin diffuse into the cytoplasm and are re-sequestered in the SR. When Ca^{2+} ions are no longer bound to the troponin, the thick and thin filaments can no longer interact, and contraction is terminated.

MECHANICS OF MUSCLE CONTRACTION

99. What is the difference between an isotonic and an isometric contraction?

Isotonic contraction refers to a contraction in which a muscle shortens while it exerts a constant force that matches the load being lifted by the muscle.

Isometric contraction refers to a contraction in which the external length of the muscle does not change because the force being generated by the muscle is insufficient to move the load to which it is attached. In the body, most contractions are a combination of isometric and isotonic components. The isometric phase occurs until the muscle generates enough force to lift the load. At this point, the isotonic phase begins and the muscle shortens at a constant force as it lifts the load. The rate and extent of muscle shortening during an isotonic contraction is less with heavier loads, and the duration of the isometric phase of the contraction is longer with heavier loads.

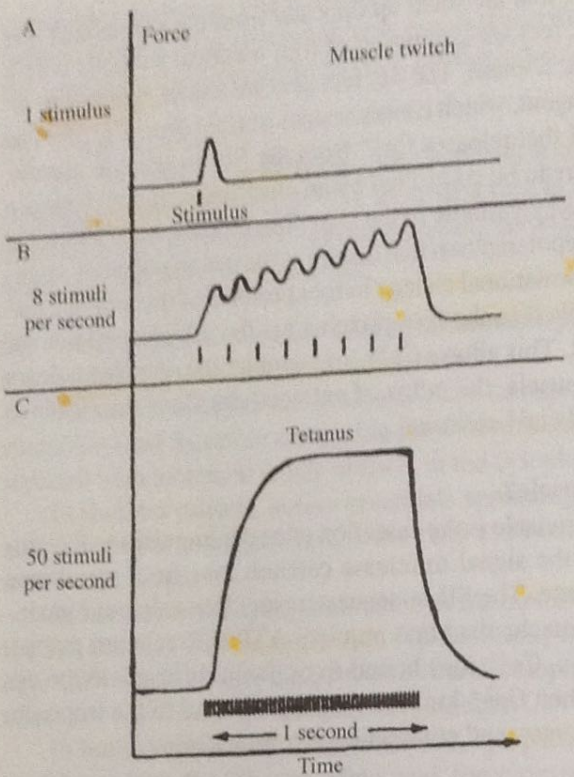
100. What is the difference between a twitch contraction and a tetanic contraction?

A **twitch contraction** is a single brief contraction of the muscle that occurs in response to a single threshold or suprathreshold stimulus.

A **tetanic contraction,** or tetanus, is a maintained contraction of a skeletal muscle owing to the continuous excitation of the muscle fibers. During a tetanic contraction, the muscle exhibits multiple action potentials, which serve to release Ca^{2+} continually from the SR and to maintain high levels of Ca^{2+} bound to troponin. Cross-bridges cycle continuously, and contractile force is maintained until excitation stops and cytoplasmic Ca^{2+} levels fall below the threshold needed to initiate muscle contraction. Tetanic contractions can arise from rapid stimulation of the muscle at frequencies greater than those at which individual twitch contractions can be resolved. The magnitude of a tetanic contraction is substantially greater than that of a twitch contraction because the elastic elements of the muscle are fully stretched, and the Ca^{2+} regulatory sites are completely saturated.

101. What are temporal and multiple motor unit summation?

Summation refers to the addition of contractile force in skeletal muscle. There are two types of summation. In **temporal summation,** with rapid frequencies of stimulation, the muscle is re-



Recordings of contractile force during a twitch contraction (upper panel), temporal summation of contractile force (middle panel), and tetanic contraction of skeletal muscle (lower panel). (From Berne RM, Levy MN: Principles of Physiology, 2nd ed. St. Louis, Mosby, 1996, with permission.)

activated before it is fully relaxed from the previous stimulus. **Multiple motor unit summation** occurs when stronger stimuli cause the activation of additional motor units with lower excitability (i.e., higher thresholds), leading to an increased force of muscle contraction.

102. How can the power output of a muscle be calculated?

The **power output** of a muscle is the mechanical force (work × distance shortened) per unit of time and can be calculated as the **product of load times shortening velocity**.

103. Can twitch contractions be of different magnitudes?

Yes. Single-twitch contractions can be of different magnitudes, depending on the number of motor units that are activated and the position of the muscle on the length-force curve. A motor unit consists of a motor nerve fiber and all of the muscle cells innervated by that nerve fiber. At low stimulus strengths, the more excitable, smaller motor units are activated. With increasing stimulus strength, motor units having higher thresholds (i.e., less excitable, larger motor neurons) are activated, adding to the force of the contraction. A maximal stimulus of the muscle activates all the motor units, and supramaximal stimuli (stimuli that are greater than the maximal stimulus) do not produce any further increase in the magnitude of the twitch contraction. As a muscle is stretched, its position on the length-force curve also changes, and the amplitude of contraction increases with the degree of overlap between thick and thin filaments. At the rest length or optimal length (L_o) of the muscle, the number of myosin heads that can combine with active sites on the thin filament is at its maximum, and twitch contractions have their maximal amplitude for a given set of conditions.

104. What is treppe?

Treppe (or the **staircase effect**) refers either to the progressive increase in the magnitude of twitch contractions of skeletal muscle to a plateau value during repetitive stimulation after a period of rest or to the progressive increase in the magnitude of cardiac muscle contractions to a plateau value that can occur immediately after an increase in heart rate. The phenomenon is due to progressive increases in cytoplasmic Ca^{2+} levels after successive activations of the muscle and

reflects the inability of the SR and Ca^{2+} extrusion mechanisms to restore cytoplasmic Ca^{2+} completely to the levels existing before the contraction.

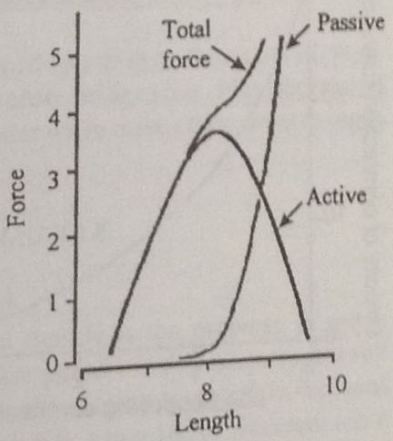
105. What is the difference between preload and afterload?

Preload is the load that a muscle experiences before the onset of contraction. An example of preload is the amount of stretch on a resting muscle during the determination of the length-force relationship or the amount of stretching of cardiac muscle cells as a result of changes in end-diastolic volume.

Afterload is a load that is encountered by the muscle only after it starts to contract. An example is the load being lifted from the floor during a weight-lifting exercise or the arterial pressure that the heart muscle encounters at the onset of systole.

106. What is the length-force (length-tension) relationship?

The **length-force relationship** is the relationship between the length of the muscle and the amount of active and passive force on the muscle, which can be measured by a transducer attached to the muscle. **Active force** refers to the force generated by the contractile machinery when the muscle is activated, and **passive force** refers to the elastic force acting on the muscle because of stretching of the connective tissue and other elastic components of the muscle. **Total force** on the muscle is the sum of the passive and active forces.



Length-force relationship from skeletal muscle. (From Rhoades RA, Tanner GA: Medical Physiology. Boston, Little, Brown, 1995, with permission.)

107. Describe how the length-force relationship works.

At short muscle lengths, the muscle is slack and the elastic components of the muscle are not stretched. As a result, there is no passive force on the muscle prior to activation, and the active force measured when the muscle contracts is significantly smaller than it is at longer lengths. As the muscle is stretched, the amount of passive force on the muscle increases exponentially because of the stretching of the elastic elements of the muscle. Lengthening the muscle at this point also increases the amount of active force generated by the muscle because the thick and thin filaments are stretched into a more optimal alignment, and more myosin heads on the thick filaments can reach active sites on the thin filament. A muscle generates force that is proportional to the number of cross-bridges that are formed simultaneously. At the rest length (also known as the optimum length [L_o]) of the muscle, all of the myosin heads on the thick filaments can reach active sites on the thin filaments, and the muscle can generate the maximal amount of contractile force. As the muscle is stretched further, the thick and thin filaments are drawn out of optimal overlap, and fewer myosin heads can reach active sites on the thin filaments, leading to a reduction in the active force that can be generated by the muscle. If the muscle is stretched to a sufficient degree, there is no overlap between thick and thin filaments, and the muscle cannot generate any contractile force. At that point, active force is 0, and the passive and total forces are the same. As the muscle is stretched further, passive force increases exponentially until the tissue tears or the muscle becomes dislodged from the force transducer.

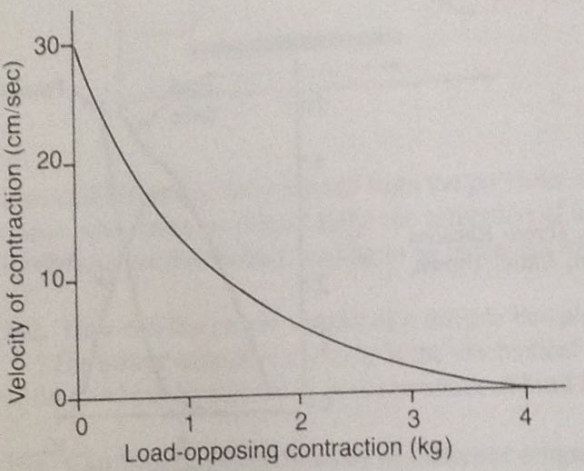
108. What is the difference between the rest length (L_o) of a skeletal muscle and the equilibrium length?

The **rest length** of a skeletal muscle is the length at which the contractile force generated by the muscle is maximum. This is also referred to as optimal length of the muscle and is close to the length of a muscle at rest in the body.

The **equilibrium length** of the muscle is the length to which the muscle recoils after the tendon is cut. This is the length at which passive force on the muscle just equals 0. The equilibrium length is shorter than the rest length, and the contractile force exerted by the muscle at the equilibrium length is less than that occurring at rest length, owing to the changes in the length-force relationship.

109. What is the force-velocity relationship?

The hyperbolic relationship between the force generated by a muscle during an isotonic contraction and the velocity of muscle shortening. The velocity of the shortening of an isotonic contraction depends both on the intrinsic properties of the muscle and on the load on the muscle. Although skeletal muscles of different types can vary substantially in their velocity of contraction at a given load, the velocity of shortening decreases as the load is increased, regardless of muscle type.



Force-velocity relationship for skeletal muscle contraction. (From Guyton AC, Hall J: Textbook of Medical Physiology, 9th ed. Philadelphia, W.B. Saunders, 1996, with permission.)

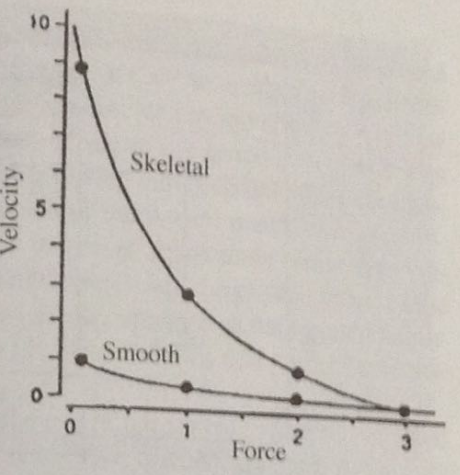
110. How does the force-velocity relationship differ among muscle types?

In **skeletal** and **cardiac muscle,** the force-velocity relationships have a similar shape, with an increase in the load on the muscle resulting in a reduced velocity of contraction. As the load on the muscle is increased, the muscle reaches a point where it cannot generate enough force to lift the load, and the contraction becomes isometric. At this load, shortening velocity is 0, and the force-velocity curve intersects the x-axis. As the load on the muscle is reduced, shortening velocity increases. The shortening velocity at 0 load (where the curve intersects the y-axis) is the **maximal velocity of shortening** (V_{max}). In skeletal muscle, V_{max} is constant for a given muscle and is a specific characteristic of the muscle. In cardiac muscle, V_{max} can change as a result of the inotropic state (contractility) of the heart.

Smooth muscle exhibits a similar force-velocity relationship as striated muscle, but the velocity of contraction is much slower than skeletal and cardiac muscle (see figure). The velocity of shortening in smooth muscle can exhibit substantial variation, depending on the level of phosphorylation of the regulatory light chains on the head of the myosin molecule.

111. What determines V_{max} for a specific muscle type?

- V_{max} for specific muscle types is determined by the myosin isoform that exists in the muscle. Different isoforms of myosin have different rates of ATP hydrolysis, and faster rates of ATP hydrolysis correspond to a greater V_{max}.



Force-velocity relationship in smooth muscle. Note the much slower velocity of contraction in smooth muscle compared with skeletal muscle. (From Rhoades RA, Tanner GA: Medical Physiology. Boston, Little, Brown, 1995, with permission.)

- In **skeletal muscle,** V_{max} is a constant for a given muscle and is determined by the myosin isoform in that muscle.
- In **cardiac muscle,** V_{max} can change, with increases in V_{max} occurring during positive inotropic states such as sympathetic stimulation and treatment with cardiac glycosides such as digitalis. Decreases in V_{max} occur during negative inotropic states such as vagal stimulation. These changes in V_{max} are generally related to changes in the availability of Ca^{2+} ions in the cytoplasm for excitation-contraction coupling.
- In **smooth muscle,** V_{max} can exhibit substantial variation, depending on the extent of phosphorylation of the regulatory light chains on the myosin cross-bridges (i.e., phosphorylated cross-bridges cycle faster and shortening velocity is greater when more of the cross-bridges are phosphorylated).

COMPARATIVE PHYSIOLOGY OF MUSCLE

112. How does cardiac muscle differ from skeletal muscle?

A major difference between cardiac muscle and skeletal muscle is the property of **automaticity** in the heart, which arises from spontaneous pacemaker potentials that occur as a result of complex changes in ionic conductance in special pacemaker cells. Action potentials in the heart exhibit a substantial regional variation, and cardiac muscle exhibits a number of different ionic currents that are not found in skeletal muscle.

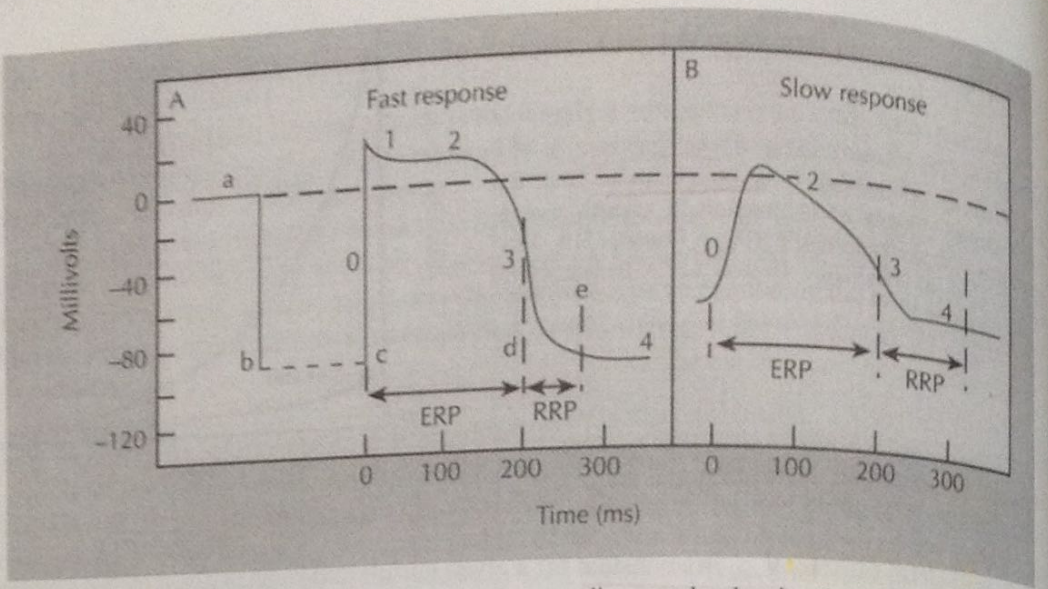
In contrast to skeletal muscle, the heart acts as a **functional syncytium,** with excitation spreading from cell to cell through low-resistance pathways, enabling the contractile activity of the heart to be coordinated to ensure the efficient pumping of blood.

Cardiac muscle also exhibits some differences in **excitation-contraction coupling** (greater reliance on extracellular Ca^{2+} influx) and **mechanical properties** (ability to change V_{max} and a slower contraction velocity) relative to skeletal muscle.

113. What are the two general types of cardiac action potentials?

- **Fast-response action potentials** have a rapid depolarization (phase 0) with a substantial overshoot, a rapid reversal of the overshoot owing to a partial repolarization of the cell (phase 1), a long plateau (phase 2), and a rapid repolarization (phase 3) to return to the resting potential (phase 4).
- **Slow-response action potentials** exhibit a slower initial depolarization, less overshoot, a shorter and less stable plateau, and a repolarization to an unstable resting potential that exhibits a progressive, slow diastolic depolarization that is a major feature of pacemaker activity.

Fast-response and slow-response action potentials both exhibit an effective (absolute) and a relative refractory period.

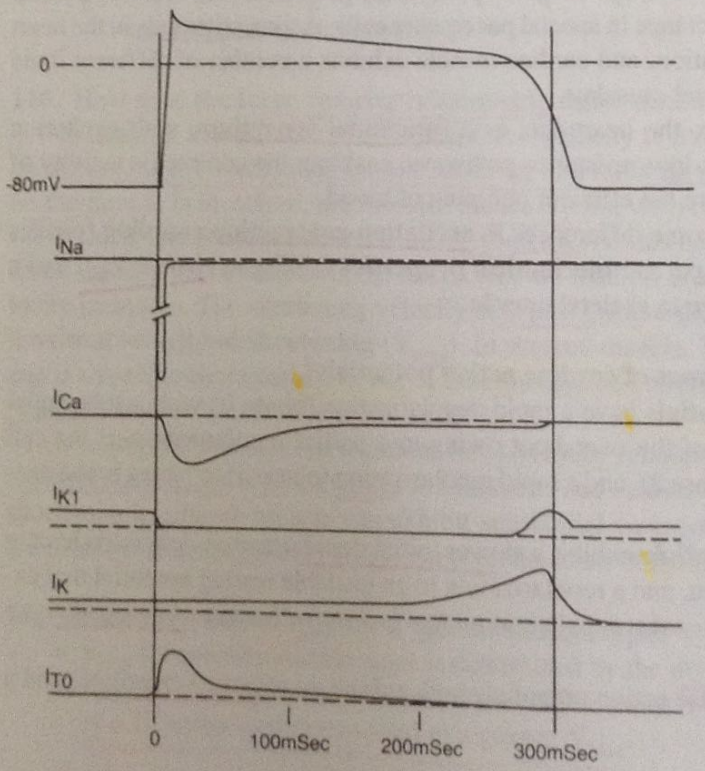


Fast-response and slow-response action potentials from cardiac muscle, showing the different phases of the action potential and the effective (ERP) and relative (RRP) refractory periods. (From Berne RM, Levy MN: Cardiovascular Physiology, 7th ed. St. Louis, Mosby, 1997, with permission.)

114. What is the ionic basis of the fast-response cardiac action potential?

The different phases of the fast-response action potential in cardiac muscle are due to changes in membrane permeability to different ions, which result in complex ionic currents that produce changes in membrane potential (see figure).

- **Phase 0** refers to the initial depolarization phase of the fast cardiac action potential, which is due to the opening of tetrodotoxin-sensitive, voltage-gated Na^+ channels. These channels are rapidly voltage inactivated, stopping the inward Na^+ current.
- **Phase 1** refers to the transient repolarization phase, which is mediated by a transient outward K^+ current that drives the initial repolarization, aided by the inactivation of the fast Na^+ current.

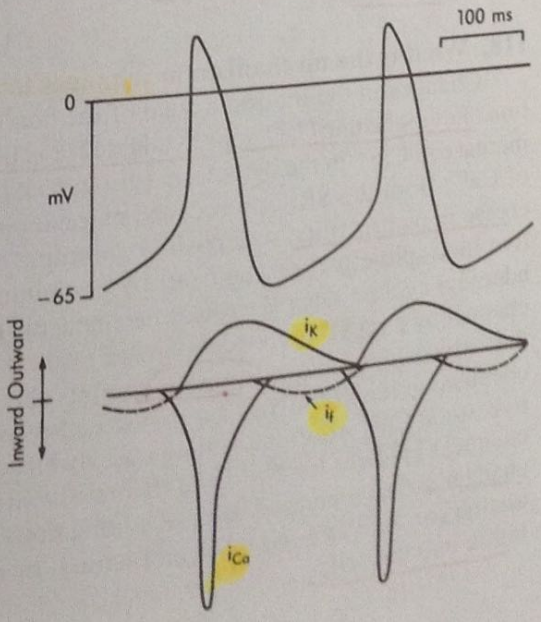


Changes in ionic currents during the action potential of a ventricular muscle cell. I_{Na} indicates inward Na^+ current, I_{Ca} indicates inward Ca^{2+} current, I_{K1} indicates current through inward rectifier K^+ channels, I_K indicates K^+ current through delayed rectifier channels, and I_{TO} indicates transient outward current during partial repolarization phase. (From Sperelakis N, Banks RO (eds): Essentials of Physiology, 2nd ed. Boston, Little Brown, 1996, with permission.)

- **Phase 2** refers to the plateau phase of the action potential, which is mediated by an inward Ca^{2+} current carried by L-type Ca^{2+} channels. The influx of Ca^{2+} ions through these channels contributes to excitation-contraction coupling and to calcium-induced Ca^{2+} release from the SR. The depolarization during the plateau phase of the action potential is also maintained by a low K^+ conductance that allows the inward current to maintain the depolarization. This reduced K^+ conductance is the result of the inward rectifier (K_{IR}) potassium channels, which allow inward K^+ current to be passed much more easily than outward K^+ current. In addition to aiding the depolarization during the plateau phase of the action potential, the decrease in the conductance of the K_{IR} channels at the onset of the action potential is important in preventing excessive K^+ loss from the cell during the action potential.
- **Phase 3** refers to the repolarization of the cell at the end of the plateau, which is mediated by a large, slowly developing K^+ current through delayed rectifier K^+ channels that are activated early in the action potential but exhibit slow activation kinetics. As the membrane potential approaches its normal resting value, the inward rectifying K^+ current, which is a crucial determinant of resting potential, also begins to contribute to the repolarization of the cell.

115. What causes the automaticity of the heart?

The automaticity of the heart is normally mediated via the spontaneous electrical activity of the pacemaker cells in the sinoatrial node. The atrioventricular node and Purkinje fibers can also serve as pacemakers but are normally overridden by the faster rate of the sinoatrial node. The pacemaker cells undergo spontaneous changes in membrane potential because of fluctuations in ionic conductances that allow the membrane potential to reach threshold values and to initiate conducted action potentials throughout the heart (see figure). The pacemaker potential exhibits a slow diastolic depolarization that eventually reaches threshold, resulting in an action potential. The diastolic depolarization is mediated by three different currents. One of these (I_f, or "funny" current) is an inward depolarizing current that is activated by hyperpolarization of the cell and is carried mainly by Na^+ ions through channels that are different from the tetrodotoxin-sensitive, voltage-gated Na^+ channels. The other depolarizing current is an inward Ca^{2+} current, which accelerates the diastolic depolarization, leading to the upstroke of the action potential. These inward currents are opposed by an outward K^+ current that repolarizes the cell after the upstroke of the action potential, then decreases its influence during phase 4 of the action potential, allowing the inward currents to trigger another diastolic depolarization. The heart rate is determined by the



Changes in ionic current during pacemaker potentials in the sinoatrial node of the heart. i_{Ca} indicates inward Ca^{2+} current, i_f indicates inward Na^+ or "funny" current, and i_K indicates outward K^+ current. (From Berne RM, Levy MN: Cardiovascular Physiology, 7th ed. St. Louis, Mosby, 1997, with permission.)

slope of the diastolic depolarization, the absolute value of membrane potential, and the value of the threshold potential, all of which determine how fast the diastolic depolarization reaches the threshold value required to initiate the next action potential.

116. Which two pathways mediate the coordinated spread of excitation and contraction in the heart?

1. The **His-Purkinje system** provides a specialized system for conduction of excitation that consists of modified cardiac muscle fibers that have fewer myofibrils than other cardiac muscle cells.
2. The **intercalated disks** provide low-resistance pathways between individual cardiac muscle cells. The intercalated disks contain gap junctions. The gap junctions are low-resistance pathways composed of connexons, which are hexameric structures consisting of six polypeptides with a central core that serves as a low-resistance pathway for cell-to-cell conduction. The combined function of the His-Purkinje system and the intercalated disks permits the heart to function as a syncytium, enabling cardiac contractile activity to be coordinated to ensure the efficient pumping of blood.

117. Which aspects of excitation-contraction coupling are different in cardiac muscle compared to skeletal muscle?

- The terminal cisternae of cardiac muscle are much less extensive than those of skeletal muscle, and hence excitation-contraction coupling in cardiac muscle is much more dependent on the influx of extracellular Ca^{2+} ions.
- The T-tubules in cardiac muscle are much larger than those of skeletal muscle, allowing easier exchange of ions, nutrients, and waste products between the cardiac myocyte and the extracellular fluid. To aid in their function, the T-tubules also contain negatively charged mucopolysaccharides that bind Ca^{2+} ions, making more Ca^{2+} available for excitation-contraction coupling.
- Changes in the number of Ca^{2+} ions released from the SR can have a much greater effect on cardiac muscle contraction than on skeletal muscle contraction. For example, the increases in cytoplasmic Ca^{2+} that result from sympathetic stimulation of the heart or reduced Ca^{2+} extrusion during treatment with cardiac glycosides result in a greater sequestration of Ca^{2+} by the SR. This ultimately leads to a greater Ca^{2+} release from the SR during the next activation of the cell and to an increased force of contraction.
- Calcium-induced Ca^{2+} release, by which increases in cytosolic Ca^{2+} levels lead to a rapid and massive release of Ca^{2+} from the SR in cardiac muscle cells, does not occur in skeletal muscle.

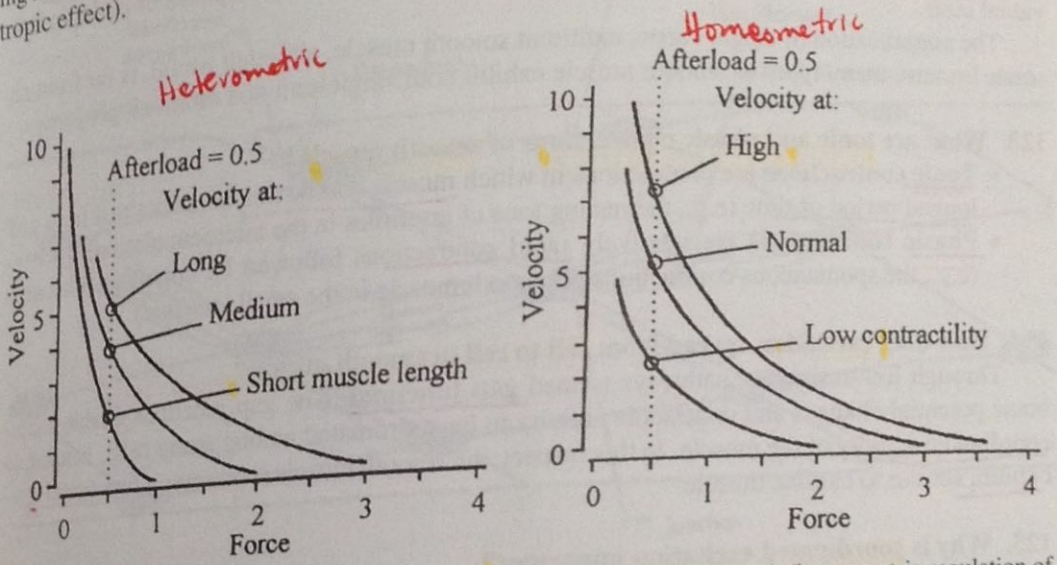
118. What is the mechanism for changes in the contractility (inotropic state) of the heart?

Changes in the inotropic state of the heart are due mainly to the changes in the concentration of cytoplasmic Ca^{2+} ions available for activation. Any stimulus that can lead to a maintained increase in Ca^{2+} in the cytoplasm (through an increased influx of Ca^{2+} ions, an increased release of Ca^{2+} from the SR, or a reduced extrusion of Ca^{2+} from the cytoplasm) can result in an increase in contractility, or a positive inotropic effect. For example, catecholamines exert a positive inotropic effect on the heart by combining with a β-adrenergic receptor, which activates adenylyl cyclase via a G-protein mechanism. The resulting phosphorylation of the L-type Ca^{2+} channel by a cAMP-dependent kinase leads to an increased influx of Ca^{2+}. Treatment with cardiac glycosides such as digitalis inhibits the Na^+, K^+ pump, resulting in a reduced electrochemical gradient for Na^+ across the cell membrane. The energy for the Na^+, Ca^{2+} exchanger to extrude Ca^{2+} from the cell against its electrochemical gradient is derived from the electrochemical gradient for Na^+, and this results in a reduced Ca^{2+} extrusion via the Na^+, Ca^{2+} exchanger and an increased force of contraction (positive inotropic effect). In contrast, vagal stimulation can lead to a reduced contractility, or negative ionotropic state, owing to reduced Ca^{2+} influx into the cell.

119. What are heterometric and homeometric regulation of contractile force in cardiac muscle?

Heterometric regulation of contractile force in cardiac muscle (see figure, left panel) refers to changes in contractile force occurring as a result of changes in the length of the muscle fiber at a constant inotropic state. These changes can occur during increases or decreases in end-diastolic volume and are due to changes in the position of the muscle fiber on the length-force curve.

Homeometric regulation of contractile force in cardiac muscle (see figure, right panel) refers to changes in the contractile force of cardiac muscle at the same muscle fiber length (or end-diastolic volume). This occurs during changes in the inotropic state of the muscle. For example, sympathetic stimulation or treatment with cardiac glycosides has a positive inotropic effect, resulting in an increase in the force generated by the muscle at a given end-diastolic volume. During heart failure or parasympathetic stimulation, the force of contraction decreases (negative inotropic effect).



Changes in force-velocity curve of cardiac muscle during changes in fiber length (heterometric regulation of contractile force) in the left panel and during changes in the inotropic state of the heart (homeometric regulation of contractile force) in the right panel. (From Rhoades RA, Tanner GA: Medical Physiology. Boston, Little, Brown, 1995, with permission.)

120. How do the contractile properties of cardiac muscle differ from those of skeletal muscle?

Cardiac muscle has a slower velocity of contraction than skeletal muscle, and cardiac muscle can exhibit changes in the V_{max} during changes in the inotropic state of the heart.

In contrast to skeletal muscle, cardiac muscle normally operates at lengths that are much shorter than the optimal, or rest, length (L_o). This property is important in allowing the heart to increase its force of contraction in response to increases in end-diastolic volume that are associated with increases in venous return (Frank-Starling mechanism or heterometric autoregulation).

121. What are the sources of metabolic energy for cardiac muscle contraction?

Oxidative phosphorylation is the primary source of metabolic energy in the heart. The primary substrates for oxidative metabolism in the heart are either fatty acids or carbohydrates. Lactate is an important substrate, and ketones and amino acids can also serve as substrates during periods of increased activity. Similar to skeletal muscle, cardiac muscle contains creatine phosphate as a buffer system to supply the short-term demands of the contractile system for ATP.

Anaerobic glycolysis can also briefly compensate for a transient lack of aerobic ATP production, but the capacity of anaerobic glycolysis to meet the energy needs of the heart is limited. The formation of ATP depends on a steady supply of oxygen via coronary blood flow. Because

of the dependence of the heart on aerobic metabolism, there is a good correlation between the oxygen consumption of the heart and the amount of work performed by the heart. Oxygen consumption is nearly proportional to the product of the tension that occurs in the heart muscle during contraction times the duration of contraction (**tension-time index**).

122. Define single-unit (unitary) and multiunit smooth muscle.

Single-unit or **unitary** applies to a smooth muscle in which the excitation spreads from cell to cell through low-resistance pathways, allowing the muscle to respond as a syncytium, or single unit. Single- unit smooth muscle often exhibits spontaneous activity, as in the intestine.

Multiunit refers to smooth muscle that requires external activation by nerves or hormones to generate contractile force. In multiunit smooth muscle, each individual cell is viewed as an independent unit, and the response of the whole muscle is a result of the response of multiple individual units.

The classification of single versus multiunit smooth muscle, although useful, is far from absolute because many types of smooth muscle exhibit both single-unit and multiunit properties.

123. What are tonic and phasic contractions of smooth muscle?

- **Tonic contractions** are contractions in which muscle contraction is maintained for a prolonged period of time (e.g., the resting tone of arterioles in the microcirculation).
- **Phasic contractions** are relatively rapid contractions followed by complete relaxation (e.g., the spontaneous contractions of smooth muscle in the small intestine).

124. How does excitation spread from cell to cell in smooth muscle?

Through low-resistance pathways termed **gap junctions**. The gap junctions enable membrane potential changes and contractile activity to be coordinated among many cells, leading to coordinated activity of the muscle. In this respect, the smooth muscle represents a functional syncytium, similar to cardiac muscle.

125. Why is coordinated excitation important?

Conducted excitation with coordinated activity of smooth muscle cells is especially important in organs such as the intestine, where extensive areas of the organ work together to mix or propel the luminal contents.

126. How do individual smooth muscle cells serve as integrators of information?

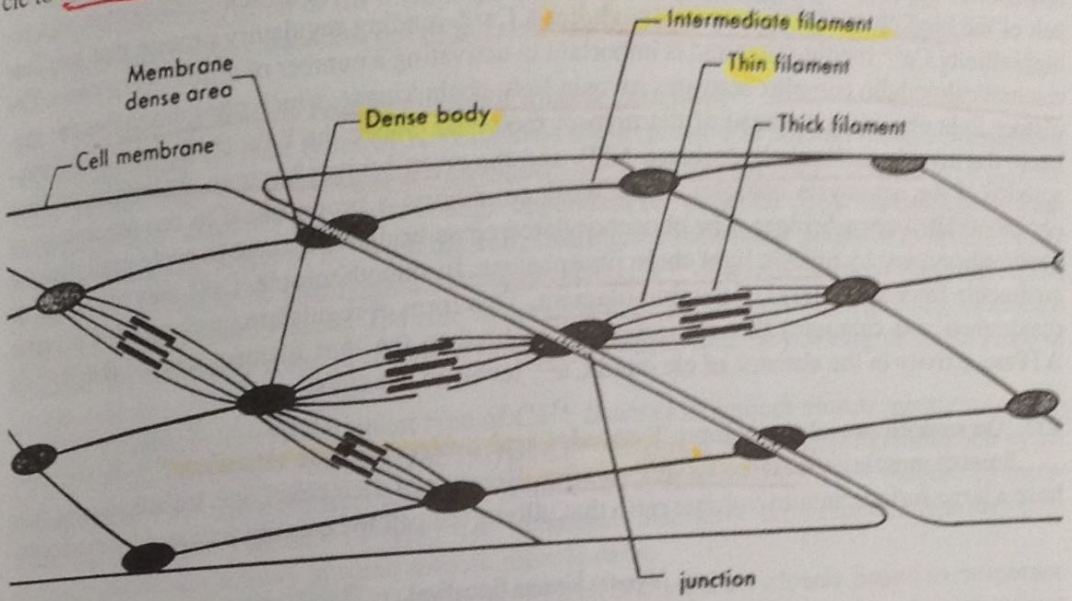
The amount of force that is generated by a smooth muscle at any given time is a function of the overall effect of a variety of excitatory and inhibitory inputs. These can include excitatory and inhibitory neural inputs, circulating hormones, autacoids, or local paracrine factors produced in the tissue. In blood vessels, the endothelium releases a number of contracting and relaxing factors that affect the active tone of the smooth muscle. Many smooth muscles are also sensitive to stretch and to local conditions such as PO_2, PCO_2, and pH. The latter factors are important in regulating physiologic functions, such as the local control of blood flow in the microcirculation. In this way, smooth muscle cells sample excitatory and inhibitory inputs to provide an integrated response that is determined by the combined influence of these inputs.

127. Compare and contrast the contractile proteins of smooth muscle and striated muscle.

Smooth muscle and striated muscle both contain myosin that has cross-bridges, hydrolyzes ATP, and interacts with actin to generate contractile force. In contrast to striated muscle, the thin filaments of smooth muscle contain only actin and tropomyosin, but not troponin. Also in contrast to striated muscle, regulation of contractile activity by Ca^{2+} in smooth muscle is mediated by the binding of Ca^{2+} to calmodulin, which activates myosin light chain kinase and phosphorylates the regulatory light chain of myosin. This results in subsequent ATP hydrolysis and cross-bridge cycling.

128. Compare and contrast the arrangement of the contractile filaments in smooth muscle with that in skeletal muscle.

The arrangement of the contractile filaments in smooth muscle is depicted in the figure. Smooth muscle contains both thick and thin filaments. As in striated muscle, the thick filaments in smooth muscle are composed of myosin. The thin filaments of smooth muscle contain actin and tropomyosin, but no troponin. The contractile filaments in smooth muscle also are not arranged in orderly arrays as in striated muscle, and the actin-to-myosin ratio in smooth muscle (14–16:1) is much greater than that in skeletal muscle (2:1). Thin filaments in smooth muscle are attached to dense bodies rather than Z lines, and myosin cross-bridges from the thick filament can interact with thin filaments along a much greater length of the thin filament, allowing smooth muscle to shorten to a much greater fraction of its length than skeletal muscle.



Arrangement of contractile filaments in smooth muscle. (From Berne RM, Levy MN: Principles of Physiology, 2nd ed. St. Louis, Mosby, 1996, with permission.)

129. How do smooth muscle cells shorten if they do not have sarcomeres as in skeletal muscle?

As in the case of skeletal and cardiac muscle, smooth muscle cells shorten as a result of an interaction between thick and thin filaments. In contrast to the regular sarcomeric structure of skeletal and cardiac muscle, thin filaments in smooth muscle are attached to structures in the cytoplasm known as the **dense bodies**, and to dense areas or attachment plaques on the sarcolemma. Dense bodies are connected to each other by **intermediate filaments** generally consisting of the protein desmin, although the intermediate filaments of some smooth muscles contain vimentin. The contractile filaments and dense bodies form an interlacing structure attached to the cytoskeleton. Interaction between the thick and thin filaments with cycling of the myosin cross-bridges results in shortening of the smooth muscle cell.

130. How do the sources of activator Ca^{2+} differ between skeletal, cardiac, and smooth muscle cells?

In both smooth and striated muscle, excitation contraction coupling involves an increase in the cytoplasmic Ca^{2+} levels of the cell. The increase in cytoplasmic Ca^{2+} in skeletal muscle is due entirely to release of Ca^{2+} from the SR stores, whereas in cardiac muscle, both the SR stores and the influx of extracellular Ca^{2+} ions are important in regulating contraction. In smooth muscle, activator Ca^{2+} can either enter the cell from the extracellular fluid or come from the SR. In

most cases, smooth muscle depends substantially more on the entry of extracellular Ca^{2+} ions than striated muscle. The contraction of smooth muscles that have a sparse SR is much more sensitive to inhibition by calcium channel blockers and Ca^{2+} free solutions.

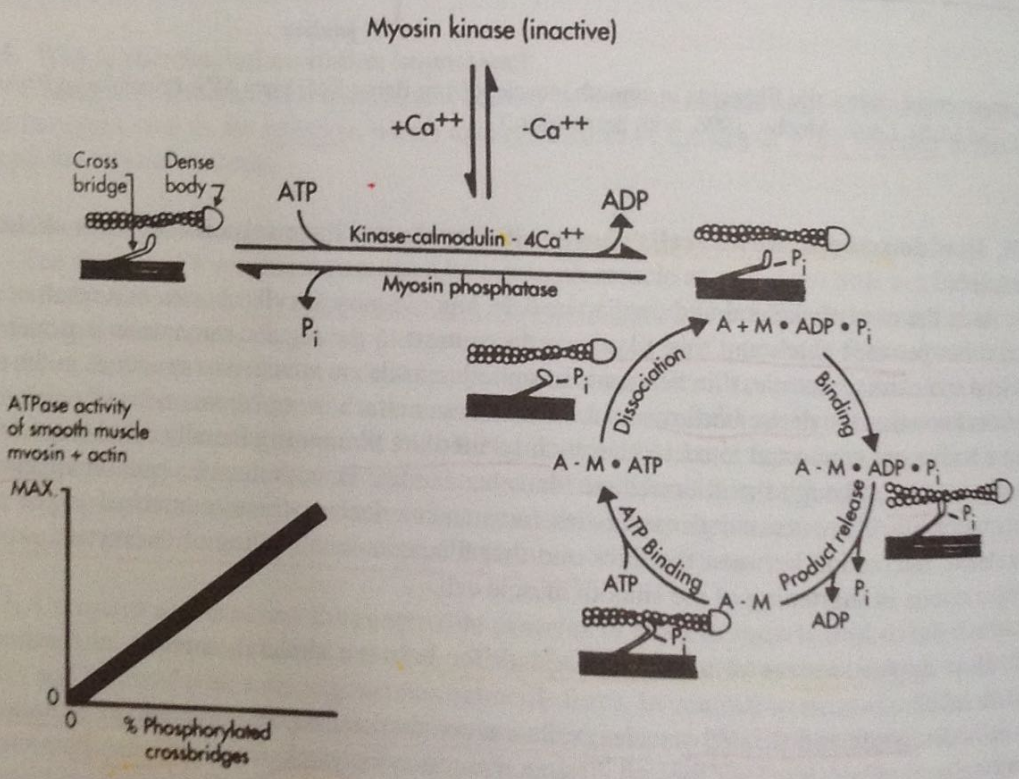
131. How do Ca^{2+} ions regulate contractile protein interactions in striated and smooth muscle?

In **striated muscle,** the Ca^{2+} ions bind to troponin C, causing a change in the position of the troponin-tropomyosin complex that unmasks the active sites on the thin filament, allowing the cross-bridge cycling that leads to muscle contraction.

In contrast to striated muscle, **smooth muscle** does not contain troponin, and regulation of contractile force occurs at the level of the thick filament (see figure). Initiation of contraction in response to increases in cytoplasmic Ca^{2+} concentration in smooth muscle cells occurs as a result of the binding of Ca^{2+} ions to calmodulin, a Ca^{2+}-binding regulatory protein that has four high-affinity Ca^{2+} binding sites and is important in activating a number of different enzymes. The calcium/calmodulin complex activates myosin light chain kinase, which phosphorylates the regulatory light chains on the head of the myosin molecule. When the light chains are phosphorylated, the myosin molecule hydrolyzes ATP, and the cross-bridges begin to cycle. The ATPase activity of the actomysin complex under these conditions is proportional to the percentage of phosphorylated cross-bridges. The phosphorylated cross-bridges continue to cycle until they are dephosphorylated by myosin light chain phosphatase. In smooth muscle, Ca^{2+} may also regulate contractile force at the level of the thin filament. This form of regulation involves other proteins (caldesmon and calponin) that are proposed to bind to the thin filament and inhibit myosin ATPase activity in the absence of elevated Ca^{2+} levels in the cytoplasm.

132. Do smooth muscle cells have T-tubules and a sarcoplasmic reticulum?

Smooth muscle cells *do not* have T-tubules. Because of their small size, smooth muscle cells have a large surface area-to-volume ratio that allows the cell to be easily activated by extracellu-



Steps in cross-bridge cycling and effect of cross-bridge phosphorylation on myosin ATPase activity in smooth muscle. (From Berne RM, Levy MN: Principles of Physiology, 2nd ed. St. Louis, Mosby, 1996 with permission.)

lar Ca^{2+} influx without the need for conduction of excitation to the center of the cell by a T-tubule system. Smooth muscle cells *do* have a sarcoplasmic reticulum that can be either fairly extensive or relatively sparse. Smooth muscles with an extensive SR are more resistant to inhibition by reductions in extracellular Ca^{2+} concentration or calcium entry blockers.

133. Which three factors determine the level of cytoplasmic Ca^{2+} in smooth muscle cells?

1. The influx of Ca^{2+} through activation of Ca^{2+} channels in the cell membrane
2. The release of Ca^{2+} ions from the SR
3. The removal of Ca^{2+} from the cytoplasm of the smooth muscle cell by several different mechanisms:
   - The active transport of Ca^{2+} into the SR by the SR-bound Ca^{2+} ATPase
   - The active extrusion of Ca^{2+} from the cell by the sarcolemmal Ca^{2+} ATPase
   - Secondary active transport out of the cell by the Na^+, Ca^{2+} counter-transporter

134. How do ion channels regulate smooth muscle function?

K^+ channels: Several types of K^+ channels are expressed in smooth muscle membranes. These include large Ca^{2+}-activated K^+ channels (K_{Ca}), ATP-sensitive K^+ channels (K_{ATP}), inward rectifier K^+ channels (K_{IR}), and voltage-dependent K^+ channels (K_V). Increases in K^+ conductance lead to the efflux of K^+ from the cell, causing the membrane potential to become more negative. This leads to the inactivation of voltage-gated Ca^{2+} channels, reduced Ca^{2+} influx, and relaxation of the smooth muscle. The role of specific K^+ channel types in regulating membrane potential and contractile force in response to various stimuli can vary among different kinds of smooth muscle.

Ca^{2+} channels: The predominant type of Ca^{2+} channel in smooth muscle membranes is the L-type, voltage-gated Ca^{2+} channel. The L-type Ca^{2+} channels are sensitive to inhibition by dihydropyridine Ca^{2+} entry blockers and control the entry of extracellular Ca^{2+} induced by membrane depolarization. Transient (T-type) Ca^{2+} channels also have been reported and may contribute to pacemaker activity in some smooth muscle cells.

Nonspecific cation channels: These ligand-gated channels are closely linked to membrane receptors and open in response to some contractile agonists. Nonspecific cation channels permit the influx of Na^+ and K^+ as well as Ca^{2+} ions and may provide the initial depolarization that triggers the opening of L-type Ca^{2+} channels.

Chloride channels: These channels may modulate the level of excitability of some smooth muscle cells by regulating electromechanical coupling. Because the Cl^- equilibrium potential is more positive than the membrane potential, opening of Cl^- channels may result in Cl^- efflux and provide a depolarizing influence to promote smooth muscle contraction.

Stretch-activated channels: The properties of these mechanosensitive channels are still being characterized. They appear to be insensitive to pharmacologic block by dihydropyridine drugs and may mediate Ca^{2+} influx during stretch of the smooth muscle cell.

135. How do membrane receptors regulate smooth muscle activity?

Membrane receptors are proteins that serve as targets for binding by specific ligands, such as neurotransmitters, hormones, and other humoral factors. The binding of the ligand to its receptor results in a specific response within the cell. In smooth muscle, excitatory receptors increase cytoplasmic Ca^{2+} and cause contraction by increasing the permeability of the cell membrane to Ca^{2+}, leading to an influx of extracellular Ca^{2+}, or by causing the release of Ca^{2+} from the SR. In other cases, occupancy of receptors by ligands can lead to smooth muscle relaxation. Receptor-mediated relaxation is often associated with hyperpolarization of the membrane mediated by activation of K^+ channels. This hyperpolarization of the cell membrane inhibits Ca^{2+} influx through voltage-gated Ca^{2+} channels. In many cases, the binding of ligands to their receptors causes an elevation in cAMP or cGMP that leads to relaxation of smooth muscle via a variety of mechanisms including activation of K^+ channels, increases in the active transport of Ca^{2+} from the cytoplasm, or alterations in the force-generating capacity of the contractile filaments.

136. How do second messengers regulate smooth muscle function?

Smooth muscle function can be regulated by a number of important second messenger systems, including:

- **Phospholipase C,** which hydrolyzes membrane lipids to produce inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (IP_3 causes the release of Ca^{2+} ions from the SR, and diacylglycerol can activate protein kinase C (PKC), which leads to activation of membrane ion channels (e.g., a PKC-dependent phosphorylation of the L-type Ca^{2+} channel stimulates Ca^{2+} influx).
- **Phospholipase A_2,** which hydrolyzes membrane lipids to liberate arachidonic acid, whose active metabolites can regulate smooth muscle contractile force.
- **Adenylyl and guanylyl cyclase,** which increase cAMP and cGMP levels.
- **Calcium ions,** which can also be viewed as second messengers because they activate the contractile system via Ca^{2+}-calmodulin–dependent activation of myosin light chain kinase and trigger other responses such as the opening of Ca^{2+}-activated K^+ channels in the cell membrane

137. How do the mechanical properties of smooth muscle differ from those of skeletal muscle and cardiac muscle?

- Skeletal muscle contracts faster than cardiac muscle, which, in turn, contracts much faster than smooth muscle.
- When normalized to cross-sectional area, smooth muscle cells can generate an equal or greater amount of force than cardiac or skeletal muscle cells, can operate over a much wider range of lengths, and can generate contractile force at much shorter lengths than skeletal or cardiac muscle. The ability of smooth muscle to generate contractile force over a wide range of lengths is important in allowing smooth muscle to adapt to large changes in the volume of hollow organs, such as the intestine or urinary bladder.
- The velocity of smooth muscle contraction can change, depending on physiologic conditions. Smooth muscle also exhibits a **latch state,** in which it can generate contractile force for prolonged periods of time with minimal energy consumption.

138. What is the latch state of smooth muscle?

The **latch state** refers to a condition in which the muscle maintains high levels of active force without rapid cross-bridge cycling and with low rates of ATP consumption.

139. What is the mechanism of the latch state?

When smooth muscle is initially activated, the rapidly developing phase of contraction coincides with a transient peak in intracellular Ca^{2+} levels, leading to activation of myosin light chain kinase, phosphorylation of cross-bridges, and cross-bridge cycling with ATP hydrolysis. During the latch state, the initial peak Ca^{2+} concentration falls to a moderately elevated steady-state level while force is sustained. This is accompanied by a reduction in cross-bridge phosphorylation and a reduction in ATP consumption. The existence of high force with moderate levels of cross-bridge phosphorylation means that cross-bridges that are attached but dephosphorylated also contribute to contractile force in the muscle. Therefore, both the number of attached cross-bridges (which determines force) and the cycling rate of the cross-bridges (which determines velocity and ATP consumption) can be regulated.

140. Why is the latch state important?

It enables the muscle to maintain contractile force for prolonged periods of time with minimal energy expenditure in the form of ATP consumption.

141. What is stress relaxation and reverse stress relaxation?

Stress relaxation and **reverse stress relaxation** refer to the ability of smooth muscle to adjust its length after abrupt changes in muscle length or organ volume. When smooth muscle length

or organ volume is abruptly increased, the total force on the smooth muscle or the pressure within the organ increases substantially. Over the next minute or so, the force on the muscle or the pressure inside the organ gradually returns to near the control value as the muscle lengthens to accommodate the stretch or the increased volume within the organ. This compensatory response of the smooth muscle to stretch is called **stress relaxation**. When smooth muscle is abruptly shortened or when organ volume is abruptly decreased, the force on the muscle or the pressure inside the organ drops. Muscle force and organ pressure are soon restored to near the control value as the muscle shortens to maintain force at the new length or pressure at the reduced volume (**reverse stress relaxation**). Stress relaxation and reverse stress relaxation result from readjustment of the position of the myosin cross-bridges on the thin filament and are important in allowing smooth muscle to maintain a constant pressure in hollow organs, despite changes in the length of the smooth muscle cells.

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