Lecture 1, Jan 10, 2023

Homeostasis

- Something staying "relatively same" – an equilibrium of sorts
- A self-regulating process by which an organism maintains stability and adjusts to external conditions
- Analogy to a feedback controller from control theory

Lecture 2, Jan 12, 2023

The Nucleus

- "Control center"
- 2 layers on the surface, nuclear pores connects the two barriers
- At the center is the nucleolus, contains stuff for making RNA
- Chromatin comes out from the center, which are threads of DNA in different proteins
- At the large scale we have chromosomes, which are made of coiled chromatin, which are coils of units of nucleosomes, which are made of spools of histones, which are made of a DNA helix of two complementary strands

Nucleosome

- DNA thread winds around histone structure, with proteins with tails
  - The proteins hold the DNA in place with latches, and through acetylation the latches unlatch and the DNA becomes loosely packed
- Nucleosome packing can be either loose (euchromatin) through acetylation or tight (heterochromatin) through methylation
  - Loosely packed nucleosomes are easier to read
  - Heterochromatin are harder to read, used to store stuff that isn't read much
- Abnormal methylation or acetylation coiling lead to abnormal chromatin structure, which can lead to cancer (in addition to regular DNA mutation)

DNA

- DNA is made of two complementary strands, one is the template and one is the coding strand
  - Strands have direction, 3' or 5'; template goes from 3' to 5'; coding goes from 5' to 3'
  - The template and coding strands are always going in opposite directions
- Mnemonic: for the template, we "read up", we go from 3' to 5'; for the code, we "write down", go from 5' to 3'
- DNA is made of 4 nitrogenous bases: *adenine* (A), *thymine* (T), *guanine* (G), *cytosine* (C)
  - Adenine and thymine match together, guanine and cytosine match together
- DNA is not a homogeneous coil – some parts have a bigger gap and some parts have a smaller gap due to its structure, making some parts more exposed and easier to read and other parts protected
- The backbone is made of sugars and phosphate

DNA Construction

- A *nucleobase* is the nitrogenous base, adenine, thymine, guanine, or cytosine
  - This is the stuff in the middle of the helix, which actually stores data
- A sugar molecule (deoxyribose) is attached to it to make it a *nucleoside*
  - The sugar goes into a third dimension (above and below the base) due to its structure
- A phosphate can be added to the sugar to make it a *nucleotide*, which helps bonding due to its reactivity
- All the carbon atoms are numbered: 1 is attached to the nucleobase, then clockwise to 2, 3, and 4, then 5 connects to the oxygen that connects to the phosphate
  - 3' would be going down and 5' goes up near the phosphate

  - The 3' end is the sugar, and 5' is the phosphate
- Cytosine and thymine are *pyrimidines*, which have one cycle; they hydrogen bond with *purines*, adenine and guanine, which have two cycles
  - The donor is a hydrogen bonded to an electronegative atom like oxygen, which makes it positive; it sticks to an electron pair on the acceptor (typically another oxygen or nitrogen)
  - Cytosine has one positive hydrogen, and two negative (oxygen and nitrogen) which fits perfectly into guanine
    * Similar for thymine and adenine
    * This is why you can't mix and match nucleobase pairs

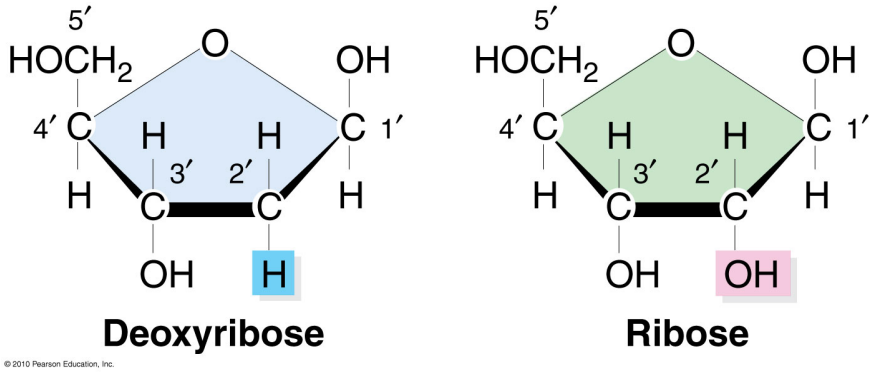

Figure 1: Numbering of carbons

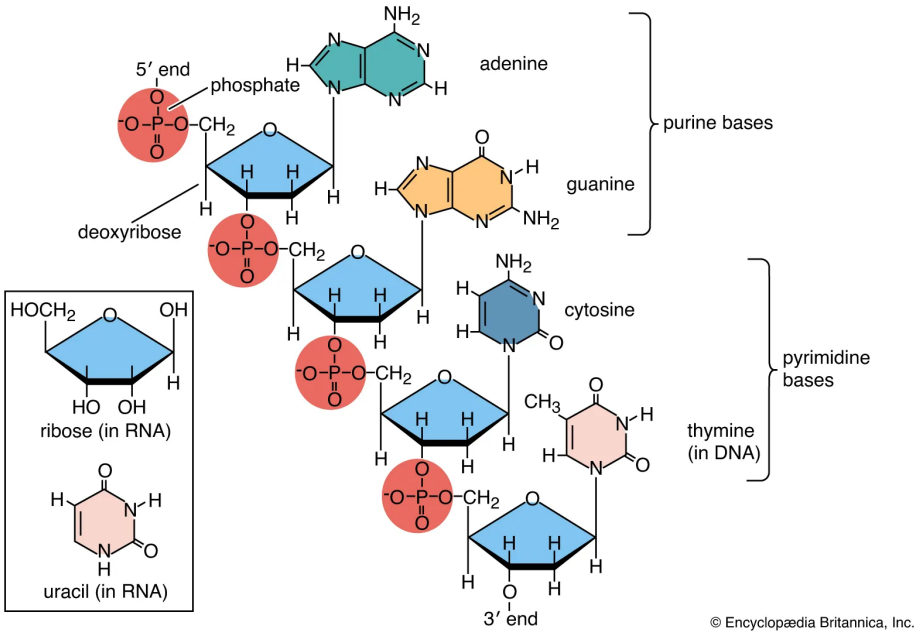

Figure 2: Structure of DNA

Lecture 3, Jan 17, 2023

RNA

- Like DNA, but instead of thymine we have uracil, which is the same as thymine but the CH_3 is not there
  - Uracil still pairs with adenine
  - The extra methyl on thymine makes the molecule more stable since it blocks the molecule, so RNA is less stable
- The sugar molecule is now only a ribose, not a deoxyribose
  - At the 2 spot there is now an OH group instead of just hydrogen
  - Not having the oxygen also makes DNA more stable and gives it space to coil
- Overall RNA is much less stable than DNA and more prone to mutations
  - DNA can last a lifetime but RNA degrades in 30 minutes
  - RNA is mostly a temporary molecule; when it degrades the cell reuses its parts
- RNA comes in only one strand, unlike the double helix of DNA
  - The ribose backbones still cause it to twist
  - RNA is also shorter than DNA
- A *primary structure* is when the RNA is still in a single strand; coiling may occur
  - Messenger RNA (mRNA) is just a single strand without bonds within itself, i.e. a primary structure
  - Transfer RNA (tRNA) is a tertiary structure
  - When the RNA folds it can start hydrogen bonding within itself; in 2D it begins forming a secondary structure, then in 3D it forms a tertiary structure
  - "The collection of base pairs in the tertiary structure is the secondary structure"

The Central Dogma (DNA Transcription)

- DNA makes (messenger) RNA, which then makes proteins
- Consider a template strand of DNA; RNA nucleotides will come in and attach to the DNA nucleobases, and form an RNA strand piece by piece
  - The hydroxyl is exposed on the 3' end of the RNA, which drives the reaction
  - This process goes from the 3' end of the DNA (which matches the 5' end of the RNA) to the 5' end of the DNA (which matches the 3' end of the RNA)
  - The RNA created is the same as the coding strand of the DNA, except thymine is replaced with uracil
  - "read up, write down" mnemonic
- Cells in different parts of the body may only be able to produce certain things
  - Every cell in your body has your complete DNA, but only in certain cells can certain parts of the DNA be activated
  - e.g. only cells in the liver can produce albumin
- There may also be inducible gene expression
  - e.g. the pancreas responds to blood glucose level (glucagon) which expresses a gene that stops glucagon
- Transcription factors assemble on a certain part of the DNA (maybe in response to environmental stimulus); it contains DNA polymerase, which splits apart the DNA locally, allowing RNA nucleotides to come in and attach, producing an RNA strand
- Eukaryotic gene structure:
  - Control elements in the DNA (enhancers/silencers and the TATA box) indicate where to start transcribing (upstream regulatory sequence)
    - Transcription factors assemble at the TATA sequence
    - Positive transcription factors indicate to the DNA polymerase where to start
      - If there is a negative transcription factor attached, it prevents positive transcription factors and DNA polymerase from attaching to the gene and copying it
  - *Introns* and *exons* in the open reading frame (ORF)
    - The introns join together the exons, but the introns are not needed and are spliced away later

  - A termination sequence and other control mechanisms are at the end (downstream regulatory sequence)
- The resulting raw RNA strand is processed by a *spliceosome*, which cuts the DNA at the introns and throws those parts away
  - This leaves us with the exons only, giving us the mature mRNA

Lecture 4, Jan 19, 2023

Transfer RNA (tRNA) and Translation

- Translation is the process of building proteins
- tRNA forms tertiary structures
- tRNAs are about 4 times smaller than ribosomes (7nm vs 30nm) and they can interact
- The ribosome consists of RNA coiled together with proteins
- The ribosome reads a messenger RNA and makes proteins
  - Transfer RNAs have anticondons that match codons on the mRNA
  - Each tRNA has an amino acid which is used to build the final protein
- Every group of 3 bases form a *codon*; condon charts tell us which condon is formed by a combination of 3 bases
  - e.g. an AUG sequence forms a methionine, which is the "start" condon; UAA, UAG, and UGA are the "stop" codons
- The tRNA gets attached to the amino acid through other molecules
- The process:
  - Initiation: the AUG codon gets read, translation starts
  - Elongation: the next tRNA enters and grows the chain of amino acids; the previous tRNA gets ejected and a new one flies in and repeats
  - Termination: there is no amino acid attached to the tRNA with anticondon matching the "stop" codon, so the translation stops there; tRNAs are ejected and the protein is detached

Summary

Transcription and Translation: Summary

1. Aleration in chromatin structure (DNA uncoils)
2. Initiation of transcription by positive transcription factors and enchancers attracting DNA polymerase
3. Transcript elongation: the RNA is built one base at a time
4. Termination of transcription
5. RNA processing: introns are removed, leaving only the exons
6. Nucleocytoplasmic transport: RNA is transported out of the nucleus
7. Translation: protein is built from amino acids by ribosomes using tRNAs and mRNAs
8. RNA degradation

Lecture 5, Jan 24, 2023

Mitochondria and ATP

- Mitochondria produce adenosine triphosphate (ATP)
  - A long chain of 3 phosphates attached to a ribose, which is attached to an adenine
- Mitochondria aren't static; they move around within the cell
- Within a mitochondrion:
  - Outer and inner membranes surround the cell
  - The intermembrane space is between them
  - Cristae stick out, increasing surface area

        * Bigger surface area produces more ATP
    - The matrix is inside the mitochondrion
- Glucose goes through glycolysis, producing pyruvate, then undergoes pyruvate decarboxylation, producing acetyl CoA, and undergoes a citric acid cycle and then oxidative phosphorylation, producing ATP at each step
    - Oxidative phosphorylation produces the most ATP (34 ATP vs 2 for most others)
    - Under ideal conditions we can get 38 ATP going through the entire cycle
    - In reality some processes take up ATP, and may be less than 100% efficient, so the real production is 30-32 ATP per glucose
- The production of ATP requires oxygen; without it the process stops at glycolysis, and instead of ATP you get lactic acid

The Cell Membrane

- Thin layer of molecules on the surface of the cell
- The membrane is made of phospholipid molecules
    - One side (head(is hydrophilic and one side is hydrophobic
    - Two lipid tails, one is unsaturated so it has a bend
- The membrane is composed of a bilayer of these molecules; the hydrophobic tails match each other, the hydrophilic head is on the outside and inside of the cell
- For a cell these form a giant sphere, surrounding all the organelles
- There are many structures embedded within the membrane:
    - Various proteins
    - Cholesterol molecules help the membrane be more flexible
    - Channel proteins allow stuff to pass through the membrane

Membrane Transport

- Unassisted membrane transport
    - Passive (simple) diffusion: with enough time molecules like gases naturally diffuse through the membrane, reaching an equilibrium concentration across both sides given enough time
        * Gases like oxygen, carbon dioxide etc can get across the membrane very easily
        * Water gets across less easily due to the polarization, but is still readily available (4 orders of magnitude lower compared to gases)
            - Water travels by osmosis
            - A hypertonic solution has more concentration of solutes outside the cell; isotonic has equal concentration; hypotonic has less concentration of solutes inside the cell
                - In a hypertonic solution, water comes out of the cell and the cell shrivels; in a hypotonic solution water goes in the cell and the cell may burst
        * Glucose is large and uncharged, but slightly polarized, so it does not go across (8 orders of magnitude lower compared to water)
        * Ions are charged, so they are repelled by the lipids and do not get across
        * ATP and amino acids are much bigger and usually charged and do not get across
- Assisted membrane transport
    - Channels or carriers facilitate the transport
        * Channel proteins are always open, allowing molecules in
            - There are specific channels for specific ions
        * Carrier proteins are first open, then captures the molecules, and then release them on the other side (these are slower)
            - Bigger molecules like glucose are transported by channel proteins
        * These are still passive processes based on concentration differences (no energy is needed)
    - By passive diffusion, the rate of transport is directly proportional to the concentration difference
        * With carrier-mediated transport, there is a maximum rate that after which increasing the concentration difference would not increase the transport rate anymore (limited by number of

carriers)
  - Sodium and potassium concentrations are important
    * On the order of a hundreds milli-moles per litre outside the cell and tens inside the cell for sodium, and the reverse for potassium
    * This concentration difference is achieved by sodium and potassium pumps that transport sodium ions outside the cell and potassium into the pump
    * These are sodium-potassium ATPase pumps; they require energy (ATP) since the concentration gradient is in the reverse direction
  - Primary active transport process:
    1. Cytoplasmic sodium ions bind to the pump
    2. ATP phosphorylates the pump, making it change shape
       * During this process, ATP changes to ADP and releases its energy
    3. The pump changes its shape to open to the outside, so the sodium gets out
    4. Potassium ions on the outside now stick to the cell, causing dephosporylation
    5. The pump returns to the original shape
    6. Potassium is released
  - Secondary active transport process:
    * The sodium and potassium concentration differences established by the primary active transport can now be used to bring certain molecules in and outside the cell
    * The sodium outside the cell pulls in molecules and ions; potassium inside the cell pushes them out
      - Importantly the sodium ions can drag glucose in via special carrier proteins

Lecture 6, Jan 26, 2023

Resting Membrane Potential

- Ions are constantly leaking in/out of the membrane through leak channels (aka background channels, open rectifier channels) as the potassium and sodium is pumped in/out of the cell
  - There are way more potassium channels than sodium or chloride channels
  - For sodium, we have 150mmol/L outside and 15mmol/L inside with a relative permeability of 1/50 to 1/75
  - For potassium, we have 5mmol/L outside and 150mmol/L inside with a relative permeability of 1
  - For chlorine we have 110mmol/L outside the cell and 20mmol/L inside with a relative permeability of about 1/2
  - Amino acids only exist inside the cell and has a relative permeability of 0
- Suppose we have a higher concentration of potassium inside the cell; the ions are going to leak out due to the concentration gradient, which creates an electric potential due to the charge being carried outside by the potassium; as the charge builds up, it becomes harder for the ions to leak out, eventually reaching an equilibrium potential
- The equilibrium potential is the point at which the ion exchange rate caused by a concentration gradient matches the rate caused by the attraction of the charges
  - For potassium this is -90mV, for sodium it's $+61$mV
  - The overall membrane potential is $V_m = -70$mV

Nernst Equation

- The equilibrium potential can be calculated by the Nernst equation
- $E_x = \dfrac{61}{Z_x} \log_{10} \dfrac{[C]_o}{[C]_i}$ for a single type of ion
  - E is the equilibrium potential in millivolts (difference between two sides of the cell) (x denotes the ion, e.g. E_{K^+} is the equilibrium potential of potassium)
    * The ground is outside the cell
  - Z is the valence of the ion

  - $[C]_o, [C]_i$ denote concentration outside and inside the cell
    * This concentration difference is controlled by the ATP pumps
  - The full version of the equation is $E_x = \dfrac{RT}{Z_x F} \ln \dfrac{[C]_o}{[C]_i}$
    * Converting this to give you volts and changing the base of the log gives the factor of 61
- Note the individual equilibrium potentials are not the same as the overall membrane potential V_m
- If we want to consider multiple types of ions, we need to use the Goldman-Hodgkin-Katz equation
  - The concentration of each type of ion on one side is multiplied by the selectivity P and summed
- We can visualize this with an electrochemical graph:
  1. Set up the graph, with concentration on the horizontal axis and electric potential on the vertical
  2. Write down the concentrations inside and outside the cell and look at how the concentration would move the ions; put this on the horizontal axis
  3. Consider the equilibrium potential and put it on the vertical axis
  4. Draw a line between the two points
  5. Follow this line for a specific potential value, project this onto the horizontal axis and look at which side of the axis it's on
- Note the equilibrium potential for a specific ion has nothing to do with permeability, but the resting membrane potential does
  - If permeability changed for an ion, its equilibrium potential would not change
  - The overall membrane potential shifts to reflect the change

Free Energy

- "Energy to do useful work"
- The concentration difference and electrical potential creates free energy
- $\Delta G_{\text{chem}} = RT \ln \dfrac{[C]_o}{[C]_i}$, $\Delta G_{\text{elec}} = ZFV_m$
- At equilibrium they are equal to each other
  - We can rearrange this to derive the Nernst equation
- $\Delta G = \Delta G_{\text{chem}} - \Delta G_{\text{elec}}$
  - If $\Delta G < 0$, the ion moves out of the cell
  - If $\Delta G > 0$, the ion moves into the cell

Lecture 7, Jan 31, 2023

Energy Needed for Active Transport

- About 40% of ATP generated by cells is purely dedicated to the sodium-potassium-ATPase pumps

Membrane Potential Continued

- *Depolarization* is when the resting membrane potential becomes less negative than normal (closer to zero), resulting in a positive change
  - After depolarization, the membrane undergoes *repolarization* to return to the normal potential in a negative change
- *Hyperpolarization* is when the resting membrane potential becomes more negative than normal, resulting in a negative change
- Depolarization/repolarization/hyperpolarization occurs due to gated ion channels; these are normally closed, but when ligands attach to them, they allow ions to flow through
  - The gated channels are all over the cell body
  - Ligands are also known as neurotransmitters
- These gated channels and ligands allow graded potentials to propagate
  - When a ligand attaches to a gated channel, sodium ions are able to come into the cell; due to the positive ions coming in, there is a little bit of depolarization around the channel

  - When the ligand is gone, positive ions on the outside of the cell move to fill the holes on the outside, and the sodium on the inside move to the negative potential
  - The result is that the depolarization spreads out in a gradient; the potential returns to normal about 1 mm away
- Voltage-gated ion channels respond to voltage differences
  - Sodium channels have 3 different states: closed but capable of opening, open (active, happens rapidly), or closed and not capable of opening for some time
  - Potassium channels are either closed or open (takes some time to close)
  - These are located on the axon hillock (the trunk), and not everywhere over the cell like ligand-gated channels
- If graded potentials transmit to the axon hillock, they will cause a small depolarization followed by a repolarization at the voltage-gated channels; more neurotransmitters cause a larger depolarization
  - If we have enough neurotransmitters to cause a depolarization above the *threshold*, all these voltage-gated ion channels open quickly
  - First the sodium channels open and cause rapid depolarization; then they close and the potassium channels open and cause rapid repolarization and a little hyperpolarization; then finally both channels are closed and everything returns to normal
  - The duration where the channels are inactive is called the *absolute refractory period*
    * This starts at where the potential crosses the threshold for the first time and ends where the potential is below the threshold again
    * In this period stimulation cannot occur
  - Once the potential is below the threshold again and until the potential returns to normal from hyperpolarization, this is called the *relative refractory period*
    * In this period it is difficult to stimulate the cell, but not impossible

Neuron Structure

- Dendrites are branch like structures coming out of the neuron
- The soma is where the nucleus lives
- The axon is the long cable part
- The axon branches out into terminal end bulbs
- The membrane is along the axon and there are voltage gated sodium and potassium channels along it
  - A signal would start at the axon hillock, and travel along the axon
  - A signal that travels one step at a time this is referred to as *contiguous*
  - *Saltatory* signals travel instead in big leaps – this is possible due to myelin sheaths in the neuron
    * The myelin sheaths wraps around the axon; there are bare spots where the axon is exposed (*nodes*), and in every other spot the axon is enclosed
    * The voltage gated sodium and potassium channel are at the nodes
    * Saltatory conduction travels from one node to another, which makes the signal travel much faster
- The factors that affect the speed of propagation are the degree to which myelin sheaths cover the axon, the axon diameter and the temperature

Lecture 8, Feb 2, 2023

The Synapse

- Two types:
  - Electrical synapse
    * Almost direct connection between two cells
    * Functionally in terms of depolarization it acts like one continuous cell
    * A small gap junction with connexons to allow ions to pass through
      - These could be closed or open

        - When one cell depolarizes, the ions can go through the channels and depolarize the other cell
    - Chemical synapse
        * Release of neurotransmitters/ligands that diffuse to another cell, attach to a receptor and depolarize another cell
- Before the synapse is the presynaptic neuron; after it is the postsynaptic neuron
    - The presynaptic neuron sends a signal which the postsynaptic neuron receives
- At the axon terminal (synaptic knob, looks like buttons), synaptic vesticles release neurotransmitters that diffuse through a synaptic cleft (gap) of 5-20 nm, resulting in a 0.5 ms delay
    - The receptors (ligand-gated ion channels) on the postsynaptic neuron receives this
- Different neurotransmitters exist:
    - Amino acids: Glutamate, GABA, glycine (these are smaller molecules)
    - Biogenic amines: norepinephrine (aka noradrenaline), epinephrine (aka adrenaline) (larger molecules)
    - Acetylcholine
    - Neuropeptides (opioids)
    - Oxytocin
    - Gases
- Steps of chemical synapse transmission:
    1. Neurotransmitters are synthesized and stored in vesticles
        - The axon carries these to the terminals
    2. An action potential arrives at the presynaptic terminal
    3. Voltage-gated Ca^{2+} channels open, allowing calcium ions to flow in
        - The calcium doesn't contribute to depolarization much
        - Ca is a secondary messenger; about 1.0mmol/L out of the cell and 0.001mmol/L in the cell; extremely low permeability
    4. Calcium ions enable exocytosis, allowing vesticle docking and neurotransmitter release
        - The calcium allow structures on the membrane to attach to the vesticle more strongly, which allows the membrane to be broken
    5. Neurotransmitters bind to receptors on the postsynaptic cell, allowing them to open or close
    6. Excitory or inhibitory postsynaptic potential is generated, which travels down the neuron
    7. To get rid of the neurotransmitters:
        - Recycled back into the presynaptic neuron through secondary active transport
        - Transported into glial cells, which destroys them
        - Diffuse away
        - Enzymes also actively degrade the neurotransmitter outside the cell
    8. Vesticles can also be recycled

Ligand-Gated Ion Channels Details

- Aka postsynaptic receptors
- Nonspecific cation channels:
    - NMDA channels: glutamate and glycine activate it, allowing ions (nonspecific) to go through
    - AMPA channels: two glutamate activate it, allowing sodium and potassium but not calcium transport
    - Ionotropic glutamate receptors
- When glutamate opens the channel, more sodium comes in than potassium leaks out, resulting in overall depolarization
    - Find out via graphical method
    - Much larger potential difference driving sodium than potassium
- There are specific ion channels, e.g. glycine or GABA attaching to a receptor that only lets in chloride
    - These are still ionotropic
- There are also non-ion channels
    - These are metabotropic receptors, protein structures in the membrane that can attach to neuro-

transmitters (mainly norepinephrine or epinephrine)
  - They don't directly allow ions to go through but go through a series of metabolic steps to open other channels
  - G-protein-coupled receptors (GPCR)
  - There is a long lasting effect (minutes to hours)

Neurotransmitter	Ionotropic receptor	Metabotropic receptor
Amino acids		
Glutamate	Yes	Yes (but less common)
GABA	Yes	Yes
Glycine	Yes	
Biogenic amines		
Norepinephrine		Yes
Epinephrine		Yes
Acetylcholine	Yes	Yes

Figure 3: List of neurotransmitters and activated receptors

Lecture 9, Feb 9, 2023

Activation of Postsynaptic Cell

- Presynaptic axon terminals are the synaptic inputs, which are near the cell body of the postsynaptic neuron
- EPSP: Excitatory PostSynaptic Potential
- IPSP: Inhibitory PostSynaptic Potential
- Glutamate is predominately excitatory; GABA is always inhibitory (but could change based on cellular concentration of ions); glycine is inhibitory
- Norepinephrine and epinephrine depends on the receptors
- Acetylcholine is always excitatory
- Two types of summation for activation:
  - *Temporal summation*: when stimuli are near each other in time, the depolarization caused by them would add on top of each other, and with enough of them the action potential would fire
    * One axon firing fast enough
  - *Spacial summation*: when multiple types of stimuli are present at the same time, the depolarization caused by them adds together
    * Two axons firing at the same time, with some distance in between
- *Inhibitory synapses*: when these fire, the membrane hyperpolarizes; this would cancel out any excitatory synapse signals
- *Presynaptic inhibition*: inhibitory synapses can attach to excitatory synapses (instead of to the postsynaptic neuron body); when these fire, they would inhibit the excitatory synapse from firing at all
  - Inhibitors only affect the synapse they attach to

Central Nervous System

- From the brain, the nerves travel down the spine and branch out
  - Cervical, thoracic, lumbar and sacral in order
  - On the face is the trigeminal nerves
  - Some nerves come directly out of the brain

- Tracts are neurons grouped in certain regions of the spinal cord
  - Ascending tracts are sensory pathways that start in the periphery regions (e.g. fingertips) that go to the brain
    * Different senses go to different regions of the brain (somatosensory homunculus); more space is allocated to more sensitive regions
  - Descending tracts are motor pathways that start in the brain and go down the spine to muscles
  - Note neurons are unidirectional
- Spinal cord structure:
  - Dorsal side is the back, ventral side is the front
  - Thicker neurons are typically motor neurons since signals travel faster
  - Mnemonic: SAME (Sensory - Afferent, Motor - Efferent), DAVE (Dorsal - Afferent, Ventral - Efferent)
  - Sensory/afferent neurons go through the dorsal side
  - A group of axons get bundled into *fascicles* to become a nerve (typically inside a fascicle, all the neurons are either all sensory or all motor)

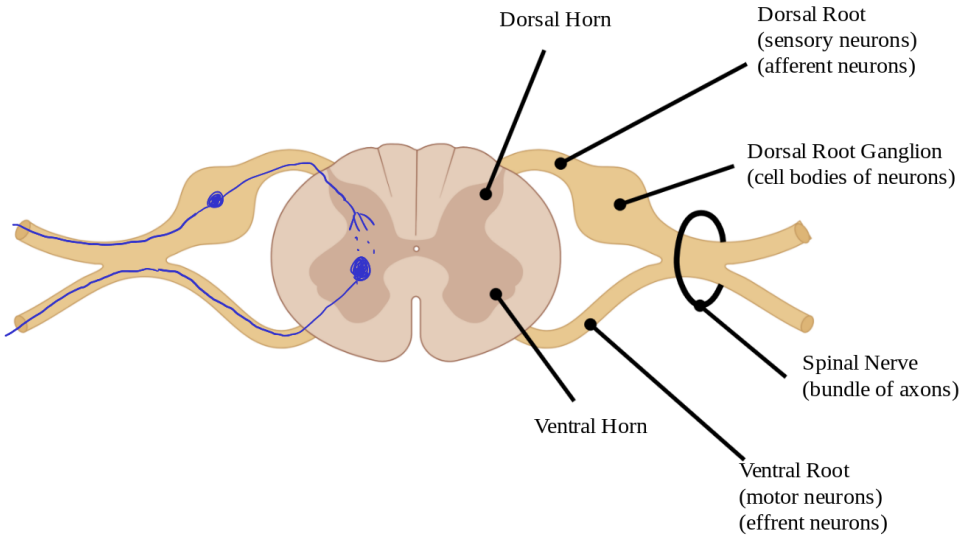

Figure 4: Spinal cord structure, with typical reflex arc in blue

Reflex Arcs

- Can be monosynaptic or polysynaptic
- Classical example of tapping the patellar tendon with a hammer
  - Cells measure how much the tendon is stretched, which gets sent to the spinal cord
  - Without needing to go into the brain, the synapse activity happens right at the spinal cord and goes back to a muscle group, causing movement of the leg
- A monosynaptic reflex only has one synapse, which has to go all the way to the spinal cord and back, so there is a delay
- A polysynaptic reflex (e.g. withdraw reflex) takes the same path, but excite multiple interneurons in the spinal cord that can excite and inhibit motor neurons for different parts of the body
  - e.g. exciting the biceps and inciting the triceps to withdraw your hand when you touch a hot object

Lecture 10, Feb 14, 2023

White and Grey Matter

- Grey matter is where the synapses are (inner region of the spinal cord)

- White matter are the tracks for messages to run through
  - Myelinated axons

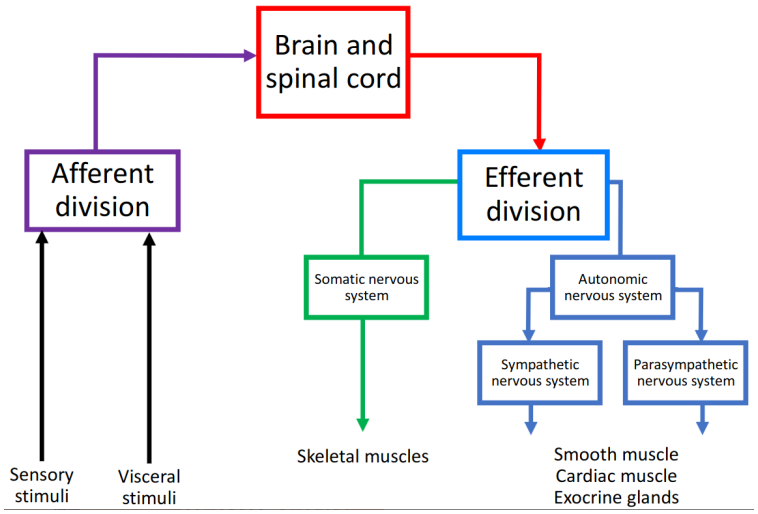

Figure 5: Strcture of the nervous system

Mechanically-Gated Ion Channels

- Also known as mechanoreceptors
- PIEZO channels open and let ions through when the membrane is being depressed through mechanical force
- These are non-selective cation channels, so more sodium is going to come in and depolarize the cell
  - This can then open the voltage gated ion channels and generate an action potential
- There are also other receptor cells, e.g. photoreceptor cells

Triggering Receptors

- MILD: modality, intensity, location, duration
- Modality
  - Mechanoreceptors:
    * Somatosensory: touch
    * Barorceptors: pressure
    * Proprioceptors: joint angles
    * Osmoreceptors: osmotic pressure between cells
  - Thermoreceptors: temperature
  - Nociceptors: pain
  - Photoreceptors: light
  - Chemoreceptors: smell
  - No sensor that detects "wet" directly
- Nerve endings can be free or encapsulated (e.g. in tissue layers)
- Sensory cells release neurotransmitters to activate a synapse
  - e.g. photoreceptors
  - These have cell bodies midway along the neuron
- For peripheral processes (e.g. olfactory receptor, stomach) the cell body is at the tip
- Intensity
  - Frequency coding: the higher the receptor potential, the greater the frequency of action potentials

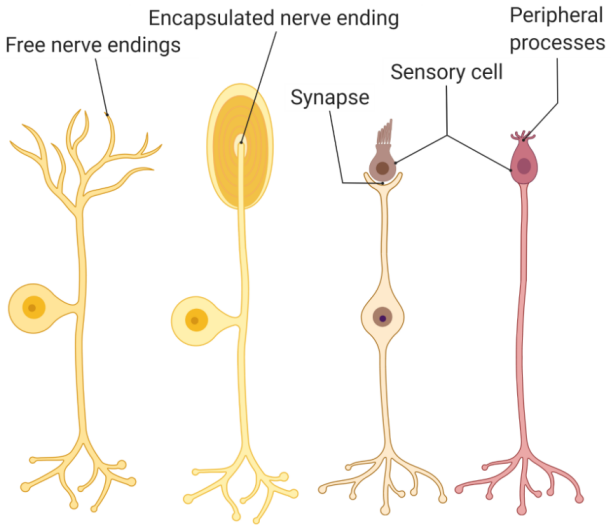

Figure 6: Sensory cells

  - Larger signals are generated when more receptors or neurons are activated (e.g. with more pressure, larger area of force)
- Location
  - Receptive field: in some places there are more receptors closer together
    * Smaller receptive field means greater acuity
  - Lateral inhibition: to figure out where exactly the stimulus comes from, the sensory neuron connects with interneurons with IPSPs and inhibits the neurons next to it
    * In places with more receptors, often multiple receptors are triggered by a single stimulus
    * Lateral inhibition reduces the signal coming from sensory neurons next to where the stimulus is the strongest, so the signal is sharper
    * Good lateral inhibition happens in places like touch on the skin
    * Poor lateral inhibition would be like cold or pain, which aren't often localized

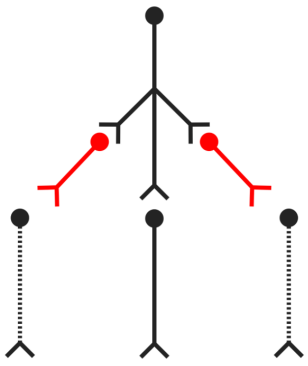

Figure 7: Lateral inhibition; red neurons pictured are IPSPs (inhibitory)

- Duration
  - *Phasic* receptors are rapidly adapting; *tonic* receptors are slowly adapting
  - Phasic receptors activate immediately to stimulus, then return back to normal; when the stimulus goes away there is also a small depolarization and repolarization
    * This gives action potentials immediately when the stimulus comes, and a few more when the stimulus is removed
    * If the stimulus is held down, there are no action potentials

    * Meissner's corpuscle detect things like grip; they are phasic receptors
    * Pacinian corpuscles are also phasic and have even more rapidly adapting action potentials
      - This is for perception of vibrations
  - Tonic receptors stay depolarized while the stimulus is held (might gradually repolarize); the receptor repolarizes when the stimulus is removed
    * Action potentials fire continuously while the stimulus is held
    * Ruffini endings are tonic; there may be background activity happening stochastically when there is no stimulus; when there is a stimulus it behaves tonically
      - This is for muscles and sensing where limbs are
    * Merkel's discs are also tonic (this one has no background activity)
      - This is for continuous touch and pressure
      - There are a lot of them so there is great resolution
  - Phasic receptors have an on-response and off-response; tonic receptors adapt slowly and have sustained action potentials

Lecture 11, Feb 16, 2023

Somatic Nervous System

- The somatic motor system consists of a somatic neuron exciting a muscle
  - The synapse between the neuron and the muscle is called a neuromuscular junction
    * Works on the same mechanism with calcium
    * Acetylcholine (ACh) is used as neurotransmitter
  - The neuron is myelinated

Autonomic Nervous System

- The autonomic motor system has a chain of two neurons
  - The cell body outside the CNS is the ganglion
  - The preganglionic neuron is myelinated, the postsynaptic neuron is not
  - The postganglionic fibre can go to gland cells, smooth muscles (surrounding organs and blood vessels) or cardiac muscles (heart)
- The autonomic nervous system is split into the *sympathetic* and *parasympathetic* nervous systems
  - These systems work against each other – sympathetic is the accelerator, parasympathetic is the brake
  - Almost every organ is controlled by both systems, but in different ways
  - Note there is always some tonic activity happening – it's not either on or off

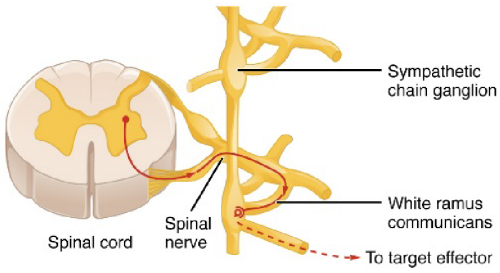

Figure 8: A central neuron synapses with a ganglion at the same level

- In the sympathetic nervous system:
  - The nerves come out of the thorax and lumbar regions (middle of the spine)
  - The preganglionic fibre is very short – the synapse is almost right outside the spinal cord and the postsynaptic fibre goes to the organ

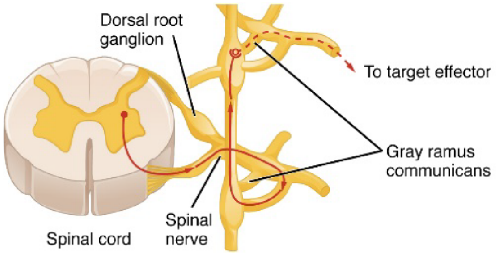

Figure 9: A central neuron synapses with a ganglion at a different level

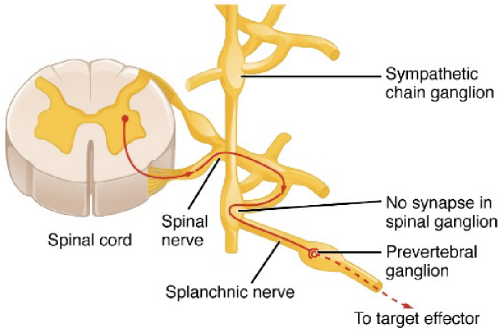

Figure 10: A central neuron that does not synapse within the chain ganglion

    * Near the spinal cord there are chain ganglia, which nerves can travel up and down and then go out
    * Some of them might have the synapse (collateral ganglion) past the chain (this is usually with abdominal muscles related to digestion)
  - The adrenal gland, sweat glands, and arterials (vasoconstriction, constriction of blood vessels) only have sympathetic nerves
- In the parasympathetic system:
  - Most nerves come out from the cranial nerves
  - The vagus nerve goes to all the organs
    * This has a very long preganglionic fibre and goes to a bunch of organs
  - At the very bottom of the spine there are a few more nerves
  - The postganglionic fibre is very short – the ganglion is almost on the organ
  - The cranial and sacral nerves only have parasympathetic nerves
- Sensory and somatic motor neurons are big and heavily myelinated, so they are the fastest; the preganglionic autonomic neurons are myelinated and the postganglionic ones are not, so the parasympathetic nervous system is faster, as it has a longer preganglionic nerve and shorter postganglionic nerve
  - Myelination takes up a lot of room, so there is a tradeoff

Cholinergic and Adrenergic Receptors

- The autonomic nervous system has a web of connections
  - Varicosities hold neurotransmitters, which are released when calcium triggers exocytosis
  - This is called a neuroeffector junction (NEJ)
- The sympathetic nervous system uses norepinephrine to signal the effector cells
  - Adrenergic receptors respond to NE and E, separated into alpha and beta receptors
    * Alpha receptors respond more to NE than to E
      - $\alpha 1$ excites, $\alpha 2$ inhibits (e.g. inhibiting digestive organs during a sympathetic response)
    * Beta receptors
      - $\beta 1$ excites (responds equally to NE and E), $\beta 2$ inhibits (responds more to E than NE)

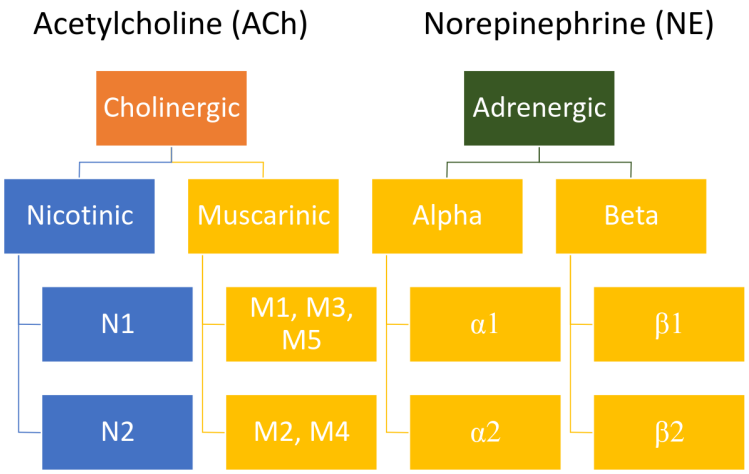

Figure 11: Types of receptors

  - Epinephrine is used indirectly
- The parasympathetic nervous system always uses acetylcholine (vagusstoff)
  - Cholinergic receptors respond to ACh, separated into nicotinic and muscarinic receptors
    * Nicotinic are ionotropic (fast-acting)
    * Muscarinic, alpha and beta adrenergic receptors are metabotropic (slow-acting)
  - Nicotinic receptors are all excitatory; there are N1 and N2 subtypes
    * N1 go at the neuromuscular junctions
    * N2 excite the dendrites on the postganglionic nerve fibres (these are faster, goes on the postganglionic fibres for both sympathetic and parasympathetic systems)
  - Muscarinic receptors have 5 subtypes; M1, M3, M5 excite, M2, M4 inhibit
- For both systems, the preganglionic fibres all release ACh, with nicotinic receptors on the postsynaptic neuron to respond quickly
  - In the parasympathetic system, ACh is released by the postsynaptic neurons and muscarinic receptors respond to them
  - In the sympathetic nervous system E and NE are released by the postsynaptic neurons, with adrenergic receptors responding to them
- The sympathetic nervous system actives chromaffin cells (via ACh) in the kidney which release mostly E (80%) and some NE (20%)
  - The NE goes into the blood stream and becomes a hormone to reach its target
- Sweat glands have cholinergic muscarinic receptors

Lecture 12, Mar 7, 2023

Skeletalmuscular System Structure

- Muscle surrounds bone like concrete surrounds rebar; muscle provides flexibility while bone provides stability
- 3 types of contractions:
  - Concentric: muscle contraction
  - Eccentric: muscle extension
  - Isometric: no movement, but still exerting a force

Skeletal Muscle Structure

- Sarcolemma: cell membrane of a muscle cell (aka muscle fibre)

- Muscle fibres are bound together into muscle fascicles, packed together with blood vessels and satellite cells (which help repair muscle cells)
- Each nerve will stimulate a collection of muscle fibres, which are all in the same motor unit
  - A bigger muscle has more fibres/fascicles in the motor unit
- Muscle cells are packed full of myofibrils, which do the actual contraction
  - Within myofibrils there are myofilaments, which can be thick (myosin) or thin (actin)
  - Myofilaments are attached together and overlap in some places
  - Within the myofibrils there are repeating patterns called sarcomeres
  - The thick (myosin) fibres have little extrusions called myosin ATPase
  - The Z-line is the zigzag pattern in the middle of the actin pattern
  - The M-line is in the middle of the sarcomere
  - The titin are where the myosin attach to which have a spring structure
  - I-bands are where the thin filament is, A-bands are where the thick filaments are
  - The H-zone is in the middle of the A-band and appears a little brighter
  - When the muscle contracts, the I band gets shorter; the A band doesn't change size; there is more overlap between the two filament types (the H zone also gets smaller)
- Skeletal muscles are striated, which has bands

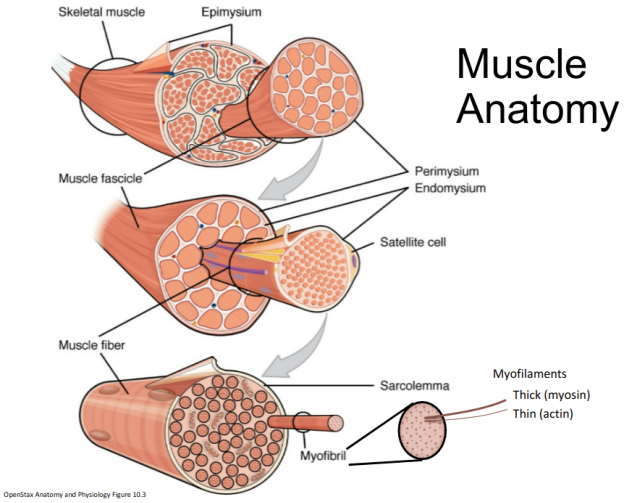

Figure 12: Skeletal muscle anatomy at a high level

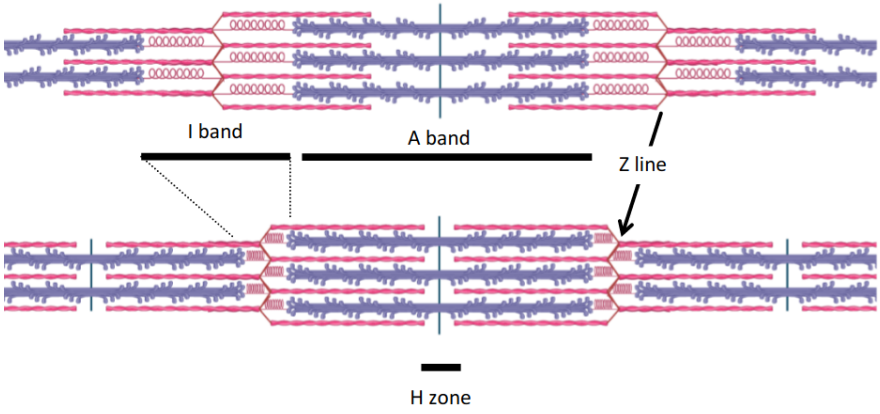

Figure 13: Process of muscle contraction; red filaments are actin (thin filaments), blue filaments are myosin (thick filaments)

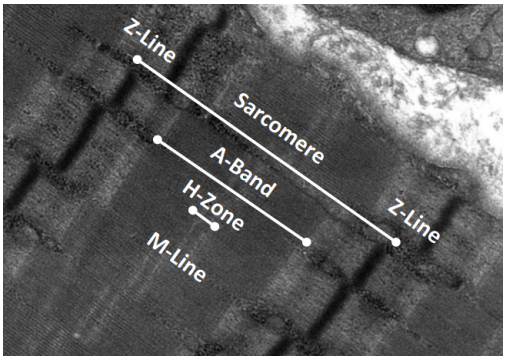

Figure 14: Skeletal fibre under a microscope

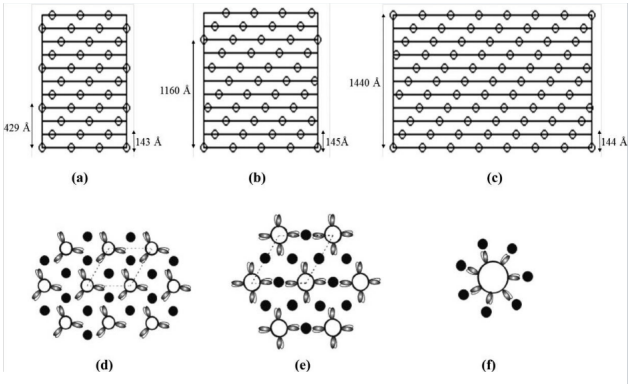

Figure 15: Cross sectional view of muscle fibres; the leftmost case is found in humans, the middle case in insect wings, and the right case is found in strong muscles such as the ones responsible for closing shells

Neuromuscular Junction

- Axon terminals attach to terminal buttons, which have wavy patterns that give them a high surface area and thus high sensitivity
- The process of a potential travelling through the junction is the same as any other synapse, except ACh is always used
  - 2 ACh binds to each receptor to open it
  - An end-plate potential is the sarcolemma depolarizing, an action potential in the muscle; this then spreads through the muscle fibre
  - After excitation ACh is removed by acetylcholinesterase (AChE)
    * AChE is an enzyme that lives on the membrane of the muscle cells (instead of just floating around)
- Since ACh is always used, these junctions are always excitatory, so if a signal were to be inhibited, we need an inhibitory interneuron higher up in the chain
- Some toxins that can mess with these junctions:
  - Black widow spider venom causes explosive release of ACh
  - Botulism toxin blocks release of ACh so muscles cannot move
  - Curare (reversibly) binds to ACh receptors and blocks ACh from attaching

Excitation-Contraction Coupling

- Transverse-tubules (T-tubules) allow the action potentials to quickly travel from the sarcolemma to the myofibrils, so that when the membrane is depolarized, almost all the myofibrils get depolarized simultaneously to get coordinated action
  - These dive deep into the cell, with reservoirs (sarcoplasmic reticulum, SR) of calcium for excitation
    * The calcium can't just be floating around because too much of it signals a cell to self-destruct
  - The combination of the T-tubules and SR on each side form a triad
- Process of excitation:
  1. ACh release at the NMJ from a neuron
  2. Action potential along the surface of the sarcolemma, travels along the T-tubules
  3. Action potential in the T-tubules causes the sarcoplasmic reticulum to release calcium
  4. Calcium ions unlocks the actin (thin) filaments (kind of like opening a latch)
     - Once the filaments are unlocked, binding can occur
  5. Binding between myosin and actin leads to contraction
     - The myosin heads create the cross-bridge to the actin filaments
     - The troponin-tropomyosin structure is the latch that opens and allows binding

Lecture 13, Mar 9, 2023

Cross-Bridge Cycle

1. Binding
   - Calcium from the SR (released when muscles are excited via ACh) allows the attachment of myosin heads to binding sites on the actin
   - This forms cross-bridges that attach the myosin to the actin
   - Without calcium binding cannot start
   - ATP is used to push calcium back into the reservoirs using SERCA pumps
2. Bending
   - Once the binding happens, the head of the myosin rotates
   - Each head is about 5 piconewtons of force
   - ADP is used here to power this
3. Detachment
   - ATP attaches to the myosin head, which breaks the cross-bridge
   - Without ATP, the myosin heads are stuck and cannot be detached, so no further muscle movement

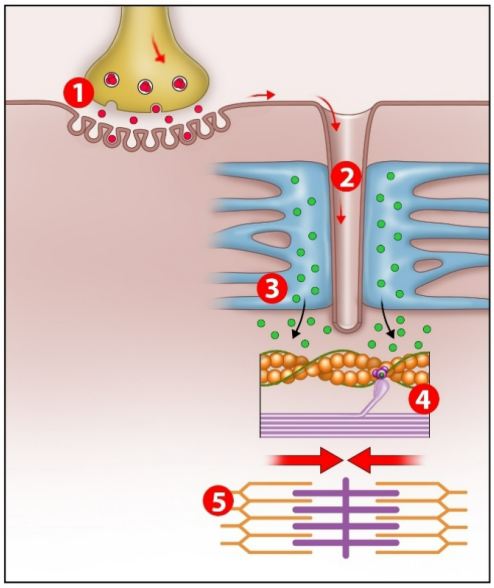

Figure 16: Process of excitation

can occur
- This is the reason for rigor mortis – without ATP muscles are stuck

4. Energization
   - As soon as ATP is attached, it becomes ADP, and the head becomes energized
   - If there's more calcium available, the cycle repeats again

What Affects Tension of a Single Fibre?

1. Action potential frequency
   - Each action potential causes a muscle twitch
   - For a single action potential, after a few ms to allow the calcium being pumped, tension increases during the contraction phase; then tension decreases during the relaxation phase
     - The latent period is the time between the stimulation and contraction
     - Contraction and relaxation time together is about 100 ms
   - Multiple action potentials cause twitch summations like spatial summations of action potentials
   - As the frequency of action potentials increase, the tension increases up to an upper limit (*tetanus*) and the muscle stays contracted instead of twitching
     - This happens at around 60 Hz for some muscles
2. Fibre length
   - Muscles can be much longer or shorter than resting length
   - At resting muscle length, there is optimal overlap, when the most tension could be produced; if the muscle gets longer or shorter the force decreases
     - At 70% (contracted muscle) there is more overlap, and force drops sharply
     - At 130% (stretched muscle) there is less overlap, force also drops but less sharply
   - Between 70% and 130% is usually what happens within the body; under experimental conditions it's possible to stretch the muscle so much that there is no more binding so no tension can be produced
   - There is also some passive tension produced by the muscle as it gets stretched, like a spring
     - The passive tension is added onto the active tension
3. Fibre diameter
   - If each myofibril gets bigger, it can develop more tension (fibre hypertrophy)
   - If more myofibril gets packed into a single fibre, it can also develop more tension (fibre split-

ting/hyperplasia)
  - Bigger filaments will exert more tension on z-disc connections when fibres contract, which can cause it to snap
  - When z-discs snap, they become separate myofibrils which is how hyperplasia happens
4. Fatigue
   - Different types of fibre types have their tension fall off in different ways
     - Slow-oxidative fibres have nearly constant tension, up to an hour
     - Fast-oxidative glycolytic fibres exert good tension up to 10 minutes but decrease after that; after an hour they exert nearly no tension
     - Fast-glycolytic fibres get fatigued much faster, with tension dropping rapidly at around 2 seconds
       * e.g. chicken breast because chickens can fly for a very short duration
5. Fibre Type

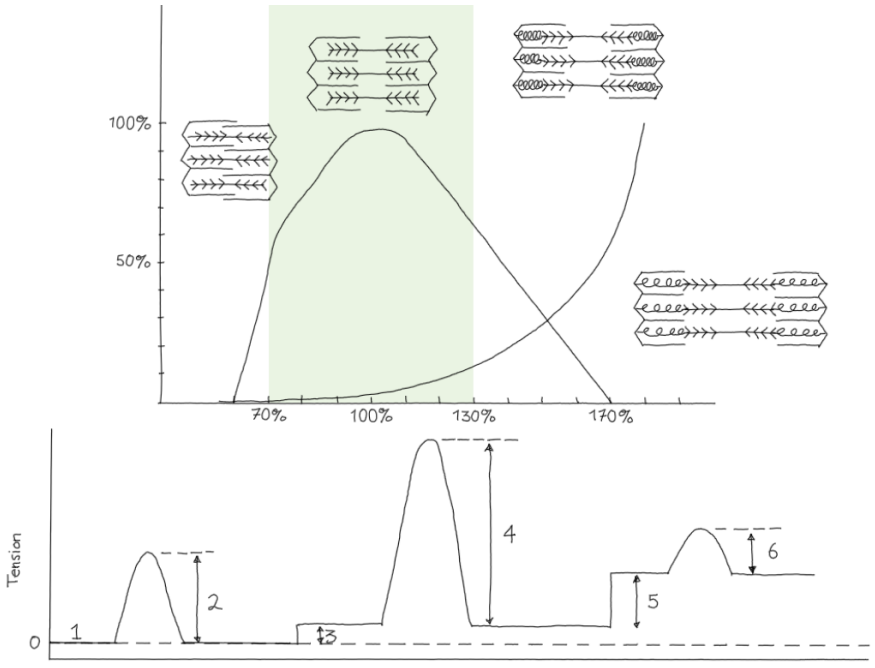

Figure 17: Combination of the effects of active (stimulated) and passive tension

What Affects Tension of Multiple Fibres?

1. Number of fibres per motor unit
   - Motor units are stimulated together by nerves
   - More fibres in a single motor unit means more power
   - Motor units can consist of multiple muscle cells in a single fascicle, but they don't have to consist of the whole fascicle
     - This can account for fatigue as different motor units are switched around
   - Different types of fibres can be stimulated to produce tension that is a sum of the different types
2. Number of active motor units
   - Different neurons excite different motor units
   - More neurons stimulate more motor units which creates more power
   - All these motor units would be within the same fascicle

	Slow-Oxidative Fibers (Type 1)	Fast-Oxidative-Glycolytic Fibers (Type 2A)	Fast-Glycolytic Fibers (Type 2X)
Fiber diameter	Small	Largest	Large
Rate of fatigue	Slow	Intermediate	Fast
Size of motor neuron innervating fiber	Small	Intermediate	Large

Figure 18: Comparison of fibre types

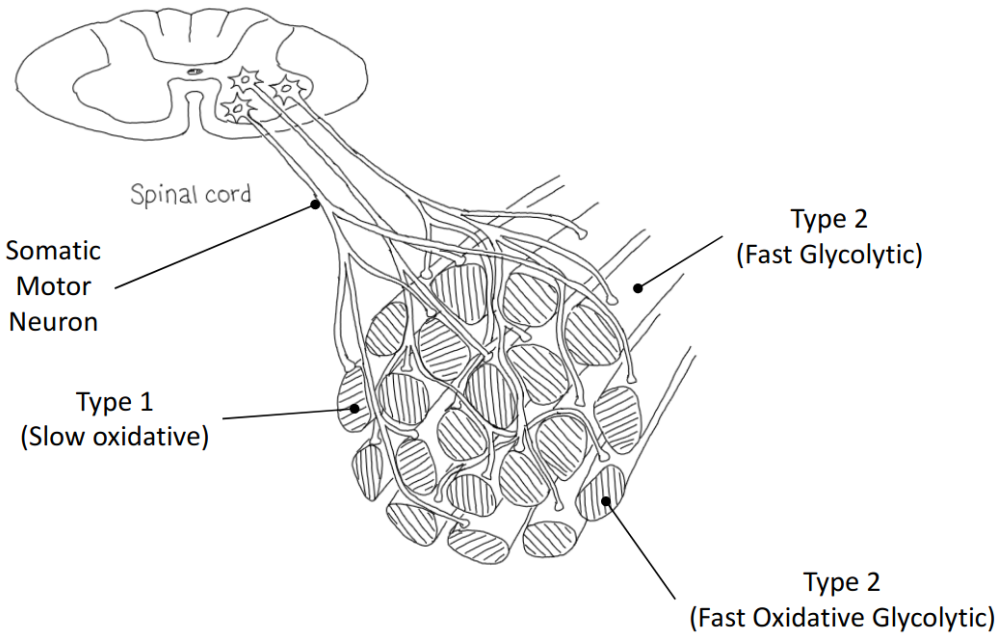

Figure 19: Structure of somatic neurons to muscle fibres

Lecture 14, Mar 14, 2023

Cardiac Muscle

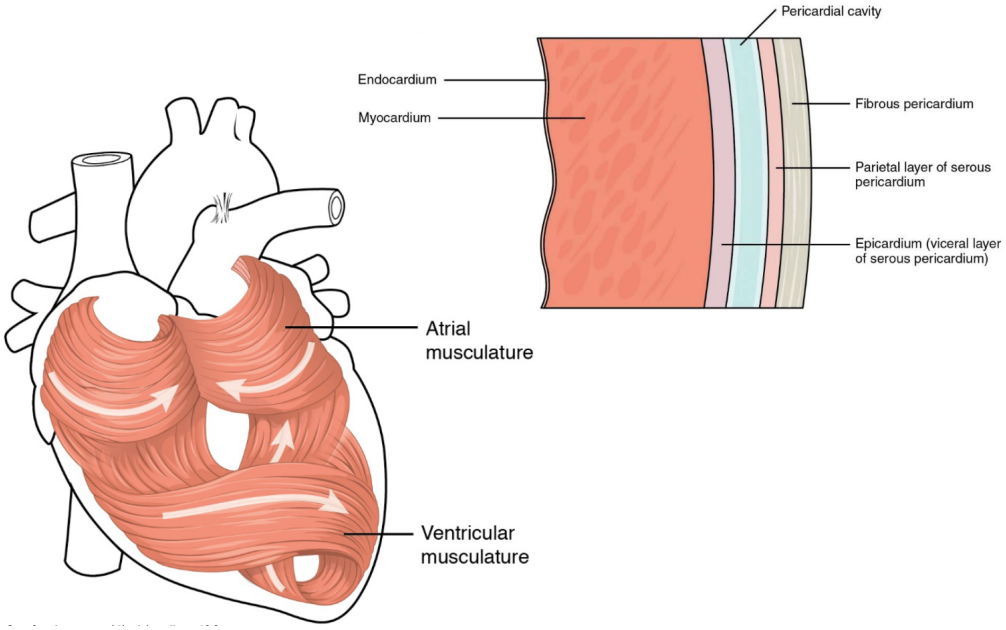

Figure 20: Arrangement of cardiac muscle in the heart

- Controlled by the autonomic nervous system
  - Both types are striated muscles, but the heart is involuntarily controlled
- Cardiac muscles are myogenic (they initiate themselves, without the need of a signal from the nervous system)
  - The nervous system just modifies the contraction strength and speed
- Unlike skeletal muscles the length of fibre controls the strength and the calcium concentration
- Hormones also modify the effect of cardiac muscle
- The SR isn't as developed, so the ECF is playing a larger role in bringing calcium in
- Gap junctions exist, unlikely in skeletal muscle
  - Gap junctions in an electrical synapse let ions pass from one cell to another if they are open
  - Once an action potential is started, it spreads through the whole heart
- While skeletal muscles are linear, cardiac muscle has branches; they are connected by desmosomes and gap junctions
- Cardiac muscle cells only have a single nucleus while a skeletal muscle cell can have multiple nuclei
- RMP is about -80 mV
- There are 2 sub-types of voltage gated calcium channels: L-type (long-lasting) and T-type (transient)
  - Different areas of the heart have different types of channels, to allow for different patterns of action potential

Types of Action Potentials

- Ventricular myocyte action potential (main muscle in the heart)
  0. Membrane depolarization
     - This happens very fast
  1. Rapid, transitory repolarization
     - Potassium channels open, but only a small number of them open for a short period of time
  2. Plateau phase
     - Other potassium channels open

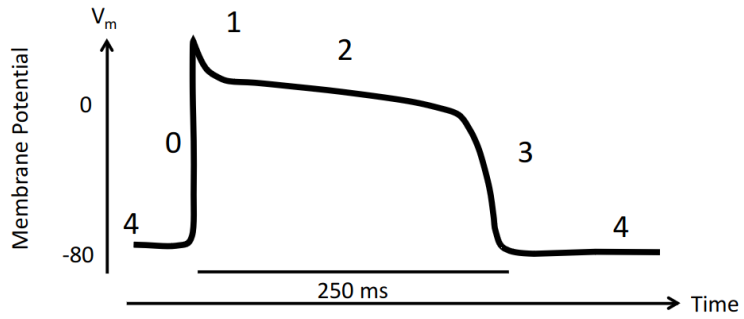

Figure 21: Shape of ventricular myocyte action potential

  - Calcium channels also open
  - Since these act against each other, this makes the membrane potential change slowly
  - The length of this phase can be altered by hormones
  - Functionally this causes a very long refractory period, which matches the contractile response of the heart; this way we won't get a tetanic response (because that does not pump blood)
3. Repolarization
  - More potassium channels open, overwhelming the calcium channels, which are now closing
4. Electrical diastolic phase
  - Kind of like a resting membrane potential (for this type of action potential)
  - Heart relaxes in this phase

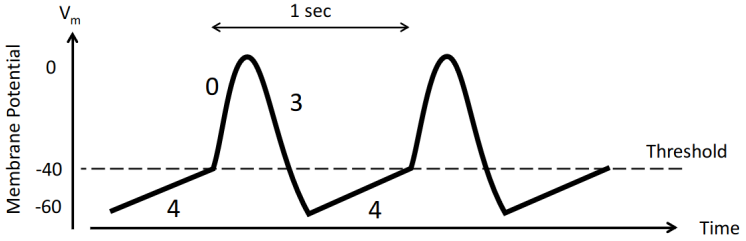

Figure 22: Shape of the nodal cell action potential

- Nodal cell (aka pacemaker) potential (autorhythmic cells that drive the heartbeat; these start the action potential that spreads through the heart)
  0. Membrane depolarization
    - This is only caused by calcium, not sodium
    - The slope isn't as steep due to this reason
    - In this phase, it's the L-type (long-lasting) calcium channels that depolarize the membrane
  1. Repolarization
    - Potassium leaks out of the cell
    - Highest permeability occurs right at the peak of the potential, and then decreases to allow for repolarization
  2. Minimum diastolic potential
    - There is no more resting potential; the cell membrane potential is always changing
    - The membrane potential hits a minimum, then slowly depolarizes until it hits a threshold, at which point it repeats the cycle
    - Sodium channels open in this phase, which is what leads to the gradual depolarization
      * This is unlike normal cells in which the sodium channels only open when the membrane is depolarized, not hyperpolarized
    - As the potential gets close to the threshold, T-type (transient) calcium channels open to provide a final boost to get to the threshold potential

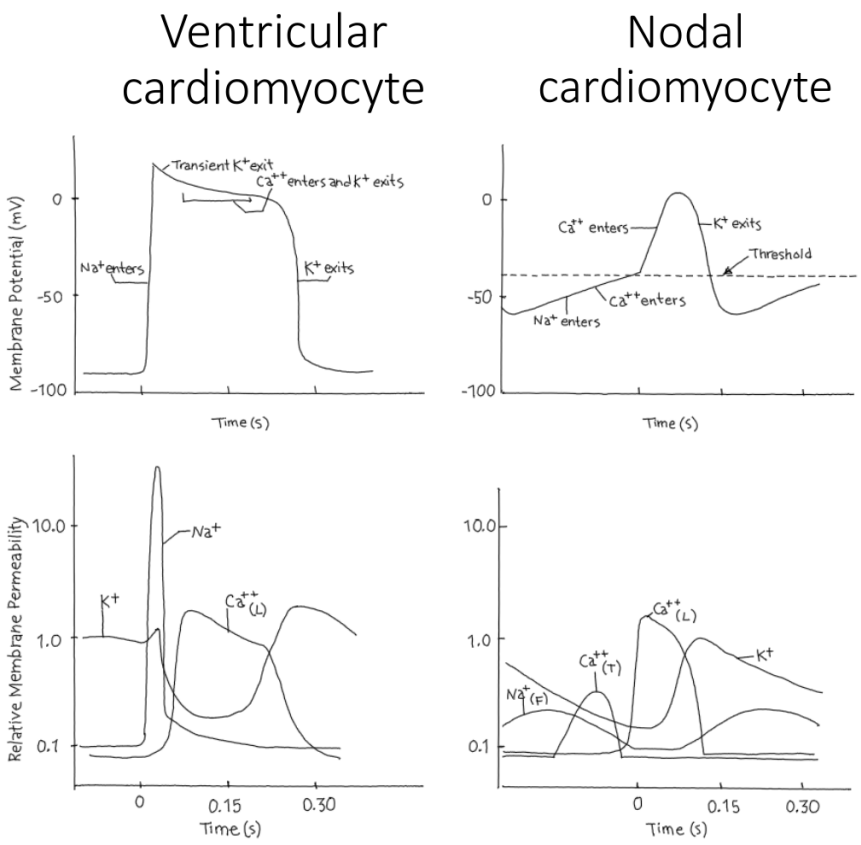

Figure 23: Comparison of the two types of action potentials and the ion permeabilities causing them

- Skeletal muscle cells are made of only 12-15% mitochondria; cardiac muscles are about 35% mitochondria

Lecture 15, Mar 16, 2023

Electrocardiogram (ECG)

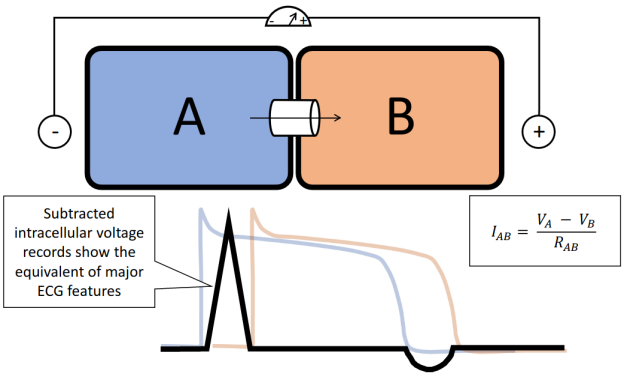

Figure 24: Subtraction of action potentials

- Consider 2 cells attached with a gap junction; what if we measure the potential of the entire unit?
  - Since the action potential has to go through the 2 cells, the second cell's action potential is delayed
  - An electrode outside the cells shows the voltage difference on the two sides
- First the sinoatrial node fires, then the atrial muscle depolarizes; the atrioventricular node depolarizes and then spreads the action potential to the other heart tissue

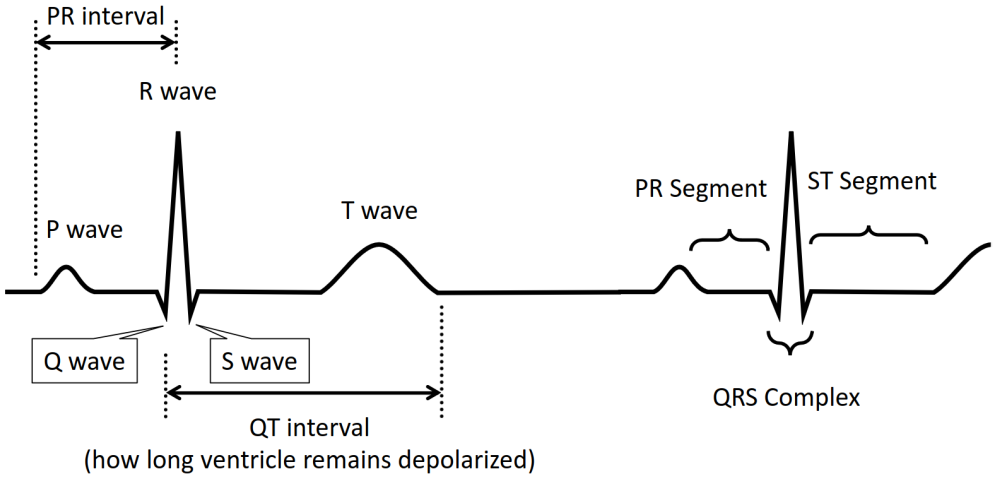

Figure 25: Structure of an ECG wave

- The P wave is caused by the atrial action potential; because there isn't as much atrial muscle mass, the P wave is small
- After a short delay the ventricular action potential fires, and since there is more ventricular muscle, it creates a large spike (the R wave)
  - Since ventricular muscles are synchronized this is a very sharp peak
- Cardiac muscles conduct much slower than neurons and skeletal muscles and have a large range of speeds

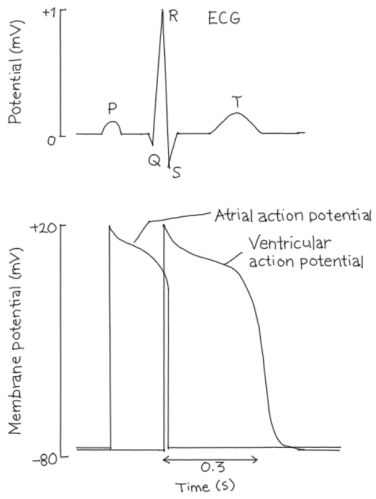

Figure 26: ECG wave forming as a result of depolarization of different parts of the heart

Cell	Velocity (m/s)
Neuron: Large and myelinated	100
Muscle: Skeletal	3 – 5
Muscle: Cardiac	0.05 - 4
Muscle: Smooth	0.015 – 0.15

Figure 27: Comparison of conduction velocity

Sequence of Depolarization/Repolarization

- Depolarization sequence:
  1. The sinoatrial node depolarizes
     - The SA node has a very slow conduction velocity (0.05 m/s), since only calcium is used to depolarize
  2. The depolarization spreads through atrial pathways (1 m/s)
  3. The action potential reaches the atrialventricular node
     - This also spreads very slowly (0.05 m/s)
     - Passing through this node is the only way to depolarize the ventricular muscles
  4. Action potential goes through bundle of his (muscle in the middle of the cell) (1 m/s)
  5. Purkinje system (septum, the muscle separating the 2 sides of the heart, is depolarized) (4 m/s)
  6. The bulk of the ventricular muscles are depolarized (anteroseptal region, near the side of the chest) (1 m/s)
     - This goes down and spreads back up
  7. The posterior portion of the base of the left ventricle is depolarized
- Repolarization sequence starts with the ventricular muscles, starting at the epicardial side (i.e. outside in, opposite to the direction of depolarization)

ECG Waveform

- Positive electrode below the heart, negative electrode above the heart defines the direction
  - The depolarization moves from the negative electrode to the positive electrode
- Sequence of the waveform:
  1. The atrial muscle depolarizes, creating the small P wave
  2. After a short delay through the atrialventricular node
  3. The septum is depolarizes from left to right, which is away from the positive electrode, creating the negative deflection of the Q node
  4. The ventricular muscles all depolarize towards the positive electrode, causing the large R wave
  5. The depolarization goes through the rest of the ventricular muscles, moving away from the positive electrode and causing the S node
  6. After a delay, the ventricular muscles repolarize, moving away from the positive electrode and creating the T wave; this isn't as coordinated, so the T wave is spread out
- Disturbances during the T wave could lead to ventricular fibrillation
  - Depolarization during the 20 ms upstroke of the T wave causes an action potential going in the wrong direction, messing up the heart rhythm
  - This could happen due to being hit by a ball, fist, etc

Cardiac Cycle

- Ventricular diastole happens in 2 phases, first a passive filling and then an active atrial ejection
  - This is where the P wave happens
- At the end of diastole the mitral valve (valve between the left atrium and left ventricle) closes
  - This happens because the ventricle starts to squeeze (mitral valves are one way and are not muscles)
  - The start of this phase is the isovolumic ventricular contraction phase, when the contraction is enough to close the mitral valve but not enough to open the atrial valve
  - The contraction leads to a build up in pressure
- The pressure becomes enough that the aortic valve opens, leading to ventricular ejection
- At the end, the aortic valve closes as the muscles relax; the mitral valve opens after this
  - This is the isovolumic ventricular relaxation phase
- The mitral and aortic valves closing create audible sounds
- Where the left ventricular pressure exceeds the left atrial pressure, the mitral valves close; then after the left ventricular pressure comes back down, the mitral vales open as the pressure flips

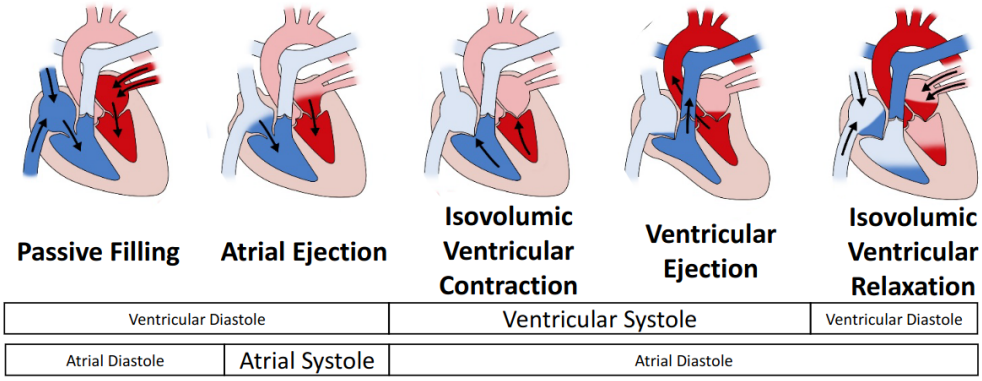

Figure 28: The cardiac cycle

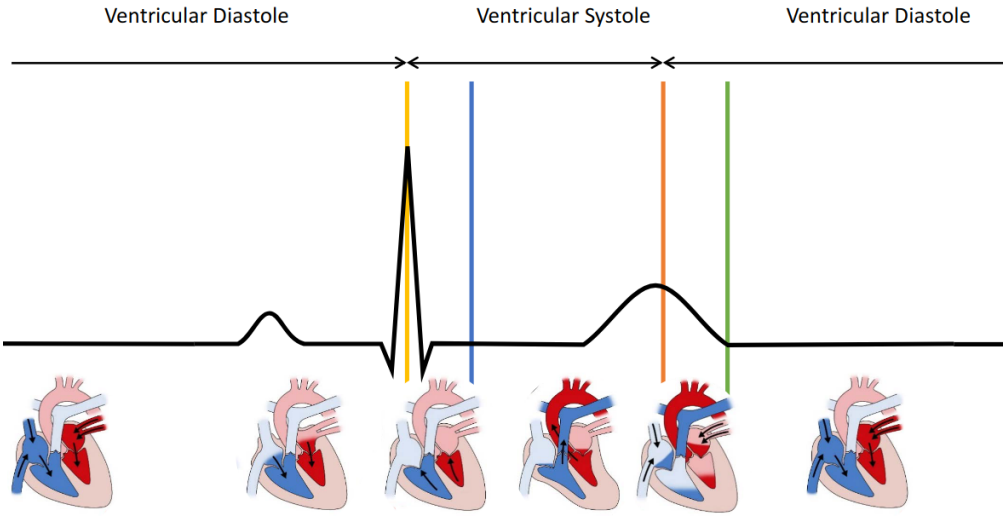

Figure 29: Mapping cardiac cycle events to the ECG waveform

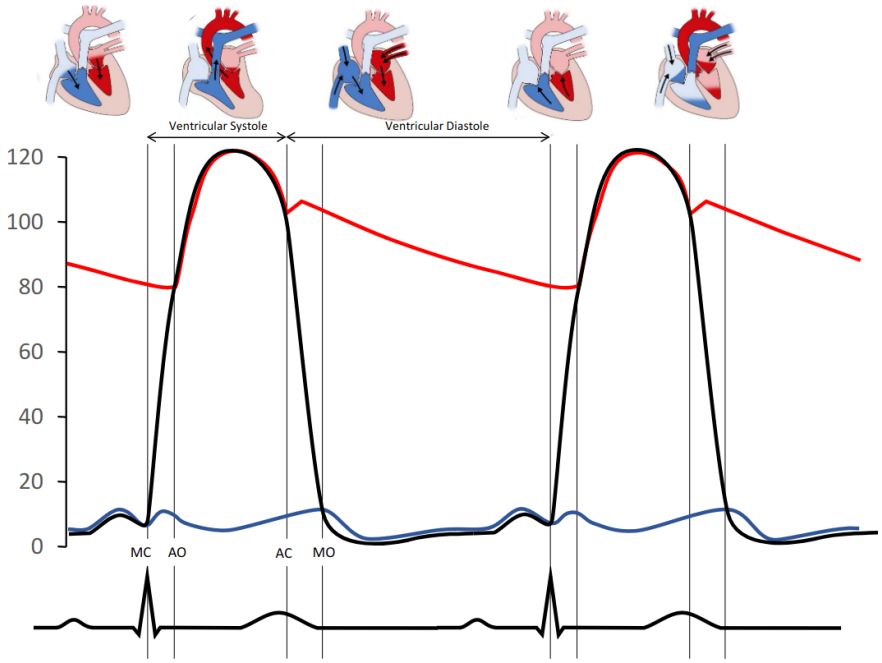

Figure 30: Blood pressure variations in the heart; blue shows the left atrial pressure, black shows the left ventricular pressure, red shows the pressure in the arteries

  - This is why blood pressure has a high value and a low value

Lecture 16, Mar 21, 2023

Volume Changes in the Cardiac Cycle

- Changes in left ventricular volume during the cardiac cycle:
  - During the isovolumic contraction and relaxation, the volume stays constant (the two plateaus in the figure)
  - After the isovolumic contraction, the volume in the left ventricle decreases as blood is pumped out to the arteries
  - Then after isovolumic relaxation, the ventricle begins to fill passively, resulting in a gradual filling
  - At the end of the passive filling, the atrial contraction gives another boost to the LV volume, pushing it to the EDV
- During a normal, slow heart rate, the contribution to ventricular volume due to the atrial contraction is not as noticeable; however with faster heart rates, the ventricle has less time to fill, so the filling caused by atrial contraction becomes a lot more important
- The *end-diastolic volume* is the volume in the ventricle after it fills (diastole), or at the beginning of the isovolumic ventricular contraction
  - This is about 135 mL
- The *end-systolic volume* is the volume still left in the ventricle after it pushes the blood out (systole), or at the beginning of isovolumic ventricular relaxation
  - This is about 65 mL
- *Stroke volume* is the amount of blood pumped by the heart every beat; it is the difference between the EDV and ESV
  - This is typically about 135 mL - 65 mL = 70 mL
- *Cardiac output* is defined as the product of stroke volume multiplied by heart rate, in units of litres per minute

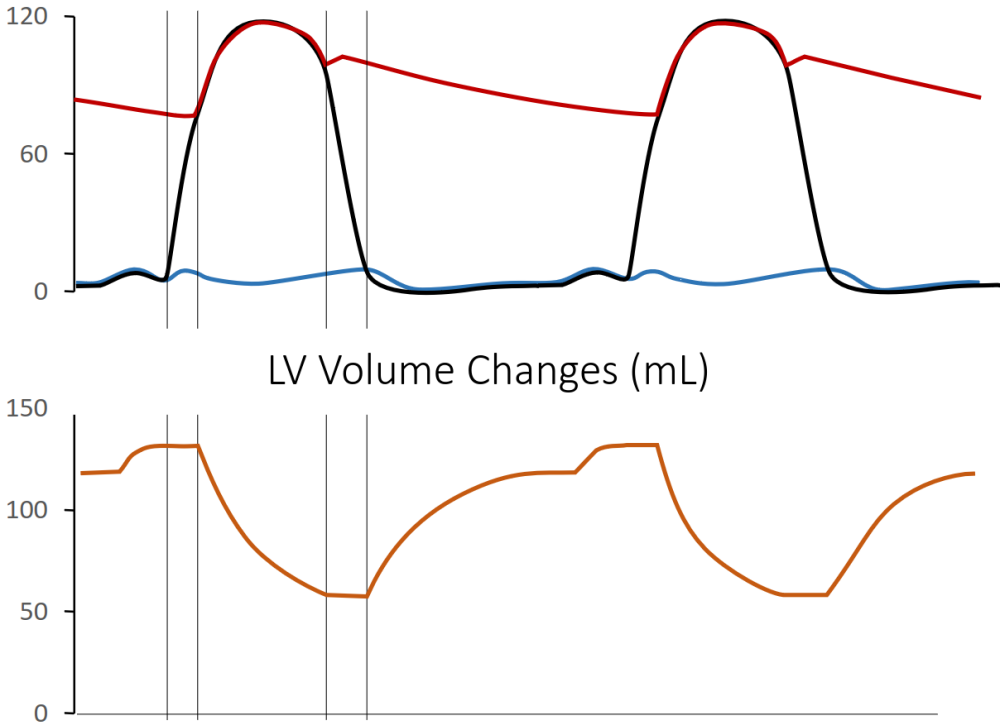

Figure 31: Changes in the left ventricular volume throughout the cardiac cycle

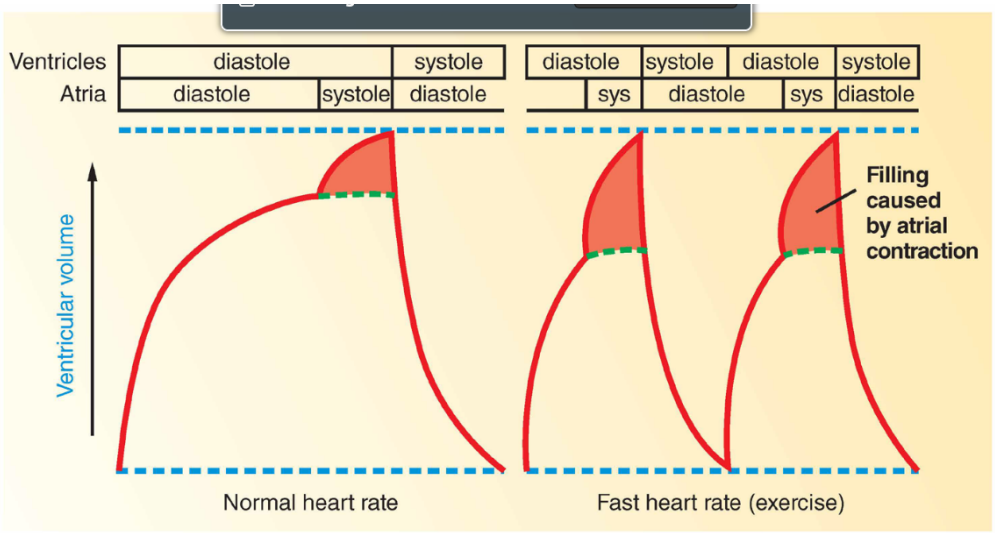

Figure 32: Effect of heart rate on left ventricular volume

- e.g. with a 70 bpm heartbeat and 70 mL stroke volume, the output is about 5 L/min

Modifying the Heart Rate

- Heart rate is directly proportional to cardiac output; this can be modified through the behaviour of the sinoatrial nodal myocyte (pacemaker):
  1. Rate of depolarization (funny current)
     - With faster rate of depolarization, after a beat, the membrane potential takes less time to reach the threshold
  2. Shift in minimum diastolic potential
     - Increasing the minimum diastolic potential means after the heart beat, the potential doesn't go as negative, which also makes it easier to reach the threshold
  3. Shift in threshold
     - Lowering the threshold (making it more negative) also makes it faster to reach the threshold and start a beat

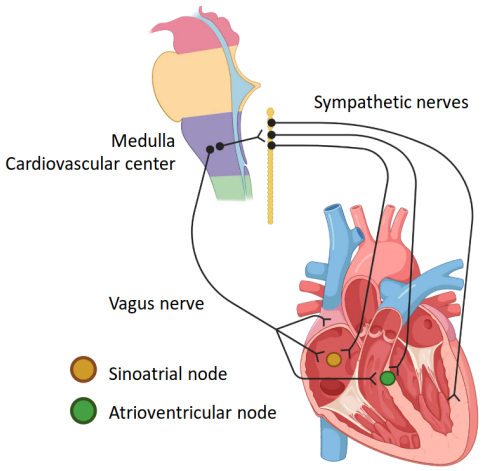

Figure 33: Autonomic effects on the heart

- The heart rate is controlled extrinsically (i.e. autonomically)
  - Signals originate from the cardiovascular centre in the medulla
- The vagus nerve (parasympathetic nervous system) comes out from the medulla, and only targets the atrial muscles, sinoatrial node and atrioventricular node
  - SA nodal cells have M2 receptors, which inhibits target cells
  - The effect of this would be to hyperpolarize the minimum diastolic potential or to reduce the depolarization rate of the SA node, both reducing the heart rate
    - The receptors enhance K+ permeability of the SA node; this hyperpolarizes the minimum diastolic potential, and also opposes the funny current that depolarizes after a beat
- Sympathetic nerves also go to the sinoatrial node, atrioventricular node and also ventricular muscles
  - Sympathetic stimulation increases permeability to calcium, which increases the conduction velocity of the AV node and Purkinje fibres (because only calcium is used for depolarization in cardiac muscle cells)
  - SA nodal cells have $\beta 1$ adrenergic receptors, which excite target cells
    - Increased calcium permeability makes the funny current stronger, making depolarization faster and reducing the time between heart beats
    - The increased calcium currents also make calcium channels more active, thereby reducing the threshold and decreasing the time between heart beats
- The two PNS and SNS are always effecting the heart; they're not on/off, but rather more/less
  - *Autonomic tone* is the balance between the influences from the two systems

– The intrinsic heart rate (completely unaffected by both systems) would be 100 to 110 bpm

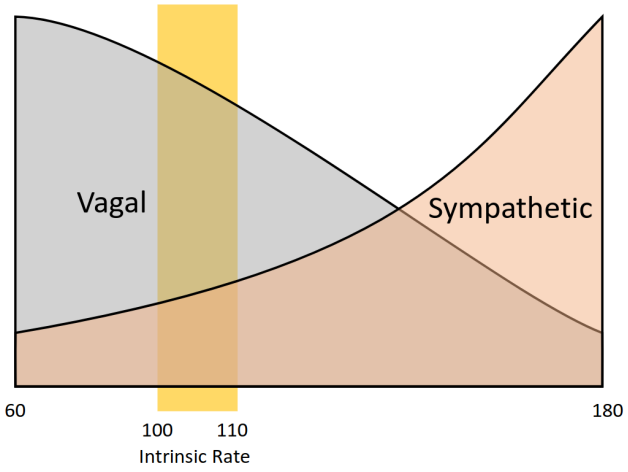

Figure 34: Balance of vagal (parasympathetic) and sympathetic tones

Extrinsic Control of Stroke Volume

- Only the sympathetic nervous system controls the stroke volume (since only the sympathetic nerves innervate the ventricular muscles)
- Enhanced calcium currents caused by sympathetic stimulation cause stronger contractions
- The end-diastolic volume stays the same, but the stronger contractions reduce the end-systolic volume, so more blood is pushed out every beat
  - This is called a positive ionotropic effect
- e.g. the ESV can be reduced from 65 mL to 35 mL, which would increase SV from 70 mL to 100 mL

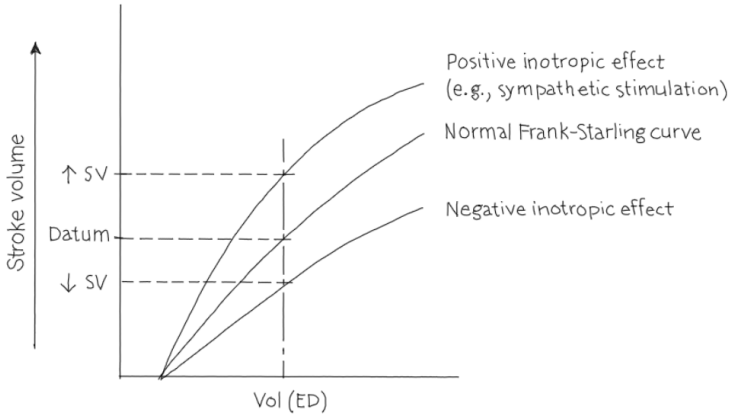

Figure 35: Effect of sympathetic simulation on stroke volume

- Putting it all together, PNS decreases the heart rate, SNS increases both the heart rate and stroke volume; both heart rate and stroke volume combine to produce cardiac output
  - Note if the heart rate becomes too fast (120+ bpm), the stroke volume begins to fall off as the heart doesn't have enough time to fill

Lecture 17, Mar 23, 2023

Smooth Muscle

- Smooth muscle is usually found in organs that aren't "solid"
- Found in STOVE:
  - Skin (the muscles that make your hair stand up)
  - Tracts (e.g. gastrointestinal, respiratory, reproductive)
  - hollow Organs (e.g. bladder, uterus)
  - Vessels (e.g. aorta, arterioles, but not capillaries)
  - Eye (controlling iris)

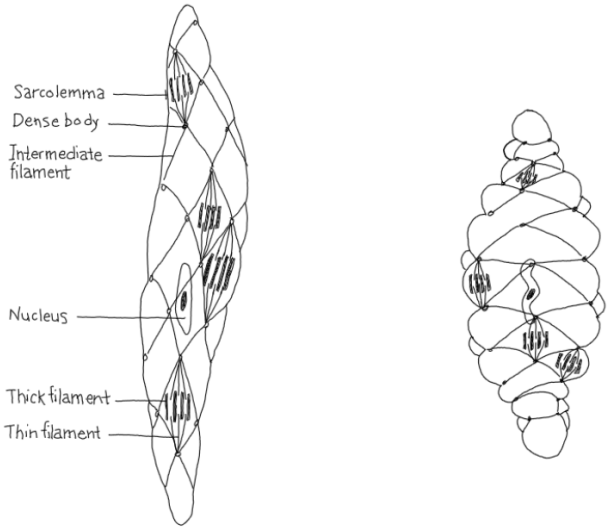

Figure 36: Structure of smooth muscle

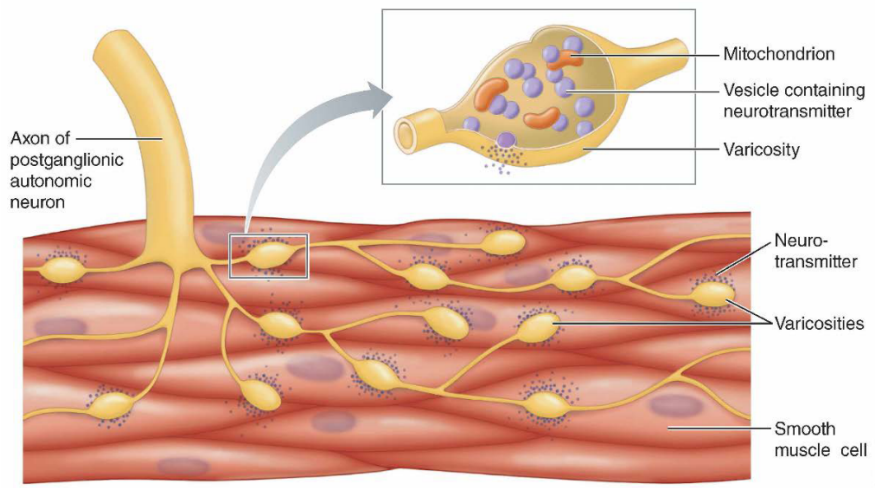

Figure 37: Innervation of smooth muscle

- Smooth muscle have a net-like structure connected by dense bodies; between all dense bodies are the thick and thin filaments (actin, myosin)
  - When smooth muscle contracts, the "net" squishes
- Smooth muscle is more flexible; generally very slow but efficient, and fatigues slowly

- Smooth muscles are innervated by the SNS and PNS; instead of a terminal junction, there are a network of varicosities
- Autonomic stimulation (neurotransmitters) change the availability of calcium ions in the cytosol of smooth muscle cells
- They have sufficient calcium levels to maintain a low level of tension, and are sensitive to neurotransmitters depending on the distribution of receptors

Characteristic	Smooth
Innervation	Autonomic nervous system
Initiation	Neurogenic & Myogenic
Role of nervous stimulation	Modifies contraction; Can excite or inhibit; Contributes to gradation
Gradation mainly accomplished via:	• Varying number of muscle fibres contracting • Varying cytosolic Ca2+ • Autonomic, hormonal, mechanical stretch, local metabolites
Modifying effect of hormones	Yes
Sarcoplasmic reticulum	Poorly developed
Source of increased cytosolic Ca^{2+}	Extracellular fluid; Sarcoplasmic reticulum
Presence of gap junctions	Yes

Figure 38: Characteristics of smooth muscle

Basic Structure of the Vascular System

- The aorta is the major systemic artery, which supplies blood to all the organs
  - Long, rigid, gets blood to where it needs to go
  - More of a conduit
- Veins have a much larger capacity; there is a reservoir where blood can pool as it returns
- Types of arteries:
  - Elastic arteries go from 3 cm in diameter to 250 microns
    - The structure makes it very flexible and elastic
  - Muscular arteries go from 100 to 40 microns
    - Less elastin, more smooth muscle (hence the name)
    - Smoot muscle dominates behavior
    - Can't stretch as much
  - Arterioles go from 40 to 10 microns
    - No elastin, only smooth muscle

Factors Effecting Arterioles

- Extrinsic factors (signals from the nervous system)
  - In the normal case, the blood vessel is slightly constricted
  - More sympathetic stimulation leads to more vasoconstriction, decreasing the diameter and leading to higher blood pressure
  - Less sympathetic stimulation leads to vasodilation, increasing the diameter
  - No parasympathetic innervation to arterioles
  - Different tissues have opposite responses to the SNS
    - All arteriolar smooth muscle (exception in the brain) all have $\alpha 1$ type receptors – they are excited by NE and constrict

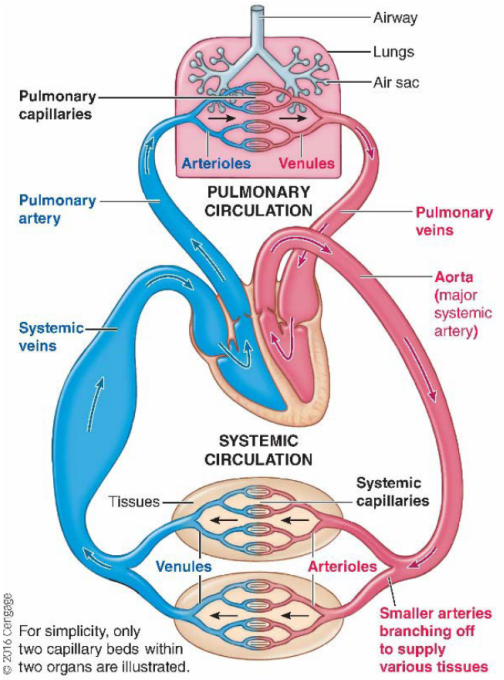

Figure 39: Basic structure of the cardiovascular system

* However the arteriolar smooth muscle in the heart and skeletal muscle have $\beta 2$ receptors, which are more sensitive to E and are inhibited
* Different types of receptors allow the SNS to either dilate or constrict

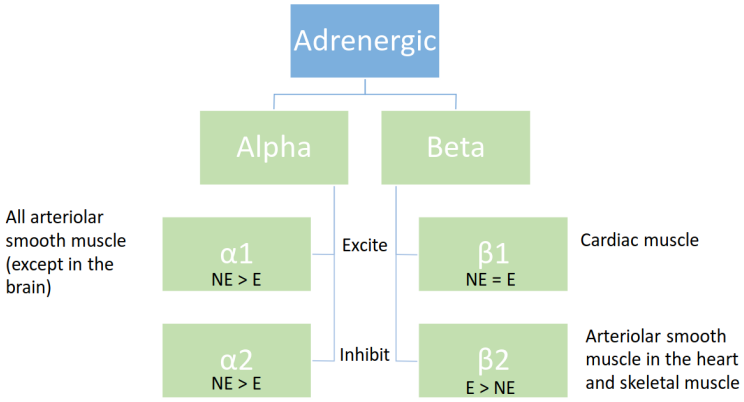

Figure 40: Types of receptors on smooth muscles

- Smooth muscles can myogenically contract due to intrinsic factors
  - More myogenic activity leads to more constricting
  - Less oxygen or more carbon dioxide leads to dilation; more oxygen or less carbon dioxide leads to constriction
    * More activity lowers the oxygen level in the blood; the vessels dilate to provide more oxygen to active muscles
  - The inner layer of cells around the vessel releases neurotransmitters that lead to myogenic behaviour
    * Endothelin leads to constriction, nitric oxide leads to dilation
    * e.g. beet juice contains nitric oxide, which dilates the vessels and increases muscle performance

- Stimulation from SNS leads to a global vasoconstriction effect, but local factors (depending on the muscle type or local muscle activity) will alter the local effects
  - e.g. during exercise, sympathetic stimulation causes constriction globally, but dilation to the exercising muscles; the lowered oxygen and increased carbon dioxide levels lead to vasodilation of exercising muscles
- Cold temperatures lead to constriction, hot temperatures lead to dilation
- Histamines released by the immune system also lead to dilation (helping the immune response)
  - This makes it possible to be allergic to the cold

Pressure and Flow Relationships in Vessels

- Hagen-Poiseuille equation: $\Delta P = Q\frac{8\eta L}{\pi r^4}$; ΔP is the pressure difference, Q is the flow, r is the vessel radius, L is the length, and η is the dynamic viscosity
  - $\frac{8\eta L}{\pi r^4}$ is referred to as the *total peripheral resistance* (TPR)
  - ΔP is the product of cardiac output (flow) and resistance
- $R \propto \frac{1}{r^4}$ so a small increase to the radius significantly lowers the resistance
  - Vessel radius can be effected by local metabolic control and extrinsic vasoconstrictor control (i.e. Sympathetic innervation)
- $R \propto \eta$ and viscosity can be effected by the number of red blood cells (e.g. dehydration leads to thicker blood, increasing resistance)

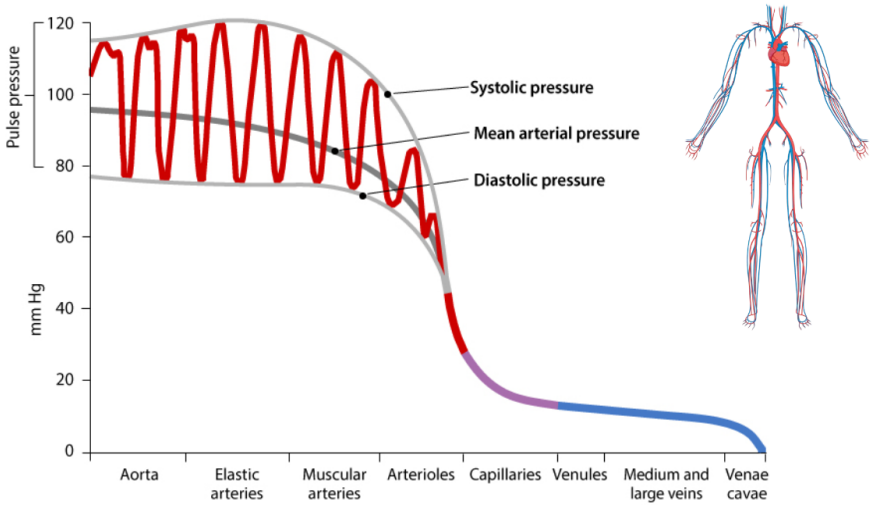

Figure 41: Blood pressure in different types of vessels

- The mean blood pressure is always lowering with smaller vessels; since pressure is the driving force for flow, the smaller vessels will have less flow
  - Pressure also fluctuate with every heart beat
  - The biggest pressure drop happens across the arterioles
  - Arterioles are called "resistance vessels" because of this, due to their inelasticity from only having smooth muscle
  - Barely any resistance happens on the venous side; only a small pressure changes happen in the arteries before arterioles
- The mean arterial pressure (MAP) is the average between the systole and diastole pressures
  - Since diastole occurs for much longer, the diastolic pressure has about twice the weight as the systolic pressure
  - $MAP \approx DBP + \frac{1}{3}PP$ where DBP is the diastolic blood pressure and PP is the pulse pressure

(difference between the 2)
– However with increased heart rate diastole shortens first (before systole shortens), so the weights can change

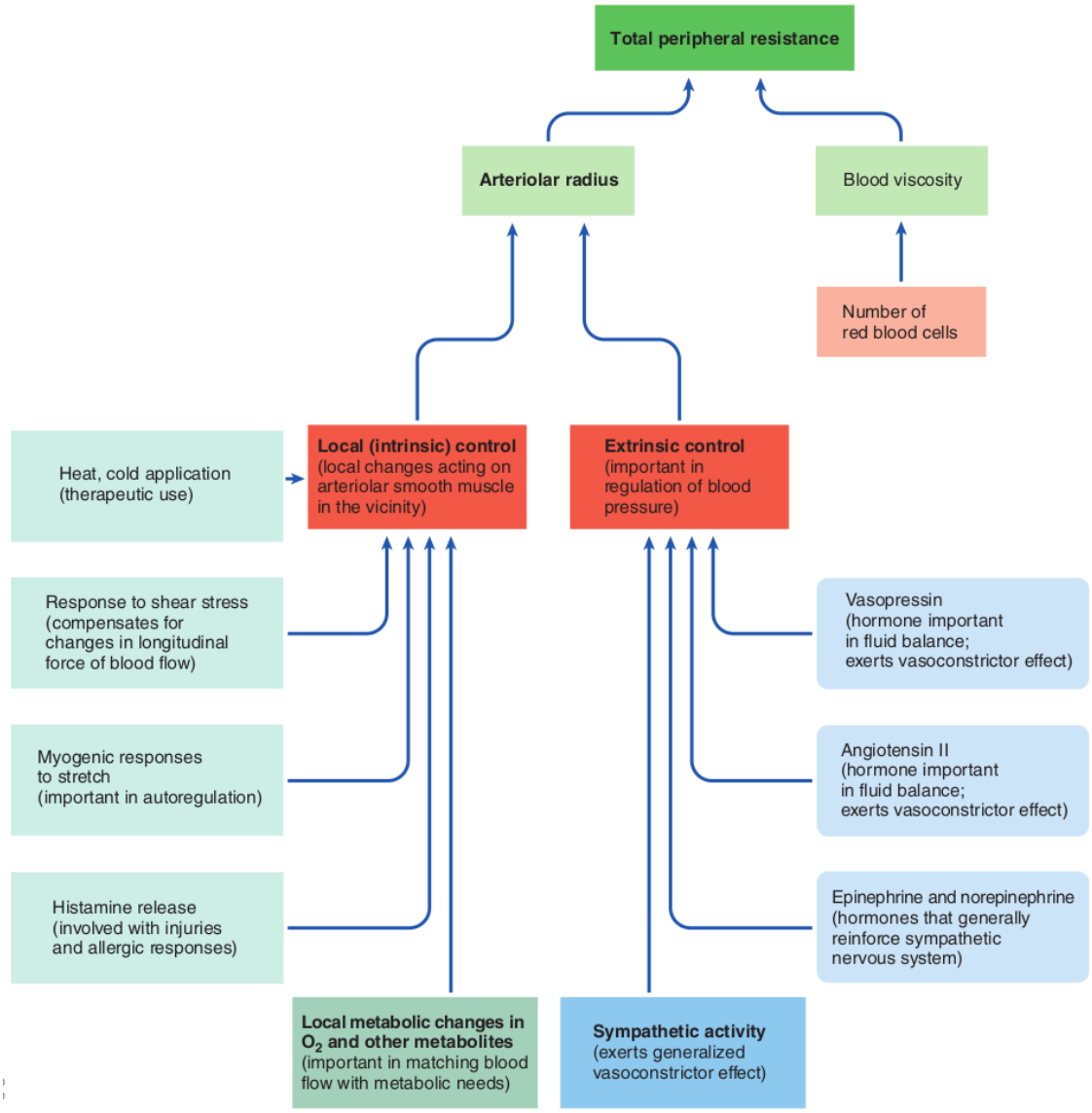

Figure 42: Summary of factors affecting total peripheral resistance

Lecture 18, Mar 28, 2023

Changes in Blood Flow

- At rest, flow is only 5 L/min, while with exercise the blood flow can get up to 12.5 L/min
- Most of the extra blood flow goes to skeletal muscle (taking up 64% of the total flow, up from 15% without exercise)
- Flow is diverted away from the digestive system, the kidneys, etc; they end up having lower blood flow, despite the increase in overall blood flow
- Skin blood flow is also increased

- All arteriolar and venule smooth muscle (except the brain) has $\alpha 1$ receptors, so release of NE leads to excitation (constriction)
- Arteriolar smooth muscle that supplies skeletal and cardiac muscle cells have $\beta 2$ receptors, which dilate instead with release of NE
  - There are still $\alpha 1$ receptors, but the $\beta 2$ receptors overwhelms

Venous Return

- At any given time most (65%) of the blood volume is stored in the systemic veins
- Because arterioles are inflexible, the flow rate back into the heart is limited; if venous return is not increased, the heart will eventually run out of blood to pump since the blood is not returning fast enough
- Factors affecting venous return:
  1. Sympathetic activity: "squeezing" blood out of the veins and into the heart
     - A lot of sympathetic innervation in the spleen, kidney, etc
     - This vasoconstriction pushes the "stored" blood volume in these organs out
  2. Blood volume: having more blood volume (e.g. with a transfusion) has the same effect
  3. Venous valves: one-way valve-like structures in the veins prevent backflow of blood when the vessels are squeezed
  4. Skeletal muscle pump: the skeletal muscles around the valves create pressure, and combined with the venous valves it pushes blood back into the heart

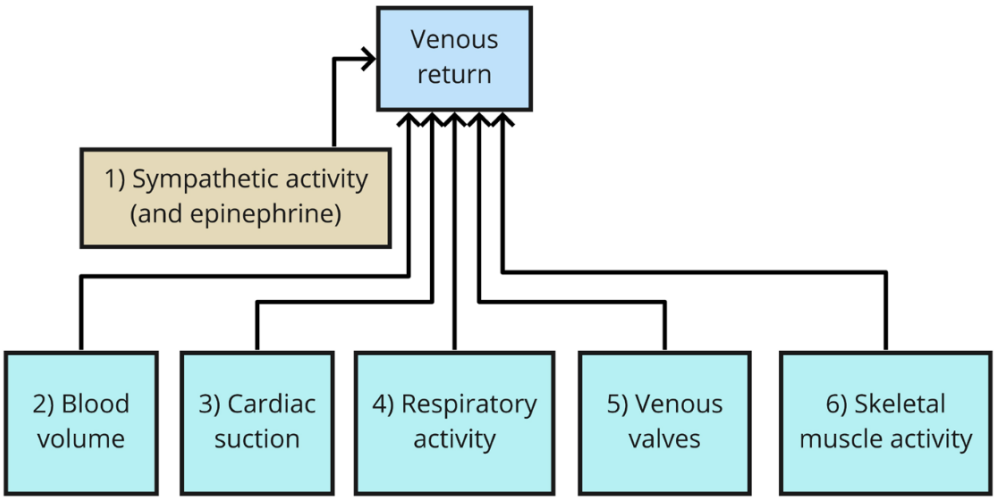

Figure 43: Summary of factors affecting venous return

Regulation of Blood Pressure

- Heart rate, stroke volume, and total peripheral resistance are the system effectors
- To sense blood pressure, the body has baroreceptors; these receptors wrap around the arteries, so with higher blood pressure, the vessels stretch and the receptors are activated
- There are carotid sinus baroreceptors (neck) and aortic arch baroreceptors (heart)
- Baroreceptors are tonic receptors, with firing rate proportional to blood pressure
  - With an increase in pressure the receptor sees a spike in potential, which then dies down and stabilizes
  - This means there will first be a transient spike in the firing rate right after a pressure change
- The afferent signals from the baroreceptors come into the medulla, which contains two cardiovascular control centres; one centre increases sympathetic excitation, the other depresses it; there is also a control centre for parasympathetic control (vagus nerve)

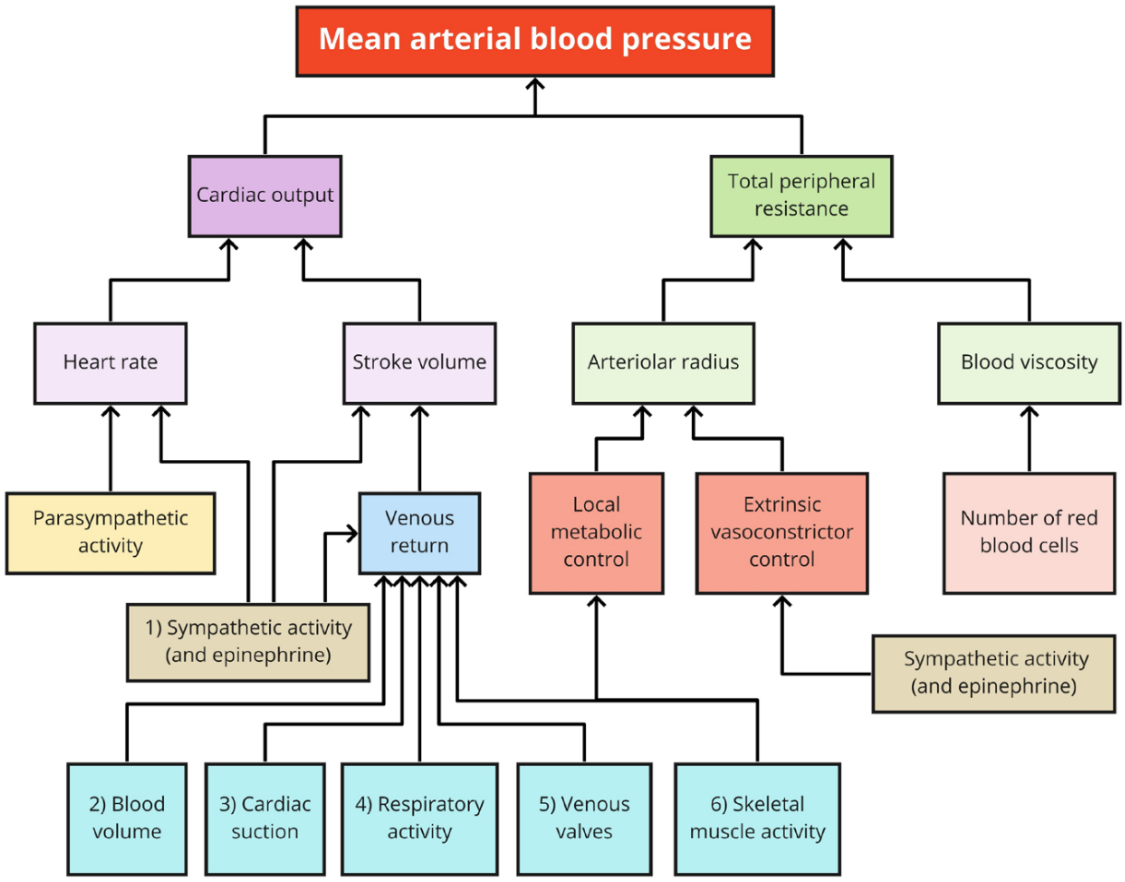

Figure 44: Summary of influences on mean arterial blood presure (MAP)

  - We can break this down into a cardioaccelatory side (increase SNS, decrease PNS) and a cardioinhibitory side (increase PNS, decrease SNS)
    * Both of these affect the heart rate and stroke volume
  - Signals from the baroreceptors are combined with environmental stimuli (exercise, injury, etc)
  - There is also a vasomotor centre (where there is no parasympathetic response); on the vasoconstrictor side there is more sympathetic response, on the vasodilator side there is less sympathetic response
    * Both of these affect the resistance, and also the stroke volume through squeezing blood out for more venous return
- e.g. when standing up, sympathetic activity increases the heart rate; this is because when standing up all the blood pools at the feet, which drops the blood pressure at the head, activating the carotid sinus baroreceptors and triggering the sympathetic response to increase blood pressure
  - This increases the heart rate at first, and then after some time the stroke volume also catches up since affecting venous return takes some time
  - This also activates vasoconstriction, which increases venous return (which increases stroke volume) and resistance (which increases pressure)

Lecture 19, Mar 30, 2023

Respiratory System – Ventilation and Respiration

- *Ventilation* is the movement of air in and out of the lungs, exchanging oxygen and CO2 with the blood
  - Ventilation is only external
- *Respiration* can be both internal (within the cell, at the mitochondrial level) and external (transfer from lungs to capillaries)
- Supply of oxygen to body cells is usually rate limited by the circulatory system (e.g. stroke volume, heart rate) instead of how much oxygen is breathed in

Lung Structure

- When the diaphragm muscle contracts, the entire muscle is pulled down, drawing air into the lungs
- Bronchioles are the branches in the lung; smooth muscles warp around this
- Alveolar sacs are made from alveoli (alveolus); venules and arterioles surround the alveolar sacs with capillaries, which lets oxygen transport happen
- There are 2 types of alveolar cells: type I and type II
  - Type I cells are very flat, which gives them surface area for oxygen diffusion
    * They are only 1 micron thick
    * Oxygen transfer happens through these cells
  - Type II alveolar cells are bigger than type I cells, and they excrete a mucus
    * The fluid layer is about 2 microns thick
    * Their thicker size makes it so that oxygen doesn't really transport through them much
  - Type I cells take up 95% of the area, but only 1/3 of the number of cells
- Capillaries surrounding the alveolar sacs have their own cells, which form a tube that carries fluid and red blood cells
  - The distance between the capillaries and the sacs is about 0.5 microns
- Every fluid, cell membrane, and cytosol between the red blood cell and the inside of the alveolar sacs forms a barrier to diffusion
- Alveoli are connected via pores of Kohn, which equalize their pressure
- Law of Laplace: $P = \frac{2T}{r}$ where T is the surface tension and P is the internal pressure of a fluid bubble
  - The surface tension of the fluid coating means the sacs want to contract back when they are expanded (recoil)
  - With just a normal fluid layer, a bigger sac would have a lower pressure, so the smaller sacs would get smaller and the larger sac gets larger – this leads to alveolar collapse

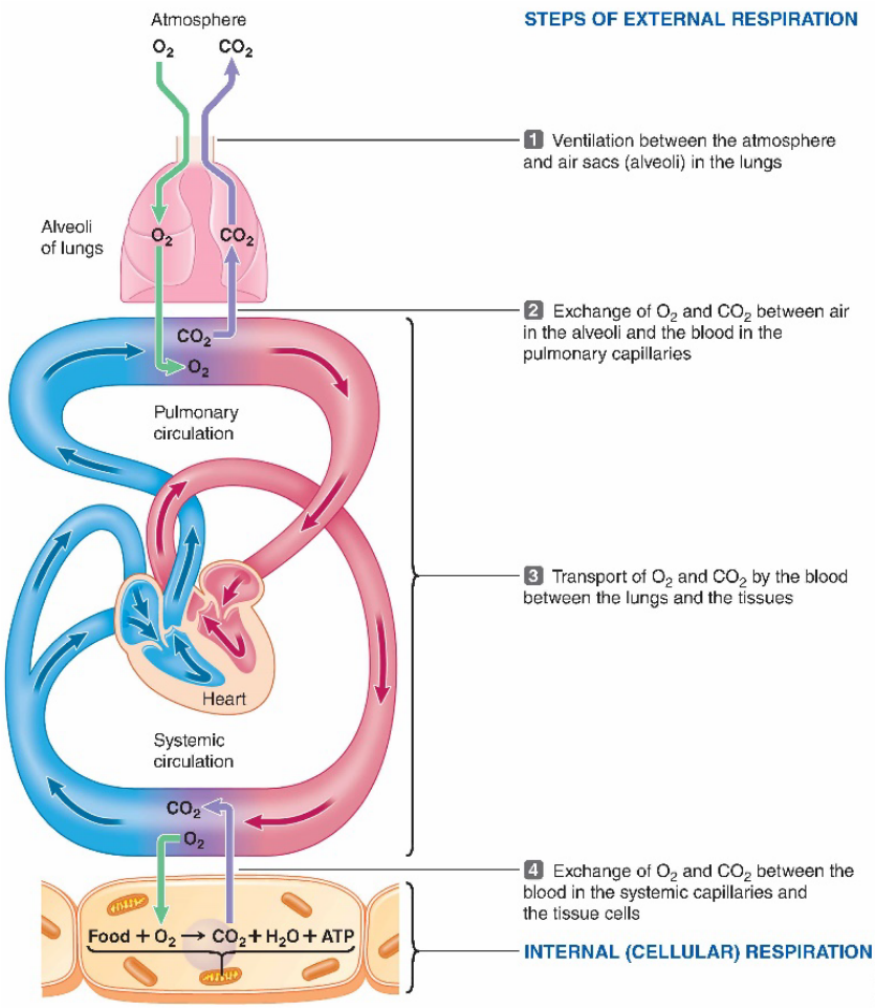

Figure 45: Overall structure of the respiratory system

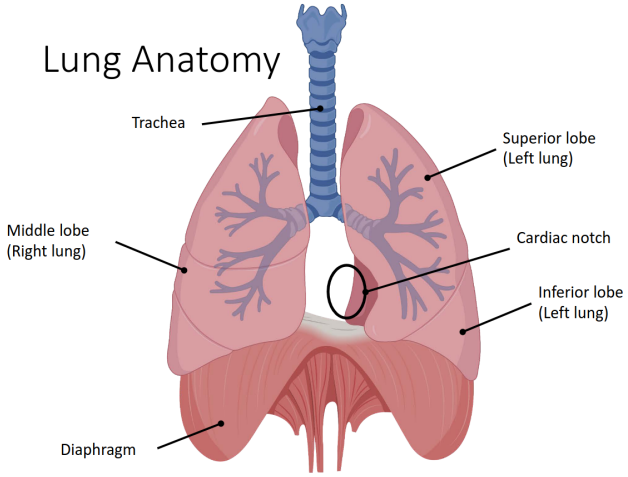

Figure 46: High-level structure of the lung

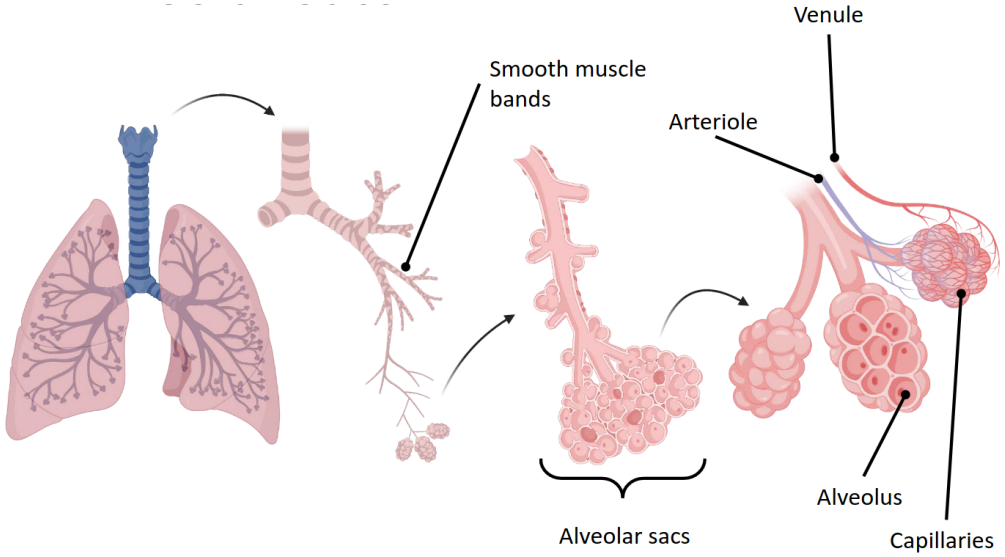

Figure 47: Low-level structure of the lung

  - The Type II cells also secrete a surfactant; now as the sac gets smaller, the surfactant concentration per area increases, which decreases the surface tension, avoiding alveolar collapse

Muscles Responsible for Ventilation

- The lung is surrounded by a self-contained sac (membrane)
  - This is made of 2 layers of membrane; from the inside of the lung: the visceral pleura, a pleural cavity (space), and then a parietal pleura which then connects to the intercostal muscles
- External intercostal muscles contract and expand the ribcage during inspiration
- Internal intercostal muscles pull and contract the ribcage
- During expiration, muscles relax and the recoil from the fluid pulls the lung back
- A range of muscles can affect inspiration and expiration
  - About 75% of inspiration is due to diaphragm alone; the other 25% is due to extra intercostal muscles
  - The intercostal muscles are only used during active (forceful) expiration; otherwise, expiration is due to the recoil alone

Mechanics of Ventilation

- Pressure gradient drives air flow
  - Main pressures: atmospheric pressure (considered as 0), alveolar pressure P_A, pleural pressure P_{pl} (inside the pleural cavity), the lung recoil (aka transmural, transpulmonary) pressure, $P_{\text{recoil}} = P_A - P_{pl}$
    * P_{pl} is lower than atmospheric pressure during normal breathing (the lung wants to collapse and the chest wall wants to expand)
  - A pressure difference between atmospheric pressure and P_A is needed to drive ventilation

Lecture 20, Apr 6, 2023

Changes During Normal Breathing

- Changes during normal breathing:
  1. Lung volume

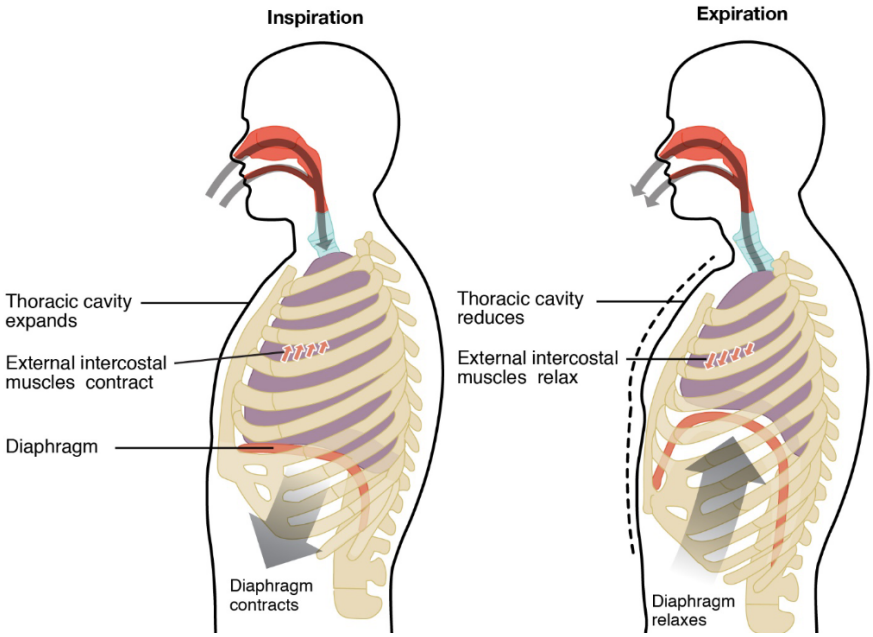

Figure 48: Diaphragm movement causing inspiration and expiration

  - Volume increases until the completion of inspiration, where P_A equalizes with the outside atmosphere
  - Then during exhale P_A becomes higher than atmospheric
2. Pleural pressure
  - Before inspiration begins, $P_{pl} = -5$
  - Halfway through inspiration, the pleural pressure gets more negative, $P_{pl} = -6.75$ because you're expanding the size of the cavity
  - Pleural pressure reaches a minimum at the completion of respiration, $P_{pl} = -7.5$; at this point the lung recoil (transmural pressure) reaches a maximum, $P_{LR} = 7.5$
  - As the diaphragm relaxes during expiration, both pressures return to normal; halfway through respiration $P_{LR} = 6.65$
  - At the end of expiration everything returns to normal
  - The two ends of the path for pleural and lung recoil pressures are the same but the paths are slightly different
    * Negative pleural pressure drives inspiration, lung recoil pressure drives expiration
    * During inspiration the lung recoil pressure lags the pleural pressure and catches up at the end of inspiration
    * During expiration the pleural pressure lags the lung recoil pressure
  - The flow rate is directly proportional to the alveolar pressure, which is the difference between the pleural and lung recoil pressures

- Minute ventilation $\dot{V}_E = V_T \times f$ is the volume of gas breathed per minute; V_T is the tidal volume and f is the respiratory rate
  - Air exchange only happens at the ends of the lungs, so the upper airways are functional dead spaces that do not transfer oxygen
  - Expired gas is a combination of alveolar and dead space air, $\dot{V}_E = \dot{V}_A + \dot{V}_D$
  - If you breathe too fast, the breaths will be very shallow and only dead space air will be exchanged, which is why you feel lightheaded since you're not getting fresh air
  - Dead space volume is a constant offset subtracted from the total ventilation, about 0.15L
- In alveolar gas, the composition of water vapour and carbon dioxide get much higher and oxygen lowers

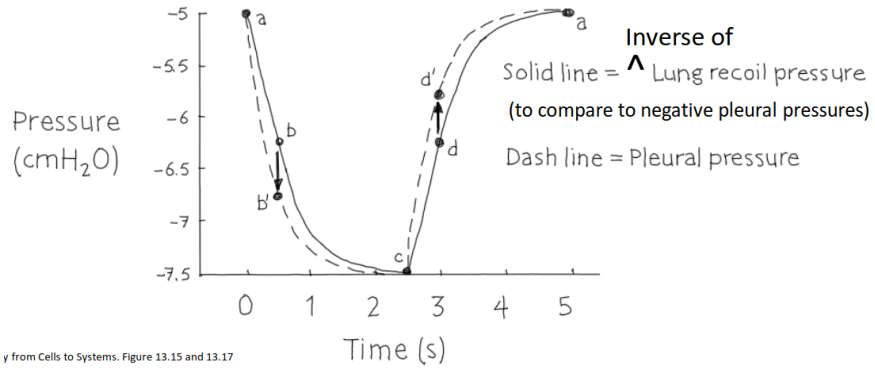

Figure 49: Changes in pleural and lung recoil pressure during breathing

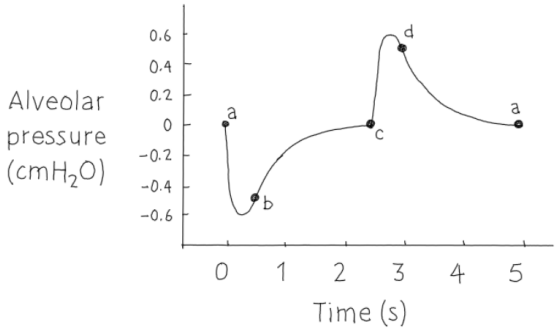

Figure 50: Changes in air flow during breathing

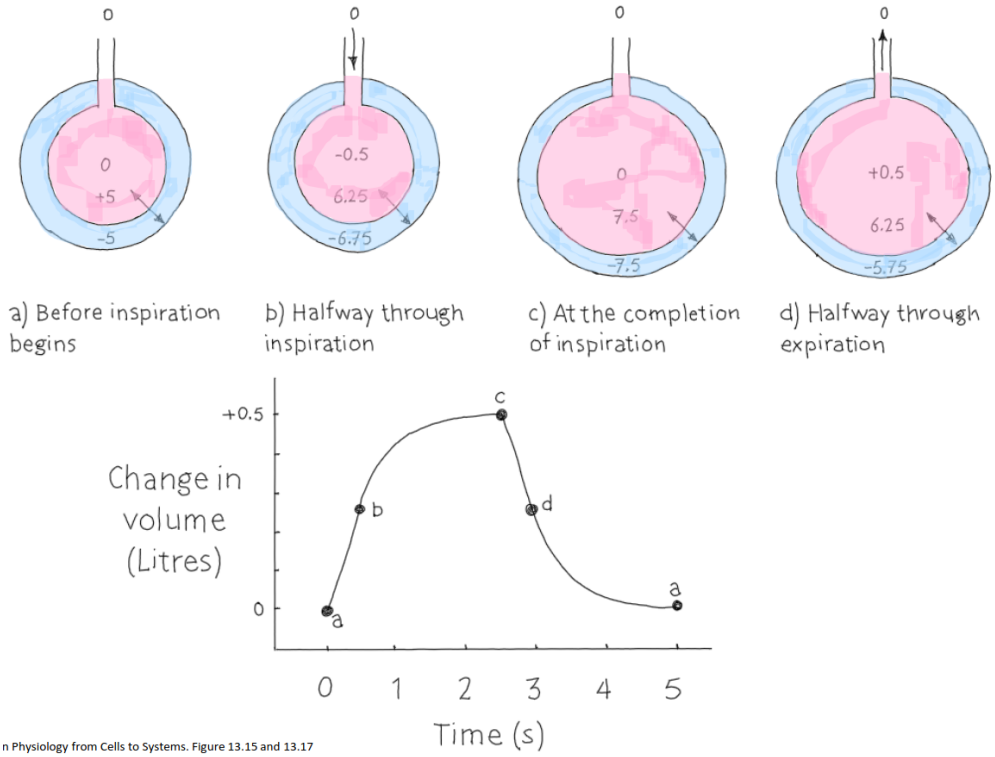

Figure 51: Changes in lung volume and pressure during breathing (relative change)

Spirometry and Lung Volume

- Residual volume is the amount of air left in the lungs no matter how hard you breathe
- Expiratory reserve volume is the amount of air you have left after expiration during normal breathing; this gives a functional residual capacity (ERV + RV)
- The tidal volume is the normal volume change during breathing
  - This is the sum of dead space and alveolar volumes
- The difference between the total lung capacity and the normal lung capacity after inspiration is the inspiratory reserve volume
- During typical breathing, only the tidal volume is exchanged; in forceful breathing, the IRV and ERV can be exchanged
- The total lung capacity cannot be changed, but IRV/ERV can be increased with training (with a stronger diaphragm muscle)
- The vital capacity is the sum of IRV, ERV and VT, and is the maximum volume you can exchange during breathing
- Inspiratory capacity is the sum of tidal volume and IRV, from the end of normal expiration to total capacity
- Total lung capacity is the sum of vital capacity and residual volume
- RV cannot be measured directly with spirometry since it can only measure air coming out of or going into the lungs

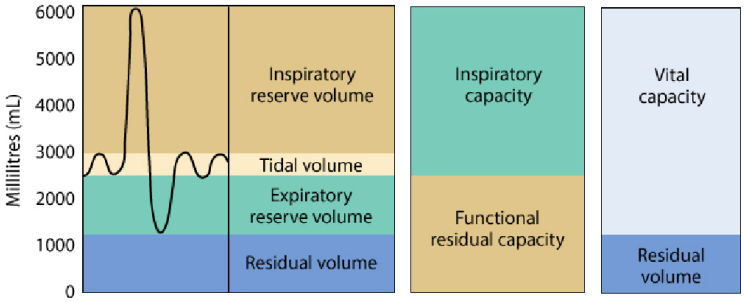

Figure 52: Lung volume and capacity breakdown

Lecture 21, Apr 11, 2023

Gas Exchange During Ventilation

- Exchange of O2 and CO2 are driven by partial pressures; normally, alveolar and arterial $P_{aO_2} = 100\text{mmHg}$ and $P_{aCO_2} = 40\text{mmHg}$
  - In hyperventilation the body is breathing faster, so the oxygen partial pressure goes up and CO2 partial pressure declines
  - Hypoventilation is the opposite
  - By the time oxygen gets back to the lungs, the partial pressure will be about 40 mmHg, so the pressure gradient of 100 to 40 drives oxygen diffusion
  - P_{vO_2} is the partial pressure in venous blood (before alveoli), P_{aO_2} is the partial pressure in arterial blood (after alveoli) and P_{AO_2} is the partial pressure in the alveoli themselves (not blood)
  - $P_{AO_2} = P_{aO_2} = 100\text{mmHg}$ is higher than $P_{vO_2} = 40\text{mmHg}$ allowing oxygen to diffuse
- Dissolved gases also exert a partial pressure (more gases dissolved has a greater pressure)
- Blood plasma itself has a very low solubility for oxygen, so hemoglobin proteins are used as the main transporter of oxygen
  - About 270 million hemoglobin molecules in each red blood cell
  - Each hemoglobin has 3 heme sites (iron) where oxygen can bind to
  - Oxygen bound to hemoglobin consists of 98.5% of oxygen transport; only 1.5% is dissolved in the plasma

- For carbon dioxide, the main carrier is bicarbonate ions
  - Dissolved carbon dioxide produces carbonic acid: $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3{}^-$
  - 5-10% are physically dissolved, with another 5-10% bound to hemoglobin; the rest 80-90% exist as bicarbonate ions
- Hemoglobin's affinity for oxygen and carbon dioxide can be changed; with higher carbon dioxide concentration, acidity, and temperature the affinity for oxygen decreases, which releases oxygen to the cells that need it most

Nervous Control of Ventilation

- Under rest (normal breathing), arterial carbon dioxide P_{aCO_2} is the most important factor regulating ventilation
  - Levels are kept constant, so even small changes have big ventilation effects
  - Normal P_{aCO_2} is about 40; increasing this to 44 almost doubles the resulting minute ventilation
- Central chemoreceptors exist in the medulla in the brain stem to measure P_{aCO_2} indirectly via blood pH, caused by increased hydrogen ion concentration from dissolved carbonic acid
  - An increase in P_{aCO_2} causes carbon dioxide to diffuse across the blood-brain barrier, which creates more hydrogen ions and makes ECF surrounding brain cells more acidic
  - The chemoreceptors pick up this change and sends a signal to the brain
  - There are still O_2 sensors but they are less effective and affects heart rate more than breathing
- At the dorsal side of the medulla is the control centre for ventilation and breathing rhythm
- A reverberating circuit (aka rhythm generator, central pattern generator, oscillation pattern) generates periodic innervations to the diaphragm muscles under normal breathing
  - Note unlike the heart, this is not just one pacemaker cell, but a loop of neurons feeding back on themselves
  - Pattern of contracting respiratory muscles for 2 seconds, and then releasing for 3 seconds leads to the breathing cycle
  - The dorsal respiratory group (DRG) innervates the diaphragm and external intercostal muscles
  - Under more forceful breathing, the ventral respiratory group (VRG) innervates other muscles such as the internal intercostal muscles to breathe more air
- More controls in the pons (right above the medulla) further affect breathing (pontine respiratory group, PRG)
  - Pneumotaxic center is the higher one which inhibits the dorsal respiratory group in the medulla
  - Apneustic center is the lower one which excites the DRG
- Example: a disturbance, an increase in P_{aCO_2}, causes the pH level to drop in the brain ECF, which makes the central chemoreceptors fire, that then causes more forceful and frequent berating to expel the extra carbon dioxide in order to bring the body to homeostasis
- Increase in blood P_{aCO_2} directly leads to a higher minute ventilation
- In general P_{aCO_2}, P_{aO_2} are held remarkably constant by minute ventilation
- Neural control of breathing is very complex, since it is subject to both voluntary and involuntary control

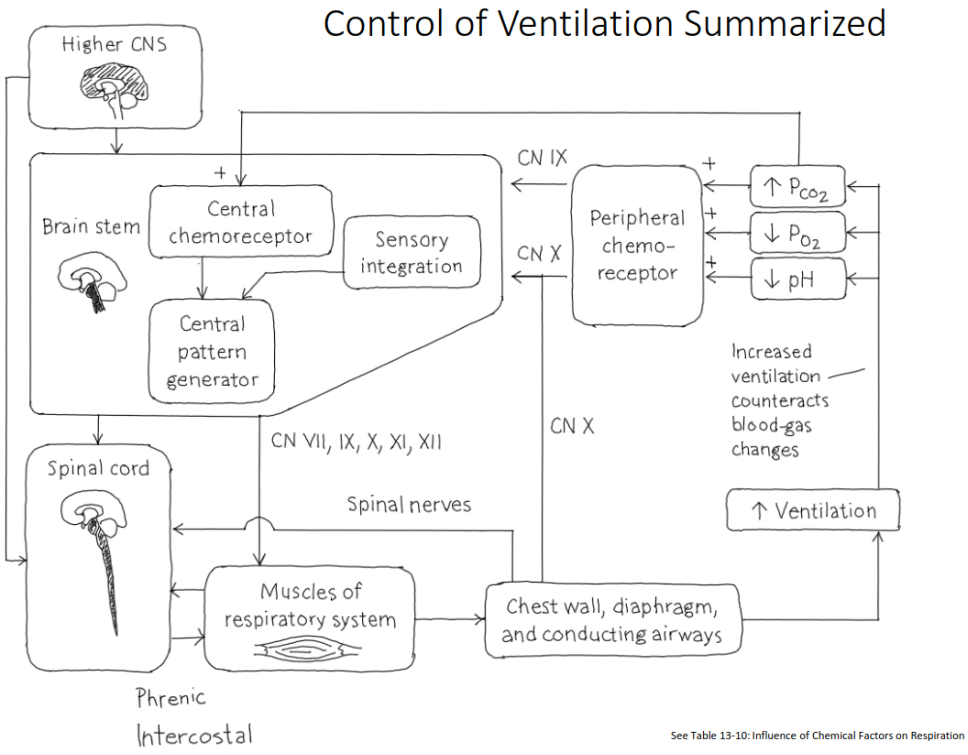

Figure 53: Summary of control of nervous control of ventilation