Chapter Guides:
http://virtual.yosemite.cc.ca.us/rdroual/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202011/chapter_5%20Fall%202011.htm

"One time, we had a guy perform who was supposed to be a master of kung fu. Turns out he was a male stripper. Surprised the hell out of us all."
"If you ever get stung by an anemone off the Great Barrier Reef, I want your last thought as you die to be 'damn, Higgins told me about this shit.'"
"They knew the dose for this furry meatloaf; some of you know it as a cat."
"Experience and treachery will always overcome youth and exuberance."
**holding up a shoe* "So this is urine, right?"*
"Isn't that great? That's almost pornographic!" - in reference to a flowchart
"The next time your roommate goes to vomit, run in and check their pupils and blood pressure. It's all for science….the next time you get the stomach flu, think of me."

Lecture 1: Multicellularity & Homeostasis

Homeostasis (Chapter 1)

Why multicellularity?

- surface:volume problem (nutrients), greater specialization, compartmentalization, homeostasis
- homeostasis – maintenance of a constant, optimal internal environment

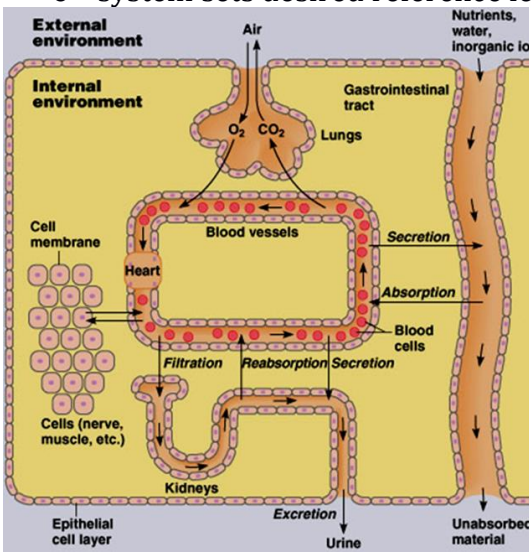
Solute	ICF (mM)	ECF (mM)
K^+	140.0	4.0
Na^+	15.0	145.0
Mg^{2+}	0.8	1.5
Ca^{2+}	$<0.001^{\dagger}$	1.8
Cl^-	4.0	115.0
HCO_3^-	10.0	25.0
P_i	40.0	2.0
Amino acids	8.0	2.0
Glucose	1.0	5.6
ATP	4.0	0.0
Protein	4.0	0.2

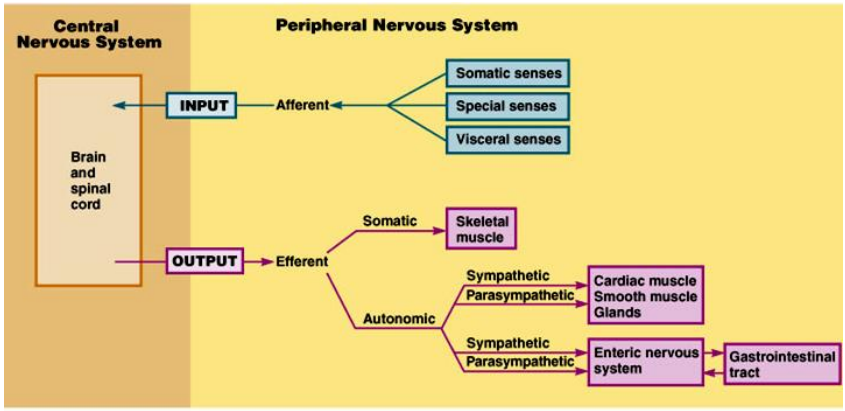
Identify 4 basic cell types in mammalian systems

- neuron, muscle, epithelial (exocrine vs endocrine), connective
- organ systems: endocrine, nervous, musculoskeletal, cardiovascular, respiratory, urinary (osmotic pressure, pH, & ion content), gastrointestinal (absorb & excrete), reproductive, immune, integumentary

Understand concept & examples of homeostasis

- by isolating internal body fluids by regulating the composition of the fluids surrounding the cells & tissues, organ systems eliminate the need for each cell to respond to changes in the external environment
- system sets desired reference level, and makes adjustment via feedback





Design closed loop, negative feedback system to control a physical parameter

- levels go beyond set point → error signal to integrating center → regulatory mechanisms activate effectors → response → change in regulated variable
- stimulus → sensory system → comparator with reference → effector for output
- e.g. CNS is integrator & comparator, PNS is sensory system & effector
- intercellular communication, types of signaling molecules, receptors for them, secondary messenger pathways & amplification
- design system to control blood pressure, blood to brain, body temperature

Draw & label 3 basic components of the mammalian nervous system

- general structures (afferent & efferent), cellular components (10^11 neurons), blood-brain barrier, membrane potential
- cell types: bipolar (sensory neurons in nose & retina, cell body parallel), pseudo-unipolar (most afferent neurons, cell body perpendicular), mutlipolar (most neurons)
- glial cells – guidance & survival of neurons, synapse formation, myelination, control of synaptic function, homeostatic regulation of [NT] & [K+]

Lecture 2: Vm & Action Potentials

basis for equilibrium potential & membrane potential

- Vm approaches the E of the most permeable ion
- all cells leak K+ out and Na+ in
- permeability of K+ is greater than that of all other ions in most cells
- selective permeability & concentration gradient are needed to establish a membrane potential

potential difference (voltage), current (I), and conductance

- movement of ions across membrane creates a current, which establishes a voltage, which changes based on the conductance of each ion
- if an ion doesn't move, it doesn't contribute to the membrane potential
- Na/K pump sets up concentration gradient, but does not establish the membrane potential
- conductance/rate of diffusion: high if permeability (# channels open) is high & VM is far from EK
- I = V/R = VG

calculations for E & Vm

- approximate Vm = Nernst of highest permeability ion, calculate Vm = Goldman
- EK = RT/zF * ln([K]out /[K]in)
- R = 1.987 cal/mol*K, T = 278+degC, F = 23,062 cal/V-mol
- in biological systems: RT/F = 61.5 if ln=log10 @ 37degC
- model tissue: squid giant axon, Nernst constant of 58 due to water temp of 20degC
- calculation method: put the largest ion concentration on top, then predict the sign based on the concentration gradient
- Vm = RT/F*ln([(Pk)[K+out] + (Pna)[Na+out] + (Pcl)[Cl-in]]/[(Pk)[K+in] + (Pna)[Na+in] + (Pcl)[Cl-out]]
- Pk is normally set to 1, and Pca is normally assumed to be 0

structure & function of voltage-gated ion channels

- Na+ voltage gate: positively-charged polypeptide
- 4 activation gates, 1 inactivation gate

- ionotropic: receptor is coupled with a channel, inducing a fast by week response (e.g. nicotinic cholinergic receptor – 5 subunits)
- metabotropic: receptor is coupled with a G-protein; both pathways elicit a slow but powerful postsynaptic potential (e.g. muscarinic cholinergic receptor)

properties of local, graded potentials

- graded potential – small change in membrane potential whose strength is relative to the stimulus that produced it, which triggers opening/closing of ion channels
- local – not propagated, graded – resistance causes it to fade
- duration, amplitude, potential change can vary
- comparison: weak strength, can be EPSP or IPSP, spatial or temporal summation, no refractory period, ligand (synaptic potential) or mechanical (receptor potential) gated, Na+/K+/Cl-, ms to sec duration, expands in all directions
- hyperpolarization: Pk increase, Pna decrease, Pcl increase
  K+[out] decrease, Na+[out] decrease, Cl-[out] increase
- action potential – large, rapid change in Vm produced by a depolarization of an excitable cell's (has voltage-gated channels) PM to threshold Vm
- equilibrium potential – Vm that counters chemical forces moving an ion across a membrane
- look out for: no permeability → no Em, must calculate direction of Cl- diffusion & effect of changing Pcl

properties and conduction of action potentials

- frequency coding (greater response magnitude): longer stimulus, greater suprathreshold stimulus, temporal summation, spatial summation → more action potentials, closer together

factors influencing AP conduction velocity

- larger diameter → less resistance to interior flow (invertebrate strategy)
- myelination → saltatory conduction, decreases resistance in the axoplasm (vertebrate strategy)
- myelin: Schwann in PNS, Oligodendrocyte in CNS
- sheaths are half as far apart as they theoretically could be (safety factor of 2)

Lecture 3: Synapses

Ionic events responsible for post-synaptic potentials

- intracellular & extracellular ions and permeability are constant
- myelination is constant
- APs on a neuron are always the same height → always opens the same # of Ca2+ gates, which allows the same # of vesicles with the same # of signal molecules/neurotransmitter of the same type contained in it to fuse with the axon terminal membrane
- changes to these constants changes conduction, which causes disease (e.g. MS, depression)
- information carried by a neuron is coded by the frequency of Aps
- [Na+] changes alters AP height, [K+] changes will kill you due to higher permeability

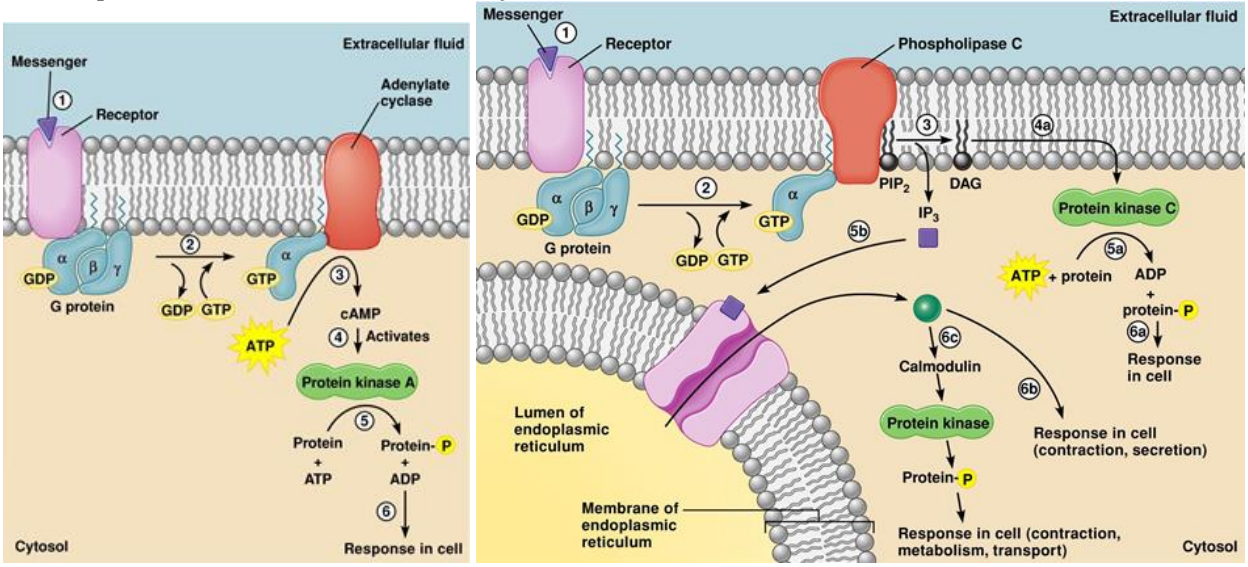
Exocytotic release of signal molecule

- electrical synapse (gap junctions) vs. chemical synapse
- paracrines vs. autocrines (closed loop negative feedback to reduce secretion)

- paracrines: growth factors, clotting factors, cytokines
- reuptake & destruction enzymes (nerve gas blocks these)
- lipophilic signal molecule: steroids hormones & eicosanoid paracrines
  diffuse through membrane; binds to carrier; bind to intracellular receptor; binds to hormone response element which alters transcription
- lipophobic: amino acid NT, amine paracrines/hormones, peptides NT/P/H
  exocytosis; ligand to PM receptor; activate ion channels, membrane-bound enzymes, or secondary messengers; fast response by short duration & half-life

Signal transduction pathways

- cAMP/cGMP: alpha subunit activates AC/GC, which converts ATP to cAMP/cGMP, which removes the regulatory segment from PKA/PKG, which phosphorylates the K+ channel to close it
- DAG/IP3: alpha subunit activates phospholipase C, which catalyzes the conversion of PIP2 into DAG, which activates PKC to phosphorylate stuff, and IP3, which triggers the release of Ca2+ from the ER, activating another PK
- Ca2+ ligand-gated channel: Ca2+ can change electrical properties of the cell, initiate muscle contraction, initiate secretion, or bind to calmodulin to act as a secondary messenger
- tyrosine: ligand binding activates tyrosine kinase receptor, which catalyzes the phosphorylation of protein-tyr, which elicits a cell response
- drugs act on this pathway (e.g. Cialis is a phosphodiesterase inhibitor, which prevents destruction of cAMP)



Receptors – agonists & antagonists

- signal molecule receptors: specificity (1me-4me structure, polarity, charges, etc), affinity for ligand, transduces signal from exterior to interior of cell, binds agonists & antagonists
- agonists last longer because the normal destruction enzymes don't work

Dose-response & receptor occupancy curves

- enzyme kinetics: Km is concentration that gives Vmax/2
- receptor affinity: Ka
- dose-response curve: tissue response vs. log10[signal molecule]

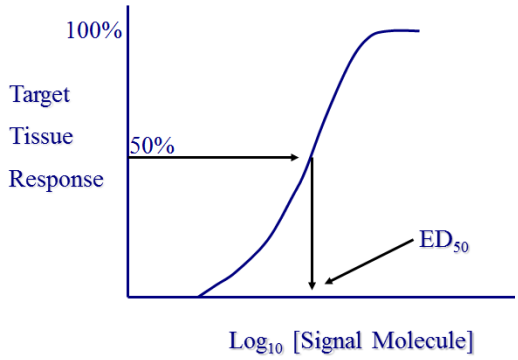
- for agonists & antagonists, ED50 decreases, but the curve shape does not change

Cholinergic & adrenergic receptor sub-types

- cholinergic motor neuron to skeletal muscle: Ach vesicle = quantum = ~1000 Ach molecules = 0.4mV mepp (occur spontaneously in multiples of this voltage)
- experiment that determined this confirmed synaptic delay
- neurons are characterized by the neurotransmitters they release
- muscarinic: M1 to M5, distinguished by G-protein linkages, all have 7 transmembrane regions with differing extracellular & cytosolic regions

Discussion Questions

- Explain what happens to the post-synaptic response of a neuron to a neurotransmitter following a reduction in extracellular Ca++.
- Explain the effect on a post-synaptic structure of a drug that inhibits the re-uptake of signal molecule from the synapse.
- Draw a dose – response curve to a typical receptor agonsist.
- Now draw the new curve(s) for:
  - The agonist in the presence of a non-competitive antagonsist
  - The agonist in the presence of a competitive agonist
  - The agonist in the presence of a second agonist.



- Why have organisms evolved multiple receptor types for many neurotransmitters?
- What properties of a molecule make it suitable to serve as a signal molecule?
- How can Epinephrine act on a receptor and increase the activity of one target tissue while decreasing the activity of another?
- How can epinephrine cause two different excitatory effects (rate and strength of beat) on two different cell types in your heart?

Lecture 4: PNS - ANS

Understand structure of the 3 branches of efferent peripheral nervous system

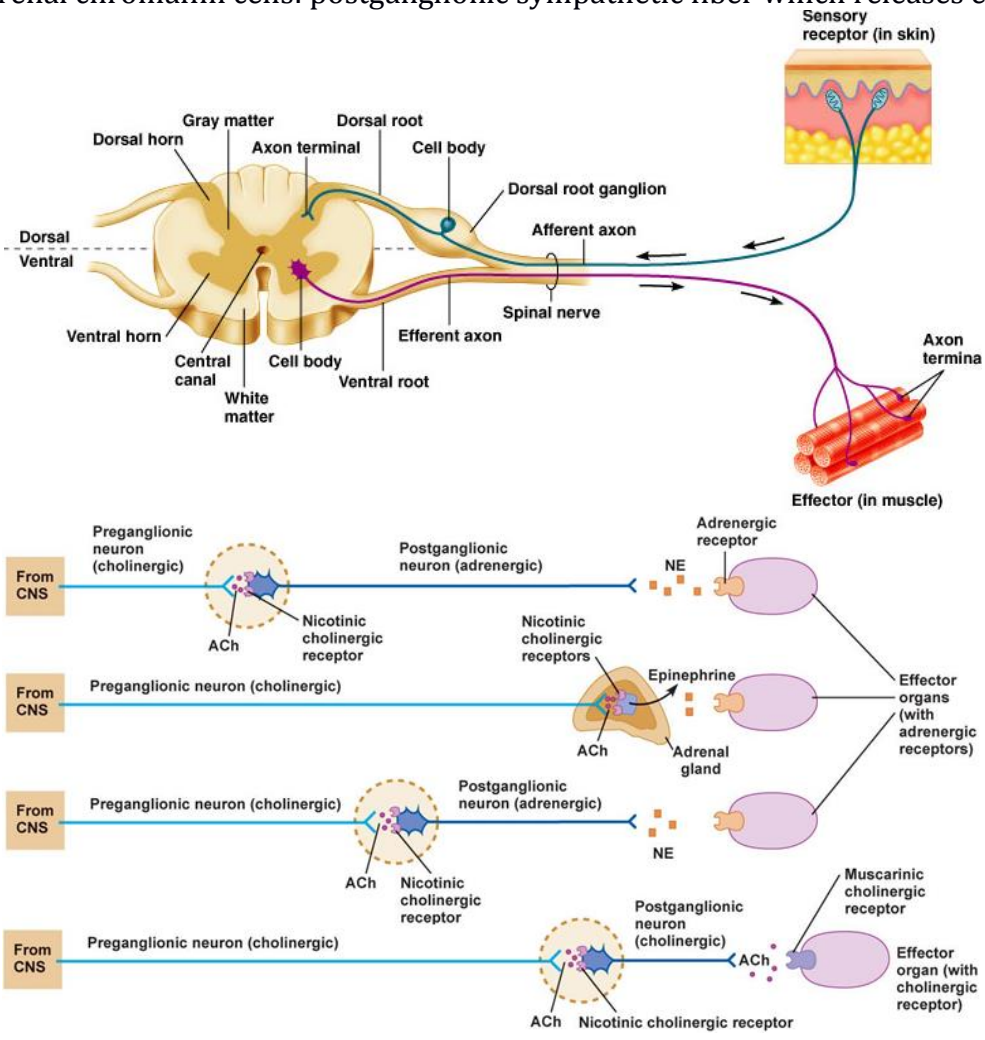
- visceral reflexes – controlled by hypothalamus (fight or flight, temperature, food intake, water balance) & pons/medulla (cardiovascular & respiratory)
- ANS neuron classifications: (non) – myelinated (myelinated neurons follow pathways guided by Schwann cells, whereas nonmyelinated neurons tend to branch more to less specific targets), cholinergic/adrenergic, pre/post-ganglionic
- ventral horn/ root → motor neurons, dorsal horn/root → sensory neurons
- somatic vs. autonomic: structures innervated, mode of action, & effect of denervation
  - somatic: striated muscle; myelinated, cholinergic, nicotinic receptor, no ganglion, always excitatory; paralysis
  - autonomic: smooth muscle, cardiac muscle, glands, adipose tissue; ganglia, excitatory or inhibitory; lost ability to regulate ANS (e.g. quadriplegic)
- SNS: motor unit: each neuron & the muscles they innervate (e.g. large postural motor unit, small finger motor unit), NT released from varicosity
  - 1 neuron → many muscle fibers, but 1 muscle fiber → 1 neuron

terminal boutons → end plate potential → motor end plate

- neuromuscular junction: be able to relate frequency of AP to degree of contraction

Be able to describe effects of sympathetic and parasympathetic nerves and their NTs on any organ or tissue

- ANS pathway: preganglionic (myelinated, long, cholinergic, nicotinic receptor) → ganglion → postganglionic (unmyelinated, short)
- SANS pathway (thoracic/lumbar): preganglionic → ganglion (paravertebral/adrenal medulla/peripheral) → postganglionic (adrenergic (NE))
- PANS pathway (cervical/sacral): preganglionic → ganglion (peripheral) → postganglionic (cholinergic, muscarinic receptor on effector organ)
- vagus nerve/cranial nerve X: PANS innervation of lungs, bronchioles, heart, liver, spleen, pancreas, stomach, intestines
- adrenal chromaffin cells: postganglionic sympathetic fiber which releases epi



Know the receptors on each tissue

Receptor type	Effector organ with receptor type	Relative affinities*	Signal transduction mechanism	Effect on effector organ†
α_1	Most vascular smooth muscle, pupils	NE > Epi	Activates IP_3	Excitatory
α_2	CNS, platelets, adrenergic nerve terminals (autoreceptors), some vascular smooth muscle, adipose tissue	NE > Epi	Inhibits cAMP	Excitatory
β_1	CNS, cardiac muscle, kidney	NE = Epi	Activates cAMP	Excitatory
β_2	Some blood vessels, respiratory tract, uterus	Epi ≫ NE	Activates cAMP	Inhibitory
β_3	Adipose tissue	NE = Epi	Activates cAMP	Excitatory

- α1: vessels (arterioles → none), lungs (bronchial glands), salivary glands (mucus → water), digestive tract (motility), sweat glands, eye (iris radial muscle → circular muscle), liver (glycogenolysis/gluconeogenesis**++** → none)
- α2: lungs (bronchial glands), digestive tract (motility, secretions), platelets (release granules), presynaptic inhibition
- β1: heart (SA node bpm, AV node conduction → none, contraction force → none)
- β2: vessels (skeletal muscle arterioles & veins → none), lungs (bronchial muscle), digestive tract (motility), liver (glycogenolysis/gluconeogenesis**++** → none)
- β3: adipose tissue (lipolysis)
- *exceptions*: excitatory muscarinic receptors on sweat glands
  on some blood vessels to skeletal muscle, muscarinic receptors → NO release from endothelial cells to dilate
- blood vessels to muscle: three stages
  posture → α1 shunts blood flow to other areas; preparing to run → β2 responds to epi from adrenal medulla; continuing to run → muscarinic (must release Ach because adrenergic receptors already stimulated)
- only SANS innervates blood vessels due to branching (excitatory response, α 1)
- look out for: in tissue vs on effector; all NT vs those released from ganglia

Understand mechanism of pre-synaptic inhibition

- α2/NE for SANS on PANS, muscarinic of PANS on SANS
- occurs in: SA node (pacemaker), radial/circular iris muscles, SANS in GI tract inhibits PANS via α2 receptors on postganglionic nerve terminals
- method: depolarization → driving force for Ca2+ entry-- → Ach release--

Lecture 5: PNS Pharmacology, Part I

Basic Concepts

- receptors at most peripheral site are acted upon first
  e.g. Ach → PANS response, but muscarinic antagonist + Ach → SANS response
- as a drug's lipid solubility is increased, its CNS action increases (BBB)
  blood-tissue barrier in systemic capillaries
  astrocytes build impermeable barrier (e.g. methamphetamine has a lower ED50 due to methyl group lending decreased polarity)
  hydrophilic molecules need selective transporters to get through the tight junction (vs. pore)

Axonal agents

- Tetrodotoxin (TTX) - blocks Na+ channels → death due to diaphragm paralysis
- Na+ channels locked open → longer AP → more NT release → tetanic contractions
- Procaine (Novocain)/Lidocaine/Benzocaine – local anesthetics that block Na+ channels
    - lipid soluble so they dissolve through the membrane
    - lipophilicity → absorbs into muscles in injection, increasing local effect

Presynaptic agents

- blocks or locks exocytotic docking to alter NT release

Muscarinic antagonists

- atropine → muscarinic antagonist

Nicotinic agonists and antagonists

- Hexamethonium – blocks nicotinic receptor only at ANS ganglia
- d-Turbocararine/curare – South American arrow poison, blocks receptor exclusively at SNS, zombification; used as muscle relaxant

Acetylcholinesterase Inhibitors

- reversible & competitive: esterine
- acetylcholinesterase on postsynaptic membrane

Lecture 6: PNS Pharmacology, Part II

Adrenergic antagonists

- α antagonists: very nonpolar, so high CNS activity
- α1-specific: Phenylephrine
- β agonist: Isoproterenol
- β antagonist: Propranolol (low CNS activity, lowers blood pressure, vasoconstriction has minimal effect)

Catecholamine synthesis

- tyrosine → +catechol (-OH) → L-dopa → -COOH → dopamine → +OH → NE → +CH3 → epinephrine
- feedback inhibition of tyrosine hydroxylase (L-Dopa) by NE in nerve terminal
- alpha-methyl-p-tyrosine: competitive inhibitor of tyrosine hydroxylase
- problem: inhibitors are temporary, requiring an increased dosage of the inhibitor → must increase dosage
- alpha-methyl-DOPA (Aldomet): nerve terminals synthesize same amount of NT, but some of it is inactive

Catecholamine reuptake/MAO inhibitors

- MAO breaks down catecholamines after reuptake → more NT in nerve terminal

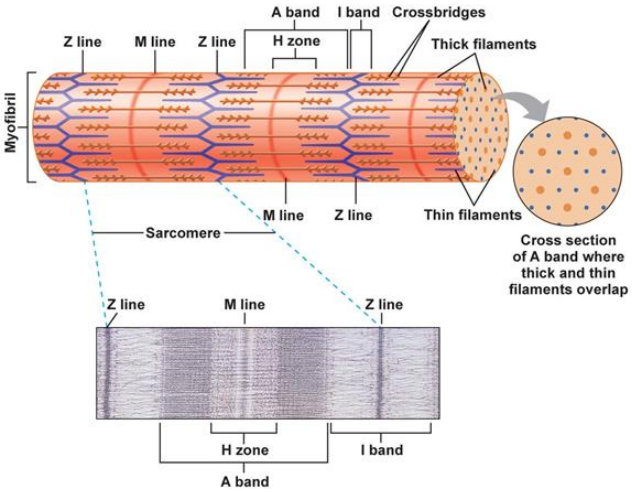
Histaminergic Agents

- receptors: 3 types, each with its own signal transduction pathway
- functions: relaxes vascular smooth muscle, contracts airway smooth muscles (asthma), contracts intestinal smooth muscle (diarrhea), increases capillary permeability (edema), increases secretion of stomach acid

Lecture 7: Muscle

Structure and function of skeletal muscle components

- striation organization: hexagonal, can be more organized into larger n-gons in muscles with higher contraction rates (e.g. humming birds)
- strength of a muscle is proportional to the number of cross-bridges it can form
- twitch – mechanical response to a single AP → highly reproducible, but varies from fiber to fiber

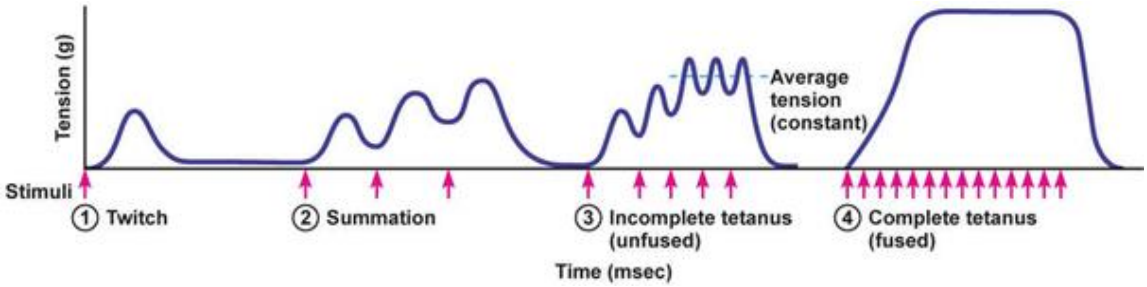


Cross bridge cycling and excitation – contraction coupling

- thin filaments: G-actin with myosin binding sites link to form F-actin, which forms a double-helix and binds with tropomyosin & troponin complex
- thick filaments: double-helix tail with 2 heads with an actin-binding site and an ATPase site
- contraction cycle: myosin binds to actin, phosphate released → powerstroke → ADP released, rigor (low-energy form) → new ATP binds, actin released → ATP hydrolysis, myosin head cocked (high-energy form)
- excitation cycle: Ach binds to receptors on motor end plate, eliciting EPP → EPP propagates down T tubules → AP changes conformation of DHP receptor in T tubule, activating ryanodine receptors in SR membrane, releasing Ca2+ → Ca2+ binds to more ryanodine receptors, opening them → Ca2+ binds to troponin, exposing binding sites → Ca2+ is pumped back into SR lumen

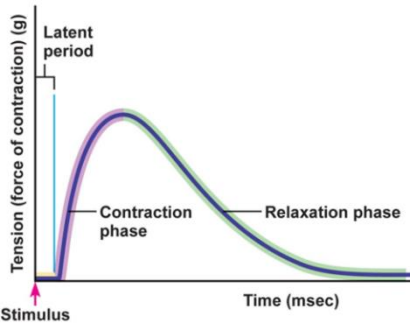
Mechanism for regulating tension in a muscle fiber and a whole muscle

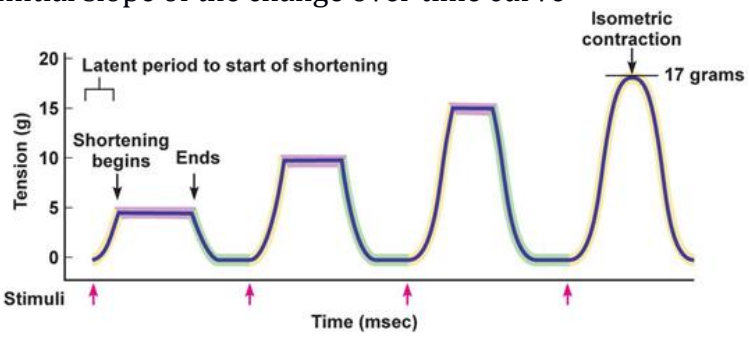
- the structure has evolved to meet the function
- force = cross-bridge activity (frequency of stimulation, fiber diameter, changes in fiber length) + # muscle fibers (recruitment)
- frequency of stimulation: when the Ca2+ release from the SR > Ca2+ active transport back into SR
  - peak tetanic/isometric twitch tension = force-generating capacity
  - treppe: peak tension rises until a plateau is reached
  - sustained contractions = asynchronous activation
- fiber diameter: larger diameter with sarcomeres in parallel = more cross-bridges
- fiber length: sarcomere length matters more than # sarcomeres in series
- size variety: # motor units, # fibers, diameter & strength of fibers
  - motor units with larger fibers tend to have more fibers
- size principle – larger motor units tend to be recruited last, because larger neurons control them, which are harder to depolarize, thus smaller graded potentials will activate smaller motor neurons first

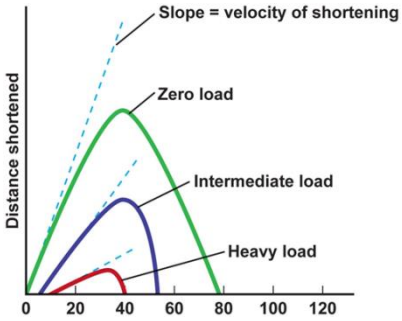


Isometric vs. Isotonic

- isometric: sarcomeres cannot shorten, all-or-nothing response
- latent period delay for excitation-contraction coupling
- measured with length & force transducer to strip-chart recorder
- load-tension curves: only shortens during the plateau; isometric curves don't have a plateau
- heavier load → tension++, latent period++, velocity of shortening--, duration--
- velocity = initial slope of the change over time curve

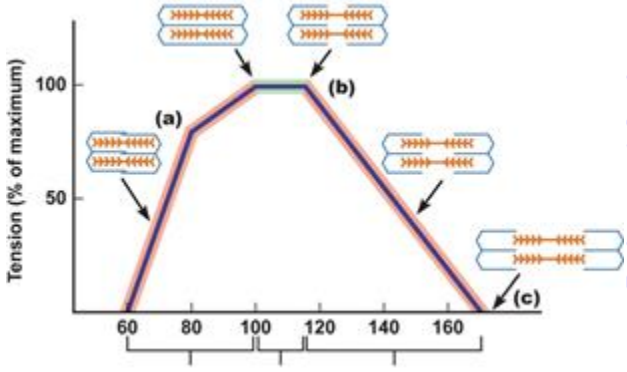


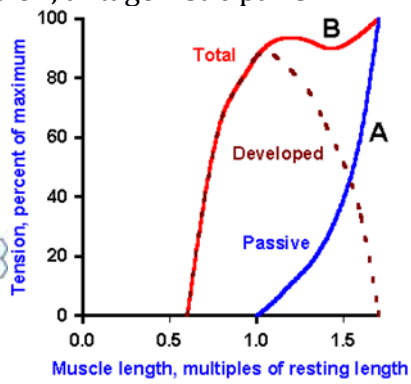




Length-tension curve

- shape determined by sarcomere structure
- passive tension: due to elasticity of muscle, stretching from L0/resting length
- past L0, passive tension increases while active tension decreases due to decreased actin-myosin interaction at each increase in length
- developed tension: passive + active/stimulated
- contractile component: sarcomeres generate force
- series elastic components: passively transmit force to end of muscle cell, needed for isotonic contractions
- muscles usually operate within optimum range
- terms: origin, tendon, insertion, flexion, extension, antagonistic pairs





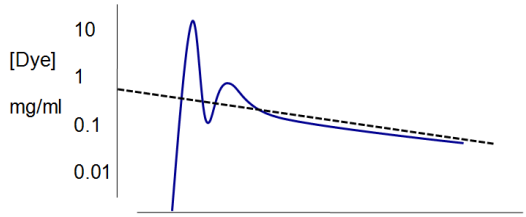
Types and functions of skeletal muscle fibers

- speed of contraction:
  - slow/fast twitch: rate of ATPase activity (measure liberated phosphate)
  - cross-bridge cycling is rate-limiting step
- primary mode of ATP production:
  - substrate-level phosphorylation: creatine phosphate → creatine + ATP OR glucagon → glycolysis → ATP
  - oxidative phosphorylation: glucose + fatty acids → pyruvic acid → lactic acid +2ATP → glycolysis → CO_2 + H_2O + 36ATP
  - glycolytic: more enzymes, larger, fewer capillaries, white muscle, more efficient
  - oxidative: more mitochondria, contain myoglobin, red muscle (no lactic acid)
- combination: slow oxidative, fast oxidative, fast glycolytic
  - progression: glycolytic capacity++, contraction speed++, myosin ATPase activity++, resistance to fatigue--, fiber diameter++, motor unit size++, force-generating capacity++
  - fatigue: strong contractions compress capillaries, generating more lactic acid

Lecture 8: Blood

Measuring blood volume

- blood volume: 6-8% x 70kg = 4.2L
- internal fluid compartments: total body water(42L) = intracellular fluid (blood & somatic cells, 28L) + extracellular fluid (plasma (serum + clotting factors, 3L) + interstitial fluid (11L) + CSF, 14L)
- how to measure: select a solute molecule that distributes within the desired compartment but is not transported out of it, not metabolized, high MW, nontoxic & measurable



- dye dilution technique: inject certain amount, measure concentration at equilibrium (e.g. spectrophotometry) → volume = weight injected/concentration measured
- correction for loss of injected solute: must measure concentration in urine & rate of urine formation, then subtract this from the total originally injected
- blood doping: centrifuge out RBCs, then add back in before race; improves available oxygen if your heart is powerful enough to pump the thick blood

Measuring volumes of other compartments

- plasma: dextran, 69kD (high MW means won't travel outside capillaries)
- blood: take plasma volume & correct for hematocrit
  centrifugation: 55% plasma, 45% hematocrit (38-47% normal), >1% buffy coat (leukocytes & platelets)
  blood volume = plasma volume/(1-hematocrit%)
- extracellular: inulin, 5.2kD
- total body water – use labeled water (D_2O or ^3H_2O)

Blood components

- plasma: proteins (albumin, clotting factors, antibodies, hormones), small nutrients (lipids, carbohydrates), metabolic waste, gases, ions, 90% water
- erythropoiesis: hematopoetic stem cells → maturity in bone marrow (except T lymphocytes, which mature in the thymus gland)
  HGF erythropoietin → lose nucleus, gain hemoglobin
- Wright stain: polymorphonuclear/granulocyte (neurtrophil - neutral, basophil - basic, eosinophil - acidic) vs monomorphonuclear/agranulocytes (monocytes → marcrophages, B & T lymphocytes)

Erythrocytes

- spectrin net, biconcave disks (max SA)
- size of RBC determines size of capillaries & vice versa
- #: male: 4.5-6.5 x 10^6 cells/uL, female: 3.8-5.8 x 10^6 cells/uL; look for correct ratio of # to volume for healthy cells

Hemoglobin

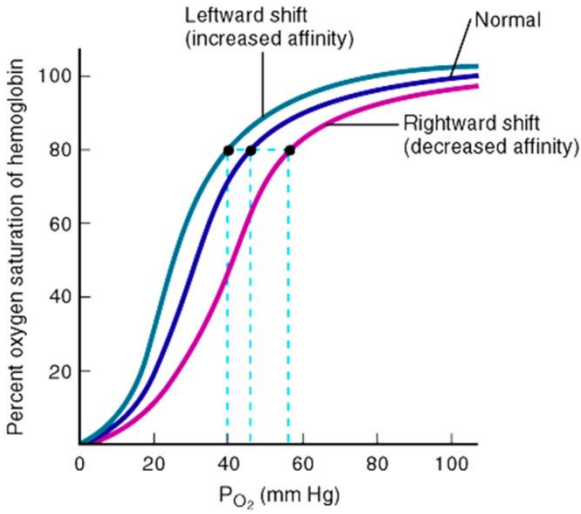
- 2-3 x 10^8 molecules/RBC, 12-16g/100mL blood (cannot be dissolved)
- [O2] + [Hb] <--> [Hb(O2)4]
- 98% of O2 in blood is bound to Hb
- 1.34mL O2/g Hb → 20.1mL O2/100mL blood
- structure: MW = 64,458, 4 polypeptide chains (2 alpha 141aa; 2 beta 146aa), 4 heme groups (Porphyrin, Iron)

- fetal hemoglobin: gamma chain expressed instead of beta chains; replaced 12wk post partum because affinity too high
- sickle cell anemia: replace #6aa glutamic acid with valine on B subunit
- other genetic variations also on chromosome 11 (beta) vs chromosome 16 (alpha)

Hemoglobin-Oxygen Curves

- curve is sigmoidal because binding is cooperative
- all oxygen-binding proteins in animal blood has cooperative binding and has subunits
- P50 = [O2] in mm Hg that yields 50% saturation of Hb → higher value means right shift, lower affinity
- you cannot change the oxygen saturation → the problem is always unloading O2
- for HbA (26.8mmHg), HbF(19-20), HbS(34)
- factors that affect affinity: temperature--, pH++
- carbonic anhydrase catalyzes: CO2 + H2O <-> H2CO3 <-> H+ + HCO3- → as [CO2]++, pH --
- hyperventilation decreases [CO2], yet will cause you to faint before you alter your pH too severely
- Mt Everest: curve shifts left in a positive feedback loop (less oxygen → lower metabolism → colder → less oxygen)

  low O2 → 2,3-DPG++ → Hb affinity--
- eventually, heart will overwork and cause pulmonary edema, decreasing available oxygen even more
- exercise: increased 2,3 Diphosphoglycerate; glycolysis: glucose-P → 2 (1,3 DPG) → 2 pyruvate; elevated plasma Epi → stimulates glycolysis in RBC via beta receptor (cyclic AMP) → 1,3 DPG increases and via DPG isomerase so does 2,3 DPG → Hb affinity for O2 is decreased



Lecture 9: Blood Blood

Understand basis for ABO blood groups

- determined by carbohydrate groups on peptide backbone of RBC transmembrane glycoprotein (glycophorin) → Karl Landsteiner in 1920s
- detected with antibodies, purpose is to recognize foreign cells
- antibodies: proteins secreted by B lymphocytes (differentiate into plasma cells) which binds specifically to an antigen after exposure
- 2 heavy chains + 2 light chains (variable region + constant region)
- heavy chains categorize immunoglobulins: IgG (dimer), IgM (pentamer, first response), IgA (secretions), IgD (response to parasites), IgE (allergic responses & on basophils)
- why have antibodies against other blood antigens? → you have suppressed B cells against your own antigens, but not against certain bacteria in your intestines

Rh blood groups & pregnancy

- Rh type: inject rhesus monkey RBC into rabbit → extract anti-Rh antibodies (antigenic (-) types cannot receive nonantigenic (+) blood)

- Rh- pregnancy with Rh+ fetus: fetal RBC leaks into maternal circulation, causing anti-Rh IgM production (cannot cross placenta because too large) → second Rh+ child attacked by IgG → child is born hypoxic & anemic (erythroblastosis fetalis)
- Rhogam/passive immunization: administer anti-Rh to mother to cover the child's fetal RBC groups
- why not ABO? → IgM response only

Feedback loop for the regulation of number of RBCs

- maturity in bone marrow: hematopoietic stem cells → erythroblast (myeloid stem cell) → normoblast → reticulocyte → biconcave mature RBC (2.3 x 10^8 per day)
- organelles in precursors: nucleus, free ribosomes to make hemoglobin, ER to make porforin ring, mitochondria to make ATP, other protein synthesis structures
- kidney synthesizes & releases EPO/ESF/erythropoietin (small amount produced in liver)
- renal blood flow is constant (1L/min) → oxygen sensor resides here → kidney is a sensor for negative feedback loop
- EPO synthesis necessary for patients undergoing chemotherapy
- regulation of EPO synthesis: constitutive (always produced) transcription factors called hypoxia inducible factors (HIFs) are hydroxylated and digested by proteosomes in presence of oxygen
- EPO receptor: activates JAK cascade (tyrosine kinase promotes gene expression & cell differentiation), works on mature RBCs in circulation to protect them from apoptosis
- stimulus is tissue hypoxia → closed negative feedback loop

Anemia

- hemorrhagic (blood loss)
- aplastic (marrow damage due to organics/xrays)
- hemolytic (sickle cell, snake venoms, transfusion with wrong blood type)
- pernicious (vitamin B12 deficient, destroyed in stomach acid unless bound to extrinsic factor to pass into intestines)
- iron deficiency

Processes utilized to remove and destroy aged RBCs

- bilirubin: get
- proforin ring is very lipid soluble, so cannot be released into circulation or would enter tissues
- albumin binds bilirubin (conjugated) and goes to gall bladder as bile salt (amphipathic = detergent), which go to small intestines & are released with fats from meals; bacteria process
- 90% of bile salts are released into circulation & recycled in liver (free)
- jaundice: babies (destroying fetal hemoglobin), alcoholics, & hepatatis patients
- increased conjugated bilirubin: hepatic; kidney malfunction or gall bladder problems
- increased unconjugated bilirubin: hemolytic; liver problems

Lecture 10: Blood Blood Blood

Understand the clotting process

- stages of hemostasis: vascular spasm (pain → SANS response; NE & 5HT release → local vasoconstriction); platelet plug; clot formation
- platelets – non-nucleated, membrane-bound bits of cytoplasm & vesicles from megakaryocytes (too few = thrombocytopenia purpura, spontaneous bruising, such as bone marrow diseases)
- platelet plug: platelets adhere to negatively charged surface (collagen in cut blood vessels)
    - this means implants cannot have any charge
    - binding promoted by von Willebrand Factor (vWF), which binds collagen (synthesized by megakaryocytes, platelets, & endothelial cells)
    - degranulation: release of 5HT & epi; ADP causes adhesion & aggregation; TXA2 causes aggregation, ADP, & vasoconstriction
    - positive feedback loop
    - blood thinner = clot inhibitors
    - 80mg aspirin inhibits TXA2 synthesize, but more inhibits other products of the COX pathway
    - happy endothelial cells release prostacyclin & NO, which prevent platelet aggregation

Clot formation

- fibrinogen (inogen = inactive precursor) converted to fibrin
- fibrin stabilizing factor (FSF/factor XIII) covalently links fibrin threads
- prothrombin → thrombin, which is converted by factor X (which must first be activated)
- extrinsic pathway: tissue thromboplastin (III) + lipids
- intrinsic pathway: IX via XI via XII (activated by collagen or negative charge)
- factor X – hemophilia of the royal families of Europe, most important factor
- positive feedback loop
- get figures!
- Used to be studied by adding clotting factors from normal blood to hemophilic blood

Anti-coagulants

- ca2+ chelators (e.g. EDTA, syringes)
- siliconized glass (non-wettable surface) – slides would otherwise clot
- heparin – natural anti-coagulants made from mast cells & basophils; localized in precapillary area
- coumarin derivatives (vitamin K analogs): vitK catalyzes carboxylation of glutamic acid residues of clotting factors, coumarin inhibits this process
- warfarin – rat poison

Clot retraction

- activation of fibrinolysin & plasmin by thrombin, factor XII, & tissue enzymes

Forces that determine fluid flow across systemic capillaries

- arteries vs veins: smooth muscle thickness, oxygenation, & valves
- fenestrated vessels: don't have basement membrane
- capillary barrier is selectively permeable to solutes < 69kD; repels negatively charged
    - electrophoresis of plasma proteins

- Starlin's capillary hypothesis: blood travels through capillaries down hydrostatic pressure gradient)
    - pressure is highest in arterioles near heart & lowest in venoules near heart
    - negative pressure across capillaries into ISF, opposing force (osmotic pressure) returning fluid to capillaries to prevent edema
    - plasma osmotic/oncotic pressure (pi = 25mmHg): due to concentration of proteins in plasma too large to leave capillaries
    - blood pressure decreases across capillaries, but pi remains constant (filtration → reabsorption)
    - filtration++ → edema, reabsorption++ → tissue dehydration
    - predict effects of plasma proteins in ISF, dehydration, hypertension, overhydration, elephatiasis parasite, histamine release (cuts blood flow to prevent allergen travel), saline administration
    - get table 14.3
- factors causing edema
- factors causing tissue dehydration
- lymphatic system collects leaking plasma proteins & dumps them back into circulation via thoracic? duct
- duct can also be blocked by edemas & cancers
- add saline + plasma "expander" (usually dextran) to prevent edema

Lecture 11: Cardiac Function, Part 1

Overview

- effect of SANS & PANS on cardiac output
- structures
- ionic events of pacemaker & cardiac muscle cell action potentials
- evolutionary need for these events

Blood flow

- systemic & pulmonary circuits
- cardiac output: fluid flow Q (mL/min) = deltaP/R = SV * HR
- pressure: (aorta) 90mmg → (venae cavae) 0mmHg
- resistance: radius & length of vessels and viscosity of blood
- pressure drops due to resistance, ventricle creates suction (negative pressure) force during systole → if cannot relax, venous pooling occurs
- RV (-4 to -8mmHg) has lowest pressure, LV has highest pressure

Heart structures

- pericardium (pericarditis is inflammation of this layer) & phrenic nerve to diaphragm → epicardium
- coronary arteries: right, left, circumflex, left anterior descending → occlusion leads to higher blood pressure to circumvent
- larger animals with greater metabolic demands leads to 4th ventricle
- 4 valves: bicuspid/mitral and tricuspid; pulmonary & aortic semilunar → open and close based on amount of pressure in ventricle (valves broken → backflow of blood → heart murmur)

- chordae tendinae & papillary muscles – develop isometric tension during contraction of ventricles
- rheumatic/scarlet fever/strep – immune response can cross-react with valve tissue, leading to heart murmur; secondary infection can lead to serious heart problems

Cardiac cell structures

- small (better S:V ratio, cannot afford to lose many), discrete cells with intercalated disks with desmosomes & gap juntions (syncytium), many mitochondria, SR & t tubules, striated (maximum tension)
- no resting length
- **<get cell figure + active tension curve>**
- Starling's law of the heart: EDV++ → ventricular muscle stretching towards optimal length → SV++

Cardiac contraction coupling

- SA node → atrial depolarization → AV node (pause, overlaps with AV's spontaneous depolarization) → bundle of His, right & left bundle branches, Purkinje fibers → ventricular depolarization
- Purkinje fibers – smaller diameter (low velocity) modified muscle fibers
- **<get pacemaker conductance graph & table 13.1>**
- no resting membrane potential
- slow initial depolarization (Pk--) → funny channels (Pna++) → T channels open briefly (Pca++) → L channels (Pca++) → Pca--, Pk++
- spread of excitation: **<figure 13.11>**
- **<get contractile cell graph & table 13.2>**
- contractile cell: long AP rather than multiple fast APs to maintain diastolic pressure & to give long refractory period (prevent fibrillation)
- myocardial infarction – death of muscle tissue from heart attack
- phases: 0 (Pna++) → 1 (Pna--) → 2 (Pk-- rectifier channels, Pca++ L-type channels) → 3 (Pk++, Pca--) → 4 (Pk++)
- K+ inward rectifier channels operate to <0:46>

Blood flow

- vagus nerve (cranial nerve X) → PANS nerve from medulla to SA & AV, various other efferent & afferent functions
- sympathetic cardiac nerve from thoracic paravertebral nerves → SANS to SA, AV, & ventricular myocardium
- there are some muscarinic receptors on ventricles, but no one knows why (normally allow EDV to determine contractility)
- inotropic (+/-) drugs: affects strength of contraction
- chronotropic (+/-) drugs: tachycardia (+) or bradycardia (-)
- **<see impt concepts slides>**
- B1 receptor: phosphorylates funny (Na+) & T (Ca2+) channels
- muscarinic receptor: 2 G-proteins will open K+ channel & close T (Ca2+) channel
- 4 subunits of PK → opens L channel, opens Ca2+ channels in SR, increases rates of myosin-ATPase, activates SR Ca2+-ATPase
- understand how they increase rate of contraction, rate of relaxation, & tension
- at rest, you have a balance between PANS & SANS (presynaptic inhibition), with PANS stimulation dominating

- the problem: as HR increases, EDV does not increase, so you must increase VR (training involves increasing this)

Lecture 12: Cardiac Function, Part 2

EKG

- intracellular (MPs) vs extracellular (differences in polarity between electrodes) recordings
- EKG gives repeatable standard record of blood flow through the heart by measuring differences between leads
- direction of waves doesn't matter
- P wave: atrial depolarization
- QRS wave: ventricular depolarization (+atrial repolarization), always largest
- T wave: ventricular repolarization
- know when channels & valves open, diastole/systole, nodal delays
- heart rate increase decreases T-Q segment
- sinus rhythm: generated by AV node

tachycardia: so fast that T & P overlap, inverting T wave
bradycardia: so slow that

- 3rd degree heart block (SA-AV conductance pathway broken, so atria beat independently from ventricles): P wave completely independent from QRS complex
- extra systole: PAC or PVC
- fibrillation: loss of coordinated electrical activity (ventricular = death)

Cardiac Output

- EDV: filling due to ventricular diastole, with extra bit from atrial systole
- CO = HR x SV = VR
- BP = CO x TPR
- Starling curve: VR++ → EDV++ → closer to optimal length → increased troponin affinity for Ca2+ → contraction strength++ → SV++
- La Place's law: P = 2T/r (spheres) of T/r (cylinders)
- pressure in aorta/ventricle at ejection = 2*myocardial tension/radius of ventricle as start of systole
- SANS: as HR++, filling time-- and CO does not ++ unless VR++
- LV PV graph: entire block is larger
- PANS: as HR--, SV++
- VR++ without CO++ → venous pooling & edema
- to VR++, must inc pressure difference between left & right ventricle (greater pressure gradient)
- think about CO & BP eq (SV) as it relates to fitness

Lecture 13: Blood Flow

Blood flow

- to increase MAP, you must increase pressure differences between left & right ventricles
- inc constriction → inc TPR → problem is heart has greater resistance to pump against

- ways to increase flow: inc CO (HR x SV) or TPR (CO/BP)

Lecture 15: BV & BP Regulation

Blood flow

- do practice exams for discussion
- see graph slide for discussion question
- watch CPR videos
- no SANS stimulation: TPR++, SV & CO--
- SANS stimulation: TPR++, contractility & VR++ → SV & CO++
- factors contributing to CO: HR, SV, VR, TPR, & CVP
- fitness: as you increase HR, you must also increase VR to increase SV (curves with & without SANS) → stress test
- digitalis: slows pacemaker exclusively → give to people with hypertension → **why can't you give these to everyone?**

Venous Return

- abdomino-thorasic (respiratory) pump squeezes vena cava
- skeletal muslce pump
- arterial pressure
  - ventricular systole (SV++)
  - arterial TPR
  - determines flow through arteries
- venous pressure (CVP) determines flow from veins to right ventricle → **do you experience these changes in the pulmonary system?**
- ventricular diastole (filling)

Baroreceptors

- why do we measure pressure instead of flow? → baroreceptors evolved because flow to high for flow meters (e.g. inner ear)
- Is pressure a good measure of flow? → yes, CO = BP/TPR, problem is when TPR is at abnormal levels (hypertension & shock)
- How does one build a baroreceptor? → mechanically gated channels, stretch-sensitive Na+ channels
- major baroreceptors: aortic arch & carotid sinus (brain, protected by jaw bone, vulcan pinch)
- draw negative closed feedback loop for BP

Vagus Nerve

- efferent (PANS – pacemaker & upper GI tract) & afferent (baroreceptor from aortic arch, stretch receptors from lungs)
- stimulation will drop HR, drop HR, & stop respiration
- stretch receptors in lungs tell medulla to stop inhaling
- input into nucleus tractus solitarius in medulla

Chemoreceptors

- PO2 receptors in carotid & aortic bodies & maybe in medulla
- only important at low PO2 (<60mmHg in arteries)
- can only measured dissolve oxygen, so not very accurate
- unimportant to BP regulation normally (e.g. suffocation, during surgery)

- **how can you prevent vasovagal syncope?**
- Practice graphs & up/downs with negative feedback loop

Pharmacology
- if TPR++exclusively (a1 agonist) → SV--
- if TPR-- exclusively (histamine) → SV--

Renal Control
- BV: inc Na+ reabsorption → inc water absorption → inc BV → raise BP
- ADH/vasopressin: released from posterior pituitary in response to elevated oncotic pressure, lowered BP/BV, & dec atrial EDV/baroreceptor distension
- ANP: atrial natriuretic peptide, released from atrial myocytes in response to distension/high atrial EDV (inhibits Na-K ATPase)
- renin: released by justaglomerial cells in response to low renal blood flow
- angiotensinogen –renin-> angiotension I –ace-> angiotension II (most potent known vasocontrictor) → constrict peripheral arterioles & inc aldosterone (inc transcription of Na-K ATPase) & inc ADH
- angiotension conversion enzyme → in pulmonary veins to spread throughout systemic system, but not pulmonary arteries
- ace inhibitors (angiotension II inhibitors also work)
- inc TPR → VR → CO → renal bloodflow

Lecture 15: Autoregulation

Autoregulation: Intrinsic Regulation of Blood Flow
- over a wide range of pressures in arterioles, the blood flow does not change → isolated tissues regulate their own blood flow independent from systemic regulation (eg ANS)
- as MAP++, TPR++
- myogenic mechanism: as smooth muscle stretches, it responds with contraction (high BF)
- tissue metabolism: don't remove CO2/lactic acid to dec pH, release NO & adenosine/adenine & Krebs cycle intermediates (low BF)

Lecture 17: Respiratory System

Anatomy
- external respiration: pulmonary ventilation (inspiration + expiration), CO2/O2 exchange between alveolar space & blood via diffusion, transport of gases in blood, CO2/O2 exchange between blood & tissues via diffusion
- thoracic cavity: diaphragm distends to increase volume & decrease volume
- trachea: cartilage rings, lymph nodes, receptors (histamine, mAChr, β2)
- alveoli: air space, endothelial cell, collagen basal membrane, endothelial cell & capillary walls
- as soon as O2 diffuses into plasma, it is bound to hemoglobin to maintain pressure gradient
- conducting zone: trachea, bronchi, bronchioles, terminal bronchioles (no exchange → dead space)
- respiratory zone: respiratory bronchioles, alveolar ducts, alveoli (exchange)

Alveoli

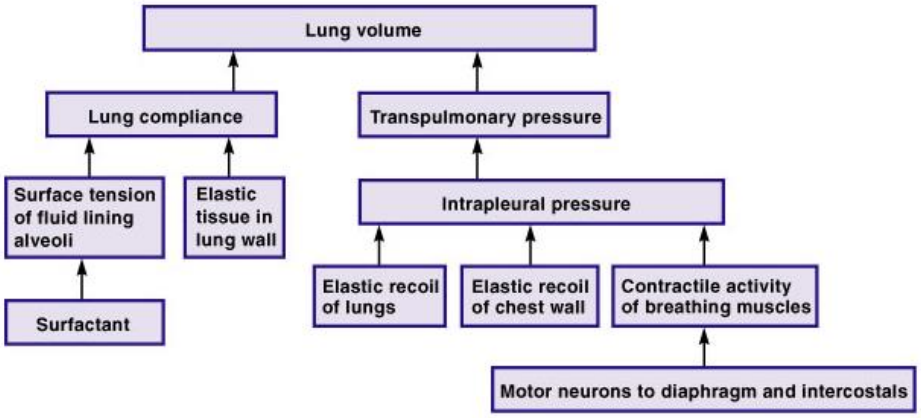
- SA: 75m^2, 300-500 million → short diffusion difference
- pneuomocytes (type II) cells: watery coating (animals prevent water loss via condensation in long nasal passages)
- macrophages (motility slowed by tar)
- inc diffusion distance by factor → inc time by factor^2 (tar, edema, etc)
- challenge: how do you spread air flow evenly to all branches and match blood flow?

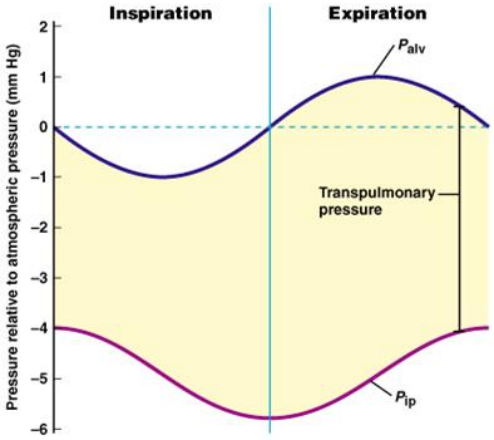
Thoracic Cavity

- pneumothorax: when air enters one side of the intrapleural space → lung collapses
- left lung has one lobe, right lung has two
- intrapleural space (between visceral & parietal pluera) → negative pressure due to lungs recoiling inwards & chest cavity recoiling outwards
- you can't isolate the pressure in your lungs from that of the environment
- when you dive, as the pressure increases, gas is driven into solution → you must slowly adjust to lower depths so that gases comes out of solution into your lungs rather than into your tissues

Breathing

- **graphs: breath volume, pressures**
- inspiration: diaphragm & external intercostals contract (ribs raise)
- expiration: diaphragm & external intercostals relax (passive); internal intercostals & abnominal muscles contract (active)
- Boyle's Law: for a set volume of gas, pressure is inversely related to volume
- Pip follows Boyle's law because it is a closed system, but Palv does not follow it strictly (eg pressure equilibrates at the end of inspiration, but volume still increases)
- PV = nRT and flow = (Patm-Palv)/R





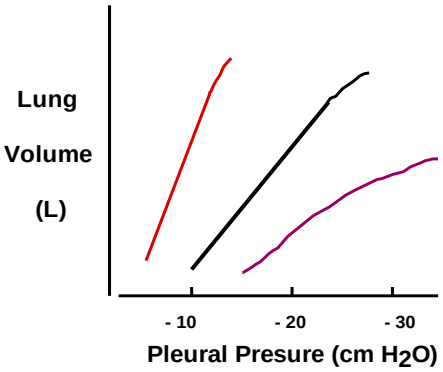
- inspiration: neural input++ → diaphragm & external intercostals contract → chest wall expands → parietal pleura expand → pull on intrapleural fluid → Pip-- → transpulmonary pressure++ → lung volume → Palv-- → Ralv++ → (Patm-Palv)++ → air flow into alveoli → Palv++ → negative feedback loop

Airway Resistance

- airway resistance: smooth muscles on bronchioles, mucus secretion, passive forces → higher resistance means must achieve greater pressure differences to get the same volume of air
- lung compliance = ΔV/Δ(Palv-Pip)
- La Place's Law: transpulmonary pressure = 2*(surface tension + elastic recoil)/R
- problem: some alveoli are smaller than others, and according to La Place's law, they must collapse into larger ones → T must decrease to match R
- water has surface tension (70nM/m) due to polar adhesion → attempts to collapse large alveoli, acting against transpulmonary pressure
- water → dec compliance, but present in higher concentrations in smaller alveoli so that the surface tension inside is lower to prevent collapse
- dec compliance → have to work harder (greater Palv) for the same volume of breath → higher load on cardiovascular system (similar to TPR++ PFL)

Surfactant

- surface tensions: 30mN/m at 100% TLC, 1-6 at 40-60% TLC in a healthy lung
- phosphatidylcholine/DPL: detergent/surfactant (amphipathic molecule – nonpolar fatty acids + polar choline) secreted by alveolar type II pneumocytes
- SP-A & SP-D have carbohydrate recognition domains which coat bacteria & vira (innate immunity); SP-B & SP-C are hydrophobic membrane proteins
  - hyaline membrane disease: premature babies have not produced enough surfactant, so they must undergo positive pressure ventilation
  - **if killing type II pneumocytes makes you more susceptible to infection due to reduced secretions, why do increased secretions also promote infections?**



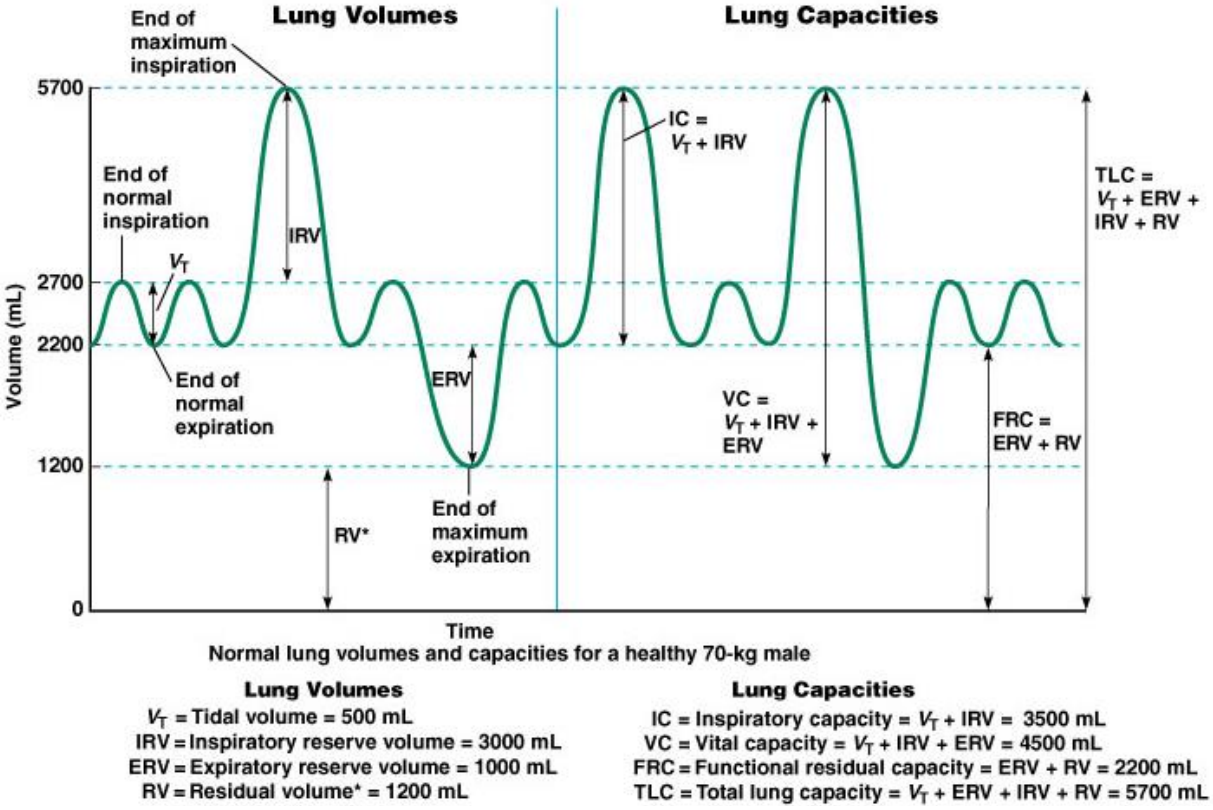
Clinical Problems

- CF: dec surfactants → increased resistance in alveoli → need a larger pressure gradient
- COPD: emphysema, chronic bronchitis, & asthma (treat with β2 agonists)
  - emphysema: chronic inflammation → macrophages secrete proteases → connective tissue destruction → (SA++ → diffusion--) && (compliance++ → IRV++ but VC-- due to increased effort to exhale)
  - chronic bronchitis: inflammation & secretions → alveolar diameter-- & tissue destruction
  - asthma: spastic smooth muscle contractions & secretions & inflammation
  - pulmonary edema: diffusion distance++ & compliance—

Lung Capacity

- **design a test to measure someone's lung capacity**
- **graph: pleural pressure v. lung volume (CF & emphysema)**
- spirometer: total lung capacity = vital capacity (IRV + ERV + TV) + residual volume
- residual volume can be measured by breathing helium & comparing expired concentration to inspired concentration
- obstruction → rate changes (airway resistance++) → low FVC; capacity reduced → volume changes (lung compliance--) → low FEV (should be 80% of VC)
- minute ventilation = [tidal volume (500mL)]*[respiratory rate (12/min)]

- alveolar ventilation rate = [TV – dead space (150mL)]*[RR] = volume of fresh air
- it is more efficient to inc TV than RR because the effect of dead space decreases
- however, deeper breaths → oxygen requirement is higher for deeper breaths than the volume advantage you gain



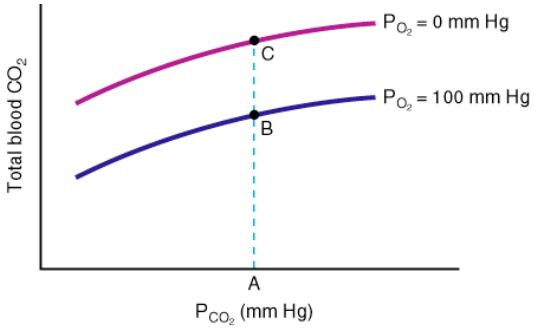
Lecture 18: Respiratory System II: Gas Exchange & Breathing

Diffusion Equation

- diffusion of gases: rate of change (ds/dt) = DARTΔC/L(MR)$^{1/2}$
- D = diffusion coeff (relates to ability to dissolve molecule in aqueous phase); A = SA; C = conc gradient; L = path length of the membrane; MR = radius of gas molecule
- CO2 has a much higher D because it is more soluble in water (cm/s^2) due to H bonds
- solubility depends on temperature, partial pressure of gas, chemical properties
- Henry's law: k = c/P → c1/P1 = c2/P2, so pressure++ → gas dissolved++
- lung diffusion capacity: DL = Vgas/(P1-P2) = Xml/min/mmHg, rate at which O2 diffuses from alveolar space into blood **→ how would you design an experiment to test this?**

Gas Exchange

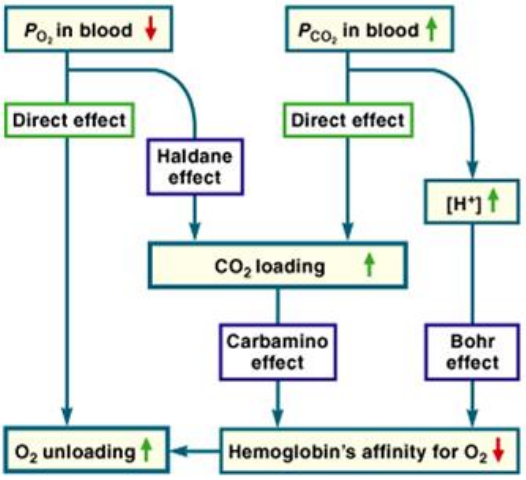
- 95% of O2 carried by hemoglobin + 5% carried by plasma
- PCO2: 40mmHg in systemic arteries (pH=7.4), 46mmHg in systemic veins (pH =7.3)
- eg given Patm of each gas = 100mmHg: 0.15 mM O2 dissolve, 3.0 mM CO2 dissolve
- PO2/PCO2 in: alveolar air/pulmonary veins/systemic arteries (100/40), cells (<40, >46), systemic veins/pulmonary arteries (40/46), atmosphere (160/0.3)



- in alveoli, water vapor (47mmHg) & CO2 (40mmHg) displace incoming O2 (160→100mmHg) and N2 (600→573mmHg)
- as you increase altitude, CO2 & water vapor occupy larger percentages of your alveolar space, displacing more O2
- alveolar partial pressures are determined by alveolar ventilation & respiratory quotient (O2 consumed by tissues/CO2 produced by tissues = 0.8)
- air is 21% O2, .04% CO2, 79% N2, and .5% H2O

Respiratory Physiology

- **graph: Haldane effect (PCO2 vs total blood CO2)**
- hypocapnia/hypercapnia (CO2), hypoxia/hypoxemia (O2 in tissues/blood)
- hypoventilation/hyperventilation, hyperpnea (inc ventilation to meet metabolic demand), apnea (cessation), dyspnea (labored breathing)
- as the length of the capillary increases, PO2++ & PCO2-- → exchange reaches equilibrium at 33% of length → safety factor of 2 (complete exchange even if CO++)
- O2 travels down conc gradient from alveoli to blood until hemoglobin is saturated
- CO2: 7% CO2 + 23% carbamino compounds on Hb (Hb-NH3+ + CO2 ↔ HB-NH-CO2; dec affinity for O2) + 70% HCO3- via carbonic anhydrase
- CO2 carried on terminal amino group, not in porforin ring
- Haldane effect: as Hb binds O2, Hb becomes a stronger acid and gives up H+ (picked up from carbonic anhydrase) → H+ binds HCO3-, converting it to CO2 & H2O → O2 binding also releases CO2 from carbamino groups on Hb → CO2 release into exhalation
- in respiring tissues, the Haldane effect promotes CO2 loading while the Bohr & carbamino effect promote O2 unloading

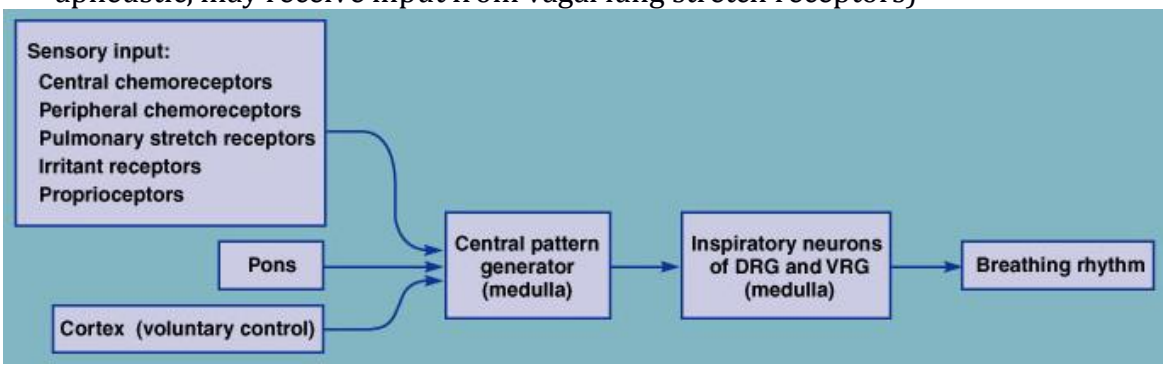


Lecture 19: Respiratory System III: Breathing Cycle & Regulation of Respiration

Central Regulation of Respiration

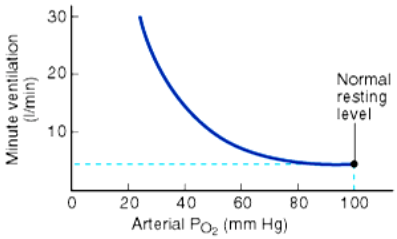
- **graphs: phrenic & intercostal nerve activity; inspiratory & expiratory muscle tension; lung volume (quiet & active ventilation)**
- all respiratory nerves are somatic (phrenic → diaphragm & intercostals → intercostals)
- ventilation regulation by CPG or by VRG/DRG interaction
- central pattern generator – network of neurons that can spontaneously generate a series of APs, then stop (exhalation), then change frequency based on input
- frequency increases at the end of inhalation → **why?**
- NTS - medullary center for respiratory & cardiovascular control; responds to peripheral input
- DRG: VRG, pons, apneustic center, sensory neurons → DRG (part of solitary nucleus) → respiratory rhythm via inspiratory neurons

- VRG: inspiratory & expiratory, especially active during exercise
- PRG: apneustic center (prolonged inspiration) & pneumotaxic center (inhibits apneustic, may receive input from vagal lung stretch receptors)

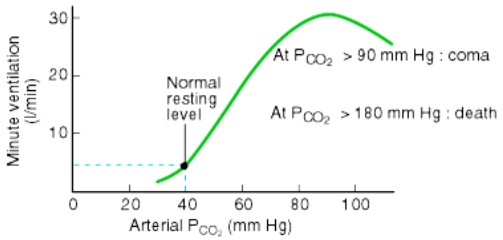


Inputs

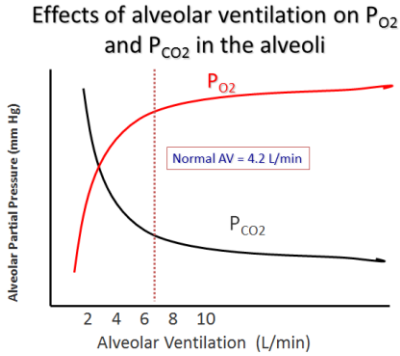
- **graph: PO2 & PCO2 vs minute ventilation**
- chemoreceptors: central (pH) & peripheral (aortic arch & carotid bodies, PO2 & PCO2)
- at PO2, hemoglobin binding affinity dives steeply
- **is the PO2 response different for newborns?**
- CO2 equilibrates rapidly between blood & CSF
- inputs during exercise: temperature, pH changes (lactic acid), muscle/joint receptors, proprioreceptors, learned response, motor cortex
- glomus cells: when PO2 < 60mmHg, O2 stops binding a K+ channel, closing the channel and depolarizing the cell → dopamine to DRG
- usually only occurs when patient is anesthetized



(a) Effects of arterial P_{O_2} on ventilation



(b) Effects of arterial P_{CO_2} on ventilation



Air vs Blood Flow

- ventilation perfusion ratio = (air flow/min) / (blood flow/min)
- pulmonary obstruction → VPR < 1; cardiac obstruction → VPR > 1
- PCO2++ or PO2++ → bronchodilation → resistance-- → ventilation++ & vasoconstriction → resistance++ → perfusion--

D in lung gas	Bronchioles	Pulmonary arterioles
Incr. P_{CO2}	dilation	Weak const
Decr. P_{CO2}	constriction	Weak dilation
Incr. P_{O2}	Weak const	dilation

Decr. P_{O2}	Weak dilation	constriction

Lecture 20: Deep Diving & High Altitudes

Human Deep Diving

- For every 33 feet you descend, the pressure doubles → the amount of gas dissolved in your tissues doubles, volume of air in lungs halves, & air in tank lasts half as long
- deep water blackout, shallow water blackout, & big squeeze
- scuba regulator delivers gas at pressure of atmosphere around you
- must also purge additional dead space
- combat the bends withed decompression to allow equilibration in alveoli → enter hypobaric chamber to fix
- gases under high pressure: nitrogen narcosis (rapture of the deep), CO2 narcosis, O2 toxicity due to free radicals
- nausea, twitching, disturbed vision, disorientation, dizziness, coma
- replace N2 with helium, remove CO2 with increased air flow at deeper depths

Animal Physiological Adaptations

- slight/no change in hematocrit, 1.5x hemoglobin (diffusion++ → requires pulmonary vascularization++), 7x myoglobin (no cooperative binding b/c 1 subunit), 10x brain O2 binding globins, TV is >80% lung volume, exhale before dive to prevent bends
- CO drops to 20%, vasoconstriction, BF to skeletal muscles reduced to nearly nothing (run anaerobically → prevent chemoreceptor response), RBC stored in spleen during shallow diving & released during deep dive
- reflex bradycardia: sphincter on posterior vena cava constricts to drop CO & deliver blood to critical tissues only (temperature-dependent response learned response by Japanese ama women)

High Altitude Adaptations

- At >13,000ft, PO2 is 60% of that at sea level, thus alveolar PO2 < 60mmHg
- hyperventilation, hypothermia, pulmonary edema → reduced PO2, increased PCO2
- acclimatization: kidneys reverse alkalosis by excreting bicarbonate to match H+ lost in CO2 reduction & secrete erythropoietin
- increased: Hb, hematocrit, capillaries in skeletal muscles, myoglobin, mitochondria, & 2,3-DPG (curve right shift)
- pulmonary arterial pressure++ → RV hypertrophy
- hematological adjustments take n km x 11.4 days
- Andes: higher [Hb] + higher TV → higher O2 carrying capacity
- Himalayas: higher RR + broader capillaries + higher NO levels
- on ch1 & 22: 10 unique Tibetan oxygen-utilization genes, EGLN1 & PPARA most prevalent, linked to Hb genes

Lecture 21: Renal Structure

Clearance

- renal plasma flow is 1L/min
- filtration (20% extraction ratio, passive) → reabsorption (lower clearance, active) → secretion (higher clearance, active) → excretion (net reabsorption)
- clearance of solute: volume of plasma from which it was removed in 1 minute

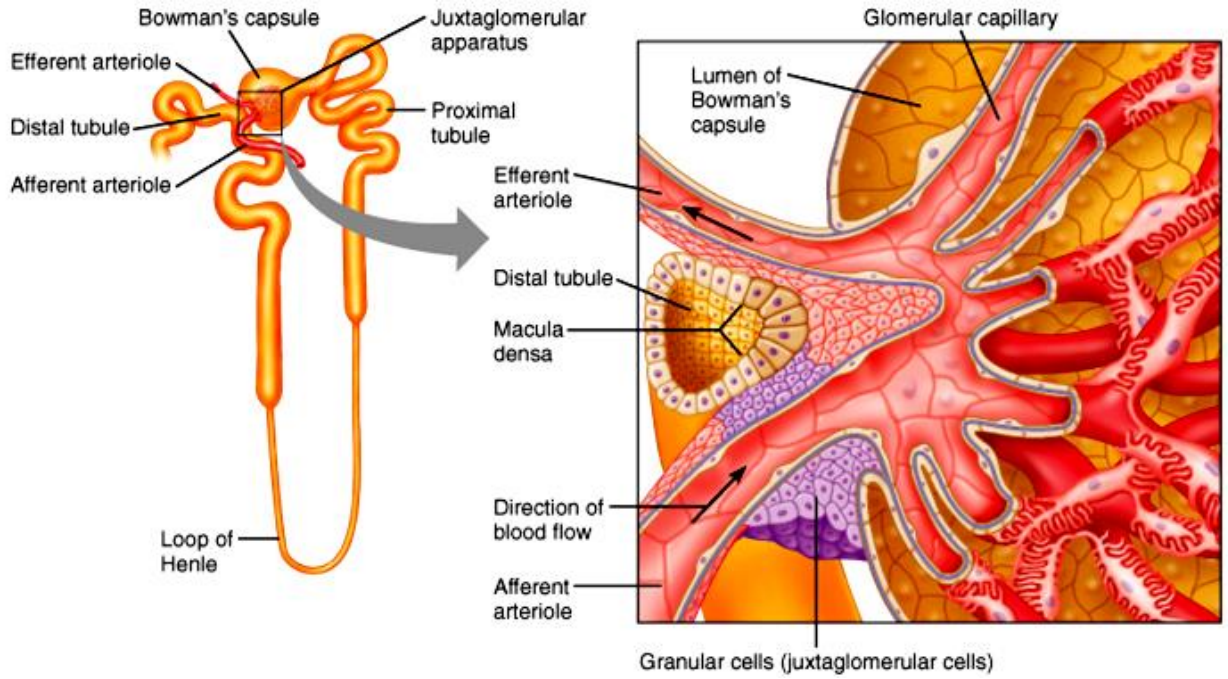
(filtration or secretion)
- inulin – only filtered, not secreted or reabsorbed

Kidney Functions
- regulate plasma [ion] (Na, K, Ca, Mg, Cl, HCO3, HPO4, H2PO4, H → pH & neural function), volume → blood pressure, & osmotic pressure → dehydration/edema
- remove metabolic wastes & foreign substances (urea & uric acid; food additives, drug metabolites)
- filtration: contains every plasma solute smaller than 69mw (20%)
- reabsorption: active selective transport of solutes from filtrate into plasma, M-M kinetics
- secretion: transport of undesirable molecules from plasma

Structures
- renal pyramids → nephrons → vascular & tubular supply
- afferent & efferent arterioles → peritubular capillaries around tubules for reabsorption → vasa recta around loop of Henle
- nephra: 80% are cortical (high in cortex with short dip in medulla), 20% are juxtameduallary (dips length of medulla)
- water in collecting duct is slightly dilute compared to plasma → can reabsorb more water via ADH → juxtameduallary nephra sets pressure gradient in medulla to reabsorb water from collecting duct
- blood is 300 milliosmoles → urine can be 1200-1400milliosmoles

Bowman's Capsule
- filtration in Bowman's capsule (solute conc same as in plasma) → proximal CT (reabsorption & some secretion) → proximal straight tubule → loop of Henle (descending & ascending; reabsorption & some secretion) → distal CT (excretion) → collecting duct (collects from 100+ nephra)
- filtration: elevate blood pressure to force edema → achieved by having large radius on afferent arteriole & small radius on efferent arteriole
- parietal & visceral layers
- podocytes lay down collagen filter over capillaries

Tubular Components
- distal CT exits between afferent & efferent arterioles → macula densa
- reabsorption ability is directly related to flow through tubules
- must maintain correct GFR to maintain homeostasis
- renal artery stenosis → filtration decreases
- low renal BF → low tubular fluid flow → high reabsorption → low fluid [Na+] & [Cl-] → macula densa change MP → gap junctions to juxtaglomerular cells → release renin into arterioles → vasoconstriction → renal BF++ & Na-K ATPase



Lecture 22: Renal Clearance

Kidney Function Experiments

- **calculations: clearance (ml/min), RPF & RBF, GFR (ml/min), extraction ratio (%), rate of filtration/reabsorption/secretion (mg/min)**
- clearance: hypothetical volume of plasma from which a substance was removed in one pass through the kidneys (volume of plasma/min needed to excrete the quantity of solute appearing in the urine/min)
- to calculate clearance: inject solute, equilibrate, measure solute conc coming into & out of kidneys: [solute] in any artery (mg/100mL), [solute] in renal vein (mg/100mL), [solute] in urine (mg/mL → why is this different?), & rate of urine formation (mL/min)
- inulin can be difficult to use because enters tissues, so must constantly reinjected
- instead, monitor [creatinine] in plasma (produced at constant rate) → filtered with minimal secretion; C only changes significantly from 10-20% of GFR if muscle mass changes significantly

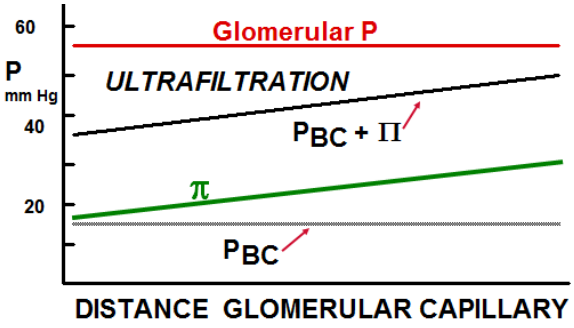
Solute Calculations

- *clearance* = [solute] in urine * rate of urine formation/[solute] in arterial plasma (C = U*V/Pa) → incl units!
- *extraction ratio*: fraction of substance that is removed in one pass through kidney (0-.74) = (Pa-Pv)/Pa
- extraction ratio & clearance is higher for filtered & secreted, lower for filtered & reabsorbed, & .20 for filtered only
- *RPF* = C/E; *RBF* = RPF/(1-ht) → use solute with highest E for accuracy reasons
- *filtration fraction* = GFR/RPF (normally 0.2)
- paramino hyperic acid & creatinine (doesn't need to be reinjected, only changes following to major muscle inc): filtered & secreted → GFR++, Pcr--
- rate solute enters urine = U*V

- filtration rate = GFR*Pa
- reabsorption rate = mg filtered - mg in urine = (GFR*Pa) – (U*V)
- secretion rate = mg in urine – mg filtered = (U*V) – (GFR*Pa)
- reabsorption/secretion: C vs GFR, E vs FF, U*V vs GFR*Pa (= is filtered, > is filtered & secreted, < is filtered & reabsorbed)

Lecture 23: Glomerular Filtration

Glomerular Filtration



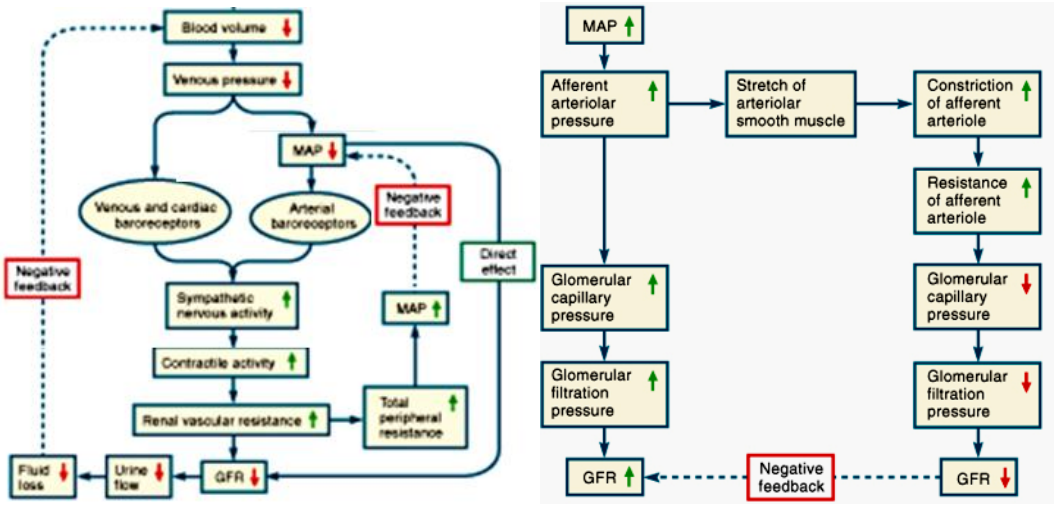
- when Pcr changes, filter is broken (not blood flow)
- fenestrated capillary endothelial cell → basement membrane (permeability barrier) → epithelial cell (podocytes)
- collagen: negative charge retards albumin, 72kD → .001 that gets through is reabsorbed
- [filtrate]/[plasma] → lower means low membrane permeability
- GFR is constant over range of BPs that kidney can autoregulate flow for (80-180)
- πp + Pbc opposes filtration
- BP in BC can be raised by GFR++ or obstruction in PT capillary (e.g. kidney stones)
- to inc GFR: dilate afferent & constrict efferent arteriole; overhydration; nephritis (pH + ion balance problems)

Factors Affecting GFR

- **graph: GFR & renal BF regulation (MAP vs flow rate)**
- glomerular ultrafiltration coeff (Kf) – size cutoff, integrity of filter (normally 1, no proteins pass through)
- hydrostatic pressure of plasma & BC
- osmotic pressure of plasma & BC
- renal blood flow
- GFR → filtration fraction (20% in humans) → renal blood flow

Regulation of Renal BF

- SANS stimulation (α1) – constricts afferent arteriole
- ANP – dilates, inhibits Na-K ATPase
- ADH – constricts
- NO – dilates, released from JG cells & endothelial cells upon stimulation from macula densa
- endothelin, adenosine, & ATP – constricts, release from JG & endothelium
- angiotensin II – constricts afferent & efferent → ask about



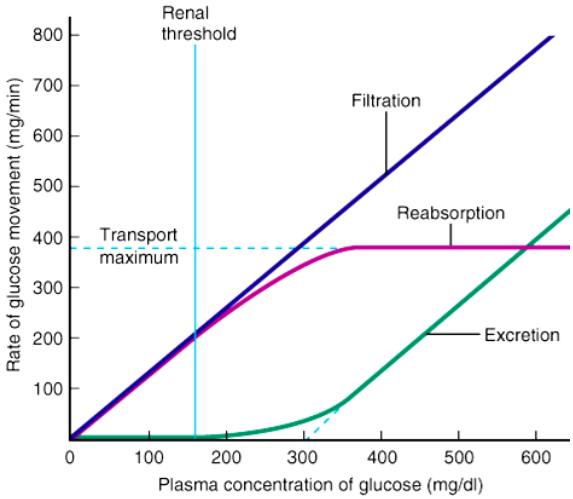
Lecture 24: Tubular Function

PCT Transport

- passive reabsorption via diffusion – small nonpolar molecules (like urea)
- apical (filtrate) & basolateral (peritubular) membranes
- Na – diffusion (apical, drives solute symports & H+ antiports) & Na/K ATPase (basolateral) → most reabsorption done here
- glucose – symport (apical) & facilitated diffusion (basolateral)
- water follows osmotic solutes through aquaporins & tight junctions
- reabsorption in PCT: AT of Na, Ca, glucose, aa, choline, urea, & phosphates; water & Cl follow osmotic gradients
- K reestablished by leak channels → the woes of light salt

Transport

- Tmax – where saturation occurs at high concentrations
- normal levels: 80-100mg/dL
- diabetic: [glucose]p drops → excretion → large urine volume, kidney damage, edema, neuropathy (due to poor circulation), vision problem (due to changing focal length)



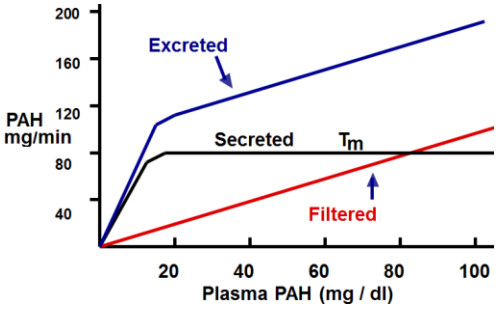
DCT Transport

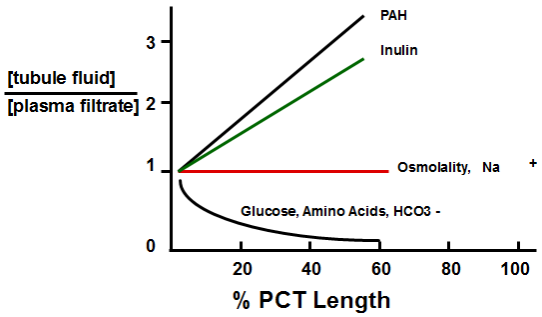
- **describe how DCT handles certain substances (draw & label)**
- Na – diffusion (apical, through leak channels & Cl- symports) & Na/K ATPase (basolateral)
- apical face has K+ leak channels, basolateral face has Cl- leak channel
- plasma K+ levels → aldosterone → Na/K ATPase in DCT
- K+ deficiency normally due to sweating/vomiting/etc, not lack of intake
- sports drink – almost isotonic to body fluids to increase absorption in intestines, should dilute it with water to prevent excess intake of K+
- PCT: leaky tight junctions & more microvilli

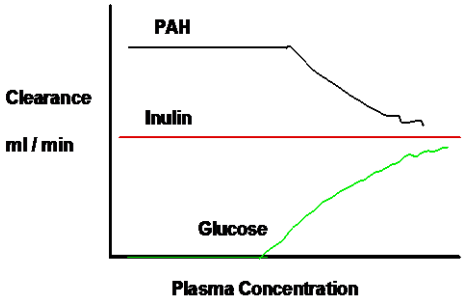
- ADH: add aquaporins

Secretion & Excretion

- graph: plasma [PAH] vs rates, PCT length vs [tubule]/[plasma], [plasma] vs clearance
- you secrete all drugs → how can this happen if you need specific transport sites for each solute? → R group is neutral, basic, or acidic
- drugs go to liver → oxidation & reduction on ER → transport sites look for those particular sites → only need 3-4 transporter types
- how would you measure these (not antibodies)?
- secretion: K+, H+, phenol red, PAH, creatinine, penicillin, acetazolamide, furosemide, histamine, NE, quinine, creatinine
- PAH – used to measure secretion (0.72)
- excreted = secreted + filtered (know how to calculate these)
- PCT length: [inulin]++ because water is reabsorbed → lines below are reabsorbed, lines above are secreted
- Na+ line: water follows Na+
- as plasma conc++ → cannot reabsorb all (higher clearance) or secrete all (lower clearance)
- could glucose clearance ever = inulin clearance?







Lecture 25: Water Balance

Ureau Gradient

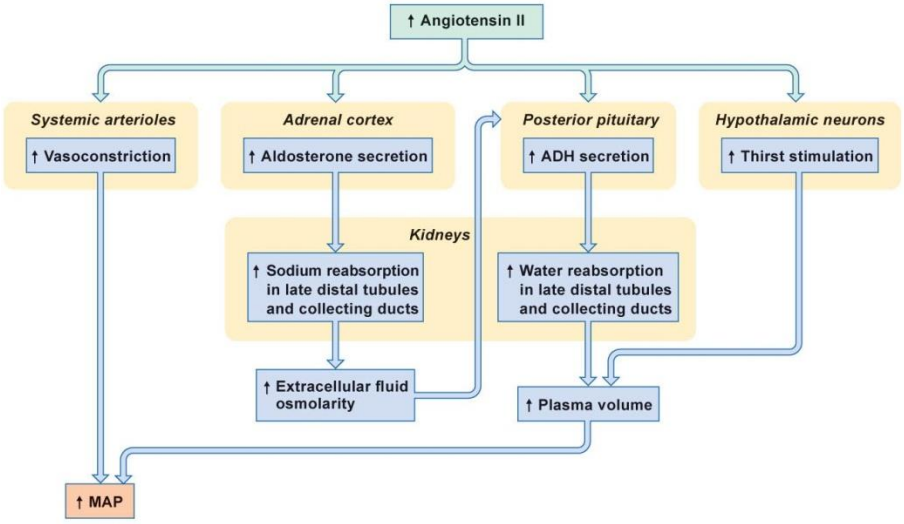
- nitrogeous waste: NH3 (aquatic, very toxic but highly solubule in water), uric acid (conserve water, crystallizes to not poison eggs), & urea (makes sharks isotonic)
- DCT: Na & solutes actively reabsorbed; urea (conc equilibrates) & H2O follow
- CD & DCT: adjust water reabsorption to regulate π of body fluids
- Hypothalamus (posterior pituitary): as π++ → cells dec in volume → stretch receptors → release ADH → G-protein/cAMP pathway → releases aquaporin-2 into apical membrane → reabsorb H2O into medulla
- also triggered by baroreceptors (low MAP)
- countercurrent exchange: eg in tunafish, warmed blood from muscles passes cooled blood from gills to warm up
- eg in fish, blood moves opposite to water to absorb most O2
- solutes pumped out of asc limb, H20 follows gradient from desc limb → SHIFT → higher osm fluid enters asc loop → solutes pumped out, H20 follows → repeat
- medulla gradient allows water to exit CD via aquaporins
- blood (300mOsm) → BC (285) → PCT (285) → LoH (285 → 1200 → 200) → DCT

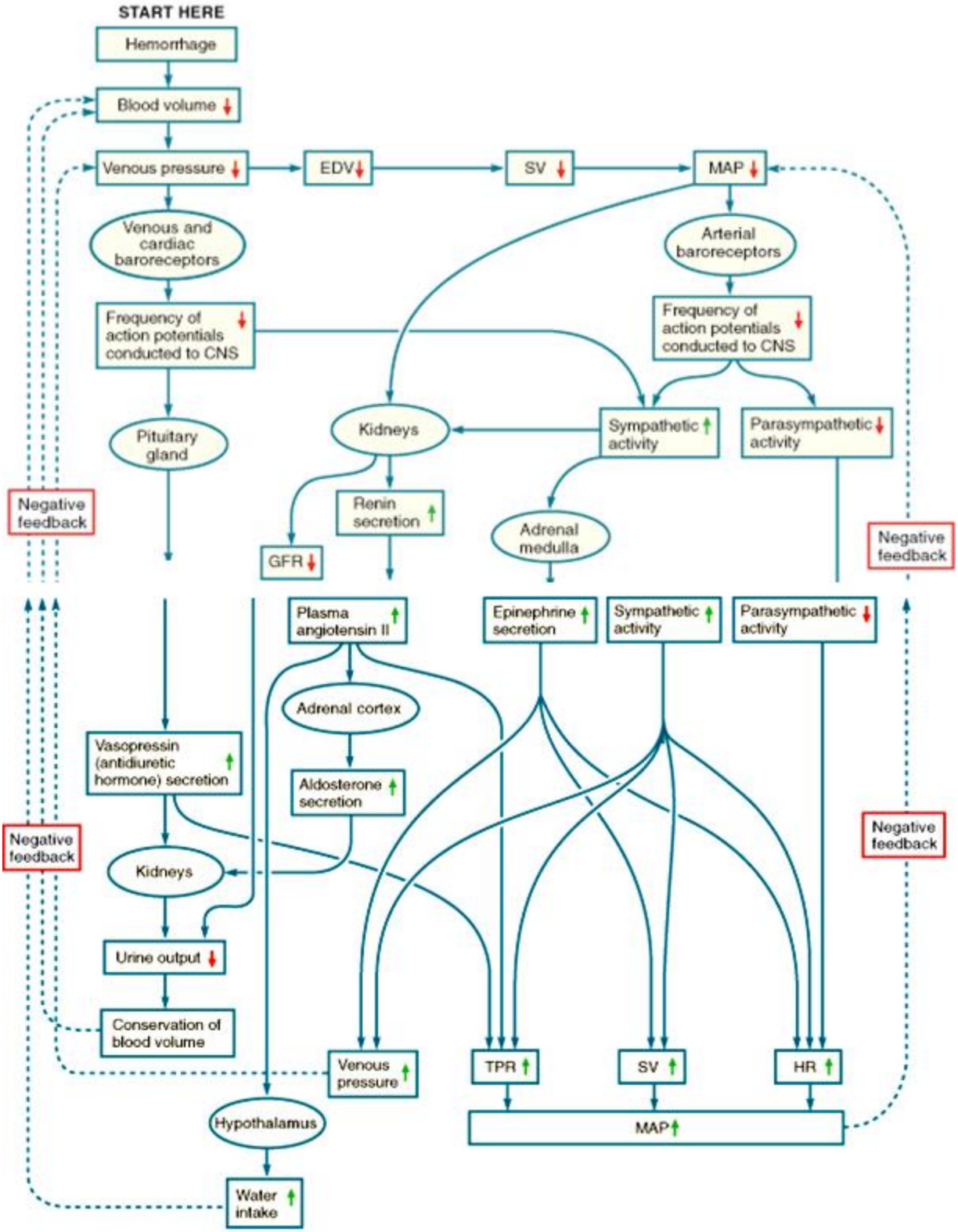
(200 → 100 → 200) → CD (200 → 285 → up to 1200)

- must match vasa recta flow; too fast flow will cause too high reabsorption, reducing gradient & making urine more dilute → regulate GFR & RBF
- diuretics: drinking water & non-reabsorbed solutes; LoH & CD Na/K-ATPase inhibitors (caffeine, theophylline, furosamide); ADH inhibitor (alcohol); inc renal BF, GFR, or vasa recta BF; CA inhibitors (can't reabsorb/create HCO3-)

Potassium Ions

- K+ is freely filtered, reabsorbed in PCT, secreted (aldosterone regulation) & reabsorbed in DCT/CD
- aldosterone: secreted by adrenal cortex; excretion greatly inc when [K+]p reaches 4.5mM; triggered by renin/angiotensin & elevated [K+]p → synthesize more K+ channels & Na/K ATPase
- steroid hormone → cytosolic receptor
- liver releases angiotensinogin → juxtaglomerular cells release renin → angiotensin I → capillary endothelium releases ACE → angiotensin II → adrenal cortex → aldosterone
- ANP: atrial stretch receptors → dec Na+ reabsorption by dec aldosterone & renin
- *review feedback loops in figures 19.16-18*

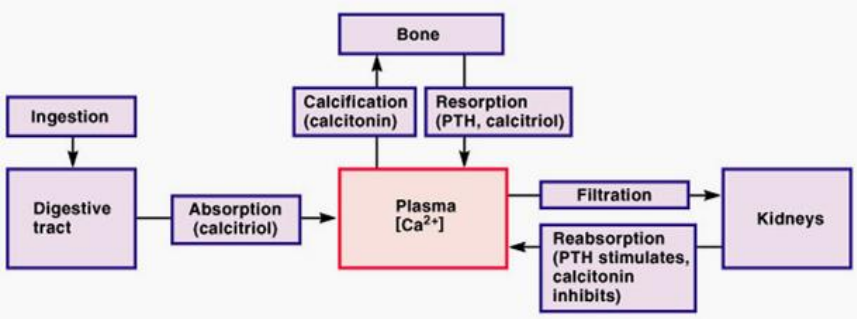


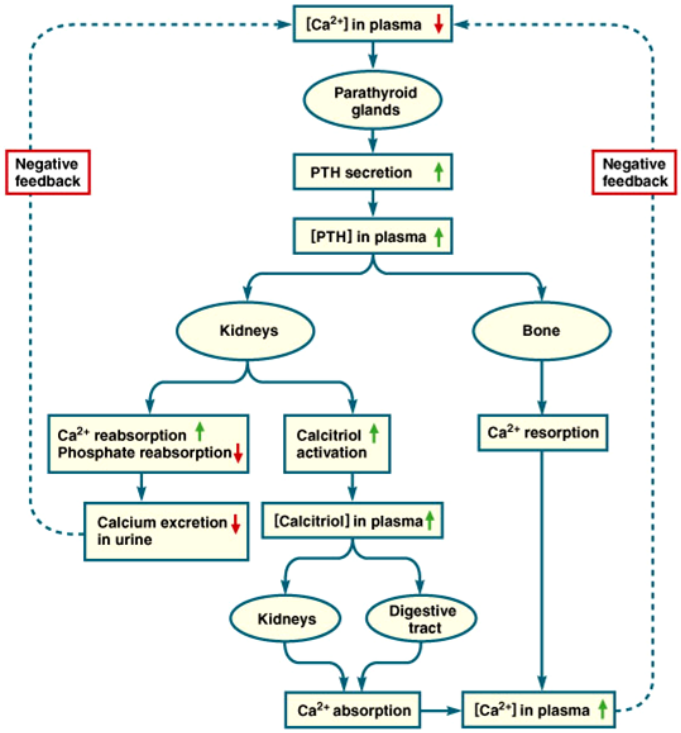


Calcium

- calcium-phosphate relationship: increased [Ca2+] must be accompanied by a dec in [phosphate] (or else will precipitate out of solution)

- blood Ca2+: bound to carrier protein; free calcium is freely filtered
- 70% reabsorbed in PCT, 20% reabsorbed in asc limb of LoH, 10% reabsorbed in DCT
- DCT & LoH reabsorption regulated by PTH
- inc Ca2+ → release PTH → Ca reabs in kidney & H3PO4 excretion/dec H3PO4 abs & Ca excretion; inc transport in GI tract; release calcitriol to resorb from bone
- calcitriol – steroid, cytoplasmic receptor promotes synthesis of Ca2+ binding protein → reduces intracellular concentration to maintain conc gradient





Lecture 26: Acid-Base Balance

Buffers

- buffer – resists changes in pH at pH = pKa (HA ↔ H+ + A-)
- arterial blood: pH = 0.05 off → acidosis/alkalosis
- complications with pH shifts: protein conformation, neuron excitability, K+ balance, cardiac arrhythmias, vasodilation
- Henderson-Hasselbach: pH = pKa + log([A-]/[HA])

Proton Sources

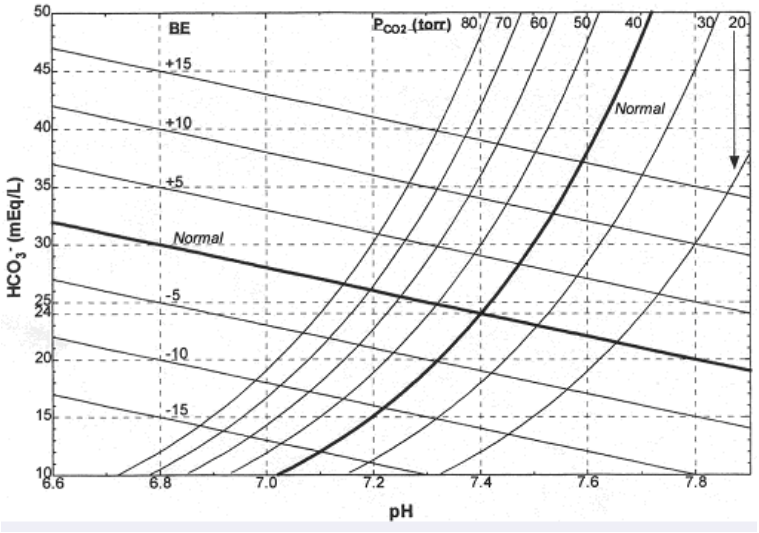
- sources of H+: diet (fats & proteins) + metabolism (CO2, lactic acid, ketoacids)

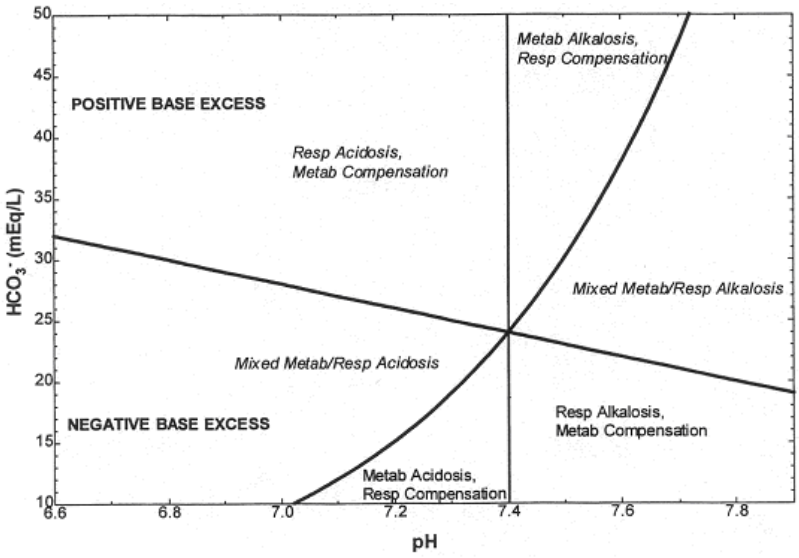
- proteins → H_2SO_4, HCl, H_3PO_4
- fats → ketone bodies (acetone & β hydroxybutryic acid)
- diabetics & high protein diet → burn lots of fat → acidosis → BP++ & RR++

Regulation

- **draw the renal mechanism in PCT & DCT**
- plasma buffers: $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$ (Pka = 6.1) → pH = 7.4 not on flat part of curve, but this is an open system
- acidosis: $[HCO_3^-]/[CO_2] < 20:1$ (0.03 * PCO_2 mmHg = $[CO_2]$ mM)
- others: H_3PO_4, organic phosphates (Pka = 2.16)
- R groups: -COOH (2.3) -NH_2 (9.6)
- buffers → respiration (min) → kidneys (hour/day)
- pH-- → peripheral chemoreceptors → ventilation++ → Pco2-- → pH++
- renal response: secrete H^+ (DCT + collecting duct), reabs HCO_3^- (PCT), synthesize HCO_3^- (DCT)
- PCT: H^+ in filtrate → $H_2O + CO_2$ in filtrate (left shift) → $H^+ + HCO_3^-$ in epithelium (right shift) → H^+ secretion into filtrate via pumps & Na/H antiport; HCO_3^- reabs via Na & Cl symports
- DCT: CO_2 in epithelium → right shift → H^+ secretion via pumps & K/H antiport; HCO_3^- reabs via Cl antiport
- severe pH stress: glutamine → PCT metabolism → $2\ HCO_3^- + 4CO_2 + H_2O$ → release HCO_3^- into plasma & secrete H^+ as NH_3

Davenport Diagram





- normal: pH = 7.4, H_2CO_3: 23-24mEq/L
- a – normal, renal will take you back here eventually
- b – hypoventilation
- c – too much H_2CO_3 or too little CO_2, but normal pH
- d – hyperventilation (high altitude, aspirin OD)
- e – marathon runners/high fat diet
- f – too little H_2CO_3 or too much CO_2, normal pH
- g – stomach flu

Midterm 3

- renal clearance (1st problem, PRACTICE), 8 graphs, respiratory regulation (input & output), acid/base conditions (essay), hemoglobin, how tubules handle solutes (draw these), blood volume regulation (hormones), ion regulation (hormones)
- no high altitude or deep diving adaptations
- review countercurrent exchange mechanism (countercurrent.mov)

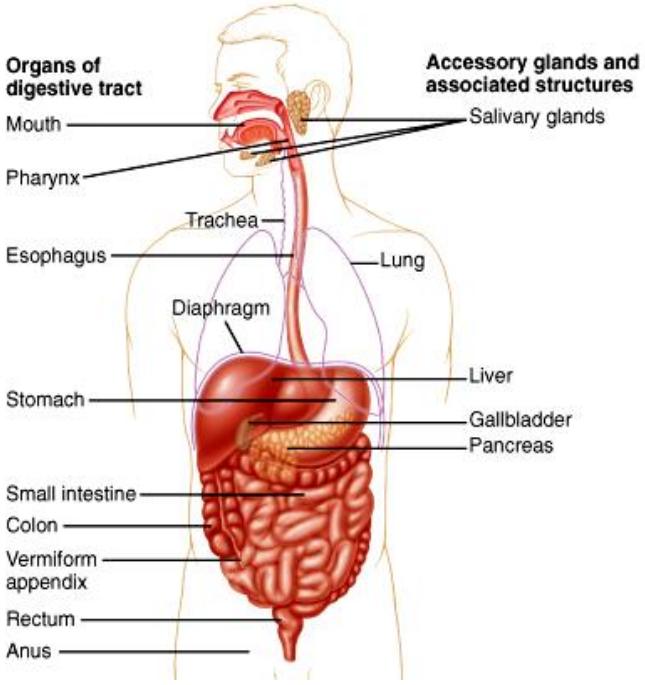
Lecture 27: GI System 1: Smooth Muscle & Neuronal Control

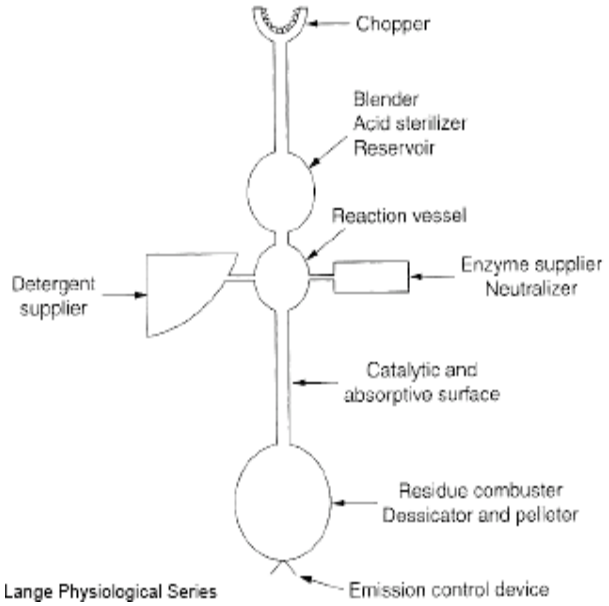
Digestion Overview

- processes: secretion, motility, digestion, absorption
- secretions (correct enzymes & emulsifiers) & motility (time for digestion & absorption; must be body temp & isotonic) must respond to size (stretch registered by enteric NS) & composition (receptors specific to proteins/carbs/fats; temp; osmolarity) of meal
- fats take a long time to digest
- you crave carbs because they are a fast source of energy, and salt (terrestrial vertebrates)
- protein leaves you more satisfied due to release of leptin (hormones that tell you you're full; stop eating so you have time to digest all essential amino acids)
- **review smooth muscle & enteric muscle system**

Structures

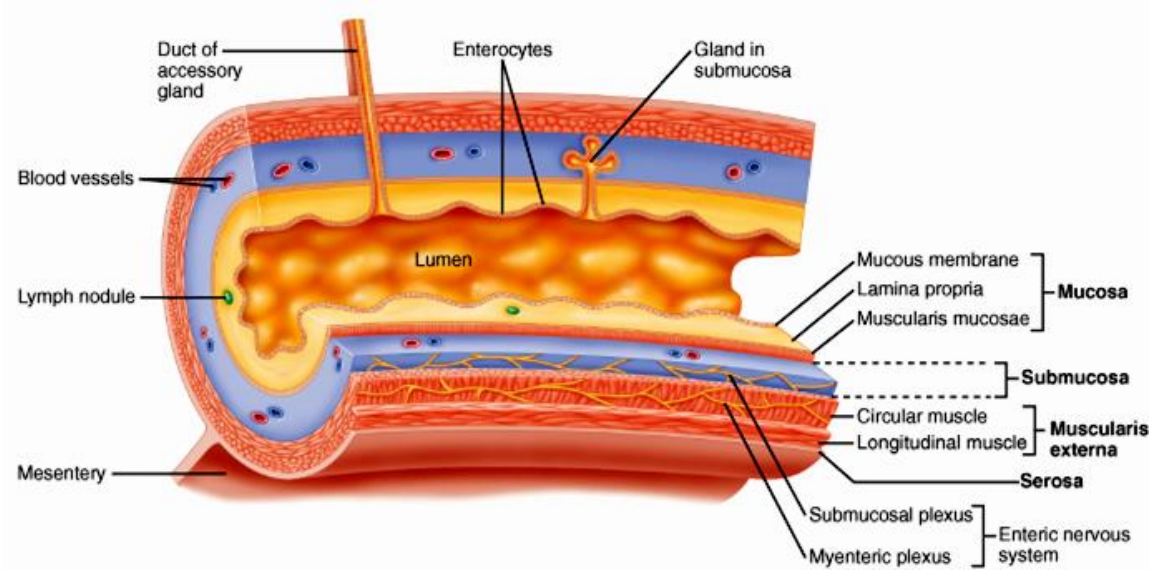
- entirely extracorporeal
- stomach: reservoir (holds material & releases at controlled rate to intestines)
- pancreas: enzyme supplier releases base to neutralize HCl → rate of stomach emptying & rate of basic secretion (H2CO3) must match
- liver: detergent: bile salts from bilirubin, an amphipathic salt which breaks up fats in duodenum so that lipases can
- small intestine: duodenum → jejunum → ileum





GI Regulation

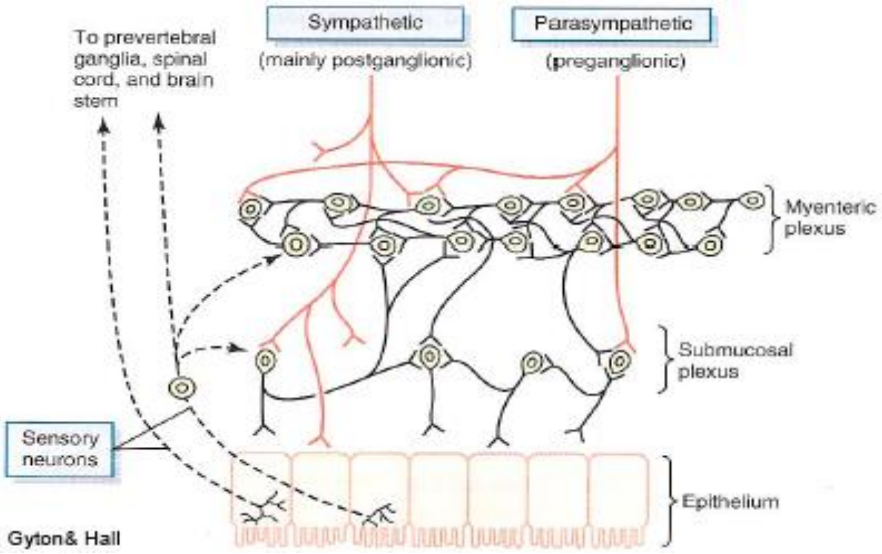
- layers: mucosa (mucous membrane + goblet cells + lamina propria + muscularis mucosae) → submucosa (connective tissue + ENS) → muscularis externa (circular + longitudinal + ENS) → serosa/adventitia (outer connective tissue)
- suspended in mesentery in abdominal cavity



Enteric NS

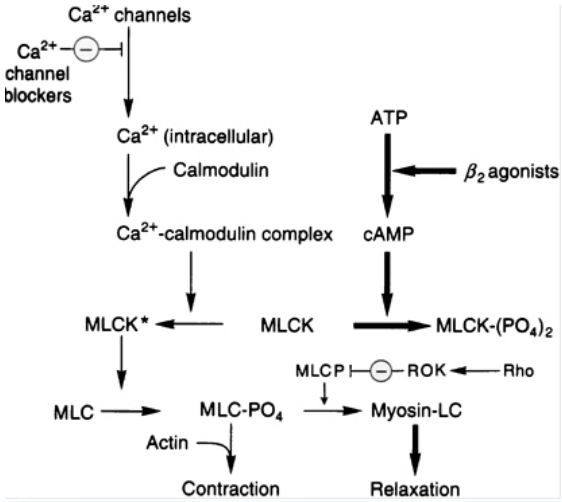
- local intrinsic neurons with cell bodies in ganglia in GI walls
- sensory, motor, & interneurons; glial support cells; diffusion barrier; integrating center
- networks: submucosal plexus & myenteric plexus
- input: chemical composition, volume, ANS enervation
- mechano, chemo, & thermo receptors → reflex + "motor" interneurons → efferent neurons to smooth muscle, BV, & secretory cells
- peristalsis: stretch → contract → relax downstream

- vagus: connects ENS (afferent & efferent) with CNS
- interstitial cells of Cajal cells: pacemakers of GI tract motility (spontaneous slow waves of depolarization that spread via gap junctions)
- PANS input causes depolarization above threshold
- varicosities instead of nerve terminals
- SANS inhibition: alpha2 & beta2 motility & secretions, alpha1 BV, alpha2 NT release via presynaptic nerve terminals
- PANS excitation: muscarinic motility, secretions, EPSP



Smooth Muscle

- **graphs: length vs tension, force vs velocity, Vm vs action potentials & muscle tension**
- small, discrete cells with gap junctions, membrane invaginations, most Ca2+ from outside cell, actin & myosin & intermediate filaments but no striations
- don't need to generate powerful or fast tension, but must perform over a wide range of lengths for a long period of time (due to cross-hatched filament arrangement)
- ionic properties: oscillating Vm due to Na & Ca leak; responds to stretch
- muscarinic receptor → phospholipase & IP3 pathway → MLCK → phosphorylates myosin chains to activate ATPase
- Ca2+ from leak channels, voltage-gated channels, ligand-gated channels, SR (IP3)
- Ca directly proportional to tension generated → **which ligands (maybe PANS?) increase this?**
- Ca2+ removal via SR & membrane ATPase, Na-Ca antiport
- genetics → ANP acts on Na/Ca antiport in BV smooth muscle → hypertension
- **would a high salt diet also inhibit the Na+/Ca2+ pump?**



Property	Skeletal	Smooth	Cardiac
Striations (sarcomeres)	Yes	No	Yes
Actin and myosin	Yes	Yes	Yes
Level of control	Voluntary	Involuntary	Involuntary
Neural input	Somatic	Autonomic	Autonomic
Neuroeffector junction	Neuromuscular junction–specific	Varicosities–diffuse	Varicosities–diffuse
Hormonal control	None	Several depending on location	Epinephrine
Source of calcium	SR	SR and ECF	SR and ECF
Regulatory protein that binds calcium	Troponin	Calmodulin	Troponin
Gap junctions	No	Yes (single unit)	Yes
Pacemaker activity	No	Yes (single unit)	Yes
Myosin ATPase activity	Fastest	Slowest	Intermediate
Recruitment	Yes	Yes (multi-unit)	No

Peristalsis

- requires only ENS for short distances
- duration, velocity, & amplitude enhanced by PANS
- reflex relaxation & sphincter opening ensures direction
- segmentation

Lecture 28: GI System 2: Mouth to Stomach

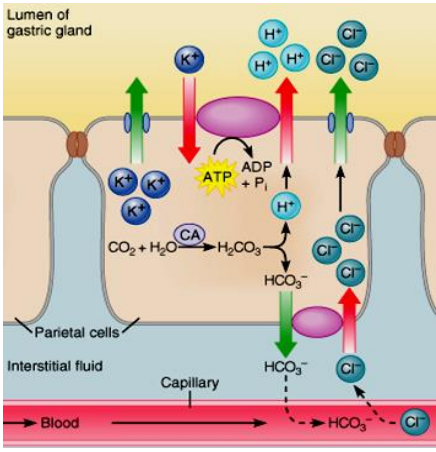
Salivary Secretions

- purpose: chopper; salivation; start digesting carbohydrates & fats
- glands: parotid (alpha amylase on 1-4 hexose linkages), sublingual & submandibular (mucin for lubrication)
- starch: alpha 1-4 & 1-6 linkages; cellulose: beta 1-4 linkages
- acinus type glands: primary section → modified in duct cells (remove Na & Cl in exchange for K & HCO3, pi drops to be hypotonic)
- flow rate increases → exchange less complete → more acidic saliva
- cavities via H+ pumps in bacteria dissolving Ca in teeth
- other components: muramidase (cleave bacterial cell walls), lactoferrin, epidermal growth factor (regrow oral cavity cells), IgA, lingual lipase (carnivores), ABO

antigens

Salivary Inputs

- Ach from PANS, VIP from ENS
- glands release kallikrein → activates kininogen to form bradykinin → local vasodilation
- cephalic & gastric phase
- distension – stretch receptors in stomach
- secretagogues – stimulation stomach & mouth; salivation to protect mouth from acid secretions
- caffeine & theophylline, peptides, spices, alcohol & aspirin
- vagal-vagal: vagus nerve from esophagus to CNS to stomach



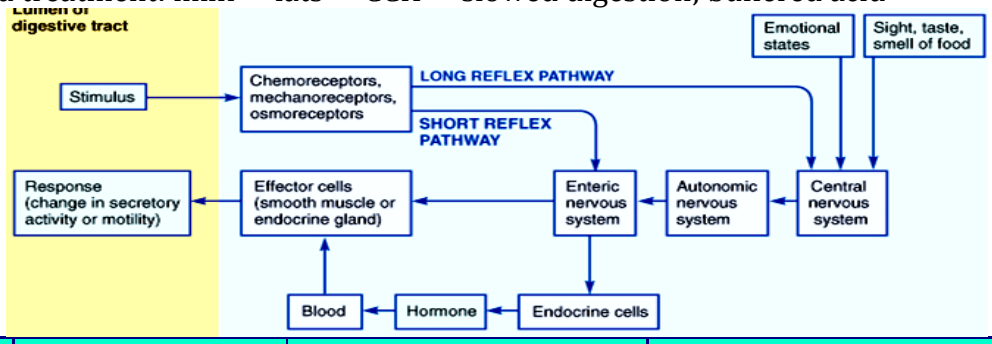
Stomach

- purpose: blender; secrete acid, pepsinogen, & intrinsic factor; digest proteins; secrete gastrin into blood; food → chyme
- acid: activates pepsinogen, breaks cell walls, kills bacteria, denature proteins
- swallowing: epiglottis moves down & closes glottis → upper esophageal sphincter opens → stretch receptors → wave of peristalsis → upper sphincter closes → lower sphincter opens → wave of peristalsis
- achalasia: reflex relaxation to open upper sphincter fails
- William Beaumont: Alexis St. Martin developed a fistula following shotgun accident → Beaumont would drop pieces of food in to measure secretions
- stomach structures: lower sphincter → fundus, rugae (increase secretion SA), antrum, pylorus → pyloric sphincter
- gastric pits/oxyntic glands: mucosa, neck cells (mucus), chief cells (pepsinogen), parietal cells (HCl & intrinsic factor for B12), G cells (gastrin)
- acid secretion driven by CA (HCO3- released back into blood), regulation via proton pump
- postprandial alkaline tide: urine is more basic after a large meal or stomach flu

Hormones

- vagal-vagal reflex: stomach distension → vagus → parietal cell & endocrine cell (releases histamine) + D cell (releases somatostatin) + G cell (gastrin) → also all activate parietal cell
- enterochromaffin cells (ECL) produce, store, & release histamine; activated by Ach, gastrin, & secretagogues
- hyperacidity treatment: atropine (remember the side effects), cimetidine (H2 antagonist), nexium (proton pump inhibitor)
- pepsin – family of endopeptides (cut internal peptide bonds) activated by low pH; happy at pH = 1.8-3.5 (optimal over small range so as to deactivate in intestines & mucosal layer of stomach)
- carnivores have greater concentrations
- haptacorrin binds B12 in salivation to protect from digestion → digested by pancreatic proteolytic enzymes in duodenum → now bound to intrinsic factor → complex uptake by endocytosis in duodenum

- ulcers: when gastric mucosal barrier is penetrated by acids
- old treatment: milk → fats → CCK → slowed digestion; buffered acid



Hormone	Site of secretion	Stimuli	Actions
Gastrin	Stomach	Protein digestion products in stomach, distention, and PANS input	Stimulates HCl & pepsinogen secretion & motility, relaxes ileocecal sphincter, stimulates mass movement of colon
CCK	Duodenum and jejunum	Fat or protein digestion products in duodenum	Inhibits gastric secretion & motility, potentiates secretin action, stimulates pancreatic enzyme secretion, stimulates bile secretion, contracts gall bladder, relaxes sphincter of Oddi
Secretin	Duodenum and jejunum	Acid in duodenum	Inhibits gastric secretion & motility, stimulates pancreatic HCO_3^- secretion, potentiates actions of CCK, and stimulates bile secretion by liver
GIP	Duodenum and jejunum	Glucose, fats or acid in duodenum and distention of the duodenum	Inhibits gastric secretion & motility, stimulates insulin secretion by the pancreas

Gastrin

- cephalic phase: thought → PANS activity → gastrin
- gastric phase: distension + proteins → chemo/mechano/osmo-receptors → short & long reflexes → gastrin
- intestinal phase: peptides + distension → gastrin + intestinal cells release CCK, secretin, & GIP → gastroilleal reflex
- acid/fats/hyperosmotic solutions in duodenum → enterogastrones → secretin & CCK → inhibits secretion & motility
- vomit reflex: SANS response; relax stomach muscles, esophageal muscles, & sphincters; abdominals contract rapidly

Other Hormones/NT

- ENS NT: serotonin, VIP, NO, somatostatin
- smooth muscle: excitatory: Ach & substance P; inhibitory: VIP, NO, & enkephalins
- GLP-1: carbs & fats → more insulin, less glucagon

- motilin: fasting → migrating motor complex

Lecture 29: GI System 3: Intestine, Chemical Digestion & Absorption

Liver

- intestinal villus: lacteal + BV → hepatic portal circulation
- purposes: bile secretion, nutrient processing, removing old RBCs (Kupffer cells), eliminate waste, synthesize plasma proteins, secrete & modify hormones
- mesenteric veins → hepatic portal vein from intestines + hepatic artery from aorta → sinusoids (blood) run antiparallel to canaliculi (bile) in lobule
- bile: hepatic ducts → gallbladder or common bile duct → combines with pancreatic duct at ampulla or vater → sphincter of Oddi (relaxed by hormones & peristalsis) → duodenum
- bile acids: from cholesterol by –OH & -COOH addition; also formed by resident bacteria; conjugated to taurine/glycine → fat emulsification & bicarbonate
- gallbladder: removes Na & water from bile → concentration can lead to gall stones → have to eat small, low-fat meals after gallbladder is removed
- 95% of bile salts & acids are reabsorbed from ileum into portal blood → liver reabsorbs & reconjugates → NFL (bile-dependent & -independent flow)
- liver problems → more conjugated bilirubin in blood

Pancreas

- CCK acts on acinar cells → ecbolic (enzyme) secretion activates proteases (endo – trypsin, chymotrypsin, elastase; exo – carboxypeptidase, aminopeptidase; alpha amylase, lipase, ribonuclease, & deoxyribonuclease)
- secretin acts on duct cells → hydrelatic (HCO_3) secretion neutralizes HCl & dilutes chyme
- secretions contain trypsinogen & competitive trypsin inhibitor → inhibitor diluted by chyme & enterokinase (luminal membrane of epithelial cells) activates trypsin → activates rest of peptidases
- cephalic phase: vagus → gastrin → secretions
- gastric phase: proteins in chyme → gastrin + distension → vagus → secretions
- intestinal phase: acid in chyme → secretin + fatty acids/proteins in chyme → CCK + vagal-vagal reflex → secretions
- enzymes: proteases + amylases + lipases

Small Intestines

- purpose: digestion via brush border & pancreatic enzymes; absorption of end products, water, ions, vitamins; secretion of enterogastrones into blood; secretion of bicarbonate

Lipoproteins

- fat globule → broken up into fat droplets by bile salts (emulsification) → lipase from pancreas breaks up phospholipids & triglycerides into fatty acids (may form micelles) → diffuses down concentration gradient into endothelium → triglyceride formation in smooth ER → protein-lipid matrix (chylomicron) formation in Golgi → into lacteal → thoracic duct
- **why not into blood?**
- lipoproteins circulate to provide fatty acids & cholesterol to cells → released by

lipoprotein lipase on endothelium of capillaries → denser as they get smaller
- HDL carries cholesterol back to liver (>40mg/dL is healthy)
- LDL deposits cholesterol in arteries (atherosclerosis: Poiseille's law, must drop tension to maintain pressure given reduced radius)

Carbohydrates
- starch → maltose + limit dextrins → disaccharidases on luminal membrane of epithelial cells → glucose/Na symport → GLUT facilitated diffusion
- lactose → glucose + galactase (if no lactase, consumed by anaerobic bacteria in ileum)
- diabetes mellitus: impaired insulin regulation of blood glucose or impaired metabolism
- insulin: inhibits GLUT, more synthesis of glycogen, break down of pyruvate into fatty acids
- any nutrient can be converted into fatty acids
- Splenda/sucrolose: binds carbohydrate taste receptors, but has Cl groups

Diabetes
- insulin-dependent DM: secretion is reduced or absent, need injections
- insulin-independent DM: loss of responsiveness to insulin (too much hormone → receptor is downregulated) & eventual reduced secretion
- symptoms: hyperglycemia (fasting levels should be 80-100mg/dL)+ glucosurea
- hyperlipidemia
- ketosis + ketoacidosis (fat metabolism)
- diuresis + electrolyte loss (urine glucose++ → pi++)
- retinopathy (neurons + heat use almost exclusively glucose → unregulated metabolism → high [glucose] leads to O2 radicals, low [glucose] leads to tissue death
- neuropathy + edema → cannot control local BF → low BF → necrotic tissue

Lecture 30: Immune System 1: Innate Immunity

Terminology
- innate (no exposure required) vs acquired (more specific & prolific)
- self vs non-self – membrane glycoproteins, autoimmune disease
- pathogenic – causing disease
- antigen – generates a (typically acquired) immune response
- inflammation – response to introduction of a foreign agent
- leukocyte – granulocytes & agranulocytes
- allergy – histamine response, treated with epi

Granular Polymorphonuclear Leukocytes
- gram/Wright stain: neutrophils (white, neutral, first responders)
- eosinophils (red, acidic, parasite)
- basophils (blue, basic, IgE + histamine)
- other phagocytes: macrophages, dendritic cells (antigen-presenting cells that release cytokines to trigger acquired response; in skin, nose, lung, stomach, & intestines)
- macrophages: free + fixed (alveolar, hitiocytes in connective tissues, Kupffer cells in

liver, microglia in CNS)
- lymphocytes: B (develop into plasma cells that secrete antibodies), T (memory & cytotoxic), Null (include killer T)
- lymphoid tissues: primary/central (bone marrow, thymus, fetal live), peripheral (adenoids, tonsils, spleen, lymph nodes, appendix, Peyer's patches in intestines)
- innate/nonspecific responses: physical barriers, inflammation, phagocytosis, complement system

Inflammation
- rubor, tumor, calor (fever) & dolor (pain)
- fixed macrophages engulf foreign materials → local edema via histamine release → containment of foreign materials by defensive proteins → heparin recruits clotting proteins → recruitment of additional leukocytes via diapedesis → final foreign material removal
- diapedesis: endothelium produces IL-1 & P-selectin → neutrophil binds selectin, IL-1 & ICAM-1 → neutrophil migrates
- itching: neural response to decreased BF & O2; spontaneous nerve activity from dendrite healing
- phagocytosis: phagosome fuses with secondary lysosome → endocytic vesicle
- opsonization: releasing cytokines to bind foreign material to identify it for neutrophils (eg antibodies & interleukin cytokines)
- interleukin cytokines released (IL-1, IL-6, TNF-alpha) → act as pyrogens to stimulate liver to produce acute phase proteins (speed up reactions, denature bacterial proteins) → IL-1 also stimulates T & B lymphocytes
- prolonged fever → medullary failure & ion channels denature → seizures

Infected Cell Response
- interferons (alpha, beta, & gamma) produced by host cells infected by a virus → released as cell lyses → induces other cells to produce anti-viral proteins which shuts down viral DNA/RNA replication
- IF-gamma also stimulates killer & cytotoxic T cells
- infected cell presents modified cell surface proteins → NK cells bind infected cells → activate → release perforin granzymes
- spinal cord injury → BBB damage → granzymes released in CNS
- complement system: complement protein binds bacterium (induced by IgM & IgG) → cascade of protein activation → pore activated → cell lyses

Lecture 31: Immune System 2: Acquired Immunity

Small Pox & Immune Responses
- inoculation using material from pustule conferred immunity
- Edward Jenner – observed that small pox survivors & milk maids were immune → injected James Phipps with material from cow pox lesions
- Washington vaccinated his troops at Valley Forge after major troop loss at Battle of Quebec
- humoral (B lymphocytes → plasma cells that secrete antibodies) & cell-mediated (T lymphocytes → cytotoxic T cells that bind & kill infected cells)
- properties: specificity, diversity, memory, & self-tolerance

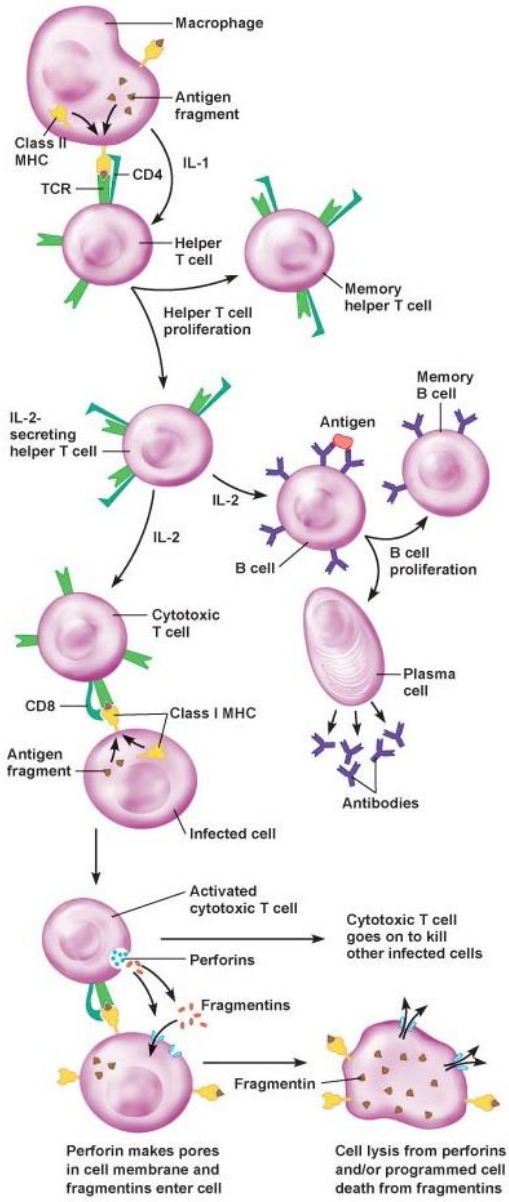
Specificity
- antigens (multiple epitopes per antigen can be targeted by multiple antibodies)
- strength of a vaccine dependent on # of epitopes injected
- problem: Group A strep → rheumatic fever → cross-reactivity of Ig with connective tissue → inflammation → attack heart valve glycoproteins → carditis
- secondary response of greater magnitude & faster than primary response
- antibody: 2 heavy chains + 2 light chains; constant (Ig type) + variable (epitope-binding) regions
- **why do antibodies have two binding regions?**

Diversity
- B cell presents antibody, T cell presents antigen-binding site (TCR)
- how many antibodies can you express? → limitless, must have monoclonal antibodies to deduce structure
- B cell ch14: thousands of Vh genes + diversity segments + joining segments + constant segments → excise all DNA except one Vh + D + J + Ig
- heavy chain class switching: IgM → excise constant regions → IgG
- clonal selection: antigen binds antibody on T cells → cell proliferation & differentiation → plasma/effector cells secrete antibodies, memory B cells
- HIV → attacks T cells → no humoral immunity

Memory
- short-term memory in B cells, long-term memory in T cells that maintain expanded B cell clone population
- different antigens have varied long-term responses (eg how long tetanus vaccines last)

Self-Tolerance
- T & B cells mature in bone marrow & thymus → antigen receptors screened for ability to recognize self proteins → cells inactivated/apoptosed
- some self proteins are never exposed to immune system (eg in CNS & eye) → can trigger immune response later (eg spinal cord injury)
- early vaccination to some disease not possible due to this

Ig
- types: IgM (primary response), IgD (B cell receptor), IgG (secondary response & opsonization), IgE (allergies), IgA (secretions & binds epithelial cells)
- purposes: neutralization (blocks pathogen activity), agglutination (pathogen aggregation), opsonization (IgG marks for phagocytosis), complement activation, enhanced NK activity (also IgG)
- production: helper T bind antigens → release cytokines (eg IL-2) → stimulate B cells → plasma cells & memory cells
- T-independent antigens do not require T cells to initiate this response
- cell-mediated immunity: helper T produce cytokines to



stimulate B cells, macrophages, & NK cells; cytotoxic T destroy foreign cells; suppressor T produce cytokines to reduce activity of B & helper T cells

MHC

- cell surface proteins that provide diversity of immune response throughout species
- high mutation rate: facial features, fingerprints, & MHC
- class I on surface of all nucleated cells & unique to individuals → binds abnormal antigens inside infected/tumor cells → presents to cytotoxic T cells → binds TCR & CD-8
- class II on macrophages/dendritic cells/activated B cells/thymus cells → presents antigens engulfed by macrophages/dendritic cells to helper T cells → binds TCR & CD-4

Other Responses

- allergies: pollen exposure → plasma cell proliferation → IgE antibodies → excess presented on surface of mast cell → releases histamine → etc
- autoimmune diseases: lupus, rheumatoid arthritis, insulin-dependent DM, MS
- MS: cytotoxic T cells invade CNS, causing demyelination