LECTURE 2

For the second lecture, one part that I found interesting had to do with control loops which is one of the fundamentals of exercise physiology. There are two types of control loops: positive and negative. Positive feedback loops are less common which basically results in an action potential having a giant effect on the body's system. The example given in the lecture had to do with the amount of oxytocin released during pregnancy. While giving birth, the body shifts from smaller signals of oxytocin to larger signals of oxytocin. This shift from smaller to larger signaling is a sign of positive control loops. On the other hand, negative feedback loops are more common and occur on a moment-to-moment basis. An example of this is when body temperature rises, your body begins to sweat as a cooling mechanism. Since the body is going from a high temperature to a lower temperature (instead of it having an increase in temperature), this makes it a negative feedback loop. Similarly, if we are cold, our body starts to shiver in order to increase our body temperature. This is also an example of a negative feedback loop, despite going from a lower temperature to a higher temperature which is an increase (which I tend to think of as positive). However, it is important to note that your body temperature is going in the opposite direction (feeling cold means your body shivers to increase temperature as feeling hot means your body sweats to decrease body temperature). On the other hand, positive feedback loops go in the same direction (small increases in oxytocin levels turn into larger increases in oxytocin levels when giving birth).

-have the same components , tho performance may be different
-how to improve performance (ask yourself different questions-- tissue development/decay, running faster/farther, reactions to different stresses, etc)

-metabolism
-early in life, people were dying bc of teeth decay(viral/bacterial infections)
- years ago people didn't know why people were dying (diseases, physiology)

What causes illness
-Early stages of physiology: identify causes of illness, infection, disease, decay, etc----and come up with countermeasures in order to survive

Body has great capacity of healing itself if you activate those tissues----foundation of PT (cell stresses: inputs into cell metabolism)(nonsurgical interventions)

-Move into areas of human performance, **optimize performance --understand how to apply appropriate loads onto tissues**

-Physiology addresses the person, the context of their own body. In exercise physiology it's in you, so easier to remember because it is your muscles/tissues/body (memorable context)

-find ways to tie info to interesting concepts (help to remember)

-"Gym science"---gives advice, people might follow it -do they have authority in that field to make those comments/claims

-may be inaccurate (some may be true)

decipher/distinguish between gym science that's real, and the one that isn't -goals can be: physical appearance, athleticism/performance, health/longevity, injury therapy -better at fitness, fundamentals might be squats and sit ups and push ups etc

-the ones that are effective, if one becomes more effective then that would become a fundamental

*organ systems: different systems in the body
Homeostasis: pH, sugar, BP, blood gases, hot/cold---maintain in a narrow physiological window
-control loops: positive (less common, with an action potential, giant effect---little bit that gets a lot bit-----in pregnancy, oxytocin--signals of birth mode little signals become big signals) and negative (more common---body is hot, so temp rises, so we sweat to reduce body temp, etc)

LECTURE 3

Macrostructure: you have ~430-640 muscles (some people may have more muscles than others--right side may differ from your left side)

Purpose of skeletal muscles: moves us around (moves our bones)

Can tell what a muscle does by its origins and insertions

Long muscles: increased amount of shortening and increased speed of shortening (faster, less force)

Thicker muscle: increase force development (slower, more force)

Different shapes

- All of your skeletal muscles have similar macro/microanatomy; all skeletal muscles are covered by an epimysium 9inside are a bunch of contractile proteins + connective tissues + more myisiums)
    - Epimysium-outer layer, surrounds muscle
    - Perimysium- surrounding each fascicle
    - Endomysium-surrounds each fiber

1. Muscle
2. Fascicles (bundles)
3. Muscle fiber (cell)
    a. Number of muscle fibers varies in different muscles
    b. Often extend the whole length of the muscle (not always)
4. Myofibril
5. Sarcomere
    a. ~2.2-3.3 micrometers in length each
    b. 15,000 sarcomeres= muscle of ~3,000 micrometers
    c. Contains
        i. Contractile proteins
6. Myofilaments
    a. Actin (2nd most abundant)
        i. Nebulin (assembly of actin)
    b. Myosin (most abundant)
        i. Heavy + light chains
            1. Heavy: isoform affects function; composed of tail region and globular head; actin binding site + ATP binding site)
            2. Light: regulatory functions; stiffening of neck)
        ii. -Z to M line (Titin=3rd most abundant; stabilizes myosin)

*Increase in both = muscle hypertrophy

Muscles get longer: sarcomerogenesis

Muscles get shorter: sacromerolysis

Regulatory proteins:

-Tropomyosin: stiffens the thin filament; cover myosin binding sites

-Troponin: 3 polypeptides= Troponin T, I (inhibition-bound to actin; movies from binding sites), C (calcium-causes confirmation change)

- ACTN3 has multiple alleles

- Strong form RR
- Intermediate form RX
- Nonsense form XX (stop codon halts production all together)

-Cross-bridge cycling: actin/myosin r contractile proteins + filaments in the sliding filament theory.

-myosin=thick tube (has to be activated before binding);actin=thin +has binding site

-no flex = binding sites covered

-release phosphate (from ATP or ADP)

-ATP hydrolysis

-power stroke

- How many fibers contribute to contraction, how much actin/myosin are in fibers; how well cross-bridges are functioning

LECTURE 4

Neural Recruitment/Motor Activation

Peripheral Nervous System (not in core bones, branches out from spine)

Autonomic (controls self-reg action of internal organs + glands)--heart

Sympathetic (arousing) vs Parasympathetic (calming)

Somatic (controls voluntary movements of skeletal muscles)--muscle

Central Nervous System (in bones, skull, spine)

Upper motor nerves

Lower Motor nerves: exit the spine; activated by upper motor nerves

1. **Primary motor cortex** in the brain =start of muscle recruitment (place where your nerve impulses for voluntary muscle contraction start)
    a. There's a premotor cortex and a primary motor complex (+supplementary motor area, etc)
    b. Primary Motor Cortex:primary portion brain tissue that controls execution of movement
        i. Betz cells: largest cells in the CNS ---(synapse with) project out of the brain and send their axons down the spinal cord to the ventral horn
        ii. overlap ; system of integrated movements
2. Premotor cortex: involved in support of motor control; sensory + spatial guidance of movement
3. Supplementary Motor area: might be involved in movement planning and coordination of bilateral functioning
4. Posterior parietal motor cortex: has associative motor roles; seems to transfer sensory info into motor channels

--(w/in Primary motor cortex) Impulse is carried w/in an alpha motor nerve (live in CNS + axons extend out of spine toward extrafusal muscle w/ somatic appointment) in the spine, exits thru ventral root

- Motor unit: a motor nerve and all of the muscle fibers it innervates; several hundred muscle fibers per motor unit (~2-2,000)
- All or None: principle states that every single muscle fiber in a specific motor unit is activated maximally if activated (each fiber innervated by single motor nerve; fibers belong to one motor unit)
- Charge gradients/neural activation: based on voltage ; gradients
- Action Potential: absolute v relative refractory period
- Saltatory Conduction
    - Myelin: spiral wrappings of tightly packed membranes
    - Nodes of ranvier: action potential gradient; high concentration of sodium and potassium ion channels
- Rate coding: how quickly the nerves are refiring
- Neuromuscular junction: synaptic clefts
- Excitation-Contraction Coupling

LECTURE 5

- Excitation-Contraction Coupling:
  An action potential goes down a t-tubule and eventually the voltage reaches the dihydropyridine receptor. This action potential begins in the upper motor nerve (also known as the alpha motor nerve in the primary motor cortex) where motor action begins. Specifically, voluntary activity begins at the primary motor cortex where the alpha motor nerve descends and reaches the lower motor nerve and then goes out to the target tissue. This voltage ends at the dihydropyridine receptor. The t-tubules could be seen as the “ending place” as this is what leads to the dihydropyridine receptor. The dihydropyridine receptor changes the confirmation and depolarizes its shape. The ryanodine receptor is the door to the sarcoplasmic reticulum. Calcium gets out of the sarcoplasmic reticulum from the ryanodine receptor. Therefore, changing the shape of the dihydropyridine receptor causes the ryanodine receptor to open and which leads to the calcium ions being released. This is called “depolarization-induced calcium release.” (Calcium then binds to troponin C, which initiates muscle contraction.) This is also an example of a positive feedback loop.

  (Overall, this means that an action potential reaches the voltage-dependent calcium channels through the t-tubules until it reaches the dihydropyridine receptors which ultimately changes its shape. Since they are linked to the ryanodine receptors which are connected to the sarcoplasmic reticula, this causes calcium ions to be released.)

LECTURE 6

-differences in motor unit recruitment (size of motor nerve=size principle)

-Type I, Type IIA, Type IIB (not in humans)----type IIx is what we could recruit, but not always

- Around minute 34 there are characteristics of muscle fiber types
- I, Ic, IIc, IIac, IIa, IIax, IIx (other categorization)
- Classify: (skeletal muscle fibers vary morphologically and physiologically)
    - **Myosin heavy chain**: head and tail of myosin
    - Myosin light chain: 2 per head, they bind heavy chains in neck to the tail
- From the motor unit: fibers belonging to a single motor unit will be the same fiber type, based on ATPase activity and MHC isoform. Those fibers have similar enzymatic capacities. (for the most part true)

-Type I: slow twitch, oxidative, red (weak, energy efficient, fatigue resistant, injury resistant)

- Marathon (involvement high)
- Really reliable, everyday/daily tasks, energy efficient (example: think of something like a bus), not fast, slow acceleration + top speed

-Type II: Fast twitch, glycolytic, white (explosive, bigger, stronger, more susceptible to injury, less energy efficient)

- Sprinting (involvement high), vertical jump (lots of type I for most of it, but you have to have a lot of type II power in order to succeed). Pitching (anyone can stand on the mound, but remember you need to have a lot of type II fibers to succeed)
- (example: think of racecars) super energy inefficient, breaks down easy, fatigue + burnout, “lot of horsepower and very little bodyweight”

LECTURE 7

One of the main concepts that I enjoyed learning about had to do with the fact that controlling exertion is dependent on the number of motor units that you recruit. If you know that something is heavy, you will recruit more motor units in order to exert more force. On the other hand, doing something like lifting up a pencil means that you will be recruiting fewer motor units. This has to do with the fact that the more motor units you recruit, the more muscle fibers will be activated during that activity. In other words, we control how much force we exert by recruiting more or less motor units depending on what action we are doing. If we see a box, and we interpret that the box is empty, then we will recruit fewer motor units because we understand that we don't need to exert a lot of force to pick it up. If we interpret that the box is empty, but it is actually full, then we won't be able to pick the box up as easily because not enough motor units were recruited. Once we know that the box is heavy, then we recruit more motor units in order to pick it up.

*pretty much the basics (I know the example had to do with a carton of milk, but I like to think about it with either picking up boxes or opening doors.)

LECTURE 8

-if you are newer to exercise, more agonists (like biceps)/muscles will flex in order to stabilize (since it is trying to learn)

-"the individual axons ceased firing in the inverse order that they were recruited after the stimulus: first recruited, last decruited…….synaptic inhibition leads to decruitment according to axon size: the last one recruited was the most susceptible to inhibition, presumably bc there was less surplus excitation"'

-postactivation potentiation: the more type II fibers you have, the more pronounced your postactivation potentiation is ---more training/type II fibers/better athletes=tend to respond to this better; time points to get this effect (postactivation potentiation vs postactivation performance enhancement;" cellular phenomena are a little diff between both; time-course can vary --heat accumulation, water content, elasticity--how long can elevated performance persist?

-pain: impair neural recruitment, reduce recruitment of muscle fibers if you feel PAIN! Alter neural recruitment, delay in recruitment; affects peak force production; peak force development rate is slower in the cold---generate force at a rate

-fatigue: manifest in different performance compromising ways (more difficult in type I fibers); if type I fibers are fatigues, then type II fibers won't work as well.

-training for baseball while doing aerobic exercises won't be helpful bc baseball mostly uses type II fibers (so why not just train the type II fibers)

-best way to recruit high threshold motor units is to load up the tissue to get max voluntary contraction (MVC)---reliable

-recruitment is based on need. Need is based on intensity. Intensity involves a lot.

-climbing Henneman's ladder

-size principle not solely based on load: can also involve amount of force, duration of tension, speed of contraction, angles, muscle length, etc

("functional exercise" stretching---may not help reduce the risk of injury--hgh loads while being lengthened, high force/speed --slow static stretching won't help)

LECTURE 9

-Changes to be more compatible to the environment

- Biological things respond to their environments: learn that cells spend their lives making changes to tolerate their environment; every living thing respond to the threats and stresses they endure: “life finds a way”
- Every creature has its own environment where it thrives (humans can’t survive in the snow, but polar bears can)----humans can get killed by everything (too cold too hot, too acidic/basic----gas pressure too low, not enough nutrient/hydration, etc----always adjust to certain conditions)
- Make changes to be more compatible with the environment. Some of the changes are relatively permanent; others are relatively impermanent.---toleration
    - Habituation: exposed to something repeatedly; familiarity diminishes your response (train keeps you up all night, later on you become used to it)---decreased sensitivity to a stimulus
    - Sensitization: becoming more sensitive to it, ability to tune (wine taster, musician tuning their instrument)---increased sensitivity to a stimulus
    - Accommodation: gradual tolerance (first get into hot tub it’s painful, slowly get used to it-- after you don’t notice it)---brief, acute tolerance of pains/stresses/senses----you get used to stuff (go outside where it’s bright, rapidly focus/accommodate) ---short term
    - Adaptation: permanent-ish (more than accommodation), muscle mass, blood volume, skin tans---a chronic change ---generally follows accommodation
        - oversimplification
    - Genetic Adaptation
    - All of these are different, but have to do with how they affect us
- Energy pathways, enzymes changes, mitochondria adapt/multiple (same with transporter molecules), receptor cells can be up or down regulated, glands can be affected by afferent signals, immune system needs exposure to stress (w/o stress=weakness)

LECTURE 10

Good v Bad stress

- Reason study was conducted (high v no dose of radiation--also low dose) bc wanted to find if radiation was bad, found high dose workers had lower all-cause mortality (circulatory, etc) 24% lower in that group (toxins not ruining health, boosting it---adapt/strengthen itself---physiological relationship between stress and protection)
- Studies of high stress (exercise vigorously)----idea that an amount of stress is good (too little stress=tissues may decay; increase stress to optimal stress zone would help; increase that and too much stress would be bad ---overreaching, metabolic problem/overtraining)
    - Good zone is where we want to be in terms of stress (bell curve)
    - Functional training---enormous amount of stress (some people can handle this and it would be in their good zone of the bell curve---others can go through the same amount of stress and their tissues would break down----all bodies are different and all bodies can get break down due to different stresses)

- Every source of stress has a unique fingerprint. The way we respond to those stresses are specific to those fingerprints. Every cell and tissue adapts according to its exact functional need

LECTURE 11

(Barefoot Running-Evaluating feet as our point of contact-a transition point - between specificity of adaptation and biomechanics)

- Know how a cell behaves in terms of stresses and loads---inventive to have perfect prescription (know physiology ---knee hip back are a mess)---biomechanics
- Feet striking the ground----start at the foundation (the shoe) work the way up leg from load profiles (4 components that impact the mechanical functions of a foot)
- The higher the heel gets you alter the biomechanics (minimilist v maximalist)
    - min:feet barely change with how it interacts with ground
    - max: neutral footwear grips arch,(changes your interaction with ground, neuromuscular characteristics)
- Minimalist shoes- minimalist running is about letting the foot behave - mechanically - as though it's barefoot ---stops from having mechanical tension, minimize limit mechanical loads
- Why not barefoot: consider interaction with environment---think wounds, bacteria, and disease---don't stab ourselves with the environment
    - May have led to minimalist movement
        - Pronated foot posture (inward sagging of the foot) may be a risk factor for medial tibial stress syndrome + may risk for patellofemoral pain development---tends to predict elevated injury
        - Daniel Lieberman, persistence hunting
        - Injury rates are higher with minimalist shoes (response to witching shoe types)--partial + full minimalist resulted in greater risk of injury than neutral footwear; partial had greatest injury rate overall, runners in full minimalist reported greater shin and calf pain than those with other footwear
    - Balance:shoe can't be problem or solution
    - Flip-flops aren't minimalist
    - PT as load patterns
    - Pronation: foot rolls inward while walking/jogging

I actually do a lot of barefoot running so this strangely applies to me. I have noticed that I get more sore when I run either barefoot or use a minimalist shoe, but for some reason I still continue to do so.

LECTURE 12

- Biomechanics
    - Physiology and biomechanics share much of the same domain of “exercise science”
    - Environmental and biological loads and stresses put on tissues
    - **Application**: Crumple tests, golf swings (where are you in space and where is the club going, where will golf ball land)
        - Speed, projection, height above ground, angle of attack (orientation)
        - “carpal tunnel syndrome and keyboard ‘ergonomics’”
        - Kyphosis (gets to extreme you’ll see) and brachial plexus
            - Hunch forward (specificity of adaptation) so can get muscle weakness
        - Lifting with your leg instead of back addresses “materials handling tasks’”--component of occupational biomechanics. Biomechanists use mechanical models of the trunk to figure out risk and stress to the low back.
        - Machines to replicate earth gravity in space (think of how in space affects your movement)
        - Children not good at walking, old people at risk of falling---biomechanists study factors that predict falls (mechanical characteristics of safe landings; how forces are sustained and distributed upon impact)
        - Every major sport (wind tunnel experiments; pole vaulting poles being appropriately flexible and stiff--balance these variables for optimal materials, techniques, and performance; ski boots and bindings to prevent ankle injuries so load gets transferred to the knee
- Kinetics:cause of a motion, internal and external forces associated with motions
- Kinematics : motions themselves, appearance of a biological thing moving around

LECTURE 13

Work Strength and Power

- Testing strength and power: power has to be measured dynamically, but strength can be measured in 3 ways
    - Isometric: how hard can you push on it (increase and decrease strength/force)
    - Isokinetic: isotonic and isometric 9ni matter how hard you push you aren't accelerating it, still moving at exact same speed), go through airport, door that rotates, push on door goes at same speed
    - Isotonic: weight stays the same (dumbbells), doesn't measure power
        - can measure power, but badly

Biomechanical Factors of Human Strength

1. Neural recruitment
2. Muscle Cross Sectional Area: not volume (which includes length) determines strength from the perspective of biological real estate
3. Arrangement of Muscle fibers: lots of architectural styles of muscle (parallel, circular, pennate, etc)--there is variation in the arrangement and the alignment of the sarcomeres in a muscle fibers
    a. parallel=faster but weaker
    b. pennate=stronger and slower
4. Muscle length
    a. How stretched the sarcomere affects the proportion of actin and myosin filaments that can interact.
    b. At rest: actin and myosin are in proximity; facilitates cross-bridge binding
    c. When stretched: fewer actin and myosin are in proximity; fewer potential cross-bridge sites available
    d. When contracted: actin filaments overlap; number of available cross-bridge sites is reduced
5. Joint Angle (longer moment arm--distance from fulcrum to the load--- means a heavier load)(moment arm of the load is largest when the muscle is at its optimal length
6. Muscle contraction Velocity: as the velocity increases, the force a muscle can exert decreases
7. Strength to mass ratio: sprint/ jump=affects ability to accelerate; weight class sport=ratio determines relative success
8. Body Size
9. Physiological explanations (cross-bridge cycling, etc)

LECTURE 14

- Loads placed on the upper body are transmitted through the spine to the legs and the musculature in the back functions at a considerable mechanical disadvantage. It produces more force internally than it generates externally.
    - Discs get compressed
    - When squatting, the compressive forces are minimized when the back is either flat or in a slight lordotic curvature (different squat postures --consider the athlete, patient, client)
        - Increasing intra abdominal pressure also reduces the need for the erector spinae to generate force to provide mechanical support. Intra Abdominal pressure can reduce compressive forces on the discs, which can reduce risk of injury (strong core=good thing to have)
        - Improvement in intra abdominal pressure which reduces spinal compression which salvages intra vertebral discs which don't heal well--weight lifting belts
            - Debate on how bad this is--women seem to maintain appropriate lordotic curvature better than men do (hunches
    - Should you lift with your legs? --maybe? a semi-squat is better because the full squat doesn't eliminate compression; it just shifts the compression changing what's being compressed (article this answer came from was biased)
    - Faces heal very effectively (quads won't heal as fast)---what's the pain coming from, what does healing look like look like in different situations
    - Once experienced pain: conscious altering of muscular recruitment characteristics to the pain associated with the activation of the affected tissue; unconscious reflexive alteration in recruitment

LECTURE 15

- If I patient is not currently feeling pain, total force output may return to somewhat normal vibes
- There can be long-term consequences of pain: extended nociceptor activity (pain sensation) can hypersensitive the nervous system so that otherwise-innocuous movements now transmit messages of pain
- Nociceptors: pain notifies you about possible threats and that triggers a protective response; sometimes pain outlives its role a a threat alarm; it continues to trigger protective responses
- ATP example: gets released from damaged tissue (or a distending bladder). When a bladder distends, ATP is released from the epithelial cells. ATP activates the nociceptors → the nociceptor then sends its pain signal to the dorsal horn and up to the brain. It also initiates “neurogenic inflammation”: the nerve releases neurotransmitters, including substances P and calcitonin gene related peptides which induce vasodilation and activate non-neural cells. These contribute more to the inflammatory environment. More inflammation while the depolarization of the nerve continues is neurogenic inflammation.
- Under excessive inflammatory conditions or repeated injury, chemical receptors can be made more sensitive and can increase in number. More receptors=more binding=more triggering of the nerve. More responsive to the same concentration of chemicals.
- Neuronal sensitization means there is an increased excitability of afferent neurons. There are lots of causes. Nobody knows them all but the consequence is pain signals get amplified. Nociceptors fire with relative ease to innocuous stimuli
- Lots of sensory fiber types (but not all of them are nociceptors)---some respond to mechanical stimuli, others to chemical stimuli, and others are silent nociceptors that will only transmit signals after they woke up from a tissue injury

LECTURE 16

- Injuries, Rehab, Reconditioning
    - Indication: a valid reason to take medication do a test, a procedure, etc
        - Potassium sparing diuretics are indicated in the treatment of congestive heart failure
    - Contraindication: a reason not to do a test, take a medication, do a procedure
        - Massage is contraindicated in burn patient's open blistering wounds full of puss
        - Statins are contraindicated in patients who have horrible alcoholic livers
    - Dislocation: complete displacement of the joint surfaces
    - Subluxation: partial dislocation of the joint surfaces followed by relocation. This can affect ligaments, nerves, cartilage, etc. and can lead to instability/laxity
    - Sprain v strain: ligament v muscle/tendon
    - Phases of healing
        - Inflammation: pain, swelling, redness, decreased collagen synthesis, increased number of inflammatory cells
        - Repair: collagen fiber production, decreased collagen fiber organized, decreased number inflammatory cells
        - Remodeling: proper collagen fiber alignment, increased tissue strength
    - Exercise Stats:
        - During inflammation phase: prevent disruption of new tissue, train uninjured extremities
        - During repair phase: prevent atrophy and joint deterioration in injured area, maintain muscular and cardiovascular function, consider specificity of adaptation, improve neuromuscular control
        - During remodeling phase:begin adding more advanced sport-specific exercises, able to begin increasing velocity/speed of movements
    - The repair of musculoskeletal tissues
        - Muscle
        - Ligament
        - Bone
        - Tendon
        - Articular structures
    - Either there is macrotrauma (overwhelming force --force vector and body position determine which tissues are involved) or microtrauma (gradual accumulation of micro--insults; anabolism v catabolism: catabolic signal predominates)

LECTURE 17

- Internal clot=provisional matrix=weak fibrin-fibronectin clot
- fibrin= fibrous protein involved in blood clots
- fibronectin = glycoprotein that binds to stuff
- Among the components of blood and lymph (a bunch of interstitial fluid. Collects in lymphatic vessels and eventually dumps into the subclavian vein, where it gets mixed with blood flow)
    - Fibrinogen
    - Fibronectin
    - Prothrombin
    - Prothrombin gets converted to thrombin---thrombin is an enzyme---its effect turns fibrinogen into fibrin---fibrin cross-links with fibronectin---platelets adhere to that---functional clot
        - In the presence of calcium, prothrombin gets converted into thrombin. When fibronectin is present, thrombin turns fibrinogen into fibrin.
        - Whenever there's bleeding, platelets show up and produce more thrombin. So now more thrombin converts into fibrinogen which converts into fibrin. No shortage of fibrin at the site of injury.
        - Bunch of fibrin and fibronectin cross-link and gunk up the area of where it's bleeding. Produce the fibrin with thrombin.
        - Platelets adhere to exposed ECM--when activated, platelets change shape and begin degranulating
        - Matric itself becomes a hub for chemotactic signaling
        - Always some macrophages in the area. Put out chemotactic signals to help recruit a neutrophil army.
        - Helps direct a bunch of chemicals to site of injury (first to show up are neutrophils)

1. Injury
2. Blood and lymphatic vessels disrupted
3. Few macrophages in area
4. Platelets first responders
5. Platelets and macrophages secrete pro-inflammatory cytokines
6. Vascular endothelium stars to get leaky
7. Leakiness is why you swell
8. Leakiness allows migrating immune cells into the area
9. Incoming cells show up by chemotaxis
10. The platelets and macrophages are both responsible for chemotaxis

LECTURE 18

Continuing on from prev lecture stuff (doesn't include stuff on fibroblasts or timing or good/bad healing environment--other stuff you need to heal)

- Insoluble fibronectin: already hanging out in the extracellular matrix
- Soluble fibronectin: major component of blood plasma
- Cross-linking provides a provisional mechanical stabilization of the wound
- Lots of stuff increases permeability: summation of all these components (damage, cytokines, kinin cascade, complement proteins, etc) leads to a huge vasodilatory effect which gets blood and cells into the area to initiate repair.
    - These cells don't just cause vascular change; they also interact with each other (ex: mast cells--resident cells in lots of tissue types)
        - Causes of mast cell degranulation: physical injury (then the complement proteins can activate them, which results in the release of histamine, which causes further vasodilation
- Healing: you need a bunch of blood and cells to initiate healing (injury→ bleed→ clot → clean → repair→ heal→)
    - Before any repair happens tho, need to clean
    - Neutrophils are great biological custodians; bacterial agents-go in and squirt superoxide and hydrogen peroxide all over the place killing everything. ---secrete proteases (enzymes perform proteolysis) that live few couple of days; they perform their custodial duties until they die
    - Pus is a bunch of dead neutrophils accompanied by some living neutrophils, a few plasma proteins, and whatever detritus got stuck in that same space.
    - Then macrophages follow the neutrophils-go in and eat up the garbage, which includes the dead neutrophils. Then you have to clean the habitat. (time this takes depends on the severity of injury)-
        - Neutrophils and macrophages also release pro-inflammatory cytokines (based on how much damage there is
    - Once site of injury/infection is clean, transition to remodeling your provisional matrix (few days out from the initial injury when the macrophages have their custodial duties under control--secrete growth factors which help initiate the proliferation phase

LECTURE 19

- "Functional hyperemia" or "reactive hyperemia" =the pump
    - Metabolism determines blood flow
    - muscle fiber contracts=metabolic activity; after one second from initiation of exercise=increase in blood flow in that fiber's direction. Substrates + products of that metabolism include numerous vasoactive molecules diffused into the blood, which provides info about the internal metabolism of that cell ---> informs the **circulatory system to provide more blood. delivery by vasodilation**
    - **Size principle ensures you recruit motor units in a specific order, some fibers active, others inactive; fibers in a single motor unit are distributed throughout the muscle, not grouped together → scattered muscle cells receive their nutrition by capillaries (no smooth muscle so unable to adjust their volume) (diameter adjusts made upstream)**
    - Muscle fibers are longer than the capillaries supplying them so they have multiple suppliers coming from upstream branches (not all of those arterioles come from the same parent so vast arteriolar network supplies a single fiber)---> capillaries receive lots of chem info from the muscle cells; RBC and endothelial cells are probably secreting additional info. Increased intravascular pressure, more sheer stress in arterioles, and mech contraction = lots of news available to guide circulation
    - Detour management at capillary level isn't really happening, the plasma traffic jam seems to contribute to the pump.
        - Hydrogen ion accumulation , lactate nitric oxide , adenosine, prostaglandins,eicosanoid explanations, potassium, bradykinin activity, sympathetically-mediated vasodilation effects

- A few days from the initial injury---macrophages secrete some growth factors which helps initiate the proliferation phase (growth of new tissue)
    - Angiogenesis (new blood vessels) = wound contraction begins
- If you spend your post-injury life in supine/prone postures, healing =limited
-Fibroblasts adhere to fibrin, req presence of fibronectin
- Key for fast/quality healing: robust+brief inflammatory reaction --leaving inflammation in a tissue impairs the action of fibroblasts (want inflammation to start receding w/in 72 hrs)

LECTURE 20

Review lecture, stuff I might not have written down in the previous notes:

- Fleshy/direct attachment: epimesium continuous w/ periosteum
- Fibrous attachment: tendinous attachment
- Muscle-tendon junction
- Origin: Proximal insertion
- Insertion: distal insertion
- Agonist: prime mover
- Antagonist: opposite
- Synergist: indirect assister (stabilizer, etc)
- Work: Force x displacement x cosine of angle
- Toque: Force that produces rotation
- Rotational work: torque and angular displacement
- Power: work/time
- Lever Arm + Moment Arm
- Variable Resistance: variable moment arm through ROM
- First class Lever: axis between force and load
- Second class lever: axis, load, force
- Third class lever: axis, force, load
- Mechanical advantage/disadvantage: trade-off btween force + speed.
- Pain and injury induced neuromuscular alterations: pain, injury, and fear of pain and injury result in conscious and unconscious changes in motor recruitment
- Transition from acute to chronic pain: inflammation occasionally is good, but when it stays for too long it's bad. Re-injuring a re-injured injury turns inflammation into something that is seemingly long-term
- Injuries classified as: acute, subacute, chronic, acute on chronic

1. Get an injury
2. Blood + lymphatic vessels are disrupted
3. The local vascular briefly vasoconstricts
4. A clot forms
5. Platelets are first responders + contribute more thrombin
6. Once the wound is stabilized, both platelets and resident macrophages send out chemotactic signals
7. Locally, blood vessels dilate and the vascular endothelium gets leaky. This allows migrating immune cells to reach the site of damage/injury
8. This leakiness is why you swell; water follows the extravasated proteins. The pain is caused by nociceptor depolarization. The redness is increased blood flow. The heat is metabolism

- Fibroblasts adhere to fibrin, req presence of fibronectin---cross-linked provisional matrix is where they adhere and begin remodeling the ECM (synthesizing collagen + fibronectin)
- If you wear shoes, specify of adaptation happens

LECTURE 21

Endocrine System

- Hormones do lots of things in your body (sleep/wake cycle, immune system, metabolic stuff, hypertrophy v atrophy, sexual function, hunger/thirst/food seeking behavior, fight/flight, etc)
- Endocrine and Nervous System: Neuro-Endocrine System
- Endocrine: pituitary, adrenal, gonad, thyroid, pancreas
    - System of glands that secrete different types of messenger molecules into the blood to regulate cells, tissues, organs, systems, etc
- Neuroendocrinology: neuro-brain-hypothalamus (blood brain barrier) --- refers to the interaction of the two “organ systems”
    - Hypothalamus to pituitary to the thyroid glands
    - Hypothalamus to pituitary to adrenal glands
    - Adrenal medulla (get epinephrine)
    - Epi is a messenger secreted upon CNS stimulation
- Messenger molecules: long range v short range
    - A chemical messenger is a compound that transmits a message
    - Hormones are long-ish range communicators
        - Synthesized, stored, and released into the blood by endocrine glands - body structures specialized for this function - and certain other cells
        - Pituitary: LH, ACTH, GH
        - Adrenal: Epinephrine, cortisol
        - Teste: Testosterone
        - Pancreas: Insulin, Glucagon
        - Thyroid: Thyroid hormones (T3 and T4)
        - System of glands that secrete different tyes of messenger molecules. They enter the bloodstream, travel around, eventually bind, and regulate stuff. Neural signals frm the brain connect to remote glands throughout the body and the hormones regulate cells and tissues all over the place
        - Signaling molecule produced mostly by a gland--often transported in a circulation to a distant tissue or organ--influence behavior of that tissue by interacting with its cells
        - Polypeptides: target receptors integrated into cell membranes
        - Steroid: interact directly with the regulatory elements of the DNA
        - Eicosanoids
    - Neurotransmitters are communication to adjacent cells
    - Hypothalamus considered the link between endocrine and nervous system
    - Pituitary regulates: stress, BP, water balance, thyroid function/temperature reg, growth, reproduction/sex organ function, lactation

LECTURE 22

Hypothalamic-Pituitary ____ Axes

- HP-Adrenal: Corticotropin-Releasing Hormone, Adrenocorticotropic Hormone…
- HP-Thyroid: Thyrotropin-Releasing Hormone, Thyroid Stimulating Hormone…
- HP-Gonadal: Gonadotropin-Releasing Hormone, Luteinizing Hormone and Follicle-Stimulating Hormone…
- HP-Liver: Growth Hormone-Releasing Hormone or Somatostatin, Growth Hormone

Neuroendocrine System: Chemical Messengers=compound that transmits a message

- Hormones are long range communication
    - Amine Hormone: amino acids modified groups
    - Peptide Hormone: short chains of linked amino acids=target receptors that are integrated into cell membranes. This initiates a signal transduction pathway
    - Protein Hormone: long chains of linked amino acids
    - Steroid hormones: derived from the lipid cholesterol=interact directly with the regulatory elements of the DNA
        - Epinephrine
        - Testosterone
        - Triiodothyronine
        - Made from cholesterol; fat soluble (diffuse across membrane/sarcolemma); adrenal cortex, testes, ovaries; nuclear or cytosolic receptors; slow initiation, long action
    - Most hormones come from gland, shuttled around in circulation, and exert some physiological effect on a distant bunch of cells (tissue or organ). The sig frm a hormone (consequence of that signal) only affects cells that express a specific receptor, one that is specific to that exact hormone. Otherwise, it would affect any cell in the body
    - Autocrine secretion: cell releases a hormone by itself for itself. The hormone never exits the tissue that produced it
    - Paracrine secretion: hormone gets released ,acts with adjacent cells, doesn't need to enter circulation to get there.
        - Pancreas get everywhere, pancrea cures everything
    - Binding proteins: these carry hormones through circulation, prolonging the half-life of the hormone. Major role in endocrine function
- Neurotransmitters are communication to adjacent cells
- Lipolysis is regulated by: growth hormone, catecholamines, insulin, glucagon, cortisol, TNF-(insert alpha symbol here)

LECTURE 23

There are many variants of growth hormones. The pharmacological human growth hormone (HGH) doesn't seem to be very effective. However, many things affect growth hormones such as sleep, meals, and exercise. The majority of HGH is released during deep sleep and low levels are released during the daytime. Denying yourself sleep will be problematic and will affect the release of the HGH. Food and exercise also have an influence, but the effects vary depending on the food and exercise. Women tend to have higher baseline levels than men, but their peaks are not as high. Post workout, women will usually be higher than men. The characteristics of exercise, specifically volume training (long and intense training), that help to increase the HGH include the increase of lactate in order to lower your body's pH. At least 8 hours later, you will then see IGF being released from the liver. The changes in these hormones take time before it spikes. Additionally, the growth hormone is initiated by the hypothalamus which then stimulates the anterior pituitary to release GH. The hypothalamus can also release somatostatin which inhibits the release of GH. It also has its own signaling cascade.

LECTURE 24

8 Arguments people commonly make against the use of steroids in sports

3 Major Ones People Tend 2 Make:

1. steroids aren't natural
2. They make sports unfair
3. They cause health problems

More ethical arguments against the use of steroids in sports

1. The athlete's health
    a. At what cost do these peaks arrive? is the athlete's health so compromised that it is not worth the benefits?
2. Unnecessary risk for harm, undue social coercion.
    a. Others are taking steroids, so you might have to do steroids too in order to keep up (you have the unfair disadvantage---coerced)
    b. Other people's decisions force you into an undue risk for harm as well
3. Steroids are unfair
    a. Unnatural (if I'm natural, unfair that I would have to compete against someone who isn't---ties into argument #2)
4. Steroids strips the soul from the sport
    a. Contravenes the spirit of the sport ; if we eliminate doping, the sport is in its purest form
5. Natural v Unnatural
    a. Steroids aren't a natural way of achievement ; something unwholesome about unnatural undertakings)---alter natural force of life
6. Rules (makes sense; but more to discuss)
    a. If on banned list, you're cheating
    b. Signing up to participate and not following the rules is wrong
7. Harm to other people
    a. Professionals can do harm to other people
    b. Think contact sports; at risk when competing against steroid user
8. They don't work anyway, so there's no reason to use them (weakest argument)
    a. "No definitive evidence that they work anyway so why take the risk"

LECTURE 25

Argument: The athlete's health

Whether or not an athlete does steroids, this does not affect the health of the person arguing for the athlete to not use steroids. If the concern was really the health of the athlete, then that would mean that there should be more factors to limit. Too much of a good thing is a bad thing, so consuming something like "too much cupcakes" would be bad as it could give you diabetes. You could do something like drinking too much medicine, and it could potentially kill you. Stating that medicine like Tylenol is less dangerous than steroids may potentially be wrong as more people can overdose on Tylenol. However, this does not mean there is a recall for all Tylenol (as you could only die via overdose). This is similar to steroids as many articles have misinformation about the side effects of steroids. With oral steroids, cholesterol levels will be affected. With the oral steroid stanozolol, HDL levels decrease while LDL levels increase. With testosterone that is delivered intramuscularly, HDL levels stay about the same while LDL levels decrease. However, if you eat testosterone, blood-filled cysts can potentially form in the liver, but it is rare. Another argument could be that taking steroids can cause left ventricular hypertrophy, but the athlete would have to take a lot of drugs for this to occur. Statistically, the sport itself is what would be injuring the athlete, not the steroids. Therefore, it would not be entirely accurate to state the athlete's health as an argument as to why athletes should not take steroids.

LECTURE 26

Argument: The unnecessary risk for harm and the social coercion that facilitates it.

This argument basically states that because others are taking steroids, an athlete might feel pressured to also take steroids in order to "level the playing field." However, no one is forcing the athletes to take steroids as it is completely voluntary. There are even laws against social coercion which means that the athlete would never be forced to take steroids. In a lot of sports, steroids are likely a requisite in order to compete at the elite level. However, no one is obligated to compete in elite competitions. For example, within the NFL it is necessary to take steroids (even if there are some minor side effects due to the size of the doses. These NFL players will face side effects from playing football against other athletes who could potentially be 300lbs. This aspect of the game is more dangerous than the steroids that the athletes are taking. Injuries are also the reason why most professional football players only play for approximately 3 and a half years. Additionally, no one is coercing the players to play, and the players already know the risks of playing at this point. Steroids are part of the game. It is ultimately the athlete's choice as to whether or not they take steroids.

LECTURE 27

8 ways to modify enzyme activity

1. Allosteric Control
    a. Allosteric activation (alternative binding site where inhibitors bind that interacts and modifies the shape) = positive modulation
    b. Allosteric deactivation (consumes ATP, abundance of ATP, want to do oxidative phosphorylation ; changes shape of active site, no longer the shape to fit the substrate; shuts down glycolysis) = negative modulation
2. Competitive inhibition (substrate and inhibitor competing for the same enzyme)
3. Noncompetitive inhibition (binds to an allosteric site, but there is no change in substrate affinity----no pref regarding binding state. Blocks the reaction/conformational change gets blocked---change the effect of what is happening)
4. Uncompetitive inhibition (potentiated by the substrate. Only binds to the enzyme after the enzyme has bound to the substrate)
5. Mixed inhibition (like noncompetitive inhibition, except the inhibitor does have a preference of whether the enzyme is bound or unbound--can affect affinity for a substrate, decreases reaction rate)
6. Suicide inhibition (the inhibitions are substrates that are derived from the enzyme's normal substrate. When the enzyme initiates catalysis-- after binding to the inhibitor--that inhibitor gets modified in a way that irreversibly inhibits the enzymes. ----wrong substrates and then its the wrong substrates)
7. Accumulation of product (hexokinase converts glucose into G6P, inhibits hexokinase---preserves blood sugar while exercising)
8. Phosphorylation toggling active/inactive forms (proteins modified by phosphorylation states. ---example with glycogen synthase and phosphorylase-----active/inactive states---phosphorylate it and it turns off)
    a. Phosphorylation activates glycogen phosphorylase
    b. Phosphorylation deactivates glycogen synthase

LECTURE 28

Hypertrophy can be described as a relay race. Things such as resistance training can cause muscle hypertrophy.

The reason why we adapt to exercise is because exercise threatens us so our body begins to reinforce its tissues and rebuild its structure so that it can be stronger. Our bodies begin to create specific adaptations in order to adapt to the exercise that we do. This is why hypertrophy happens; since our bodies are unable to withstand heavy loads and stresses, this induces adaptations. One of the adaptations that reinforces skeletal muscles just so happens to be hypertrophy (making our muscles bigger and more capable). Specificity of adaptation as well as fitness compatibility are reasons why hypertrophy occurs. This occurs via cell signaling cascades. Something binds to a receptor which then turns on the receptor which leads to the activation of a protein. This protein at the membrane then activates a protein in the cytosol. Eventually, you get your final response that ends at a specific intracellular response, which in this case would lead to hypertrophy. Additionally, this specific cell signaling would be phosphorylation cascades (phosphorylating a protein to alter its behavior). Eventually this signaling cascade ends in hypertrophy (translate some proteins and favor anabolism/hypertrophy). Resistance training causes hypertrophy because of mTOR (specifically complex 1).

LECTURE 29

-you see growth in mTOR complex 1 (adapt/grow/hypertrophy)---interact w/ it---accelerate growth----way of improving

-how to make progress

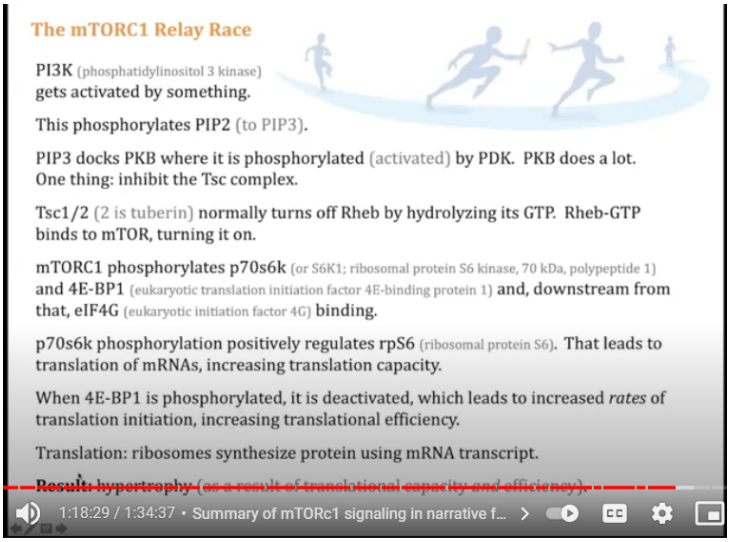
-checks/balances---spending ATP =going bankrupt, if accumulate=bad in the body----want to balance (mTOR is well regulated)

Dif regulatory upstream variables in complex 1 and 2 (different mTOR enzymes)---dif controlled upstream and downstream variables

- **Complex 1**: mTOR enzyme, Raptor (reg protein of target of rapamycin), MLST8 (mammalian lethal w/ SEC13-protein 8)----need regulation (try to go back to around minute 40)
    - The most critical reg of skeletal muscle metabolism (protein synthesis + degradation)
    - Complex 2 is more about promoting stress responses necessary for cell survival
    - **mTOR enzyme---**phosphorylates
    - **Raptor**---critical, function:recruiting downstream targets for mTOR complex 1 to phosphorylate them --abundant in skeletal muscle---major point of interaction--whether it turns on or off (MAPK--anabolic, grow, turn on mTOR signaling; AMPK-catabolic, waste away, turn off)
        - Responsible for assembly of protein complex
    - **MLST8**
        - Required for some assembly (core protein in complex 1 tho)
    - PKB/Akt--opposite effect on tuberin
    - **TSC1/2**-upstream from mTOR enzyme
    - **Rheb**-gets inhibited, promotes phosphorylation/turns on mTOR
        - Facilitating hydrolysis of GTP
    - FKBP12---interacts with rapamycin
    - **4EBP1**-downstream target of mTOR-inhibit growth
    - **P70S6K**-downstream target-promote
    - **rpS6**-ribosomal protein
        - grow
    - **DEPTOR**-inhibitor--negative regulator
        - Inhibiting the kinase of mTOR
        - mTOR is preventing atrophy, cell death, etc
        - DEPTOR inhibits mTOR, it is also prohibiting apoptosis
    - **PRAS40**-inhibitor
        - If phosphorylated (+DEPTOR, then that gets rid of inhibition)
    - Rapamycin-->raptor/mTOR/g(beta thingy)L → cell growth
    - RSK-suppresses (?)
    - (mTOR→ S6K1→ rpS6)
    - Rapamycin--- promotes inhibition of the mTOR enzyme via FKBP12 (and then raptor function) + inhibits S6K1's phosphorylation of rpS6

- Complex 2: mTOR enzyme, Rictor (rapamycin-insensitive companion of target of rapamycin), MLST8, MSIN1 (mammalian stress-activates protein kinase interacting protein 1)

-just go to minute 1:17:00 to find the summary :3



LECTURE 30

(Go over insulin signaling ---classic growth signaling---PI3K, PKB, mTOR---map going everywhere, some go in the same direction, others in other directions)
-things that turn on mTOR (4 categories)

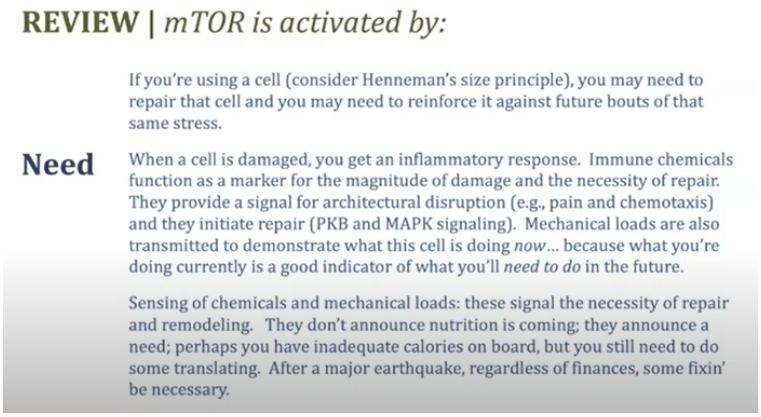
- immune/chemicals
    - In phospholipid bilayer, has arachidonic acid (abundant in skeletal muscle)
    - When you exercise, you release a bunch of arachidonic acid which is a substrate for COX so you synthesize a bunch of prostaglandins. Prostaglandins signal the MEK-ERK (MAPK) pathway. MEK-ERK and mTOR "cross-talk" which leads to growth.
    - Taking an NSAID may block COX 1 (which is abundant in gastric tissues)
    - Cross-talk upstream (cross-talk also seen with Raptor)
    - MAPK cascades (signaling)
        - Tuberin (TSC2), Raptor (hub 4 cross-talk)
    - RSK
    - PI3K, PTEN→ opposites
    - Tissue damage→ body responds with immune + inflammatory cells (neutrophils, macrophages, cytokines, etc)
        - Interleukin-15 (cytokines
            - Abundantly released during tissue damage (proportionate to the amount of damage)
            - Promotes protein synthesis and inhibits protein degradation
            - Regulators of skeletal muscle released during time of tissue damage and connected to tissue repair
            - Expression induces hypertrophy
        - Many interleukins (2 and 15) (cytokines--among 36 identified human interleukins)
            - Shut off Forkhead, Bad (agonist of cell death), GSK-3 (which shuts off glycogen synthase---> turning on the synthesis of glycogen by turning it off)
            - GLUT
            - Raptor recruiting downstream targets, while mTOR phosphorylates (leads to growth)
            - PI3K---> PDK1
            - IL2
            - Interferon (gamma) ---cytokine that interferes with viral replication
            - GF (IGF=insulin-like growth factor)
            - Insulin
            - AMPK turning TSC1 + TSC2 and deactivating Rheb (not activating mTOR so stop translation)
        - Myotatin (Myokine=muscle made cytokine that's mostly autocrine, member of the TGF-beta subfam)
            - Inhibition of PKB; promoter of growth?

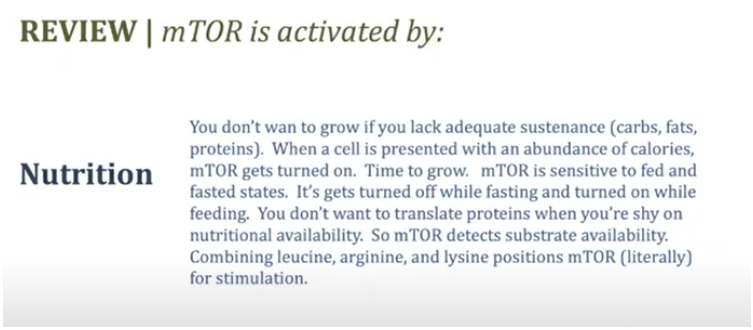
    - Reactive oxygen species (complicated relationship w/ mTOR)
    - ***mTOR can be activated by: inflammatory/immune activation of cell surface receptors: prostaglandins, interleukins 2 and 15, interferon gamma, reactive oxygen species, Wnt proteins, TNFalpha, myostatin (neg receptor). Works thru MAPK + PI3K
- Mechanical tension
    - Mech receptors sensing dif variables gets converted into chem+electrical signals tht triggers cascades=protein synthesis
    - Intercellular v intracellular signals
    - Titin resp 4 passive elasticity of muscle
    - Mech sig created when muscle resists load, signals converted to chem, “mechanotransduction,” initiate hypertrophic cell signaling--mostly integrins, titin, caherens---lots of pathways
- Endocrine system
- Nutrition

LECTURE 31

- Endocrine system
  - Glandular responses
  - Testosterone : primary effect is steroid/genomic
    - Binds to androgen receptors ; cross phospholipid bilayer and change shape and bind to hormone response element------metabolic fitness (reg size of self)---cell signaling
    - 2ndary effects are non-genomic (messenger cascades)
      - Calcium release from inside cell
    - Regulates the anabolic cell signaling cascades (in part thru facilitation of IGF-1 signaling)
    - Activates both PKB + MAPK
    - Inhibits LKB1 (inhibits atrophy thru mTOR)
    - When you put on pounds (fat) -- your strength goes up (increased calcium)
  - Estrogen: primary effects are steroidal/genomic
    - Anabolic effects
    - 2ndary effects are non-genomic
    - Phosphorylates (deactivates) tuberin (impairs activation of mTOR thru hydrolysing Rheb-GTP)
    - Promotes LKB1 + AMPK
  - Insulin and IGF1: binding proteins,
    - Insulin → PI3K → PKB → GLU4 translocation, turning off glycogen synthase kinase (assembling glycogen)
  - Growth Hormone: Hypothalamic-Pituitary (IGF doing most of interaction), lots of signaling
  - Thyroid Hormone: mimic what a steroid hormone would do to a degree
  - ****mTOR can be activated by Endocrine system by:
    - Insulin
      - PI3K
    - Thyroid hormone
      - PI3K
    - hGH/IGF
      - PI3K
      - MAPK
      - JAK-STAT
    - Testosterone
      - Ca2+ dependent MAPK activation
      - Increased IGF signaling
      - Inhibition of LKB1
    - Estrogen (good guy but tricky)
      - Inhibition of Tuberin
      - Promotion of Rheb

        - Promotion of LKB1 and AMPK
    - **Goal: To get Rheb to activate mTOR (send mTOR to the lysosome)**
- Nutrition
    - 20 Amino acids (some more important than others for mTOR signaling)
        - **Leucine (anabolic)**, arginine, lysine
    - Many proteins involved
        - SLC38A9=transmembrane protein=senses intra-lysosomal arginine (use CASTOR and SLC38A9 to eliminate that detection)
    - Need lots of stress for AMP to bind AMPK so that LKB1 can promote it (promote tuberin + inhibit Raptor)
    - LKB1 = liver kinase B1---activates AMPK
    - *****
        - Fats: lipids hv reg roles---cholesterol rich diets elicit elevations in circulating steroid hormones
        - Carbs: glycogen binds to beta subunits on AMPK; increases blood glucose; insulin response stimulates PI3K
        - **Proteins: cell capable of rec intracellular amino acids. leucine=important; signals thru vps34 + Rag GTPases. Proteins attach to raptor +cause movement of mTOR complex to lysosome (facilitates interaction w/ Rheb). mTOR + Rheb dissociate w/o AAs**





REVIEW | *mTOR is activated by:*

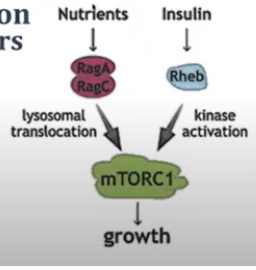
Assumption of nutrition

There are multiple ways of showing your cells that you have an abundance of calories. 1) Provide the actual energy substrates. 2) Don't provide any substrates, but promise the cell that they're are on the way, i.e., initiate PI3K signaling independent of cellular damage. Insulin does this. An injection of insulin provides no new calories, but it turns on mTORc1 anyway. Because evolution could not anticipate the invention of the hypodermic needle. Our bodies assume insulin is only released in response to a feeding. So when it binds, it triggers mTOR and GLUT4 translocation simultaneously. "Start synthesizing proteins; calories are on the way!", it tells the cell, exclamation point in tow. This is similar to how the scent of food can induce salivation before any calories actually enter your mouth. Insulin is the mechanism by which a muscle cell smells its coming substrates.

REVIEW | *mTOR is activated by:*

Combination of activators

We have a diverse set of nutrients coming in. Protein for the Rags, carbs for the Rheb. We're eating a broad, colorful, abundant diet. In this situation, growth seems okay. Unthreatening to fitness.



Or... we have enough protein on board to make more useful proteins out of them (rearrange their building blocks). And although we might be a bit shy on gross calories (low on carbohydrate availability) to offset the ATP expense, we have some upstream chemicals (prostaglandins, cytokines, IGF, etc.) informing us of the importance to translate those proteins anyway.

LECTURE 32

AMPK: metabolic dictator

- mTOR = enzyme (kinase). Lots of enzymes influence athletic perf; many of those do so via mTOR
- Enzymes that enhance endurance metabolism
    - Mitochondrial enzymes
    - Glycolotic enzymes
    - Those involved in fatty acid metabolism
- Enzymatic adaptations for strength + hypertrophy: reduce activity of some of these enzymes
    - Reducing the supply, simulating catabolic enzymes
    - Helps reg the energy status of ur muscles during endurance sports
    - Phosphorylates (inhibits) raptor and tuberin (turning on tuberin) preventing rheb from activating mTOR + phosphorylate mTOR directly
- Key enzyme in cellular energy deficits---inhibt metabolic pathways tht consume energy (senor and it regulates)
- AMP-activates protein kinase (normally don't have a bunch of AMP, so AMPK is inactive-----exercise)
- Building up ADP + losing ATP
    - Adenylate kinase
- AMP binds to AMPK which promotes it. When ATP binds to AMPK, it inhibits it. (AMPK has subunits)
    - You can deaminate your AMP
    - Regulatory subunits are beta and gamma (where AMP binds)
    - If you have a bunch of glycogen, it can bind to the beta subunit
    - ATP hydrolysis→ adenylate kinase reaction → ATP and AMP compete for binding on gamma subunits on AMPK; Atp inhibits alpha phosphorylation; AMP promotes it → binding of first AMP on gamma enhances binding of a second → w/ 2 AMPs bound, an upstream kinase activates AMPK by phosphorylating the alpha subunit
        - Promoted by: exercise, hypoxia, starvation/glucose deprivation , exercise in the presence of those things
        - Minute 47:47
    - Inhibit, mTOR is the hoarder, AMPK is cleaning out
    - Ubiquitin proteasome pathway (degrades)
    - reactive oxygen species (all over the place)
    - Healthy for cardiovascular health
    - Cytokines and drugs can also activate AMPK
        - Metphorman

-Once activated, switches on pathways that produce ATP + inhibits pathways that consume ATP

Trying to turn off ATP consumption + turn on ATP synthesis (cost body ATP, turned off; helps ATP production/gen=turned on)

- Mice who r deficient of AMPK get huge, increasing AMPK facilitates muscle atrophy
- AMPK affects behavior (inhibits food intake, inhibiting AMPK; stimulating intake=stimulating AMPK)
- Summary at 1:12:00

LECTURE 33

-AMPK applications: general health (life span, cardiovascular, etc)

-AMPK and healing: early healing can be enhanced; angiogenesis=early restoration of blood, access to nutrients in diabetic patients

-mTOR and *eccentric loading*: more disruption to sarcolemma where arachidonic acid lives. More PLA2 activity, more COX activity, greater buildup of prostaglandins, more MAPK sig, and cross talks, etc

- exercise-induced muscle damage = major trigger for the increase in MGF lvls and eccentric stress = more potent trigger

- activation of the tissue associates w/ greater reductions in myostatin, a myokine (little protein by the muscle) w/ autocrine, paracrine, + endocrine functions ----PKB inhibition

-add some additional resistance

-Speed of contraction: slow eccentric stress may gen more MGF fast eccentric stress

-Size Principle: mechanotransduction belongs to the fibers tht were activated; passive fibers rn't participating in the sensation of + response to the application of mechanical tools

-need a high load (want to adapt)

-Blood Flow Restriction: elicit mTOR response---restricting blood flow from exiting, reason for MAPK activation ---chem impression of high intensity---cortisol goes up

-Aerobics + Anaerobics: stopping tuberin (anaerobic) and turning on tuberin (aerobic)----aerobic is opposing anaerobic---stop aerobics for muscle hypertrophy? Maybe----expect beginners to improve

-Specificity of Adaptation: hard to grow in every direction; adapt to different situations ---diff mechanical forces cells respond to (nature of stress affects how you will adapt---the load is going to be applied differently)

Involves proteins and tissue remodeling

Resistance training stimuli cause mTOR/p70s6k

Aerobic/oxidative stimuli promote mitochondrial biogenesis (don't activate mTOR)

Frequency, intensity, duration of signaling responses

Your body detects, quantifies, and responds to different variables (diversity of mechanical loads/stresses)

Angular specificity

-Nutrition:

cabs and AMPK (inhibitory of mTOR)

Leucine, lysine, arginine= mTOR to lysosome (+other growth factors 1:07)---eat the right stuff (give your body the metabolic signals of value)(give body right nutrients)

LECTURE 34

- Supplements: PDE; effective at performance and attention; mobilization of energy substrates---but doesn't impair muscle responses;;greater muscle protein synthesis with leucine (HMB-stimulates protein synthesis, exhibits anti-catabolic effect---preserve muscle mass)
    - Previously untrained, HMB might help show improvement (at least for a month)
    - Well-trained, ergogenic effect isn't as good
    - Change up routine, HMB should work better (more adapted to routine, won't help)
    - Phosphatidylserine: tempers some of the spikes in cortisol (cortisol inhibitor, but doesn't eliminate)
    - Arachidonic Acid: effect on arachidonic supplementation and performance (cell signaling)---evidence that it works (bottom of list tho-know how it works, pros/cons)
    - Phosphatidic acid: in mechanical loading, convert to phosphatidic acid (can just eat it)---seems to work---binds to mTOR (lysophosphatidic acid and then get some MAPK signaling---so not direct activation as done thru mechanical loading)---increased MAPK signaling
- Catabolic Supplements: good if you are an aerobic athlete; endurance (AMPK helpful for endurance)
- All enzymes are trainable
- mTOR - muscle adaptation relationship: altered in many different ways
    - What to do for hypertrophy
    - Heavy lifting, with multiple muscle groups or large muscle groups
    - chemical , mechanical, hormonal, nutritional responses maximize activation
    - Amino acids → rag → lysosomal translocation → mTOR C1 → hypertrophy
    - Growth factors→ Rheb → kinase activation → mTOR C1 → hypertrophy
    - mTOR turns on protein translation which is the linking of amino acids
    - Optimize tissues, cells, adapt to the environment--why hypertrophy happens
    - How: **mTOR (signaling--interpretation of upstream signals and the relaying of the downstream signals)**, steroid hormones
    - What enzyme stiffarms mTOR: AMPK
    - AMPK-ways to save ATP and increase storage; alpha is catalytic, beta and gamma are regulatory
    - Eliminate AMP with AMP deaminase
    - 1:05:00

LECTURE 35

While exercising, hydrogen ions cause your pH to decrease which leads to your nerves sensing this change. This leads to fatigue and muscle burning. (What usually gets blamed, however, is anaerobic metabolism with lactic acid being its byproduct.) There are steps that lead to the release and consumption of hydrogen ions. It begins with glucose being converted into glucose 6-phosphate (which could also be made from glycogen). During this step, ATP gets converted to ADP and you release a hydrogen ion (at the hexokinase step). At the phosphofructokinase (PFK) step, ATP also gets consumed and converted into ADP; therefore, another hydrogen ion is released. At the glyceraldehyde 3-phosphate dehydrogenase (G3PD) step, two hydrogen ions get released as there are two reactions occurring (since the glucose has split in half, rather than working on one molecule, there are two 3-carbon molecules where the reactions occur from). After this, we get to pyruvate kinase where we consume two hydrogen ions. In total, there is a net total of two hydrogen ions being released. Glycolysis doesn't yield any protons if it begins with glucose so there is no change in your pH. If you begin with glycogen, then your body consumes one proton (which would make your pH more basic). In other words, lactic acid accumulation does not cause muscle burning or fatigue.

LECTURE 36

Causes of Muscle Burning + Fatigue:

- ATP : ADP ratio (prev lecture)---reg; state of perf alteration (resting potential of the cell can be affected)----as ATp =hydrolyzed, more ADP builds up
- Hydrogen ion
    - During exercise, pH goes down---accumulation of hydrogen ions--might contribute to fatigue
    - Elevated proton concentrations (sarc reticulum/CA kinetics affected; contractile unit obstruction--weaken cross-bridge activity)
    - Relative refractory period = hyperpolarization
    - During exercise, muscle cells prog lose K+; as it seeps out, the excitability of cell decreases; ability of that cell to initiate an action potential diminishes; intercellular buildup of H+ ions//t-tubules less permeable to chloride; neg charge stops leaking in, membrane potential preserved
- Phosphate
    - Increase in phosphate in muscle during exercise; impairment of cross-bridges (decreases myofibrillar calcium sensitivity---impairs cross-bridge itself)
    - Phosphates do more than just buffer the free calcium; it impairs the release of it (takes time tho for ATP concentration to drop----ATP hydrolysis=fast, bt creatine phosphates donates donates nearly as fast ---> when it slows, the concentration of ATP drops as well--------quick build up of phosphates + decline in ATP)
    - Time frame for this cause of muscle fatigue: ~ 1 min
- Magnesium
    - Lives in skeletal muscle
    - Complexed or uncomplexed
    - Free magnesium have a lower affinity----during exercise, it increases---compromise release of calcium in the SR---competitive inhibition (compete for binding sites)
- Reactive oxygen species
    - Antioxidants combat free radical damage
    - Antioxidants inhibit oxidation of molecules
    - Electron transfer
    - impaired----ETC -- have an effect on fatigue
    - Intense exercise--free radicals--affect performance (calcium sensitivity, SR, depolarization-induced calcium release)
- Local inflammation
    - DOMS
    - Induce fatigue
    - Many inflammatory cells affect fatigue
- Structural damage to tissues
- Generation of heat
    - Temperature rises
    - Enzymes (denaturing---even b4 that, losing function)
    - Blood distribution changes

    - Oxygen dissociation curve shifts right
    - Increase production of ROS
    - Electrolyte balances across sarcolemma
    - Reduce stroke volume, increase HR
    - Increased RPE, decreased central drive
- Carbohydrate availability
    - When carbs get low, performance suffers
    - Glucose + fructose to increase oxidation rate
- Tryptophan and serotonin
- Central fatigue

LECTURE 37

After you eat carbohydrates, you have an increase in insulin production. Insulin alters the branch chain to tryptophan ratio. Based on this, one could make the assumption that we should avoid eating carbohydrates during exercise. However, this is not the case. In reality, carbohydrates do not make you sleepy while you are exercising. During exercise, we have non-insulin dependent glucose uptake as AMPK mobilizes your GLUT4 for you. This means that you will not get an insulin response while you are exercising. You are already oxidizing BCAAs during exercise; therefore, you do not need insulin as your muscles are doing it for you. Additionally, you are also mobilizing free fatty acids as you are undergoing lipolysis. This means that the free fatty acids are binding to albumin and the increase free tryptophan. While you are not getting an insulin response, you are changing the lipolytic activity to favor carbohydrates in place of fat. This therefore reduces the amount of free fatty acids in the blood. In other words, during exercise carbohydrates will reduce sleepiness.