Exercise Physiology

Facts & Stats
- Tapering allows the testosterone to cortisol ratio to increase thus increasing the anabolic processes.
- anabolic steroids most likely attenuate the effects of cortisol (in overtraining) induced decrease in training adaptations
- training at a pace that exceeds Vo2max may be a more important component than training volume to stimulate an increase in muscle oxidative potential
- ventilatory threshold....point at which ventilation rate increases out of proportion to workrate (similar to lactate threshold)
- people use less of their lung volume as they become more sedentary w/age. Total lung capacity changes very little as one ages. People are losing elastic recoil of the lung as they become more sedentary.
- cortisol release is in proportion to exercise intensity
- warmup prior to sprint exercise results in an increase in aerobic ATP production
- warm-ups used to bring a decrease in the change in Vo2 from rest to exercise…..a high intensity warmup [6 min at 90% Vo2 max] with a 3 minute rest can decrease the change in Vo2 by 60%
- Creatine phosphate acts as a carrier of phosphate from production site to site of utilization

Half lives
-- cytochrome C [and other mitochondria proteins] = 6 – 10 days
-- glut 4 = 1 – 2 days

Sweating & Heat Loss
- sedentary person has daily water requirement of ~ 2 liters
- heat acclimation = 50 - 60% of it is by way of decreased heat generation by way of a decrease in RMR
- 10% of blood flow goes to skin during exercise in the heat.
- Skin blood flow increases in proportion to exercise intensity and heat production.
- Skin blood flow increases until the body temp gets to 38C, then it levels off reguardless of further increases in intensity or temperature.
- At 90% Vo2peak, skin blood flow is 60% higher in trained vs. untrained people.
- The energy that is stored in heat is used to convert water into water vapor.
- Water can pull 200 times more heat away from skin than air can.
- Elevation in core temp tells brain to turn on sweating, increase in osmality of blood turns on thirst drive.
- There is a core temp that serves as a threshold point to be reached for dialation of skin blood vessels.
- hot day sweat rate = .5 - 1.5 liters per hour. = 8 - 25ml per minute
- 1 liter of water = 1kg body weight
- should take in about 1 gram of sodium per hour
- fit athletes acclimated sodium loss…… ~40mmol/liter of sodium or less
- unfit athletes sodium loss……60mmol/liter or greater
- Hypontremia……low plasma sodium = less than 135mmol/liter……..normal = 136 – 142mmol/liter
- get symptoms when plasma sodium goes 125 – 135mmol./liter……..more severe below 125….major problems below 120
- Training adaptations may allow for reduced heat production during exercise in the heat. Training decreases the temp. needed to cause the same skin blood flow increases as untrained.
- At 85% humidity or above, body heat dissapation is reduced significantly.
- water immersion precooling increases exercise endurance in hot, humid conditions
  - lowers starting body temperature and allows more work to be completed prior to reaching critical limiting temp.
- skin blood flow becomes stable by 30 minutes or earlier into exercise....there is a large increase during the first 5 - 15 minutes
- core temperature increases are large during the first 10 - 20 minutes
- any attempt to do something about body temperature should definitly be done during the first 5 - 15 minutes of exercise

Cramps
- doubling of extracellular potassium [cell membrane depolarizes]
- hydrogen modulates activity of potassium channels in muscle [ATP closes the channel, H+ opens it]

RMR
A 1kg increase in muscle = 50kcal per day increase in RMR. RMR declines with the decline in muscle mass. Menopause is correlated with a decrease in energy expenditure, along with a dramatic increase in body fat stored in central location. The main difference in fat oxidation between trained and untrained people is in muscle triglyceride oxidation. Weight loss = 75% fat mass, 25% fat free mass, and decrease RMR. Strength training increases fat free mass and sympathetic activity, thus increases RMR. Small decreases in fat mass with increase in fat free mass cause an increase in RMR. RMR decreases when weight loss is accompanied by decreased fat free mass. Diet + aerobic exercise = decreased RMR. Must have strength training to maintain fat free mass, and thus RMR. Lower metabolic rate is significant risk factor for later weight regaining. A small increase in RMR or maintaining it due to increased fat free mass have significant effects.

EPOC (Excess Postexercise Oxygen Consumption)
- exercise intensity maintains higher levels of postexercise energy cost than does duration

- high intensity keeps elevated longer than low intensity
- exercise intensity is the primary determinent of the magnitude of EPOC
- duration of EPOC may be brief w/short duration exercise, but the magnitude can be quite high w/high intensity exercise
- when exercise energy expenditure is held constant, high intensity exercise affects the magnitude, but not the duration, of EPOC
- Vo2 has further to fall after exercise if it is high during exercise

Post Workout Recovery
- after removal of debri from damaged myofibers....satellite cell activation stimulates myoblast activity
- damage to sarcolema results in necrosis mediated by;
    - increased intracellular calcium activates proteases
    - C56b-9 membrane attack complex located on the membrane is activated by membrane damage and causes cell lysis and attracks immune cells
- befor regeneration can occur, necrotic tissue must be phagocytosed by macrophages....they are attracted by products of complement cleavage
- angiogenesis follows phagocytosis....revascularization is required for successful regeneration
- satellite cells are located between the basal lamina and plasmalemma.....are a pool of stem cell progenator cells that are recruited for muscle regenaration
- satellite cells proliferate and differentiate, and then fuse to form new myotubes which are immature muscle fibers

during reinerveration, the old synapse site is used to reform a new synapse. Fast muscle specific isoforms of muscle genes are expressed in the new myofibers prior to innervation, reguardless of the muscle fiber type. Once innervated, fast and slow isoforms are differentially expressed.

NSAID's may block platelet aggregation and accentuate the initial swelling at the injury

Sprinting
Optimal Sprinting -- produce the smallest braking force possible, produce the largest horizontal propulsive force possible. You can decrease braking force by decreasing it muscularly, or by decreasing braking time (time spent applying the braking force to the ground).
- Pronghorn Sheep……sustain running speeds of 20 meters/sec by taking up oxygen at 9.5 liters/minute……
…….similar size goats that have only 1/5th the aerobic capacity, run only 1/5th as fast

Cold weather running
- with vasoconstriction and other blood flow alterations, lactate production will increase as oxygen delivery decreases
- more glycogen depletion exercising lightly at 48 degrees F, compared to 70 degrees F.
- shivering may deplete glycogen stores
- thirst drive is depressed
- 3 fold higher incidence of EIB among elite cold weather athletes compared to warm weather athletes (possibly due to increased immune suppression or disruption)

Muscular Force & Rate of Force
- Jump height is determined by take-off velocity
- loaded jump squats (loaded at 30% of 1-RM) produces greatest improvement
- training induced improvements in maximal force during slow movements fail to produce great improvements in the rate of force production
- vertical jump training with light loads increaes ability to rapidly develop force
- 30% of 1-RM produced greatest mechanical power
- nervous system can grade muscle tension by varying the stimulation frequency
- contraction velocity is also increased by increased stimulation frequency
- power = tension x velocity
- stimulation frequency influences the magnitude and rate of tension generation
- the rate of tension generation continues to increase at stimulation rates beyond what is necessary to achieve maximal tetanic tension
- maximal shortening velocity may not be reached at the same stimulation rate that produces maximal tension
- the rate of stimulation needed to produce max shortening velocity exceeds the rate of stimulation needed to produce max tension.
- muscle fiber conduction velocity correlates with frequency of stimulation
    - low frequency stimulation.....those muscles have low rate of supply of ATP
- with fatigue, the rate of brain signals to muscle decreases
- fast twitch muscle becomes slower with increased weight bearing, slow twitched becomes faster with decreased weight bearing
- Calcium ATPase that works in the sarcoplasmic recticulum sequesters calcium in the SR
    - is the rate limiting protein for muscle relaxation
    - has isoforms similar to the muscle fiber type….each isoform has a gene
- Troponin T (TnT) is the tropomyosin binding subunit of the troponin complex
    - has isoforms similar to the muscle fiber type….each isoform has a gene
    - there is a large diversity of isoforms expressed
- increases in muscle fiber area may approach 20% with endurance training….similar to what is seen with high resistance training
    - thus it is training volume that affects muscle hypetrophy
- Vastus lateralis has ~ 300 motor units.....~ 450,000 muscle fibers
    - motor unit.....average ratio of 1 neuron for 1500 fibers
- Vastus medialis has ~ 230 motor units
-muscle contains 3.3% of phenylalanine

Cheetah

- can go from 0 to 45mph [20 meters per second] in 2 seconds
- max velocity ~71mph [~32 meters per second]…can maintain for ~275 meters [8 sec.]
- hunts about every 3 days
- hunts in early morning and late afternoon [does little when sun is hottest]
- it will chase prey for 5000 meters, at average velocity of 45 miles per hour
- full sprint during the hunt lasts ~20 seconds to 1 minute
- weighs about 60kg……2 meters long…….shoulder height about 3 feet
- lives 10 – 12 years in wild, around 17 in captivity
- in captivity, adults are fed 6 – 9 pounds of meat per day
- when running at19 miles per hour [about 9 meters per sec], it can stop in one stride

Pronghorn Sheep [Antilocapra]

- muscle tissue is densely packed with mitochondria
- max velocity around 60 miles per hour [~28 meters per second]
- can go 18 meters per second for long distances [6 – 8 miles]
- can go 30 – 45 miles per hour for long distances
- weigh about 100 – 130 pounds
- eat vegetation [shrubs, forbs, flowers, fruits]
- eat in morning and afternoon
- spend 60% of day resting/loafing
- their turf is a 200 – 600 meter area
- their predators are coyotes and bobcats, and bucks chase each other for territorial rights

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Sport Biomechanics

Facts & stats

- 1% higher velocity requires 3% higher power output (due to air resistance).
- air resistance and extra O2 uptake -- middle distance paces = 7-8%, still air sprinting = 13-16%
- drafting 1 meter behind decreases air resistance 80%, energy cost decreases 6% (4 sec. per lap)
- drafting 2 meters behind decreases air resistance 40%, energy cost decreases 3% (1.4 sec. per lap)
- On windy day, as compared to maintaining a steady pace, less energy is expended when accelerating into wind, and decelerating with the wind at back.
- ground contact time
    - running at 4.0m/sec = .19 - .21 seconds
    - running at 5.5m/sec = .15 - .17 seconds
    - running at 7.65m/sec = .12 seconds
    - running at 9.19m/sec = .09 seconds
- hamstring can extend hip and knee during propulsion phase to counter anterior tibial shear
- latency of stretch reflex = 45 – 60 milliseconds during the ground contact phase of the stride

Equations/Definitions

1kg x 9.81 = 9.81 newtons
force = mass x acceleration
impulse = force x time
power = work/time
work = force x distance, 400lbs moved 2 feet = 400 x 2 = 800 foot pounds (ft-lb)
momentum = mass x velocity, momentum is a quantity of motion
angular momentum = mass x velocity x (radius) squared
moment of intertia = mass x (radius)squared
centripetal force = force acting toward the center of rotation
centrifugal force = force acting away from the center of rotation
Acceleration is the rate of change in speed.
Derivative = measure of the rate of change in distance, speed, acceleration.

Mitochondria
- citrate synthase and other mitochondrial enzymes (50% decrease) in 6 - 7 days of detraining
- membranes of mitochondria have a high protein to lipid content (3 to 1), and within the lipid portion, three major types of phospholipids predominate --- lecithin, cephalin, cardiolipin, also known as photidylcholine, phosphatidylethanolamine, diphosphatidylcholine.
- mitochondria located in two areas in muscle
    - subsarcolemal mitochondria
    - intermyofibrillar mitochondria
- may have a continuous membrane where new mitochondria fuse with the existing membrane network
--- have receptors for infra-red light

Formulas based on Vo2max and lactate threshold
Formulas for estimating the velocities to train based on Vo2max and lactate threshold; LA threshold at 85% = Vo2 x .2936 + 2.6481 x 1000 / 3600 and adjust by 5% to account for air resistance when on track rather than treadmill; LA threshold at 80% = Vo2 x .2878 + 1.5867 x 1000 /3600 and adjust by 5%; LA threshold at 75% = Vo2 x .2779 + 1.2499 x 1000 /3600 and adjust by 5%.

Muscle
- Acetylcholine receptors increase in number at the motor endplate.
- muscle mass for total body is ~30-40kg.
- muscle is ~ 50% of body weight
- Muscle is responsible for 75% of insulin stimulated glucose uptake.
- During hypoxia, the ADP to ATP ratio increases = increased AMP = increased glycogenolysis. The ADP to ATP ratio is turns on mitochondria.
- AMP and phosphate accumulation in muscle during exercise turns on glycogen phosphoralase to cause breakdown of glycogen
- Muscle that is stretched without loading, has longer fibers.
- the number and affinity of calcium binding sites on troponin can change due to training....activation dependent troponin has different isoforms in different muscle fiber types.
- Lactate can be produced during exercise by non-exercising muscle.
- hydrogens inhibit PFK activity
- pyruvate dehydrogenase allows pyruvate to enter the mitochondria
- skinned human muscle fibers contract even at very low Ph's
- as few as 10 contractions per strength training session is enough to elevate expression of myosin genes ~ 250%....pre-translational mechanisms are sensitive to small amounts of high resistance training
- there are ~ 300 grams of fat in total body muscle
- Moystatin……regulates muscle size by controlling embryonic myoblast proliferation……it's a negative regulator of muscle growth…..not myostatin = large muscles
Myogenic Regulatory Factors [MRF's]
-- muscle transcription factors [4]
-- myogenin
    -- MRF4
    -- MyoD
    -- Myf5
-- they regulate several muscle genes such as desmin, troponin I, myosin light chain

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MCT-1.....monocarboxylate transporter 1
- lactate transporter, improves clearance from blood into muscle, probably works the same as glucose transporters.
- found predominately in oxidative muscles
- There are MCT-1 through MCT-7
- lactate transport is enhanced by training…..MCT-1 enhanced by high intensity training
- Rate of transport of lactate and H+ increases due to training
- transport can increase by at least 12% and MCT-1 can increase by at least 76%
- speed endurance trained athletes have a higher capacity to transport lactate than less trained and untrained

Glycogen Phosphorylase (Phos)
- glycogen phosphorylase catalyzes the rate limiting step in glycogenolysis and sets the upper limit for the rates of glycolysis.
- Phos a…..more active form….can be de-phosphorylated to a form by Phos Phosphatase
- Phos b….less active form…is transformed to a form by Phos Kinase
- Phos is regulated by reversible enzymatic phosphorylation and exists in two interconvertible forms a & b, regulated at the hormonal level by

cAMP and at the contractile level by calcium release from the sarcoplasmic recticulum
- transformation from a form to b form can reach peak within first 6 seconds of maximal effort exercise
- rate of phos transformation & rate of glycogenolysis is determined by the exercise intensity
- G-6-P is an inhibitor of Phos b
- elevated hydrogen levels inhibit Phos kinase, reducing transformation of phos b to phos a

Pyruvate Dehydrogenase (PDH)

- PDH
  - ----- phosphorylated…….in-active [in-activated by PDH kinase =PDHK…..pyruvate decreases PHDK]
  - ----- un-phosphorylated….active [activated by PDH phosphatase = PDHP]
- PDH kinase…..phosphorylates PDH to it's inactive form
- PDH kinase…..inhibited by pyruvate, elevated ratios of CoASH to acetyl CoA, NAD to NADH
- PDH kinase…..stimulated by elevated ratio of ATP to ADP, elevated acetyl CoA
- PDH phosphatase…..dephosphorylates PDH, to activate PDH
- PDH phosphatase…..stimulated by calcium release from sarcoplasmic recticulum
- PDH phosphatase…..inhibited by acetyl CoA
- PDH catalyzes the oxidative decarboxylation of pyruvate to acetyl CoA
- phosphorylase = regulates rate of pyruvate production….and PDH regulates rate of pyruvate oxidation
- regulates the entry of pyruvate into the krebs cycle
- when rate of pyruvate production exceeds the rate of oxidation through PDH, it is converted to lactate
- lactate accummulation not primarily due to insufficient oxygen availibility. Primarily due to mismatch of pyruvate production and pyruvate oxidation
- citrate synthase is the enzyme that breaks down acetyl CoA, dependent on oxaloacetate presentation
- extent of PDH activation is dependent on power output
- activity of PDH is determined by the amount of PDH that is in the active form
- PDH can be fully active within 15 seconds
- following previous bouts, PDH can be fully active within 6 seconds
- Oxidative ATP production early in exercise is limited by acetyl CoA availability….the availability of acetyl groups may the limiting factor to Oxidative ATP production…….ability of metabolic processes to be activated limits oxygen use in the transition from rest to exercise……a high intensity warm-up, may affect this

Pyruvate Production & Oxidation stats

First 6 seconds of first of (3) 30 second maximal bouts…..[no info. on who the subjects where]
= 4.31mmol/kg/second
From 6 seconds – 15 seconds = 3.89mmol/kg/second
From 15 seconds – 30 seconds = 1.36mmol/kg/second

Pyruvate Oxidation by PDH (active form)…….

First 6 seconds of first of (3) 30 second maximal bouts…..[no info. on who the subjects where]
= .09mmol/kg/second
From 6 seconds – 15 seconds = .20mmol/kg/second
From 15 seconds – 30 seconds = .27mmol/kg/second
PDH activation……..
Bout 1……14% at rest……..to 48% at 6 seconds…….95% at 15 seconds. PDH remained fully activated during rest interval
Bout 3……42% during prior rest interval……nearly 100% by 6 seconds

ATP Production stats

First 6 seconds of first of (3) 30 second maximal bouts…..[no info. on who the subjects where]
ATP-PC = 7.0 mmol/kg/second…….48%
Glycolysis = 6.2 mmol/kg/second…..42%
Oxidative = 1.32 mmol/kg/second…..9%
Total = 14.52 mmol/kg/second

Vo2 & Vo2max
- 5% change in Vo2max = a 2.7% change in 800m time
- 5% change in Vo2max = a 3.9% change in 5000m time
- Peter Snell hypothesises that a person with a pr for 200m at 22.5 would need a Vo2max of 75ml to run a 1:45 800m. A person with a faster 200m pr may need a Vo2max of only 60ml to run the same 800m time.
- Alveolar Po2 decreases with the decrease in environmental P02, thus saturation in blood decreases
- The rate of oxygen uptake by the body during exercise may increase by 10 to 15 times. Oxygen flux in the active muscle may increase by ~100 times.
- oxygen flux to the mitochondrion has been identified as the major component that sets V02max

Vo2 phases

- early component…attributed to the increase of pulmonary blood flow…completed within 15 – 20 seconds on exercise onset
- fast component…decrease in venous oxygen content
- slow component…80 – 200 seconds into exercise
- steady state component…..3 – 6 minutes

PDK4

- kinase that inactivates pyruvate dehydrogenase [PDH]….which causes inhibition of conversion of pyruvate to acetyl CoA, turning off glycolysis
- causes transition from glycolysis to use of FFA……..happens during prolonged exercise

Lactate

--- D-lactate = neurotoxic
--- L-lactate = can be used as fuel by brain cells, allows glucose to be used to produce glutathione

Lactate transporters

--- monocarboxylate transporter MCT2 belongs to a large family of membrane proteins involved in the transport of lactate, pyruvate and ketone bodies
--- expression of MCT2 observed in a large number of neurons
--- expression of MCT2 in fibers both in grey and white matter
--- expression of MCT2 in some astrocytes
--- expression of MCT2 preferential postsynaptic localization of synaptic MCT2 expression.
--- strong MCT2 expression at asymmetric synapses in the postsynaptic density and also within the spine head but not in the presynaptic terminal

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Blood

- 200ml increase in RBC's with exposure to altitude, 7% increase in RBC, 6% increase in o2 consumption.
- with altitude training, the increase in RBC's is about one third of the increase in Vo2max
- with altitude training, in trained athletes, there may be no increase in hemoglobin mass
- atltitude greater than 1700 meters may be necessary to induce an increase in hemoglobin
- performance decrements occur with the reduced intensity that can be trained at altitudes above 1000 meters
- plasma volume can increase 20% w/training
- hematocrits can change following workouts/races by 7 - 10% due to fluid loss

Blood vessels

--- Nitric oxide induces VEGF production
-- Weightlessness
----- Endothelial dysfunction at microcirculatory sites might contribute to cardiovascular deconditioning
---- changes in the morphology and gene expression of endothelial cells, apoptosis of microvascular endothelial cells

Endothelial Progenitor Cells

- endothelial progenitor cells can attach to endothelial cells and transmigrate into tissues and induce angiogenesis
- can differentiate into arterial or venous endothelial cells, induce angiogenesis
- mobilize from bone marrow into peripheral blood
- shear stress caused by blood flow promotes differentiation into arterial endothelial cells
- high intensity interval training....promoted the migration and tube formation of endothelial progenitor cells
- capillary endothelial cells sense neuronal activity that increases in extracellular K+ via K+ channels
--- the hyperpolarization travels upstream along the vascular network, reaching arterioles and evoking vasodilation

Angiogenesis

- VEGF receptors [they're located in vascular endothelium on endothelial cells]
--- KDR main one for inducing angiogenesis
--- Flt-1 a ligand binding molecule
- exercise may increase VEGF receptors
- VEGF isoforms…. 121, 165, 189, and 209 amino acids
---121 and 165 are secretable
--- 189, 209 bound to membrane
- copper can stimulate blood vessel production
- copper controls endothelial cell migration
--- copper causes production of fibronectin
--- fibronectin gets deposited on surface of endothelial cells
--- fibronectin allows endothelial cell tracking and forming of a blood vessel
- copper has a role in production of collagen and elastin matrix
- copper deficiency decreases angiogenesis

- proangiogenic factors
    --- IL-6, IL-7, IL-8, VEGF, bFGF
- angiogenic factors function maximally when copper levels are adequate or high

Angiotensin Converting Enzyme [ACE]
- ACE cleaves angiotensin-I to make angiotensin II [a vasoconstrictor]
- ACE inhibitors decrease vascular resistance, leading to increased blood flow
- ACE inhibitors increase angiogenesis

Erythropoeitin.....EPO Production

- ROS can decrease EPO production
- vitamin A (retino-acetate) can increase EPO production by increasing hypoxia-inducible factor-1 alpha (HIF-1 alpha)
- short term (ie. 2 hour) changes in blood pH fails to increase EPO
- adenosine is a modulator of regional blood flow in tissues.....adenosine is increased by decrease in oxygen availabity.....renal adenosine content is increased by hypoxia
- adenosine release from kidney is increased during hypoxia
- stimulation of adenosine alph-2 receptors (A2 receptors) on EPO producing cells, increases EPO production
- A2 receptors stimulate adenylate cyclase.....cAMP may increase EPO production
- extracellular adenosine decreases renal blood flow
- the renal outer medulla releases adenosine
- EPO produced in kidney interstitial cells adjacent to proximal tubial
- EPO levels during hypoxia elevate substantially after 90 minutes to 2 hours
- EPO levels following hypoxia can continue to increase for another 90 minutes
- No stores of EPO are available in the body
- mRNA of EPO can be detected within 1 hour of the beginning of hypoxia
- EPO in kidney preceed the rise in blood EPO levels by about 30 minutes
- half-life for disappearance of EPO is around 5 hours (take 5 hours to decrease to half the levels it had increased to)
- EPO production rates can increase 2 to 3 times at very high levels of hypoxia (ie. 4000 meters)
- EPO production is small a low levels of hypoxia
--- production of EPO protein has been identified in astrocytes and neurons in various regions of the brain
--- EPO-receptors (EPO-R) in neurons, glial cells and neurovascular endothelium
--EPO receptor found in the hippocampus, temporal cortex, amygdala and cerebellum
-- EPO crosses the blood–brain barrier
-- Epo increases dopamine release in the hippocampus
-- Epo protects neurons from glutamate neurotoxicity
-- in neuronal cells, Epo produces a rapid and transient increase in intracellular calcium necessary for neuroprotection
-- A specific neurotrophic sequence of 17 amino acids within the Epo molecule has been identified which triggers differentiation, increases choline-acetyltransferase activity and prevents cell death
-- may shorten survival in cancer patient by fueling tumor growth
-- elevated mortality rate in cancer patients
-- cancer cells have EPO receptors [breast, prostate, ovarian], causes cell proliferation

---The first demonstration of age-related decreases in Epo expression in the cerebral cortex and hippocampus may provide useful data for investigating the pathogenesis of age-related neurodegenerative diseases, suggesting that age-related decreases in Epo may contribute to degenerative events following age-related decreases in brain flow and oxygen supply.
- exercise induced production in muscle & kidneys
- many cells have EPO receptors
- has anti-apoptotic effects
- has trophic effects
- has anti-inflammatory effects
- promotes neuro-genesis
- promotes angio-genesis
- oxygen sensors are located in the brain stem
- regulation of EPO production may be located in hypothalamus-hypophyseal area
- electrical stimulation of hypothalamus increases EPO production
- an increase in brain hypoxia stimulates increased EPO production by kidney

Damaged erythrocytes
-- accumulate in pathological conditions
    ----- hemolytic anemia
    ----- anemia of inflammation
    ----- sickle cell disease
-- In mice challenged with damaged erythorcytes, a monocyte subset migrates to the liver (but not to the spleen)
    ----- this subset differentiates into a transient macrophage population that removes the damaged erythrocytes preventing organ damage

Red Blood Cell Production
- Primitive progenitor cell.....called burst forming unit erythroid (BFUe)...stimulated by interlukin-3 and granulocyte-macrophage colony stimulating factor.

- The BFUe matures into a colony forming unit (CFUe).....stimumlated by EPO.
- Following stimulation by EPO, the CFUe matures into a reticulocyte within 2 - 3 days. Reticulocytes remain within the bone marrow for 2 more days. Going from BFUe to erythrocyte takes about 7 days. With high EPO levels, it can take about 5 days.
- a single day of protein deprivation can decrease EPO production after hypoxia. CHO levels have no effect on EPO production. Magnesium levels have effects on erythropoiesis.
- Subnormal serum ferritin levels ALWAYS indicates iron deficiency.....can be iron
- production of red blood cells can increase from 2 - 7 times the normal rate depending on iron availability. Hemoglobin levels can more than double in 3 weeks time.
- to achieve maximal results, Iron supplementation must keep pace with iron demand
- bone marrow can undergo hyperplasia in response to hypoxia stimuli such as high altitude. This may be the mechanism by which people who are born at altitude are able to adapt faster and more extensively when returning at altitude than sea level born athletes.
- red blood cells are commonly found in urine……increased glomerular permeability in kidney may allow RBC's to pass through the nephrons.
- Blood flow reduction through the kidney = 30% at 50% Vo2max, and 75% at 65% Vo2max
- ferritin levels decrease following erythropoiesis

Plasma Volume
Dietary sodium intake is strongly associated with training induced increases in plasma volume, and is an influencial factor in determining the magnitude of plasma volume expansion induced by training. Sodium is a major regulator of extracellular fluid volume. Training induced plasma volume expansion is in part due to an enhanced capacity for renal tubular resorption of sodium. Plasma volume expansion is delayed in people that have a low sodium diet. Plasma volume lost during exercise is restored faster when sodium is added to the rehydration drinks. With long term training/living in the hot environments, failure to maintain sodium balance may result in a net loss of plasma volume, or a reduced net gain. High training intensities in addition to adequate fluid + sodium intake will yield optimal increases in plasma volume as an adaptation to training.

Hemoglobin
- hemoglobin
    - 14 - 16 grams per 100ml
    - endurance athletes can have 1400g....sedentary people have 700g...severely ill people have 400g
    - Andean mountain residents have 20g per ml, hematocrit 59% at 4500 meters, 52% at 3700 meters, 50% at 3200 meters
    - 1 gram can hold ~ 1.34ml of oxygen
    - ~20ml of oxygen per 100ml of blood
    - ~ .3ml of oxygen per 100ml of plasma

AMPK [AMP-Activated protein kinase]
--- responds to changes in concentrations of energy metabolites [ie. Carbos]
--- AMPK is activated by AMPK kinase [AMPKK].....which are activated by depletion of cellular ATP
--- the rate [rather than magnitude] of carbo depletion increases activity of both isoforms of AMPK
--- AMPKalfpha1
--- AMPKalpha2
--- either directly or indirectly stimulates glut-4 production, mitochondria biogenesis, glycogen storage
--- activity over time depends on progressive increases in training intensity and volume

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Calcium pumps
--- in fast twitch muscle = SR Ca ATPase isoform [SERCA1a]
--- ATP is needed to drive the pumps
--- these pumps can use up to 55% of total ATP production
--- calcium taken up by mitochondria can trigger ATP production by stimulating dehydrogenase enzymes

Sodium/Potassium pumps
--- production of pump isoforms [there are 9] is specific to training velocity
--- the enzyme is composed of binding sites for ATP, sodium, potassium, on the alpha subunit
--- not beta subunits have been detected in humans
--- alpha 1 may be the fastest

Potassium Channels
- Types of potassium channels…Voltage gated….Calcium gated
- categories of potassium channels…..Eag, ELK1, Erg
- Elk1 = sub-category of Eag potassium channel gene group
- comprised of 3 genes…....KCNH3, KCNH4, KCNH8
- primarily in human nervous system

Vo2
- exponential rise in O2 consumption reaches steady state at 10ml per min at 2 – 3 minutes into exercise
- rise in Vo2 is linear with increase in exercise intensity independent of age, health, fitness, etc
- slow component = delayed onset rise in Vo2 past 10ml per minute

Nitric Oxide
Nitrate = NO3
Nitrite = NO2
Nitric Oxide = NO
- bacteria mouth/stomach convert nitrate in diet to nitrite
- in stomach nitrite can be converted nitric oxide
- nitrite can be absorbed in intestines into the blood stream
- beet root juice high source of nitrate, reduces O2 cost of exercise, reduces systolic blood pressure
- conversion of nitrite to nitric oxide is done by removal of one electron via…..
    --- electron transport in mitochondria
    --- endothelial nitric oxided synthase
    --- hemoglobin, myoglobin, etc
    --- xanthine oxidoreductase
- diet accounts for most nitrate consumption
- vegetables comprise 60 – 80% of nitrate consumption from diet
- 3 days consumption of 500ml beet root juice doubled plasma nitrite, reduced O2 cost of exercise [20%], increased time to exhaustion
- killing bacteria in mouth via mouth was can decrease conversion of nitrate to nitrite, as does spitting before swallowing
- mouth bacteria contain nitrate reductases
- nitric oxide can be made from L-arginine via nitric oxide synthase
- nitric oxide is an inhibitor of cytochrome oxidase activity
- nitric oxide has a strong affinity for cytochrome C oxidase
- nitrite may function in mitochondria as an electron acceptor, thus reducing the need for O2
- nitric oxide relaxes smooth muscle of blood vessels, thus reduction blood pressure
- may lead to increase in muscle vasodialation during exercise, increase in hemoglobin
- nitric oxide --- guanosine monophosphate synthesis --- smooth muscle relaxation
- synthesis of nitric oxide…..
    --- oxygen dependent pathway with L-arginine [rate limited by lack of O2 during exercise]
    --- independent of oxygen pathway via nitrite
- should probably avoid consuming nitrate with protein.....in the stomach, nitrate converted to nitrite, may interact with protein to form nitrosamines [carcinogen, related to esophageal cancer]
- should probably avoid consuming nitrate without anti-oxidants
- arginine supplementation increases plasma nitric oxide levels
- NO synthase enzymes convert arginine into NO and citrulline
- arginine paradox = eventhough there is abundant intracellular arginine, supplying exogenous arginine increases NO production

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Hormones

Thyroid Hormone
Thyroid hormone influences gene expression. The major form of thyroid hormone is thyroxine (T4), which is peripherally transformed into tri-iodothyronine (T3), the most biologically active form. T3 is transported into the nucleus of target cells, where it interacts with binding proteins known as thyroid hormone receptors. The T3-binding protein complex is then able to interact with a regulatory element located near the start site on all thyroid hormone responsive genes. This element is called the thyroid response element (TRE). This interaction alters the transcriptional activity (transcription rate) of specific genes. Thyroid hormone can also affect muscle protein synthesis at the post-transciption/pretranslation, translation, and post-translation levels. At a minimum, thyroid hormone affects transcription of genes for type I myosin heavy chain, alpha actin, and sodium/potassium pumps. Thyroid hormone affects transcription of genes that do not have a TRE by modulating the expression of a nuclear factor that acts as a direct transcription factor for a target gene. The mitochondrial genes located in the nucleus of the muscle fiber have been shown to be responsive to thyroid hormone. Thyroid hormone represents a powerful stimulus for mitochondrial biogenesis, particularly in skeletal muscle.
- Catecholimines stimulate a cascade reaction leading to an accumulation of intracellular cAMP. cAMP is implicated as an important transcription factor for several genes.
- There is a possibility that local polypeptide growth factors (ie. IGF-1) act in a messenger role, impacting transcription factores.

Insulin-like Growth Factor (IGF)
- IGF-1 molecule is a 70 amino acid single chain polypeptide.
- IGF-1 stimulates red blood cell production
- zinc deficiency decreases IGF-1 production and decreases growth hormone receptors
- IGF-1 binds to IGF-1 receptors, which activates a signal-transduction pathway. This results in mitogenic/anabolic responses.

Calcitrol
- steroid hormone that regulates calcium metabolism and cell differentiation. Stimulates gene transcription, interacts with nuclear receptor (vitamin D receptor)

Growth factors produced by kidneys
- IGF
- platlet derived growth factor
- NGF
- hepatocyte growth factor
- transforming growth factor beta (potent inhibitor of cellular proliferation....tumor suppressor)
- epidermal growth factor

Growth Hormone
- Binds to transmembrane receptor. The receptor forms a dimer, activating an intracellular signal-transduction pathway. This results in synthesis of IGF-1. Then IGF-1 binds to IGF-1 receptors, which activates a signal-transduction pathway. This results in mitogenic/anabolic responses. It is uncertain if GH has anabolic effects independent of IGF-1.
- acute exercise causes an increase....levels increase as exercise intensity increases.
- the major daily growth hormone surge occurs during non-rapid eye movement sleep. The inhibition of growth hormone releasing hormone, decreases during sleep

Insulin
It is known that protein synthesis is sensitive to the presence of insulin. Insulin increases amino acid uptake in muscle, and is the most anabolic hormone.
- increase mRNA production
- increase number of ribosomes (by increase production and decrease destruction)
- increase amino acid pool
- activates phosphatidylinositol 3-kinase (PI 3-kinase)....enzyme in muscle that leads to glut-4 translocation
    - is inactive in people who are insulin resistant

Androgens
- Low concentration Epi or at rest = alpha inhibition controls rate of lipolysis.
- Lipolysis is highest between low to high levels of Epi.
- High concentration Epi or at exercise = beta inhibition controls rate of lipolysis.
- Obese people take less to induce alpha inhibition and decreased lipolysis. They are more prone to inhibition of lipolysis. Thus commercial vendors of fat loss drugs etc. should focus on alpha blockers rather than beta stimulators.
- With exercise in the heat, as you get hot, catecholimines increase, thus increasing glycogenolysis. At low levels, epi increases lipolysis, at higher levels it increases glycogenolysis. Epi may restrain blood glucose uptake by muscle, thus increasing reliance on muscle glycogen.
- Sympathetic nervous system activity in relation to adipose tissue can help in maintenance of normal body fat levels.
- The lipolytic action of catecholimines is at least 10 times greater in fat cells from abdominal adipose tissue than from extremeties.
- Alpha andrenergic receptors -- mainly norepinephrine
- Block adipose alpha receptors at rest, increases lipolysis
- Beta andrenergic receptors -- mainly epinephrine
- total and free testosterone levels of distance runners are only about 75% of the levels found in sedentary men
--- dihydro-testosterone [DHT] is –not- aromatized to estrogen

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Sport nutrition

Facts & Stats
- Takes 12 hours for food to move through large intestine. Bile gives feces brown color.
- peanuts....essential fatty acids….35 peanuts have ….50mg magnesium…..7 grams protein…..1 mg zinc
- liquid meals….reduce the need to defecate

consume 30 - 60 grams of carbo per hour during exercise
use spreads/margerines made from liquid vegetable oils

-- high protein diet
- prevents the impaired leukocyte redistribution in response to acute exercise caused by a large volume of high-intensity exercise training

- high protein diet restored leukocyte kinetics to similar levels observed during normal-intensity training
- High-intensity training while consuming a high protein diet was associated with fewer symptoms of upper respiratory tract infection compared to performing high-intensity training with a normal diet

Iron

places of storage -- blood, bone marrow, muscle (myoglobin, mito. enzymes), other tissues enzymes. Absorb 10% of that ingested. 1 ounce of meat = 1 mg of heme iron. Need to replace .5-1.5 mg per day. Vit. C prevents the oxidation of ferrous iron thus aiding absorption. Zinc to iron ratio in intake should be -- zinc 1.5mg to 1mg of iron. Iron demand increases 6-10 times with exposure to altitude.

- total iron stores in the body = 2 - 5 grams....lose about 2mg/day
    - 1/3 of total body iron stored in liver
    - 2/3 of total body iron located in myoglobin
    - iron loss in sweat = 300 - 400 nanograms per liter
- 23% of heme iron is absorbed
    - 10% nonheme iron is absorbed
    - during iron deficiency, absorption may increase to 50%
- at altitude and probably highly hypoxic sea level training, iron is used at 10 times the normal rate

Glucose/Glycogen

- 1 gram of CHO + 2.7g of water = glycogen
- max glucose oxidation rate from an exogenous source ~ 1 gram per minute
- ventral-media hypothalamus controls liver glycogen
- when glycolytic rate exceeds the rate of oxidation = lactate formation
- Glycogen content of muscles increases with strength training.
- increases in glycogen increases the capacity for prolonged strenuous exercise
- low initial glycogen levels associated with more rapid development of fatigue
- Muscle glycogen resynthesis rate = 15-36 mmol/kg/hour following high intensity exercise. Following prolonged exercise = 5 - 8 mmol/kg/hour. Optimal carbohydrate supply following exercise = .7g/kg/hour…….7 x 60kg = 42g per hour
- With carbohydrate supplementation post exercise, glycogen resynthesis rate increases 2 to 4 times, the result of an increased glucose supply to an already activated glucose transport system.
- Carbo feedings during exercise (1g/kg/min) at moderate to high intensities (70-80% Vo2 max), fails to increase carbo oxidation. It does increase carbo oxidation at lower exercise intensities (60-65%). This may be caused by a lack of a significant insulin response. If you increase the amount fed, that may be sufficient to yield a high enough insulin response to increase carbo oxidation. A pre-exercise meal will increase carbo oxidation. Carbo feedings during exercise will yield a proportional match in the decrease of liver glucose output. Carbo oxidation is higher during exercise where you fail to drink, than if you drink water.
- At intensities beginning at 5% below lactate threshold and higher, insulin response to glucose feeding is very low. When exercising above LA threshold, liver glucose output will be higher than when exercise is below LA threshold.
- glycerol can be converted to glucose...in the liver

-- Resistin…….decreases activity of cell surface glucose transporters, reducing glucose transport

-- Resistin produced by adipocytes

-- levels increase in obesity as compared to lean people

Glycolysis

- rate of glycolysis increases with increasing exercise intensity
- glycogenolysis is increased with epinephrine/high intensity training and decreases blood glucose uptake
- liver gluconeogenesis contributes over 50 - 60% of blood glucose formation
- liver glycogen contributes 40 - 50 % of blood glucose formation
- one molecule of glucose produces 38 ATP and uses 6 molecules of oxygen
- reduction in blood glucose concentration is linked to hypothalmic-pituitary-adrenal activation, an increase in adrenocorticotrophic hormone and cortisol. Carbo supplementation during intense exercise maintains or elevates plasma glucose levels which attenuates the normal rise in stress hormones.

Endogenous glucose production (EGP)

- CHO ingestion during exercise, decreases oxidation of endogenous (liver glycogen/blood glucose -- not muscle glycogen) CHO
- exogenous glucose oxidation is limited to 1 gram per minute
    - higher ingestion rate does not increase the oxidation rate to greater than 1 gram per minute
    - gastric emptying is not rate limiting either
- ingestion of 35grams per hour markedly suppresses EGP
- ingestion of 175grams per hour completely blocks EGP
- ingestion of 10 - 15 grams per 10 minutes [60 – 75 grams per hour] = 50 - 70% decrease in EGP

If you feed pre-exercise carbo (prior to long exercise period), the insulin response decreases the exercise induced increase in lipolysis. The maximal effect is between 1 - 2 hour marks of exercise. If you feed pre-exercise carbo (prior to long exercise period), FFA oxidation will decrease below fasting levels due to insulin, glycogen oxidation will increase to compensate, compensation will be incomplete because of limited glycogen stores. Thus you must feed enough pre-exercise carbo (200-400 grams) to compensate by supplying enough blood glucose such that muscle glycogen isn't the main source of compensation.

Glycogenin

- primer for glycogen synthesis is a protein called glycogenin
    - catalyzes the addition of glucosyl units to the tyr-194 binding site

Regulator of glycogen metabolism……bound to glycogen
Glycogen synthesis is catalyzed by a protein primer, glycogenin
Generates an oligosaccharide primer of 7 to 11 glucosyl units, which serves as a substrate for glycogen synthase.
Glycogen synthase and branching enzyme then act to catalyze the formation of two pools of glycogen (proglycogen, macroglycogen)

Pro-glycogen

- Pro-glycogen…….Small glycogen entity
- less resistant to mobilization…PG used most during moderate to intense exercise as compared to MG
- has same amount of protein as MG, but less CHO
- associated with PG synthase
- 1 mole of PG = 6% of the CHO contained in MG…even so, 65 – 75% of all glycogen is in PG form
- post exercise, muscle selectively produces PG first, then MG after PG levels have returned to normal

Macro-glycogen

Macro-glycogen……..Large glycogen entity

They differ in size, rates of degradation, rates of synthesis
- more resistant to mobilization
- supercompensation is due to increased synthesis of MG
- high ratio of CHO to protein

Glut-1
– blood/brain barrier

Glut-2
- pancreas Beta cells, liver cells [important for blood glucose]

Glut-3

- neurons

Glut-4
- activation of AMPK increases Glut-4
- the higher the exercise intensity, the higher the glut4 content after training
- transcription factors = Myocyte Enhancer Factor [MEF-2A, MEF-2D]
- in muscle, translocate to the T-tubules
- adipocytes contain glut-4
- nerve derived neurotrophic factors affect transcription of glut-4 mRNA
- glut-4 binds to glycogen
- there are 2 intracellular pools of glut4
    - one responsive to insulin
    - one responsive to contraction (released from glycogen)
- phosphatidylinositol 3-kinase (PI 3-kinase)
    - enzyme in muscle.....activated by insulin, leads to glut-4 translocation
    - is inactive in people who are insulin resistant
- the significance of the increase in Glut 4 in response to training is to facilitate glycogen repletion when carbos are ingested between exercise bouts
- stimulus for Glut 4 production is glycogen depletion
    - there will be fewer inactive muscle fibers after 40 minutes of exercise than after 5 minutes
    - there will be as few inactive muscle fibers after 10 minutes at high intensity as after 40 minutes at low intensity
- glycolytic rate reflects muscle activation frequency
- glycogenolysis is activated by calcium (ie. muscle activation)
- Muscle contraction increases glut 4 activity/translocation

- an adaptation to exercise muscle activity is to increase glut 4 content of the muscle fiber membrane.
- Changes in Glut 4 may precede changes in muscle mitochondrial enzymes.
- Glut 4 content is the same in obese and lean, thus glut 4 activity level/translocation ability may be what has gone wrong in obese people. This is what decreases glucose transport capacity.
- The definition of reduced activity is that glut 4's move to the cell surface but fail to do anything when they get there.
- Insulin increases cell surface glut 4 in lean, but in obese this fails to happen.
- Contraction stimulate glucose transport in lean and obese is the same.
- Contraction + insulin increases cell surface glut 4 beyond the levels of either one by itself (has additive effect). Contraction increases insulin's ability to stimulate glut 4.
- Glut 4 cell surface content increases in trained vs. untrained.
- Glucose transport during resting conditions is the same in trained and untrained indicating that glut 4 content goes up but transport at rest remains the same.
- glycogen level is a signal for glucose transport
- Exercise training may result in the increase of glut4 within the plasma membrane, rather than an increase in glut 4 in the intracellular pool located in the cytisol. This location (plasma membrane) allows insulin to affect translocation to the cell surface in a facilitated manner since in obese, insulin fails to make glut 4 move from the intracellular pool, to the plasma membrane, to the cell surface.
- Subjects with the highest glut 4 concentrations have the highest glycogen concentrations after feeding post exercise.
- Reduction in insulin stimulated glucose transport precedes changes in glut 4.
- Muscle activity regulates glut 4 increase/decrease
- hypoxia increases glucose transporters (thus altitude training will increase glucose transporters)

Glut 4 Gene Expression

- signal for Glut 4 gene expression
    --- build-up of AMP
    --- activates AMA Activated Protein Kinase [AMPK]
    --- AMPK causes phosphorylation of transcription factors, which causes Glut4 gene transcription
- AMPK is activated by phosphorylation …..phosphorylized by AMPKK…which is also activated by AMP
- AMPK activates transcription of some mitochondrial genes as well
- AMP kinase actitivity is exercise intensity dependent

Glut-5
- fructose transporter

Glut-6
-

Glut-7
-

Glut-10
-

Glut-12
- muscle, fat cells, small intestine

Carbohydrates
Glucose polymers are chains of glucose molecules. They have less of an effect on osmo receptors in stomach, thus gastric emptying may increase, in theory. Gastric emptying regulation.... volume of presentation is most important. Higher caloric intake slows down gastric emptying due to osmo receptors in small intestine. Isotonic = Iso - same, tonic - concentration. Same concentration as blood is best (290-300 milliosmols.
monosaccharides = glucose, fructose, galactose
disaccharides = table sugar (sucrose), milk sugar (lactose), grain sugar (maltose)
polysaccharides = glycogen, starch, cellulose
Carbohydrate digestion
1. salivary amylase, in mouth, begins breakdown of starch into oligosaccharides, 2 - 8 mono's long.
   Shuts down when food gets to stomach, inactivated by stomach acid.
2. pancreatic amylase, in small intestine, breaks starch to grain sugar (maltose -- from poly's to di's).
3. intestinal brush border enzymes, breaks from di's/oligo's to mono's. Dextrinase/glucoamylase break oligo's with more than 3 mono's in a chain. Maltase/sucrase/lactase break maltose, sucrose, and lactose. Digestion ends in small intestine beacause colon has none of these enzymes. Colon bacteria digest the rest.

Overeating Carbohydrate
Once muscle glycogen stores are full, excess glucose will be oxidized rather than be stored as fat. Using this glucose as a fuel source will decrease use of fat, thus creating a situation where this reduction in fat oxidation with deposition of fat from the diet continuing as normal can result in a net gain in fat mass. Continuing to overeat carbohydrate over a period of several days results in the conversion and storage of excess carbohydrate as fat. Eating frequently throughout the day will keep insulin levels high, and cause an insulin induced reduction in lipolysis and fat oxidation, yielding a continued increase in fat mass by conversion of excess glucose to fat while simultaneously decreasing

fat oxidation. One of the most useful purposes of exercise in weight loss is that it keeps muscle glycogen levels down, creating a place for excess glucose consumed in the diet to be stored, with no increase in fat deposition.

Fat Matabolism

Facts & Stats
- Fat oxidation during 20 - 30 minutes at moderate intensity is 1.5 times higher than low intensity exercise, carbo oxidation is 4 times highers, and glycogen use is 5 times higher.
- Exogenous triglycerides take ~3 hours to get to muscle following ingestion.
- When plasma FFA fall below .5mmol, muscle glycogen use increases.
- A pre-exercise meal drives plasma FFA below .5mmol.
- There are Three main limits on fat oxidation.
    - lack of mitochondria.
    - exercise intensity increase, there is a failure to mobilize more fat (increase lipolysis),
    - failure to oxidize more fat... intramuscular glucose flux and reliance/shift to muscle glycogen utilization.
- FFA oxidation is highest at 50-75% Vo2max. Plasma FFA and intramuscular triglycerides are oxidized at this level.
- With glucose feeding, rdFFA is decreased because RaFFA is decreased.
- Decreased lipolysis rather than decreased oxidation is what happens first.
- Decreased lipolysis causes decreased oxidation.
- With glucose feeding, rdFFA is decreased because RaFFA is decreased.
- Decreased lipolysis rather than decreased oxidation is what happens first.
- Decreased lipolysis causes decreased oxidation.
- Insulin concentration needs to be 30-60 microunits/ml to maximally suppress fat oxidation by way of decreased lipolysis.
- 50 grams of carbohydrate will elevate insulin to 30-60 microunits/ml, which decreases fat oxidation by ~50%.
- 10 microunits/ml will have some limiting effect on fat oxidation by way of decreased lipolysis.
- 5 microunits/ml has no limitation on fat oxidation.
- At moderate exercise intensities, the insulin response to glucose feeding is reduced. It does reduce lipolysis but insufficiently enough to reduce fat oxidation.
- Insulin increases within 5 - 10 minutes following the pre-exercise carbo meal.
- Insulin decreases within 10 - 20 minutes into low intensity exercise (ie.45% Vo2max)
- training at higher intensities decreases epinephrine's effects of elevating lipolysis
- fat derived compounds
    - ketone bodies
    - acetoacetate
    - beta hydroxybutyrate
- glycerol can be converted to glucose...in the liver

Fat Transporters
- when the oxidative capacity of muscle increases there is a parallel increase in the rate of fatty acid transport and transporters
- fat carried in membrane vessicles
- fat binding protein associated with the plasma membrane (FABPpm)
    - 2 integral membrane proteins…..fat translocase (FAT/CD36)….and fat transport protein (FATP)

Fat Oxidation
- long and medium chain fatty acids undergo beta-oxidation once they have entered the mitochondria
- LCFA (long chain fatty acid) must bind to carnitine, a reaction catalyzed by acyl-carnitine palmitoyl transferase (CPT-1)...to enter into the mitochondrial matrix
- the product of this reaction is fatty acylcarnitine....is transported across the inner mitochondrial membrane by carnitine-acylcarnitine translocase system
- increased pyruvate availability increases Malanyl-CoA.....Malanyl-CoA inhibits CPT1, thus decreasing fat oxidation
- Glucose results in decreased CPT1 activity. Diet can increase CPT activity directly, or indirectly by decrease in glycogen/glucose use. The same happens during exercise
- Insulin decreases intramuscular lipolysis more so than it decreases CPT activity
- Glycogen, glucose, and insulin all decrease CPT activity
- FFA enter into cytoplasm of muscle, bind to protein transporter, and are taken to mitochondria
- outside of mitochondria...enzyme acyl-CoA synthase....produces Acyl-CoA from the FFA
- inner-membrane of mitochondria....impermeable to acyl-CoA
    - acyl-CoA converted inot acyl-carnitine by carnitine-acyl-CoA transferase (CAT-1)
    - carries it across inner-membrane....then converts back to acyl-CoA by CAT-2
    - medium/short chain fatty acids may simply diffuse across inner-membrane
    - Malanyl-CoA inhibits CAT-1

Malanyl-CoA.....formed by acetly CoA carboxylase (ACC0
    - glucose/insulin activity increases ACC
    - which increases Malanyl-CoA

- which decreases fat oxidation by causing inhibition of CAT-1, thus keeping fatty acids out of mitochondria
- AMPK phosphorylates and inhibits ACC-beta
- ACC is inhibited by epinephrine
- people deficient in carnitine have little way to use fat as fuel
- beta-oxidation....stepwise degradation of acyl-CoA to acetyl-CoA and acyl-CoA residue
- acyl-CoA residue....used as substrate for beta-oxidation
- medium chain fatty acids are more rapidly oxidized than long chain
- oxidation rates decrease with increasing chain lengths
- there is ~ 300 grams of fat in total body muscle
- one molecule of fat produces 147 ATP and uses 26 molecules of oxygen

Lipolysis & Re-esterification

- within the adipocyte.....hormone sensitive Lipoprotein Lipase (HSL), cleaves the fatty acids (2 are removed) the remaining one is freed from glycerol by monoglyceride lipase
- the glycerol cannot be reused by the adipocyte
- adenylate cyclase activates cAMP....stimulates protein kinase which activates HSL
- caffeine stimulates adenylate cyclase
- phosphodiesterase breaksdown cAMP preventing activation of HSL
- HSL is the rate limiting step in the mobilization of fatty acids
- HSL is stimulated primarily by epinephrine
- caffeine
- growth hormone
- glucocorticoids
- norepinephrine
- TSH
- HSL is inhibited primarily by insulin
- lactate
- ketones
- adipose tissue receptors
- alpha adrenergic = inhibitory on rate of lipolysis
- regulates lipolysis at rest
- beta adrenergic = stimulatory on rate of lipolysis
- regulates lipolysis during exercise
- beta 1 receptors
- beta 2 receptors
- removal rate of FFA from adipocytes....dependent upon concentration of plasma albumin and blood flow through the adipose tissue (during exercise, increases 3 fold)
- glycerol in adipocytes is derived from the breakdown of glucose
- low blood glucose levels decreases glucose availability for glycerol formation...thus decreases re-esterification....the excess FFA are released into the blood
- fat loss increases plasma levels of organochlorine [OC]……agricultural and industrial compounds
- OC can inhibit enzyme activities of mito electron transport system

Fat

- fatty acid synthesis..... 2 enzymes = acetyl-CoA carboxylase, and fatty acid synthase
- glucose to acetyl-CoA.....to palmitate.....occurs primarily in the liver and adipose tissue
- insulin increases synthesis of fatty acid synthase
- Short Chain Triglycerides -- 6 carbon chains
- Medium Chain Triglycerides (MCT's) -- 8 - 10 carbon chains
- Long Chain Triglycerides -- 14 - 24 carbon chains
- palmitic acid and oleic acid are the most abundant long chain fatty acids
- C20:4 (n-3) = 20 carbon fatty acid with 4 double bonds, first double bond starts from the 3rd carbon counting from the methyl group
- saturated fatty acids
- no double bond in their hydrocarbon chains
- unsaturated
- have one or more double bonds in their hydrocarbon chains
- monounsaturated
- have one double bond in their hydrocarbon chains
- polyunsaturated fatty acids
- have two or more (poly) double bonds in their hydrocarbon chains
- Fat digestion

1. emulsion in bile induodenum-- nonpolar part of bile salt clings to fat globlet, polar end repels the other salts attached to other fat globlets, thus spreading the fat apart for digestion.
2. lipase from pancreas into small intestine, breaks triglycerides/triacylglycerols, cleaves 2 fatty acid chains, yields 2 free fatty acids and 1 fatty acid attached to glycerol.

- Can get into mitochondria when long chains are prevented due to insulin. MCT's can go to liver and be converted in to ketones, then go to muscle and be used as a fuel for energy production. Feeding MCT's with carbohydrate triples oxidation of MCT's. Presence of MCT's accelerates gastric emptying of carbohydrate. Can only oxidize ~20% of the MCT's ingested. Ingestion of greater than 25 grams at a time causes gastro-intestinal discomfort, thus you cannot ingest enought MCT's during exercise to make a difference in sparing muscle glycogen or blood glucose.

- As fat cell size increases due to storage of more triglycerides, the membranes become less sensitive to insulin (insulin resistant). Trained people are insulin sensitive, untrained are insulin resistant.
- Obese people have high fat free mass, high fat mass, and no decrease in BMR
- Cell surface glut 4 content is less in obese, thus insulins effects are less.
- Glut 4 translocation may be impaired in obese. Insulin fails to increase cell surface glut 4 in obese.
- Obese may have fewer beta receptors than non-obese, thus alpha receptor stimulation may be higher, thus lipolysis is lower.
- Disorder eating may keep insulins high throughout the day, thus inhibiting lipolysis, though insulins effects may be decreased due to their insulin resistant state. Some fat cells in the body are resistant to insulin inhibition.
- Overeating causes increase of carbohydrate use in muscle, which causes fat utilization to decrease. Some carbohydrate will be converted to fat, with the rest being oxidized, replacing fat as the fuel source.
- Training may increase neuropeptide Y in obese, which regulates hypothalamus hunger drive. Insulin supresses neuropeptide Y release.
- Oxidize 6-9grams of fat per hour at 85% Vo2max.
- Greater fat mass yields high raFFA but it is still less than what is seen in trained subjects.
- Takes approx. 4 days of overeating to turn on lipogenic hormones that will convert carbo to fat. Until then the excess carbo will be oxidized. An increased muscle mass serves as an increased storage space for excess calories.

Essential Fatty Acids
- Essential Fatty Acids
    - alpha-linoLEnic acid (LNA)
    - docoshexaenoic acid (DHA)
    - eicosapentaenoic acid (EPA)
- EPA can be formed endogenously
- fish oil is enriched in 20 carbon and 22 carbon n-3 fatty acids
    - eicosapentaenoic acid (EPA)
    - docosahexaenoic acid (DHA)
- flax seed oil
    - has high levels of linoLEnic acid (alpha-LNA)
    - has low levels of linoLEIc acid (LA)
- the ratio of LNA to LA is important because it affects the efficiency of LNA to elevated cell EPA
- LA levels also affect how well EPA elevates EPA levels
- high LNA ingestion inhibits TNF-alpha, and IL-1 beta ~ 30%
- high EPA ingestion inhibits TNF-alpha, and IL-1 beta ~ 70-80%
    - inhibition occurs when cell EPA levels are ~1% of total fatty acid content
    - 1.6 - 2.7 grams per day EPA + .7 - 1.8 grams per day DHA cause suppression
    - n-3 fatty acids inhibit synthesis of n-6 fatty acids....n-6 fatty acids affect synthesis of TNF-alpha, and IL-1 beta
    - thromboxane B2 is suppressed by high n-3 fatty acid intake
- canola oil is high in omega 3 fatty acids

Branched Chain Amino Acids [BCAA]
- leucine, isoleucine, valine
- ~30% of muscle protein is comprised of BCAA…….~30 - 35% of that is comprised of leucine
- increase RDA from 14mg to 45mg per kg for sedentary people
- rate limiter of BCAA oxidation = Branched Chain 2-Oxoacid Dehydrogenase [BCOAD]

Chromium
- potentiates the action of insulin
- best absorption when complexed with organic compounds such as
    - nicotinic acid.....picolenate
- typical American diet contains ~ 15mcg/1000 kcals
- chromium competes with iron for binding to transferrin

Copper
- needed for ;
    - superoxide dismutase 1
    - cyctochrome C oxidase
    - dopamine beta hydroxylase
    - transciption factor
- copper deficiency leads to
    - decrease in T-cell proliferation
    - decreased IL-2

- decreased number of neutrophils

Vitamin D

-- RDA = 400IU [10mcg]

Calcium

Absorption
- calcium carbonate = 26 – 29%
- calcium citromalate = 32 – 37%
- calcium citrate = 23%
- milk calcium = 32%
- hydroxy appetite……may be highly absorbable form
- calcium binding protein [paravalbumin] in muscle is used for re-uptake into the sarcoplasmic recticulum
- as paravalbumin increases in amount, calcium is removed faster
- calcium citrate malate= combo of calcium with citric and malic acids….used to fortify fruit juices….30 – 40% absorption

Magnesium
- minimum intake should be 7 - 10mg/kg per day [perhaps closer to 10mg/kg]
- RDA's 280 – 350mg…….70% of RDA is considered adequate
- 50% of population may have marginal deficiencies due to food processing that removes magnesium
- intakes have declined from ~500mg to 175 – 225mg
- negative magnesium balance occurs with intakes below 6mg/kg per day
- whole wheat grains, dark green vegetables, spinach, brocholi
- any reaction that requires ATP involves magnesium
- level of magnesium has significant impact of G protein activation....G proteins = guanine nucleotide-binding regulatory proteins intracellular signal transduction system
- without adequate levels of magnesium, there is no G protein activation ....at low magnesium levels, G protein activation is low
- calcium and magnesium compete for common absorption pathways
- magnesium deficiency decreases activity of the sodium/potassium pump
- blood levels of magnesium are only 1% of body levels, thus a blood test is no good....leukocyte levels may match muscle levels
- relieves PMS symptoms
    -- people with headaches have decreased brain blood vessel smooth muscle magnesium levels
    -- increased levels of progesterone and increased levels of estrogen cause decreased magnesium in vascular smooth muscle in brain…….may result in decreased cerebral blood flow
- magnesium levels affects brain and peripheral tissue glutathione levels
- Glutathione synthesis enzymes are magnesium dependent
    -- glutanylcysteine synthase
    -- glutathione synthase
- controls neuronal activity, neuromuscular transmission, forms magnesium adenosine triphosphate [MgATP] used by enzymes that break down fatty acids, amino acids, and glucose
- regulates DNA and RNA synthesis
- magnesium citrate may be highly absorbable form

Zinc
- Intake of 13mg, cut in half, the duration of common cold when taken within 24hours of symptom onset. Duration was 4.4 days w/zinc, and 7.6 days with placebo.
- availability affects liver release of retinol binding protein
- used for DNA synthesis enzyme = deoxythymidine Kinase (TK)
- affects ability of growth hormone to bind to liver cell receptors
    - deficiency results in failed binding, thus decreased IGF-1
- zinc finger loop proteins provide one of the fundamental mechanisms for regulating gene expression
- zinc competes with copper and iron for absorption
- zinc deficiency causes decreases om IL-2, TNF-alpha, leptin, IGF-1 production and growth hormone receptors
- pools found in amygdala, hippocampus, cerebral cortex, spinal cord
- zinc enriched neurons [ZEN] are a subset of glutamatergic neurons
- zinc is in some synaptic vessicles
- zinc transporter [ZnT3] transports zinc into synaptic vessicles
- zinc may act as a neuromodulator of amino acid receptors
- zinc transporters…..protect cells against zinc toxicity
- 2 families of zinc transporters…..ZIP imports zinc……ZnT releases or sequesters zinc into vesicles
- ZnT comprised of 4 membrane proteins [contains histidine, essential amino acid]
- ZnT…..4 member family……ZnT-1, ZnT-2, ZnT-3, ZnT-4
- ZIP 3 member family…..hZIP1, hZIP2, hZIP3
- Zinc exists in the synaptic vesicles of hippocampal mossy fibers in high concentrations. Zinc concentration in the vesicles in the giant boutons of hippocampal mossy fibers is estimated to be approximately 300 M [5.], which is higher than in the cell body. This zinc is histochemically reactive (as revealed by Timm,s sulfide-silver staining method) [4.], contained in a subclass of glutamatergic neurons and released by a calcium- and impulse-dependent manner [1. and 8.]. The hippocampal and amygdalar regions may possess zinc-containing

glutamatergic neuron terminals in high densities
-- Neural circuits of the zinc-containing glutamatergic neurons are considered to be associated with the episodic memory function and are important for behavior, emotional expression, and cognitive-mnemonic operations [19. and 23.]. Vesicular zinc may play a role in synaptic neurotransmission in the mammalian brain and serve as an endogenous neuromodulator of several important receptors including the -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)/kainate, N-methyl--aspartate (NMDA) and -amino butyric acid (GABA) receptors

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Antioxidants

Beta Carotene
- Transported by LDL.
- body uses an enzyme to cleave beta carotene……to form retinal/retenoids
- cleavage by an enzyme [beta carotene dioxygenase] to retinal….from retinal it can be metabolized to retinol or retinoic acid

Alpha-Tocopherol
- 1mg of d-alpha tocopherol = ~1.49 IU
- 1 gram = 1500IU
- 600mg = 400 IU
- membrane concentrations (vit.E to lipid ratios)
    - RBC's = 1:1000
    - mitochondria = 1:2000
    - other tissues = 1:3000
- absorbed in small intestine, transported to liver by chylomicrons
- alpha is the most biologically active form
- in liver, there is an alpha tocopherol protein that transfers Vit E to VLDL's
    - Vit. E is incorporated into VLDL's, which enter the blood

Ascorbic Acid (Vitamin C)
- Ascorbic acid has been suggested to be the most effective antioxidant in human blood plasma
- Ester C = mixture of calcium ascorbate and calcium threonate.....
- Ester C = a complex consisting of ascorbic acid and calcium
    - ester C has more available ascorbate activity/potency than ascorbic acid
    - mechanism of increased potency is facilitated transport into the cell by threonate
        - threonate is a normal metabolite of ascorbic acid
    - ester C is in higher levels in plasma and excreted less rapidly than acorbic acid
- rapid cellular uptake and delayed renal excretion of ascorbic acid is conducive to providing optimum cellular concentration for biochemical activity
--- glucose-derived molecule ascorbate (vitamin C) functions as an enzyme cofactor and antioxidant.
--- reactions require oxidation of ascorbate to dehydroascorbic acid (DHAA),
--- Muscle and brain cells cannot synthesize vitamin C de novo from glucose and so must obtain it from the extracellular fluid.
--- 40% of the body's ascorbate is stored in skeletal muscle because this tissue is relatively abundant and its intracellular concentration of ascorbate is 10-fold higher than the plasma level
--- intracellular concentration of ascorbate in brain greatly exceeds the level in the extracellular fluid The high concentration of ascorbate in brain cells has been attributed to activity of the Na+-ascorbate cotransporter SVCT2 in neurons and astrocytes as well as DHAA uptake and reduction back to ascorbate (i.e., recycling)
--- Astrocytes are relatively abundant in brain and may be the major cell type that clears DHAA from the extracellular fluid
--- DHAA induces lethal oxidative stress in neuronal cells. After DHAA is taken up by astrocytes, it is reduced to ascorbate that then becomes available for release back into the extracellular fluid
--- Glucose inhibits competitively the DHAA uptake that is mediated by facilitative hexose transporter (GLUT) isoforms 1, 3 and 4
--- involvement of glucose transporters in DHAA uptake…….hyperglycemia of diabetes is associated with elevated plasma levels of DHAA

Selenium
An essential component of the anti-oxidative capacity of muscle fibers has been found to be the selenium dependent glutathione peroxidase enzyme. Selenium is a non-metalic element that occurs in four oxidation states -- elemental selenium, selenite, selenide, and selenate. Major dietary sources = meat, poultry, grain, grain products, sea food. Intake by Americans is ~ 60 - 216 micrograms per day. 50 - 200 micrograms is considered to be adequate (USRDA). Vitamin C inhibits absorption. Total body selenium is ~ 14,600 micrograms (14.6mg). The valence state effects bioavailability. Selenium compounds are easily absorbed in the small intestine (rats 95%). Nutritional supplements = selenium-enriched yeast products --- sodium selenite .5 - 2 mg per week --- selenite. Muscle contains the highest proportion of total body selenium. Selenium is incorporated into tissue proteins as the amino acid selenomethionine. Selenium functions as a cofactor of glutathione peroxidase, an enzyme that requires glutathione as its substrate for the scavenging of hydrogen and other peroxides. Vitamin B6 facilitates the availability of selenium for glutathione peroxidase.
- selenomethionine may be a better form of selenium than sodium selenite
-- Selenium depletion in animals is associated with decreased activities of Se-dependent enzymes and leads to enhanced cell loss in models of neurodegenerative disease.

B-Vitamins

B-Vitamins	RDA	potential needs
B1 = Thiamin	= 1.8mg	25mg
B2 = Riboflavin	= 2.1mg	10mg
B3 = Niacin	= 20mg	100mg
B4 = Choline Chloride		
B5 = Pantothenic Acid	= 10mg	100-200mg
B6 = pyridoxine	= 2mg	50mg
B7 = Biotin		
B8 = Inositol		
B9 = Folic Acid	= 200ug	
B10= PABA [Para-amino-benzoic acid]		
B11 = ??? Lipoic Acid		
B12 = Cobalamin	= 6mcg	500 – 1000mcg

General Info. On B-Vitamins
- Folate.....Deficiency can lead to DNA strand breaks of p53 gene. Folate is essential for synthesis of purines and thymidylate (affecting DNA replication and cell division). There is measurable chromosomal damage in circulating blood of folate deficient humans. DNA strand breaks by DNA damaging agents is enhanced in folate deficiency. 30% of "healthy" populations have folate deficiency.
- B6.....Used in the enzyme.....cystathionine beta-synthase
- B12....used in the enzyme methionine synthase
- Riboflavin is used in the hydrogen acceptor FAD
- Niacin is used in the hydrogen acceptor NAD
- Pantothenic Acid is used in coenzyme A that is used to make Acetyl CoA

Choline
- TDA = 1 - 3 grams per day

Creatine
Made from;
- arginine
- methionine
- glycine

- beta-guanidinoproprionic acid (beta-GPA)
  - competes with creatine for access into muscle
  - causes decrease in creatine phosphate and creatine kinase
- there is ~ 400 - 500mg of creatine per kg of body weight
- human body has greater than 100grams of creatine...95% of it is in muscle
- synthesize ~ 2 grams per day
- 1 pound of beef contains 2 grams of creatine

Plant (Phyto) Estrogens
- foods containing plant estrogens
  - flax seed, peas, soy beans, tofu, apples, almonds, cashew nuts, almonds
- two principle types of plant estrogens
  - isoflavonoids found mainly in
    - soy products
  - lignans found mainly in
    - fiber of
      - whole grains
      - berries
      - fruits
      - vegetables
      - flax seed

- compete with estrogens for nuclear binding sites
    - inhibit growth and proliferation of hormone dependent cells
- stimulate production of liver sex-hormone-binding-globulin
    - decreases availabity of free, biologically active estrogen
- inhibit aromatase, the enzyme that converst androstenedione to estrogen
    - decreases amount of circulating estrogen
- high intake of phyto-estrogens decreases brain calcium binding proteins, which may lead to calcium induced apoptosis,degenerative diseases, cerebrovascular deaths.

Protease Inhibitors
- soy foods contain Bowman-Birk Inhibitor (BBI)
    - a protease inhibitor
    - inactivates chymotrypsin and trypsin
    - heat from cooking inactivates the inhibitors thus reducing some of their activity

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Water, Dehydration
1% loss in body water weight = 8 beat increase in HR, 1 liter increase in Q, .3 degree increase in temp. To increase water absorption, add sodium -- .5-.7 grams per hour. Person, 65% water, 65% of that is intracellular, 35% is extracellular. Muscle is 75% water. Plasma volume is approx. 5 liters. 1 liter of water weighs about 1kg. Increase in osmality, turns on thirst drive. Dehydration can increase cortisol levels, thus decreased adaptation, decreased immunocompetence. 1 liter of sweat has 2-3grams of sodium chloride. 1 teaspoon of sodium chloride = 4 grams sodium chloride. Osmo receptors perceive the osmality of extracellular fluid (interstitial fluid). Water movement in dehydration -- intracellular to extracellular, to blood plasma, to sweat. People stop drinking before they restore osmality. When rehydrating without replacing sodium osmality goes down below original levels that existed prior to exercise. The best way to rehydrate is to drink water with a meal. Caffine ingestion, decreases ADH, retain only 40% of fluid ingested. 60% is formed into urine. Sport drink, retain 70%, if salt added = 80-90%, water, retain 50-60%. Aldosterone causes resorption of sodium.

Dehydration & Performance
- Power output decreases with dehydration either because of glycogen depletion or an inability to use it.
- Power output is 20% lower than when fluids are given.
- There are negative effects of any amount of dehydration. Need to drink enough to match sweat rate.
- 1% dehydration results in .3C, HR increases 8 beats/min., and cardiac output decreases 1 liter/minute.
- The lowest levels of dehydration = the highest levels of perceived exertion.
- Heat balance = heat production vs. heat loss. Even in well hydrated conditions, heat production at high rates due to high intensity exercise can far exceed heat loss rates (sweat rates).
- Wet bulb considers evaporation, black bulb considers heat, heat index considers air temp + humidity.
- Whole body dehydration rather than dehydration of blood (decreased plasma vol.) causes the series of events that impair body heat dissapation.
- Once there is a significant decrease in plasma volume (20%), drinking will have no effect on body temp. At a decrease of 7% or less, drinking may affect hyperthermia.
- Carbo oxidation is higher during exercise where you fail to drink, than if you do drink water. Carbo use in the heat goes up during exercise w/drinking gatorade, less w/water.
- As you get hot, catecholimines increase, thus increasing glycogenolysis. In the heat, though you may be training at low Vo2, glycogen depletion can still be quite high. Total carbohydrate use increases in the heat, due mainly to muscle glycogen utilization.
- Lactate is higher during exercise with no fluid (one hour into exercise).

Obesity/Weight loss
More vigorous skeletal muscle contraction will result in proportionally more Lipoprotein Lipase (LPL) expression. People with a malfunctioning LPL gene or protein, may be unable to get sufficient quantities of fat into muscle for oxidation. Another cause of obesity is when there is something wrong with the gene responsible of lipolysis within the adipocytes. The other most likely physical cause is impairment in glut 4 which would result in more glucose being stored as fat in adipocytes since it would be unable to enter muscle for oxidation. High intensity exercise favors a negative energy balance to a greater extent than low intensity exercise. Lean sedentary people have the same muscle oxidative capacity as obese people who are matched for age and fitness. Thermic effect of eating ~ 10%. Basal metabolic rate accounts for ~60-75% of daily energy expenditure.

Neuropeptide Y (NPY)
- NPY is a 36 amino acid polypeptide
- one of the most abundant brain peptides.
- concentrated in the hypothalamus
- arcuate nucleus (ARC)
- paraventricular nucleus (PVN)
- Neuropeptide Y modulates immune responses.....NPY inhibits natural killer cell activity
- NPY may be produced in increased amounts from stress
- NPY increases hunger
- Insulin increase may turn down hunger drive in hypothalamus by inhibiting NPY
- NPY stimulates eating, drinking, preovulatory LH
- Affects hypothalamus and medulla. May potentiate release of norepinephrine.
- NPY secretion may be high in obese people
- Nicotine decreases NPY, this may account for "skinny" smokers and explain weight gain w/smoking cessation.
- NPY reduces energy expenditure by decreasing sympathetic nerves that stimulate brown adipose tissue.
- NPY is a potent central appetite stimulant and induces powerful carbohydrate selective hyperphagia.
- Under conditions such as food restriction, high intensity exercise, the ARC-PVN is stimulated, and NPY is released.
- It decreases energy expenditure while stimulating energy intake.
- The ARC-PVN may be overactive in obese people, it is overactive in the zucker rat.
- NPY is low in people with depression

Leptin
- product of ob gene
- hormone derived from adipocytes
- signals presence of excessive energy stores
- reduces apetite
- decreases during food restriction
- leptin is a cytokine
- decrease in leptin = decrease in T-cells during starvation
- decrease in leptin = decrease growth hormone
- decrease in leptin = thyroid hormone
- decrease in leptin = increase in cortisol
- has high-affinity binding sites on hypothalamus
- leptin levels in obese humans are elevated
- strong correlation between blood leptin levels and % body fat
- adipocytes of humans produce leptin when adipose tissue mass increases

Amylin
Pancreatic hormone (37 amino acid chain), co-secreated with insulin at a 1 - 10 ratio amylin to insulin.
It increases blood glucose levels and blood lactate levels by inhibiting glucose uptake by muscle. It inhibits glycogen synthase activity by causing a decrease in the glycogen synthase I to D ratio, thus it is an antagonist to glycogen synthesis, even in the presence of high insulin levels. Amylin increases glucose 6 phosphate (G6P) which causes inhibition of hexokinase. Amylin causes an increase in cAMP.