F2

Chapter 25 structure and function of the respiratory system

introduction

- contraction of diaphragm→ inspiration → negative pressure

gross anatomy

upper airways

- nose volume 20ml; 50% resistance in nose by quiet breathing;
- condition air by humidifying, heating,

lower airways

- penumothorax will involve just 1 lung wing→ separated
- mainstem bronchi→ lobar bronchi→ segmental bronchi→ terminal bronchioles
    - anatomic dead space 150ml→ no gas exchange
- cartilage disappear by 1mm
- bronchiols: less 1mm increase decrease, cuboidal epithelium,
- gas exchanging units→ respiratory bronchioles→ alveolar ducts→ alveoli
    - blood from pulmonary arteries

blood supply to the lung

- bronchial circulation from aorta for bronchial tree
- 1-2% of cardiac output→ cystic fibrosis 10-20%
- small alveolar-arterial oxygen difference

muscles of respiration

- force of contraction increases with increasing lung volume,
- diaphragm: inspiratory pressure 150-200cm H20, tidal breathing 1cm up and down,
    - paralization: moves up in inspiration
    - C3-5; above C3 no own breathing
- diaphragm and external intercostals for inspiration; abdominal muscles for and internal intercostals expiration
- muscles limit maximal in and expiration
- passive expiration by recoil of lung
- O2 2-3% consumption by resting; disease and exercise 20-30%

cells of the airways

- ciliated cells
    - chloride secretion, sodium absorption, → regulating dept of periciliary fluid for cilia transport system CL- secretion regulated by cAMP and Ca and Na absorption
- mucus production
    - SSC or goblet cells (increase by smoking→ obstruction) disappear beyond 12th,
    - submucosal glands: increase by bronchitis
    - clara cells

cells of the alveoli

- type I: 95% of surface, gas exchange, thin, prone to injury
- type II: small, 2%, synthesize surfactant, regeneration, can change into type I cell, until late gestation, in fibrosis just type II cells
- type III: or brush cells in whole lung, chemoreceptor

surfactant

- 90% lipids, 10% protein
- reduce surface tension, major lipid is phosphatidylcholine (mainly DPPC, 2nd is PG→ spreads surfactant)
- protein SP-A: surfactant turnover, immune, formation of myelin
- protein SP-B stabilizes;
- exocytosis of lamellar body→ stimulated by beta adrenergic agonists, activators protein kinase C, leukotrins
- reducing work of breathing, preventing collapse and sticking of alveoli

surfactant and surface tension

- pressure in sphere=2*wall tension/ radius of sphere
- without surfactant: we need highe rtransmural pressure to produce increase in alveolar volume at lower lung volumes than at higher lung volumes
- surfactant stabilizes the inflation of alveoli because it allows the surface tension to decrease as the alveoli become larger→ transmural pressure required to keep alveolus inflated increases as lung volume and pressure increases
- pores of kohn and the canals of lambert provide collateral ventilation and prevent alveolar collapse due to opposing traction from surrounding alveoli

lymphoid tissue and the lymphatic system

- fluid filtration and host defense
- lymphatic capillaries have no tight junctions, connection with filaments to ct, valves
- bronchus-associated lymphoid tissue BALT (similar to GALT in intestine), lack germinal center, antigens,

smooth muscle, connective tissue and other cells

- collagen major component of lung structure that limits distensibility
- elastin major contributor to elastic recoil of the lung
- cartilage disappears at level of bronchioles
- kulchitsky cells secreting amines → bronchial carcinoid tumor

innervation

- parasympathetic: nerve X, constriction, blood vessel dilation, glandular secretion, innervation is stronger in larger airways and diminishes towards smaller, smooth muscle
- sympathetic relaxation: relaxation, vessel constriction, inhibition of glandular secretion
- vagal excitatory ACH and substance P; inhibitory VIP and dynorphin, PNS innervation greater in larger airways
- no pain fibers only in pleura, no voluntary movement innervation,
- preganglionic and postganlionic fibers contain excitatory cholinergic and inhibitory nonadrenergic motor neurons
- no adrenergic fibers

central control of respiration

- brainstem control center, CPG is pacemaker,
- input from stretch receptors, oxygen from carotid body, from amygdale and hypothalamus

growth and development: congenital lung disease

- intrauterine events that occur prior to 16 weeks of gestation (bronchial tree) will affect the number of airways
- alveoli develop after birth up to 8 years
- congenital diaphragmatic hernia

Chapter 26 BL mechanical properties of the lung and chest wall: static and dynamic

static lung mechanics

lung volumes

- capacity 2 or more volumes
- TLC= total lung capacity; VC+RV
- vital capacity= max exhaled air to max inhaled air
- residual volume= air that remains in lung after complete exhalation
- functional residual capacity FRC= end of exhalation during quiet breathing or resting volume of lung
    - RV + ERV (volume possible to exhale from FRC to RV)
- elevated RV/TLC ratio more than 0,25→ pulmonary disease obstruction of airways, RV more TLC reduction

determinants of lung volume

- TLC not more because inspiration force do not overcome force to distend lung and chest wall
- RV determined because exhalation could not overcome recoil of lung
- FCR: decreases if chest wall is weak; increases by airway obstruction
- RV and TLC can not be measured with spirometry but with helium and body plethysmographie
    - helium dilution change of concentration of inert gas is proportional to new volume where inert gas has been distributed
    - does not function FRC measurement in lung disease, FRC in body plath larger

lung compliance

- lung compliance changes with lung volume
- volume increase→ lung recoil negative pressure increases
- C=change in volume/ change in pressure
- normal is 0,2 L/cm H2O
- emphysema more compliant; fibrosis less
- specific lung compliance (by dividing by lung volume) is not affected by reduction of lung but static compliance

lung-chest wall interactions

- chest wall and lung move together
- transpulmonary pressure= alveolar pressure – pleural pressure (PL=PA-PPL)
    - has to be positive to distending lung, 0 lung is smallest
    - PA= elastic recoil pressure of lung + pressure surrounding lung pleural pressure
- transmural pressure= pleural pressure – pressure surrounding the chest wall (Pw=PPL-PB)
- pressure across respiratory system is Prs=Pa-Pb
- TCL: lung and chestwall are positive
- Prs is at FRC
- resting volume of chest wall is by 60% of TLC
    - greater than 60% TLC chest wall recoiled inward
    - resting volume of lung is 10% TCL

pressure-volume relationship

- gas moves from high to low pressure
- into lungs; into
- minute ventilation= tidal volume* number of breaths/m
- Pa and Prs 0 if no air flow occurs
- negative pressure in pleural space, alveolar pressure 0→ inspiration→ alveolar pressure falls, intraleural pressure falls

dynamic lung mechanics

dynamic compliance

- hysteresis between inflation and deflation pressure volume curves is due to surface tension variation with changes in lung volume
- dynamic compliance less than static compliance
- more surfactant in air liquid make lung more compliant
- by exercise→ large changes in tidal volume→ more surfactant→ lung more compliant

airflow in airways

- contraction of diaphragm causes negative pressure (gradient)→ air flows in
- laminar and tubular flow
- poiseuill law; V=pressure*radius/viscosity
- resistance inversevly proportional to radius and proportional to length and viscosity
- Reynolds number greater then 2000 → turbulences in straight tubes
    - Re=2rvd/η,where d is fuid density, v average velocity, r radius, η viscosity
- turbulences in trachea also in quiet breathing → further down gas flow becomes more laminar (is silent)

lung resistance

- resistance in small arteries small due to parallel circuits 1/r is inverse
- large bronchi major site of resistance, 80% of resistance by airways greater then 2mm
- n poor test of detecting small airway obstruction

factors that contribute to resistance

- increase lung volume decrease resistance→ larger airway
- resistance increase by: dens air, mucus, edema, constriction sm,
- O2 helium in status asthmaticus
- normal air resistance is 1-3 cm H2O

neurohumeral regulation of airway resistance

- vagal= airwayconstriction; stimulation by smoke, dust, cold air,
- sympathetic dilation
    - histamine, ACH, thromboxane A, prostaglandins, leukotrins→ recruit airway cells→ constriction
- metacholine→ constriction asthma

measurements of expiratory flow

- FCV= total amount of exhaled air; 72% can be exhaled in first second
- FCV/FCV1 ratio smaller then 72%--> problems by expiration

determinants of maximal flow

- maximum inspiratory: combination of inspiratory muscle force, the static recoil of the lung and the changes in airway resistance cause maximal inspiratory flow to occur about halfway between TLC and RV
- no change of effort during expiration will change the exhaled volume→ effort independent
    - events early in expiration are effort dependant first 20% ; increasing effort increasing flow rate

flow limitation and the equal pressure point

- expiration→ transmural pressure across the airways decreases due to friction loss and gas velocity increases
- driving pressure = elastic recoil pressure and the pleural pressure
- transmural pressure decreases: expiratory airflow resistance and cross sectional area decrease with increasing gas velocity
- equal pressure point: pressure in and out airways the same→ no amount of effort will increase flow further
    - occur in airway with cartilage
    - lung volume decreases and elastic recoil pressure decreases EPP moves closer to aveoli
    - premature closure can be heard as crackles
- airway resistance is greater during exhalation

uses of spirometry and body plethysmography

work of breathing

- work of breathing= pressure*change in volume
- work is required to overcome elastic and flow resistive forces
- by fibrosis work increases due to lower compliance

- breathing adapts due to condition
- work increases by deeper and faster breathing

clinical implications

- emphysema→ damage of alveolar and capillary walls
    - increased lung compiance, less tethering causes EPP to move towards alveoli, air trapping and increases in RV, TLC and FRC, Raw is also increased
- chronic bronchitis→ EPP also moves closer to alveoli due to inflammation, increases in RV, FRC, TLC, CL normal
- pulmonary fibrosis→

Chapter 38 pulmonary circulation, pulmonary edema, pleural fluid

- high pressure low-flow circulation supplies systemic arterial blood
- low pressure high flow circulation venous blood

physiologic anatomy of the pulmonary circulation system

- pulmonary vessels: pulmonary artery high compliance, low pressure high flow, thin, distensible, exchange
- bronchial vessels: oxygenated blood supplies lung and enters in pulmonary vein→ left ventricular output 1-2% bigger, high pressure, low flow, nutrition
- lymph vessels

pressures in the pulmonary system

- pressure pulse curve in right ventricle 0-25mmHg
- pressures in the pulmonary artery 8-25mmHg; mean 15mmHg
- pulmonary capillary pressure 7mmHg
- left atrial pulmonary venous pressures 2mmHg
    - pulmonary wedge pressure in pulmonary artery small branch, stop blood flow connection to left atrium just 2-3mmHg greater

blood volume of the lungs

- 9%; 450ml; 70mml in capillaries
- lung serves as a blood reservoir→ under pressure blood leaves lung
- increase in alveolar pressure can decrease volume
- cardiac pathology may shift blood from the systemic circulation to the pulmonary circulation by failure of left side, mitral stenosis and regurgitation

blood flow through the lungs and its distribution

- peripheral factors determine co→ determine pulmonary blood flow
- decreased alveolar oxygen reduces local alveolar blood flow and regulates pulmonary blood flow distribution
    - oxygen saturation falls in lungs→ constriction → due to shift blood in oxygen rich areas which are better ventilated

effect of hydrostatic pressure gradients in the lungs on regional pulmonary blood flow

- uppermost 15mmHg less then pulmonary arterial pressure and lowermost point 8mmHg greater
- zones 1, 2, 3 of pulmonary blood flow
    - any time the lung alveolar air pressure becomes greater than the capillary blood pressure→ capillaries close and there is no blood flow
    - zone 1: no blood flow during all portions of the cardiac cycle because alveolar capillary pressure never higher than alveolar air pressure → not in healthy lungs
    - zone 2: intermittent flow systolic arterial pressure rises higher than alveolar air pressure
        - 10cm over heart top highest lung point by standing
    - zone 3: continuous blood flow capillary pressure greater than air pressure
        - when person lies down; and 10cm above heart to lowermost point of lungs

    - zone 1 blood flow occurs only under abnormal conditions→ systole to low or air pressure to high, by breathing against resistance or severe blood loss
    - effect of exercise on blood flow through the different parts of the lungs
        - blood flow rises, pressure rises everywhere zone 3, in top rises 700%
- increased cardiac output during heavy exercise is normally accommodated by the pulmonary circulation without large increases in pulmonary artery pressure
    - opening, distending and increasing capillary pressure→ save energy for right heart, no edema
- function of the pulmonary circulation when the left atrial pressure rises as a result of left sided heart failure
    - left atrial pressure never over 6mmHg → failure rise op to 50mmHg → excess work of right heart and edema

pulmonary capillary dynamics

- pulmonary capillary pressure mean 7mmHg
- resistance 10* lower as in systemic
- length of time blood stays in the pulmonary capillaries 0,8 sec normal→ increase CO 0,3 sec (shortening not so much because more capillaries open)
- capillary exchange of fluid in the lungs and pulmonary interstitial fluid dynamics
    - lower capillary pressure in lungs 7mmHg; interstitial more negative; more leaky to protein so colloid pressure high in interstitium; easy rupture if bigger than air pressure
    - interrelations between interstitial fluid pressure and other pressure in the lung
        - slight filtration out in interstitial space
    - negative pulmonary interstitial pressure and the mechanism for keeping the alveoli dry
        - due to negative pressure fluid is carried away by lymph or absorbed in capillaries
- pulmonary edema
    - by left sided heart failure; mitral valve disease→ increase in pulmonary capillary pressure
    - damage to pulmonary capillaries → fluid loss→ drowning; flun interstitial space and alveoli
    - safety factor
        - lymph system increases adapts to higher pressure carry more fluid away; pressure must raise from 7 to 28 capillary pressure;
        - death is quick by acute pulmonary edema

fluid in the pleural cavity

- very narrow just a potential space
- negative pressure in pleural fluid; under -4mmHg to prevent collapsing (keep expanded); negative pressure due to lymph system
- pleural effusion – collection of large amounts of free fluid in the pleural space→ edema in pleural cavity due to lymph and heart failure, great reduction of plasma colloid osmotic pressure

Chapter 39 physical principles of gas exchange; diffusion of oxygen and carbon dioxide through the respiratory membrane

physics of gas diffusion and gas partial pressures

- molecular basis of gas diffusion
    - diffusion rate depends on partial pressure
    - in fluid the higher the attractive force the more molecules can be dissolved
    - partial pressure=concentration of dissolved gas/solubility coefficient
    - CO2 is 20 times more soluble then O2→ partial pressure is 20 times less than exerted by O2
    - vapor pressure is 47mmHg→ PH20 in air at body temperature→ water is evaporated in airways
    - 21% O2, 79% N2
- diffusion of gases through fluids – pressure difference causes net diffusion
    - pressure difference for causing diffusion; partial pressure difference
    - affected by: solubility; cross section area of fluid; distance to which gas must diffuse; weight of gas; temperature;
    - diffusion rate= partial pressure*cross sectional area*solubility/distance of diffusion*wurz molecular weight
        - diffusion coefficient of gas= solubility/molecular weight

        - diffusion coefficient for O2 is 1; for CO2 is 20

composition of alveolar air and atmospheric air are different

- alveolar air is not the same as atmospheric air→ humidified, CO2, O2 differences
- humidification of the air in the respiratory passages → dilutes all other gases in air; alveolar air pressure can not rise over 760mmHg atmospheric pressure
- rate at which alveolar air is renewed by atmospheric air
    - 350ml tidal volume; 2300ml FRC
    - the faster you breath the faster the air is renewed but also after 16 breaths you still have old air
    - important to prevent sudden gas changes in lung→ makes control easier
- oxygen concentration and partial pressure in the alveoli
    - O2 concentration determined by: rate of absorption into blood, rate of entry of new O2 into lungs
    - at increased O2 expenditure higher alveolar ventilation is required to keep normal alveolar Po2
- CO2 concentration and partial pressure in the alveoli
    - determined also by absorption and excretion and rate of ventilation
- expired air is a combination of dead space air and alveolar air
    - collectin alveolar air by taken a sample at end of forceful expiration

diffusion of gases through the respiratory membrane

- respiratory unit, gas exchange at membrane
- respiratory membrane: 0,6 mm in average thin; red blood cell touches capillary endothelium
- factors affect the rate of gas diffusion through the respiratory membrane
    - thickness (increased by edema); surface area (decrease by emphysema); diffusion coefficient (CO2 20 times more than O2); partial pressure difference
- diffusing capacity of the respiratory membrane
    - respiratory membranes diffusing capacity= volume of a gas that will diffuse through the membrane each minute for a partial pressure difference of 1mmHg
    - diffusing capacity for oxygen: 21ml/min/mm;  230ml O2/m through membrane each minute;
    - increased oxygen diffusing capacity during exercise
        - increasing up to 65ml/min/mm due to opening up of many previous dormant capillaries, dilation, increase in ventilation perfusion ratio
    - diffusing capacity for carbon dioxide; Co2 heart to gain; measure CO in alveoli and in blood→ bind in no time to hemoglobin multiplied with factor

effect of the ventilation perfusion ratio on alveolar gas concentration

- if there is imbalance between alveolar ventilation and alveolar blood flow
- expressed as alveolar ventilation/ blood flow (Q) by same alveolus
    - Va is 0 still perfusion; adequate ventilation but 0 perfusion ratio is infinity → both no exchange of gases
- alveolar O2 and Co2 partial pressure when Va/Q equals zero→ same as venous blood free diffusion
- alveolar O2 and Co2 partial pressures when Va/Q equals infinity→ no blood so alveolar air becomes equal to the humidified inspired air
- gas exchange and alveolar partial pressure when Va/Q is normal→ between venous and humidified air values Po2 104mmHg and Pco2 40mmHg
- when value is under normal→ inadequate ventilation to provide the oxygen needed o fully oxygenate the blood flowing through the alveolar capillaries; part of venous blood do not become oxygenated (greater physiological shunt)
- when va/q is greater than normal→ ventilation is wasted, physiological dead space
- abnormalities of ventilation-perfusion ration
    - upper lung low flow and ventialation but flow lower→ in upper part wasted ventilation
    - lower lung is physiological shunt more flow then ventilation
    - smoke some areas shunt some wasted ventialtion

Chapter 40 transport of oxygen and carbon dioxide in blood and tissue fluids

transport of oxygen from the lungs to the body tissues

- diffusion of oxygen from the alveoli to the pulmonary capillary blood
    - uptake of oxygen by the pulmonary blood during exercise
        - by resting blood stays 3 times longer in capillaries as needed→ so still full saturation by exercise; and surface area for perfusion increases and better ventilation perfusion ratio in upper lung
- transport of oxygen in the arterial blood→ shunt blood from aorta (40mmHg) to deep lung bypass gas exchange→ fall from 104mmHg to 95mmHg P02
- diffusion of oxygen from the peripheral capillaries into the tissue fluid→ concentration gradient from 95mmHg to 40mmHg→ rapid diffusion
    - blood flow increases→ tissue P02 saturation also increases
    - tissue Po2 determined by rate of o2 transport and rate of usage by tissue
- diffusion of oxygen from the peripheral capillaries to the tissue cells → 5mmHg to 40mmHg, 1-3mmHg is normal required for chemical functions→ large safety factor
- diffusion of carbon dioxide from the peripheral tissue cells into the capillaries and from the pulmonary capillaries into the alveoli
    - pressure difference for CO2 is far less then for O2 (20)
    - intracellular PCO2 46mmHg and interstitial 45mmHg→ just 1mmHg difference
    - arterial blood PCO2 40→ tissue PCO2 45→ venous PCO2 45→ equilibrium between interstitium and blood
    - PCO2 of blood entering lung 45→ leaving lung 40
    - effect of rate of tissue metabolism and tissue blood flow on interstitial PCO2
        - increasing blood flow reduces interstitial Pco2 down to 41mmHg
- role of hemoglobin in oxygen transport
    - hemoglobin 97%; 3 % of O2 dissolved
- reversible combination of oxygen with hemoglobin
    - if Po2 is high O2 binds to hemoglobin in pulmonary capillaries
    - if Po2 is low O2 released in tissue capillaries
    - oxygen-hemoglobin dissociation curve
        - increase in P02→ higher % of O2 bound to hemoglobin
        - when venous blood returns from tissue saturation is 75%
    - maximum amount of oxygen that can combine with the hemoglobin of the blood
        - 15gr of hemoglobin in 100ml blood can bind 20ml O2
    - amount of O2 released from the hemoglobin when systemic arterial blood flows through the tissues
        - 5ml of O2/100ml of blood from lungs to tissue in normal
    - transport of oxygen during strenuous exercise 15ml/100ml
    - utilization coefficient→ percentage of blood that give up its O2 normal 25% can increase to 100%
- effect of hemoglobin to buffer the tissue Po2
    - role of hemoglobin in maintaining nearly constant PO2 in the tissues
        - fall in PO2 cause large amounts of O2 released from blood
        - low PO2= large change in saturation for a small change in PO2 and vice versa
        - hemoglobin delivers O2 to tissues by a pressure from 15 to 40mmHg
    - when atmospheric oxygen concentration changes markedly, the buffer effect of hemoglobin still maintains almost constant tissue PO2
        - alveolar Po2 vary between 60-500mmHg→ tissue Po2 just vary slightly
    - factors that shift the oxygen-hemoglobin dissociation curve – their importance for oxygen transport
        - shift to right→ more PO2 pressure is needed to saturate hemoglobin
            - caused by: acidic pH, increased CO2, increase temperature, increase BPG
    - increased delivery of oxygen to the tissues when CO2 and H+ ions shift the O2-hemoglobin dissociation curve – the bohr effect
        - CO2→ into blood→ rise in H2CO3 and H+→ O2 hemoglobin curve shift to right→ forcing O2 away from hemoglobin→ more O2 to tissue
        - in lungs exactly the OPPOSITE
    - effect of BPG (biphosphoglycerat) to cause rightward shift of the oxygen-hemoglobin dissociation curve
        - hypoxia→ BPG increases→ shift to right→ release more O2
    - rightward shift to the oxygen-hemoglobin dissociation curve during exercise
        - more CO2 from muscles, temperature rises

- metabolic use of O2 by the cells
    - effect of intracellular PO2 on rate of O2 usage
        - if above 1mmHg not limiting factor→ is ADP
        - O2 usage increase with ATP
    - effect of diffusion distance from the capillary to the cell on oxygen usage→ distance could become the limiting factor→ diffusion limited
    - effect of blood flow on metabolic use of O2→ if blood flow is to low→ limiting factor
- transport of oxygen in the dissolved state
    - decrease by exercise, O2 poisoning if one breath 100% o2
- combination of hemoglobin with carbon monoxide – displacement of oxygen
    - 250 more affinity to hemoglobin→ just 0,6mmHg CO pressure can be lethal
    - PO2 level normal so no response against CO → help is 100% high pressure O2→ displace CO

transport of carbon dioxide in the blood

- normal 4ml/100ml of CO2 transported from tissue to lungs
- chemical forms in which CO2 is transported
    - transport of CO2 in the dissolved state
        - 7% CO2 transported in dissolved form, venous blood 45mmHg PCO2, arterial 40
    - transport of carbon dioxide in the form of bicarbonate ion
        - CO2 reacts with H2O of blood cell, catalyzed by carbonic anhydrase
        - dissociate in H+ and HCO3-→ H+ bind to hemoglobin and HCO3- out and therefor chloride in→ chloride content of venous red blood cells is greater than that of arterial red blood cells
        - CO2 attached to hemoglobin and to plasma protein→ around 20%
- CO2 dissociation curve
    - 40mmHg in arterial and 45mmHg in venous blood;
    - CO2 pressure rises→ CO2 in blood also rises
- when oxygen binds with hemoglobin, carbon dioxide is released (the Haldane effect) to increase CO2 transport
    - binding of O2 with hemoglobin displace CO2 → Haldane effect?
    - because O2 + hem→ hem becomes stronger acid→ less tendency to combine with CO2 and increase acidity release of CO2
    - Haldane effect doubles amount of CO2 release in lungs and double the pickup of CO2 in tissues
    - arterial pH 7,41 venous pH 7,37

respiratory exchange ratio

- respiratory exchange ratio= rate of CO2 output/ rate of O2 uptake
- 1 just carbohydrates; 0,7 just fats

Chapter 41 regulation of respiration

respiratory center

- dorsal respiratory group of neurons – its control of inspiration and of respiratory rhythm most important
    - neurons in NTS nucleus tractus solitaries
    - responsible for quiet breathing
    - signals from chemoreceptors, baroreceptors, lung receptors
    - rhythmical inspiratory discharges from the dorsal respiratory group
        - generation of basic rhythm, repetitive discharge, cutting still functional→ independent
    - inspiratory ramp signal
        - enervates diaphragm, ramp 2 seconds, ceases for 3 seconds→ elastic recoil of lung
        - control of the rate of increase of the ramp signals→ heavy respiration→ ramp increases heavily
        - control of limiting point at which the ramp suddenly ceases→ the earlier ramp ceases→ the shorter the duration of inspiration→ higher frequency
- a pneumotaxic center limits the duration of inspiration and increases the respiratory rate
    - in nucleus parabrachialis to inspiratory area
    - switch off of inspiratory ramp

    - strong penumotaxic signal→ short inspiration → increase respiration rate
- ventral respiratory group of neurons – functions in both inspiration and expiration
    - nucleus ambiguus and retroambiguus
    - inactive during normal breathing
    - if respiratory drive for increased ventilation becomes greater→ signals spill over→ ventral extra drive as well
    - for heavy exercise, control expiration abdominal muscles
- lung inflation signals limit inspiration – the hering-breuer inflation reflex
    - stretch signals→ into dorsal respiratory group if lungs are overstretched→ switch off inspiratory ramp→ reflex for preventing excess lung inflation; active by 1,5L TV
- control of overall respiratory center activity

chemical control of respiration

- direct chemical control of respiratory center activity by carbon dioxide and hydrogen ions
    - chemosensitive area of the respiratory center detect changes in Pco2, H+, concentration
    - O2 act via chemoreceptors of carotid body
- excitation of the chemosensitive neurons by hydrogen ions is likely the primary stimulus but do not cross BBB
- carbon dioxide stimulates the chemosensitive area
    - indirect effect→ forms H+ with H2O behind BBB
    - CO2 more effect on receptors because of blood brain barrier and H+ can not get through
    - decreased stimulatory effect of CO2 after the first 1-2 days
        - just acute effect, weak chronic effect, renal adjustment, H2CO3 diffuse back and binds H+ outside receptor brain area
    - quantitative effects of blood PCO2 and hydrogen Ion concentration on alveolar ventilation
        - PCO2 huge effect on ventilation; pH change is not so great
    - changes in O2 have little direct effect on control of the respiratory center
        - hem O2 buffer system effective→ normal O2 delivery between 60-1000mmHg Pco2
        - chemoreceptors respond if Po2 under 70mmHg

peripheral chemoreceptor system for control of respiratory activity – role of O2 in respiratory control

- aortic and carotid chemoreceptors→ to dorsal medullary respiratory area
- exposed at all times to arterial blood
- decreased arterial O2 stimulates the chemoreceptors, sensitive by 30-60mmHg
- increased CO2 and H+ concentration stimulates the chemoreceptors (peripheral faster, important in exercise), stronger action directly in respiration center
- basic mechanism of stimulation of the chemoreceptors by oxygen deficiency
- effect of low arterial PO2 to stimulate alveolar ventilation when arterial CO2 and H+ concentration remain normal
    - low Po2 drives ventilation process quite strongly under 100mmHg
- chronic breathing of low O2 stimulates respiration even more – the phenomenon of acclimatization
    - 2-3 days respiratory center in brain stem loses about 4/5 of its sensitivity to changes in Pco2 and H+→ excess ventilation blow of CO2→ low O2 drive respiration much higher
- composite effects of Pco2, pH, Po2 on alveolar ventilation

regulation of respiration during exercise

- by the onset of exercise stimulation reach muscles and also respiratory center→ increased ventilation, not by changing Po2, H+, Po2 because they do not change during exercise
- interrelation between chemical factors and nervous factors in the control of respiration during exercise
    - respiratory signals to strong or to weak→ chemical factors do fine adjustment
    - exercise onset ventilation increases and decrease PCo2→ release of excess Co2 from muscles maybe equals Pco2 los out
- neurogenic control of ventilation during exercise may be partly a learned response

other factors that affect respiration

- voluntary control of respiration
- pulmonary irritant receptors→ coughing, constriction, as asthma, emphysema
- function of lung J receptors → edema, feeling dyspnea
- brain edema depress the respiration center
- anesthesia overdose
- periodic breathing→ cheyen-stokes breathing
- basic mechanism of cheyne stokes breathing
    - excess breathing→ more O2 less CO2→ stop breathing→ no O2 much CO2
    - often in severe heart failure due to slow blood flow→ delay from lungs to brain; to strong response from respiratory center by brain damage
- seep apnea → absence of spontaneous breathing
    - 500 times each night 10sec or longer
    - obstructive sleep apnea is caused by blockage of the upper airway, muscles relax normally keep pharynx open
    - relaxation of larynx→ to narrow opening, large tongue, enlarged tonsils, damage to central respiratory centers
    - apnea→ Po2 decreases but Pco2 increases → strong respiration

Chapter 62 general principles of gastrointestinal function – motility, nervous control, and blood circulation

general principles of gastrointestinal motility

- physiologic anatomy of the gastrointestinal wall
    - serosa, longitudinal smooth muscle, circularly smooth muscle, submucosal, mucosa
    - gastrointestinal smooth muscle functions as a syncytium
        - connected by gap junctions, syncytium, AP travels a lot,
    - electrical activity of gastrointestinal smooth muscle
        - slow waves: activated by smooth muscle and interstitial cells of cajal (electrical pacemaker)→ excite spike potentials→ excite muscle contraction
            - 5-15mv, 3-12/minute
            - slow waves only cause contraction in stomach
        - spike potentials: normal AP, threshold -40mv, Ca influx mainly and bit Na→ slow voltage gates Ca Na channels
        - changes in voltage of the resting membrane potential
            - -56mv RMP, depolarization by→ stretching, ACH, hormones;
            - hyperpolarization→ norepinephrine, epinephrine, sympathetic stimulation
        - calcium ions and muscle contraction
            - Ca→ calmodulin→ myosin actin→ contraction
            - by spike potentials→ Ca enters
        - tonic contraction of some gastrointestinal smooth muscle
            - tonic contraction long time
            - caused by repetitive spike potentials, hormones, continuous Ca entry

neural control of gastrointestinal function – enteric nervous system

- differences between the myenteric and submucosal plexuses
    - myenteric: chain of neurons, tone and contraction, intensity, rhythm, velocity; also inhibitory by relax sphincter
    - submucosal plexus: secretion, absorption, local contraction
- types of neurotransmitters secreted by enteric neurons
    - ACH excites; nor and epinephrine inhibit
    - autonomic control of the gastrointestinal tract
        - parasympathetic stimulation increases activity of the enteric nervous system
            - cranial sacral; vagus for esophagus, stomach, pancreas, bit intestines
            - sacral parasympathetics for end intestines
        - sympathetic stimulation usually inhibits gastrointestinal tract activity
            - celiac and mesenteric ganglia → postganglionic→ innervates all parts of GI system, secrete mainly norepinephrine less epinephrine

                - norepinephrine→ inhibit tract smooth muscle (but excite mucosal muscle), inhibits neurons of enteric nervous system
        - afferent sensory nerve fibers from the gut
            - stimulated by irritation, over distension, chemicals→ reflex
        - gastrointestinal reflexes
            - reflexes that are integrated entirely within the gut wall enteric nervous system for secretion, peristalsis
            - reflexes from gut to the prevertebral sympathetic ganglia and then back to the gastrointestinal tract→ reflexes from stomach to colon
            - reflexes from gut to the spinal cord or brain stem and back to the gastrointestinal tract
                - pain reflexes, vagus nerve stomach brain, defecation reflex
- hormonal control of gastrointestinal motility
    - gastrin: protein, distension nerve→gastric acid secretion, growth of mucosa
    - cholecystokinin: food→secretion of pancreatic enzyme, bicarbonate, gallbladder contraction, exocrine pancreas and inhibits gastric emptying and appetite→ slow down
    - secretin: small intestine, secrete pepsin, bicarbonate, growth of exocrine pancreas, inhibit gastric acid secretion → against acid, fat
    - gastric inhibitory peptide: small intestine, insulin release; against protein, fat, carbohydrates
    - motilin: motility

functional types of movements in the gastrointestinal tract

- propulsive movements – peristalsis
    - due to stretch,vagal innervation, irritation
    - function of the myenteric plexus in peristalsis → plexus is necessary, atropine paralyzes
    - directional movement of peristaltic waves toward the anus
        - myenteric or peristaltic reflex and the law of the gut→ relaxation of intestine more descend to allow food to be propelled more easily towards anus than towards the mouth
- mixing movements by peristalsis and constrictive movement, accumulation before sphincter

gastrointestinal blood flow – splanchnic circulation

- reticuloendothelial cells remove bacteria and foodstuff from blood
- blood from spleen, pancreas, gut→ to liver by portal vein; fat via lymph
- anatomy of the gastrointestinal blood supply
- effect of gut activity and metabolic factors on gastrointestinal blood flow
    - blood flow increases with activity
    - possible causes of the increased blood flow during gastrointestinal activity
        - vasodilator: vip, gastrin, secretin, cck; kallidin, bradykinin
        - lack of O2 during activity→ more vasodilation, adenosine
    - countercurrent blood flow in the villi→ O2 exchange, O2 lack in tip of villi→ necrosis of villi
- nervous control of gastrointestinal blood flow→ vagal dilation, sympatethics constriction
    - autoregulatory escape if sympathetic is active→ local vasodilator activated by ischemia return blood flow
    - importance of nervous depression of gastrointestinal blood flow when other parts of the body need extra blood flow→ constriction also of large veins like intestinal and mesenteric veins

chapter 63 propulsion and mixing of food in the alimentary tract

ingestion of food

- mastication
    - chewing reflex, up and down, bigger surface→ better for digestive enzyme work
- swallowing
    - voluntary stage of swallowing→ automatic swallowing after tongue no stop
    - pharyngeal stage of swallowing reflex
        - reflexes due to presents of food bolus→soft plate up to close nasal cavities; palatopharyngeal folds medially; epiglottis close, larynx up, opening of esophagus bigger; pharyngoesophageal sphincter prevents air entry;

- nervous initiation of the pharyngeal stage of swallowing
    - nerve ring posterior to mouth→ trigeminal and glossopharyngeal nerve→ tractus solitaries controlled by swallowing center
    - motor impulse by5, 9, 10, 12,
- effect of the pharyngeal stage of swallowing on respiration → to short
- esophageal stage of swallowing
    - primary peristalsis: every 8-10 seconds to stomach
    - secondary wave by distention up by vagus back by glosso and vagal → cut vagal nerve swallowing still possible
    - striated becomes smooth muscle
- receptive relaxation of stomach before peristalsis wave comes
- function of the lower esophageal sphincter (gastroesophageal sphincter)
    - prevent reflux of acid, relaxes also by peristalsis wave
- additional prevention of esophageal reflux by valve like closure of the distal end of the esophagus

motor functions of the stomach

- storage function of the stomach: if full→ vagovagal reflex→ brain stem→ reduces tone, 1,5 L
- mixing and propulsion of food in the stomach – basic electrical rhythm of the stomach
    - gastric juice, mixing waves by basic electric rhythm (slow waves)→ become stronger towards antrum and force content in antrum
    - retropulsion: moving peristaltic constrictive ring and upstream squeezing→ mixing
    - chime: after stomach
    - hunger contractions: strong titanic 2-3 minute constriction; by starvation pain greatest 3-4 days
- stomach emptying
    - intense antral peristaltic contractions during stomach emptying – pyloric pump
    - role of the pylorus in controlling stomach emptying→ water can pass by ease, chime must be on water level
- regulation of stomach emptying
    - duodenum regulates more
    - gastric factors that promote emptying
        - effect of gastric food volume on rate of emptying → stretching→local myenteric nerves reflex→ activity of pyloric pump
        - effect of the hormone gastrin on stomach emptying→ promotes stomach emptying because it enhances the pyloric pump
    - powerful duodenal factors that inhibit stomach emptying
        - inhibitory effect of enterogastric nervous reflexes from the duodenum
            - if duodenum is to full→ directly from duodenum to stomach by enteric nervous system; by extrinsic nerves that go to the prevertebral sympathetic ganglia and back to inhibitory; by vagus nerve→ increase tone of sphincter and inhibit pyloric pump
            - degree of duodenal distension; irritation of mucosa; acidity (pH to low?); osmolarity of chime (no hypertonic chyme); presence of breakdown products
        - hormonal feedback from the duodenum inhibits gastric emptying – role of fats and the hormone cholecystokinin
            - fats (slow digestion)→ receptors→ hormones via blood→ inhibit pyloric pump and contract sphincter
            - CCK, gastric inhibitory peptide GIP, secretin
- summary of the control of stomach emptying

movement of the small intestine

- mixing contractions (segmentation contractions)
    - chime→ contraction→ segmentation mixing food with secretations
        - determined by electrical slow waves
        - atropine blocks enteric nervous system
- propulsive movements
    - peristalsis in the small intestine
        - slow 1cm/m; 3-5 hours from pylorus to ileocecal valve

    - control of peristalsis by nervous and hormonal signals
        - chime stretches duodenum wall→ peristalsis
        - hormones, nerves
    - propulsive effect of the segmentation movements similar to peristalsis
    - peristaltic rush→ caused by infection of mucosa → chime fast into colon to relax small intestine
- function of the ileocecal valve
    - prevent backflow, can sustain 50-60 cm water ileocecal sphincter
    - feedback control of the ileocecal sphincter
        - cecum is distended→ delay of emptying
        - appendix inflammation→ prevents ileal emptying

movements of the colon

- absorption of water (proximal) and electrolytes and storage of feces (distal portion), sluggish movement
- mixing movements – haustrations
    - circular constrictions, longitudinal contractions→ bulging→ haustrations
    - propulsive movements – mass movements
        - 8-15h from ileocecal valve to end, just 3 times a day in 1 h after eating for 15min bf
        - constrictive ring in transverse colon→ 20 cm distal from this point entire colon contracts as unit→ as mass further down, last 10-30 minutes→ defecation
- initiation of mass movement by gastrocolic and duodenocolic reflexes→ by distension of stomach and duodenum, also caused by irritation
- defecation
    - most of the time rectum is empty; if feces in rectum reflex for defecation immediately
    - external sphincter controlled voluntary, internal subconscious
    - defecation reflex
        - feces enters rectum→ distension→ signals myenteric plexus→ peristalsis → internal inhibit by myenteric plexus→ defecation occurs if external is relaxed voluntary, but weak reflex
        - enforced by parasympathetic nerves circuit to spinal cord
        - enforced by contraction ob diaphragm and abdomen
        - by spinal cord injury→ defecation occurs involuntary

other autonomic reflexes that affect bowel activity

- peritoneointestinal reflex→ by irritation of peritoneum → intestinal paralysis nerve damage
- renointestinal and vesicointestinal reflexes inhibit intestinal activity by bladder or kidney irritation

chapter 64 secretory functions of the alimentary tract

general principles of alimentary tract secretion

- anatomical types of glands
- basic mechanisms of stimulation of the alimentary tract glands
    - contact of food with the epithelium stimulates secretion – function of enteric nervous stimuli
    - autonomic stimulation of secretion
        - parasympathetic stimulation increases alimentary tract glandular secretion rate
        - sympathetic stimulation has a dual effect on alimentary tract glandular secretion
            - sympathetic innervation alone slightly increase secretion
            - is parasympathetic and hormones already cause secretion→ sympathetic inhibit secretion
        - regulation of glandular secretion by hormones – liberated from mucosa→ absorbed and carried to glands
- basic mechanism of secretion by glandular cells
    - secretion of organic substances
        - secreted material reaches glandular cells by blood; many mitochondria; ATP ER; golgi secretory vesicles→ hormone→ ca influx→ release
    - water and electrolyte secretion
    - lubrication and protective properties of mucus, and importance of mucus in the gastrointestinal tract

        - composed of water and electrolytes, is adherent to food, coat mucosa, sliding, stick fecal particles together, resistant to digestion, buffer function

secretion of saliva

- saliva contains a serous secretion and a mucus secretion
    - 800-1500ml, ptyalin for starches (parotid gland), mucus for lubrication, pH 6-7
- secretion of ions in saliva
    - K+, bicarbonate but less Na and cl- → smaller by faster secretion→ reconditioning reduced
    - acini secrete primary secretion with ptyalin→ Na ions are reabsorbed from saliva and potassium secreted→ -70mv in salivary duct→ chloride reabsorbed→ bicarbonate secreted
    - wash away bacteria and food; destroy bacteria; contain protein antibodies
- nervous regulation of salivary secretion
    - controlled by parasympathetic system, salivatory nucleus excited by smell and taste, sour taste, tactile stimuli, rough objects inhibit salivation, excited by appetite and smell area of brain,
    - saliva removes irritating factor in gastrointestinal tract by diluting or neutralizing the irritant substances
    - sympathetic can increase salivation slightly
    - blood supply also influences secretion→ supply of nutrients
    - kallikrein→ bradykinin from salivary cells vasodilation→ more salivation

esophageal secretion; compound gland protection against acid, mucos in proximal part prevent excoriation

gastric secretion

- characteristics of the gastric secretions
    - oxyntic acid gland: contain oxyntic HCL intrinsic factor glands, chief cells pepsinogen, mucus in proximal 80%
    - pyloric glands→ mucus for protection, gastrin in distal 20%
    - secretions from the oxyntic (gastric) glands
        - basic mechanism of hydrochloric acid secretion
            - pH 0,8, 3mio times hydrogen ion concentration as in blood→ need 1500 calories/ liter of gastric juice → during secretion bicarbonate ion into venous blood higher pH then arterial blood
            - HCL formed by canaliculi→ secreted by hydrogen potassium pump
            - formation:
                - H2O → H+ and OH- in cell→ H+ in canaliculus in exchange for K+
                - basolateral Na-K ATPase creates low Na→ Na reabsorption from canaliculus
                - formation in cell of HCO3-→ exchanged for Cl-→ diffusion into canaliculus→ form HCL
                - H20→ ECF→ cell→ canaliculus
            - gastric barrier alkal prevents damage by HCL due to back flow, over tight junctions
        - basic factors that stimulate gastric secretion are ACH, gastrin and histamine just HCL
        - secretion and activation of pepsinogen → pepsin activated by low pH values under 5→
        - secretion of intrinsic factor by parietal cells→ essential for absorbing B12 (for RBC) in ileum is secreted by parietal cells (lack of HCL B12 lack pernicious anemia)
- pyloric glands – secretion of mucus and gastrin
- surface mucous cells→ 1mm thick layer of mucus shell, alkaline
- stimulation of gastric acid secretion
    - parietal cells of the oxyntic glands are the only cells that secrete HCL
        - protein→ gastrin→ ECL cells secrete histamine→ parietal cells secrete HCL, proportional
    - stimulation of acid secretion by gastrin
        - gastrin from G cells in distal stomach→ gastrin into blood→ to ECL→ histamine→ HCL
- regulation of pepsinogen secretion
    - acid in stomach or vagus stimulation→ pepsinogen secretion by peptic cells in oxyntic glands→ activated by acid→ protein digestion
- phases of gastric secretion
    - cephalic phase → 30% of gastric secretion before food enters by smell, appetite

    - gastric phase→ food enters→ 60% →
    - intestinal phase→ food in duodenum but it releases little gastrin→ 10% secretion
- inhibition of gastric secretion by other post-stomach intestinal factors
    - food in duodenum inhibits stomach secretion
    - food break down products or irritation→ secretin for duodenum→ inhibits gastric secretion
    - → reduce chime propelling, and stomach motility
    - little secretion during interdigestive period→ enhanced by emotional stress-> ulcer
- chemical composition of gastrin and other gastrointestinal homones

pancreatic secretion

- pancreatic digestive enzymes by acini
    - bicarbonate ions, trypsin and chymotrypsin split proteins into peptides → boxypolypeptidase→ amino acids;
    - carbohydrates by pancreatic amylase except cellulose;
    - lipase and cholesterol esterase and phospolipase for fat digestion→ activated by entering duodenum
    - secretion of trypsin inhibitor prevents digestion of the pancreas itself because trypsin inhibitor inhibits trypsin and trypsin all other enzymes, if accumulate to much→ self digestion→ pancreatitis
- secretion of bicarbonate ions by epithelial cells
    - bicarbonate to buffer acidity in duodenum
    - bicarbonate formation by CO2→ H+ exchanged for Na to provide electrical neutrality by secretion bicarbonate→ bicarbonate and Na in duct lumen drag water with them
- regulation of pancreatic secretion
    - basic stimuli that cause pancreatic secretion
        - ACH, CCK→ stimulate acini→ just enzymes; secretin→ H20 and bicarbonate ,CCK (by food) and secretin (by acid) both from duodenum
        - multiplicative effects of different stimuli→ all 3 instantaneously biggest effect
    - phases of pancreatic secretion
        - cephalic and gastric phases→ same as by stomach but little secretion because lack of water
        - intestinal phase → chime enters duodenum→ secretin→ H20 Na→ full secretion
        - secretin activated under pH 4,5 →HCL+NaHCO3→NaCl+H2CO3 → H20+CO2
        - cholecystokinin – its contribution to control of digestive enzyme secretion by the pancreas
            - stimulated by peptones

secretion of bile by the liver; functions of the biliary tree

- physiologic anatomy of bilary secretion
    - secondary to bile contains bicarbonate and Na stimulated by secretin → neutralizing acid
    - storing and concentrating bile in the gallbladder
        - 12 h of bile can be stored in bladder normal just 60ml but mucosa absorbs water, Na, Cl→ concentrating bile 5-20 fold
    - composition of bile→ huge secretions of bile salts, bilirubin, cholesterol, lecithin, electrolytes
    - emptying of the gallbladder – stimulation role of cck stimulated by fat→ secreted from duodenum→ cause gallbladder contraction
- function of bile salts in fat digestion and absorption
    - cholesterol→ cholic acid + glycine→ glycol tauro conjugated bile acids
    - salts action: detergent→ break fat called emulsifying or detergent function of bile salts; help in absorption of fatty acids, monoglycerides, cholesterol→ form micelles→ absorbed into blood
    - enterohepatic circulation of bile salts
        - reabsorbed by blood 94% → back in hepatic cells
        - secretin can double bile secretion
- liver secretion of cholesterol and gallstone formation

secretions of the small intestine

- secretion of mucus by brunners glands in the duodenum

    - secrete mucus by tactile or irritating stimuli, vagal stimulation, hormones especially secretin → protection of mucosa; inhibit by sympathetic stimulation→ ulcers
- secretion of intestinal digestive juices by the crypts of lieberkühn
    - contain goblet cells for mucus; enterocytes secrete water and electrolytes and absorb end products of digestion
    - mechanism of secretion of the watery fluid: secretion of electrolytes into crypt drag water with them
    - digestive enzymes in the small intestinal secretion
        - digest fats, proteins carbohydrates while they are absorbed
- regulation of small intestine secretion – local stimuli

secretion of mucus by the large intestine

- mucus secretion: liberkühn, no enzymes, no villi, by parasympathetics
- diarrhea caused by excess secretion of water and electrolytes in response to irritation→ dilute irritating factors

chapter 65 digestion and absorption in the gastrointestinal tract

digestion of the various foods by hydrolysis

- hydrolysis of carbohydrates
    - 2 monosaccharides bound to each other→ $H_2O$
    - hydrolysis is reverse: R2-R1+$H_2O$→digestive enzyme→ R2OH+R1H
- hydrolysis of fats → add $H_2O$ to triglyceride→ split fatty acid away from glycerol
- hydrolysis of proteins same
- digestion of carbohydrates
        - carbohydrate foods of the diet: sucrose, lactose, starches
    - digestion of carbohydrates in the mouth and stomach
        - ptyalin from saliva→ starch→ maltose; 30-40%
- digestion of carbohydrates in the small intestine
    - digestion pancreatic amylase
        - α amylase→ carbohydrates→ maltose
    - hydrolysis of disaccharides and small glucose polymers into monosaccharide's by intestinal epithelial enzymes
        - enterocytes has 4 enzymes→ split disaccharides → monosaccharide's → into portal blood
- digestion of proteins
    - proteins of the diet
    - digestion of proteins in the stomach
        - active pH 2-3 inactive above 5, important in collagen digestion for meat
    - most protein digestion result from actions of pancreatic proteolytic enzymes
        - most in upper intestine by trypsin, chymotrypsin, carboxypolypeptidase, proelastase
        - most remains as di or tri peptides
    - digestion of peptides by peptidases in the enterocytes that line the small intestinal villi
        - peptidase aminopolypeptidase and several dipeptidases project from villi
        - split proteins→ into interior of enterocytes; 99% are amino acids absorbed
- digestion of fats
    - fats of the diet
        - cholesterol has no fatty acids but is fat,
    - digestion of fats in the intestine
        - 10% in stomach but unimportant
    - the first step in fat digestion is emulsification by bile acids and lecithin
        - emulsification of fat by bile (lecithin, bile salts→ have water and fat soluble part→ make fat watersoluble)→ break fat → reduce surface tension→ increase total surface area for lipase
    - triglycerides are digested by pancreatic lipase
    - end products of fat digestion are free fatty acids
    - bile salts form micelles that accelerate fat digestion

        - bile salts removing the monoglycerides and free fatty acids from the vicinity of the digesting fat globules → form micelles (if concentration is high enough)→ ferry the fats to villi and are released later
    - digestion of cholesterol esters and phospholipids
        - hydrolyzed by cholesterol ester hydrolase and phospholipase→ micelles ferry them

basic principles of gastrointestinal absorption

- anatomical basis of absorption
    - absorbed fluid=ingested fluid (1,5L + secreted fluid in gastrointestinal secretions 7L)
    - stomach poor absorption due to tight junctions and lack of villi
    - folds of kerckring, villi, and microvilli (brush border) increase the mucosal absorptive area by nearly 1000 fold, central lacteal absorb lymph vessel

absorption in the small intestine

- absorption of water by osmosis
    - isosmotic absorption→ diffusion; water could also be added to hyperosmotic chime
- absorption of ions
    - sodium is actively transported through the intestinal membrane; very little amounts are excreted;
        - sodium glucose co transporter; sodium amino acid co transporter; sodium hydrogen exchanger → Na K pump into interstitial fluid
        - 142mEq/L Na in chime= plasma
    - osmosis of the water
        - aldosterone greatly enhances sodium absorption (and water),from adrenal gland
    - absorption of chloride ions in the small intestine; in upper part by diffusion follow Na, more distal by bicarbonate exchanger
    - absorption of bicarbonate ions in the duodenum and jejunum
        - Na exchanged with H+→ H+ bicarbonate form $H_2CO_3$ in small intestine→ into $H_2O$ and $CO_2$ (into blood expired)→ called active absorption of bicarbonate ions
    - secretion of bicarbonate ions in the ileum and large intestine – simultaneous absorption of chloride ions
        - neutralizes acid production by bacteria
        - extreme secretions of CL-, water from large intestines epithelium in some types of diarrhea
            - toxins of cholera and other diarrheal bacteria can stimulate epithelial fold secretion so greatly that this secretion often becomes much greater as absorption
                - cause Cl- channels to open→ loss → Na with Cl→ drags water with them→ try to wash out bacteria→ prevention
            - active absorption of Cl-, iron, potassium, magnesium, phosphate
- absorption of nutrients
    - carbohydrates are mainly absorbed as monosaccharides
        - 80% glucose
        - glucose is transported by a sodium co transport mechanism
            - low Na in cell drags Na inside and glucose comes with it
        - absorption of other monosaccharide
            - fructose by facilitated diffusion no Na involved
    - absorption of proteins as dipeptides, tripeptides, amino acids
        - co transport with Na, some by facilitated diffusion
    - absorption of fats
        - micelles are soluble in chime, ferrying function, →taken up by smooth ER→ new triglycerides→ in lymph; in absence of micelles just 50% fat absorbed
        - direct absorption of fatty acids into portal blood → if they are short chain fats

absorption in the large intestine: formation of feces

- absorption and secretion of electrolytes and water
    - Na, Cl-→ absorption against much higher concentration gradient due to tighter tight junctions
    - excrete bicarbonate for Cl-

    - absorption of water
- maximum absorption capacity of the large intestine
    - 5-8 liters if more→ diarrhea
    - bacteria form gases and vitamin K
    - composition of feces ¾ water, ¼ solid matter (30% dead bacteria,10-20%fat, 10-20% inorganic matter, 2-3% protein, 30% undigested roughage)
        - brown color caused by stercobilin and urobilin derived from bilirubin

chapter 70 the liver as an organ

physiologic anatomy of the liver

- central vein→ hepatic vein→ vena cava
- sinusoids lined by endothelial cells and large kupfer cells contain macrophages, large pores, spaces of disse

hepatic vascular and lymph systems

- blood flow through the liver from portal vein and hepatic artery
    - the liver has high blood flow and low vascular resistance
        - 1300ml/ minute; portal vein 9mmHg; hepatic vein 0mmHg;
    - cirrhosis of the liver greatly increases resistance to blood flow by alcohol or fat→ fibrosis
    - portal vein occlusion→ hypertension→ fluid los death in short time
- the liver functions as a blood reservoir, expandable by heart failure
- the liver has very high lymph flow
    - high hepatic vascular pressures can cause fluid transudation into the abdominal cavity from the liver and portal capillaries – ascites
- regulation of liver mass – huge regeneration is severely impaired by liver disease
- hepatic macrophage system serves a blood-cleansing function, remove 99% of bacteria

metabolic functions of the liver

- carbohydrate metabolism
    - storage of glycogen, conversion of galactose and fructose to glucose, gluconeogenesis,
    - glucose buffer function of liver
- fat metabolism
    - oxidation of fatty acids to supply energy for other body functions
    - synthesis of large quantities of cholesterol, phospholipids, lipoproteins
    - synthesis of fat from proteins and carbohydrates
    - fatty acids→ citric acid cycle
    - cholesterol into bile salts
    - proteins, carbs→ fat
- protein metabolism
    - deamination of amino acids; formation of urea for removal of ammonia from the body fluids; formation of plasma proteins; interconversions of various amino acids and synthesis of other compounds from amino acids
    - liver forms urea, if not plasma ammonia concentration rises→ hepatic coma
    - form plasma proteins except gamma globulins
    - formation of non essential amino acids
- other metabolic functions of the liver

measurement of bilirubin in the bile a clinical tool

- bilirubin from hemoglobin degradation
- RBC→hemoglobin→ macrophages unconjugated bilirubin into blood→ in liver→ conjugated bilirubin→ feces stercobilin, urine urobilin
- jaundice – excess bilirubin in the ECF
    - unconjugated or conjugated, caused by increase destruction of RBC, obstruction of bile duct
    - obstructive (total bilirubin test negative) and hemolytic jaundice (unconjugated form van den bergh reaction)

chapter 71 dietary balances; regulation of feeding; obesity and starvation; vitamins and minerals

- energy intake and output are balanced under steady-state conditions
- dietary balances
    - energy available in foods
        - physiologically available energy carbs 4, fat 9, protein 4
        - average daily requirement for protein is 30-50 grams
            - partial proteins: inadequate quantities of certain essential amino acids like plants
            - kwashiorkor: protein deficiency, hunger belly→ lack of proteins→ edema in belly not in legs due to muscle pump
        - carbohydrates and fats act as protein sparers, starvation use of proteins
    - methods for determining metabolic utilization of carbohydrates, fats, proteins
        - respiratory quotient is the ratio of CO2 production to O2 utilization and can be used to estimate fat and carbohydrate utilization
            - carbs are oxidized  1 O2 consume and 1 CO2 output→ respiratory quotient 1
            - fat needs 100 O2 output is 70 CO2→ respiratory quotient 0,7
            - proteins quotient is 0,8 → O2 combines with H+ so less CO2
            - respiratory exchange ratio = respiratory quotient is 1 body uses carbs
            - immediately after meal 1 RQ use just carbs→ after 8-10 h 0,7RQ use just fats
            - in diabetes 0,7→ no insulin
        - nitrogen excretion can be used to assess protein metabolism
            - protein contains nitrogen 90% of its is excreted 10% via feces→ amount of protein break down measured by nitrogen concentration in urine
            - negative nitrogen balance→ protein body store decreases

regulation of food intake and energy storage

- neural centers regulate food intake
    - the hypothalamus contains hunger and satiety centers
        - lateral nuclei feeding center
        - ventromedial nuclei is satiety center → inhibit feeding center
        - hypothalamus recives signals from gastrointestinal tract about → stomach filling, chemicals from nutrients in blood, adipose tissue, cerebral cortex sight smell,
        - orexigenic substances stimulate feeding
        - anorexigenic inhibit feeding
    - neurons and neurotransmitters in the hypothalamus that stimulate or inhibit feeding
        - in arcuate nucleus: POMC neurons that produce α-MSHormone together with CARTranscript
            - decrease food intake, increase energy expenditure
            - MRC receptors → mutation→ obesity; anorexia
        - neurons that produce the orexigenic substances neuropeptide Y NPY and AGRProtein
            - increase food intake and reduce energy expenditure
            - AGRP increase→ increased food uptake, antagonist of MCR
        - arcuate nuclei convergence of many signals that regulate energy stores, neurons targets of hormones
    - neural centers that influence the mechanical process of feeding
        - mechanics of feeding are controlled by center in brain stem
        - amigdala: control appetite, quality of food, smell
- factors that regulate quantity of food intake
    - short term regulation of food intake
        - gastrointestinal filling inhibits feeding → stretch inhibitor signals by vagus suppress feeding center
        - gastrointestinal hormonal factors suppress feeding
            - CCK→ act on receptors on duodenum→ vagal signals→ prevents overeating
            - PYY decrease food intake
            - GLP and insulin suppress appetite
        - ghrelin – a gastrointestinal hormone – increases feeding
            - from oxyntic cells; rise by starvation→ stimulate eating

        - oral receptors meter food intake
            - chewing, salivation, swallowing, tasting inhibit feeding center
    - intermediate and long term regulation of food intake
        - effect of blood concentration of glucose, amino acids, and lipids on hunger and feeding
            - drop in glucose causes hunger (also drop of amino and fatty acids in blood)
            - rise in blood glucose increase signals of glucosereceptors→ into satiety center
            - increase in blood glucose decrease firing of glucosensitiv neurons in the hunger center
        - temperature regulation and food intake
            - cold increase feeding
        - feedback signals from adipose tissue regulate food intake
            - adipose tissue increases→ adipocytes produce more leptin→ act on POMC neurons→ decrease NPY AGRP, release of MSH, hormones that decrease food intake like corticotrophin releasing hormone, increase sympathetic activity, decrease insulin secretion (decrease energy storage)
            - obesity linked to leptin resistance
        - summary: energy storage falls below→ search food; energy abundant→ lost hunger
    - importance of having both long and short term regulatory systems for feeding
        - long term maintains constant store of nutrients preventing them from becoming to low or to high
        - short term force people to eat smaller quantities, preventing of eating to much for storage

obesity

- BMI= Kg/ height m2
- obesity results from greater energy intake than energy expenditure
    - 9,3 cal excess 1 gram fat is stored
- decreased physical activity and abnormal feeding regulation as causes of obesity
    - sedentary lifestyle is a major cause of obesity
    - abnormal feeding behavior is an important cause of obesity
    - environmental, social, psychological factors contribute to abnormal feeding
    - childhood overnutrition a sa possible cause of obesity
    - neurogenic abnormalities as a cause of obesity
        - hypophyseal tumors damage to hypothalamus
    - genetic factors as a cause of obesity
        - mutations of MCR4; congenital leptin deficiency; mutation of the leptin receptor
- treatment of obesity
    - negative energy balance; amphetamines inhibit feeding center; negative adaption to drug, hypertension

inanition, anorexia and cachexia

- extreme weight loss
- caused by cancer
- anorexia: reduction of food due to reduced appetite
- anorexia nervosa: person loses desire for food
- cachexia: metabolic disorder of increased energy expenditure, tumor AIDS

starvation

- depletion of food stores in the body tissues during starvation
    - fat 100 times more energy than in stored carbs; without food body has energy for half a day
    - protein depletion: rapid (use easy accessible proteins for brain), slow (body uses proteins which are not so easy to remove, brain depends on keton bodies)→ excessive fat utilization and at the end fast (fat stores are depleted) before death (when proteins are used to 50%)
- vitamin deficiencies in starvation
    - fast consume of vitamin B, C

Chapter 73 body temperature regulation and fever

normal body temperatures

- body core temperature and skin temperature
- normal core temperature
    - rectal body temperature 1F higher

body temperature is controlled by balancing heat production and heat loss

- heat production
    - by metabolism, factors are basal rate of metabolism of all cells, extra rate of metabolism by muscles, extra caused by thyroxine growth hormone testosterone, by hormones, sympathetic stimulation, chemical activity, processes
- heat loss
    - heat generated by brain, liver, heart→ transferred to tissue
    - determined by how fast heat can be conducted and how fast can it be conducted
    - insulator system of the body
        - skin, fat great insulator, ct,
    - blood flow to the skin from the body core provides heat transfer
        - high rate of skin flow causes heat to be conducted from core of body to skin
        - control of heat conduction to the skin by the sympathetic nervous system, venous plexuses
    - basic physics of how heat is lost from skin surface
        - radiation: 60% of total heat loss, heat rays
        - conduction: 15% to air, air convention, moving of skin
        - convection: 15% air gets hot by skin and elevates→ first conduction of theat to air then convection
        - cooling effect of wind: 4 miles wind twice as effective for cooling as 1 mile wind, faster replacement of air layer on skin
        - conduction and convection of heat from a person suspended in water: each water molecule can absorb much more heat from skin then air molecule, cant from a thin layer of water for heating
        - evaporation: 1gr water vapors=0,58 calorie
        - evaporation is a necessary cooling mechanism at very high air temperatures
            - air higher temperature as body→ body get rid of heat by evaporation
        - effect of clothing on conductive heat loss: have of heat lost to clothes is by radiation→ thin gold layer reflects back, clothes are wet no effect due to heat conduction of water, in arctic prevent sweating
    - sweating and its regulation by the autonomic nervous system
        - anterior hypothalamus→ cause sweating, cholinergic sympathetic fibers !!!--> to glands; also innervated by nor and epinephrine
        - mechanism of sweet secretion
            - precursor secretion lack plasma proteins
            - slow secretion→ Na and Cl and water reabsorbed→ high concentration of K, urea, lactic acid
            - fast secretion no concentration→ high water and Na Cl loss
        - acclimatization of the sweating mechanism to heat – role of aldosterone
            - adaption to hot weather→ more sweat production→ adaption of gland
            - increased secretion of aldosterone→ reduce of NaCl concentration in extracellular fluid→ save NaCl by sweating (15→ to 3g/day)

regulation of body temperature – role of the hypothalamus

- nude person can maintain body temperature between 10-55
- role of the anterior hypothalamic-preoptic area in thermostatic detection of temperature
    - preoptic and anterior hypothalamic nuclei of the hypothalamus sensitive to cold or heat
        - heat sensitive neurons increase firing 2-10times in respond to a 10C increase in body temperature and vice versa

- detection of temperature by receptors in the skin and deep body tissues
    - periphery skin more cold then warm receptors
    - cold→ shivering, no sweating, skin vasoconstriction
    - deep body receptors in spinal cord, abdominal viscera, great veins
    - --> prevent hypothermia
- posterior hypothalamus integrates the central and peripheral temperature sensory signals
- neuronal effector mechanisms that decrease or increase body temperature
    - temperature-decreasing mechanisms when the body is too hot
        - vasodilation of skin blood vessels, inhibit sympathetic
        - sweating
        - decrease in heat reduction inhibit shivering
    - temperature increasing mechanisms when the body is too cold
        - skin vasoconstricition throughout the body by posterior hypothalamus
        - piloerection
        - increase in thermogenesis (heat production), shivering, sympathetic stimulaton, thyroxine secretion
    - hypothalamic stimulation of shivering
        - primary motorcenter of shivering, inhibited from heat center, excited from cold signals
        - can increase heat production 5 times, muscle tone rises above level→ shivering
    - sympathetic chemical excitation of heat production
        - chemical thermogenesis: increase in rate of cellular metabolism caused by sympathetic, nore and epinephrine
        - increase oxidative phosphorylation in brown fat tissue→ norepinephrine stimulates mitochondrial uncoupling protein→ increase thermogenesis (foodstuffs are oxidized but no ATP release)
            - important in neonates they have brown fat
    - increased thyroxin output as long-term cause of increased heat production
        - cooling anterior hypothalamus→ thyrotropin-releasing hormone→ pituitary gland→ thyroid stimulating hormone → thyroxine → chemical thermogenesis
        - requires several weeks
- concept of a set point for temperature control
    - 37,1°C set point, above more heat los then gain
    - feedback gain for body temperature control
        - high feedback gain→ effectiveness of control system; 1° for 30° elevation
    - skin temperature can slightly alter the set point for core temperature control
        - skin and deep body signals after the set point of the hypothalamic temperature
        - set point increases when skin temperature decreases
        - when skin temperature was high, sweating began at a lower hypothalamic temperature than when the skin temperature was low
        - similar in shivering: when skin becomes cold it drives hypothalamic centers to the shivering threshold even when hypothalamic temperature itself is still on the hot side of normal
- behavioral control of body temperature
    - signals to brain-→ cold, warm→ wear clothes, heated room
- local skin temperature reflexes
    - local sweating and vasoconstriction
    - regulation of internal body temperature is impaired by cutting spinal cord above sympathetic outflow→ hypothalamus cant reach skin or blood flow

abnormalities of body temperature regulation

- fever
    - caused by brain, toxins,
    - resetting the hypothalamic temperature-regulating center in febrile diseases – effect of pyrogens
        - pyrogens→ cause set point to rise, body temperature approaches set point, can act directly or indirectly and also delayed
        - mechanism of action of pyrogens in causing fever – role of cytokines

- bacteria are digested by leukocytes, macrophages→ release cytokines like interleukin-1 or leukocyte pyrogen→prostaglandin E2→ act on hypothalamus→ fever
- drugs inhibit prostaglandin like asperine called antipyretics
- 1/10000000 gr of bacteria is enough to cause reaction

▪ fever caused by brain lesions
- by brain tumor squeezing hypothalamus, operation on brain

▪ characteristics of febrile conditions
- chills: if set point is set higher the body temperature needs time to adapt→ person feels cold and shivers although the body temperature is already above normal
- crisis or flush: set point reestablishes→ body temperature falls

▪ heatstroke
- if air is dry person can withstand several hours at 54C
- if air is wet or in water is just 94F
- harmful effects of high temperature
  - hyperpyrexia→ local hemorrhages, cell damage
- acclimatization to heat
  - increase in sweating, increase in plasma volume, prevention of salt los by aldosterone

▪ exposure of body to extreme cold
- under 30C hypothalamus lost regulation function
- frostbit→ damage of smooth muscle→ vasodilation→ heat to skin
- artificial hypothermia by heart surgery to slow town cell metabolism

chapter 72 energetics and metabolic rate

- adenosine triphosphate ATP functions as an energy currency in metabolism
  - ATP from foodstuff, 12000 cal in physiological conditions
  - ATP is generated by combustion of carbohydrates, fats, proteins
    - carbs: glucose, fructose in cytoplasm→ anaerobic glycolysis or in mitochondria aerobic by citrate cycle
    - fat in mitochondria by beta oxidation
    - proteins hydrolysis→ amino acids→ citrate cycle→ acetyl coenzyme A
- ATP energizes the synthesis of cellular components
  - ATP for peptide linkage between amino acids
  - ATP for lactic acid→ glucose
  - ATP ammonia→ urea important
- ATP energizes muscle contraction, releases energy ADP→ bending
- ATP energizes active transport across membranes
- ATP energizes glandular secretion
- ATP energizes nerve conduction
- Phosphocreatine functions as an accessory storage depot for energy and as an ATP buffer
  - phosphocreatine: store of high energy phosphate bonds, more abundant, more energy
  - ATP used to build up phosphocreatine→ storehouse; releases also ATP
- Anaerobic versus aerobic energy
  - carbs can provide energy without O2→ anaerobe
  - glucose→ into pyruvic acid release of 2 ATP; glycogen 3 ATP (best source of energy in anaerobic state→ already phosphorylated)
  - anaerobic energy utilization during hypoxia
    - hem and lungs have O2→ 2 minutes→ then glycolysis
  - anaerobic energy utilization during strenuous bursts of activity is derived mainly from glycolysis
    - anaerobic glycolysis faster, used by exercise 10s to 2 min, lactic acid is the result→ oxidation in liver→ glucose and pyruvic acid→ glucose stored again as glycogen in cell
  - extra consumption of O2 repays the oxygen dept after completion of strenuous exercise
    - O2 used for reconvert lactic acid into→ glucose; ADP→ ATP; creatin and P→ phosphocreatine; rise O2 concentration to normal
    - oxidative process can continue as long fat exists

control of energy release in the cell

- rate control of enzyme-catalyzed reactions
    - rate of reaction is determined by concentration of enzyme and substrate
    - role of enzyme concentration in regulation of metabolic reactions
        - if substrate is high→ rate is determined by enzyme, enzyme saturation
    - role of substrate concentration in regulation of metabolic reactions
    - rate limitation in a series of reactions→ determined by slowest step
    - ADP concentration as a rate controlling factor in energy release
        - ADP decreases with activity; ADP increases with rate of food energy metabolism

metabolic rate

- heat is end product of all energy released in body, just 27% of food used by functional system
- exception is if muscles perform work outside the body
- 1 calorie is the quantity of heat required to raise the temperature of 1 gram water 1°C; 1Calorie=1000 calorie
- measurement of the whole body metabolic rate
    - dirct calorimetry measures heat liberated from the body; heat tight room→ body heats air→ air is cooled→ maintaining temperature
    - indirect calorimetry – the energy equivalent of oxygen
        - quantity of energy liberated per liter of O2 used in the body averages about 4,8 Calories→ called energy equivalent of O2

energy metabolism – factors that influence energy output

- basal metabolic rate, physical activity, processing food, maintain body temperature
- overall energy requirement for daily activities
    - 70kg man in bed 1650 kcal, 2000 kcal performing essential functions
- basal metabolic rate BMR – the minimum energy expenditure for the body
    - 50-70% BMR → minimum level of energy required→ measure rate of O2 utilization
        - sleep, no food, no ativityy, constant temperature,
        - normal 70kcal/h; 30% of BMR resting muscles;
        - lower BMR in woman and older people
    - thyroid hormone increases metabolic rate, BMR higher in colder areas
    - male sex hormone, growth hormone, fever increase metabolic rate
    - sleep, malnutrition decrease metabolic rate
- energy used for physical activities
    - short heavy exercise most increase in metabolic rate
- energy used for processing food – thermogenic effect of food
    - specific dynamic action of protein→ rises metabolic rate long
- energy used for nonshivering thermogenesis – role of sympathetic stimulation
    - brown tissue mitochondria produce heat but no ATP (uncoupled oxidative phosphorylation) due to nor and epinephrine
    - buffer against obesity

chapter 75 pituitary hormones and their control by the hypothalamus

pituitary gland and its relation to the hypothalamus

- the pituitary gland has 2 distinct parts – the anterior and posterior lobes
    - anterior adenohypophysis from epithelium
        - growth hormone; adrenocorticotropin metabolism of glucose, proteins, fats; thyroid stimulating hormone; prolactin milk production; follicle stimulating hormone and luteinizing hormone growth of ovaries and tests
    - posterior neurohypophysis from neural tissue; pars intermedia
        - ADH; oxytocin express milk form glands of brest
- anterior pituitary gland contains several different cell types that synthesize and secrete hormones
    - 1 cell for each major hormone

        - 40% somatropes hGH cidophils; 20% corticotropes ACTH; thyrotropes TSH; gonadotropes LH and FSH; lactropes PRL
- posterior pituitary hormones are synthesized by cell bodies in the hypothalamus
    - hormones are secreted in hypothalamus and transported by neurons in pituitary gland

hypothalamus controls pituitary secretion

- hypothalamus stimulates anterior part by hormones via hypothalamic-hypophysial portal vessels and posterior part by neurons
- hypothalamic- hypophyseal blood vessels
    - hypothalamic releasing and inhibitory hormones are secreted into the median eminence
        - hypothalamic neurons into tuber cinerum (median eminence), endings → secrete hypothalamic releasing and inhibitory hormones into hypophyseal portal system→ control secretion of anterior pituitary hormones
    - hypothalamic releasing and inhibitory hormones control anterior pituitary secretion
        - TRH; CRH; GHRH and GHIH; GnRH; PIH inhibition exception special
    - specific areas in the hypothalamus control secretion of specific hypothalamic releasing and inhibitory hormones

physiological functions of growth hormone

- no target gland→ direct on tissue
- growth hormone promotes growth of many body tissues
    - somatropin, growth of all tissues and cells,
- growth hormone has several metabolic effects
    - increase rate of protein synthesis, mobilization of fatty acids from tissue to energy, decreased rate of glucose utilization→ GH enhances body protein uses fat stores but conserves carbs
    - growth hormone promotes protein deposition in tissues
        - enhancement of amino acid transport through the cell membrane→ in cell, more protein synthesis
        - enhancement or RNA translation to cause protein synthesis by the ribosomes
        - increased nuclear transcription of DNA to form RNA most important in long run
        - decreased catabolism of protein and amino acids
    - growth hormone enhances fat utilization for energy
        - release of fatty acids→ conversion into acetyl co enzyme A→ energy
        - takes longer
        - ketogenic effect of excessive growth hormone
            - too much fat release→ ketosis→ fatty liver
- growth hormone decreases carbohydrate utilization
    - insulin resistance→decrease glucose uptake (muscle, liver), increase glucose production in liver, increased insulin secretion
    - insulin resistance → diabetogenic like diabetes type II
    - rising blood fatty acids→ decrease insulin sensitivity
    - necessity of insulin and carbohydrate for the growth promoting action of growth hormone
        - no growth without pancreas, carbs
- growth hormone stimulates cartilage and bone growth
    - increased deposition of protein by chondrocytic and osteogenic cells that cause bone growth; incrased reproduction of these cells; specific effect of converting chondrocytes into osteogenic cells→ new bone
    - grow in length at epiphyseal cartilage; osteoblaste deposit more new bone thickness increases
- growth hormone exerts much of its effect through intermediate substances called somatomedins (also called insulin like growth factors)
    - GH→ liver forms somatomedins IGF (like insulin)→ increase whole bone growth
    - alternative but not always necessary, pigmens lack somatomedins c
    - short duration of action of growth hormone but prolonged action of somatomedin C
- regulation of growth hormone secretion
    - GH secretion decease with age

    - stimulation by starvation by severe protein deficiency; hypoglycemia or low concentration of fatty acids in blood; exercise; excitement; trauma; ghrelin (before meals);
    - decreased by: glucose; free fatty acids; obesity; aging;
    - only adding of proteins reduces growth hormone in starvation
    - role of the hypothalamus, growth hormone-releasing hormone and somatostatin (inhibition) in the control of growth hormone secretion
        - GHRH by ventromedial nucleus which is sensitive to blood glucose, hunger, satiety→ nutrition alters GH
        - emotional, stress, trauma increase GH
        - GHRH more important→ receptors→ adenylyl cyclase sytem inside cell membrane→ increasing cAMP→ Ca influx and release of GH
        - GH secretion by negative feedback mechanism
        - long term regulation by protein nutrition
- abnormalities of growth hormone secretion
    - panhypopituitarism: decreased secretion of all hormones of anterior hypophysis
    - dwarfism: from panhypopituitarism in childhood; proportions equal; never develop sexual functions; 30% just GH absent, Lorain dwarf normal GH but lack of somatomedin C
        - therapy: maybe from some monkeys GH, human GH from e.coli
    - panhypopituitarism in the adult: craniopharyngiomas, chromophobe tumors→ compression; thrombosis of pituitary blood vessels if mother develops circulatory shock
        - hypothyroidism, depressed production of glucocorticoids and gonadotropic hormone→ gain weight, lost sexual functions,
    - gigantism: excess GH, tumor, 2,5m if epiphyse is still open, hyperglycemia→ diabetes mellitus
    - acromegaly: membranous bones enlarge, thicker bones, organs enlarge but not size
    - lack of GH in age: more fat, lock older, less protein content but therapy cause insulin resistance

posterior pituitary gland and its relation to the hypothalamus

- neurohypophysis, glial cells, pituicytes, fibers from supraoptic (ADH) and paraventricular (oxytocin)nucleus,
- ADH and oxytocin chemical very similar→ if pituitary stalk is cut→ continue secretion; carried by neurophysins
- physiological functions of ADH
    - cause collecting tubules to be permeable to water, prevent fluid loss
    - ADH→ cAMP→ vesicles have pores fuse with membrane→ permeability
    - regulation of ADH production
        - increased extracellular fluid osmolarity stimulates ADH secretion
            - change in minutes, hyperosmolarity→ osmoreceptors  decrease size
    - low blood volume and low blood pressure stimulate ADH secretion – vasoconstrictor effects of ADH
        - higher amounts cause vasoconstriction→ increase pressure
        - stimulated by decreased blood volume signals from atria stretching
- oxytocic hormone
    - oxytocin causes contraction of the pregnant uterus
    - oxytocin aids in milk ejection by the breasts
        - suckling stimulates nipple→ signals to oxytocin neurons→ in blood to breasts→ contraction of myoepithelial cells→ milk letdown

chapter 76 thyroid metabolic hormones

synthesis and secretion of the thyroid metabolic hormones

- 93% thyroxine T4; 7% triiodothyronine T3 stronger but less present
- physiologic anatomy of the thyroid gland
    - follicles filled with colloid (thyroglobulin) must be reabsorbed back through follicular epithelium→ blood, high blood flow
- iodine is required for formation of thyroxine
    - fate of ingested iodides
        - 20% are absorbed by thyroid gland, 80% excreted
- iodide pump – the sodium-iodide symporter (iodide trapping)

    - 2 sodium- 1 iodide symporter from blood into cell (energy from Na-K pump concentration gradient)→ from cell into follicle by chloride-iodide ion counter transport molecule called pendrin
    - rate iodide trapping by concentration of TSH
- thyroglobulin and chemistry of thyroxine and triiodothyronine formation
    - formation and secretion of thyroglobulin by the thyroid cells
        - ER and golgi→ thyroglobulin contain tyrosine amino acids →thyroid hormones form within the thyroglobulin molecule
    - oxidation of the iodide ion
        - iodine→ oxidation by peroxidase (if absent no thyroid hormone), H+peroxide to nascent iodine I or I3→ combine with tyrosine
    - iodination of tyrosine and formation of the thyroid hormones – organification of thyroglobulin
        - organification: iodine + thyroglobulin
        - tyrosine→ monoiodotyrosine→diiodotyrosine
        - 2 diiodotyrosin= thyroxine T4; diiodotyrosine + monoiodotyrosine= triiodothyronine T3
    - storage of thyroglobulin
        - each thyroglobulin contain 30 thyroxine; 2-3 month supply unusual; stored in follicle
- release of thyroxine and triiodothyronine from the thyroid gland
    - thyroglobulin not released
    - T4, T3 cleaved from thyroglobulin; pinocytic vesicles, lysosomes→ T4, T3 into blood capillaries
    - ¾ of thyodine never becomes hormone→ iodine recycled by deiodinase (lack→ iodine deficiency)
    - daily rate of secretion of T4 and T3
        - most T4 converted into T3, mainly T3 delivered to tissue
- transport of T4 and T3 to tissues
    - T4 and T3 are bound to plasma proteins
    - T4 and T3 are released slowly to tissue cells
        - due to high affinity of T4 to plasma binding proteins, T3 lower affinity
        - stored also in target cells
    - T4 have slow onset and long duration of action
        - T4 does max effect after 10 days; T3 max effect after 3 days

physiological functions of the thyroid hormones

- T4 increase the transcription of large numbers genes
    - activate nuclear transcription of many genes
- most of the T4 secreted by the thyroid is converted to T3→ remove of iodine by iodinase before transcription
- thyroid hormones activate nuclear receptors
    - thyroid hormone receptor forms heterodimer with RXR receptor at DNA→ become active if by binding→ transcription→ proteins
    - also nongenomic cellular effects on cAMP, ion channels
- thyroid hormones increase cellular metabolic activity
    - BMR up to 100%, increase growth rate, mental process, food utilization
    - thyroid hormones increase the number and activity of mitochondria
    - thyroid hormones increase activity transport of ions through cell membranes
        - more permeable to Na ions, increase Na K pump activity
- effect of thyroid hormone on growth
    - rapid growth, brain development
- effects of thyroid hormone on specific bodily mechanisms
    - stimulation of carbs metabolism: fast glucose uptake, glycolysis, gluconeogenesis, absorption, more insulin
    - stimulation of fat metabolism: lipids mobilized from fat tissue→ decrease fat store
    - effect on plasma and liver fats: decrease cholesterol, phospholipids, triglycerides but increase free fatty acids; decrease cause deposit of fat
    - increased requirement for vitamins, hyperthyroidism→ cause lack of vitamins
    - increased BMR
    - decreased body weight sometimes counterbalance because the increase appetite
    - effect of thyroid hormones on the cardiovascular system

        - increase blood flow and cardiac output: more O2 needed, vasodilation→ increased blood flow
        - increased heart rate: excessive or diminished thyroid hormone
        - increased heart strength: long term protein use→ death
        - normal arterial pressure: but pulse pressure increases
        - increased respiration: rate and depth
        - increased gastrointestinal motility: more secretion, diarrhea
        - excitatory effects on the central nervous system:
        - effect on the function of the muscles: moderate makes them stronger, excess weak because of protein usage
        - muscle tremor: hand vibration
        - effect on sleep: always tierd but difficult to sleep; hypothyroidism→ sleep to 12h
        - effect on other endocrine glands: increased glucose consumption→ increased insulin, increase in parathyroid hormone
        - effect on thyroid hormone on sexual function: lack less libido, excess impotence,

regulation of thyroid hormone secretion

- TSH increases thyroid secretion
    - increased proteolysis of the thyroglobulin→ release of hormone
    - increased activity of the iodide pump→ increase iodine trapping
    - increased iodination to tyrosin to form the thyroid hormones
    - increased size and increased secretory activity of the thyroid cells
    - increased number of thyroid cell cuboidal to columnar cells
- cyclic adenosine monophosphate mediates the stimulatory effect of TSH→ protein kinase-→multiple phosphorylation
- anterior pituitary secretion of TSH is regulated by thyrotropin-releasing hormone from the hypothalamus
    - TRH→ TSH, if blood flow is cut TSH is not zero
    - bind to TRH receptors on pituitary cell membrane→ phospholipase 2nd messenger→ phospholipase C→ Ca diactyle glycerol→ TSH release
    - effects of cold and other neurogenic stimuli on TRH and TSH secretion→ mediated by hypothalamus
        - cold increase TRH and TSH secretion
        - excitement and anxiety cause decrease in TSH
- feedback effect of thyroid hormones to decrease anterior pituitary secretion of TSH
    - T4, T3 decrease secretion of TSH by direct inhibition not via hypothalamus, constant levels
- antithyroid substances suppress thyroid secretion
    - thiocyanate ions decrease iodide trapping: inhibition of iodide transport, rise in TSH→ enlargement of thyroid gland
    - propylthiouracil decrease thyroid hormone formation: prevent formation of thyroid hormone from iodides and tyrosine, block peroxidase (coupling)→ TSH, enlargement of thyroid gland
    - iodided in high concentrations decrease thyroid activity and thyroid gland size: decrease rate of iodide trapping???, decreased bleeding by surgery

disease of the thyroid

- hyperthyroidism
    - caused by toxic goiter, thyrotoxicosis, graves disease
    - increased gland size, increased secretion, autoimmune disease→ antibodies TSI bind same membrane receptors as→ continuous stimulation of thyroid gland→ high level hormone secretion→ TSH to 0
    - thyroid adenoma: secretes huge amounts of hormone, depress TSH production
- symptoms of hyperthyroidism
    - high excitability, intolerance to heat, increased sweating, weight loss, diarrhea, muscle weakness, nervous, tired, shaking hands
    - exophthalmos: eyeball protrusion, eye damage, autoimmune, edema in eye
    - diagnostic tests for hyperthyroidism
        - BMR, TSH concentration, TSI,
    - treatment in hyperthyroidism

        - removal of gland
        - radioactive iodine destroy cells
- hypothyroidism
    - autoimmune against gland hashimotot disease, destruction not stimulation,
    - edemic goiters→ lack of iodine
    - no thyroid hormones in blood→ increased TSH→ increasing in size and production of thyroid gland but no iodide present→ just production of thyroglobulin→ follicles increase in size
    - idiopathic nontoxic colloid goiter
        - no iodide deficiency, secretion is depressed, signs of mild thyroditis TSH elevated
        - no iodide trapping, no peroxidase,
    - physiological characteristics of hypothyroidism
        - fatigue, slow heat rate, weak muscles, decreased co, increased body weight, decrease hair growth,
    - myxedema: swelling of face, increased fluid in interstitial tissue
    - atherosclerosis: increased cholesterol→ deafness, coronary artery disease
    - diagnostic tests in hypothyroidism: low BMR, low T4,3, high TSH
    - treatment of hypothyroidism: T4 ingestion,
    - cretinism: extreme hypothyroidism,  no body growth

chapter 77 adrenocortical hormones

synthesis and secretion of adrenocortical hormones

- the adrenal cortex has three distinct layers
    - zona glomerulosa: under cortex, secrete aldosterone stimulated by angiotensin II and potassium
    - zona fasciculate: cortisol, corticosterone, adrenal androgens, estrogen controlled by ACTH
    - zona reticularis: androgens DHEA and androstenedione, estrogen controlled by ACTH
- adrenocortical hormones are steroids derived from cholesterol
    - all steroid hormones are synthesized from cholesterol
    - 80% of cholesterol form LDL, also de novo cholesterol→ uptake by adrenocortical cell membrane Endocytosis
    - ACTH (but also K and  angiotensin II)→ increase receptors for LDL and activity of enzymes for LDL degradation→ cholesterol into cell→ form pregnenolone (rate limiting step)
    - synthetic pathways for adrenal steroids
        - formation occur in mitochondria and ER
    - adrenocortical hormones are bound to plasma protein
        - 95% of cortisol binds to plasma proteins globulin and more less to albumin; half life 60-90%
        - 60% of aldosterone bind with plasma protein; half life 20min
        - → uniform distribution without fluctuation
    - adrenocortical hormones are metabolized in the liver
        - excretion by bile and kidney

functions of the mineralocorticoids – aldosterone

- mineralocorticoid deficiency causes severe renal sodium chloride wasting and hyperkalemia
    - total loss of mineralocorticoid→ rapid loss of NaCl and rise of K+→ decrease in extracellular fluid and blood volume→ death
    - lifesaving hormones
- aldosterone is the major mineralocorticoid
    - aldosterone 90% of activity 3000 times more then cortisol but 2000 higher concentration
    - renal epithelial cell convert cortisol to cortisone by 11β
    - lack of 11β→ excess cortisol called apparent mineralocorticoid excess syndrome AME
- renal and circulatory effects of aldosterone
    - aldosterone increases renal tubular reabsorption of sodium and secretion of potassium
        - in principal cells of collecting tubules
    - excess aldosterone increases extracellular fluid volume and arterial pressure but has only a small effect on plasma sodium concentration
        - due to co absorption of water

        - aldosterone escape→ rise in pressure→ again excretion of salt and water → +-0 gain of water and salt but hypertension and excess aldosterone
        - 0 aldosterone decrease ECF and circulatory shock
    - excess aldosterone causes hypokalemia and muscle weakness; too little aldosterone causes hyperkalemia and cardiac toxicity (weak heart contraction, arrhythmia, )
        - K lost in urine and transported into cells
    - excess aldosterone increases tubular H+ ion secretion in exchange for Na in intercalated cells and causes alkalosis
- aldosterone stimulates sodium and potassium transport in sweat glands, salivary glands and interstitial epithelial cells
    - increases reabsorption of NaCl in sweat and salivary glands but secretion of K+
    - also increases  Na absorption in intestine, colon
- cellular mechanism of aldosterone action
    - aldosterone lipid soluble→ diffuse into cell→ binds to MR receptor protein→ into nucleus→DNA→ RNA→ protein → enzymes for electrolyte transport like NA-K pump, epitheilia sodium channel (ENac)
    - wait 45 minute for effect
- possible nongenomic actions of aldosterone
    - increase cAMP
- regulation of aldosterone secretion
    - aldosterone secretion is independent
    - increased K in ECF increases aldosterone
    - increased angiotensin II in ECF increases aldosterone
    - increased Na slightly decrease aldosterone
    - ACTH necessary for secretion but no effect of rate, permissive role

function of the glucocorticoids

- in long run as important as mineralocorticoid
- 95% of activity from cortisol
- effects of cortisol on carbohydrate metabolism
    - stimulation of glucogenesis
        - cortisol increases the enzyme required to convert amino acids into glucose in liver via DNA transcription
        - cortisol causes mobilization of amino acids from the extrahepatic tissues mainly from muscle → more aa in blood
        - increased glycogen storage in liver
    - decreased glucose utilization by cells, delay NAD to NADH (necessary for glycolysis)
    - elevated blood glucose concentration and adrenal diabetes→ stimulates insulin but cells are insensitive to insulin due to glucocorticoids→ adrenal diabetes
- effects of cortisol on protein metabolism
    - reduction in cellular protein but not in liver, weak muscles less RNA formation
    - cortisol increases liver and plasma proteins→ cortisol enhances aa transport to liver
    - increased blood amino acids, diminished transport of amino acids into extrahepatic cells and enhanced transport into hepatic cells→ increase protein and plasma protein formation in liver, aa→ to glucose
- effects of cortisol on fat metabolism
    - mobilization of fatty acids→ more in blood→ energy; enhanced oxidation of fats; use of fats is important to maintain body glucose and glycogen
    - obesity caused by excess cortisol, stimulated by excess food intake fat storage in chest and head→ buffalo look fat generated in some tissue more quickly
- cortisol is important in resting stress and inflammation
    - stress (infection, inflammation, cold, surgery)→ ACTH→ cortisol
    - cause aa and fat release for energy
    - inflammation can be more damaging than disease itself
    - anti-inflammatory effects of high levels of cortisol

        - 5 steps of inflammation: damaged tissue releases chemicals→ activate inflammation→ increased blood flow called erythema→ leakage of plasma→ clotting of interstitium edema→ leukocytes infiltration→ ingrowth of fibrous tissue
        - cortisol inhibit early inflammation or stop of inflammation and faster healing
        - cortisol prevents the development of inflammation by stabilizing lysosomes and by other effects
            - stabilized lysosomal membrane, decrease permeability of the capillaries , decrease migration of white blood cells into the inflamed area and phagocytosis of the damaged cells, suppresses the immune system causing lymphocytes reproduction to decrease markedly, attenuates fever mainly because it reduces the release of interleukin-1 from the white blood cells
        - cortisol causes resolution of inflammation
            - but rate of healing is enhanced→ use of aa to repair, extra glucose and fat
- other effect of cortisol
    - block response to allergic reactions prevent shock or death
    - decrease eosinophils and lymphocytes
    - decrease output of T cells and antibodies from lymphoid tissue→ death by normal diseases
    - no immune reaction to transplanted organs
    - increase RBC
- cellular mechanism of cortisol action
    - receptors in target cell because lipid soluble diffusion in cell→ hormone receptor complex act on DNA
- regulation of cortisol secretion by adrenocorticotropic hormone from the pituitary gland
    - ACTH stimulates cortisol secretion
    - chemistry of ACTH
    - ACTH secretion is controlled by corticotrophin-releasing factor CRF essential from the hypothalamus
    - ACTH activates adrenocortical cells to produce steroids by increasing cAMP→ enzyme formation of adrenocortical hormones
        - most important is enzyme protein kinase A which cause initial conversion of cholesterol to pregnenolone → this is rate limiting step; ACTH is NECESSARY for secretion
    - physiological stress increased ACTH and adrenocortical secretion
        - physiological, mental stress, damage, trauma → ACTH
        - inhibitory effect of cortisol on the hypothalamus and on the anterior pituitary to decrease ACTH secretion
    - summary of the cortisol control system
- cardiac rhythm of glucocorticoid secretion
    - CRF high in morning low in evening
- synthesis and secretion of ACTH in association with melanocyte-stimulating hormone, lipotropin and endorphin
    - ACTH causes several other hormones secretion POMC, MSH (appetite, skin pigment melanin but ACTH more important), lipoprotein, endorphin → no effect just if ACTH is very high like in addisons disease

adrenal androgens

- important in fetal life; dehydroepiandrosterone; female growth of pubic hair; some converted into testosterone

abnormalities of adrenocortical secretion

- hypoadrenalism adrenal insufficiency – addisons disease
    - 80% autoimmune against cortices, cancer, no adrenocortic hormones, fail of ACTH
    - mineralocorticoid deficiency
        - lack of aldosterone→ ECF decreases, hyponatremia, hyperkalemia, acidosis, plasma volume decreases, RBC rise, CO and BP decrease
    - glucocorticoid deficiency: loss of cortisol secretion makes it impossible for a person with addisons disease to maintain normal blood glucose between meals→ no gluconeogenesis, no aa and fat release

    - melanin pigmentation: because no cortisol→ no negative feedback→ no ACTH inhibition→ pigmentation due to excess ACTH MSH
    - treatment administration of gluco and mineralocoticoids
- hyperadrenalism – cushings syndrome
    - caused by adenomas excess ACTH, abnormal hypothalamus excess CRH, adenomas of adrenal cortex
    - → mainly excess cortisol
    - dexamethasone test ACTH independent or not; 25% ACTH decreases due to negative feedback
    - cause→ fat in buffalo form, acne, moon face edema,
    - effects on carbs and protein metabolism
        - increase blood glucose, enhanced gluconeogenesis, decreased utilization of tissue,
        - aa loss from muscles, weakness, osteoporosis
        - → cut adrenal gland or block steroidogenesis, destroy tumor
    - primary aldosteronism
        - tumor→ excess aldosterone , muscle weakness due to hypokalemia, decreased renin as indicator
    - adrenogenital syndrome
        - excess androgens→ masculinization

chapter 78 insulin, glucagon and diabetes mellitus

- isles of Langerhans: glucagon and insulin; acini: digestive juice
- alpha cells: glucagon; alpha cells:insulin, amylin; delta: somastotatin

insulin and its metabolic effects

- insulin is a hormone associated with energy abundance
    - store excess energy as glycogen in liver and muscles→ to much carbs stored as glycogen by insulin as fats
    - insulin promotes aa uptake and conversion into proteins, inhibit breakdown of proteins
- insulin chemistry and synthesis
    - synthesized by beta cells; plasma half life of 6 minutes; cleared after 15 minutes → turn off and on insulin effect rapidly→ degraded in liver by insulinase
- activation of target cell receptors by insulin and the resulting cellular effects
    - insulin→ receptor on cell surface, enzyme lined receptor→ autophosphorylation on inside→ activate tyrosin kinase→ phosphorylation of other intracellular enzymes like IRS →
        - cell increase glucose uptake by glucose transport proteins for muscle and adipose cells (no neurons in brain)
        - cell more permeable to many aa, k, p, → inside
        - insulin remodels cellular enzymatic machinery
- effect of insulin on carbohydrate metabolism
    - carbs→ insulin→ glucose uptake by muscles, liver, adipose tissue
    - insulin promotes muscle glucose uptake and metabolism
        - muscle normally takes fat because membrane is just slightly permeable for glucose
        - exercising muscle more permeable to glucose
        - after meal excess insulin→ muscle uses glucose, more permeable
        - storage of glycogen in muscle if muscle is not exercising
        - quantitative effect of insulin to assist glucose transport through the muscle cell membrane
        - insulin can increase the rate of transport of glucose into the resting muscle cell by 15 fold
    - insulin promotes liver uptake, storage and use of glucose
        - insulin inactivates liver phosphorylase→ prevent breakdown of glycogen to glucose
        - increase activity of glucokinase→trapps glucose by phosphorylation
        - increase glycogen synthesis by glycogen synthase
        - → increase glycogen in liver
        - glucose is released from liver between meals
            - decreased blood glucose→ decreased insulin→ stopping syntheses of glycogen and prevent glucose uptake by liver→ lack of insulin splitting of glycogen into glucose phosphate→ glucose diffuse back into blood

        - insulin promotes conversion of excess glucose into fatty acids and inhibits gluconeogenesis in the liver
            - glucose exceeds storing capacity of liver→ glucose into fatty acids → adipose tissue
    - lack of effect of insulin on glucose uptake and usage by the brain
        - brain cells are permeable to glucose do not need insulin, use only glucose→ to low hypoglycemic shock
    - effect of insulin on carbohydrate metabolism in other cells increase transport and utilization
- effect of insulin on fat metabolism
    - long term lack of insulin→ atherosclerosis, heart attacks, cerebral shocks
    - insulin promotes fat synthesis and storage by
        - insulin sparse fat; promote fatty acid synthesis
          excess glucose forms fat
        - ions from citric cycle→ from acetyl-CoA carboxylase (first step of fatty acid)
        - formation of triglycerides in liver→ lipoprotein→ uptake form adipose tissue
        - role of insulin in storage of fat in the adipose cells
            - inhibit hormone sensitive lipase→ inhibit release of fatty acids from adipose tissue
            - promotes glucose uptake of fat cells→ syntheses of fatty acids
    - insulin deficiency increased use of fat for energy
        - insulin deficiency causes lipolysis of storage fat and release of free fatty acids→ become main energy source; rise blood glucose, fatty acids, acetoacetic acid
        - insulin deficiency increases plasma cholesterol and phospholipid concentration→ high lipid concentration→ atherosclerosis
        - excess usage of fats during insulin lack causes ketosis and acidosis
            - increased transport of fats into mitochondria→ formation of acetyl –CoA→ acetoacetic acid
            - lack of insulin→ inhibit utilization of acetoacetic acid in peripheral tissue→ acidosis also excess keton bodies
- effect of insulin on protein metabolism and on growth
    - insulin promotes protein synthesis and storage
        - insulin stimulates transport of many of the amino acids into the cell
        - increases translation of mRNA, RNA increase ribosome work→ protein formation
        - insulin inhibits the catabolism of proteins→ no release of proteins
        - depresses rate of gluconeogenesis conserve proteins
    - insulin deficiency causes protein depletion and increases plasma amino acids→ protein wasting severe, gluconeogenesis or used for direct energy
    - insulin and growth hormone interact synergistically to promote growth; alone no effect
- mechanisms of insulin secretion
    - insulin rise proportional to blood glucose
    - GLUT 2 transporters in beta cells cause glucose influx → glucose phosphorylated to glucose 6 phosphate by glucokinase (rate limiting) → form ATP→ inhibit K channels → depolarization of cell membrane→ Ca channels open→ secretion of insulin
- control of insulin secretion
    - increased blood glucose stimulates insulin secretion
        - increase in 2 stages
            - insulin increases 10 fold by 3-5 minutes→ decrease back to normal in 5-10 minutes→ after 15 minutes insulin rises a second time reach plateau in 2-3 h
    - feedback relation between blood glucose concentration and insulin secretion rate
- other factors that stimulate insulin secretion
    - aa: little alone but multiply effect together with glucose
    - gastrointestinal hormones:  increase sensitivity of insulin receptors, double effect
    - (glucagon), GH, cortisol, estrogen,→ to long present→ diabetes mellitus
    - parasympathetic pancreas stimulation
- role of insulin and other hormones in switching between carbohydrate and lipid metabolism
    - insulin use carbs but depress fat utilization
    - blood glucose is switch mechanism between energy usage

- GH, cortisol→ secreted in response to hypoglycemia→ promoting fat utilization stop carbs usage; epinephrine→ releasing glucose by stress gluconeogenesis and release fats by lypolytic effect usage; glucagon

glucagon and its functions

- secreted by alpha cells→ active by low blood glucose→ increase blood glucose; hyperglycemic hormone
- effects on glucose metabolism
  - glucagon causes glycogenolysis and increased blood glucose concentration
    - glucagon→ activates adenylyl cyclase in hepatic cell membrane→ cAMP→ protein kinase regulator protein→ protein kinase→ phosphrylase b kinase→ into phsophorylase a→ glycogen into glucose 1 phosphate→ removal of p→ glucose released in blood
    - second messenger function, kaskading system every next product in higher quantity→ amplifying
  - glucagon increases gluconeogenesis
    - aa uptake by liver and conversion to glucose, pyruvate to p pyruvate rate limiting
  - other effects of glucagon
    - activates adipose cell lipase→ more free fatty acids; prevent liver from removing fatty acids; enhances heart strength; increased blood flow in kidneys; more bile; inhibit gastric secretion
- regulation of glucagon secretion
  - increased blood glucose inhibits glucagon secretion
  - increased blood amino acids stimulate glucagon secretion (but also insulin)→ glucagon converts aa into glucose;
  - exercise stimulates glucagon secretion→ prevents decrease in blood glucose

somatostatin inhibits glucagon and insulin secretion

- delta cells of islets of Langerhans secrete somatostatin
- stimulated by: increased blood glucose, aa, fatty acids, gastrointestinal hormones
- inhibitory effect on: depress insulin and glucagon; decreases gastrointestinal motility and decreases secretion and absorption
- → make food longer available, GHIH

summary of blood glucose regulation

- 80-90mg/100ml blood glucose
- liver is glucose buffer; low blood glucose→ epinephrine increases release of glucose; hypoglycemia→ GH and cortisol activation→ fat utilization→ return blood glucose towards normal
- insulin more important then glucagon→ is in exercise and stress important
- importance of blood glucose regulation
  - glucose level maintenance is important because brain, retina, germinal epithelium of gonads exclusively use glucose
  - glucose from gluconeogenesis into brain, if insulin is present glucose would go to muscles
  - glucose to high→ cellular dehydration, loss in urine→ cause diuresis of kidneys, damage of blood vessels, stroke, blindness

diabetes mellitus

- type I: insulin dependent diabetes mellitus→ lack of insulin secretion
- type II: non insulin dependent diabetes mellitus→ decreased sensitivity of target tissue towards insulin
- type I diabetes – deficiency of insulin production by beta cells of the pancreas
  - viral infections, autoimmune, age 14, but can occur at any age; 5-10%
  - blood glucose concentration rises to high levels in diabetes mellitus
  - increased blood glucose causes loss of glucose in the urine; 180mg/100ml is threshold for excretion
  - increased blood glucose causes dehydration→ increased osmotic pressure→ water out of cells; decrease water reabsorption of kidneys because shift of concentration gradient to urine→ water follows glucose in urine
  - chronic high glucose concentration causes tissue injury

        - decreased blood supply→ kidneys disease, stroke, heart attack, blindness, ischemia, gangrene, damage of nerves
    - diabetes mellitus causes increased utilization of fats and metabolic acidosis
        - shift to fat metabolism→ keto acids→ acidosis under 7pH → diabetic coma
        - prevent by increased ventilation and kidney buffer
    - diabetes causes depletion of the bodies proteins
        - weight loss, lack of energy,
- type II diabetes – resistance to the metabolic effects of insulin
    - after age of 30, obesity biggest risk
    - obesity, insulin resistance, metabolic syndrome usually precede development of type II diabetes
        - increased plasma insulin concentration→ compensatory response but later beta cells become exhausted
        - metabolic syndrome: obesity; insulin resistance; hyperglycemia; lipid abnormalities; hypertension → cardiovascular disease
        - insensitivity or damage of insulin receptors
    - other factors that can cause insulin resistance and type II diabetes
        - excess GH, mutations of insulin receptor, pregnancy, obesity
        - PCOS: increase ovarian androgen, insensitivity,
    - development of type II diabetes during prolonged insulin resistance
        - depends on how long pancreas can adapt and excrete excess amounts of insulin
        - in early stages prevention with exercise, caloric restriction, weight reduction
        - thiazolidinediones→ increase insulin sensitivity; metformin→ suppress liver glucose production; sulfonylureas→ additional release of insulin by pancreas
- physiology of diagnosis of diabetes mellitus
    - urinary glucose; fasting blood glucose over 110mg/100ml;
    - after meal insulin is absent in type I and present in large amounts in type II
    - glucose tolerance test: glucose uptake→ after 2 h still elevated, do not fall back under control beginning level
    - acetone breath: not in early stages
- treatment of diabetes
    - severe type I: 1 single dose of long lasting action
    - people develop immunity against animal insulin
    - relation of treatment to arteriosclerosis
        - due to circulating cholesterol,
- insulinoma – hyperinsulinism
    - excess production of insulin→ hypoglycemia
    - insulin shock and hypoglycemia
        - 50-70mg/100ml neurons become extremely excitable

chapter 79 parathyroid hormone, calcitonin, calcium and phosphate metabolism, vitamin D, bone and teeth

overview of calcium and phosphate regulation in the extracellular fluid and plasma

- hypocalcemia: nervous system more excited
- calcium in the plasma and interstitial fluid
    - 41% bound to plasma protein; 9% diffusible bound to anions; 50% diffusible and ionized
- inorganic phosphate in the extracellular fluid
    - 85% stored in bones; 14% in cell; 1% in ECF; not so well regulated as Ca
- nonbone physiologic effects of altered Ca and P concentration in the body
    - P change no big effect
    - hypocalcemia causes nervous system excitement and tetany→ more leaky to Na→ self excitation→ tetany, seizures, by reduction of 35% lethal at 4mg/dl
    - hypercalcemia depress nervous system and muscle activity, slow reflex, no appetite,
- absorption and excretion of calcium and phosphate
    - interstitial absorption and fecal excretion of calcium and phosphate
        - 90% of Ca uptake excreted in feces; almost all P is absorbed but later excreted in urine
    - renal excretion of Ca and P→ secretion and absorption depends on concentration in blood and ECF
        - renal tubules reabsorbe 99% of Ca, overflow mechanism by P

bone and its relation to extracellular Ca and P

- organic matrix of bone 30%: 95% collagen, ground substance ECF + proteoglycans
- bone salts 70%: Ca, P crystals hydroxyapatite; mg, na, k and radioactive compounds and other elements can bind to bone
- tensile (collagen) and compressional (salts) strength of bone
- precipitation and absorption of Ca and P in bone – equilibrium with the extracellular fluids
    - hydroxyapatite does not precipitate in ECF despite supersaturation of Ca and P→ inhibitor is pyrophosphate
    - mechanism of bone calcification
        - osteoblasts produce osteoid (collagen + ground substance)
        - Ca salts precipitate on the surface of the collagen→ forming nidi → hydroxyapatite crystals
        - few remain in armorphous form→ important they can be absorbed in ECF
    - precipitation of Ca in nonosseous tissues under abnormal conditions→ arteriosclerosis, old blood clots
- Ca exchange between bone and extracellular fluid
    - adding and loss of Ca quickly equilibrated due to exchangeable Ca in all tissues (liver GI) and bone
- deposition and absorption of bone – remodeling of bone
    - deposition of bone by the osteoblasts, constantly
    - absorption of bone – function of the osteoclasts (villi projections, ruffled border, proteolytic enzymes, acids) stimulated by PTH (PTH→ bind to osteoblasts→ release OPGL or RANK→ activate preosteoclasts to osteoclasts→ reabsorb bone);
        - osteoblasts also inhibit OPGL with OPG (estrogen stimulated it, but vitamin D and PTH inhibit OPG)
    - bone deposition and absorption are normally in equilibrium
        - except by growing bone; osteoclasts form tunnel→ is invaded by osteoblasts→ new bone develop in layers called lamellae, haversian canal is remain, osteon
    - value of continual bone remodeling
        - replacement of old bone, strength and bone stress, shape rearranged
    - control of the rate of bone deposition by bone stress
        - more load→ thicker bone;
    - repair of a fracture activates osteoblasts→ bone stress to accelerate fracture healing

vitamin d

- cholecalciferol vitamin D3 is formed in the skin
    - formed in skin by UV light and 7-dehydrocholesterol
- cholecalciferol is converted to 25-hydroxycholecalciferol in the liver→ high feedback prevents excessive action of vitamin D, converse it for further use in vitamin D form
    - high vitamine D uptake has little effect on 25 dihydroxycholecalciferol
- formation of 1,25-dihydroxycholecalciferol (active form of vitamin D) in the kidneys and its control by parathyroid hormone; essential for vitamin D function, conversion requires PTH → absorbes Ca in intestine
- Ca ion concentration controls the formation of 1,25-dihydroxycholecalciferol
    - Ca prevent 25 hydroxycholecalciferol conversion to 1,25 dihydroxycholecalciferol
    - Ca inhibits PTH secretion
    - slight decrease in plasma Ca→ increase 1,25 dihydroxycholecalciferol
- actions of vitamin D
    - hormonal effect of vitamin D to promote intestinal Ca absorption→ increase calbindin a Ca binding protein, proportional, stays several weeks in brush border, Ca ATP
    - vitamin D promotes P absorption by the intestines
    - vitamin D decreases renal Ca and P excretion→ increase reabsorption
    - effect of vitamin D on bone and its relation to parathyroid hormone activity
        - excess D→ bone absorption
        - absence of D → PTH bone absorption is reduced
        - vitamin D in small quantities promote bone calcification

parathyroid hormone

- physiologic anatomy of the parathyroid glands; PTH from chief cells, 1 gland still enough
- chemistry of PTH: kidney remove hormone quickly but not all fragments→ still active
- effect of PTH on Ca and P concentration in the ECF
    - parathyroid hormones increased Ca and P absorption from bone
        - rapid phase of Ca and P absorption from bone – osteolysis
            - PTH removes bone salts from matrix adjacent to osteoblasts
            - osteocytic membrane system separates the bone itself from ECF→ bone fluid in between→ Ca ions pumped from bone fluid into ECF activated by PTH by increasing Ca permeability
        - slow phase of bone absorption and Ca P release – activation of the osteoclasts
            - PTH→ activates osteocytes and blasts→ signals to osteoclasts OPGL→ activation and proliferation of osteoclasts
            - can lead to weak bone and to stimulation of osteoblasts
    - PTH decreases Ca excretion and increase P excretion by the kidneys
        - inhibit tubular reabsorption of P→ loss of P
        - increase absorption of Ca, Mg, H+, diminish reabsorption of Na, K, AA
    - PTH increases intestinal absorption of Ca and P, cAMP
- control of PTH secretion by Ca ion concentration
    - hyperthrophy by rickets lack of Ca, lactation, pregnancy
    - decreased activity: excess Ca diet, increased vitamin D, bone absorption other then caused by PTH
    - changes in ECF→ sensed by CaSR PTC→ if stimulated activate phospholipase C→ increase IP3 (intracellular inostiol), DAG (diacylglycerol)→ Ca release from stores → decrease PTH in turn
    - small deflection causes strong feedback
    - PTH: bone reabsorption; ca reabsorption kidney p excretion; vitamin D pathway intestine Ca absorb

calcitonin from thyroid gland

- increased plasma Ca concentration stimulates calcitonin secretion
    - increased Ca→ increase calcitonin, weak feedback system
- calcitonin decreases plasma Ca concentration
    - decrease absorptive activities of the osteoclasts, osteolytic effect of osteocytic membrane, formation of new osteoclasts
- calcitonin has a weak effect on plasma Ca concentration in the adult human
    - PTH feedback is stronger, bigger effect in children and in disease

summary of control of Ca ion concentration

- buffer function of the exchangeable Ca in bones – the first line of defense and exchangeable Ca also in liver and mitochondria
- hormonal control of Ca ion concentration – the second line of defense
    - long term Ca control due to PTH and vitamin D

pathophysiology of parathyroid hormone, vitamin D and bone disease

- hypoparathyroidism:
    - PTH decreased→ osteocytic Ca reabsorption decreases + osteoclasts inactive→ Ca decreases→ tetany in laryngeal muscles
    - P increase
    - treatment with vitamin D in extremely high amounts ( and PTH)
- primary hyperparathyroidism:
    - tumor mainly in women due to pregnancy
    - excess PTH→extreme osteoclastic activity bone eaten away→ Ca increase P decrease, high alkaline P as diagnostic,
    - weak muscles, depression CNS, $CaHPO_4$ crystals in lung parathyroid poisoning, kidney stones (excess excretion),
    - secondary hyperparathyroidism result of hypocalcemia caused by vitamin D lack renal disease
- rickets caused by vitamin D deficiency
    - lack of vitamin D→ slightly Ca decrease but big P decrease

    - in spring month after depletion of stores
    - Ca decline prevent by PTH but eat bone, no regulatory mechanism for P→ decline
    - rickets develop, tetany later if no Ca store anymore
    - treatment: diet Ca, P, vitamin D
    - osteomalacia: steatorrhea (failure to absorbe fat); adults seldom have rickets no new bones must growth,
        - vitamin d resistanc rickets: may be due to kidney damage→ do not form active from of vitamin D 1,25…→ treated by P
- osteoporosis
    - poor bone matrix not calcification, weak osteoblastic activity,
    - due to lack of stress, malnutrition, lack of vitamin C, postmenopause lack of estrogen, no GH in old age, cushions syndrome elevated glucocorticoids

physiology of the teeth

- functions of the different parts of the teeth
- enamel: ameloblasts, absorb electrolytes, hard, resistant protein, hydroxyapatite
- dentin: collagen, hydroxyapatite crystals, nourished by odontoblasts, does not contain osteoblasts, cites, clast
- cementum: tooth socket,
- pulp: cavity, ct,
- dentition: 28-32 permanent; development influenced by GH, salts, Ca availability if one factor is absent no calcification of teeth
- mineral exchange in teeth
    - salts composed of hydroxyapatite with absorbed carbonates and various cations
    - new salts deposit
    - deposition in dentin and cementum slightly in enamel
- dental abnormalities
    - caries: bacteria, streptococcus mutans→ plaque film of saliva and food on teeth, bacteria use carbs secrete acids
        - enamel primary barrier, problem is candies small regular amounts of carbs
    - role of fluorine in preventing caries: enamel more resistant, replace hydroxyl ions in hydroxyapatite crystals→ enamel less soluble
    - malocclusion

chapter 80 reproductive and hormonal functions of the male (and function of the pineal gland)

physiological anatomy of the male sexual organs

spermatogenesis

- steps of spermatogenesis
    - in seminiferous tubules during active sexual life by stimulation of anterior gonadotropic hormones, by 13 years but decrease in old age
    - inner surface lined with 3 layers of spermatogonia→ migrate towards central lumen
    - meiosis
        - spermatogonia→ primary spermatocytes→ 1 division forms 2 secondary spermatocytes→ spermatids→ spermatozoa or sperm; 74 days
    - sex chromosomes
    - formation of sperm: cap on top, acromosom with lysosomes and enzymes→ enter ovum; flagellum; move 1-4mm/min in fluid
    - hormonal factors that stimulate spermatogenesis
        - testosterone: from Leydig cells, for growth and division of testicular germinal cells first step
        - luteinizing hormone: from anterior pituitary gland→ stimulate Leydig cells
        - follicle-stimulating hormone: from anterior pituitary gland→ stimulate Sertoli cells involved in spermatogenesis
        - estrogens: from Sertoli cells
        - GH: division, absent cause infertility

    - maturation of sperm in the epididymis
        - travels several days through epididymis, after 1 day capable of motion
        - storage of sperm in testes: 120 sperm/day stored in vas deferens up to 1 month
        - physiology of the mature sperm: activity enhanced in neutral and alkaline medium temperature, acid death, 1-2 days in female genital tract
- functions of the seminal vesicles
    - secrete mucus containing fructose, citric acid, fibrinogen, prostaglandins (react with female mucus more receptive for sperm movement, reverse peristaltic contraction)
- functions of the prostate gland
    - secret Ca, citrate ion, P, clotting enzyme, profibrinolsin, alkalie helps to neutralize female acidity active above pH6
- semen
    - fluid and sperm from vas deference 10%; fluid from seminal vesicle 60% secreted last; fluid from prostate gland 30%
    - pH 7,5; coagulum holds sperm by cervix in place→ dissolves sperm becomes motile
    - capacitation of spermatozoa is required for fertilization
        - factors inhibit motility in of sperms in man→ become activated by female fluids, 1-10h
        - uterine and fallopian tube fluids wash away various inhibitory factors
        - membrane acrosome of head of sperm becomes weak→ lack of cholesterol→ Ca enters sperm→ activates flagellum stroke, release of acrosome enzymes
    - acrosome enzymes the acrosome reaction and penetration of the ovum
        - in acrosome are hyaluronidase (dissolve cement which holds granulosa cells together) and proteolytic enzymes (digest elements adherent to ovum)
        - sperm anterior membrane→ bind to receptors on zona pellucid→ acrosome dissolve and release enzymes→ open tunnel for sperm head→ fuse with oocyte
        - Ca influx of oocyte→ release of cortical substances prevent binding of additional sperm
- abnormal spermatogenesis and male fertility
    - mups→ cause inflammation→ destroying seminiferous tubular epithelium
    - increase temperature can prevent spermatogenesis→ degradation of sperm and seminiferous cells
    - cryptochidism: failure of testis to descent, incapable of sperm formation,
    - effect of sperm count on fertility: 3,5ml sperm, 1ml 120mio sperms, under 20 mio infertile,
    - effect of sperm morphology and motility on fertility:

male sexual act

- neuronal stimulus for performance of the male sexual act
    - glans highly sensitive, but also urethra etc
    - psychic element of male sexual stimulation
    - integration of the male sexual act in the spinal cord: genital stimulation possible with cut spinal cord
- stages of the male sexual act
    - penile erection – role of the parasympathetic nerves: sacral nerves, release nitric oxide (activates GMP→ relaxes arteries of the penis and sm→ blood into penis→ further release of NO) and vasoactive intestinal peptide
    - lubrication is a parasympathetic function: mucus secreted from glands
    - emission (for sperm) and ejaculation are functions of the sympathetic nerves
        - hypogastric and pelvic plexuses
        - vas deference and ampulla contract, everything contract, ejaculation,

testosterone and other male sex hormones

- secretion, metabolism, and chemistry of the male sex hormone
    - secretion of testosterone by the interstitial cells of Leydig in the testes
        - testosterone is eventually converted into dihydrotestosterone
        - Leydig cells numerous in new born and after puberty, 20% of testis mass
    - androgen means masculinizing effects, adrenal gland 5 other androgen hormones but just 5% effect, ovary also some androgens
        - chemistry of androgens steroid compounds

        - metabolism of testosterone: bind to albumin or sex hormone binding globulin, circulate several hours,
        - degradation and excretion of testosterone: in liver into androsterone and dehydroepiandosterone→ excreted in bile or kidneys
        - production of estrogen in the male: Sertoli cells convert testosterone to estradiol, also in liver 80% maybe
- functions of testosterone
    - functions of testosterone during fetal development
        - from 7th week, Y chromosom has SRY sex determining region → protein called testis determining factor→ genital ridge cells change to secrete testosterone, suppress female organs
        - effect of testosterone to cause descent of the tests in last 2-3 month of pregnancy, descend by additional testosterone or gonadotropic hormone which acts on Leydig cells
    - effect of testosterone on development of adult primary and secondary sexual characteristics
        - effect on distribution of body hair
        - baldness: genetic background and much androgenic hormones
        - effect on the voice: enlargement or larynx and mucosa
        - testosterone increases thickness of skin and can contribute to development of acne; increase protein formation and muscle development; increase bone matrix and causes Ca retention (narrows pelvis and reinforce it); increase basal metabolic rate; increase RBC; increase Na reabsorption
- basic intracellular mechanism of action of testosterone
    - increase protein formation;
    - in prostate → 5α reductase converts testosterone→ dihydrotestosterone → binds receptor protein→ DNA RNA transcription→ increase of protein→ increase of prostate cells
- control of male sexual functions by hormones from the hypothalamus and anterior pituitary gland
    - GnRH from hypothalamus every 1-3h frequency and quantity acts more on LH→ anterior pituitary gland→ LH and FSH
    - GnRH and its effect in increasing the secretion of LH and FSH
- gonadotropic hormones: LH and FSH
    - secreted by gonadotrope, glycoproteins activate cAMP
    - regulation of testosterone production by LH, proportional, LH causes cells to mature into Leydig cells
    - inhibition of anterior pituitary secretion of LH and FSH by testosterone negative feedback control of testosterone secretion; GnRH→ LH, FSH→ testosterone→ decrease GnRH
    - regulation of spermatogenesis by FSH and testosterone
        - FSH bind to receptors on sertoli cells→ grow, secrete various spermatogenic substances; man need FSH and LH together
        - role of inhibin in negative control of seminiferous tubule activity
            - sertolic cells secrete inhibin acts on anterior pituitary gland inhibit FSH and GnRH
    - human chorionic gonadotropin secreted by the placenta during pregnancy stimulates testosterone secretion by the fetal tests
    - puberty and regulation of its onset
        - during childhood no GnRH; sex hormone inhibit GnRH; male climacteric

abnormalities of male sexual function

- prostate gland and its abnormalities: hypertrophy not by testosterone but cancer
- hypogonadism in the male: loss of testosterone before puberty eunuchism, castration after puberty secondary signs (loss of bass voice, sexual desire, sexual organs decrease, loss of masculine hair)
- testicular tumors and hypergonadism in the male: excess testosterone ,→ fast growth but also fast uniting of epiphyses
- tumors of germinal epithelium: teratoma, estrogens gynecomastiain male

erectile dysfunction in the male

- nicotine, alcohol, antidepressants, hypertension, diabetes, atherosclerosis→ no dilation
- sildenafil, Viagra→ increase cGMP duration by inhibiting phosphodiesterase 5→ prolonged effect of CGMP to cause erection

pineal gland – its function in controlling seasonal fertility in some animals

- enhancing sex, staving off infection, promoting sleep, enhancing mood, increasing longevity
- light, time pattern
- tumor hyper hypogonadal function

chapter 81 female physiology before pregnancy and female hormones

physiologic anatomy of the female

female hormonal system

- GnRH every 90 minutes ; FSH; LH; estrogen; progesterone;

monthly ovarian cycle; function of the gonadotropic hormones, 28 days

- gonadotropic hormones and their effects on the ovaries
    - changes in ovarian cycle due to LH, FSH; onset by 11-15; menarche first cycle
    - act on ovarian membrane, activat cAMP receptors
- ovarian follicle growth – follicular phase of the ovarian cycle
    - after birth around each ovum granulosa cells→ nourish ovum and secrete oocyte maturation-inhibiting factor keeps it in prophase state→ ovaries grow and ovum
    - development of antral and vesicular follicles
        - first days of cycle FSH (more) and LH elevated→ accelerate growth of 6-12 follicles
        - theca interna secrete estrogen and progesterone→ antrum appear just by FSH, estrogen built more FSH receptors on granulosa cells more sensitive→ FSH and estrogen→ promote LH receptors on original granulosa cells→ estrogen and LH cause proliferation of thecal cells and increase their secretion→ explosive follicular growth
        - theca external capsule ct
    - only one follicle fully matures each month and the remainder undergo atresia
        - 1 follicle outgrowth others die called atresia
        - estrogen from most rapidly growing follicles suppress hypothalamus; biggest continue to grow due to intrinsic positive feedback → prevent more then 1 child
    - ovulation
        - 14 days after onset of menstruation
        - stigma fluid into ovum→ rupture→ovum surrounds itself by granulosa cells called corona radiate
        - surge of LH necessary for ovulation:
            - before ovulation LH rises strongly peak 16h before; FSH also rises
            - LH converts granulosa and theca cells that they secrete progesterone → estrogen declines
            - LH activates progesterone depress estrogen post ovulation// pre ovulation estrogen depress FSH
        - initiation of ovulation: LH→ progesterone→ theca externa release enzyme and dissolve follicular capsule, prostaglandins into follicular tissue→ plasma transduction→ follicle swelling→ rupture releases ovum
- corpus luteum – luteal phase of the ovarian cycle
    - granulosa and theca cells→ into lutein cells, luteinization→ from corpus luteum biggest 8 days after ovulation → corpus albicans
    - smooth ER secrete progesterone and estrogen,
    - luteinizing by LH and exclusion of ovum
    - secretion by the corpus luteum: an additional function of LH, chorionic gonadotropin similar to LH acts on corpus luteum maintain it 2-4 month of pregnancy
    - involution of the corpus luteum and onset of the next ovarian cycle→ due to secretion of inhibin (negative feedback of estrogen)→ decreases FSH and LH→ degradation of corpus luteum 26 day, 2 days before menstruation starts again

functions of the ovarian hormones – estradiol and progesterone

- chemistry of the sex hormones
    - estrogens: from ovaries granulosa cells, mainly beta estradiol
    - progestins: progesterone from corpus luteum
    - synthesis of the estrogens and progestins: steroids, from cholesterol CoEA→ progesterone and androgens→ estrogens by aromatase
    - theca cells lack aromatase→ androgens diffuse out and are converted then by granulosa cells (FSH activates aromatase)→ into estrogen
    - estrogens and progesterone are transported in the blood bound to plasma proteins albumin
    - functions of the liver in estrogen degradation: estrogen→ glucuronides, sulfates→ bile, urine liver failure increases estrogen in body
- functions of the estrogens – their effects on the primary and secondary female sex characteristics
    - effect of estrogens on the uterus and external female sex organs
        - external internal female sex organs increase in size, change of vaginal epithelium into stratified more resistant
    - effect of estrogens on the fallopian tubes: increase cilia,
    - effect of estrogens on the breasts: fat, ductile system, stromal tissue
    - effect on skeleton stimulate bone growth; osteoporosis of bone caused by estrogen lack in old age; increases protein deposition; increase fat deposition and body metabolism; little effect on hair distribution hair from androgens from adrenal gland; skin becomes smooth more vascular; Na and water absorption
- functions of progesterone
    - progesterone promotes secretory changes in the uterus→ decrease contraction prevent expulsion of ovum
    - effect of progesterone on the fallopian tubes→ increased secretion, nutrition for ovum
    - progesterone promotes development of the breast→ alveola, lobes,
- monthly endometrial cycle and menstruation
    - proliferation phase estrogen phase of the endometrial cycle, occurring before ovulation
        - increase number in stroma cells, thicker, new vessels,
    - secretory phase progestational phase of the endometrial cycle, occurring after ovulation
        - estrogen and progesterone from corpus luteum increase endometrium, nourishment
    - menstruation: if ovum is not fertilized corpus luteum dissolve, caused by reduction of estrogen and progesterone, vasospasm, loss of hormones→ necrosis, lost 40ml blood no clotting due to fibrinolysin, many leukocytes called leucorrhea released,

regulation of the female monthly rhythm – interplay between the ovarian and hypothalamic-pituitary hormones

- the hypothalamus secretes GnRH which causes the anterior pituitary gland to secrete LH and FSH
    - intermittent, pulsatile secretion of GnRH by the hypothalamus stimulates pulsatile release of LH from the anterior pituitary gland every 90min LH peak
    - hypothalamic centers for release of GnHR in arcuate nuclei
- negative feedback effects of estrogen and progesterone to decrease LH and FSH secretion
    - estrogen inhibit LH and FSH directly on anterior pituitary gland
    - inhibin from corpus luteum inhibits FSH and LH secretion, more FSH
- positive feedback effect of estrogen before ovulation – the preovulatory LH surge (progesterone→ estrogen→ LH surge)
- feedback oscillation of the hypothalamic-pituitary-ovarian system
    - postovulatory secretion of the ovarian hormones and depression of the pituitary gonadotropins: between ovulation and menstruation
    - follicular growth phase: corpus luteum secretion stops→ secretion of FSH and slightly LH by start of menstruation; also estrogen secretion→ decrease slightly due to negative feedback→ increase LH preovulatory
    - preovulatory surge of LH and FSH causes ovulation
    - if LH is not sufficient elevated no ovulation called anovulatory cycle→ no corpus luteum→ no progesterone, cycle shortened; at beginning puberty and at end of cycles menopause
- puberty and menarche
- menopause

- 40-50 fail ovulation, outburn of ovaries, no estrogen→ no inhibition→ large amounts of FSH LH, fatigue, hot flush, anxiety, decreased Ca

abnormalities of secretion by the ovaries

- hypogonadism – reduced secretion by the ovaries: female eunuchism, atrophy of sexual organs same as by menopause
  - irregularity of menses; amenorrhea cycle not present no corpus uteum no ovulation,
- hypersecretion by the ovaries: excess estrogen→ inhibit GnRH→ no ovarian hormones

female sexual act

- stimulation of the female sexual act: psychic and local stimulation, desire on peak by ovulation,
- female erection and lubrication: NO, VIP, ACH dilation; mucus form bartholin gland;
- female orgasm: more fertile with real sexual intercourse; orgasm cause contraction, oxytocin,

female fertility

- fertile period of each sexual cycle: 4-5 days fertile during month before ovulation and 1 day after
- rhythm method of contraception: avoidance of intercourse 4 days before and 3 days after ovulation
- hormonal suppression of fertility the pill: estrogen progesterone prevent LH surge
- abnormal conditions that cause female sterility: failure to ovulate, no progestational effects→ anovulary cycle pregnanediol; hyposecretion of LH, FSH→ hCG same as LH; endometriosis fibrosis; salpingitis in fallopian tubes, abnormal mucus

chapter 82 pregnancy and lactation

maturation and fertilization of the ovum

- entry of the ovum into the fallopian tube (uterine tube)
- fertilization of the ovum
- what determines the sex of the fetus that is created?
- transport of the fertilized ovum in the fallopian tube
- implantation of the blastocyst in the uterus 7 days after fertilization, trophoblast cells invade endometrium

early nutrition of the embryo progesterone on endometrium→ contains nutrition, decidual cells

function of the placenta

- development and physiologic anatomy of the placenta: umbilical veins and arteries exchange gases and nutrients like lung with placenta villi
  - umbilical arteries contain deoxygenated blood; umbilical veins contain O2 blood
  - placenta permeability and membrane diffusion conductance:
    - conductance increases after time
    - diffusion of O2 through the placental membrane:
      - like in lung pressure gradient, maternal Po2 50mmHg→ 20mmHg difference → Po2 of fetus 30mmHg→
        - at low Po2 fetal hemoglobin can carry 20-50% more O2 then maternal,
        - 2nd the hemoglobin concentration is 50% greater
        - double Bohr effect hemoglobin carry more O2 at low PO2 values; loss of CO2 makes fetal blood more alkaline, and increased CO2 in maternal blood makes it more acidic→ enhancing O2 uptake from fetal blood
    - diffusion of CO2 through the placental membrane→ extreme solubility in placental membrane
    - diffusion of foodstuffs through the placental membrane→ easy diffusion, glucose important
    - excretion of waste products through the placental membrane

hormonal factors in pregnancy

- human chorionic gonadotropin causes persistence of the corpus luteum and prevents menstruation

    - syncytial trophoblasts→ secrete human chorionic gonadotropin
    - function of hCG like LH
        - prevent involution of corpus luteum it growth→ secrete more progesterone and estrogen for next month→ prevent menstruation, endometrium grow and store
        - corpus luteum involutes slowly after 3 month, placenta overtake function
    - effect of hCG on the fetal tests→ stimulates tests of fetus→ grow of male sex organs
- secretion of estrogen by the placenta
    - first from corpus luteum than→syncytial trophoblasts form estrogen from androgenic steroid compounds from adrenal gland→ converted into estradiol, estrogen, estriol
    - function of estrogen in pregnancy: enlargement of uterus, bigger breasts, larger external genitalia, relax pelvic ligaments
- secretion of progesterone by the placenta
    - cause decidual cells to develop in endometrium for nutrition; prevent uterine contractions; development of conceptus; prepare mothers breasts for lactation
- human chorionic somatomammotropin
    - from placenta; cause breast development and lactation, bit GH action, decreased insulin sensitivity and decreased glucose utilization in mother thus making more glucose available for fetus
- other hormonal factors in pregnancy
    - anterior pituitary gland enlarges 50% during pregnancy→ LH and FSH suppressed by estrogen but excess corticosteroids, thyroid hormones, prolactin,
    - corticosteroid slightly elevated: mobilize aa, maybe hypertension
    - increased thyroid gland secretion: enlarges 50%
    - increased parathyroid gland secretion: PTH, enlarge Ca supply from mothers bones
    - secretion of relaxin by the ovaries and placenta: relaxation of ligaments

response of mothers body to pregnancy

- weight gain in the pregnant woman 11-16kg
- metabolism during pregnancy higher: BMR up 15%
- nutrition during pregnancy: fetus double weight in last 2 month; iron supply; vitamine D; Ca, protein
- changes in the maternal circulatory system during pregnancy
    - blood flow through the placenta 625ml and maternal cardiac output increases during pregnancy, but falls to normal in last 8 weeks
    - maternal blood volume increases during pregnancy, 2 liters more for safety factor for mother
    - maternal respiration increases during pregnancy, decrease in PCO2
    - maternal kidney function during pregnancy: 50% more salt and water retaining→glomerular filtration increases also RBF up to 50% due to renal vasodilation NO relaxin;
    - amniotic fluid and its formation: from fetal excretion
    - preeclampsia and eclampsia: hypertension and protein in urine at end of pregnancy due to excess water and salt reabsorption, weight gain

parturition

- increased uterine excitability near term, mechanical and hormonal change
    - hormonal factors that increase uterine contractility
        - increased ratio of estrogens to progesterone: estrogen→ increased contractility
        - oxytocin causes contraction of the uterus: muscle increase oxytocin receptors, neurohypophysis more oxytocin,
        - effect of fetal hormones on the uterus: secrete oxytocin
    - mechanical factors that increase uterine contractility
        - stretch of the uterine musculature: sm stretch→ contraction
        - stretch or irritation of the cervix:
- onset of labor – a positive feedback mechanism for its initiation
    - rhythmical Braxton hicks contractions of uterus→ change into strong labor contractions
    - baby stretches cervix and uterus more→ more contraction
    - oxytocin from pituitary gland due to stretching
    - positive feedback cycle every step must be greater as previous one
- abdominal muscle contractions during labor due to pain from uterus

- mechanics of parturition
    - contractions strong at top weak at cervix→ force baby out
    - breech presentation→ baby first with butt or legs
- separation and delivery of the placenta: vasoconstriction, 30 mins after, 400ml blood loss
- labor pains: uterine hypoxia, stretching of birth canal
- involution of the uterus after parturition:4weeks, suppression of gonadotropin and ovarian hormone

lactation

- development of the breasts
    - estrogen stimulates growth of the ductal system of the breasts
    - progesterone is required for full development of the lobule-alveolar system
- prolactin promotes lactation by suckling → keeps breasts on producing milk
    - estrogen and progesterone inhibit milk secretion→ decrease after labor
    - clostrum like milk but without fat,
    - hypothalamus secretes prolactin inhibitory hormone
    - suppression of the female ovarian cycle in nursing mothers for many months after delivery
        - suckling inhibit gonatropin releasing hormone, LH FSH
- ejection or let down process in milk secretion – function of oxytocin
    - suckling→ hypothalamus secretes oxytocin → to breasts and cells contract→ milk flow
    - also baby crying
- milk composition and the metabolic drain on the mother caused by lactation; mother need Ca and vitamine D
    - antibodies and other anti infectious agents in milk

chapter 83 fetal and neonatal physiology

growth and functional development of the fetus

development of the organ systems:

- no weight and length growth in first 12 weeks
- GI system produce meconium

adjustment of the infant to extrauterine life

- onset of breathing 1 min after labor, hypoxia due to cut umbilical vein, cooing of skin→ onset
- collapsed lungs need high negative pressure -25mmHg to open, first breath extremely strong
    - need to expel fluid from airways
- blood by umbilical vein→ ductus venosus baypass the liver→ right atrium→ foramen ovale into left atrium→ into head and forelimbs; blood from SVC enters right ventricle→ lung → ductus arteriosus into aorta→ umbilical arteries into placenta
- decreased pulmonary (due to expansion of lung) and increased systemic vascular resistance at birth (closing of umbilical arteries)
- closure of foramen ovale
- closure of ductus arteriosus (reverse bood flow, constriction), venous

nutrition

- liver notable for gluconeogenesis, first days weight drop fluid loss no milk

special functional problems in the neonate

- 40 breaths/m, 16ml; blood 300ml; 500ml CO; BB 70-50mmHg;
- liver not at work for 100% after birth, hyperbilirubinemia; not able to form plasmaproteins, hypoproteinemic edema; no gluconeogenesis so blood glucose falls; no normal blood coagulation
- no pancreatic amylase→ problems with starch; smaller fat absorption
- poor body temperature regulation
- need of Ca, VD; iron; V C lack

- immunity decreases but then elevates until 20 month, protection from mothers antibodies, allergy occur when child produce its own antibodies
- endocrine problems
    - diabetic mother→ hypoglycemia in infant; maternal diabetes II→ big babies opposite by diabetes type I
    - many die due to respiratory distress syndrome
    - mother hyperthyroidism→ child hypothyroidism

special problems of prematurity

- small ventilation, inadequate GI system, Ca absorption poor,
- danger of blindness by excess O2→ stop grow of blood vessels → retrolental fibrplasia

growth and development of the child

- nervous system functional after 1 year

chapter 84 sports physiology

- female and male athletes: just muscle amount is higher in male

muscle in exercise

- strength, power and endurance of muscles
    - 3-4kg/cm2, quadriceps up to 6000 newton
    - holding strength greater then contractility
    - mechanical work= force*distance
    - power measured in time in watts
    - power unequal to efficiency
    - endurance determined by amount of glycogen stored
    - high carbs→ mixed diet→ high fat diet
- muscle metabolic system in exercise
- ATP p=7300 calories , just 3 seconds muscle power
- phosphocreatine system
    - creatine PO3-
    - more energy then ATP bond → restore ATP
    - phosphagen energy system ATP and phosphocreatine (10,3 Cal)→ energy 8-10 seconds
- glycogen lactic acid system→ glycolysis without O2 anaerobic→ glucose→ pyruvic acid → 4 ATP→ pyruvic acid into mitochondria and with O2 form more ATP → if NO O2 pyruvic acid into lactic acid (cause fatigue→ converted into glucose or pyruvic acid)
    - anaerobic part very rapid, 1,5min max muscle activity
    - restore ATP and phosphagen
- aerobic system
    - foodstuff and O2 in mitochondria
    - restore ATP, phosphagen, glycogen lactic acid
- ATP amount: phosphagen system 4; glycogen lactic acid 2,5; aerobic system 1
- time: aerobic system unlimited→ glycogen lactic acid 1,5 m→ phosphagen 10 sec
- oxygen dept: 2L stored O2, restoring after exercise → 9L additional for phosphagen and lactic acid system
- recovery of muscle glycogen: requires days and carb supply in diet
- nutrients used during muscle activity
    - fats at beginning →then carbs later →fats again
- effect of athletic training on muscles and muscle performance
    - importance of max resistance training: 3*6 3 days a week
    - muscle hypertrophy:
        - increased muscle diameter, number of fibers slightly
        - increased numbers of myofibrils, mitochondrial enzymes, more glycogen, more fat
    - fast twitch and slow twitch fibers
        - fast twitch: larger, more enzymes faster for max power

        - slow twitch: endurance, aerobic energy, more mitochondria, more myoglobin O2 carrier, more capillaries

respiration in exercise

- O2 consumption and pulmonary ventilation in exercise 250ml/min at rest→ marathon runner up to 5100ml/min
- limits of pulmonary ventilation
    - max breathing capacity 50% greater then needs safety for high altitudes, hot temperature, abnormal respiratory system
- effect of training on Vo2 max
    - just increase over weeks up to 10%, determined by respiratory muscles and chest size
    - long term effect but not big short term effect just
- O2 diffusion capacity of athletes: O2 diffusion from alveoli into blood expressed in ml of O2 /min of pressure difference, endurance training play important role, better perfusion of cross section area of lung
- blood gases during exercise: do not change
- effect of smoking on pulmonary ventilation in exercise: constriction, swelling, immobile cilia,
    - emphysema: chronic bronchitis, obstruction of many terminal bronchioles, destruction of many alveolar walls

cardiovascular system in exercise

- muscle blood flow: in muscle contraction decreases blood flow due to compression, blood flow increases huge, increase 25 times
- work output, O2 consumption and cardiac output during exercise, increase 4-6 times from 5L
- effect of training on heart hypertrophy and on cardiac output: chambers and mass of heart enlarge,
    - co in athletes and normal person same but slower heart rate larger stroke volume
- role of stroke volume and heart rate in increasing co
    - stroke volume rises faster then heart rate→ further increase in co just over heart rate
- relation of cardiovascular performance to Vo2 max
    - heart more limiting
- effect of heart disease and old age on athletic performance, co decreases in age

body heat in exercise

- also convertion f muscle energy into heat due to friction, just 25% effectiveness
- heat proportional to 02 consumption,
- heatstroke
    - exercise elevates body temperature upt o 42° by hot and wet climate
    - treatment with water wind ice

body fluids and salts in exercise

- weight los in exercise
- replacement of NaCl and P: sweat glands can acclimate→ less salt los more aldosterone but also then more K loss

drugs and athletes: caffeine improve, testosterone, amphetamines

body fitness prolonged life: reduce cardiovascular disease; more reserves in sickness; less insulin resistance, rduce LDL increase HDL

ZUSATZ: vitamins

- daily requirements of vitamins
    - small compound needed for normal metabolism, essential,
- storage of vitamin in the body
    - in cells, major in liver, water soluble vitamins cause fast symptoms
- vitamin A:
    - in animal tissue as retinol, precursors in vegetables, formation of retinal pigments→ prevent night blindness, growth of cells (epithelium), lack cause keratinization, anti infection vitamin
- thiamine vitamin B1
    - deficiency called beriberi
    - needed for metabolism of carbs and proteins
    - deficiency cause lesion of the central and peripheral nervous system, degeneration of myelin sheats, muscle atrophy, weak cardiac muscle→ failure, cause vasodilation→ incrase venous return, edema
- niacin or nicotinic acid
    - form NAD, NADP are H+ acceptors
    - lack→ no oxidative delivery of energy from the foodstuffs to the functioning elements, muscle weakness, tissue death, no skin repair, black tongue, pellagra, caused also by lack of tryptophan
- riboflavin vitamin B2
    - form with phosphoric acid FMN and FAD, hydrogen carriers,
- vitamin B12
    - cause pernicious anemia, DNA replication, RBC formation, demyelination of large nerve fibers of the spinal cord
- folic acid
    - required for formation of DNA, replication, maturation of RBC,
- pyridoxine vitamine B6
    - coenzyme in synthesis of amino acids,
- pantothenic acid
    - lack lead to depressed metabolism of carbs and fats
- ascorbic acid vitamine c
    - lack weaks collagen fibers, scurvy→ no wounds heal, no collagen, no bone growth, fragil vessels, bleading
- vitamine d
    - increase ca absorption and ca deposition in bone,
- vitamine e
    - lack→ steril, antisterilic vitamin, prevent oxidation of unsaturated fats,

- vitamine K
    - for blood coagulaton, coenzyme, form bacteria in colon

mineral metabolism

- magnesium: enzymatic reaction by carbs, increase extracellular concentration depress nervous system, vasodilation,
- calcium: in bone, excess stop heart, lack tetany
- phosphorus: anion of intracellular fluid,
- iron: hemoglobin,
- important trace elements in body
    - iodine: formation of thyroxine, triiodothyronine
    - zinc: part of enzymes like carbonic anhydrase, in RBC,
    - fluorine: teeth protection,
- FVC= TLC-RV
- pleural pressure always negative -5—7
- blood flow is lowest in lung apex
- brain increases respiration by exercise not PCO2 change because it does not change
- ovolution → progesterone increases
- PTH→ loss of P in urine
- peptide hormones bind to cAMP… insulin NOT

aviation

- people can stay conscious until 50% of arterial O2 saturation→ dizzy, fatigue,
    - acclimatization to low O2:
        - increase in pulmonary ventilation: chempreceptors; but increase ventilation→ PCO2 decrease→ PH increase→ inhibition on respiration in brain stem→ 2-5 days inhibition fades away→ HCO3- decrease→ pH decrease → increase respiration
        - RBC stimulated by hypoxia
        - diffusion capacity of lung,
        - increased vascularity of peripheral tissue,
        - tissue ability to use O2 up, better usage of O2 by mitochondria
- mountain sickness: cerebral edema due to vasodilation by hypoxia; pulmonary edema vasoconstriction high blood flow
- blood can be transferred by accelerating forces