Metabolism notes

Human Anatomy and Physiology III (Algonquin College)

Regulation of Metabolism and Body Temperature (January 28, 30; February 6, 11; David Lohnes)

2.1 Review the metabolic pathways and their interactions

6 Classes of nutrients: carbohydrates, lipids proteins – major. Vitamins, minerals, water – minor

- **Food pyramid**: emphasis on reducing animal fats, restricting red meats, sweets, starch; 8 glasses of water a day; 30 mins exercise daily

Nutrient	Dietary Sources	Requirements	Uses
Carbohydrates	Most come from plants • Sugars (fruit, honey), starches (grains, legumes), cellulose (fibre)	• 100g/day *minimum* • 130g/day recommended intake as complex carbs (Avoid spike in BS) • 45-65% total calorie consumption • *If carb intake less than 50g/day, muscle breakdown occurs*	• *Glucose* used to make ATP (galactose, fructose converted to glucose via isomerization) • *Neurons & RBCs* rely 100% on glucose • *Nucleic acids, glycoproteins, glycolipids* • Excess converted to glycogen
Lipids	• Saturated fats (meat, dairy, coconut) • Unsaturated fats (seeds, nuts, olive oil) • Cholesterol • Linoleic & linolenic acids = essential for life fatty acids as body can't manufacture	• Should be <30% of caloric intake • *Saturated fats* should be equal to or less than 10% total fat • *Cholesterol* should be less than or equal to 300mg/d (1 egg yolk)	• Absorption of *fat-soluble vitamins* • Major fuel for *hepatocytes & skeletal muscle* • *Phospholipids for myelin sheaths and plasma membranes* • *Fatty deposits* • Production of *prostaglandins, steroids and bile*
Proteins	• Animal products (essential amino acids (complete proteins have all amino acids) • Legumes- protein rich but not complete proteins **EXCEPT FOR TOFU/SOYA**	• Requirement dictated by age, size, nitrogen balance • 0.8g/kg recommended • **All or nothing rule:** for a cell to make a protein, all amino acids need to be present or it will not be made	• *Structural*: keratin in skin, collagen and elastin in connective tissue • *Functional*: enzymes, hemoglobin, peptide hormones • *Energy*: last resort when carbs are too low • ***Anabolic hormones*** will generate muscle
Vitamins (vita=life)	• Not made in the body, need to be consumed • *Fat-soluble*: A, D, E, **K** (cannot be stored in body); absorbed with dietary lipids; storable; some toxic • *Water-soluble*: B-complex, C; absorbed with water; not stored- need to consume regularly. • *Found in all major food groups; need balanced diet*	• Minute amounts of all vitamins • Need to regularly consume water soluble vitamins as not stored in body	• Needed for growth and good health; essential for use of proteins/carbs in diet • *Coenzumes* of metabolic reactions • *Antioxidants:* neutralize free radicals and have anti-cancer properties
Minerals	• Vegetables, milk and meat	• *Moderate amounts*: **calcium**,	• Give added strength to

	• *Need to maintain balance between excretion and ingestion*	**phosphorus,** potassium, sulfur, sodium, chloride, magnesium • *Trace amounts*: iron, iodine, manganese, copper, zinc, cobalt, fluorine, selenium, chromium	bone • Act as cofactors • Electrolytes • Hormone production
Water	•	• 8 glasses a day	• Carries nutrients throughout the body • Cleanses wastes • Solvent • Lubricant • Regulation of body temp

Metabolism: anabolism and catabolism; used to construct molecules or to generate energy through ATP

Redox reactions: reduction of compounds through oxidation; passing of electrons by hydrogen.

Carbohydrates: metabolized via *glycolysis* producing some energy via phosphorylation, followed by Kreb's cycle which produces some ATP but most ATP is produced by oxidative phosphorylation:

$$C_6H_{12}O_6 + 6O_2 – 6H_2O + 6CO_2 + 32\ ATP\ and\ heat$$

- Amino acids and glycerol can also feed into glycolysis

Glycolysis: 10 steps; see sheet below

Oxidative Phosphorylation: FADH2 and NADH carry energy that must be converted into ATP; coupled to formation of water from electrons, oygen and H+. Stepwise pattern to prevent too much heat from being developed. H+ re-entry drives a motor in ATP synthase which converts ADP + Pi to ATP – reverse proton pump.

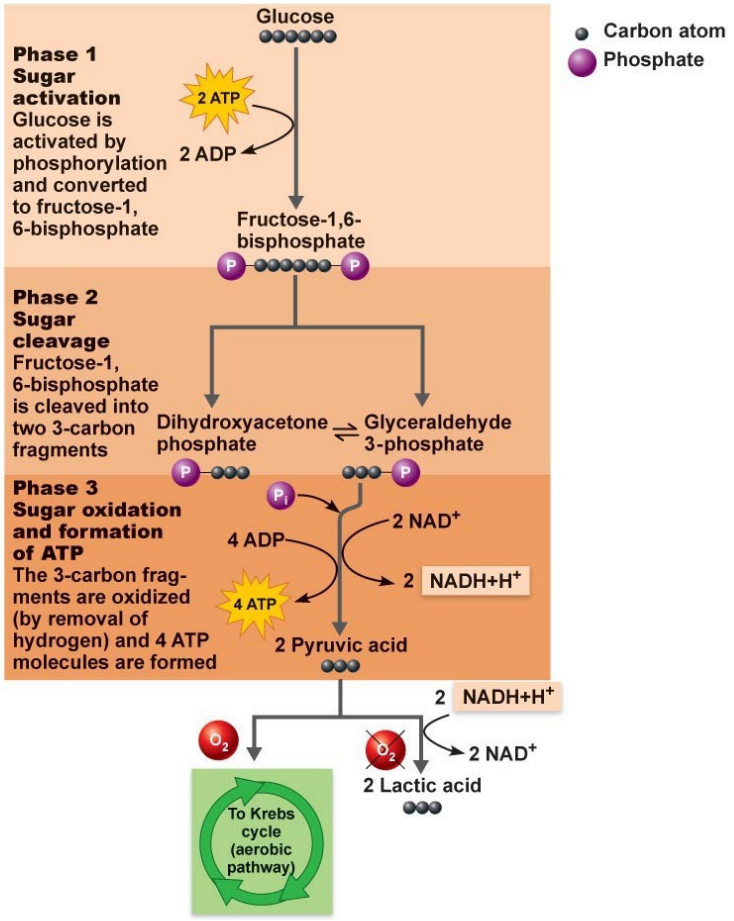
One molecule of glucose yields 32 ATP, rest of energy is lost as heat. 55kg of ATP is developed by one person daily, which is used almost immediately for brain function and for other bodily functions

Lipogenesis vs. lipolysis: amino acids are not stable or stored; excess is converted to fat or burned for energy.

- Glycerol and free fatty acids can be used for energy but only glycerol can use the glycolytic pathway.
- **Amino acids** undergo transamination and deamination reactions to remove the amine group and to generate *keto acid* as a source of energy; ammonia is generated as a by-product which is converted to urea and excreted as it is toxic if it builds up and can lead to gout/toxicity.

2.2 Define the absorptive state and justify the key role of insulin in its metabolic regulation

Absorptive state: fed state; time during and shortly after eating; nutrients entering circulation provide an energy supply. *Anabolism exceeds catabolism*. Glucose serves as the major fuel. Dietary amino acids and fats are used for anabolic processes (making new proteins and fat stores). Excess metabolites of all sources used to make fat once anabolic and energy demands met.

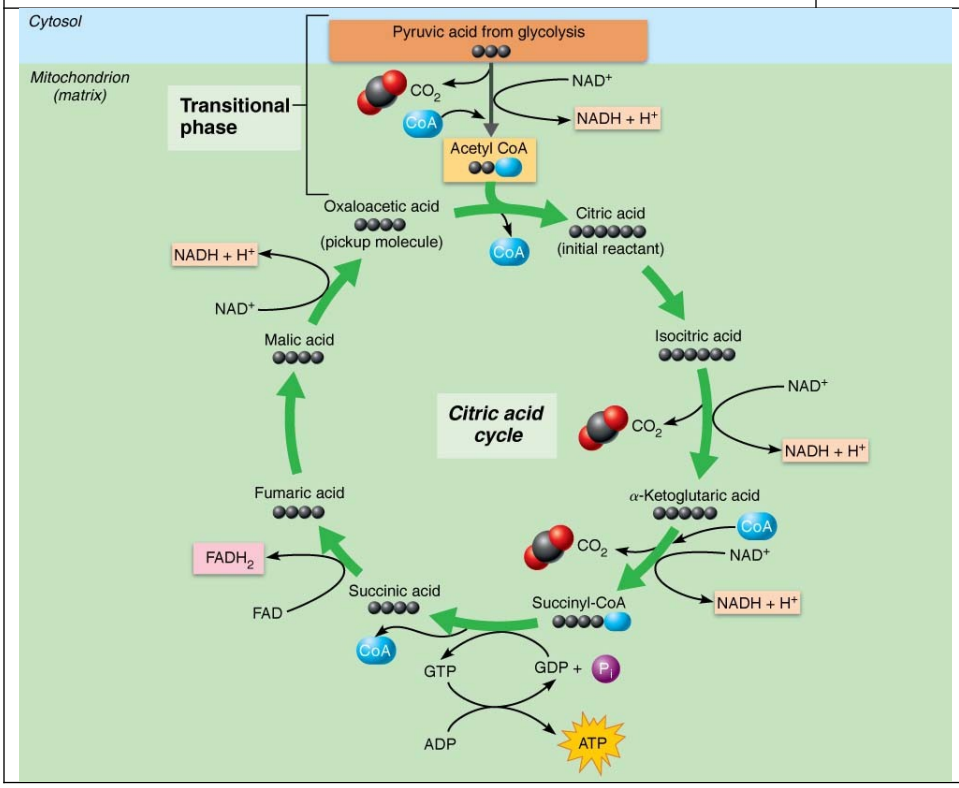


Glycolysis:

1) **Sugar activation**: glucose enters cell and is activated by phosphorylation and converted into Fructose-1,6-bisphosphate (picks up 2 phosphate molecules); *serves purpose so that the transformed molecule cannot go out the concentration gradient*
2) **Sugar cleavage**: Fructose-1,6-biphosphate is cleaved into 2 3-carbon fragments, each with a phosphate molecule
3) **Sugar oxidation and formation of ATP**: the 3-carbon fragments are oxidized (by removal of hydrogen from 2 NAD, which converts to 2 NADH+H) and 4 molecules of ATP are formed, resulting in pyruvic acid, and 2 NADH+H.
   a. In the *presence* of oxygen (Aerobic) pyruvic acid goes to the Krebs cycle
   b. In the *absence* of oxygen (anaerobic) 2 NADH+H+ give hydrogen to 2 pyruvic acids leaving 2 lactic acid molecules.

Cycle is ***reversible***

$C_6H_{12}O_6 - 2X(C_3H_4O_3)$: 2 hydrogen molecules missing, went with NADH+H+.



Citric Acid Cycle/ Kreb's Cycle

Occurs in the *mitochondria* of cells; ***nonreversible***

1) Pyruvic acid has C02 removed from it to form acetic acid then conjugated to -CoA to form acetyl CoA.
2) Oxaloacetic acid picks up acetyl CoA which intermediates
3) Keto acids decarboxylates X2 and oxidized x4
4) Oxaloacetate regenerated and cycle begins again

Some intermediates can be used to make amino acids or fats, and Krebs cycle can also burn triglycerides and amino acids as needed.

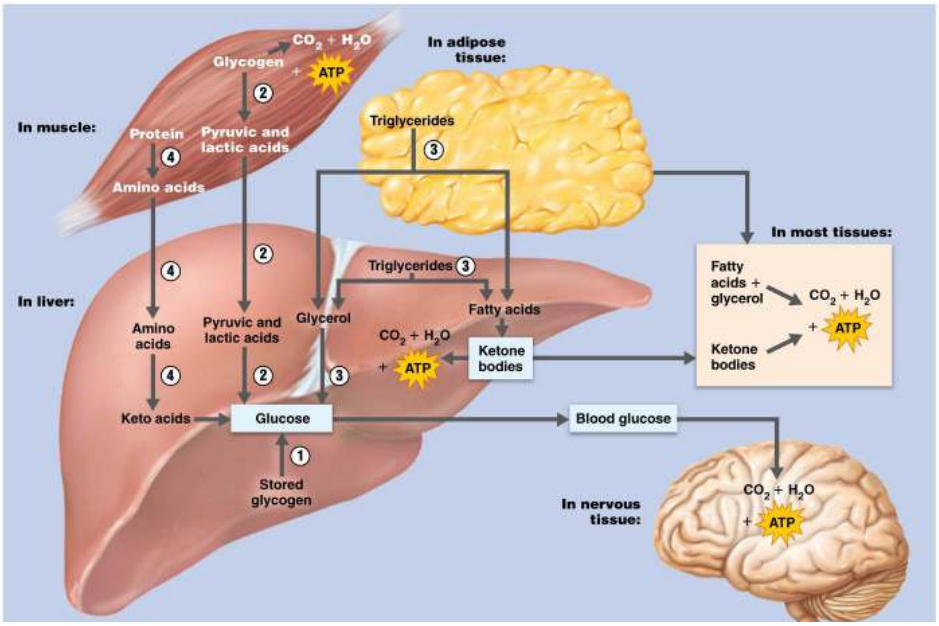
Insulin: directs all events of absorptive state. Produced by beta cells of islets of Langerhans in pancreas. Primary *stimulation* is a rise in blood sugar but also stimulated by increased blood amino acids, glucose-dependent insulinotropic peptide (GIP) and PNS stimulation; anabolic, hypoglycemic hormone.

- Effect: activates carrier mediated facilitated diffusion of glucose into cells. *INSULIN NOT NEEDED FOR GLUCOSE ENTRY INTO LIVER, KIDNEY, BRAIN OR INTESTINAL EPITHELIAL CELLS.*
  - Enhances glucose oxidation for energy
  - Stimulated conversion of glucose to glycogen and TGs
  - Increases active uptake of amino acids and promotes protein synthesis
  - Controls virtually all liver enzymes that promote gluconeogenesis and inhibits hydrolysis of glycogen to glucose

2.3 Define the post absorptive state and describe the roles of glucagon and other supporting mechanisms in the maintenance of blood glucose levels

Post absorptive state: fasting state; GI tract empty; energy needs are met by breakdown of food reserves; between meals, blood glucose drops and a net synthesis of fat, proteins, glycogen stops and catabolism of these substances begins. Primary *goal* is to maintain blood glucose within homeostatic range. Important as the brain needs glucose

- Major events geared toward sparing glucose for brain cells, and making more glucose available to the circulatory system
- Making glucose available to the blood: from glycogen, tissue proteins, fat
  - *Glycogenolysis* in the liver: liver has 100g of glycogen reserves which are the first source of glucose and can normally maintain blood sugar for about 4hrs.
  - *Glycogenolysis in skeletal muscle:* 100g of reserve; oxidized to pyruvic acid or lactic acid → blood → liver and → glucose. Skeletal muscle cannot directly provide glucose to the circulation as it is missing the enzyme to breakdown. *Indirect source of glucose*.
  - *Lipolysis in adipose tissues and liver:* adipose tissues and liver cells produce glycerol → liver converts to glucose. Free fatty acids can only → Krebs cycle.
  - *Catabolism of cellular protein:* **LAST RESORT**; used only if fasting is prolonged and during stress (secretion of glucocorticoids). Process required deamination of amino acids in the *liver* to generate keto acids → glucose.
- *Glucose sparing*: mechanisms which use non-carbohydrate fuel molecules for energy in order to conserve glucose. As the body moves to post absorptive state, all tissues and organs except the brain switch to using fats as their major energy source.
  - Lipolysis in adipose tissue frees fatty acids and glycerol
  - Liver oxidizes free fatty acids to ketone bodies which are released into the blood and used by the cells for energy
  - If fasting is prolonged, the brain will start to use some ketone bodies for energy.



Hormonal and Neural Controls: interaction of SNS and several hormones regulate post absorptive state (varying in length).

- *Initiation*: of post absorptive state is change in blood glucose, including a decrease in blood glucose triggering the post absorptive state and leading to the inhibition of secretion of *insulin*. Decreasing blood glucose levels also stimulate secretion of *glucagon.*

Glucagon: produced by alpha cells in islets of Langerhans in pancreas. Potent hyperglycemic. 1 molecule of glucagon can release 100 million molecules of glucose into the blood.

- *Target:* liver and adipose tissue. Promoters glycogenolysis, glucose synthesis from lactic acid and via gluconeogenesis from glycerol and amino acids; in adipose cells stimulate lipolysis causing release of FFA and glycerol into blood.
- *Secretion inhibited when glucose blood levels rise.*

If eating a high protein, low carb meal- glucagon levels increase to increase blood sugar but insulin levels rise as well to counter the glucagon.

SNS response: responds to sudden drop in blood sugar; bodily injury, anxiety, anger, other stressors with the "fight-or-flight" response in which blood sugar levels rise, blood vessels constrict, heart beats faster, blood gets shunted to the brain, heart and skeletal muscle. SNS stimulation results in lipolysis and fat mobilization from adipose tissue and stimulates glycogenolysis.

Adrenal glands: responds to SNS stimulation as part of "fight or flight" response.

- *Adrenal medulla* secrete *epi* and *norepi* which stimulate glycogenolysis , lipolysis and fat mobilization, as well as gluconeogenesis.
- *Adrenal cortex* secreted glucocorticoid *cortisol* which is essential for life. If levels remain increased for too long can lead to muscle wasting and protein catabolism.

2.4 Describe the metabolic consequences of the two types of diabetes mellitus MIDTERM BEFORE THIS ^^^^^

Diabetes Mellitus: decreased insulin or absence. NO BACK-UP HORMONE FOR INSULIN. Blood sugar high but unable to get into most cell types; cells unable to utilize glucose for energy and turn to glucose sparing methods.

- Body responds by mobilizing fats. Due to loss of acetyl-coA acceptor molecule oxaloacetate (which is scavenged); can lead to a buildup of *ketone bodies* in the bloodstream; leads to ***ketoacidosis*** (pH of blood is lowered) and can disrupt CNS, heart activity and O2 transport, leading to coma and death.
- Key signs and symptoms:
    - *Polyphagia*: excessive eating due to starving due to inability to use carbs for energy
    - *Polydipsia*: excessive thirst/drinking due to body trying to flush out excess glucose
    - *Polyuria*: excessive urination due to body trying to pee out excess glucose.

	Type 1 Diabetes	**Type 2 Diabetes**
Age of onset	Childhood	Adulthood
Cause	Destruction of pancreatic beta cells by autoimmune processes, potentially by molecular mimicry (virus brought on autoimmune process)	Age, lifestyle (obesity and poor diet), sedentary lifestyle, *genetics*
Management	Insulin	Diet, weight loss and exercise but may need insulin eventually
Long term effects	Vascular: atherosclerosis, stroke, MI, gangrene Neurological: loss of sensation, impaired bladder function, impotence	Same as Type 1
Acute issues	Ketoacidosis	

2.5 List the various hepatic functions associated with metabolism

Hepatic Functions: liver the most biochemically complex organs in body conducting over 500 metabolic functions and processing nearly every class of nutrients, and regulation of plasma cholesterol levels.

- Carb metabolism:
    - isomerizes monosaccharides to glucose
    - packages glucose as glycogen and fats to store it
    - glycogenolysis to release glucose
    - gluconeogenesis to convert amino acids or glycerol to glucose when needed
- fat metabolism:
    - primary site for beta oxidation
    - generates ketone bodies from acetyl-coA
    - generates lipoproteins for triglyceride transport
    - metabolizes cholesterol, bile salts

- protein metabolism:
    - principle site for amino acid deamination
    - forms urea for removal of ammonia
    - generates most plasma proteins
    - major site of generation of non-essential amino acids
- storage:
    - stores 1-2yrs worth of vit A, 1-4mo supply of vit D and B12
    - stores iron from degraded RBCs for release when needed
- biotransformation:
    - inactivates compounds such as ethanol, drugs
    - will activate a number of drugs
    - processes bilirubin from heme
    - catabolizes many hormones for excretion

2.6 List and describe the 4 major types of lipoproteins

Lipoproteins: triglycerides and cholesterol are insoluble in aqueous environment and cannot circulate freely in the blood and are transported as lipoproteins- composed of varying proportions of triglycerides, phospholipids and cholesterol, in addition to protein (important for regulation into specific target cells). In general, the higher % of lipid, the lower (and

worse it is) its density. Excess cholesterol linked to elevated risk of atherosclerosis and associated stroke and heart attack.

- Chylomicron: lowest density, transports newly adsorbed lipids from Gi tract
- Very low density lipoprotein (VLDL): made in liver, transports triglycerides to peripheral tissues. At target cells, triglycerides are unloaded and VLDL become LDL.
- Low density lipoprotein: (LDL) primary role to deliver cholesterol to peripheral tissues (not all bad as cholesterol needed for steroid hormones, bile salts, membranes, signaling molecules in development). **LOUSY.** Bad as excessive amounts can lead to deposition of cholesterol in blood vessel walls
- High density lipoprotein: (HDL) protein component of HDL made in liver and secreted in collapsed form. Primary purpose to transport cholesterol from peripheral tissues to the liver where they are broken down into bile. Will also deliver cholesterol to some tissues for use in steroid hormone synthesis. **HEALTHY**. Good because cholesterol associated with HDL mainly destined for degradation. **Ratio to LDL important**

Cholesterols:

- **Saturated fatty acids:** stimulate liver synthesis of cholesterol and inhibits cholesterol excretion, **NOT TOO GOOD**
- **Unsaturated fatty acids:** promote catabolism and excretion of cholesterol, **GOOD**
- **Trans fats:** stimulate greater increase in LDL and decrease HDL; **BAD**

2.7 Describe the synthesis of thyroid hormones and its regulation

Thyroid: butterfly shaped located on trachea just inferior to larynx. 2 bilateral lobes connected to an isthmus. Largest pure endocrine gland in the body; supplied by very rich blood supply from carotid arteries.

T4 and T3 are transported in blood bound to **thyroxine binding globulin (TBG)** which transports them throughout the body. *Transport protein needed because hormones are very tiny and may be filtered out through the kidneys and also can recognize targets that may need thyroid hormones*. Bind in nucleus to **thyroid hormone receptor (TR)** which results in the increased expression of target genes (T3 is approx. 10x more active than T4).

Follicles: thyroid gland composed of hollow follicles surrounded by cuboidal or squamous epithelial cells called follicles that produce thyroglobulin (glycoprotein). Filled with colloid consisting of iodinated thyroglobulin serving as precursos for thyroid hormone.

Parafollicular cells: interspersed between follicles produce calcitonin.

Thyroxine (T4): principle secretory product of thyroid follicles
Triiodothyronine (T3): more *active* hormone and derived largely from T4

Transport and regulation of thyroid hormone:
Falling TH levels lead to secretion of TSH (thyroid stimulating hormone) by the anterior pituitary which elicits 2 general responses in the thyroid gland:

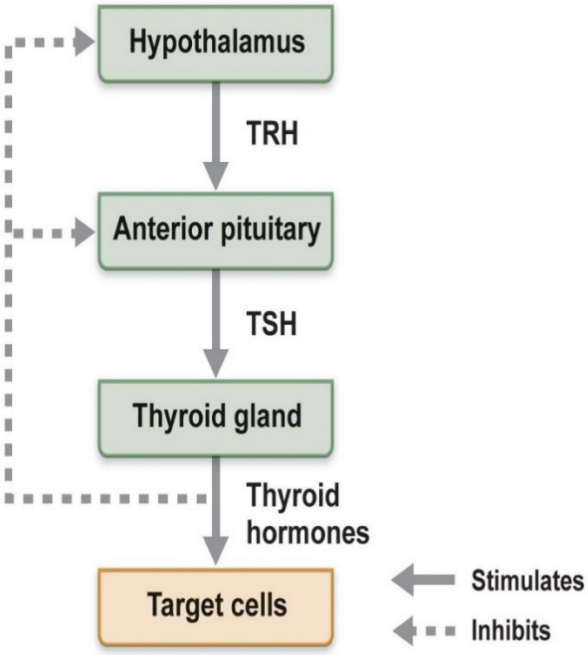
- Causes thyroid to secrete stored TH
- Resynthesizes thyroglobulin and to replenish the colloid; typically enough hormone in colloid to support secretion for several months

Unique because colloid is extracellular, which is unique to the thyroid

Negative feedback system

- Inhibit TSH secretion by anterior pituitary
- Inhibit secretion of TRH by hypothalamus

TH affects essentially every cell of the body except for the brain, spleen, testes, uterus and thyroid. Acts to regulate basal metabolic rate and heat production (calorigenic effect); regulates BP, tissue growth and development.



2.8 List the metabolic processes regulated by thyroid hormones

Myxedema: mucous swelling in adults that occurs in inadequate TSH or TRH release, removal of thyroid gland, or inadequate iodine (Endemic goiter). Results in lethargy, low metabolic rate, chills, dry skin, edema, mental sluggishness. Occurs in hypothyroidism. Congenital hypothyroidism in infants (can result in mental retardation, thick tongue, nexk, disproportionate body size and is reversible if caught early, but irreversible once signs are present).

Hyperthyroidism: can lead to grave's disease – bulging eyes. Can be autoimmune, pt develops Ab that mimic TSH and constantly stimulate output of thyroid hormones leading to elevated BMR, sweating, rapid and irregular HR. Treatment with radioactive iodine that will destroy the thyroid, or by surgical removal of the thyroid.

Calcitonin: hormone produced by parafollicular cells of thyroid. Lowers blood calcium by inhibiting bone reabsorption and stimulating Ca++ uptake and incorporation into bone. Is secreted in response to rising blood levels of calcium; very important in childhood with minimal role in adults.

2.9 Define basal metabolism and total metabolism and identify the factors that influence them

Basal metabolic rate: body's rate of energy expenditure per hour = total heat produced by all of the chemical reactions and mechanical work of the body. Measured 12 hours after a meal while the body is at rest. "Lowest point of metabolism". Influenced by **SURFACE AREA**, gender, stress, hormones. THYROID HORMONE is most important hormonal regulator.

Regulation of metabolic rate: Influenced by stress, temperature

Total metabolic rate: total rate of kcal consumption to fuel all ongoing activities. Influenced by thermogenesis, and fasting or low caloric intake.

2.10 Discuss the mechanisms of appetite regulation

Energy intake = total energy output (heat + work + energy storage)

Energy intake = energy provided by food oxidation (energy released when the bonds linking the subunits of complex food molecules are broken

Energy output = energy lost as heat + work (ATP) ; the majority of this is in the form of heat. Even when muscles do work, much of this energy is from food breakdown is lost in the form of heat.

Energy storage = excess of energy intake that is stored as fat or glycogen

Heat works to warm tissues and blood to a comfortable temperature and allows metabolic reactions to occur at efficient levels.

Regulation of food intake: when energy intake = energy output in the form of heat + work, body weight remains stable. In most people, body weight remains fairly stable, suggesting that physiological mechanisms must exist to control food intake or heat production, or both. No single signal or receptor identified to date which balances food intake with energy output, but there are some pathways that are clearly involve.

Appetite: desire for specific types of food, dependent on memory and associations but doesn't necessarily reflect the body's caloric needs

Hunger: physiological need to eat

Satiety: satisfaction of hunger

Arcuate nucleus: in the hypothalamus and the **solitary nucleus** in the brainstem are key centers in appetite regulation.

- **AN**: as 2 important groups of neurons:
    - **stimulation of NPY** (Neuropeptide Y/agouti related peptide) which stimulates appetite via the LHA.
    - **POMC/CART** (proopiomelanocortin/cocaine and amphetamine-regulated transcript neurons release melanocortins, which suppress appetite via corticotropin releasing hormone by the VMH.

Short term regulation of appetite:

- *Neural signals*: via vagal stimulation. Stretch receptors in GI tract inhibit appetite. Protein and carbohydrates stimulate vagal afferents to inhibit appetite. Protein stimulates longer response
- *Nutrients*: plasma levels of glucose, amino acids, FFA, and glycerol signal to the brain. During eating, plasma glucose levels rise and activate glucose receptors in the brain and eating is depressed. Elevated plasma amino

acids depress and low plasma amino acids stimulate eating. Blood concentrations of FFA and glycerol play a similar role.

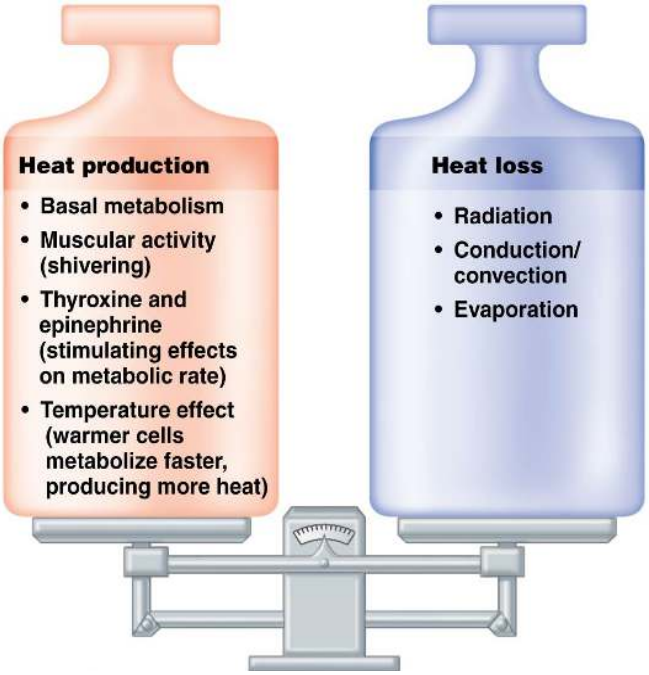
- *Hormones*:
    - Insulin: satiety signal
    - Cholecystokinin: depresses hunger
    - Glucagon: stimulates hunger
    - Ghrelin: released by stomach, potent stimulator of hunger
- Body temperature
- Psychological factors

Long term regulation of hunger:

- *Leptin*: peptide hormone secreted by adipose tissue that serves as sensor for adipose stores. Inhibits NPY secretion and increases CART expression. Leads to inhibition of appetite until adipose stores decrease.

2.11 Describe and explain the mechanisms of heat exchange

Temperature is a balance between heat production and heat loss. Heat produced by skeletal muscle can be more than that of the rest of the body. Change in activity is a key way of modifying body temperature.



If temperature goes too high: neurons depressed, and proteins start to be denatured.

Average temperature is 37C degrees

Heat exchange:

- *Radiation*: loss of heat by infrared waves, movement from warmer to colder
- *Conduction*: transfer of heat between objects in direct physical contact with one another
- *Convection*: warm air rises and is replaced by cool air
- *Evaporation*: water molecules absorb enough heat for energy to escape as gas.

Hypothalamus: major integrating centre for thermoregulation, comprised of 2 thermoregulary centers: *heat loss center and heat promoting center*. Received input from peripheral thermoregulators (in shell), and central thermoregulators (in core, sensitive to blood temp). Initiates heat-loss or heat-promoting mechanisms. GOAL to preserve core temp.

Heat promoting mechanisms:

- Vasoconstriction of cutaneous blood vessels: activation of **sympathetic** vasoconstrictor fibres serving skin results in decreased blood flow, restricting blood to deep body areas, largely bypassing skin. Results in sharp drop in shell temp and conservation of core temp. Okay for brief period but if extended, skin will be deprived of O2 and can lead to frostbite.
- Shivering: involuntary reacting but very effective as generates a lot of heat.
- Increase in metabolic rate: cold stimulates release of epi and norepi resulting in increased metabolic rate and more heat production. Known as chemical or nonshivering thermogenesis.
- Enhanced thyroxine release: lowering of temp results in increased secretion of TRH by hypothalamus causing TSH secretion by anterior pituitary which increases secretion of T3 and T4. This increases metabolic rate and

body heat production and improves the ability to maintain constant body temp as environment cools. Not seen in adults but only children.

- Behavioural modifications: putting on warmer clothing, changing posture to reduce exposed body surface area, increasing physical activity.

Heat loss mechanisms:

- Vasodilation of cutaneous blood vessels: turn off sympathetic vasoconstriction, resulting in increased blood flow to skin and increasing hat loss by radiation, conduction and convection.
- Enhanced sweating: if body is overheated, sweat glands are activated by sympathetic nervous system, increasing perspiration.
- Behavioural modifications: reducing level of activity, seeking cooler environment or increasing convection. Wearing light, loosely fitted clothing to reflect radiant energy and reduce heat gain.

Hyperthermia: occurs when normal heat loss processes become ineffective. Elevated body temp depresses hypothalamus and suspends heat control mechanisms resulting in a vicious positive feedback loop, increasing metabolic rate and increasing heat production. This causes more and more damage and leads to heat stroke.

- Fever: controlled hyperthermia usually due to infection. Pyrogens released by macrophages cause a reset of hypothalamic thermoregulatory center