NUTRITION AND METABOLISM

(a) ***To define basal metabolic rate and to describe its measurement.***

(b) ***To describe the factors that influence metabolic rate.***

Metabolic rate (MR):

- Defined rate of energy output or production in a subject
- BUT since all energy produced ultimately appears as heat (as this form as energy has the highest entropy) → MR can also be defined as energy output of heat production in a subject

Basal metabolic rate (BMR):

- Defined as energy output of heat production in a subject (or metabolic rate) measured under a defined set of standard conditions:
  - (i) Subject in a state of mental and physical rest
  - (ii) Comfortable environment (Eg. room temperature)
  - (iii) 12 hours after a meal
- Expressed as "watts" (1 W = 1 J/sec) → can be indexed to BSA (W/m^2)
- BMR for 70 kg adult ♂ = 100 W or 58 Wm^2 → 70-100 kcal/min (or 2000 kcal/day)

> Note: Standard measurement conditions of BMR are of importance → allows:
> - (1) Reproducibility of measurement for an individual
> - (2) For comparison of MRs between individuals or for an individual at different times (Ie. before/after treatment)

> Note: BMR is NOT the lowest possible MR → MR during sleep is lower!

Measuring MR and BMR:

- (1) Direct calorimetry
  - Person stays in a special insulated chamber for several days → total heat energy output by the body (as amt heat energy produced per hour) is directly measured
  - Issue → difficult to measure and impractical
- (2) Indirect calorimetry
  - O_2 consumption by the body is measured to indirectly estimate the total heat energy output by the body → this is based on the fact that metabolic rate of the body is proportional to its O_2 utilisation (such that 1 L O_2 used = 4.8 kcal of energy produced)

> Note – This is because:
> - Vast majority of body's energy is derived from aerobic metabolism → where ATP is produced via [O] phosphorylation in mitochondria → this process requires O_2 consumption in the final reaction in the ETC:
>
> $2\ H + ½\ O_2 \rightarrow H_2O$ (irreversible reaction catalysed by cytochrome oxidase)

  - Three methods exist:
    - (i) Benedict-Roth spirometer – Closed-circuit breathing system filled with 6L O_2 and held in drum → subject breathes in from drum via inspiratory valve, then exhales back into drum via expiratory value (but CO_2 removed via CO_2 absorber) → drum volume decreases with each breath → this is proportional to the rate of O_2 consumption
    - (ii) Douglas bag technique – Expired air is collected using a mouthpiece with inspiratory/expiratory valves → air is analysed for O_2 (and CO_2) content → O_2 consumption (and CO_2 production) then determined

        - (iii) Max-Plank respirometer (used when very ↑ rate of O_2 consumption or prolonged measurements required) – Dry gas meter is used to measure the volume of expired gas → a device in the machine then diverts an adjustable volume of expired gas into a breathing bag → gas analysed like Douglas bag technique

<u>Factors that influence MR and BMR</u>:

- (1) Body size (BSA → height and weight)
    - ↑ BSA → ↑ MR
- (2) Fat/LBM body content
    - LBM produces a ↑ MR cf. fat → this explains why MR of ♂ > MR of ♀ (as ♀ have more fat content than LBM)
    - Note – There is no gender difference in MR based on LBM alone
- (3) Age
    - MR is highest in newborn (MR 2x ↑ cf. adult) and childhood/puberty → due to growth needs
    - MR ↓ with age (due to declining growth rate) → in adults, MR ↓ 2% per decade
- (4) Food intake
    - MR ↑ (by 10-15%) 4-6 hrs postprandial due to processing of food → due to "Specific dynamic action" (SDA) of food (esp of hepatic oxidative deamination of proteins from food)
    - MR ↓ due to starvation/malnutrition → due to ↓ tissue metabolism and cell mass
- (5) Temperature
    - (i) Ambient temperature:
        - ↑ ambient temperature (> core body temp.) → ↓ MR due to ↓ heat loss efficiency
        - ↓ ambient temperature (< core body temp.) → ↑ MR due to heat conserving mechanism activated (esp shivering)

        > Note → BMR is 10% ↓ in tropics than it is in temperate climates

    - (ii) Core body temperature → 1°C ↑ = 10% ↑ in MR (likewise for ↓ temp.)
        - Fever → cellular metabolism → ↑ MR
        - Slight ↓ core body temp. → shivering → ↑ MR
        - Severe hypothermia → ↓ cellular metabolism → ↓ MR
- (6) Skeletal muscle activity → MAJOR factor in influencing MR → this is b/c it is the largest organ in the body and its heat energy production is variable (can ↑↑↑ with activity)
    - ↑ skeletal muscle activity (Eg. exercise, shivering) → ↑ MR
    - ↓ skeletal muscle activity (Eg. sleep, sitting, paralysis with GA) → ↓ MR
- (7) Hormones
    - Thyroxine and SNS outflow (Adr/NAd) → ↑ cellular oxidative metabolism and heat production → ↑ MR
    - GH → ↑ MR (10-15%)
    - Testosterone → ↑ MR
- (8) Pregnancy
    - MR ↑ progressively to 20% above normal levels (esp 2nd and 3rd trimesters) → due to foetal metabolism, placenta, ↑ cardiorespiratory demands, metabolism of additional tissue (esp uterine and breast tissue)
- (9) Lactation → ↑ MR due to milk production and secretion
- (10) Emotional state
    - Anxiety/tension → ↑ SNS activity and muscle tensing → ↑ MR

(c) ***To describe relevant, cellular biochemical pathways and the control of fat, carbohydrate and protein metabolism, including the role of vitamins and trace elements.***

Cellular Energy Metabolism: Overview

Metabolism:

- Defined as sum of chemical processes in the cell → involves (i) anabolism (synthesis of macromolecules) and (ii) catabolism (breakdown of macromolecules)

Generation of cellular energy:

- Cellular energy is generated from aerobic oxidation of metabolic fuels (carbohydrates, fats, proteins) derived from digestion of meal or from breakdown of internal stores:
    - These metabolic fuels are broken down into basic substrates (glucose, a.a., FFA, glycerol) → electrons removed (Ie. oxidation) at high potential from these substrates and transferred to a lower potential → release energy in doing so
    - Reduced coenzymes (NAD^+ and FADH) are intermediate energy storage compounds that aid electron (and energy) transfer from metabolic reactions (glycolysis and TCA cycle) to the electron transport chain (ETC)
    - In the ETC, electrons are transferred through a series of carriers of lower potential → energy released by this is used to form ATP → electrons finally combine with the end electron acceptor (O_2) to form H_2O

> With aerobic metabolism → O_2 consumed at the end of ETC; CO_2 produced (via TCA cycle)

- Cellular energy can also be generated anaerobically → via anaerobic glycolysis of glucose only (see below)

Cellular energy compounds:

- (1) ATP
    - "Energy currency" of the cell – energy stored in high-energy PO_4^{3-} bond → loss of PO_4^{3-} group via hydrolysis forms ADP → this releases energy required for most cellular reactions
    - Body uses 100 mol ATP daily but at any time the body stores only 25 mmol ATP (sufficient for 1.5 mins of resting metabolic functions only) → thus, ATP needs to be continuously recycled from ADP (Ie. very rapid turnover)
    - ATP is generated by harnessing energy from metabolic fuels via:
        - (i) Substrate phosphorylation (glycolysis, TCA cycle) → 5% only
        - (ii) Oxidative phosphorylation (ETC) → 95%

> Aerobic metabolism (glycolysis, TCA cycle, ETC) → 1 mol glucose produces 38 mol ATP
> Anaerobic metabolism (anaerobic glycolysis) → 1 mol glucose produces only 2 mol ATP

> Note – Production of 1 mol ATP by addition of PO_4 to ADP requires ~ 7 kcal

- (2) Creatine phosphate
    - Acts as a back-up energy store in brain and muscle cells → it is formed by transfer of high-energy PO_4^{3-} bond from ATP to creatine

$$\text{ATP + creatine} \leftrightarrow \text{ADP + creatine phosphate}$$

    - With ↑ cellular activity → ATP regenerated for cellular use by transfer of PO_4^{3-} from creatine phosphate back to ADP
- (3) Reduced coenzymes (NAD^+, FADH, NADP)

- Intermediate energy storage compounds that transfer electrons to ETC to generate ATP via oxidative phosphorylation
- NADH (and NADPH) donate electrons early in ETC → 3 ATP made per NADH (or NADPH) oxidised
- $FADH_2$ donate electrons late in ETC → 2 ATP made per $FADH_2$ oxidised

Note: During catabolic reactions → large energy fall forms NADH, intermediate energy fall forms $FADH_2$, small energy fall produces ATP

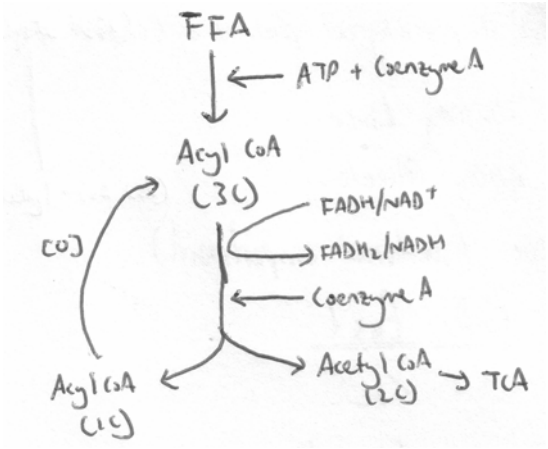
Cellular Energy Metabolism: Catabolic pathways

Overview of catabolic pathways:

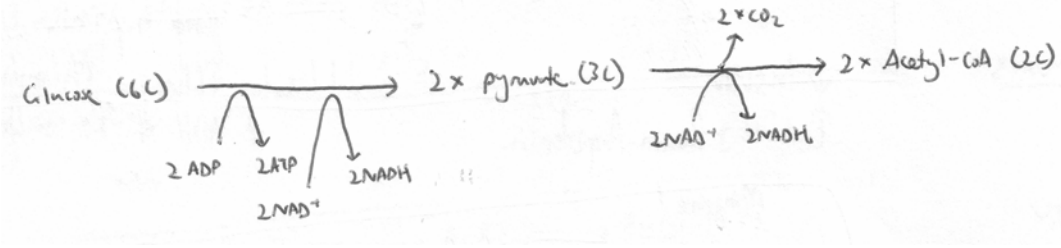
- Metabolic fuel substrates (glucose, a.a., FFA, glycerol) undergo 3 catabolic phases:
  - Phase 1 reactions – Partial oxidation of metabolic fuel substrates (via glycolysis, β-oxidation, oxidative deamination) → 33% of total energy of substrates released
  - Phase 2 reactions – Complete oxidation of phase 1 reaction products via TCA cycle → remaining 66% of substrates' total energy released
  - Phase 3 reaction – Oxidative phosphorylation via ETC

Phase 1 reactions:

- (1) β-oxidation of FFA
  - FFA derived from diet and lipolysis of fat stores (via lipoprotein transport) is partially oxidised in mitochondrial matrix by removal of 2-C moieties (as acetyl CoA) at a time
  - Lipolysis of fat stores is ↑ by GH, GC and Adr (stimulates TAG lipase)

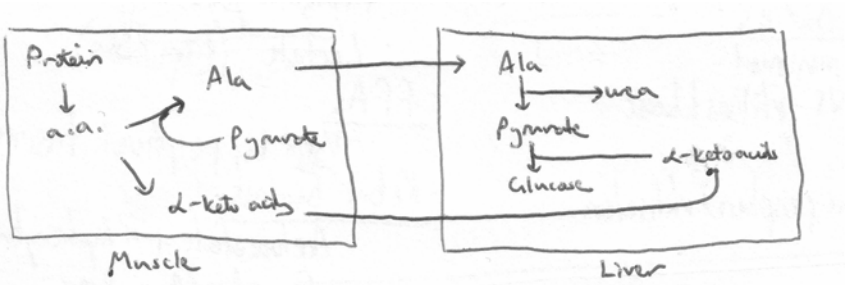


- (2) Glycolysis of glucose
  - Glucose (6-C) derived from diet, GCN (liver) or glycogenolysis (liver, muscle) is partially oxidised via a series of 10 reactions in cytoplasm to 2x pyruvate (3-C):
    - Glucose converted to fructose diphosphate (using 1 ATP) → later cleaved into 2x triose phosphate units → each triose phosphate unit is converted to produce pyruvate (while forming NADH and 2x ATP)
    - Produces net 2x ATP (4x ATP made via substrate phosphorylation, but 2x consumed by hexokinase) and 2x NADH
  - Pyruvate then enters mitochondria and irreversibly reacts with Coenzyme A to produce → (i) Acetyl-CoA (2-C), (ii) CO_2, and (iii) NADH + H^+
  - Glycolysis is ↑ by insulin (stimulates hexokinase, phosphofructokinase, pyruvate dehydrogenase)



- (3) Oxidative deamination of a.a.
  - A.a. derived from breakdown of protein in liver (↑ by glucagon/GC) and muscle (↑ by GC) undergoes oxidative deamination as follows:
    - (i) Transamination – Amino group transferred from C-residue of an a.a. to an α-keto acid to form a new a.a. → this recurs repeatedly until glutamate and aspartate are formed → glutamate dehydrogenase then converts glutamate to NH_3
    - (ii) Urea cycle – NH_3 is converted by liver to urea (see "urea cycle" in liver physiology)

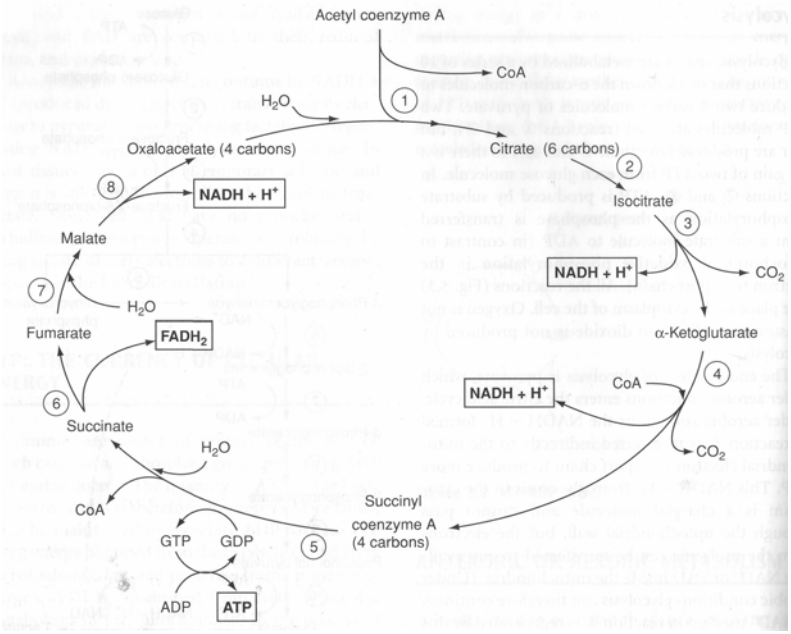
Nb. Muscle transports transaminated a.a. to liver via "glucose-alanine cycle" → b/c muscle cannot produce urea!



    - (iii) C-residue of a.a. (α-keto acid) is partially oxidised to form intermediates that can (a) enter TCA to produce energy , or (b) be converted to glucose and FFAs

Phase 2 reactions (TCA cycle):

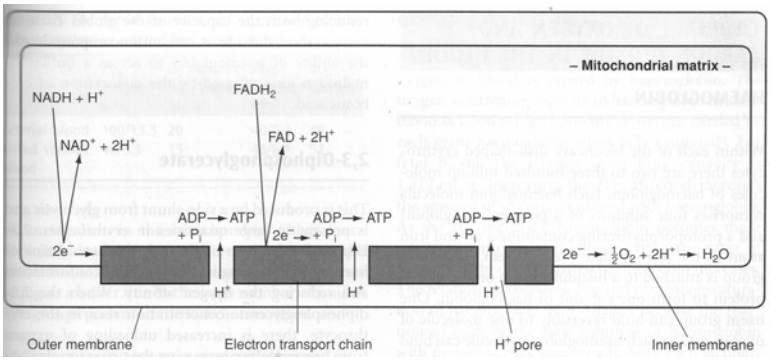
- TCA cycle occurs in mitochondrial matrix under aerobic conditions only → consumes breakdown products of glucose (as acetyl CoA), FFA (as acetyl CoA) and a.a (as TCA intermediates – α-ketoglutarate, oxaloacetate, fumarate, succinyl CoA) to produce → (i) 2x CO_2, (ii) 1x ATP, (iii) 3x NADH + H^+ / 1x $FADH_2$ – per acetyl-CoA metabolised



- TCA cycle stimulated by ↓ $NADH/NAD^+$ ratio (as NADH inhibits dehydrogenase enzymes of the cycle)

Phase 3 reactions (ETC):

- Electrons donated to ETC by $NADH/FADH_2$ → passed along series of cytochromes (along inside surface of inner mitochondrial membrane) down its energy gradient until they are accepted by O_2 at the end (via cytochrome a)
- At each cytochrome, $NADH/FADH_2$ are re-oxidised → releases energy to extrude H^+ across IMM from matrix into inner membrane space → produces a [ ] gradient of H^+ → also regenerates NAD^+/FADH for reuse in phase 1 and 2 reactions (see above)
- At 3 separate points in IMM, channels allow H^+ to flow down its [ ] gradient back into matrix → this releases energy to produce ATP from ADP (via oxidative phosphorylation)
- At end of ETC → O_2 is reduced by H^+ released by re-oxidation of $NADH/FADH_2$ along IMM → forms H_2O

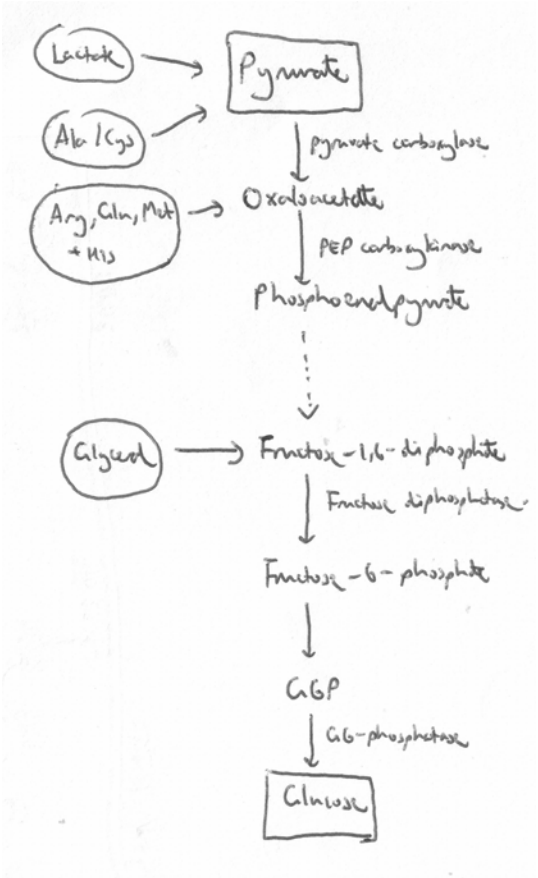


Remember:
- NADH donates electrons at start of ETC → 3 ATP made per NADH oxidised
- $FADH_2$ donates electrons later in ETC → 2 ATP made per $FADH_2$ oxidised

- ETC stimulated by ↓ $NADH/NAD^+$ ratio (as NADH ↓ oxidation rate of ETC enzymes)

Gluconeogenesis:

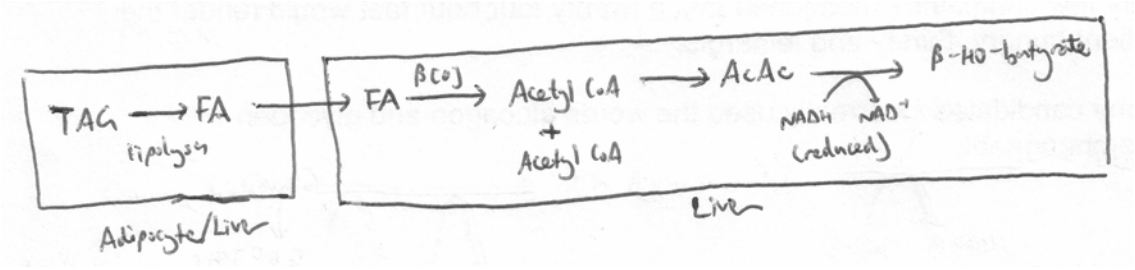
- Occurs 1°ly in liver but also in kidney → glucose is synthesised from non-CHO precursors derived from anaerobic glycolysis, fat and protein catabolism – (i) Lactate (muscle and RBC), (ii) Glycerol (fat), (iii) Glucogenic a.a. (muscle) → released into blood
- Cytoplasmic process → except conversion of pyruvate to oxaloacetate (mitochondria)



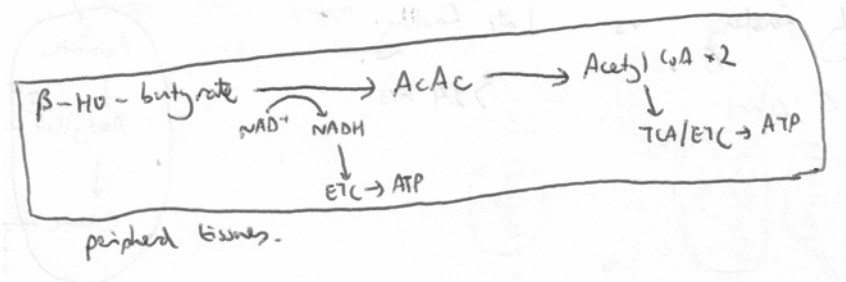
- Gluconeogenesis ↑ with glucagon, Adr, and GH (stimulates fructose diphosphatase and pyruvate carboxylase); ↓ with insulin

Ketone body metabolism:

- Ketone bodies (acetoacetate, β-OH-butyrate) are formed in liver only when there is extra acetyl CoA formed by β-oxidation of excess FFA (2° to ↑ lipolysis by GH, GC, Adr)



- Ketone bodies are released from liver → utilised peripherally by skeletal muscle, heart, kidney (and brain/nervous tissue during starvation)



Nb. Liver cannot utilise ketone bodies as they lack oxo-acid CoA transferase → cannot transfers CoA from succinyl CoA to AcAc → cannot cleave AcAc into 2x acetyl CoA

<u>Cellular Energy Metabolism: Anabolic pathways</u>

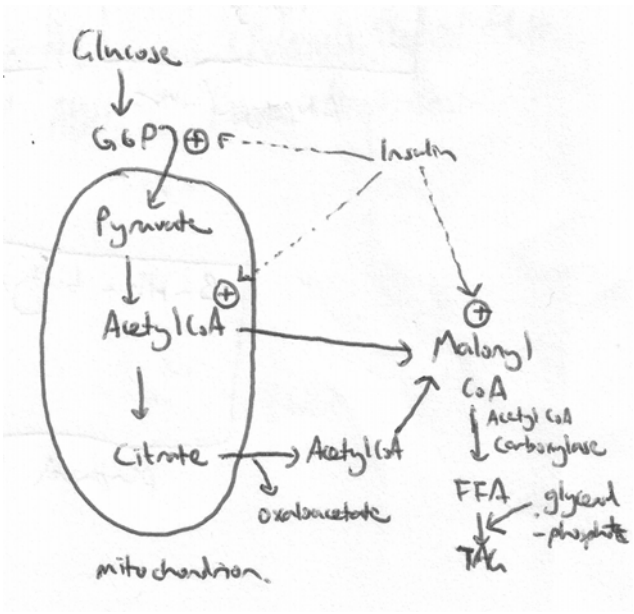
Glycogen synthesis:

- Glycogen stores → branched polymer of glucose (α1,4 and α1,6 links) → (i) Liver (100 g; ½ day supply), (ii) Muscle (400 g), (iii) Brain (minimal; 4 mins supply)
- Glycogen synthesis (glycogenesis) → when excess glucose available:
  - ↑ BGL → ↑ insulin level → (i) promotes glucose entry in muscle (Nb. glucose entry in liver is insulin-independent → dependent on [ ] gradient), and (ii) stimulates glycogen synthetase → builds glycogen store from glucose
- Glycogen breakdown (glycogenolysis) → during glucose deficiency:
  - ↓ BGL → ↑ glucagon/Adr → stimulate glycogen phosphorylase → break down glycogen to G6P → liver has enzyme to convert this into glucose and release it into blood (but muscle/brain lack this enzyme and must use G6P locally only)

Fat synthesis:

- FFA synthesis occurs mainly in liver (and adipose tissue) in the presence of excess glucose → stimulates ↑ insulin which causes:
  - (i) ↑ glycolysis → ↑ formation of acetyl CoA → acetyl CoA diffuses out of mitochondria → ↑ conversion to malonyl CoA (via acetyl-CoA carboxylase) in cytoplasm → finally to FA
  - (ii) ↑ TCA cycle → ↑ formation of citrate → diffuses out of mitochondria → splits into acetyl CoA and oxaloacetate in cytoplasm → acetyl CoA converted to malonyl CoA then FA (as above)

- Nb. NADPH from pentose phosphate shunt is required for FFA synthesis



- FFA can be used to:
  - (i) Store excess chemical energy of foods as TAGs → in liver and adipocyte
    - Lipogenesis (TAG synthesis) → within cytoplasm and ER → 3x Acyl CoA + glycerol phosphate → TAG
    - Lipolysis (TAG breakdown) → forms FFA + glycerol → both released systemically (except in liver where glycerol is converted to glycerol phosphate and utilised locally)
  - (ii) Form phospholipid

Protein synthesis

- Protein (such as muscle protein, plasma proteins, CT, enzymes) is synthesised from a.a. → note that synthesis is limited by availability of essential a.a.'s (which body cannot synthesise and must extract from diet)
- Protein can be catabolised to a.a. → a.a. used for (i) gluconeogesis, (ii) tissue energy production via TCA cycle (during fasting), or (iii) conversion to FFA

<u>Factors Influencing Cellular Energy Metabolism</u>:

- (1) Cellular energy demands
  - ↑ IC [ATP] → inhibits [O] phosphorylation → accumulation of NADH (↑ $NADH/NAD^+$ ratio) → inhibits dehydrogenase enzymes of TCA cycle and oxidation rate of ETC enzymes → ↓ ATP production
  - ↓ IC [ATP] → opposite happens
- (2) Hormonal regulation (Eg. insulin, glucagon, GC, GH, Adr)
  - Acute control → rapid modification of enzyme activity
  - Chronic control → control expression (and quantity) of enzymes present

Aside: Nutrition and metabolic energy of food.

Nutrition: Types of nutrients

Carbohydrates:

- Provide 50% of total caloric intake (1200-2000 kcal/day) → avg intake of 300-500 g/day (with caloric value 4 kcal/g)
- Derived from → starch (esp plant foods – polymer of glucose), sucrose (table sugar – glucose-fructose), lactose (milk – glucose-galactose), and glycogen (meat)

Fats:

- Provide 40% of total caloric intake (1200 kcal/day) → avg intake of 140 g/day (with caloric value of 9 kcal/g → very ↑ energy-concentrated nutrient)
- Derived from 1°ly TAGs but also cholesterol/phospholipids (plants and animals)

Proteins:

- Provide 10% of total caloric intake (300-400 kcal/day) → avg intake of at least 1 g/kg/day (with caloric value of 4 kcal/g)
- Derived from plant/animal proteins → MUST include essential a.a.'s (isoleucine, leucine, valine, lysine, methionine, phenylalanine, threonine, tryptophane) → as body CANNOT synthesise these via transamination

> Note – Body catabolises 200-400 g/day of protein, but a.a. formed is reused → thus, a minimum intake of 20-40 g/day is required for protein balance (although > 1 g/kg/day recommended)

Vitamins:

- Organic compounds that cannot be synthesised by the body and must be derived from diet → they are vital to enzyme systems and metabolic pathways in body
- Two types:
    - (i) Fat-soluble → stored in large amounts in liver
        - Vit A – Derived from β-carotene (fruits/veg) → retinal pigment (rhodopsin) and epithelial tissue repair
        - Vit D – Ca^{2+} homeostasis, bone formation/deposition
        - Vit E – Mixture of tocopherols → anti-oxidant
        - Vit K – Coagulation (CF II, VII, IX, X, C/S)
    - (ii) Water-soluble → freely circulate in body (not stored in any large amount) and excreted in urine
        - Vit C (ascorbic acid) – Prevents scurvy (haemorrhage of skin/internal organs)
        - Vit B1 (thiamine) – Required in pyruvate dehydrogenase → deficiency causes peripheral neuropathy and CCF
        - Vit B2 (Riboflavin) – Required for $FADH_2$ synthesis for oxidative phosphorylation
        - Vit B3 (Nicotinic acid) – Required for NADH/NADPH synthesis for oxidative phosphorylation → deficiency causes dermatitis and diarrhoea
        - Vit B12 (cyanocobalamin) – Contains Co in porphyrin ring → required for nucleic acid synthesis, RBC maturation, and myelin integrity → deficiency causes peripheral neuropathy/spinal degeneration and anaemia
        - Folic acid – Me group transfer and RBC maturation → deficiency causes anaemia and neural tube defects

Minerals:

- Inorganic trace elements (Eg. Zn, Fe, Cu, Mn, Co, Se, I, Cr, Mb) that cannot be synthesised by the body and must be derived from diet → they are vital to enzyme systems and metabolic pathways in body

Metabolic energy of food:

Overview:

- Chemical energy of food is transformed to heat, even in the absence of external work → BUT when external work is done, up to 20% of energy is converted to it (and > 80% of energy is still transformed to heat)

Measuring chemical energy of food:

- Calorie (cal) → amount of energy needed to raise temperature of 1 g of H_2O by 1°C (from 15 to 16ºC) → used as the standard unit of heat energy
- Kilocalorie (kcal or Cal) → amount of energy needed to raise temperature of 1 kg of H_2O by 1°C (from 15 to 16ºC) → unit of energy used for metabolic studies

> Important to note → 1 kcal or Cal = 1000 cal = 4.18 kJ

- Caloric value of food (CVF) → energy released from oxidation of a gram of food (CHO and proteins → 4 kcal/g; Fats → 9 kcal/g)
- Caloric energetic equivalent of O_2 (CEEO) → amount of energy released by food for each mol of O_2 consumed (kcal/L O_2)
- Respiratory quotient (RQ) → ratio of volume CO_2 produced to volume of O_2 used

> Note – RQ varies with non-metabolic factors also → Eg. RQ ↑↑ with exercise and metabolic acidosis (due to ↑ CO_2 expired with hyperventilation); opposite occurs with metabolic alkalosis and sedentary activity

Nutrient	CVF	CEEO	RQ
Glucose	4 kcal/g	5 kcal/L O_2	1.0
Protein	4 kcal/g	4.6 kcal/L O_2	0.8
Fat	9 kcal/g	4.7 kcal/L O_2	0.7

(d) ***To explain the physiological principles of parental nutrition.***

Overview of parental nutrition:

- Parental nutrition is the delivery of nutrients into venous circulation (peripherally or centrally) instead of the enteral route → it can be used to supplement nutrient delivery via enteral route, or supplement nutrient delivery in its entirety (total parental nutrition)
- It is prepared by sterile technique → typically a 3L bag of hyperosmolar solution (containing glucose, amino acids, lipids, H_2O, electrolytes, vitamins and trace elements)
- It can only be administered by CVC due to its ↑ tonicity (Nb. issues with irritation and thrombosis if given via PIVC) → infused over 24 hrs
- It also requires multidisciplinary team involvement

Indications for parental nutrition:

- Indicated for those unable to ingest or digest nutrients or to absorb them from GI tract for a prolonged period of time (> 3-4 days) → includes those who have:
    - (1) A failed trial of enteral feeding
    - (2) Contraindications to enteral nutrition:
        - GI obstruction
        - Upper GI strictures and fistulae (Eg. enterocutaneous fistulae)
        - Severe pancreatitis
        - Prolonged ileus (Eg. major abdominal surgery where feeding not anticipated for days, paralytic ileus)
        - Inflammatory conditions (Eg. IBD or mucositis due to chemotherapy)
        - Short gut syndromes (Eg. major SB resection)

Daily nutritional requirements for parental nutrition:

Nutrient	Requirement
H_2O	30-40 mL/kg/day
Energy	25-30 kcal/kg/day (can ↑ up to 1.5-1.75x with disease/stress)
Nitrogen	0.5 g/kg/day (can ↑ to 1-1.5 g/kg/day with disease/stress)
Glucose	3 g/kg/day
Lipid	2 g/kg/day
Na^+	1-2 mmol/kg/day
K^+	0.7-1 mmol/kg/day
Ca^{2+}	0.1 mmol/kg/day

BUT these vary according to:

- (1) Physiological factors:
    - Age, gender, body size
    - Pregnancy
    - Activity level
    - Hydration status
- (2) Pathological factors
    - Burns and sepsis → ↑ protein and caloric intake
    - Renal failure → ↓ volume, protein and electrolyte (esp K^+) content
    - CCF → fluid reduction
    - Hepatic failure → ↓ a.a/protein content to prevent encephalopathy
    - Respiratory failure → ↓ glucose to minimise CO_2 production

Components of parental nutrition:

- (1) Energy source → glucose:lipid mixture (60:40 or 50:50)
    - (a) Glucose (as 50% dextrose)
        - Used as an energy substrate → provides 50% of daily caloric needs

        - Glucose has ↓ energy density → 3.4 kcal/g only (cf. 4 kcal/g for carbohydrates) → 50% dextrose needs to be given (1 L = 940 kcal) → BUT this is hypertonic (1900 mosm/L) and requires delivery via CVC
        - Insulin can be given to aid glucose utilisation (esp in stressed patients)
        - Need to avoid excess glucose delivery → risk of ↑ BGL, lipogenesis (liver disease), ↑ MR and ↑ CO_2 production (delayed ventilatory wean)
    - (b) Lipid (as 10% or 20% intralipid)
        - Used as (i) an energy substrate (provides 30-40% daily caloric needs), and (ii) provision of essential FAs (vital for cell membranes and PG synthesis)
        - ↑ energy density cf. glucose → 1.1 kcal/mL (10%) and 2 kcal/mL (20%) → thus 1000 kcal can be achieved by 500 mL of 20% or 1L of 10%
        - Can be infused separately (Ie. not mixed with glucose/a.a. solution) → can be given 1x/week BUT usually given daily to aid caloric delivery in the smallest volume of solution
- (2) Nitrogen-source (as symthamin 17)
    - Used for (i) tissue protein synthesis (Eg. enzymes) and (ii) caloric needs
    - Includes > 50% essential a.a.'s (isoleucine, leucine, valine, lysine, methionine, phenylalanine, threonine, tryptophane) and > 25% branched chain a.a
    - Nb. A.a. are all L-isomers (as the body cannot use D-isomers)
- (3) H_2O → to maintain body H_2O balance and replace losses (Eg. dehydration, bleeding)
- (4) Electrolytes ($Na^+/K^+/Cl^-/PO_4^{3-}/Mg^{2+}$, Ca^{2+}) → to maintain and replace losses
- (5) Vitamin/trace elements → vital to enzyme systems and metabolic pathways in body
    - Vitamin solutions – both H_2O and fat-soluble vitamins (esp folic, thiamine, vitamin K)
    - Trace elements (Zn, Fe, Cu, Mn, Co, Se, I, Cr, Mb)

<u>Monitoring of parental nutrition</u>:
- Needed to assess for (i) progress of nutritional state and (ii) complications of therapy
- Involves:
    - (i) Clinical r/v (Eg. fluid balance, weight, nutritional assessment, infections)
    - (ii) Frequent ward glucose testing (until BGL stabilises)
    - (iii) Investigations → daily EUC, CMP, BGL; weekly FBC, LFT (incl albumin), Coags, Lipid studies, and plasma/urine osmolality

<u>Complications of parental nutrition</u>:
- (1) Catheter-related (MOST common) → PTX, chylothorax, embolism (air/thrombus), infection, Etc.
- (2) Fluid/electrolyte disturbances
    - Fluid overload or hyperosmolar dehydration
    - Electrolyte disturbances
    - Normal AG metabolic acidosis (due to ↑ Cl^- content)
- (3) Metabolic disturbances
    - Hyperglycaemia (initially) → delay in ↑ endogenous insulin (thus supplemental insulin required)
    - Rebound hypoglycaemia (with abrupt cessation of TPN) → due to ↑ levels of endogenous insulin
    - Metabolic bone disease
- (4) Others:
    - Immune suppression (due to fat component)
    - Liver disease → initially deranged LFTs → later fatty liver/steatohepatitis
    - ↑ $PaCO_2$ (due to excessive glucose metabolism)

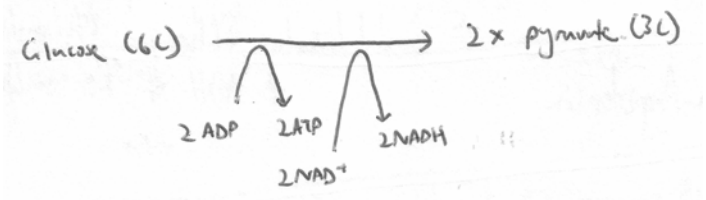
(e) ***To describe the consequences of anaerobic metabolism.***

Anaerobic metabolism:

- Anaerobic metabolism occurs when there is a cellular environment that is either:
  - (i) Lacking mitochondria (Eg. RBC) → this is b/c mitochondria is required for aerobic metabolism of metabolic substrates (Ie. via TCA cycle, ETC, β-oxidation)
  - (ii) Hypoxic (↓ PO_2) → this is b/c aerobic metabolism requires O_2

> Note – In the absence of O_2:
> - ETC cannot function as it requires O_2 as a terminal acceptor of electrons → causes accumulation of NADH/$FADH_2$ and loss of oxidative phosphorylation
> - TCA cycle cannot function because → pyruvate is no longer converted to acetyl CoA (↑ NADH inhibits pyruvate dehydrogenase), and there is lack of NAD^+/FADH (due to ↑ NADH/$FADH_2$ levels 2° to defunct ETC)
> - β-oxidation and KB metabolism cannot function because → lack of NAD^+/FADH and their products cannot be fed into TCA cycle/ETC

- During anaerobic conditions, glycolysis is the ONLY catabolic pathway that can occur:
  - (i) Glucose (6-C) is partially oxidised via a series of 10 cytoplasmic reactions to 2x pyruvate (3-C) → this also produces net 2x ATP (4x ATP made via substrate phosphorylation, but 2x consumed by hexokinase) and 2x NADH + H^+



  - (ii) Under anaerobic conditions, pyruvate is instead reduced to lactate within the cytoplasm → this requires LDH (lactate dehydrogenase) and NADH (as a reducing agent)

  - (iii) This is vital for anaerobic glycolysis to continue b/c this allows NADH to be reoxidised to regenerate NAD^+ for reuse in glycolysis

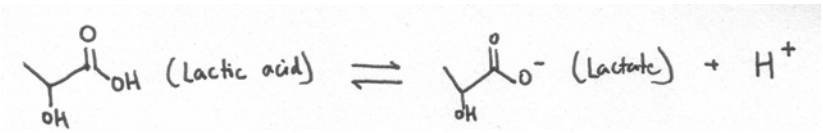
> Note: Under aerobic conditions, pyruvate is instead oxidised to acetyl CoA → fed into TCA cycle (producing CO_2 and NADH/ATP) → then into ETC (consuming O_2 to produces H_2O and ATP)

Consequences of anaerobic metabolism:

- (1) ↓ ATP production → total 2 ATP produced per glucose via substrate phosphorylation alone (cf. aerobic metabolism where total 38 ATP produced per glucose via both substrate and oxidative phosphorylation)
- (2) Unable to metabolise other metabolic substrates (Ie. FFA, KB, a.a) → glycolysis is the only catabolic pathway available
- (3) Production of lactate (see below)

Anaerobic metabolism: Lactate

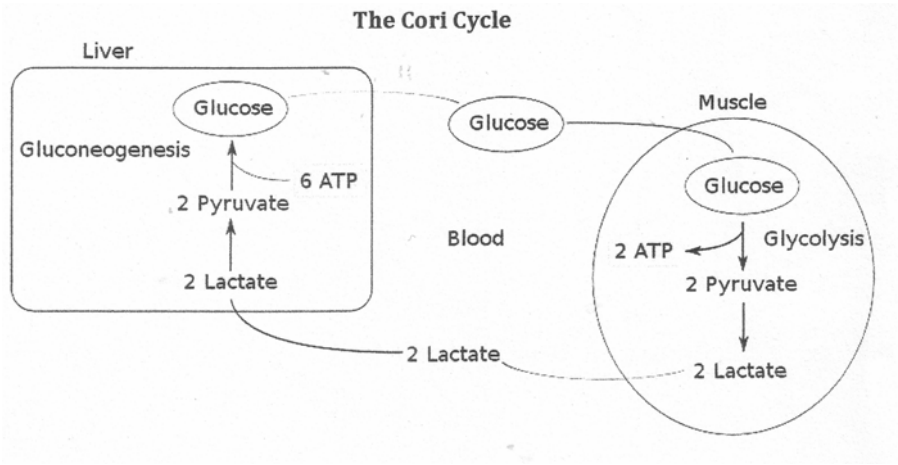
- Lactate is the conjugate base of lactic acid (an organic 3-C acid)



- It is produced by anaerobic metabolism of pyruvate (see above reaction) either:
    - (i) Physiologically → in RBC (no mitochondria), renal medulla (↓ PO_2), cornea/ lens (↓ PO_2) → hence, normal plasma [lactate] is 0.5-2 mM (and NOT zero!)
    - (ii) Pathologically → reduced tissue perfusion and/or O_2 delivery (Eg. shock, hypoxaemia) → thus, plasma [lactate] ↑↑↑ (> 2 mM)

> Note: Plasma [lactate] is an indicator of anaerobic metabolism → so ↑ [ ] = ↑ anaerobic metabolism

- Plasma [lactate] is 0.5 – 2 mM (and NOT zero) due to physiological production → it can be measured clinically as an indicator of anaerobic metabolism (Ie. ↑ anaerobic metabolism due to pathological situations lead to ↑ [lactate])
- Fate of lactate:
    - (1) Persistent anaerobic metabolism (Ie. ongoing hypoxia) causes an accumulation of cellular lactate → this diffuses out of the cell into plasma along its [ ] gradient → lactate can then be: (a) Used as a fuel source by the heart and brain
        - (b) Transported to the liver where it is:
            - (i) Converted back to glucose via gluconeogenesis (requires 6x ATP), which is then transported back peripherally for use → "Cori cycle"
            - (ii) Converted to pyruvate intermediate → utilised locally in TCA cycle for ATP production via oxidative phosphorylation



    - (2) Resolution of hypoxia (Ie. tissue O_2 tension restored) → intracellular lactate can be oxidised back to pyruvate for use in local tissue aerobic metabolism (Ie. fed into TCA cycle)

(f) ***To describe the physiological consequences of starvation.***

Body energy substrate reserves and utilisation:

- Body energy substrate reserves:
  - Glycogen stores → (i) Liver (100 g; ½ day supply), (ii) Muscle (400 g), (iii) Brain (minimal; 4 mins supply) → source of glucose
  - Fat stores (as TAG) → liver and adipose tissue → source of FFA and glycerol
  - Protein stores → muscle protein, plasma proteins, CT, enzymes → source of a.a.
- Body energy substrate utilisation:
  - Brain/nervous tissue – 1°ly uses glucose for energy, but uses KBs with fasting
  - Cardiac muscle – Use FFA, lactate and KB for energy
  - RBC – 1°ly uses glucose for energy
  - Skeletal muscle
    - Uses FFA and ketone bodies for energy
    - Glucose can be used for energy (esp with hyperglycaemia or anaerobic conditions (Eg. exercise)) or glycogen storage
  - Adipose tissue – Uptake of glucose, glycerol and FFA → forms TAG for storage (lipogenesis); also breaks TAG into FFA/glycerol (lipolysis)
  - Liver → integral role in starvation
    - Control BSL by controlling glycogen stores and gluconeogenesis
    - Takes up all metabolic fuel substrates → can interconvert them (Eg. gluconeogenesis, ketogenesis)
    - Vital source of circulating metabolic fuel substrates

Body fluid reserves and utilisation:

- Body fluid reserves:
  - TBW 60% of weight (~ 42 L in 70 kg adult) → 1°ly intracellular (Eg. adipose, muscle, liver, lungs, GIT, interstitium, Etc.)
  - Metabolic H_2O (350 mL/day)
- Body fluid utilisation:
  - IWL from skin/lungs (900 mL), faecal loss (100 mL) and sweat loss (50 mL)
  - Renal loss can be varied

Physiological effects of early fasting (< 24 hrs):

Nature of fasting	Fasting 6-12 hrs is a daily occurrence (Ie. sleeping) → generally well-tolerated due to adequate fuel/fluid body reserves → a/w mild hunger/thirst and minimal lethargy
Caloric losses	Up to 25-30 kcal/kg in 24 hrs (~ 1 kcal/kg/hr)
Effect on energy substrate source	Initially → glucose main energy substrate → derived from: - Food intake prior to fast → continued absorption of glucose from food remaining in the GI tract - Glycogenolysis → glycogen stores rapidly exhausted within 12-24 hrs: o Liver stores → glucose released systemically (important) o Peripheral stores (muscle, brain) → glucose used locally only (cannot release it systemically due to lack of glucose-6-phosphatase) - Gluconeogenesis in liver (and kidneys) → very minor role Later → other fuel sources become main energy substrates: - FFA → released from adipose tissue by lipolysis → next major energy source - Ketone bodies (acetoacetate, β-OH butyrate) → small amounts produced by liver from FFA derived from lipolysis → minor energy source
Effect on energy substrate utilisation	- Brain/nervous tissue maintains glucose utilisation for energy - ↑ utilisation of FFAs and KBs by other tissues for energy (Eg. heart, kidney, skeletal muscle, adipose, Etc.) → preserves glucose use for brain/nerve tissue - ↓ glucose uptake and utilisation by insulin-dependent tissues (muscle, adipose)
Fluid losses	Up to 25-35 mL/kg in 24 hrs (~ 1-1.5 mL/kg/hr)
Effect on water balance	- Mobilisation of body fluid reserves - Ongoing losses as part of IWL, and in faeces/sweat

	- ↓ renal loss (↓ urine output) → produce ↑ concentrated urine

Hormones	- ↓ insulin levels → causes:
	  - Liver: ↑ glycogenolysis and GCN (with glucose release), ↑ ketogenesis
	  - Muscle: ↓ glucose uptake, ↑ glycogenolysis, ↓ protein synthesis
	  - Adipose: ↑ lipolysis (with FFA/glycerol release), ↓ glucose/TAG uptake
	- ↑ ADH and AII/aldosterone levels → causes thirst and ↑ tubular reabsorption of H_2O/Na^+

Physiological effects of sustained fasting (> 24 hrs):

Nature of fasting	Rare occurrence→ poorly tolerated due to significant mobilisation of fuel/fluid reserves needed to compensate for lack of fluid/caloric intake → a/w significant hunger, thirst and lethargy
Caloric losses	25-30 kcal/kg per day
Effect on energy substrate source	- Gluconeogenesis is main source of glucose as glycogen stores depleted → synthesises glucose using glucogenic a.a. (esp alanine; from skeletal muscle protein), glycerol (from TAGs in adipose and liver stores), and pyruvate/lactate (from RBC, skeletal muscle) Note: Glucose generated in liver from (i) alanine derived from skeletal muscle via "Glucose-Alanine cycle"; and (ii) lactate/pyruvate from peripheriess via "Cori cycle" - ↑ plasma levels of FFA and glycerol due to ↑ lipolysis of fat stores - ↑ plasma levels of ketone bodies due to ↑ ketogenesis by liver - ↑ plasma levels of a.a. due to ↑ catabolism of protein stores (esp in muscle) Note: Protein sparing occurs with prolonged fasting (Ie. 75 g protein catabolism/day in first few days of fasting → ↓ to 20g/day after 3 weeks) → due to (i) ↓ gluconeogenesis (Ie. ↓ utilisation of glucogenic a.a. from protein stores) a/w ↓ glucagon levels, and (ii) ↑ tissue reliance on FFA/ketone body (Ie. ↑ lipolysis of fat stores instead)
Effect on energy substrate utilisation	- Brain/nervous tissue → ketone bodies replace glucose as main fuel source - Other tissues → heavily reliant on FFA/KB as fuel sources
Fluid losses	25-35 mL/kg per day
Effect on water balance	- Fluid reservoirs depleted - Ongoing IWL, losses in faeces and sweat - Obligatory urine loss (430 mL/day)

Hormones	- ↓↓↓ insulin levels
	- ↑↑↑ ADH and AII/aldosterone levels
	- ↑ glucagon levels → causes:
	  - Liver: ↑ glycogenolysis and GCN (with glucose release), ↑ ketogenesis
	  - Muscle and adipose: Minimal effects
	  - Nb. Levels peak at day 4 then ↓ to prefasting levels at day 10 → a/w ↓ gluconeogenesis (esp using a.a.'s) → protein-sparing mechanism
	- ↑ cortisol levels → causes:
	  - Liver: ↑ glycogenolysis and GCN with glucose release
	  - Muscle: ↑ protein catabolism (and a.a. release), ↓ glucose uptake
	  - Adipose: ↑ lipolysis (and FFA/glycerol release)
	- ↑ Adr levels → causes:
	  - Liver: ↑ glycogenolysis and GCN (with glucose release), ↑ ketogenesis
	  - Muscle: ↑ FFA utilisation, ↑ glycogenolysis, ↓ glucose uptake
	  - Adipose: ↑ lipolysis (and FFA/glycerol release), ↓ glucose uptake
	- ↑ GH levels over first 24-48 hrs → then ↓

(g) ***To describe the metabolic consequences of sepsis, burns and trauma.***

Metabolic consequences of sepsis, burns and trauma → involve "stress" response which is characterised by:

- (1) General hypercatabolic state → involves breakdown of:
  - Carbohydrates → ↑ BGL due to ↑ hepatic glycogenolysis and gluconeogenesis
  - Fat → ↑ lipolysis of TAG stores, ↑ FFA utilisation peripherally, ↑ ketogenesis
  - Protein → ↑ skeletal muscle breakdown (lose LBM), net –ve N-balance, conversion of a.a. to glucose in liver
- (2) Hypermetabolic state (↑ BMR and MR) due to ↑ catabolism
- (3) Pyrexia → due to pyrogen- or cytokine-induced rise in core body temperature (via central hypothalamic effect)
- (4) ↑ resting energy expenditure (and ↑ energy intake demands) due to:
  - (i) hypermetabolic state
  - (ii) ↑ thermogenesis (a/w pyrexia and loss of body heat (Ie. 2° to wounds))
- (5) "Stress" hormonal response → promotes hypercatabolic response
  - ↑ plasma levels of glucagon, catecholamine, cortisol → hypercatabolic response
  - ↑ plasma levels of insulin BUT a/w tissue insulin resistance
  - ↓ plasma GH levels
- (6) Tissue hypoxia → due to arterial hypoxaemia, tissue hypoperfusion, autoregulatory dysfunction and DIC
  - Anaerobic metabolism occurs due to insufficient tissue O_2 delivery → ↑ diversion of pyruvate substrate from glycolysis to form lactic acid → inefficient production of energy (2 ATP with substrate phosphorylation vs 38 ATP with oxidative phosphorylation)
  - Hepatic hypoperfusion means lactic acid cannot be processed in liver via Cori cycle back into glucose
- (7) Metabolic acidosis
  - ↓ pH due to depletion of HCO_3^- and ↑ H^+ production from tissue metabolic acid production (Eg. Lactic acid)
  - Compensated by buffering (acute), respiratory compensation (hrs-days), renal correction (days-weeks)