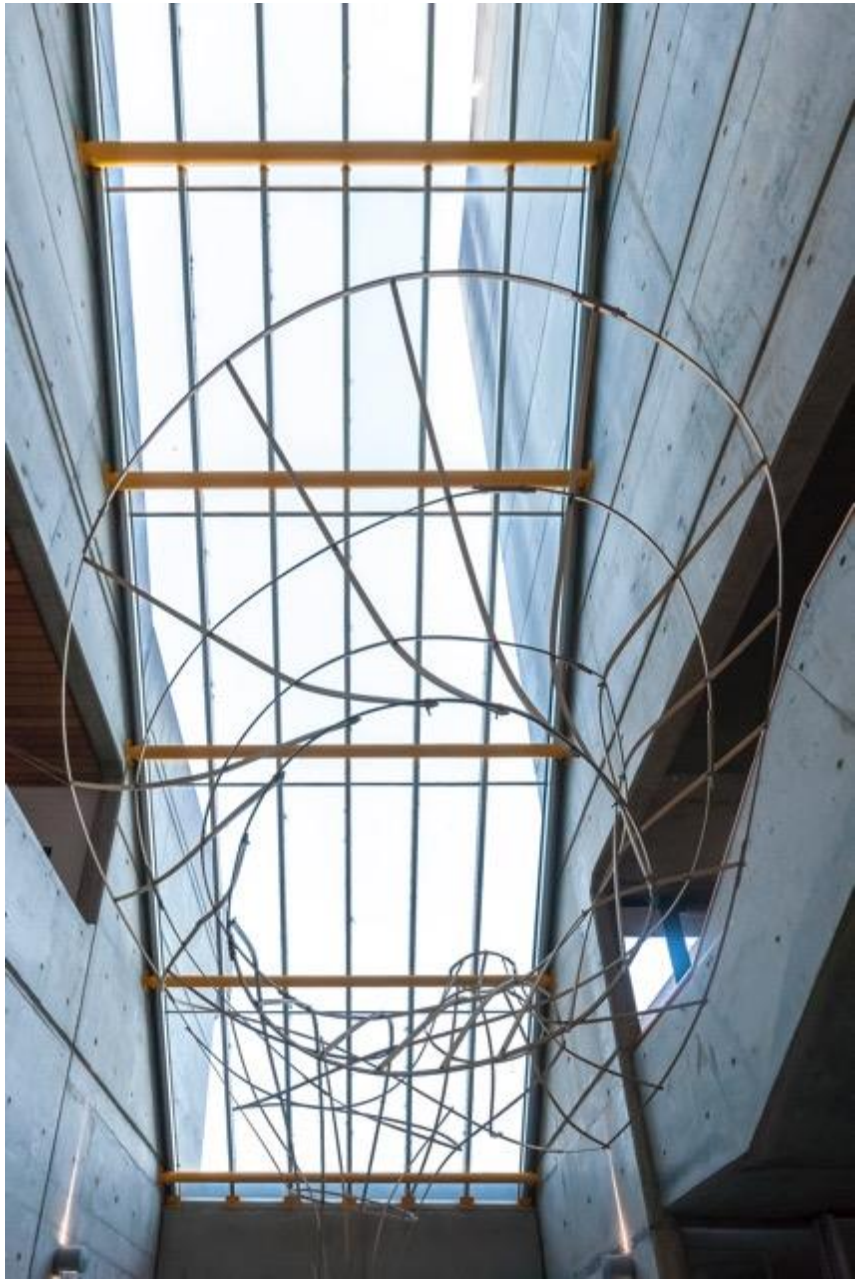
Ask Weber
Session 7

Topics 18 and 19

Energy & metabolic pathways



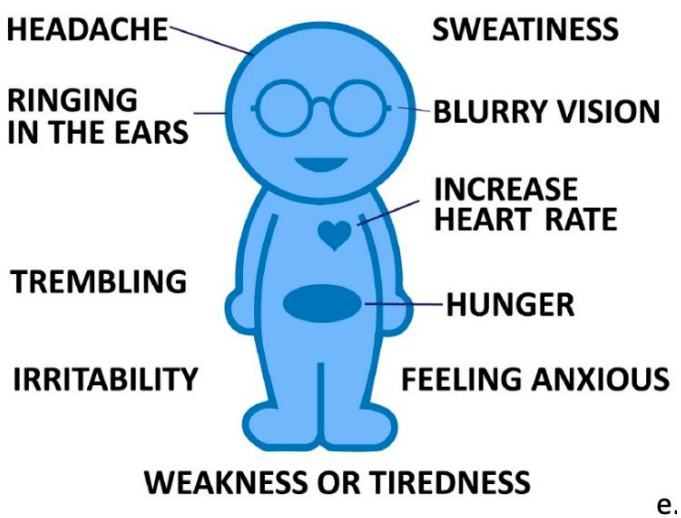
THE UNIVERSITY OF SYDNEY

Fuels

Energy utilization and sources

1. **What energy source does the brain, heart muscle and skeletal muscle use?**
    1. The brain uses glucose primarily (not in lecture, but brain can also function off ketone bodies when in starvation)
    2. cardiac muscle uses fatty acids, lactate, ketone bodies
    3. Skeletal muscle can use both glucose and fatty acids as well as ketone bodies

1. **What are the signs of hypoglycaemia?**
    - Headache, hunger
    - Sweatiness, blurry vision, anxiety, trembling, increased HR, irritability
    - Weakness/fatigue



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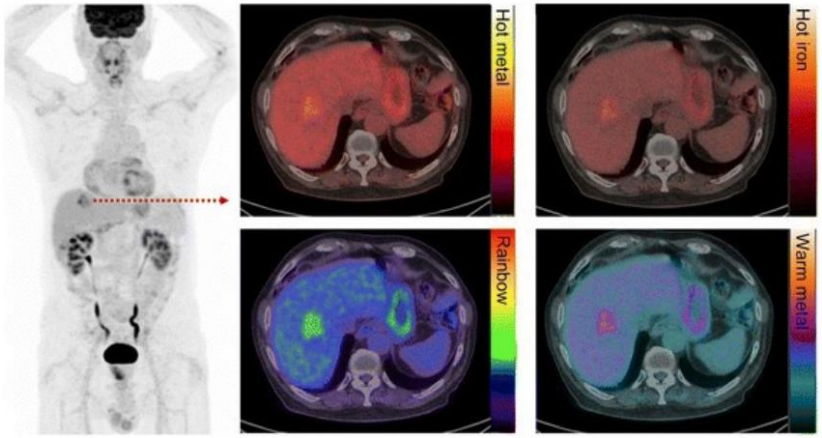
Radiolabelling

- **How does the Warburg effect relate to radiolabelled imaging for cancers and metastases?**
  - Cancers primarily metabolise glucose (Warburg effect). By radiolabelling glucose (e.g. FDG) and injecting it into the patient, we can see regions of high glucose utilization. These areas will light up in the body scan. The scan itself is called a PET scan.



Energy generation from alternative sources

1. **How is energy generated cellularly (i.e. respiration) from glucose?**
    1. Aerobic respiration: Glucose undergoes glycolysis to form pyruvate
        1. Pyruvate can be converted to acetyl CoA, and enter the citric acid cycle
    2. Anaerobic respiration: Glucose undergoes glycolysis to form pyruvate (which then forms lactate) – doesn't enter citric acid cycle, but generates 4 ATP (uses 2 in process – i.e. net 2 ATP production)

1. **How is energy generated from fatty acids?**
    1. Fatty acids can be broken down into Acetyl-CoA
    2. Acetyl CoA can enter the citric acid cycle to form ATP in aerobic respiration

ATP production rates

1. **How is exercise proposed to increase ATP production in the long run?**
   - More exercise = more calcium in muscle (for contractions)
   - More contraction = more ATP usage = more AMP in muscle (recall ATP can break down into AMP)
   - More calcium AND more AMP = more mitochondrial production (via some upregulation mechanism?)

Feeding, fasting, starving

1. **Describe the absorptive state in feeding**
    1. Occurs 4h after a meal
    2. The meals TYPICALLY contain glucose (either directly or via carbohydrates)
    3. All tissues will utilize glucose in this state
2. **Describe the post-absorptive state (fasting)**
    1. Occurs 4-30h after a meal
    2. Glucose has either been initially utilized or is currently being stored (as glycogen)
    3. Tissues will reduce glucose utilization (except brain – brain always wants glucose when available)
    4. Glucose can be additionally re-utilized through breakdown of glycogen (glycogenolysis) and amino acids

1. **Describe what happens to the body after 30 hours of no feeding (starving)**
    1. Non-brain tissues stop using glucose (recall – brain ALWAYS wants sugar)
    2. Liver and kidney needs to remobilise glucose (from stored glucose – glycogenolysis and amino acids)
    3. If glucose runs too low, brain can start using ketone bodies (via ketogenesis – fatty acid breakdown)

Starvation

1. **What is the order of biomolecular utilization in starvation?**
    1. Fats are used first – fatty acids can be converted into Acetyl CoA, which can then be used in the citric acid cycle to produce ATP, as well as be used in the production of ketone bodies (ketogenesis). Ketone bodies can be used by the brain
    2. Amino acids (i.e. protein, muscle breakdown) can then be used – at this point, you will start looking cachexic. These amino acids get turned into pyruvic acid or acetyl-CoA, which can enter the citric acid cycle as well

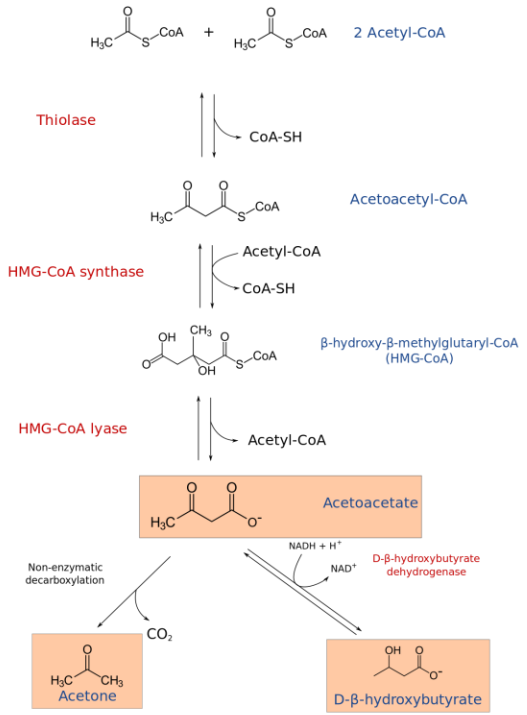
What is ketogenesis?

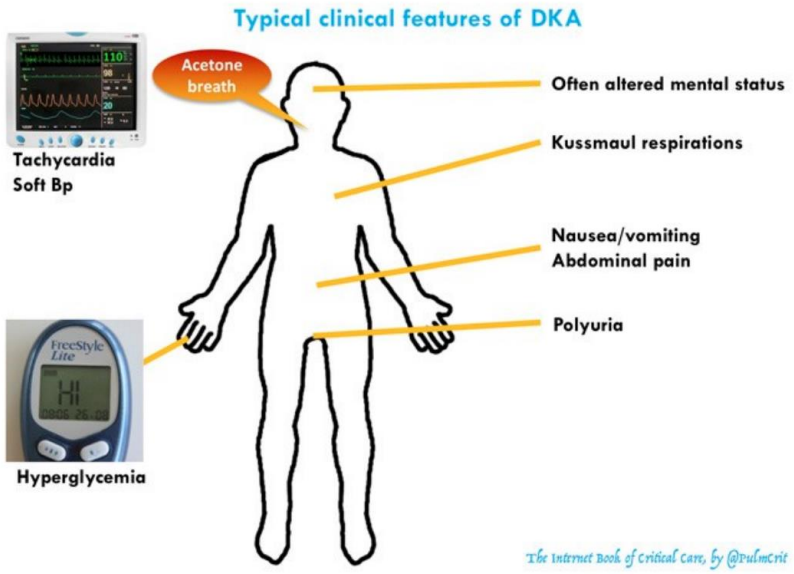
In type 1 diabetics, patients are unable to produce insulin. If they don't take their insulin medication, a few things happen

1. Glucagon levels increase – liver undergoes gluconeogenesis and glycogenolysis – this can form ketone bodies
2. Adipose tissue will undergo lipolysis – this can form ketone bodies

The result of this is called diabetic ketoacidosis, as the ketone bodies and the process of production will acidify the blood. What clinical signs/symptoms do you expect to see in someone with DKA, and why?

1. Hyperglycaemia
2. Tachycardia
3. Fruity breath
4. Kussmaul breathing
5. Polyuria
6. Altered mental status





Microbiome

Microbes on our body

1. **What is the difference between a pathogen/parasite and a commensal?**
   - Pathogens and parasite can cause pathologies (i.e. diseases)
   - Commensals (99% of microbes) may potentially even help us

– **Where on the human body do microbes typically colonise?**
  – Skin
  – Gut, oral mucosa, etc.
  – ?Internal, extracellular – can't really think of where…

- **In what manners can microbes trigger an immune response?**
  - Cell or tissue damage - body responds by trying to get rid of the causative agent
  - Simply colonizing might trigger an immune response

Immune responses

- **What are the 2 main types of immune responses and what do they do?**
  - Innate immunity – a general immune response that initiates inflammation and attacks anything foreign
    - Might also induce programmed cell death for identified infected cells
  - Adaptive immunity – a specific immune response to a target organism/microbe, can produce specific antibodies

- **How does a strong immune response potentially hurt us?**
  - Ongoing damage can occur
  - Inflammation might kill the bacteria/microbe, but inflammation is NOT good for us (think of this – chronic inflammation is considered a precursor to cancer)
    - Chronic inflammation will result in tissue damage
  - Immune complex formation – antibodies can form clumps and deposit in random places where we don't want them to (e.g. Henoch-Schonlein purpura, an IgA vasculitis)
  - Autoantibody formation (e.g. rheumatic fever after a Group-A Streptococcus infection – can cause endocarditis, higher risk in Indigenous children)
  - Cell death, inflammation, etc.

DAMP, MAMP, PAMP, Lamp?

- **What is the function of a DAMP, and what is the function of a PAMP in the case of an organism such as Vibrio cholerae?**
  - Vibrio cholerae is a pathogen. All pathogens will activate an innate and adaptive response. DAMP and PAMPs are part of the innate response
    - DAMP – Damage associated molecular patterns; essentially any molecules which are found on HUMAN CELLS WHICH ARE DAMAGED
    - PAMP – Pathogen associated molecular patterns (which is now called MAMP – microbe associated molecular pattern) are molecules which are found on MICROBES

- **What do MAMPS, DAMPS do?**
  - The body's immune cells will recognize MAMPs and DAMPs
  - Just note that DAMPs should not really be present in the normal, healthy human – MAMPs might be (as not all microbes are bad), but they shouldn't really be in the blood…
  - These cells in the innate immune system respond by activating inflammation, etc.

The microbiome

- **How do microbes affect our gut function postnatally?**

- **Does the large or the small intestine have more microbes?**
  - Large intestine has mode
- **Difference between small and large intestine microbiome? What about in herbivores vs carnivores?**
  - SI – stable occupation by distinct microbes
    - Microbes in herbivores allow for fermentation in herbivores, but tends not to be as common in carnivores
  - LI – higher density

Microbiome in the large intestine

- **What are the most common microbes in the gut?**
  - Bacteria most common
    - Bacteroidetes – involved in fermentation and breakdown of large chain polysaccharides into short chain fatty acids
    - Firmicuties – fermentative metabolism
    - Proteobacteria – metabolically diverse, fermentation, more commonly break down sugars, amino acids, small chain fatty acids
  - Archaea
    - Methanobrevibacter- involved in methanogenesis, breakdown of small carbons into methane!

- **How do intestinal microbes allow us to maximise carbohydrate consumption in vegetables?**
  - Large intestine microbes secrete enzymes, ferment sugars and synthesize biomolecules
  - They allow slow transit of 'fibre', in the process breaking down insoluble polysaccharides (e.g. cellulose – in plant walls) and exposing nutrients within cells that can then be altered and absorbed (incl. SCFA, amino acids, vitamins, etc.)

Microbiome benefits to us

- **What short chain fatty acids are produced by the microbiome in the large intestine?**
  - Via fermentation, simple carbohydrates can be converted into
    - Acetate
    - Propionate
    - Butyrate
    - Etc
- **What is the function of butyrate in our gut?**
  - Butyrate acts as an energy source for the colon – It is produced BY bacteria in the colon, FOR the colon!

– **How can a gut microbiome dysregulation result in formation of a toxic metabolite?**
  – Sulfate reduction can occur, which converts short chain fatty acids into H2S (rotten egg gas) via an anaerobic respiratory process

Microbiome benefits to us

- **What is nutrient control?**
  - Control of nutrients available to different segments of the digestive tract
    - Small intestine has all nutrients absorbed quickly, quick passage means limited time to grow
    - Large intestine works much slower, creates a different nutritional milieu
  - Fermentative metabolism in large colon allows release of SCFA and fibre metabolism
    - Low iron = low oxygen = anaerobic/fermentative respiration
    - Nitrogenous wastes (urea, uric acid) allows growth on fibre