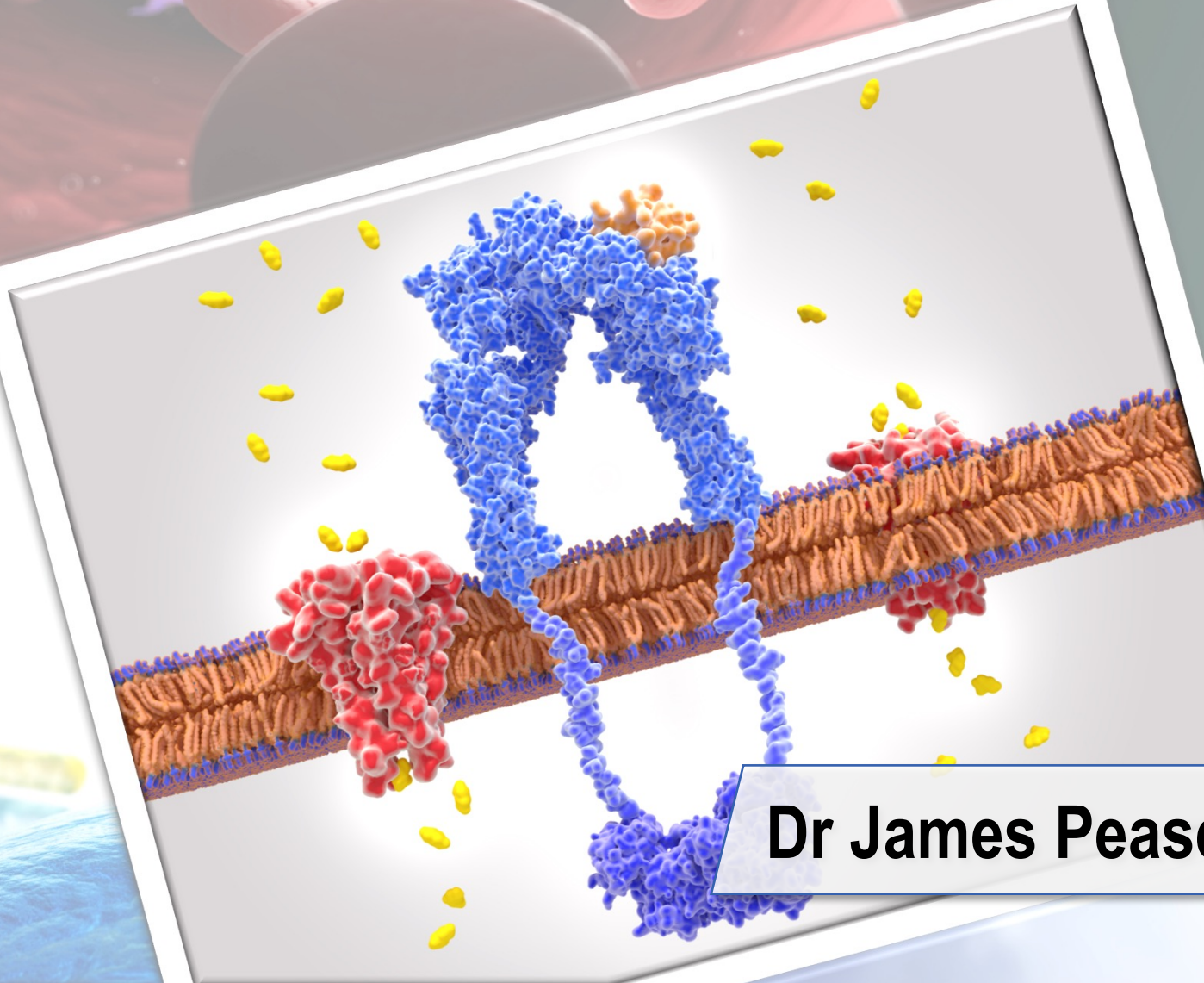


Integration of metabolism



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Session Plan



Part 1

Energy intake vs expenditure

Metabolic features of tissues

- Skeletal muscle
- Brain
- Heart
- Liver

Part 2

Gluconeogenesis

Energy stores and consumption

- Aerobic respiration
- Anaerobic respiration

Part 3

Control of metabolic pathways

- Enzymatic control
- Hormonal control

Diabetes mellitus

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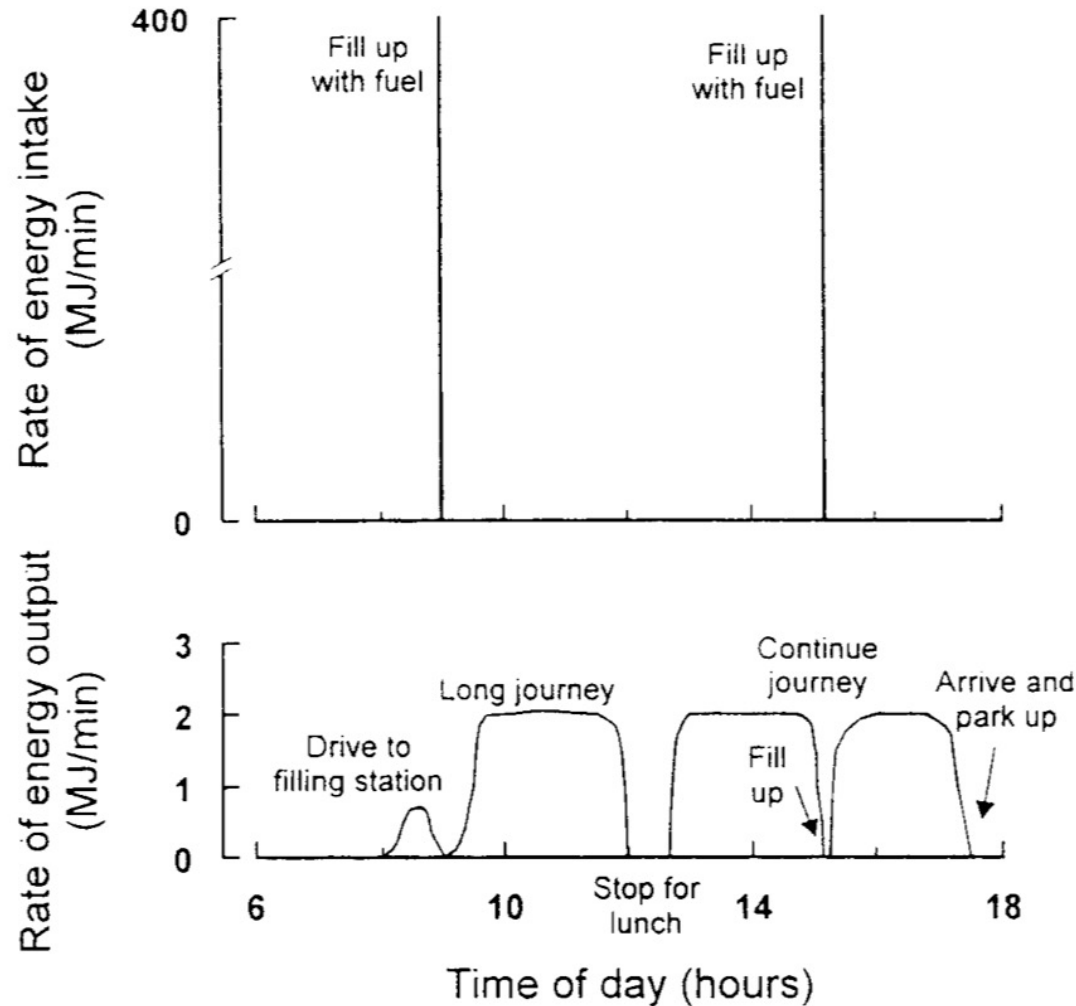
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Energy intake v energy expenditure – an analogy

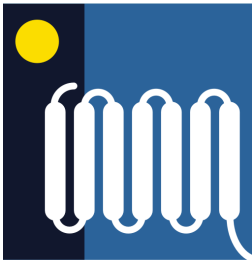


Energy intake needs to be **tightly coordinated** with energy expenditure

Different tissues often have **distinct** fuel requirements.

From: 'Metabolic Regulation: A Human Perspective' by K.N. Frayn (1996)

Metabolic features of tissues – key facts



Muscle (40 % of total body weight) can have periods of very high ATP requirement (vigorous contraction) and relies upon carbohydrate **and** fatty acid oxidation

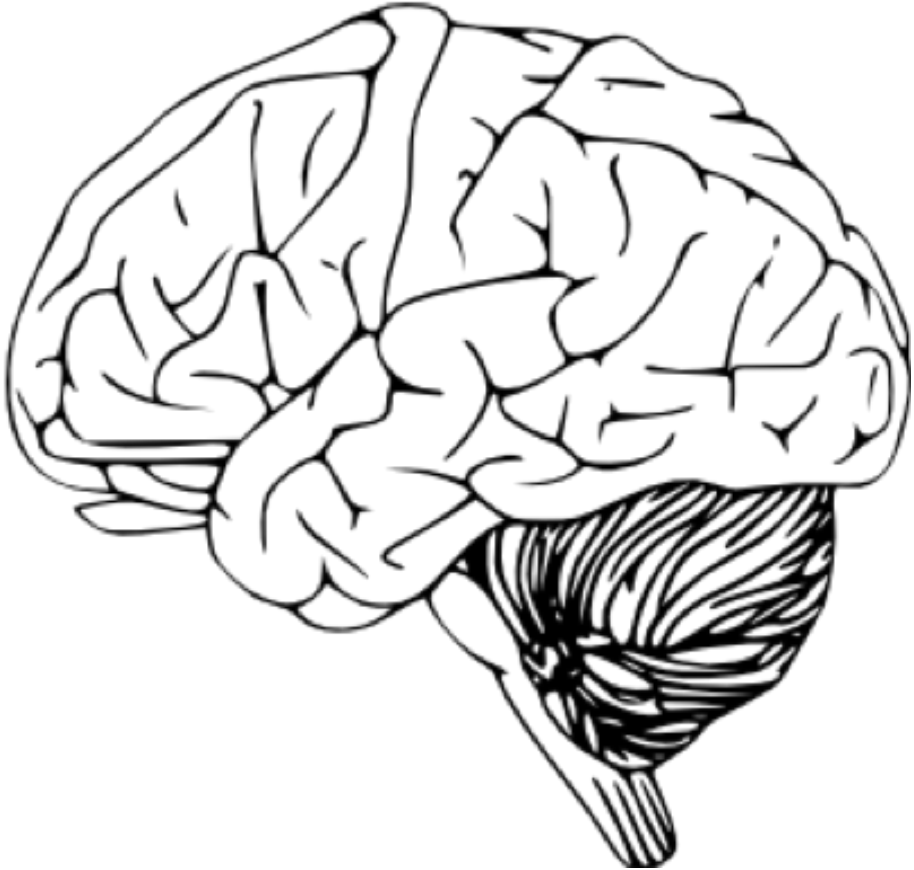
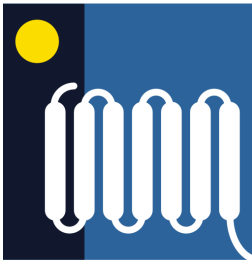
Brain and nervous tissue (2 % of total body weight) uses 20 % of resting metabolic rate as it has a continuous high ATP requirement; **cannot utilise fatty acids** as a fuel source

Adipose tissue (15 % of total body weight) and a long term storage site for triglycerides.

Heart (1 % of total body weight) 10 % of resting metabolic rate and can oxidise fatty acids **and** carbohydrate

Liver (2.5 % of total body weight) 20 % of resting metabolic rate; the body's main carbohydrate store (glycogen) and a **source of blood glucose**

Metabolic features of tissues - brain



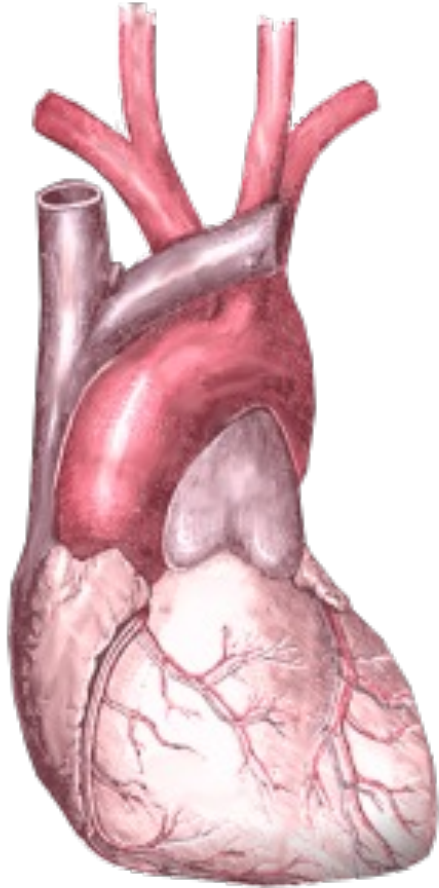
- The brain requires a continuous supply of glucose
- The brain cannot metabolise fatty acids
- Ketone bodies (e.g. β -hydroxybutyrate) can partially substitute for glucose
- Too little glucose (**hypoglycaemia**) causes faintness and coma
- Too much glucose (**hyperglycaemia**) can cause irreversible damage

Metabolic features of tissues – skeletal muscle



- ATP requirements vary depending on exercise undertaken
- Light contraction – requirements met by OxPhos
- Vigorous contraction - O_2 becomes a limiting factor
 - glycogen breakdown (muscles)
 - lactate formation

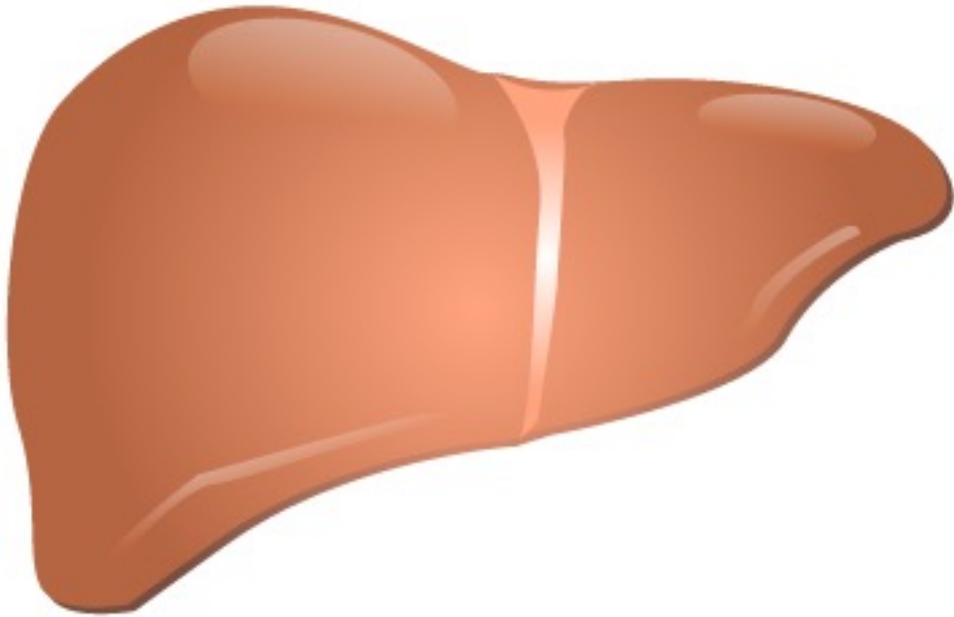
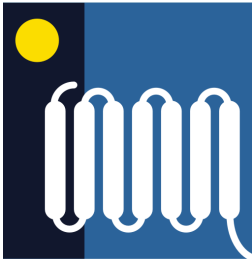
Metabolic features of tissues - heart



- The heart must beat **constantly**
- It is designed for completely aerobic metabolism, and is rich in mitochondria
- The heart utilises TCA cycle substrates, e.g. **free fatty acids, ketone bodies**
- Loss of O₂ supply to the heart is devastating
- Leads to cell death and myocardial infarction (energy demand >>> energy supply)

1-POM-1-5
1-POM-1-6

Metabolic features of tissues - liver



- Undertakes a **wide repertoire** of metabolic processes
- Is highly metabolically active
- Can interconvert nutrient types
- Plays a central role in maintaining blood [glucose] at 4.0-5.5 mM
- Is a glucose **storage organ** (glycogen)
- Plays a key role in lipoprotein metabolism (transport of triglycerides & cholesterol)

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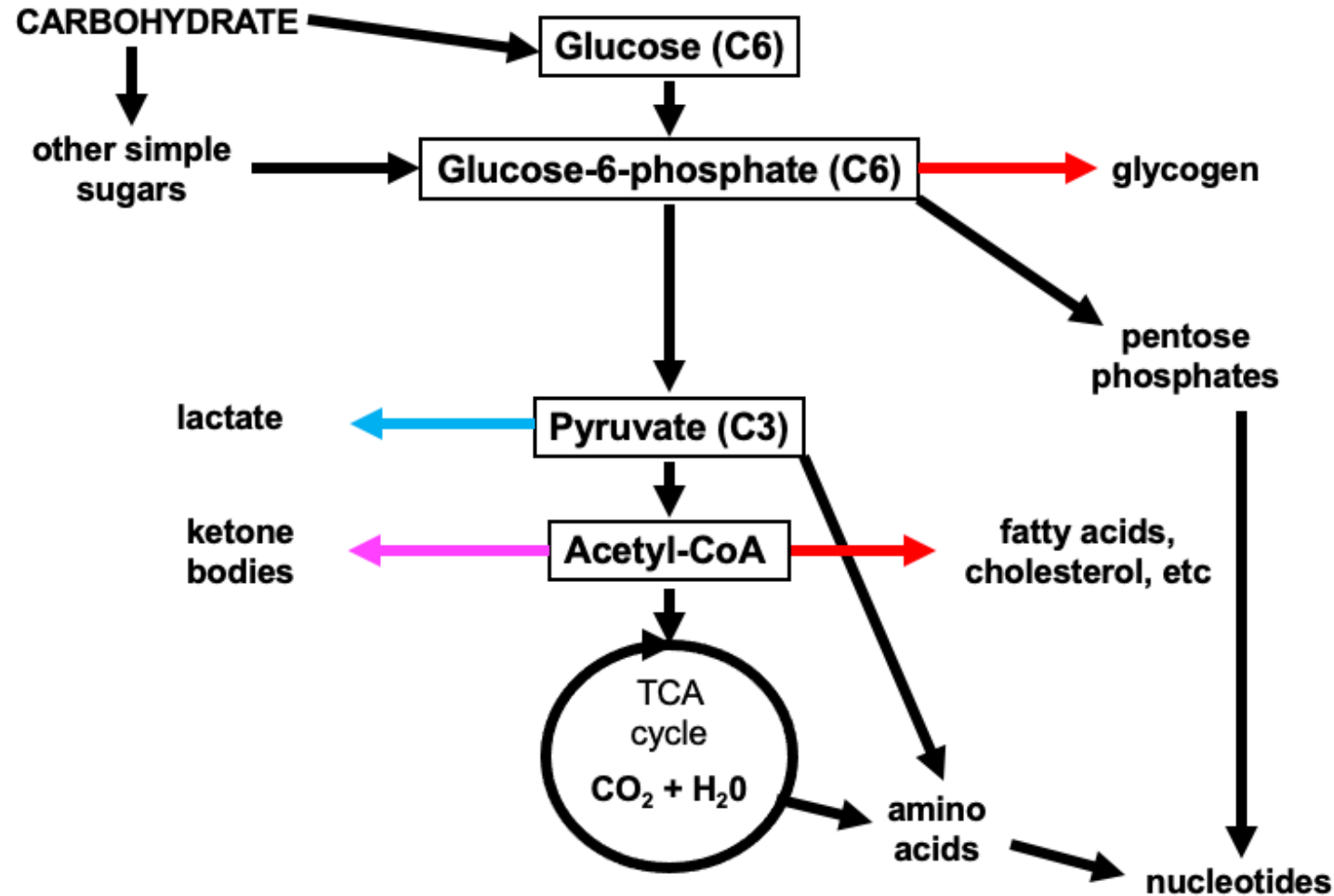
- Enzymatic control
- Hormonal control

Diabetes mellitus

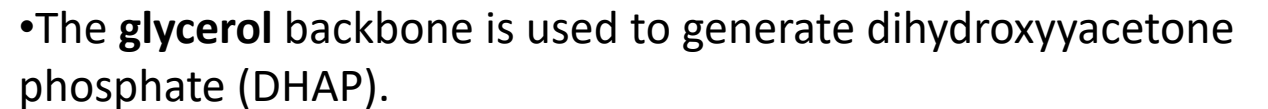
An overview of carbohydrate metabolism



Glycolysis : lysis of glucose



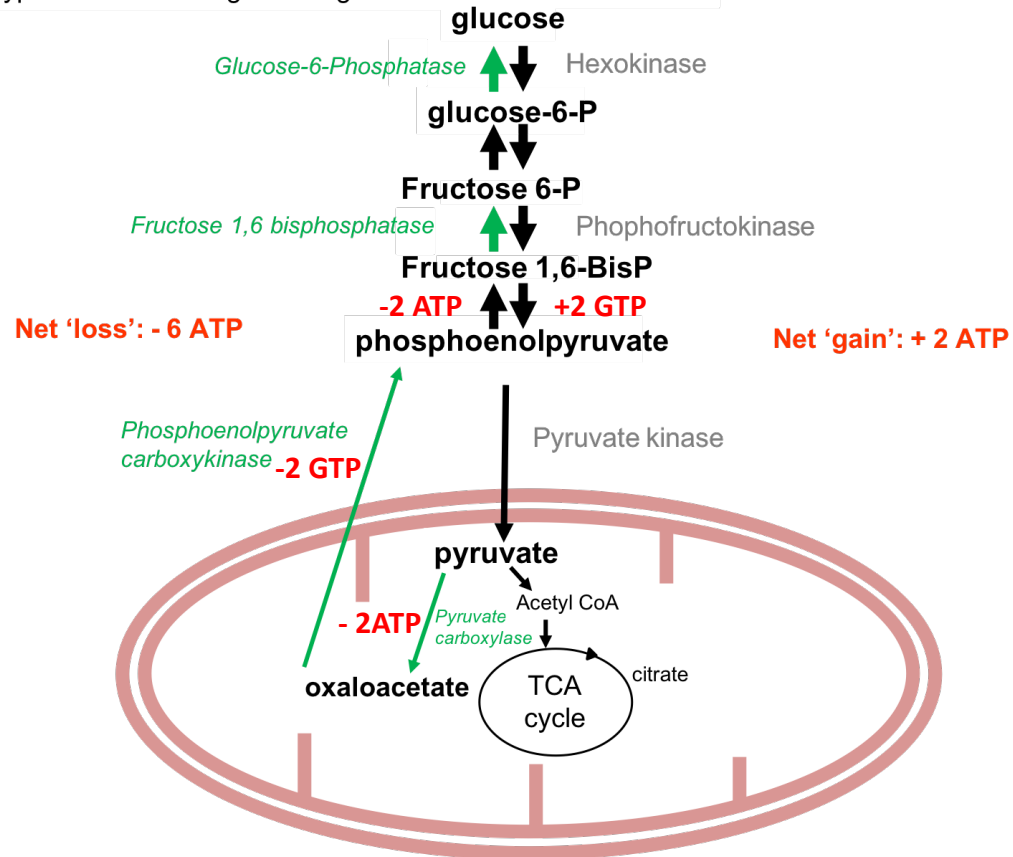
- During extreme exercise, the ATP demands of the muscle outstrip the oxygen supply needed for aerobic respiration and **lactate** is produced (blue arrow).
- During fasting, rather than enter the TCA, much of the acetyl CoA produced results in **ketone body** production (purple arrow).



The bypass reactions of gluconeogenesis



Bypass reactions of gluconeogenesis

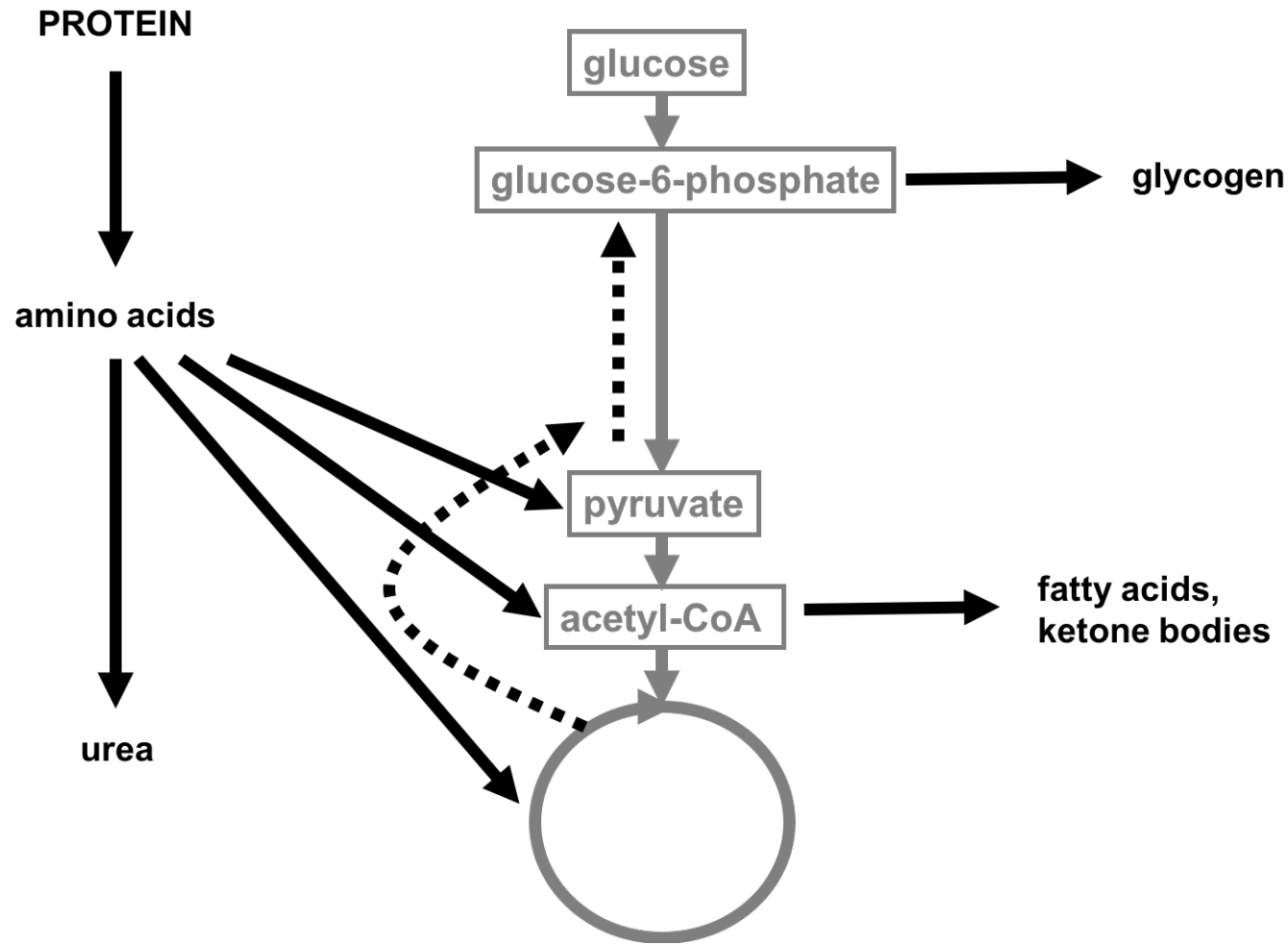
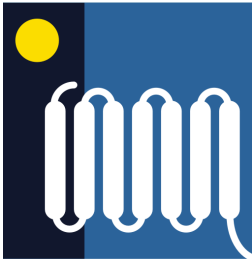


ΔG value for a straight reversal of glycolysis would be +90 kJ/mol

Six phosphoanhydride bonds are required to turn an energetically unfavourable process into an energetically favourable one:

ΔG for gluconeogenesis is -38 kJ/mol.

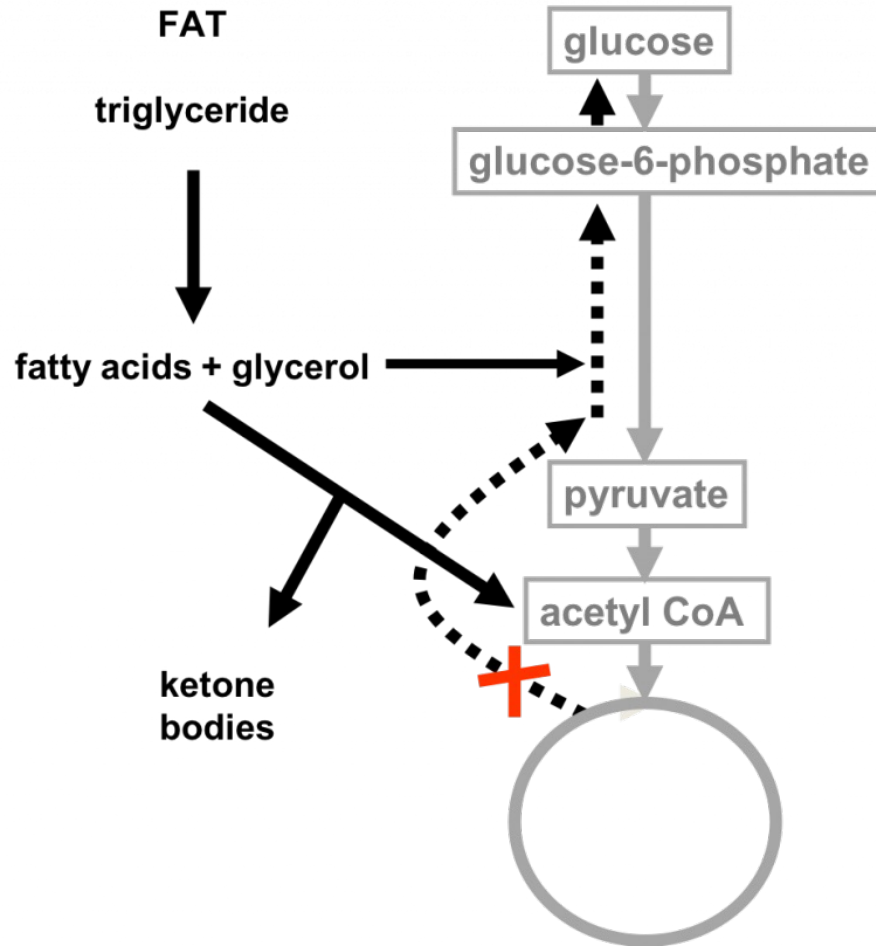
Protein as fuel sources – a recap



Glucogenic amino acids are used to generate glucose via gluconeogenesis (dashed lines)

Ketogenic amino acids are used to synthesis fatty acids and ketone bodies.

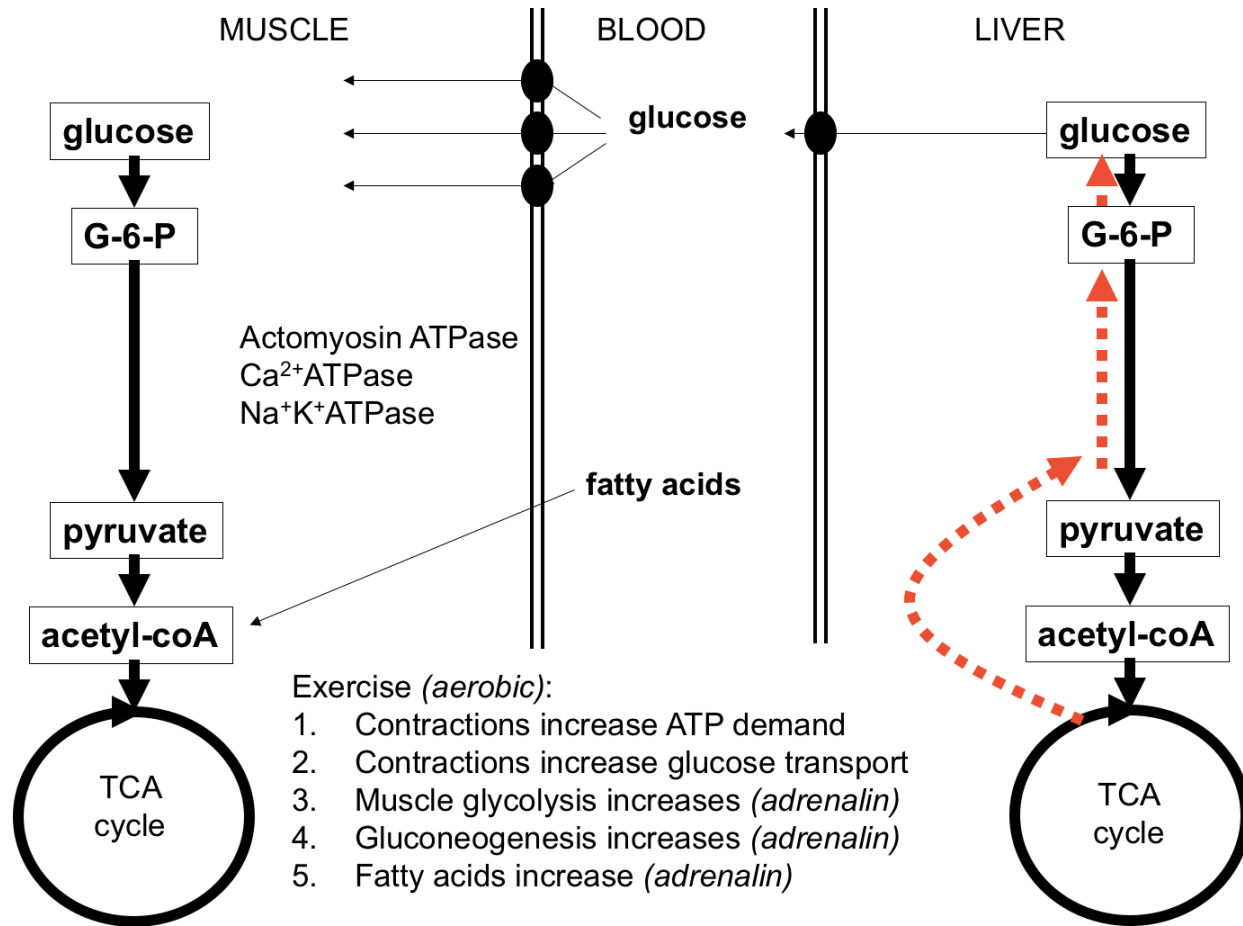
Fats as fuel sources – a recap



Triglycerides are broken down into **fatty acids** and **glycerol**

Fatty acids can be converted into **ketone bodies**

Energy stores and energy consumption – Aerobic respiration



With adequate oxygen, ATP demands of muscle can be met by OxPhos using glucose and other substrates.

Contracting muscle requires:

↑ATP

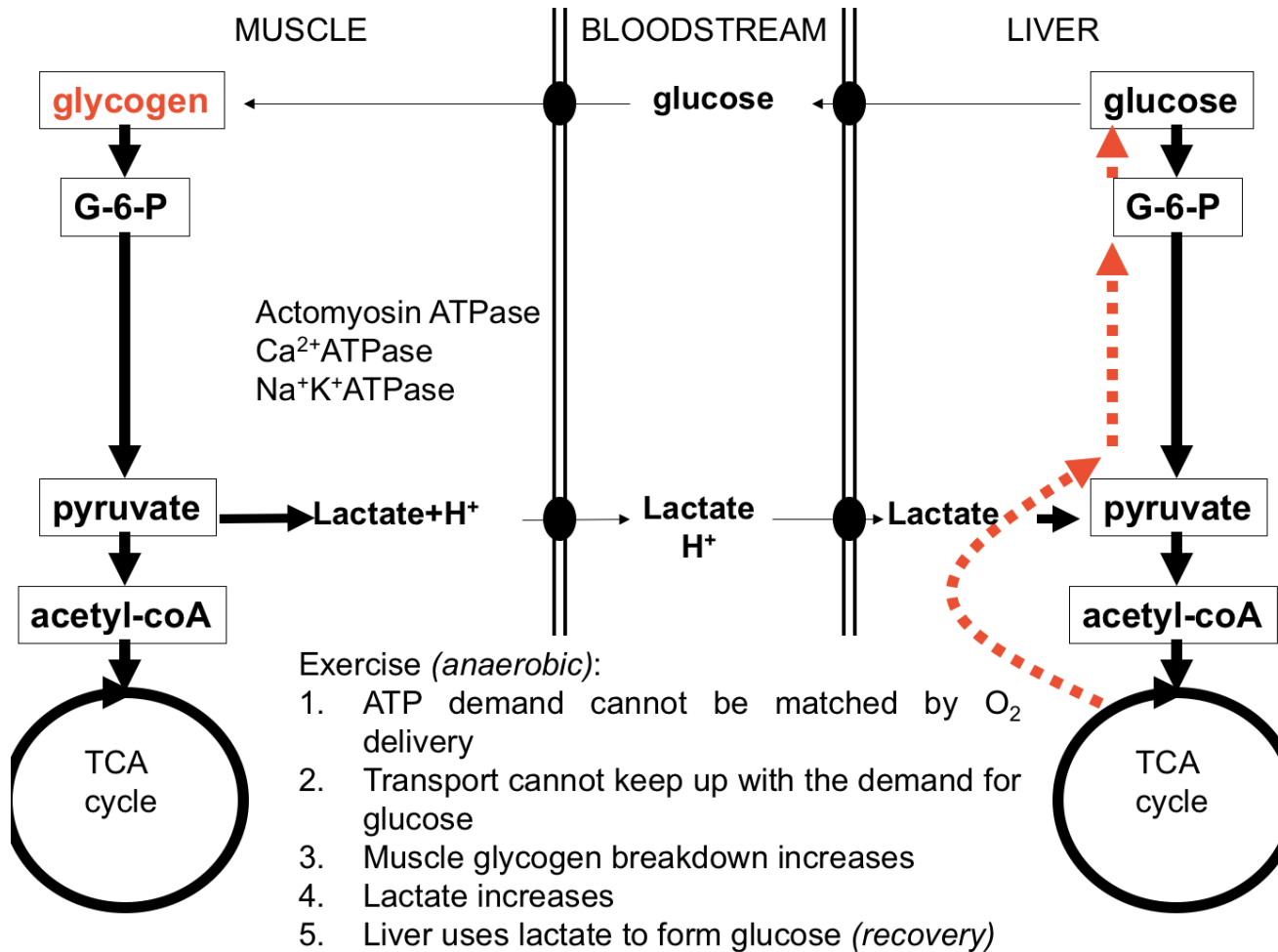
↑glucose transporters

Adrenalin helps increase the rate of **glycolysis** in muscle by:

↑ **gluconeogenesis** by the liver (red arrows)

↑ release of **fatty acids** from adipocytes.

Energy stores and energy consumption – Anaerobic respiration

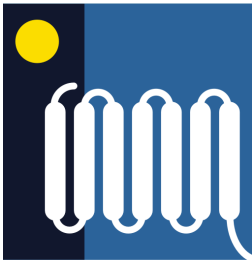


Glycogen is broken down to meet the glucose demands of the muscle

Lactate synthesis replenishes NAD⁺ levels

Lactate is used in **gluconeogenesis** to synthesize more glucose

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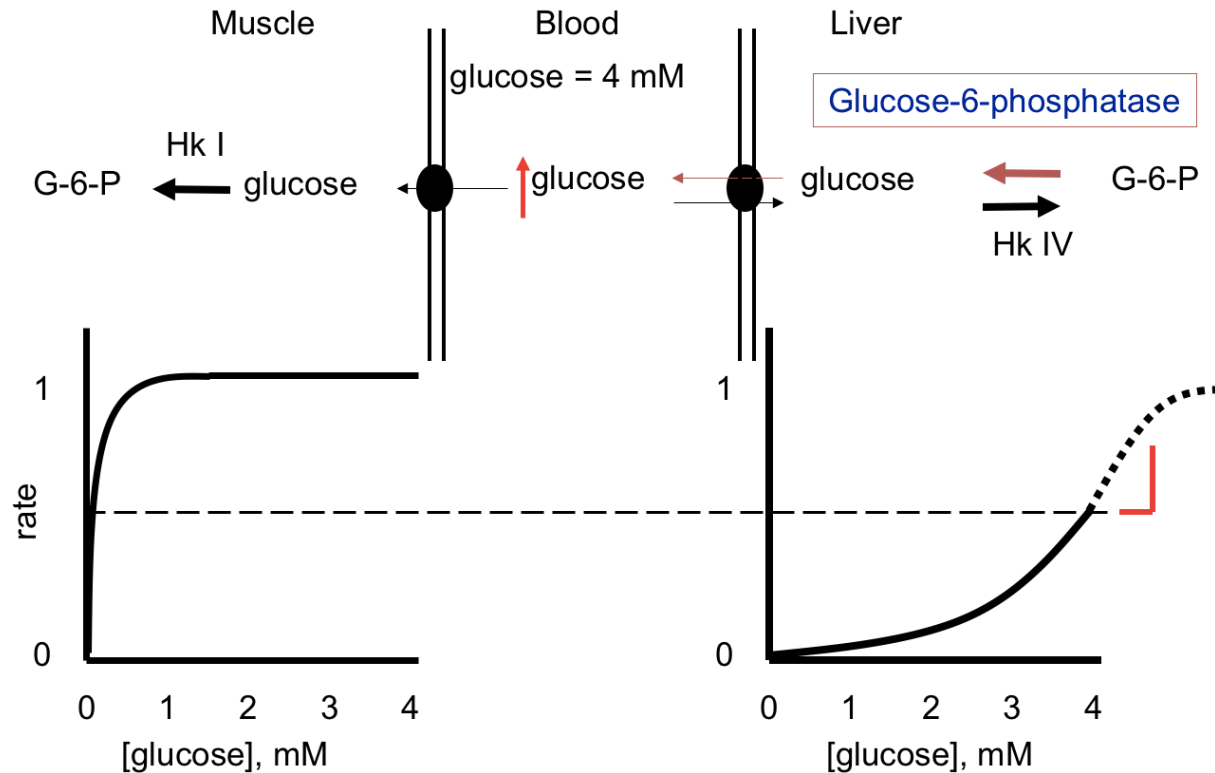
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Diabetes mellitus

Control of metabolic pathways



The Michaelis constant (K_M) which is the concentration of substrate at which an enzyme functions at a half-maximal rate (V_{max}).

Hk I in muscle is active at **low** [glucose]

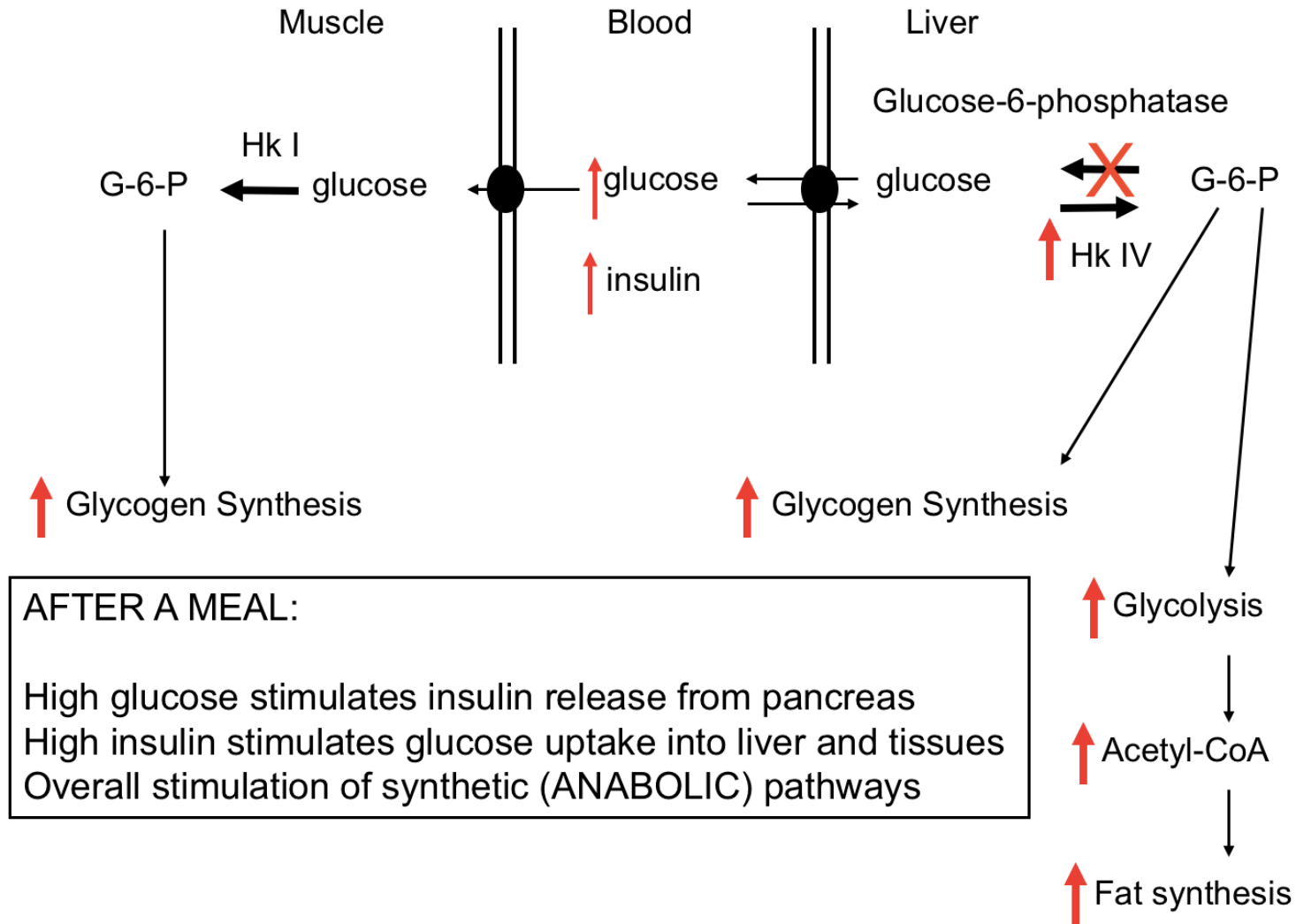
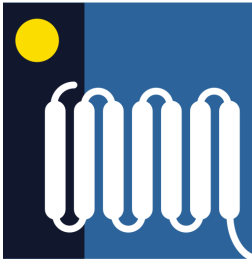
Hk IV in liver is active at **high** [glucose]

Hormonal control of blood [glucose]



- **Insulin** is secreted when glucose levels rise: it stimulates uptake and use of glucose and storage as glycogen and fat.
- **Glucagon** is secreted when glucose levels fall: it stimulates production of glucose by gluconeogenesis and breakdown of glycogen and fat.
- **Adrenalin** (or epinephrine): strong and fast metabolic effects to mobilise glucose for “flight or fight”.
- **Glucocorticoids**: steroid hormones which increase the synthesis of metabolic enzymes concerned with glucose availability.

Hormonal control of blood [glucose]



Hormonal control of blood [glucose]



After a meal blood glucose levels start to fall and are controlled by:

- \uparrow glucagon secretion and \downarrow insulin from pancreas.
- glucose production in liver resulting from glycogen breakdown and gluconeogenesis.
- fatty acid breakdown as alternative substrate for ATP production
- adrenalin stimulates glycogen breakdown and glycolysis (skeletal muscle) and lipolysis (adipose)

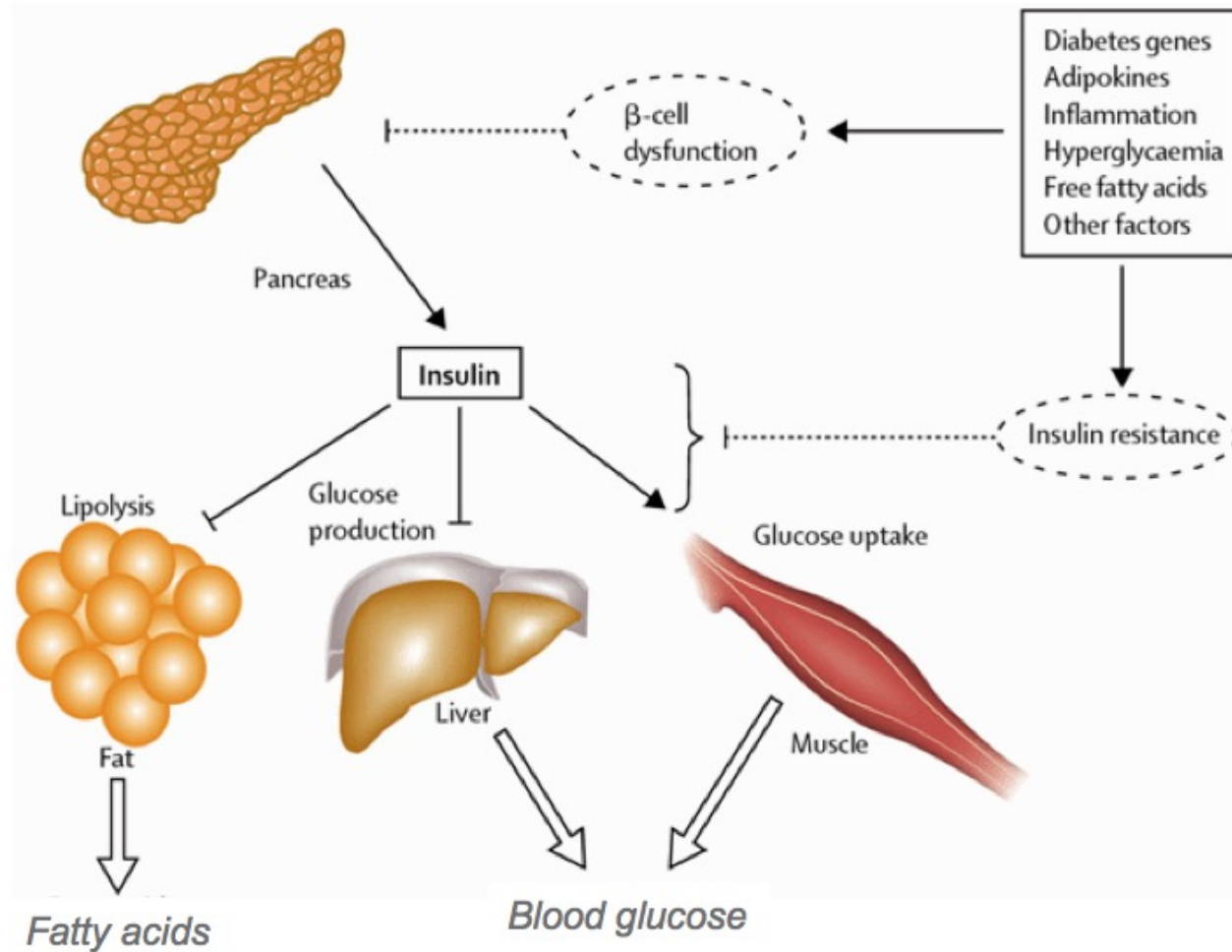
Hormonal control of blood [glucose]



After prolonged fasting:

- Glucagon/insulin ratio increases further
- Adipose tissue hydrolyses triglyceride to provide fatty acids for metabolism
- TCA cycle intermediates are reduced in amount to provide substrates for gluconeogenesis
- Protein breakdown provides amino acid substrates for gluconeogenesis
- Ketone bodies are produced from fatty acids and amino acids in liver to partially substitute the brain's requirement for glucose

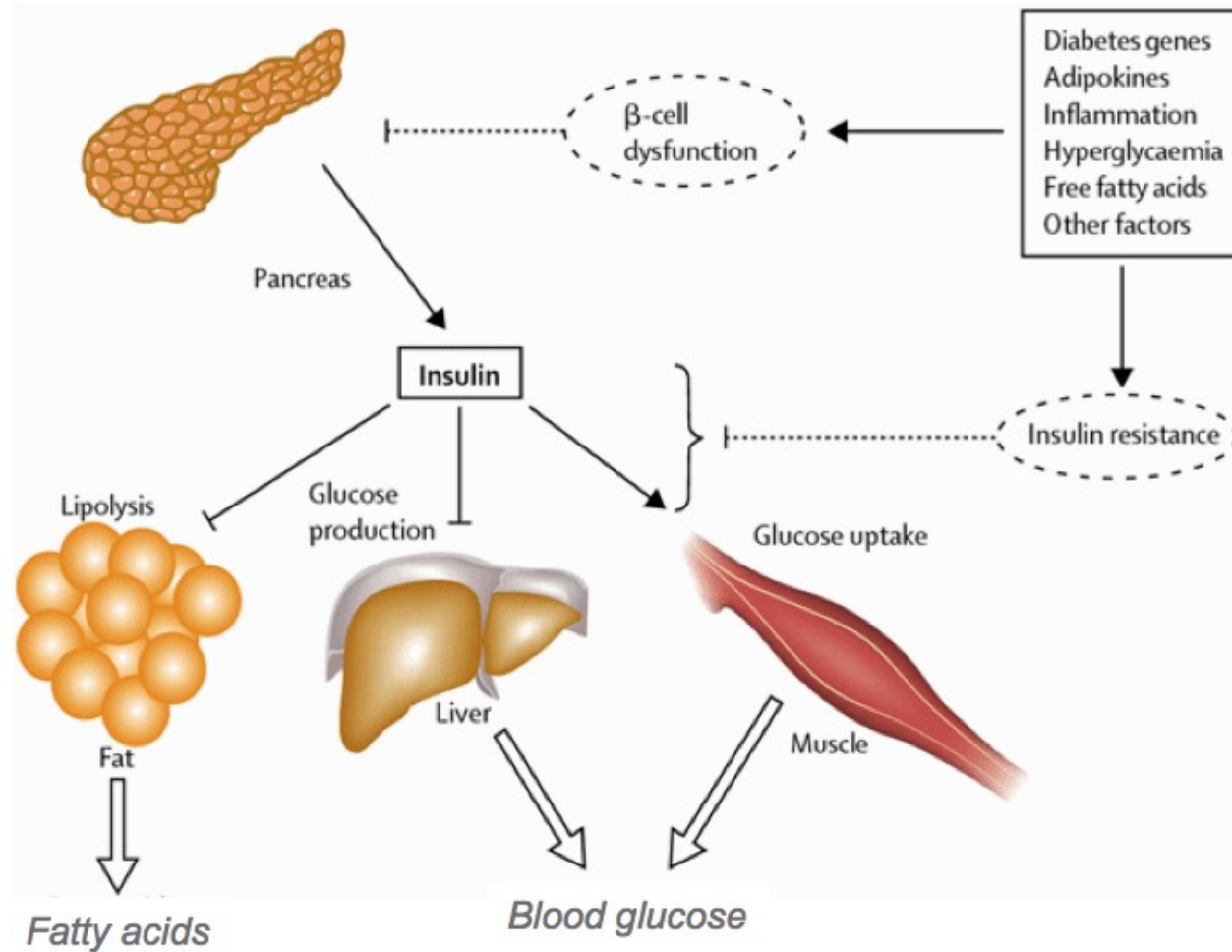
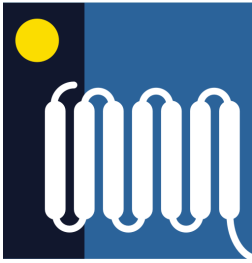
Diabetes mellitus



Type I diabetes - failure to secrete enough insulin (β -cell dysfunction).

Type II diabetes - failure to respond appropriately to insulin levels (insulin resistance).

Diabetes mellitus



Complications of diabetes include:

- hyperglycaemia
- cardiovascular complications
- ketoacidosis
- hypoglycaemia