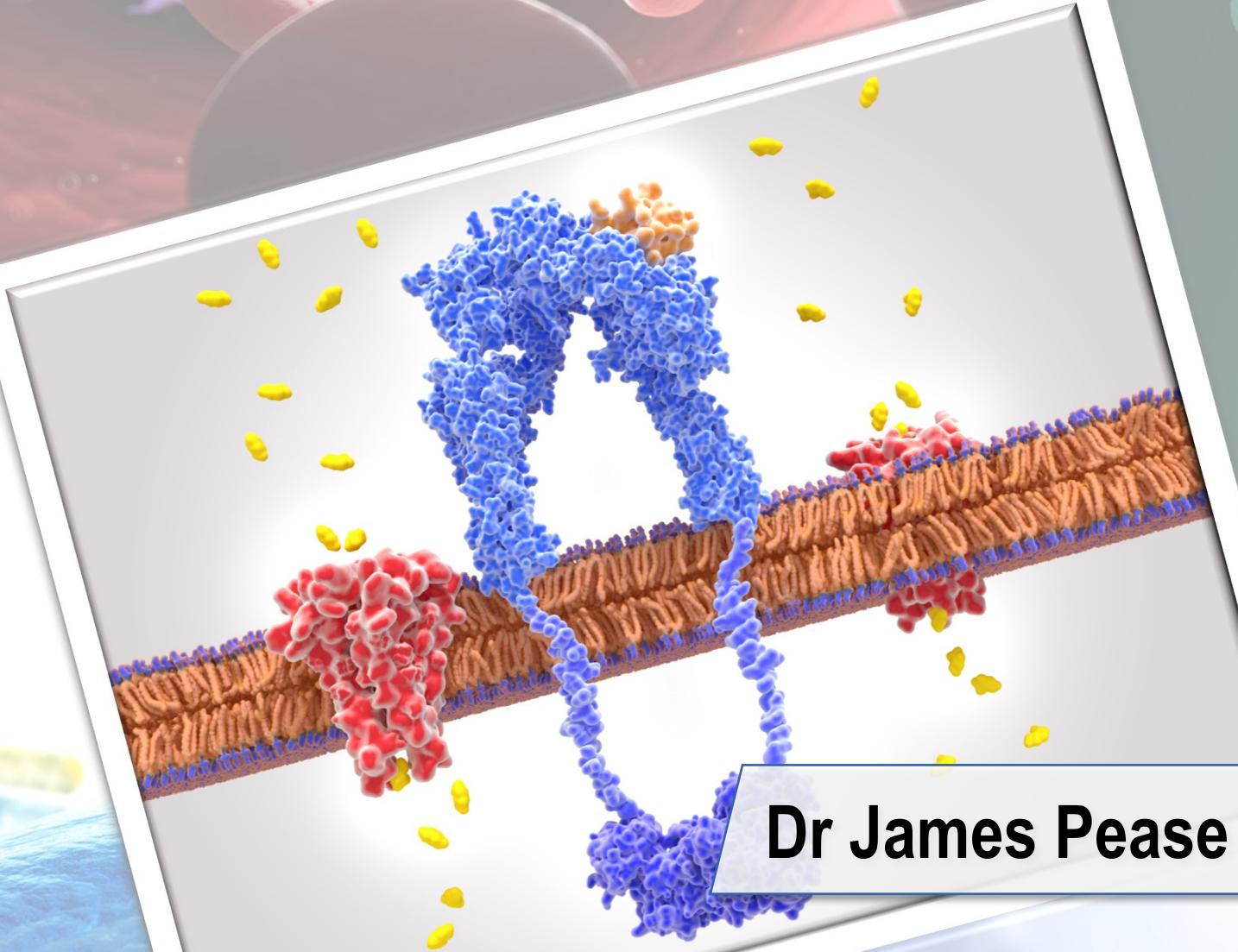
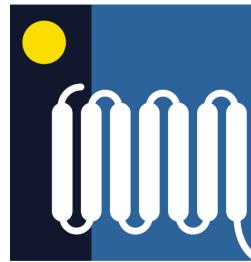


# Integration of metabolism



Dr James Pease [j.pease@imperial.ac.uk](mailto:j.pease@imperial.ac.uk)

# 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

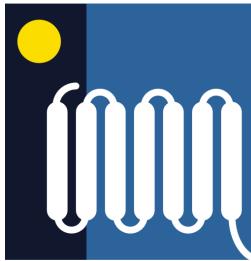
## Part 3

Control of metabolic pathways

- Enzymatic control
- Hormonal control

Diabetes mellitus

# Session Plan



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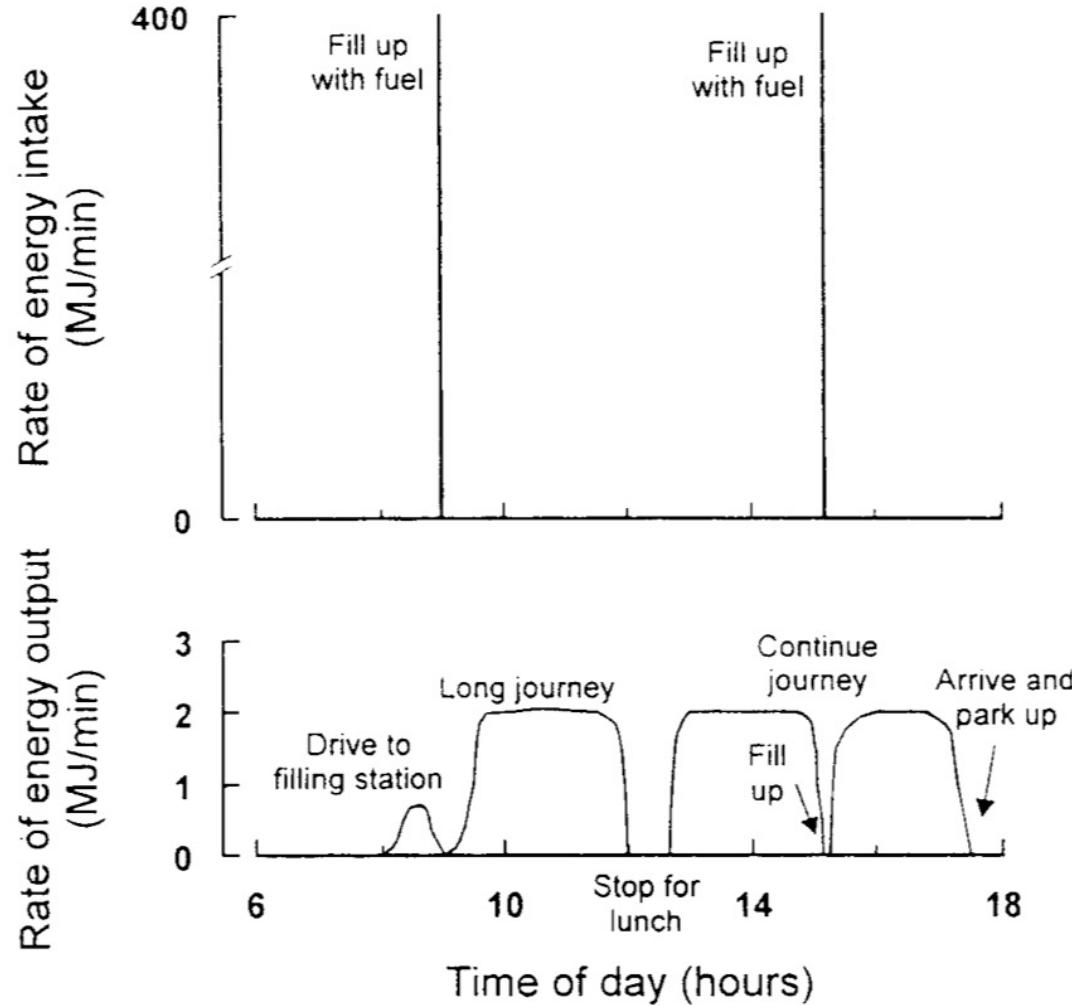
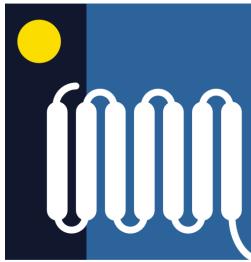
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# Energy intake v energy expenditure – an analogy



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

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

From: 'Metabolic Regulation: A Human Perspective' by KN 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

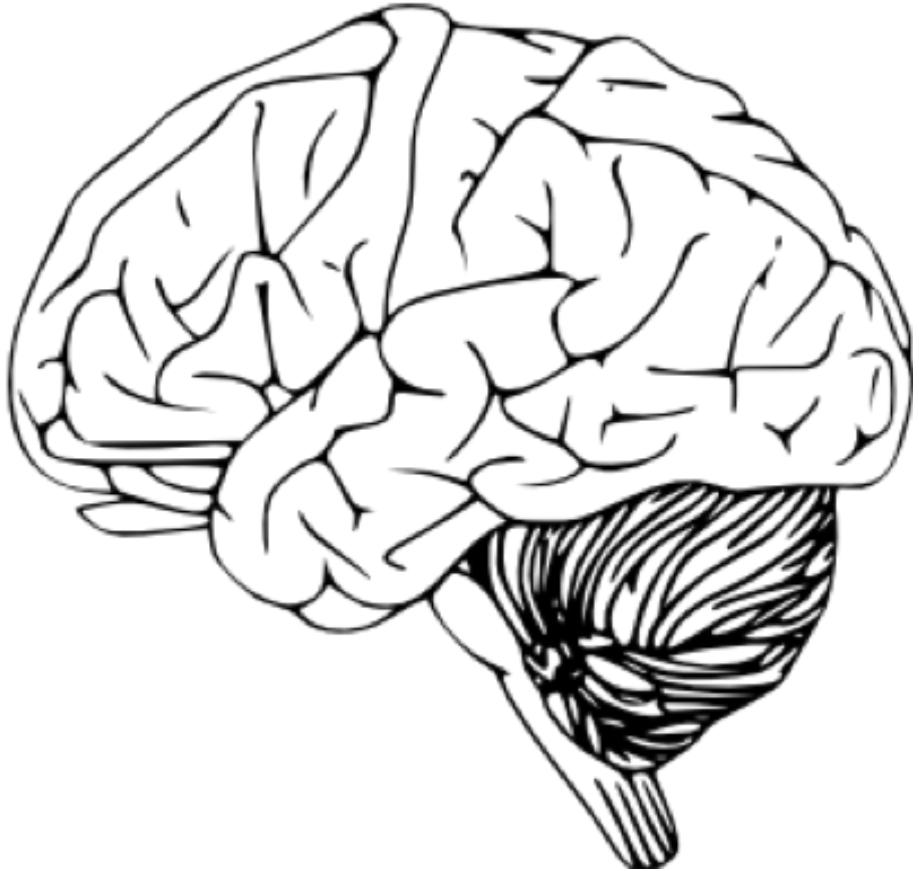
**Brain and nervous tissue** (2 % of total body weight) uses 20 % of resting metabolic rate as it has a continuous high ATP requirement; **cannot utilise fatty acids** as a fuel source

**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



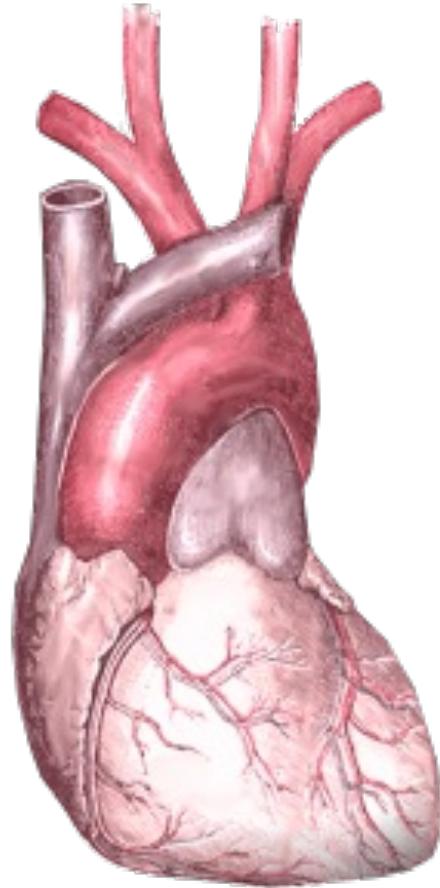
- The brain requires a continuous supply of glucose
- The brain cannot metabolise fatty acids
- Ketone bodies (e.g.  $\beta$ -hydroxybutyrate) can partially substitute for glucose
- Too little glucose (**hypoglycaemia**) causes faintness and coma
- Too much glucose (**hyperglycaemia**) can cause irreversible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

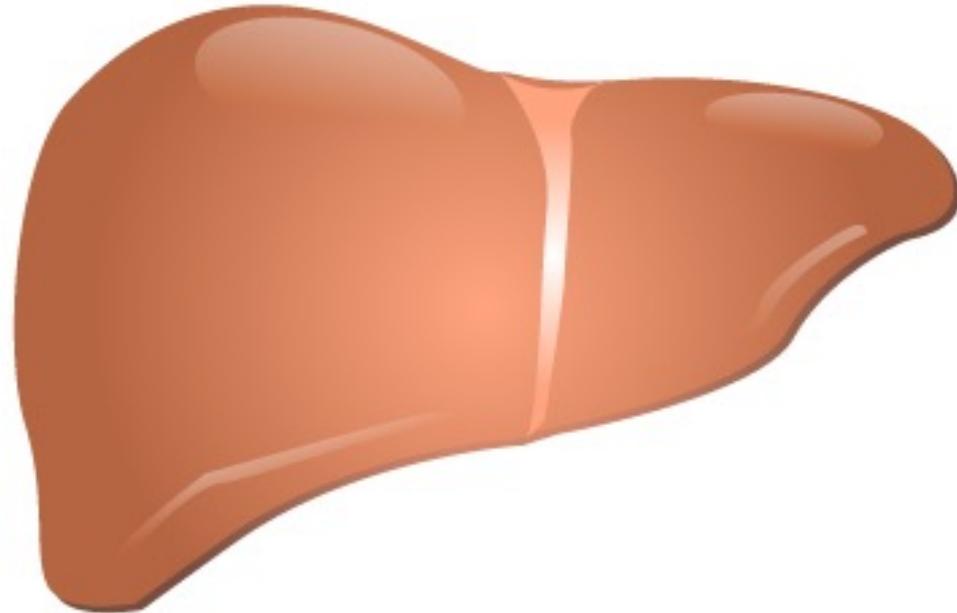
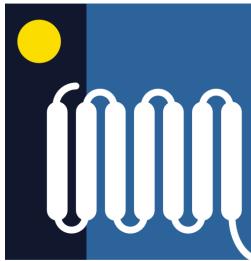
# Metabolic features of tissues - heart



- 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 O<sub>2</sub> supply to the heart is devastating
- Leads to cell death and myocardial infarction (energy demand >> energy supply)

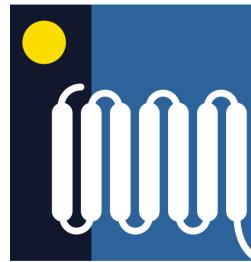
1-POM-1-5  
1-POM-1-6

# 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)

# Session Plan



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Gluconeogenesis

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- Anaerobic respiration

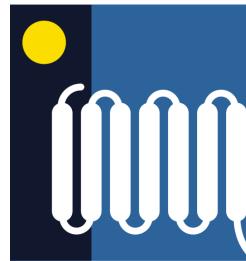
## Part 3

Control of metabolic pathways

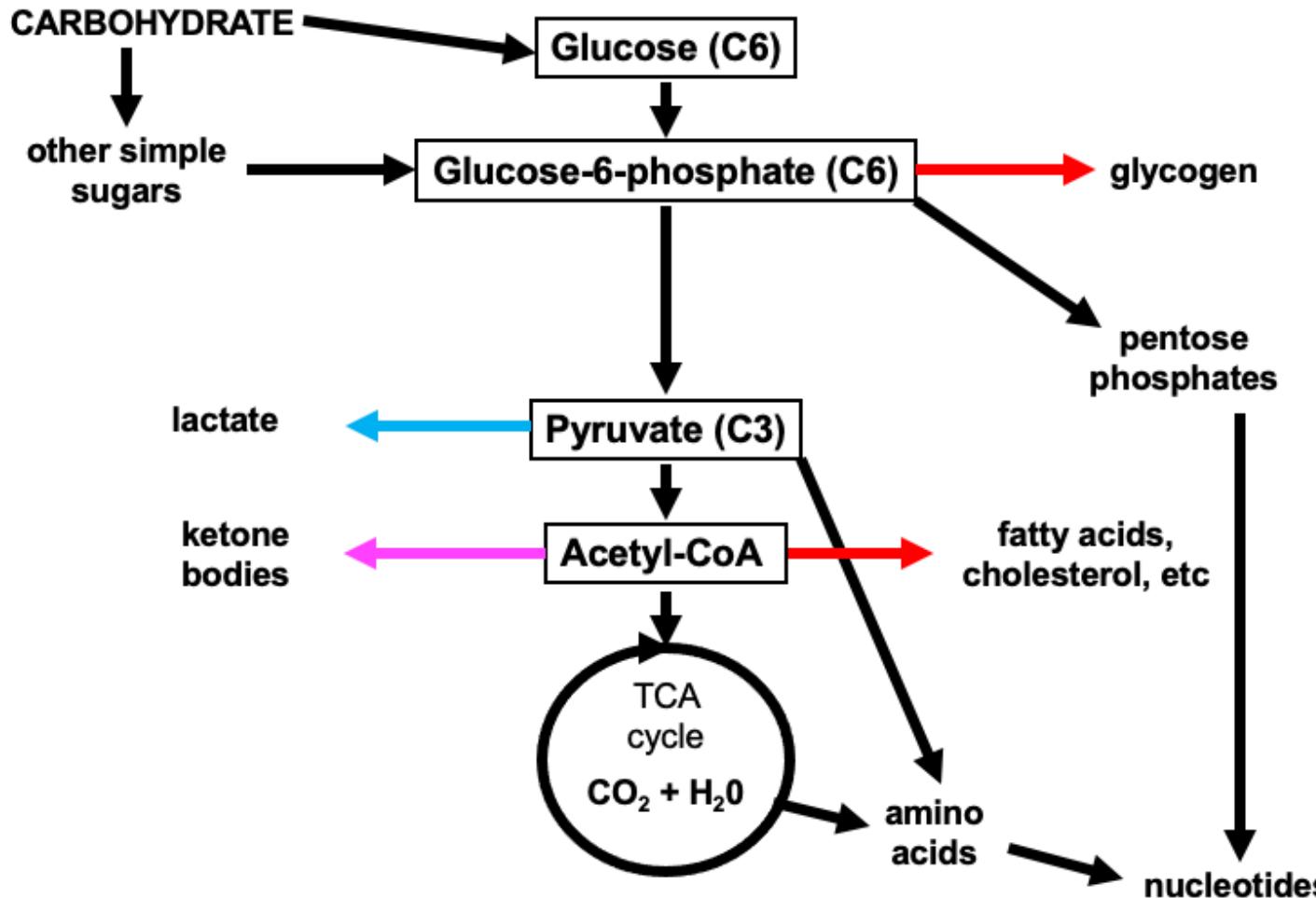
- Enzymatic control
- Hormonal control

Diabetes mellitus

# An overview of carbohydrate metabolism

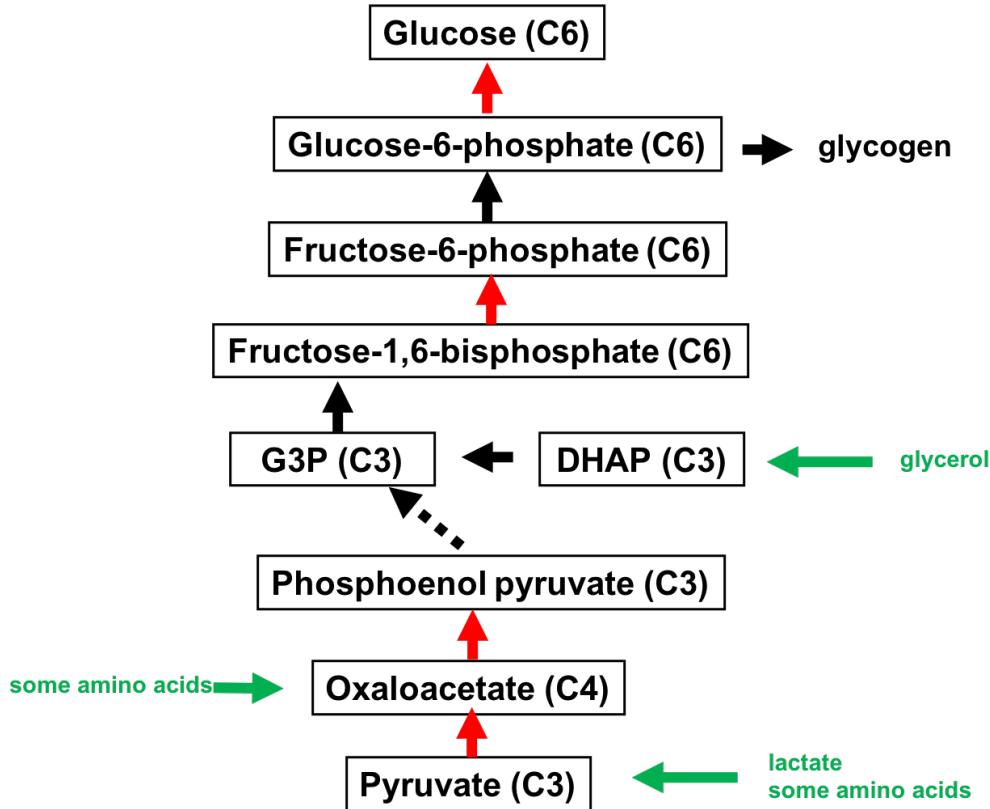
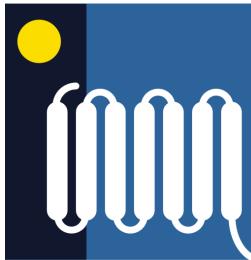


Glycolysis : lysis of glucose



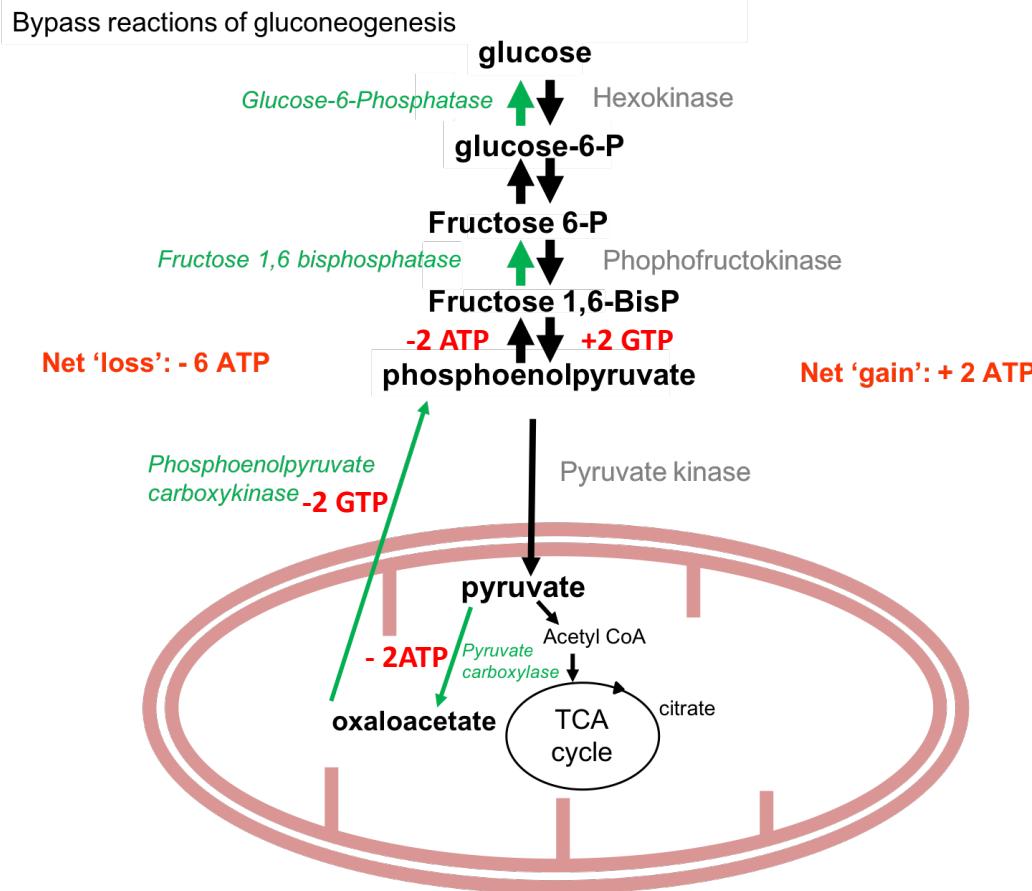
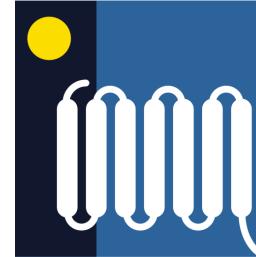
- During extreme exercise, the ATP demands of the muscle outstrip the oxygen supply needed for aerobic respiration and **lactate** is produced (blue arrow).
- During fasting, rather than enter the TCA, much of the acetyl CoA produced results in **ketone body** production (purple arrow).

# Gluconeogenesis



- **Lactate** is utilised to regenerate pyruvate by lactate dehydrogenase (LDH).
- **Amino acids** can be derived from the diet or the breakdown of skeletal muscle.
- The **glycerol** backbone is used to generate dihydroxyacetone phosphate (DHAP).

# The bypass reactions of gluconeogenesis

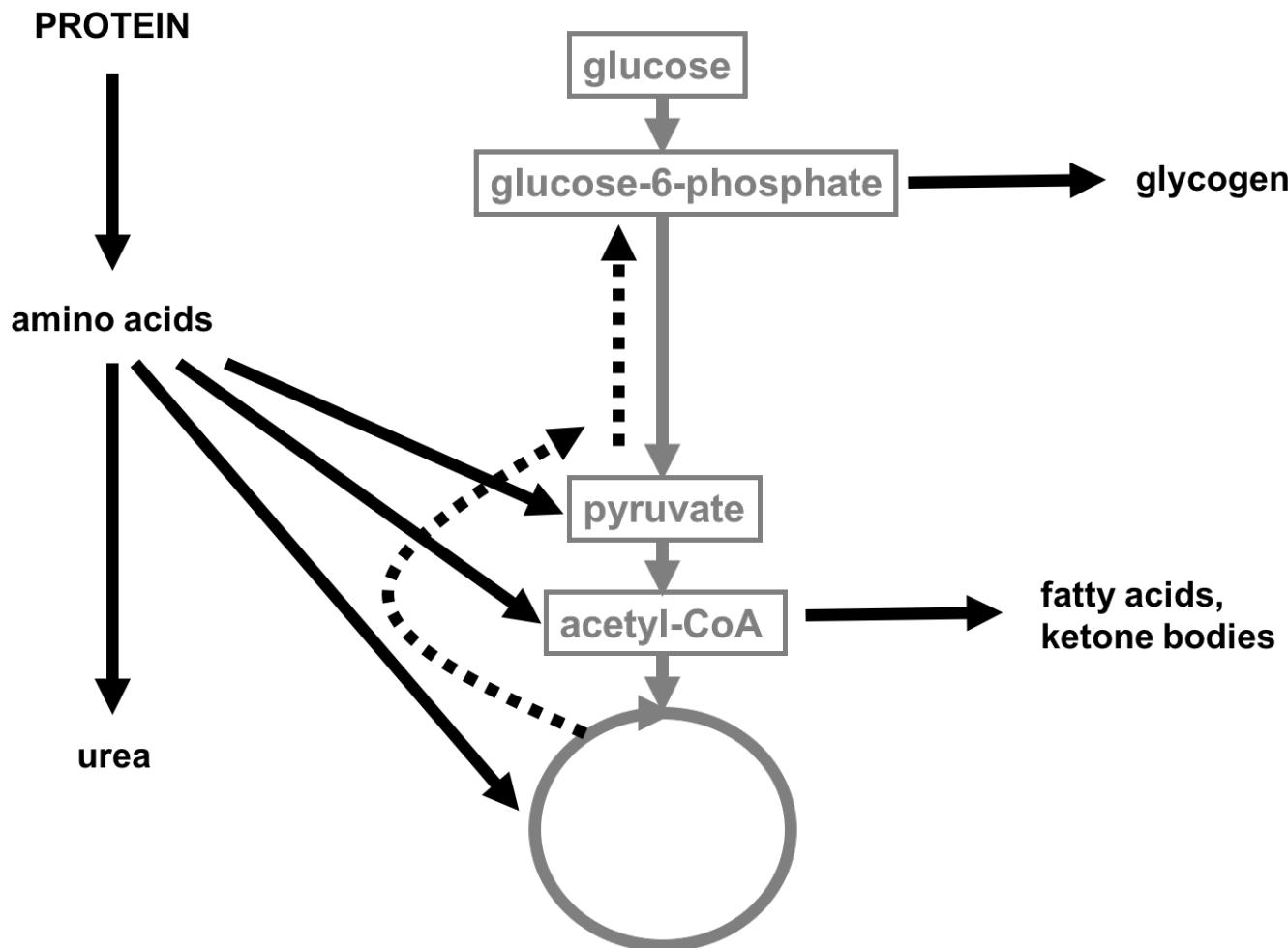


$\Delta G$  value for a straight reversal of glycolysis would be +90 kJ/mol

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

$\Delta G$  for gluconeogenesis is -38 kJ/mol.

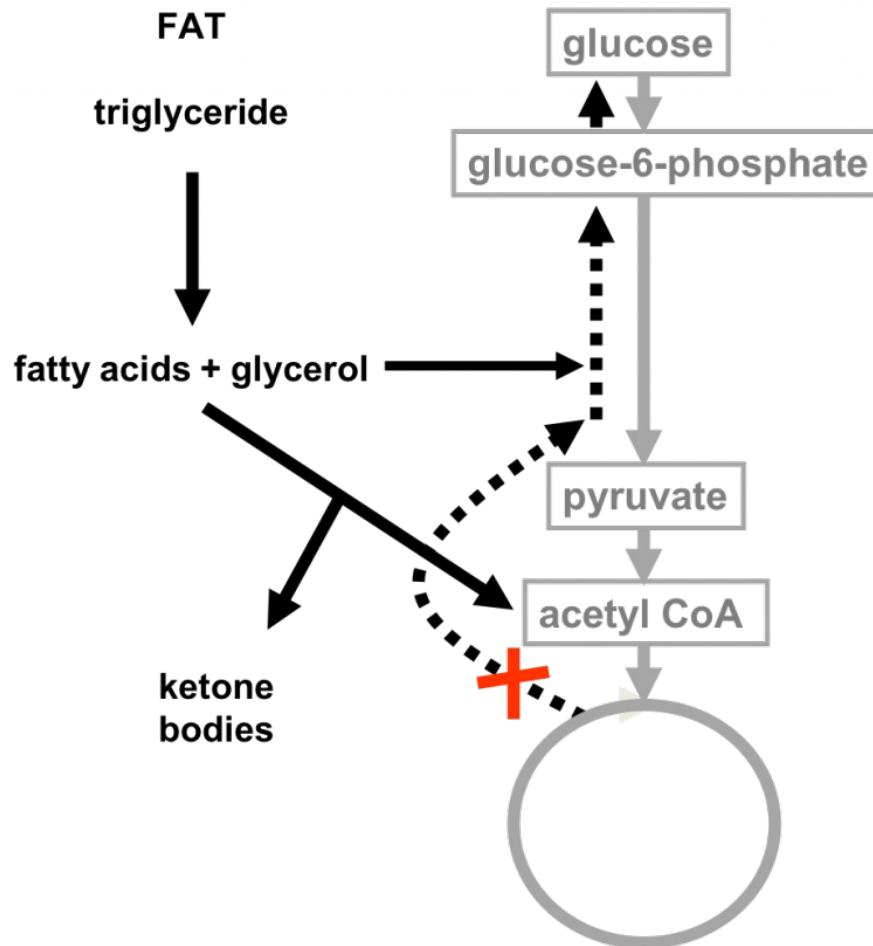
# Protein as fuel sources – a recap



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

**Ketogenic** amino acids are used to synthesize fatty acids and ketone bodies.

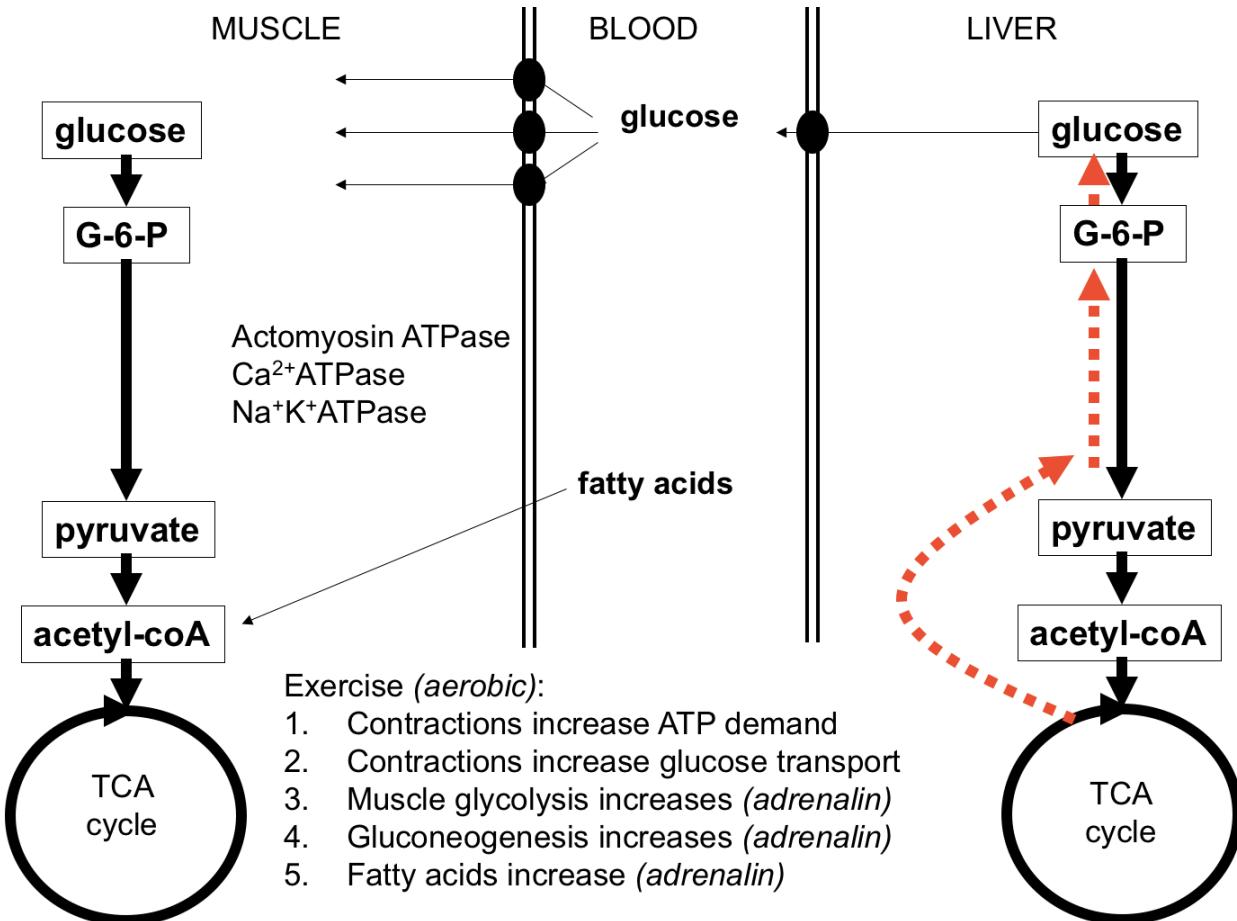
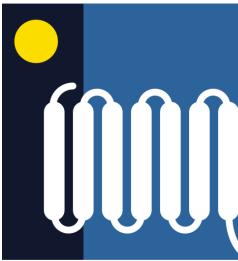
# Fats as fuel sources – a recap



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.

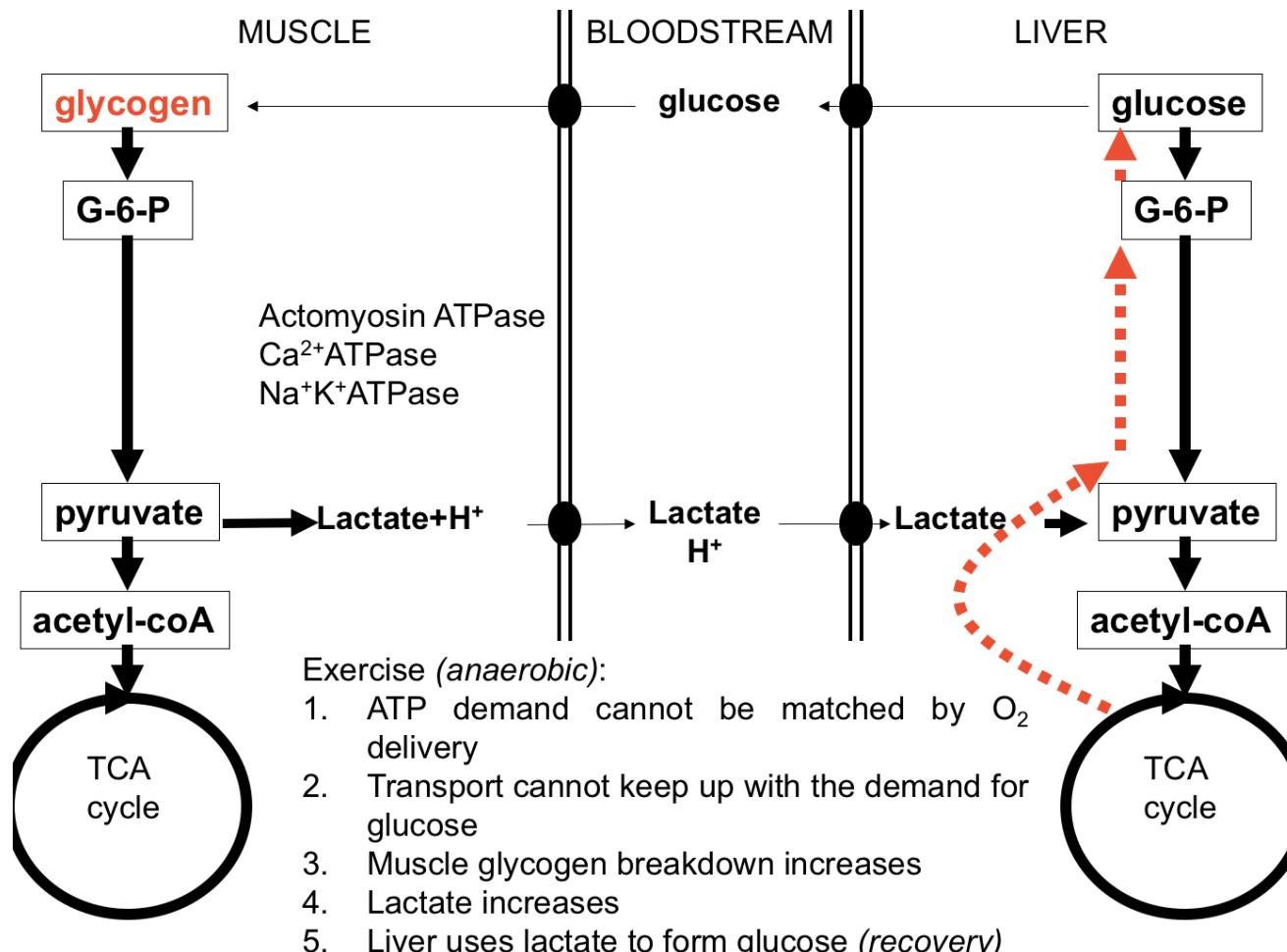
Contracting muscle requires:

↑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

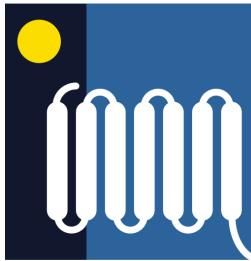


Glycogen is broken down to meet the glucose demands of the muscle

Lactate synthesis replenishes NAD<sup>+</sup> levels

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

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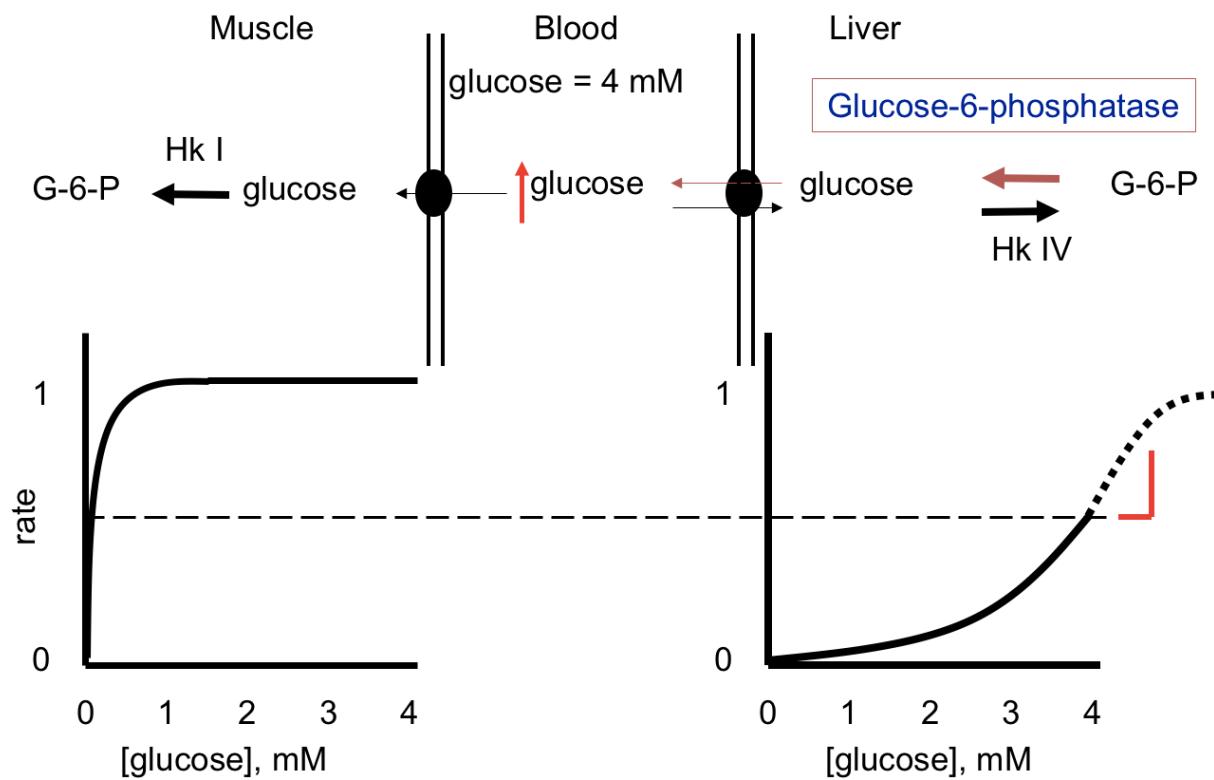
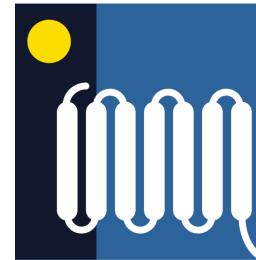
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- Hormonal control

Diabetes mellitus

# Control of metabolic pathways



**Muscle Hk:**  
-high glucose affinity  
( $K_M$  of 0.1 mM)  
-highly sensitive to G-6-P inhibition

**Liver Hk:**  
-low glucose affinity  
( $K_M$  of 4 mM)  
-less sensitive to G-6-P inhibition

**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]

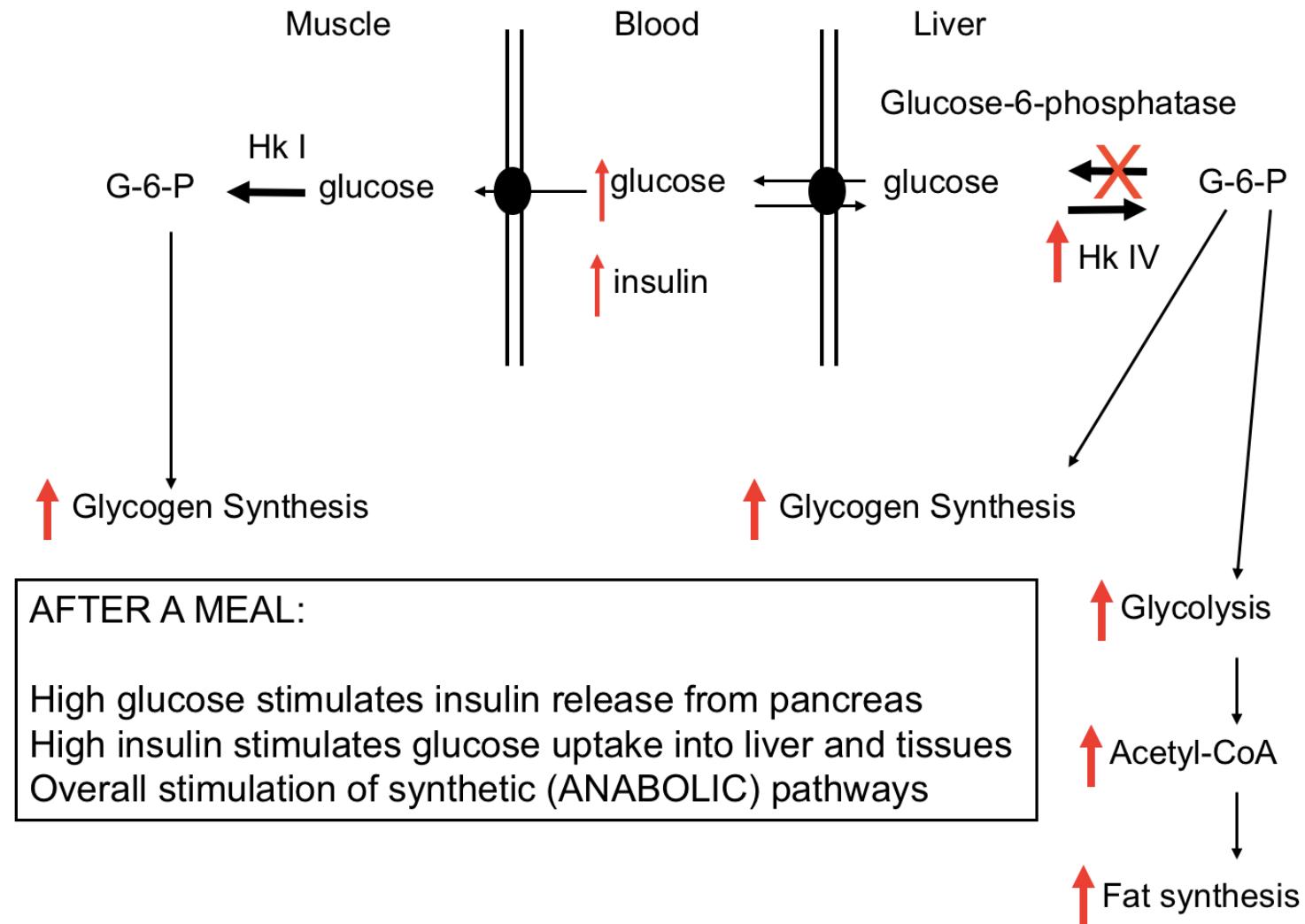
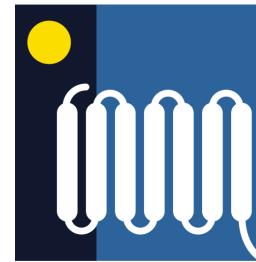
Hk IV in liver is active at **high** [glucose]

# 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]

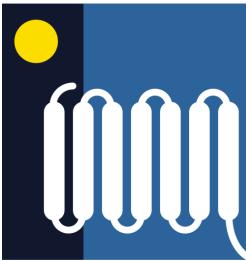




# Hormonal control of blood [glucose]

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

- ↑ glucagon secretion and ↓ 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)

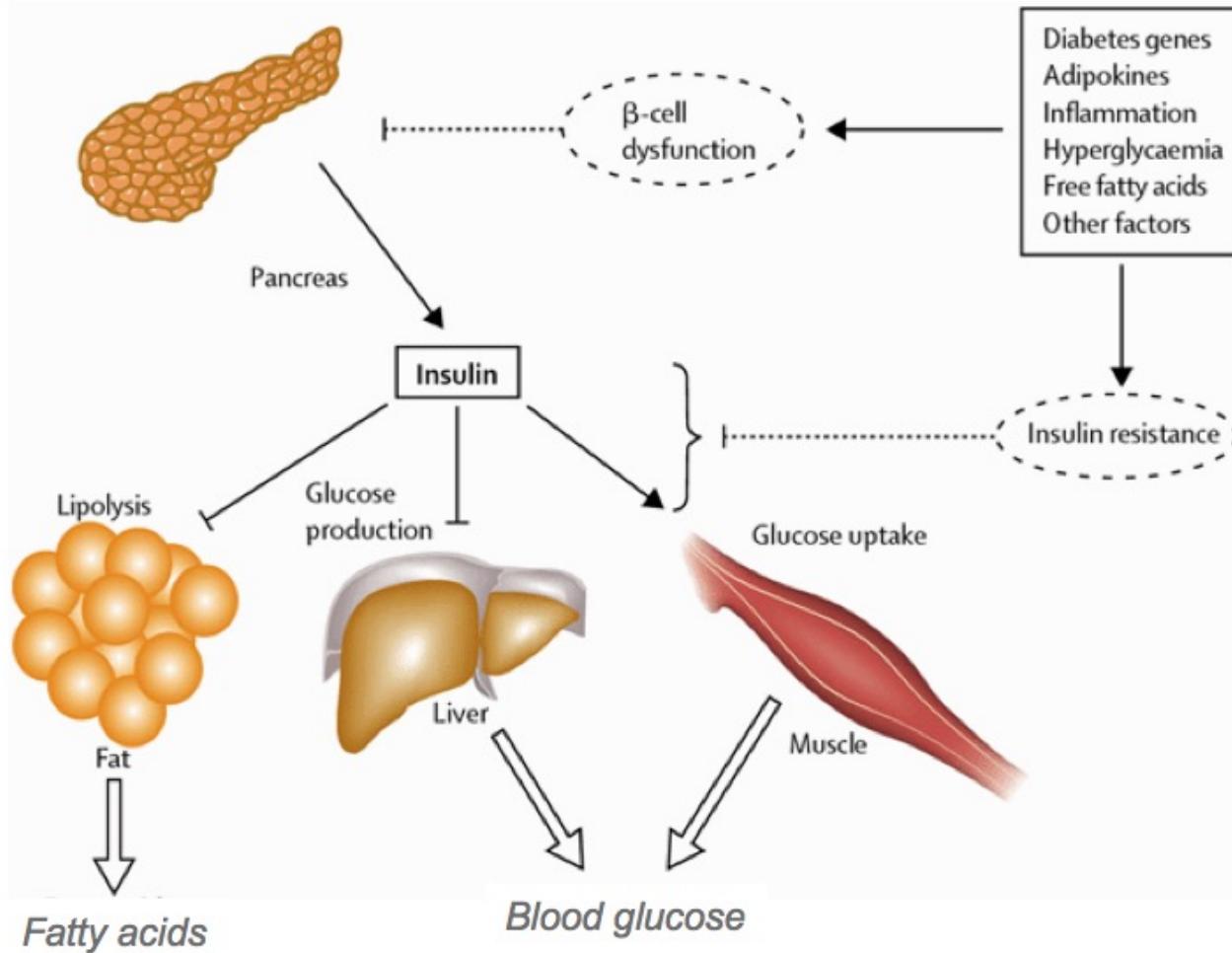
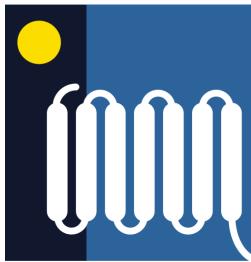


# Hormonal control of blood [glucose]

## 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

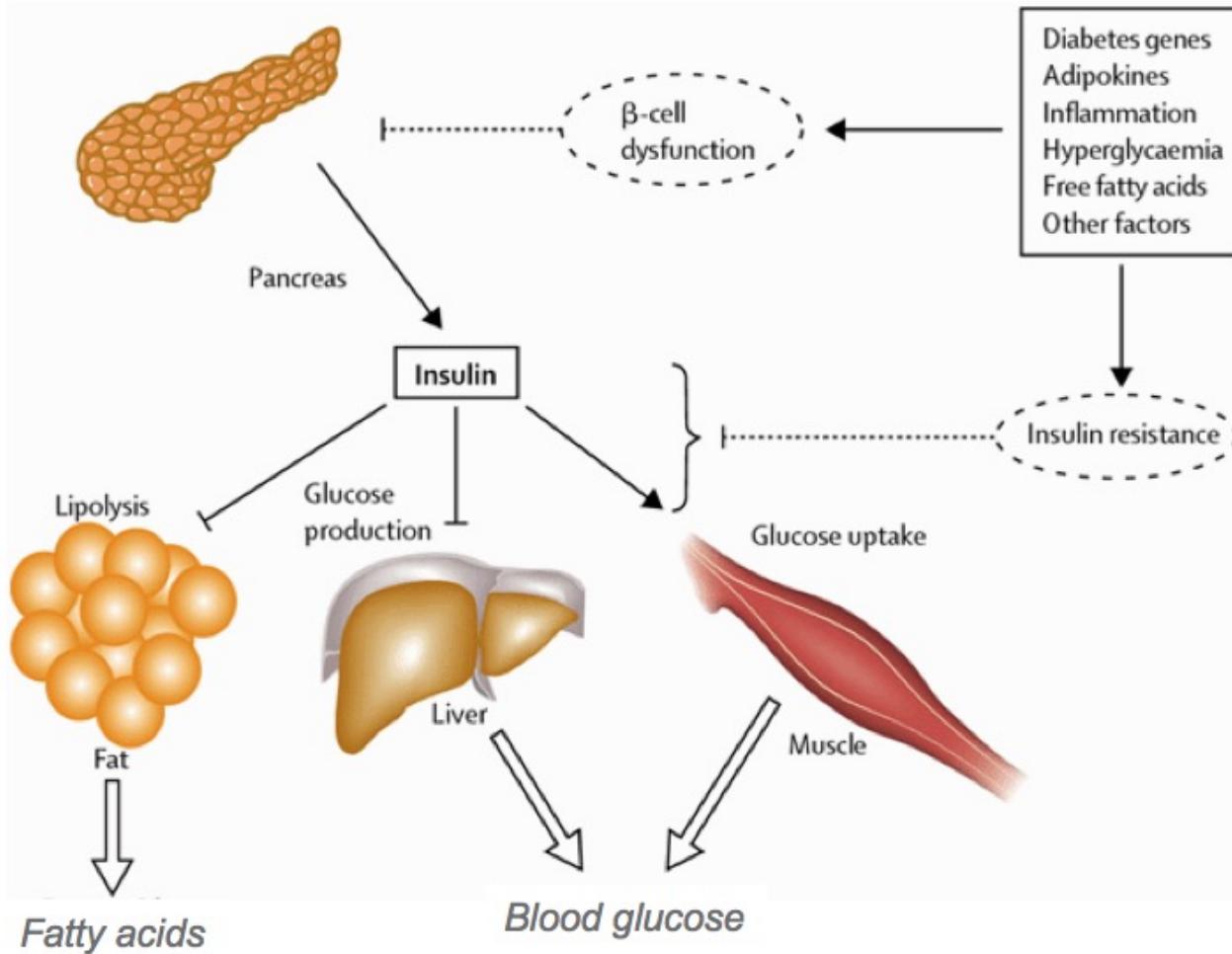
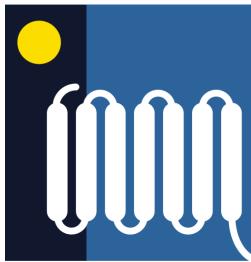
# Diabetes mellitus



Type I diabetes - failure to secrete enough insulin ( $\beta$ -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