THE UNIVERSITY OF MELBOURNE

Melbourne Veterinary School

The role of the liver in fatty acid, amino acid and carbohydrate metabolism

Dr Nick Bamford
Senior Lecturer, Veterinary Biosciences

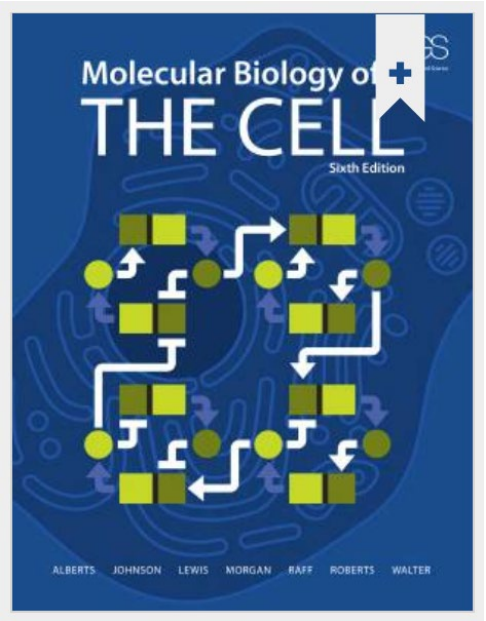
n.bamford@unimelb.edu.au

VETS30017 / VETS90125

Role of the liver in metabolism & energy production

- Lecture 3 – Health
  - Key pathways of metabolism

- Lecture 8 – Disease
  - Metabolism of negative energy balance
  - Ruminant metabolism
  - Syndrome of ruminant ketosis



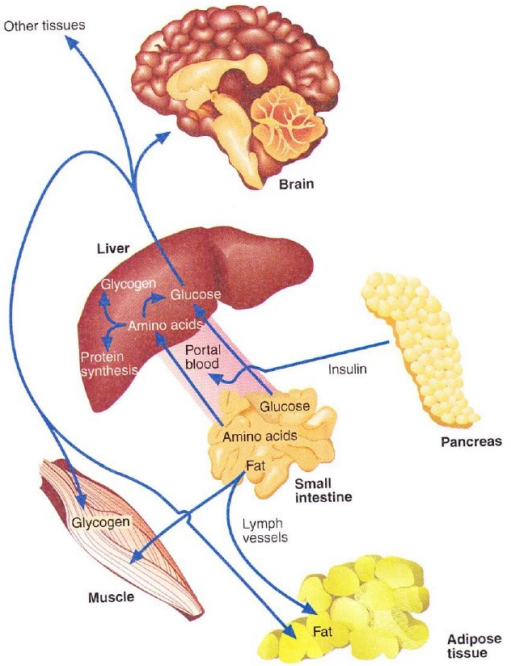
Chapter 2 & 14

Intended learning outcomes

- Outline how energy is derived from:
    1. Carbohydrates (glucose)
    2. Fats (fatty acids)
    3. Protein (amino acids)
- Key biochemical processes that occur in the liver
- Major metabolic effects of insulin and glucagon
- Metabolic fates of acetyl-CoA

Purpose of metabolism

- Chemical processes in the body that sustain life
  - Oxidation of food to provide energy (ATP)
  - Food molecules converted into new cellular material
  - Processing of waste products to facilitate excretion
  - Generation of heat
- Liver is central to these processes!

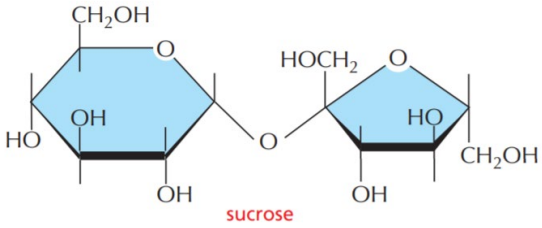


Constituents of food

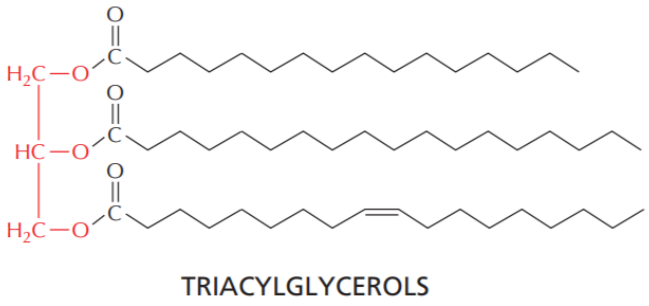
1. Carbohydrates
2. Fats
3. Proteins
4. Vitamins
5. Minerals
6. Fibre
7. Water

Constituents of food

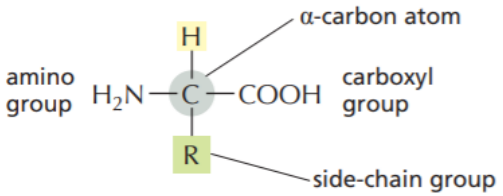
- Carbohydrates
  - Sugars mostly as disaccharides (e.g. sucrose, lactose) or polysaccharides (e.g. starch)



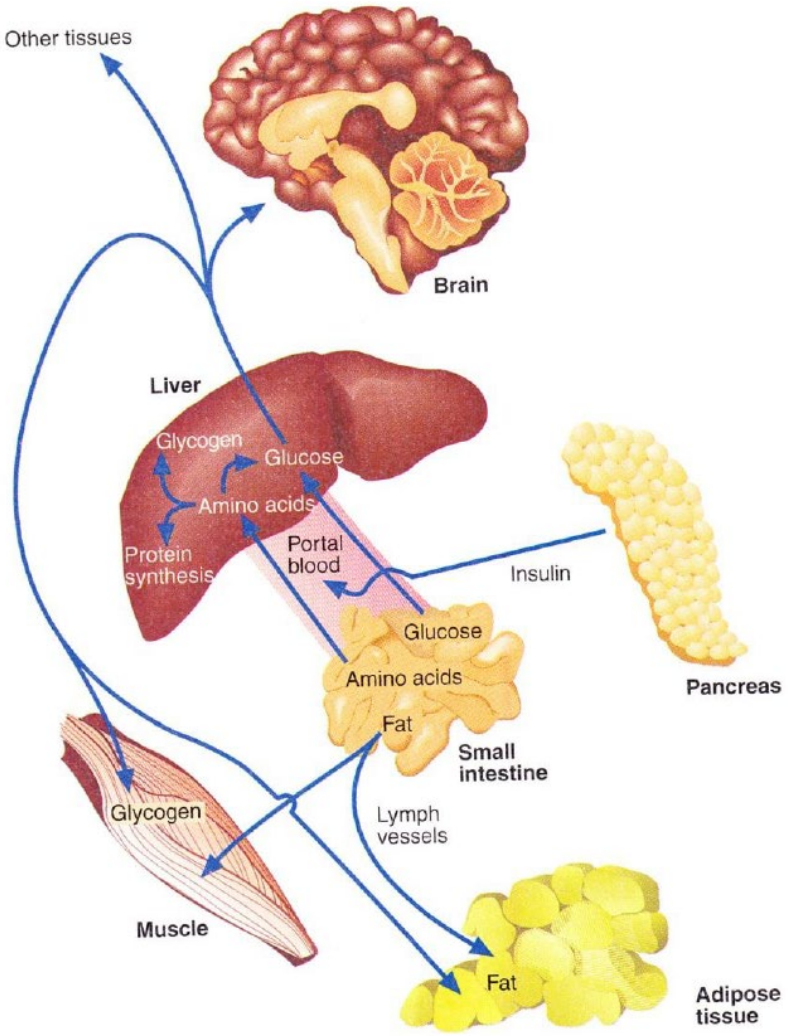
- Fats
  - Triacylglycerols (TAGs)



- Proteins
  - Polypeptides of amino acids

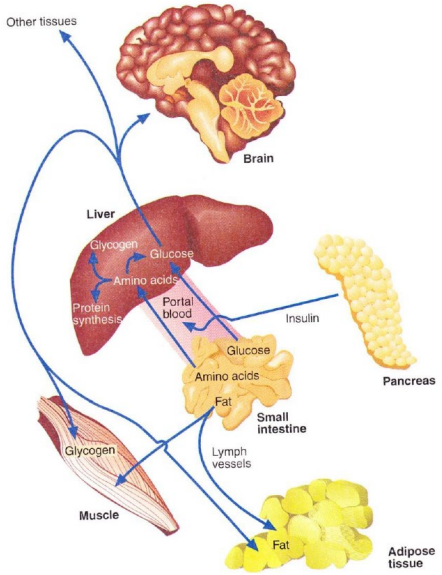


Highly regulated system



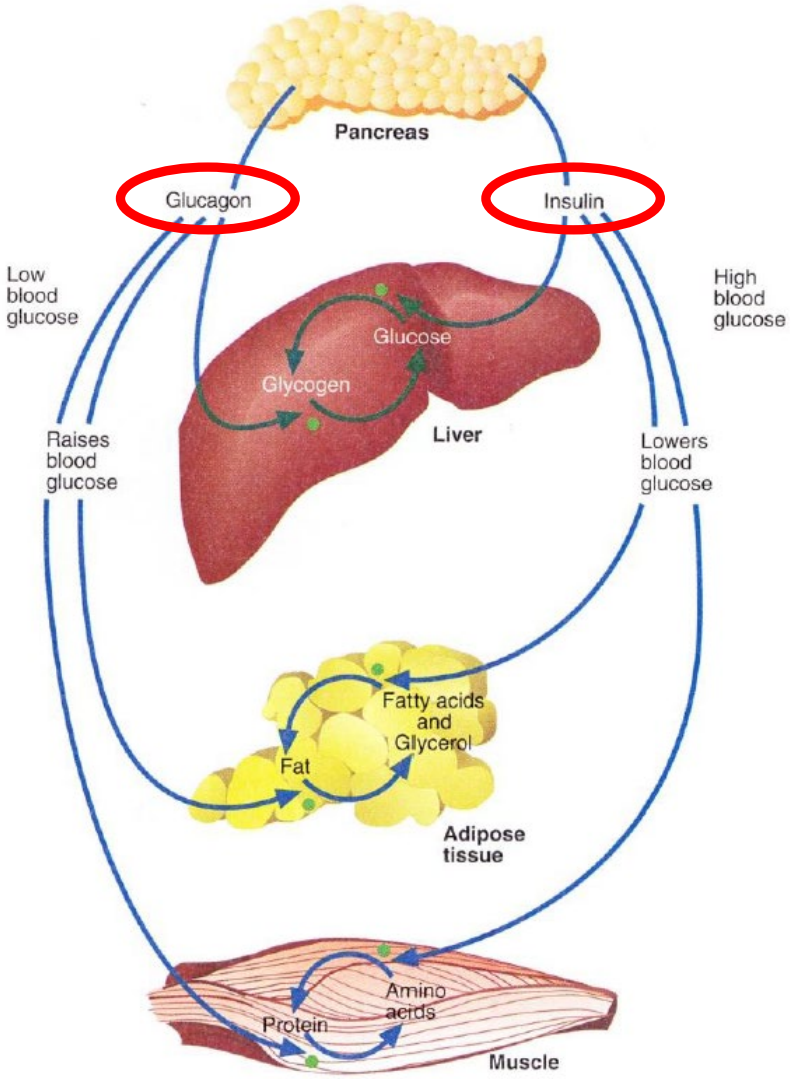
Postprandial state

- High levels of nutrients in the blood
- Glucose
  - Replenish glycogen stores in liver & skeletal muscle
  - Excess converted to TAGs
- Fats
  - TAGs stored in adipocytes
- Amino acids
  - Utilised by tissues for de novo protein synthesis
  - Excess converted to fat or glycogen



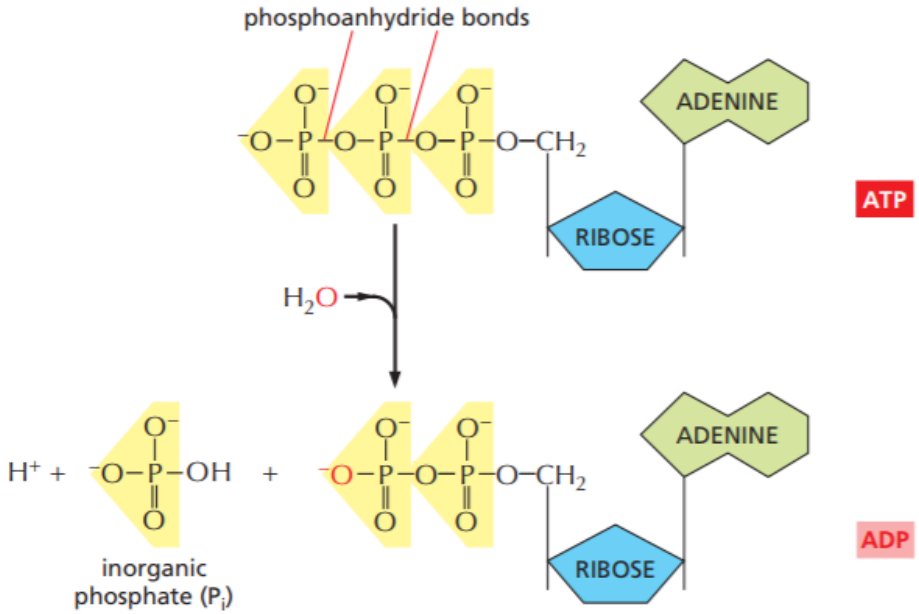
Hormonal control

- Insulin
  - Main signal to ‘store’
  - Pancreatic β cells in response to high glucose
- Glucagon
  - Main signal to ‘release’
  - Pancreatic α cells in response to low glucose
- Reciprocal control



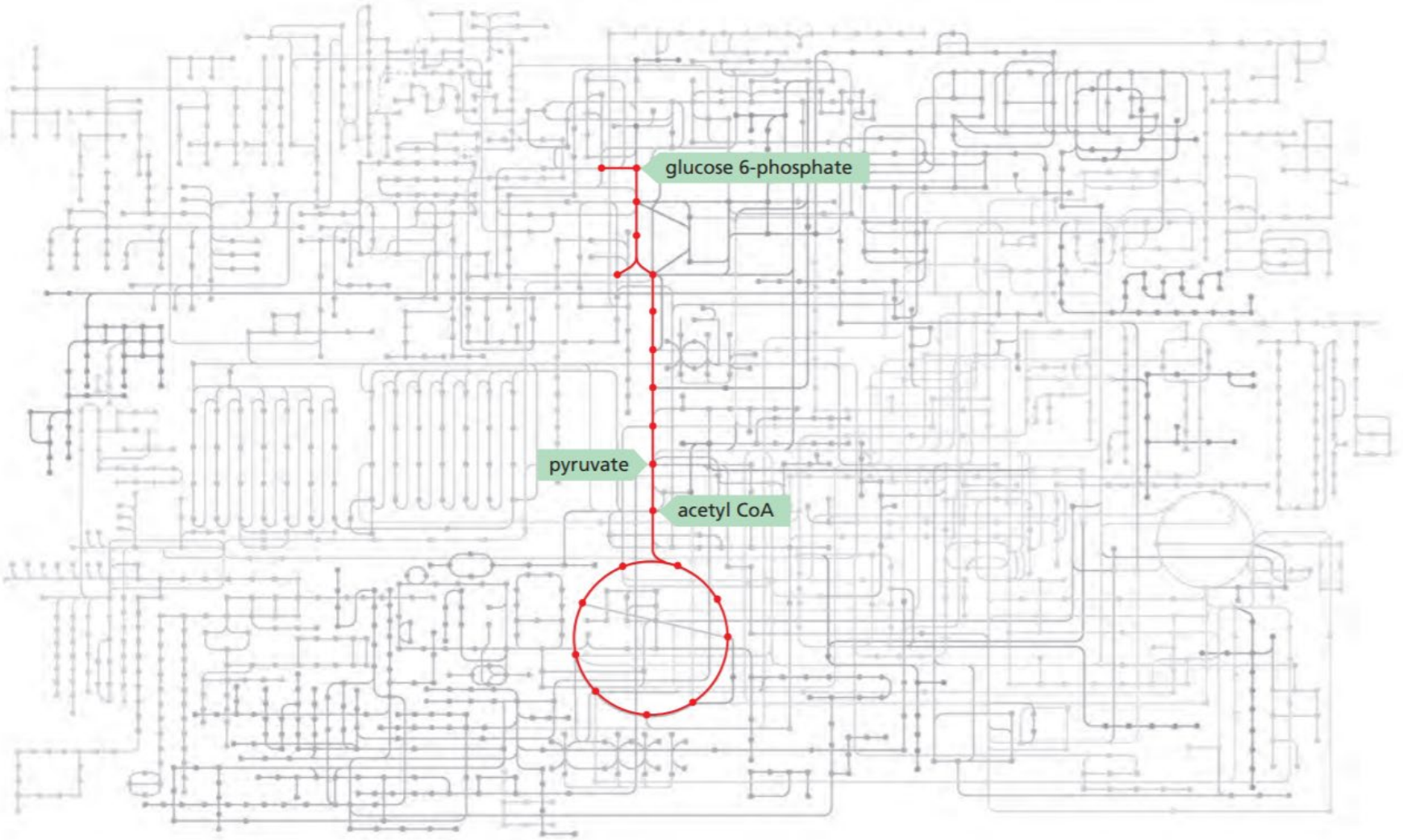
Energy release from food

- Energy is derived from glucose, fat and amino acids in the form of adenosine triphosphate (ATP)



Hydrolysis of ATP to ADP & inorganic phosphate

Energy release from food



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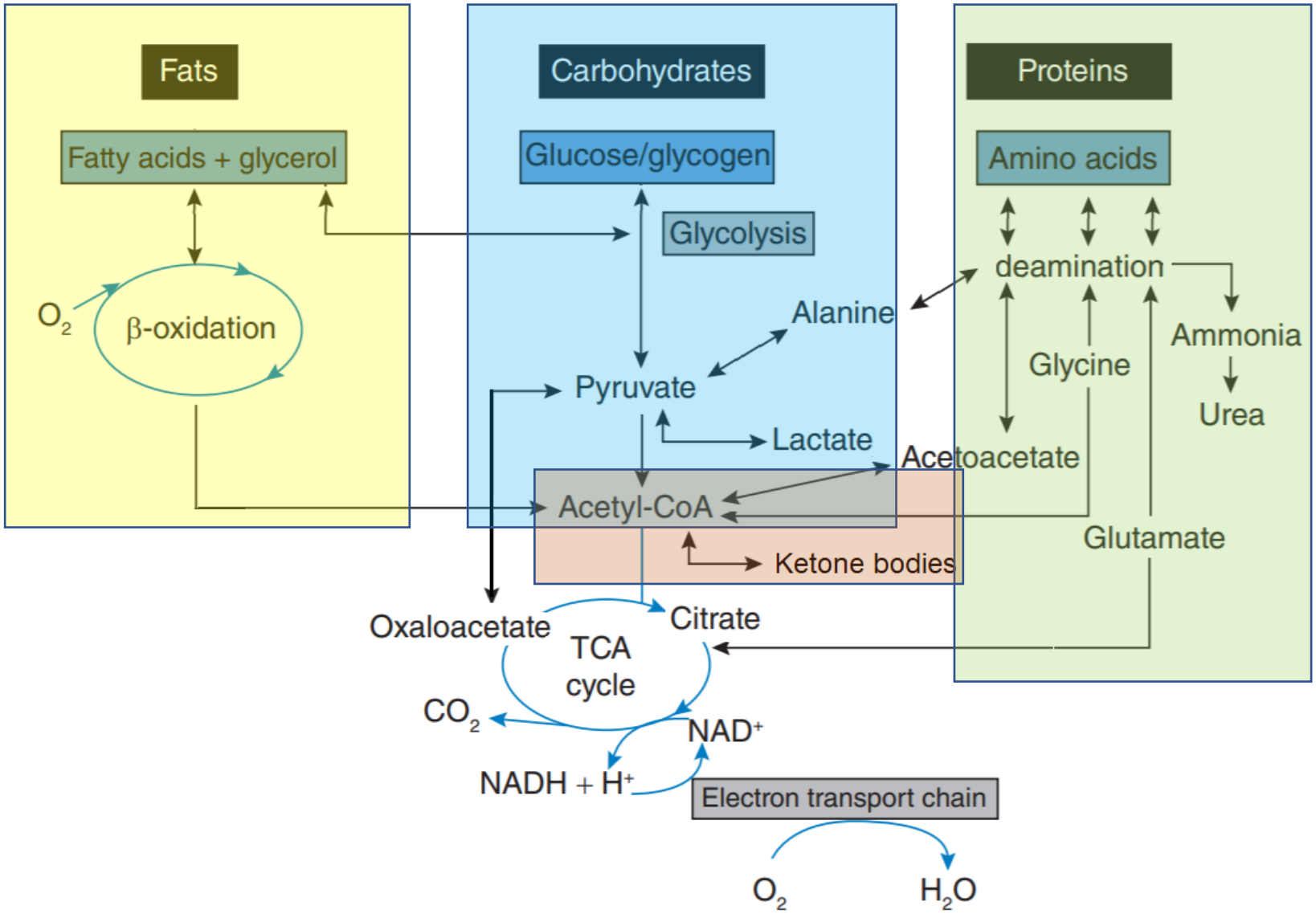
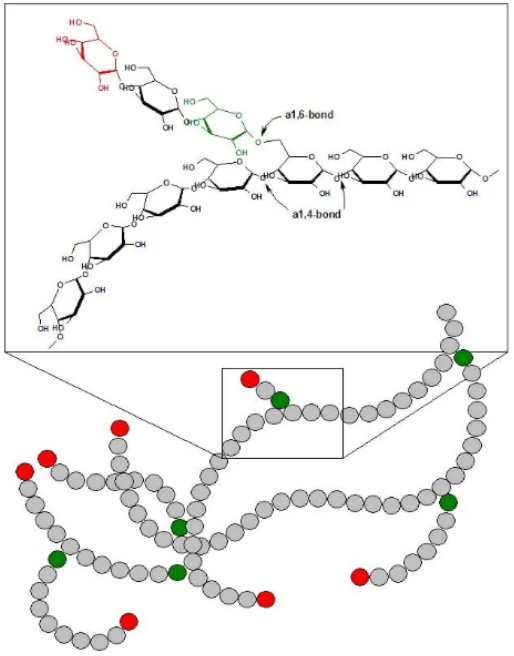
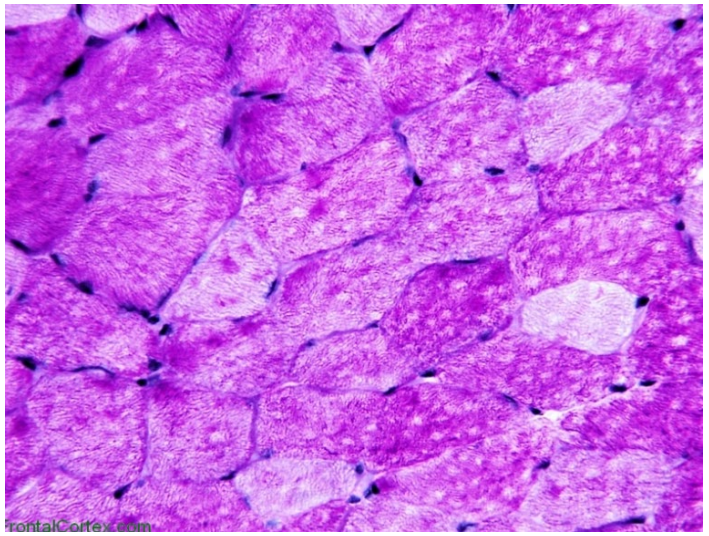


Energy release from glucose

- Glucose or other sugars as ‘glucose-like’ substrates
- Stored as glycogen in liver & skeletal mm.

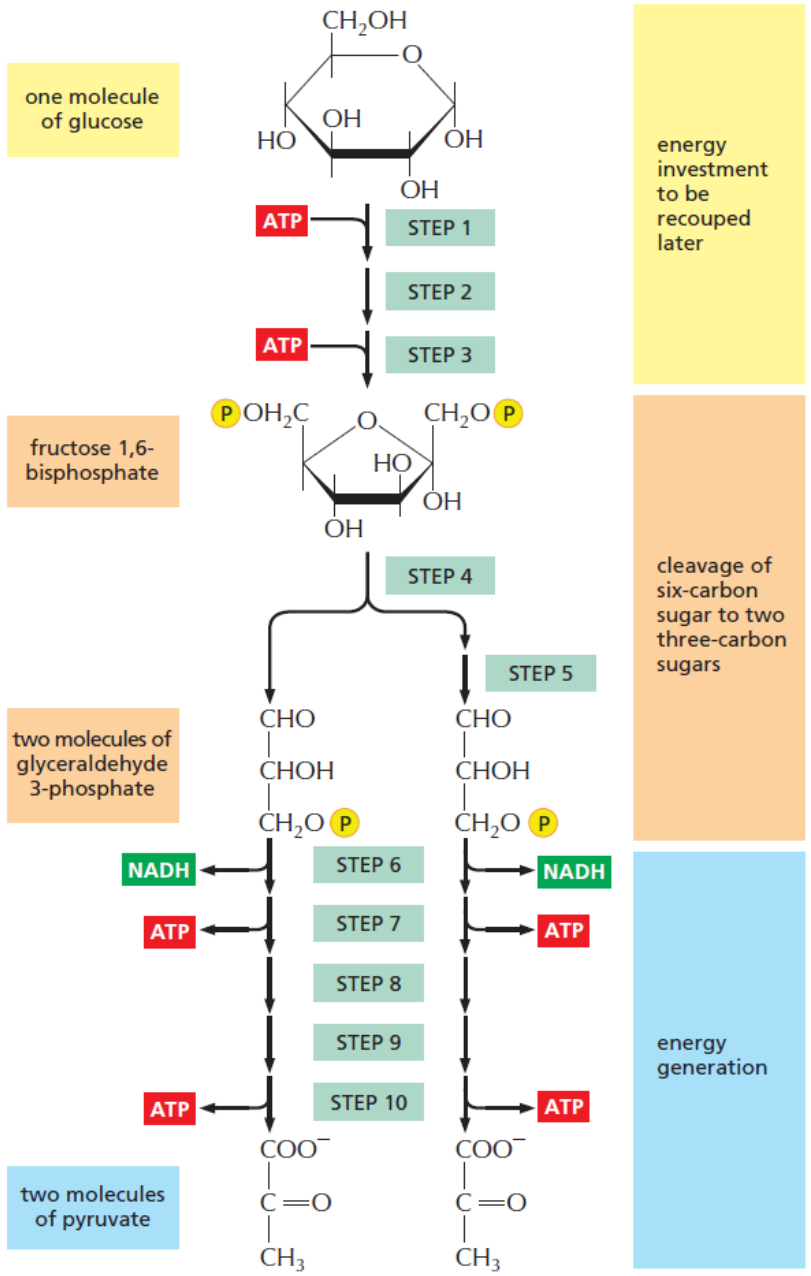




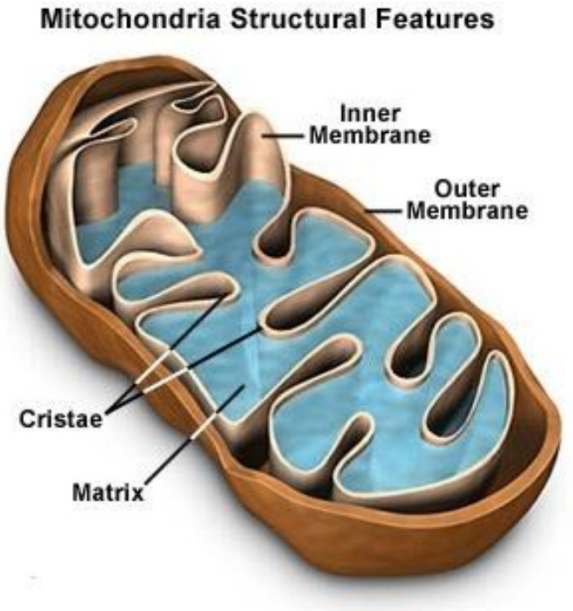
Periodic Acid Schiff (PAS) stain of muscle

Stage 1: Glycolysis

- Cytoplasmic
- Splitting of glucose (6C) → 2x pyruvate (3C)
  - Net 2ATP & 2NADH
- Does not require O_2



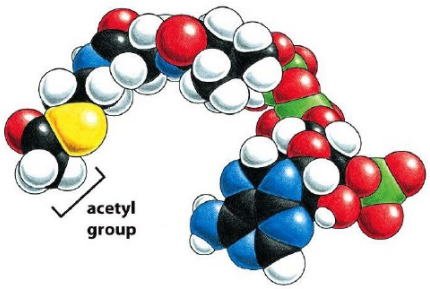
Stage 2: TCA cycle

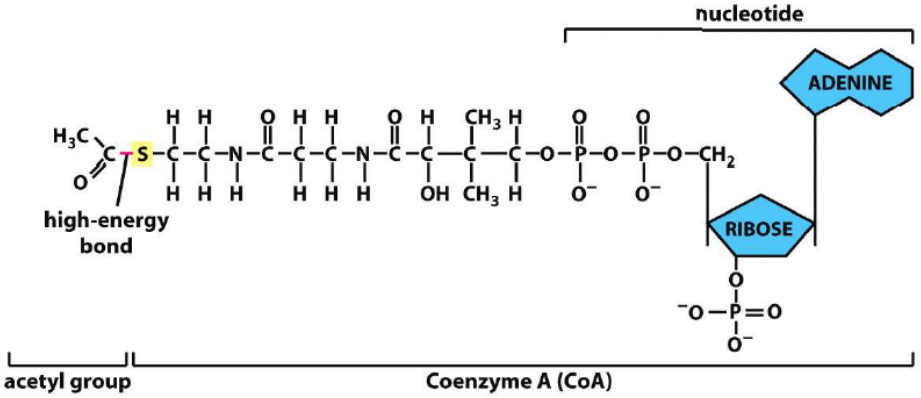


- Mitochondrial matrix

<u>First step</u>

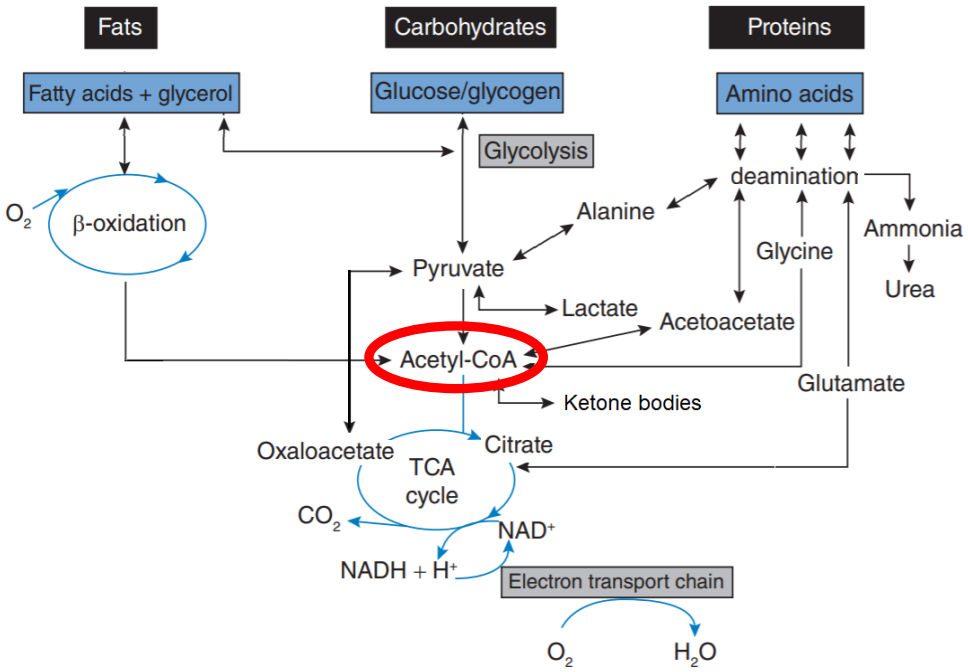
- Oxidative decarboxylation of pyruvate
  - Irreversible release of CO_2
- Acetyl group (2C) transferred to carrier Coenzyme A → acetyl-CoA





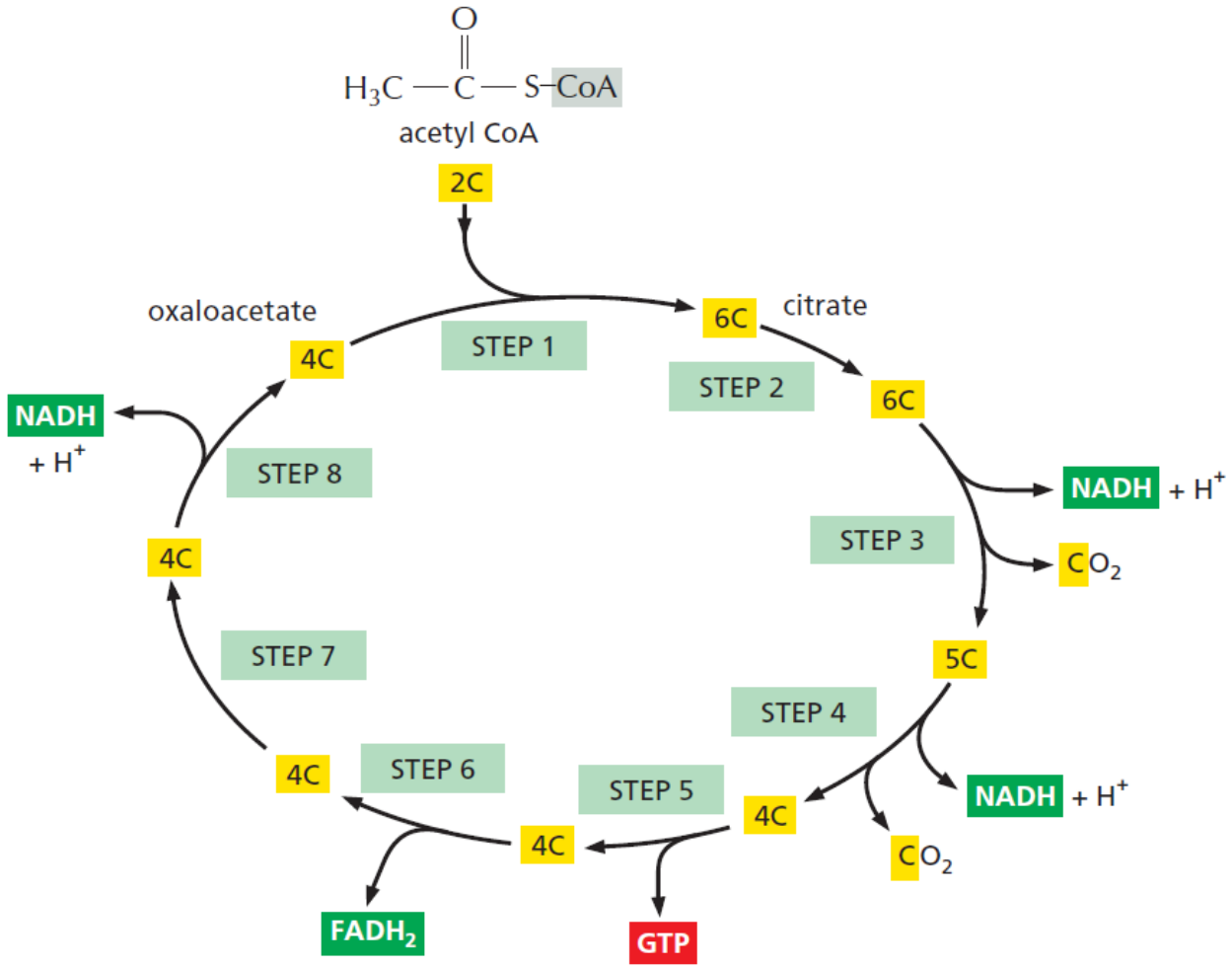
Acetyl-CoA

- Coenzyme A (CoA) is an acyl group carrier
- Incorporates pantothenic acid (Vit. B5)
- Acetyl-CoA is at the cross-roads of metabolism!
- Fate of acetyl-CoA:
    1. Feed into TCA cycle
    2. Lipogenesis
    3. Ketogenesis



Stage 2: TCA cycle

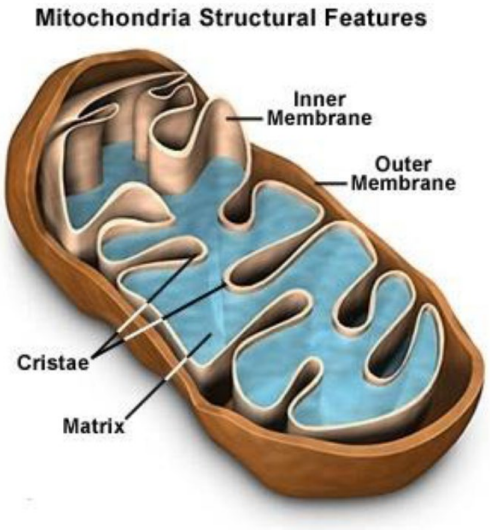
AKA Krebs cycle/Citric acid cycle

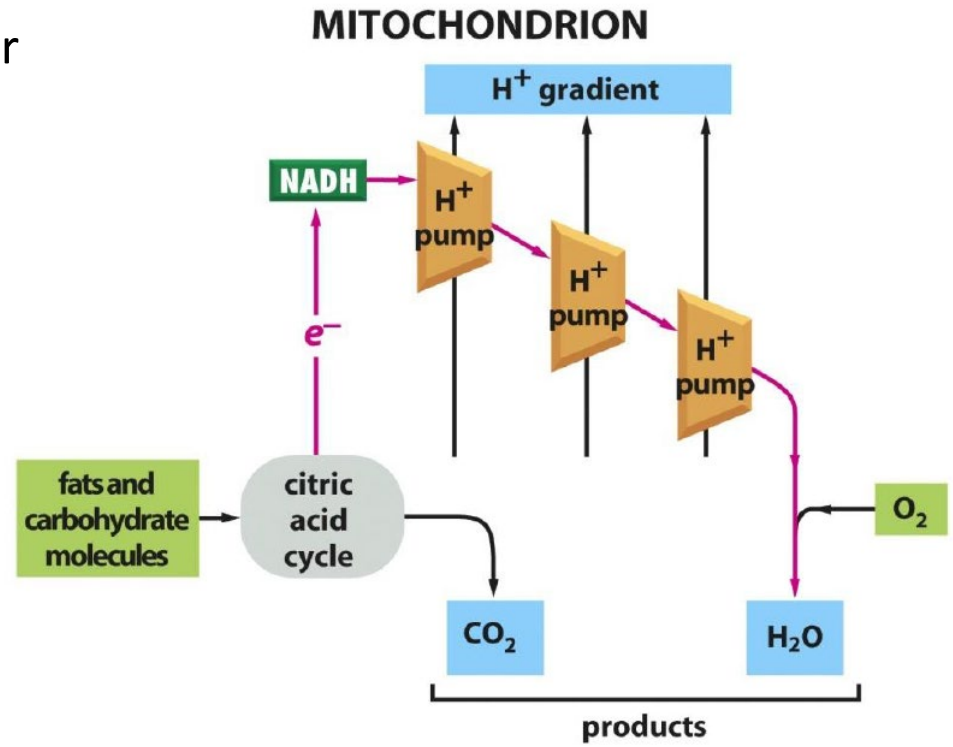


NET RESULT: ONE TURN OF THE CYCLE PRODUCES THREE NADH, ONE GTP, AND ONE $FADH_2$ MOLECULE, AND RELEASES TWO MOLECULES OF CO_2

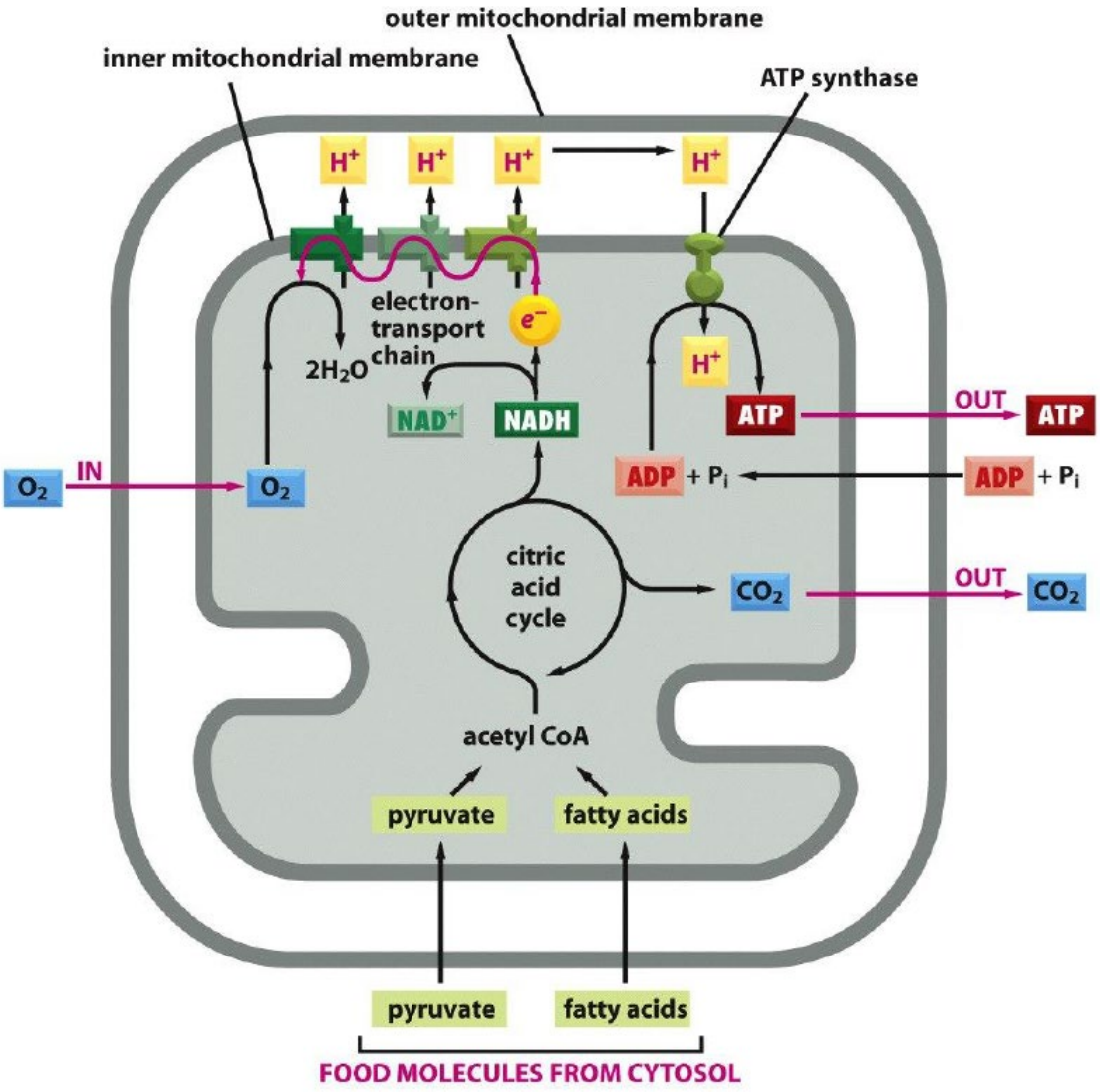
Stage 3: Oxidative phosphorylation

- AKA Electron transport chain
- Electrons from NADH/FADH2 “bump down a staircase”
  - Each fall releases energy
  - O_2 is final electron acceptor



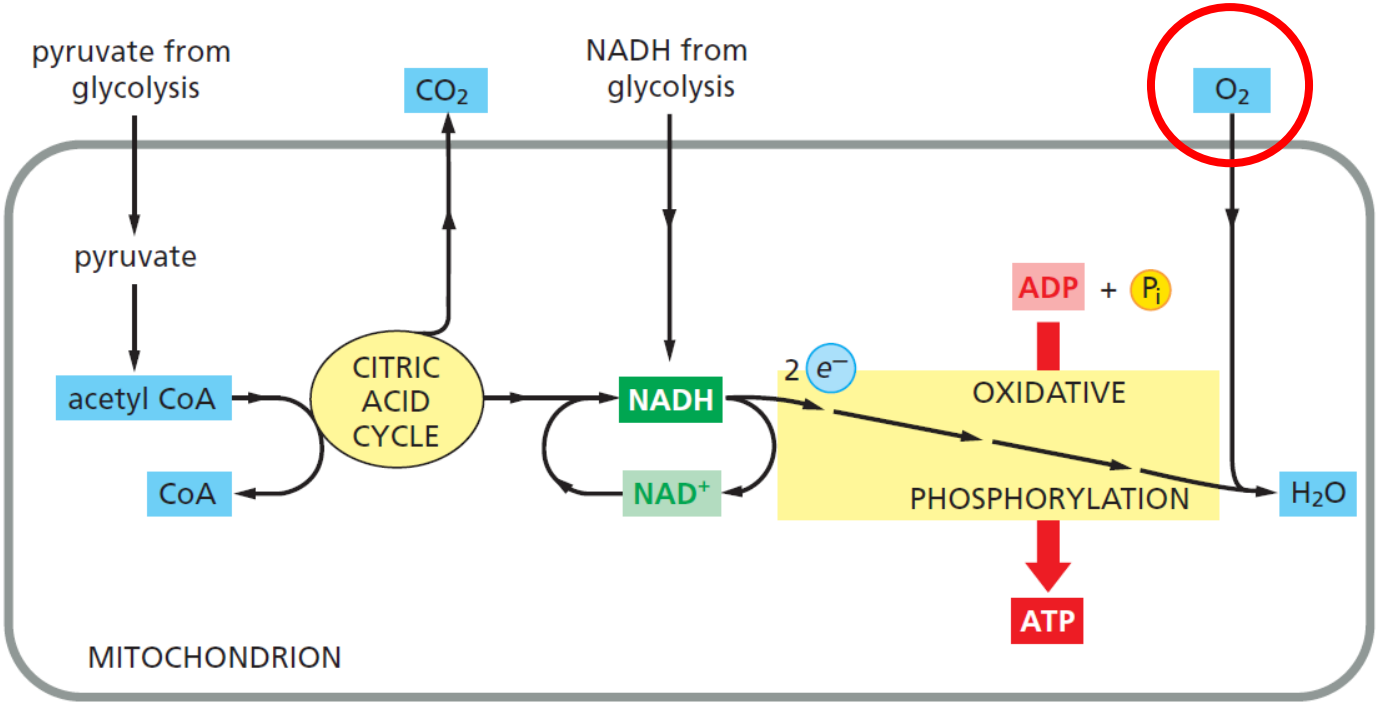


Stage 3: Oxidative phosphorylation



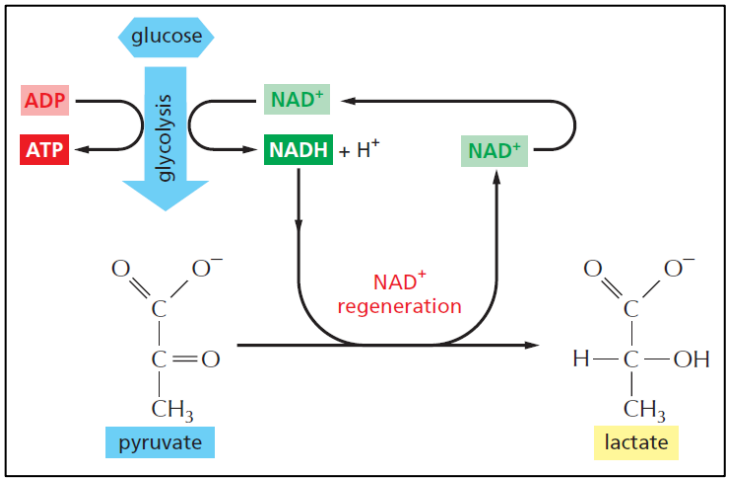
Aerobic cellular respiration

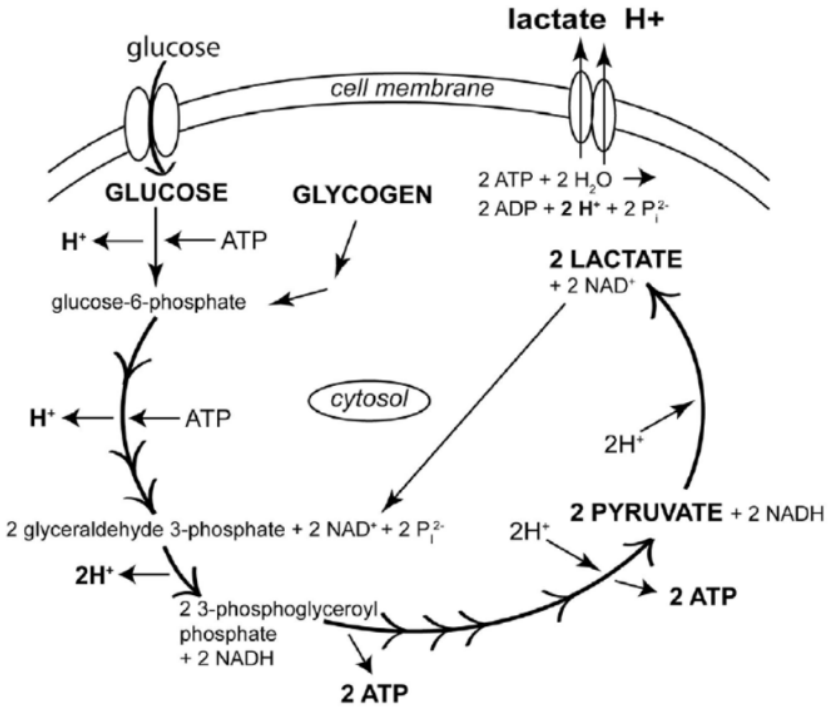
- Oxygen required as final electron acceptor in ETC
- Although oxygen not utilised directly in TCA cycle, the availability of NAD^+ becomes limiting when oxygen is not present



Anaerobic cellular respiration

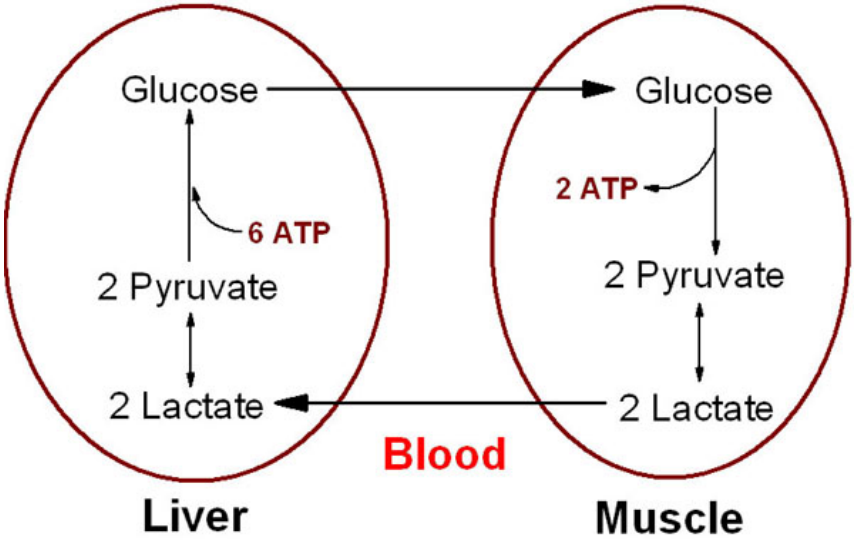
- Anaerobic glycolysis: pyruvate → lactate
- Lactate sustains glycolysis:
  - Yields only 2 ATP (net) per glucose (c.f. 38 ATP)
  - But 100x speed ox. phos.





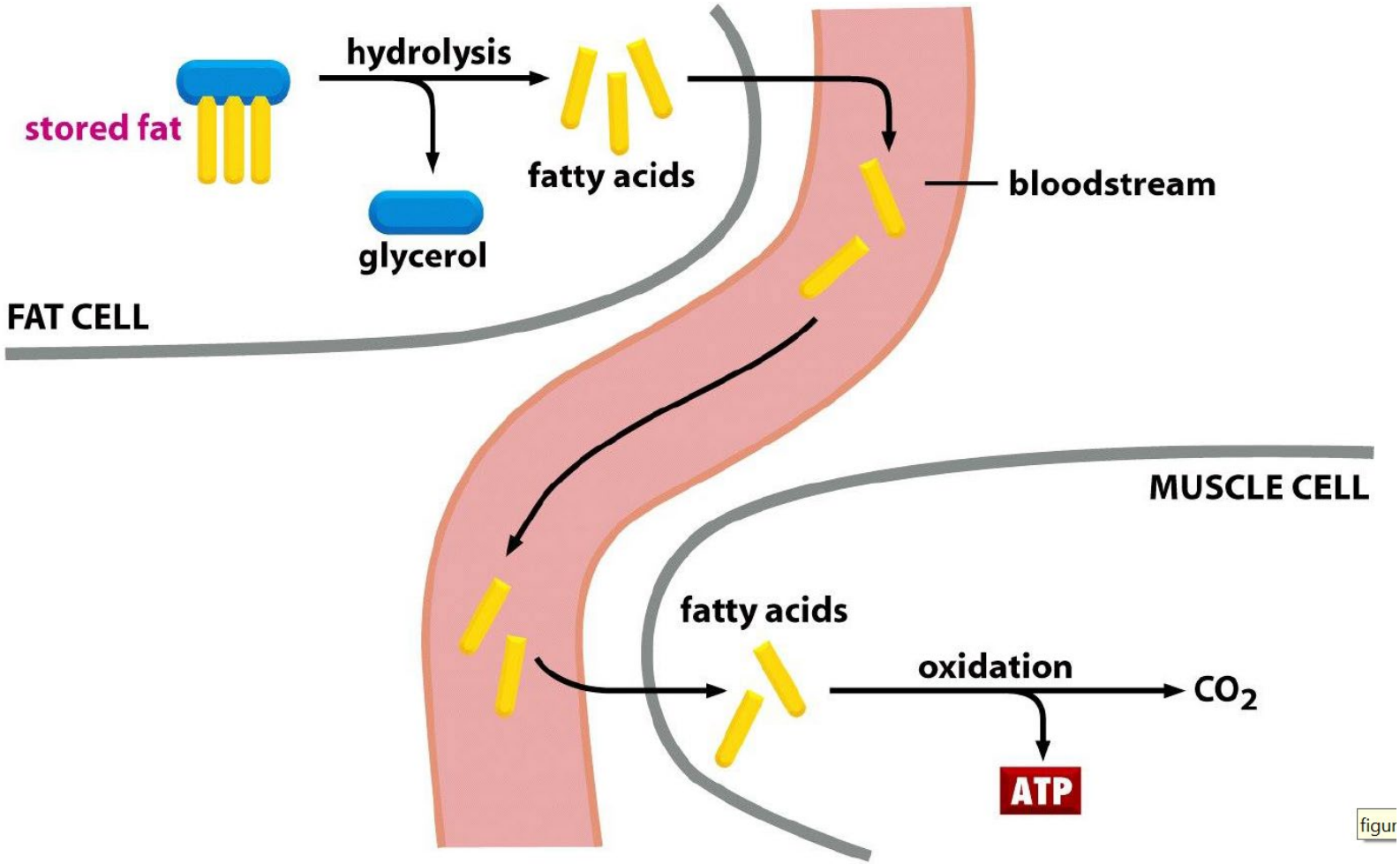
Lactic acid cycle

- Lactate released from tissues and transported to liver
- Lactate converted to glucose (requires energy)

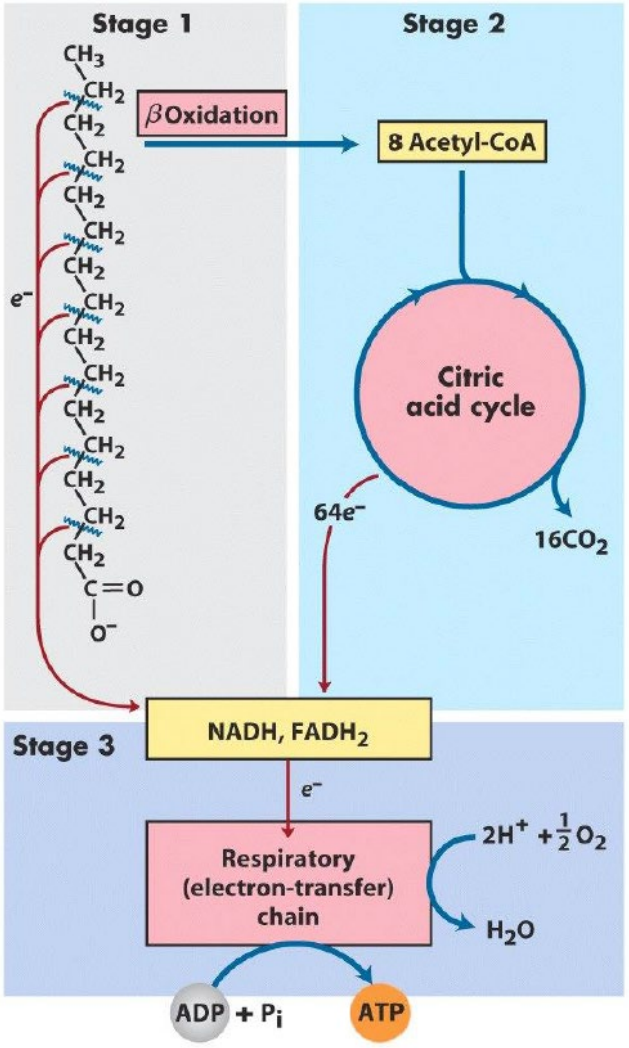


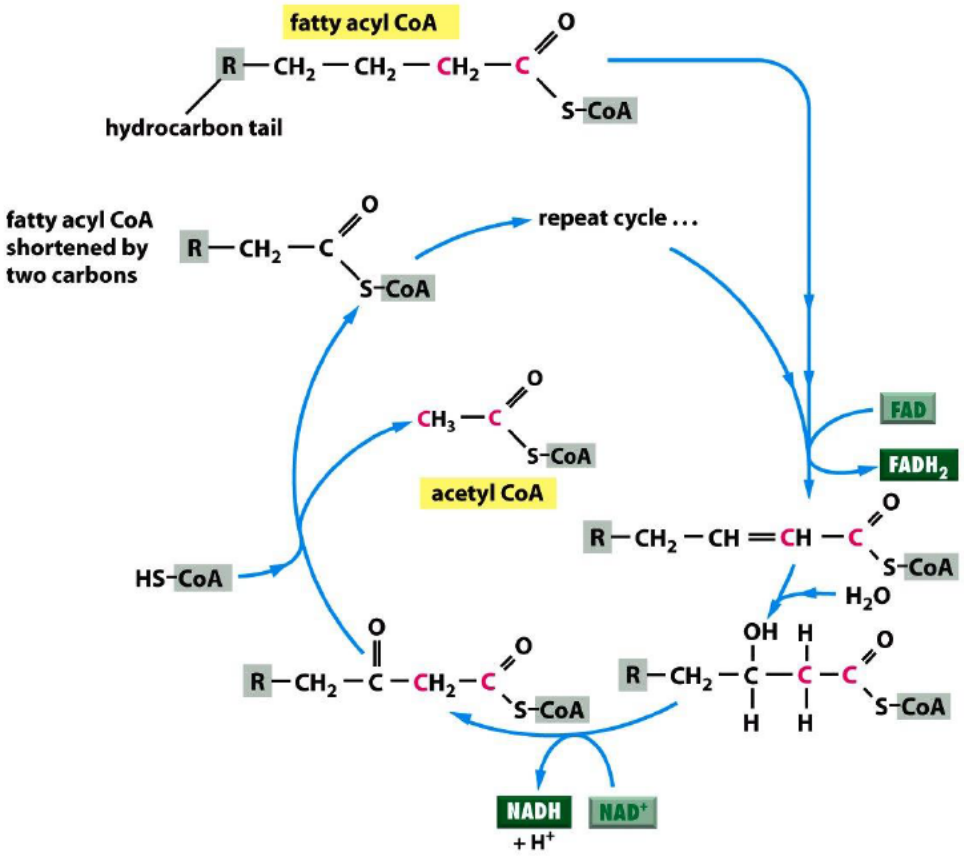
Lactic acid (Cori) cycle

Energy release from fats



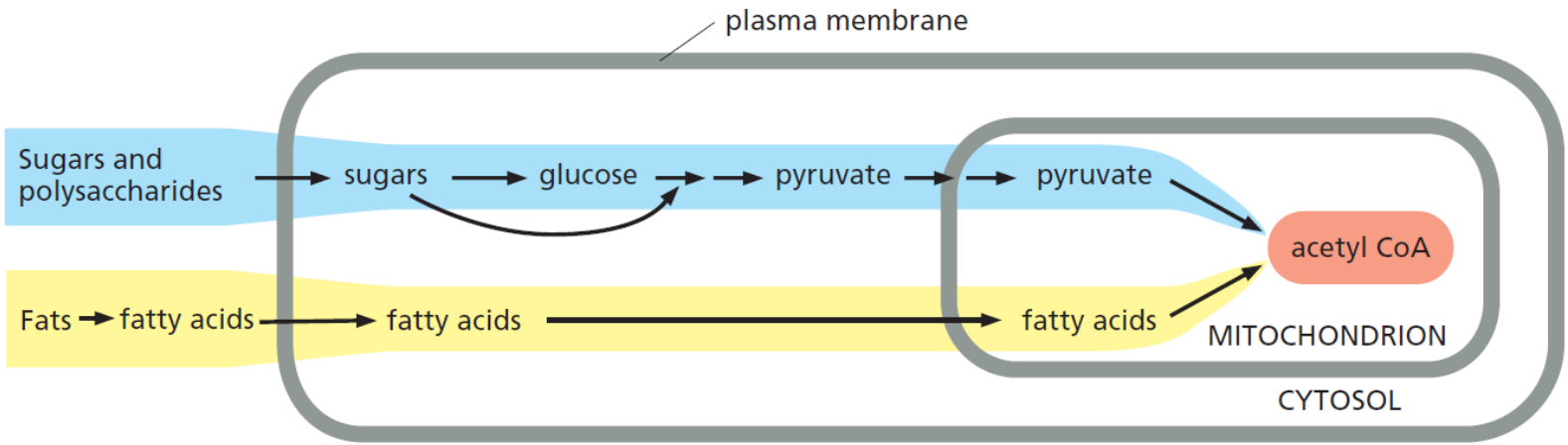
Fatty acid (β) oxidation





C atoms detached 2 at a time as acyl group
→ acetyl-CoA → TCA cycle

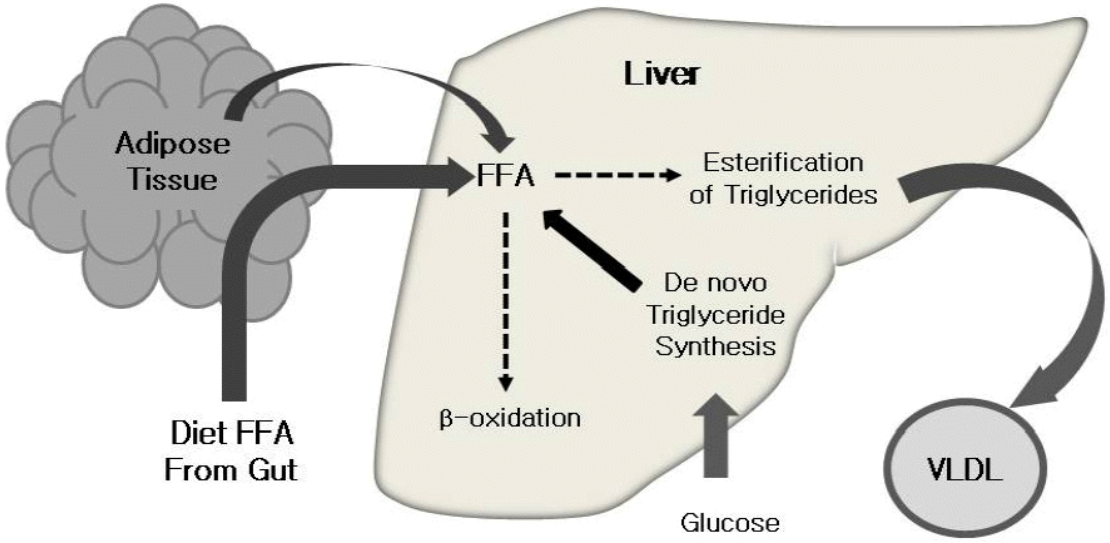
Energy release from fats



- Fatty acid oxidation differs from glucose oxidation in the preliminary formation of acetyl-CoA

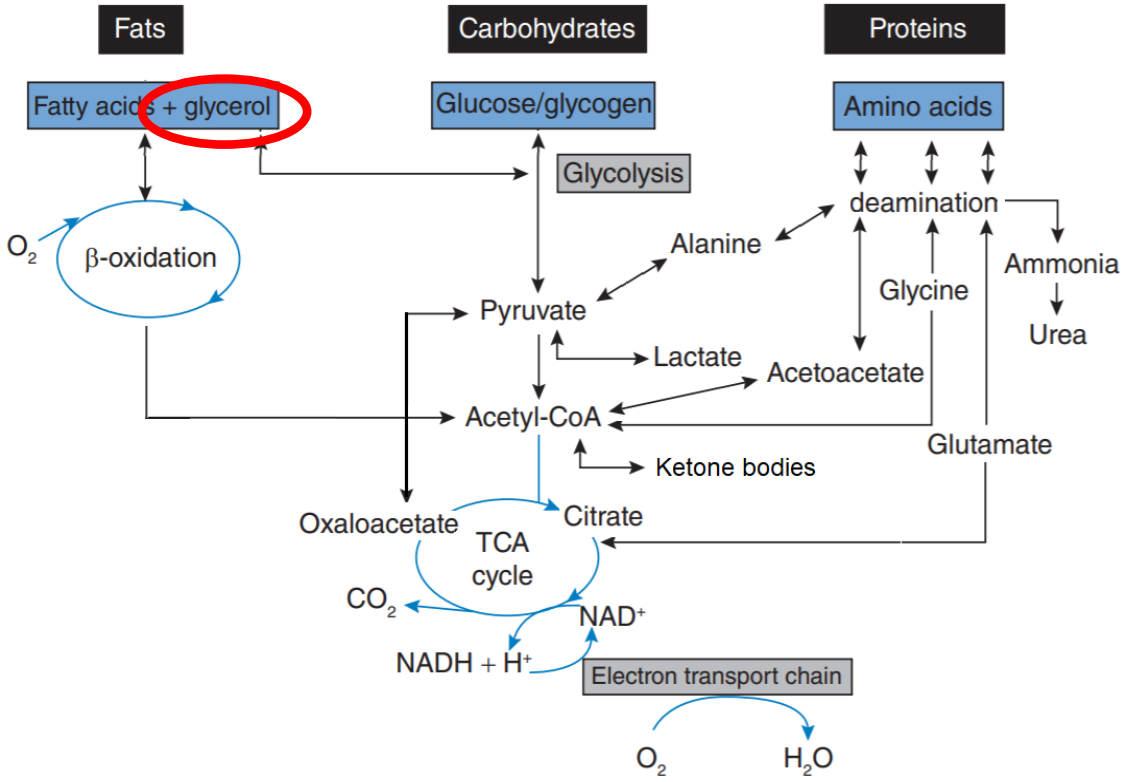
Role of the liver in fatty acid metabolism

- Can utilise fatty acids as energy (β oxidation)
- Lipogenesis/TG synthesis
- Package TAGs with apoproteins as VLDL

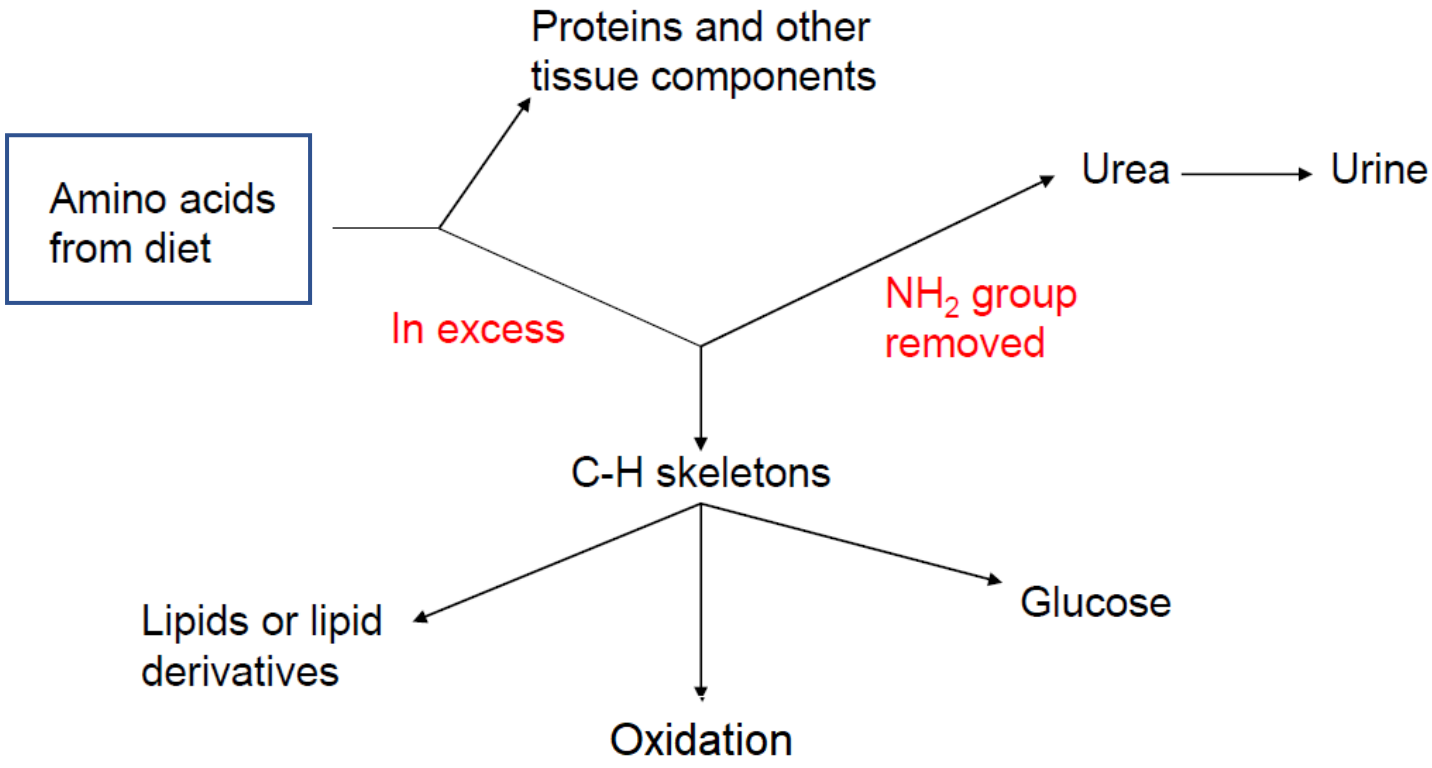


Fate of glycerol

- Directed to liver or kidneys to be converted to glycolytic intermediates → feeds into glycolysis

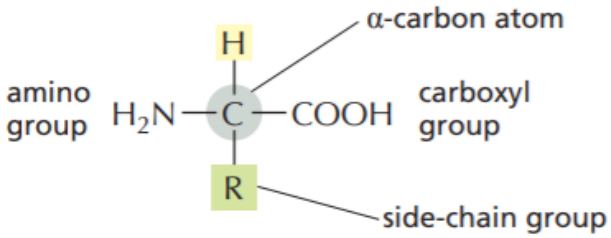


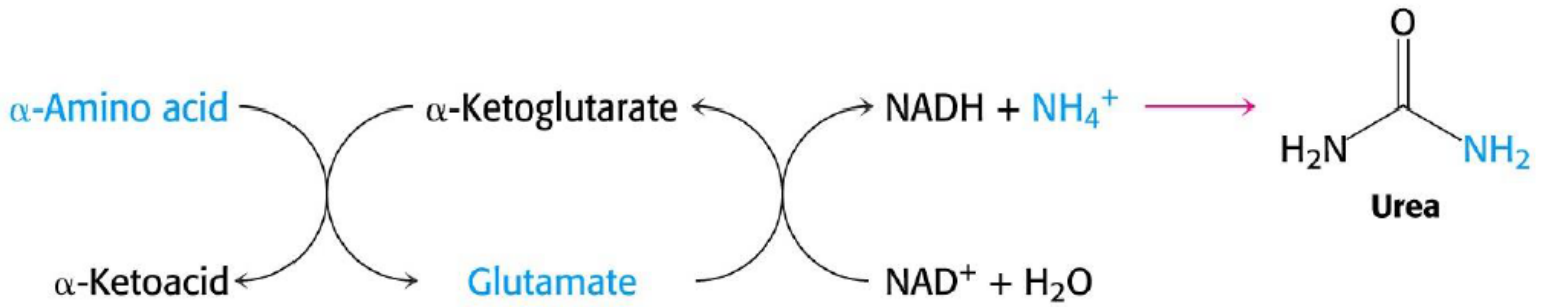
Fate of amino acids



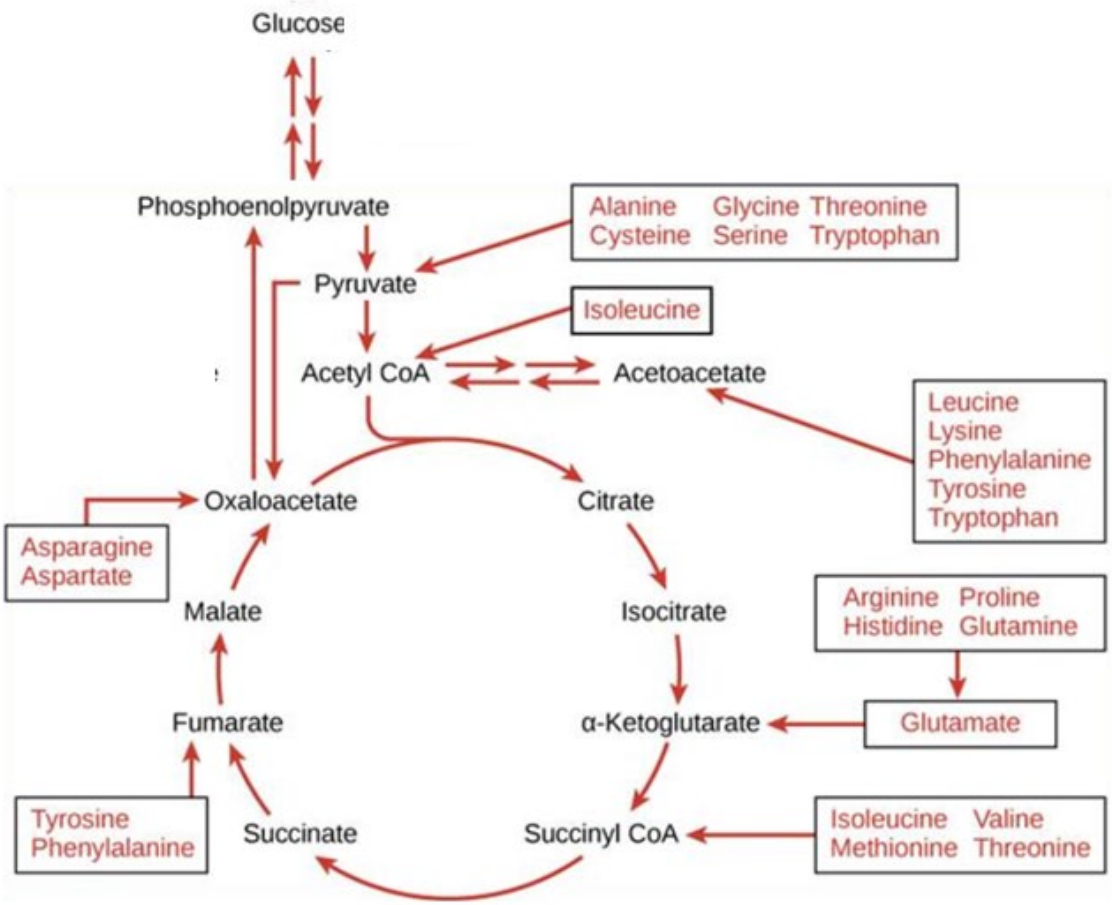
Energy release from amino acids

- Deamination via transaminase
- C-H skeletons used as fuel:
  - Pyruvate
  - Acetyl-CoA
  - TCA cycle intermediates





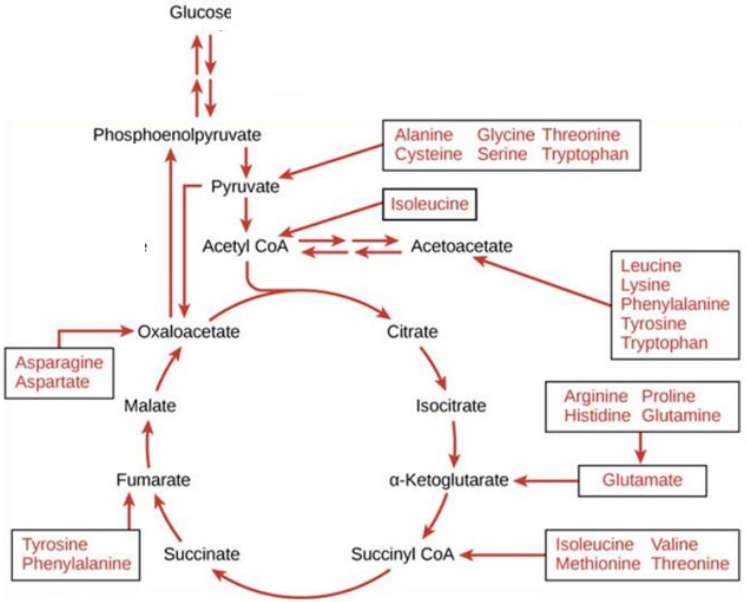
Energy release from amino acids



Amino acids can be glucogenic, ketogenic or both

Gluconeogenesis

- Most reactions opposite of glycolysis
- Glucose production from non-carbohydrate substrates
  - Glycerol
  - Lactate, pyruvate
  - Gluconeogenic amino acids (esp. alanine, glutamine)
  - (Propionate – ruminants)
- Acetyl-CoA is not gluconeogenic!
- Mainly in liver (also in kidney)



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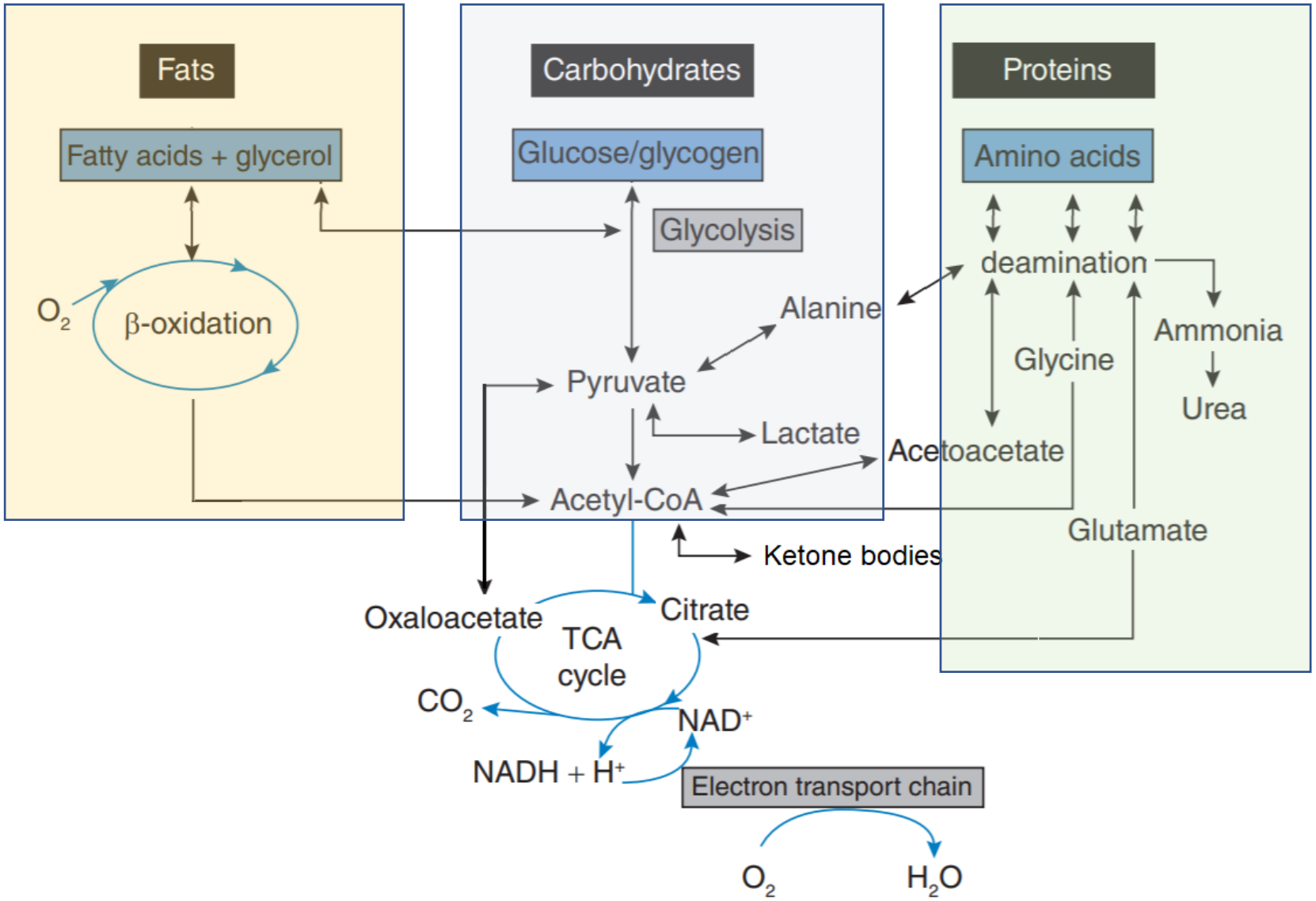

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Key role of the liver

- Glycogenesis/glycogen storage (also skeletal mm.)
- Gluconeogenesis
- Ketogenesis
- Fatty acid metabolism – TAG/VLDL synthesis
- Lactic acid metabolism
- (Generation of energy through glycolysis & β oxidation just as in other tissues)

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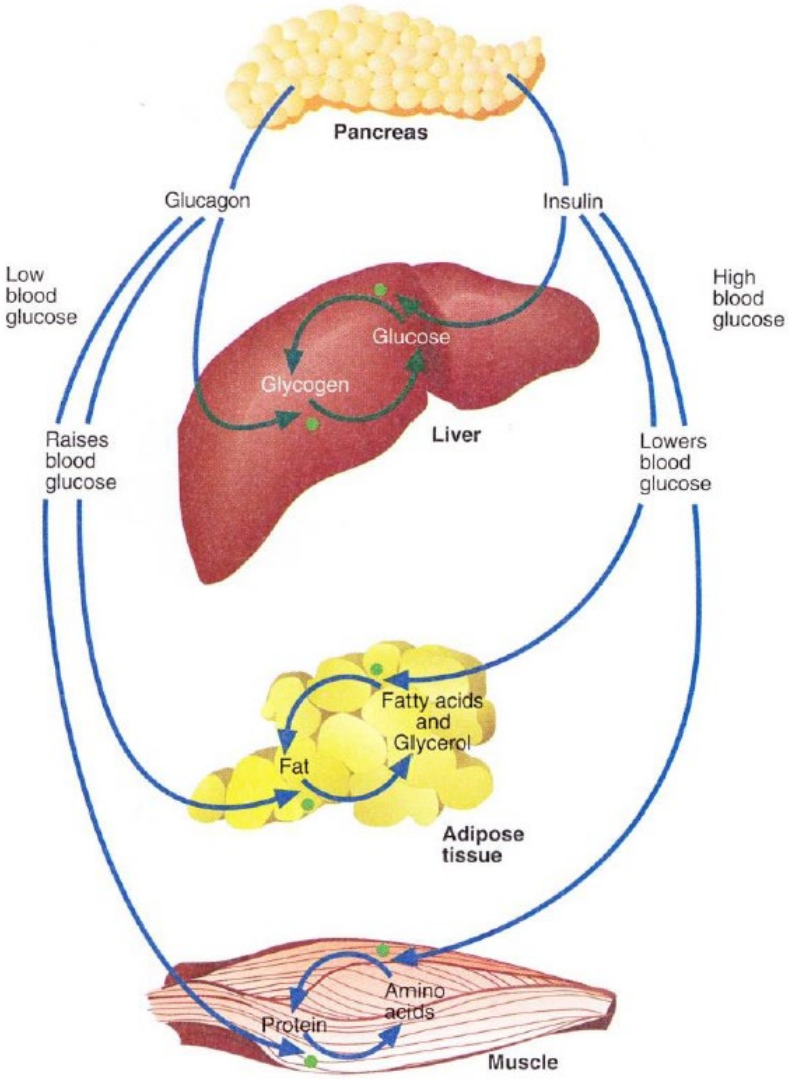

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