THE UNIVERSITY OF MELBOURNE

Melbourne Veterinary School

Bovine ketosis and other fatty liver syndromes in domestic animals

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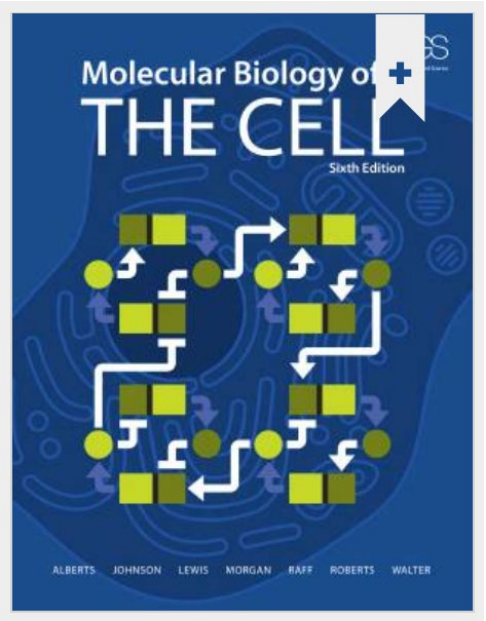
VETS30017 / VETS90125

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
  - Fatty liver syndromes in other species

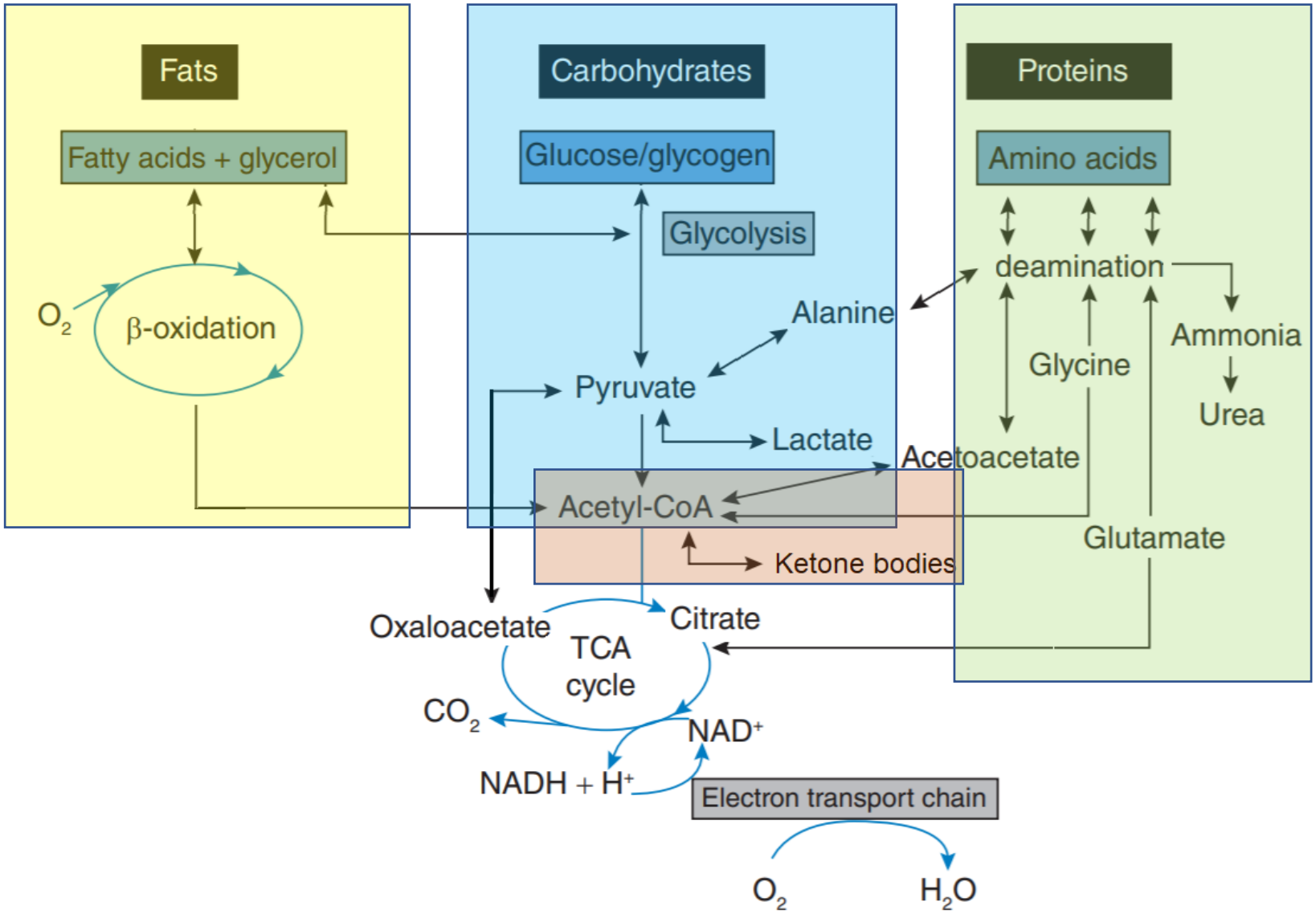


Chapter 2 & 14

Intended learning outcomes

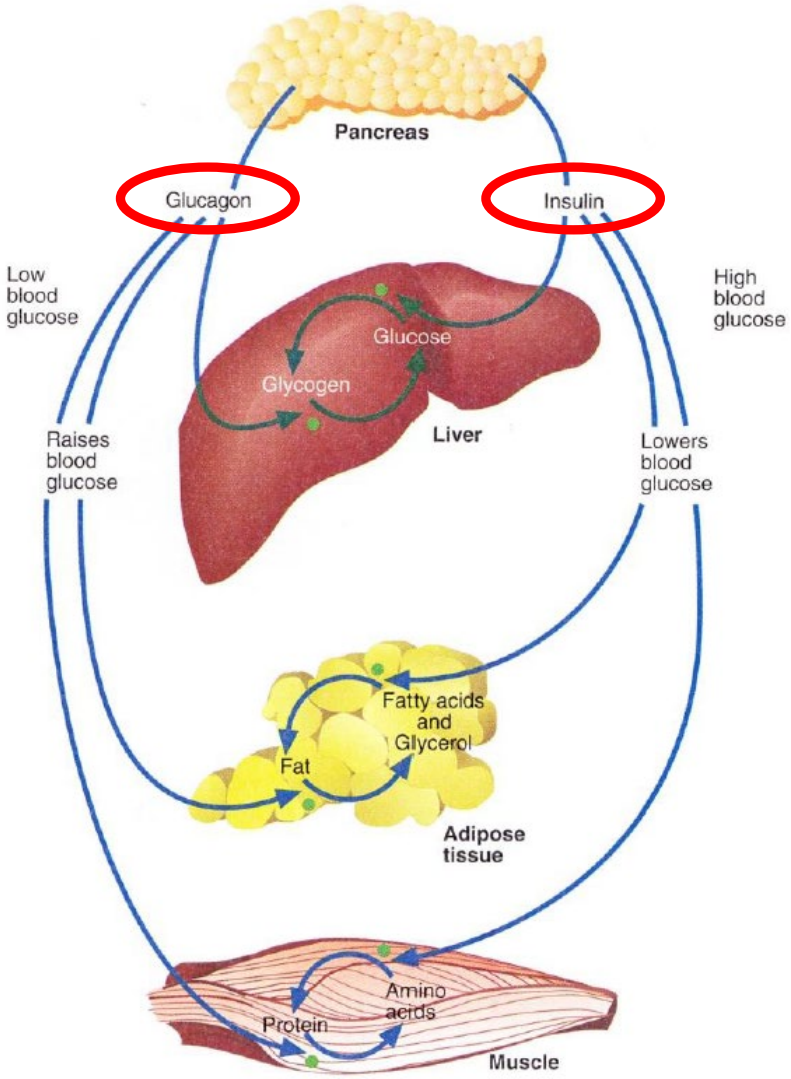
- Describe the metabolism of negative energy balance
  - Role of the liver in these processes
- Outline how ruminants digest complex carbohydrates to derive energy
- Apply knowledge of metabolism to clinical cases
  - Biochemistry of ketosis
  - Fatty liver syndromes
  - Principles of treatment

Recap: Energy release from food



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

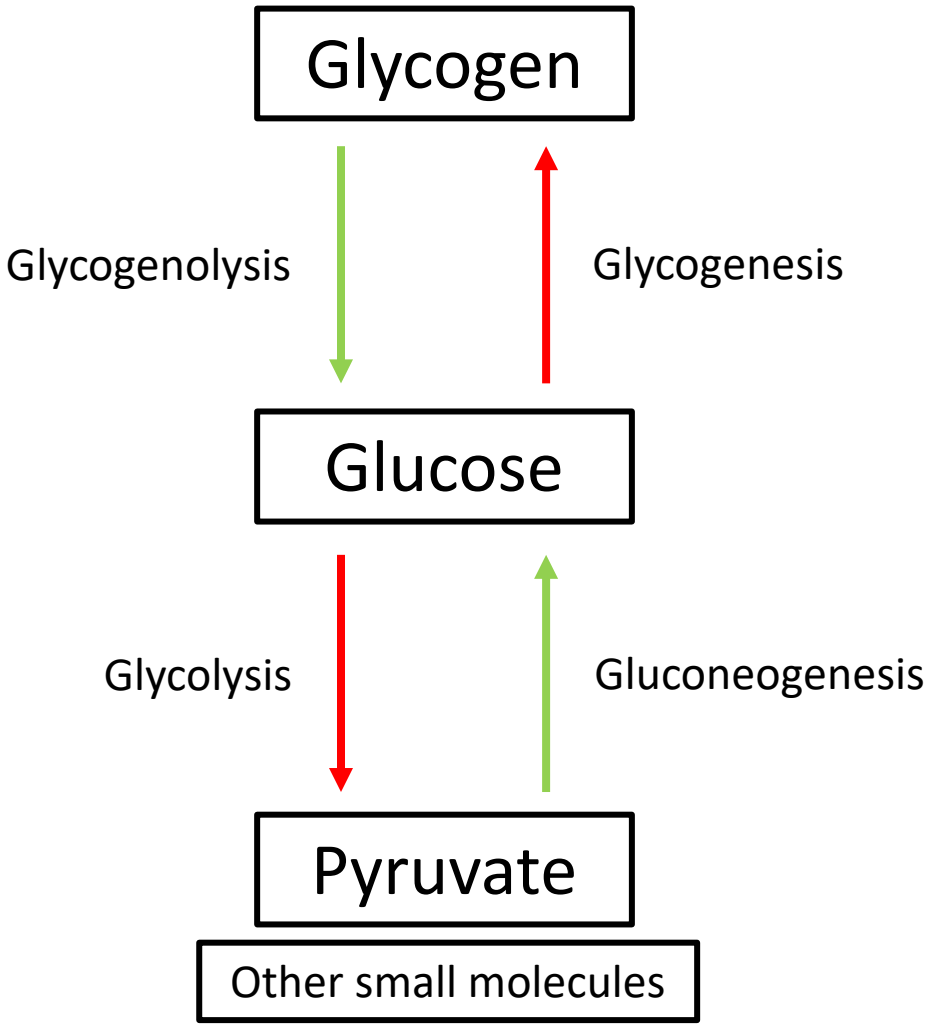


Metabolic balance in the liver

Hormones:

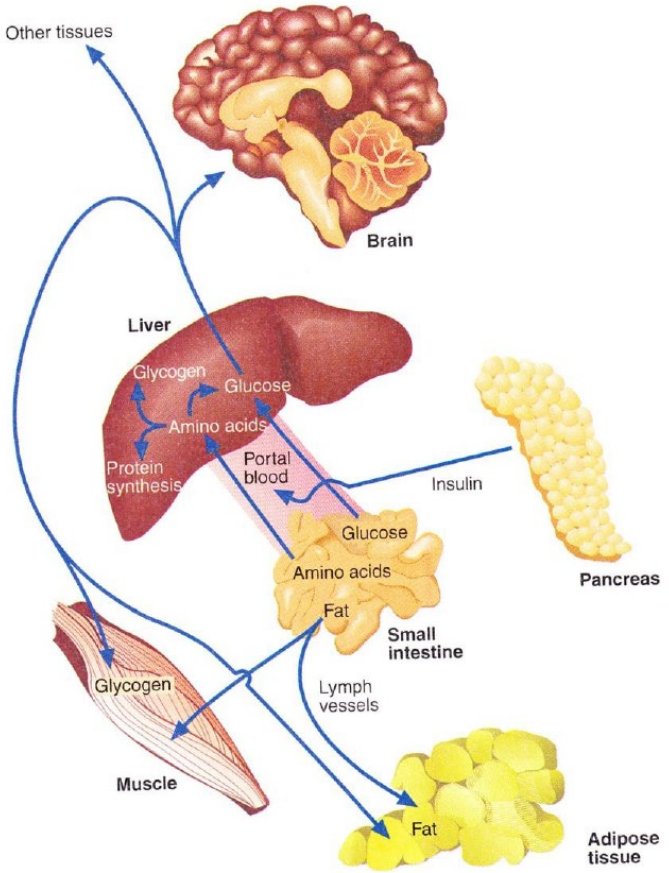
Insulin

Glucagon



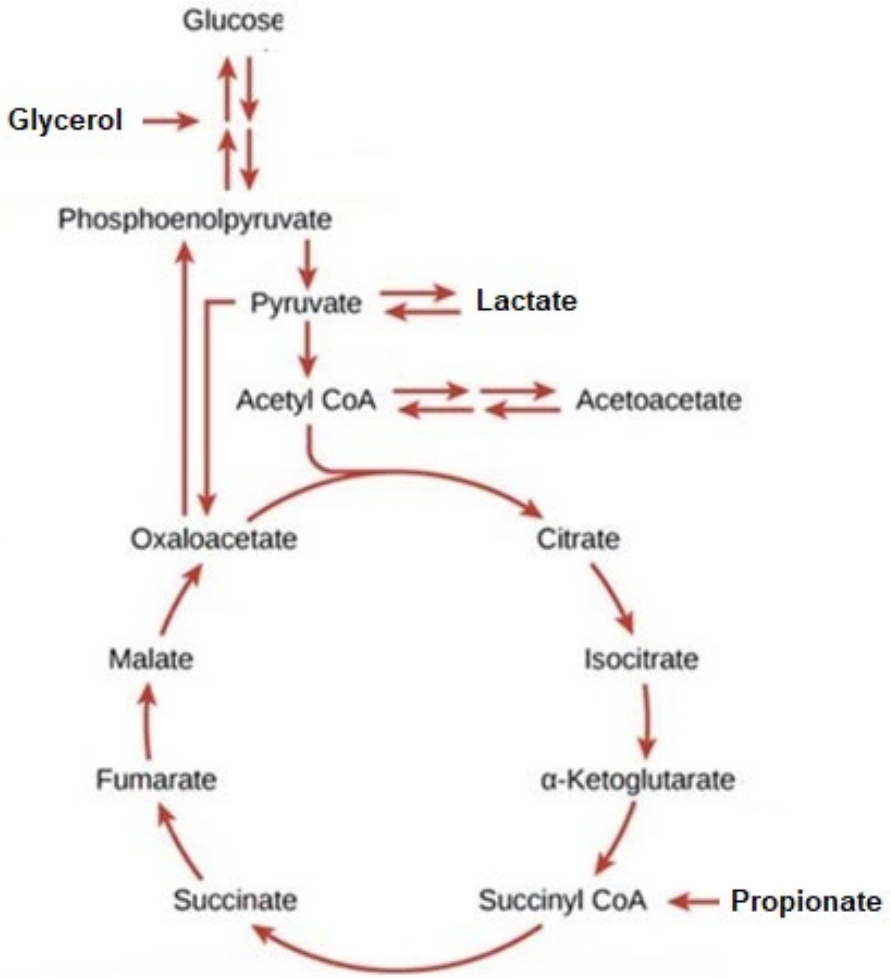
Negative energy balance (early)

- Mobilisation of energy stores to maintain blood glucose
  - Depletion of glycogen stores (≈ 24 hrs)
  - Release of FFA from adipose stores
    - β-oxidation in tissues
    - (Spare precious glucose for brain)
  - Breakdown of proteins to amino acids
    - Gluconeogenesis
- Glucagon >> insulin

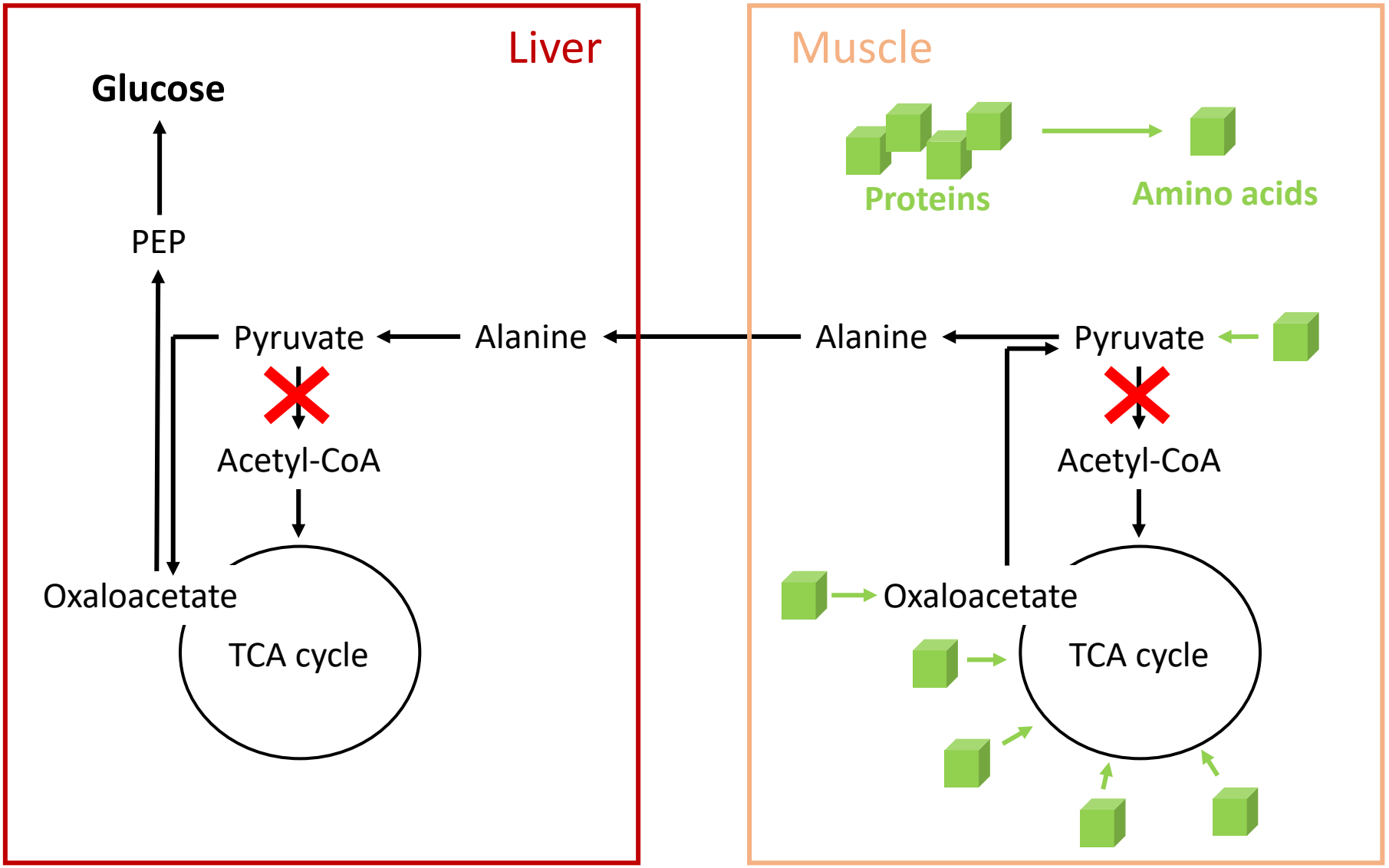


Recap: Gluconeogenesis

- Glucose production from non-carbohydrate substrates
  - Glycerol
  - Pyruvate, lactate
  - Certain amino acids
  - Propionate – ruminants
- Acetyl-CoA is not gluconeogenic!
- Mainly in liver (also in kidney)

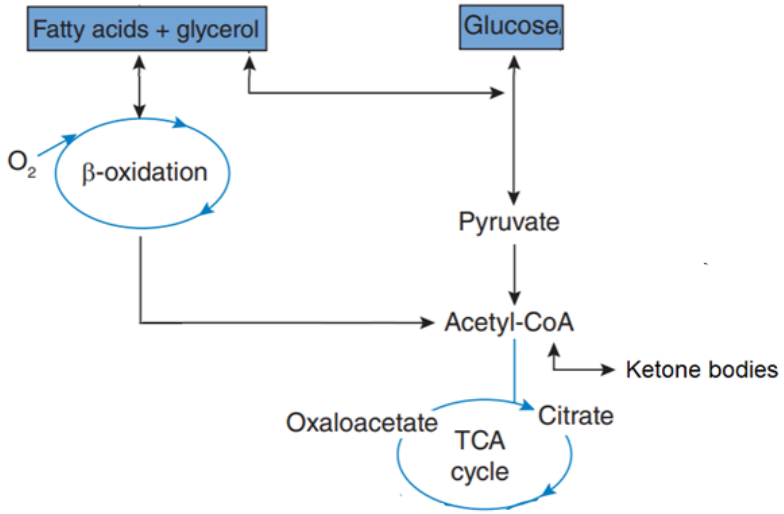


Protein degradation for gluconeogenesis



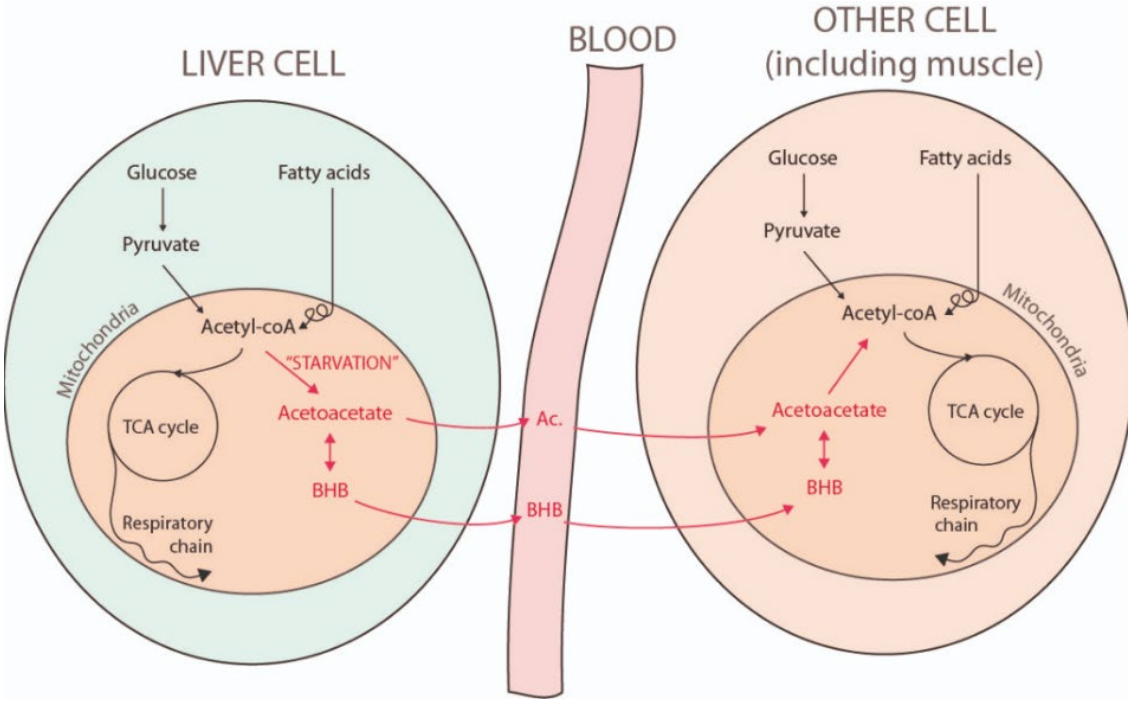
Negative energy balance (later)

- Continued fasting/starvation:
  - Glucagon remains high / glycogen stores depleted
  - FFAs continue to be released into circulation
    - Overwhelm TCA cycle
    - Oxaloacetate concurrently diverted to gluconeogenesis
  - Acetyl-CoA converted to ketone bodies by liver



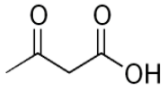
Ketogenesis

- Acetyl-CoA accumulates beyond capacity for oxidation or lipogenesis
- Ketone bodies produced by liver – alterative fuel source for tissues
  - AcAc & BHB (4C) converted to acetyl-CoA
  - Acetone (3C) utilized via different pathway → pyruvate

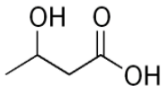


Ketone bodies

Acetone



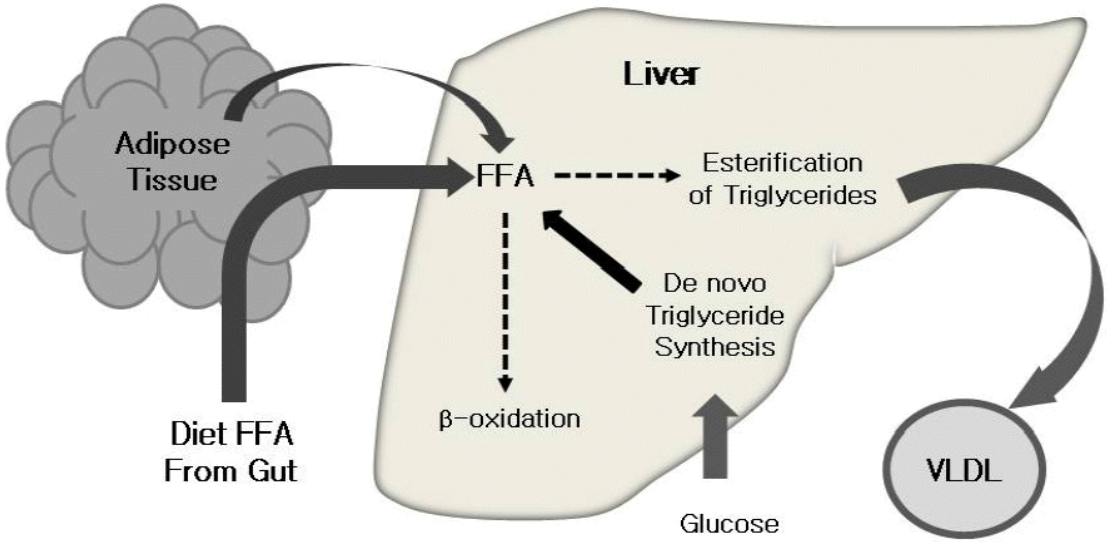
Acetoacetate



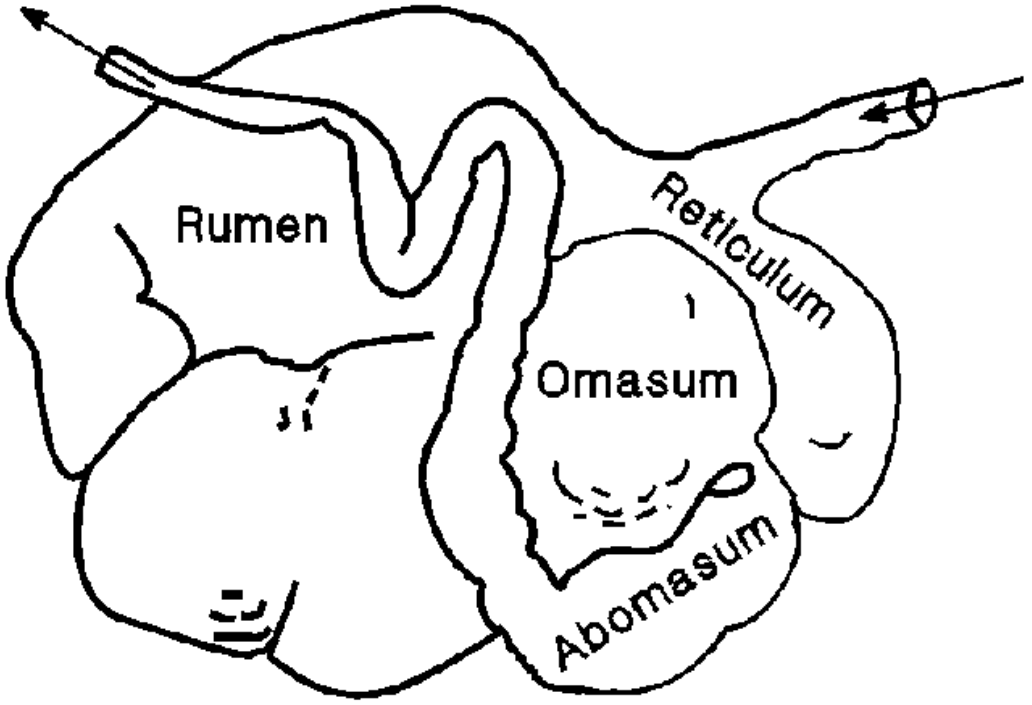
β-hydroxybutyrate

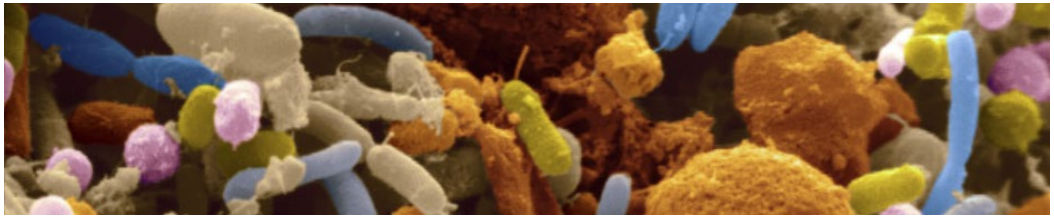
Recap: Fatty acids and the liver

- Liver packages TAGs with apoproteins as VLDL
- Negative energy balance: process can be overwhelmed (plus apoproteins can be scarce)
- Accumulation of TAGs within hepatocytes → hepatic lipidosis



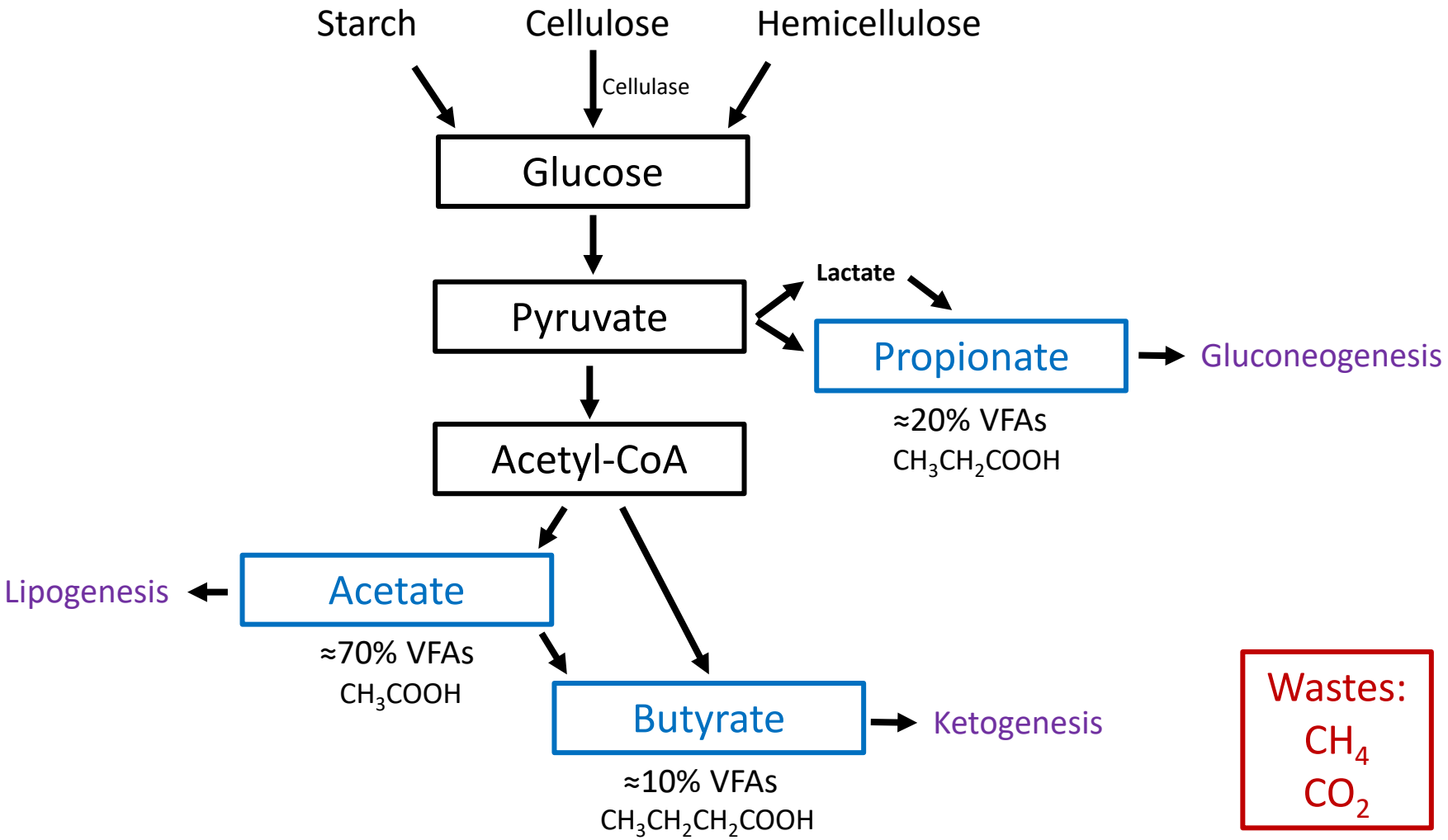
Ruminant metabolism



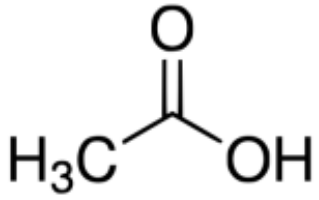


Ruminant metabolism

- Microbial fermentation of feed to produce volatile fatty acids (VFAs)

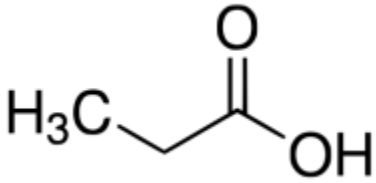


VFAs: Acetate

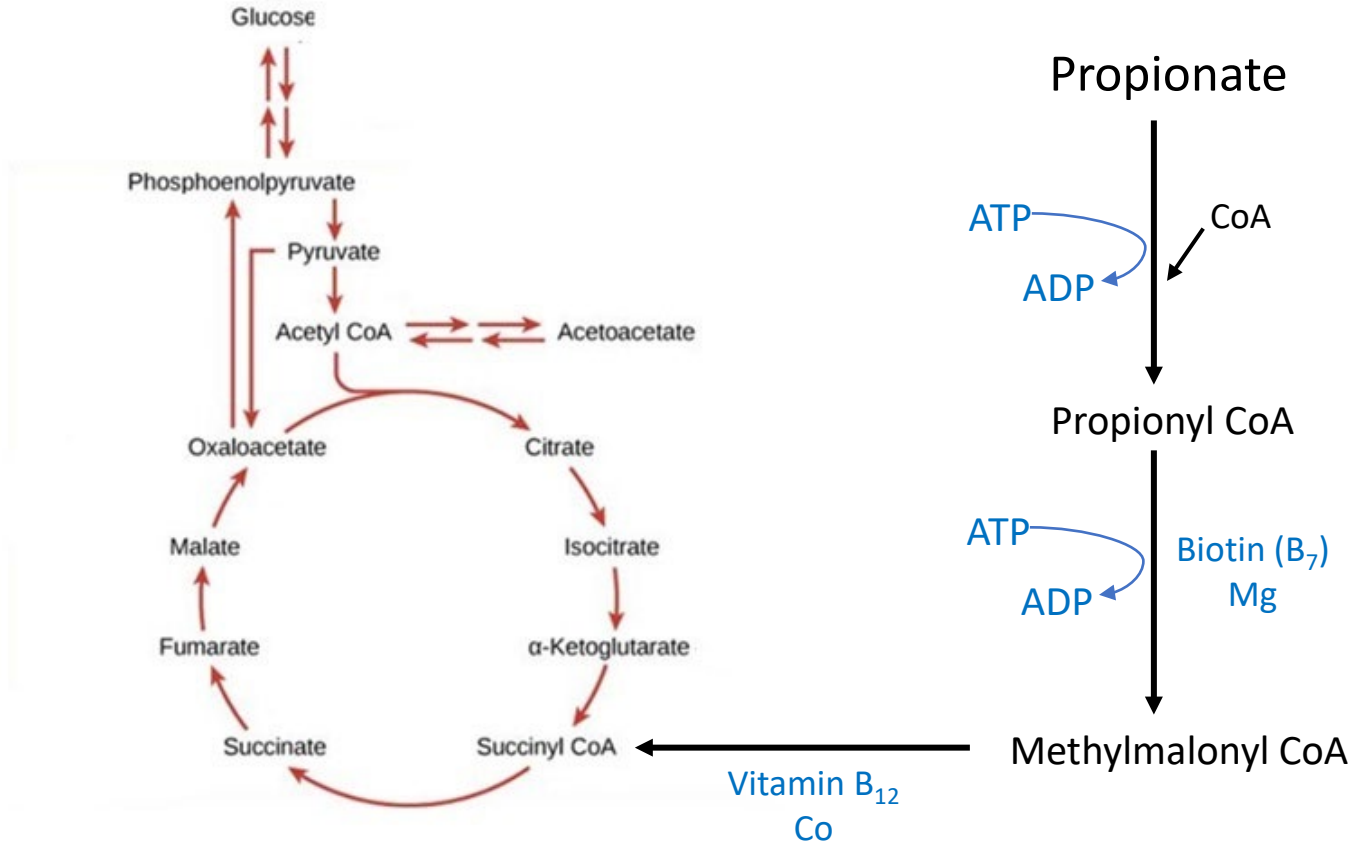


- Absorbed across rumen epithelium
- Minimal uptake by liver
- Oxidised as acetyl-CoA in tissues to generate energy
  - Skeletal muscle, heart, kidneys
- Important precursor for *de novo* fatty acid synthesis
  - Adipose tissue
  - Mammary gland
- Utilisation dependent on energy balance (Which hormones?)
  - Oxidised when energy is low
  - Lipogenesis when energy is high

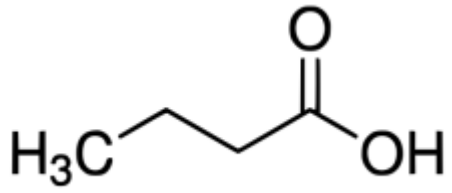
VFAs: Propionate



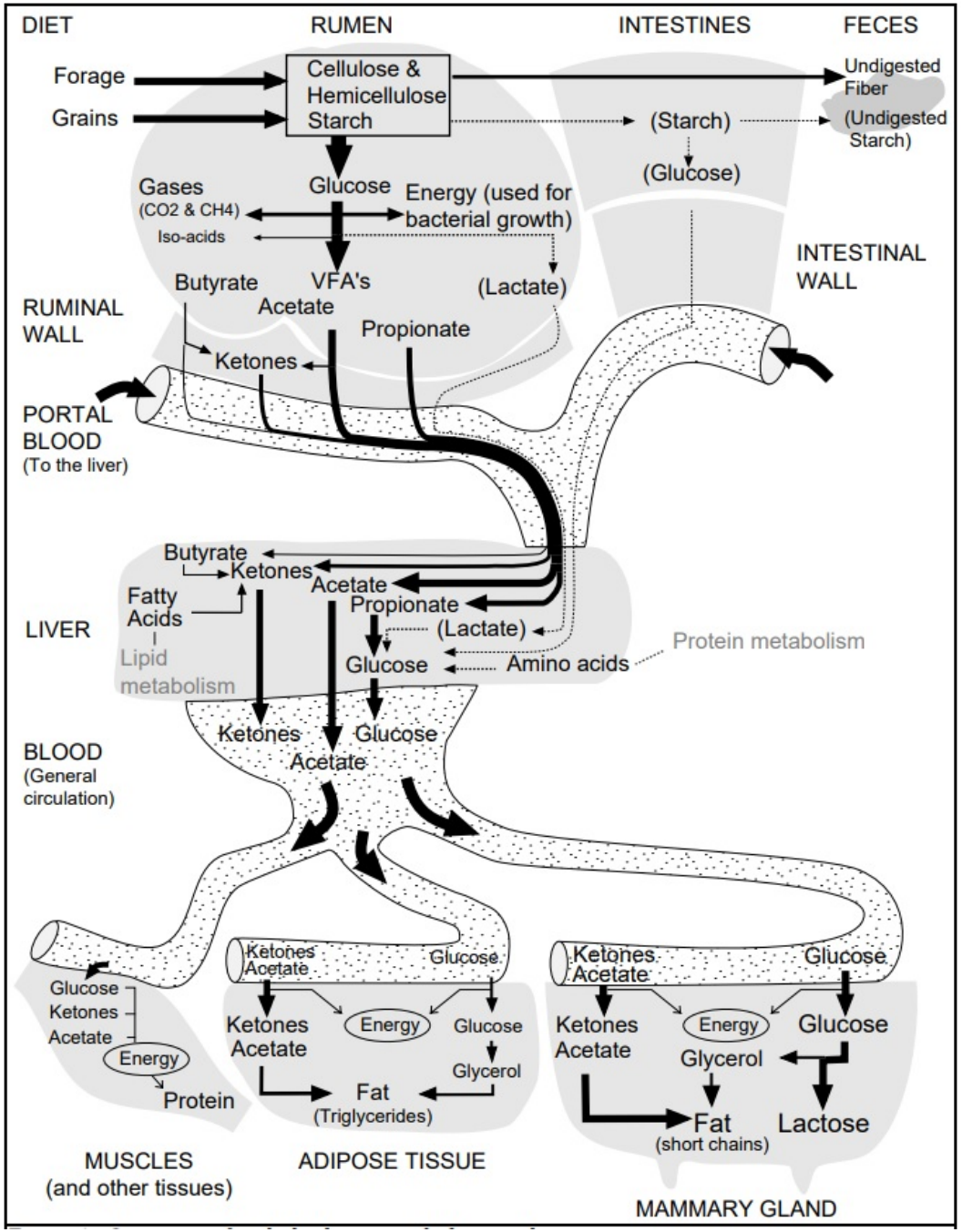
- Principal gluconeogenic precursor in ruminants
  - > 70% glucose derived from propionate



VFAs: Butyrate



- Absorbed across rumen epithelium
- Metabolised in rumen wall to ketone bodies (β-OH-butyrate)
    - Utilised by liver and other tissues


DIET
RUMEN
INTESTINES
FECES
Forage
Grains
Cellulose & Hemicellulose Starch
Undigested Fiber
(Starch)
(Undigested Starch)
(Glucose)
Gases (CO2 & CH4)
Iso-acids
Glucose
Energy (used for bacterial growth)
INTESTINAL WALL
Butyrate
VFA's
Acetate
(Lactate)
RUMINAL WALL
Propionate
Ketones
PORTAL BLOOD (To the liver)
Butyrate
Ketones
Acetate
Propionate
Fatty Acids
LIVER
(Lactate)
Lipid metabolism
Glucose
Amino acids
Protein metabolism
Ketones
Glucose
Acetate
BLOOD (General circulation)
Ketones Acetate
Glucose
Glucose
Ketones
Acetate
Energy
Protein
Ketones Acetate
Energy
Glucose
Glycerol
Fat (Triglycerides)
Ketones Acetate
Glucose
Ketones Acetate
Energy
Glucose
Glycerol
Fat (short chains)
Lactose
MUSCLES (and other tissues)
ADIPOSE TISSUE
MAMMARY GLAND

Ketosis: A system under stress

- Applied understanding of ruminant metabolism in the context of negative energy balance

Bovine ketosis

- History
  - 7 year-old Holstein Friesian cow
  - Calved 3 weeks ago
  - Inappetent and losing weight
  - Poor milk yield
  - Diet: lush pasture

Bovine ketosis

- Physical examination
  - Dull and depressed, not interactive, disinclined to move
  - Dry coat, body condition score 2/5
  - TPR normal
  - Reduced rumen contractions
  - Dry manure

Bovine ketosis

- Clinical pathology
  - Stallside – Ketostix reagent strips
    - Detect ketone bodies in urine
  - Blood collected

		RESULTS	REFERENCE VALUES
Glucose	mmol/L	1.9	2.3 – 5.1
Urea	mmol/L	8.7	2.0 – 9.5
Creatinine	mmol/L	0.14	0.08 – 0.18
Protein	g/L	70	63 – 85
Albumin	g/L	35	32 – 42
Globulin	g/L	35	32 – 53
Total bilirubin	µmol/L	7.3	0 – 8
Conjugated bilirubin	µmol/L	2.0	0 – 8
GLDH	U/L	47	0 – 20
ALP	U/L	126	40 – 100
AST	U/L	380	50 – 150
GGT	U/L	43	10 – 32
β-OH butyrate	mmol/L	5.3	0 – 0.9
CPK	U/L	560	30 – 250
Cholesterol	mmol/L	4.8	2.0 – 6.5
Magnesium	mmol/L	1.0	0.6 – 1.2
Calcium	mmol/L	2.3	2.0 – 3.05
Phosphate	mmol/L	2.0	1.0 – 2.5
Sodium	mmol/L	145	143 – 151
Potassium	mmol/L	3.9	4.1 – 5.3
Chloride	mmol/L	108	97 – 111
Bicarbonate	mmol/L	13.5	18 – 33
Anion gap	mmol/L	27.4	6 – 14

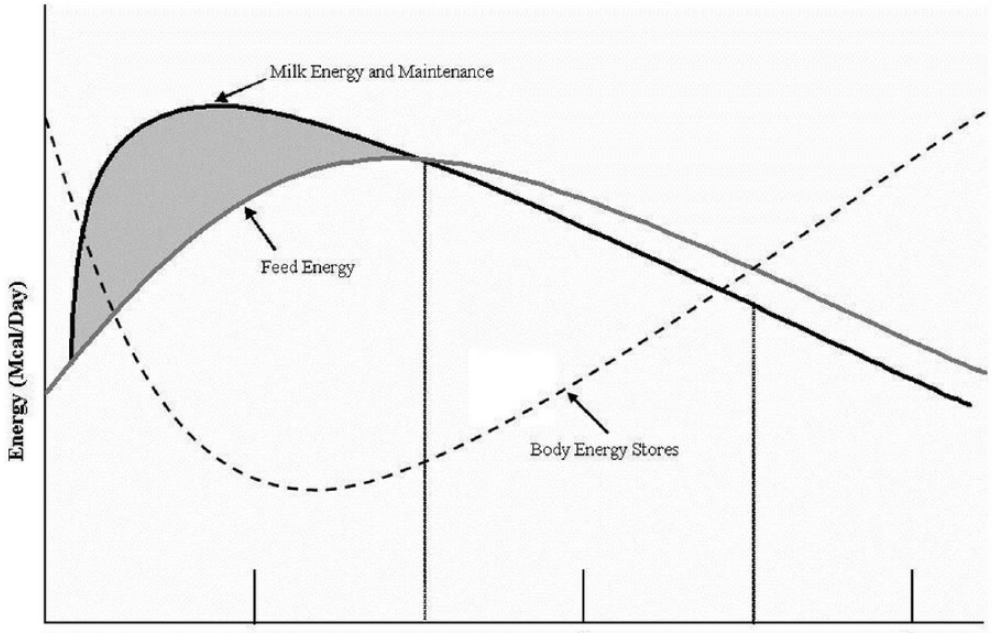
Bovine ketosis

- Diagnosis
  - Ketosis!
  - Clinical manifestation of negative energy balance
  - 1° or 2°
  - Can also be subclinical if noticed early – how?
  - Why?!

Bovine ketosis

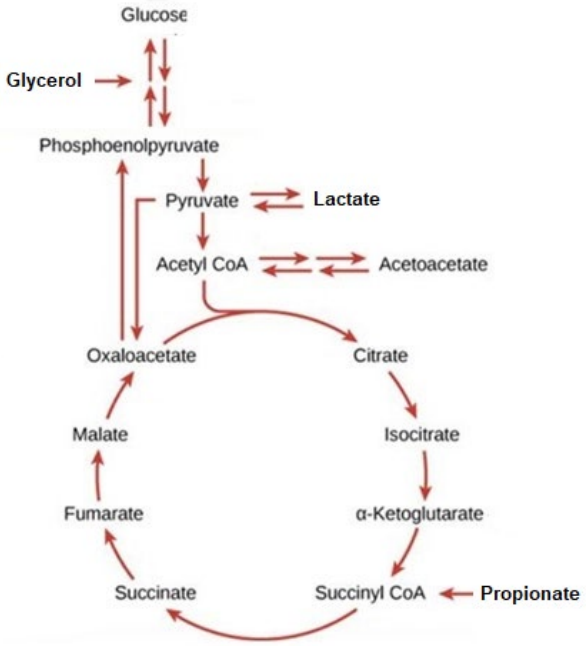
- Pathophysiology
  - Intense demand of early lactation → negative energy balance
  - Peak energy demand 4-7 weeks post-calving
  - Peak feed intake 8-12 weeks post-calving

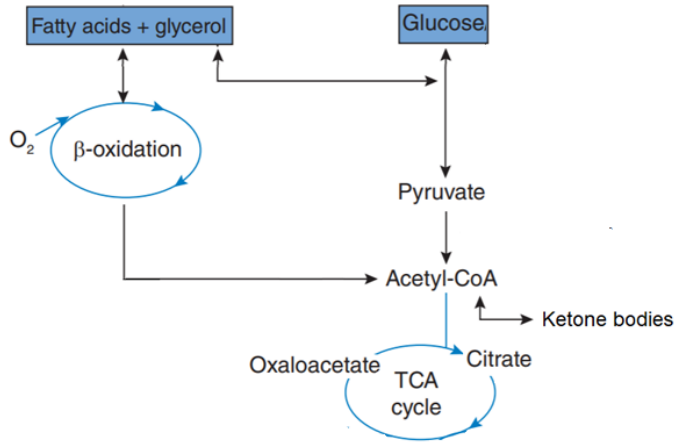
But the cow had access to lush pasture…



Bovine ketosis

- Negative energy balance (dominance of glucagon)
  - Glycogen stores depleted
  - Protein breakdown for gluconeogenesis
  - FFAs released into circulation
    - Overwhelm TCA cycle
    - Oxaloacetate diverted to gluconeogenesis
  - Acetyl-CoA converted to ketone bodies by liver





Bovine ketosis

- Treatment
  - Provide glucose
    - Intravenous bolus/infusion
    - Short term but immediate improvement
  - Provide gluconeogenic substrate
    - Propylene glycol
    - Converted to pyruvate (propionate)
  - Address energy drain if possible
  - (Corticosteroids?)

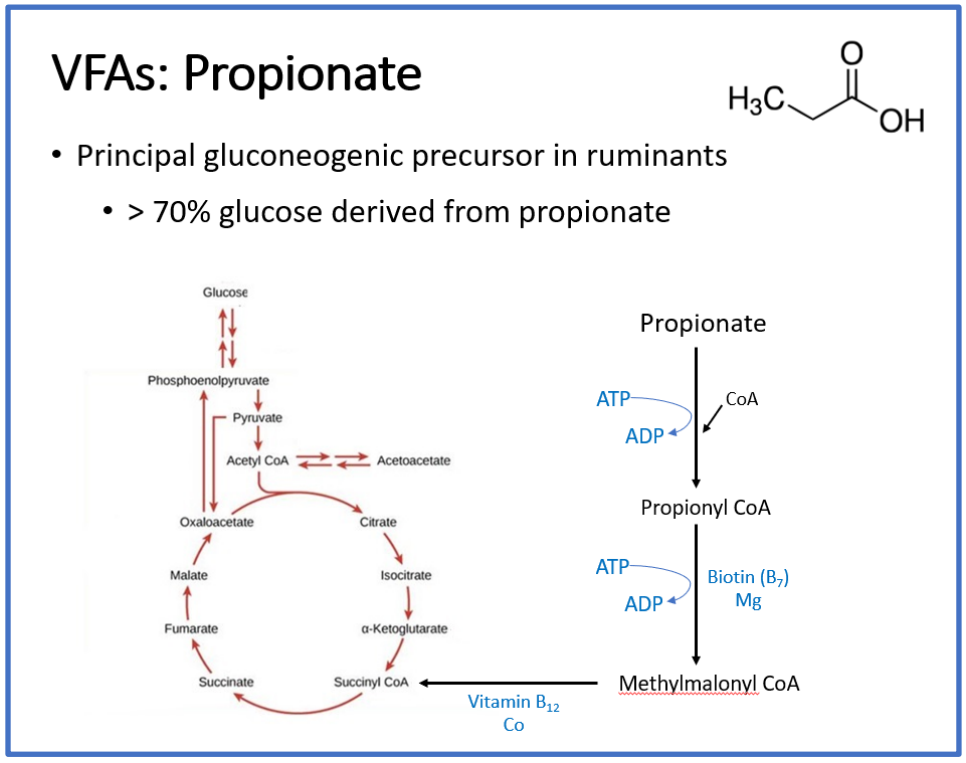
Ketosis in other contexts

- Pregnancy toxaemia
  - Beef cattle
  - Sheep (‘twin lamb disease’)
  - Intense energy demand of late developing foetus coupled with inadequate feed intake
  - Often severe clinical signs due to failure to notice early signs
    - Depressed & inappetent
    - Weight loss
    - Neurological signs (circling)
    - Weakness & recumbency
    - Death

Ketosis in other contexts

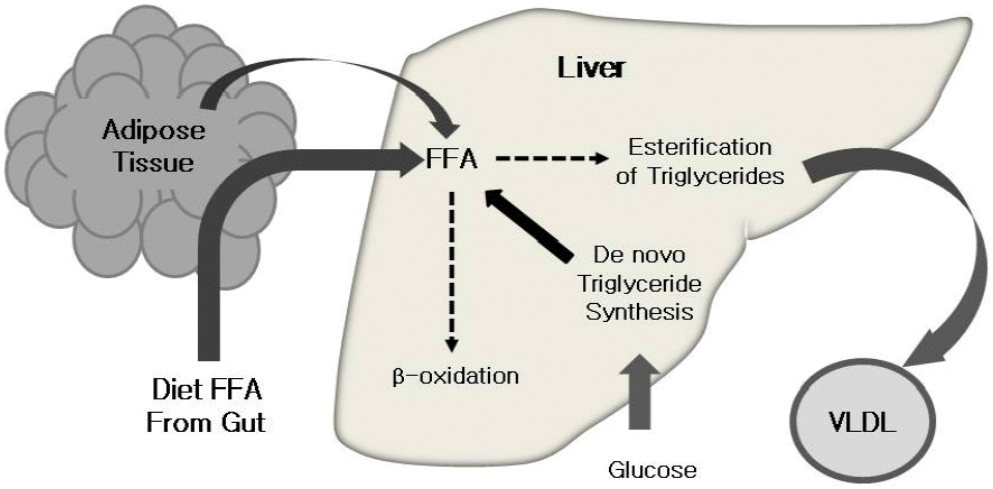
- Is feed intake the only factor?
- Vitamins and trace minerals involved in metabolic pathways

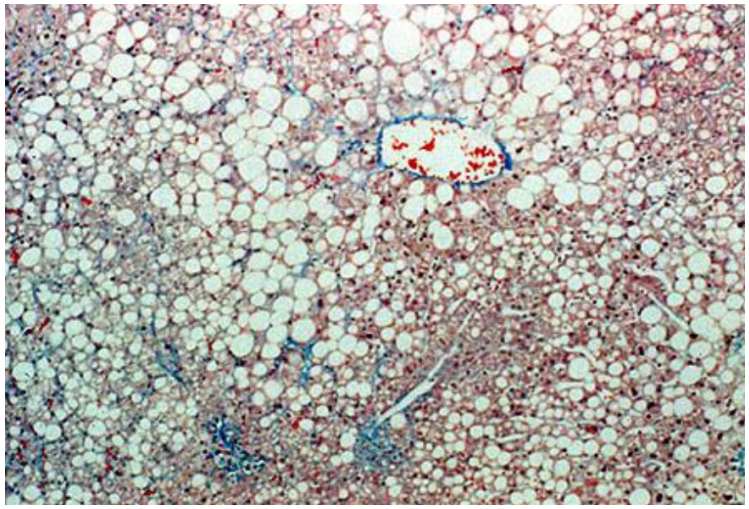
- Cobalt is a cofactor for Vit B12 → dietary deficiency of Co leads to ineffective methylmalonate pathway → impaired gluconeogenesis
- 'Illthrift' (ketosis)



Fatty liver disease (hepatic lipidosis)

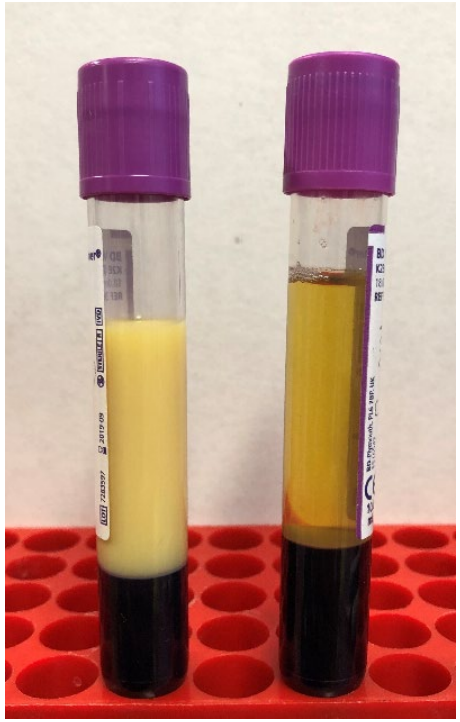
- Potential sequelae to ketosis
- Especially in overconditioned animals
  - Large adipose reserve to flood the liver with FFAs
  - Overwhelm VLDL formation → FFAs accumulate in hepatocytes





Fatty liver disease (hepatic lipidosis)

- Not only ruminants
- e.g. Horses (esp. fat ponies)
  - During negative energy balance develop hyperlipaemia
  - Ketone pathway poorly developed
    - Do not develop overt ketosis
  - Mobilisation of FFAs occurs
    - VLDL pathway in liver well developed
    - But still overwhelmed
    - FFA accumulation → Hepatic lipidosis



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