NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

SCHOOL OF MEDICINE

BIOCHEMISTRY II – 3nd SEMESTER

Metabolic correlations: Starve-feed cycle Mechanisms involved in the transduction of hepatic metabolism between well-fed and fasting states

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Metabolic correlations: Starve-feed cycle
Mechanisms involved in the transduction of hepatic metabolism between well-fed and fasting states

Learning aims

- Understand and describe how glucose, amino acids and fat are disposed by various tissues in a well-fed state
- Understand and describe how diet supplies provide energy requirements in a well-fed state
- Understand and describe how blood glucose is maintained in the early fasting state through hepatic glycogenolysis
- Understand and describe how blood glucose is maintained in the early fasting state through hepatic glycogenolysis
- Understand and describe how gluconeogenesis occurs in the fasting state
- Describe metabolic interrelationships of major tissues in early fasting state
- Describe metabolic interrelationships of major tissues in fasting state
- Understand and describe how glucose homeostasis is maintained during different nutritional states
- Describe how allosteric effectors control hepatic metabolism in the well-fed state
- Describe how allosteric effectors control hepatic metabolism in the fasting state
- Describe how covalent modifications control hepatic metabolism in the well-fed state
- Describe how covalent modifications control hepatic metabolism in the fasting state
- Understand and describe how gene transcription is regulated in the well-fed and fasting state in the liver

INTRODUCTION

- Interdependence of metabolic processes of the major tissues of the body will be discussed.
- Not all of the major metabolic pathways function in every tissue at any given time.
- Depending on the nutritional and hormonal status of a patient it is critical to know which pathways are functional and how they are associated.
- Association of:
  - Glycogenesis
  - Glycogenolysis
  - Glyconeogenesis
  - Glycolysis
  - Fatty acid synthesis
  - Lipogenesis
  - Lipolysis
  - Glyceroneogenesis
  - Fatty acid oxidation
  - Glytaminolysis
  - Tricarboxylic acid (TCA) cycle activity
  - Ketogenesis
  - Amino acid oxidation
  - Protein synthesis
  - Proteolysis
  - Urea synthesis

INTRODUCTION

- **It is necessary to know:**

1. **Which tissues are most active in these processes**
2. **When these processes gain control**
3. **How these processes are regulated in different metabolic states**

1. **Variable fuel input: Feed**
2. **Fuel storage (glycogen and triacylglycerol)**
3. **To meet metabolic needs of fasting**

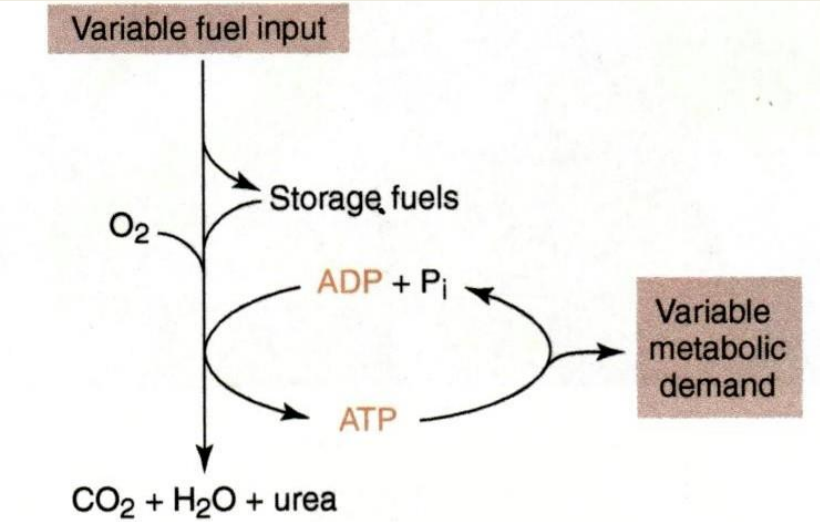


Figure 21.1 Humans can use a variable fuel input to meet a variable metabolic demand.

Consequences of metabolic dysregulations

- **Obesity and the Metabolic Syndrome**

- Unlimited capacity of the human body to store food excess as triacylglycerols (or else triglycerides)

- Risk factor for:

  - Diabetes mellitus
  - Hypertension
  - Endometrial carcinoma
  - Osteoarthritis
  - Cirrhosis
  - Gallstones
  - Cardiovascular diseases

Consequences of metabolic dysregulations

- **Metabolic Syndrome (or Syndrome X)**

Clinically:

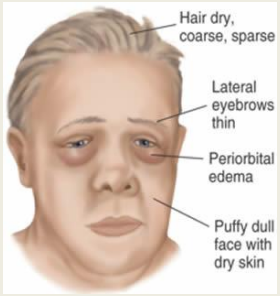
1. **Obesity**
2. **Insulin resistance**
3. **Dyslipidemia**
4. **Hypertension**

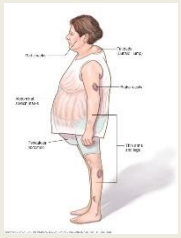
- high rate of cardiovascular deaths in western countries

Consequences of metabolic dysregulations

- **Why obesity occurs?**

- An obese person has eaten more calories than he/she expended
- Cultural changes in food preparation and consumption
- Reduced physical activity
- Aberrant neural control of calory intake to balance energy consumption
- Secondary to another disorder (rarely)
  - Hypothyroidism
  - Cushing syndrome (increased secretion of glycocorticoids causing fat deposition in the face and trunk, wasting of the limbs, glucose intolerance), increased protein breakdown in muscle, conversion of the amino acids to glucose and fat

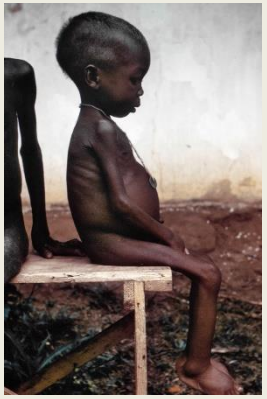




Consequences of metabolic dysregulations

- **Obesity**
- **Larger adipocytes**
- **Men: visceral fat/high waist-to-hip circumference ratio (predictive of premature coronary heart disease)**
- **Women: hips**
- **Dieting**

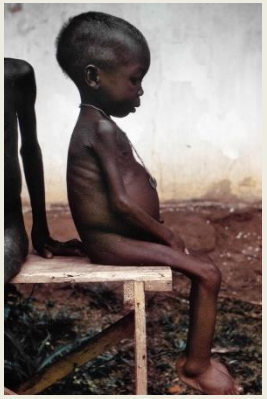
Consequences of metabolic dysregulations



- **Protein-Calorie Malnutrition - Kwashiorkor**
- Nutritional problem of young children in the developing countries
- 1-3 years old
- Transition from breast feeding to low protein diet
- Kwashiorkor: “the sickness of the older child when the next baby is born”
- Diet adequate in calories but deficient in protein
- Poor growth
- Low plasma protein (total proteins and albumin)
- Low levels of aminoacids
- Muscle wasting
- Edema
- Diarrhea
- Increased susceptibility to infection

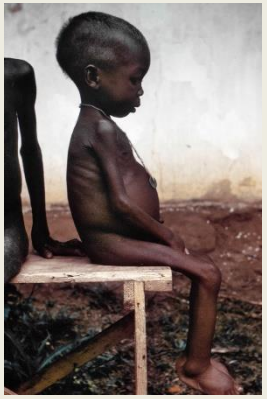
Consequences of metabolic dysregulations

- **Protein-Calorie Malnutrition - Kwashiorkor**



- Subcutaneous fat – high carbohydrate intake
- High insulin levels
- Therefore they cannot break down fat, produce ketones, transfer amino acids from skeletal muscle to the liver, kidneys, heart, and immune cells.
- Decreased protein synthesis
- Large liver with fat
- Need for hepatic protein synthesis to release VLDL
- Dysregulation of gut function: decreased absorption of carbohydrates, proteins and vitamins

Consequences of metabolic dysregulations



- **Protein-Calorie Malnutrition - Kwashiorkor**
- Children with low weight for height – “wasted” – treatable
- Children with low height for weight – “stunted” – never recover

- Also found in elderly when they get sick
  - Deficiency of iron, calcium and vitamins
  - Loss of body mass and strength
  - Anemia
  - Loss of bone strength (breaking of the hip during falls)

- Liver cirrhosis
  - Low serum albumin
  - Dietary deficiency and dysregulation of oxidation of branched-chain amino acids (leucine, isoleucine, valine)

Consequences of metabolic dysregulations

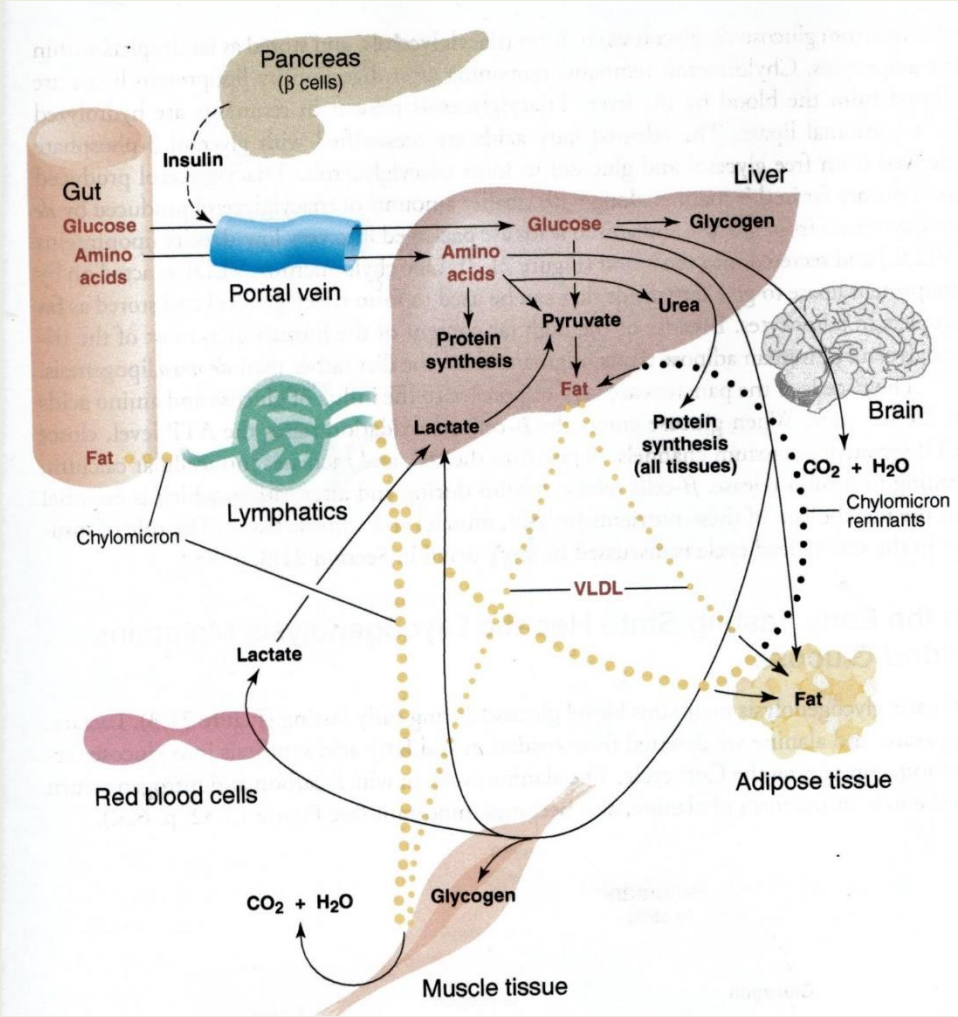
- **Starvation**
- Marasmus syndrome
- Children <1 year of age
- Early weaning of breast milk
- Low insulin levels
- Fat and protein mobilization for energy
- Starvation to death
- Usually from pneumonia

Consequences of metabolic dysregulations

- **Starvation**
- Adults
- Throat or esophagus cancer
- Stroke/dementia
- Reduced absorption: Crohn’s disease, celiac disease
- Short-bowel syndrome from surgical resection
- Cachexia (anorexia)

Starve-Feed Cycle / Well-Fed State

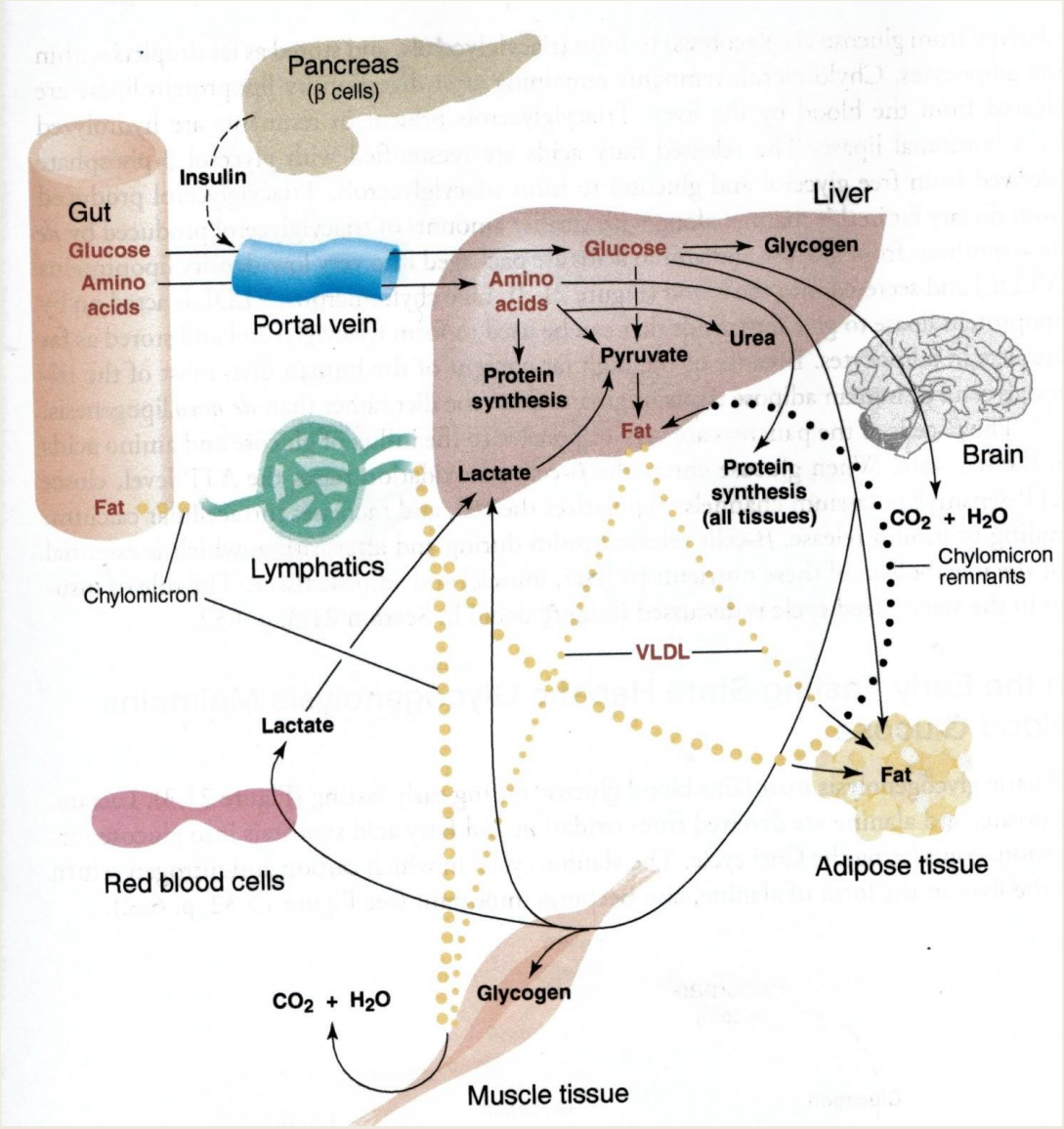
- ***Disposition of glucose, amino-acids, and fat by various tissues in the well-fed state***



Starve-Feed Cycle / Well-Fed State

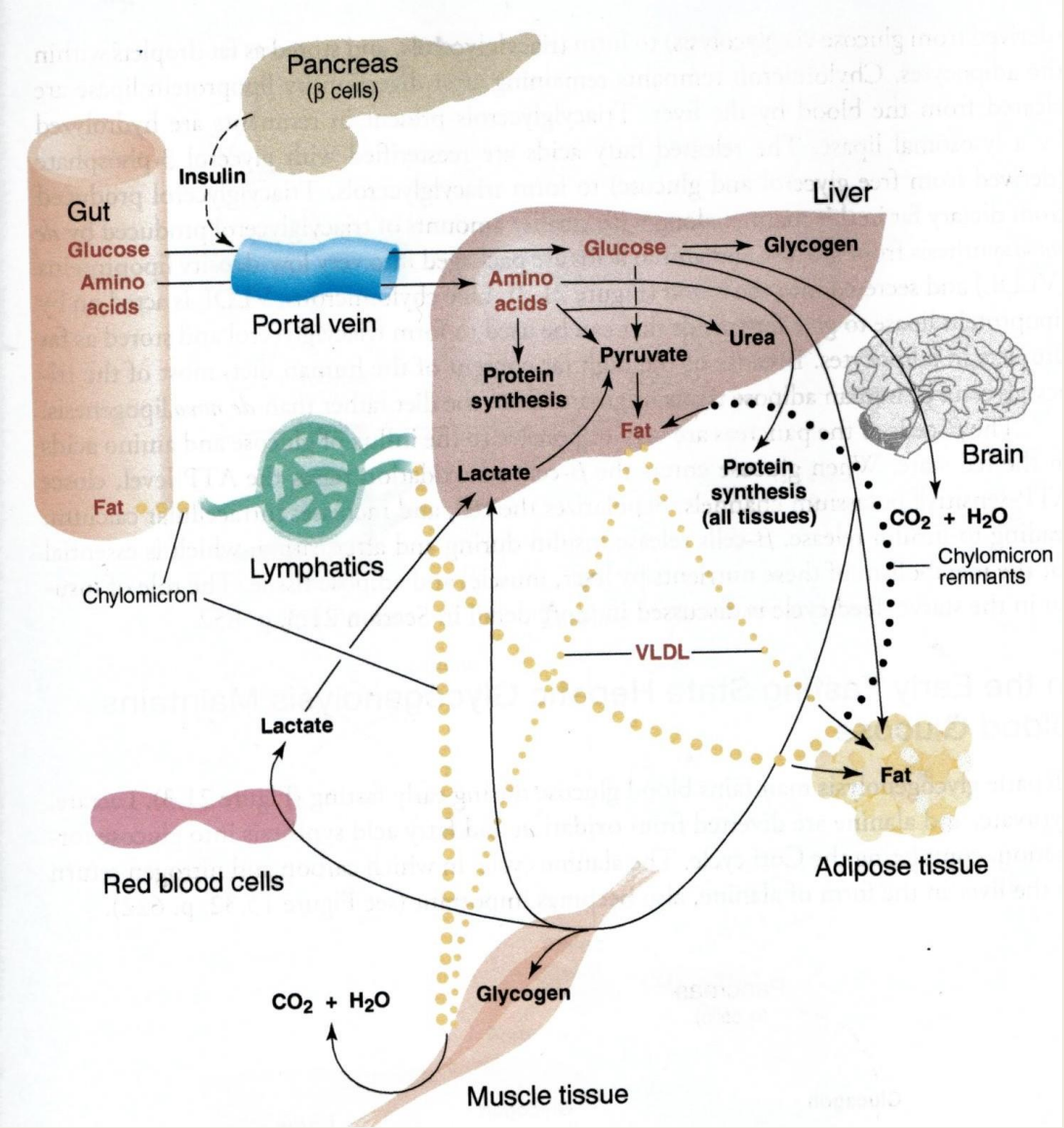
- ***Amino-acids and glucose pass from the intestinal epithelial cells to the blood circulation and through the portal vein arrive to the liver.***

- ***Chylomicrons (carriers of the food-associated triacylglycerols) are secreted from intestinal epithelial cells to the lymphatic circulation – thoracic duct – subclavian vein – body tissues***



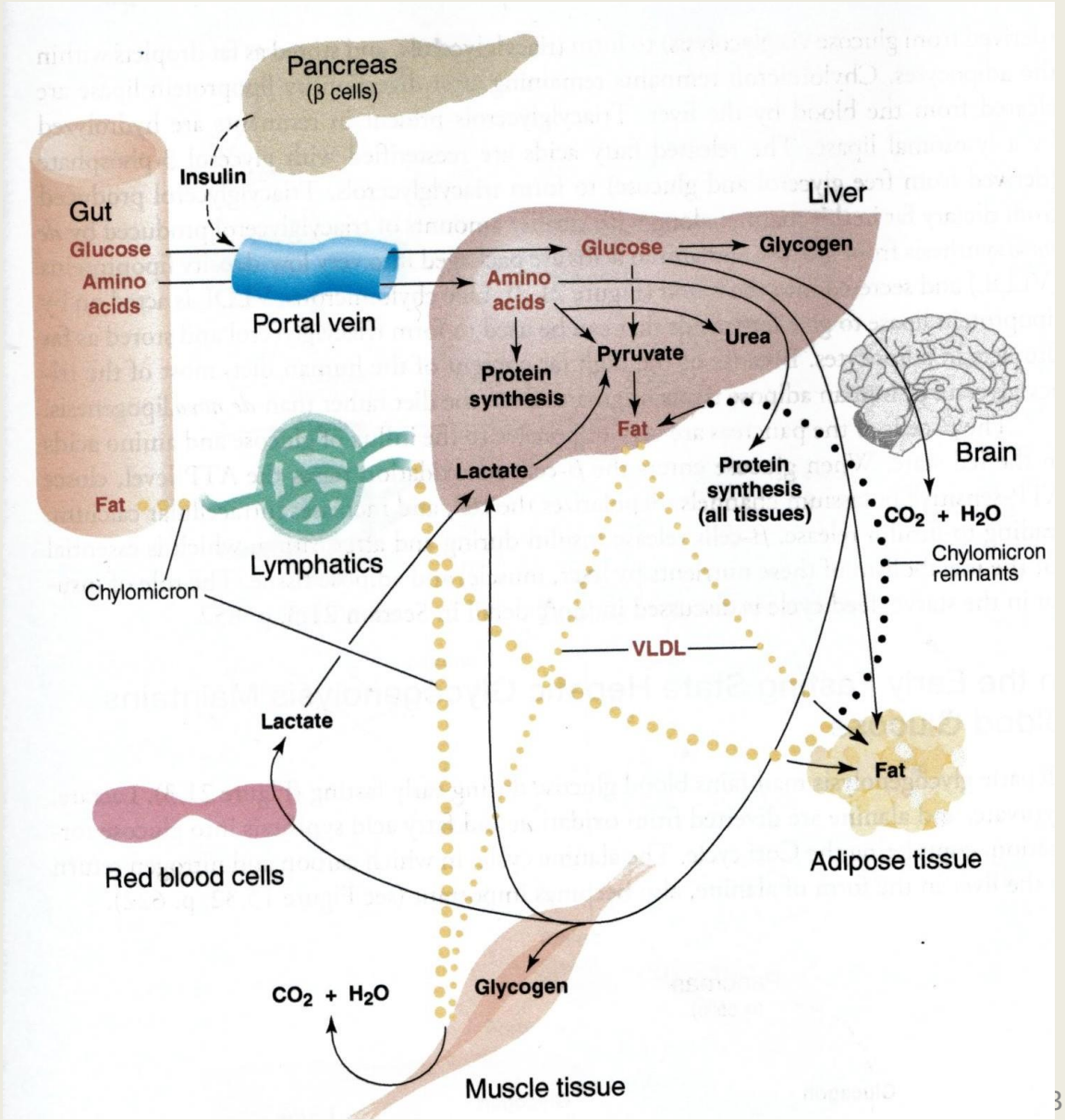
Starve-Feed Cycle / Well-Fed State

- ***Fates of the dietary glucose in the liver***
- ***Glycogenesis – converted to glycogen***
- ***Glycolysis – to pyruvate or lactate***
- ***Pentose phosphate pathway***
- ***Pyruvate oxidization to fat (acetyl-CoA to triacylglycerols)***
- ***Pyruvate oxidization through the TCA cycle***



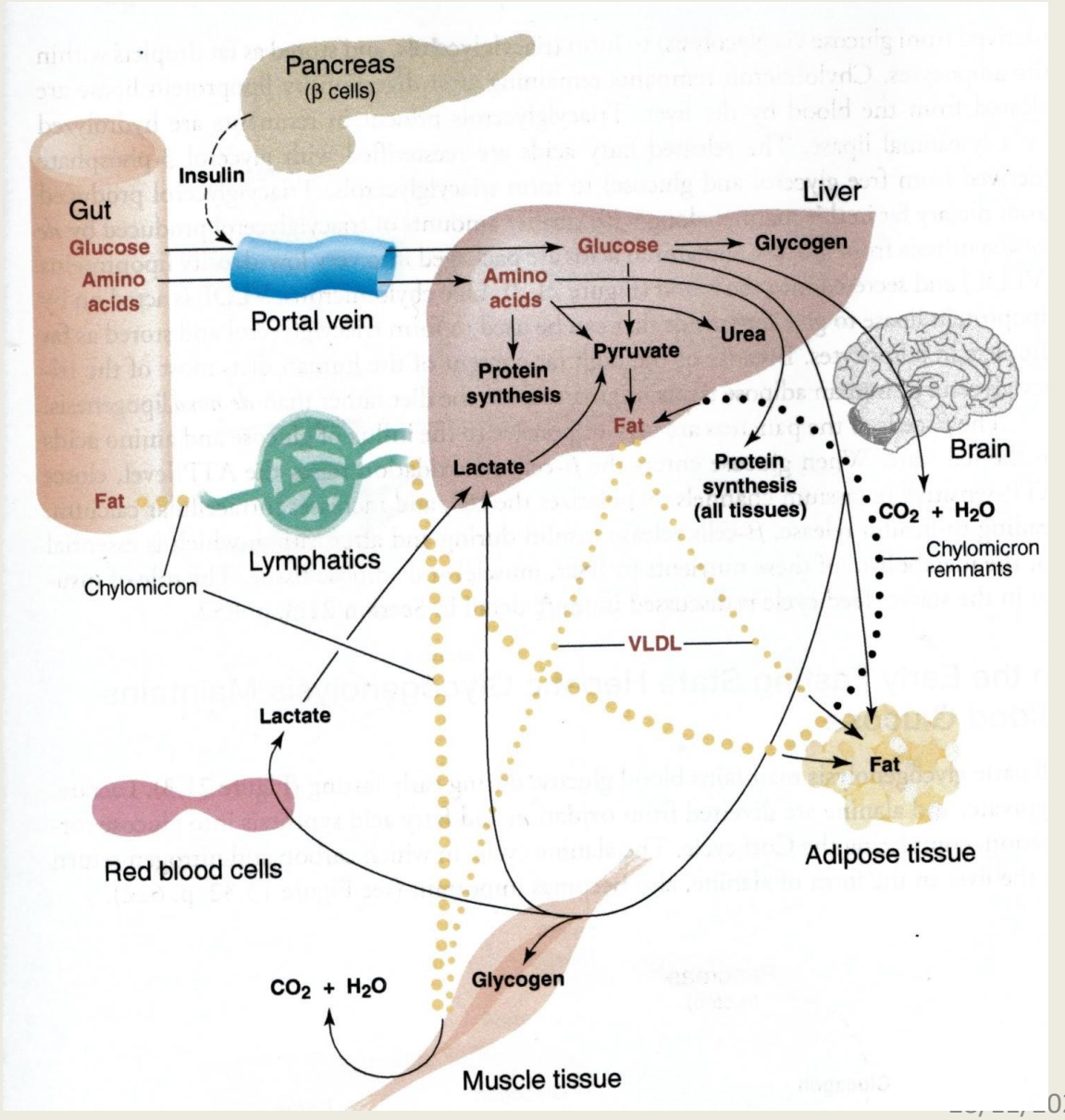
Starve-Feed Cycle / Well-Fed State

- *Glucose can pass from the liver to other organs*
- *Brain, RBC, renal medulla only depend on glucose*
- *Adipose tissue (convert it to glycerol)*
- *Muscles: glycogen or glycolysis/TCA*



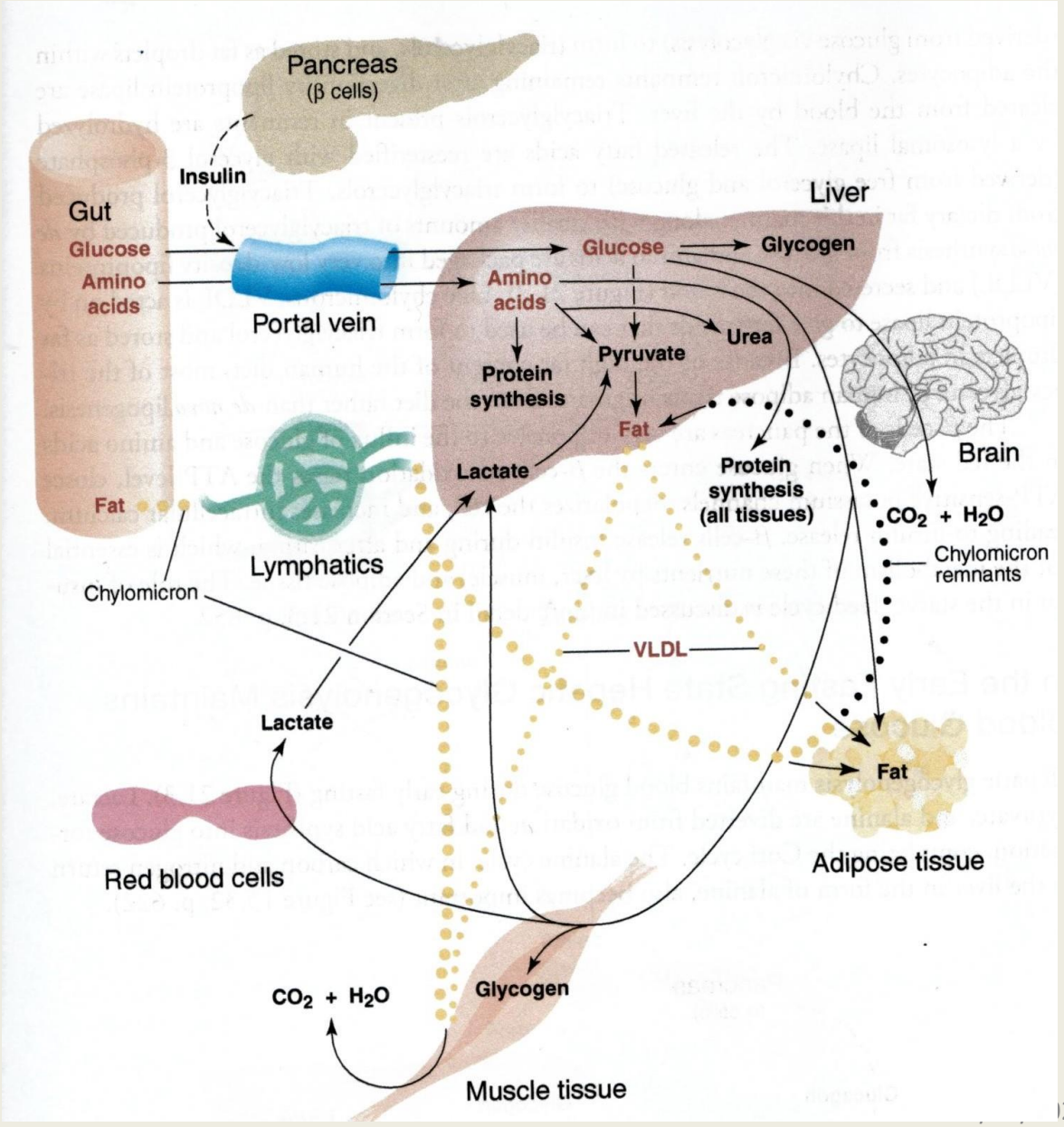
Starve-Feed Cycle / Well-Fed State

- ***Dietary Amino-acids transferred through the portal vein to various tissues***
- ***High Km of the enzymes for amino acid catabolism (must be present in the liver in high concentrations before break down)***
- ***Low Km of tRNA enzymes – protein synthesis***
- ***Excess amino acids are oxidized to urea, CO2 and water***
- ***The intermediates are used for lipogenesis***



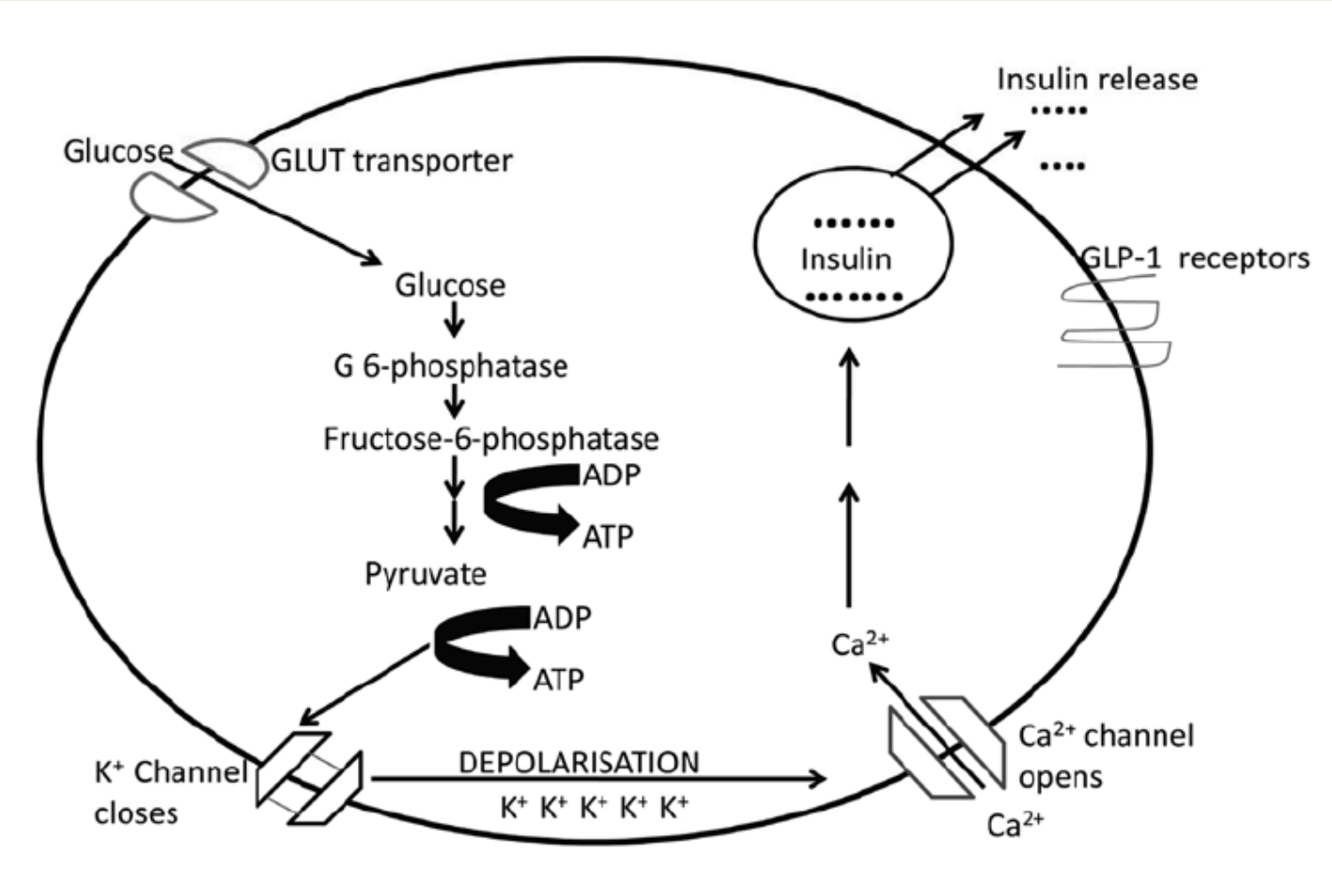
Starve-Feed Cycle / Well-Fed State

- ***Dietary triacylglycerols – chylomicrons in the bloodstream***
- ***Lipoprotein lipase in the surface of endothelial cells in the lumen of capillaries of various tissues***
- ***Adipose tissue***
- ***Triacylglycerols hydrolysis***
- ***Released fatty acids again form triacylglycerols and are stored inside the adipocytes (reesterified with glycerol-3-phosphate)***
- ***Packaged into VLDLs (very low-density lipoproteins and are secreted into the blood) and travel to various tissues, especially adipose tissue***



Starve-Feed Cycle / Well-Fed State

- ***Glucose causes the secretion of insulin from pancreatic β-cells***



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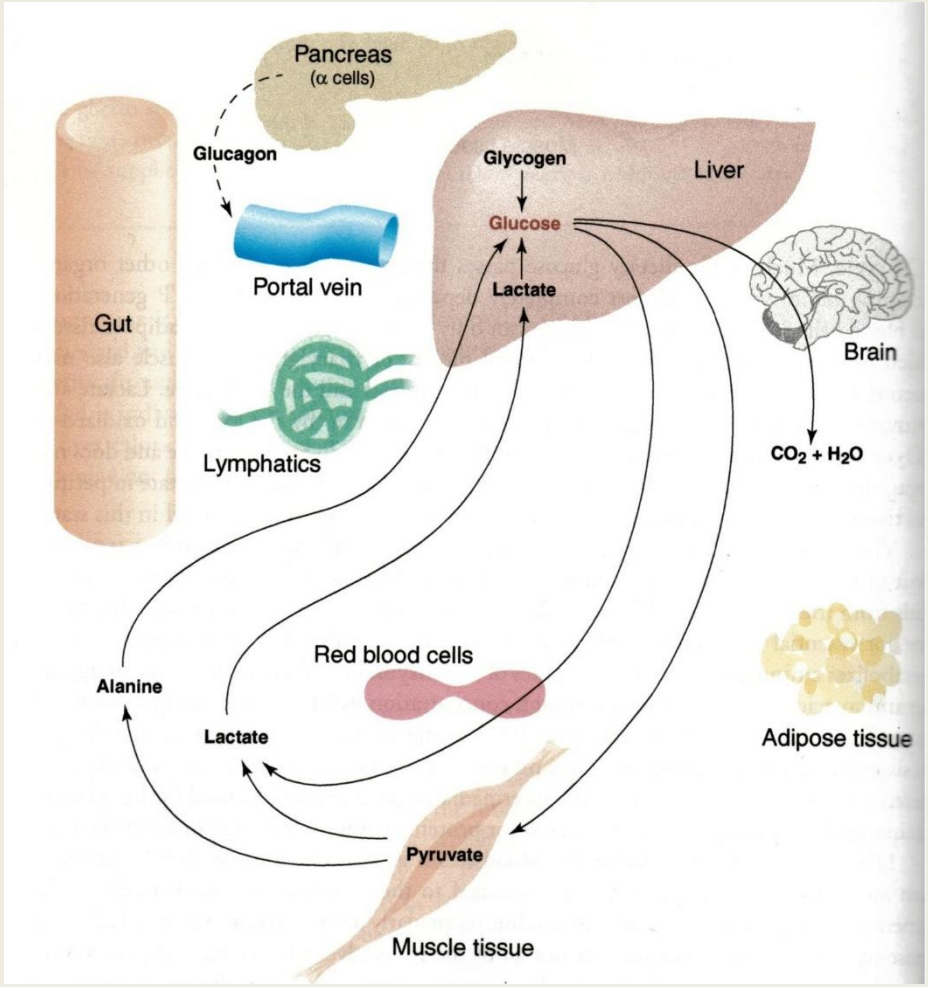
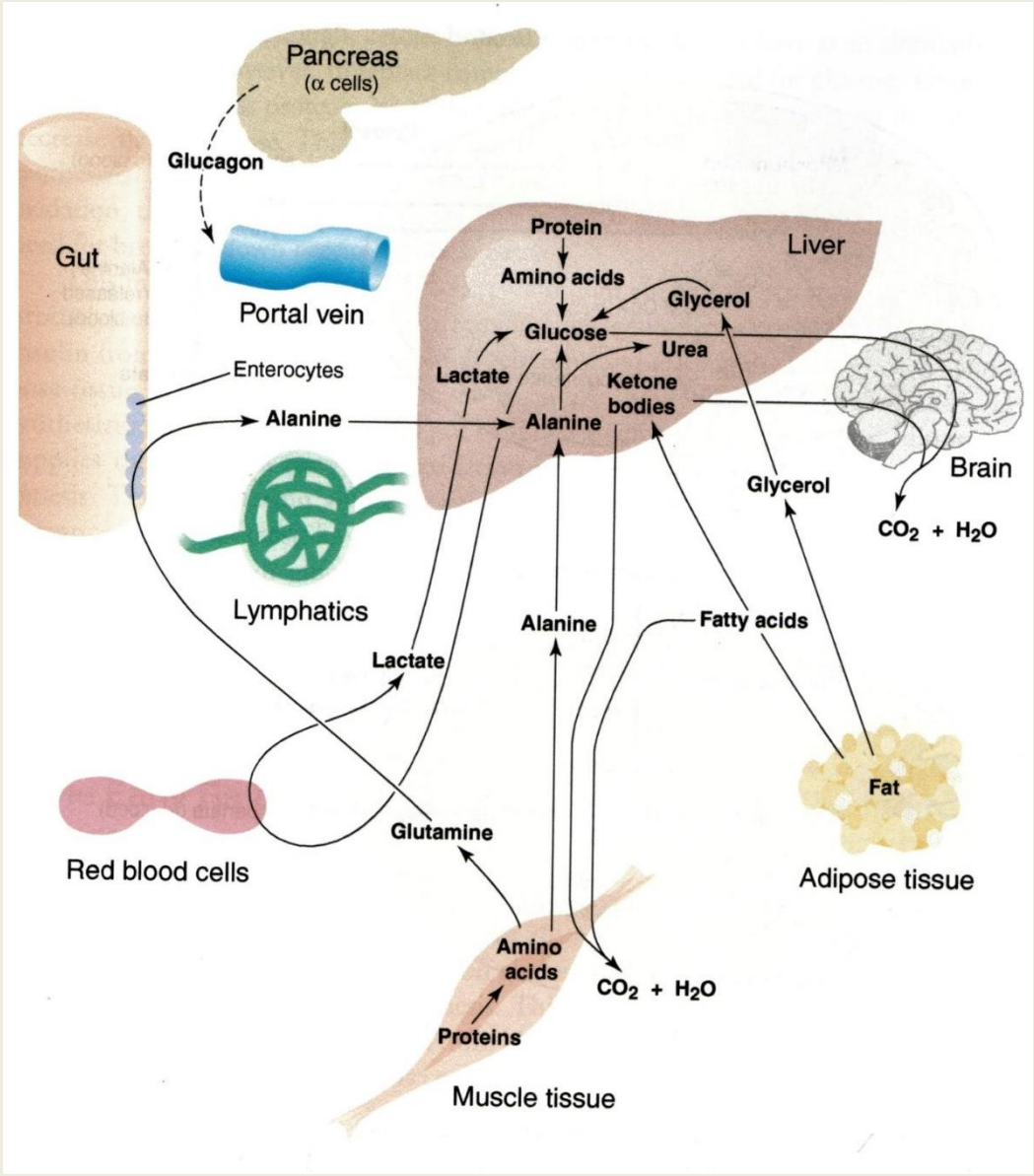
Starve-Feed Cycle / Early-fasting state

- *Hepatic glycogenolysis maintains blood glucose*
- *Cori cycle, alanine cycle: lactate, pyruvate and alanine used for glucose formation*



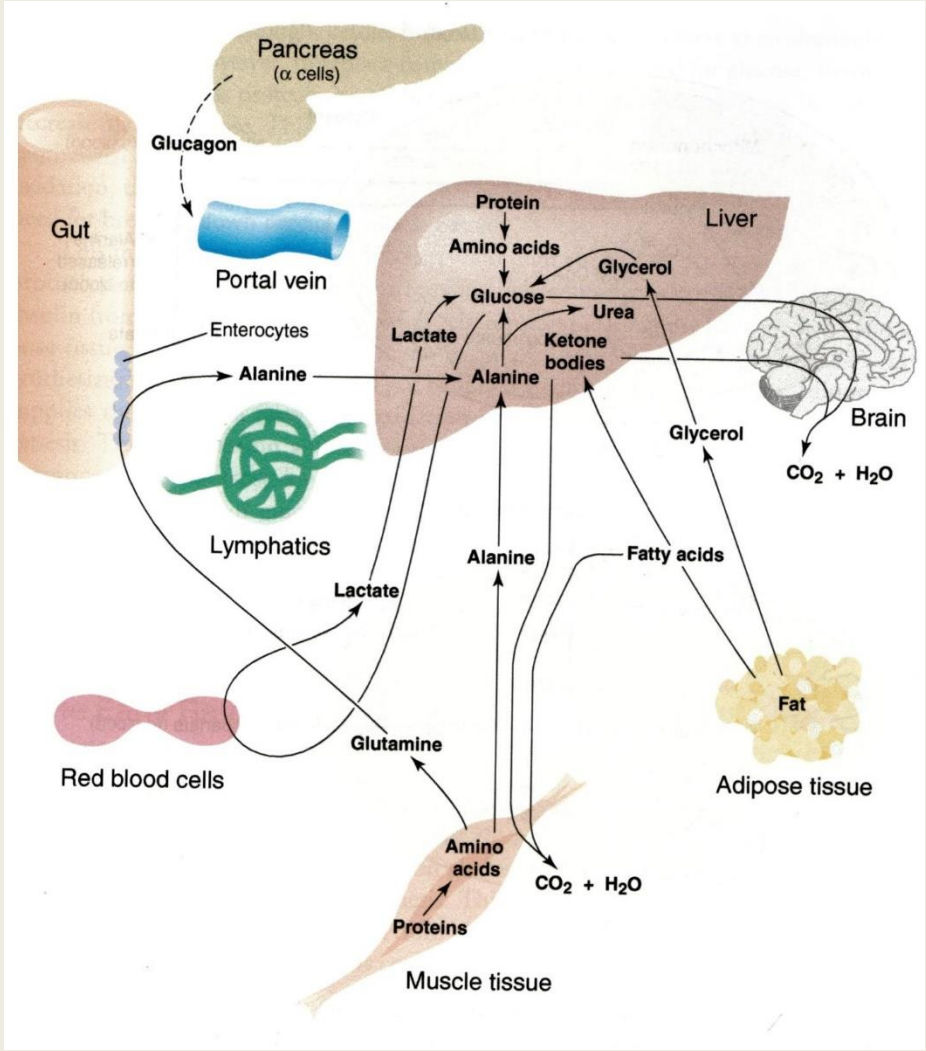
Starve-Feed Cycle / Fasting state

- *Little glycogen after 10-12 hours of fasting*
- *Hepatic gluconeogenesis (from lactate, glycerol and alanine)*
- *Cori and alanine cycles replace glucose breakdown in other tissues by glucose formation in the liver*
- *The brain completely oxidizes glucose*
- *Can fatty acids be converted into glucose?*
- *No path for acetyl-CoA conversion into glucose*
- *Glycerol for glucose synthesis*
- *Protein breakdown from skeletal muscles for glucose synthesis*



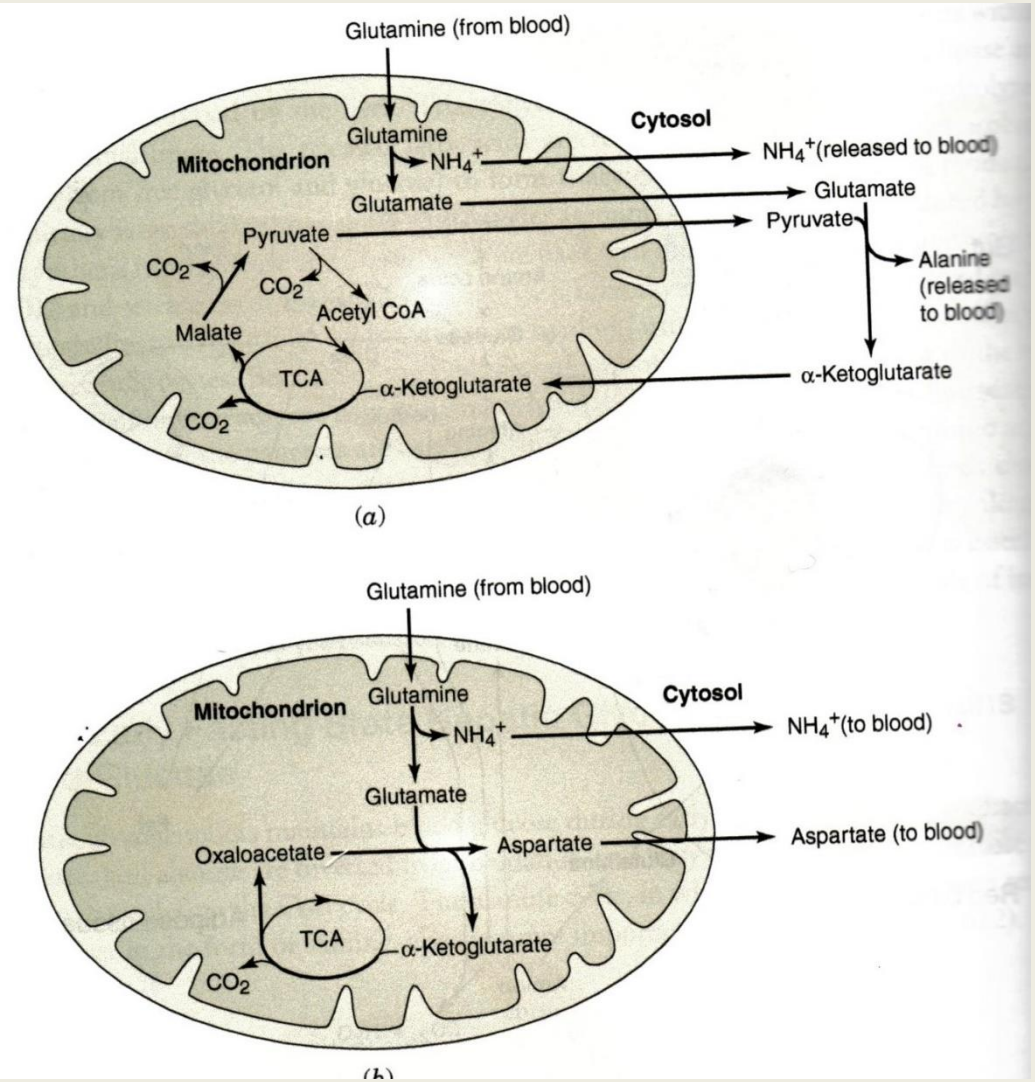
Starve-Feed Cycle / Fasting state

- *Protein breakdown from skeletal muscles for glucose synthesis*
- *Glutamine and alanine released*
- *Other amino acids are metabolized to intermediates (pyruvate and α-ketoglutarate) – they can produce glutamine and alanine*
- *Branched-chain amino-acids (valine, leucine, isoleucine) provide nitrogen for alanine and glutamine in muscle cells*



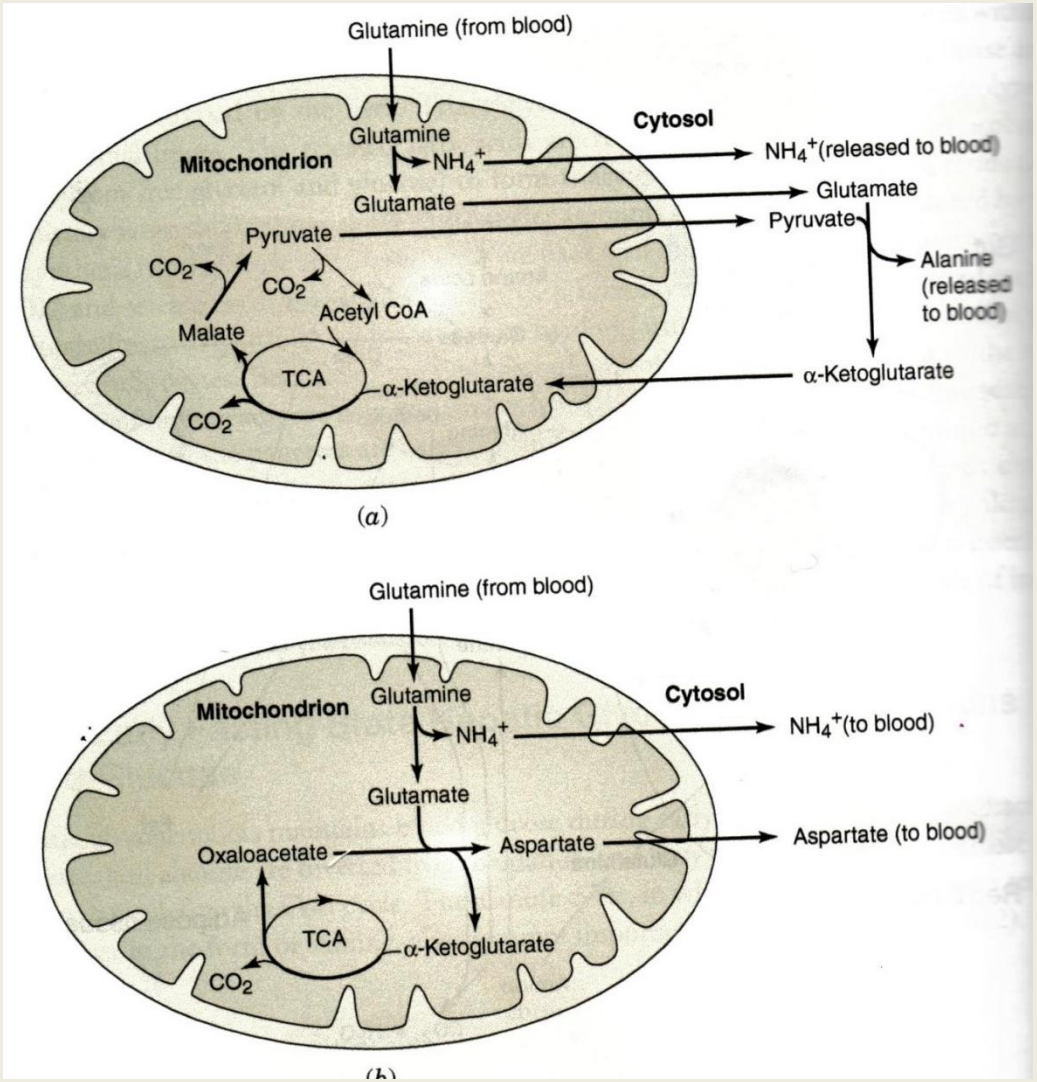
Starve-Feed Cycle / Fasting state

- *Glutamine released from muscle is used by intestinal epithelium, lymphocytes and macrophages*
- *Conversion of glutamine to glutamate*
- *Transamination with pyruvate to form alanine and α-ketoglutarate*
- *In the TCA cycle malate is produced in order to finally produce puryvate for alanine formation*
- *Also glutaminolysis can have aspartate as the end product*



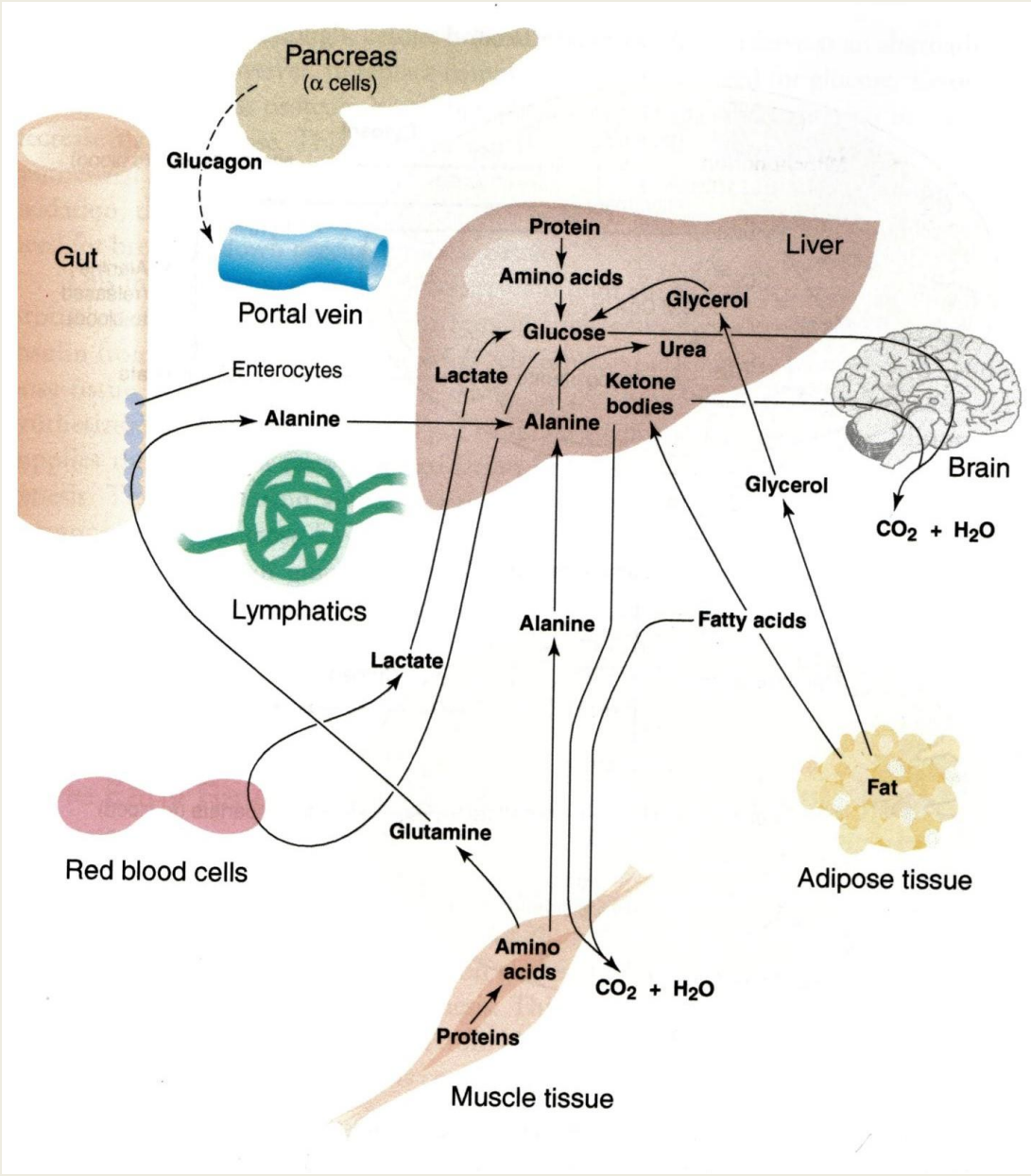
Starve-Feed Cycle / Fasting state

- ***Synthesis of urea***
- ***Glutamate provides nitrogen for urea through ammonia and aspartate***



Starve-Feed Cycle / Fasting state

- *Low blood insulin – lipolysis*
- *Free fatty acids for breakdown*
- *Fatty acid oxidation*
- *In liver fatty acid oxidation provides ATP for gluconeogenesis*
- *Acetyl-CoA is not oxidized completely*
- *It is converted into ketone bodies (aceto-acetate and β-hydroxybutyrate) in liver mitochondria*
- *They are preferred instead of glucose (alternative fuel of the brain)*
- *Less need for glucose, gluconeogenesis and breakdown of muscle tissue*



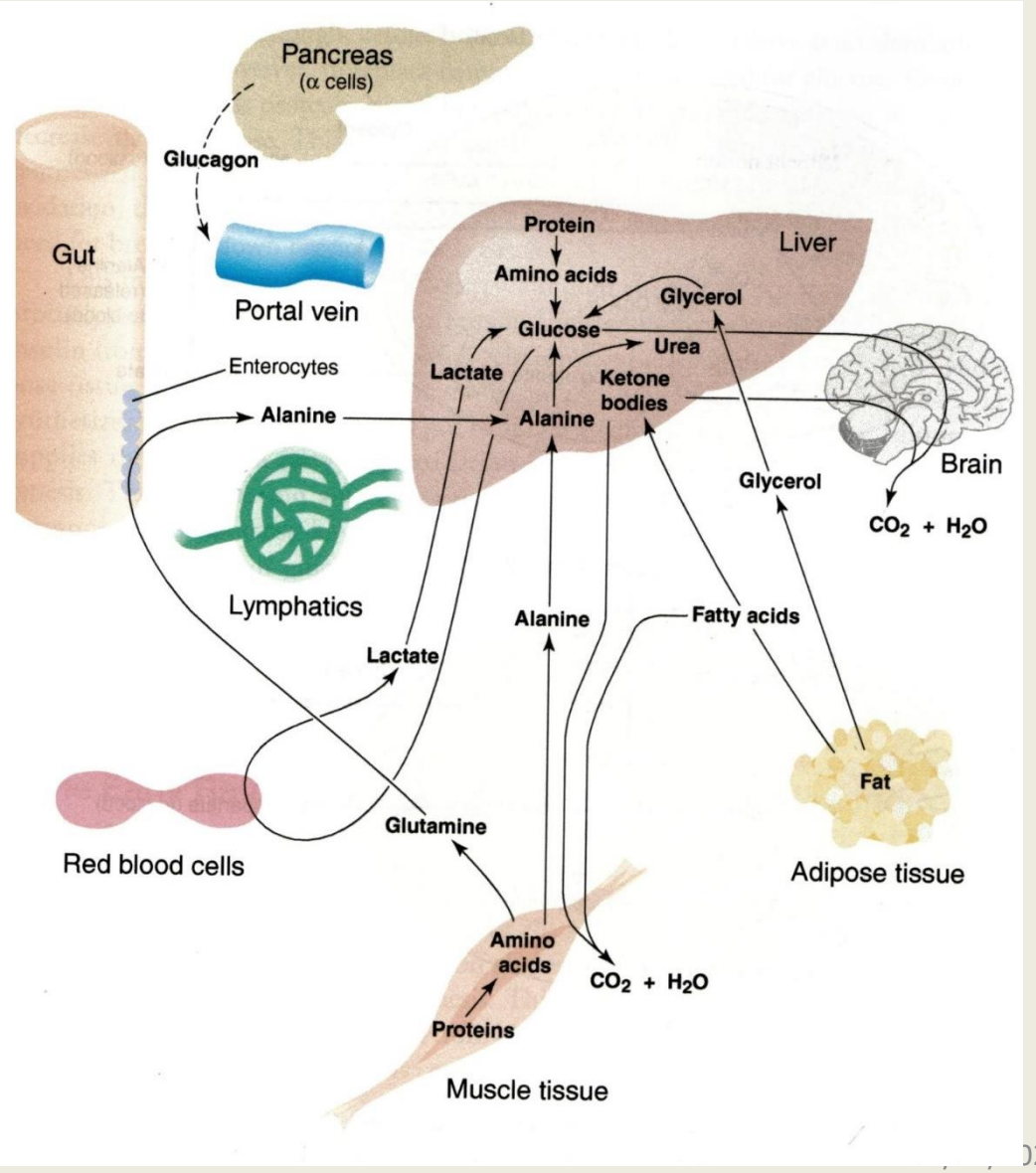
Starve-Feed Cycle / Fasting state

- *Hepatic gluconeogenesis*

1. *Liver produces the glucose*
2. *Muscle and gut provide the substrate (alanine)*
3. *Adipose tissue provides ATP (fatty acid oxidation)*

- Low glucose – low insulin – increased glucagon (pancreas)

And epinephrine from adrenal medulla



Energy requirements and reserves

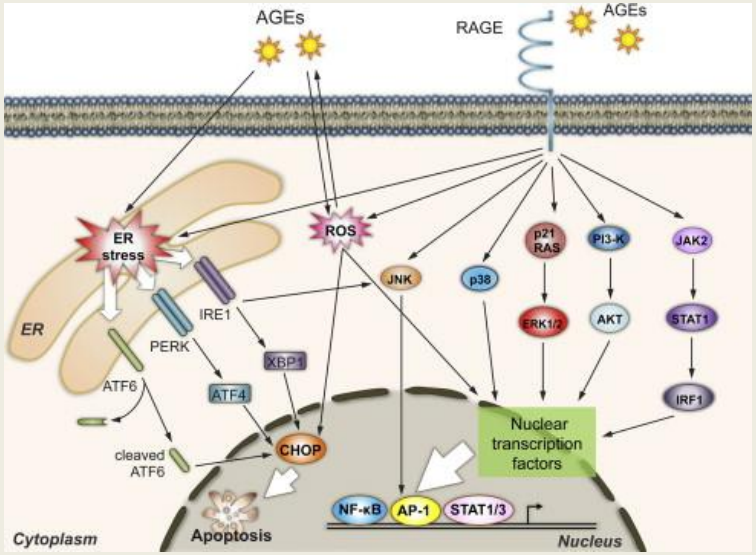
- *An average person consumes daily 180-280g carbohydrate*
- *70-100 g protein*
- *70-100 g fat*
- *1600-2400 kcal daily*

Tight control of glucose homeostasis

- *Too low glucose concentrations < 30 mg/dl – comma and death*
- *Too high*
- *Hyperglycemic / Hyperosmolar comma*
- *Patients with type 2 diabetes*
- *Elderly who obtain fluids less, after an infection, heart attack or not taking their medication properly*
- *Urinary losses of water, glucose and electrolytes (sodium, chloride, potassium)*
- *Osmotic diuresis reduces circulating blood volume*
- *Worsen insulin resistance and hyperglycemia*
- *Glucose >1000 mg/dl*
- *Dehydration, comma*
- *High mortality*

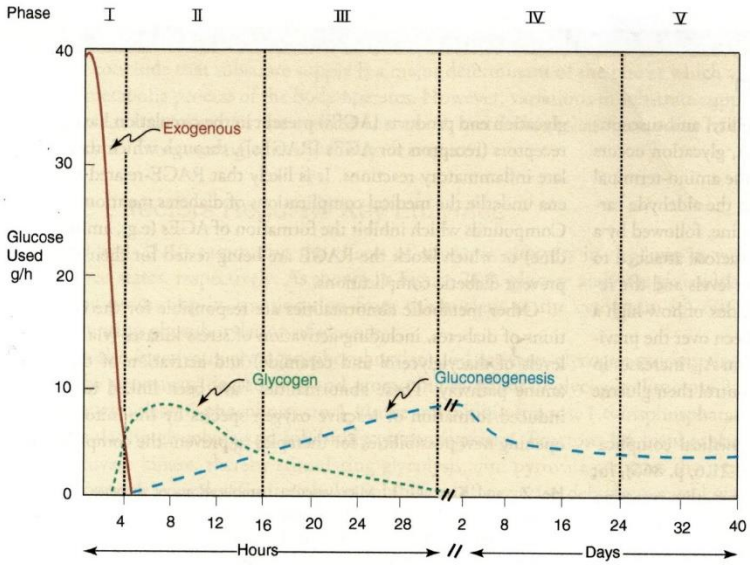
Tight control of glucose homeostasis

- *Chronic hyperglycemia and protein glycation*
- *Enzyme glycation – non-enzymatic reaction*
- *e.g. HbA1c*
- *Glycation of proteins contribute to medical complications of diabetes: coronary heart disease, retinopathy, nephropathy, cataracts, neuropathy*
- *Glycation of matrix proteins*
- *Advanced-glycation end products (AGEs) bind to their receptor RAGE and induce inflammation*



Five phases of glucose homeostasis

- ***Phase I**: the well-fed state*
- ***Phase II**: hepatic glycogenolysis*
- ***Phase III**: hepatic gluconeogenes is (20h of fasting)*
- ***Phase IV**: hepatic, renal gluconeogenes is and ketone bodies catabolism*
- ***Phase V**: ketone body and fatty acid oxidation*



Phase	ORIGIN OF BLOOD GLUCOSE	TISSUES USING GLUCOSE	MAJOR FUEL OF BRAIN
I	Exogenous	All	Glucose
II	Glycogen Hepatic gluco–neogenesis	All except liver. Muscle and adipose tissue at diminished rates	Glucose
III	Hepatic gluconeogenesis Glycogen	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Glucose
IV	Gluconeogenesis, hepatic and renal	Brain, RBCs, renal medulla. Small amount by muscle	Glucose, ketone bodies
V	Gluconeogenesis, hepatic and renal	Brain at a diminished rate, RBCs, renal medulla	Ketone bodies, glucose

Mechanisms involved in the transduction of hepatic metabolism between well-fed and fasting states

- ***Liver of a well-fed person***
  - ***Glycogenic***
  - ***Glycolytic***
  - ***Lipogenic***
- ***Liver of a fasting person***
  - ***Glycogenolytic***
  - ***Glyconeogenic***
  - ***Ketogenic***
  - ***Proteolytic***

- ***Store calories when food is available***

- ***Mobilize them when the other tissues are in need***

Mechanisms involved in the transduction of hepatic metabolism between well-fed and fasting states

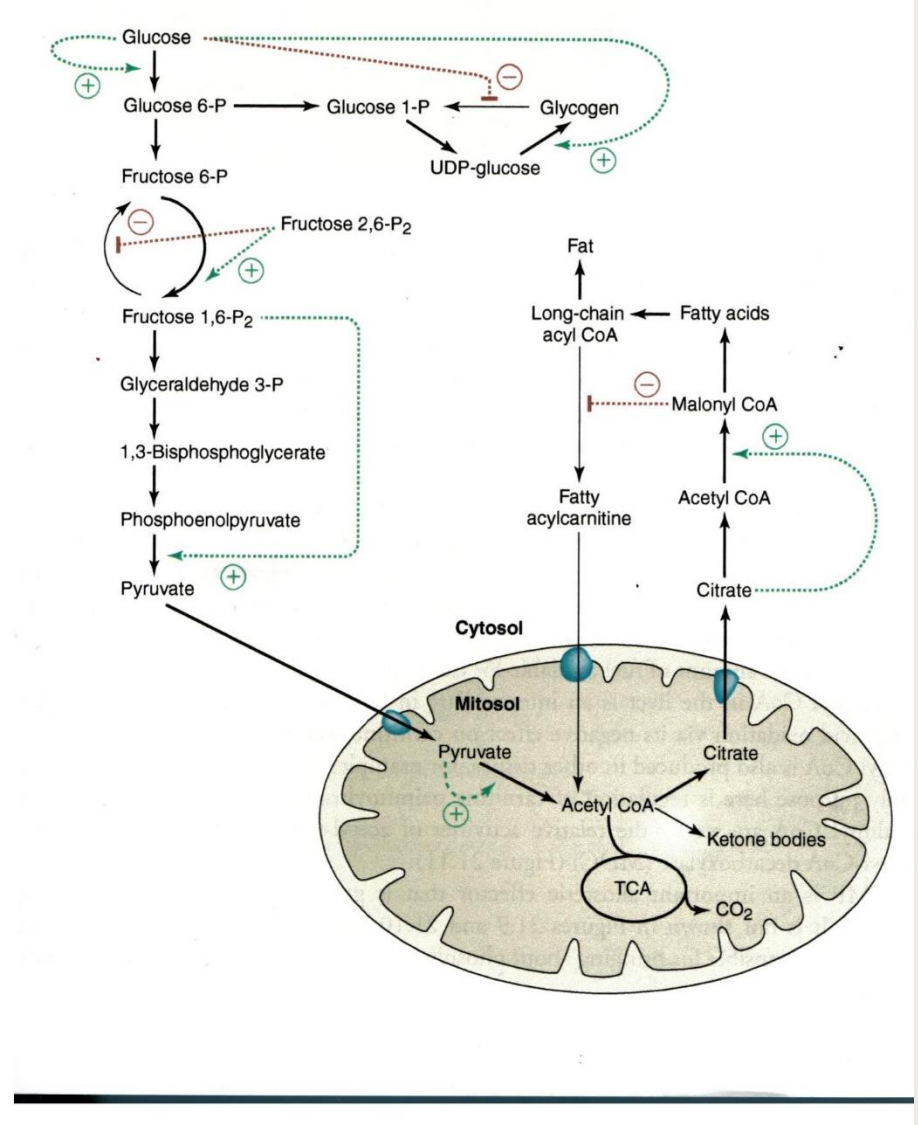
- *1. Substrate supply*
- *2. allosteric effectors*
- *3. covalent modifications*
- *4. induction-repression of enzymes*

Control by substrate availability

- *Concentration of fatty acids in the liver – rate of ketogenesis*
- *Glucose synthesis – rates of gluconeogenic substrates flow*
- *Amino acids concentration in diabetes – gluconeogenesis / hyperglycemia*
- *Low glucogenic substrate concentration – hypoglycemia*
- *Finer-tuners of pathways are required*

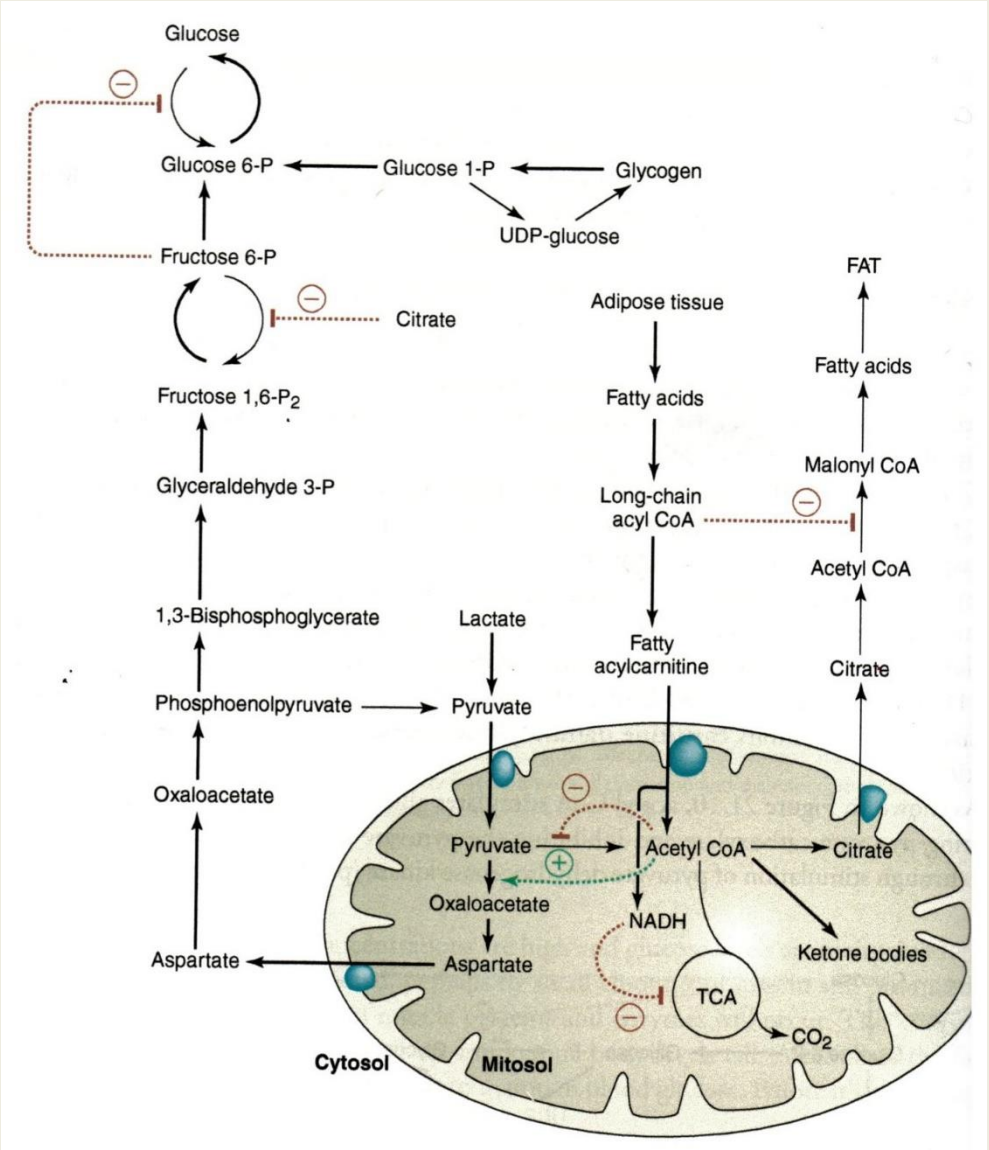
Control of hepatic metabolism by allosteric effectors in the well-fed state

- *Glucose activates glucokinase – favors glycolysis*
- *Glucose inactivates glycogen phosphorylase – inhibits glycogen catabolism*
- *Glucose activates glycogen synthase - favors glycogen synthesis*
- *2,6 Fructose diphosphate stimulates PFK-1 - favors glycolysis*
- *2,6 Fructose diphosphate inhibits 1,6 biphosphatase – inhibits gluconeogenesis*
- *Fructose 1,6-P2 activates pyruvate kinase - favors glycolysis*
- *Pyruvate activates PDH complex - favors acetyl-CoA*
- *Citrate activates acetyl-CoA carboxylase – favors fatty acids synthesis*
- *Malonyl CoA inhibits carnitine palmitoyltransferase I – inhibits fatty acids breakdown*



Control of hepatic metabolism by allosteric effectors in the fasting state

- *Acetyl-CoA activates pyruvate carboxylase – favors gluconeogenesis*
- *Acetyl-CoA inhibits PDH – favors gluconeogenesis*
- *Long chain acyl-CoA decreases malonyl CoA – increases fatty acid oxidation*
- *Fructose 6-P inhibits glucokinase – inhibits glycolysis*
- *Citrate inhibits PFK1 – inhibits glycolysis*
- *NADH inhibits TCA cycle*
- *Other allosteric effectors include malonyl-CoA, cAMP, AMP/AMPK (activation of glycogen phosphorylase, PFK1, inhibition of fructose -1,6-biphosphate)*

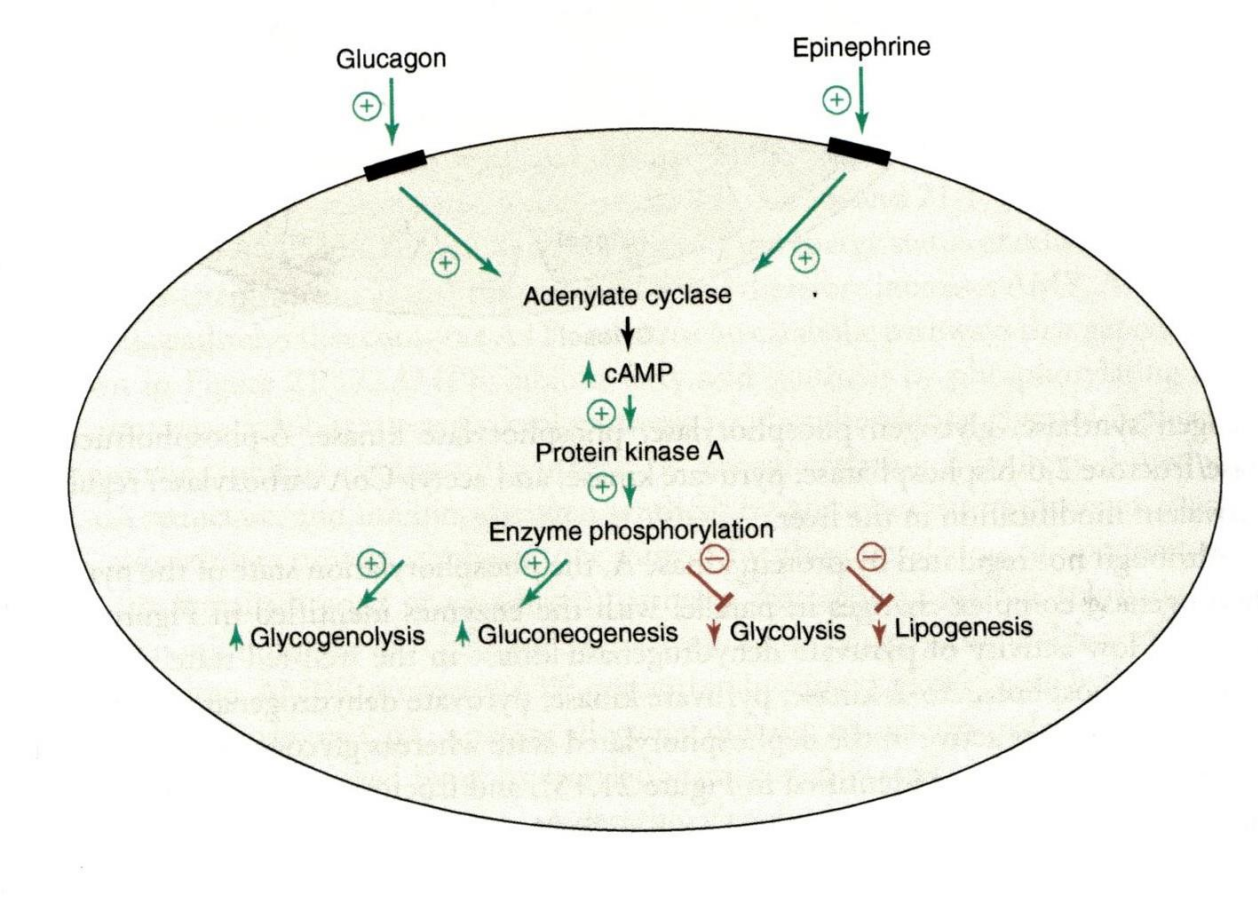


Covalent modification regulates key-enzymes

- ***Phosphorylation status affects the catalytic activities of the enzymes***
- ***Other enzymes active in the dephosphorylation***
- ***Other in the phosphorylation state***
- ***cAMP/PKA axis***

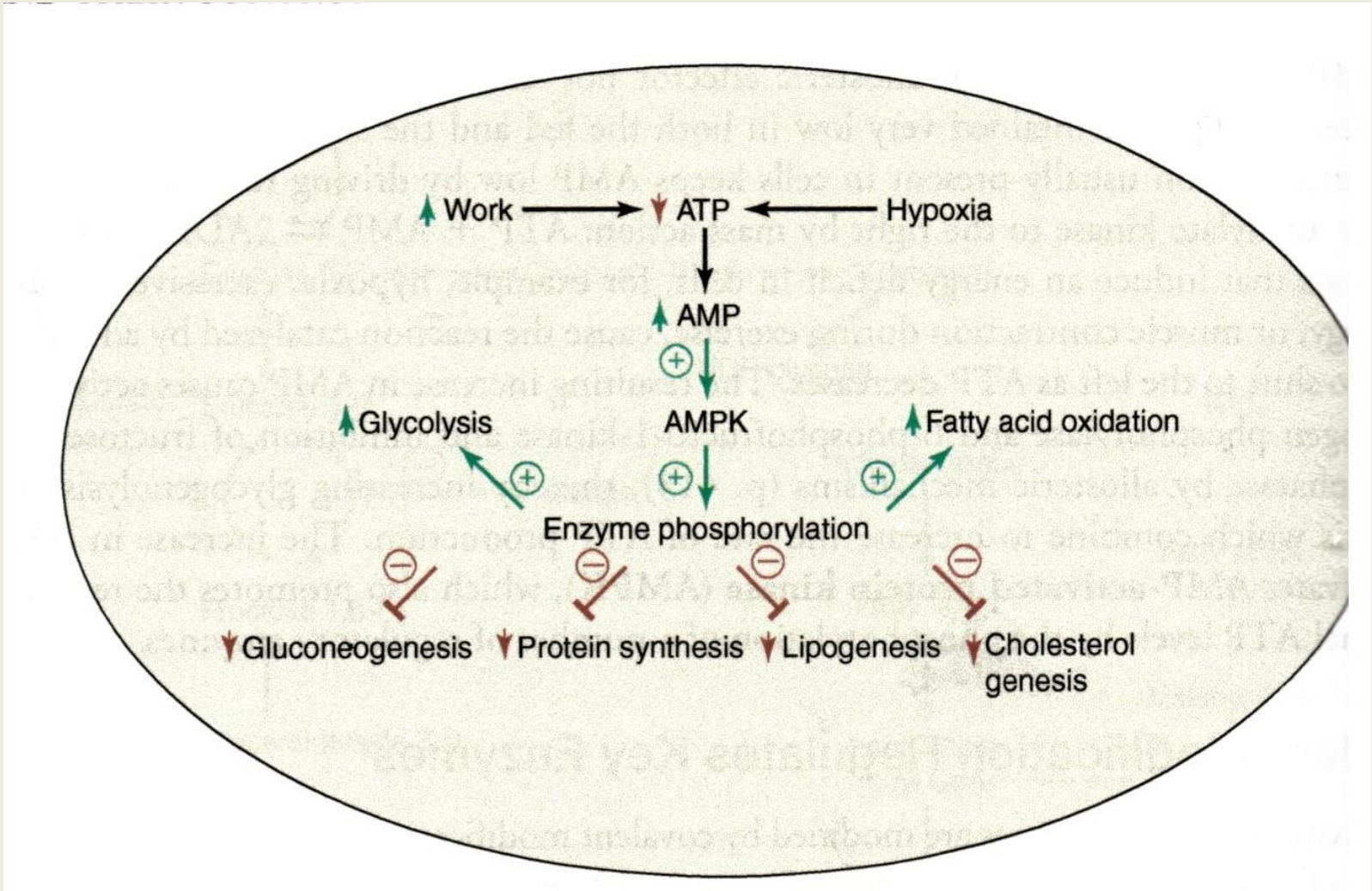
Covalent modification regulates key-enzymes

- ***Glucagon and epinephrine activate glycogenolysis / gluconeogenesis and inhibit glycolysis and lipogenesis in liver***



Covalent modification regulates key-enzymes

- ***Activation of AMPK suppresses ATP-requiring processes and upregulates ATP-producing processes***

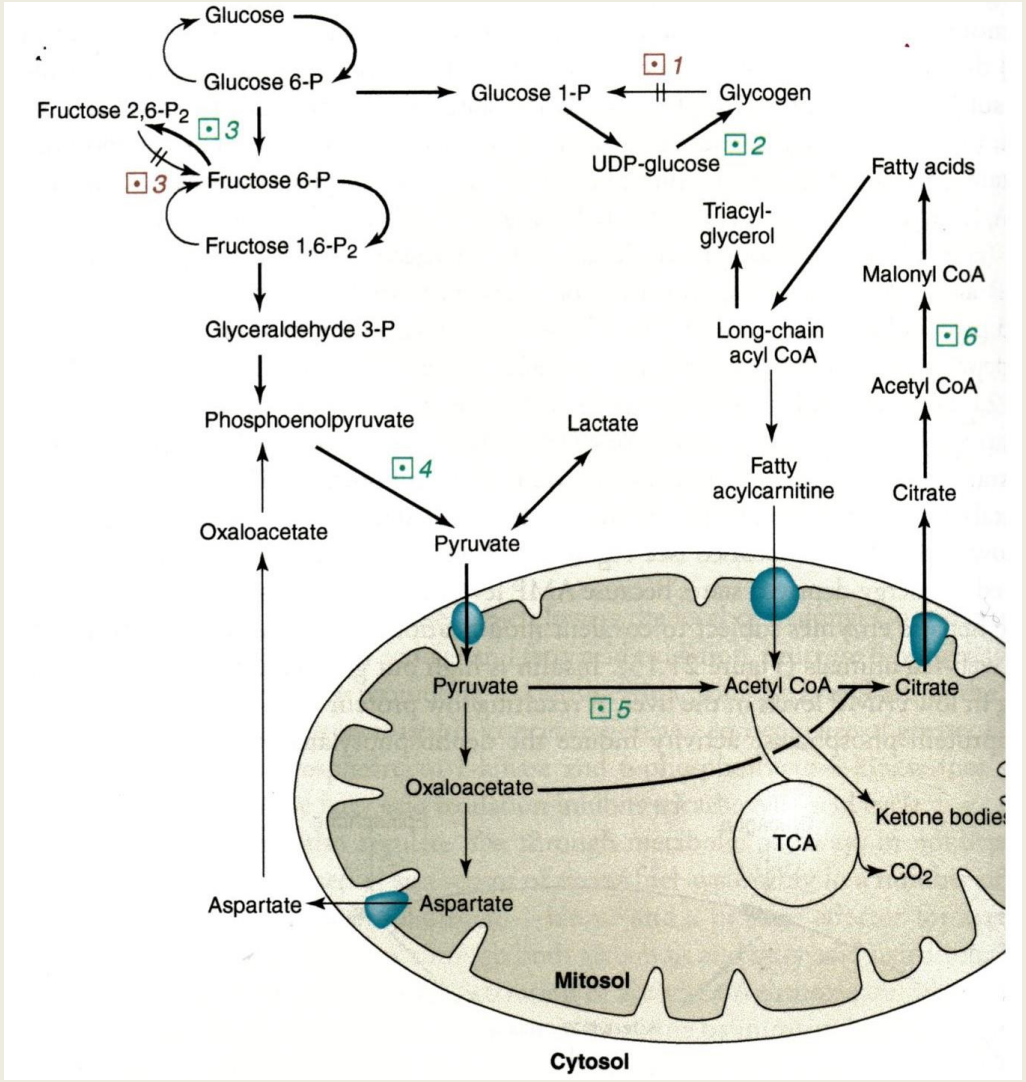


Control of hepatic metabolism by covalent modification in a well-fed state

- *Insulin / Low PKA activity / high phosphatase activity*
- *Dephosphorylation of*

1. *Glycogen phosphorylase*
2. *Glycogen synthase*
3. *6-phosphofructo-2-kinase/fructose-2,6-biphosphatase*
4. *Pyruvate kinase*
5. *Pyruvate dehydrogenase*
6. *Acetyl-CoA carboxylase*

- Enhancement of glycogenesis, glycolysis and lipogenesis

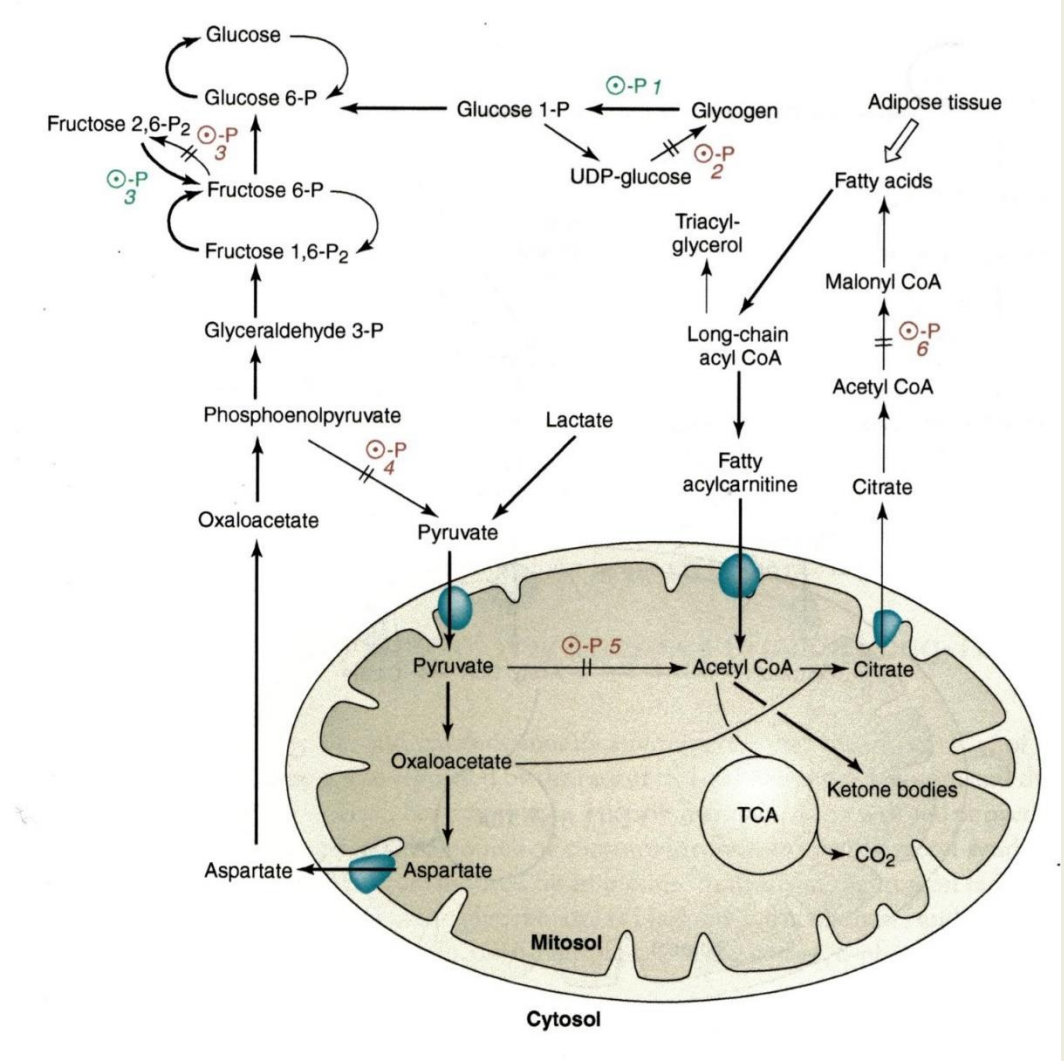


Control of hepatic metabolism by covalent modification in the fasting state

- *Glucagon / high PKA activity and cAMP / low phosphatase activity*
- *Phosphorylation of*

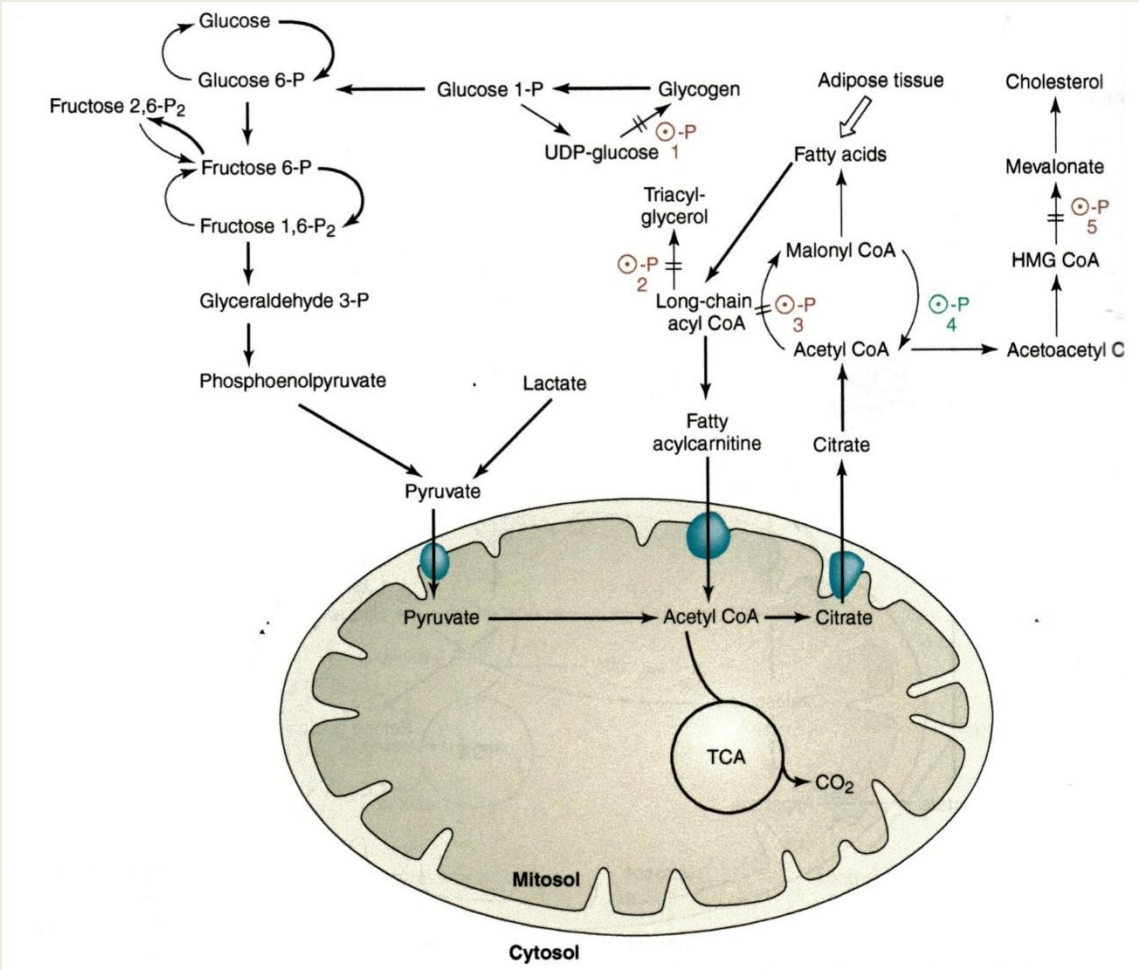
1. *Glycogen phosphorylase*
2. *Glycogen synthase*
3. *6-phosphofructo-2-kinase/fructose-2,6-biphosphatase*
4. *Pyruvate kinase*
5. *Pyruvate dehydrogenase*
6. *Acetyl-CoA carboxylase*

Enhancement of glycogenolysis, gluconeogenesis and ketogenesis



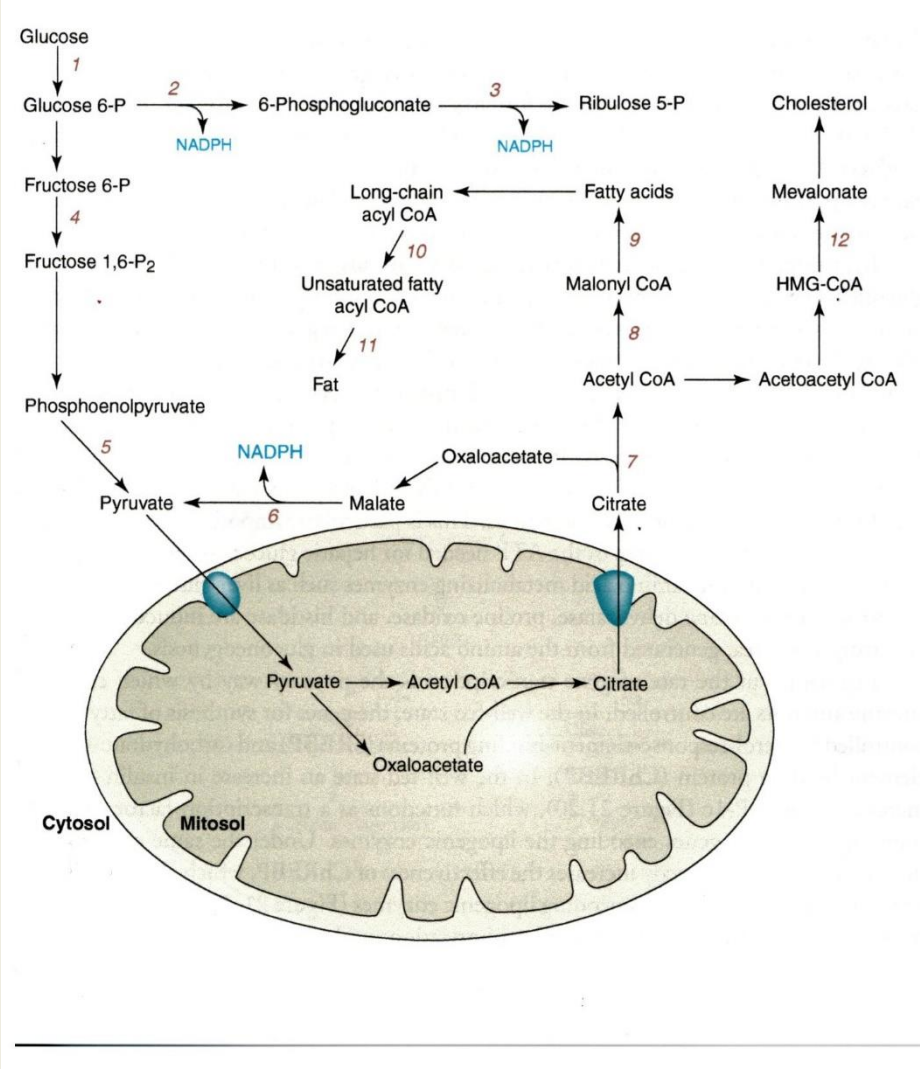
Control of hepatic metabolism by AMPK in the fasting state

- *High AMP concentration*
- *Phosphorylation of*
- *Glycogen synthase*
- *Glycerol-3-phosphate acyltransferase*
- *Acetyl-CoA carboxylase*
- *Malonyl-CoA decarboxylase*
- *HMG-CoA reductase*



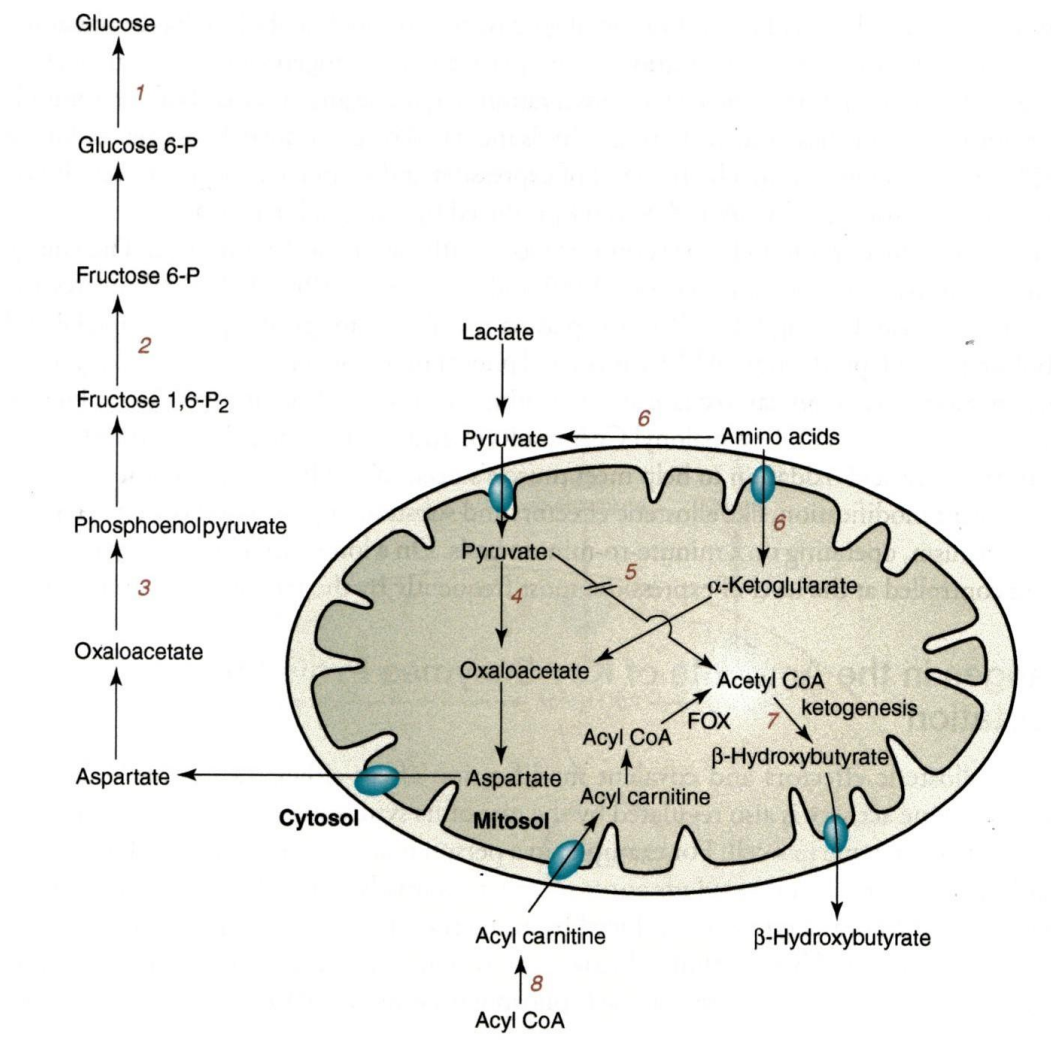
Hepatic enzymes induced in the well-fed state

- ***Changes in the production of key-enzymes***



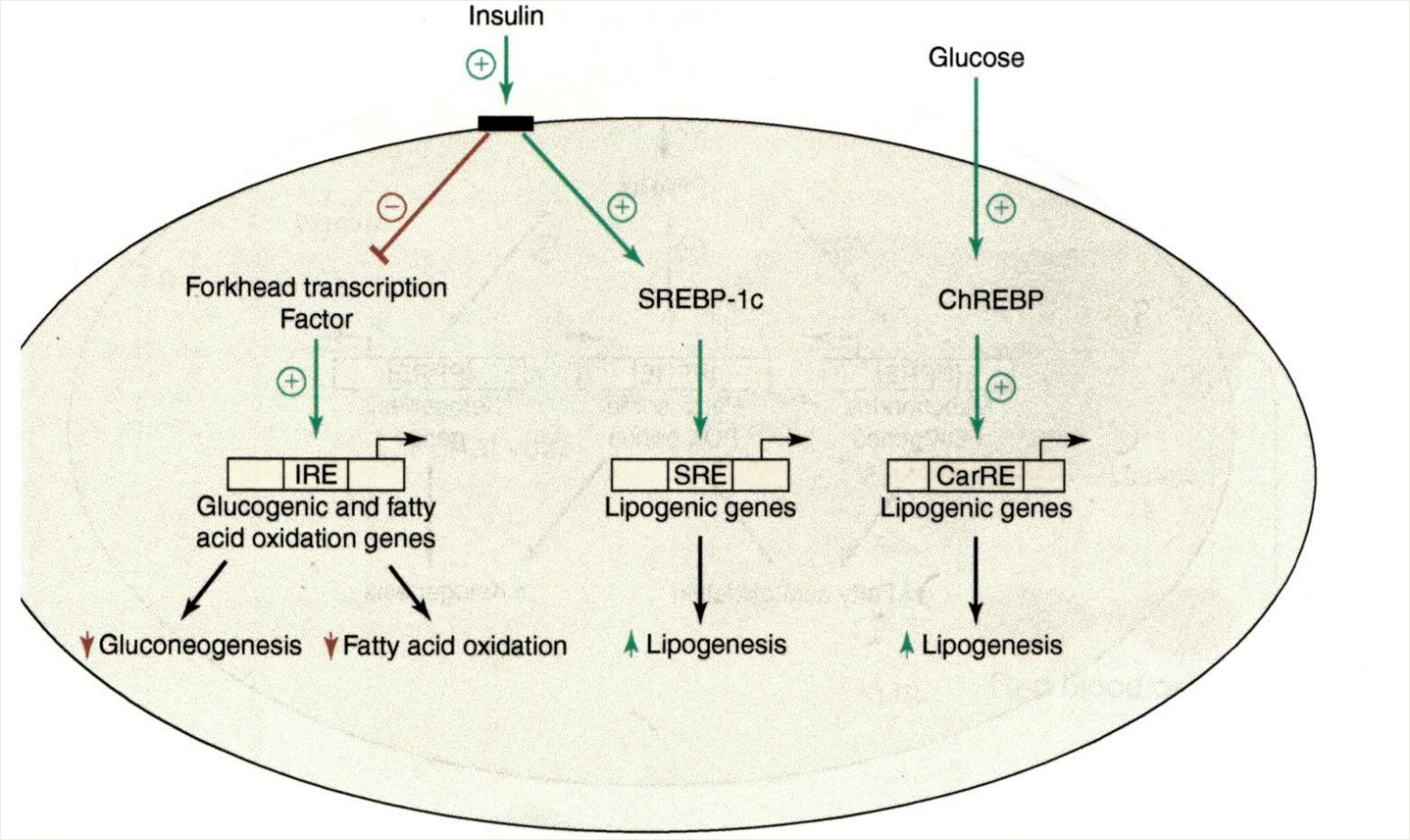
Hepatic enzymes induced in the fasting state

- ***Changes in the production of key-enzymes***



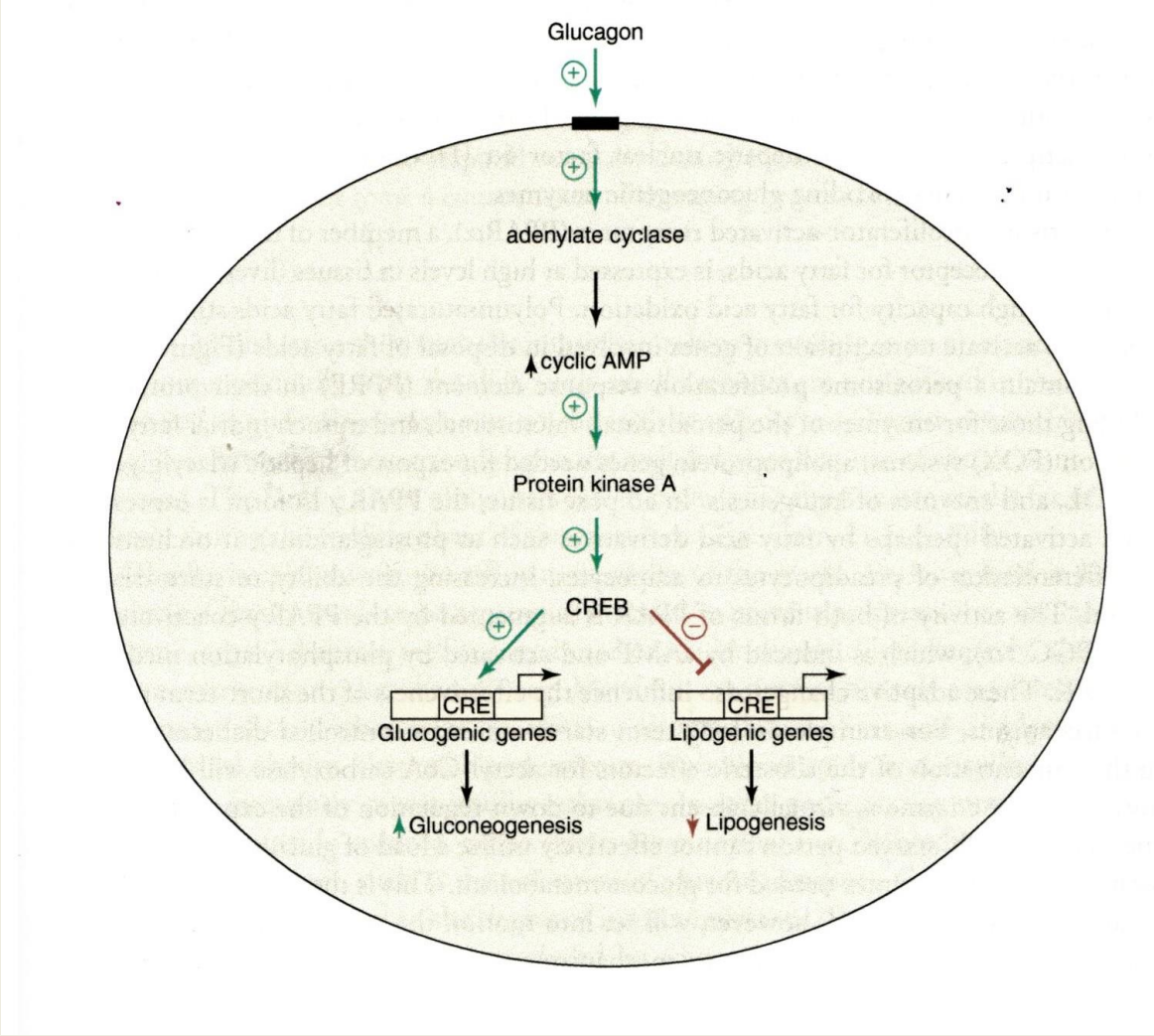
Regulation of gene transcription

- ***Changes in the production of key-enzymes by insulin and glucose***



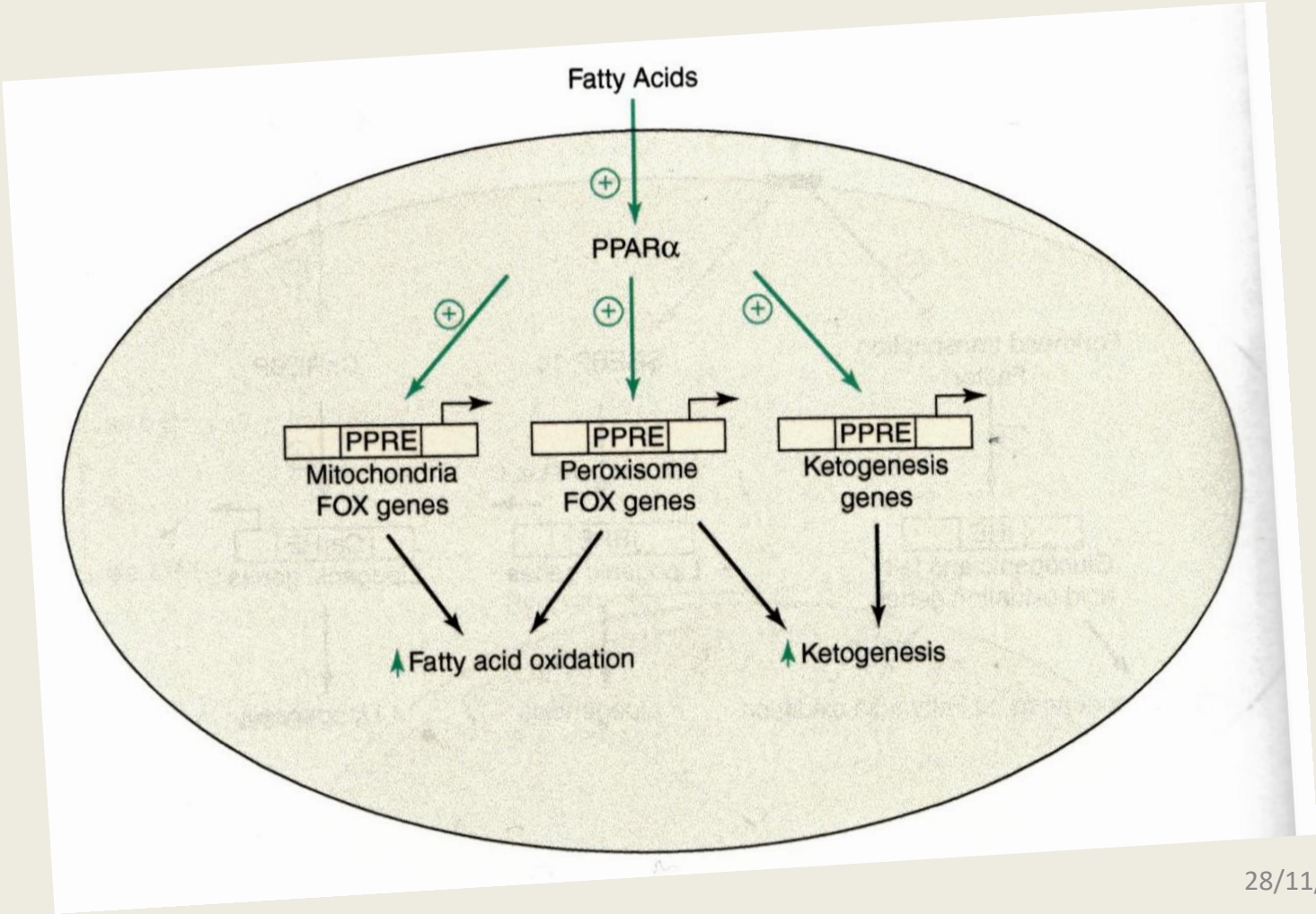
Regulation of gene transcription

- ***Changes in the production of key-enzymes by glucagon***



Regulation of gene transcription

- ***PPARa activation by fatty acids promotes transcription of fatty acid oxidation (FOX) and ketogenesis genes***



Devlin chapter 21

Which sentence is incorrect?

1. Insulin promotes glycogen synthesis in the liver

2. Insulin promotes the synthesis of fatty acids in the liver

3. Insulin promotes gluconeogenesis in the liver

4. Insulin is secreted as a response to high blood glucose concentration

Which sentence is incorrect?

1. Glucagon promotes the breakdown of glycogen in the liver

2. Glucagon inhibits glycolysis in the liver

3. Glucagon promotes gluconeogenesis in the liver

4. Glucagon promotes protein synthesis

5. Glucagon promotes the production of ketone bodies to be used as fuel in neurons

6. Glucagon promotes the degradation of triacylglycerols

Which sentence is incorrect? In the well-fed state

1. Amino-acids and glucose pass from the intestinal epithelial cells to the blood circulation and through the portal vein arrive to the liver.

2. Chylomicrons are secreted from intestinal epithelial cells to the lymphatic circulation towards body tissues

3. Glycogen synthesis is induced

4. Glycolysis is induced

5. Proteins are catabolized in skeletal muscles for glucose synthesis

Which sentence is incorrect? In the fasting state

1. Cori and alanine cycles replace glucose breakdown in other tissues by glucose formation in the liver

2. Synthesis of urea is enhanced

3. Glycogen synthesis is induced

4. The brain completely oxidizes glucose

5. Branched-chain amino-acids (valine, leucine, isoleucine) provide nitrogen for alanine and glutamine in muscle cells

Which of the following would favor gluconeogenesis in the fasted state?

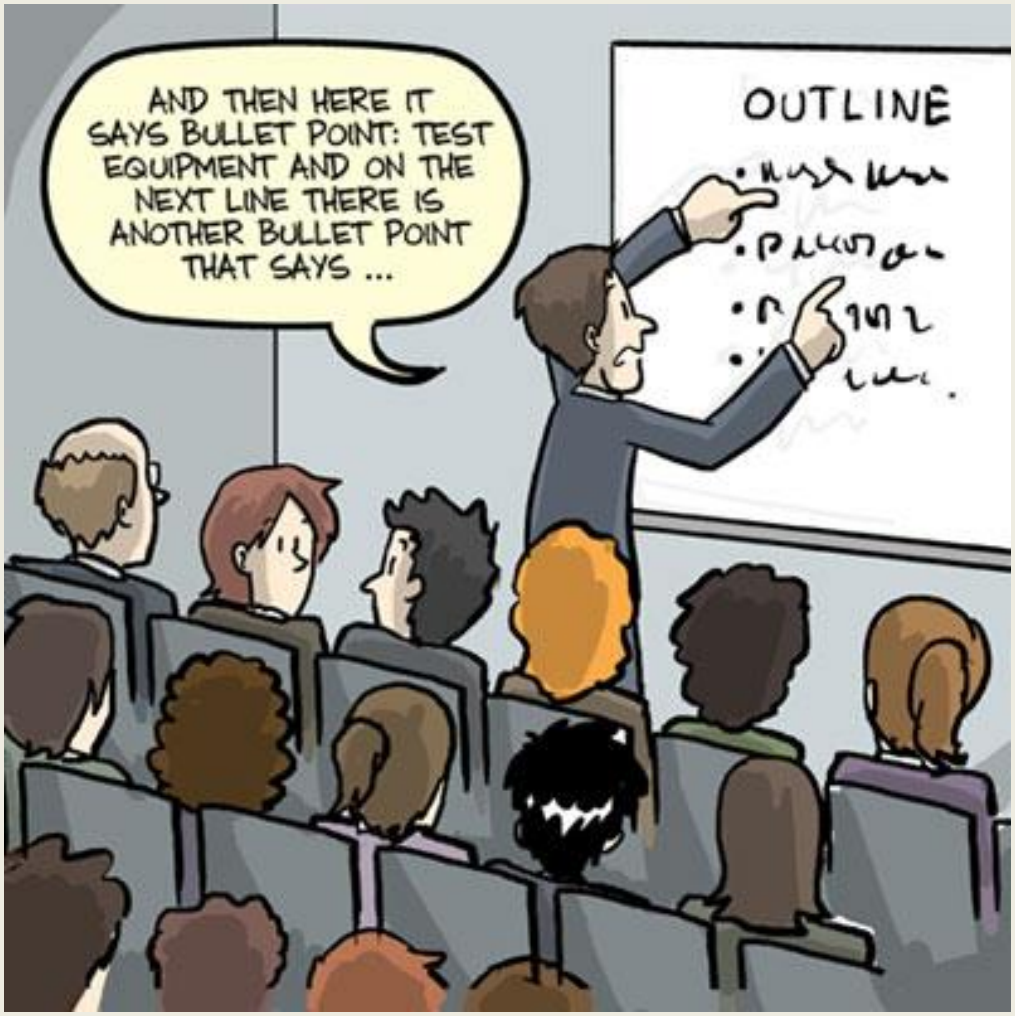
1. Fructose 1,6-biphosphate stimulation of pyruvate kinase

2. Acetyl-CoA activation of pyruvate carboxylase

3. Citrate activation of acetyl-CoA carboxylase

4. Malonyl-CoA inhibition of carnitine palmitoyltransferase I

5. Fructose 2,6-biphosphate stimulation of 6-phosphofructo-1-kinase


AND THEN HERE IT SAYS BULLET POINT: TEST EQUIPMENT AND ON THE NEXT LINE THERE IS ANOTHER BULLET POINT THAT SAYS ...
OUTLINE

Thank you!