NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

SCHOOL OF MEDICINE

BIOCHEMISTRY II – 3nd SEMESTER

Metabolic correlations: : Interrelationships of tissues in nutritional and hormonal states.

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Metabolic correlations: : Interrelationships of tissues in nutritional and hormonal states.

Learning aims

- Understand and describe metabolic interrelationships of tissues in various nutritional, hormonal and disease states
- Understand and describe metabolic interrelationships of tissues in obesity
- Understand and describe metabolic interrelationships of tissues in dieting
- Understand and describe metabolic interrelationships of tissues in cancer
- Understand and describe metabolic interrelationships of tissues in exercise
- Understand and describe metabolic interrelationships of tissues in pregnancy
- Understand and describe metabolic interrelationships of tissues in lactation
- Understand and describe metabolic interrelationships of tissues in stress and injury
- Understand and describe metabolic interrelationships of tissues in liver disease
- Understand and describe metabolic interrelationships of tissues in kidney failure
- Understand and describe metabolic interrelationships of tissues in consumption of alcohol
- Understand and describe metabolic interrelationships of tissues in acidosis

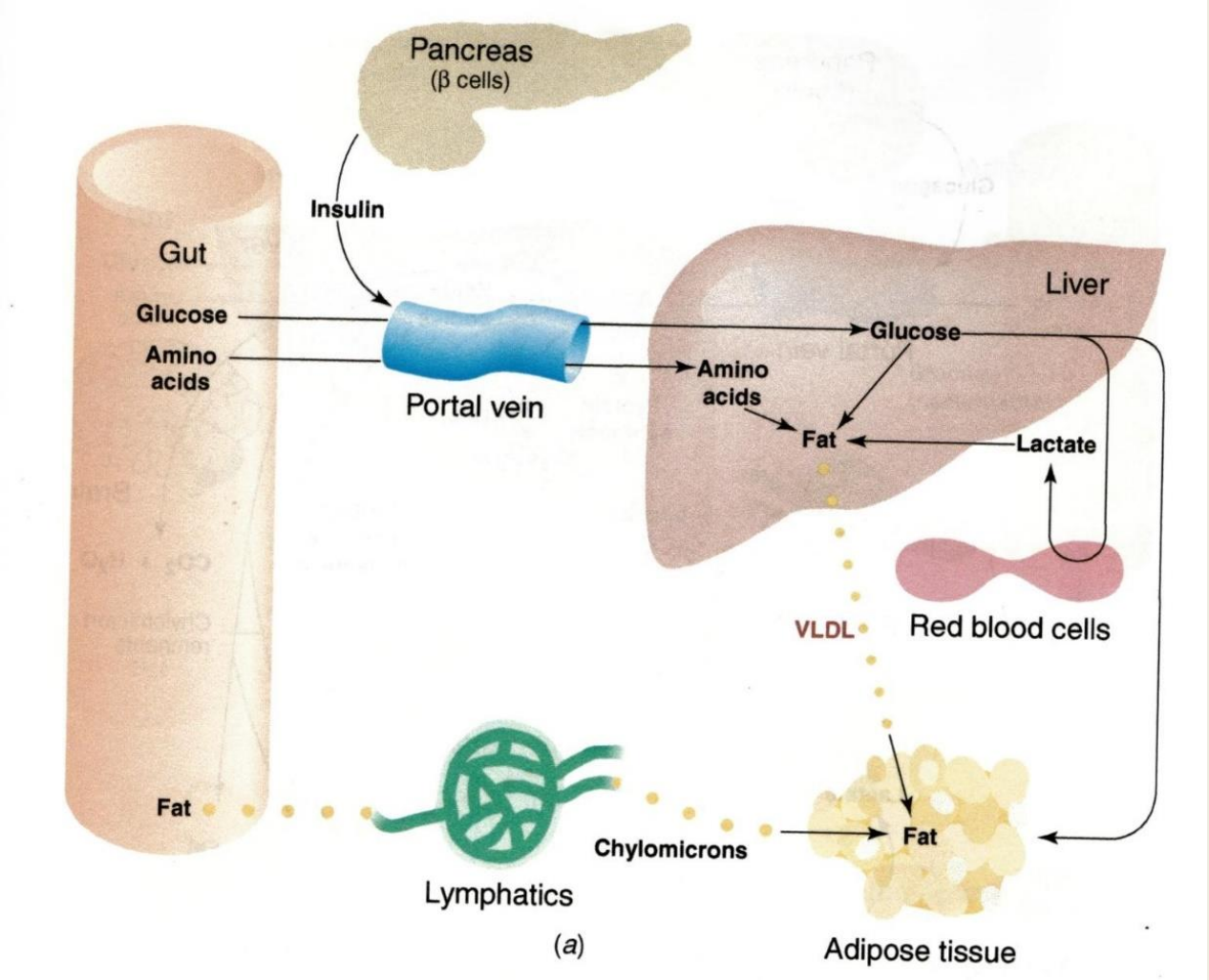
INTRODUCTION

- Changes occur in the different nutritional and hormonal states as variations of the starve-feed cycle.

- **Examples in physiology:**

- Rapid growth of children

- Aging

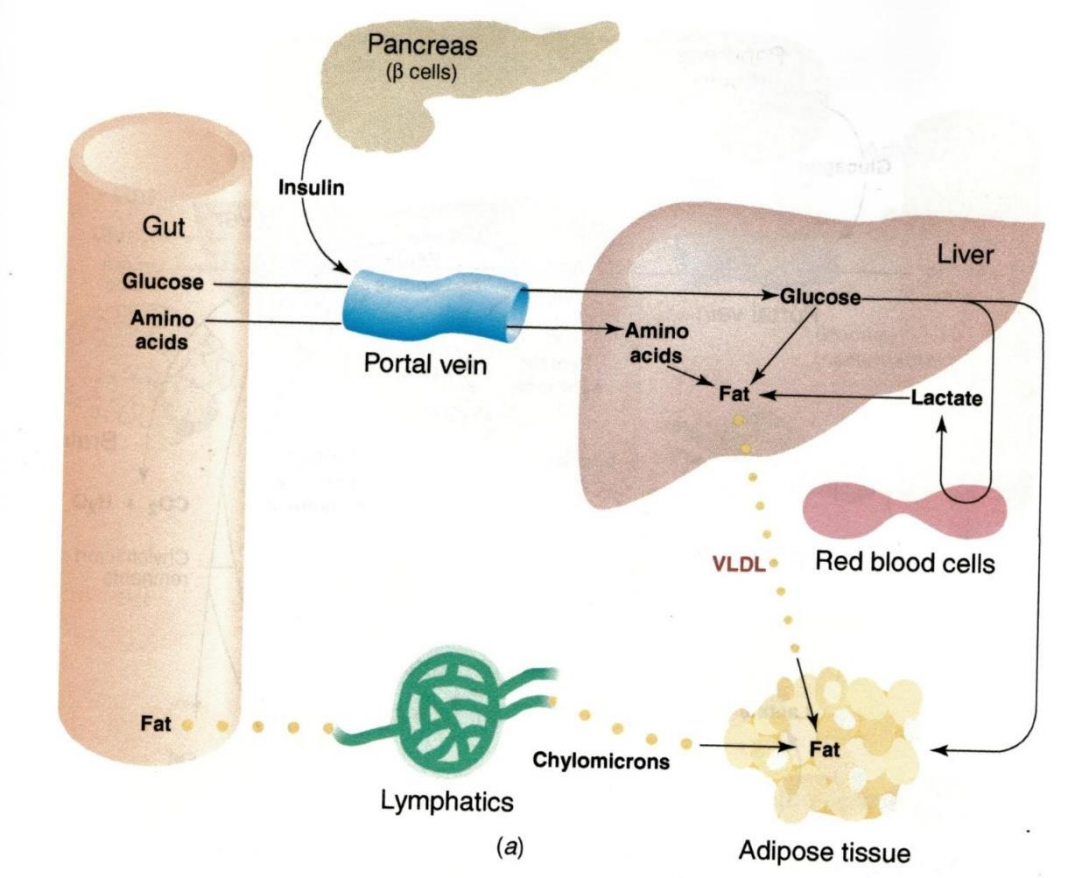


Obesity

- Primary origin of body fat comes from the diet
- Low liver and adipose tissue synthesis of triacylglyceroles
- **Well-fed state – long time-period**
- Fasting state – short time-period
- Sequence:

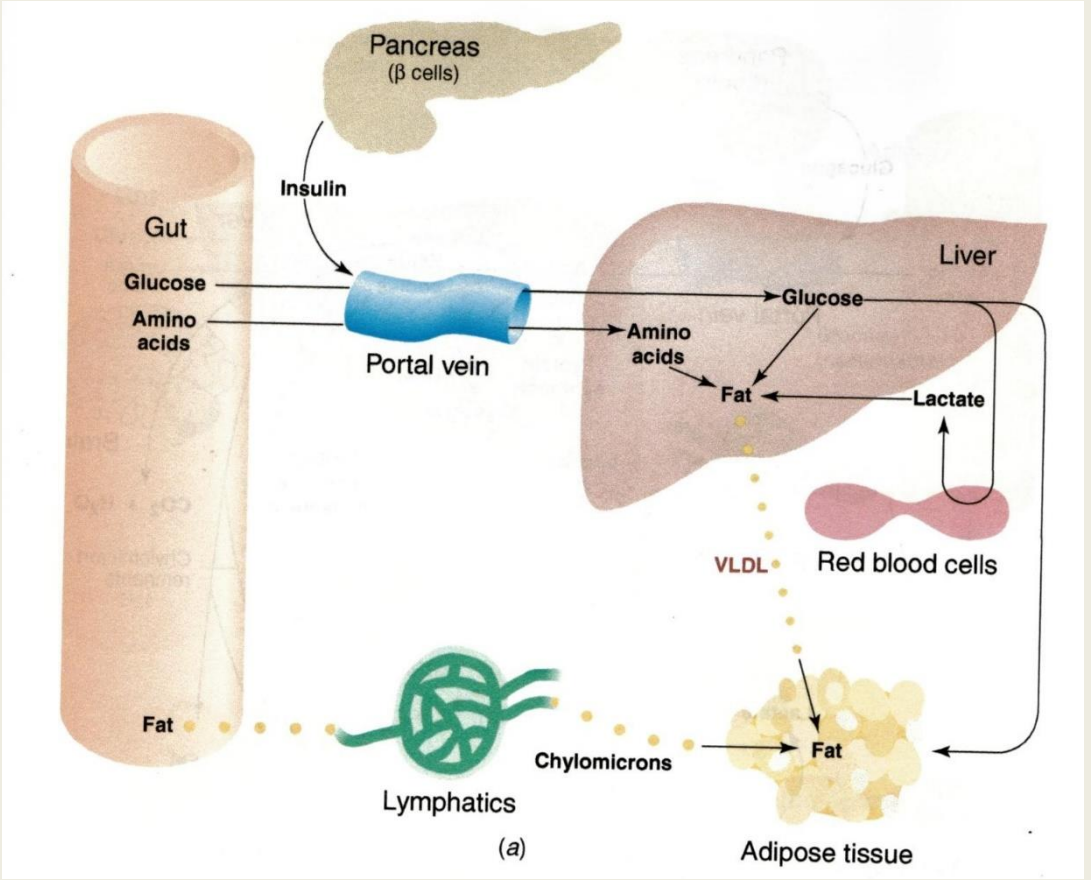
- Obesity
- metabolic syndrome
- type 2 diabetes mellitus
- cardiovascular disease

- ***Treatment: dieting – dieting – dieting***
- Metabolic syndrome
  1. Abdominal obesity
  2. High blood pressure
  3. high blood lipids
  4. Insulin resistance

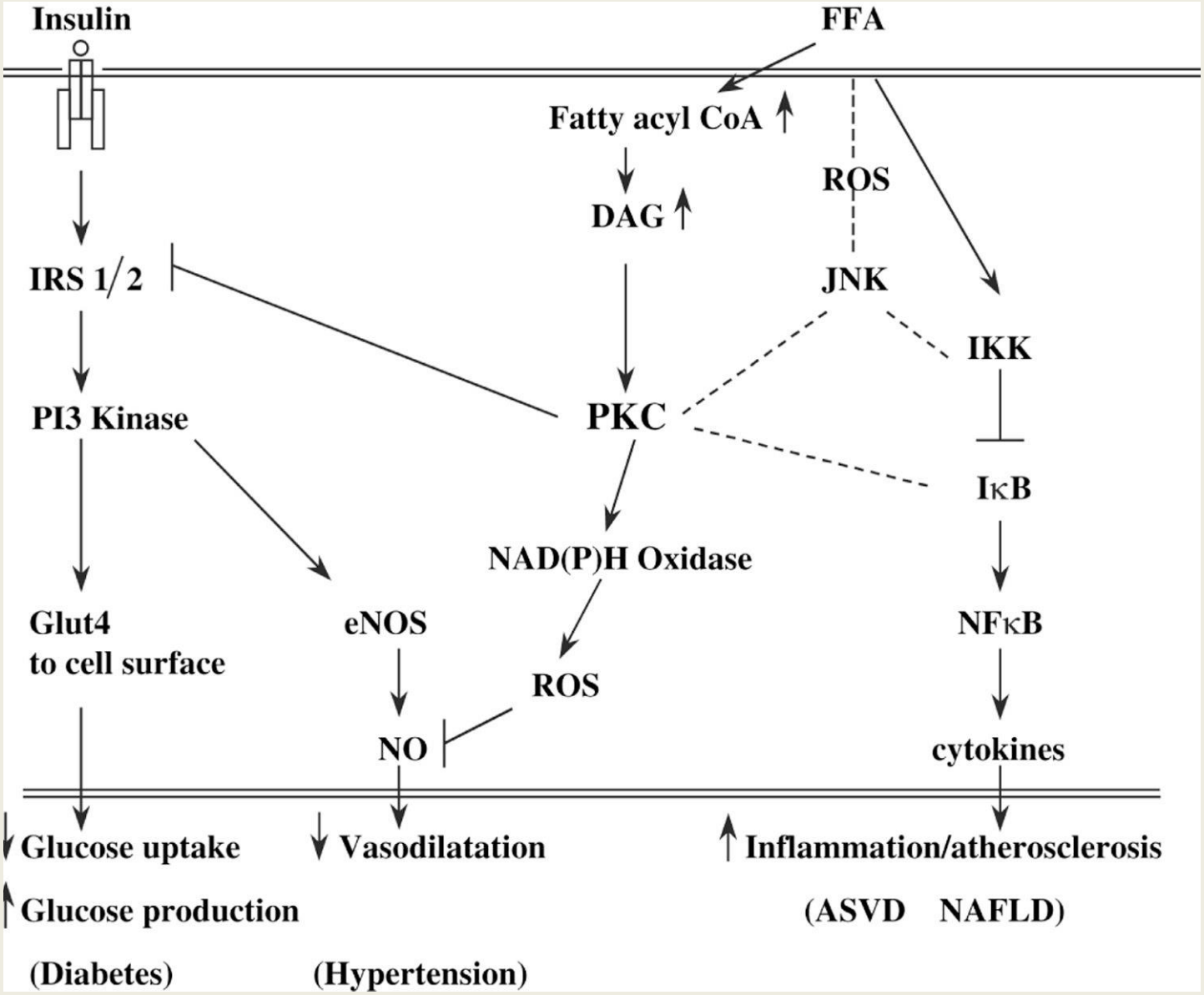


Obesity

- **Insulin resistance**
- **Causes**
- **Reduced number of insulin receptors**
- **Reduced affinity of receptors**
- **Normal insulin binding – abnormal responses – activation of glucose transport**
- **Quantity of body fat – association with the degree of insulin resistance**
- **Resistance by peptides (TNFα, resistin) produced by adipocytes opposing the action of insulin**
- **Low adiponectin in obesity – insulin resistance**
- **High plasma insulin levels**

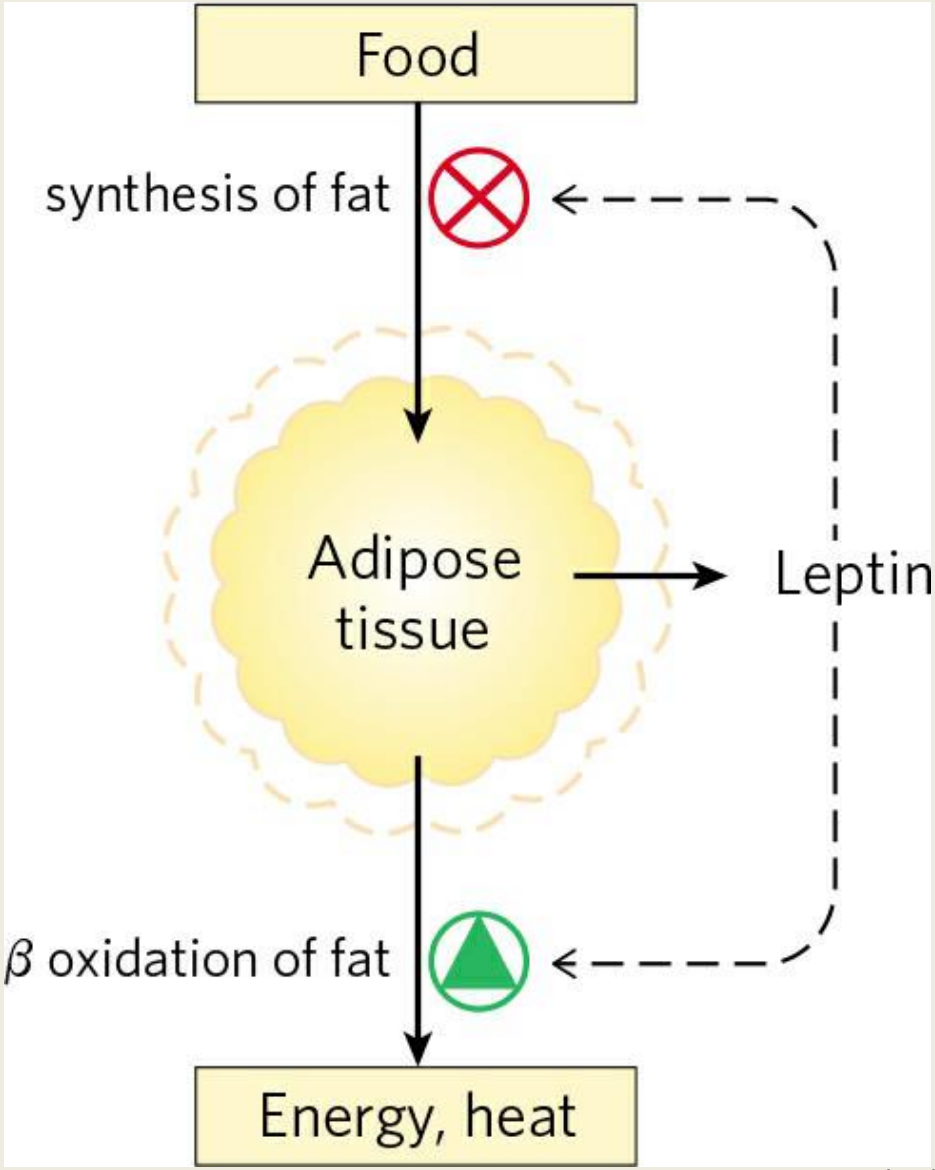


Association of fatty acids with insulin resistance



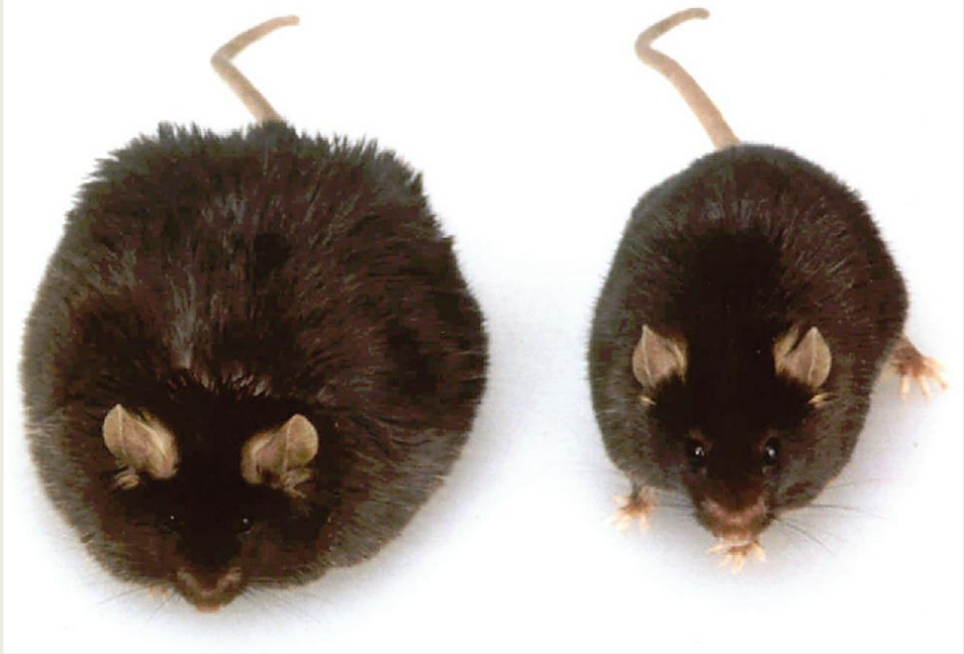
Obesity

- **Set-point model for maintaining constant mass.**
- **When the mass of adipose tissue increases, released leptin inhibits feeding and fat synthesis and stimulates oxidation of fatty acids.**
- **When the mass of adipose tissue decreases, lowered leptin production favors greater food intake and less fatty acid oxidation.**



Obesity

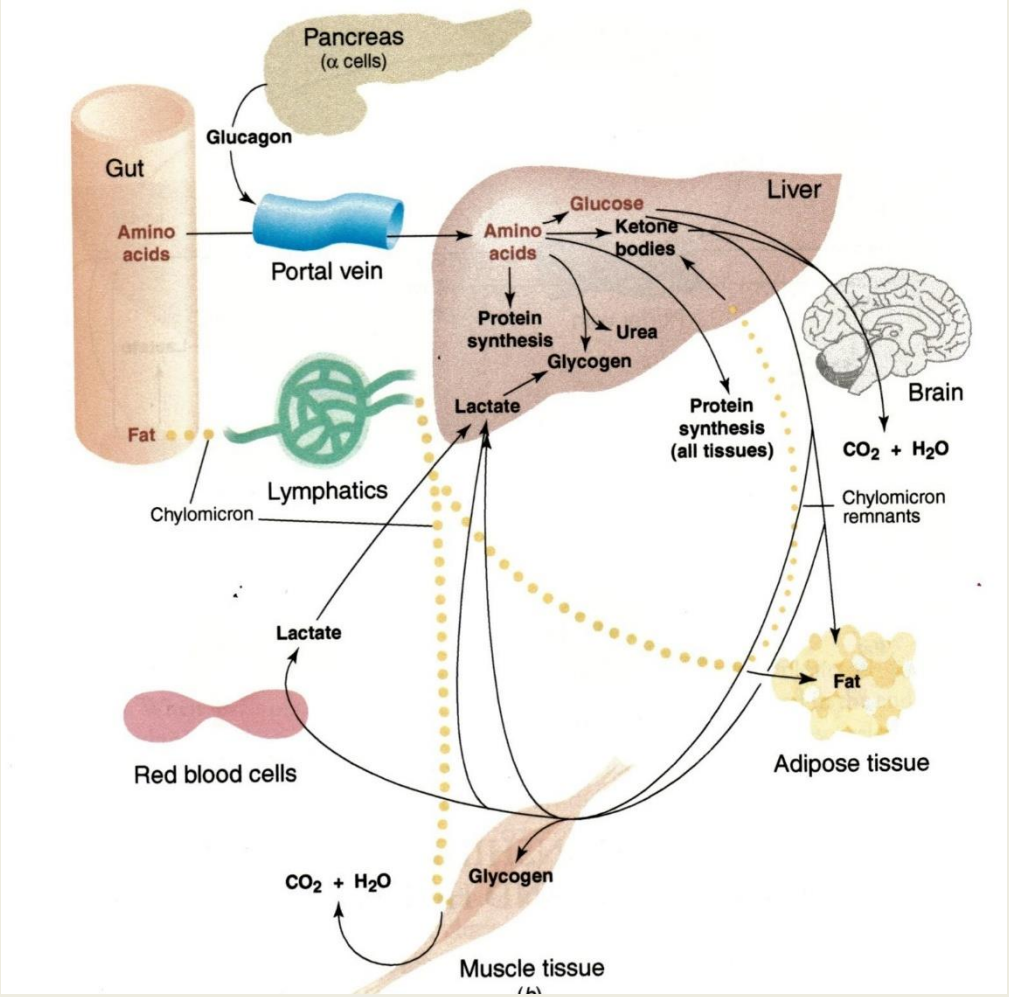
- Leptin (Greek leptos, “thin”) is an adipokine (167 amino acid residues)
- reaching the brain, acts on receptors in the hypothalamus to suppress appetite.
- Mice with two defective copies of this gene (ob/ob genotype) show the behavior and physiology of animals in a constant state of starvation
- plasma cortisol levels are elevated
- They exhibit unrestrained appetite
- They are unable to stay warm,
- They grow abnormally large
- They do not reproduce.
- They weigh as much as three times more than normal mice



Obesity caused by defective leptin production. defects in the *OB* gene. The mouse on the right was injected daily with purified leptin and weighs 35 g. The mouse on the left got no leptin and consequently ate more food and was less active;.
[Source: The Rockefeller University/AP Photo.]

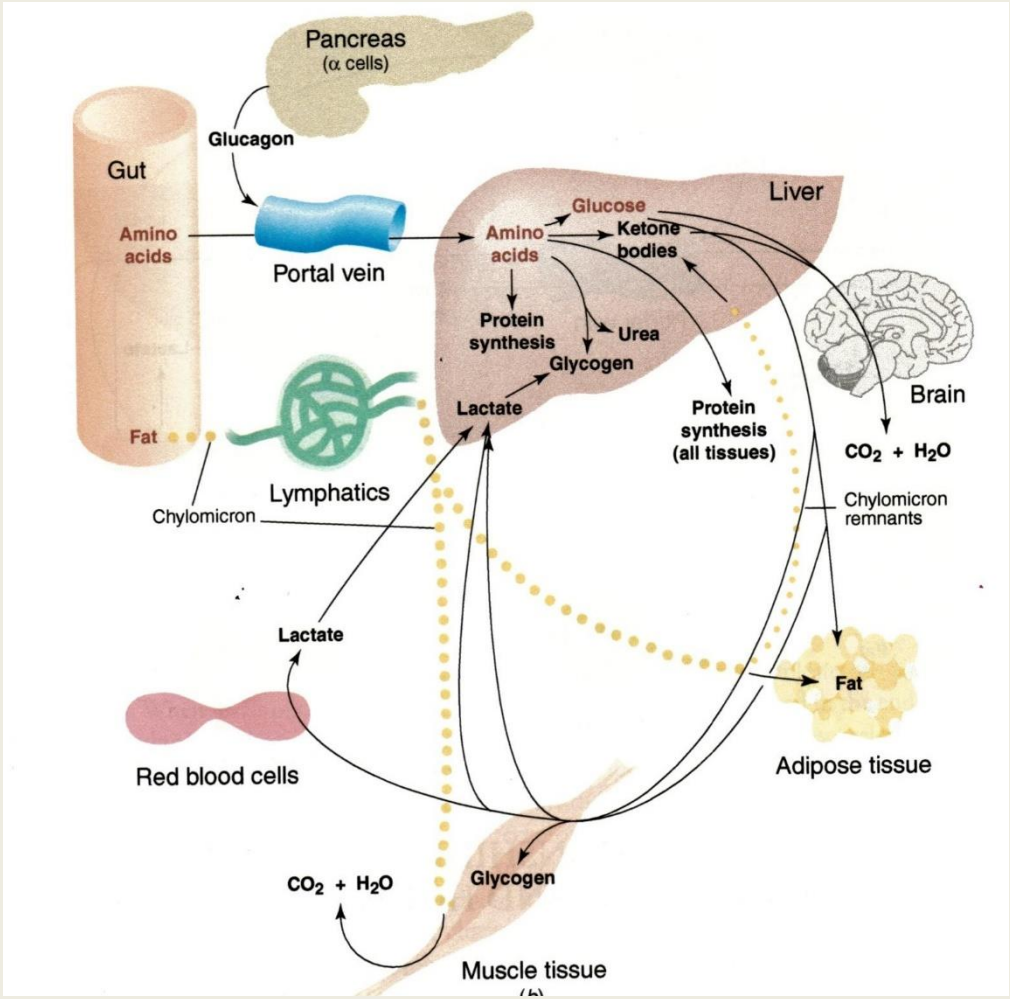
Dieting

- Losing weight requires a negative energy balance
- Short length of the well-fed state
- Less glycogen and TGs stored
- Switch sooner to the fasting state (Unless carbohydrates compensate for fat intake)
- *Ketogenic diet* (extremely low carbohydrate, moderate fat and high protein)



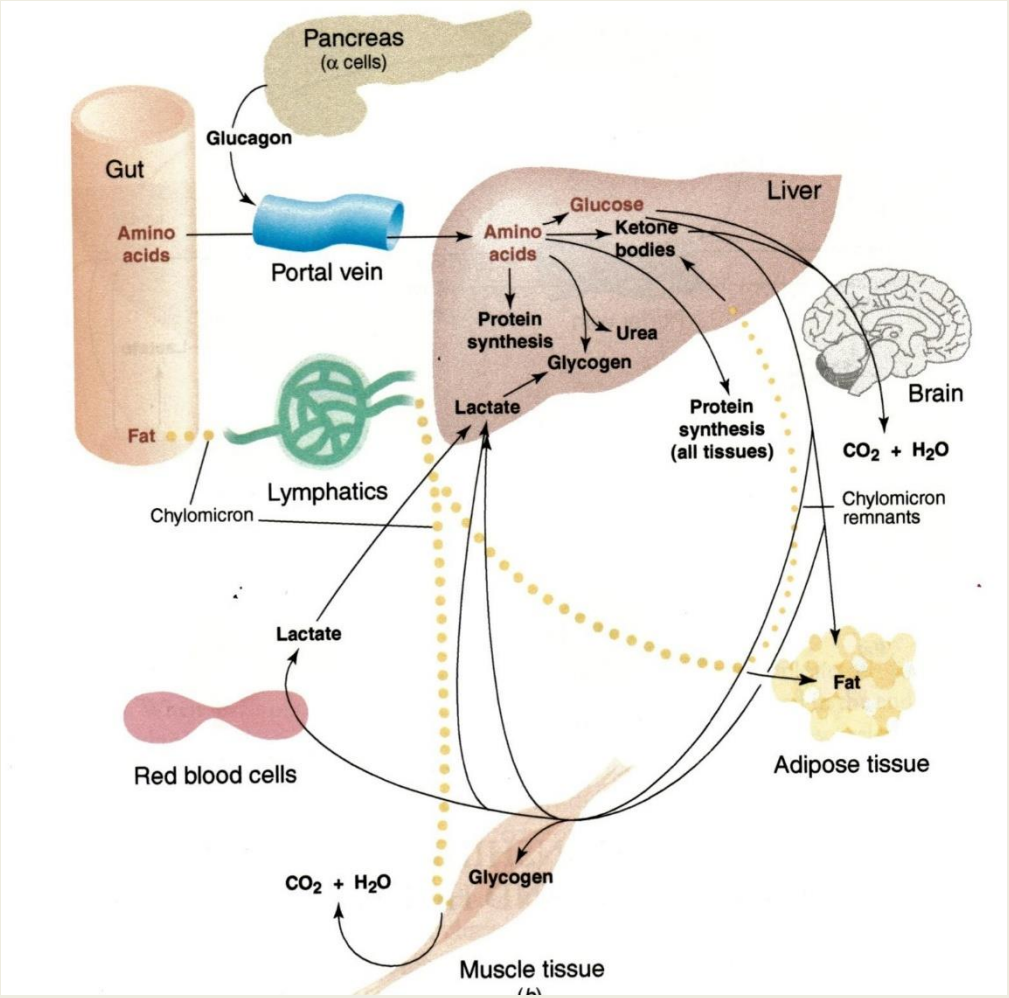
Dieting

- *Ketogenic diet*
- Gluconeogenic liver (well-fed state)
- Ketogenic liver (well-fed state)
- Little rise in glucose and insulin
- Amino acids are converted to glycogen, blood glucose and ketone bodies following protein synthesis
- Amino acids arrive to the liver from nutrients
- Chylomicron remnants to the liver – ketone bodies for ATP - gluconeogenesis



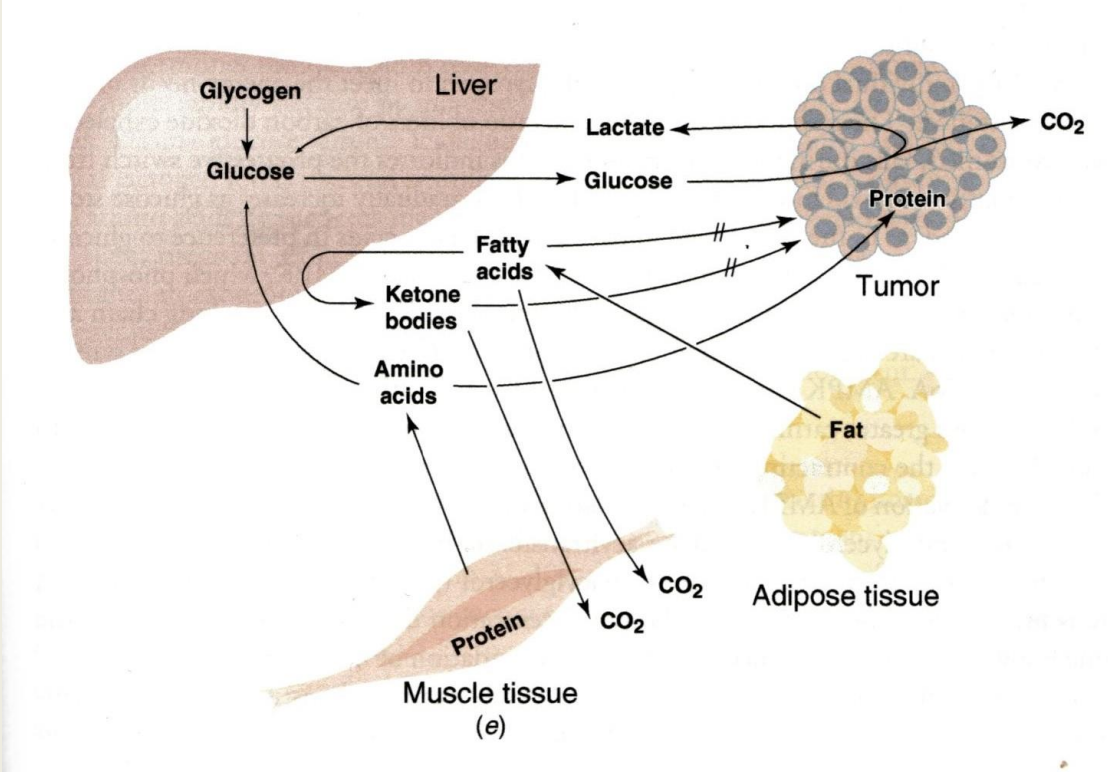
Dieting

- Glucose and ketones are produced both in the fasting and fed state
- Ketone bodies production balances the need for them by peripheral tissues
- Does not increase blood lipids



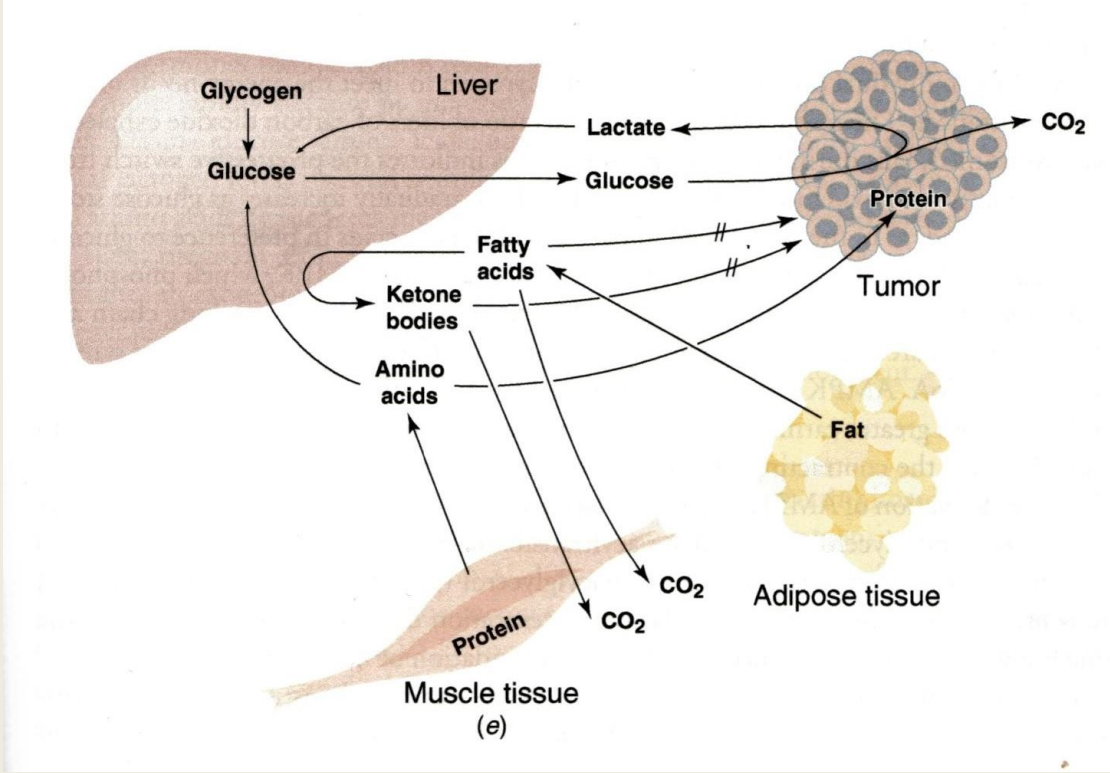
Cancer

- Tumors function independently from the starve-feed cycle
- Tumors continuously demand glucose for energy and amino acids for protein synthesis
- Tumors prefer glucose, not fat or ketone bodies
- Unresponsive to hormonal changes



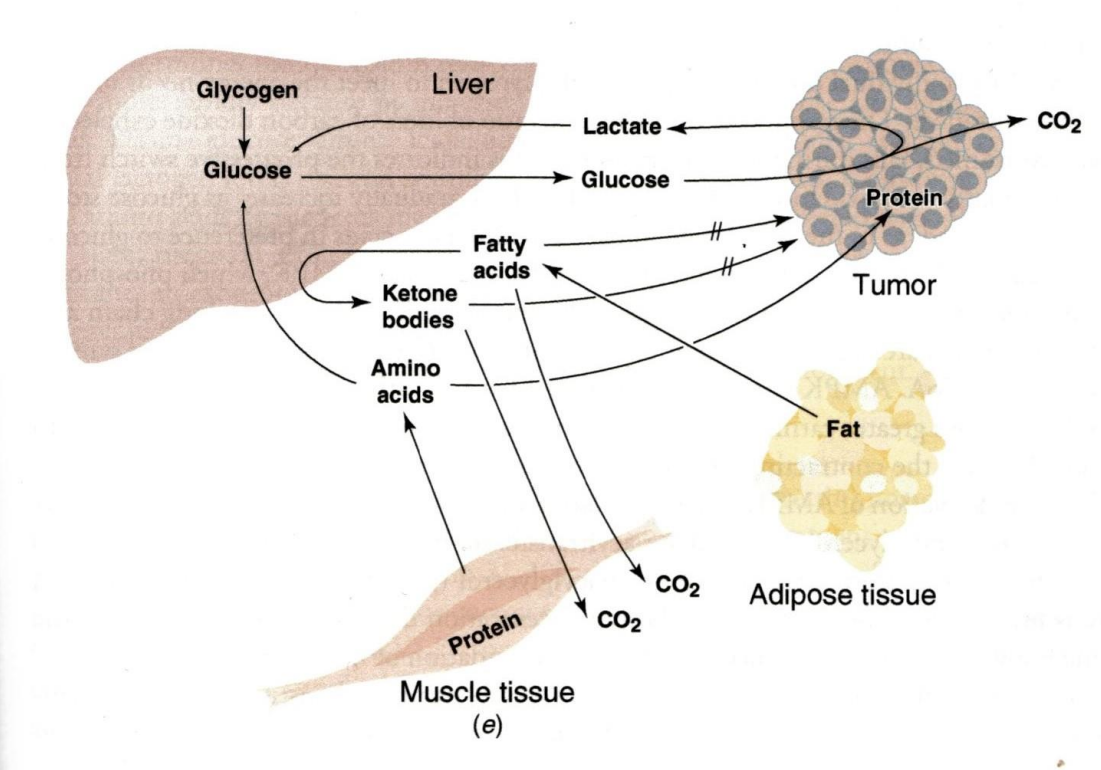
Cancer

- Cori cycle with the liver
- They can still oxidize glucose
- Hypoxia of core cancer cells
- Induction of hypoxia-inducible factor 1α (HIF-1α)
- Genes encoding glucose transporters, enzymes of glycolysis, inactivation of the PDH complex
- Constitutively active due to mutations
- ATP generation from glycolysis



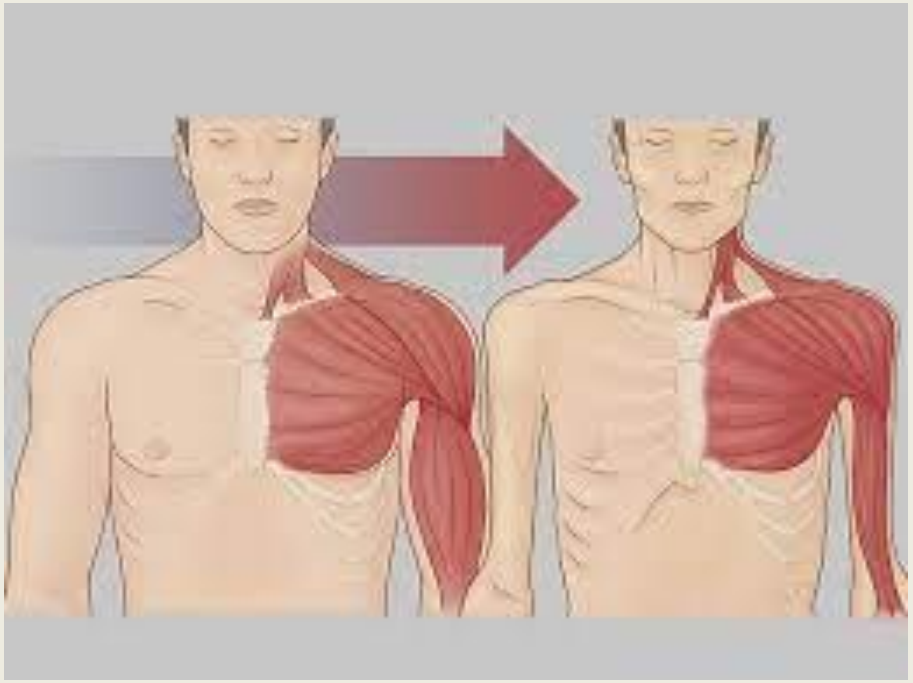
Cancer

- Glycolysis without complete oxidation
- Cancer dysregulation
- Reduces production of ROS
- They survive and invade in low oxygen status



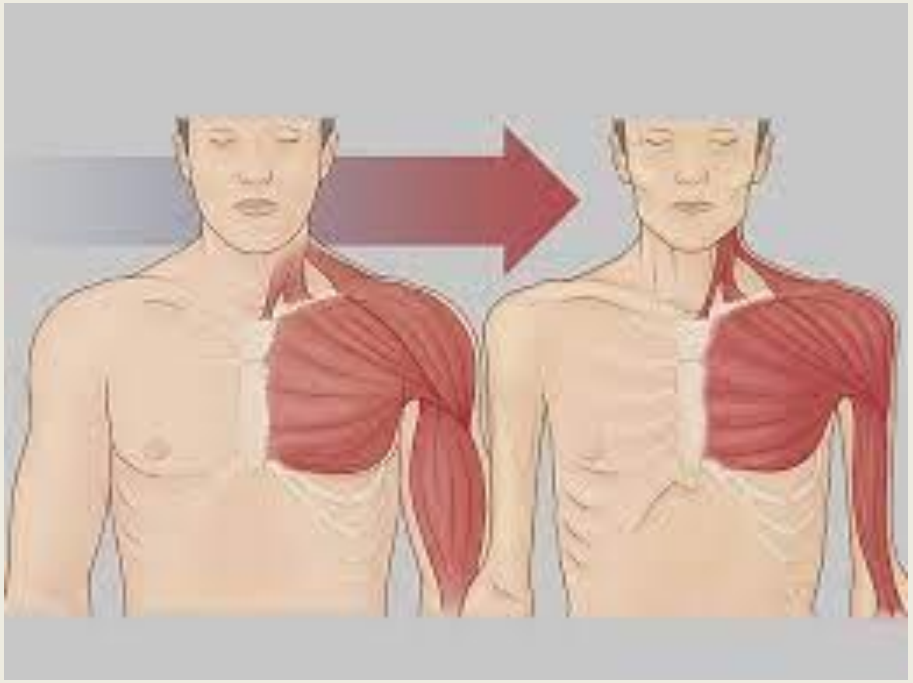
Cancer

- Cancer cachexia
- Unexplained weight loss
- Weight loss in advanced cancer
- Loss of skeletal muscle and adipose tissue
- Preservation of liver, kidney and heart protein
- Skeletal muscle: protein degradation by lysosomes, cytosolic proteins and the ubiquitin-proteasome pathway



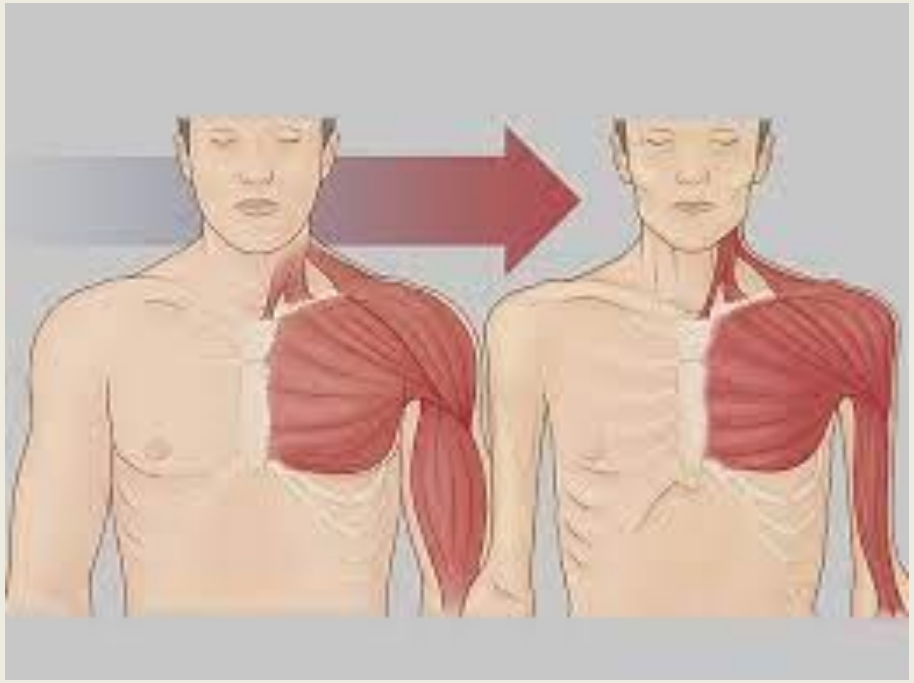
Cancer

- Endocrine abnormalities
- Insulin resistance
- Higher cortisol levels
- Higher metabolic rate
- Tumors secrete peptides such as ACTH, NGF, IGFs – modification of energy metabolism
- Immune cells: IL-1, IL-6, IFN-γ, TNFα
- TNFα (cachexin) – causes wasting



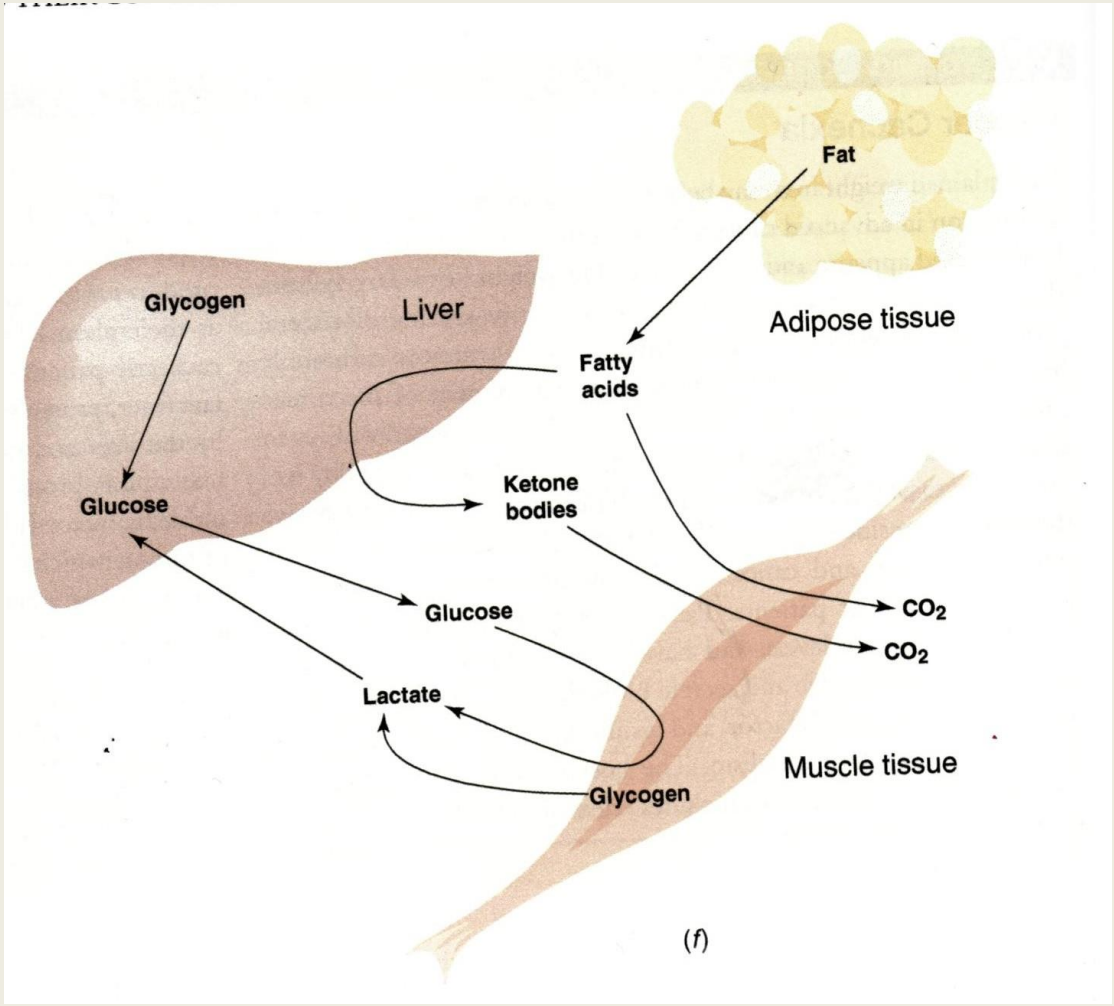
Cancer

- Cytokines stimulate fever, protein break down, fat break down
- Proteolysis-inducing factor (PIF)
- Lipid mobilizing factor (LMF)
- Skeletal protein catabolism
- Wasting of adipose tissue



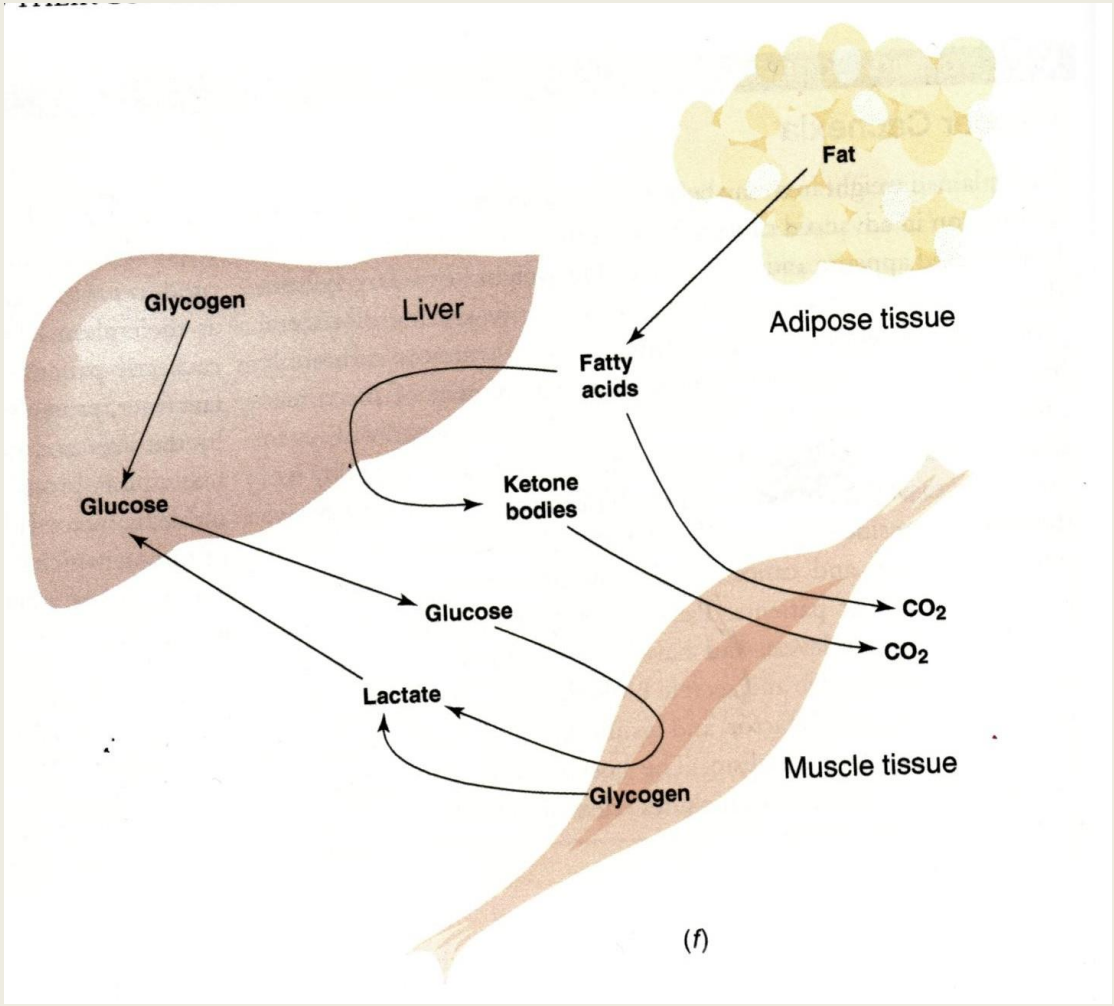
Exercise

- Anaerobic exercise (sprinting or weight-lifting)
- Cells rely on their own glycogen and phosphocreatine – little interorgan cooperation
- Aerobic exercise – glycolysis for ATP
- Glycolysis of muscle glycogen
- Increase of glucose uptake (GLUT4 translocate to the plasma membrane)



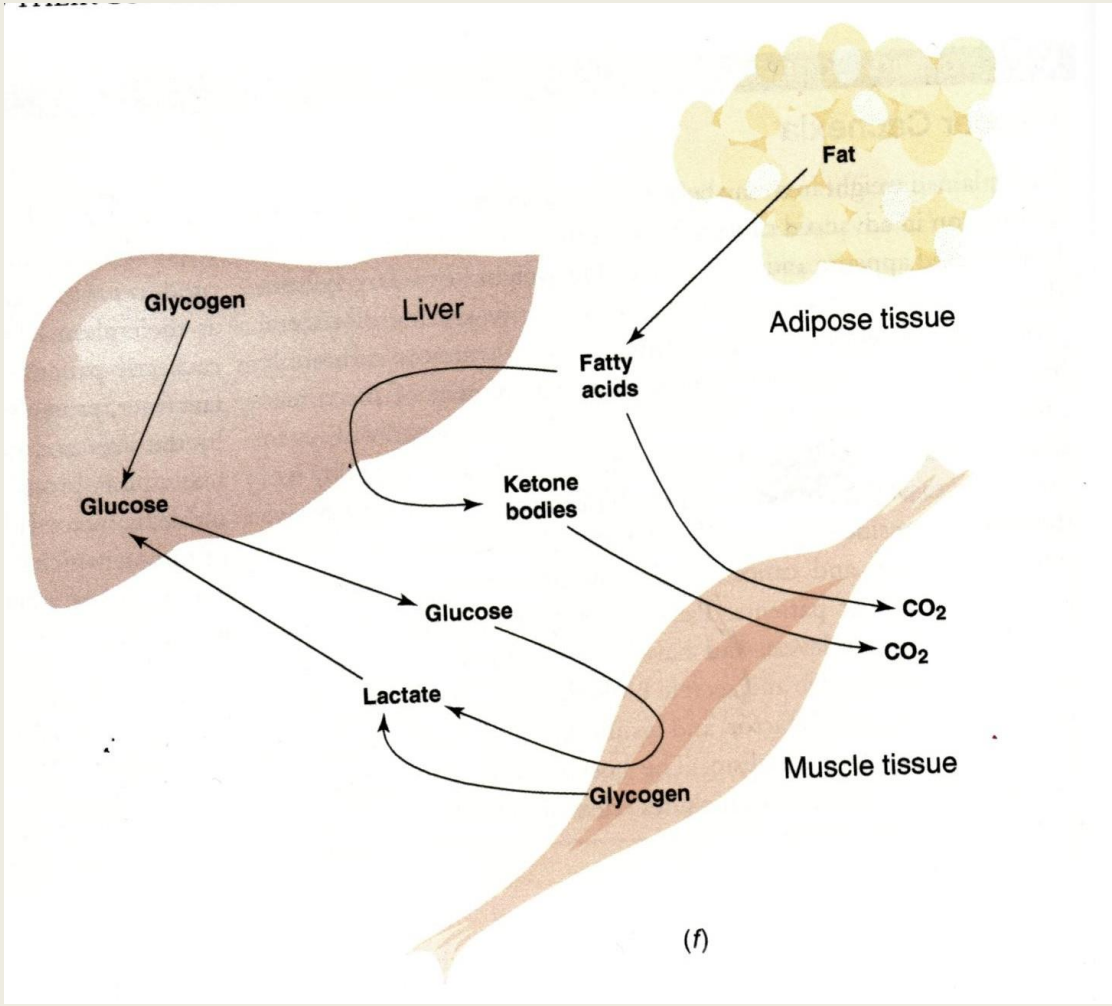
Exercise

- Decrease in ATP (muscle contraction)
- Higher AMP
- AMP/AMPK
- AMP (allosteric effector) – activates glycogen phosphorylase, PFK-1 and AMPK
- ATP for muscle contraction
- Branched-chain amino acid oxidation, ammonium, alanine release



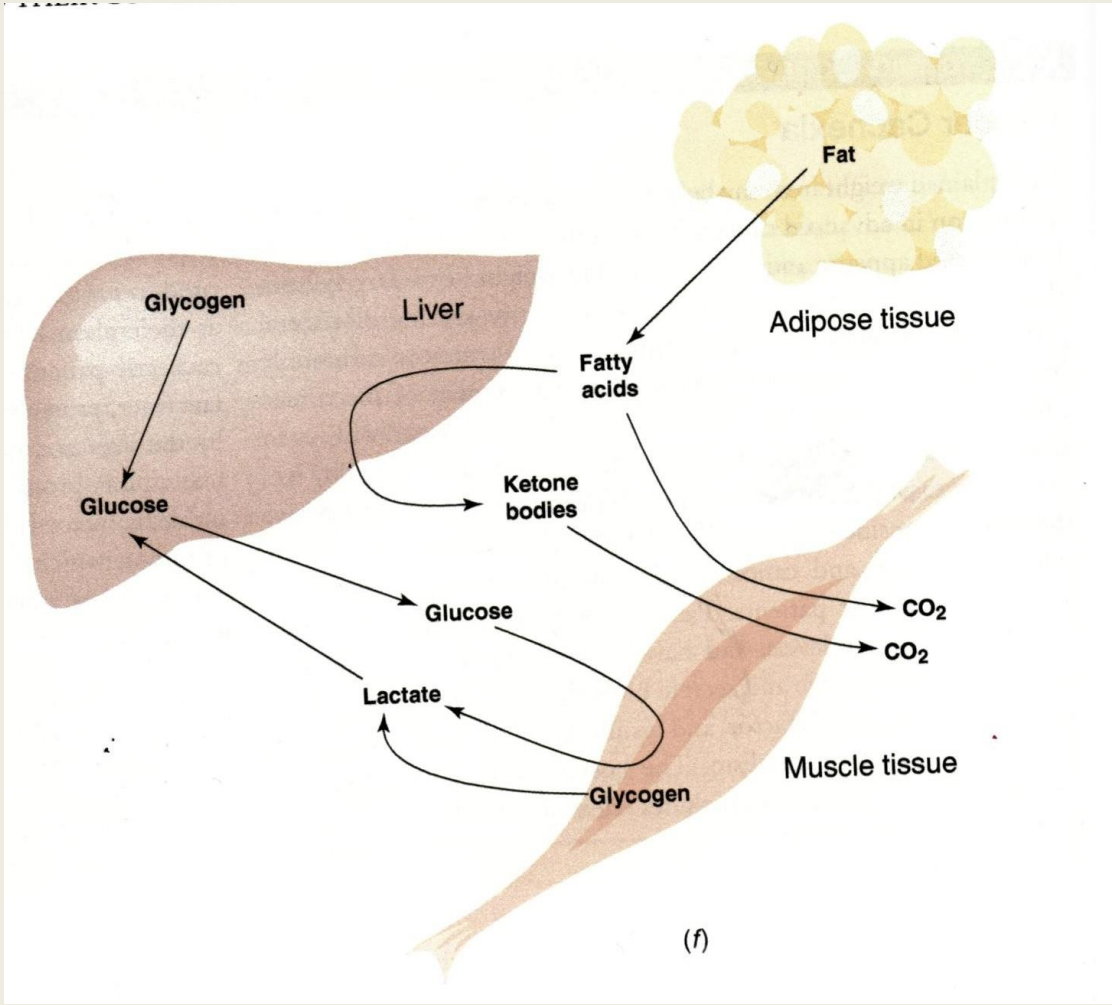
Exercise

- Long distance run
- Glycogen is not enough
- Switch from glycogen to fatty acid oxidation
- Muscles oxidize fatty acids
- AMP/AMPK – inactivation of acetyl-CoA carboxylase
- Reduction of malonyl-CoA
- Fatty acid oxidation



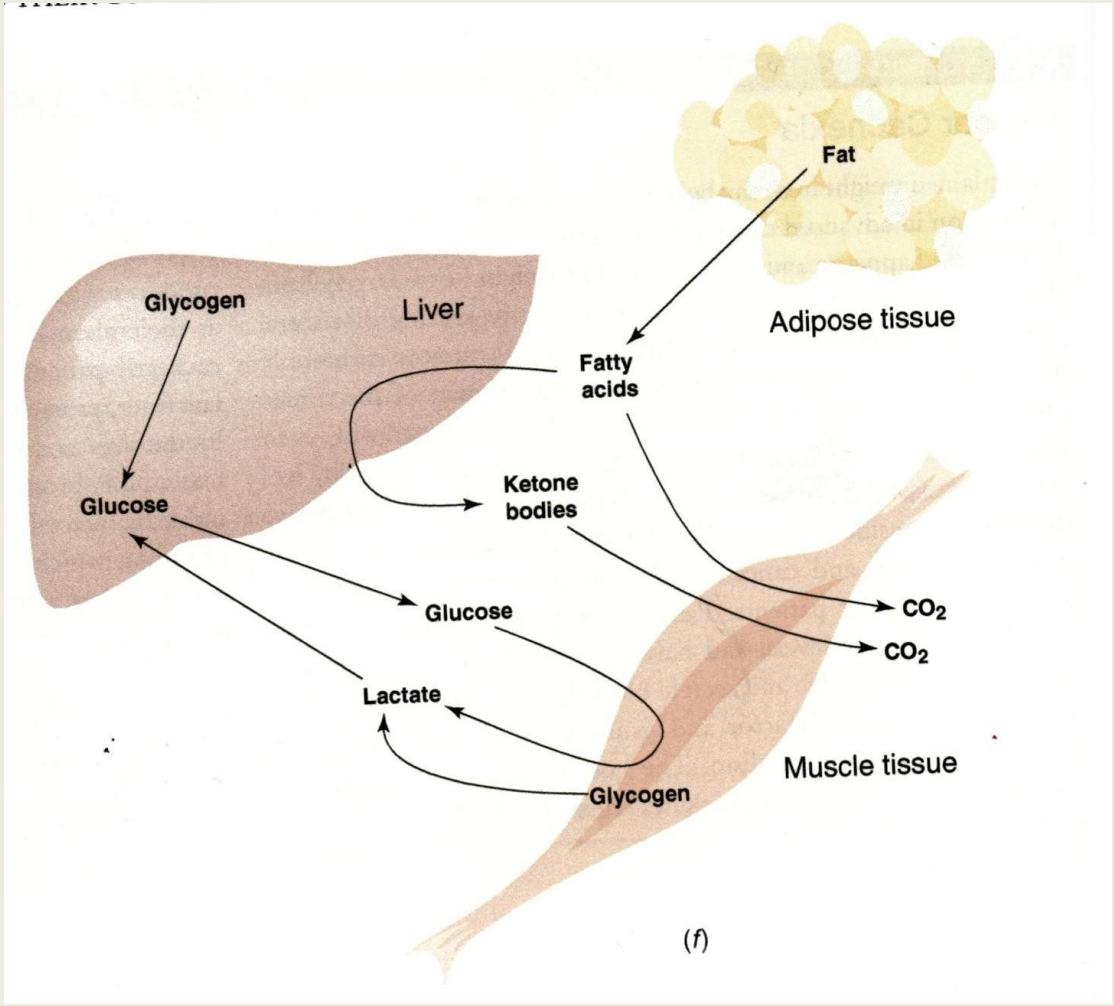
Exercise

- Oxidation of fatty acids instead of formation of triacyglycerols
- Little increase in blood ketone
- They are consumed by muscle ketone break down for energy
- High lactate levels in exhaustive exercise, especially in anaerobic exercise
- High lactate production/lactate of gluconeogenesis ratio



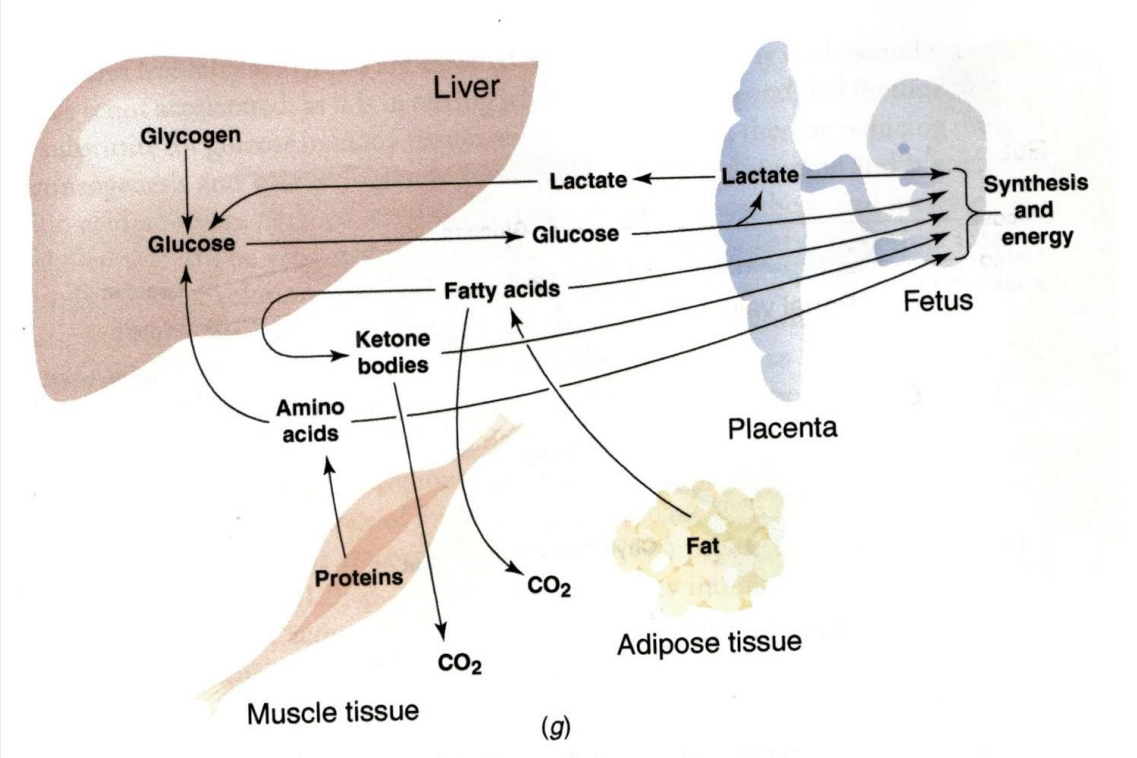
Exercise

- High blood lactate levels pass through the BBB (blood brain barrier – fuel)
- Prevents energy consumption for conversion of lactate to glucose



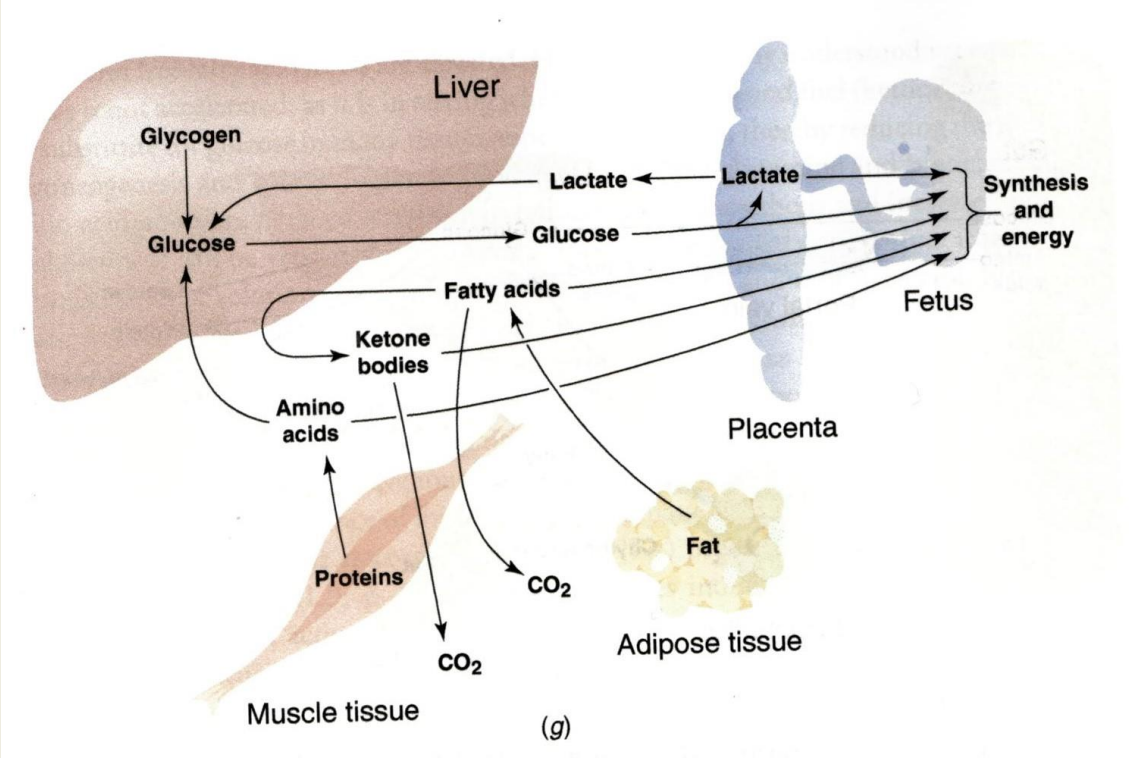
Pregnancy

- The fetus is a nutrient-requiring organism
- Mainly glucose
- Amino acids
- Lactate
- Fatty acids
- Ketone bodies
- Lactate is produced in the placenta by glycolysis
- 1. lactate to the fetus
- 2. Cori cycle with the mother's liver



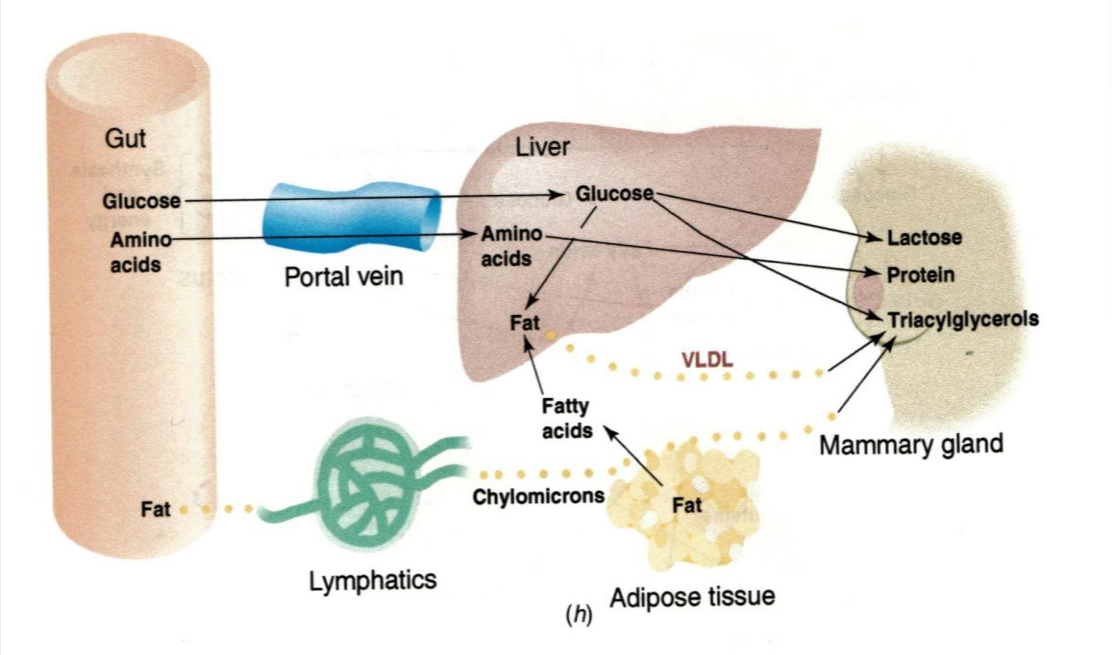
Pregnancy

- Placental lactogen – lipolysis in adipose tissue
- steroid hormones (estradiol and progesterone) induce insulin resistance
- Rapidly to the fasting state (consumption by the fetus)
- Decrease of plasma glucose, amino acids and insulin levels
- Increase of glucagon and placental lactogen
- Stimulation of lipolysis and ketogenesis
- Consumption of glucose and amino acids by the fetus – maternal hypoglycemia



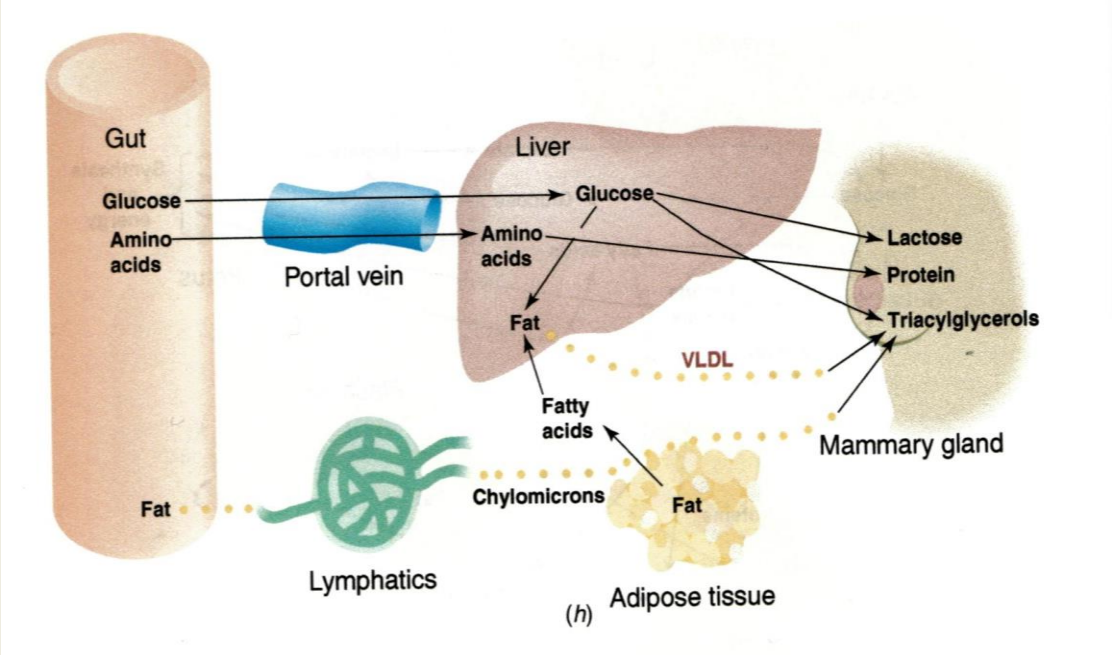
Lactation

- Breast tissue uses glucose for lactose and triglycerides
- Amino acids for protein synthesis
- VLDLs and chylomicrons for triacylglycerols synthesis
- Fasting state
- Proteolysis
- Gluconeogenesis
- Lipolysis
- Maternal malnutrition – milk of poor quality



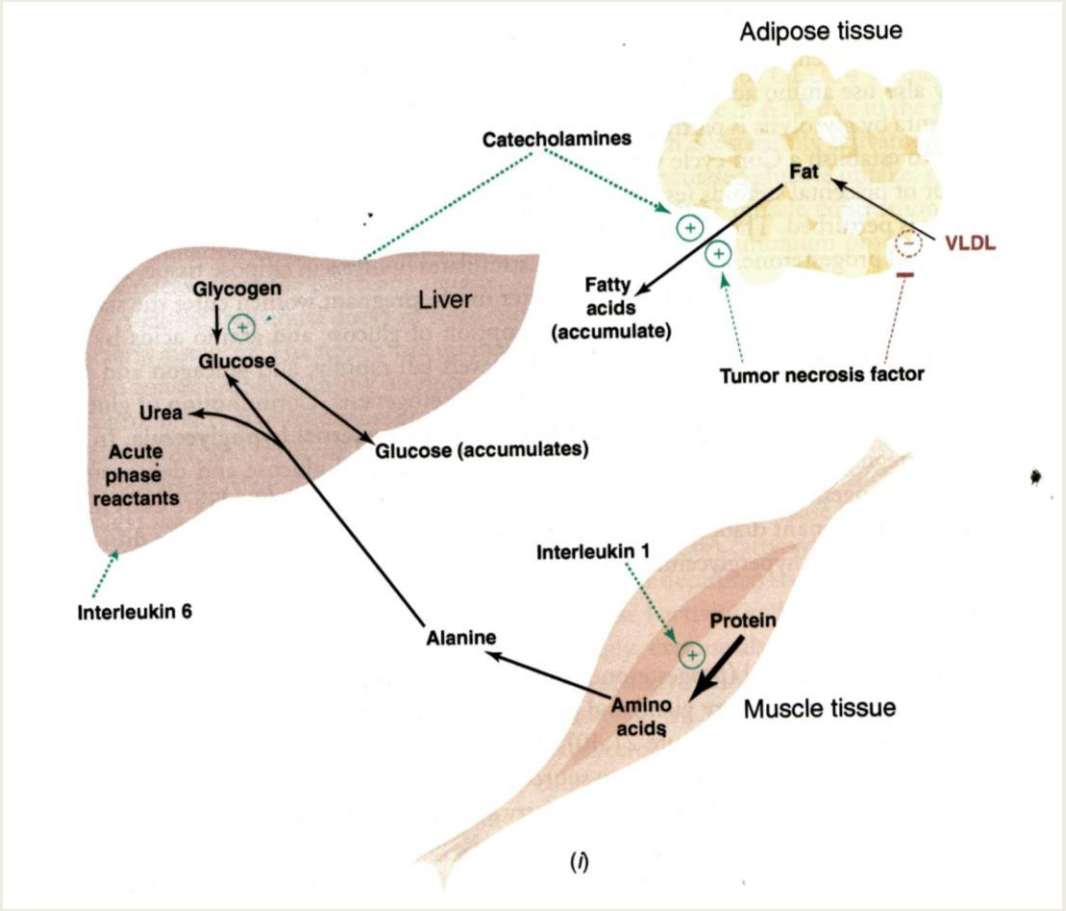
Lactation

- Parathyroid hormone-related protein (PTHrP)
- Mimics PTH
- Absorption of calcium and phosphorus from the gut and bone
- Calcium sensing receptor



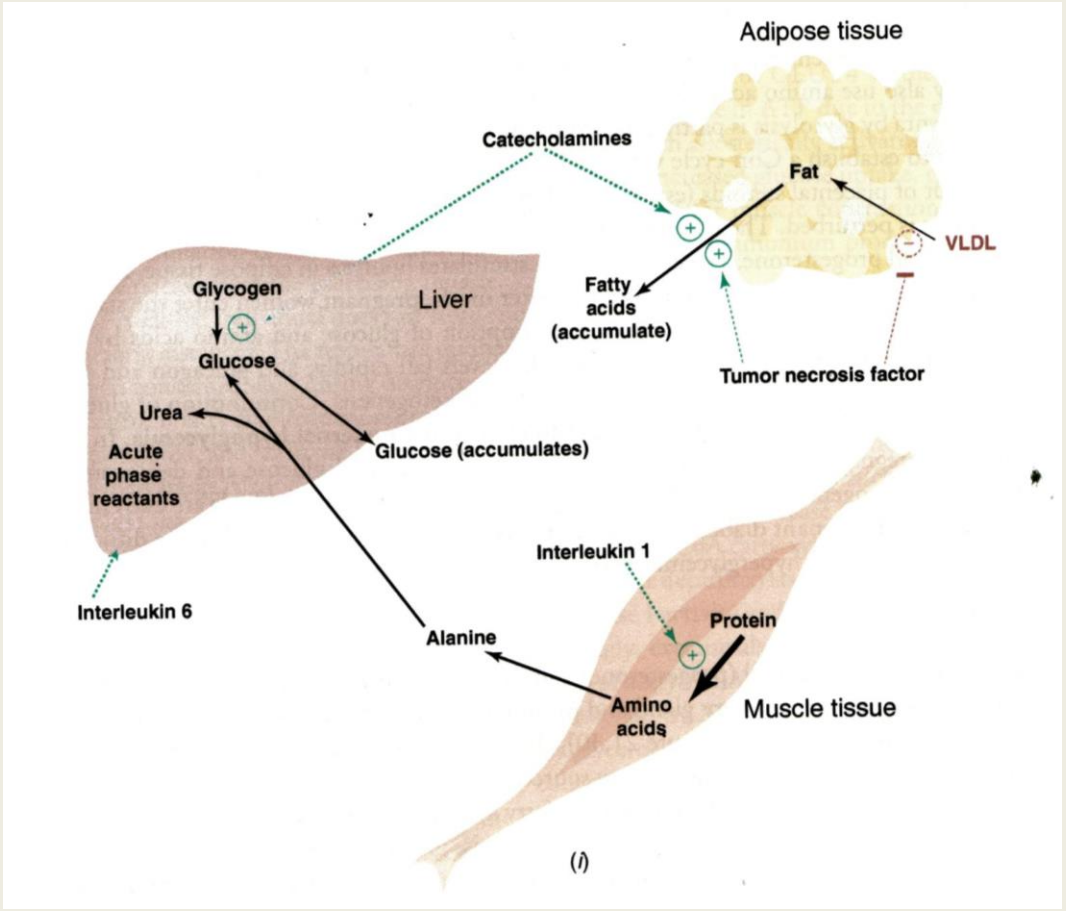
Stress and Injury

- Stresses: injury, surgery, renal failure, burns, infections
- Increase of
  - Blood cortisol
  - Glucagon
  - Catecholamines
  - Growth hormone
- Resistance to insulin
- Elevated
  - Metabolic rate
  - Blood glucose
  - Free fatty acids
- ~~Ketogenesis~~



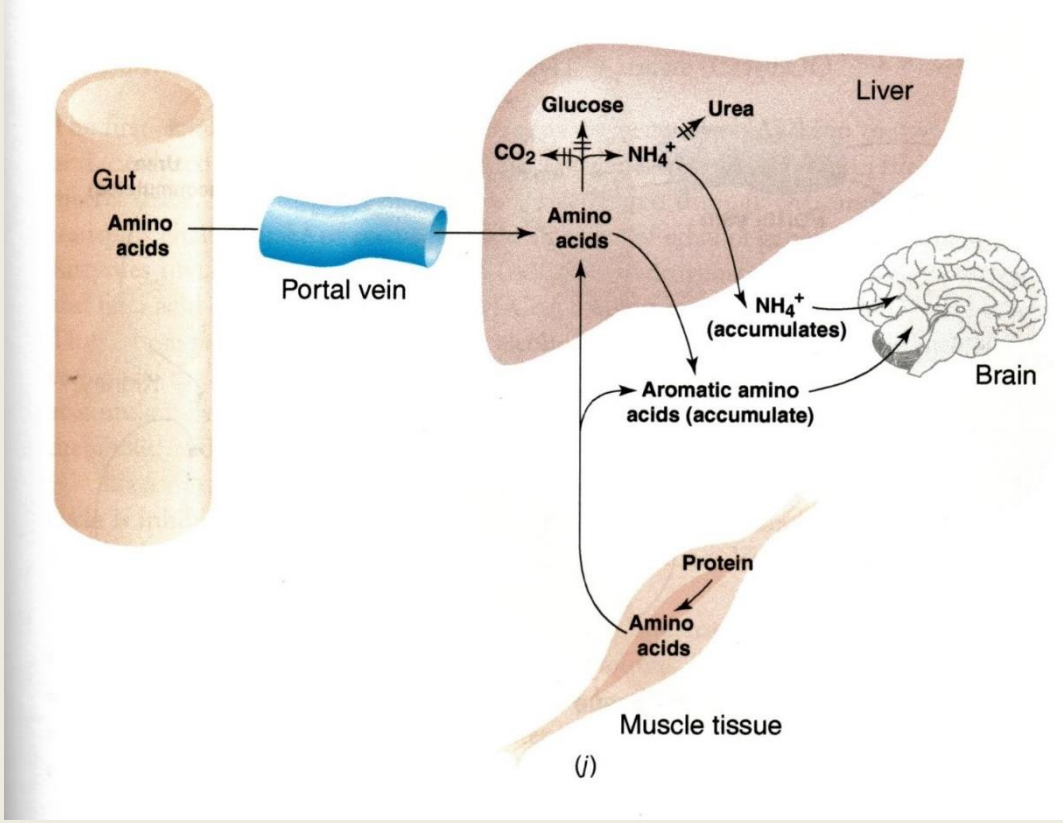
Stress and Injury

- Reduced protein synthesis
- Increased protein breakdown
- Better treatment with enteral feeding than intravenous feeding (amino acids)
- Cytokines induce
  - Proteolysis
  - Lipolysis
  - Insulin resistance
- Myopathy of chronic ICU patients (malnutrition and increased cytokines)



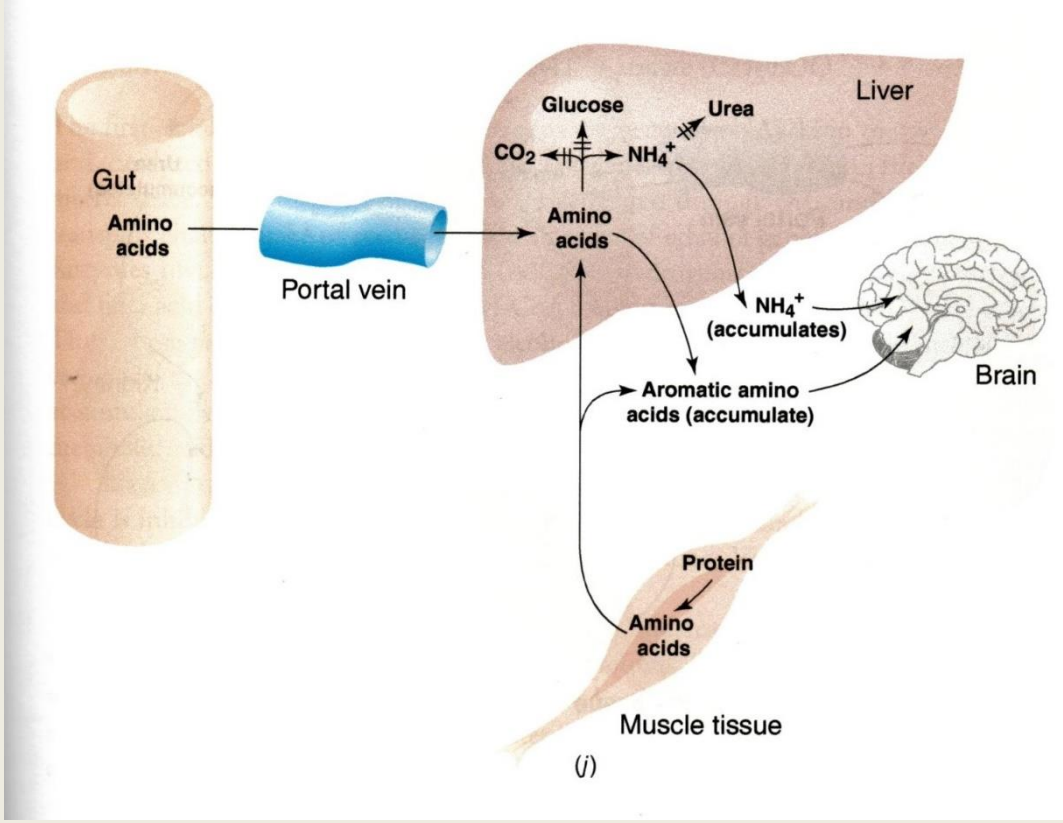
Liver disease

- Major metabolic derangements
- Cirrhosis
- Unable to convert ammonia to urea and glutamine
- High blood ammonia
- Shunting of blood around the liver – disturbed intercellular glutamine cycle
- Ammonia production: glutaminase, glutamate in intestine and liver
- Intestine: bacterial urease produces ammonia from urea



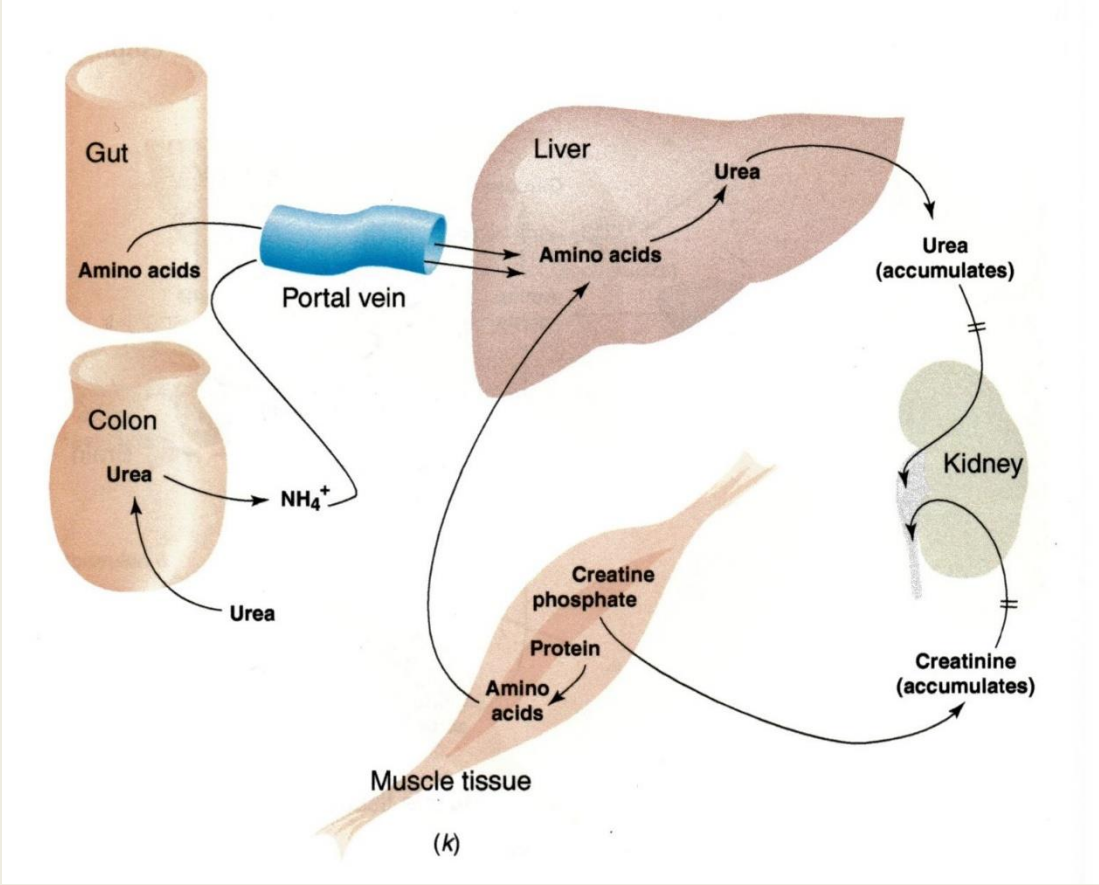
Liver disease

- High ammonia levels after upper GI bleeding (unusual amino acid composition of hemoglobin)
- Reduction in plasma isoleucine
- High ammonia in liver failure
- Comma
- Muscle wasting because of deficiency of IGF-1
- Decrease of branched-chain aa, increase of aromatic aa – brain abnormalities
- hypoglycemia



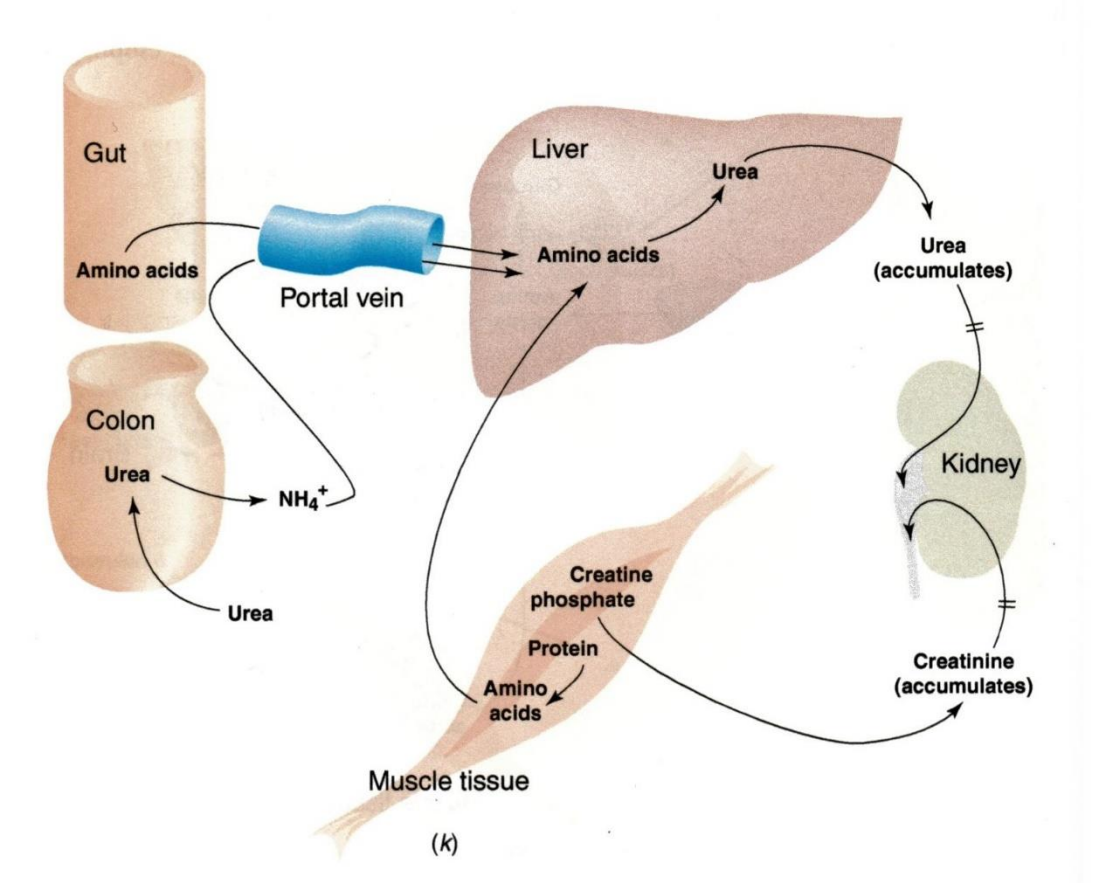
Renal disease

- Chronic renal disease
- Increase of aminoacids metabolized by kidney (glutamine, glycine, proline, citrulline)
- Increase of nitrogen end products (urea, uric acid, creatinine)
- Diet high in protein – increased proteolysis
- Diet high in carbohydrates and adequate in essential aminoacids – liver synthesizes nonessential aminoacids



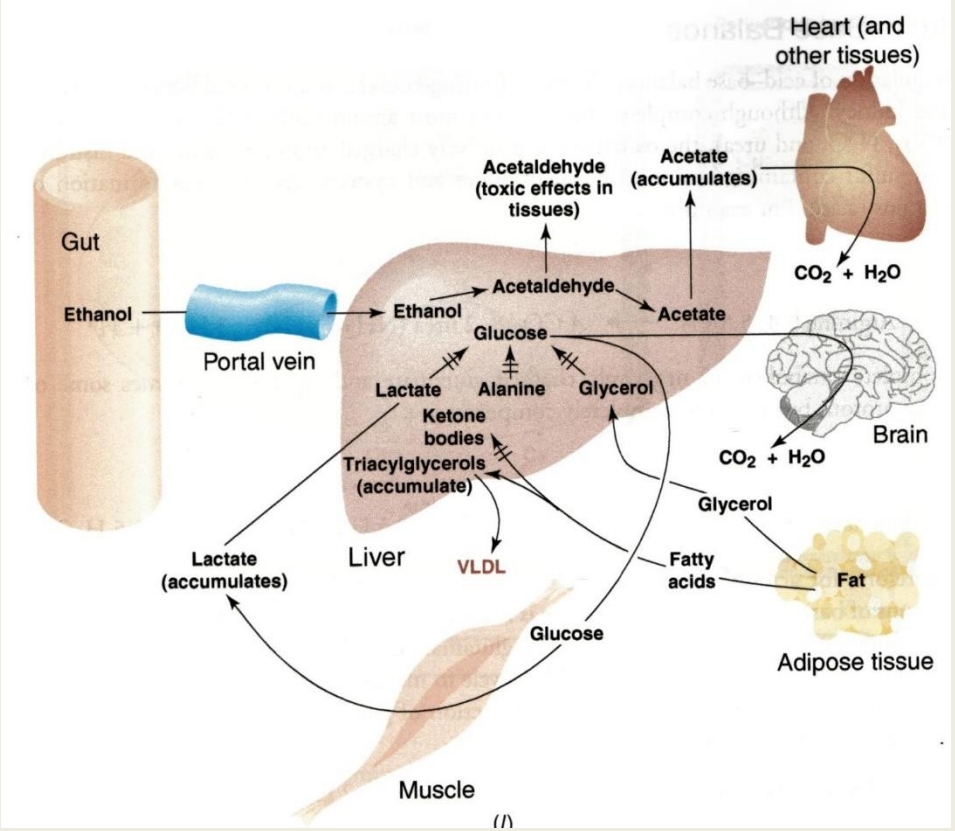
Renal disease

- Carnitine deficiency
- Cardiac and skeletal myopathy – reduced ability of these tissues to oxidize fatty acids



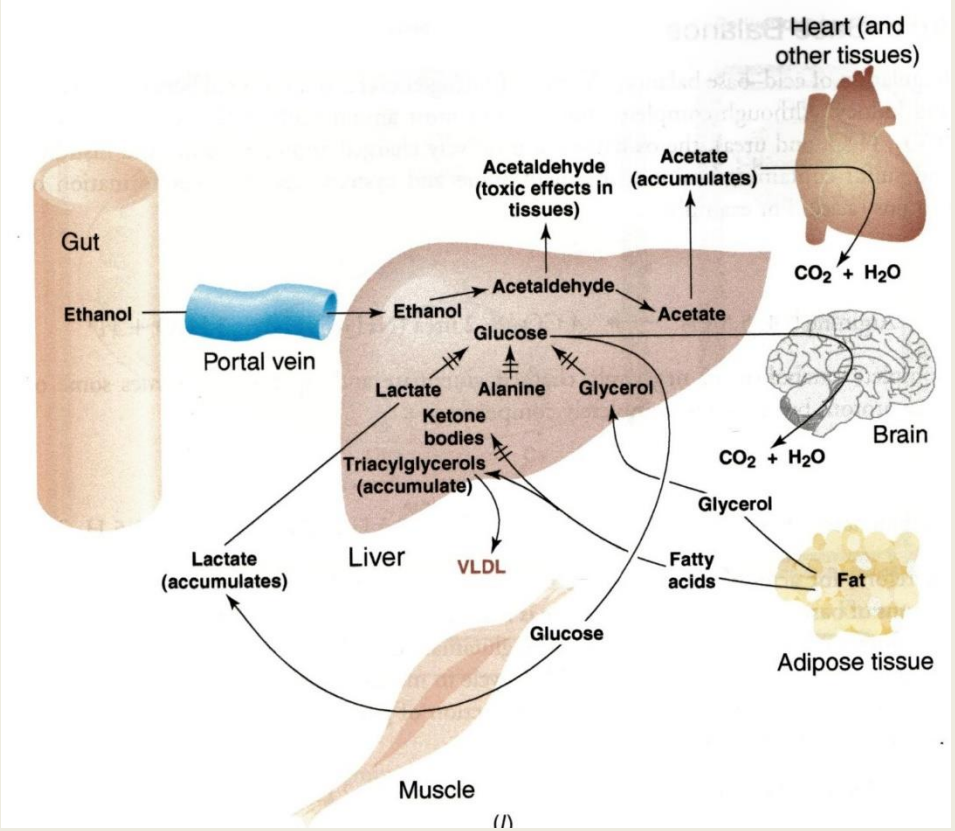
Alcohol consumption

- Liver – ethanol catabolism
- Ethanol + NAD=acetaldehyde + NADH + H
- Acetaldehyde + NAD +H2O=acetate + NADH + 2H
- NADH inhibits gluconeogenesis and fatty acid oxidation
- Fasting hypoglycemia
- Fatty liver (accumulation of triglycerides)



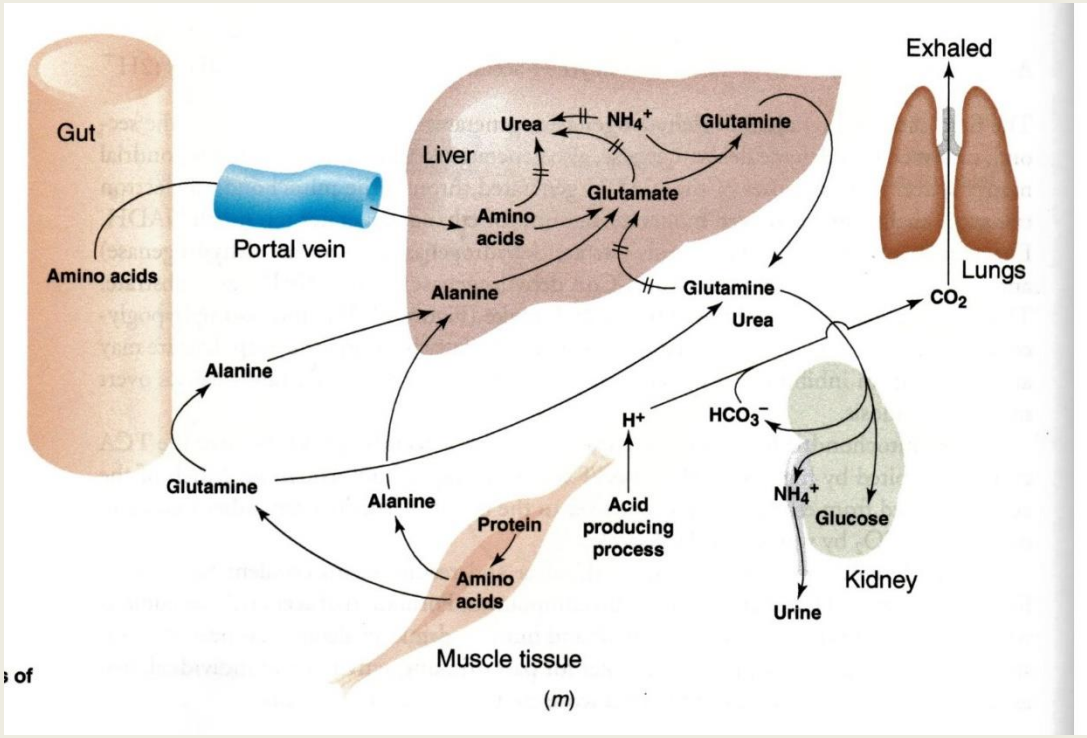
Alcohol consumption

- High lactate
- Limited capacity to oxidize acetate
- Blood circulation
- Acetaldehyde adducts with proteins



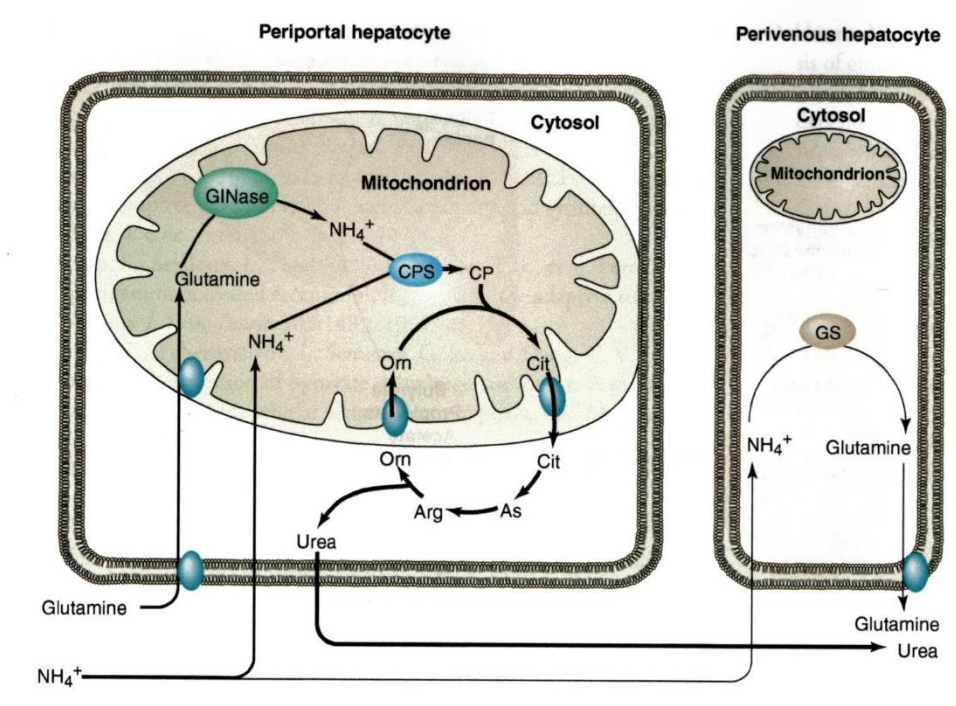
Acid-Base Balance

- Acid-base balance (liver and kidney)
- Catabolism of positively charge aa (arginine, lysine, histidine, methionine, cysteine) – acids
- Glutaminolysis
- Ammonium ions – urine
- CO2 - lungs



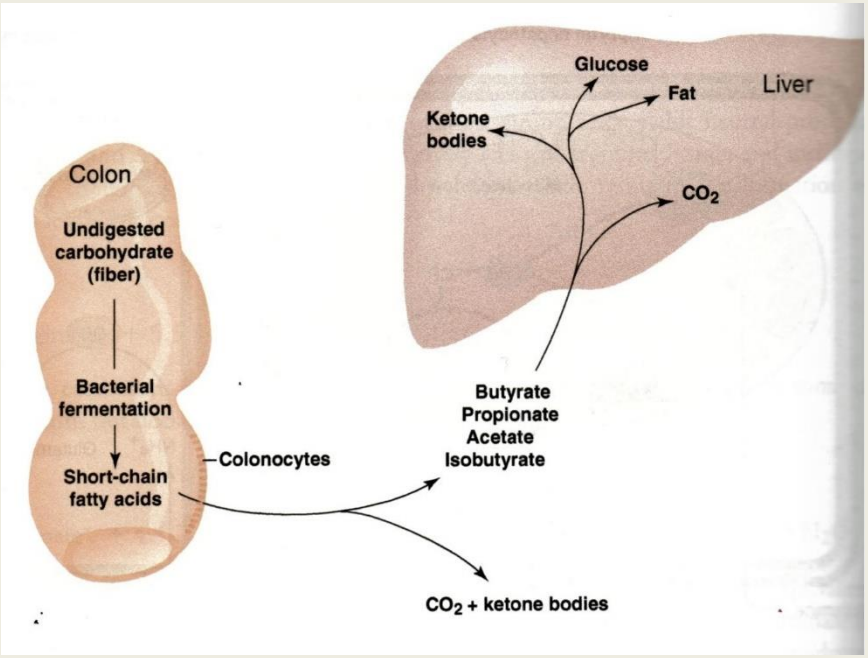
Acid-Base Balance

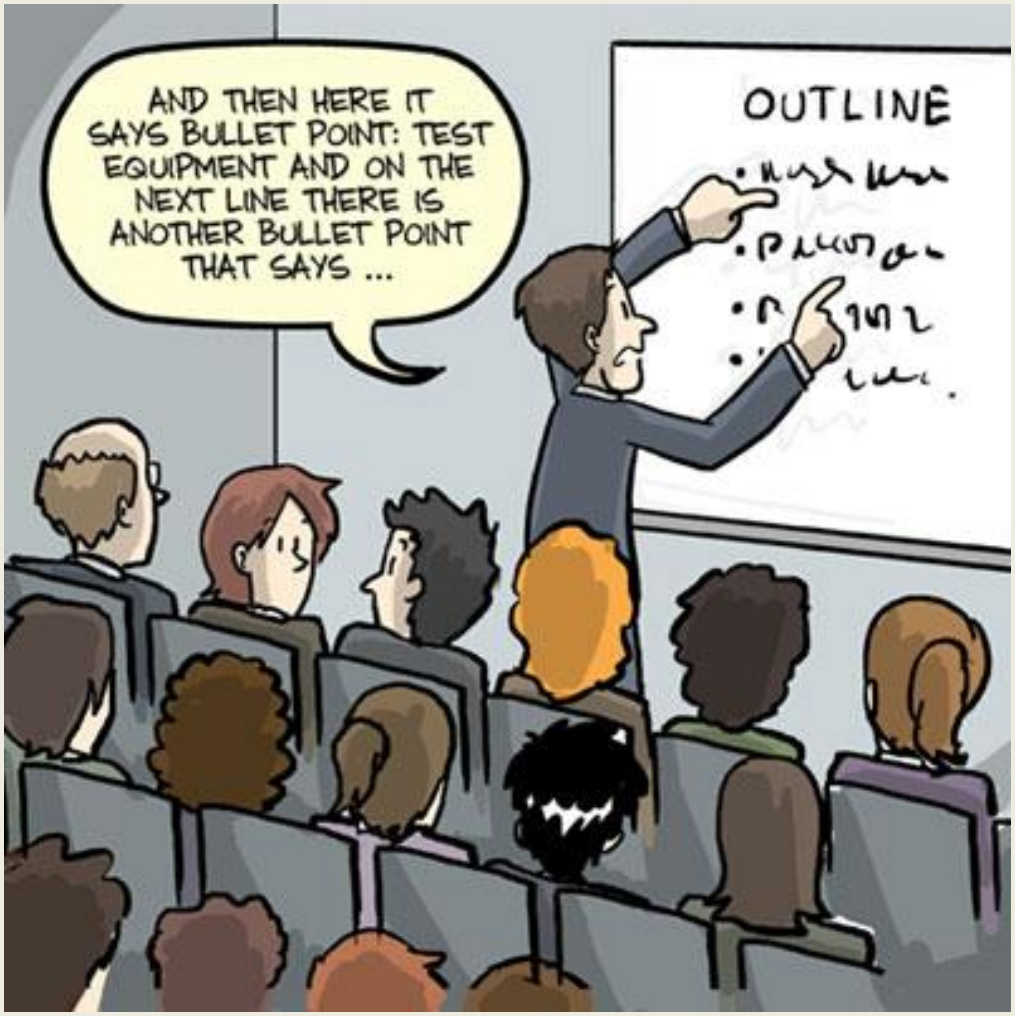
- **Intercellular glutamine cycle of the liver**



Acid-Base Balance

- **Bacterial fermentation in colon**




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

Thank you!