

THE METABOLISM OF KETONE BODIES

KETOGENESIS

CLINICAL SIGNIFICANCE OF KETOGENESIS

- **The production of ketone bodies occurs at a relatively low rate during normal feeding and under conditions of normal physiological status.**
- **Normal physiological responses to carbohydrate shortages cause the liver to increase the production of ketone bodies from the acetyl-CoA generated from fatty acid oxidation. This allows the heart and skeletal muscles primarily to use ketone bodies for energy, thereby preserving the limited glucose for use by the brain.**
- **The most significant disruption in the level of ketosis, leading to profound clinical manifestations, occurs in untreated insulin-dependent diabetes mellitus. This physiological state, diabetic ketoacidosis (DKA), results from a reduced supply of glucose (due to a significant decline in circulating insulin) and a concomitant increase in fatty acid oxidation (due to a concomitant increase in circulating glucagon).**
- **The increased production of acetyl-CoA leads to ketone body production that exceeds the ability of peripheral tissues to oxidize them.**
- **Ketone bodies are relatively strong acids (pKa around 3.5), and their increase lowers the pH of the blood. This acidification of the blood is dangerous chiefly because it impairs the ability of hemoglobin to bind oxygen.**

- It is important to note that animals are unable to convert fatty acids into glucose.
- Specifically, acetyl CoA cannot be converted into pyruvate or oxaloacetate in animals.
- The two carbon atoms of the acetyl group of acetyl CoA enter the citric acid cycle, but two carbon atoms leave the cycle in the decarboxylations catalyzed by isocitrate dehydrogenase and α -ketoglutarate dehydrogenase.
- Consequently, **oxaloacetate is regenerated but it is not formed de novo when the acetyl unit of acetyl CoA is oxidized by the citric acid cycle.**

- **REMEMBER!!** When fatty acid oxidation in the liver is uncontrolled, as in *diabetes or starvation*, ketone body production becomes excessive and life-threatening, because they are acids and lower the pH of blood.
- This condition is called *ketosis or ketoacidosis* and can often be detected by the odor of acetone on the breath.

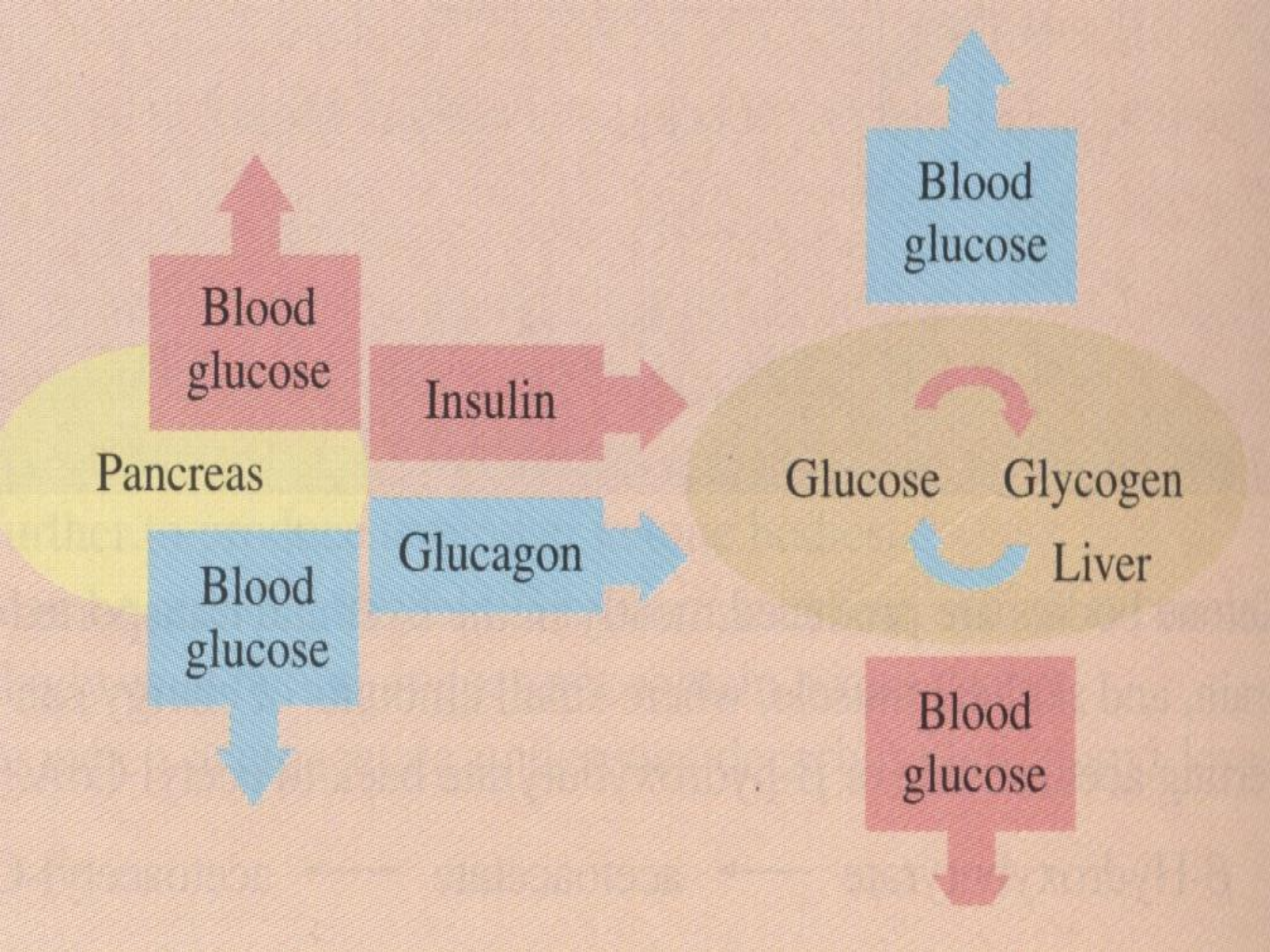
- When ketone bodies accumulate, they may not be completely metabolized by the body.
- This may lead to a condition called **ketosis**, which is found in severe diabetes, diets high in fat and low in carbohydrates, and starvation.
- **Because two of the ketone bodies are acids, they can lower the blood pH below 7.4, which is acidosis, a condition that often accompanies ketosis.**
- A drop in blood pH can interfere with the ability of the blood to carry oxygen and cause breathing difficulties.

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- **There is excessive production of ketone bodies in diabetes mellitus in DKA (diabetic ketoacidosis)**
- When the rate of formation of ketone bodies is greater than the rate of their use, **their levels begin to rise in the blood (ketonemia) and eventually in the urine (ketonuria).**
- These two conditions are seen most often **in cases of starvation or severe diabetes mellitus.**
- In diabetic individuals with severe ketosis, urinary excretion of ketone bodies may be as high as 5000 mg/24 hr, and the blood concentration may reach 90 mg/dL (versus less than 3 mg/dL in normal individuals).
- **An elevation of ketone body concentration in the blood results in acidemia.**
- The carboxyl group of a ketone body has a PKa around 4. Therefore, **each ketone body loses a proton (H⁺) as it circulates in the blood, which lowers the pH of the body.**
- **Also, excretion of glucose and ketone bodies in the urine results in dehydration of the body. Therefore, the increased number of H⁺ circulating in a decreased volume of plasma, can cause severe acidosis (ketoacidosis).**

Ketone Bodies and Diabetes

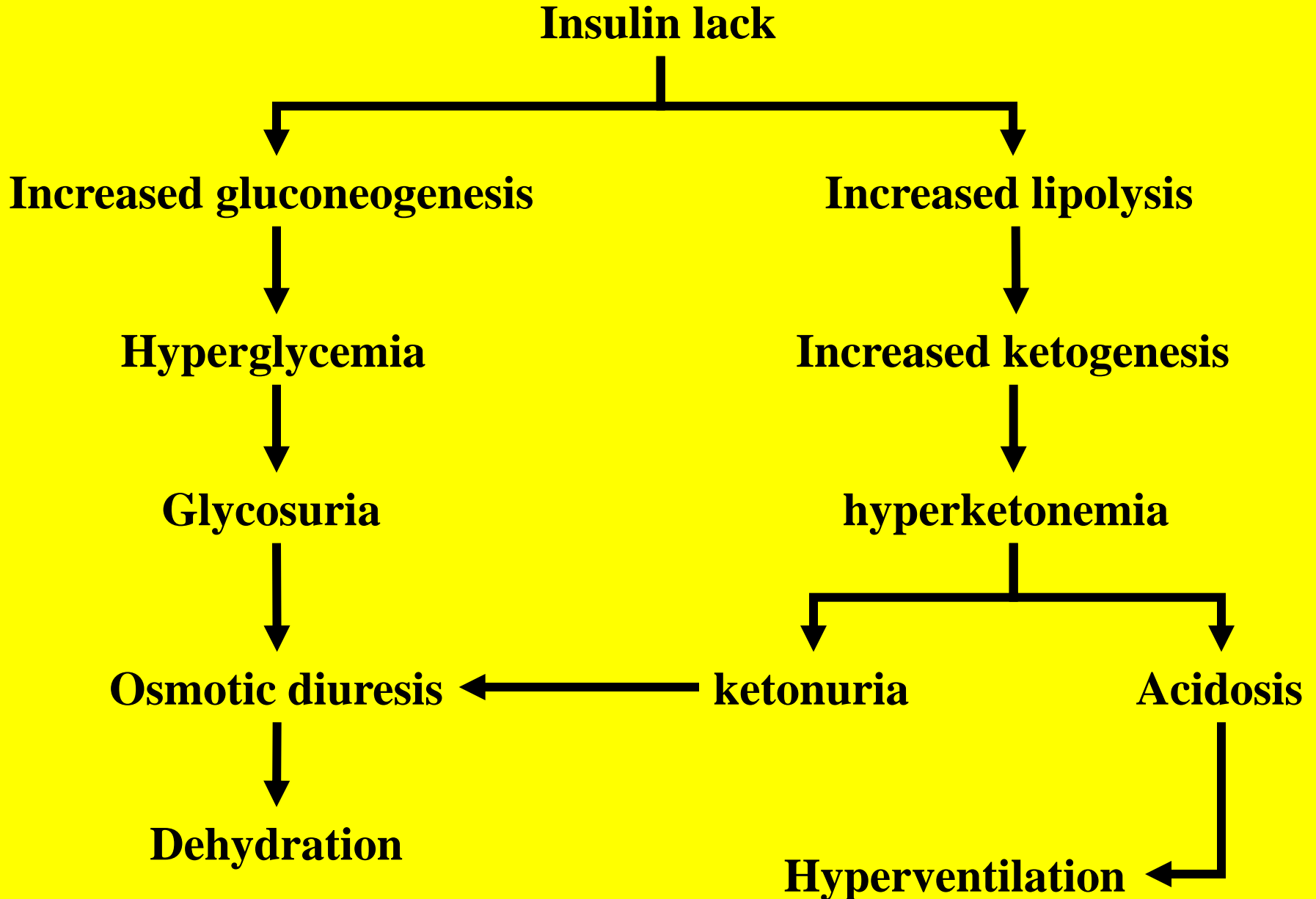
- The blood glucose is elevated within 30 minutes following a meal containing carbohydrates.
- The elevated level of glucose stimulates the secretion of the hormone insulin from the pancreas, which increases the flow of glucose into muscle and adipose tissue for the synthesis of glycogen.
- As blood glucose levels drop, the secretion of insulin decreases. When blood glucose is low, another hormone, glucagon, is secreted by the pancreas, which stimulates the breakdown of glycogen in the liver to yield glucose.
- **In diabetes mellitus, glucose cannot be utilized or stored as glycogen because insulin is not secreted or does not function properly.**



- In Type I, insulin-dependent diabetes, which often occurs in childhood, the pancreas produces inadequate levels of insulin.
- This type of diabetes can result from damage to the pancreas by viral infections or from genetic mutations.
- In Type II, insulin resistant diabetes, which usually occurs in adults, insulin is produced, but insulin receptors are not responsive. Thus a person with Type II diabetes does not respond to insulin therapy.
- Gestational diabetes can occur during pregnancy, but blood glucose levels usually return to normal after the baby is born.
- Mothers with diabetes tend to gain weight and have large babies.
- **In all types of diabetes, insufficient amounts of glucose are available in the muscle, liver and adipose tissue. As a result liver cells synthesize glucose from noncarbohydrate sources (gluconeogenesis) and break down fat (lipogenolysis), which elevates the acetyl CoA level.**
- **Excess acetyl CoA undergoes ketogenesis and ketone bodies accumulate in the blood.**
- As the level of acetone increases, its odor can be detected on the breath of a person with uncontrolled diabetes who is in ketosis.

- In uncontrolled diabetes, the concentration of blood glucose exceeds the ability of the kidney to reabsorb glucose, and glucose appears in the urine (glycosuria).
- High levels of glucose increase the osmotic pressure in the blood, which leads to an increase in urine output.
- Symptoms of diabetes include **frequent urination and excessive thirst**. Treatment for diabetes includes a change to a diet to limit carbohydrate intake, and may require medication such as a daily injection of insulin.

DIABETIC KETOACIDOSIS



A 15-year-old girl is admitted to the ER. She is confused and her breath smell as ripe fruits (acetone). She has dry skin and tongue, which are the signs of dehydration. She also takes quick, deep breaths (hyperventilates). *WHAT IS YOUR DIAGNOSIS? Are the laboratory results below in keeping with your opinion?*

Laboratory

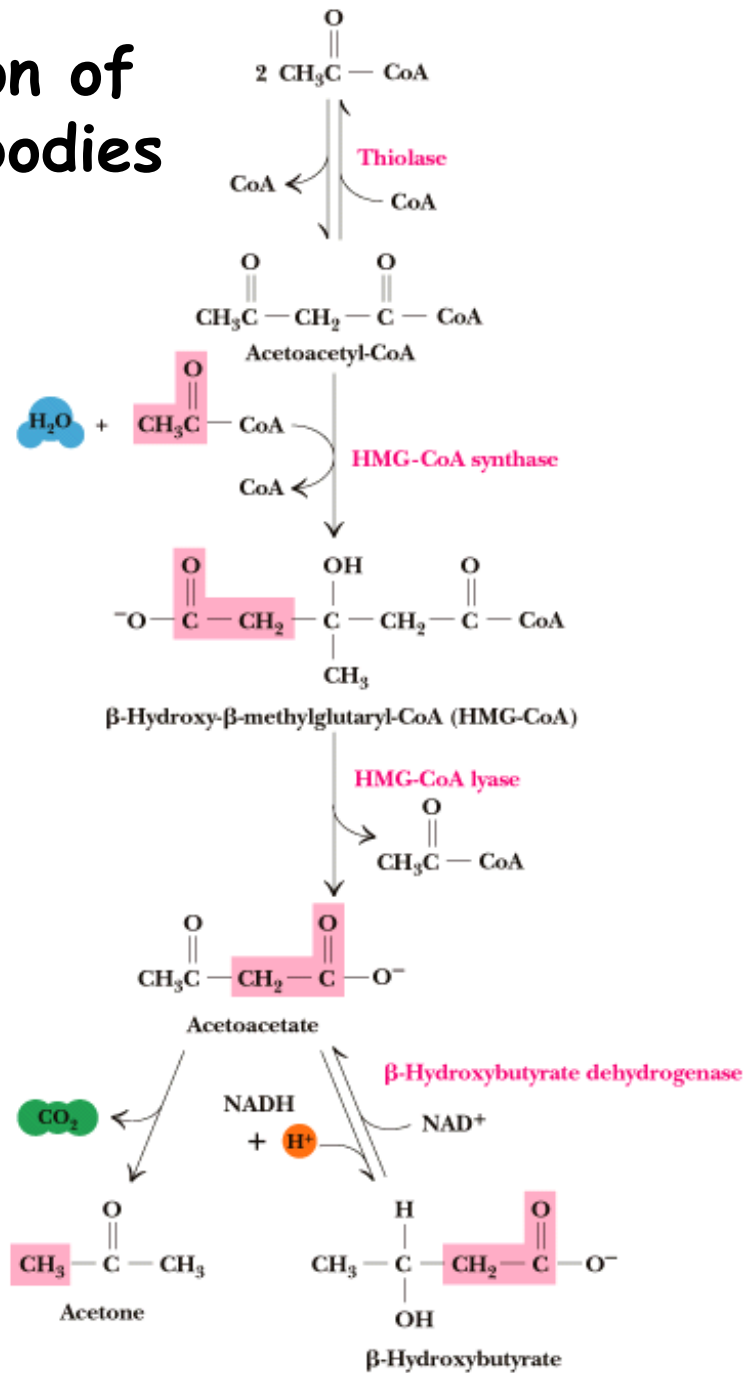
- **Glucose in urine**
- **Ketone bodies in urine**
- **Glycemia**
- **Potassium**
- **Blood pH**

Results

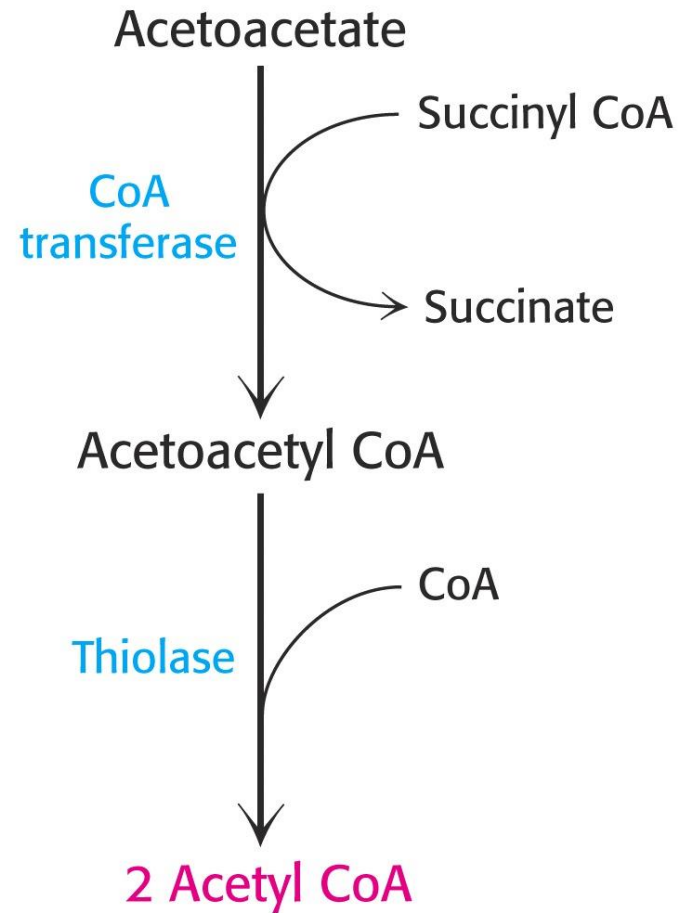
- **Positive**
- **Positive**
- **18,0 mmol/l (324 mg%)**
- **3,5 mmol/l**
- **7,21**

- REVIEW
- The following slides are a very good capsule of **KETONE BODY METABOLISM**

Formation of ketone bodies

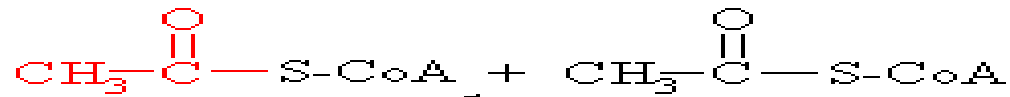


Re-utilization of ketone bodies

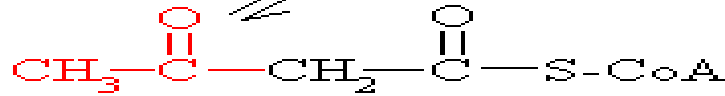


- **THE FIRST THING TO REALIZE AND REMEMBER is.....that**
- **If a person is not getting enough glucose through the diet (rare!) because of fasting, starvation, etc. or if glucose is not being transferred from the blood to body cells (as in diabetes mellitus), then oxaloacetate from the Krebs Cycle is converted to new glucose via gluconeogenesis.**
- **Without oxaloacetate, Acetyl CoA cannot be used and accumulates.** The liver then converts excess acetyl CoA into ketones (acetone, acetoacetate, etc.). **These ketones are acidic and as they accumulate, they cause ketoacidosis.**

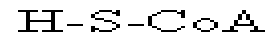
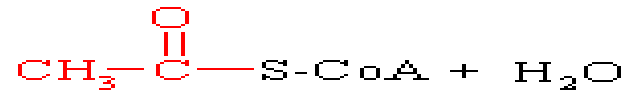
- **TO REPEAT!**
- **If the body is deficient in oxaloacetate (due to fasting, diabetes, starvation), acetyl CoA from the β -oxidation pathway cannot enter the citric acid cycle, and oxaloacetate is diverted to gluconeogenesis.**
- Acetyl CoA is diverted to form the three compounds referred to as ketone bodies-- acetoacetate, D-3-hydroxybutarate and acetone.
- Liver is the site of major production of ketone bodies.



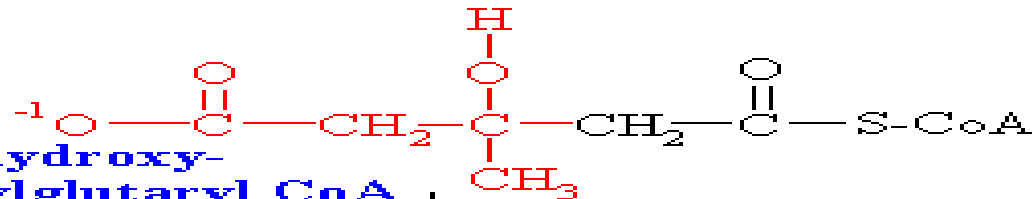
3-Ketothiolase



acetoacetyl CoA

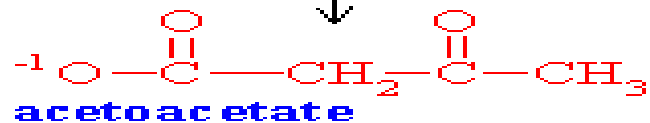


**Hydroxymethylglutaryl
CoA Synthetase**

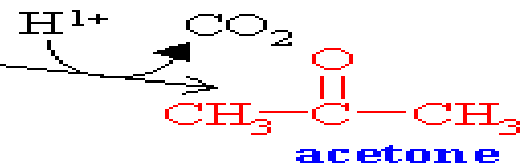


**3-hydroxy-
3-methylglutaryl CoA**

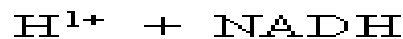
**Hydroxymethylglutaryl
CoA Cleavage Enzyme**



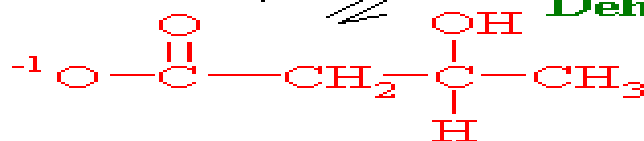
acetoacetate



acetone



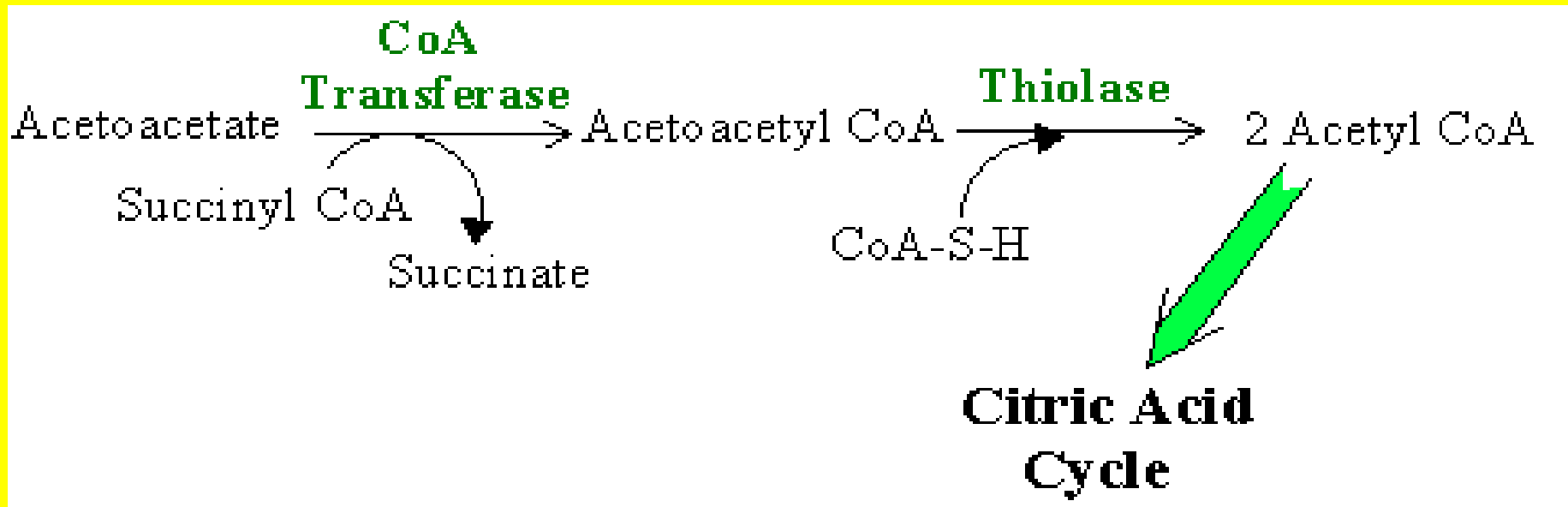
**D-3-Hydroxybutyrate
Dehydrogenase**



D-3-hydroxybutyrate

- **Ketone Bodies are a special source of fuel and energy for certain tissues produced when acetyl-CoA levels exceed the capacity of the TCA cycle (depends on OAA levels)**
- **Under starvation conditions no carbohydrates to produced anpleorotic intermediates**
- **Some of the acetyl-CoA produced by fatty acidoxidation in liver mitochondria is converted to acetone, acetoacetate and β -hydroxybutyrate**
- **These are called "ketone bodies"**
- **Source of fuel for brain, heart and muscle**
- **Major energy source for brain during starvation**
- **They are transportable forms of fatty acids!**

- Acetoacetate and 3-hydroxybutyrate are normal fuels of respiration for some tissues- e.g Heart muscle and renal cortex use acetoacetate over glucose.
- In prolonged starvation, the brain adapts to using acetoacetate.



- **KETONE BODY METABOLISM**
- **In the fasting state**, the liver converts excess acetyl-CoA from [beta-oxidation of fatty acid ketone bodies, acetoacetate and 3-hydroxybutyrate (beta-hydroxybutyrate), which are used by extrahepatic tissues.
- Cardiac and skeletal muscles and renal cortex metabolize acetoacetate and 3-hydroxybutyrate to acetyl-CoA.
- Normally during a fast, muscle metabolizes ketones rapidly as the liver releases them, preventing their accumulation in blood.
- After a week of fasting, ketones reach a concentration in blood high enough for the brain to begin metabolizing them.
- **If ketones increase sufficiently in the blood, they can lead to ketoacidosis.** Ketogenesis and ketogenolysis are shown in Figure 1-16-4.

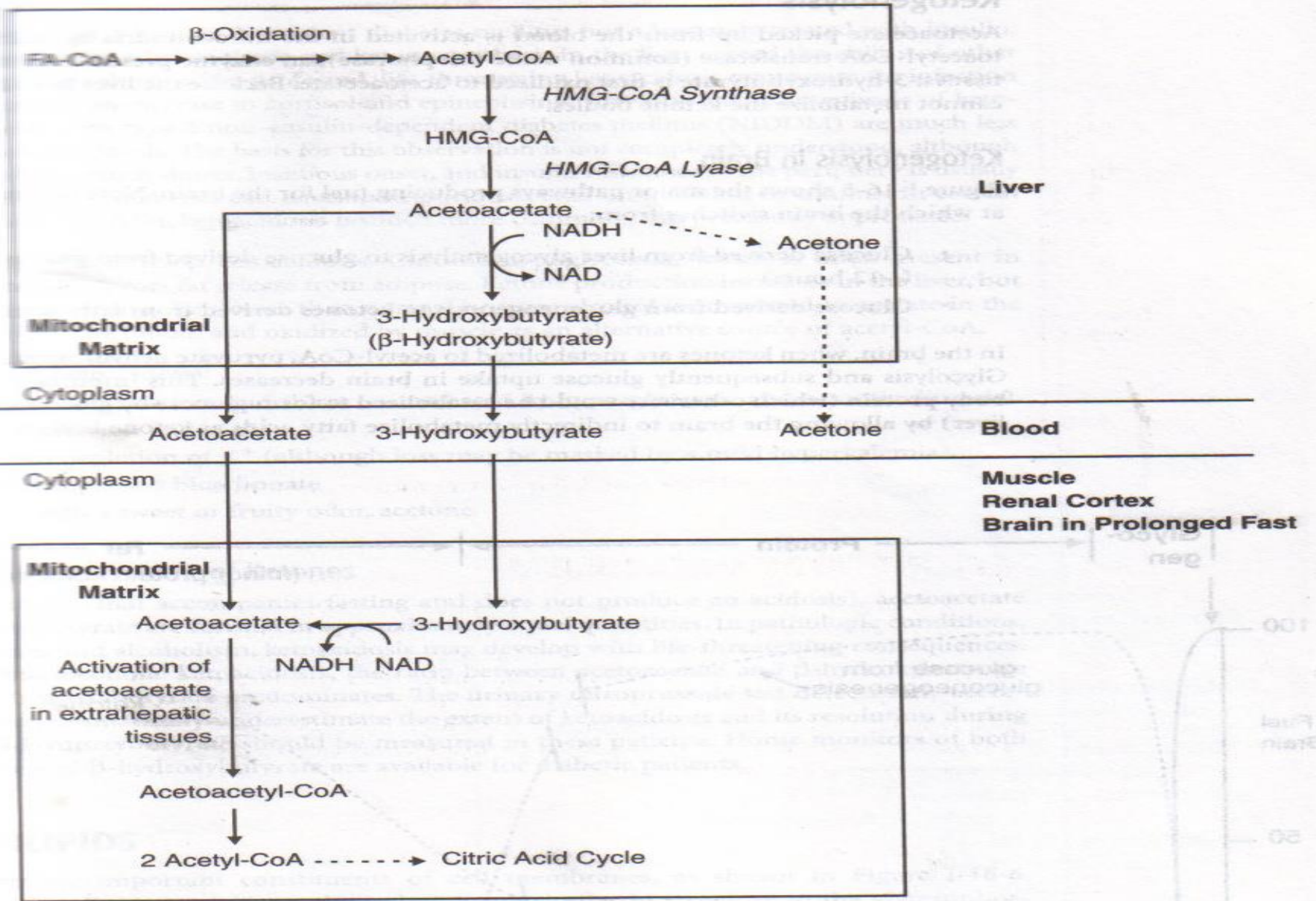


Figure I-16-4. Ketogenesis (Liver) and Ketogenolysis (Extrahepatic)

- **Ketogenesis**
- Ketogenesis occurs in mitochondria of hepatocytes **when excess acetyl-CoA accumulates in the fasting state.**
- HMG-CoA synthase forms HMG-CoA, and HMG-CoA lyase breaks HMG-CoA into acetoacetate, which can subsequently be reduced to 3-hydroxybutyrate.
- **Acetone** is a minor side product formed nonenzymatically but **is not used as a fuel in tissues.** It does, however, **impart a strong odor (sweet or fruity) to the breath, which is almost diagnostic for ketoacidosis.**

- **Ketogenolysis**
- Acetoacetate picked up from the blood is activated in the mitochondria by **succinyl-CoA acetoacetyl-CoA transferase (common name thiophorase)**, an enzyme **present only in extrahepatic tissues**; 3-hydroxybutyrate is first oxidized to acetoacetate.
- **Because the liver lacks this enzyme it cannot metabolize the ketone bodies.**

- **Ketogenolysis in Brain**

- Figure 1-16-5 shows the major pathways producing fuel for the brain. Note the important times at which the brain switches from:

- **Glucose derived from liver glycogenolysis to glucose derived from gluconeogenesis (~12 hours)**

- **Glucose derived from gluconeogenesis to ketones derived from fatty acids (~1 week)**

- **In the brain, when ketones are metabolized to acetyl-CoA, pyruvate dehydrogenase is inhibited.**

- Glycolysis and subsequently glucose uptake in brain decreases. This important switch spares body protein (which otherwise would be catabolized to form glucose by gluconeogenesis in the liver) by allowing the brain to indirectly metabolize fatty acids as ketone bodies.

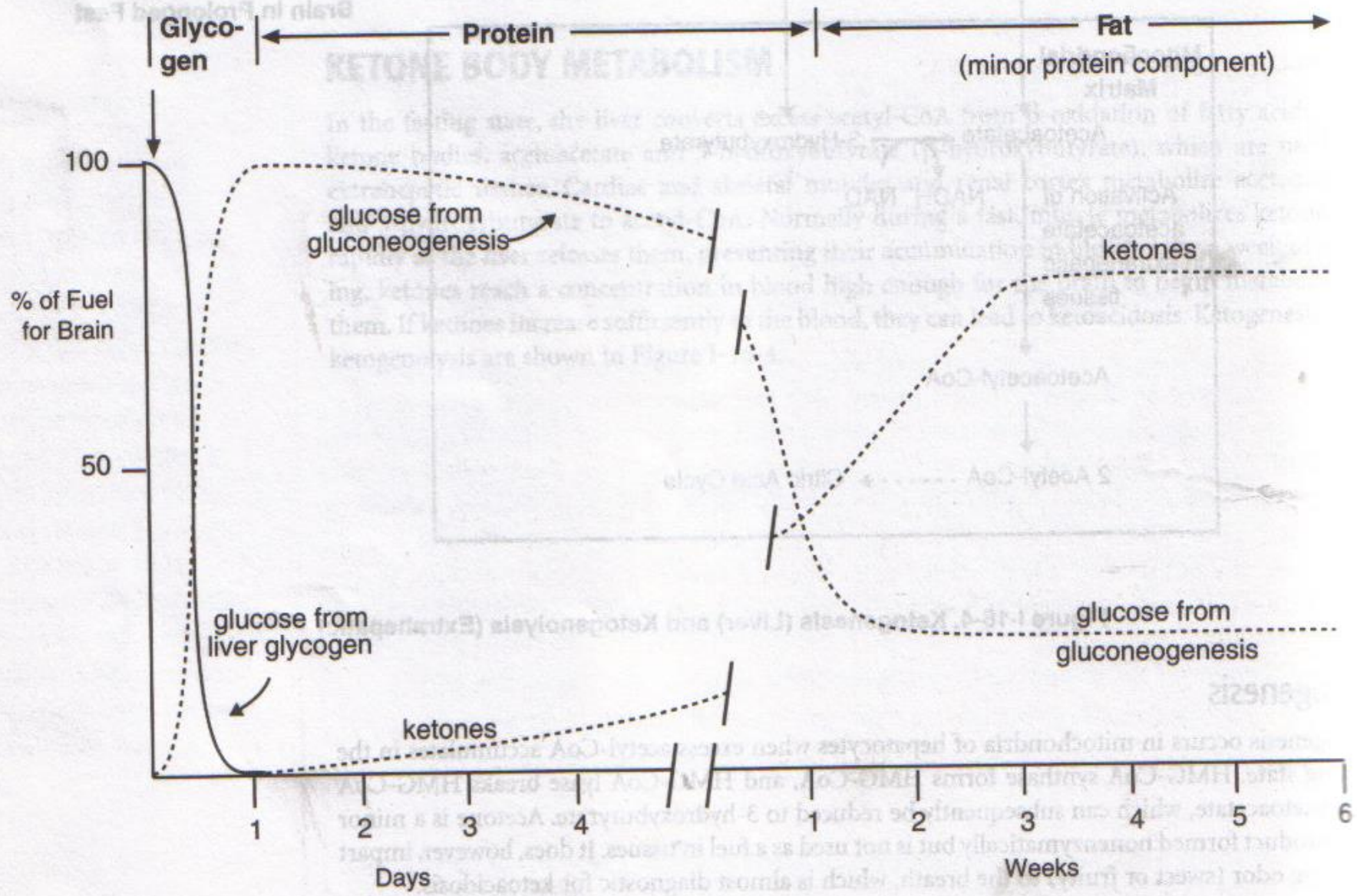


Figure 1-16-5. Fuel Use in the Brain During Fasting and Starvation

- **Ketoacidosis**
- In patients with type 1 insulin-dependent diabetes mellitus not adequately treated with insulin, **fatty acid release from adipose tissue and ketone synthesis in the liver exceed the ability of other tissues to metabolize them, and a profound, life-threatening ketoacidosis may occur.**
- **An infection or trauma (causing an increase in cortisol and epinephrine) may precipitate an episode of ketoacidosis.**
- **Patients with type 2 non-insulin-dependent diabetes mellitus (NIDDM) are much less likely to show ketoacidosis.** The basis for this observation is not completely understood, although type 2 disease has a much slower, insidious onset, and insulin resistance in the periphery is usually not complete.
- **Type 2 diabetics can develop ketoacidosis after an infection or trauma. In certain populations with NIDDM, ketoacidosis is much more common than previously appreciated.**

- Alcoholics can also develop ketoacidosis.
- Chronic hypoglycemia, which is often present in chronic alcoholism, favors fat release from adipose.
- Ketone production increases in the liver, but utilization in muscle may be slower than normal because alcohol is converted to acetate in the liver, diffuses into the blood, and oxidized by muscle as an alternative source of acetyl-CoA.

- **Associated with ketoacidosis:**
 - **Polyuria, dehydration, and thirst**
(exacerbated by hyperglycemia and osmotic diuresis)
 - **CNS depression and coma**
 - **Potential depletion of K^+ (although loss may be masked by a mild hyperkalemia)**
 - **Decreased plasma bicarbonate**
 - **Breath with a sweet or fruity odor, acetone**
 - **Potential depletion of K^+ (although loss may be masked by a mild hyperkalemia)**
 - **Decreased plasma bicarbonate**

- Potassium deserves special attention in the patient with DKA. **As a rule, the total body potassium levels in the patient with DKA are decreased.**
- **However, the patient may be hyperkalemic or have a normal serum potassium level at presentation. This falsely normal or elevated plasma potassium level is multifactorial.**
- **First, the osmotic pull of the extracellular fluid shifts water and potassium out of the intracellular fluid of the muscle cells.**
- **The shift is then further increased by the breakdown of intracellular protein which liberates more potassium.**
- **Additionally, potassium moves out of cells in exchange for hydrogen ions which are present in excess during DKA.**

- **Finally, in the absence of insulin potassium is unable to move back into cells once it has been pulled out.**
- **All of this potassium that is pulled from the intracellular arena is initially brought to the kidneys, where it is lost in the osmotic pull present due to the extreme glucosuria.**
- **When the patient finally becomes so dehydrated that they cannot maintain adequate glomerular filtration, the potassium present in the extracellular fluid appears as a normal or increased amount, despite severe total body depletion.**

- **Laboratory Measurement of Ketones**
- **In normal ketosis** (that accompanies fasting and does not produce an acidosis), **acetoacetate and (beta-hydroxybutyrate are formed in approximately equal quantities.**
- **In pathologic conditions, such as diabetes and alcoholism, ketoacidosis may develop with life-threatening consequences.**
- **In diabetic and alcoholic ketoacidosis, the ratio between acetoacetate and (beta-hydroxybutyrate shifts and beta-hydroxybutyrate predominates.**
- **The urinary nitroprusside test detects only acetoacetate and can dramatically underestimate the extent of ketoacidosis and its resolution during treatment. beta-Hydroxybutyrate should be measured in these patients.**
- Home monitors of both blood glucose and beta-hydroxybutyrate are available for diabetic patients.

- **Ketone Bodies and Diabetes**
- **Lack of insulin related to uncontrolled fat breakdown in adipose tissues**
- **Excess β -oxidation of fatty acids results in ketone body formation.**
- **Can often smell acetone on the breath of diabetics.**
- **High levels of ketone bodies leads to condition known as diabetic ketoacidosis.**
- **Because ketone bodies are acids, accumulation can lower blood pH.**

Ketones in Diabetes Mellitus

In presence of insulin:

- **Enhanced glucose uptake by tissues**
- **Decreased mobilization of lipids by adipocytes**

In absence of insulin:

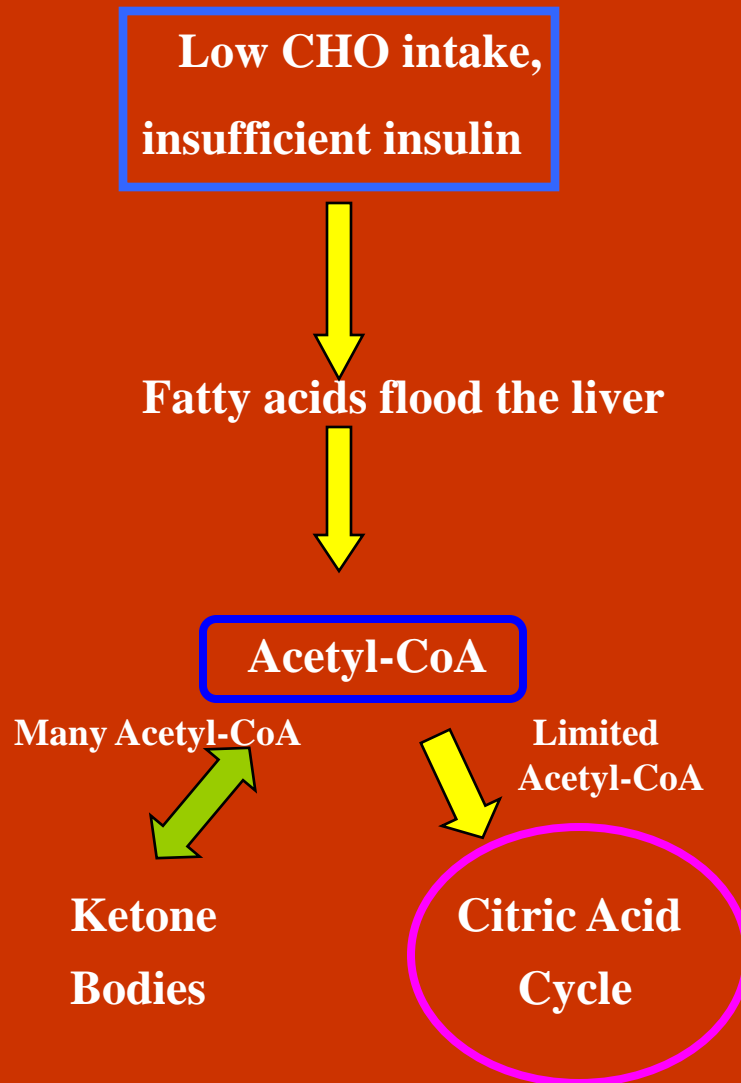
- **Decreased glucose uptake by tissues**
- **Increased mobilization of lipids by adipocytes**

Ketones in Diabetes Mellitus

Biochemical consequences of decreased insulin production:

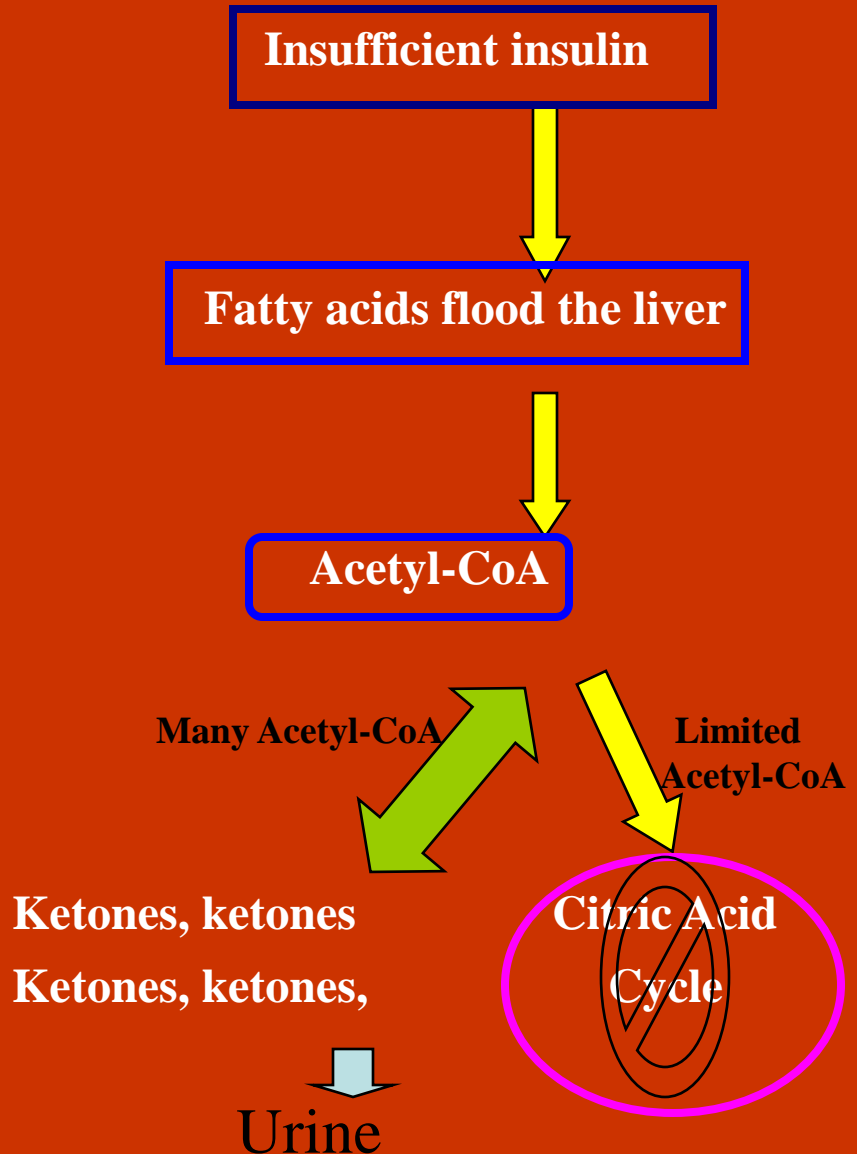
- **Glucose not taken up by liver**
 - Decreased oxaloacetate to combine with acetyl CoA to enter TCA
- **Adipocytes release fatty acids into blood**
 - Increased production of ketone bodies in liver

Ketogenesis in Diabetes Mellitus



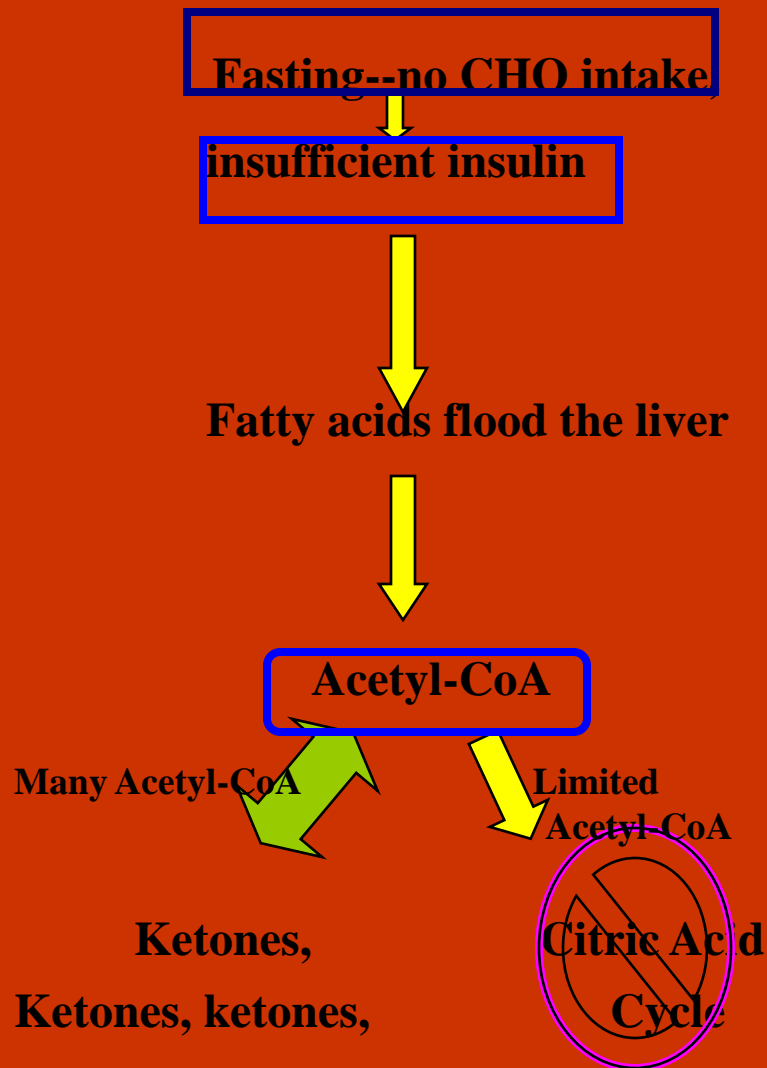
- **Ketones are products of incomplete fatty acid oxidation**
- **Usually a result of faulty blood glucose balance**

Ketogenesis in Diabetes



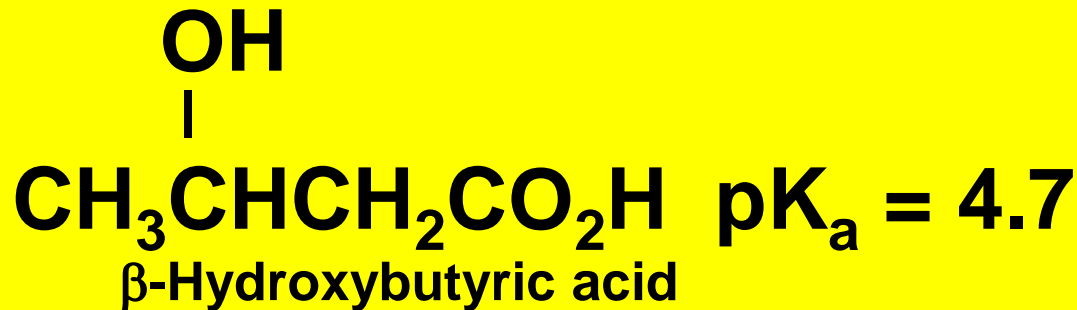
- Not enough insulin produced
- CHO metabolism is limited
- Oxaloacetate is needed to produce glucose
- Citric Acid Cycle is limited
- More ketones produced; ketones spill into urine

Ketogenesis in Fasting



- Insulin production falls
- Fatty acids flood the blood stream
- Oxaloacetate is needed to produce glucose
- Citric Acid Cycle is limited
- More ketones produced

Metabolic Acidosis in Untreated Diabetes Mellitus



↑ Concentration of acetoacetic acid can result in metabolic acidosis (pH 7.1) → ↓ affinity of Hb for O₂.