Diabetic Ketoacidosis (DKA)

Endocrine Block

Lecture's Outlines:

- **Diabetic Complications**
- **Ketone bodies metabolism**
- **DKA**:

Definition

Causes and Mechanisms

Manifestations

Precipitating Factors

- **Hyperosmolar hyperglycaemic state (HHS) = Hypperosmolar non-ketotic acidosis (HONK):**

Definition

Causes and Mechanisms

Manifestations

- **Hypoglycemia:**

Causes

Manifestations

Hormonal mechanisms preventing or correcting hypoglycemia

- **A case of DKA:** (Presentation, Examination, Lab results & their interpretation)
- **Metabolic changes in DKA**:

- Changes in CHO, protein and lipid metabolism
- Changes in water, electrolytes, and pH

Diabetic emergencies

1. Diabetic Ketoacidosis (DKA)
2. Hyperosmolar hyperglycaemic state (HHS)=

   Hypperosmolar non-ketotic acidosis (HONK)
3. Hypoglycemia

Diabetic Ketoacidosis (DKA)

Diabetic Ketoacidosis (DKA):

- **Triad of hyperglycemia, high anion gap metabolic acidosis, and ketonemia**
- **Characteristically associated with T1DM**
- **It has become increasingly common in T2DM**
- **DKA may be the first presentation of T1DM**

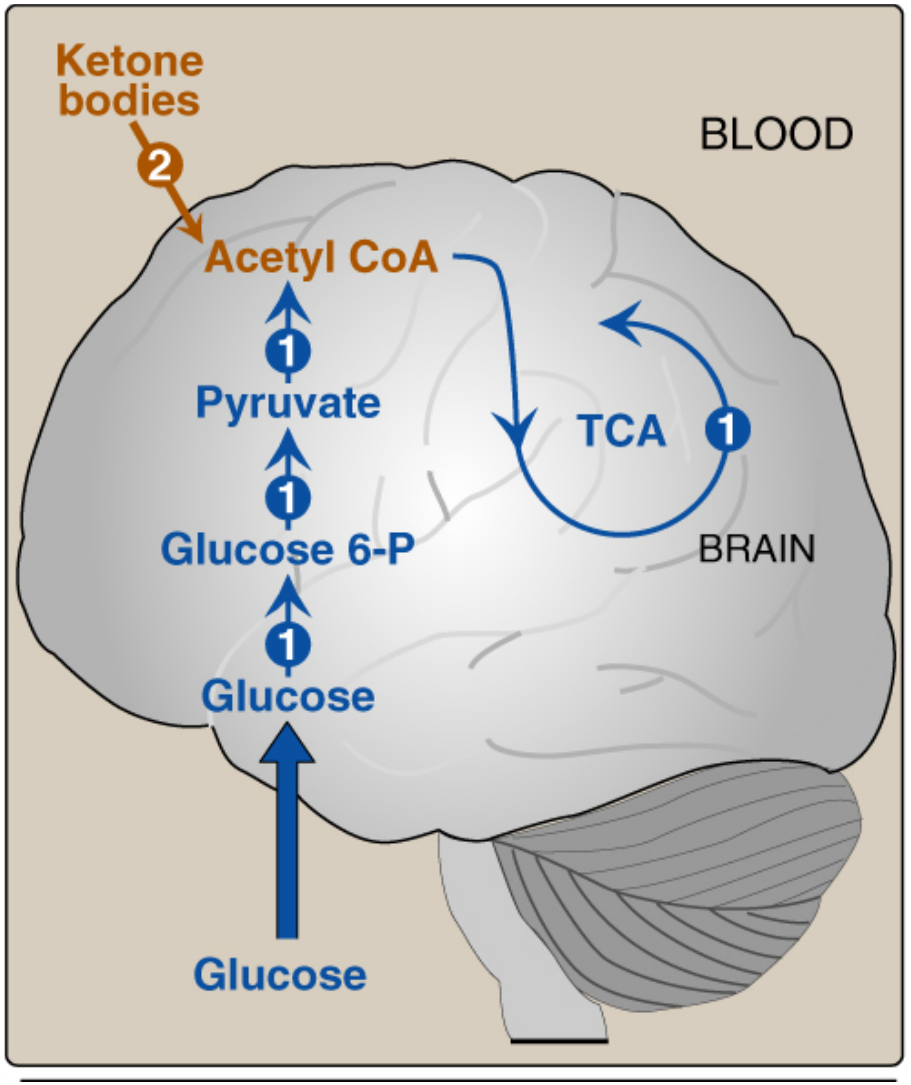
Ketone Bodies

1. Acetoacetate
2. Acetone
3. β-Hydroxybutyrate

- They are produced by the liver (ketogenesis) and utilized for energy production by peripheral tissues (Ketolysis)

Normally, glucose is the primary fuel for the brain.
It can penetrate the blood brain barrier.
The brain's GLUT is insulin-independent.

If glucose is not available for the brain, the brain can utilize plasma ketone bodies, that can penetrate the blood brain barrier, and serve as fuel molecules.



Ketone bodies synthesis = Ketogenesis

- Occurs in the hepatocyte mitochondria
- In uncontrolled DM there is ↑lipolysis in adipose tissue → ↑ [FFA] mobilization to liver

  → ↑hepatic FA oxidation → ↑ acetyl CoA which will be channeled into KB synthesis
- HMG CoA synthase is the rate limiting enzyme
- The first KB to be synthesized is acetoacetate.
- Acetoacetate can be:
  - reduced to β–Hydroxybutyrate, or
  - spontaneously decarboxylated to acetone.

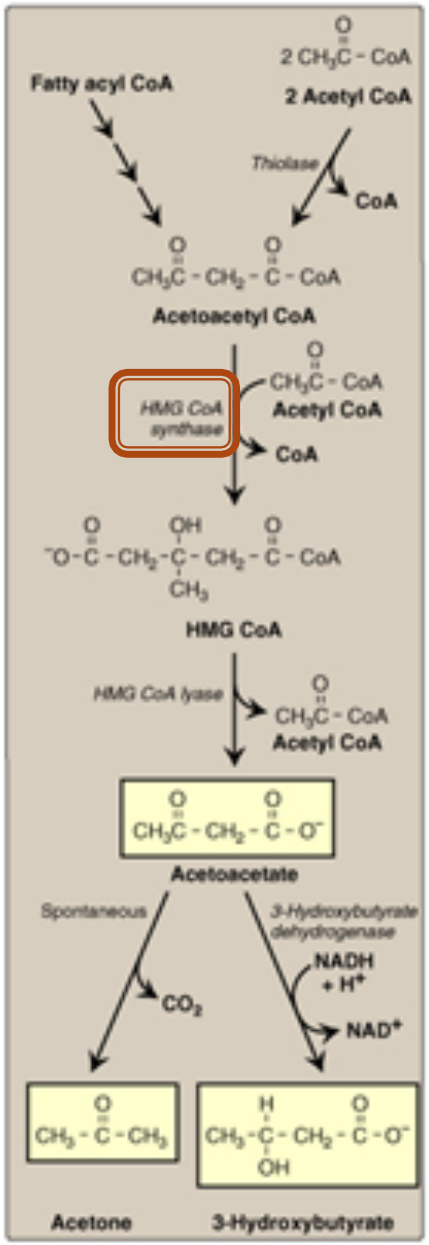
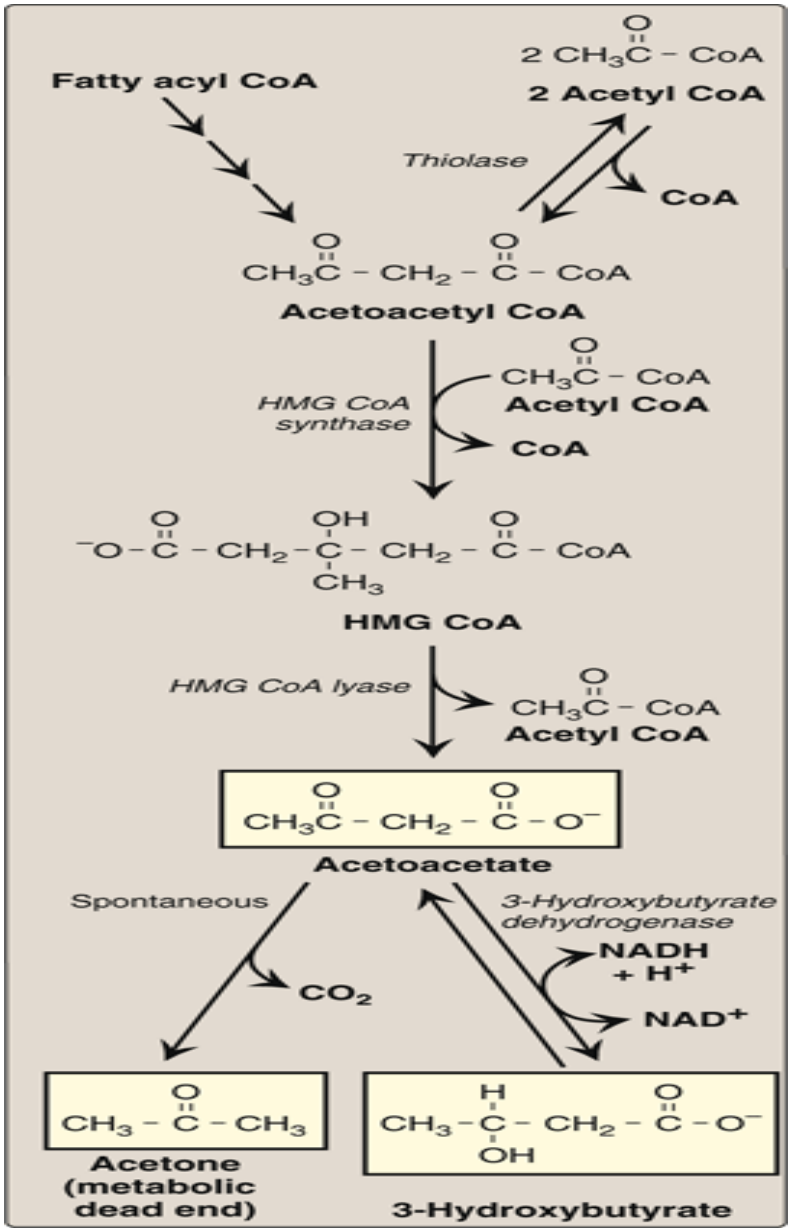


Figure 16.22
Synthesis of ketone bodies. HMG = hydroxymethylglutaryl CoA.



Synthesis of Ketone bodies

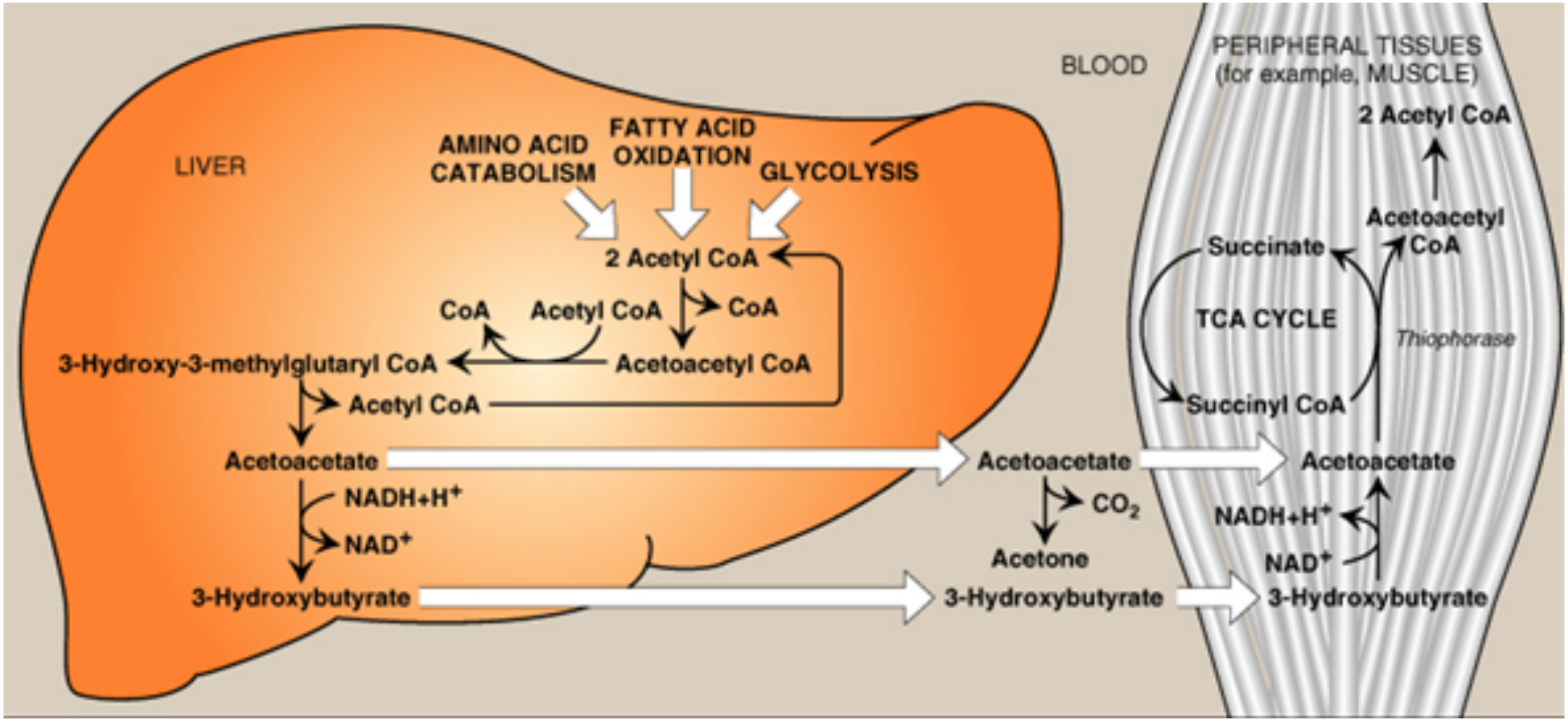
Ketogenesis

- ↑hepatic FA oxidation → ↑ acetyl CoA which will be channeled into KB synthesis
- Acetyl CoA + oxaloacetate (OAA) → Krebs cycle
- ↑ Acetyl CoA production activates pyruvate carboxylase
- Pyruvate carboxylase converts pyruvic acid into OAA
- OAA is used for gluconeogenesis (rather than Krebs cycle)
- Acetyl CoA is channeled into KB synthesis

Ketone Bodies Utilization=Ketolysis

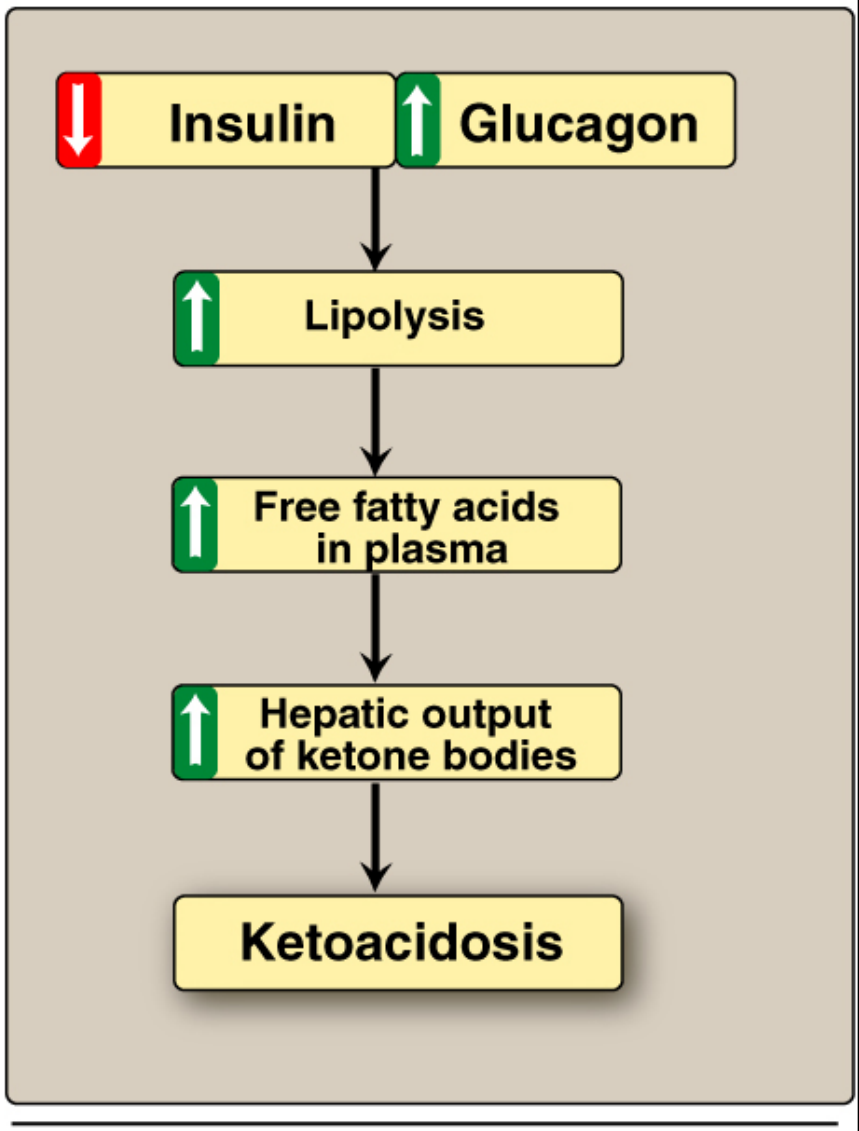
- Takes place in extrahepatic tissues
- Occurs in the mitochondria (so cannot occur in RBCs)
- Does not occur in the liver (as the liver lacks the thiophorase enzyme required for ketolysis)
- β-Hydroxybutyrate is oxidized to acetoacetate (by a dehydrogenase)
- Acetoacetate is converted to acetoacetyl CoA (catalyzed by thiophorase)
- Acetoacetyl CoA is converted to acetyl CoAs.

Ketone Bodies Utilization=Ketolysis



Mechanisms of DKA:

In uncontrolled DM there is ↑lipolysis in adipose tissue → ↑ [FFA] → ↑ mobilization of FFA to liver → ↑hepatic FA oxidation → ↑ hepatic acetyl CoA which will be utilized in KB synthesis (ketogenesis) → ketoacidosis



Mechanisms & Manifestations of DKA

- In uncontrolled DM the rate of ketogenesis is > the rate of ketolysis → ketonemia (↑[KB] in blood)→ ketonuria (↑[KB] in urine).

- **Manifestations of DKA:**
  - Fruity odor on the breath (acetone)
  - Acidosis (low pH of blood because KBs are acids)
  - Dehydration (due to glucosuria)

Precipitating factors for DKA

- Infection (30–40%)
- Inadequate insulin treatment or non-compliance (20%)
- Severe illness e.g., Myocardial infarction
- Trauma
- Drugs: e.g., steroids

Hyperosmolar hyperglycaemic state (HHS)= Hypperosmolar non-ketotic acidosis (HONK)

Hyperosmolar hyperglycaemic state (HHS)= Hypperosmolar non-ketotic acidosis (HONK

- Little or no accumulation of ketone bodies
- Serum [glucose] is often >50 mmol/L
- Plasma osmolality may reach 380 mosmol/Kg (normal 275-295)
- Neurological abnormalities are frequently present
- Insulin levels are insufficient to allow appropriate glucose utilization but are adequate to prevent lipolysis and subsequent ketogenesis
- Usually occurs in elderly patients with T2DM
- Has a substantially higher mortality than DKA (up to 15%)

Hypoglycemia

Hypoglycemia:

- Common complication of treatment with insulin or oral hypoglycaemics
- More common in patients with T1DM
- Manifestations: Characterized by:
  1. CNS Symptoms (confusion, aberrant behavior, or coma): *see details later*
  2. Low blood [Glucose]
  3. Symptoms resolved within minutes following the administration of glucose

Hypoglycemia is a medical emergency, Why ?

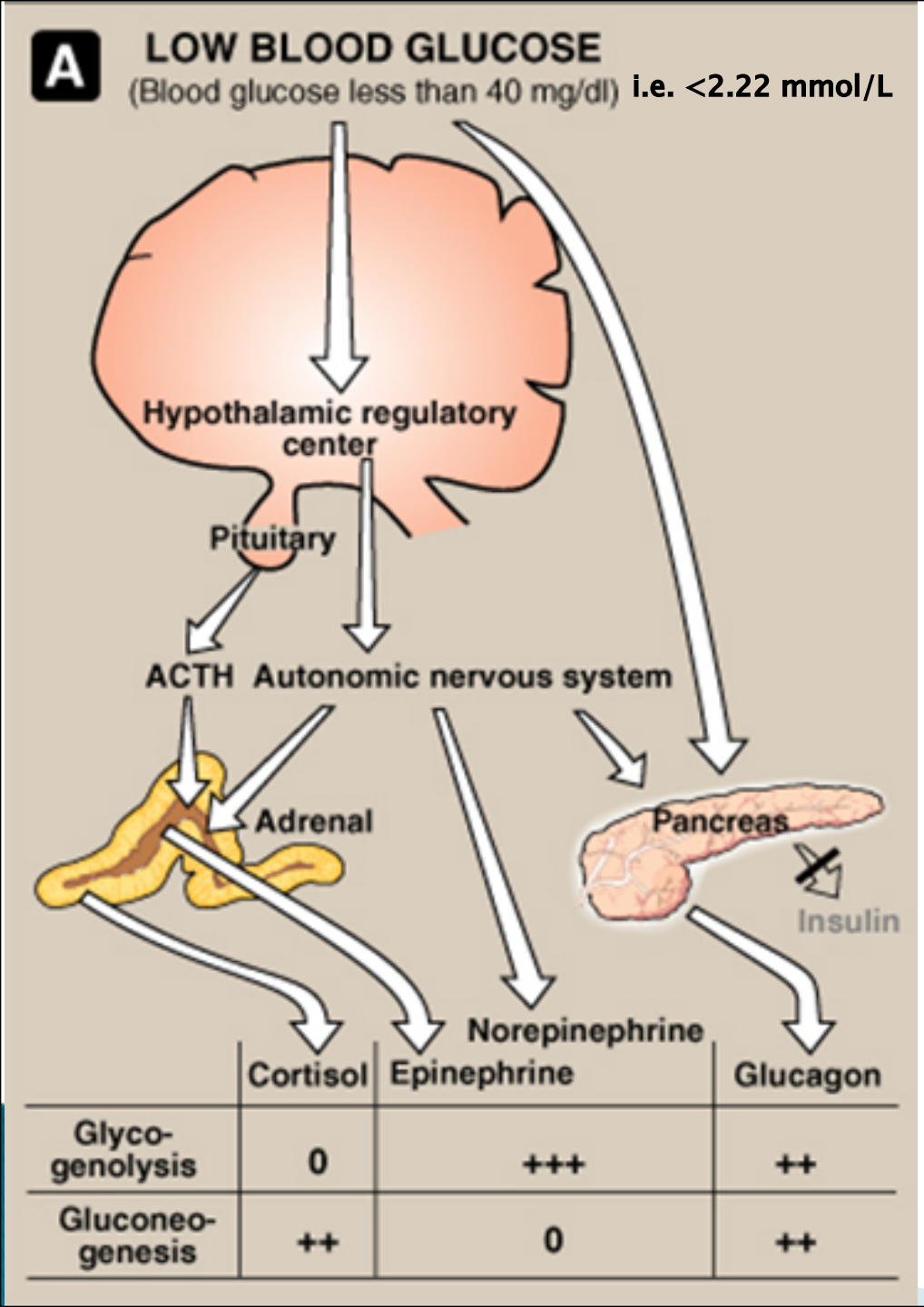
- The brain has absolute requirement for a continuous supply of glucose
- Transient hypoglycemia → cerebral dysfunction
- Severe, prolonged hypoglycemia → brain death

Hypoglycemia, continued..

- **Hypoglycemia occurs due to impaired protective responses to hypoglycemia:**
  - **Insulin is supplied exogenously and its release cannot be turned off**
  - **Glucagon & adrenaline response to hypoglycemia becomes impaired later in the course of DM**

Hypoglycemia, continued..

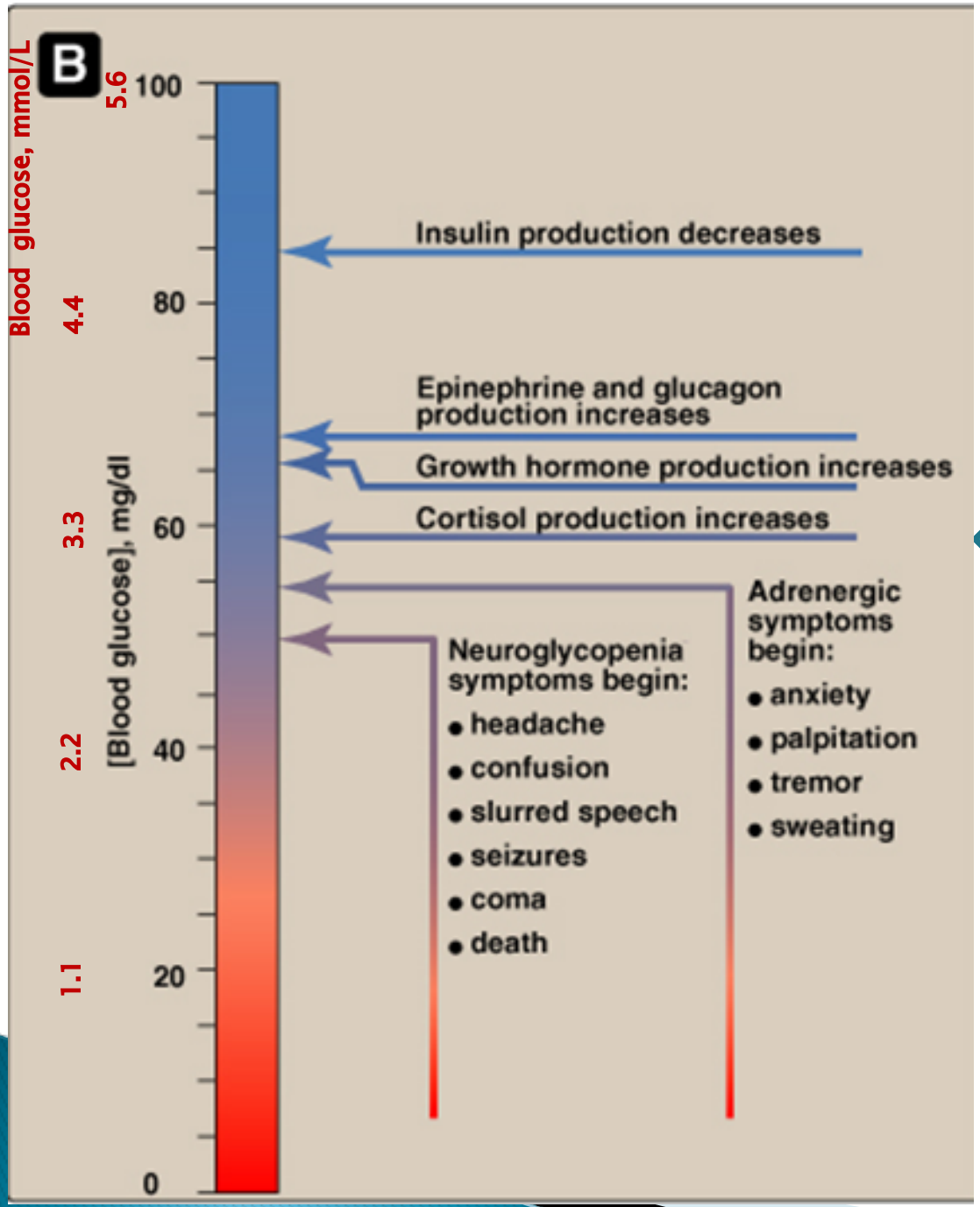
- **Clinical presentation:**
  - Symptoms of sympathetic overactivity (plasma [glucose] <3.6 mmol/L, abrupt fall): anxiety, tremors, sweating & palpitation
  - Symptoms of neuroglycopenia (plasma [glucose] <2.6 mmol/L, gradual fall): headache, confusion, drowziness and ultimately loss of consciousness or seizures (at plasma [glucose] <1.5 mmol/L)



Hormonal mechanisms to prevent or correct hypoglycemia:

⇐ ↓ Production of insulin

⇐ ↑production of:
- Epinephrine & glucagon
- Growth hormone
- Cortisol



Glycemic thresholds for the various responses to hypoglycemia:

A CASE of DKA

- A 14-year-old girl was admitted to a children's hospital in coma. Her mother stated that the girl had been in good health until approximately 2 weeks previously, when she developed a sore throat and moderate fever. She subsequently lost her appetite and generally did not feel well.

A CASE of DKA .....Cont'd

- **Several days before admission she began to complain of undue thirst and also started to get up several times during the night to urinate. However, on the day of admission the girl had started to vomit, had become drowsy and difficult to arouse, and accordingly had been brought to the emergency department.**

A CASE of KDA, continues..

On examination:

- She was dehydrated
- Her skin was cold
- She was breathing in a deep sighing manner (Kussmaul respiration)
- Her breath had a fruity odor
- Her blood pressure was 90/60 mmHg (N: 120/80)
- Her pulse rate 115/min.
- She could not be aroused

A provisional diagnosis of T1DM with complicating ketoacidosis and coma (DKA) was made by the intern on duty

Laboratory findings: blood results

The admitting diagnosis was confirmed by the laboratory findings shown below:

Plasma analytes	Patient's results	Normal levels
Glucose (mmol/L)	50	3.9–5.6
Ketoacids	++++	(trace)
Bicarbonate (mmol/L)	6	22–30
Arterial blood pH	7.07	7.35–7.45
Na^+ (mmol/L)	136	136–146
Cl^- (mmol/L)	100	102–109

Laboratory findings : blood results,

continued..

Plasma analytes	Patient's results	Normal levels
PCO_2 (kPa)	2.7	4.3–6.0
*Anion gap (mmol/L)	35.5	7–16
K^+ (mmol/L)	5.5	3.5–5.0
Urea nitrogen (mmol/L)	15	2.5–7.1
Creatinine (μmol/L)	200	44–80
Albumin (g/L)	50	41–53
Osmolality (mOsm/kg serum water)	325	275–295
Hematocrit	0.500	0.354–0.444

*Anion gap (A^-)= (Na^+ + K^+)– (HCO_3^- + Cl^-)

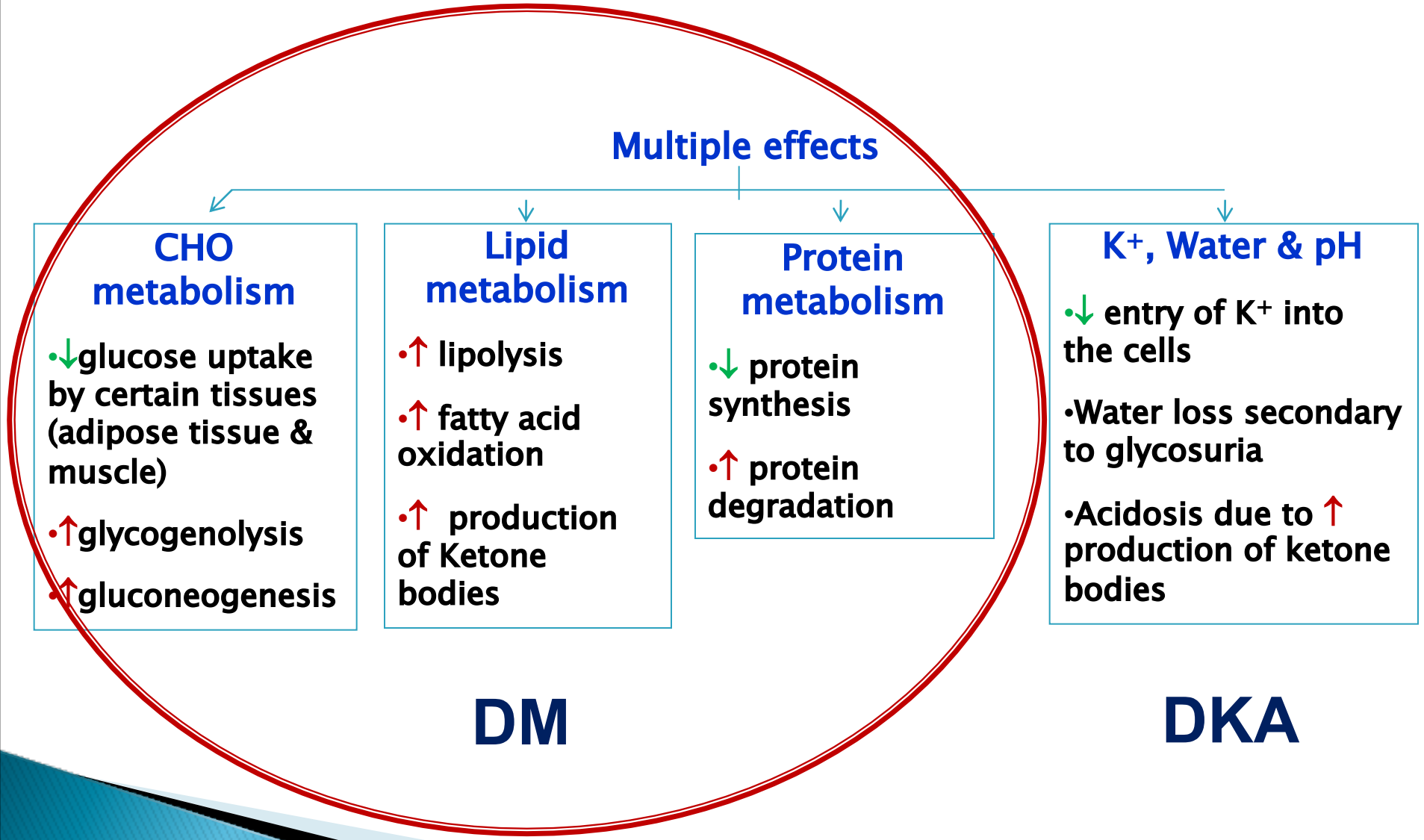
Laboratory findings: Urine results

Urine analyte	Patient's results	Normal level
Glucose	++++	–
Ketoacids	++++	–

Interpretation of Laboratory findings

Results	Interpretation
Hyperglycemia	Confirm the diagnosis of DKA
Glucosuria	
Ketonemia	
Ketonuria	
↓ pH	Severe metabolic acidosis due to ↑ production of ketone bodies
↓ bicarbonate and PCO_2	Metabolic acidosis with partial respiratory compensation (the hyperventilation)
↑ anion gap	Due to ↑ ketone bodies in the blood
↑ urea & creatinine	1. Renal impairment (dehydration → ↓ blood volume →↓ renal perfusion) 2. Dehydration 3. Degradation of protein (for urea)
↑K^+	↓ Uptake of potassium by cells in the absence of insulin
↑ Plasma osmolality	Due to hyperglycemia and fluid loss

Metabolic Changes in DM and DKA



Take Home Message

- Acute complications of DM include: DKA, HHS, and hypoglycemia
- DKA is a triad of hyperglycemia, ketonemia and high anion gap metabolic acidosis, and can be precipitated by several stressful factors.
- Ketone bodies (KB) are synthesized in the liver (HMG CoA synthase is the rate limiting enzyme) and utilized by peripheral organs and not the liver (liver lacks thiophorase enzyme)
- KB can serve as energy source (this is important for the brain in case of hypoglycemia)

Take Home Message

In DKA there is excessive ketogenesis (more than ketolysis) *(details of the mechanisms and consequences are required)*

HHS is a serious condition, usually occurs in elderly with T2DM, and has high mortality rate.

Hypoglycemia is a medical emergency that might be caused by DM treatment (intensive) and impaired protective mechanisms against hypoglycemia. Its clinical manifestations are due to sympathetic overactivity and neuroglycopenia.

Case presentation, examination of DKA can provide provisional diagnosis, and should be confirmed by comprehensive blood and urine lab investigation including measuring blood glucose, KB, pH, pCO_2, electrolytes, osmolality, protein, and kidney function test; anion gap calculation; hematocrit; and urine glucose and KB.

THANK YOU!