2018-2-17 Describe ketone bodies including their synthesis and metabolism.

Introduction:
- Ketone bodies are three water-soluble molecules (acetoacetate, beta-hydroxybutyrate, and their spontaneous breakdown product, acetone) containing the ketone group
- Provide an alternative source of substrate for energy production
- Ketones can only be produced by the liver, and only used as a substrate by the kidney, as well as skeletal and cardiac muscle
- Production of ketones is accelerated by glucagon and adrenaline

Ketogenesis:
- They are produced by the mitochondria in liver cells from fatty acids
  - β-oxidation of fatty acids in the liver produces acetyl-CoA
  - Acetyl-CoA usually enters the citric acid cycle to produce ATP
  - When large amounts of acetyl CoA are produced, they may instead condense to form acetoacetate, which can then be reduced to β-hydroxybutyrate (These three molecules are called ketone bodies)

Ketone bodies:
- **Acetoacetate**: When two acetyl-CoA molecules lose their -CoAs, (or Co-enzyme A groups) they can form a (covalent) dimer called acetoacetate.
- **Beta-hydroxybutyrate**: Beta-hydroxybutyrate is a reduced form of acetoacetate, in which the ketone group is converted into an alcohol (or hydroxyl) group. Both are 4-carbon molecules, that can readily be converted back into acetyl-CoA by most tissues of the body, with the notable exception of the liver.
- **Acetone**: Acetone is the decarboxylated form of acetoacetate which cannot be converted back into acetyl-CoA except via detoxification in the liver where it is converted into lactic acid, which can, in turn, be oxidized into pyruvic acid, and only then into acetyl-CoA.

Circumstances:
- Ketogenesis takes place in the setting of low glucose levels in the blood, after exhaustion of other cellular carbohydrate stores, such as glycogen.
  - Low food intake (fasting), carbohydrate restrictive diets, starvation, prolonged intense exercise, alcoholism
  - State of low insulin and high glucagon is what stimulates the liver
- It can also take place when there is insufficient insulin (e.g. in type 1 (but not 2) diabetes), particularly during periods of "ketogenic stress" such as intercurrent illness.
  - Untreated (or inadequately treated) type 1 diabetes mellitus.

Transport:
- Ketone bodies are readily transported into tissues outside the liver and converted into acetyl-CoA, which then enters the citric acid cycle and is oxidized in the mitochondria for energy.
- In the brain, ketone bodies are also used to make acetyl-CoA into long-chain fatty acids.
Metabolism:

- Ketone bodies can be utilized as fuel in the heart, brain and muscle, but not the liver. They yield 2 GTP and 22 ATP molecules per acetoacetate molecule when oxidized in the mitochondria.

- **Liver**: cannot use them for energy because it lacks the enzyme thiophorase (β-ketoacyl-CoA transferase). Acetone is taken up by the liver in low concentrations and undergoes detoxification through the methylglyoxal pathway which ends with lactate. Acetone in high concentrations, as can occur with prolonged fasting or a ketogenic diet, is absorbed by cells outside the liver and metabolized through a different pathway via 1,2-propanediol. Though the pathway follows a different series of steps requiring ATP, 1,2-propanediol can eventually be turned into pyruvate.

- **Heart**: Preferentially utilizes fatty acids as fuel under normal physiologic conditions. However, under ketotic conditions, the heart can effectively utilize ketone bodies for this purpose.

- **Brain**:
  - The brain gets a portion of its fuel requirements from ketone bodies when glucose is less available than normal (e.g., during fasting, strenuous exercise, low carbohydrate, ketogenic diet and in neonates).
  - In the event of a low glucose concentration in the blood, the brain has an obligatory requirement for some glucose.
  - After the diet has been changed to lower blood glucose utilization for 3 days, the brain gets 25% of its energy from ketone bodies.
  - After about 24 days, ketone bodies become the major fuel of the brain, making up to two-thirds of brain fuel consumption.

**Examiner Comments:**

35% of candidates passed this question.

Whilst most candidates understood that ketones provided an alternative source of substrate for energy production, many lacked a basic understanding of their synthesis and metabolism. Important facts included what ketone bodies are, where they were synthesised, where they were taken up and used as fuel, under what circumstances they are used and the integral role of insulin. Many candidates accurately reproduced the glycolytic and/or the TCA cycle, but this was not being examined, and did not score additional marks. Many candidates incorrectly stated that ketone production was the result of anaerobic metabolism.