# Lecture 1
# Session Six

## Control of Energy Metabolism

# Control of fuel concentration

- Fuel concentrations are controlled hormonally
- insulin lowers fuel concentrations in the blood while glucagon, adrenaline, growth hormone and cortisol increase their concentrations
- Those oppose insulin action are called anti-insulin hormone

# Diversity of fuel

- **Glucose** can be used by all cells and is the preferred fuel.
- Very little free glucose is present in the body.
- About 12g is present in solution in the body fluids and this would support the metabolism of the CNS for ~2hr.
- More glucose (~300g) is stored as **glycogen**, principally in liver and muscle. Only the glucose stored in the liver (~100 g) can be made available to tissues such as the CNS.
- Many cells, (Except RBCS & CNS) can also use **fatty acids** derived from triacylglycerol stored in adipose tissue.

# Diversity of Fuel

- In a typical 70kg individual there is 10-15kg of fat, enough to supply the body's fuel needs for about two months
- Fatty acids can be converted to **ketone bodies** in the liver to be used as fuel by tissues including the CNS when glucose is low.
- Some of the **protein** in muscle (~6kg) can be broken down (proteolysis) to amino acids that can also be used to provide fuel in times of shortage, either by conversion to glucose and ketone bodies or by direct oxidation. This fuel reserve corresponds to about two weeks supply of fuel at normal rates of metabolism.

# Importance of Glucose for CNS

- CNS depends on glucose to produce energy.
- Glucose has to be available at all times as metabolism in the CNS (~140g/24hr) and other glucose-dependent tissues (~40g/24hr).
- The rate of glucose uptake by the CNS depends on the blood glucose concentration
- In a healthy individual, blood glucose concentration is maintained in the range 4.0-6.0mM.
- The blood glucose concentration is controlled via the endocrine system

# Hypoglycaemia

- A reduction in blood glucose to 3.0mM or lower, is known as hypoglycaemia.
- The acute effects of hypoglycaemia can include: trembling, weakness, tiredness, headache, sweating, sickness, tingling around the lips, palpitations, changes in mood (angry/bad temper), slurred speech, and a staggering walk and confusion.
- Hypoglycaemia may rapidly lead to unconsciousness and death if untreated as the CNS is starved of glucose.

# Hyperglycaemia

- Elevation of the fasting blood glucose above 7.0 mM is known as hyperglycaemia.
- The chronic effects of hyperglycaemia are serious and reduce both the quality and duration of life.
- Many systems of the body including the nervous, cardiovascular and renal systems may be affected.
- There is glucoseuria , polyuria‘ and polydipsia.
- Hyperglycaemia activates the non-enzymatic glycosylation of plasma proteins such as lipoproteins that leads to disturbances in their function

# *Feeding/fasting cycle*

**Effects of feeding**

- The absorption of glucose, amino acids and lipids from the gut stimulate the endocrine pancreas to release insulin which has the following actions:
    - increases glucose uptake and utilisation by muscle and adipose tissue.
    - promotes storage of glucose as glycogen in liver and muscle.
    - promotes amino acid uptake and protein synthesis in liver and muscle.
    - promotes lipogenesis and storage of fatty acids as triacylglycerols in adipose tissue.

# *Feeding/fasting cycle*

**Effects of fasting**

- Low glucose concentration inhibits insulin secretion. This reduces the uptake of glucose by adipose tissue and muscle.
- The falling blood glucose concentration also stimulates glucagon secretion i.e. insulin/anti-insulin ratio ↓. This stimulates:

  glycogenolysis in the liver

  lipolysis in adipose tissue

  gluconeogenesis

# Starvation

- Fasting must proceed for more than 10h in order to start the changes associated with starvation begin.
- It is relatively rare for individuals to eat no food at all for long periods, but poor nutrition is very common worldwide.
- Diets poor in different components have a variety of effects

# Response to Starvation

- At first blood glucose falls, but is maintained at an adequate level (3.5mM) by the actions of glucagon, which stimulates the breakdown of hepatic glycogen (12-16h).
- As these stores last only a few hours, low BGL stimulates the secretion of ACTH which enhances cortisol secretion. This hormone, amongst other effects, acts to maintain blood glucose by stimulating gluconeogenesis, and at the same time making gluconeogenic substrates available (mainly alanine and glycerol) by stimulating the breakdown of protein and fat.
- Cortisol and glucagon also stimulates gluconeogenesis

# Response to Starvation

- Lipolysis occurs at a high rate, because of the fall in plasma insulin and rise in lipolytic hormones such as glucagon, cortisol and growth hormone with elevation of free fatty acids in blood.
- The continuing action of cortisol stimulates fat breakdown, and prevents most cells from using glucose but can use the fatty acids
- Glycerol is an important substrate for gluconeogenesis, reducing the need for breakdown of proteins.

# Response to Starvation

- Under the influence of the change in the insulin/anti-insulin ratio, fatty acids are also oxidized in the liver to produce ketone bodies, which can replace glucose as a fuel for the brain. This further reduces the need for gluconeogenesis in the liver, and further spares body protein.
- As adaptation to starvation proceeds two factors become important:
  - ❖ the brain becomes able to use ketones as fuel, reducing its glucose requirement from 140g/day to 40g/day.
  - ❖ The kidneys begin to contribute to gluconeogenesis.

# Response to Starvation

- After 4-5 weeks starvation gluconeogenesis has fallen to ~30% of that at early starvation.
- Urinary nitrogen excretion initially about 12g/day (mostly urea) eventually falls to about 4g/day (approx. equal amounts of urea and $NH_4^+$).
- The reduction in urea synthesis during starvation leads to a marked decrease in the amount and activities of the enzymes involved in urea synthesis. This has important implications during the re-feeding .

# Response to Starvation

- Once all of the body's fat stores are depleted, the body will use proteins rapidly. Death follows shortly
- Death results from a number of causes related to loss of muscle mass including serious respiratory infections due to loss of respiratory muscle.