Starvation, exercise and the stress response

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Abstract

Starvation, exercise and the stress response have a physiological impact on the body. Many patients are malnourished, have impaired exercise tolerance or undergo the stress response. We describe how the body adapts to decreased nutrient supply, increased energy demands and to stress.

Keywords Carbohydrate; exercise; fat; protein; starvation

Royal College of Anaesthetists CPD Matrix: 1A01, 2A03

Learning objectives

After reading this article you should be able to:

- describe how the body uses its energy stores during starvation to maintain a glucose supply to the brain, while minimizing the loss of protein
- compare the differing phases of response to starvation
- explain the mechanisms that maintain substrate supply and the physiological changes that occur during exercise
- describe the metabolic and endocrine changes that occur when the body is under stress
- describe the stress response and its consequences

Starvation

Starvation occurs due to a failure to ingest, digest or absorb enough calories to maintain normal function. It results in metabolic, physical and behavioural changes and necessitates a reliance on endogenous energy stores.

During starvation an adaptive hypometabolic response occurs, accompanied by the conservation of energy. The blood glucose concentration needs to be maintained because brain tissue, the renal medulla and red blood cells are dependent on it for their metabolism. Both red blood cells and the renal medulla can obtain glucose via glycolysis, whereas the nervous system requires glucose directly.

The changes that occur differ depending on duration of starvation and can be subdivided into three stages (Box 1). Ultimately, total starvation would result in death.

Glycogenolytic phase

During the initial phase, hepatic and muscle glycogen stores are mobilized by glucagon. The liver contains about 100 g of glycogen and the muscles contain about 300–400 g of glycogen. Hepatic glycogen can be broken down to glucose-6-phosphate and subsequently glucose, to be released into the circulation. In contrast to this, the muscle glycogen store can only be used within the muscles themselves.

Ketone bodies (acetoacetate and β-hydroxybutyrate) begin to be produced from the high acetyl-CoA concentration, secondary to β-oxidation of fatty acids.

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During anaerobic glycolysis within the muscles, some of the pyruvate produced is converted to lactate. This enters the Cori cycle (Figure 1); it passes to the liver and is converted to glucose for export back into the circulation.

Gluconeogenic phase

After 24–48 hours glycogen stores become exhausted. Fat is used during this phase as the primary energy source, via β-oxidation of fatty acids. Protein catabolism and subsequently gluconeogenesis also occur during this phase of starvation. These changes result from the on-going influence of high plasma glucagon, but also due to raised levels of cortisol and epinephrine. The brain requires 100–120 g of glucose a day. This requirement is met by gluconeogenesis, primarily in the liver but also in the kidneys. The substrates for gluconeogenesis are glycerol (derived from lipolysis of triglycerides), lactate and amino acids.

Not all amino acids can be utilised for gluconeogenesis; alanine is the principal gluconeogenic precursor for the liver, whilst glutamine is used in the kidney. About 1.75 grams of protein has to be broken down to provide 1 g of glucose.

Urinary nitrogen begins to fall during the first week (having peaked between the second to fourth days), due to the on-going lack of protein intake and a reduction in muscle catabolism (relative to fat). Muscle wasting and weakness progresses over the duration of starvation, because amino acids are liberated for gluconeogenesis.

Another hormonal change is decreasing tri-iodothyronine (T3) levels. This contributes to a fall in metabolic rate and may also have a protein-sparing effect.

Ketogenic phase

Following a few days of starvation, lipolysis continues under the influence of increased glucagon, and decreased T3 and insulin levels. This results in energy production, manufacture of substrate for gluconeogenesis (glycerol) and rising levels of ketone bodies.

There is no decline in metabolic demand in the nervous system. Ketone bodies become increasingly utilised as fuel as the duration of starvation extends. The brain can derive up to two-thirds of its metabolic requirement from ketone oxidation, which could result in the conservation of up to 80 g of glucose per day. Ketones are also used in this manner by the myocardium and liver.

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Phases of starvation

Initial 24–48 hours (glycogenolytic phase)

- Due to rise in glucagon (and fall in insulin)
- Liver and muscle glycogen stores exhausted by 24 hours
- Lipolysis and release of fatty acids, which subsequently undergo β-oxidation

After 24–48 hours up to a few days (gluconeogenic phase)

- Utilisation of glycerol, lactate (via the Cori cycle) and amino acids
- Plasma insulin very low. Cortisol and epinephrine rise initially
- Growth hormone rises after 24–48 hours and then decreases
- β-oxidation continues and ketone body production increases

Days-weeks (ketogenic phase)

- Gluconeogenesis begins to decline
- Tissues (including the central nervous system) adapt to using ketones bodies as fuel
- Basal metabolic rate falls by up to 30%

Box 1

The glucose requirements of red blood cells and the renal medulla, as mentioned earlier, also need to be met. These tissues can use the anaerobic metabolism of glucose to provide energy and produce lactate, which can then be recycled via the Cori cycle (Figure 1).

During this phase, urate levels increase and potassium levels fall initially, before stabilising at about 3.0 mmol/litre.

In severe starvation behavioural changes occur and only essential movement by the individual takes place. In extreme circumstances movement may only occur if survival is threatened. A reduction in sympathetic nervous system activity causes abnormalities in the maintenance of blood pressure and thermoregulation.

Death occurs after 40–60 days of starvation, with survival dependent on remaining triglyceride stores (and supply of water). When the final fat stores are exhausted, amino acids from remaining muscle mass are utilised. Ultimately death may occur as a result of the individual becoming too weak to cough and clear secretions followed by developing pneumonia.

Refeeding syndrome

Refeeding syndrome describes the characteristic metabolic disturbances that occur following reinstitution of nutrition to patients who have been starved for 5 days or more or who are severely malnourished. Plasma insulin levels rise due to an increase in serum glucose following intake of food. This causes cells to uptake glucose, potassium, magnesium and phosphate, resulting in serum levels of these ions falling to levels that are low enough to precipitate arrhythmias. Sodium is retained by the kidneys, resulting in water retention, increased extracellular volume and may lead to cardiac failure. The rise in carbohydrate metabolism also increases the respiratory quotient and therefore production of carbon dioxide. Removal of this excess carbon dioxide can place further stress on the weak respiratory system. Therefore the re-introduction of nutrition to a patient in a state of starvation must occur in a controlled fashion, with monitoring of exact calorific intake, electrolytes and fluids. Dieticians play a crucial role in planning the safe reintroduction of food and in calculating the specific nutritional requirements for patients at risk of refeeding syndrome.

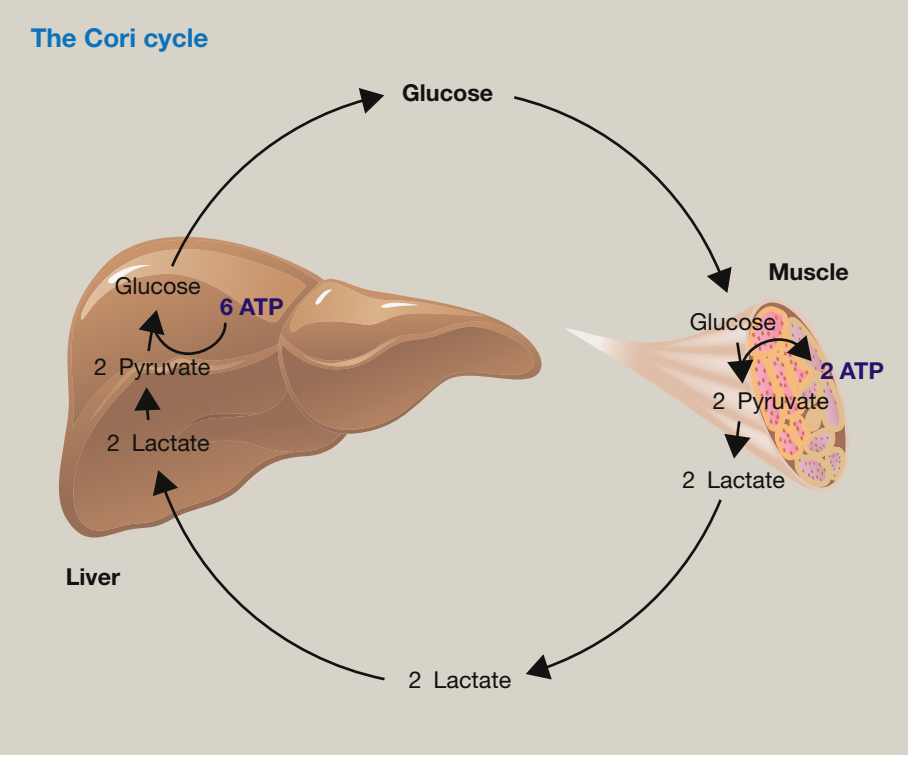

Figure 1

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