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Educational Paper

# Basics in clinical nutrition: Metabolic response to injury and sepsis

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## 1. Learning objectives

- To characterize the metabolic changes during injury and sepsis;
- To be able to understand the metabolic priorities for survival during a critical illness;
- To know the changed metabolic needs in injury and sepsis.

## 2. Introduction

All processes, in living animal cells, are dependent on a constant supply of substrate to generate high-energy phosphate bonds e.g. ATP. Energy is then harnessed to cellular activity by the hydrolysis of ATP. The turnover of ATP is extremely high reaching 1.3 mmol/kg/sec. As the total body pool of ATP in an individual of average size is between 60 and 100 mmol, this would cover energy requirements for less than a minute even when all ATP is fully hydrolyzed. It can be estimated that the mass of ATP hydrolyzed daily is equivalent to the body weight of the individual and that insufficient generation of ATP leads to irreversible destruction of the whole organism within less than one 1 minute. Continuous regeneration of ATP is therefore essential for survival under all conditions.

Carbohydrates (CHO), fat and proteins are the substrates, which are oxidized to generate ATP. Under normal circumstances these substrates are supplied in food, which is, after absorption, processed by different metabolic pathways. As food intake is not a continuous process the organism in between meals has to utilize energy substrates from its reserves. Under normal (non-stress) situations ingested CHO, fat and protein are partly stored as glycogen and lipid. Accumulation of protein can only occur in a quantatively modest manner, and may happen during growth of the individual, recovery after illness, training or postprandially. In healthy individuals, eating food of normal quantity and composition, as much nitrogen is excreted in urine, stools, skin, hair and sweat as is eaten during the day. The non-nitrogen part is oxidized or stored as fat or glycogen. During fasting, the body mobilizes these stores for tissue energy supply.

## 3. Stress response

During evolution energy requirements could not be supplied by food intake during critical illness, trauma or severe infection, because voluntary food intake generally stopped. The organism then had to consume its own energy stores to cover energy needs. However, trauma, critical illness, sepsis, burns, and other critical situations have distinct features that differ from short- or long-term starvation.

Cuthbertson originally described the metabolic response to injury in three phases:

1. The ebb or early shock phase of decreased metabolism.
2. The flow or catabolic phase.
3. The convalescent or anabolic phase when resynthesis of lost tissue can take place.

The flow phase of the metabolic response to stress can be characterized as an »all or nothing« response, which means that substrate supply must cover needs for »fight or escape« reactions,

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for prevention of bleeding, bacterial invasion, etc. Although this response is essential for survival in the short term, it carries the seeds of destruction when sustained or extreme, since the tissues such as muscle, adipose tissue, skin and others melt away. We therefore need to understand this paradox in its modern clinical context where it is modified by treatment and by all the weapons of critical care.

The metabolic reaction to stress is mediated by catabolic hormones (glucagon, catecholamines and corticoids) and by insulin resistance as well as by cytokines, eicosanoids, oxygen radicals, and other local mediators. These mediators have anabolic and catabolic actions. The catabolic action takes place largely in peripheral tissues like muscle, adipose tissue and skin and serves to furnish substrates for the healing response. In addition to the delivery of fuel the production of amino acids, which serve as building blocks for crucial acute phase proteins, participating in the healing response is crucial to successful recovery from disease. The amino acids required are not only those necessary for protein synthesis but also special non-essential amino acids like glutamine, alanine and may be arginine.

## 4. Substrate metabolism

### 4.1. Carbohydrates

One of the important metabolic goals during the general response to critical illness is to supply suitable substrate for tissues in which mitochondrial respiration is not (yet fully) possible as in white blood cells, macrophages and compromised tissues. Therefore injury initiates a strong increase in endogenous glucose production and turnover (up to 150% above control levels). Glucose is an indispensable substrate in this respect because part of the glucose breakdown (glycolysis) does not require oxygen, while still furnishing energy.

As a source of energy it can therefore be utilized in hypoxic and inflammatory tissues and in healing wounds in which mitochondria are not yet developed, or where fat cannot reach the cells due to the absence of capillaries. Therefore, immune cells, fibroblasts and granulation tissue, as well as the brain chiefly utilize glucose. Moreover, its metabolite – pyruvate – can accept $NH_2$ groups for transfer to the liver as alanine.

Glycogen, chiefly liver glycogen, supplies glucose for only 12–24 hours and during critical disease states glycogen stores are exhausted in an even shorter period. Therefore, formation of new glucose by the liver (gluconeogenesis) from lactate and amino acids is increased immediately. This augmentation in endogenous glucose production is related to critical illness and cannot be fully suppressed by exogenous glucose or by insulin, suggesting that gluconeogenesis is an obligatory process, initiated by stress hormones and cytokines, which cannot be suppressed in a similar manner to the fasted state. In fact this increased glucose production is vitally important for survival of the (human) organism in critical conditions (see above).

Quantitatively, lactate is the most important precursor of gluconeogenesis. As this substrate is the result of anaerobic glucose metabolism, the glucose carbons circulate between peripheral tissues and liver (Cori cycle) (Table 1). Under normal conditions about 150 g of lactate is metabolized in the liver, but this amount can increase greatly in stress conditions. The total energy loss in this cycle is 4 ATP molecules (see Fig. 1). In a similar manner glucose is produced from alanine (alanine is formed mainly in muscle from lactate and amino-groups; in this manner part of the waste nitrogen derived from amino acid breakdown in muscle is released into the circulation and can be metabolized in the liver to produce glucose). Glucose is also formed from glycerol, released from adipose tissue during lipolysis.

**Table 1**
Glucose metabolism during starvation and critical illness

| | Postprandial state | Prolonged starvation | Stress reaction |
|---|---|---|---|
| Gluconeogenesis | ↓ | ↑ | ↑↑↑ |
| Glycolysis | ↑ | ↓ | ↑↑↑ |
| Glucose oxidation | ↑↑↑ | ↓ | ↓ |
| Glucose cycling | ↑ | ↓ | ↑↑↑ |

### 4.2. Proteins and amino acids

Amino acids, released into the circulation by peripheral tissues are predominantly derived from muscle (Table 2). They are, together with glycerol, the main substrates for »de novo« glucose production in the liver because Cori-cycling does not furnish net "de novo" glucose (Fig. 1). The degree of protein catabolism in sepsis is large, reaching 260 g per day. This corresponds to a daily loss of more than 1 kg of muscle tissue, which implies that, when protein catabolism continues at this rate and when patients do not receive nutritional support, muscle tissue will be lost rapidly, hampering weaning from the ventilator and recovery. Moreover, particular amino acids, such as glutamine and branched-chain amino acids (BCAA), are the only substrates that can be utilized in some peripheral or wounded tissues as a source of energy. A large part of the BCAA derived from muscle protein breakdown is irreversibly degraded to yield part of the carbon skeleton and the amino-nitrogen of glutamine and alanine. This explains why re-utilization of the amino acids from muscle protein degradation for protein synthesis in liver, immune system and wound is inefficient in the sense that at the whole body level a negative nitrogen balance is achieved.

Amino acids released from muscle tissue are also used for the synthesis of acute phase proteins, albumin, fibrinogen, glycoproteins, complement factors, etc. In the flow phase, muscle catabolism can be reduced by nutritional support, by promoting protein synthesis, although complete suppression of muscle catabolism is impossible. Net muscle protein gain can only be achieved in the convalescent or anabolic phase of disease, provided adequate nutrition is administered and physical activity undertaken. In this phase the turnover of muscle protein turnover will slowly diminish

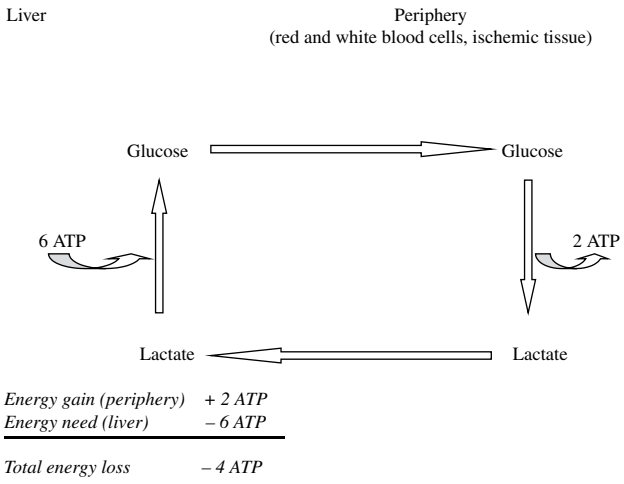


**Fig. 1.** Glycolysis and gluconeogenesis during critical illness (Cori cycle).

**Table 2**
Protein metabolism during starvation and critical illness

| | Postprandial state | Prolonged starvation | Stress reaction |
|---|---|---|---|
| Proteolysis | ↓ | ↓ | ↑↑↑ |
| Proteosynthesis | ↑ | ↓ | ↑↑ |
| Amino acid oxidation | ↑ | ↓ | ↑↑↑ |

**Table 3**
Lipid metabolism during starvation and a critical illness

| | Postprandial state | Prolonged starvation | Stress reaction |
|---|---|---|---|
| Lipolysis in fat tissue | ↓↓ | ↑↑↑ | ↑↑ |
| Lipid oxidation | ↓ | ↑↑↑ | ↑ |
| Ketogenesis | ↓↓ | ↑↑↑ | ↑ |
| Fatty acids – triglyceride cycling | – | ↓ | ↑↑ |

and protein gain will largely be achieved by a decrease in protein degradation as well as increased synthesis.

### *4.3. Lipids*

The energy, which is necessary for increased gluconeogenesis, either from lactate or from amino acids in the liver, is supplied by oxidation of fat which is probably the main energy substrate for liver cells (Table 3). As glucose is only partly oxidized and 80–90% of energy necessary for gluconeogenesis is derived from fat oxidation, the respiratory quotient of the whole organism is between 0.8 and 1.0.

Body lipid stores are substantial. Although an accelerated rate of lipolysis is part of the metabolic response to severe illness, regardless of its aetiology, the resulting fatty acid release can exceed energy requirements. The fatty acids that are released from adipose tissue are only partly oxidized in the liver and resting muscles and the remainder is re-esterified to triglycerides. This can lead to fatty infiltration of liver and muscle tissue, especially when high doses of glucose (above oxidation limit 4–5 mg $kg^{-1}$ $min^{-1}$ in an adult patient) are administered continuously. This may occur more readily when patients have diabetes, are obese or are septic.

Because of high insulin levels, hepatic ketogenesis is stimulated to a lesser degree during acute illness combined with starvation than in starvation alone. Because of this, glucose and amino acids are utilized in peripheral or wounded tissues as a source of energy.

## 5. Summary

The metabolic response to stress is mediated by catabolic hormones (glucagon, catecholamines and corticoids), insulin resistance as well as by cytokines, eicosanoids, oxygen radicals, and other local mediators. It is characterized as an acute substrate supply for prevention of bleeding, bacterial invasion, etc. It is essential for survival in the short term; however, it is destructive when sustained or extreme.

The stress response can only be reversed effectively by reducing infection, inflammation, heat loss, etc. Nutritional support can compensate by reducing negative energy and protein balance, but it cannot reverse a negative protein balance until the convalescent phase begins. Special substrates may however help to ameliorate some of the metabolic changes and improve outcome.

## Conflict of interest

There is no conflict of interest.

## Further reading

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