# Metabolic Response to Injury

## BASIC CONCEPTS IN HOMEOSTASIS

Homeostasis is the state of steady internal, physical, and chemical conditions maintained by living systems. This is the condition of optimal functioning for the organism and includes many variables, such as body temperature and fluid balance, being kept within certain pre-set limits (homeostatic range).

Resuscitation, surgical intervention and critical care can return the severely injured patient to a situation in which homeostasis becomes possible once again

## MEDIATORS OF THE METABOLIC RESPONSE TO INJURY

The classical neuroendocrine pathways of the stress response are bi phasic

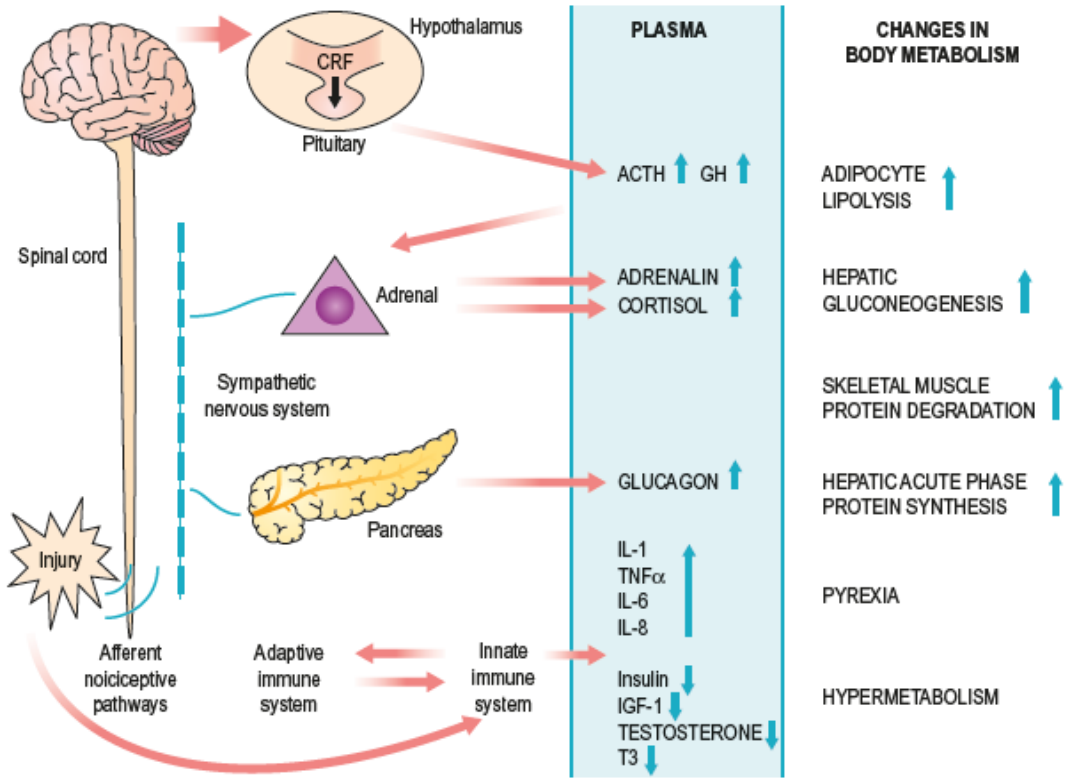
**Acute phase**

consist of Corticotrophinreleasing factor (CRF) released from the hypothalamus increases adrenocorticotrophic hormone (ACTH) release from the anterior pituitary. ACTH then acts on the adrenal to increase the secretion of cortisol. Hypothalamic activation of the sympathetic nervous system causes release of adrenalin and also stimulates release of glucagon. Intravenous infusion of a cocktail of these 'counter-regulatory' hormones (glucagon, glucocorticoids and catecholamines) reproduces many aspects of the metabolic response to injury.

**Chronic phase** associated with hypothalamic suppression and low serum levels of the respective target organ hormones. Changes contribute to chronic wasting.

The innate immune system (principally macrophages) interacts in a complex manner with the adaptive immune system (T cells, B cells) in co-generating the metabolic response to injury

Proinflammatory cytokines including interleukin-1 (IL-1), tumor necrosis factor alpha (TNF_), IL-6 and IL-8 are produced within the first 24 hours and act directly on the hypothalamus to cause pyrexia. Such cytokines also augment the hypothalamic stress response and act directly on skeletal muscle to induce proteolysis while inducing acute phase protein production in the liver. Proinflammatory cytokines also play a complex role in the development of peripheral insulin resistance.

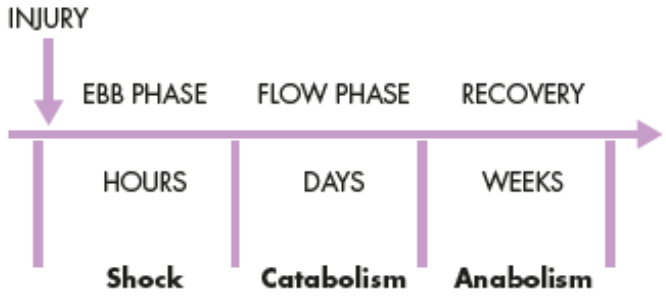



Within hours of the upregulation of proinflammatory cytokines, endogenous cytokine antagonists enter the circulation (e.g. interleukin-1 receptor antagonist (IL-1Ra) and TNF soluble receptors (TNF-sR-55 and 75)) and act to control the proinflammatory response.
changes include the development of a Th2-type counter-inflammatory response (regulated by IL-4, -5, -9 and -13 and transforming growth factor beta (TGF_)) which, if accentuated and prolonged in critical illness, is characterized as the CARS compensatory anti-inflammatory response syndrome and results in immunosuppression and an increased susceptibility to opportunistic (nosocomial) infection

## Physiological response to injury ((THE 'EBB AND FLOW' MODEL))

In the natural world, if an animal is injured, it displays a characteristic response, which includes immobility, anorexia and catabolism
The ebb phase begins at the time of injury and lasts for approximately 24–48 hours. It may be attenuated by proper resuscitation, but not completely abolished.
The ebb phase is characterized by hypovolemia, decreased basal metabolic rate, reduced cardiac output, hypothermia and lactic acidosis. The predominant hormones regulating the ebb phase are catecholamines, cortisol and aldosterone.

Following resuscitation, the ebb phase evolves into a hypermetabolic flow phase, This phase involves the mobilization of body energy stores for recovery and repair, and the subsequent replacement of lost or damaged tissue. It is characterized by tissue oedema (from vasodilatation and increased capillary leakage), increased basal metabolic rate (hypermetabolism), increased cardiac output, raised body temperature, leukocytosis, increased oxygen consumption and increased gluconeogenesis. The flow phase may be subdivided into an initial catabolic phase, lasting approximately 3–10 days, followed by an anabolic phase, which may last for weeks if extensive recovery and repair are required following serious injury.




During the catabolic phase, the increased production of counter-regulatory hormones (including catecholamines, cortisol, insulin and glucagon) and inflammatory cytokines (e.g. IL-1, IL-6 and TNF_) results in significant fat and protein mobilization, leading to significant weight loss and increased urinary nitrogen excretion. The increased production of insulin at this time is associated with significant insulin resistance and, therefore, injured patients often exhibit poor glycemic control.

## Insulin resistance

Following surgery or trauma, postoperative hyperglycemia develops as a result of increased glucose production combined with decreased glucose uptake in peripheral tissues. Decreased glucose uptake is a result of insulin resistance which is transiently induced within the stressed patient. Suggested mechanisms for this phenomenon include the action of proinflammatory cytokines and the decreased responsiveness of insulin-regulated glucose transporter proteins. The degree of insulin resistance is proportional to the magnitude of the injurious process.

Following routine upper abdominal surgery, insulin resistance may persist for approximately 2 weeks.

Postoperative patients with insulin resistance behave in a similar manner to individuals with type II diabetes mellitus. The mainstay of management of insulin resistance is intravenous insulin infusion.

## AVOIDABLE FACTORS THAT COMPOUND THE RESPONSE TO INJURY

### Continuing hemorrhage

During simple hemorrhage, pressor receptors in the carotid artery and aortic arch, and volume receptors in the wall of the left atrium, initiate afferent nerve input to the central nervous system (CNS), resulting in the release of both aldosterone and antidiuretic hormone (ADH). Pain can also stimulate ADH release. ADH acts directly on the kidney to cause fluid retention.

Decreased pulse pressure stimulates the juxtaglomerular apparatus in the kidney and directly activates the renin–angiotensin system, which in turn increases aldosterone release.

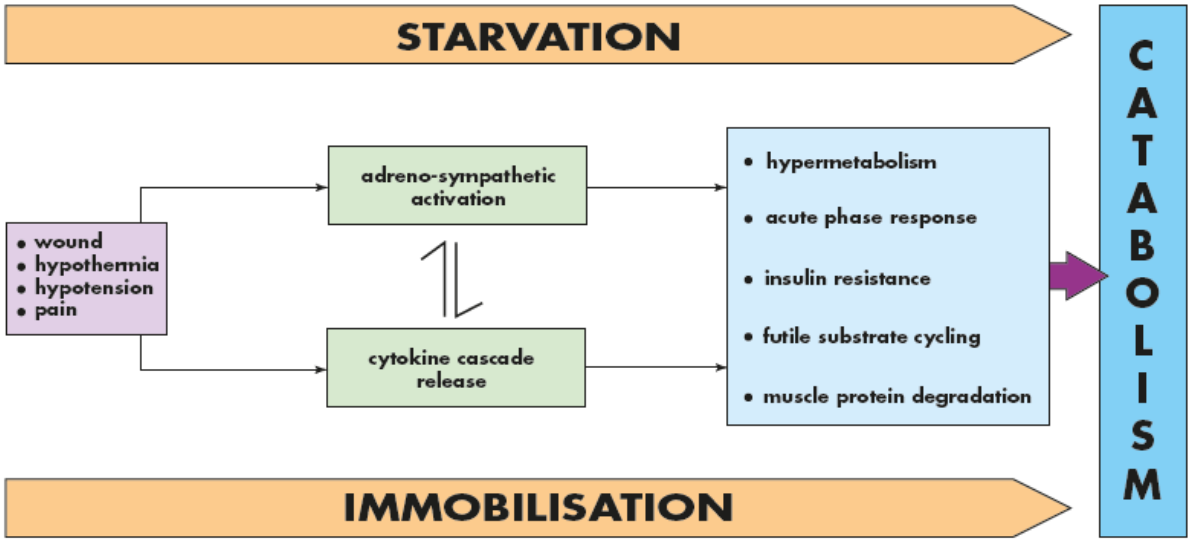
### Hypothermia

Hypothermia results in increased elaboration of adrenal steroids and catecholamines. When compared with normothermic controls, even mild hypothermia results in a two- to three-fold increase in postoperative cardiac arrhythmias and increased catabolism.

### Tissue oedema

During systemic inflammation, fluid, plasma proteins, leukocytes, macrophages and electrolytes leave the vascular space and accumulate in the tissues. This can diminish the alveolar diffusion of oxygen and may lead to reduced renal function.

Increased capillary leak is mediated by a wide variety of mediators including cytokines, prostanoids, bradykinin and nitric oxide. Vasodilatation implies that intravascular volume decreases, which induces shock if inadequate resuscitation is not undertaken.



## Systemic inflammation and tissue response

### Under-perfusion

The vascular endothelium controls vasomotor tone and microvascular flow, and regulates trafficking of nutrients and biologically active molecules. When endothelial activation is excessive, compromised microcirculation and subsequent cellular hypoxia contribute to the risk of organ failure. Maintaining normoglycemia with insulin infusion during critical illness has been proposed to protect the endothelium and prevent organ failure via preservation of the microcirculation in vital organs.

### Starvation

During starvation, the body is faced with an obligate need to generate glucose to sustain cerebral energy metabolism (100 g of glucose per day). This is achieved in the first 24 hours by mobilizing glycogen stores and thereafter by hepatic gluconeogenesis from amino acids, glycerol and lactate. The energy metabolism of other tissues is sustained by mobilizing fat from adipose tissue.

Such fat mobilization is mainly dependent on a fall in circulating insulin levels. Eventually, accelerated loss of lean tissue (the main source of amino acids for hepatic gluconeogenesis) is reduced as a result of the liver converting free fatty acids into ketone bodies, which can serve as a substitute for glucose for cerebral energy metabolism.

Avoiding unnecessary fasting in the first instance and early oral/enteral/parenteral nutrition form the platform for avoiding loss of body mass as a result of the varying degrees of starvation observed in surgical patients. Modern guidelines on fasting prior to anesthesia allow intake of clear fluids up to 2 hours before surgery.

### Immobility

Immobility has long been recognized as a potent stimulus for inducing muscle wasting. Inactivity impairs the normal meal-derived amino acid stimulation of protein synthesis in skeletal muscle. Avoidance of unnecessary bed rest and active early mobilization are essential measures to avoid muscle wasting as a consequence of immobility.