1 Homeostasis and Metabolic Response to Injury

Specific Learning Objectives

By the end of this chapter, the student must know:

- Basic concepts of homeostasis
- Body's response to trauma
- Mediators causing metabolic changes after trauma
- Pathophysiology of metabolic response to trauma
- The phases of metabolic response
- The steps to be taken to minimise the deleterious effects of metabolic response to trauma
- Concepts behind good perioperative care

"Big surgeons take big incisions" —was an old saying. It is now replaced with big surgeons doing minimal access surgery.

Competency achievement: The student should be able to:

SU1.1 Describe the basic concepts of homeostasis. Enumerate the metabolic changes in injury and their mediators.

SU1.2 Describe the factors that affect the metabolic response to injury.

BASIC CONCEPTS IN HOMEOSTASIS

It is a well-known fact that the human body tries to maintain a constant internal environment so as to allow the body to function at maximum efficacy. Thus homeostasis, i.e. the tendency of the body to maintain internal consistency, forms the foundation of normal physiology. So as to achieve the state of "milieu interieur", healing and repair are the most important elements as they are sufficient to ensure survival in the case of mild or sometimes moderate injuries. But they demand support in case of extensive/severe injury. So, stress-free perioperative care is indispensable in restoring the homeostasis after an elective surgery. It is possible for a severely injured patient to reach a situation of homeostasis again by the means of **resuscitation, surgical intervention and critical care**.

As a result of recently developed understanding of metabolic response to an injury, elective surgical practice seeks to decrease the need for a homeostatic response by reducing the primary insult to its absolute minimum (e.g. minimal access surgery).

RESPONSE COMPONENTS

In a conquest to attain the homeostasis, there is a wide array of responses happening. These responses form a complex interconnected pathway (Fig. 1.1) which insures the internal consistency. The components of this response are as follows:

- Physiological consequences
- Metabolic manifestations
- Clinical manifestations
- Laboratory changes

Physiological consequences

- Increased cardiac output
- Increased ventilation
- Increased membrane transport
- Weight loss
- Wound healing

Metabolic manifestations

- Hypermetabolism
- Accelerated gluconeogenesis
- Enhanced protein breakdown
- Increased fat oxidation

Clinical manifestations

- Fever
- Tachycardia
- Tachypnea
- Presence of wound or inflammation
- Anorexia

Laboratory changes

- Leucocytosis/leucopenia
- Hyperglycemia
- Elevated CRP/altered acute phase reactants
- Hepatic/renal dysfunction

GRADED NATURE OF THE INJURY RESPONSE

It is to be understood that the nature of response is also graded just like the injury which means the response received will be of same intensity as that of the injury. This concept is applicable on all the components of response mentioned earlier. The

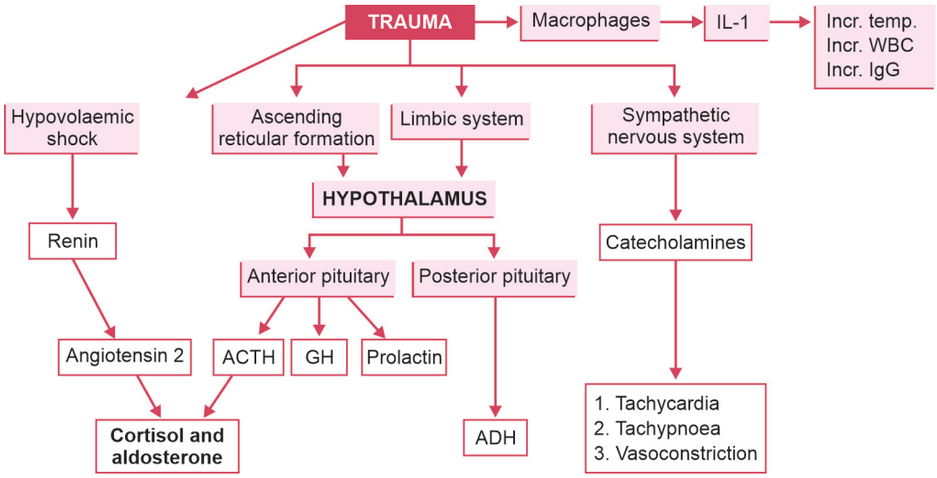

Fig. 1.1: Various responses to a trauma

catabolised structures help in the repair of the injured parts and at the same time maintaining the vital functions as illustrated in Fig. 1.2.

Thus, following an elective surgery that is mildly invasive in nature, there may be a mild fever, tachycardia, tachypnoea, increased BMR, and a slight peripheral leucocytosis. These changes would be intensified in case of a major injury where the patient could be severely febrile with a systemic inflammatory response syndrome, accompanied with hypermetabolism, shock resulting in multiple organ dysfunction syndrome and sometimes death. One must always keep into consideration the variability in the response intensity caused due to the genetic factor which plays a key role in expression of the same. Also, the metabolic response, along with being graded, evolves over time. This is due to the fact that the inflammatory response which will form the immunological sequelae of the insult, primarily evolve from the proinflammatory agents which are secreted by the innate immunity of the subject.

Mediators of Injury Response

The response has to be mediated and co-ordinated in the body for that there are two types of mediators, namely neuroendocrine (hormonal) and metabolic and cytokine axes.

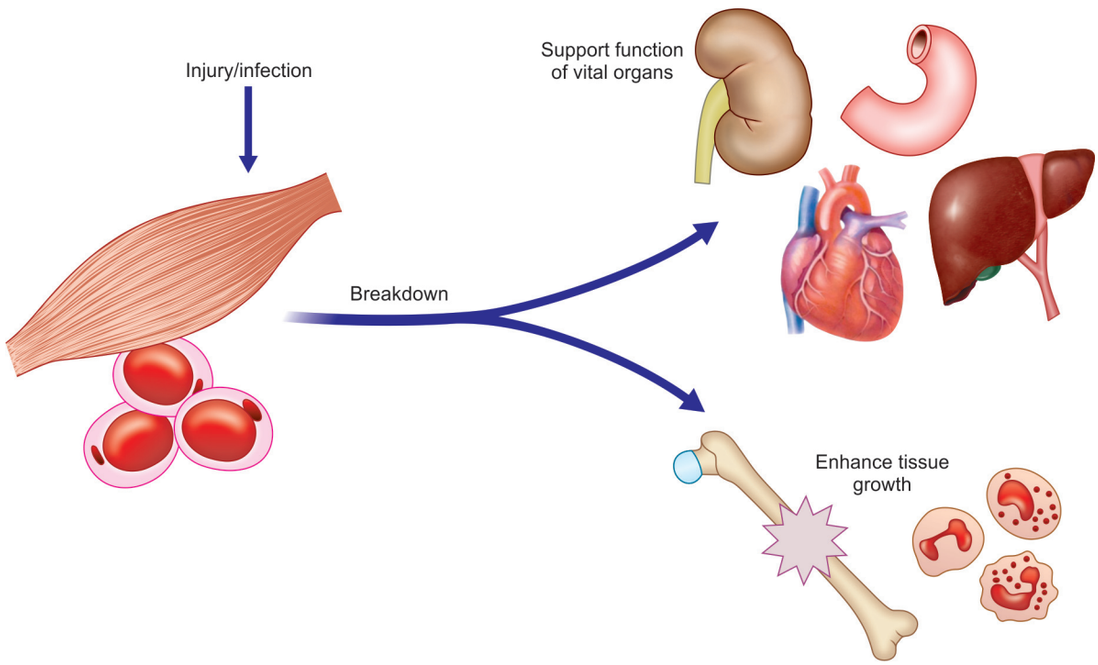

Fig. 1.2: The response cycle

Neuroendocrine Response to Injury/Critical Illness (Fig. 1.3)

This kind of response to an injury or critical illness occurs in two phases; namely **acute** and **chronic**.

1. **Acute phase:** The changes occurring in this phase are thought to be beneficial for **short-term survival**. This phase has an actively secreting pituitary and elevated counter-regulatory hormone (cortisol, glucagon, and adrenaline).
2. **Chronic phase:** The changes of this phase contribute to chronic wasting. The phase is characterized by hypothalamic suppression and low serum levels of the respective target organ hormones.

The group of events in neuroendocrine changes following injury acts so as to ensure survival by providing essential substrates, delays anabolism, reinforce host defence.

To the severely injured patient, these changes may be helpful in the short term, but may be harmful in the long term, especially when he would otherwise not have survived without medical intervention.

Metabolic and Cytokine Axes of Injury Response

Proinflammatory cytokines

1. IL-1, IL-6, TNF-α
2. NO
3. Endothelin 1

Cytokine antagonist: Interleukin receptor antagonist, TNF soluble receptors are released within hours of injury.

Physiological response to injury: The natural response to injury includes:

1. Immobility
2. Anorexia
3. Catabolism

The metabolic response to injury in humans was derived into "Ebb and Flow" phases by Sir David Cuthberstson in 1930 (Fig. 1.4).

Ebb (untreated shock): Starts at the time of injury and lasts for approximately 24–48 hours. Main hormones in Ebb phase are catecholamines, cortisol, and aldosterone. Although it may be reduced in intensity by proper resuscitation but is never completely stopped. The main physiological role of this phase is to conserve both circulating volume and energy stores for recovery and repair.

It consists of:

- Decreased body temperature
- Decreased O_2 consumption
- Lactic acidosis
- Increased stress hormones
- Decreased insulin
- Hyperglycaemia

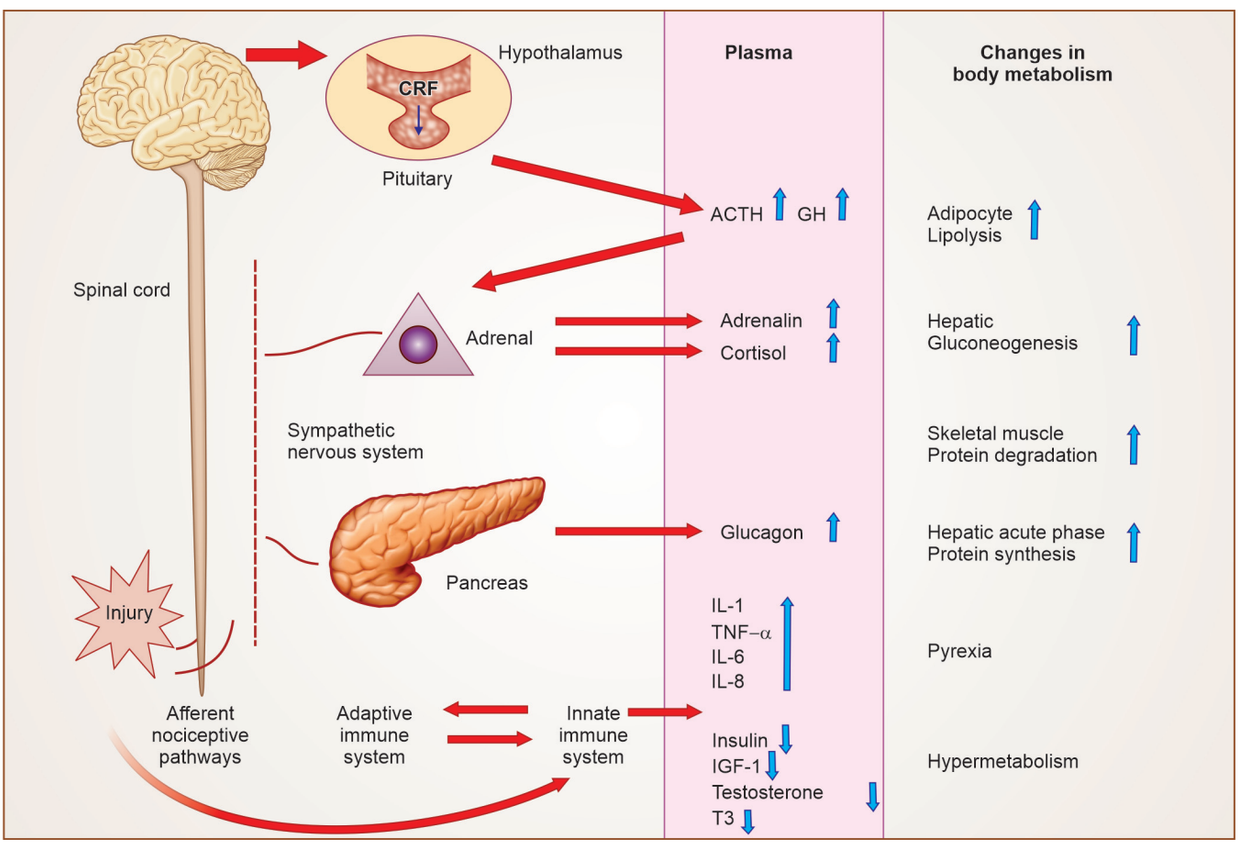

Fig. 1.3: Hormonal response

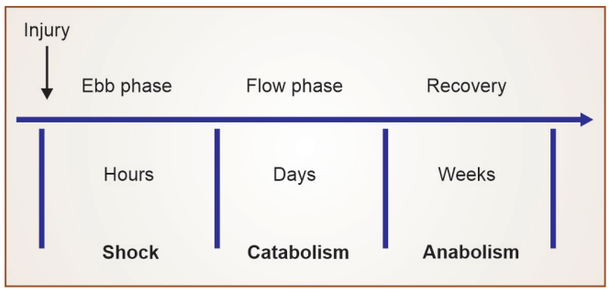

Fig. 1.4: Metabolic changes after major trauma (Cuthbertson, Lancet, 1942)

- Gluconeogenesis
- Increased substrate consumption
- Hepatic acute phase response
- Immune activation

Flow phase: It lasts for several weeks. This phase involves mobilization of body energy stores for repair and recovery. Following resuscitation, Ebb phase evolves into hypermetabolic flow phase, which corresponds to systemic inflammatory response syndrome (SIRS).

It consists of:

- Increased body temperature
- Increased O_2 consumption
- Negative nitrogen balance
- Increased stress hormone
- Normal to increased insulin
- Hyperglycaemia
- Gluconeogenesis
- Proteolysis (autocannabalism)
- Lipolysis
- Immunosuppression

A basic idea about Ebb and flow phases has been summarized in Table 1.1.

Hypermetabolism: Majority of trauma patients show an excess of approximately 15–25% in energy expenditure above predicted healthy resting values. Factors which increase this metabolism are central thermodysregulation, increased sympathetic activity, increased protein turnover, wound circulation abnormalities, etc.

Key catabolic elements of flow phase

- Hypermetabolism
- Alterations in skeletal muscle protein
- Alterations in liver protein
- Insulin resistance

Hypermetabolism following injury is predominantly caused by an acceleration of futile metabolic cycles and is minimal in modern practice due to elements of routine critical care.

Skeletal muscle wasting: Skeletal muscle protein is the source of amino acids for protein synthesis in central organ/tissues. It is carried out at a molecular level mainly by activation of the ubiquitin-protease pathway and it can cause immobility and be a contributing factor to hypostatic pneumonia and death, if in excess and for longer duration.

Hepatic acute phase response: The hepatic acute phase response demonstrates a priority bases reordering of body protein metabolism towards the liver and is characterized by:

- Positive reactants (CRP): Plasma concentration increases
- Negative reactants (albumin): Plasma concentration decreases

Insulin resistance: The degree of insulin resistance is directly proportional to grievousness of the injurious process. After a routine upper abdominal surgery, insulin resistance may occur for nearly 14 days. Postoperative patients with insulin resistance demonstrate similar behaviour to individuals with type 2 diabetes. The treatment of choice is IV insulin. Intensive insulin infusions are better over conservative approach.

Changes in Body Composition Following Injury

- Most readily available energy reserve in the body is **fat**.

TABLE 1.1 Ebb and flow phases

Phase	*Duration*	*Role*	*Physiological*	*Hormones*
Ebb	<24 hr	Maintenance of blood volume, catecholamines	↓ BMR, ↓ temp. ↓ O_2 consump, vasoconst, ↑ CO, ↑ heart rate, acute phase proteins	Catechol, cortisol, aldosterone
Flow				
• Catabolic	3–10 days	Maintenance of energy	↑ BMR, ↑ Temp, ↑ O_2 consump, –ve N2 balance	↑ Insulin, glucagon, cortisol, catechol but insulin resistance
• Anabolic (MOORE)	10–60 days	Replacement of lost tissue	+ve nitrogen balance	Growth hormone, IGF

- Most readily available protein reserve in the body is **skeletal muscle**.
- While fat mass can be decreased without major impairment of function, loss of protein mass leads to skeletal muscle wasting, and depletion of visceral protein mass.
- Following major injury, and especially in the presence of evident septic complications, the adaptive change does not occur, and there is a state of autocannibalism, leading to continuous urinary nitrogen losses of 10–20 g/day (500 g lean tissue/day).
- In case of total starvation, once loss of body protein mass has achieved a level of 30–40% of the total, survival is unlikely.

Avoidable factors that increase the response to injury:

1. Continuing haemorrhage
2. Hypothermia
3. Tissue oedema
4. Tissue under perfusion
5. Starvation
6. Immobility

Volume loss: Careful restriction of intraoperative administration of colloids and crystalloids so that there is no net weight gain.

Hypothermia: RCT have shown that wound infection, cardiac complications and bleeding and transfusion requirements are decreased by an upper body forced air heating cover which causes normothermia.

Tissue oedema: During systemic inflammation, fluid, plasma proteins, leucocytes, macrophages and electrolytes leave the vascular space and get collected in the tissues. This can diminish the alveolar diffusion of oxygen and may lead to reduced renal function.

Systemic inflammation and tissue under perfusion: The vascular endothelium controls vasomotor tone and microvascular flow and regulates movement of nutrients and biologically active molecules.

Administration of activated protein C to critically ill patients has been shown to reduce organ failure and death and is thought to act, in part, via preservation of the microcirculation in vital organs. To protect the endothelium, maintaining the normoglycaemia with insulin infusion during critical illness has been proposed, probably in part, via inhibition of excessive iNOS-induced NO release, and thereby resulting in the prevention of organ failure and death.

Starvation: During starvation, the body is challenged with an obligate need to generate glucose to maintain cerebral energy metabolism (100 g of glucose per day). This is done in the first 24 hours by mobilizing glycogen stores and after that by gluconeogenesis in liver from amino acids, glycerol and lactate. The energy metabolism of other tissues is maintained by providing fat from adipose tissue. Such fat mobilization is primarily dependent on a drop in circulating insulin levels. Eventually, accelerated loss of lean tissue is decreased as a result of the liver converting free fatty acids into ketone bodies, which serves as a substitute for glucose for cerebral energy metabolism. Provision of 2 litres of IV 5% dextrose as IV fluids for surgical patients, who are fasted, provides 100 g of glucose per day and has a significant protein sparing effect. Intake of clear fluids up to 2 hours before surgery is allowed in modern guidelines of anaesthesia. Perioperative anxiety and thirst and postoperative insulin resistance are decreased by administration of a carbohydrate drink at this time.

Immobility: It has been identified as a potent stimulus for inducing muscle wasting. Early mobilization is vital to avoid muscle wasting.

A prospective approach to restrict unnecessary aspects of the surgical stress response and optimize perioperative care and recovery includes:

1. Early mobilization
2. Minimal access techniques
3. Blockade of afferent painful stimuli (epidural anaesthesia)
4. Minimal periods of starvation

THERAPEUTIC IMPLICATIONS

The catabolic response to injury is continually a key concern in postoperative care. Three types of interventions were tried to reduce this.

These are:

- Nutritional
- Hormonal
- Biologic

Nutritional Treatment

Three central facets of nutrition need to be considered.

1. *Route of administration* (enteral/parenteral): Enteral nutrition is favoured. It improves the protein balance and clinical result.
2. *Timing* (early versus late feeding): Enteral nutrition is started as early as possible. Early feeding is better in its effects on catabolic and hypermetabolic response to injury.
3. A slower rate of fluid resuscitation after trauma haemorrhage leads to a faster restoration of the depressed cell-mediated immunity. However, rapid fluid resuscitation produces an extended depression of immune responses.

Hormonal Treatment

Anabolic hormones, GH, IGF-1 and insulin, promote positive nitrogen balance. GH supplementation

improves wound healing and decreases postoperative wound infection rate. IGF-1 mediates most of the metabolic effects of GH. Exogenous IGF-1 reduces gut mucosal atrophy in trauma. Both GH and IGF-1 are powerful modulators of the effector function of phagocytic cells.

Biologic Treatment

Several approaches have been tried, which include antibodies to endotoxin, TNF or IL-6. But most patients with sepsis have elevated levels of cytokines and other mediators. So, this can be given as "prophylaxis" for patients with high risk, e.g. those undergoing major surgical procedures. Genetic modifications can occur during injury and infection. Therefore, gene therapy will have a role in the management of trauma patients who are critically ill in the near future.

Key Points

Basic concepts in homeostasis

1. Homeostasis is the basis of normal physiology.
2. Stress-free perioperative care aids in restoring homeostasis following elective surgery.
3. **Resuscitation, surgical intervention and critical care** can return the severely injured patient to a situation in which homeostasis becomes possible once again.

As a consequence of modern understanding of metabolic response to injury, elective surgery practice seeks to reduce the need for a homeostatic response by minimizing the primary insult.

A prospective approach to prevent unnecessary aspects of the surgical stress response and optimize perioperative care and recovery includes:

1. Minimal access techniques
2. Blockade of afferent painful stimuli (epidural anaesthesia)
3. Minimal periods of starvation
4. Early mobilization.