1 Metabolic response to injury

- RESPONSE
- Starvation
- Systemic inflammation and tissue
- Tissue oedema
- Volume loss
- b b o
- l i i
- s s m m
- t a a
- underperfusion

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Within hours of the upregulation of proinflammatory cyto kines, 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 initial proinflammatory response and limit any systemic organ damage caused by it. A complex further series of adaptive c hanges includes the development of a counter-inflammatory response regulated by IL-4, -5, -9 and -13 and transforming growth factor beta (TGF β). Within inflamed tissue the duration and magnitude of acute inflammation as well as the return to homeostasis are influenced by a group of local mediators known as specialised pro-resolving mediators (SPMs), which include essential fatty acid-derived lipoxins, resolvins, protectins and maresins. These endogenous resolution agonists orchestrate the uptake and clearance of apoptotic polymorphonuclear neutrophils and microbial particles, reduce proinflammatory cytokines and lipid mediators as well as enhance the removal of cellular debris. Thus, both at the systemic level (endogenous cytokine antagonists – see earlier) α α and at the local tissue level, the body attempts to limit the inflammatory response, but further tissue damage, sepsis or other complications challenge these processes of resolution. As with the initial inflammatory response to tissue injury , it - appears that the degree of the secondary anti-inflammatory response varies between individuals, probably on a genetic basis. If the anti-inflammatory response dominates or is accentuated and prolonged in critical illness, it is characterised as a compensatory anti-inflammatory response syndrome (CARS), resulting in immunosuppression and an increased susceptibility to opportunistic (nosocomial) infection. Further sepsis, with its associated catabolism, results. CARS can be prolonged by ongoing critical illness as part of an ongoing vicious cycle of chronic critical illness (also known as Persis - tent Inflammation, Immunosuppression and Catabolism) syndrome. Thus both the initial inflammatory response to tissue injury and the secondary modulating r esponses can be seen to di ff ering degrees in di ff erent individuals or at di ff erent stages of the critical illness. Either circumstance can cause harm, and rapid restoration of homeostasis and preventing secondary inflammation or sepsis are key therapeutic principles that influence late outcomes as well as immediate ones.

BODY ME TA BOLISM ACTH GH ADIPOCYTE LIPO LY SIS HEPATIC ADRENALINE GLUCONEOGENESIS CO RT ISOL SKELE TA L MUSCLE PROTEIN DEGRAD AT ION HEPATIC ACUTE PHASE GLUCAGON PROTEIN SYNTHESIS IL-1 TNF PYREXIA IL-6 IL-8 Innate immune INSULIN HYPERMETABOLISM system IGF-1 TESTOSTERONE T3 , tumour necrosis factor alpha.

The metabolic response to surgery and injury: key characteristics /uni25CF α /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

Rapid onset driven by proin /f_l ammatory cytokines (e.g. IL-1, IL-6 and TNF) Broadly related to injury severity; most severe in sepsis, burns and major trauma Varies in severity between individuals (genetic) Causes catabolism, muscle breakdown, immunosuppression and organ dysfunction/failure Counterbalanced by antagonist response but the balance may be imperfect Prolonged by sepsis and other secondary insults Can become chronic Associated with most late deaths from injury or surgery in developed health systems

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CHANGES IN BODY COMPOSITION FOLLOWING INJURY

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The average 70 /uni00A0 kg male can be considered to consist of fat (13 /uni00A0 kg) and fat-free mass (or lean body mass: 57 /uni00A0 kg). In such an individual, the lean tissue is composed primarily of protein (12 /uni00A0 kg), water (42 /uni00A0 kg) and minerals (3 /uni00A0 kg) (Figure 1.5). The protein mass can be considered as two basic compartments: skeletal muscle (4 /uni00A0 kg) and non-skeletal muscle (8 /uni00A0 kg), which includes the visceral protein mass. The water mass (42 litres) is divided into intracellular (28 /uni00A0 litres) and extracellular (14 litr es) spaces. Most of the mineral mass is contained in the bony skeleton. - ↓ Figure 1.5

70 Fat 60 50 Protein 40 FFM or LBM Intracellular Mass (kg) 30 water 20 Extracellular 10 water Minerals 0 The chemical body composition of a normal 70 kg male. FFM, fat-free mass; LBM, lean body mass.

The main labile energy reserve in the body is fat, and the main labile protein reserve is skeletal muscle. While fat mass can be reduced without major detriment to function, loss of protein mass results not only in skeletal muscle wasting but also in depletion of visceral protein status. Within lean tissue, each 1 /uni00A0 g of nitrogen is contained within 6.25 /uni00A0 g of protein, which is contained in approximately 36 /uni00A0 g of wet weight tissue. Thus, the loss of 1 /uni00A0 g of nitrogen in urine is equivalent to the break down of 36 /uni00A0 g of wet weight lean tissue. Protein turnover in the whole body is of the order of 150–200 /uni00A0 g per day . A normal human ingests about 70–100 /uni00A0 g protein per day , which is metab olised and ex creted in urine as ammonia and urea (i.e. approx imately 14 /uni00A0 g /uni00A0 N/day). During total starvation, urinary loss of nitrogen is rapidly attenuated by a series of adaptive changes. Loss of body weight follows a similar cour se (Figure 1.6 accounting for the survival of hunger strikers for a period of 50–60 days. Follo wing major injury , and particularly in the presence of ongoing septic complications, this adaptive change fails to occur and there is a state of ‘auto-cannibalism’, result ing in continuing urinary nitrogen losses of 10–20 /uni00A0 g /uni00A0 N/day (equivalent to 500 /uni00A0 g of wet weight lean tissue per day). As with total starvation, once loss of body protein mass has reached 30–40% of the total, survival is unlikely . Critically ill patients admitted to the intensiv e care unit with severe sepsis or major blunt trauma undergo massive changes in body composition (Figure 1.7). Body weight increases immediately on resuscitation with an expansion of extracellular water by 6–10 litres within 24 hours. Thereafter, even with optimal metabolic care and nutritional support, total bod y protein will diminish by 15% in the next 10 days, and body

weight will reach negative balance as the expansion of the extracellular space resolves. In marked contrast, it is now possible to maintain body weight and nitrogen equilibrium following major elective surgery . This can be achieved by blocking the neuroendocrine stress response with epidural analgesia/other related techniques and providing early oral/ enteral feeding. Moreover, the early fluid retention phase can be avoided by careful intraoperative management of fluid balance, with avoidance of excessive administration of intravenous saline. Figure 1.6 Summary box 1.7 Changes in body composition following major surgery/ critical illness /uni25CF /uni25CF - - -

14 12 10 (%) 8 Sepsis and multiorgan Weight gain 6 4 2 2 24 68 10 12 14 16 18 20 22 days 4 6 8 Uncomplicated major (%) 10 12 Weight loss 14 16 Starvation failure surgery Changes in body weight that occur in serious sepsis, after uncomplicated surgery and in total starvation. Catabolism leads to a decrease in fat mass and skeletal muscle mass Body weight may paradoxically increase because of expansion of /f_l uid within the extracellular /f_l uid space

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The main labile energy reserve in the body is fat, and the main labile protein reserve is skeletal muscle. While fat mass can be reduced without major detriment to function, loss of protein mass results not only in skeletal muscle wasting but also in depletion of visceral protein status. Within lean tissue, each 1 /uni00A0 g of nitrogen is contained within 6.25 /uni00A0 g of protein, which is contained in approximately 36 /uni00A0 g of wet weight tissue. Thus, the loss of 1 /uni00A0 g of nitrogen in urine is equivalent to the break down of 36 /uni00A0 g of wet weight lean tissue. Protein turnover in the whole body is of the order of 150–200 /uni00A0 g per day . A normal human ingests about 70–100 /uni00A0 g protein per day , which is metab olised and ex creted in urine as ammonia and urea (i.e. approx imately 14 /uni00A0 g /uni00A0 N/day). During total starvation, urinary loss of nitrogen is rapidly attenuated by a series of adaptive changes. Loss of body weight follows a similar cour se (Figure 1.6 accounting for the survival of hunger strikers for a period of 50–60 days. Follo wing major injury , and particularly in the presence of ongoing septic complications, this adaptive change fails to occur and there is a state of ‘auto-cannibalism’, result ing in continuing urinary nitrogen losses of 10–20 /uni00A0 g /uni00A0 N/day (equivalent to 500 /uni00A0 g of wet weight lean tissue per day). As with total starvation, once loss of body protein mass has reached 30–40% of the total, survival is unlikely . Critically ill patients admitted to the intensiv e care unit with severe sepsis or major blunt trauma undergo massive changes in body composition (Figure 1.7). Body weight increases immediately on resuscitation with an expansion

of extracellular water by 6–10 litres within 24 hours. Thereafter, even with optimal metabolic care and nutritional support, total bod y protein will diminish by 15% in the next 10 days, and body weight will reach negative balance as the expansion of the extracellular space resolves. In marked contrast, it is now possible to maintain body weight and nitrogen equilibrium following major elective surgery . This can be achieved by blocking the neuroendocrine stress response with epidural analgesia/other related techniques and providing early oral/ enteral feeding. Moreover, the early fluid retention phase can be avoided by careful intraoperative management of fluid balance, with avoidance of excessive administration of intravenous saline. Figure 1.6 Summary box 1.7 Changes in body composition following major surgery/ critical illness /uni25CF /uni25CF - - -

14 12 10 (%) 8 Sepsis and multiorgan Weight gain 6 4 2 2 24 68 10 12 14 16 18 20 22 days 4 6 8 Uncomplicated major (%) 10 12 Weight loss 14 16 Starvation failure surgery Changes in body weight that occur in serious sepsis, after uncomplicated surgery and in total starvation. Catabolism leads to a decrease in fat mass and skeletal muscle mass Body weight may paradoxically increase because of expansion of /f_l uid within the extracellular /f_l uid space

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ENHANCED RECOVERY AFTER SURGERY

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Modern understanding of the metabolic response to surgical injury and the mediators involved has led to a complete reappraisal of traditional perioperative care and the process known as ERAS. ERAS is evidence based on the strong scien tific rationale for avoiding unmodulated exposure to stress, prolonged fasting and excessive administration of intravenous (saline) fluids (Figure 1.8). ERAS principles are now applied by protocol to many types of major surgery , bringing considerable benefit in terms of improved outcomes. Reductions in length of hospital stay after surgery of 30–50% are common, with associated savings in healthcare costs . ERAS depends on a multimodal approach where the combined e ff ects of several interventions achieve significant benefits. The widespread adoption of minimal access (e.g. laparoscopic) surgery is a key Figure 1.8 of surgical injury and enhance the rate of patients' return to homeostasis and recovery . Modulating the stress/inflammatory response at the time of surgery may have long-term sequelae over periods of months or longer. For example, β -blockers are associated with improved short- and long-term survival after major surgery , perhaps by modulating the e ff ects of the hyper - adrenergic state induced by surgical stress. Equally , in 'open' surgery the use of epidural analgesia to reduce pain, block the cortisol stress response and attenuate postoperative insulin resistance may , via e ff ects on the bod y's protein economy , favourably a ff ect many of the patient-centred outcomes that are important to postoperative recovery . However, because of the reduction in wound size and tissue trauma, it should be noted that epidural analgesia is no longer recommended for laparoscopic surgery . Patient-controlled analgesia is usually su ffi cient and avoids the fluid shifts and hypotension seen with epidurals. Adjuncts such as 'one-shot' spinal diamorphine and/or a 6–12-hour infusion of intravenous lidocaine have been suggested to be opiate sparing, to improve gut function and to enhance overall recovery . Summary box 1.9 A proactive ERAS approach to prevent unnecessary aspects of the surgical stress response /uni25CF /uni25CF /uni25CF /uni25CF -

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Homeostasis

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Homeostasis is the concept of maintaining a constant internal environment that allows cellular processes to function optimally . Many aspects of surgery , trauma and injury a ff ect homeostasis and can lead to organ dysfunction. Traditionally the metabolic response to injury is divided into an initial period of catabolism (which may include a period of shock) followed by an anabolic phase of repair and tissue healing. The catabolic phase begins at the time of injury and is characterised by hypovolaemia, decreased basal metabolic rate, reduced cardiac output, hypothermia and lactic acidosis. The main physiological role of this phase is to conserve both circulating volume and energy stores and thus maximise sur - vival chances for future recovery . A series of neurohormonal responses accompany these e ff ects and trigger a systemic inflammatory response syndrome (SIRS), where body stores are mobilised for recover y and repair. The catabolic e ff ects include muscle breakdown, weight loss and hyperglycaemia, which themselves increase the risk of complications, especially sepsis. As the catabolic phase subsides, an anabolic (rebuilding) phase develops, which may last for weeks if extensive recovery and repair are required following serious injury .

Avoidable factors that compound the metabolic response • to injury How the metabolic response to injury in /f_l uences surgical • outcomes Concepts behind optimal perioperative care •

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There are several factors that prolong the acute-phase response to injury (Table 1.1) and keep the patient in a - catabolic state. Other factors can exacerbate or compound the metabolic stress response both in elective surgery and in the emergency setting. These include anaesthesia, dehydra - tion, starvation (including preoperative fasting), acute medical illness, frailty , chronic diseases or even severe psychological stress (Figure 1.7) . Attempts to limit or contr ol these factors can also be beneficial to the patient. Summary box 1.8 Avoidable factors that compound the metabolic re - sponse to injury during elective surgery /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

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Immobilisation

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Adreno-sympathetic activation Wound Hypothermia Hypotension Pain Cytokine cascade release

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Immobility has long been recognised 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 mobilisation are essential measures to avoid muscle wasting as a consequence of immobility . Pre-habilitation programmes provide a better starting point before surgery . Immobility

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Introduction

INTRODUCTION

As surgeons we are inextricably linked with tissue injury and its e ff ects, both from the damage which operating inevitably causes and from the treatment of accidental traumatic injury . The body responds to significant local tissue injury , whether surgical or accidental, with a series of systemic changes which a ff ect the functions of vital organs. This surgical stress response is brought about by several pathways involving hormones, inflammation-related cytokines and neural circuits. It leads to alterations in body metabolism, wound healing and immunity and in the function of specific organs. These changes are known collectively as the metabolic response to injury . While these responses are designed to limit damage and begin repair processes, not all the e ff ects are beneficial by any means. They can lead to complications, especially sepsis, which can then amplify and prolong the abnormal processes and lead to or prolong multiple organ dysfunction syndrome (MODS). Given that these metabolic e ff ects of injury can have a significant impact on recovery and survival from many types of surgery and surgical illness, surgeons require an understanding of them in order to care optimally for their patients. Successful management of the metabolic response improves outcomes and forms the basis of modern perioperative care after major surgery as well as the treatment of severely injured and septic patients. This chapter will look primarily at the metabolic responses to injury while shock, fluid balance, sepsis and nutrition are covered in greater depth in Chapters 2 and 25

Learning objectives

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To understand: How the body responds to accidental injury and surgery • Physiological and biochemical changes that occur during • injury and recovery Mediators and pathways of the metabolic response to • injury Learning objectives

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MANAGING THE CATABOLIC STRESS RESPONSE

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There are several key elements that determine the extent of catabolism and thus govern the metabolic and nutritional care of the surgical patient. It must be remembered that, during the response to injury , not all tissues are catabolic. Indeed, the essence of this coordinated response is to allow the body - to reprioritise limited resources away from peripheral tissues (muscle, adipose tissue, skin) and towards key viscera (liver, immune system) and the wound (Figure 1.3) . However the damage to skeletal muscle can be catastrophic. Figure 1.3

Central tissues Liver During the metabolic response to injury, the body reprioritises protein metabolism away from peripheral tissues and towards key central tissues such as the liver, Immune system immune system and wounds. One of the main reasons why the reutilisation of amino

acids derived from muscle proteol

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The majority of trauma patients (except possibly those with extensive burns, in whom a greater e ff ect can be seen) demonstrate energy e xpenditures approximately 15–25% above pr edicted healthy resting values. The predominant cause appear s to be a complex interaction between the central control of metabolic rate and peripheral energy utilisation. In particular, central thermodysregula tion (caused by the proinflammator y cytokine cascade), increased sympathetic activity , abnormalities from wound circulation (ischaemic areas produce lactate, whic h must be metabolised by the adenosine triphosphate [ATP]-consuming he patic Cori cycle; hyperaemic areas cause an increase in car diac output), increased protein turnover and nutritional support may all increase patient energy expenditure. Theoretically , patient energy expenditure could rise even higher than observed levels f ollowing surgery or trauma, but several features of standard intensive care (including bed rest, paralysis, ventilation and external temperature regulation) limit the hypermetabolic driving forces of the stress r esponse. Furthermore, the skeletal muscle wasting experienced by patients with prolonged catab olism actually limits the volume of metabolically active tissue (see Alterations in skeletal muscle protein metabolism MANAGING THE CATABOLIC STRESS RESPONSE

There are several key elements that determine the extent of catabolism and thus govern the metabolic and nutritional care of the surgical patient. It must be remembered that, during the response to injury , not all tissues are catabolic. Indeed, the essence of this coordinated response is to allow the body - to reprioritise limited resources away from peripheral tissues (muscle, adipose tissue, skin) and towards key viscera (liver, immune system) and the wound (Figure 1.3) . However the damage to skeletal muscle can be catastrophic. Figure 1.3

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Tissue injury is sensed in several ways. Tissue damage causes the release of cellular and other molecular fragments known as damage-associated molecular patterns (DAMPs) or alarmins. These DAMPs are sensed by pattern recognition receptors (PRRs), such as Toll-like receptors and NOD-like receptors (or nucleotide-binding leucine-rich repeat receptors) on cells of the innate immune system, which includes macrophages, neutrophils and dendritic cells. These cells are attracted and activated, triggering the formation of complex intracellular proteins known as inflammasomes. This results in the activation of caspases; these are enzymes that, in turn, activate key inflammatory cytokines including interleukin-1 (IL-1), IL-6 and many others. PRR activation also leads to release of tumour necrosis factor alpha (TNF), interferons, chemokines and other mediators. Thus begins a sterile systemic inflammatory cascade tha t leads to local inflammation and, when su ffi ciently severe, to a clinically detectable SIRS. Once activated by DAMPs, inflammasomes also contribute to cell death, tissue damage and immune suppression. DAMPs can activate inflammasome formation in endothelial cells and platelets, resulting in leaky capillaries and coagulopathy; these are changes that can result in the production of more DAMPs owing to local ischaemia from microcirculatory e ff ects. Local inflammation begins the process of tissue repair but SIRS, when uncontrolled or prolonged, becomes a risk factor for acute kidney injury , acute lung injury and coagulopathy , and hence for MODS and organ /uni00A0 failure. Within the injured brain, secondary brain injury can occur. DAMPs thought to be important in tissue trauma include heat shock proteins, high mobility group protein B1 (HMGB1), S100 proteins and fragments of nucleic acids . Commonly , DAMPs can activate several di ff erent receptors and pathways. This crossover, or redundancy as it is termed, is a characteristic of inflammation and has been one of the barriers to developing

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TABLE 1.1 Some secondary triggers of the metabolic response to injury. Secondary triggers of in /f_l ammatory pathways in trauma and surgery Sepsis Haemorrhage Massive transfusion Acidosis Surgery Crush syndrome Ischaemia–reperfusion These events can amplify or prolong the catabolic phase, leading to organ failure or immune dysfunction.

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Modern surgical care

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The role of surgical critical care, including resuscitation and/ or organ support, must be to work alongside the metabolic e ff ects of injury while the patient is restored to a situation from which homeostatic mechanisms can achieve a return to normality . The systemic e ff ects of injury still impact heavily on survival and complications through loss of muscle mass, sepsis and MODS. In fact, modern treatment of major trauma can now be so successful that the great majority of hospital deaths . in developed countries occur after some days as a result of complex physiological processes, rather than as a direct and rapid consequence of organ damage or blood loss, although it is the initial injury and blood loss that sets the scene for the later systemic e ff ects. Parallel with the catabolic e ff ects introduced above, inflammatory-type processes cause immune suppression. While this inflammation is often initially sterile, the nature of surgery and injury predisposes to infection and sepsis. Impaired immunity as part of the metabolic response failure is a key part of perioperative care and a leading mode of death among our patients. Even in modern trauma systems, MODS carries a mortality of around 25%. As a consequence of modern understanding of the meta bolic response to injury , elective surgical practice now seeks to actively reduce the need for a homeostatic response by mini mising the primary insult via minimal access surger y and by ‘stress-free’ perioperative care or enhanced recovery after sur gery (ERAS). This chapter will review the mediators of the str ess response, the physiological and biochemical pathway changes associated with surgical injury and the changes in body composition that occur following surgical injur y . Empha sis is placed on why knowledge of these events is important to understand the rationale for modern ‘stress-free’ perioperative and critical care. Summary box 1.1 Basic concepts /uni25CF /uni25CF /uni25CF /uni25CF Figure 1.1

Homeostasis is the foundation of normal physiology ‘Stress-free’ perioperative care helps to preserve homeostasis following elective surgery Resuscitation, surgical intervention and critical care can return the severely injured patient to a situation in which homeostasis becomes possible once again The metabolic response to surgery in /f_l uences these processes profoundly, particularly through catabolic effects, MODS and impaired immunity 140 Major trauma 130 Minor trauma 120 110 Normal 100 range 90 Starvation Resting metabolic rate (%) 80 0 1 0 2 0 3 0 4 0 5 0 6 0 7 0 Major trauma 25 Minor trauma 20 15 Normal (g N/day) 10 range Nitrogen excretion 5 0 Hypermetabolism and increased nitrogen excretion are closely related to the magnitude of the initial injury and show a graded response.

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Neuroendocrine response to injury

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Patients also respond rapidly to injury by the classical neuroen docrine pathways of the stress response, consisting of a ff erent nociceptive neurones, the spinal cord, thalamus, hypothalamus and pituitary (Figure 1.2). Nociceptive neurones are ex by the e ff ects of local inflammation as well as by direct injury . The neurones terminate in the hypothalamus and release corti cotropin-releasing factor (CRF). CRF stimulates adrenocorti cotropic hor mone (ACTH) release from the anterior pituitary , which then acts on the adrenals to increase the secretion of cortisol within hours of injury . Hypothalamic activation of the sympathetic nervous system causes release of adrenaline (epinephrine) and also stimulates release of glucagon. An intravenous infusion of a cocktail of these ‘counter-regulatory’ hormones (glucagon, glucocorticoids and catecholamines) reproduces many aspects of the metabolic response to injury . The metabolic e ff ects of the acute rise in the levels of these hormones is to liberate glucose from carbohydrate stores and to begin the breakdown of fat and protein as metabolic substrates for energy and repair. There are, however, many other e ff ects, including alterations in insulin release and sensitivity , hypersecretion of prolactin and growth hormone (GH) in the presence of low circulatory insulin-like growth factor-1 (IGF-1) and inactivation of peripheral thyroid hormones and gonadal function. Of note, GH has direct lipolytic, insulin-antagonising and proinflammatory properties. Neuroendocrine response to injury/critical illness - /uni25CF /uni25CF - As described above, the innate immune system (principally macrophages), once activated by DAMPs, interacts in a complex manner with the adaptive immune system (T cells, B cells) in co-generating the metabolic response to injury (Figure 1.2) . Proinflammatory cytokines including IL-1, TNF alpha (TNF α), 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 pr oteolysis while inducing acute-phase protein production in the liver. Proinflammatory cytokines also play a complex role in the development of peripheral insulin resistance. Other import - ant proinflammatory mediators include nitric oxide ([NO] via inducible nitric oxide synthetase [iNOS]) and a variety of prostanoids (via cyclooxygenase-2 [Cox-2]). Changes in organ function (e.g. renal hypoperfusion/impairment) may be induced b y excessive vasoconstriction via endogenous factors such as endothelin-1. Complement and kinin pathways are also activated and processes of programmed cell death and - phagocytosis are triggered to clear damaged tissues. There are many complex interactions among the neuroendocrine, cytokine and metabolic axes. For example, cited although cortisol is immunosuppressive at high levels, it acts synergistically with IL-6 to promote the hepatic acute-phase - r esponse. ACTH release is enhanced by proinflammatory - cytokines and the noradrenergic system. The resulting rise in cortisol levels may form a weak feedback loop, attempting to limit the proinflammatory stress response. Finally , hyperglycaemia may aggravate the inflammatory response in the mitochondria, causing the formation of excess oxygen free

radicals and also altering gene expression to enhance cytokine production. At the molecular level, the changes that accompany systemic inflammation are extremely complex. In one study using network-based analysis of changes in mRNA expression in leukocytes following exposure to endotoxin, ther e were changes in the expression of more than 3700 genes, with over half showing decreased expression and the remainder increased expression. The cell surface receptors, signalling mechanisms and transcription factors that initiate these events are also complex. Although the detailed mechanisms are being steadily identified, specific molecular therapies remain elusive and certainly subservient to optimal clinical care.

The neuroendocrine response to severe injury/critical illness is biphasic: Acute phase (hours) characterised by elevated counter- regulatory hormones (cortisol, glucagon, adrenaline). Changes are thought to be bene /f_i cial for short-term survival Chronic phase (days) associated with hypothalamic suppression and low serum levels of the respective target organ hormones. Changes may contribute to chronic wasting

Figure 1.2

CRF Pituitary Spinal cord Ad re nal Sympathetic nervous system Pancreas Injury Afferent Adaptive noiciceptive immune pathways system The integrated response to surgical injury (/f_i rst 24–48 hours): there is a complex interplay between the neuroendocrine stress response and the proin /f_l ammatory cytokine response of the innate immune system. ACTH, adrenocorticotropic hormone; GH, growth hormone; IGF , insulin-like growth factor; IL, interleukin; T3, triiodothyronine; TNF

Neuroendocrine response to injury

Patients also respond rapidly to injury by the classical neuroen docrine pathways of the stress response, consisting of a ff erent nociceptive neurones, the spinal cord, thalamus, hypothalamus and pituitary (Figure 1.2). Nociceptive neurones are ex by the e ff ects of local inflammation as well as by direct injury . The neurones terminate in the hypothalamus and release corti cotropin-releasing factor (CRF). CRF stimulates adrenocorti cotropic hor mone (ACTH) release from the anterior pituitary , which then acts on the adrenals to increase the secretion of cortisol within hours of injury . Hypothalamic activation of the sympathetic nervous system causes release of adrenaline (epinephrine) and also stimulates release of glucagon. An intravenous infusion of a cocktail of these ‘counter-regulatory’ hormones (glucagon, glucocorticoids and catecholamines) reproduces many aspects of the metabolic response to injury . The metabolic e ff ects of the acute rise in the levels of these hormones is to liberate glucose from carbohydrate stores and to begin the breakdown of fat and protein as metabolic substrates for energy and repair. There are, however, many other e ff ects, including alterations in insulin release and sensitivity , hypersecretion of prolactin and growth hormone (GH) in the presence of low circulatory insulin-like growth factor-1 (IGF-1) and inactivation of peripheral thyroid hormones and gonadal function. Of note, GH has direct lipolytic, insulin-antagonising and proinflammatory properties. Neuroendocrine response to injury/critical illness - /uni25CF /uni25CF - As described above, the innate immune system (principally macrophages), once activated by DAMPs, interacts in a complex manner with the adaptive immune system (T cells, B cells) in co-generating the metabolic response to injury (Figure 1.2) . Proinflammatory cytokines including IL-1, TNF alpha (TNF α), 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 pr oteolysis while inducing acute-phase protein production in the liver. Proinflammatory cytokines also play a complex role in the development of peripheral insulin resistance. Other import - ant proinflammatory mediators include nitric oxide ([NO] via inducible nitric oxide synthetase [iNOS]) and a variety of prostanoids (via cyclooxygenase-2 [Cox-2]). Changes in organ function (e.g. renal hypoperfusion/impairment) may be induced b y excessive vasoconstriction via endogenous factors such as endothelin-1. Complement and kinin pathways are also activated and processes of programmed cell death and - phagocytosis are triggered to clear damaged tissues. There are many complex interactions among the neuroendocrine, cytokine and metabolic axes. For example, cited although cortisol is immunosuppressive at high levels, it acts synergistically with IL-6 to promote the hepatic acute-phase - r esponse. ACTH release is enhanced by proinflammatory - cytokines and the noradrenergic system. The resulting rise in cortisol levels may form a weak feedback loop, attempting to limit the proinflammatory stress response. Finally , hyperglycaemia may aggravate the inflammatory response in the mitochondria, causing the formation of excess oxygen free radicals and also altering gene expression to enhance cytokine production. At the molecular level, the changes that accompany systemic inflammation are extremely complex. In one study using network-based analysis of changes in mRNA expression in leukocytes following exposure to endotoxin, ther e were changes in the expression of more than 3700 genes, with over half showing decreased expression and the remainder increased expression. The cell surface receptors, signalling mechanisms and transcription factors that initiate these events are also complex. Although the detailed mechanisms are being steadily identified, specific molecular therapies remain elusive and certainly subservient to optimal clinical care.

The neuroendocrine response to severe injury/critical illness is biphasic: Acute phase (hours) characterised by elevated counter- regulatory hormones (cortisol, glucagon, adrenaline). Changes are thought to be bene /f_i cial for short-term survival Chronic phase (days) associated with hypothalamic suppression and low serum levels of the respective target organ hormones. Changes may contribute to chronic wasting

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RESPONSE

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It is important to recognise that, in general or population terms, the metabolic response to injury is graded: the more severe - the injury , the greater the response (Figure 1.1). This concept applies not only to physiological and metabolic changes but - also to immunological changes and other sequelae. Thus, following major elective surgery , there may be a transient and - modest rise in temperature, heart ra te, respiratory rate, energy expenditure and peripheral white cell count. Following major trauma, emergency surgery , sepsis or burns, these changes are accentuated, resulting in SIRS, with hypermetabolism, - marked catabolism, shock and even MODS. However, genetic variability also plays a key role in determining the intensity of the inflammatory response, with some individual patients responding much more dramatically than others to apparently similar conditions. RESPONSE

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Starvation

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Figure 1.7

Factors that exacerbate the metabolic response to surgical injury include hypothermia, uncontrolled pain, starvation, immobilisation, sepsis and medical complications.

Starvation

During starvation, the body is faced with an obligate need to generate glucose to sustain cerebral energy metabolism (100 /uni00A0 g of glucose per day). This is achieved in the first 24 hours by mobilising glycogen stores and thereafter by hepatic glucone - ogenesis from amino acids, glycerol and lactate. The energy metabolism of other tissues is sustained by mobilising fat from adipose tissue. Such fat mobilisation is mainly dependent on a fall in circulating insulin levels. Eventually , accelerated loss of neogenesis) 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. Provision of 2 litres of intrav enous 4% dextrose/0.18% sodium chloride as maintenance intravenous fluids for surgical patients who are fasted provides 80 /uni00A0 g of glucose per day and has a significant protein-sparing e ff ect. Avoiding unnecessary fasting in the first instance and early oral/enteral/par enteral 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 anaesthesia allow intake of clear fluids up to 2 hours before surgery . Administration of a carbohydrate drink at this time reduces perioperative anxiety and thirst and decreases postoperative insulin resistance. Starvation

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Systemic inflammation and tissue

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Tissue oedema

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Volume loss

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During simple haemorrhage, baroreceptors in the carotid artery and aortic arch and volume receptors in the wall of the left atrium initiate a ff erent nerve input to the central nervous system, resulting in the release of both aldosterone and antid iuretic hormone (ADH). Pain can also stimulate ADH release. ADH acts directly on the kidney to cause fluid retention. Decreased pulse pressure stimulates the juxtaglomerular appa ratus in the kidney and directly activates the renin–angiotensin system, w hich in turn increases aldosterone release. Aldosterone causes the renal tubule to reabsorb sodium (and consequently conserve water). ACTH release also aug ments the aldoster one response. The net e ff ects of ADH and aldosterone result in the natural oliguria observed after sur gery and conserva tion of sodium and water in the extracellular space. The tendency towards water and salt retention is e erbated by resuscitation with saline-rich fluids. Salt and wa retention can result in not only peripheral oedema but also visceral oedema (e.g. in the stomach). Such visceral oedema has been associated with reduced gastric emptying, delayed resumption of food intake and pr olonged hospital stay . Careful limitation of intraoperative administration of balanced crys talloids so that there is no net weight gain following elective surgery has been proven to reduce postoperative complications and length of stay . Volume loss

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b b o

b b o

o l

Insulin resistance Futile substrate cycling

b b o

o l

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b b o

o l

Insulin resistance Futile substrate cycling

l i i

l i i

Muscle protein degradation

l i i

Muscle protein degradation

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Muscle protein degradation

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t a a

Acute phase response

t a a

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t a a

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underperfusion

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