Understanding the metabolic response to trauma

Introduction

The management of the polytrauma patient is still a great challenge and trauma remains the leading cause of death in people under 40 years of age in the developed world (Keel and Trentz, 2005). The pattern of death following injury is classically described as having a trimodal distribution:

1. Occurring at the scene as a result of catastrophic injuries, such as aortic transection and massive haemorrhage
2. Within the first 24–48 hours often as a result of neurological dysfunction
3. In the days and weeks following the initial insult, largely as a result of sepsis and multiple organ failure (Baker et al, 1980).

'There is a circumstance attending accidental injury which does not belong to disease, namely, that the injury done, has in all cases a tendency to produce both the disposition and the means of cure' (Hunter, 1794).

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Trauma triggers a complex, coordinated metabolic response geared towards the restoration of homeostasis (*Figure 1*). The success of this response has a direct impact on the survival of the patient and a greater understanding of the response to injury is invaluable in tailoring care to improve outcome.

First described by Cuthbertson in 1942, the metabolic response to trauma can be divided into two distinct phases: an 'ebb' and a 'flow' phase. The ebb phase is a period of diminished vitality, which occurs almost immediately after a moderate or severe insult and typically lasts 24 hours, clinically manifesting as shock. This is followed by a period of increased metabolic activity (hypermetabolism) lasting a few days to a couple of weeks – the flow phase (Cuthbertson, 1980). This article outlines the key metabolic aberrations associated with trauma; discussion of the important role played by the immune system and inflammation (namely chemokines, alarmins (Lenz et al, 2007), and cytokines (Moshage, 1997)) is beyond its remit.

Catecholamines in trauma

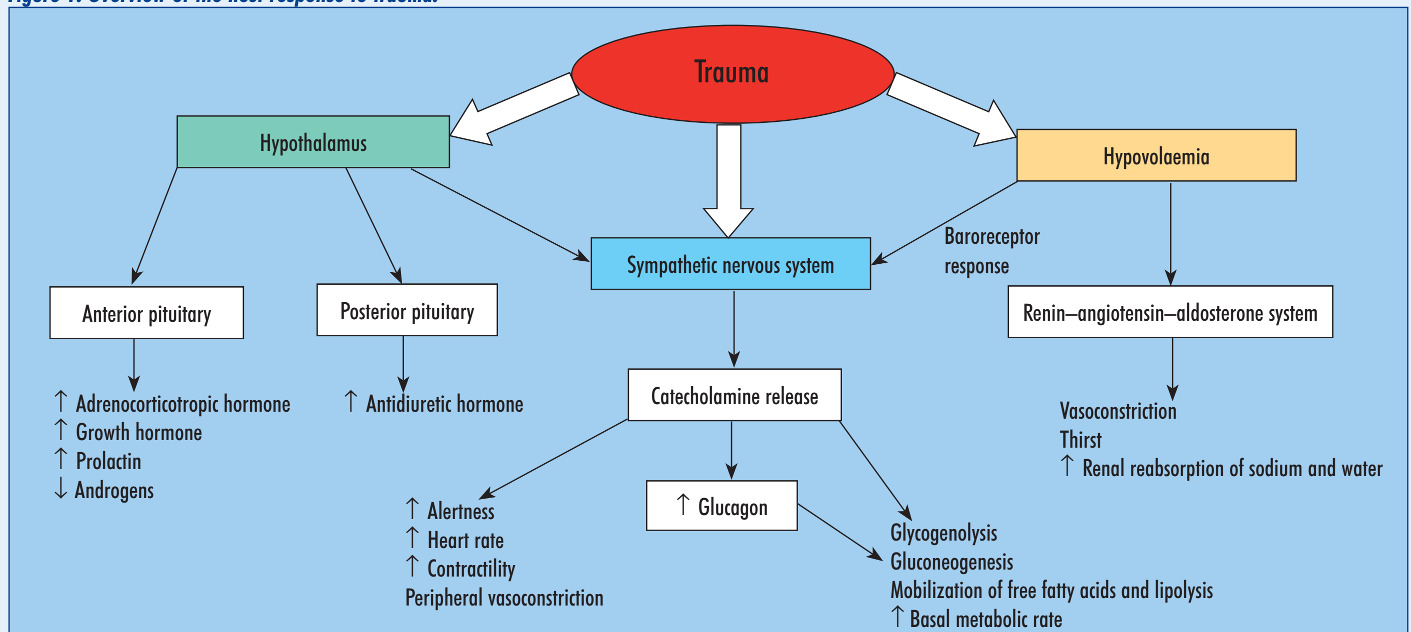
Physical injury and emotional stress result in activation of the sympathetic nervous system with subsequent release of catecholamines, namely adrenaline and noradrenaline, from the adrenal medulla (Cannon, 1934). The net effect is an increase in cardiac output which is achieved through increases in heart rate and cardiac contractility by β1-receptor activation. Peripheral vasoconstriction also occurs primarily as a result of the action of noradrenaline on α1-receptors, with diversion of blood to key organs, such as the brain, lungs and heart, and a reduction in perfusion of the splanchnic bed, kidneys and skeletal muscle (Keel and Trentz, 2005).

In addition to effects on the circulation catecholamines also have an impact on cognitive and metabolic function, increasing alertness, promoting glycogenolysis and gluconeogenesis within the liver and skeletal muscle, and encouraging the mobilization of free fatty acids from adipose tissue. They also increase basal metabolic rate and thereby increase energy expenditure and heat production.

Baroreceptor and osmoreceptor responses in trauma

Hypovolaemia following trauma leads to a fall in venous return and consequently a fall in cardiac output. This results in a decrease in mean arterial pressure, which is detected in the first instance by baroreceptors located at the carotid sinus and aortic arch. Reduced 'stretch' within these

Figure 1. Overview of the host response to trauma.



receptors results in a reduction of impulses via the glossopharyngeal and vagus nerves to the cardiovascular centre located in the medulla, causing inhibition of the parasympathetic and upregulation of the sympathetic nervous systems. The effect is an increase in heart rate, cardiac contractility and systemic vascular resistance – responses geared towards improving mean arterial pressure and therefore tissue perfusion.

Following injury the body also has a number of compensatory strategies which aim to restore circulating blood volume. The fall in renal perfusion which follows the reduction in mean arterial pressure together with the increase in sympathetic activity stimulates the juxtaglomerular apparatus to trigger the release of renin. Renin acts on the plasma protein angiotensinogen, which is produced by the liver, to convert angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates both thirst and the secretion of aldosterone which promotes the renal reabsorption of sodium and water.

Additionally, increased osmotic pressure which is observed following trauma is detected by osmoreceptors in the anterior hypothalamus. This triggers the secretion of antidiuretic hormone by the posterior lobe of the pituitary. Antidiuretic hormone acts to reduce renal water loss and this manifests clinically as oliguria or anuria (Keel and Trentz, 2005).

Hormone secretion in trauma

In addition to the vast catecholamine release seen, trauma stimulates the hypothalamus to secrete corticotropin-releasing hormone, with the subsequent secretion of adrenocorticotropic hormone, growth hormone and prolactin from the anterior lobe of the pituitary (adenohypophysis).

Adrenocorticotropic hormone stimulates the adrenal cortex to release glucocorticoids (e.g. cortisol) or mineralocorticoids (e.g. aldosterone) and increased levels of these can be detected in the serum within minutes of injury (Wanek and Wolf, 2007). At the same time there is an inhibition of the secretion of the anabolic hormones insulin and somatomedin and an increase in glucagon. These effects are largely mediated by catecholamines (Keel and Trentz, 2005). The duration of the initial pattern of hormone release depends on the severity of the injury and will differ for each hormone (Keel and Trentz, 2005).

The sex hormones are also thought to play a role in the metabolic response to trauma. Levels of endogenous testosterone, the main anabolic sex hormone in men, are diminished following injury. Furthermore, the use of the synthetic analogue oxandrolene in burns patients significantly reduces muscle wasting and improves nitrogen balance and net protein synthesis (Hsieh et al, 2007), suggesting testosterone plays an important role in protein metabolism.

Oxygen consumption and basal metabolism

In the ebb phase a decrease in oxygen consumption and basal metabolic rate is seen which is proportional to the severity of shock. This reduction may be as great as 50% (Cuthbertson, 1980). Conversely, there is an increase in metabolic activity in the flow phase with marked increases in cardiac output, basal oxygen consumption (up to 25%) and glucose production (Cuthbertson, 1980).

Temperature changes

Perhaps not surprisingly, temperature changes mirror those of metabolic activity. During the ebb phase, heat production, and hence body temperature, is reduced. However, in the flow phase both rise, although rarely exceeding 39°C. The rise in body temperature parallels that of heart rate and respiratory rate, peaking between days 2 and 3 after injury, and this is generally viewed as a good prognostic sign (Cuthbertson, 1980). Both temperature and pulse rate slowly decline and return to normal values in the ensuing weeks.

Carbohydrate metabolism

Hypermetabolism and catabolism are central to the flow phase of the metabolic response and are largely mediated by catecholamines (Wanek and Wolf, 2007). A key feature is the generation of abundant substrate, predominantly glucose, from the body's endogenous stores, mainly of protein and fat, to support the increased cellular activity required for the repair of damaged tissues and recovery. The increase in cellular activity and energy expenditure typically reaches a maximum at 5–10 days (Keel and Trentz, 2005), but the hypermetabolic state and its associated metabolic derangements can persist for several months (Wanek and Wolf, 2007).

Glucose is the substrate of choice in the brain and in those tissues where mitochondrial respiration may be absent, such as white blood cells, macrophages and injured tissue. Since the body's established stores of glucose are rapidly depleted, an increase in plasma glucose is advantageous and the observed rise is proportional to the severity of the injury sustained (Bahten et al, 2008). However, high glucose levels ≥200 mg/dl are associated with higher infection and mortality rates, and insulin therapy aimed at maintaining blood glucose levels <110 mg/dl reduces morbidity and mortality in critically ill patients (van den Berghe et al, 2001).

Post-trauma hyperglycaemia is mediated by both catecholamines (as discussed earlier) and other hormones. Following trauma increased circulating glucagon levels and reduced insulin levels are observed and the net effect is enhanced hepatic production of glucose (glycogenesis and gluconeogenesis). Concurrently, peripheral glucose uptake and use by peripheral tissues is reduced and this, combined with peripheral insulin resistance, ensures a high supply of this substrate to the predominantly glucose-consuming cells (Hsieh et al, 2007).

Glucocorticoids (cortisol) also play an important role in promoting hyperglycaemia and cortisol concentrations following injury are significantly increased and proportional to the degree of injury (Wanek and Wolf, 2007). Cortisol acts by increasing hepatic gluconeogenesis and glycogenesis, inhibiting protein synthesis, and increasing muscle (proteolysis) and fat breakdown (lipolysis) to liberate amino acids and free fatty acids respectively. Interestingly, gluconeogenesis cannot be limited by infusions with glucose, and it has been suggested that it may serve another purpose, namely to maintain body temperature by increasing energy production by the liver.

Glucose is taken up into cells and undergoes oxidative phosphorylation to form pyruvate, which is subsequently reduced to form serum lactate. Both lactate and base deficit are sensitive and useful clinical markers of tissue hypoperfusion and of prognosis in patients following severe injury (Bahten et al, 2008).

Fat metabolism

Injury leads to enhanced lipolysis and there is an increase in both free fatty acids and very low density lipoproteins (Hsieh et al, 2007). This is largely brought about by the action of catecholamines and glucagon (Wanek and Wolf, 2007). The free fatty acids liberated are taken up by the liver and used to generate energy through mitochondrial fatty acid oxidation. Glycerol also acts as a substrate for gluconeogenesis but these processes are often inefficient following injury (Wanek and Wolf, 2007).

Any excess fatty acids produced under these circumstances undergo re-esterification to triglycerides in the liver. Owing to a combination of inefficient very low density lipoprotein formation and defective very low density lipoprotein-triglyceride secretion, they may become sequestered here leading to hepatic steatosis (Romijn, 2000; Wanek and Wolf, 2007).

Protein metabolism

Although fat provides between 80 and 90% of the total energy expended in trauma, there is evidence that skeletal muscle plays the greater role during the first 10–12 days following injury (Cuthbertson, 1980).

Increased plasma levels of nitrogen and urinary levels of urea were first observed in soldiers who were severely injured during the First World War. It was not until the 1930s, in studies conducted in patients with fractures, that the relevance of this was delineated. In these studies, Cuthbertson (1930) noted that patients with normally healing fractures had significant urinary losses of phosphorus, nitrogen (urea) and sulphur.

Further studies in a similar cohort of patients showed the maximum urinary loss of nitrogen to be proportional to the degree of injury and to parallel the basal oxygen consumption, reaching a maximum between day 2 and 6 following injury, before gradually declining to normal values 1–2 months later (Cuthbertson, 1930). Subsequent measurements and evaluation of nitrogen:sulphur and nitrogen:potassium ratios identified skeletal muscle catabolism as the main source of the excess urinary nitrogen and this was reflected clinically by marked muscle wasting (Cuthbertson, 1930).

Although protein synthesis does occur following injury it is far outstripped by protein breakdown. Importantly, nitrogen loss can exceed levels of 20 g per day (Cuthbertson, 1931) (more than two or three times the intake) and this poses challenges in the nutritional management of the patient, where protein loss may account for anywhere between 14 and 18% of the total weight loss during the first 3 weeks following injury. Amino acids produced following proteolysis are taken up by the liver and used to generate glucose via gluconeogenesis and for protein synthesis (Kohl and Deutschman, 2006). In addition, they may be used by mononuclear cells to synthesize inflammatory mediators, for enzyme synthesis and by the liver for the synthesis of acute phase proteins (Keel and Trentz, 2005).

Acute phase proteins

Following injury, the local and systemic release of pro-inflammatory cytokines (the acute phase response) induces the liver to synthesize so-called acute phase proteins, while reducing its production of constitutive hepatic proteins such as prealbumin, albumin and transferrin. Acute phase proteins are plasma proteins which are present under normal conditions in low concentrations, but which increase in amount following injury. These include fibrinogen, α2-macroglobulin, C-reactive protein, serum amyloid A, α1-acid glycoprotein, α1-antitrypsin, haptoglobin and caeruloplasmin (Keel and Trentz, 2005). The function of these acute phase proteins is unclear, but they are thought to play a protective role and are useful clinically as a marker of recovery (Keel and Trentz, 2005; Kohl and Deutschman, 2006).

Conclusions

Trauma or injury triggers a complex, well-orchestrated cascade of events with recruitment of immune, inflammatory and hormonal mediators. Although its chief goal is to restore normal homeostatic function, prolongation of the hypermetabolic phase of the response has deleterious effects and can result in systemic inflammatory response syndrome or multi-organ dysfunction syndrome (Kohl and Deutschman, 2006). An improved understanding of the metabolic response to trauma will allow the clinician to take a more targeted and considered approach to therapy. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The pattern of death following trauma has a trimodal distribution.
- A better understanding of the metabolic response to trauma will prove invaluable to guiding management and reducing mortality associated with second and third peaks.
- The metabolic response to trauma is complex and classically characterized by an ‘ebb’ and a ‘flow’ phase.