The metabolic and endocrine response to trauma

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Learning objectives

After reading this article, you should be able to:

- describe the response of the hypothalamic-pituitary-adrenal axis to trauma
- describe how this response results in volume conservation, mobilization of fuel sources and improved haemostasis
- outline the current controversies surrounding the management of trauma patients

Abstract

Metabolic and endocrine pathways are central to the body's compensatory response to trauma. They drive mobilization of energy substrates, volume conservation and haemostasis via activation of the hypothalamic pituitary adrenal axis, the sympathetic nervous system and an inflammatory response. As clinicians, we can intervene in these pathways, however optimal management of anaesthesia, fluids, transfusion, nutrition and the use of steroids remains controversial and to be determined.

Keywords Catecholamines; coagulation; cortisol; enhanced recovery pathway; fibrinogen; gluconeogenesis; glutamine; hypothalamic pituitary axis; inflammatory mediators; regional anaesthesia; renin angiotensin aldosterone system; transfusion

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Introduction

Prior to the modern era of resuscitation, humans have long developed crucial physiological responses to survive traumatic insults. As many insults and conditions elicit similar physiologic responses to those in trauma, for the anaesthetist 'trauma' is a broad term just as readily encompassing surgery as well as burns, traumatic brain injury, chest and abdominal injuries. All these circumstances result in significant physiological changes, essentially via metabolic and endocrine pathways but also intrinsically involving the inflammatory and autonomic systems, all with the ultimate aim of optimizing tissue repair.

To achieve this, it is vital to maintain perfusion and energy supplies to vital organs. Hence the metabolic and endocrine responses focus on mobilizing fuel sources, conserving volume and minimizing blood loss. There is a complex interaction between these pathways with a surge in hypermetabolism and catabolism.

Despite a robust design, these pathways are so complex there is potential for failure of negative feedback with overshooting of the response to actually lead to detriment. It is vital for the anaesthetist to have a sound understanding of these mechanisms to minimize the consequences of injury and to optimize and support the body's physiological responses.

The hypothalamic pituitary axis plays a central role in coordinating these endocrine and metabolic responses. The hypothalamus receives multiple inputs including from baroreceptors, volureceptors and pain fibres stimulated during trauma; in response a number of vital pathways are activated via the pituitary and adrenal glands, and sympathetic nervous system.

Mobilization of energy resources

Corticotrophin releasing hormone (CRH) from the hypothalamus results in release of adrenal corticotrophin hormone (ACTH) from the anterior pituitary into the blood. This acts on the adrenal cortex resulting in a surge of cortisol. The key aim of cortisol is to mobilize energy stores and hence it induces gluconeogenesis. Cortisol serum levels should result in negative feedback into the hypothalamic pituitary axis, decreasing release of further corticotrophin releasing hormone. This can fail in trauma leading to a persistently high ACTH and cortisol resulting in catabolism, with protein and, ultimately, muscle breakdown. The latter is particularly detrimental to patients.

There is also a release of growth-hormone releasing hormone (GHRH) from the hypothalamus leading to a release of growth hormone (GH) from the anterior pituitary. This acts via insulin like growth factors to increase catabolism, but to a lesser extent than cortisol.

The pancreas also plays a role by decreasing the secretion of insulin while increasing the secretion of glucagon. There is also a state of relative insulin resistance, which when combined with decreased insulin secretion, leads to decreased glucose uptake by cells and increased circulating blood glucose levels.

These pathways all result in an increase in gluconeogenesis via glycogenolysis, lipolysis and proteolysis. Overall this increase in circulating glucose increases the supply of glucose at cellular level. This is important in generating ATP via aerobic respiration in the processes of glycolysis, the Krebs cycle and ultimately oxidative phosphorylation to support the body post trauma.

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Volume conservation and redistribution

Trauma often results in a shocked state with hypoperfusion of vital organs. In an attempt to maintain organ perfusion several physiological responses occur, with the overall aim of ensuring redistribution of blood flow to vital organs, volume conservation and optimal haemostasis.

Hypothalamic stimulation results in increased sympathetic outflow leading to two important effector responses. Firstly, the preganglionic fibres synapsing with the adrenal medulla cause an increased release of catecholamines into the circulation. Secondly, there is an increase in output down all postganglionic sympathetic fibres. Those most important during trauma are the cardioacceleratory fibres and those to the smooth muscle of the vasculature. These postganglionic fibre outputs, together with increased circulating catecholamines, mediate their effects via the alpha and beta adrenoreceptors of the end organs leading to the essential 'flight or fight responses'.

Increased sympathetic outflow leads to positive cardiac inotropy and chronotropy. Sympathetically mediated peripheral venoconstriction mobilizes blood from reservoirs, such as muscle, to increase venous return. Arteriolar vasoconstriction redistributes blood flow from peripheral to central structures.

In an attempt to correct volume loss, various compensatory processes are activated, namely the renin angiotensin aldosterone system (RAAS) and ADH release from the posterior pituitary. Renin is secreted from juxtaglomerular cells in the kidney as a result of increased sympathetic activity, renal hypoperfusion and reduced sodium delivery to the macula densa. Renin converts angiotensinogen to angiotensin I, which is further cleaved via angiotensin converting enzyme (ACE), to angiotensin II (AT II). AT II has multiple effects. Primarily, it stimulates the release of aldosterone from the zona glomerulosa of the adrenal cortex and via its actions on the hypothalamus, results in thirst and additional ADH secretion. It is also a potent peripheral vasoconstrictor. At the glomerulus, it causes preferential efferent arteriole constriction in an attempt to conserve glomerular filtration rate (GFR). ACTH and hyperkalaemia stimulate aldosterone release to a lesser extent.

Aldosterone acts predominantly on the distal convoluted tubule of the nephron resulting in reabsorption of sodium and loss of potassium and hydrogen ions. This increases water reabsorption and hence volume conservation. This is further accentuated by the aldosterone like effect of circulating cortisol.

From the posterior pituitary, ADH is released and acting via V2 receptors in the kidney, results in an increase in aquaporins into the collecting duct and hence water reabsorption into the systemic circulation, to support the circulation during this time of injury.

The immunological response

Trauma induced tissue damage activates the complement pathway. This results in neutrophil and macrophage activation with subsequent release of inflammatory mediators including interleukin-1, TNF-alpha and platelet activating factor. Consequently there is upregulation of other acute phase proteins including fibrinogen, oxygen free radicals and proteases as well as arachidonic acid metabolites including thromboxanes and prostaglandins. The end result of this earliest phase of tissue trauma is propagation of the coagulation cascade, neutrophil accumulation at the site of injury and a lymphocytosis with induction of both cell mediated and humoral pathways, all with the aim of limiting further tissue damage and promoting repair. However, there is a delicate balance between these pro- and anti-inflammatory pathways and interfering with these in an attempt to optimize outcomes in trauma patients, for example by administration of steroids, is complex.

Haemostasis

In an attempt to prevent ongoing blood loss and conserve volume, various haemostatic mechanisms are activated. These include vasoconstriction and platelet adhesion and aggregation, ultimately leading to clot formation. These processes are augmented by the inflammatory response to trauma, namely elevated arachidonic acid metabolites such as thromboxane A2, which acts as a potent vasoconstrictor and increases platelet activation and aggregation. Serum levels of acute phase proteins, such as the procoagulant fibrinogen, are also elevated whilst others such as the anticoagulant, protein C are decreased altering the balance between pro- and anticoagulant factors. The ultimate aim of these pathways is a hypercoagulable state.

Management of the metabolic and endocrine pathways activated in trauma: current controversies

All these processes seek to preserve vital organ functions and allow survival following traumatic insult. However, without appropriate management these compensatory mechanisms can become overwhelmed resulting in death.

The hypermetabolic state associated with trauma increases tissue oxygen demand. If cardiac output fails to increase sufficiently, inadequate oxygen delivery to the tissues occurs. This can be further compromised by peripheral vasoconstriction and anaemia. Overall this will result in cellular hypoxia, lactic acidosis and multiorgan failure. Equally, the compensatory mechanisms of the coagulation system can become overwhelmed resulting in disseminated intravascular coagulopathy (DIC) and uncontrolled haemorrhage.

There are numerous interventions utilized in the management of trauma patients, some augment the natural physiological responses but some interfere with these responses and can lead to poorer patient outcomes. It is important that we understand how our actions interfere with these processes so we can continue to optimize our management and improve patient outcomes.

It is always difficult to demonstrate clear benefits of interventions in the perioperative period. In particular, multi trauma patients are a very heterogeneous group. Furthermore, it is impossible to study and intervene in this group before their injury and hence it is difficult to elicit the true benefit or detriment of physiological responses and how best to modulate these. However, nonetheless there has been much work looking at interventions in the perioperative period of general surgical and burns patients, and some of these findings can be extrapolated and applied to influence interventions more specifically for trauma patients.

Choice of anaesthesia agent

Induction of anaesthesia in these patients can be difficult and there is a constant debate about the competing interests to minimize the risk of aspiration and a surge in intracranial pressure but to maintain haemodynamic stability. Overall the aim is to maintain the