The metabolic and endocrine response to trauma

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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 remain controversial and to be determined.

Keywords Catecholamines; coagulation; cortisol; gluconeogenesis; glutamine; hypothalamic pituitary axis; inflammatory mediators; regional anaesthesia; renin–angiotensin–aldosterone system; transfusion

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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
- better understand the current controverseries surrounding the management of trauma patients

Introduction

In order to survive traumatic insults, prior to the modern era of intravenous fluid resuscitation, humans have developed a crucial physiological response. The priority is to maintain perfusion and energy supplies to vital organs. Hence the response focuses on mobilizing fuel sources, conserving volume and minimizing blood loss. This is achieved through a complex interaction between the metabolic, endocrine and immunological pathways.

The endocrine and metabolic pathways

The hypothalamus is central in coordinating these endocrine and metabolic responses. It 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 gland, and sympathetic nervous system.

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The anterior pituitary gland increases secretion of three key hormones: growth hormone, prolactin and adrenocorticotrophic hormone (ACTH), the latter stimulating the adrenal cortex to release cortisol. From the posterior pituitary gland there is increased secretion of antidiuretic hormone (ADH). Thyroxine-stimulating hormone secretion, from the anterior pituitary, is unchanged but there is an overall decrease in T3 and T4.

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

Physiological effects of the metabolic and endocrine responses to trauma

Increased energy substrates

Increased circulating levels of cortisol and growth hormone, together with catecholamines, result in mobilization of energy stores. This is an attempt to meet the increased energy demands of the body's vital organs during stress. The pancreas also plays a role by decreasing the secretion of insulin while increasing the secretion of glucagon. These pathways all result in an increase in gluconeogenesis via glycogenolysis, lipolysis and proteolysis. 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.

Overall this increase in circulating glucose attempts to ensure an increased supply at cellular level to generate ATP via aerobic respiration in the processes of glycolysis, the Krebs cycle and ultimately oxidative phosphorylation to support the body post-trauma.

As with all hormonal pathways, there is tight regulation with positive and negative feedback loops ensuring homeostasis so that, for example, the cortisol feeds back into the hypothalamus decreasing release of further corticotrophin releasing hormone.

Volume conservation and redistribution

Trauma can result 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.

Increased sympathetic outflow leads to positive ionotropy and chronotropy. Sympathetically mediated peripheral venoconstriction mobilises 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 and by ADH released from the posterior pituitary, which through its action on the collecting ducts leads to further water reabsorption.

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 anti-coagulant protein C are decreased altering the balance between pro- and anti-coagulant factors. As a result of these pathways a hypercoagulable state occurs.

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, tumour necrosis factor-α (TNF-α) 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 thrombus formation, accumulation of neutrophils at the site of injury and activation of cell-mediated and humoral immune pathways. These processes aim to limit further tissue damage and promote repair. There is a delicate balance between these pro- and anti-inflammatory pathways. Interfering with these in an attempt to optimise outcomes in trauma patients, for example by administration of steroids, is complex.

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

The metabolic and endocrine processes seek to preserve vital organ functions and allow survival following traumatic insult. If trauma is not managed appropriately these compensatory mechanisms can become overwhelmed and result 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 utilised 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 optimise our management and improve patient outcomes.

Conduct of anaesthesia

Given its favourable haemodynamic profile, etomidate was traditionally used as an induction agent in haemodynamically unstable trauma patients. Despite studies failing to definitively link etomidate with negative outcomes[1] concerns have been raised regarding the resultant adrenal suppression and its potential impact on survival. Ketamine has a similar haemodynamic profile to etomidate and may be more appropriate in the cardiovascularly unstable trauma patient. The neuroprotective effects of thiopentone and propofol make them ideal induction agents in traumatic brain injury but they should be used in lower doses and with caution in unstable patients due to their vasodilatory and negative ionotropic effects. Midazolam and fentanyl are alternatives to the traditional induction agents.

Regional anaesthetic techniques have been used to improve analgesia and attenuate the sympathetic response to pain. There is increasing evidence to support the safety of regional anaesthesia in trauma[2] despite prior concerns regarding risks associated with coagulopathy and concealed compartment syndrome, but no clear evidence for improved patient outcomes exists.

Steroids

Steroid use in trauma remains controversial. The initial hyperinflammatory response, aimed at limiting tissue damage, is followed by a hypoinflammatory phase. During this latter phase the body is susceptible to infection which can worsen tissue damage, the so-called 'two hit hypothesis'.[3] There is some evidence that administration of steroids to trauma patients may reduce their risk of pneumonia by interfering with the balance between this hyper- and hypo-immune response.[3] However there are concerns as etomidate was used in this trial and the results conflict with