Hormonal and metabolic response to trauma

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Learning objectives

After reading this article you should be able to:
- describe the structure of the hypothalamic-pituitary-adrenal axis
- describe the major mediators of the stress response
- list the major complications of the stress response

Abstract

Trauma induces the stress response which mobilizes physiological mechanisms to protect an otherwise threatened body homeostasis. Increasingly the maladaptive nature of this response is being recognized as a result of systemic derangements triggered by the sympathetic nervous system and hypothalamic-pituitary-adrenal axis.

Keywords Catecholamines; cortisol; homeostasis; hormones; hypothalamic-pituitary-adrenal axis

Introduction

Stress is defined as a state of threatened homeostasis resulting from exposure to adverse forces (stressors) such as trauma, infections, burns and surgery. The stress response is complex and is predominantly mediated by the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis which in turn modulate endocrine, metabolic and immunological changes. This cascade has the potential to be either physiological by protecting and repairing tissue integrity or to be pathological by inducing a maladaptive activation of organ systems.

Structure and effector pathways

Tissue damage triggers somatic and visceral afferent neurons that ascend to the central nervous system, specifically the hypothalamus and brain stem (Figure 1). The paraventricular nuclei of the hypothalamus release corticotrophin-releasing hormone (CRH) and arginine-vasopressin (AVP also known as antidiuretic hormone). CRH, synergistically aided by AVP, regulates the anterior pituitary release of ACTH which in turn stimulates adrenal cortex secretion of glucocorticoids with their wide-ranging effects. Glucocorticoids act via glucocorticoid receptors which, both upregulate and downregulate an array of genes with metabolic, endocrine and immunological activity; importantly they also act as a negative feedback signal to dampen the entire system.

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The sympathetic nervous system represents the other principal effector limb of the response to stress. Noradrenergic cell groups originate in the locus ceruleus of the medulla and pons with the majority of sympathetic preganglionic fibres terminating in the paravertebral sympathetic chain with postganglionic fibres releasing noradrenaline in peripheral tissues. Other preganglionic fibres innervate the chromaffin cells of the adrenal medulla and release acetylcholine as the principal preganglionic neurotransmitter. When stimulated the adrenal medulla releases adrenaline, and to a lesser extent noradrenaline (in an approximately 4:1 ratio), into the systemic circulation (Table 1).

Complications of the stress response

Metabolic and immunological complications arise as a direct result of the stress response, but additional deleterious effects may result either from an insufficient or an excessive response relative to the degree of initiating insult or a prolonged response outlasting the period of tissue injury. Initiation of the stress response is vital to maintaining homeostasis but equally vital is the ability to self-restrain the adaptive response and terminates the deleterious catabolic and immunosuppressive effects.

Cardiovascular: myocardial and vascular adrenergic receptors are triggered by both direct sympathetic innervations and circulating catecholamines. Hypertension and tachycardia follow, with resultant myocardial stress and ischaemia; furthermore catecholamine B1 stimulation can induce cardiomyocyte apoptosis and fibrosis.[1] Profound vasoconstriction can cause tissue ischaemia and will reduce renal blood flow.

Energy metabolism: insulin release is suppressed and glucagon secretion increased. Gluconeogenesis, glycolysis and lipolysis are induced in the liver and muscle with resulting hyperglycaemia and tissue catabolism. Circulating cortisol antagonizes the anabolic actions of growth and thyroid hormones further exacerbating tissue catabolism with the potential for a rapid decline in lean body mass. Hyperglycaemia can impair tissue healing, impair immune function and promote infection and cause an osmotic diuresis.

Renal: renin is released from juxtaglomerular cells by direct sympathetic innervations thereby promoting fluid retention. Electrolyte and fluid balance disturbances are exacerbated by the effect of AVP which promotes water resorption from collecting tubules in the kidney by increasing the number of aquaporin channels inserted into duct walls further exacerbating tissue oedema and hypokalaemia. Mineralocorticoids are also released by sympathetic stimulation of the adrenal cortex. Fluid overload can develop with congestive cardiac failure and impaired wound healing.
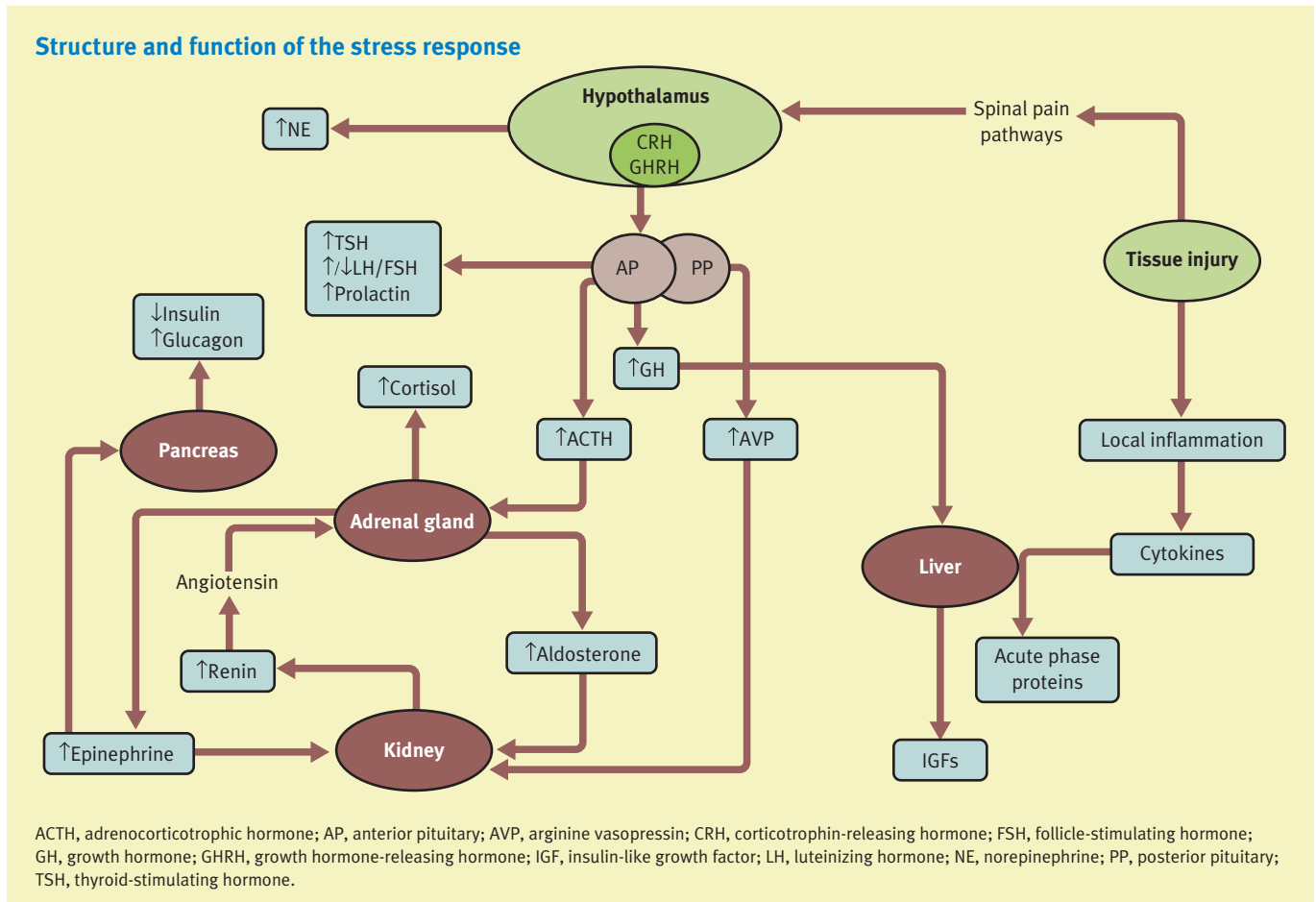
Structure and function of the stress response

ACTH, adrenocorticotrophic hormone; AP, anterior pituitary; AVP, arginine vasopressin; CRH, corticotrophin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; NE, norepinephrine; PP, posterior pituitary; TSH, thyroid-stimulating hormone.

Figure 1 Structure and function of the stress response (*figure reproduced from Guest 2008*).

Immunoregulation: immunomodulation is a major component of the stress response and is mediated by cortisol. Pro-inflammatory cytokines, namely tumour necrosis factor-α, interleukin-1 (IL-1) and interleukin-6, are released at the site of trauma. These cytokines promote the inflammatory cascade and are increasingly recognized as independent stimuli for secretion of CRH and AVP. Virtually all the circulating pro-inflammatory factors are inhibited by cortisol thereby dampening the inflammatory burst. A prolonged stress response is potentially immunosuppressive with increased infection risk. Alternatively, a relative cortisol deficiency can result in an unrestrained pro-inflammatory state with its own deleterious effects and a systemic inflammatory response syndrome type state with pyrexia and vascular permeability ensuing.

Other complications include inhibition of gastrointestinal motility with delayed gastric emptying, failure of enteral nutrition absorption and ileus. Adrenaline increases factor VIII activity, von Willebrand antigen, tissue plasminogen activator and platelet counts leading to marked hypercoagulability and thrombus formation. Additionally, during severe stress with adrenergic overstimulation bone marrow inhibition occurs.

Modulation of the stress response

Steroids: exogenous steroids have been suggested as a possible means to inhibit IL-6 production and dampen the stress response although evidence does not support its use. However there is evidence supporting the use of exogenous glucocorticoids in those patients deemed to have a relative adrenal insufficiency in relation to the expected adrenal activation deemed appropriate for critical illness. In selected patients outcomes appear improved.

Opioids: injected opioids have theoretical benefit by central suppression of the HPA axis and blocking transmission of stressor signals from the peripheries. However evidence for improved outcomes is lacking and the high doses required carries the risk of inducing respiratory depression.

Anaesthetic agents: etomidate is an induction anaesthetic agent with significant cardiovascular stability, a property advantageous in the critically ill. However this drug blocks 11-β-hydroxylase activity interrupting the synthesis of cortisol from cholesterol precursors with inhibition lasting 8 hours after a single induction dose. Some evidence suggests worse outcome in those critically ill patients administered etomidate[2] although recent other data are contradictory.[3]

Regional anaesthesia: neuraxial blockade blocks afferent pain pathways that activate the hypothalamus and efferent pathways carrying sympathetic nerves. Circulating cytokines are induced

Major mediators of stress and systemic effects

Mediator	Major effects
Adrenaline	Arterial and venous vasoconstriction, positive inotropy and chronotropy, glycogenolysis and gluconeogenesis, increased rennin release and sodium reabsorption in renal tubules, decreased smooth muscle contraction in gastrointestinal tract, lactate release from skeletal muscle, immunosuppression, release of clotting and fibrinolytic factors, bronchodilation, increased basal metabolic rate
Noradrenaline	Arterial and venous vasoconstriction, reduced hepatic and splanchnic blood flow
Arginine-vasopressin	Arterial vasoconstriction, water reabsorption in renal collecting ducts, release of von Willebrand factor
Cortisol	Required for reactivity to catecholamines by increasing adrenergic receptors number and stimulating their function, proteolysis, lipolysis, gluconeogenesis and inhibits peripheral glucose utilization, stimulates gastric acid secretion, inhibits cytokine production and release
Cytokines (TNF-α, IL-1, IL-6)	Local and systemic inflammation, mobilization of leukocytes, hepatic production of acute phase reactants

IL, interleukin; TNF, tumour necrosis factor.

Table 1

by local tissue damage so levels are not affected by regional anaesthesia. Mortality benefit has never been proven, but improved morbidity is seen in some patient subsets.[4]

B-blockade: blocking the effects of β-adrenergic stimulation is likely to have cardio-protective effects with benefit seen in high-risk cardiac patients. Recent evidence is emerging that β-blockade may also benefit head-injured patients,[5] and multi-trauma patients[6] and blunt the catabolic state seen in burn patients.[7]

α-2 agonists: clonidine and dexmedetomidine acts as α-2 agonists and stimulate presynaptic α-2 receptors which inhibit catecholamine release with some attenuation of the adrenergic stress response seen perioperatively and reduced myocardial ischaemia and mortality after non-cardiac surgery.

Glycaemic control: stress promotes glucose release and insulin suppression with resultant hyperglycaemia. Some early data suggested benefit with tight glycaemic control in intensive care patients, but more recent evidence refutes this with current recommendations favouring more moderate target glucose levels.[8,9]   ◆

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