# Hypothalamic–pituitary–adrenal function: anaesthetic implications

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## Abstract

Surgery, trauma and critical illness evoke a series of hormonal and metabolic changes commonly referred to as the stress response. Activation of the hypothalamic–pituitary–adrenal axis results in increased secretion of hormones such as cortisol. Anaesthesia can suppress adrenocortical secretion either by an effect at the hypothalamus, for example by a decrease in neural input with regional anaesthesia, or by a direct effect on the adrenal cortex, for example by etomidate. For patients undergoing routine surgery an increase in cortisol secretion is unnecessary, uneventful recovery occurs in the presence of circulating cortisol concentrations within the normal range. Patients often present for surgery taking corticosteroids for a variety of medical conditions, but excessive supplementation with hydrocortisone is unnecessary, and can cause side effects. The use of steroids in critically ill patients remains contentious. Furthermore, the immune system and neuroendocrine system are closely related and the metabolic response to surgery involves both hormonal and inflammatory processes. Attempts have also been made to obtund the perioperative inflammatory response.

**Keywords** Cortisol; cytokines; etomidate; sepsis; surgery

**Royal College of Anaesthetists CPD matrix**: 1A02

## Learning objectives

After reading this article you should understand the:

- hormonal aspects of the stress response to trauma or surgery
- inflammatory response to injury and how this is related to the hormonal response
- role of anaesthetic agents and techniques in modifying this response
- role of steroid supplementation in critical illness

Surgery evokes a series of hormonal and metabolic changes commonly referred to as the stress response. Afferent neuronal input, both somatic and autonomic from the surgical site, activates the hypothalamic–pituitary axis and the sympathetic nervous system. In addition to a marked increase in catabolic hormone secretion there is suppression of the important anabolic hormones insulin and testosterone. The hypothalamic–pituitary axis is the major neuroendocrine organ of the body. Regulation of hormone secretion is undertaken by feedback loops, both positive and negative. A typical pathway involves secretion of a releasing factor from the hypothalamus, such as a corticotrophin-releasing factor or hormone (CRF or CRH), which stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH) into the circulation. In turn, this acts on the target organ, the adrenal cortex, to secrete cortisol. An increase in the circulating concentration of cortisol acts on the hypothalamus and pituitary to inhibit release of CRF and ACTH, respectively, so restoring circulating cortisol levels to normal physiological values. These feedback control mechanisms fail in surgery, trauma and critical illness, resulting in abnormal endocrine function.

The hypothalamus is part of the anterior diencephalon and contributes to the floor and lateral wall of the third ventricle (Figure 1). There are vascular connections between the hypothalamus and the anterior lobe of the pituitary, the portal hypophysial vessels, whereas the posterior pituitary is linked to the hypothalamus by neural connections, the hypothalamohypophysial tract, arising from cell bodies in the supraoptic and paraventricular nuclei. The key difference between the anterior and posterior pituitary results from their embryological origins. The anterior pituitary is derived from Rathke's pouch, an evagination from the roof of the pharynx, while the posterior lobe arises from an evagination of the third ventricle. Other than neuroendocrine control, the hypothalamus has important functions in temperature regulation, appetite control and sexual behaviour.

The anterior pituitary secretes six hormones in response to releasing factors secreted into the hypophysial vessels in the hypothalamus:

- adrenocorticotropic hormone
- growth hormone (GH)
- prolactin (PRL)
- thyroid-stimulating hormone (TSH)
- luteinizing stimulating hormone (LSH)
- follicle-stimulating hormone (FSH).

The posterior pituitary secretes arginine vasopressin (AVP) and oxytocin.

The stress response to surgery or injury is a combination of not just hormonal, but also inflammatory changes. The systemic inflammatory response is mediated primarily by cytokines synthesized at the site of injury. Cytokines are low molecular weight (<80 kDa), heterogeneous glycoproteins, which include interleukins, interferons and tumour necrosis factor. They are synthesized by activated macrophages, fibroblasts, endothelial and glial cells in response to tissue injury from surgery or trauma. Cytokines are present locally at high concentrations when they isolate and destroy infective organisms, prevent further tissue damage and activate wound healing. Some inflammatory mediators are released into the circulation, particularly interleukin (IL)-6, and act on distant organs to stimulate the acute-phase response. This response is characterized by acute-phase protein synthesis in the liver, neutrophil mobilization from the bone marrow,

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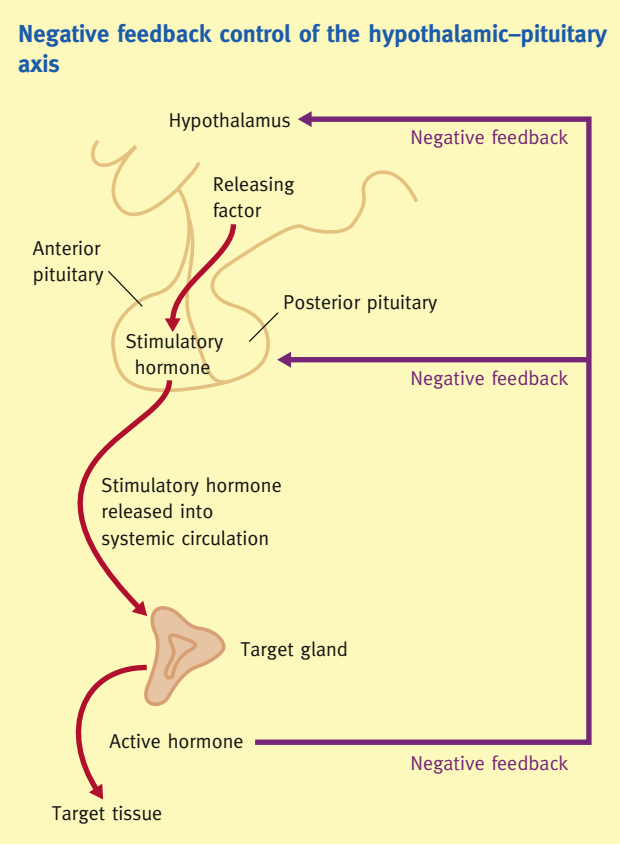


**Figure 1**

immunosuppression from altered T-lymphocyte differentiation, increased body temperature by affecting hypothalamic control and adrenocorticotrophic hormone secretion from the anterior pituitary. These widespread changes are usually considered essential for recovery from injury, although some aspects of the acute-phase response are potentially detrimental. For example, the increased synthesis of fibrinogen in the liver, peaking several days after injury, increases the risk of thromboembolism and is accompanied by a decrease in albumin synthesis.

The immune and the neuroendocrine systems are closely interconnected. Interleukin-1 and IL-6 have been shown to stimulate secretion from isolated pituitary cells. In surgical patients, circulating cytokines may augment pituitary ACTH secretion and consequently increase the release of cortisol sustaining the glucocorticoid response to injury for several days. A negative feedback system exists whereby glucocorticoids decrease cytokine production by inhibiting gene expression. Thus, the cortisol response to surgery limits the severity of the inflammatory response. It has been suggested that increased intracerebral IL-6 results in the enhanced cortisol secretion found after cerebral haemorrhage.

## Effects of surgery and anaesthesia

The onset of surgery is associated with the rapid secretion of hormones derived from the anterior and posterior pituitary gland. Adrenocorticotropic hormone (ACTH) is secreted by corticotroph cells in the anterior lobe of the pituitary gland. ACTH contains 39 amino acids and is synthesized as part of a large precursor molecule, pro-opiomelanocortin (POMC) which undergoes considerable post-translational processing. The main stimulus to ACTH secretion is corticotrophin-releasing hormone (CRH), a 41-amino acid-peptide produced in the hypothalamus and secreted into the hypophyseal portal system. Arginine vasopressin (AVP) also plays an important role in the control of ACTH secretion during stress, by directly stimulating the release of ACTH and acting synergistically with CRH, as well as regulating pituitary CRH receptor expression.

ACTH acts on the adrenal gland through a specific cell surface receptor, a member of the G-protein-coupled receptor family to stimulate cortisol secretion. Normally feedback inhibition by cortisol then prevents any further increases in CRH or ACTH production. Cortisol is a $C^{21}$ corticosteroid with both glucocorticoid and mineralocorticoid activity. Endogenous cortisol production is between 25 and 30 mg per day, circulating concentrations vary in a circadian pattern and the half-life of cortisol in the circulation is between 60 and 90 minutes.

Plasma cortisol concentrations increase rapidly in response to surgical stimulation and remain elevated for a variable time following surgery. Peak values are achieved within 4–6 hours after surgery or injury and return towards baseline after 24 hours; this increase in plasma cortisol may, however, be sustained for up to 48–72 hours following major surgery, such as cardiac surgery. The amount of cortisol secreted following major surgery, such as abdominal or thoracic surgery, is between 75 and 100 mg on the first day. Minor surgery, such as herniorrhaphy, induces less than 50 mg cortisol secretion during the first 24 hours. Increased cortisol production is secondary to ACTH secretion, but the plasma ACTH concentration is far greater than that required to produce a maximal adrenocortical response. Furthermore, the normal pituitary adrenocortical feedback mechanism is no longer effective, as both hormones remain increased simultaneously.

Cortisol has complex effects on intermediate metabolism of carbohydrate, fat and protein. It causes an increase in blood glucose concentrations by stimulating protein catabolism and promoting glucose production in the liver by gluconeogenesis. Cortisol reduces peripheral glucose utilisation by an anti-insulin effect. Glucocorticoids inhibit the recruitment of neutrophils and monocyte-macrophages into the area of inflammation and also have well-described anti-inflammatory actions, mediated by a decrease in the production of inflammatory mediators such as leukotrienes and prostaglandins. In addition there is immunoregulatory feedback between the glucocorticoid hormones and IL-6; the production and action of IL-6 is inhibited by ACTH and cortisol.

Activation of the hypothalamic–pituitary–adrenal axis in response to surgery may be modified by anaesthesia. Regional anaesthesia can prevent an increase in ACTH and cortisol secretion but only if autonomic afferent fibre activity is blocked as well as somatic afferent fibre activity. There are a limited number of operative sites at which this can be achieved: pelvis, limb and eye. For pelvic surgery an extensive afferent blockade from dermatomes T4 to S5 is necessary to prevent pituitary hormone secretion. This upper dermatomal limit is often higher than required for surgery, but is essential if sympathetic afferent blockade is to be achieved. It is presumed that complete afferent blockade of the surgical site markedly decreases the neural input to the hypothalamus.