

Endocrine and metabolic response to surgery

Deborah Burton FRCA
 Grainne Nicholson MB BCh BAO FFARCSI
 George Hall MBBS PhD DSc FRCA

Key points

- Surgery evokes a series of hormonal and metabolic changes commonly referred to as the stress response.
- There is increased secretion of pituitary hormones and activation of the sympathetic nervous system.
- Increased catabolism mobilizes substrates to provide energy.
- Salt and water retention occur to maintain fluid volume and cardiovascular homeostasis.
- Attempts have been made to modify the stress response after surgery with various anaesthetic techniques but the results are inconclusive.

The neuroendocrine, metabolic and inflammatory aspects of injury are part of the overall 'stress response' (Table 1). This has been studied most commonly in relation to surgery, because the catabolic changes that occur can be observed from a well-defined starting point, but similar features occur in trauma, burns, severe infection and strenuous exercise. These result in substrate mobilization, muscle protein loss and sodium and water retention, with suppression of anabolic hormone secretion. There is activation of the sympathetic nervous system and immunological and haematological changes. Generally, the magnitude of the metabolic response is proportional to the severity of the surgical trauma. These changes have probably evolved to aid survival in a more primitive environment, by mobilizing substrates, limiting tissue damage, destroying infectious organisms and activating repair processes. Psychological and behavioural changes accompany the physiological events. The benefits of the stress response are not obvious in modern medicine, when physiological changes can be more easily corrected and it may even have a detrimental effect. In recent years,

research has focused on methods to modify the response associated with surgery in an attempt to improve patient outcome.

Endocrine and metabolic changes

Initiation of response

The hypothalamic–pituitary axis and the sympathetic nervous system are activated by afferent nerve input, both somatic and autonomic, from the area of trauma or injury. There is a failure of the normal feedback mechanisms of control of hormone secretion. For example, enhanced cortisol secretion fails to inhibit further production of adrenocorticotrophic hormone (ACTH). In general, there is release of catabolic hormones such as the catecholamines and pituitary hormones whereas anabolic hormones such as insulin and testosterone are suppressed (Table 2).

Sympathetic nervous system

Catecholamines are released from the adrenal medulla and norepinephrine spills over from presynaptic nerve terminals in response to hypothalamic stimulation. Marked activation of the sympathetic nervous system results in tachycardia and hypertension. Hepatic, pancreatic and renal function are also modified. Renin is released from the kidneys causing the conversion of angiotensin I to angiotensin II.

Table 1 Changes occurring during the stress response

Physiological	Hormonal Metabolic Immunological Haematological
Psychological	Malaise (fatigue)
Behavioural	Reluctance to move

Table 2 Hormonal changes during surgery

	Pituitary	Adrenal	Pancreatic	Others
Increased secretion	Growth hormone (GH) Adrenocorticotrophic hormone (ACTH) β-Endorphin Prolactin Arginine vasopressin (posterior pituitary) (AVP)	Catecholamines Cortisol Aldosterone	Glucagon	Renin
Unchanged secretion	Thyroid stimulating hormone (TSH) Luteinizing hormone (LH) Follicle stimulating hormone (FSH)			
Decreased secretion			Insulin	Testosterone Oestrogen Tri-iodothyronine (T ₃)

Deborah Burton FRCA

Lecturer in Anaesthesia
 Department of Anaesthesia
 St George's Hospital Medical School
 London
 SW17 0RE

Grainne Nicholson MB BCh BAO FFARCSI

Senior Lecturer in Anaesthesia
 Department of Anaesthesia
 St George's Hospital Medical School
 London
 SW17 0RE
 Tel: 020 8725 2615
 Fax: 020 8725 0256
 E-mail: gnichols@sghms.ac.uk
 (for correspondence)

George Hall MBBS PhD DSc FRCA

Professor of Anaesthesia
 Department of Anaesthesia
 St George's Hospital Medical School
 London
 SW17 0RE

The latter stimulates the secretion of aldosterone from the adrenal cortex, which in turn increases sodium reabsorption from the distal convoluted tubule in the kidney. Glucagon release from the pancreas stimulates the breakdown of glycogen in the liver and muscle leading to increased glucose and lactate concentrations as well as mobilization of free fatty acids (FFAs) from available lipid stores. However, the effects of insulin on fat and carbohydrate metabolism are far more significant.

Pituitary gland

The anterior pituitary gland is controlled by hypothalamic releasing or inhibiting factors, which are secreted into the hypothalamic–hypophyseal portal system. The hypothalamus has direct neural control of the posterior pituitary gland. The secretion of the anterior pituitary hormones ACTH and growth hormone (GH) is stimulated by hypothalamic releasing factors, corticotrophin releasing factor (CRF) and somatotrophin (or growth hormone releasing factor). The secretion of prolactin is under tonic inhibitory control via prolactin release inhibitory factor; perioperative increased prolactin secretion occurs by release of inhibitory control. The secretion of other hormones, thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH) does not change significantly. Increased arginine vasopressin (antidiuretic hormone) release from the posterior pituitary, in addition to CRF, stimulates the production of the amino acid pro-opiomelanocortin in the anterior pituitary, which is the precursor of ACTH, β -endorphin and *N*-terminal precursor (Fig. 1). ACTH stimulates cortisol production within a few minutes of the start of surgery. The production of ACTH is far in excess of that required to produce a maximum adrenocortical response.

Cortisol

The normal baseline value of cortisol is ~ 400 nmol litre⁻¹, which can increase to >1500 nmol litre⁻¹ within 4–6 h of major surgery starting. The usual negative feedback mechanism fails and

concentrations of ACTH and cortisol remain persistently increased. The magnitude and duration of the increase correlate well with the severity of the insult and the response is not abolished by the administration of corticosteroids. The metabolic effects of cortisol are enhanced with skeletal muscle protein breakdown to provide gluconeogenic precursors and amino acids for protein synthesis in the liver, and stimulation of lipolysis. Glucose utilization is impaired, which is known as an ‘anti-insulin effect’ leading to further hyperglycaemia. There are also mineralocorticoid effects with sodium and water retention and potassium loss. Cortisol also has well recognized anti-inflammatory effects mediated by a decrease in production of inflammatory mediators such as leukotrienes, cytokines and prostaglandins.

Growth hormone

Growth hormone has mixed catabolic and anabolic effects but increased secretion after surgery has only a minor physiological role and its diabetogenic effects are not thought to be important in the perioperative period. Glycogenolysis and lipolysis are promoted by GH while glucose uptake and utilization by cells are inhibited. However, it may have a more important role in helping to prevent muscle protein breakdown and promote tissue repair. This action is achieved by the stimulation of the production of polypeptides in the liver, which are known as somatomedins or insulin-like growth factors (IGFs). The main protein is somatomedin C (or IGF-1), which reduces protein catabolism. There has been considerable interest in the potential role of recombinant growth hormone or IGFs in improving wound healing, but evidence is inconclusive.

β -Endorphin and prolactin

β -Endorphin is a peptide produced from pro-opiomelanocortin and increased concentrations during surgery reflect anterior pituitary stimulation. Prolactin has a major role during pregnancy and lactation. The physiological effects of increased secretion of both hormones during surgery are unknown, but they may alter immune function.

Arginine vasopressin

The increased production of this hormone from the posterior pituitary has an anti-diuretic effect. It is also an important vaso-pressor and enhances haemostasis. ACTH release is enhanced by AVP.

Insulin and glucagon

Insulin is a key anabolic hormone which is usually secreted in response to hyperglycaemia promoting glucose utilization and glycogen synthesis. Lipolysis is inhibited and muscle protein loss reduced. The failure of the body to secrete insulin in response to trauma is partly caused by the inhibition of the β -cells in the pancreas by the α_2 -adrenergic inhibitory effects of

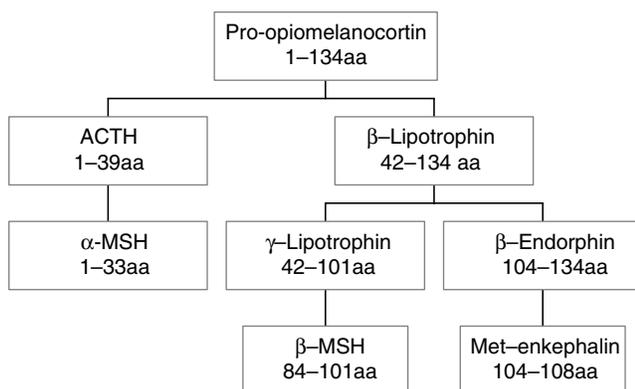


Fig. 1 Pro-opiomelanocortin, structural components and derived hormones.

catecholamines. 'Insulin resistance' by target cells occurs later because of a defect in the insulin receptor/intracellular signalling pathway. Thus, the perioperative period is characterized by a state of functional insulin deficiency. In contrast to insulin, glucagon release promotes hepatic glycogenolysis and gluconeogenesis, but insulin effects predominate. Glucagon secretion increases briefly during surgery but it is not thought to make a major contribution to the hyperglycaemia.

Other hormones

Thyroxine (T_4) and tri-iodothyronine (T_3) are secreted by the thyroid, in response to TSH. T_3 is five times more active than T_4 . They are highly bound in the circulation to albumin, thyroxine-binding pre-albumin and thyroid-binding globulin. They stimulate oxygen consumption in many organs, increase the metabolic rate and heat production. Circulating concentrations are inversely correlated with sympathetic activity and after surgery there is a reduction in thyroid hormone production, which returns to normal over a few days. The importance of the changes in gonadotrophin production and testosterone after surgery is uncertain. Testosterone concentrations are decreased for several days as are oestrogen values in females.

Substrate mobilization

The overall metabolic effect of the endocrine response is the mobilization of substrates from carbohydrate, lipid and protein stores.

Carbohydrate metabolism

Hyperglycaemia is a major feature of the metabolic response to surgery and results from an increase in glucose production, at the same time as a reduction in glucose utilization. This is facilitated by catecholamines and cortisol, which promote glycogenolysis and gluconeogenesis. The hyperglycaemic response is enhanced by the iatrogenic effects of administration of glucose infusions and blood products. The usual mechanisms, which regulate glucose production and homeostasis, are ineffective because of initial failure of insulin secretion followed by insulin resistance. The size of the hyperglycaemic response reflects the severity of surgery or injury. Glucose concentrations >12 mmol litre⁻¹ impair wound healing and increase infection rates. There is also an increased risk of ischaemic damage to the nervous system and myocardium.

Protein metabolism

Initially there is inhibition of protein anabolism, followed later, if the stress response is severe, by enhanced catabolism. Protein catabolism is stimulated by increased cortisol and cytokine concentrations. The amount of protein degradation is influenced by the type of surgery and also by the nutritional status of the patient. For example, after major abdominal surgery, up to 0.5 kg day⁻¹ of lean body mass may be lost, which can cause significant muscle wasting and weight loss. Skeletal muscle protein is mainly affected but some visceral muscle protein may also be catabolized to release

essential amino acids. The amino acids released form new proteins in the liver known as acute phase proteins, but albumin production is reduced interfering with the maintenance of the extracellular volume. Amino acids are also used for gluconeogenesis to maintain circulating blood glucose >3 mmol litre⁻¹. The amount of protein loss can be assessed indirectly by measuring nitrogen excretion in the form of urea in the urine. Attempts to prevent protein loss after surgery, by providing nutritional support, enteral and parenteral, have proved disappointing. The availability of additional substrates has little effect in overcoming the inhibition of protein anabolism and preventing catabolism.

Lipid metabolism

Increased catecholamine, cortisol and glucagon secretion, in combination with insulin deficiency, promotes lipolysis and ketone body production. Triglycerides are metabolized to fatty acids and glycerol; the latter is a gluconeogenic substrate. High glucagon and low insulin concentrations also promote oxidation of FFAs to acyl CoA. Acyl CoA is converted in the liver to ketone bodies (β -hydroxybutyrate, acetoacetate and acetone), which are a useful, water-soluble fuel source. Heparinization (for example during cardiac surgery) activates lipoprotein lipase which stimulates lipolysis, but this is less of a problem with the new 'cleaner' heparins.

Salt and water metabolism

Arginine vasopressin secretion results in water retention, concentrated urine, and potassium loss and may continue for 3–5 days after surgery. Renin is secreted from the juxtaglomerular cells of the kidney secondary to sympathetic efferent activation. It converts angiotensin to angiotensin II, which in turn releases aldosterone from the adrenal cortex promoting sodium and water retention from the distal convoluted tubule.

Cytokines

Cytokines are low molecular weight, heterogeneous glycoproteins that include interleukins (IL) 1–17, 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. Although they exert most of their effects locally (paracrine), they can also act systemically (endocrine). Cytokines play an important role in mediating immunity and inflammation by acting on surface receptors of target cells.

The most important cytokine associated with surgery is IL-6 and peak circulating values are found 12–24 h after surgery. The size of IL-6 response reflects the degree of tissue damage which has occurred. IL-6, and other cytokines, cause the acute phase response (Table 3), which includes the production of acute phase proteins such as fibrinogen, C reactive protein, complement proteins, α_2 -macroglobulin, amyloid A and ceruloplasmin. Other effects of cytokines include fever, granulocytosis, haemostasis, tissue damage limitation and promotion of healing.

Table 3 The acute phase response

Tissue injury → cytokine production, particularly IL-6
Acute phase protein synthesis, C reactive protein, serum amyloid A, serum amyloid P component, metal binding proteins, proteinase inhibitors, complement proteins, coagulation proteins
Hepatic sequestration of cations, e.g. iron and zinc
Reduction in transport proteins, e.g. albumin, transferrin, α_2 -macroglobulin
Pyrexia
Neutrophil leucocytosis
Increased muscle proteolysis
Changes in vascular permeability
Activation of hypothalamic–pituitary axis (<i>in vitro</i>)
Lymphocyte differentiation

The immune system and neuroendocrine system are closely related. Cytokines may increase the release of cortisol although this has only been demonstrated *in vitro* and cytokine production is limited by cortisol in a negative feedback system. Thus, the cortisol response to surgery limits the severity of the inflammatory response.

Modifying the response

Anaesthesia

Anaesthesia may influence some aspects of the stress response to surgery.

Opioids

Opioids are known to suppress hypothalamic and pituitary hormone secretion. At high doses (fentanyl $>50 \mu\text{g kg}^{-1}$) the hormonal response to pelvic and abdominal surgery is abolished. However, such doses prolong recovery and increase the need for postoperative ventilatory support. Even in cardiac surgery, where such doses are more often used, the stimulatory effects of cardiopulmonary bypass are so profound that the inhibitory effects of opioids are overcome.

Anaesthetic drugs

Etomidate suppresses the production of corticosteroids in the adrenal cortex by reversible inhibition of the enzyme 11- β -hydroxylase and the cholesterol side chain cleavage enzyme. An induction dose (0.3 mg kg^{-1}) blocks the synthesis of aldosterone and cortisol for up to 8 h. Benzodiazepines (midazolam $0.2\text{--}0.4 \text{ mg kg}^{-1}$ and infusion of $0.9\text{--}0.125 \text{ mg kg}^{-1} \text{ h}^{-1}$) may also have an inhibitory effect on steroid production at the hypothalamic–pituitary level, but the significance of this has not been established. Clonidine, a centrally acting anti-hypertensive, may decrease sympathoadrenal and cardiovascular responses to surgery.

Regional anaesthesia

The influence of regional anaesthesia on the stress response has been extensively investigated. Epidural/spinal anaesthesia can reduce the glucose, ACTH, cortisol, GH and epinephrine changes, although cytokine responses are unaltered. Abolition of hormonal responses occurs only when, not only somatic afferent, but also

autonomic afferent block occurs (pelvic, eye and limb surgery). An improved outcome, in terms of morbidity and mortality, with regional techniques has not been demonstrated consistently. However, the merits of excellent analgesia, reduced thromboembolic complications, improved pulmonary function and reduction of paralytic ileus are important.

Other methods

Surgical technique

Refining surgical techniques may have some benefit in reducing the inflammatory responses. Cytokine release is reduced in less invasive surgery such as laparoscopic techniques leading to quicker recovery and discharge.

Nutrition

Nutrition can also play a major part in preventing the adverse effects of the stress response. Enteral feeding, in particular immunonutrition (glutamine, arginine, omega-3 fatty acids) has been shown to improve recovery.

Hormone therapy

There may also be a role for growth hormone and anabolic steroids in improving outcome. Insulin infusions, with and without glucose, may also reduce excess protein breakdown.

Maintenance of normothermia

Maintenance of normothermia is also beneficial in reducing the extent of the metabolic response to surgery.

Conclusion

The hormonal and metabolic response to surgical and other physiological stresses is complex. It is important to reduce the deleterious effects of hypertension and tachycardia during surgery, particularly in patients with ischaemic heart disease. Modern anaesthetic practice strives to suppress sympathetic responses and maintain cardiovascular stability. However, there is no consistent method of suppressing the endocrine and metabolic changes and even when this is possible it is uncertain whether this benefits long-term outcomes.

Key references

- Baumann H, Gauldie J. The acute phase response. *Immunology Today* 1994; **15**: 74–9
- Desborough JP. The stress response to surgery. *Br J Anaesth* 2000; **85**: 109–17
- Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–17
- Sheeran P, Hall GM. Cytokines in anaesthesia. *Br J Anaesth* 1997; **78**: 201–19
- Traynor C, Hall GM. Endocrine and metabolic changes during surgery: anaesthetic implications. *Br J Anaesth* 1981; **53**: 153–60

See multiple choice questions 104–106.