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The anaesthetic modification of the endocrine and metabolic response to surgery*

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Summary

The metabolic and endocrine response to surgery has been investigated in detail for many years. The current view is that the response is detrimental to the patient and that the prevention or reduction of the changes may be beneficial in aiding recovery from surgery. Three main methods are available at present for modifying the response.

First, the use of afferent neuronal blockage, by epidural or spinal analgesia, to inhibit the transmission of impulses from the site of trauma.

Secondly, the intravenous administration of large doses of potent opiate analgesics to block hypothalamic-pituitary function.

Thirdly, the hormonal status of the patient may be changed, either by the use of agents to inhibit the secretion or action of the catabolic hormones, or by the infusion of anabolic hormones such as insulin.

Introduction

Surgery evokes an endocrine response which results in substrate mobilisation and muscle protein loss. These changes appear to have evolved to assist survival in a more primitive environment by providing appropriate substrates for gluconeogenesis and essential protein synthesis. However, in modern surgical practice, where severe physiological disturbances are prevented or rapidly treated and suitable substrates are easily provided, the benefits of this response are no longer apparent. Indeed, Kehlet *(1)* has argued that a decrease or abolition of the metabolic and endocrine changes associated with surgery may reduce postoperative morbidity.

Activation of the hormonal and metabolic response to surgery

A rational approach to the management of the hormonal and metabolic response to surgery depends on an understanding of the causative factors. Afferent nerve impulses from the injured area initiate the hormonal and physiological changes. Although early studies emphasised the importance of somatic afferent fibre activity, more recent work has demonstrated the major contribution from autonomic afferent impulses. This is shown most clearly by the failure of analgesia *per se* to prevent the endocrine response to surgery *(2)*. The increase in neuronal input to the hypothalamic area activates the autonomic nervous system and hypothalamic-pituitary secretion. Furthermore, the normal homeostatic feedback mechanism between the pituitary trophic hormones and their target hormones is disrupted so that the continuing secretion of pituitary hormones occurs.

A possible role for various circulatory factors, such as prostaglandins, 5-hydroxytryptamine and amino acids, in eliciting the metabolic changes associated with surgery received little support until recently. It has been shown however, that tissue damage causes the release of a polypeptide, interleukin-1 (also called leucocyte pyrogen, endogenous pyrogen, leucocytic endogenous mediator and lymphocyte-activating factor) from macrophages and monocytes. This low molecular weight compound may be responsible for several apparently unrelated changes observed after surgery. These include acute phase protein synthesis in the liver, T lymphocyte proliferation, antibody production, release of neutrophils from bone marrow, the febrile response to trauma and muscle proteolysis *(3)*. The hypothesis that interleukin-1 causes an increase in prostaglandin E_2 synthesis in muscle which results in augmented proteolysis has been challenged by those workers who consider muscle protein loss to be due to an inhibition of synthesis rather than increased breakdown *(4)*. The potential contribution of interleukin-1 to the metabolic response to surgery is of importance since anaesthetic techniques obviously cannot modify tissue damage.

In addition to afferent neuronal impulses and interleukin-1 a variety of other physiological disturbances may contribute to the overall changes and the most important are shown in Table I.

TABLE I *Contributory factors in the metabolic response to surgery*

1	*Preoperative*
	Partial starvation and dehydration
	Anxiety and fear
2	*Operative*
	Haemorrhage
	Hypothermia
3	*Postoperative*
	Infection
	Hypoxaemia
	Immobilisation
	Alteration in diurnal rhythms

*Based on a Hunterian Lecture given at the Royal College of Surgeons of England on October 13th 1983.

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The Editor would welcome any comments on this paper by readers

Hormonal and metabolic changes

The sequential changes in circulating hormones and metabolites occurring in surgery have been described in detail previously *(5)*. The hormones most commonly measured to quantify the response are the catabolic hormones, cortisol, catecholamines and growth hormone (GH), and the anabolic hormone, insulin. Alterations in other catabolic hormones such as glucagon and adrenocorticotrophic hormone (ACTH) have received less attention, partly due to difficulties in developing sufficiently accurate assays.

Blood glucose is the most commonly estimated circulating metabolite as the increase in concentration during surgery is roughly proportional to the surgical trauma. The mechanism of the hyperglycaemic response to surgery is complex, but increased circulating adrenaline and glucagon values raise hepatic glucose production in the presence of suppression of insulin secretion. Changes in fat metabolism are commonly assessed by measuring plasma non-esterified fatty acid (NEFA), plasma glycerol and blood 3-hydroybutyrate values. The mobilisation of fatty acids and glycerol from adipose tissue is controlled mainly by the catecholamines (lipolytic) and insulin (lipogenic) acting in opposition. Plasma amino acid profiles are sometimes used to assess protein metabolism during surgery, but the routine estimation of muscle protein loss is usually undertaken indirectly by determination of nitrogen balance. The measurement of urinary 3-methylhistidine as a specific marker for myofibrillar protein breakdown has been disputed since a significant contribution from the gut and other tissues has been reported *(6)*. Isotopic techniques to study protein turnover are not readily applicable to surgical patients and a simple, specific and sensitive method for examining acute changes in muscle protein is urgently required.

Management of the hormonal and metabolic response to surgery

It is common practice to accept the hormonal changes as an inevitable consequence of the surgical trauma and to attempt to minimise their metabolic sequelae. This is usually undertaken by the provision of appropriate substrates, either enterally or parenterally. Other measures that have been tried include nursing the patient in a thermoneutral environment after injury. Early studies showed that this was of little benefit for the general surgical patient, but more recent work indicates that the prevention of intraoperative hypothermia may be important *(7)*.

Anaesthetic and endocrine modification of the hormonal and metabolic response to surgery

There are three main methods available for modifying the response (Table II). First, the use of afferent neuronal blockade, by epidural or spinal analgesia, to inhibit the transmission of impulses from the site of trauma. Secondly, the intravenous administration of large doses of potent opiate analgesics to block hypothalamic-pituitary function. Thirdly, the hormonal status of the patient may be changed, either by the use of agents to inhibit the secretion or action of the catabolic hormones, or by the infusion of anabolic hormones such as insulin.

TABLE II *Methods for the anaesthetic and pharmacological modification of the metabolic and endocrine response to surgery*

1 Afferent neuronal blockade	—	local analgesics
	—	opiates
2 High-dose opiate anaesthesia		
3 Endocrine manipulation	—	inhibition of catabolic hormones
	—	infusion of insulin

When comparative studies are undertaken to examine the effects of the modification of the hormonal and metabolic response to surgery, there are many important variables which can influence the results obtained (Table III). It is unfortunate that in many investigations no control was exerted over these variables, and there are obvious examples in the literature of a failure to standardise even basic features such as the operation and the intravenous fluids.

TABLE III *Important variables in metabolic studies undertaken during surgery*

1	Age
2	Sex
3	Nutrition
4	Duration of preoperative starvation
5	Body type (% fat)
6	Drug therapy
7	Anaesthetic agents
8	Surgical stimulation
9	Intravenous infusion of crystalloids
10	Blood transfusion

EPIDURAL ANALGESIA (local analgesics)

The use of epidural analgesia to inhibit the metabolic and endocrine response to pelvic surgery has been investigated intensively by Kehlet and colleagues (for review see *1*). This followed the demonstration in 1977 that total abolition of the glucose and cortisol response to hysterectomy could be achieved only by neuronal blockade extending from T4 to S5 dermatome *(8)*. A less extensive blockade, which still provided excellent analgesia and operating conditions, failed to inhibit completely the increase in plasma cortisol. Although it is now commonly accepted that epidural blockade from T4 to S5 dermatome will prevent the response to pelvic surgery, it is clear from published work that some increase in cortisol may still occur during surgery. A thorough examination of the use of an extensive epidural blockade has shown beneficial effects on postoperative nitrogen balance and immunodepression (9), but no long term advantages such as a shortening of the duration of hospitalisation have been found. It is important to note that in all these studies the epidural block was established before the onset of surgery. The use of epidural analgesia *after* surgery has only limited effects on circulating glucose and cortisol values *(10)*.

The influence of epidural analgesia on the hormonal and metabolic response to upper abdominal surgery has received much less attention. In an early study of thoracic and upper abdominal surgery, epidural analgesia failed to alter the increase in plasma cortisol although the hyperglycaemia was abolished *(11)*. The interpretation advanced for these findings was that an increase in autonomic afferent fibre activity in the vagus nerve was an important factor in stimulating ACTH and thus cortisol secretion. Therefore, we attempted to examine the importance of vagal activity in mediating the metabolic and endocrine changes found during cholecystectomy *(12)*. Thoracic epidural analgesia was combined with infiltration of the vagus nerve with lignocaine at the gastro-oesophageal junction as soon as the peritoneum was opened. The results were disappointing since there was no effect on the plasma cortisol response, but the hyperglycaemia was inhibited as predicted. At first sight these findings suggest that vagal afferent activity is not important in stimulating ACTH and cortisol production; however other explanations cannot be excluded. For example, some dissection and retraction of organs were necessary to gain access to the gastro-oesophageal junction and this stimulus may have been sufficient to initiate the changes. Another possibility is that all vagal fibres were not blocked by the local analgesic.

Further recent work on abdominal surgery has examined the potential role of parasympathetic and symphathetic afferent fibre activity *(13,14)*. The results appear to support the contention that adequate blockade of sympathetic nerves from the abdomen has an important effect in decreasing the

hormonal changes. Close perusal of the studies, however, shows many methodological inaccuracies (see Table III) and thus confirmation of these findings is required.

EPIDURAL ANALGESIA (opiates)

The epidural administration of opiates for intraoperative and postoperative analgesia has been pursued enthusiastically by many anaesthetists. The possible beneficial effects of epidural opiates on the metabolic and hormonal response to surgery have also been studied. At present, all published work has been confined to the use of pelvic surgery and surgery on the lower limbs. In general, the results show that there is a decrease in plasma cortisol postoperatively compared with patients given conventional analgesia and this is attributed to the superior pain-relief with epidural opiates. It is interesting to note that in pelvic surgery epidural morphine was inferior metabolically and hormonally to epidural local analgesia from T4 to S5 dermatome *(15)*.

In view of the marked differences between pelvic and upper abdominal surgery when local analgesics are used epidurally, we examined the effects of epidural diamorphine on patients undergoing cholecystectomy (unpublished results). Excellent analgesia was achieved postoperatively and was associated with a 25% reduction in plasma cortisol values compared with patients given a conventional analgesic regimen. Epidural diamorphine had no effect on changes in circulating glucose, lactate, pyruvate and NEFA values intraoperatively and postoperatively. The use of extradural opiates seems to confer only minor hormonal benefits.

HIGH-DOSE OPIATE ANAESTHESIA

The ability of morphine to inhibit ACTH secretion was described 25 years ago *(16)*. The use of this drug to modify the hormonal response to surgery was investigated by George *et al. (17)*. They found that 1 mg morphine/kg body weight intravenously decreased the endocrine changes found during abdominal surgery and that 4 mg morphine/kg body weight inhibited the response during cardiac surgery until the start of cardiopulmonary bypass. The use of large doses of morphine during surgery resulted in an unacceptably prolonged recovery period and respiratory depression. The introduction of fentanyl, a potent opiate analgesic with a short duration of action, has enabled the effects of high-dose opiate anaesthesia on the metabolic and endocrine response to surgery to be studied in detail.

The intravenous administration of 50 μg fentanyl/kg body weight before the onset of surgery abolished the glucose, lactate, cortisol and GH response to pelvic surgery of 3 hours duration *(18)*. The same dose of fentanyl was less effective in patients undergoing gastric surgery *(19)*. The abolition of the increase in glucose, lactate and cortisol values was present for only 60–90 minutes of surgery after which surgical stimulation appeared to overcome the inhibition of hypothalamic-pituitary function. Profound respiratory depression occurred postoperatively in several patients in both studies and required careful supervision.

The use of the high-dose fentanyl anaesthesia (50 μg/kg body weight or greater) for cardiac surgery has achieved considerable popularity. It provides good cardiovascular stability, particularly in patients undergoing coronary artery bypass grafts, and the residual respiratory depression is of little consequence as patients are usually ventilated postoperatively. Several studies have examined the effects of fentanyl, and its congener sufentanil, on the metabolic and hormonal response to cardiac surgery. In summary, they show that high-dose fentanyl anaesthesia abolishes the catecholamine, ACTH/cortisol, GH, vasopression and glucose changes only until the start of cardiopulmonary bypass. The physiological changes associated with cardiopulmonary bypass, hypothermia, haemodilution and non-pulsatile flow, evoke endocrine responses that cannot be inhibited by opiates. It is unlikely that the transient suppression of the hormonal and metabolic changes before bypass confers any long-term benefits in cardiac surgical patients.

In the majority of studies using high-dose fentanyl anaesthesia the results were compared with a control group anaesthetised with a volatile agent such as halothane. The question arises whether any endogenous opioid secretion occurred in those patients given volatile agents which may have partially suppressed hypothalamic-pituitary function. The infusion of the opioid antagonist, naloxone, during pelvic surgery resulted in an exacerbation of the glycaemic response, but no significant changes were observed in cortisol, GH, insulin and glucagon secretion *(20)*. Thus endogenous opioids have only a minor role in modulating the metabolic and endocrine response to surgery; similar results have been found in other stress states such as insulin-induced hypoglycaemia and gastroscopy.

In all studies of high-dose opiate anaesthesia the analgesic was administered before the start of surgery. Since epidural analgesia is relatively ineffective in modifying the metabolic and endocrine response after the onset of surgery, it was of interest to determine the effects of high-dose fentanyl anaesthesia on the established response. Fifty μg fentanyl/kg body weight was given intravenously after one hour of inhalational anaesthesia to patients undergoing pelvic surgery and the results compared with a control group who received inhalational anaesthesia only *(21)*. Fentanyl administration had no effect on circulating glucose, NEFA and cortisol values, but did cause a decline in blood lactate possibly secondary to decreased catecholamine secretion. Thus, as was found for epidural analgesia, the metabolic and hormonal changes are easily prevented but cannot be reversed once they are established.

It is a common assumption that the effects of high-dose opiate anaesthesia on hypothalamic–pituitary secretion and sympathetic nervous system activity are mediated simply by binding of the drug to opioid receptors, particularly μ receptors. Detailed studies of the interactions between opiates and corticotrophin releasing factor suggest that the inhibitory action of the opiates is due partly to changes in neuronal input from higher centres. The failure of high-dose fentanyl anaesthesia to reverse the established metabolic response to surgery may reflect the importance of increased neuronal activity in controlling hypothalamic function.

ENDOCRINE MANIPULATION

Catecholamines Plasma noradrenaline and adrenaline values increase during surgery but it is only the latter which acts as a catabolic hormone. Epidural analgesia with local analgesics inhibits the rise in circulating adrenaline due to blockade of the innervation of the adrenal medulla. The hyperglycaemic response to surgery is easily abolished with epidural analgesia indicating that adrenaline-induced hepatic glycogenolysis is a major factor in this response. However, blockade of the direct sympathetic innervation of the liver may also be implicated.

The administration of α and β-adrenoceptor blocking drugs during surgery has been used in an attempt to define those metabolic changes subserved by different receptors. Beta-adrenoceptor blockade with 0.15 mg propranolol/kg body weight intravenously had little effect on circulating metabolites during pelvic surgery but caused an even greater insulin suppression than that observed in a control group *(22)*. The α-adrenoceptor blocking drug phentolamine was infused at 0.5 mg/minute into patients undergoing similar surgery and resulted in an increase in insulin secretion and an inhibition of the blood glucose response *(23)*. These results suggest that the increased circulating catecholamines during surgery exert their main effects on insulin secretion and blood glucose regulation. It is not clear whether α-adrenoceptor blockade modifies the hyperglycaemia of surgery by a direct effect on hepatic glucose production or indirectly by increasing insulin secretion.

Many surgical patients take a variety of adrenergic blocking drugs for the treatment of associated medical problems such as hypertension and ischaemic heart disease. Most anaesthetists concentrate on the potential cardiovascular problems associated with such patients, but the metabolic effects during surgery may be complex, particularly in diabetics.

Glucagon and growth hormone (GH) Both these hormones are considered together as their secretion is inhibited by the tetradecapeptide, somatostatin. This compound was originally postulated to be the hypothalamic growth hormone release inhibiting factor, but it was shown subsequently to also suppress glucagon, insulin and prolactin secretion. The inhibitory effects of somatostatin on pancreatic hormones are not surprising as it is located in the D-cells of the pancreas in close proximity to the insulin and glucagon secreting cells. It is thought that in the pancreas somatostatin acts as a local hormone or paracrine substance.

The infusion of somatostatin at a rate of 10 μg/minute during major abdominal surgery resulted in a ten-fold increase in circulating somatostatin values. As predicted, plasma glucagon concentrations declined significantly and this was associated with a small decrease in the hyperglycaemic response (unpublished results). The effect on blood glucose occurred in spite of further suppression of plasma insulin in the somatostatin-treated patients, and indicates that glucagon contributes to the rise in hepatic glucose output during major abdominal surgery. Fat metabolism, as assessed by circulating NEFA and glycerol values, increased during the somatostatin infusion probably secondary to the decline in plasma insulin.

The increase in GH secretion during surgery is also inhibited by somatostatin, but there is little evidence to support a short-term effect of this hormone on glucose and fat metabolism. It is likely, however, that the prolonged increase in GH secretion found after major surgery may be linked with the occurrence of insulin-resistance in the postoperative period.

Cortisol The intravenous induction agent, etomidate, has been found to be a potent inhibitor of adrenal steroidogenesis both *in vitro* and *in vivo*. An infusion of this agent during surgery will specifically block cortisol and related steroid production enabling the metabolic effects of these compounds to be assessed. Preliminary observations suggest that there is a small decrement in the glucose response to pelvic surgery, but that etomidate has no influence on other circulating metabolites (unpublished results). Although very low plasma cortisol values were found in some patients (< 100 nmol/l), no adverse cardiovascular effects were observed. This is in marked contrast to patients with septicaemia who seem to require higher circulating cortisol concentrations. Etomidate may become a useful pharmacological tool for the study of cortisol-induced metabolic changes.

Insulin The failure of insulin secretion to respond to the hyperglycaemia of surgery is a well recognised and important component of the endocrine response. There is some evidence to suggest that this is due partly to the inhibitory α-adrenergic effects of circulating catecholamines on the insulin secreting cells of the pancreas *(22,23)*.

In a recent study we examined the effects of a low-dose infusion of insulin on circulating metabolites during pelvic surgery *(24)*. Although the infusion only increased plasma insulin values from 5 to 25 mU/l, there were profound metabolic changes. Blood glucose declined progressively throughout surgery, whereas when catabolic hormone secretion is inhibited glucose values remain constant. It was not possible with this study to determine whether insulin was acting predominantly on hepatic glucose production or on glucose uptake peripherally. However, a correlation was found between the obesity of the patients and the decrement in blood glucose during surgery suggesting that an effect on peripheral glucose metabolism was present. Fat metabolism was also inhibited by the insulin infusion with a rapid decline in plasma NEFA values. This was followed by a decrease in 3-hydroxybutyrate concentrations secondary to the reduction in lipolysis. It was notable that the inhibition of substrate mobilisation during surgery occurred in the presence of a normal or augmented response of the catabolic hormones.

The results of this study imply that insulin suppression during surgery is a major factor in determining changes in glucose and fat metabolism. It is conceivable that the recent preoccupation of anaesthetists with the inhibition of the secretion of catabolic hormones during surgery may be misplaced. The possible benefits of an insulin infusion during surgery require verification using a more traumatic surgical model with particular attention to the protein-sparing effects of this hormone *(25)*. The beneficial effects on postoperative nitrogen balance reported after the administration of substances as diverse as GH and bradykinin may be mediated indirectly through increased insulin secretion.

Conclusions

The two main anaesthetic methods available for ameliorating the metabolic and endocrine response to surgery, epidural analgesia and high-dose opiate anaesthesia, have serious limitations. Autonomic afferent fibre activity is a major problem with the former and a failure to inhibit completely the response to severe surgical trauma occurs with the latter. It appears unrealistic to expect one technique to be of value except for specific operative sites such as pelvic surgery and lower limb surgery. Future investigations should be directed towards examining a combination of techniques, such as insulin infusion together with epidural blockade. Furthermore it is essential that studies are conducted on patients who are a high surgical risk, such as malnourished patients requiring extensive resection for carcinoma, to determine whether inhibition of the metabolic response confers any benefit in terms of mortality and morbidity.

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Notes on books

Nutrition Bulletin. British Nutrition Foundation, London.

The BNF Nutrition Bulletin for September 1983 discusses the F-Plan Diet, desirable weight, sweeteners, Vitamin C and nitrosamines, and enzymes in food processing.

Recent Advances in Orthopaedics 3 edited by B McKibbin. 237 pages, illustrated Churchill Livingstone, Edinburgh. £18.

Selected topics of current interest are discussed by international experts. The treatment of spinal turberculosis, osteosarcoma, anticoagulants in hip surgery and the early management of spinal injuries are discussed. Rotator cuff tendinitis, drug treatment of skeletal disorders, infected joint implants and internal fixation in fractures are next discussed. Various aspects of flexor tendon injuries are reviewed and the book ends with accident centres in civil disturbances.

Pediatric and Adolescent Sports Medicine edited by L J Micheli; 218 pages; illustrated; Little Brown & Co, Boston/Quest Publishing, Beckenham. $35.75.

This book starts by describing sports injuries in young athletes and emergencies in children's sports. It subsequently deals with injuries in the limbs and spine and considers medical and psychological problems.

Medical Textbook Review by Victor Daniels. 160 pages. Paperback. 6th edition. Cambridge Medical Books. £5.

This gives brief notices on many of the textbooks available, classified by subject with the name of the publisher and price. Anyone planning to buy a textbook would be well advised to glance through this review.

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