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Overview

Neuroimmunomodulation by regional and general anaesthesia

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Abstract

Background and Purpose: *This review presents the detailed immunological impact of neural variables, including stress, on specific cellular and molecular events that that take place over the full (time course) duration of autoimmune, inflammatory, allergic and infectious diseases.*

Materials and Methods: *A comprehensive search of literature from major injury (serious traumatic injury and major burns) to major surgical procedures that often lead to severe immunosuppression, which contributes to delayed wound healing, infectious complications and, in some cases, to sepsis, the most common cause of late death after trauma.*

Results: *Strong stimulation of the SNS and the HPA axis correlates with the severity of both cerebral and extracerebral injury and an unfavourable prognosis. The suppressed cellular immunity is associated with diminished production of IFN-γ and IL-12 and increased production of IL-10 – Th2 shift. Disbalance in relations Th1 and Th2 cytokine secreted by the T lymphocytes is considered the main difference between general and regional anaesthesia.*

Conclusions: *Considerable in-vitro data and in-vivo animal studies suggest that three factors associated with cancer surgery impair cellular immunity: the stress response to tissue injury, general anaesthesia and opioid analgesia. Regional analgesia decreases the neuroendocrine stress response to surgical tissue injury, eliminates or reduces the need for general anaesthesia and minimises opioid requirement. Thus cancer recurrence is lower after surgery with regional anaesthesia/analgesia than after surgery with general anaesthesia and opioid analgesia.*

INTRODUCTION

Major injury (serious traumatic injury and major burns) or major surgical procedures often lead to severe immunosuppression which contributes to delayed wound healing, infectious complications and, in some cases, to sepsis, the most common cause of late death after trauma *(1)*. The effect of anaesthesia on endocrine function is closely related to the actual stress concept based on studies by Cannon and Selye *(2)*. Cannon described the role of catecholamines in stress and characterised the fight-flight reaction *(2)*. Selye emphasised the role of the adrenocortical reaction defining the »general adaptation syndrome«, which evolves in three stages (»alarm reaction«, »stage of resistance«, »stage of exhaustion«) *(2)*. Anaesthesia can influence the stress response by afferent blockade (local anaesthesia), central modulation

TABLE 1

Systemic responses to surgery *(4)*.

Sympathetic nervous system activation
Endocrine »stress response«
Pituitary hormone secretion Insulin resistance
Immunological and haematological changes
Cytokine production Acute phase reaction Neutrophil leucocytosis Lymphocyte proliferation

(general anaesthesia) or peripheral interactions with the endocrine system (etomidate). Up to now, a total peripheral blockade of the nociceptive system is impossible, due to surgical technique (destruction of nerve fibres) and release of mediator substances. Spinal and epidural anaesthesia alone as well as in combination with general anaesthesia can reduce the endocrine stress response more than necessary. This is due to the sympathetic blockade, combined with an afferent blockade of central cord fibres which modulate the pituitary-adrenocortical system. Only few data are available concerning the stress response during infiltration anaesthesia or nerve block, but additional sedation seems to be beneficial *(2)*.

The stress response, anaesthesia and surgical outcome

The stress response is the term given to the hormonal and metabolic changes which follow injury or trauma *(3)*. This is part of the systemic reaction to injury which encompasses a wide range of endocrinological, immunological and haematological effects (Table 1) *(4)*.

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. These impulses travel along sensory nerve roots through the dorsal root of the spinal cord, up the spinal cord to the medulla to activate the hypothalamus *(2)*. The changes in pituitary secretion have secondary effects on hormone secretion from target organs (Table 2) *(5)*.

There is a failure of the normal feedback mechanisms of the control of hormone secretion. For example, enhanced cortisol secretion fails to inhibit further production of adrenocorticotropic hormone (ACTH) (6/4). In general, there is release of catabolic hormones such as the catecholamines and pituitary hormones whereas anabolic hormones such as insulin and testosteron are suppressed.

The overall metabolic effect of the hormonal changes is increased catabolism which mobilises substrates to provide energy sources and a mechanism to retain salt and water and maintain fluid volume and cardiovascular homeostasis *(7)*.

The stress response and immunology

The immunological effects of stress are mediated by cytokines, which are a group of low-molecular weight proteins which include the interleukins and interferons. They are produced from activated leucocytes, fibroblasts and endothelial cells as an early response to tissue injury and have a major role in mediating immunity and inflammation *(3)*. The cytokines act on surface receptors on many different target cells and their effects are produced ultimately by influencing protein synthesis within these cells. They have local effects of mediating and maintaining the inflammatory response to tissue injury, and also initiate some systemic changes which occur. After major surgery, the main cytokines released are interleukin-1 (IL-1), tumour necrosis factor – α (TNF-α) and inteleukin-6 (IL-6) *(3, 8, 9)*. The initial reaction is the release of IL-1 and TNF-α from activated macrophages and monocytes in the damaged tissues. This stimulates the production and release of more cytokines, in particular, IL-6, the main cytokine responsible for inducing the systemic changes known as the acute phase response (Table 3) *(4)*.

There are also interactions between the immune system and the neuroendocrine system. The cytokines IL-1

TABLE 2

Hormonal changes during surgery *(5)*.

	Pituitary	Adrenal	Pancreatic	Others
Increased secretion	Growth hormone (GH) Adrenocorticotrophic hormone (ACTH) b-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 (T3)

TABLE 3

Features of the acute phase response *(4)*.

Fever
Granulocytosis
Production of acute phase proteins in liver
CRP Fibrinogen α-2 macroglobulin
Changes in serum concentrations in transport proteins
Increase in ceruloplasmin Decrease in transferin, albumin and α-2 macroglobulin
Changes in serum concentrations in divalent cations
Copper increases Zinc and iron decrease

and IL-6 can stimulate secretion of ACTH and subsequently increase the release of cortisol *(5)*. A negative feedback system exists, so that glucocorticoids inhibit cytokine production. The cortisol response to surgery is sufficient to depress IL-6 concentrations.

The stress response and anaesthesia

Anaesthesia may indirectly affect the immune system of surgical patients by modulating neurohormonal stress response. In particular, regional anaesthesia attenuates this stress response and the associated effect on cellular and humoral immunity *(10)*. Additionally, anaesthetics may directly affect the functions of immune-competent cells. Mostly they have immunosuppressive effects which may be particularly important in the intensive care unit when anaesthetics are used as long-term sedatives. On the other hand, anti-inflammatory effects of anaesthetics may be therapeutically beneficial in distinct situations such as those involving ishaemia/reperfusion injury or systemic inflammatory response syndrome *(11)*.

The stress response and outcome

There has been a great deal of interest in modification of stress response with respect to the potential beneficial effects on surgical outcome. The extent to which the responses are modified depends on the choice of the analgesic techniques used. Inhibition of stress response is greatest with neural blockade (epidural) (with) by local anaesthetics *(8, 9)*. These changes in the immune system are irrelevant in young and healthy patients, but in high risk patients can potentiate cardiovascular complications, infection, MOF (multiorgan failure) and higher incidence of metastatic diseases.

Most current data support the notion that acute inflammation triggered by tumour-infiltrating host leukocytes does not exert normal immunoprotective mechanisms that lead to eradication of the evolving cancer

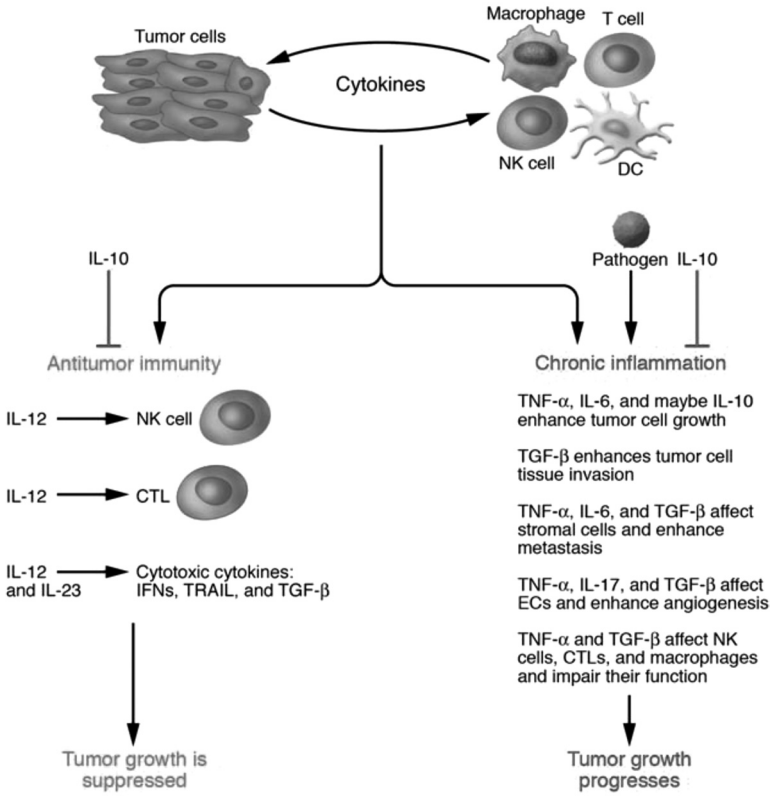

Figure 1. *A cytokine-mediated link between innate immunity, inflammation and cancer. Take from LIN W W, KARIN M 2007.*

(antitumour immunity). Instead, excessively and chronically produced proinflammatory mediators are thought to contribute to tumour promotion and progression (Figure 1) *(12)*. Thus, cancer can be promoted and/or exacerbated by inflammation and infection. A key molecular link between inflammation and tumour promotion and progression is provided by the inhibitor of NF-κB kinase/ NF-κB (IKK/ NF-κB) signalling pathway, which is activated by many proinflammatory cytokines *(12)*.

Clinical evaluation and research

Pain, surgical stress, tissue injury and invasive micro-organisms are known to modulate complex immune responses in patients undergoing major surgery, which can lead to subsequent increased susceptibility to postoperative infections. Anaesthetics may influence the immune response indirectly through modulation of the neurohumoral response or directly by acting on immune competent cells. General anaesthesia accompanied by surgical stress is considered to suppress immunity, presumably by directly affecting the immune system or activating the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Along with stress such as surgery, blood transfusion, hypothermia, hyperglycaemia, and postoperative pain, anaesthetics per se are associated with suppressed immunity during perioperative periods because all anaesthetics have direct suppressive effects on cellular and neurohumoral immunity (through) by influencing the functions of immunocompetent cells and inflammatory mediator gene expression and secretion. Particularly in cancer patients, immunosuppression attributable to anaesthetics, such as the dysfunction of natural killer cells and lymphocytes, may accelerate the growth and metastases of residual malignant cells, thereby worsening prognoses. Alternatively, the anti-inflammatory effects of anaesthetics may be beneficial in (distinct) certain situations involving ischemia and reperfusion injury or the systemic inflammatory response syndrome (SIRS) *(13, 14)*. Immunosuppressive effects may be particularly relevant in the intensive care unit when anaesthetics are used as long-term sedatives and evidence of infectious complications *(9)*.

Spinal and epidural anaesthesia alone as well as in combination with general anaesthesia and optimum postoperative analgesia can reduce the endocrine stress response more than necessary. This is due to the sympathetic blockade, combined with an afferent blockade of central cord fibres which modulate the pituitary-adrenocortical system.

Surgery remains the most effective treatment for most cancers, although it is usually associated with systemic release of tumour cells, in addition, pre-existing scattered micrometastases commonly remain. Whether minimal residual disease succeeds in establishing itself as recurrence or metastases is primarily a function of the host defence. In practice, the immune system frequently fails to neutralise remaining malignant tissues. Considerable *in vitro* data and *in vivo* animal studies suggest that three factors associated with cancer surgery impair cellular immunity: the stress response to tissue injury, general anaesthesia and opioid analgesia. Regional analgesia decreases the neuroendocrine stress response to surgical tissue injury, eliminates or reduces the need for general anaesthesia, and minimises opioid requirement. I therefore propose the hypothesis that cancer recurrence is lower after surgery with regional anaesthesia/analgesia than after surgery with general anaesthesia and opioid analgesia. Confirming this hypothesis would indicate that a minor modification to anaesthetic management reduces the risk of cancer recurrence *(15)*.

Surgery of breast cancer is the primary and most effective treatment, but minimal residual disease is probably unavoidable. Whether residual disease results in clinical metastases depends on numerous factors, including anti-tumour cell mediated immunity and angiogenic and growth signals in sites of residual disease. At least three perioperative factors adversely affect these: 1) the neuroendocrine stress response to surgery, 2) volatile anaesthetics and 3) opioids. Retrospective studies in humans also suggest that regional analgesia may reduce recurrence risk after cancer surgery. Sessler *et al. (16)* reports that local or metastatic recurrence after breast cancer surgery is lower in patients randomised to paravertebral or high-thoracic epidural analgesia combined with sedation or light anaesthesia than in patients given intraoperative volatile anaesthesia and postoperative opioid analgesia. They (enrolling) examined 1100 patients over 5 years and confirmed that a small modification to anaesthetic management, one that can be implemented with little risk or cost, will reduce the risk of cancer recurrence – a complication that is often ultimately lethal *(16)*.

Biki B *at al. (17)* evaluated prostate cancer recurrence in patients who received either general anaesthesia with epidural anaesthesia/analgesia or general anaesthesia with postoperative opioid analgesia. They concluded that open prostatectomy surgery with general anaesthesia, substituting epidural analgesia for postoperative opioids, was associated with substantially less risk of biochemical cancer recurrence *(17)*.

Many studies have shown that regional anaesthesia improves postoperative outcome and particularly lessens infection by attenuating perioperative immunosuppression related to the stress response to surgery and general anaesthesia *(8)*. However, it remains to be determined whether regional anaesthesia improves oncologic outcome after surgery. Wada H *et al.(18)* showed that the addition of spinal block to sevoflurane general anaesthesia reduces the promotion of tumour metastasis. C57BL/6 mice were subjected to laparotomy during sevoflurane general anaesthesia alone or combined with spinal block achieved with bupivacaine (5 microg) and morphine (1.25 microg). Sevoflurane anesthesia plus spinal block significantly reduced this increase to 19.8 +/- 9. The in vitro killer activity of liver mononuclear cells against EL4 cells decreased from 32.7% (control) and 29.4% (sevoflurane alone) to 18.5% after sevoflurane plus laparotomy, and the addition of spinal block increased activity to 26.6%. The interferon-gamma/interleukin-4 ratio decreas-

ed from 89.3 (control) and 95.7 (anaesthesia alone) to 15.7 after sevoflurane plus laparotomy, and the addition of spinal block increased the ratio to 46.5. The addition of spinal block to sevoflurane general anaesthesia accompanying surgery attenuates the suppression of tumoricidal function of liver mononuclear cells, presumably by preserving the T helper 1/T helper 2 (Th1/Th2) balance, and thereby reduces the promotion of tumour metastasis *(18)*.

The immune response (measured by a variety of parameters) was examined in patients undergoing transurethral resection of the prostate (TURP) for benign disease. A significant reduction in lymphocyte numbers and in the response of lymphocytes to the mitogens PPD and PWM and to histocompatibility antigens in mixed lymphocyte culture was seen in patients after TURP under general anaesthetic, although minimal changes were found in patients who had spinal anaesthetic. Cortisol levels were not elevated in either group after surgery. The immunodepression occurring after TURP appears to be due to general anaesthesia rather than the trauma of surgery *(19)*.

Surgical stress and anaesthesia cause immunosuppression that may predispose patients to postoperative infections. T helper lymphocytes play a major role in the immune response by controlling cell-mediated and humoral immunity. The type of immune response generated is determined by the differentiation of precursor T helper cells into Th1 or Th2 cells. Each cell subset secretes a particular array of cytokines that further augment the differentiation into that subset. Th1 cells produce interferon gamma and are responsible for cell-mediated immunity. Th2 cells produce interleukin-4 and are more effective in inducing humoral immunity. Cytokine concentrations are altered during surgery and anaesthesia, which may effect Th cell predominance and, therefore, subsequent immune responses. Le Cras *et al. (20)* determined Th1 to Th2 cell ratios in patients undergoing transurethral resection of the prostate (TURP) using either spinal or general anaesthesia. Mononuclear cells were isolated before anaesthesia, immediately after surgery, and after 24 h from patients undergoing TURP. T helper cell subsets were quantified by using flow cytometry, and the ratio of Th1 to Th2 cells was calculated. Results of data suggest that, from an immunological viewpoint, spinal anaesthesia, but not general anaesthesia, benefits the patient by maintaining Th1 cell numbers, thereby promoting cellular immunity. Spinal anaesthesia may result in less immunosuppression after surgery. They found that the ratio of T helper 1 to T helper 2 cells was higher in patients undergoing prostate surgery by spinal rather than general anaesthesia. Th1 cells promote protective immune responses that may result in fewer postoperative infections *(20)*.

Cytokines are significant mediators of the immune response to surgery and also play a role in parturition. The study was to investigate the impact of the anaesthetic technique (spinal and general anaesthesia) for cesarean section on plasma levels of cytokines IL-6 and TNF-α. Under the present study design anaesthetic technique did not affect IL-6 or TNF-α concentrations in parturients undergoing elective cesarean section. Serum IL-6 levels increased 24 h postoperatively independently of anaesthetic technique *(21)*.

Glial cells and pain

Today, there is a need for development of new agents and methods for the treatment and prevention of postoperative complications. Attention has recently shifted from neuronal modulation to the discovery of glial modulating agents for the treatment of a host of neurodegenerative diseases, as well as pain.

Glial cells are key neuromodulatory, neurotrophic and neuroimmune elements in the CNS. Glial cells, including resident microglia, perivascular microglia, astrocytes and oligodendrocytes constitute over 70% of the total cell population in the brain and spinal cord. Microglia, cells of monocytic origin, are the macrophages of the brain and the first cell type to respond to CNS injury *(22)*. The initial signal that triggers microglial reactivity is not fully understood; however, neuronal depolarization and extracellular ion changes following nerve injury may be major stimuli. Alternatively, neuronal signals such as nitric oxide (NO) or pro-inflammatory cytokines may induce this reactivity.

Microglia both release and respond to several cytokines including interleukin (IL)-1, IL-6, tumour necrosis factor (TNF-α) and interferon-α, all of which are instrumental in astrocytic reactivity, induction of cellular adhesion molecule expression and recruitment of T-leukocytes into the lesion. In addition, microglia may act as cytotoxic effector cells by releasing proteases, reactive oxygen intermediates and NO. Perivascular microglia are CNS antigen-presenting cells and play an important role in the communication of the CNS with the peripheral immune system, especially in pathological conditions *(22)* such as perioperative pain. Astrocytic changes in response to injury include proliferation, hypertrophy, and over-expression of glial fibrillary acidic protein (GFAP). Spinal GFAP increases following peripheral nerve injury *(22)*.

The goal of further clinical studies must be to establish the immunomodulating properties of individual anaesthetic agents so that selection can be tailored to the individual patient's pre-operative immune status and intraoperative course *(23, 24),* with regard to long-term mortality, morbidity, and the optimal prognosis.

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