EDITORIAL

Does anaesthesia have long-term consequences?

The definition of anaesthesia as a triad of hypnosis, analgesia and neuromuscular block, now seems simplistic; it ignores other less obvious effects, which may be either beneficial or detrimental to our patients. One example of a more subtle effect of anaesthesia is how it may influence communication between cells. Intact intercellular signalling underlies the ability of an organism to mount an appropriate physiological response to an insult. In many pathophysiological processes, including wound healing, ischaemia and malignancy, defective signalling is known to occur. Progress in basic science has led to the identification of, and the technology to measure, a group of intercellular mediators termed cytokines. These comprise a family of small proteins and glycoproteins (molecular weight 15–30 kDa). Under normal conditions, baseline production of cytokines is low, but when triggered by appropriate stimuli, including infection or surgical injury, production can increase markedly. Most cytokines act in an autocrine (i.e. on the producer cell) or paracrine (i.e. on neighbouring cells) manner. A few members of the family, for example tumour necrosis factor-α (TNF-α), interleukin-2 (IL-2), interleukin-6 (IL-6) and transforming growth factor-β (TGF-β) are transported in the blood to act at distant sites, and thus resemble classical hormones. After stimulation by an insult, leucocytes, macrophages and endothelial cells either release stores, or rapidly switch on the synthesis of cytokines. These mediators regulate the activity, differentiation and growth of many types of cell belonging to the inflammatory and immune systems. Generation of transgenic animals, which either over-express or under-express a specific cytokine, has provided a useful tool to help unravel the functions of these mediators.

Severe injury and infection produce well characterized neuroendocrine and metabolic changes in the host. These changes are mediated, at least partly, by cytokines. TNF-α, IL-1β, IL-2, IL-6 and interferon-α cause release of anterior pituitary hormones by acting on the hypothalamus and pituitary glands. Although such cytokine responses are generally believed to be beneficial, some individuals develop an excessive or prolonged response, manifested clinically by the systemic inflammatory response syndrome (SIRS). Many animal studies have been published demonstrating improved outcome after inhibition of cytokine responses. Most of this research has focused on sepsis. They conclude that attenuation of cytokine activity after lipopolysaccharide (LPS) administration, or caecal ligation and puncture, increases survival. For many reasons, discussed by Yentis in an editorial in this journal, the expected benefit from cytokine manipulation in sepsis has not yet been realized in human studies.

Cytokine responses to surgery have also been studied, particularly IL-1β, IL-6 and TNF-α, which have been shown to increase in proportion to the magnitude of the operation. Although there is a paucity of data on the influence of anaesthetic drugs and techniques on cytokine responses, there is evidence that anaesthesia is capable of modulating these short-term responses. In vitro studies have demonstrated that volatile agents can suppress cytokine release from blood cells. Isoflurane inhibits the secretion of TNF-α and IL-1β from LPS-stimulated human peripheral blood monocytes. In another study, sevoflurane and enflurane were found to inhibit TNF-α and IL-1β release from stimulated monocytes, but the release of IL-2 was unaffected. In vitro assessment of anaesthesia and cytokine responses has not been restricted to general anaesthetic agents. Lignocaine inhibits the effect of recombinant human granulocyte colony-stimulating factor (rhG-CSF) on human neutrophil function: it reduces rhG-CSF-induced neutrophil superoxide release and down-regulates leucocyte adhesion molecule-1 expression in a dose-dependent manner.

Few studies have been published on how anaesthesia affects in vivo cytokine responses to surgery. Crozier and colleagues compared the changes in plasma concentrations of IL-1β and IL-6 after abdominal surgery, using two different anaesthetic techniques. Compared with anaesthesia using isoflurane and nitrous oxide, total i.v. anaesthesia (TIVA) with propofol and alfentanil caused a significantly reduced and delayed increase in IL-6 concentrations. No difference was observed when concentrations of IL-1β were measured. The authors concluded that alfentanil was the agent responsible for suppressing the release of IL-6. The effect of extradural anaesthesia on the IL-6 response to abdominal surgery has also been investigated: although it caused no overall significant change in cytokine concentrations, a delayed increase in IL-6 was noted. Thus, there is evidence that anaesthesia has the potential to attenuate cytokine responses induced by surgical trauma.

For reasons which remain unclear, some individuals develop uncontrolled cytokine responses and could potentially benefit from appropriately timed
cysteine. Until recently it has not been possible to predict which patients are at risk of mounting this excessive cytokine response to surgical injury. However, molecular biology may be able to offer a solution. Polymorphism is the existence in a population of two or more relatively common alleles at a genetic locus. Polymorphism, or variation in DNA sequence, may occur in an exon (coding portion of the gene) and after transcription and translation, result in the production of a defective protein. Equally, polymorphism may occur in an intron (non-coding portion), but still modify gene expression in other subtle ways. For example, polymorphism may lie in the promoter region of the gene, a part of the gene that is important in determining initiation of transcription. Alternatively, polymorphism itself may be unimportant, except as a marker that may be linked to another, as yet unidentified, allelic variation that is responsible for the altered phenotypic response. Although it is accepted that particular genotypes can predispose individuals to long-term risks in response to environmental stress, for example the familial clustering of some types of cancer, until recently there was little evidence that genotype could alter outcome with respect to short-term stress. Stuber and colleagues have recently reported a genomic polymorphism within the TNF locus that influences concentrations of TNF-α and outcome in patients experiencing the short-term stress of severe sepsis. They used the polymerase chain reaction (PCR) to amplify a 782-base pair fragment of genomic DNA, which included the polymorphic site of a restriction endonuclease (NcoI) within the TNF locus. Each patient’s genotype was determined after digestion with NcoI and gel electrophoresis. Two TNF alleles, TNFβ1 and TNFβ2, were identified and correlated with maximum concentrations of TNF-α and outcome. The 42% of patients who were homozygous for TNFβ2 had significantly higher concentrations of TNF-α and a worse outcome. This is the first attempt at using a genetic test to predict cytokine responses and outcome, and should be investigated prospectively. In the future it may be possible, using simple blood tests, to predict which patients are likely to mount excessive cytokine responses after major surgery (high responders). Such tests may help anaesthetists to predict outcome or the need for postoperative intensive care. They may also allow us to select the most appropriate anaesthetic, in terms of its ability to modulate cytokine activity, for each patient.

In addition to modulating cytokine responses to surgical injury, anaesthesia may influence the activity of cytokines involved in coincidental pathophysiological processes. Many cytokines have been identified as pivotal mediators in a wide range of chronic processes. Transforming growth factor-β (TGF-β) may be unfamiliar to most anaesthetists, but is an example of a cytokine which is known to be vitally important in the pathogenesis of many long-term disorders, including wound healing, fracture healing and malignancy. When soft tissue is injured, TGF-β is released from degranulating platelets to trigger a cascade of events, including recruitment of inflammatory cells, angiogenesis and the synthesis of collagen. Application of topical TGF-β promotes wound healing in a variety of animal models and the topical application of anti-TGF-β antibodies reduces cutaneous scarring. Interestingly, Amento and colleagues reported that a single dose of TGF-β administered systemically before wounding also enhanced healing. Thus, transient changes in concentrations of TGF-β may have effects on the long-term process of wound healing. If anaesthesia is shown to change TGF-β activity, even for a short albeit critical period, then it could indirectly influence wound healing after surgery. TGF-β is also thought to contribute to fracture healing and embryonic bone formation. Injections of TGF-β onto the periosteum of rat parietal bones induced new bone formation.

Systemic administration of TGF-β protects against ischaemia. It was shown to have cardioprotective effects when administered after experimental myocardial infarction in rats. Systemic administration of TGF-β in a model of splanchic ischaemia–reperfusion injury was also shown to be protective. Growth of most epithelial and lymphoid cells is inhibited by TGF-β. One postulated mechanism whereby cells undergo carcinogenic transformation and escape from normal growth control appears to involve an altered response to the negative regulation of TGF-β. Studies on a TGF-β-responsive human colonic carcinoma cell line implicated TGF-β as an autocrine and paracrine negative regulator of growth, and suggest that loss of response to TGF-β may contribute to tumour progression.

Our understanding of cytokine biology is developing rapidly. Knowledge as to the identification of patients who are prone to mounting abnormal cytokine responses, and the roles of cytokines in the pathogenesis of disease, is increasing at a phenomenal rate. Anaesthesia must contribute to this exciting and expanding area of research. The study of how different anaesthetic agents and techniques affect cytokine concentrations and activity must continue. Certain agents and techniques could prove to be clinically useful in the modulation of cytokine activity in subjects who are high responders and also influence specific disease processes which are regulated by cytokines. Indeed, there may well be more to anaesthesia than sleep!

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References


