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Anesthesiology and the cytokine network

Anestezjologia w sieci cytokin

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Summary

The immune response is a highly specific reaction carried out by means of specialized cells that belong to the immune system. There are two types of immune response mechanisms aimed towards pathogens: non-specific, innate reactions, and specific, acquired reactions.

Acquired immunity, characterized by its specificity, is comprised of lymphocytes, including both T cell and B cell populations. The role of B lymphocytes is not limited to the humoral response, though the cellular immune response is carried out mainly by various T lymphocyte subpopulations.

The reactions of the humoral and cellular responses complement and stimulate one another mutually – cytokines are their common linking element. The attachment of cytokines to their specific receptors activates a sequence of signals – either intracellular or between the cells of various systems.

This organization of respective connections and reactions, including the functional relations between cells of the immune response, in its complexity, is best described as a cytokine network.

The response of the immune system to surgical trauma can be looked at from both a local and a general perspective. Not only surgical trauma caused by tissue damage, however, influences the functioning of the immune system, but also the drugs and techniques used during anesthesia.

Our article is a presentation of the effects of medications used in anesthesia with respect to their influence on the cytokine network.

Key words: immune system • cytokines • anesthetics

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THE ROLE OF CYTOKINES IN THE IMMUNE SYSTEM

To survive, an organism must protect itself by means of fighting or adapting to invading microorganisms. In short, a stranger must either be accepted or destroyed.

The highly specific immune response is carried out by specialized tissues and cells comprising the immune system which functions to protect organisms against foreign antigens.

There are 2 types of immunological responses to infectious agents: non-specific, innate reactions, and specific, acquired defenses.

The immune system plays a key role in the inflammatory response and is anatomically and physiologically designed to protect the organism against harmful pathogens. Monocytes/macrophages, B, T, NK and dendritic cells (DC) as well as granulocytes constitute the basic elements of the cellular immune response to infectious agents.

An important characteristic of acquired immunity is its specificity. The components of acquired immunity are antigen-presenting cells (APC) represented by DC and lymphocytes, including the T cell and B cell populations. Antibodies (immunoglobulins) are produced by activated, differentiated B lymphocytes. Antibodies, present in the blood, lymph and tissue fluids, have the ability to bind and neutralize antigens. The role of B lymphocytes is not, however, limited to the humoral response – functions such as cytokine synthesis, presenting antigens to T lymphocytes and helping to generate secondary lymphoid tissue are also important for the efficacy and functioning of the immune system [40].

The cellular immune response is carried out by various T lymphocyte subpopulations (helper T cells, cytotoxic T lymphocytes, and regulatory T cells), capable of recognizing specific antigens. The reactions of the humoral and cellular responses complement and stimulate one another mutually.

The 2 types of immune responses are linked by cytokines, which, in a sense, can be compared to reporters or journalists in that they play an important role in the distribution of information.

Cytokines are released by cells of the immune system. They are characterized by pleiotropy, act in an auto-, para-, and endocrine manner, and either demonstrate synergistic activity or act antagonistically towards one another.

Cytokines function via cell surface receptors. The binding of cytokines to their receptors usually activates a sequence of intracellular signals leading to a cell response.

Cytokines are therefore vital in the inflammation process, playing an important role in both strengthening and suppressing the inflammatory response.

This system of respective connections and reactions, including the functional relations between cells of the immune response, in its complexity, is best described as a cytokine network.

The response of the immune system to surgical trauma can be estimated at both local and systemic levels. However, not only surgical trauma, caused by tissue damage, may modify the function of the immune system, but also the drugs and techniques used during anesthesia. It seems, though, that at the core of immune system changes is the modulation of the cytokine network.

The main cytokines implicated in this response are IL-6, TNF- α , IL-1 and IL-8. In reaction to stress caused by surgical trauma, macrophages release TNF- α and IL-1, which subsequently trigger the synthesis and release of other proinflammatory cytokines, such as IL-6, IL-8 [50] and numerous endogenous inflammatory mediators – growth factors, elements of the complement system, adhesion molecules, thrombin and PAF, among others.

The intensity of the cytokine response is directly related to the size and scope of the surgical wound, which depends mainly on choice of operative technique [45]. Several results have confirmed the relationship between operative technique and cytokine response. They underline the importance of cytokine network changes that can play a role in the quality of post-operative care [8,19,68]. With respect to anesthesia, it is thought that cytokine equilibrium, broken down by surgical stress, is mostly influenced by medication, followed by the choice of anesthetic types and techniques.

The effect of drugs depends primarily on their plasma concentrations and duration as well as on function of the immune system.

It should be noted that findings suggesting the influence of anesthesia on the immune system were first presented by Graham as well as Gaylord and Simpson in 1911 and 1916, respectively [31,35].

It is believed that in comparison to general anesthesia, regional anesthesia suppresses the immune system to a smaller extent. This was not confirmed, however, by studies performed by Dermitzaki et al., who did not find a difference in IL-6 and TNF- α serum concentrations between groups of patients that received either general or epidural anesthesia prior to cesarean section procedures. In both groups, an increase in IL-6 with no changes in the concentrations of TNF- α was observed [14]. The same results were obtained by other authors who examined the effect of regional and general anesthesia on plasma concentrations of IL-1, IL-6 and TNF- α in patients undergoing orthopedic surgery. In both groups the authors observed an increase of IL-6 and TNF- α with low values of IL-1. The results did not confirm significant differences in plasma concentrations of TNF- α and IL-6 between patients who underwent general or regional anaesthesia [24].

Gilliland et al. confirmed the positive correlation between IL-6 concentrations and the extent of surgical trauma and also the influence of these concentrations on the healing process and on post-operative immunosuppression [22]. Studies carried out on animals by Shimada et al. did not show anesthesia to exert any effect on either TNF or IL-6 concentrations [60].

CYTOKINES IN THE FACE OF SOME DRUGS USED DURING ANESTHESIA

Intravenous anesthetics

Of all the intravenous anesthetic agents, the following are noteworthy: thiopental, a representative of the first ever synthetic barbiturates; ketamine, a drug whose 'golden age' is gone but is still, nevertheless, put to use; and propofol, a popular drug that is administered often. Intravenous anesthetics have anti-inflammatory properties which, in most septic cases, can be considered to be beneficial to the patient.

Thiopental like many anesthetics acts on GABA_A receptors whose presence on immune cells has been confirmed [1,27]. Ketamine acts via antagonism of N-methyl-D-aspartate (NMDA) receptors. The anti-inflammatory effects of ketamine are still unclear but they could be connected with the suppression of macrophage production of TNF in the presence of bacteria [11]. According to results reported by Song et al., ketamine inhibits production of proinflammatory cytokines by reduction of hepatic nuclear factor kappa B (NF- κ B) activation in experimental model of sepsis [63]. The nuclear factor kappa-B (NF- κ B) proteins belong to a family of transcription factors that play a key role in the activation of many genes that regulate a large number of process such as synthesis of proinflammatory cytokines, cell proliferation and apoptosis, for example. NF- κ B is also involved in the transcription of genes linked with sepsis. Thiopental and ketamine can inhibit the release of IL-1, IL-6, TNF- α and IL-8 triggered by endotoxin or lipopolysaccharide. Additionally, these drugs also increase the level of IL-10, an anti-inflammatory cytokine [29,30,65,71].

This situation can be beneficial for septic patients because proinflammatory cytokines' responses are well-known factors in the pathophysiology of organ dysfunction following endotoxemia. The overproduction of the proinflammatory cytokines causes the enhanced systemic inflammatory response syndrome (SIRS). However, the predominance of antiinflammatory cytokines may lead to higher risk of infections. Similarly, the effect of ketamine and thiopental on the function of mast cells appears to be disadvantageous for patients with a high risk of infection. The study of Fujimoto et al. showed that both these anesthetics have also suppressed mast cell chemotaxis and exocytosis [20]. Mast cells have a protective role in host defense against pathogens due to their involvement in innate and acquired immune responses to infection. So, the inhibitory effects of thiopental and ketamine on

mast cell function may induce a higher risk of infection. Additionally, the ability of thiopental to inhibit monocyte chemotaxis and phagocytosis may also suppress the host response against pathogens and thereby enhance the risk of infection in immunocompromised patients [48,72]. Chemotaxis plays a crucial role in the inflammatory response, because it is involved in the migration of leukocytes through the walls of blood vessels to sites of infection.

We suppose that management of well-balanced sedation technique in patients with an impaired immune response could significantly reduce the risk of infection.

The increased risk of infection in patients with continuous barbiturate therapy may provide new approaches to modulate the immune response.

Zeyneloglu et al. in their study with children undergoing cardiac surgery found no significant differences between ketamine and isoflurane on the magnitude of the systemic inflammatory response. Both anesthetics had similar effects on the concentrations of IL-6 in plasma and bronchoalveolar lavage fluid [74]. But it has also been demonstrated that a low dose of ketamine used as preemptive anesthesia caused a perioperative decrease of IL-6 concentration independently of the kind of surgery [54,55].

Moreover, the application of low-dose ketamine also suppressed the *in vitro* mitogen response and release of IL-1 β , IL-2, IL-6, and TNF- α , by peripheral blood mononuclear cells (PBMC) in patients undergoing abdominal surgery [3].

So using ketamine may be an effective preventative method of impeding inflammation in response to surgical stress. Because the overproduction of these cytokines is connected with the severity of the inflammatory response and postoperative complications this management seems to be effective in reduction of postoperative complications as well. In addition, the results of many studies have shown that ketamine could be helpful in reducing the amount of requested analgesics and postoperative pain score [44,47,48].

The preemptive epidural administration of ketamine did not change the concentrations of IL-6, TNF or IL-10 cytokines in the plasma of examined patients but diminished the pain intensity after surgery [61]. To the contrary, preemptive ketamine given intravenously not only reduced the plasma concentration of IL-6 and TNF- α but also was associated with lower pain intensity and postoperative consumption of analgesics when compared with a control group [15].

It is suggested with high probability that ketamine did not affect cytokine levels due to low blood concentration after epidural administration. Epidural ketamine improved pain relief by the inhibitory action of NMDA receptors in spinal cord without any changes in cytokine concen-

trations. In conclusion, the choice of way of ketamine administration should be associated with the patient's condition and his capacity for defense against infection.

Propofol (2,6-diisopropylphenol) is routinely used for short-term sedation, maintenance of anesthesia and for long-term sedation in critical patients. Propofol is characterized by perfect anesthetic effects and anti-inflammatory, antioxidant properties [42].

The molecular mechanisms for anti-inflammatory and antioxidant activity of propofol have been a subject of interest for many studies; however, they are still unclear.

The drug owes these properties to its chemical resemblance to endogenous tocopherols. Studies have shown that after the use of propofol patients exhibit a substantial increase in γ tocopherol, an agent causing inhibition of the inflammatory response.

The anti-inflammatory properties of propofol are also demonstrated by its ability to weaken the synthesis of prostaglandins (PGE) by LPS activated monocytes [9].

In addition, propofol blocks the expression of ICAM-1 and VCAM-1 cellular adhesion molecules, which are crucial in the migration of leukocytes through the endothelium [13].

The studies conducted by González-Correa et al. have shown that propofol reduced the concentration of cytokines (IL-1, TNF- α , IL-6) and stimulated the neutrophils to nitric oxide (NO) synthesis [23,62].

The anti-inflammatory effect of propofol has been confirmed by its inhibition of LPS stimulated macrophages, which can be regarded as a laboratory endotoxemic model [25].

The results presented by Chung-Hsi et al. indicated that propofol attenuated the inflammatory activity of LPS-induced macrophages in an animal septic model by inhibition of the signal transduction including the reactive oxygen species generation/Akt signaling/I κ B kinase/NF- κ B pathway (ROS/Akt/IKK β /NF- κ B). They confirmed the suppressive influence of propofol treatment on LPS-induced cellular inflammatory responses respectively, in macrophages. Furthermore, the authors provided evidence that the antioxidant properties of propofol have been associated with decrease of antioxidant activity capacity also via regulation of the ROS/Akt/NF- κ B pathway.

The antioxidant properties of propofol have also been confirmed by other investigators. Their results showed that propofol could reduce free radical level and the intensity of oxidative stress [2,38].

Oxidative stress is characterized as an imbalance between generation of reactive oxygen species (ROS) and inadequate antioxidant defense systems including endogenous enzymes and exogenous antioxidants. The significant in-

crease of ROS following many stressful events can initiate the damage to cellular DNA, lipids and proteins that in surgical patients may lead to the impairment of wound healing and higher risk of infection.

The anti-inflammatory effect of propofol was also observed *in vitro* in LPS stimulated macrophages. Propofol has remarkable regulatory activity on NO generation via stimulation of constitutive nitric oxide synthase and inhibition of inducible nitric oxide synthase (iNOS) [25].

The inhibitory effects were dose and time manner dependent; a higher dose of propofol attenuated synthesis more strongly when given immediately after LPS stimulation. NO synthase (iNOS) plays a role in induction of NO release from macrophages due to inflammatory reactions. The excess of NO may cause damage of tissue and organ failure. This effect should not always be beneficial to patients in acute states compared to those with chronic inflammation when suppression of the chronic inflammatory response may have more advantages.

Furthermore, propofol causes an increase in anti-inflammatory IL-10 concentrations.

The higher concentration of anti-inflammatory cytokine in patients given propofol is additional proof of the drug's anti-inflammatory properties. IL-10 blocks the synthesis of pro-inflammatory cytokines and stimulates the release of IL-1 receptor antagonist (IL-1Ra).

The use of propofol anesthesia has also been shown to be more beneficial than isoflurane from the point of view of post-operative risk of infection. The results of studies examining the IL-6/IL-10 ratio (factor indicating attenuation of the immune imbalance) demonstrated increase of this ratio after propofol and its decrease after isoflurane administration – findings which can subsequently lead to the reduction of post-operative risk of infection [69].

Like ketamine, propofol impairs the chemotaxis and oxidative ability of macrophages in a dose-dependent manner. The investigators explained that decline of macrophage activity could be followed by lowering of membrane potential of mitochondria and synthesis of cellular adenosine triphosphate [12], which in turn leads to attenuation of synthesis of TNF- α , IL-1 β and IL-6 proinflammatory cytokines.

Sung et al. showed that propofol could limit an excess of inflammatory response followed by stress involving ischemia and reperfusion [64]. In their studies, they evaluated the effect of propofol in relation to the hepatic Kupffer cells that are known as a major source of proinflammatory cytokine release during the acute phase inflammatory response. The results showed reduction of intracellular Ca²⁺ and TNF- α mRNA expression in the cells in presence of propofol. The protective function of propofol on cells after ischemia-reperfusion have also been confirmed by Feng et al. The authors demonstrated significantly lower

expression of NF-kappa B and IL-1, TNF-alpha and ICAM-1 in cells taken from animals which were given propofol during transient focal cerebral ischemia-reperfusion [16].

A study examining the influence of propofol (used in two doses, 3.5 or 10 µg/ml) and thiopental (one dose) on Th1/Th2 equilibrium evaluated by levels of IFN γ , IL-4 and IL-2 released by lymphocytes showed the different effects of these anesthetics on the immune response. In contrast to propofol, thiopental caused a decrease in IFN γ and IL-4 concentrations without affecting IL-2 concentrations. In this study, only propofol infusions at a higher dose caused an increase of IFN- γ /IL-4 ratio, while propofol used at a lower dose did not change the concentrations of cytokines [56].

T helper cells (Th lymphocytes) are a subpopulation of lymphocytes that play a supportive role in the humoral and cellular response through direct contact and *via* cytokine release. The Th1 and Th2 subtypes of helper cells are distinguished by differences in function, in types of cytokines released and in CD molecule expression. For instance, Th1 lymphocytes, releasing IL-2 and IFN- γ , strengthen the cellular immune response. Th2 lymphocytes produce IL-4, IL-5, IL-10 and IL-13 cytokines, stimulating the synthesis of many antibodies by B lymphocytes, which in turn strengthens the humoral immune response. The growth and differentiation autocrine factor for Th1 cells is IL-2 and for Th2 cells – IL-4.

In summary, the contribution of anesthetics in the functioning of the cytokine network is seen in both humoral and cellular mediated immunity.

Opioids

Studies have shown the existence of mutual connections between opioids and the immune system. Both suppressive and stimulatory effects of opioids on the immune system have been described. Opioids exert their effects either directly through receptors (μ , δ , κ) which are widely located on both neural and immune cells or *via* the autonomic and central nervous systems [17,28,39,46].

Opioids cause the modulation of both innate and adaptive immunity, including cytokine and immunoglobulin synthesis, activation of natural killer cells (NK) and phagocytosis [17,52].

Opioid receptors are commonly expressed by peripheral immune and glial cells and the suppressive activity of opioids on the immune system is demonstrated *via* both centrally and peripherally distributed receptors.

As an example, long-term (12 months) epidurally given morphine alone or with bupivacaine caused a significant increase of μ receptors mRNA in lymphocytes, which likely causes attenuation of cytokine synthesis. Additionally, at the same time a lowering of the percentage of NK was observed [7]. Opioids have the ability to modulate the

immune responses including cell proliferation and regulation of cytokine synthesis and secretion [52].

Roy et al. showed the influence of chronic morphine treatment on Th1/Th2 balance. Morphine induces the production of TGF- β by stimulated lymphocytes, monocytes and macrophages – this concerns mainly long-term therapy which also causes a rise in IL-4 and IL-5 concentrations and a decrease in IL-2 and IFN- γ [51]. Furthermore, Vassou et al. presented evidence that opioids could modulate humoral immunity by decreasing both antibody secretion by normal B-lymphocytes and proliferation of multiple myeloma cells [67].

Studies investigating the influence of opioids on the production of pro-inflammatory monocyte/macrophage-derived cytokines have demonstrated a significant diminishing of TNF α , IL-1 and IL-6 concentrations following morphine treatment [17]. In turn, studies carried out by Makimura et al. showed a correlation between the concentrations of certain cytokines (IL-8, IL-12, MIP-1 α) and analgesic tolerance to morphine. Lower concentrations of the mentioned cytokines were found in patients requiring higher doses of morphine in long-term therapy. A lower level of examined cytokines was also found in patients with symptoms of higher resistance to morphine [41].

The central activity of opioids is focused mainly on glial cells, which demonstrated proinflammatory activation and which are the main source of cytokines. Morphine causes activation of glial cells that subsequently release proinflammatory cytokines including IL-1 β , IL-6, and TNF- α acting in opposition to the analgesic effects of morphine. The stimulation of cytokine release is irrespective of the frequency and time period of morphine administration. Considering the short cytokine response time (about 5 min) to morphine, it can be assumed that morphine stimulates the release of stored reserves but not their synthesis. The results presented by Shavit et al. showed that IL-1 can decrease the analgesic potential of morphine and plays a role in developing tolerance to morphine [59].

On the other hand, Byrne et al. found that IL-1 β can affect the expression of the opioid receptors in glial cells. The authors confirmed the ability of IL-1 β to up-regulate opioid receptors (μ , δ , κ) in astrocytes [6].

The pathways of morphine-induced inhibition of pro-inflammatory cytokine production *via* μ receptors are different but finally lead to the depression of NF- κ B signaling. On one hand, the depression of NF- κ B signaling is caused by activation of the cAMP response, and on the other, it follows the increase of nitric oxide activation after stimulation of the μ_3 opiate receptor on monocytes [32]. There is evidence that Toll-like receptors (TLR4, TLR2) are involved in the immunomodulatory effect of morphine. Stimulation of TLR signaling causes activation of intracellular pathways: the NF- κ B and MAPK pathways play leading roles in the proinflammatory response, which

le the PI3K/Akt1 pathway is related more to processes of survival and apoptosis [53].

For example, in the development of morphine tolerance, hyperalgesia and respiratory depression are linked to the activity of Toll-like receptor 4 (TLR4) in glial cells. The proinflammatory glial response to opioids is stimulated through TLR4, whose activity can inhibit opioid analgesia. A study on animals showed the reduction of opioid tolerance and hyperalgesia as well stronger opioid analgesia following the blockade of TLR4 pathway signaling. According to these authors' suggestions, systemic morphine analgesia might be in opposition to TLR4 signaling [26,52].

As first, Bonnet et al. revealed morphine inhibition of TNF and IL-6 production in TLR2-stimulated monocytes. Like TLR4, the stimulation of TLR2 also provokes the synthesis of TNF and IL-6 via NF- κ B pathway signaling. In the same study the authors did not confirm their hypothesis that the elevation of IL-10 production would be involved in morphine immunomodulatory effects [4]. The presented results are important because TLR2 plays a pivotal role in identifying Gram-positive bacteria components associated with the development of severe infection.

The study of Franchi et al. demonstrated that morphine has been able to decrease TLR4 mRNA via the μ receptor. Taken together, morphine regulates the cell signaling pathway in TLR2 or TLR4 stimulated macrophages through inhibition of the receptor and NF- κ B pathway during the initial stage of pathogen recognition. This mechanism seems to explain the peripheral suppressive effect of morphine on innate immunity [18].

Thus, the anti-inflammatory activity of opioids appears to be mediated by different signaling ways.

The results of the Levis et al. study showed that one of its main metabolites – morphine-3-glucuronide (M3G) – caused enhancement of pain following stimulation of the TLR4 receptor and release of IL-1 from the glia. Such a function has not been observed with morphine-6-glucuronide (M6G) [37].

In contrast to M3G, whose activity is associated with allodynia and hyperalgesia, morphine-6-glucuronide has high affinity for the opioid receptor. Therefore, the attenuation of morphine-induced hyperalgesia though the inhibition of TLR4 signaling seems to be a noteworthy suggestion.

Studies performed in genetically modified animals confirmed the participation of μ receptor activation in TNF- α , IL-1 and IL-6 release by macrophages following morphine stimulation [10].

Remifentanyl, in comparison with fentanyl, causes a decrease in the IFN- γ /IL-10 ratio (a drop in IFN- γ), which mirrors the equilibrium of Th1/Th2. Concentrations of IL-6, TNF, IL-10 and IL-2 were not shown to change upon treatment with remifentanyl or fentanyl [5,70].

Benzodiazepines

Midazolam, a representative of benzodiazepines, is used mainly in premedication and sometimes intraoperatively during anesthesia. Midazolam exerts its action via central and peripheral benzodiazepine receptors (CBR/PBR). The expression of PBR found on the surface of macrophages allows benzodiazepine to modulate pro-inflammatory and anti-bacterial functions of macrophages by blocking their ability to produce superoxide anions as well as IL-1, TNF and IL-6 cytokines [66,73].

Both midazolam and propofol modulate the transport and release of IL-8. Activation of leukocytes via LPS in the presence of propofol and midazolam causes a decrease in the concentration of extracellular IL-8 while the intra-cellular concentration remains unchanged [21]. The suppression of IL-8 release may increase the risk of infection in the post-operative period.

INFLUENCE OF CONTROLLED VENTILATION ON CYTOKINES

Controlled ventilation, through trauma to alveolar cells and mechanical stress, can destabilize the ventilation/perfusion ratio (hyperperfusion), causing release of inflammatory mediators, leading to worsening of gas exchange in the post-operative period [34].

Damage to the alveoli from pressure changes with the use of PEEP is also a traumatizing factor, as are the inhalational anesthetics themselves [43]. The inhaled substances cause irritation of the endothelium, which can in turn lead to stimulation of endothelial cells and their subsequent release of proinflammatory cytokines and mediators.

Damage to lung tissue is directly proportional to ventilation volume and translates into lung capillary trauma and the accumulation of neutrophils. Another factor that can cause lung tissue damage leading to increased release of cytokines is intra-operative hypoxemia.

Results presented by Schilling T et al. showed that both the type of ventilation and the medication used during general anesthesia had an effect on proinflammatory cytokine concentration levels [57,58]. Concentrations of TNF- α , IL-8 and IL-1 in bronchoalveolar lavage fluid were shown to be higher in patients given propofol than in those who received inhalational anesthetics – desflurane and sevoflurane. IL-6 concentrations increased irrespective of the type of anesthetic used. Contrary to this local response, the systemic (general) response was insignificant.

Similar results were obtained by other authors with respect to isoflurane and propofol [33]. Namely, TNF- α and IL-8 concentrations in bronchoalveolar lavage fluid and plasma were higher after propofol administration in relation to patients treated with isoflurane. Isoflurane decreased the inflammatory response associated with one

lung ventilation during thoracic surgery and may be preferable to propofol in patients with expected high levels of proinflammatory cytokines.

Consequently, it can be confirmed that inhalational anesthetics have protective (anti-inflammatory) properties. This finding is important especially in patients with an altered cytokine network equilibrium, such as those with autoimmune disorders or cancer.

Sevoflurane, isoflurane and enflurane inhibit the release of IL-1- β and TNF- α from peripheral blood mononuclear cells (PBMC), which can reduce the immunological potential of these cells in the presence of cancerous cells or foreign microorganisms. This role of inhalational anesthetics may, however, be difficult to identify and therefore go unnoticed.

CONCLUSION AND OUTLOOK FOR THE FUTURE

Post-operative, immunological complications such as poor wound healing or infection are rare in patients with properly functioning immune systems. However, in patients with immune disorders – either externally inflicted or with autoimmune problems – the interaction of anesthetic drugs with their receptors found on cytokine-producing cells is substantially increased, leading to modulations in the response to surgical stress. For this reason, choices of pain relief therapy should

be carefully considered with respect to immune suppression.

Doctors currently anesthetize growing numbers of AIDS patients as well as people with autoimmune diseases in whom long-term anesthetic administration coupled with heightened surgical stress can lead to the uncontrolled development of SIRS and multi-organ failure. Patients with cancer form a separate group of subjects in whom both the disease and applied therapy cause weakening of the immune response; if these patients are then additionally subjected to the suppressive effects of anesthetics, the risk of post-operative complications and cancer proliferation increase extensively. Certain drugs, however, such as propofol, may lead to decreases in cancerous growth rates via increased activity of cytotoxic T lymphocytes (CTL) and lowered TGF concentrations [36].

Linking anesthetics to the immune system has created new therapeutic advantages as well as challenges. It should be anticipated that the growth of empirical knowledge concerning the mechanism of action of anesthetics will facilitate their more favorable administration taking into account the functioning of the cytokine network.

AUTHORSHIP

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