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Volatile Anesthetics and Immunity

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Abstract

Historically, volatile anesthetics have demonstrated interesting interactions with both the innate and adaptive immune systems. This review organizes these interactions into four phases: recognition, recruitment, response, and resolution. These phases represent a range of proinflammatory, inflammatory, and innate and adaptive immune regulatory responses. The interaction between volatile anesthetics and the immune system is discussed in the context of pathogenesis of infectious disease.

Keywords

Anesthetics; Immune response; Infectious disease

Introduction

John Snow was among the first generation of physicians who practiced anesthesia in England. He is also considered the father of infectious disease epidemiology, because of his work in tracing the source of a cholera outbreak in London, England in 1854 (Snow, 1855). Since John Snow's time, anesthetic agents have been linked to pharmacologic action on the immune response and the outcomes of infectious disease. However, during the period from 1493 to 1544, ether was reported to be used to treat the plague, pneumonia, and whooping cough (Donovan, 1968). In addition, in 1794, ether inhalation was used to treat tuberculosis (Donovan, 1968). In 1904, in the first volume of *The Journal of Infectious Diseases*, George Rubin published his studies on effects of ether and chloroform on natural immunity (Rubin, 1904). Even in veterinary medicine, studies of volatile anesthetics (VAs) on infectious disease appear. For example, Conrad Donovan demonstrated a beneficial effect of ether on canine encephalopathy secondary to a distemper virus infection (Donovan, 1968). With the development of newer VAs, studies of the interaction between VAs and the immune system have been reported over the past few decades.

Modern VAs are an essential pharmacological tool that has revolutionized perioperative medicine. They are a chemically and pharmacologically diverse group that includes the potent halogenated ethers (i.e., isoflurane, sevoflurane, desflurane, enflurane), as well as the

alkane, halothane (Miller and Eriksson, 2015). Since VA agents are absorbed and eliminated through alveolar blood–gas exchange, tissue-dependent metabolism is unnecessary for drug clearance (Miller and Eriksson, 2015). Additionally, all potent VA agents share pharmacologic responses of bronchodilation, dose-dependent decrease in skeletal muscle tone, and decrease in cerebral oxygen consumption (Miller and Pardo, 2011). The precise mechanisms whereby potent volatile-inhaled agents induce anesthesia are not known. However, the neurotransmitter-gated ion channels, in particular GABAA, glycine, and NMDA-type glutamate receptors, are putative targets of anesthetics.

The immune system is a network of molecules and cells that work together to protect the body against attacks by “foreign” invaders. In vivo, following contact with an antigen, a cascade of immunological events occurs. In this review, we have broken down the immune response into four phases: recognition, recruitment, response, and resolution. These phases represent a range of proinflammatory, inflammatory, and innate and adaptive immune regulatory responses. We will discuss the changes observed in each phase secondary to anesthetic action of commonly used volatile agents (i.e., isoflurane, sevoflurane, desflurane). We will also include halothane’s action on the immune system despite it being discontinued in the United States, as it is still one of the most commonly used anesthetics in resource-limited settings due to cost (Meara et al., 2014).

Recognition

Recognition is the primary step of immune activation. This is an essential step in order to acknowledge the type and location of a “foreign” attack. Sentinel cells including phagocytic and antigen-presenting cells are involved in recognition of antigens and are the body’s first line of defense. Sentinel cells are embedded in tissues such as the skin, lung, and gastrointestinal tract. For example, alveolar macrophages or dust cells are the sentinel cells of the lung. Their regulatory functions include recognition of pulmonary insults and initiation of responses through the release of immune/inflammatory regulators. Therefore, alveolar macrophages are a good sentinel cell model to study anesthetic-induced changes in immune/inflammatory recognition (Kotani et al., 1998).

On the molecular level, the first contact of the sentinel cells with an antigen is mediated by the binding of pattern recognition receptors (PRRs). PRRs are located on the cell surface or intracellularly and are able to make complexes with antigens, which are perceived as foreign. Some of the molecules, such as pathogen-associated molecular patterns (PAMPs, i.e., lipopolysaccharide [LPS]), are foreign entities that complex with PRRs and have the ability to activate proinflammatory responses. In cases of cell damage, leaked intracellular contents can bind to PRRs and stimulate sterile inflammation. Proinflammatory cellular materials are also known as damage-associated molecular patterns (DAMPs). For example, high-mobility group box one (HMGB1, the most studied DAMP) binds with PRRs to induce an inflammatory response, which can increase the severity of the initial injury/stress (Park et al., 2004). PRRs, such as Toll-like receptors or retinoic acid inducible genes, interact with DAMPs or PAMPs and result in formation of proinflammatory signaling molecules (such as nuclear factor kappa B [NF- κ B]). The early proinflammatory cytokines (i.e., tumor necrosis factor [TNF]) “prep the battle field” by activating leukocytes and stimulating adhesion

molecules on the surface of both leukocytes, and vascular endothelial and epithelial cells in a paracrine fashion. This early response is required for the eventual recruitment of leukocytes from the circulation into the infected/injured site (see Recruitment).

PRR-PAMP/DAMP complexes play a pathogenic role in organ injury, e.g., acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Xiang and Fan, 2010). Interaction of PRRs with PAMPs is the initiating event that is required for the recruitment of inflammatory effector cells, which are important in the pathogenesis of ALI (Xiang and Fan, 2010).

Although VAs have the potential to exacerbate lung injury (see below), they also demonstrate/exhibit anti-inflammatory effects. Sevoflurane decreases expression of PRRs secondary to anesthetic-induced decreases in gene and protein expression (Sun et al., 2015). Additionally, sevoflurane demonstrates direct inhibition of the major products of the associated intracellular signaling cascade, specifically, activation of NF- κ B, a transcription factor involved in generating inflammatory regulators and mediators (Sun et al., 2015). NF- κ B is also important in a number of other pathophysiologic processes, for example, the cellular injury secondary to ischemia–reperfusion (I/R)-mediated injury (Zeng et al., 2013, Zhong et al., 2004). Attenuation of NF- κ B by VAs is associated with a decrease in the severity of the I/R-mediated tissue injury (Zhong et al., 2004).

VA protection of I/R tissue-mediated injury also occurs as a result of anesthetic-induced preconditioning (Hemmings and Egan, 2013, Kevin et al., 2005, Miller and Pardo, 2011). I/R of an organ leads to necrosis with the leakage of the intracellular contents into the extracellular space. VAs decrease DAMP-initiated inflammation. Isoflurane preconditioning reduces circulating HMGB1 levels and suppresses signaling cascades, while sevoflurane downregulates proinflammatory genes of PRRs (Liang et al., 2014, Sun et al., 2015). The clinical importance of PRR ligation can be appreciated in renal I/R-mediated injury in the perioperative settings (including cases of shock, renal transplantation, and renal artery angioplasty), where exposure to VAs has been associated with protection against resulting acute kidney injury (Liang et al., 2014).

Recruitment

Recruitment involves cellular trafficking by signaling and activation of leukocytes into the involved tissue. An important aspect of recruitment also involves determining the type of immune/inflammatory response, as well as controlling severity and resolution of the inflammation (see below). Cytokines and chemokines are potent low molecular weight molecules that orchestrate intercellular communication and trafficking in response to recognition of a pathogen or tissue injury. However, these molecules can be injurious and play a role in the pathogenesis of a number of perioperative diseases. VAs attenuate the production of cytokines and chemokines which results in a decrease of leukocyte infiltration into the affected areas (Giraud et al., 2000, Reutershan et al., 2006, Yue et al., 2008). For example, incubation of neutrophils with sevoflurane leads to reduced chemotaxis, neutrophil adherence, and neutrophil-induced alveolar epithelial cell death (Yue et al., 2008). In further translational investigations, administration of isoflurane or halothane reduced the recruitment of polymorphonuclear neutrophils (PMNs) into the lung after exposure to LPS stimulation in murine models (Giraud et al., 2000; Reutershan et al., 2006). These findings

suggest that when VAs are used in the presence of a systemic bacterial infection, the innate immune response may not be adequate to combat the infection. Other studies have shown that VAs may induce markedly different results when used in mechanically injured lungs (Nader-Djalal et al., 1998) (see below).

Ischemic tissue injury leads to the release of cytokines and chemokines that can result in a cascade of events that further exacerbate tissue damage. For example, inflammatory cytokines are believed to play a role in the development of arteriosclerosis, promote coronary artery spasm, and thrombosis (Saini et al., 2005). The myocardium is an important site of cytokine generation during cardiopulmonary bypass (CPB) and myocardial ischemia. Reperfusion of the ischemic myocardium rapidly promotes secretion of proinflammatory cytokines and the chemotaxis of neutrophils to the site of inflammation (Sawa et al., 1998). For patients undergoing aortic cross-clamping during coronary artery bypass graft (CABG) surgeries, induction of anesthesia with sevoflurane effectively reduces the generation of cytokines, inhibits neutrophil activation, and preserves myocardial systolic function after CPB compared to the control group receiving no volatile gases (Nader et al., 2004, Yu et al., 2014).

Interestingly, researchers have successfully translated this protective observation to other organs as well (Kong et al., 2010). For example, during liver transplantation, reperfusion of the implanted organ releases proinflammatory cytokines. These cytokines, in addition to inducing local damage associated with the I/R event, can result in both liver and renal injury. However, use of sevoflurane during liver transplantation decreases subsequent injury to the kidneys. These findings are important because renal failure remains a major cause of mortality and morbidity following liver transplantation (Kong et al., 2010).

Proinflammatory factors released by surgical tissue trauma-induced release of DAMPs or bacterial infection-induced PAMPS can activate leukocytes to produce acute phase cytokines, such as Interleukins, leukotrienes, and TNFs which are released into the circulation. The release of acute phase proteins has proven to be clinically important in the pathogenesis of diseases such as ALI and ARDS (Flondor et al., 2007). Exposure to VAs attenuates release of such potent proinflammatory activators. For example, isoflurane exposure decreases the release of proinflammatory cytokines in cultured peripheral blood mononuclear cells (Hofstetter et al., 2005). Possible mechanisms by which VAs may decrease the deleterious consequences of increased proinflammatory mediators include decreasing the appearance of adhesion molecules on the cell surface and interfering with chemokine release. Both of these actions would decrease recruitment and activation of circulating PMNs, as well as in tissues such as lungs.

Increased levels of cytokines and chemokines in a vascular bed result in an increase of adhesion molecules on the surface of the vascular endothelium, as well as the surface of immune/inflammatory effector cells (Borish and Steinke, 2003). The interaction of these adhesion molecules results in the binding of the leukocytes to the vascular endothelium, an important initial step associated with infiltration of these cells into tissues. Several studies have demonstrated a direct correlation between VA exposure and adhesion molecule expression (Kowalski, 1997, Mobert et al., 1999, Nader et al., 2004). Cultured human

umbilical vein endothelial cells exposed to several VAs (halothane, isoflurane, or sevoflurane) decreased the appearance of neutrophil adhesion molecules (Mobert et al., 1999). Similar results were observed in coronary vessels of guinea pigs (Kowalski, 1997). In humans, sevoflurane anesthesia demonstrates attenuation of I/R-related inflammation, specifically, a decrease in the binding and rolling of neutrophils in vessels of patients undergoing CABG using CPB (Nader et al., 2004).

However, other researchers have found that VAs exacerbate inflammatory injury (Nader-Djalal et al., 1998). In a rat model of acid aspiration, exposure to halothane or isoflurane for two or more hours following intratracheal instillation of low-pH aspirate increases the severity of the neutrophil-dependent lung injury (Raghavendran et al., 2011). Gastric aspiration is a recognized complication of general anesthesia occurring in 1 out of every 2000–3000 cases (Nason, 2015). Therefore, these findings have important clinical implications. The mechanisms behind the increase in lung injury following acid aspiration by VAs are different than previously described. For example, VA-induced changes in pulmonary microcirculation may lead to increased infiltration of inflammatory cells to the site of injury. Second, VAs also increase perfusion to poorly ventilated, injured alveoli by inhibition of hypoxic vasoconstriction. The increased perfusion leads to an increase in proteinaceous edema fluid and infiltrating leukocytes in the injured alveoli, which may play a role in the pathogenesis of this acute inflammatory lung injury (Nader-Djalal et al., 1998).

Response

Response is the capability of the immune system to control foreign attacks by sending out “the troops” to the areas of insult and effectively eradicating the antigens involved. The immune system executes this phase by phagocytizing the insulting pathogens and, if need be, recruiting more cells to the areas. Previously in our laboratory, we observed a relationship between VAs and immune responses in children who received halothane in the setting of an acute uncomplicated respiratory tract infection during tympanostomy. Children who received halothane anesthesia exhibited a reduced prevalence of new symptoms and shorter duration of symptoms compared to children who did not receive halothane (Tait and Knight, 1987). Next, we studied the immune modulatory effects of VAs in murine and ferret models of influenza (Tait et al., 1988). The reduction by halothane anesthesia of severity of the pathogenesis of influenza virus infection in mice was associated with suppression of the number of monocytic leukocytes into the alveoli. This change in immune response occurred without any affect on the viral load. In order to further understand these immune modulating mechanisms, we isolated natural killer (NK) cells from murine spleen and incubated them with Type I interferon (IFN), in vitro, with and without prior exposure to halothane. We demonstrated that the cytotoxicity of NK cells was 20-fold higher without prior exposure to halothane. Mice exposed to halothane had a significant inhibition of interferon-induced NK cell toxicity (Markovic et al., 1993). Similar results were noticed using isoflurane. These results led our laboratory to study the effects of halothane on secondary bacterial pneumonia, a major complication of influenza infection. Halothane exposure resulted in decreased post-influenza streptococcal bacterial burden and lung injury through decreased IFN γ expression (MacDonald et al., 2015). Similarly, IFN receptor A1 knockout mice infected with influenza followed by *Streptococcus pneumoniae* without exposure to

halothane also had a decreased bacterial burden. Our work provides evidence that patients suffering from upper respiratory tract infections are not at enhanced risk for secondary pneumonia if VAs are employed for surgical procedures.

Phagocytosis is an important cellular mechanism employed in killing pathogens and removing cell debris during the Response phase. Sentinel cell phagocytosis is reduced during and following anesthesia and surgery (Cullen, 1974; Kotani et al., 1998). Decreased phagocytic activity and chemotaxis have been directly linked to the use of VAs. For example, isoflurane demonstrates a time-dependent decrease in the ability of phagocytes to engulf opsonized and non-opsonized particles (Kotani et al., 1998). Conversely, use of intravenous anesthetics, such as propofol, does not exhibit as much inhibition of phagocytosis as VA agents (Heine et al., 2000; Kotani et al., 1998).

The effect of VAs on cellular phagocytic capacity is also time-dependent. Longer durations (i.e., 6 h) of anesthetic exposure decrease neutrophilic phagocytic activity in murine models (Koutsogiannaki et al., 2016). This decrease in neutrophil function was associated with higher bacterial levels in tissues and increased mortality in animal models. Shorter durations (i.e., 2 h) of anesthetic exposure were not associated with these changes. Interestingly, even long durations of intravenous anesthetics (e.g., propofol) were not associated with the deleterious changes in the pathogenesis of sepsis (Koutsogiannaki et al., 2016). Therefore, VAs should be administered cautiously in long procedures with septic patients.

Reactive oxygen species (ROS) are classically defined as partially reduced metabolites of oxygen that at high concentrations oxidize proteins and lipids damage DNA and are released in large quantities during I/R (Mittal et al., 2014). Production of ROS by PMNs at the site of insult acts as both a signaling molecule and a major chemical effector of inflammation (Mittal et al., 2014). The attenuating effects of VAs on ROS have gained particular attention, as they are not only an integral part of combating infection but also recognized as important mediators of cardiac injury following ischemia and reperfusion (Kevin et al., 2005). Furthermore, ROS has been linked to contractile dysfunction in heart failure (Kubin et al., 2011). Although the invading pathogen is the most ideal target of ROS, the host cells are also “collateral damage.” In cardioprotection, halothane, isoflurane, and enflurane have been shown to decrease ROS production in isolated rabbit hearts (Tanguay et al., 1991). Furthermore, these agents decreased the negative effects of ROS on left ventricular pressure and coronary blood flow (Tanguay et al., 1991). Similar attenuating effects of ROS on the cardiocyte by isoflurane and halothane have been shown in rats and dogs, respectively (Glantz et al., 1997; Nakamura et al., 1999).

Paradoxically, even though large quantities of ROS may have detrimental effects on an organ, the protective effects of anesthetic preconditioning were abolished when ROS scavengers were given during anesthetic exposure (Glantz et al., 1997). Initial bursts of ROS can directly stimulate intracellular pathways that elicit cardioprotection from subsequent I/R injuries (Glantz et al., 1997; Kevin et al., 2003; Riess et al., 2005). In our laboratory, we tested this hypothesis in acid aspiration-induced inflammation and showed that injury is exacerbated in NADPH oxidase-deficient mice (Segal et al., 2007). We further showed that Nrf2 (transcriptional factor that induces antioxidative and cytoprotective pathways) is

involved in decreasing the injury produced by recruited PMNs in aspiration models (Davidson et al., 2013). Likewise, sevoflurane directly causes superoxide formation in an intact heart, which may in turn contribute to the anesthetic preconditioning which attenuates superoxide formation during subsequent ischemia and reperfusion (Kevin et al., 2003). Similar results were shown with isolated rabbit hearts in the presence of isoflurane (Riess et al., 2005).

Similar to cardiac anesthetic preconditioning, protective properties of VAs have been useful in brain ischemic injury, which can occur in procedures such as carotid endarterectomy and aortic repair (Yang et al., 2011). For example, sevoflurane preconditioning can reduce infarct volume and neurologic deficits in a dose-dependent manner. Consistent with a previously presented VA action, an initial oxidative stress generated by sevoflurane preconditioning triggers a cascade of signals that lead to ischemic tolerance (Yang et al., 2011).

A more specific continuation of the innate immunity is the adaptive immune response. The main participants of adaptive immunity are the B and T lymphocytes, which are activated by amino acid sequences from denatured infectious antigens that are internalized by sentinel cells. Being an extension of innate immunity, various aspects of the adaptive immune response are modulated by VAs. For example CD3+ lymphocytes (prothymocytes) encompass all known T-cell populations, including CD4, CD8, and Th1/Th2, all of which play a crucial role in the defense against nosocomial infections (Loop et al., 2005). Prothymocytes have been shown to be very sensitive to sevoflurane and isoflurane-induced apoptosis (Loop et al., 2005). Such findings raise concerns in post-operative immune suppression after the use of VAs in major surgeries since these patients have increased susceptibility to infectious complications, systemic inflammatory response syndrome, and sepsis (Loop et al., 2005).

Building on lymphocytic suppression by VAs, researchers observed a decrease in experimental autoimmune encephalomyelitis (EAE) progression following a single exposure to VAs (Polak et al., 2012). EAE is the oldest and most frequently used model for studying multiple sclerosis in laboratory animals (Ransohoff, 2012). Although the exact causes of multiple sclerosis are not yet precisely known, it is well established that activation of the adaptive immune system leads to proliferation and infiltration of T cells (Olsson et al., 1990). Within the central nervous system, the released cytokines lead to oligodendrocyte damage, demyelination, and axonal damage. However, in sevoflurane-treated mouse EAE models, the number of lymphocytic infiltrate areas and a glial cell activation was reduced (Polak et al., 2012).

T lymphocytes are directly and indirectly the body's major defense mechanism against viral infection and are also responsible for combatting tumors. Because T lymphocytes are sensitive to VAs, these agents should be used cautiously in patients with metastatic disease. Over the years, researchers observed that laparotomy during sevoflurane anesthesia increased the number of liver metastases compared to mice receiving sevoflurane anesthesia plus spinal block (Wada et al., 2007). The change in ratio of Th1–Th2 cells with the use of VAs may be the explanation to these findings (Inada et al., 2004). Th1 cytokines are involved in increasing the cytotoxic activities of T cells and NK cells. In contrast, Th2

cytokines are reported to be involved in increasing humoral immunity and in suppressing the Th1 response. Th2-dominant status is thought to have a negative role in oncologic immunity and susceptibility of patients to certain infections (Wada et al., 2007). Addition of spinal block to VAs attenuates, the promotion of metastasis induced through preservation of tumoricidal function of liver mononuclear cells and the Th1/Th2 cytokine balance (Inada et al., 2004; Wada et al., 2007).

Although VAs tend to cause lymphopenia in patients undergoing major surgeries, some studies have shown the contrary (Morisaki et al., 1998). The mechanism underlying the lymphocytic events, however, may not be attributed solely to the effects of VAs but rather associated with the perioperative events. For example, lymphocytosis may occur from fluid loading or acute psychological stress. This is because both administered fluids and adrenaline produced during stress cause a direct redistribution of circulating leukocyte subsets (Drobin and Hahn, 1995, Karandikar et al., 2002).

B lymphocytes are components of adaptive immunity involved in the humoral response. Similar to T lymphocytes, B cells are susceptible to apoptosis in the presence of VAs, putatively by way of disruption of intracellular calcium homeostasis (Yang et al., 2008). B lymphocytes include plasma cells capable of secreting antibodies. The relationship between IgG4 autoantibodies and VAs has been studied for many years and they appear to be responsible for autoimmune diseases such as acute liver injury (Kenna et al., 1988). For example, halothane hepatitis is a massive immune-mediated centrilobular liver necrosis that may lead to fulminant liver necrosis with up to 50% mortality. The risk is not exclusive to halothane, as it has been shown to occur with other VAs including enflurane, isoflurane, sevoflurane, and desflurane (Reichle and Conzen, 2003). In physiological situations, antibody production by plasma cells is responsible for inactivation of viruses and microbial toxins, opsonization, feedback for phagocytic cell activation, and activation of the complement system (Abbas et al., 2015). In the case of halothane hepatitis, metabolites of halothane act as haptens and bind to liver proteins causing antibodies to attack these complexes ultimately damaging the liver. However, the chance of immune-mediated hepatitis in patients intubated with more modern VAs is reduced compared to those anesthetized using halothane (Eger, 2004). Nevertheless, repeated exposure even to modern VAs has shown to cause chronic hepatitis, as well as acute liver injury (Nicoll et al., 2012).

Resolution

Resolution is the final phase of the battle. Understanding the resolution of inflammatory processes is indispensable in perioperative medicine. Even though inflammation at the incisional site may be controlled in surgical settings, operations such as CPB can be associated with the development of a systemic inflammatory response that can often lead to dysfunction of major organs (Asimakopoulos, 2001). The process of resolution begins by lowering the number of PMNs by apoptosis, active removal of debris and apoptotic PMNs from the inflamed sites by activation of macrophages, and finally cells such as fibroblasts are recruited to the area of injury for tissue remodeling and scar formation (Chiang et al., 2008). Isoflurane and sevoflurane decrease the degree of neutrophilic apoptosis, suggesting a prolongation of resolution phase (Tyther et al., 2001, 2003). On the other hand, other studies

have shown that isoflurane promotes the resolution of inflammation in mice at clinical concentrations administered over a 2-h period (Chiang et al., 2008). Isoflurane triggers the progression of PMN elimination while attenuating cytokines involved, thus shortening the time of resolution during acute inflammation (Chiang et al., 2008).

Resolution is not always the final end point of acute inflammation. In fact, the activation of the PRRs, cytokines, and adhesion factors for prolonged periods of weeks or months stops the resolution of acute inflammation and instead pushes the body into a chronic inflammatory phase with subsequent tissue damage (Hsing and Wang, 2015, Kong and Le, 2011). Chronic inflammation is mainly caused by persistence of infections (granulomatous diseases), immune-mediated inflammation (rheumatic diseases), or prolonged exposure to toxins. The types of cells involved in chronic inflammation are mainly monocytes, macrophages, and lymphocytes. Similar to acute inflammation, chronic inflammation can be modulated by VAs. For example, isoflurane has been shown to suppress chronic inflammation in collagen-induced arthritis (the animal model of rheumatic arthritis) (Lawrance et al., 2009).

Similarly, chronic inflammation is the hallmark of human allergic asthma, where the persistent inflammation causes structural and functional damage of the respiratory system. Subepithelial and airway wall fibrosis, goblet cell hyperplasia and metaplasia, smooth muscle thickening, and increased vascularity play a role in the pathogenesis (Bousquet et al., 2000, Burburan et al., 2014, Curran and Cohn, 2010). Although most VAs improve lung mechanics and lessen the damage involved in asthma, sevoflurane has shown to be the most effective in decreasing bronchoconstriction in mouse chronic allergen-induced asthma models (Burburan et al., 2014). The effect of sevoflurane in asthma is directly related to modulation of inflammatory mediators that induce fibrogenesis, angiogenesis, and leukocytic recruitment factors.

Conclusion

VAs possess immune modulatory properties that extend beyond their primary use of producing perioperative narcosis. They have the capacity to modulate the recognition of antigens, recruit proinflammatory cells, and modulate antigen response and resolution of the affected area. These anesthetic actions are also a double-edged sword, as their use may not always lead to favorable outcomes clinically. Autoimmune patients may benefit greatly from the immunosuppressive abilities of VAs, whereas their use may be detrimental in patients with metastatic disease or infections. New knowledge is surfacing daily in the off-label use of VAs outside of the scope of anesthesia. Coordinated clinical investigations, such as using biomedical informatics, represent directions to pursue in the future to further elucidate the extra-operative actions of VAs.

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