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REVIEW ARTICLE

The immune response to anesthesia: Part 1

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Abstract

Objective To review the immune response to anesthesia including mechanical ventilation, inhaled anesthetic gases, and injectable anesthetics and sedatives.

Study design Review.

Methods and databases Multiple literature searches were performed using PubMed and Google Scholar from spring 2012 through fall 2013. Relevant anesthetic and immune terms were used to search databases without year published or species constraints. The online database for Veterinary Anaesthesia and Analgesia and the Journal of Veterinary Emergency and Critical Care were searched by issue starting in 2000 for relevant articles.

Conclusion Recent research data indicate that commonly used volatile anesthetic agents, such as isoflurane and sevoflurane, may have a protective effect on vital organs. With the lung as the target organ, protection using an appropriate anesthetic protocol may be possible during direct pulmonary insults, including mechanical ventilation, and during systemic disease processes, such as endotoxemia, generalized sepsis, and ischemia-reperfusion injury.

Keywords acute lung injury, anesthesia, immune, inflammation, remote lung injury, ventilator-induced lung injury.

Introduction

When the immune response to general anesthesia was first studied, the immunomodulatory effect of each component of general anesthesia such as lung ventilation, hypotension and noxious stimulation were difficult to separate from the effects of the drugs themselves. Gradually, the differences between inhalation and injectable anesthesia, the effect of mechanical ventilation *versus* spontaneous ventilation, the effects of various volatile anesthetic gases, and the influences of various injectable anesthetics and sedatives have been documented. Despite these differences, some researchers fail to adequately account for the confounding components of anesthetic protocols when designing studies to evaluate the immune system. In addition, the activation of the hypothalamic-pituitary-adrenal axis (HPAA) in response to the stressful components of anesthesia and its subsequent effect on the immune system should also be considered. Anesthetic drugs have been evaluated *in vitro* and *in vivo* for their effect on various cell types, including inflammatory cells and various tissues, sometimes with differing results. The immune response, both pulmonary and systemic, to inhalation and injectable anesthesia has been thoroughly investigated in small laboratory mammal models, but is less well understood in larger mammals. It is important to notice that there is a distinct difference in the immune response, particularly the pulmonary immune response, among species, so care should be taken when extrapolating laboratory animal data to other species. This review presents

data available on the immune response to anesthesia in many animals including small rodents, swine, horses, rabbits, and dogs, as many of these animals have been used as models for human research.

Current research is directed towards discovering the extent of the immunomodulatory effects of anesthetics, both inhalation and injectable, in order to develop anesthetic protocols that exploit any therapeutic benefits these anesthetic drugs might exert. For example, anesthetic drugs may modulate the immune system in a positive manner for patients with acute lung injury (ALI) and ventilator-induced lung injury (VILI). This review article explores the responses of the immune system to commonly used anesthetic agents as they are currently understood in two parts. The first part will focus on the immune response to mechanical ventilation, volatile anesthetics, and inhaled gases. The second part will focus on the immune response to injectable anesthetic drugs and the difference in the immune response to total intravenous anesthesia and inhalation anesthesia.

Multiple literature searches were performed from spring 2012 through fall 2013 using online databases including PubMed and Google scholar. Relevant anesthetic and immune terms were used to search databases without year published or species constraints. Initial searches used broad terms such as 'anesthesia and immune response.' Additional searches using more specific key terms such as a drug name, disease process, immune cell, species, or authors' last name were used to obtain information for specific topics. Review articles were used as a source for additional relevant articles and provided a basis for more specific literature searches using online databases. The online database for Veterinary Anaesthesia and Analgesia and the Journal of Veterinary Emergency and Critical Care were searched by issue starting in 2000 for relevant articles.

The pulmonary immune response

The pulmonary immune response is stimulated by the introduction of foreign material or forces placed upon the lung. The foreign entities are categorized by the immune system as non-infectious damage or danger-associated molecular patterns or pathogen-associated molecular patterns. These unique, non-self patterns are recognized by transmembrane proteins called pattern recognition receptors (PRR), such as toll-like receptors (TLR), on the surface of antigen presenting cells and many tissue cells including epithelial and endothelial cells (Schaible et al. 2010). Antigen presenting cells are found in all tissues and assess the local environment for abnormal, or non-self, molecular patterns (Fig. 1). In the lung, resident antigen presenting cells include pulmonary alveolar macrophages (PAMs), dendritic cells, B lymphocytes, interstitial macrophages, and, in some mammals including horses, pigs, calves, sheep, rats, rabbits, and cats, pulmonary intravascular macrophages (PIMs) (Brain et al. 1999; Aharonson-Raz & Singh 2010). PAMs serve as a first line of defense against pulmonary insults, including mechanical ventilation and inhaled gas anesthetics (Schaible et al. 2010). Pulmonary dendritic cells reside in the pulmonary parenchyma primarily along the bronchioles (Fig. 1, Lambrecht & Hammad 2003; Vermaelen & Pauwels 2005; Schaible et al. 2010). In addition to their antigen presenting functions, these cells may directly activate cytotoxic T lymphocytes and natural killer (NK) cells within tissues, by-passing the traditional adaptive immune response (Schaible et al. 2010). Similar to Kupffer cells in the liver, PIMs are intimately associated with the endothelium of the alveolar capillaries where they take in foreign substances that have crossed the alveolar epithelial barrier and clear pathogens from the systemic circulation (Brain et al. 1999).

Once an antigen presenting cell recognizes a threat to the body, the innate immune system is activated. Intracellular signaling, through elaboration of secretory molecules or direct membrane contact, allows cells in the immediate area to communicate. Membrane receptors on cell surfaces, such as TLRs, are activated resulting in the activation of intracellular pathways resulting in production of proinflammatory cytokines and chemokines (Fig. 1, B & Table 1). The cytokines and chemokines act locally (paracrine) or remotely (endocrine) to activate and recruit inflammatory cells. Specifically, neutrophils move into the tissues by rolling (mediated by selectins), tethering (mediated by E-selectin), adhering to endothelial cells (mediated by intracellular adhesion molecules, ICAM), then diapedese between endothelial cells (mediated by platelet endothelial cell adhesion molecule, PECAM) out of the blood vessels (Fig. 1, E). Phagocytes, including neutrophils and non-resident macrophages, accumulate within the injured or infected tissue and phagocytose pathogens, foreign material, and damaged cells. Phagocytes may undergo respiratory burst where enzymes such as myeloperoxidase within cellular lysosomes produce oxygen free radicals or reactive oxygen species (ROS) as a