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Review article

Anesthetic modulation of immune reactions mediated by nitric oxide

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Abstract
Nitric oxide (NO), when produced via inducible NO synthase (iNOS) in excess under pathological conditions (e.g., inflammation, endotoxemia, and septic shock), may lead to tissue injury and organ dysfunction. The bioavailability of NO and the activity and expression of iNOS are regulated by anesthetic agents. Volatile anesthetics mostly suppress, but in some instances may upregulate, the lipopolysaccharide- and cytokine-induced expression of iNOS in blood vessels and macrophages. Intravenous anesthetics inhibit iNOS expression in macrophages and the liver. Local anesthetics decrease the production of NO by inhibiting iNOS expression in macrophages and increase NO production in glial cells. Based on the literature reported so far, the effects of anesthetics on iNOS expression and activity under conditions of inflammation are controversial, with the observed effects depending on the experimental methods and animal species used. On the other hand, it has been shown that volatile and intravenous anesthetics consistently prevent the development of multiple organ failure elicited by endotoxemia or septic shock. Information, although still insufficient, regarding the interactions between anesthetic agents and the detrimental effects of NO formed during inflammatory processes may help us to construct advanced strategies for anesthetizing and sedating patients with inflammation and sepsis and for anesthetic preconditioning against ischemic injury.

Key words Nitric oxide · iNOS (inducible nitric oxide synthase) · Inflammation · Anesthetic preconditioning · Endotoxemia

Introduction

Nitric oxide (NO) is an inorganic, labile gaseous molecule that plays an important role in a large number of biological pathways. NO is synthesized from L-arginine via the catalysis of constitutive NO synthase (cNOS), neuronal (n) NOS [1] and endothelial (e) NOS [2], and inducible (i) NOS [3,4]. NO produced by cNOS contributes to the regulation of cardiovascular and central/peripheral nerve functions, except when it is produced in excess, such as in the case of cerebral ischemia leading to neural cell death, whereas iNOS-derived NO possesses dual actions that can be beneficial and harmful under pathological conditions such as inflammation and sepsis [5].

Many reports in the literature have noted that the effects of anesthetic agents are modulated by NO produced by cNOS and iNOS. Recently, we summarized findings concerning the involvement of NO in the effects of anesthetic agents on the cardiovascular and nervous systems [6]; however, in this article, we could not cover the regulation of anesthetic agent actions by NO formed under conditions of immune reactions. The present review article describes the involvement of NO, produced through iNOS in inflammatory processes and endotoxemia, in the effects of volatile, intravenous, and local anesthetic agents.

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NO formed by iNOS

Under pathological conditions (e.g., during inflammation), high levels of NO are produced after the induction of iNOS expression, mainly in macrophages [5]. NO possesses the protective/destructive duality inherent in every other major component of the immune response. On the one hand, it exerts beneficial effects by acting as an antibacterial, antiparasitic, and antiviral agent, or as a tumoricidal agent; on the other hand, high levels of NO, if uncontrolled, elicit detrimental effects that are produced because NO reacts with concomitantly produced superoxide anions, thereby generating highly toxic compounds, such as peroxynitrite (Fig. 1) and hydroxyl radicals [7]. The suppression of mitochondrial respiration [8,9] is one of the mechanisms

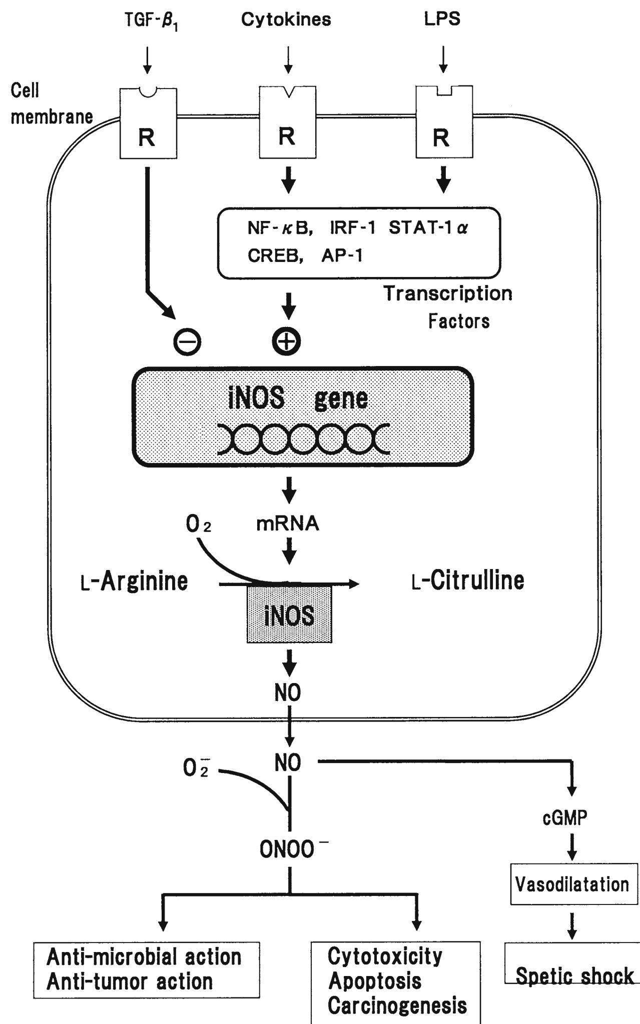

Fig. 1. Induction of inducible nitric oxide synthase (*iNOS*) in macrophages, smooth muscle cells, and glial cells, stimulated by bacterial polysaccharides or immune cytokines; and the beneficial and detrimental actions of NO produced by iNOS. *R*, receptor; +, stimulation; –, inhibition; *TGF-β_1*, transforming growth factor-β_1; *O_2^-*, superoxide anion; *ONOO$^-$*, peroxynitrite. Transcription factors: *NF-κB*, nuclear factor-κB; *IRF-1*, interferon regulatory factor-1; *STAT-1α*, signal transducer and activator of transcription-1α; *CREB*, cyclic AMP-responsive element binding protein; *AP-1*, activating protein-1; *LPS*, lipopolysaccharide; c*GMP*, cyclic guanosine monophosphate

underlying NO-induced cytotoxicity. Inducers of iNOS expression include bacterial polysaccharides and immune cytokines, such as interferon-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-1β. Suppressors of iNOS expression include dexamethasone, corticosteroids, nonsteroidal anti-inflammatory agents, estrogens, transforming growth factor-β, IL-4, IL-8, IL-10, IL-11, and IL-13 [10]. Transcription factors and the sequential pathway involved in iNOS expression are shown in Fig. 1.

iNOS is not normally present in the brain, but is detected, mainly in glial cells, after inflammatory, infectious, or ischemic damage, as well as in the aging brain. Excessive NO production by iNOS seems to participate in the pathophysiology of many diseases that involve the central nervous system (e.g., Alzheimer's disease and Parkinson's disease), as well as the cardiovascular system [11,12].

Excessive NO levels in plasma, if they are persistently associated with the expression of iNOS in macrophages and vascular smooth muscle cells, result in fatal circulatory shock because of a marked fall in vascular resistance and the venodilatation that lead to profound hypotension and acute cardiac failure [13].

Inflammation and iNOS

Vasculature

Volatile anesthetics

Exposure of rat aortic rings to lipopolysaccharide (LPS) decreased the contractile response to phenylephrine, and an additional decrease in tension was elicited by halothane; also, a nonselective NOS inhibitor, N^G-nitro-L-arginine (L-NA), reversed the LPS-induced decrease in tension, but did not affect the effect of halothane [14]. In aortic rings without the endothelium, halothane, but not isoflurane, reduced the IL-1β-induced inhibition of contraction; the cyclic guanosine monophosphate (GMP) content of the vascular smooth muscle was increased by exposure to IL-1β, and the IL-1β-induced expression of iNOS and iNOS mRNA in the rat aorta was inhibited by halothane [15]. Intravenous LPS decreased mean arterial pressure and vasodilatation in response to acetylcholine and an NO donor, sodium nitroprusside (SNP), in rats—LPS also caused acidosis, endothelial swelling, and endothelial detachment from the smooth muscle; pretreatment with isoflurane attenuated the decrease in arterial pressure, increased vasodilatation in response to acetylcholine but not in response to SNP, prevented acidosis and endothelial damage, and attenuated the increase in TNF-α associated with LPS-induced inflammation [16]. Isoflurane appears to protect the vasculature during inflammation (Table 1).

Volatile anesthetics mostly inhibit, but in some instances may augment, inflammatory responses to LPS.

Intravenous anesthetics

Treatment with L-arginine increased concentrations of cyclic GMP in the LPS-stimulated rat aorta, the effect being reduced by thiopental; L-arginine caused an increase in nitrite concentrations that was not affected

Table 1. Effects of anesthetic agents on the NO-mediated inflammatory responses of the vasculature and macrophages

Author (year)	Animal and material	Anesthetic	Effect
Shimaoka et al. (1996) [28]	Rat macrophages	Ketamine	Inhibition of inflammatory response to LPS
Li et al. (1997) [29]	Rat macrophages	Ketamine	Inhibition of inflammatory response to LPS
Kim et al. (1998) [17]	Rat isolated aorta	Thiopental	Inhibition of inflammatory response to LPS
Tschaikowsky et al. (2000) [27]	Rat macrophages	Halothane, enflurane, isoflurane, desflurane	Inhibition of inflammatory response to LPS or IF[a]
Maeda et al. (2001) [15]	Rat isolated aorta	Halothane	Inhibition of inflammatory response to LPS
Shiga et al. (2001) [33]	Rat macrophages	Lidocaine	Inhibition of inflammatory response to LPS
Chang et al. (2002) [30]	Rat macrophages	Propofol	Inhibition of cell death and apoptosis induced by SNP
Chen et al. (2003) [31]	Rat macrophages	Propofol	Inhibition of inflammatory response to LPS
Plachinta et al. (2003) [16]	Rat in vivo	Isoflurane	Inhibition of inflammatory response to LPS
Huang et al. (2006) [34]	Rat macrophages	Lidocaine, tetrodotoxin	Inhibition of inflammatory response to LPS (involvement of Na channel)
Gao et al. (2006) [19]	Human umbilical vein EN cells	Propofol	Inhibition of LPS-activated EN cell barrier dysfunction
Liu et al. (2006) [32]	Rat macrophages	Propofol	Inhibition of inflammatory responses to LPS
Kessler et al. (1997) [18]	Rat cultured aortic SM cells	Thiopental	Augmentation of inflammatory response to IL-1β
Zuo and Johns (1997) [26]	Mouse macrophages	Halothane	Augmentation of inflammatory response to LPS
	Bovine pulmonary EN cells	Isoflurane	Augmentation of inflammatory response to LPS
Tschaikowsky et al. (2000) [23]	Rat macrophages	Volatile anesthetics	Augmentation of inflammatory response to LPS + IF[b]

IF, interferon-γ; SM, smooth muscle; SNP, sodium nitroprusside; EN, endothelial
[a] Treatment with LPS or IF
[b] Treatment with LPS + IF

by thiopental, indicating that thiopental may suppress iNOS-induced cyclic GMP formation in vascular smooth muscle, without affecting NO production [17]. Of interest, IL-1β-stimulated increases in nitrite formation, iNOS protein, and mRNA abundance in cultured rat aortic smooth muscle cells were augmented in the presence of thiopental, whereas methohexital, hexobarbital, pentobarbital, and phenobarbital were without effect; thiopental did not affect the IL-1β-stimulated activation of nuclear factor-κB (NF-κB); also, this barbiturate augmented hyporeactivity to phenylephrine in rabbit carotid arteries exposed to IL-1β, an effect that was abolished by L-NA [18], These effects of thiopental could be the result of increased iNOS expression, most likely involving mechanisms distinct from NF-κB activation. Propofol inhibited NF-κB activation in LPS-stimulated human umbilical vein endothelial cells [19].

Ischemia and anesthetic preconditioning

Volatile anesthetics

In isolated, perfused rat lungs, ischemia-reperfusion caused increses in the coefficient of filtration, the wet-to-dry lung weight ratio, the rate of increase of lactate dehydrogenase activity, and TNF-α in the perfusate, and it caused a decrease in NO metabolites in the perfusate; administration of isoflurane and sevoflurane before ischemia reversed the alterations induced by the ischemic insult [20]. Postischemic left ventricular function in the rat heart was improved and iNOS expression and activity in the heart were increased after the inhalation of isoflurane; also, a selective iNOS inhibitor, 1400 W, abolished iNOS activation and cardioprotection [21]. Isoflurane appears to induce a second window of preconditioning through the overexpression and activation of iNOS in the heart. On the other hand, in the ischemic rat heart, NF-κB-DNA binding activity was increased at the end of reperfusion, and preconditioning with sevoflurane attenuated NF-κB activation and reduced the expression of TNF-α, IL-1, and iNOS, together with decreases in infarct size and creatine kinase release, and the improvement of myocardial function [22]. Attenuation of NF-κB activation and the subsequent downregulation of NF-κB-dependent inflammatory gene expression may play an important role in the protective mechanism of anesthetic preconditioning against acute myocardial ischemia-reperfusion injury.

Anesthesia with isoflurance or halothane before permanent middle cerebral artery occlusion in rats reduced infarct volumes compared with control volumes; Western blot analysis from cortical extracts of rats with

anesthetic preconditioning revealed an increase in iNOS protein, and aminoguanidine eliminated the infarct-sparing effect of the preconditioning [23]; the authors of the study suggested that iNOS may be critically involved in the prolonged neuroprotection conferred by volatile anesthetics. In 7-day-old rats subjected to left common carotid arterial ligation followed by hypoxia, isoflurane preconditioning did not alter mortality, but it did increase the weight ratio of the left/right cerebral hemispheres in the survivors; isoflurane induced a time-dependent increase in iNOS protein, and the anesthetic preconditioning-induced neuroprotection was abolished by aminoguanidine, suggesting an iNOS-dependent neuroprotection [24]. Zheng and Zuo [25] also noted that isoflurane preconditioning reduced the neurotoxicity induced by glutamate, N-methyl-D-aspartate (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazol propionic acid in rat cerebellar slices, this neuroprotection being abolished by protein kinase inhibitors or L-NA methylester (L-NAME). The neuroprotection induced by isoflurane preconditioning may be protein kinase- and NOS-dependent.

Anesthetic preconditioning appears to be protective against ischemia-induced injury in the heart and brain due to iNOS-dependent mechanisms.

Macrophages

Volatile anesthetics

Halothane and isoflurane, at clinically relevant concentrations, upregulated the mRNA, protein, and activity of NOS in LPS-treated macrophages (iNOS) and bovine pulmonary endothelial cells (eNOS) [26]. This is a novel interaction between volatile anesthetics and the NO signaling pathway (Table 1). On the other hand, Tschaikowsky et al. [27] demonstrated that volatile anesthetics, such as halothane, enflurane, isoflurane, and desflurane, suppressed nitrite production and iNOS expression in J774 murine macrophages stimulated by LPS or γ-interferon, and the inhibition was antagonized by ionomycin, but was unaffected by diacylglycerol, phorbol myristate acetate, and C2-ceramide. In contrast, in cells costimulated by LPS and interferon-γ, volatile anesthetics increased nitrite production and iNOS expression independently of ionomycin. The authors of the study [27] suggested that the inhibitory effects of volatile anesthetics on macrophages stimulated by either LPS or γ-interferon may be due to an attenuation of intracellular Ca^{2+} increase; however, mechanisms underlying the augmenting effect of anesthetics seen under costimulation remain unidentified.

Intravenous anesthetics

Ketamine inhibited nitrite production and TNF-α in LPS- and lipoteichoic acid-activated J774 murine macrophages, but the NMDA receptor antagonists, MK-801 and dextromethorphan, were without effect, suggesting that the inhibitory effect of ketamine is associated, in part, with a decrease in the production of TNF-α, an autocrine stimulatory factor for NO production, but that this inhibitory effect is not associated with the NMDA receptor pathway [28]. Similar results were also obtained with rat alveolar macrophages activated by LPS [29]. Propofol, at a therapeutic concentration, blocked SNP-induced cell death and apoptosis in murine macrophages (cell line Raw 264.7) [30]. Chen et al. [31] obtained evidence suggesting that propofol at a clinically relevant concentration could suppress murine macrophage functions, possibly through inhibiting mitochondrial membrane potentials and ATP synthesis. Propofol inhibited LPS-induced NO production, L-arginine transport, and the expression of iNOS and cationic amino acid transporter in stimulated murine macrophages [32].

Local anesthetics

Lidocaine dose-dependently attenuated the increase in nitrite/nitrate levels in murine macrophages (Raw 264) in response to LPS and interferon-γ and decreased iNOS protein levels at the highest concentration used, but failed to decrease iNOS mRNA expression, suggesting that lidocaine reduces NO production in activated macrophages at multiple levels after transcription [33]. Lidocaine also attenuated the LPS-induced upregulation of iNOS and type-2 cationic amino acid transporter and, conversely, increased GTP cyclohydrolase I transcription in LPS-stimulated murine macrophages, with the effects of tetrodotoxin being comparable to those of lidocaine; veratridine attenuated the effects of lidocaine and tetrodotoxin, leading to the conclusion that alterations by lidocaine in LPS-stimulated macrophages are mediated via a mechanism that possibly involves the voltage-sensitive Na^+ channel [34].

Modifications of the NO-mediated inflammatory response to LPS or cytokines induced by volatile, intravenous, and local anesthetics are summarized in Table 1. Volatile (with some exceptions), intravenous, and local anesthetics suppressed the LPS-induced expression of iNOS in macrophages.

Miscellaneous

Volatile anesthetics

Increases in leukotriene C_4, NO_3, and NO_2 levels in bronchoalveolar lavage fluid were observed after sevoflurane anesthesia, compared with thiopental anesthesia, in pigs, and there was a decrease in the total blood leukocyte count in sevoflurane-treated pigs, suggesting that this volatile anesthetic evokes a pulmonary inflammatory response [35]. An alteration in the production

of both IL-10 and NO has been found following surgery/anesthesia trauma. In patients scheduled to undergo elective major surgery and anesthetized with either a volatile or an intravenous anesthetic, IL-10 overproduction did not correlate with the decrease in systemic NO concentrations during the postoperative period [36].

Intravenous anesthetics

In rat lungs, urethane decreased cyclooxygenase (COX)-1 and COX-2 mRNA levels and suppressed iNOS mRNA levels, but had no effect on eNOS mRNA levels, whereas pentobarbital and ketamine did not affect the mRNA levels of COX-1 and COX-2 [37]. Urethane should be avoided as an anesthetic when lung inflammatory processes are present, as suggested by the results of animal studies. Ketamine did not prevent LPS-induced gastrointestinal ileus, nor did it improve gastric emptying in rats; however, it did decrease LPS-induced gastric luminal fluid accumulation and it blunted iNOS expression in both the stomach and ileum [38]. It was concluded that, while iNOS may play a role in LPS-induced gastric luminal fluid accumulation, it does not appear to be a major mediator of the gastrointestinal ileus caused by LPS. Administration of propofol inhibited oxidative stress, NF-κB nuclear translocation, and iNOS overexpression in the livers of rats receiving halothane [39]. Propofol treatment appears to block the production of noxious mediators involved in the development of halothane-induced injury. Pentobarbital anesthesia augmented LPS-induced systemic hypotension, attenuated LPS-induced acute lung injury, and improved the survival rate following LPS administration in rats [40]. The authors of the study [40] suggested that this mechanism was related to the inhibitory effects of increases in the production or activity of NO, free radicals, proinflammatory cytokines, nitrotyrosine, and iNOS. A recent review article by Marik [41] summarized findings showing that propofol has antiinflammatory properties, decreasing the production of proinflammatory cytokines, altering the expression of NO, and inhibiting neutrophil function; in addition, propofol is a potent antioxidant.

Local anesthetics

Although incubation with bupivacaine and tetracaine alone did not induce nitrite accumulation in rat glial cells, nitrite production induced by stimulation with LPS and interferon-γ was increased, and increased nitrite production was accompanied by increased iNOS catalytic activity, mRNA levels, and promoter activation; lidocaine and ropivacaine increased nitrite production only at high concentrations, demonstrating that submillimolar doses of bupivacaine and tetracaine can increase glial iNOS expression [42]. The number of apoptotic cells observed in the neocortex of rats treated with human immunodeficiency virus (HIV)-1 gp120 was increased by intraperitoneal cocaine, and pretreatment with MK801 (an NMDA receptor antagonist), L-NAME (a nonselective NOS inhibitor), 7-nitroindazole (a selective inhibitor of nNOS), or 1400 W (a selective inhibitor of iNOS), minimized the neurotoxicity induced by combined administration of cocaine and gp120 [43]. Cocaine, which is often abused by HIV-infected patients, has been suggested to worsen HIV-associated dementia. The findings of the above study [43] suggest that neurotoxicity associated with cocaine + gp120 may be mediated via NO formed by iNOS and nNOS.

Endotoxemia and septic shock

There is a wealth of data implicating NO formed during an abnormally enhanced host inflammatory process as a key player in the cardiac, vascular, renal, and pulmonary derangements of endotoxemia and septic shock.

Volatile anesthetics

In a dog model of septic shock utilizing halothane, isoflurane, alfentanil, and ketamine, Van der Linden et al. [44] obtained data suggesting that ketamine best preserved cardiovascular function and appeared to have the least deleterious effects on the hypoxic tissues, and halothane had the least desirable effects. Intracerebroventricularly infused bacterial LPS increased iNOS and COX-2 mRNA levels and enzyme activities, and enhanced halothane-induced increases in regional cerebral blood flow; cotreatment with the COX-2 inhibitor NS-398 attenuated but aminoguanidine or dexamethasone abolished the effect of LPS on halothane-induced increases in cerebral blood flow, suggesting that bacterial LPS augmented halothane-induced cerebrocortical hyperemia by the induction of iNOS and COX-2 [45]. Isoflurane pretreatment 1 or 12 h before LPS attenuated neutrophil recruitment into the lung interstitium and alveolar space in mice receiving an endotoxin challenge, and also reduced protein leakage and pulmonary edema; however, the production of the chemokines, keratinocyte-derived chemokine and macrophage inflammatory protein 2, in bronchoalveolar lavage fluid was reduced when isoflurane was given 1 h, but not 12 h, before LPS [46]. Isoflurane pretreatment appears to reduce acute lung injury when given 1 or 12 h before an endotoxin challenge, or within the first hour of an already established inflammation.

Intravenous anesthetics

In healthy sheep, propofol caused only minor hemodynamic changes; however, in septic sheep receiving propofol, hemodynamics deteriorated and renal blood flow was reduced; these effects of propofol were reduced when propofol was combined with fentanyl [47]. In rats

with sepsis induced by cecal ligation and puncture, propofol and midazolam, at clinical concentrations, depressed H_2O_2 production by blood and peritoneal neutrophils, with propofol causing more depression than midazolam, suggesting that midazolam may be preferable to propofol for sedation during sepsis [48]. In another study, in a sepsis group of hamsters that had undergone cecal ligation and puncture, diaphragmatic twitch, titanic tension, and tension during fatigue trials were reduced, and diaphragm malondialdehyde and iNOS activity and plasma nitrite/nitrate concentrations were increased, compared with those in the sham group; propofol attenuated these changes seen in the sepsis group [49]. The authors of the study [49] suggested that pretreatment with propofol attenuated the diaphragmatic dysfunction induced by septic peritonitis, possibly via the inhibition of lipid peroxidation in the diaphragm caused by the powerful oxidant. Of note, intraperitoneal ketamine and xylazine blunted the LPS-induced expression of iNOS in rat stomach, duodenum, jejunum, and colon [50].

Intravenous injections of *Escherichia coli* endotoxin to rats produced progressive hypotension, metabolic acidosis, and a large increase in plasma cytokine concentrations; these responses were completely abolished by pretreatment with ketamine and were modestly suppressed by post-treatment with ketamine, suggesting that the judicious use of ketamine as an anesthetic agent may offer advantages in endotoxemia [51]. Compared with an endotoxemic group of rats receiving intravenous LPS, both the pretreatment group (with propofol) and simultaneous treatment group (with simultaneous administrations of propofol and LPS) showed improvements in Pa_{O_2}, pH, mean arterial pressure, and 5-h survival rate, and decreases in the endotoxin-induced increases in iNOS mRNA, nitrotyrosine expression, myeloperoxidase activity, and malondialdehyde levels in lung tissue, as well as decreased pulmonary microvascular permeability, and decreases in TNF-α and NO in plasma [52, 53]. Propofol administration may provide protective effects against acute lung injury in endotoxin-induced shock.

Intravenous injections of endotoxins to conscious rats caused hypotension, vascular hyporeactivity, and tachycardia, as well as lung, liver, and kidney damage—propofol attenuated the hepatocellular damage and suppressed aortic superoxide anion production, but did not suppress plasma NO and TNF-α; the survival rate was increased in propofol-treated rats [54]. The inhibition of aortic superoxide production and the amelioration of liver dysfunction appeared to contribute to the beneficial effect of propofol in conscious rats with endotoxin-induced shock. Suliburk et al. [55] reported that intraperitoneal LPS increased the levels of serum aspartate aminotransferase and iNOS, and increased heme oxygenase-1 immunoreactivity in the rat liver, while ketamine, but not isoflurane, attenuated the LPS-induced liver injury, upregulated heme oxygenase-1, and downregulated iNOS, suggesting that the hepatoprotective effects of ketamine against LPS-induced liver injury appeared to be mediated by a differential modulation of the oxidation stress proteins iNOS and heme oxygenase-1. Also, authors in the same group as that carrying out the above study [55, 56] obtained data suggesting that the protective effects of ketamine against LPS-induced liver injury were mediated through a reduction in COX-2 and iNOS protein that could be regulated via changes in NF-κB-binding activity. Tsao et al. [57] discussed, in their review article, evidence that different intravenous anesthetics, such as propofol, ketamine, and barbiturates, produced different levels of inhibition of the inflammatory responses seen in sepsis.

In summary, both volatile and intravenous anesthetics prevent the development of multiple organ failure elicited by endotoxemia and septic shock.

Other aspects

Peroxynitrite is implicated in the neuropathology of several degenerative disorders, such as shock and inflammation, as well as being implicated in ischemia-reperfusion injury [58]. Studies investigating the reaction of propofol with peroxynitrite showed that the addition of peroxynitrite to propofol in alkaline solution yielded a detectable electron spin resonance signal corresponding to a phenoxyl radical [59]; however, they could not identify the endproduct of the reaction of propofol with peroxynitrite. To investigate the protective effect of propofol in oxidative processes, in which NO and peroxynitrite are involved, Cudic and Ducrocq [60] explored direct interactions and obtained evidence leading them to propose the involvement of the nitrosodioxyl radical, forming an adduct with the propofoxyl radical, to yield 4-nitrosodioxypropofol and, finally, 4-nitrosopropofol. Isoflurane induced heme oxygenase-1 in hepatocytes in the pericentral region of the rat liver, and this induction was prevented by dexamethasone and gadolinium chloride; inhibition of NOS or reactive oxygen intermediates did not affect the heme oxygenase upregulation, which was blocked by chelerythrine and quinacrine, an inhibitor of protein kinase C and an inhibitor of phospholipase A_2, respectively [61]. The isoflurane-induced induction of heme oxygenase-1 in hepatocytes is independent of NO or reactive oxygen species, but likely involves protein kinase C and phospholipase A_2. The heme oxygenase pathway represents a major cell and organ protective system in the liver.

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