Local Anesthetics and the Inflammatory Response

A New Therapeutic Indication?

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LOCAL anesthetics (LA) are known for their ability to block Na⁺ channels. However, they have significant effects in several settings other than local and regional anesthesia or antiarrhythmic treatment, the areas in which they are used traditionally. These effects result from LAs interacting with other cellular systems as well. Interestingly, some of these effects occur at concentrations much lower than those required for Na⁺ channel blockade. For example, whereas the half-maximal inhibitory concentration (IC₅₀) of lidocaine at the neuronal Na⁺ channel is approximately 50–100 μM (depending on the specific channel subtype and study preparation),¹ the compound inhibits signaling through m1 muscarinic receptors (expressed recombinantly in Xenopus laevis oocytes) with an IC₅₀ of 20 nM, that is, 1,000- to 5,000-fold lower.² This sensitivity of other targets has two important consequences. First, we assume that LAs, at concentrations that result in significant Na⁺ channel blockade, also affect a number of other systems. Second, relatively low LA concentrations (such as attained in blood during epidural anesthesia or analgesia or during intravenous LA infusion) that block neuronal Na⁺ channels to a limited extent only still can have significant pharmacologic effects. We suggest that some of these “alternative actions” may be beneficial in the clinical setting, and others may be responsible for some adverse effects of LAs. Although Butterworth and Strichartz³ a decade ago urged investigation of such actions and their mechanisms, much remains to be discovered. To demonstrate the variety of LA effects, table 1 provides an overview of various LA actions reported in the literature.

This review focuses on an area in which alternative actions of LAs show much promise for clinical application: their effects on the inflammatory response and especially on inflammatory cells (mainly polymorphonuclear granulocytes [PMNs] but also macrophages and monocytes). PMNs do not express Na channels,⁴ and LA effects on these cells therefore are not caused by Na channel blockade. LA effects on these cells are not affected by Na channel blockers such as tetrodotoxin or veratridine.⁵ Overactive inflammatory responses that destroy rather than protect are critical in the development of a number of perioperative disease states, such as postoperative pain,⁶–⁸ adult respiratory distress syndrome (ARDS),⁹–¹¹ systemic inflammatory response syndrome, and multiorgan failure.¹²–¹⁵ Perioperative modulation of such responses is therefore relevant to the practice of anesthesiology, and LAs may play significant roles in this regard.

Inflammatory Response

In general terms, inflammation can be described as a reaction of the host against injurious events such as...
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PMN = polymorphonuclear granulocytes; MA = maximum amplitude; TEG = thrombelastography; ACT = activated clotting time; CNS = central nervous system; ACh = acetylcholine; GABAergic = \( \gamma \)-aminobutyric acid–mediated; LA = local anesthetics; EAA = excitatory amino acids.
tissue trauma or presence of pathogens. Release of vasoactive mediators from tissue mast cells (histamine, leukotrienes), as well as from platelets and plasma components (bradykinin), causes vasodilation and increased vascular permeability, leading to the classic inflammatory signs of redness (rubor) and heat (calor). The resulting edema causes swelling (tumor), and interactions of inflammatory mediators with the sensory systems induce pain (dolor). Significant local inflammation causes a systemic response, termed the acute phase reaction. This response is manifested by increases in acute phase proteins (C-reactive protein, complement factor C3, fibrinogen, and serum albumin), followed by activation of several systems of mediators (kinin system, complement system, lipid mediators, and cytokines). Cytokines, in particular, are important for regulation of the inflammatory response. The local release of cytokines (interleukin-1 [IL-1], IL-8, tumor necrosis factor [TNF]) coordinates the inflammatory response at the site of injury and induces neutrophil chemotaxis to the site of inflammation. Some cytokines (IL-1, IL-6, TNF) released from inflammatory sites mediate the systemic response. They induce fever and the acute phase reaction, mobilize neutrophils from the bone marrow, and promote lymphocyte proliferation.

The inflammatory response induces cells (primarily PMNs and monocytes) to migrate into the affected area, in which they destroy pathogens, largely by phagocytosis. This process can be divided into several stages (fig. 1):

1. PMNs sense chemoattractants derived from bacteria, complement activation, and cytokine production at the site of infection.
2. PMNs roll onto and attach to endothelial cells (margination and adhesion). Adhesion is mediated by histamine, complement factors C5a and C3a, IL-1 and IL-8, and TNF and platelet-activating factor.
3. PMNs squeeze through gaps between adjacent endothelial cells (diapedesis).
4. PMNs migrate up the chemoattractant gradient to the pathogen (chemotaxis). C5a, C3a, IL-8, and leukotriene B4 (LTB4) and other cytokines are involved in chemotaxis.
5. Pathogens are opsonized (coated with specific serum proteins, such as complement fragments, immunoglobulins, or acute phase proteins) and PMNs are primed (switched to an activated state with increased surface expression of plasma membrane receptors and enhanced nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase activity).
6. PMNs generate reactive oxygen metabolites (O2•-, H2O2, OH, and particularly HOCl) using NADPH-oxidase or myeloperoxidase enzyme complexes. Increased oxygen uptake (independent from mitochondrial respiration) is required for generation of free radicals and is referred to as respiratory burst.
7. PMNs deliver free radicals to the pathogen. Pathogens are killed by phagocytosis (by PMNs and mononuclear phagocytes) and—in PMNs—by delivery of high concentrations of reactive oxygen metabolites into the phagosome.
8. This inflammatory response can be enhanced further by PMN products.

The inflammatory response is essential for structural and functional repair of injured tissue. It is, however, a double-edged sword. Excessive generation of proinflammatory signals, as occurs in several disease states, can aggravate tissue damage because of products derived from inflammatory cells. This suggests that modulation of the inflammatory response (e.g., by LAs) might prevent such tissue damage.

Effects of LAs on Inflammatory Processes

This section describes some actions of LAs on inflammatory processes. We focus on three specific disease states relevant to anesthesiologists: inflammatory lung injury, increased microvascular permeability, and myocardial ischemia-reperfusion injury. In addition, we discuss briefly the use of LAs to treat inflammatory bowel disease, an area of active clinical investigation. Finally, we refer to an issue of considerable importance: the possibility that LAs, because of their antiinflammatory properties, might increase the risk of infection in certain settings.

High LA concentrations have been used in some studies, and, in order to judge the clinical relevance of the various reports, it is important to consider the concentrations of LAs used in clinical practice. These concentrations differ widely, depending on the method of application. In order to achieve systemic effects after intravenous administration of LAs, plasma levels in the low micromolar range are required (for lidocaine, approximately 0.5–5.0 μg/ml, corresponding to 2–20 μM). For example, intravenous administration of lidocaine at 2–4 mg/min leads to plasma concentrations of 1–3 μg/ml (4–12 μM) after 150 min. After 15 min a 2 mg/kg intravenous bolus of lidocaine results in peak plasma levels of 1.5–1.9 μg/ml (6–8 μM). Similar
plasma concentrations are obtained after epidural administration\textsuperscript{19} or topical application of LAs (1 mg/cm\textsuperscript{2}) in partial-thickness burns\textsuperscript{20}. LAs applied topically on intact skin are likely to achieve substantially lower plasma concentrations. Plasma concentrations of lidocaine above 10 μg/ml tend to produce adverse effects.\textsuperscript{21} In contrast, after local application or tissue infiltration of these drugs, LA tissue concentrations are typically in the millimolar range. Similar concentrations are present around the spinal nerves after epidural or spinal administration of LAs.\textsuperscript{22} LA concentrations at specific sites vary widely, depending on the method of administration. In vivo, LAs are largely protein-bound, lowering the concentrations available for interactions with signaling systems.

Most studies have used lidocaine as a prototypical compound. Although other LAs appear to exhibit similar actions, there is clearly a lack of comparative studies with LAs from various classes, and very few structure-function studies have been performed. Data obtained with lidocaine cannot necessarily be extrapolated to other LAs.

**Effects of LAs on Lung Injury**

Polymorphonuclear granulocytes, macrophages, and cytokines play crucial roles in the pathogenesis of inflammatory lung injury. Cytokines increase the expression of adhesion molecules, thereby increasing margination of PMNs in the lung. The attachment of PMNs affects endothelial cells and microvascular permeability.

Nishina et al.\textsuperscript{23} reported that pre- or early posttreatment with lidocaine (bolus 2 mg/kg + 2 mg·kg\textsuperscript{-1}·h\textsuperscript{-1} continuous infusion, yielding plasma concentrations of 1.2–2.5 μg/ml [5–10 μM]) attenuates the late phase of acid installation–induced lung injury in rabbits. Lidocaine decreased PMN accumulation in the lung. Superoxide anion production by PMNs obtained from the pulmonary artery was inhibited, indicating reduced free radical generation. In turn, this would reduce endothelial damage and therefore might decrease pulmonary edema. The HCl-induced increase in pulmonary wet: dry ratio and albumin extravasation was attenuated in lidocaine-treated rabbits, and cytokine levels in bronchoalveolar fluid decreased. (Fluid used for bronchoalveolar lavage routinely contains high concentrations of LA in clinical\textsuperscript{24} and animal experiments.\textsuperscript{25} These concentrations of LA have been shown to affect the behavior of alveolar macrophages significantly.\textsuperscript{26}) The decrease in cytokines was more likely a result from attenuation of the inflammatory response, rather than direct suppression of cytokine production by macrophages or alveolar epithelium. Plasma levels of IL-6 and IL-8, and IL-6 concentrations in bronchoalveolar fluid, were less in lidocaine-treated animals. The antiinflammatory effects of lidocaine improved lung function after tracheal HCl installation, indicated by improved partial pressure of oxygen and attenuation of both decreased compliance and increased resistance. The protective effects observed were likely a result of inhibition of sequestration and activation of PMNs.\textsuperscript{23}

Interactions of PMNs with endothelial cells also may be important in the pathogenesis of organ dysfunction induced by endotoxin. Increased margination of activated PMN in response to an inflammatory stimulus contributes to endothelial damage. Because LAs interfere with the initial steps of inflammation in vitro, a protective effect of these drugs in endotoxin-induced lung injury might be expected. Schmidt et al.\textsuperscript{27} reported that, in a rat model of sepsis, pretreatment with lidocaine (plasma concentration 1.4–2.5 μg/ml [6–10 μM]) attenuated endotoxin-induced increases in PMN adherence, PMN activation and migration to the inflammatory site, and PMN metabolic function, as assessed by an inhibition of free radical production. The protective action of lidocaine was not a result of differences in venular wall shear rate. Instead, inhibition of PMN adherence to endothelial cells, PMN function, and suppression of histamine release by lidocaine may explain the observed decrease of microvascular permeability in lidocaine-pretreated rats. Similar results were obtained by Mikawa et al.,\textsuperscript{28} who showed that pretreatment with lidocaine (single dose of 2 mg/kg intravenously followed by continuous infusion of 2 mg·kg\textsuperscript{-1}·h\textsuperscript{-1}) significantly attenuates endotoxin-induced lung injury in rabbits, by attenuating the accumulation and the O\textsubscript{2}\textsuperscript{2} production of PMNs.

The mechanisms underlying ARDS induced by long-term exposure to high oxygen concentrations remain unclear. An inflammatory mechanism, including PMN activation and sequestration in the lung, may be pivotal in the pathogenesis of this syndrome. This hypothesis is confirmed by the fact that antioxidants protect the lung in such situations. Considering the effects of LAs on inflammatory cells, it would be expected that their antiinflammatory properties help prevent hyperoxic lung injury. Takao et al.\textsuperscript{29} demonstrated a protective effect of LAs on inflammatory responses and pulmonary function in a rabbit model of hyperoxia-induced lung injury. Lidocaine infusion to systemically relevant plasma concentrations (1.4–2.5 μg/ml [6–10 μM]) decreased chemotactic factors (C3a, C5a, TNF-α, IL-1β) in bronchoalveolar...
lavage fluid and resulted in less PMN accumulation than in saline-infused rabbits. PMN from lidocaine-treated rabbits showed a marked reduction in chemiluminescence, indicating reduced free radical release and therefore less likelihood of endothelial damage. The treated animals developed less lung edema, as demonstrated by a decrease in albumin extravasation and improved wet:dry ratio of the lung. Lidocaine infusion was associated with fewer histopathologic changes of lung damage.

LAs have been shown to be protective in various animal models of ARDS, and the underlying mechanism appears to be their antiinflammatory action.

**Effects of LAs on Microvascular Permeability**

Increased microvascular permeability is common in many inflammatory diseases. Examples relevant to anesthesiologists include ARDS, sepsis, burns, and peritonitis. Various studies have shown protective effects of LAs on this process.

In an *in vivo* model of ligature-induced obstructive ileus in rats, lidocaine, administered intravenously (2 mg/kg) or sprayed directly onto the serosa, suppressed the inflammatory reaction, as indicated by marked inhibition of fluid secretion and albumin extravasation. Although blockade of neurons in the enteric nervous system (especially the myenteric plexus), with subsequent reduction in the release of secretory mediators such as vasoactive intestinal polypeptide, may have contributed to the antisecretory action of lidocaine, this does not explain easily why lidocaine pretreatment of the serosa of the obstructed jejunum reduced the inflammatory reaction in the bowel wall even 18 h later. Lidocaine’s interference with several steps of the inflammation cascade may be a more likely explanation for the protective effect observed in this study. Similar results were obtained by Rimbäck *et al.* They studied the effects on HCl-induced peritonitis of topical pre- and posttreatment of the peritoneal surface with lidocaine (37 mM) and
bupivacaine (17.5 ms). Both anesthetics significantly inhibited Evans blue albumin extravasation, a marker of microvascular permeability. Although both drugs were titrated to the same nonionized fraction (based on pKa), lidocaine showed a more potent inhibitory effect.30

Using hamster cheek pouch, Martinsson et al.32 observed reversible inhibition by ropivacaine (100 μM) of LTB4-induced plasma exudation, indicating that the effect is not specific to lidocaine.

Thermal injury activates the complement system and other inflammatory cascades, resulting in progressive plasma extravasation with subsequent hypoproteinemia and hypovolemia. Antiinflammatory drugs inhibit burn-induced albumin extravasation,33,34 suggesting a role for inflammatory mediators in the pathogenesis of edema. Therefore investigators were interested in studying whether the anti-inflammatory properties of LAs could protect microvascular integrity, without increasing infection rate. Using skin burns in rats, Cassuto et al.35 reported that topical application or systemic administration of amide LAs, in doses resulting in plasma concentrations below toxic level,17,20 significantly inhibited plasma exudation in rats compared with placebo. This protective action could be explained by several of the known effects of LAs. Inhibition of PMN delivery to the site of inflammation,36 direct suppression of PMN-endothelial adheriveness,37 reduced generation of toxic oxygen metabolites,38,39 impaired prostaglandin and leukotriene production,40 or increased local prostacyclin production,41 and reduced PMN stickiness and adherence to injured endothelium all may contribute to the reduced plasma extravasation. These findings were not confirmed, however, by Nishina et al.,23 who did not find that LAs affect leukotrienes and prostacyclin. Inhibition of sensory neurons with resultant decreases in release of substance P, suggested to be important for edema development after thermal injury,42 is another possible explanation. Cassuto et al.35 reported that the protective effect was lost if the systemically administered concentration of lidocaine was increased from 10 to 30 μg · kg⁻¹ · min⁻¹. A potential explanation for this unusual concentration-dependency is activation or block of additional pathways at the higher lidocaine concentration. A similar and possibly related phenomenon is the concentration-dependent action of LAs on vascular smooth muscle in vitro and in vivo:43 Low concentrations (for lidocaine 1 μg/ml–1 mg/ml, corresponding to 4 μM–4 mM) induce vasoconstriction; greater concentrations induce vasodilation. It is conceivable that vasoconstriction would decrease edema formation, and vasodilation would enhance it.

Inhibiting the inflammatory response could increase the incidence of infection, but Brofeldt et al.20 reported that 5% lidocaine cream, applied to the skin of patients with partial-thickness burns in concentrations up to 2.25 mg/cm², was associated with good pain relief, plasma concentrations below toxic levels, no infections or allergic complications, and excellent wound healing. These studies suggest that benefit may be obtained from topical treatment with LAs, even in patients with extensive burns.

Effects of LAs on Inflammatory Diseases of the Gastrointestinal Tract

Inflammatory processes contribute to the development of several bowel diseases. Ulcerative colitis and proctitis are caused by both immunologic and inflammatory stimuli. In a rat colitis model, ropivacaine showed protective effects,44 and clinical studies have shown that LAs can be effective against the severe mucosal inflammation of these diseases.45,46 Arlander et al.47 reported that patients with ulcerative colitis treated rectally with ropivacaine 200 mg twice daily (mean peak plasma concentrations 1.0–1.4 μg/ml [3.6–5.0 μM]) demonstrated decreased inflammation and reduced clinical symptoms after only 2 weeks of treatment. Perturbation of the link between inflammatory and immune competent cells, as well as blockade of hyperreactive autonomic nerves (which also may play a causative role in these diseases),48 were suggested as possible explanations for the LA effect. Decreased release of proinflammatory lipoxygenase products (LTB4 or 5-hydroxy-eicosatetraenoic acid), with other potentially cytoprotective eicosanoids (15-hydroxy-eicosatetraenoic acid and prostacyclin) unaffected, also may contribute to this beneficial effect of ropivacaine.49 Lidocaine failed, however, to inhibit prostanooid release by human gastric mucosa in vitro at concentrations less than 250 μg/ml.50

Lidocaine (plasma concentration 5–15 μM) accelerated the return of bowel function in patients undergoing radical prostatectomy,51 resulting in a significant shortening of hospital stay. LAs (lidocaine 100 mg bolus intravenously + 3 mg/min continuous intravenous infusion, or bupivacaine 2 mg/kg intraabdominal installation) also shortened the duration of postoperative ileus in patients undergoing major abdominal surgery.52,53 Peritoneal surgery is associated with release of inflammatory mediators such as histamine, prostaglandins, and kinins.52,54 Activation of abdominal reflexes resulting in

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longlasting inhibition of colonic motility after surgery is likely to be a result of inflammatory reactions in the area undergoing surgery. Because LAs affect the release of inflammatory agents, beneficial effects on bowel function may result at least in part from lidocaine’s antiinflammatory effects. This hypothesis is supported by the observation that nonsteroidal antiinflammatory drugs are also effective. The antiinflammatory effect of LAs is prolonged and persists after serum levels have decreased. This might explain lidocaine’s effect on bowel function 36 h after infusion was discontinued. T

Taken together, these findings show significant promise for the use of LAs in the treatment of inflammatory bowel disease, as well as in the attenuation of postoperative ileus.

**Effects of LAs on Myocardial Infarction and Reperfusion Injury**

Acute myocardial infarction is not usually considered an inflammatory disease, but infarction, and particularly ischemia–reperfusion injury, is accompanied by a significant cardiac inflammatory response. PMN-endothelial interactions occurring during myocardial ischemia and reperfusion are thought to play a crucial role, and PMN-derived oxygen metabolites are important in myocardial injury associated with reperfusion of the ischemic heart. Activated PMN can induce structural changes in the heart through the action of free radicals and arachidonic acid metabolites. In 1984 Mullane et al. reported that drugs that impair PMN function may reduce infarct size. Recent studies have shown that IL-6 and IL-8 are important regulators of the inflammatory response in myocardial infarction, and C5a is suggested as a key mediator of tissue injury in this setting. Moreover, expression of PMN and monocyte adhesion molecules and their ligands increases in the acute phase of myocardial infarction. It is not surprising that blockade of adhesion molecules, reducing PMN accumulation in the myocardium, exerts significant protective effects on myocardial ischemia–reperfusion injury in rats. Intravenous administration of antibodies against CD11b-CD18 reduced myocardial reperfusion injury in an animal model. Similar findings were observed after treatment with 17β-estradiol, which decreased TNF-α levels and reduced intercellular adhesion molecule-1-mediated binding of PMN to injured myocardium, leading to less PMN accumulation and subsequent protection against reperfusion injury. Leukotriene synthesis inhibitors also provide significant cardioprotection in myocardial ischemia. PMN-mediated endothelial reperfusion injury can be attenuated by PMN depletion during reperfusion.

Experiments in a porcine model of myocardial ischemia have shown that lidocaine, either administered intravenously or perfused in a retrograde manner before onset of reperfusion, preserved the ischemic myocardium and reduced infarct size after reperfusion. Lido
caine infusions in dogs reduced infarct size, possibly by inhibiting release of toxic oxygen metabolites. In contrast, de Lorgeril et al. reported that, in their dog model, lidocaine (plasma concentration 13 μM) reduced neither infarct size nor myocardial PMN accumulation significantly. These discrepancies might be caused by differences between the models, particularly the duration of occlusion.

Lidocaine is used for antiarrhythmic treatment after myocardial infarction. It is conceivable that part of the antiarrhythmic effect in this setting is a result of antiinflammatory effects of lidocaine in areas of myocardial infarction. Although lidocaine administration failed to be effective in treating reperfusion arrhythmias in several experimental studies in dogs and pigs, lidocaine decreased reperfusion arrhythmias caused by free radical-induced enhanced automaticity, without effect on reentry arrhythmias.

**LAs and Increased Risk of Infection**

An important aspect of the antiinflammatory properties of LAs is a possible increase in susceptibility to infections: LA-mediated depression of the PMN oxidative metabolic response may decrease the ability to control bacterial proliferation. Investigations suggest, however, that the remaining PMN function is sufficient to minimize the risk. Peck et al. found that the microbicidal function of PMNs from patients receiving lidocaine infusions was only slightly decreased. Although Grou"
Powell et al. reported increased infection risk if eutectic mixture of local anesthetics cream was applied to contaminated wounds.

It appears, therefore, that LAs are most likely to be beneficial in settings of sterile inflammation, in which the excessive inflammatory response is a major pathogenic factor. In contrast, LAs might be detrimental in settings of bacterial contamination, in which an unmitigated inflammatory response is required to eliminate the microorganisms.

Local anesthetics, in millimolar concentrations, possess antimicrobial properties in vitro and in vivo. Lidocaine (37 mM) inhibits growth of Escherichia coli and Streptococcus pneumoniae but has no effect on S. aureus or Pseudomonas aeruginosa; 2% lidocaine (74 mM) inhibits all of these bacteria. Schmidt and Rosenkranz utilizing a larger number of bacterial pathogens, showed similar results, demonstrating inhibition of all pathogens except S. aureus and P. aeruginosa.

The mechanisms behind this antibacterial action are unclear. Recent investigations suggest that the antimicrobial activity seems to be bactericidal rather than bacteriostatic.

Recently, Sakuragi et al. showed that preservative-free bupivacaine (4.4-26.0 mM) possesses temperature- and concentration-dependent bactericidal activity against microorganisms in the human skin flora. S. aureus was more resistant to bactericidal activity of bupivacaine than were Staphylococcus epidermidis or E. coli.

Such antibacterial actions, however, are obtained only at high concentrations. Feldman et al. observed that low concentrations of bupivacaine had, at best, limited antibacterial activity and did not inhibit growth of coagulase-negative staphylococcus. They concluded that LAs are unlikely to prevent, for example, epidural catheter-related infections. Only bupivacaine concentrations of 8 mM or higher appeared to have antibacterial properties. Concentrations of LAs in the epidural environment, are in the millimolar range. Although, to our knowledge, no published studies exist, it might be possible that the antibacterial properties of epidural LAs contribute to prevention of epidural infections; if so, eliminating LAs from epidural infusions might result in a higher infection rate.

High concentrations of LAs also inhibit viruses. Using an in vitro test (plaque neutralization test in Vero cells) to study the antiviral action of LAs against herpes simplex virus 1, De Amici et al. reported that anesthetics with intermediate potency such as mepivacaine can inhibit viral replication by up to 50%, but only with concentrated solutions (more than 1% [35 mM]) and if applied in combination with epinephrine. Bupivacaine (15.5 mM) also inhibited, but again, without epinephrine the effect was reduced markedly. Inhibition was maximal with 1% (approximately 31 mM) solutions. It is likely that the inhibitory effect is directed primarily against the virus itself and not (as with most antiviral drugs) mediated by interference with the mechanisms of cellular replication. LAs can exert antiviral activity in a concentration-dependent manner. This effect is influenced by other factors such as osmolarity and presence of epinephrine (possibly a pH effect), especially if a less concentrated solution is employed.

Because the antibacterial and antiviral effects of LAs are observed only at high concentrations, antiinflammatory actions of these compounds at systemic levels in theory can increase the risk of infection. This has not been relevant in the in vitro studies reported to date, except in settings of gross bacterial contamination. One of the hallmarks of the findings described here is that these compounds can modulate excessive inflammatory responses without significant impairment of host defenses. The next section describes the cellular actions underlying this inflammatory modulation.

Effects of LAs on Inflammatory Cells and Mediators

Effects on Release of Inflammatory Mediators

Leukotrienes, particularly LTB4, play an important role in the early phase of inflammation. Reduction of leukotriene release is therefore a major option for modulating inflammation.

Leukotriene B4, formed in inflammatory cells such as PMNs and monocytes, is a potent stimulator of PMN activity. It induces margination at endothelial cells, degranulation, diapedesis, and superoxide generation and acts synergistically with prostaglandin E2 to enhance vascular permeability. It has a high chemotactic potency for PMNs (i.e., it is a potent leukoattractant) in vitro and in vivo. Blocking release of this chemotactic mediator exerts an antiinflammatory action, because PMNs no longer are recruited to the inflammatory site. LAs block leukotriene release. In vitro preincubation of human PMNs or monocytes with different concentrations of lidocaine or bupivacaine (2-20 mM lidocaine and 0.4-4.4 mM bupivacaine) inhibit LTB4 release nearly completely. This may explain some of the antiinflammatory effects of the compounds. Because LTB4, in combination
with prostaglandin E$_2$, induces edema formation, blockade of LTB$_4$ release by LAs may explain in part the beneficial effects of LAs on edema formation.\textsuperscript{50}

Interleukin-1$\alpha$ is another inflammatory mediator, which, acting on its receptor on PMNs, stimulates phagocytosis, respiratory burst, chemotaxis, and degranulation. Reduced release of cytokines such as IL-1$\alpha$ therefore also would contribute to an antiinflammatory effect of LAs. \textit{In vitro}, amide LAs, such as lidocaine and bupivacaine, dose-dependently (lidocaine 0.2-20.0 mM, bupivacaine 44-4,400 $\mu$M) inhibit IL-1$\alpha$ release in lipopolysaccharide-stimulated human peripheral blood mononuclear cells.\textsuperscript{86}

Lidocaine also inhibits histamine release from human peripheral leukocytes, cultured human basophils, and mast cells \textit{in vitro} at concentrations in the high micromolar range.\textsuperscript{87} It therefore appears that LAs can inhibit the release of several critical inflammatory mediators; in addition to direct effects on PMNs and macrophage function, this may be one of the main pathways by which they exert their antiinflammatory effects.

\textit{Effects of LAs on PMN Adhesion}

Adhesion of PMNs to endothelium, if excessive, may induce endothelial injury, which is mediated by several adhesion molecules. One of the most important for firm adhesion of PMN to endothelium and subsequent transmigration (diapedesis) is CD11b-CD18, a member of the integrin family.\textsuperscript{88} This receptor is expressed constitutively on the surface of nonactivated PMN, but expression increases markedly after inflammatory stimulation. Binding of activated PMN to endothelial cells by CD11b-CD18 increases intracellular peroxide levels in the endothelial cells, in which reactive oxygen species can have detrimental effects.\textsuperscript{89} Monoclonal antibodies against CD11b-CD18 protect \textit{in vitro} against endothelial cell injury.\textsuperscript{89} \textit{In vitro} studies have shown a reduction of TNF-$\alpha$-induced up-regulation of CD11b-CD18 surface expression on PMN after ropivacaine or lidocaine treatment. This may contribute to the beneficial \textit{in vivo} effects of ropivacaine on ulcerative colitis,\textsuperscript{32} at tissue concentrations (100-300 $\mu$M) obtained after rectal LA administration.

Recombinant human granulocyte colony-stimulating factor (rhG-CSF) participates in PMN-endothelial interactions by stimulating PMN functions and upregulating expression on PMNs of cellular adhesion molecules, such as CD11b-CD18. Lidocaine (20 mM), added to PMNs during incubation with rhG-CSF, abolished the priming effect of rhG-CSF and inhibited rhG-CSF-stimulated surface expression of CD11b. The effect was concentration-dependent (4-40 ms), and decreased PMN adherence \textit{in vitro}.\textsuperscript{90} Because increases in intracellular Ca$^{2+}$ concentration play a major role in PMN activation,\textsuperscript{91} and upregulation of CD11b is also Ca$^{2+}$-dependent,\textsuperscript{92} \textit{in vitro} inhibition by lidocaine (14 $\mu$M) of increases in intracellular Ca$^{2+}$ concentration\textsuperscript{93} may be responsible for this action.

When adhering to surfaces, PMNs flatten out the rounded cell shape characteristic for circulating cells. Conversely, rounding of PMNs prevents endothelial adhesion. Low temperature, colchicine, and cyclic adenosine monophosphate prevent PMNs from flattening and therefore from adhering to surfaces. Rounding is characterized by cell contraction, synthesis of retraction fibrils, and withdrawal of cell processes. Inhibition of phagocytosis, lysosomal enzyme release, superanion production and postphagocytic oxygen consumption all are associated with marked cell rounding and withdrawal of cell processes.\textsuperscript{26,94-97} If PMNs are exposed to LAs \textit{in vitro} (lidocaine 12 mM or tetracaine 1.5 mM), these morphologic changes also occur, followed by inhibition of adherence and therefore impaired PMN delivery to sites of inflammation.\textsuperscript{98} Perfusion with LA-free medium reverses these effects. Rounding also occurs after Na$^+$ depletion of or Mg$^{2+}$ and Ca$^{2+}$ addition to the medium. Because tetrodotoxin does not affect rounding, the LA effect seems unrelated to Na$^+$ channel inhibition. Rabinovitch and DeStefano\textsuperscript{94} reported that macrophages cultured \textit{in vitro} and incubated with either lidocaine (12 ms) or tetracaine (1.5 ms) underwent reversible cell rounding, associated with cell contraction and withdrawal of cell processes. \textit{In vitro}, lidocaine induces a dose-dependent reduction of granulocyte adherence; significant effects are obtained with concentrations $\geq$ 100 $\mu$M. \textit{In vivo}, bolus injection of 2.5 mg/kg lidocaine in rabbits caused a transient decrease in adherence (to 40% of control) 5 min later.\textsuperscript{36} Adherence recovered 15 min after injection. Continuous lidocaine infusion (0.3 mg $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$) after bolus injection maintained this inhibitory effect for the duration of infusion. Similar results were obtained in humans receiving a 100-mg bolus of lidocaine intravenously for treatment of arrhythmia.\textsuperscript{36}

Peritonitis is accompanied by a profound increase in PMN adherence and subsequent delivery into the exudate. In rabbits, lidocaine (1.5 mg/kg bolus, followed by 0.3 mg $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$) markedly inhibited both adherence (to 25% of control) and delivery (to 2% of control), measured 6 h after induction of peritonitis and initiation of lidocaine infusion.\textsuperscript{36} In this experiment, lidocaine treatment caused a more than 10-fold larger inhibition of inflammation than did methylprednisolone (2- to 3-kg

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rabbts were given 15-mg doses of the depot form subcutaneously twice at 7-day intervals, and 1–3 days after the second dose sterile peritonitis was induced). In the hamster cheek pouch preparation, ropivacaine (100 μM) markedly inhibits LTB₄-induced PMN adhesion in post-capillary and larger venules. This may be caused by an effect on PMN rolling or firm adhesion.³² Reduction of PMN rolling may result in part from alterations in blood flow and in part from effects on PMN-endothelial interactions.³²

Local anesthetics decrease the ability of PMNs to adhere to surfaces. As a result, one would anticipate a significant effect on PMN accumulation at the site of inflammation.

**Effects of LAs on PMN Migration**

Migration of PMNs is a key event during the inflammatory response. Lidocaine’s inhibitory effect on PMN migration has been reported by several investigators, using both *in vitro* and *in vivo* models.⁹⁹–¹⁰¹ Hammer et al.⁹⁹ showed *in vitro* that lidocaine (4–20 μM) concentration-dependently inhibits human PMN metabolism and random motility, with complete immobilization of PMNs occurring in the presence of 20 μM. Dickstein et al.¹⁰² reported that, *in vitro*, exposure to 1–100 μM lidocaine inhibits macrophage migration. Destruction of the functional integrity of cytoskeletal structures,¹⁰³ interference with Ca²⁺-dependent cellular processes,¹⁰⁴ and interaction with membrane lipids, causing changes in stability and fluidity of the membrane, may contribute to the observed effect of the compound.¹⁰²

**Effects of LA on PMN Accumulation**

Wound healing requires that a large number of PMNs migrate to an injured area. Effects of local administration of LAs on wound healing processes are of special interest, because these drugs often are injected into tissue for pain relief after surgery. Studies on this topic have, however, yielded contradictory conclusions. Some *in vivo* investigations have demonstrated delayed wound healing,¹⁰⁶ no effects,¹⁰⁶ or even improved wound healing¹⁰⁷ after LA infiltration.

Eriksson et al.¹⁰¹ investigated the effects of lidocaine on PMN accumulation in a wound, using an *in vivo* rat model. Inflammation was induced by implantation of a titanium chamber close to the peritoneum. Pretreatment of the wound with 10 mg lidocaine reduced the accumulation of PMN in the wound area compared with saline-treated rats. Chemiluminescence in the lidocaine group was reduced markedly, indicating suppression of metabolic responsiveness of PMN. MacGregor et al.³⁶ reported that in rats PMN accumulation during peritonitis is suppressed by lidocaine (1.5 mg/kg bolus followed by infusion of 0.3 mg · kg⁻¹ · min⁻¹ for the duration of the experiment). Scott et al.¹⁰⁸ found that lidocaine, at micromolar concentrations, impairs accumulation and adherence of PMNs in an *in vivo* canine model. These findings may be explained by inhibition of PMN adherence (and therefore inhibition of migration),³⁶,¹⁰⁹ or a direct inhibitory effect on motility and migration of PMNs.³⁶,⁹⁹,¹⁰⁰ In addition, it is conceivable that LAs inhibit chemoattractant release by impairing cell metabolism.⁸⁶,⁹⁶,⁹⁹,¹⁰¹

It appears that LAs reduce the ability of PMNs to migrate to the site of inflammation by interference with the critical steps of adhesion and migration. The result is decreased PMN accumulation.

**Effects of LAs on PMN Priming**

The priming process can be described as a potentiated response of PMNs after previous exposure to priming agents, such as TNF-α, platelet-activating factor, IL-8, lipopolysaccharide, or granulocyte-macrophage colony-stimulating factor. Priming is a key regulatory mechanism of PMN function and seems to play a pivotal role in the “overstimulation” of inflammatory pathways, which then induces tissue damage rather than protect the host. As such, the process is being investigated intensively, but mechanisms are as yet poorly understood. An excellent overview of the pathophysiologic consequences and underlying mechanisms of PMN priming was published in 1998 by Condliffe et al.¹¹⁰

The effects of LAs on PMN priming have not been investigated in detail. We have shown *in vitro* that lidocaine blocks priming of PMNs by lysophosphatidic acid in a concentration-dependent manner (IC₅₀ = 1 μM).¹¹¹ In contrast to other LA actions on these signaling systems, the LAs acted at an extracellular site; the non-permeable lidocaine analog QX314 had effects similar to those of lidocaine. It is possible that inhibition of priming contributes to the antiinflammatory actions of LAs, and in particular suppresses the deleterious effects of the uncontrolled, overactive response of inflammatory cells to a stimulating agent. This might explain how LAs can decrease tissue damage without significantly inhibiting PMN functions required for host defense.

NADPH-oxidase activity, Ca²⁺, protein kinase C, phospholipase D, and phosphatidylinositol-3-kinase are likely to be involved in the priming process. In other settings,
inhibition of NADPH-oxidase activity, Ca\(^{2+}\), transients and protein kinase C have been described for several LAs\(^{112}\) such that the compounds might be anticipated to affect priming.\(^{93,113,114}\) Effects of LAs on phospholipase D and phosphatidylinositol-3-kinase to our knowledge have not been published.

Interactions of LAs with PMN priming require more investigation.

**Effects of LAs on PMN Free Radical and Granule Enzyme Release**

Activated PMNs generate light (chemiluminescence), which can be measured as an indicator of metabolic activity, that is, free radical generation. Although some researchers have questioned the usefulness of this methodology for investigation of PMN function, because the nature of detected oxidants is uncertain, chemiluminescence is a commonly used, sensitive, noninvasive technique to measure reactive oxidant production by PMN. \(\text{In vitro}\) lidocaine and bupivacaine inhibit luminal-amplified chemiluminescence concentration-dependently (\(IC_{50} = 4.5-5.0\) ms for lidocaine and 1.4-2.0 ms for bupivacaine, depending on the manner of activation).\(^{96,38}\) Reports of effects of lower concentrations have been contradictory: Some investigators have reported no or only a slight impairment of chemiluminescence by LAs \(\text{in vitro}\)^{115–117} but Hattori et al.\(^5\) demonstrated \(\text{in vitro}\) suppression of PMN free radical generation by eight different LAs in a concentration-dependent manner (0.1 and 10 ms). The inhibitory effect correlated with the partition coefficient for each drug; that is, the more lipid-soluble LAs were more potent inhibitors of free radical production. Tetrodotoxin, veratridine, and amiloride hydrochloride were tested for their abilities to affect free radical generation by human PMNs. Because none of these compounds showed any inhibitory effects, the underlying mechanism of LA action is unlikely to be Na\(^+\) influx blockade.\(^5\) Cederholm et al.\(^{116}\) studied \(\text{in vitro}\) effects of ropivacaine, bupivacaine, lidocaine, mepivacaine, and prilocaine on both intra- and extracellular production of oxygen metabolites in human PMNs. LAs (0.5-200.0 \(\mu M\)) caused a small but statistically significant decrease in chemiluminescence response. Prilocaine's inhibitory effect on extracellular release was accompanied by an enhanced intracellular activity. This makes this drug particularly noteworthy, because excessive extracellular free radical release may cause tissue damage, and increased intracellular activity improves antimicrobial properties.\(^{118}\) Studies on surgical wounds in rats confirmed the effects of LAs on free radical release \(\text{in vivo}\).\(^{101}\) The inhibitory effect of LAs on PMN affects not only the production of \(O_2^-\) but also the generation of hydrogen peroxide and hydroxyl radical. Mikawa et al.\(^{119}\) reported \(\text{in vitro}\) that LAs at concentrations of 0.1-1.2 ms decrease release of reactive oxygen species such as \(O_2^-\), \(H_2O_2\), and \(OH^-\). LAs do not scavenge the reactive oxygen species generated but rather inhibit the ability of PMNs to produce them.\(^{119}\)

**Effects of LAs on PMN Lysosomal Enzyme Release**

Antimicrobial activity results in part from release of lysosomal enzymes by PMNs. Therefore Peck et al.\(^{38}\) investigated \(\text{in vitro}\) the effects of 8 ms lidocaine on lysozyme and myeloperoxidase release and compared these effects with the ability of lidocaine-treated PMN to kill \(E.\) coli. Lidocaine significantly impaired release of both enzymes and reduced the capability of killing \(E.\) coli from 95 to 70%. These findings were confirmed \(\text{in vitro}\) for lidocaine and tetracaine.\(^{95}\)

**Effects of LA on PMN Nitric Oxide Generation**

Nitric oxide plays multiple, at times contradictory, roles in the inflammatory process. Because nitric oxide synthase inhibitors enhance \(\text{in vivo}\) the number of PMNs adherent to endothelial cells of mesenteric vessels,\(^{120}\) increased nitric oxide production has an antiinflammatory action. Nitric oxide attenuates tissue injury during endotoxemia and sepsis \(\text{in vivo}\).\(^{121}\) In contrast, overproduction of nitric oxide by the inducible nitric oxide synthase (iNOS) expressed in macrophages or neutrophils has been implicated in the pathogenesis of septic shock or tissue injury against the host itself leading to multiple organ failure. Suppression of nitric oxide overproduction by iNOS inhibitors occasionally acts advantageously. The iNOS inhibitor aminoguanidine successfully attenuates endotoxin-induced acute lung injury \(\text{in vivo}\).\(^{122}\) \(\text{In vitro}\) blockade of TNF (by TNF-binding protein) and nitric oxide (by aminoguanidine) decreases PMN chemotaxis and sequestration and attenuates acute lung inflammation induced by ischemia and reperfusion of lower extremity.\(^{123}\)

The effects of LAs on nitric oxide metabolism have not been described in detail. \(\text{In vitro}\), LAs enhance \(N\)-formylmethionyl-leucyl-phenylalanine- or phorbol myristate acetate-induced nitric oxide generation in human PMNs.\(^{124}\) This may contribute to the protective effects of LAs, although it seems unlikely to be a major pathway.
Effects of LAs on Macrophages

Macrophages are pivotal in the inflammatory response. As the primary defense against injurious agents, they generate significant amounts of cytokines and other inflammatory mediators. In an in vitro study of human alveolar macrophages, tetracaine and lidocaine were reversible, dose-dependent inhibitors of oxidative metabolism (oxygen consumption and free radical release). This inhibition was associated with cell rounding and occurred at LA concentrations as present in effluents recovered during bronchopulmonary lavage (2–16 mM). Ogata et al. reported in vitro that LAs (10 mM) reversibly inhibited phagocytosis by macrophages, in a concentration- and pH-dependent manner. Tetracaine exerted the largest and procaine the smallest effect. Phagocytosis by monocytes in vitro also is inhibited by lidocaine. Lidocaine, in concentrations (500 μM) routinely injected into tissue, inhibits phagocytosis and metabolism of human PMNs in vitro.

Macrophage functions such as cytokine release, respiratory burst and phagocytosis are sensitive to intracellular pH changes, regulated by vacuola-type H+-translocating adenosine triphosphatase and the Na+-H+ exchanger (NHE). LAs bind to NHE and lidocaine inhibits NHE in human PMNs in vitro. Lidocaine also dose-dependently slowed intracellular pH recovery and suppressed phorbol myristate acetate-induced respiratory burst in rabbit alveolar macrophages in vitro, without decreasing metabolic activity or viability of the macrophages. Inhibition of the intracellular pH regulatory mechanism may contribute to effects of LAs on alveolar macrophage function. These findings support the hypothesis that the effect of lidocaine on phagocytosis and other macrophage processes might result in part from to an inhibitory effect on NHE.

Mechanisms of Action

A variety of actions of LAs on inflammatory cells have been described, many of which suggest that LAs might modulate the inflammatory response in various disease states. Most in vitro studies require concentrations of LAs above the clinically relevant range; in vivo studies of the same or similar phenomena often demonstrate effects at clinically feasible concentrations. The reasons for this discrepancy are unknown. The issue is particularly remarkable because one would anticipate that larger free LA concentrations would be available in many protein-free in vitro solutions, as compared with in vivo situations. It may be that the multiple molecular targets of LAs allow potentiating interactions in vivo that cannot be attained in a simplified in vitro model. Alternatively, the more prolonged exposure to LAs during in vivo investigations may play a role. We found that, in Xenopus oocytes, sensitivity of thromboxane A2 and lysophosphatidic acid signaling to lidocaine and bupivacaine increased more than five-fold if incubation times were extended from 10 min to 12 h. Unfortunately, virtually nothing is known about the specific molecular mechanisms involved in these effects. In many instances, Na+ channel blockade can be ruled out, either because in vitro Na+ channels are not detectable in the cells under study or because in vivo LAs induce effects at concentrations much lower than those required for Na+ channel blockade. Several mechanisms have been suggested (fig. 2), but only a few targets have been described in molecular detail. LA interactions with G protein-coupled receptors are an area of active investigation, because most mediators involved in the inflammatory process signal through receptors of this class. We have shown that LAs inhibit signaling of several G protein-coupled receptors mediating inflammatory responses (lysophosphatidic acid1 and thromboxane A2), as well as m1 muscarinic acetylcholine receptors. Functional findings using lysophosphatidic acid and platelet-activating factor in Xenopus oocytes were confirmed in human neutrophils. One common target on several G protein-coupled signaling pathways is the coupled Gq protein. Selective knockdown of Gq eliminates LA sensitivity of lysophosphatidic acid signaling; knockdown of Go is without effect. We have shown that the signaling pathway downstream of the G protein is not involved in the LA effect. Inhibitory effects of the compounds on NHE are described elsewhere here. Interactions of LA with PKC signaling have been described, but very little specific information is available. This area clearly deserves further research.

Conclusions

Clear evidence exists, in vitro as well as in vivo, for antiinflammatory properties of LAs. Effects on PMN mediator and free radical release, as well as migration to the site of action, appear most important. The molecular mechanisms underlying these effects are poorly delineated. Of particular relevance is the difference in concentrations required to achieve effects on inflammatory cells in vitro versus much lower in vivo concentrations. Clinical use of LAS for the explicit purpose of modulat-
ing the excessive inflammatory response may be feasible. Treatment of ulcerative colitis with topical ropivacaine is one example. It seems possible that some of the beneficial effects of epidural administration of LAs (which leads to blood levels close to those attained after intravenous infusion) may be caused by antiinflammatory effects of circulating LAs. Effects on prolonged pain and hypercoagulation are examples. In those patients not able or willing to receive intra- or postoperative epidural analgesia, intravenous infusion of LAs could be considered in order to modulate postoperative inflammatory responses. In the setting of bacterial contamination, however, there is an increased risk of infection.

Further research should be directed primarily in two areas. First, we need to gain a detailed understanding of the mechanisms of action of LAs on the inflammatory system. Structure-function studies are particularly essential, because they can lead to the development of novel compounds. Second, more well-designed clinical studies should be performed, to assess whether the effects of LAs observed in cells and in animals also can be applied to clinical practice.

The authors thank Prof. Dr. med. E. Martin, Ruprecht-Karls-Universität Heidelberg, Germany, for his support and C. DiFazio, M.D., Ph.D., Professor of Anesthesiology, Department of Anesthesiology, University of Virginia Health Sciences Center, Charlottesville, Virginia, for critically reviewing the manuscript.

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