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Review Article

Anti-inflammatory properties of local anesthetics and their present and potential clinical implications

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Development of new local anesthetic agents has been focused on the potency of their nerve-blocking effects, duration of action and safety and has resulted in a substantial number of agents in clinical use. It is well established and well documented that the nerve blocking effects of local anesthetics are secondary to their interaction with the Na^+ channels thereby blocking nerve membrane excitability and the generation of action potentials. Accumulating data suggest however that local anesthetics also posses a wide range of anti-inflammatory actions through their effects on cells of the immune system, as well as on other cells, e.g. microorganisms, thrombocytes and erythrocytes. The potent anti-inflammatory properties of local anesthetics, superior in several aspects to traditional anti-inflammatory agents of the NSAID and steroid groups and with fewer side-effects, has prompted clinicians to introduce them in the treatment of various inflammation-related conditions and diseases. They have proved successful in the treatment of burn injuries, interstitial cystitis, ulcerative proctitis, arthritis and herpes simplex infections. The detailed mechanisms of action are not fully understood but seem to involve a reversible interaction with membrane proteins and lipids thus regulating cell metabolic activity, migration, exocytosis and phagocytosis.

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Key words: bacteria; cytokines; eicosanoids; herpes simplex virus; histamine; immune system; inflammation; leukocytes; local anesthetics; phagocytosis.

'. . .AN anesthetic is not a special poison for the nervous system. It anesthetizes all the cells, benumbing all the tissues, and stopping temporarily their irritability.' With these words, Claude Bernard anticipated already in 1875 (Leçons sur les anesthésiques et sur l'asphyxie) the fact that the membrane actions of anesthetics occur in both excitable and non-excitable membranes (1). Although most of us relate the use of local anesthetic agents to their nerve blocking properties, in which capacity they have served clinicians for over a century, accumulating data suggest that they also posses a wide range of other effects related to their membrane actions and equally interesting from a clinical perspective. The purpose of this review is to summarize the effects of local anesthetics on non-nervous tissue, particularly in connection with tissue damage and inflammation, and to discuss their mechanisms of action as well as present and future clinical implications.

General aspects on inflammation

Inflammation has been described as 'the stereotyped response of vascularized tissue to injury of any kind' (2) and 'a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissue' (3). The process may be triggered by neuronal stimuli, foreign agents and tissue damage, which will set off a cascade of cellular and humoral factors aimed at tissue defense, repair and restoration. However, in certain situations the inflammatory response tends to become 'over reactive' and harmful, causing tissue destruction and reduced function (4). Inflammatory signs have pathophysiological correlates characterised by a dilatation of arterioles, capillaries and venules inducing *rubor* (redness/erythema) and *calor* (heat). The early extravasation of plasma through the capillaries and post-capillary venules (5) will give rise to tissue swelling, *tumor*, and after a while pain, *dolor*, and functional disturbances, *functio laesa*. These changes correlate well with the production and release of proinflammatory substances in the inflamed tissues, many of which originate from the cells of the innate and adaptive immune systems, i.e. the granulocytes, monocytes, macrophages and lymphocytes (6). The cells of the

innate immune system are produced in large numbers when required and then released into the circulation. Upon reaching the endothelium affected by inflammation, the leukocytes marginate and slow down, 'roll', along the vascular lining, a process generally involving activation of selectins, integrins and ligands on the surface of leukocytes and the endothelium (Figs 1 and 2) (6, 7). Being a reversible event, rolling must be replaced by a strong adhesion of the leukocyte to the endothelium, a prerequisite for successful migration out of the bloodstream. In the process of firm adhesion, the leukocyte is stimulated by chemokines produced by the endothelial cells, increasing its activity of integrins, which brings about a tight adhesion of the leukocyte onto integrin ligands on the endothelial cell surfaces, i.e. intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM) (Fig. 1) (6–8). Some chemokines are constitutively produced but most are synthesized in response to agents or mediators such as bacterial endotoxins or primary inflammatory cytokines (e.g. lipopolysaccharide, TNF-α, inerleukin-1, monocyte chemotactic proteins, macrophage inflammatory proteins) with pronounced specificity as to recruitment of different subsets of leukocytes. Once the process of adhesion has been finalized, transendothelial leukocyte migration, *diapedesis*, starts (Fig. 2). The leukocytes begin to leave the bloodstream by passing through interendothelial junctions as a result of chemotactic stimulation and active interaction with molecules localized at the junctions, which open up for transmigration (2, 6). The subsequent movement of leukocytes in the extracellular matrix towards the inflammatory sites, *chemotaxis*, is further influenced by the combined actions of proinflammatory agents on the chemokine and cytokine receptors of the leukocytes, to a substantial degree produced by leukocytes having arrived earlier to the site of inflammation (Fig. 2) (9, 10). The mechanisms behind the chemotactic cell movements involve release of various chemotactic substances, such as leukotrien B4 (LTB_4) (11), interleukin-1 (IL-1) (12), IL-8 (CXCL8) (13) and substance P (14), which stimulate chemoattractant receptors coupled to G-proteins influencing in turn the actin cytoskeleton of the leukocyte and its movements (15, 16). The stimuli also prime

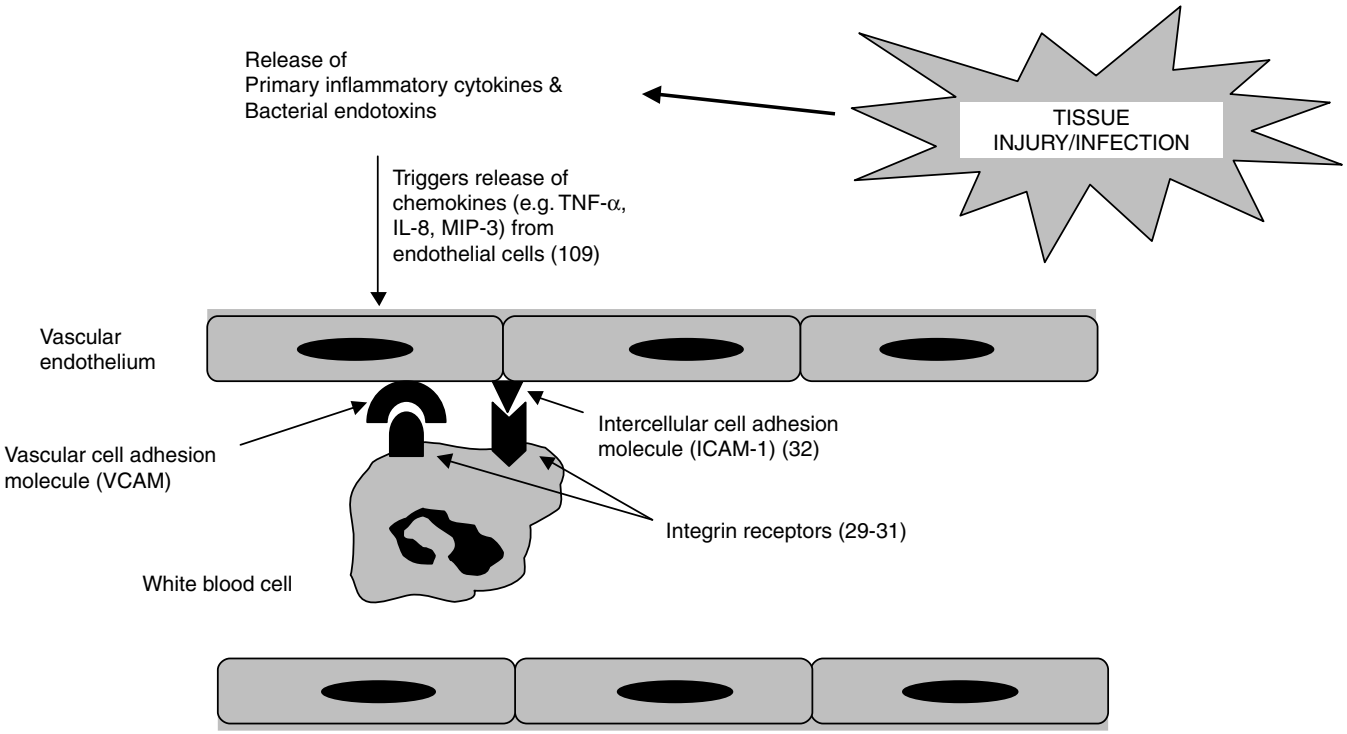

Fig. 1. Adhesion of leukocytes to the vascular endothelium is a prerequisite for succesful migration of immune cells from the blood stream to the injured/inflamed tissue. The process of adhesion involves release of chemokines from endothelial cells at inflammatory sites and a subsequent activation of integrins and adhesion molecules on leukocytes and endothelial cells. Numbers in parentheses () represent references showing an inhibitory effect by local anesthetics on specific molecules or processes. TNF, tumor necrosis factor; IL, interleukin; MIP, macrophage inflammatory protein.

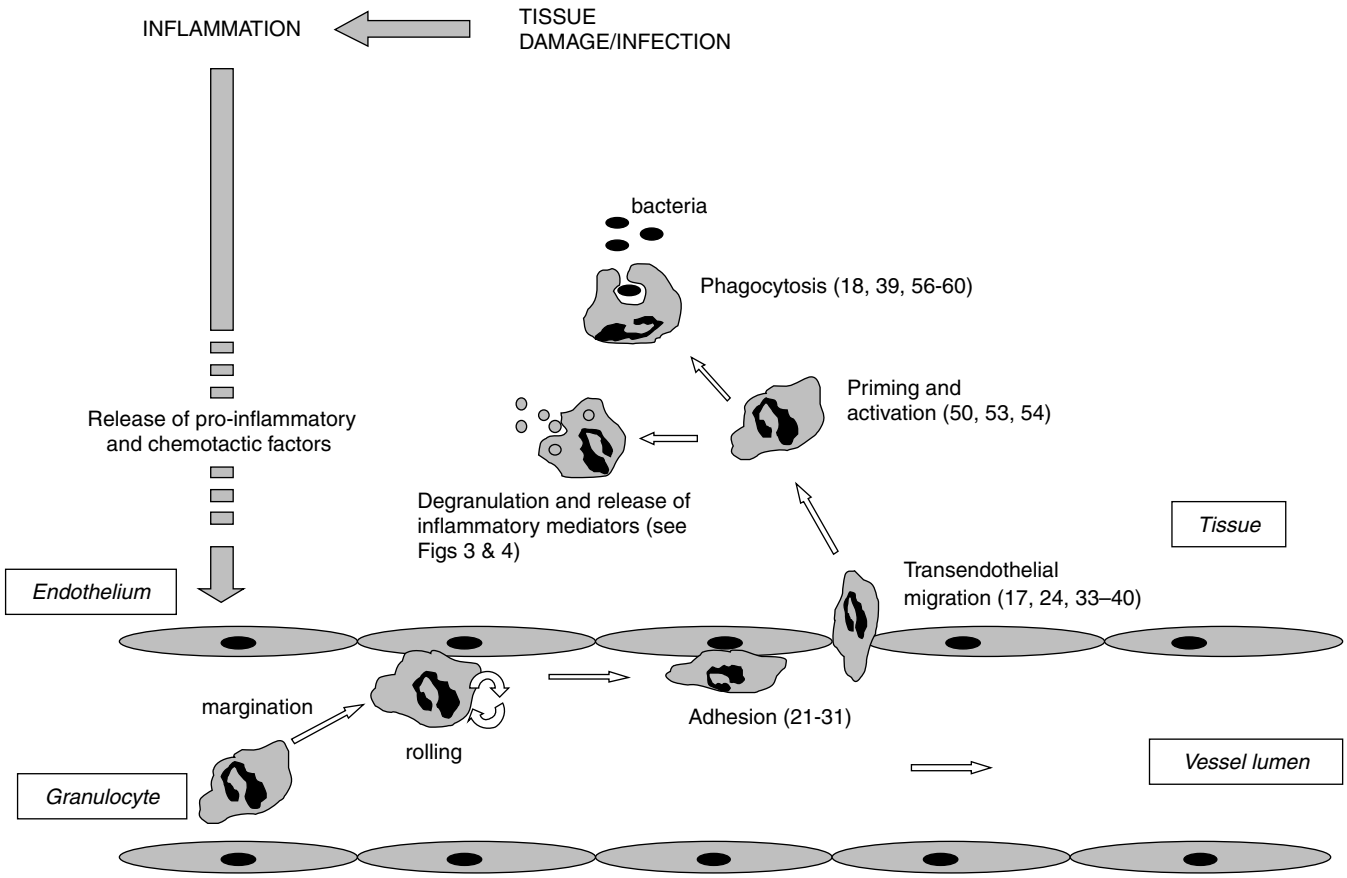

Fig. 2. Tissue injury will set off release of proinflammatory and chemotactic agents which will activate selectins, integrins and ligands in the area of inflammation leading to a slowing down of circulating leukocytes along the endothelium (rolling) followed by adhesion, extravasation and migration towards the injured/infected tissue area where immune cells are activated to initiate the process of phagocytosis of foreign agents and the release of various inflammatory mediators. Numbers in parentheses () represent references showing inhibitory effect by local anesthetics on specific process. PG, prostaglandin; TX, thromboxane; LT, leukotrien; 15-HPTE, 15-hydroperoxyeicosatetraenoic acid.

leukocytes to their phagocytic function and release of lysosomal enzymes, free radicals and various inflammatory mediators, aiming at the destruction, dilution, and digestion of both the injurious agents and the injured tissues and the subsequent restoration of tissue function and wound healing (Fig. 2).

Effects of local anesthetics on various steps of the inflammatory cascade

Leukocyte adhesion

Having arrived at the site of inflammation via the circulation, the leukocytes undergo the multi-step adhesion process described above and aimed at transferring the immune cells from the bloodstream to the tissues.

Several *in vitro* and *in vivo* studies have shown that local anesthetics dose-dependently and reversibly inhibit leukocyte adhesion to synthetic materials (17–20) and to blood vessel walls (Figs 1 and 2) (21–26). Using blood samples from patients receiving lidocaine infusions to treat arrhythmias, the authors found significantly reduced granulocyte adherence, suggesting that this inhibition can occur at plasma concentrations normally seen in clinical practice (24).

Several mechanisms accounting for the suppression by local anesthetics of leukocyte adherence to endothelial cells have been proposed. Sodium channels responsible for the nerve blocking actions of local anesthetics were ruled out because another potent blocker of sodium conductance, tetrodotoxin, lacked effect on leukocyte adhesion (27). Local anesthetic-induced release of prostacyclin from the endothelium could constitute part of the mechanism as both lidocaine and prostacyclin, when applied locally, can cause release of leukocytes previously firmly adherent to vascular endothelium (28). Recent studies have suggested that local anesthetics inhibit leukocyte adhesion to the endothelium by interfering with the actions of integrins (29–31) and leukocyte adhesion molecule-1 (29, 32) (Fig. 1).

Leukocyte migration

The endothelium, which in the resting state forms an effective barrier to the passage of cells from the circulation and into the surrounding tissues, undergoes a dramatic permeability transformation during an inflammatory response and becomes the main gateway for the exit of blood constituents and fluid. This transformation is preceded by changes in the adhesive properties of the endothelium, which is normally non-adherent to the cellular components of the bloodstream, allowing blood-borne leukocytes to adhere and subsequently begin the process of diapedesis in which the leukocyte extends itself by a pseudopod through small gaps in the junctions between apposing endothelial cells (6), a process requiring disassembly of the cytoskeleton on the apical surface and reassembly on the abluminal side of the endothelium (2) (Fig. 2).

Several studies have confirmed the dose-dependent inhibition of normal random motility of leukocytes both *in vitro* and *in vivo* by a wide range of local anesthetic agents (17, 33–38) (Fig. 2). This inhibition is reversible in nature and without interference with cell viability (36). The concentrations of local anesthetics required to induce inhibition of leukocyte locomotion are in the range normally achieved in clinical practice as suggested by an *in vivo* study showing that the delivery of granulocytes into peritonitis exudates was markedly inhibited by intravenous lidocaine infusions (24). Similarly, lidocaine was shown to inhibit the migration of leukocytes into synovial fluid in crystal-induced arthritis in dogs *in vivo* (39) as well as the infiltration of granulocytes into the tissue in experimental colitis in rats *in vivo* after subcutaneous or intrarectal administration of lidocaine (40). Several investigators have linked the inhibitory actions of local anesthetics on leukocyte mobility to their effects on the cytoskeleton (41–47) which have also been confirmed in a variety of other cell types, such as keratinocytes, erythrocytes, platelets, muscle cells, fibroblasts, nerve cells and tumor cells, also confirming the reversible nature of the inhibition. Another, indirect route, by which local anesthetics may interfere with leukocyte mobility, is by attenuating the release of chemoattracting agents from leukocytes (38, 48).

Activation and priming

Neutrophils are activated and primed by a variety of endogenous and exogenous agents, such as bacterial lipopolysaccharide (LPS), granulocyte/macrophage stimulating factor, tumor necrosis factor (TNF-α), IL-8 and platelet aggregating factor (PAF) (49, 50). The priming process is aimed at significantly boosting the activation of neutrophils and their release of tissue toxic mediators, such as superoxide anions (51) and lipid mediators (52), thereby improving the immune systems ability to take out agents that have previously been identified by the system (49). Local anesthetics may interfere with the priming process by inhibition of protein kinase C (PKC)/phospholipase C (PLC) (Fig. 3) (50, 53), probably within the Gq-coupled signaling pathway (50). The effects of local anesthetics may also involve inhibition of phospholipase D (PLD) (54), which plays an important role in the regulation of leukocyte functions of phagocytosis, degranulation and oxidant production. The actions of local anesthetics on PLD could be either by preventing the membrane translocation of PLD-activating factors and/or by direct inhibition of the enzyme (54).

Phagocytosis

Phagocytosis is the principal way by which neutrophils execute the destruction of invading microorganisms as well as the ingestion of over-aged cells and cellular debris. Particle internalization is initiated by the interaction of specific receptors on the surface of the phagocyte with ligands on the surface of the particle. This leads to the polymerization of actin at the site of ingestion, and the internalization of the particle via an actin-based mechanism involving the formation of a phagocytic cup culminating in the formation of the mature phagolysosome. Because endosome/lysosome trafficking occurs primarily in association with microtubules, phagosome maturation requires the coordinated interaction of the actin- and tubulin-based cytoskeletons (55).

Local anesthetics induce a dose-dependent and reversible inhibition of granulocyte phagocytosis (Fig. 2) (18, 56, 57). Systemic intravenous administrations of lidocaine in doses recommended for antiarrhythmic treatment (39) significantly reduced phagocytic activity of leukocytes sampled from the synovial fluid of knee joints with synovitis. Surprisingly, the novel local anesthetic ropivacaine was reported to exert weak or no effects on granulocyte phagocytic activity (53, 58), as opposed to other local anesthetic agents. The currently most plausible mechanism to account for the inhibition induced by local anesthetics on leukocyte phagocytic activity is by impairment of leukocyte surface receptor expression (59) and inhibition of actomyosin filament activity (60).

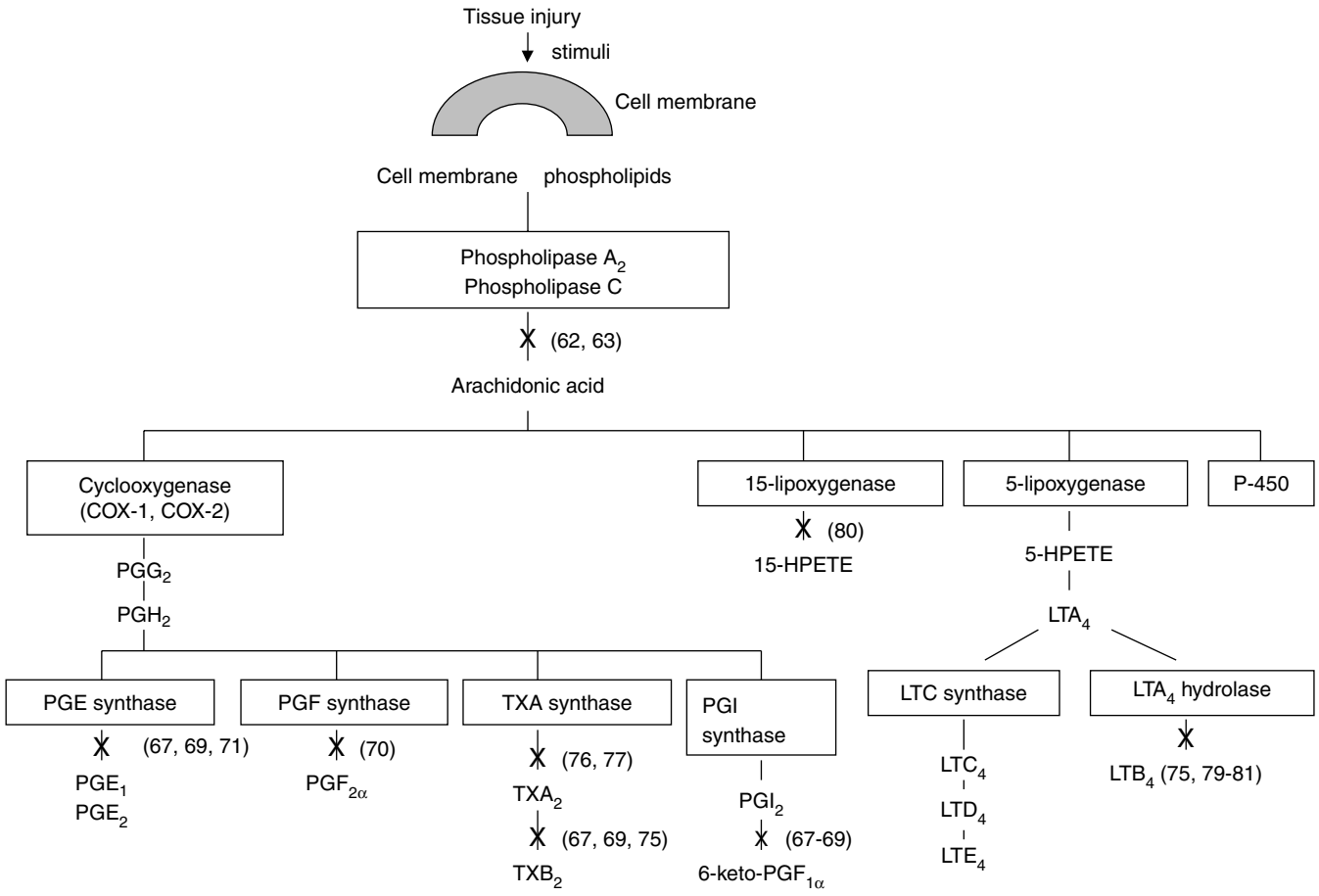

Fig. 3. The arachidonic acid cascade plays a major role in the inflammatory processes taking place in the sequel of a tissue injury. Local anesthetics have been shown to induce inhibition (references in parentheses) at various steps in the cascade.

Effects of local anesthetics on synthesis and release of inflammatory mediators

Eicosanoids

Release of arachidonic acid from membrane phospholipids by the action of the enzyme phospholipase A_2 (PLA_2) and its oxygenation by the enzymes cyclooxygenase and lipoxygenase to generate bioactive eicosanoids represent an important series of events that is thought to play a pivotal role, both in the regulation of physiologic organ function and pathologic responses to tissue damage (61). Several local anesthetics have been shown to interact in a dual fashion with PLA_2 (Fig. 3) as suggested by results showing that low concentrations of the agents induced a slight stimulation of PLA_2 activity, while higher concentrations inhibited the enzyme (62). Other investigators showed that some local anesthetic agents (procaine and lidocaine) were able to inhibit pancreatic PLA_2 at a very low surface concentration, while other local anesthetics (tetracaine, butacaine and dibucaine) required rather high concentrations (63). The authors suggested that a correlation exists between the nerve-blocking potencies of the agents and the inhibition of PLA_2 (64).

Prostaglandins

Early *in vitro* studies have shown several local anesthetics too possess inhibitory effects on spontaneous prostaglandin biosynthesis (65, 66), an inhibition that increases with lower pH, suggesting an action primarily by the ionized forms of the agents (62). Lidocaine administration significantly inhibited prostanoid (PGI_2/6-keto-PGF1-α) release from incubates of human gastric mucosa (67) as well as prostanoid biosynthesis in response to experimental damage (68, 69) (Fig. 3). A significant inhibition of $PGF_{2\alpha}$ release into the circulation was seen during systemic administration of lidocaine in dogs with cardiac arrhythmias (70). In a recent study using a technique allowing for the *in vivo* analysis of inflammatory mediators released post-burn (71), a potent inhibition of PGE_1 and PGE_2 release was

demonstrated when treating the burned skin in the intact animal with a topical local anesthetic cream (71), thus confirming an earlier report showing reduced PGE release from isolated pieces of gastric mucosa by lidocaine (67) (Fig. 3). These inhibitory effects on PGE, known to play a significant role in the mechanisms responsible for inflammatory pain, could account for some of the potent analgesic effects of intravenous lidocaine reported in burn patients (72, 73) and in patients having undergone surgery (74).

Thromboxanes

Several *in vivo* and *in vitro* studies revealed that the local anesthetics significantly inhibited thromboxane B2 (TXB_2) release (Fig. 3) (67, 69, 75). In a study investigating the effect of bupivacaine on the coagulation of human whole blood, the authors were able to demonstrate that the agent prolonged clotting time in clinically relevant concentrations and that this effect, at least in part, was mediated by inhibition of TXA_2 signaling (76). Others confirmed the inhibitory effect of lidocaine, ropivacaine and bupivacaine on TXA2-induced platelet aggregation, although higher doses of the local anesthetic agents were required (77). The inhibitory effects of local anesthetics on thromboxane synthesis probably contribute to their suppressive effects on platelet aggregation (76) and the reduced incidence of deep venous thrombosis (78).

Leukotrienes

Local anesthetics have been shown to induce inhibition of LTB_4 release from activated human granulocytes and monocytes (Fig. 3) (79, 80). In a recent *in vivo* study, topical administration of lidocaine-prilocaine cream induced a pronounced inhibition of LTB_4 release from a full-thickness burn injury of rat skin (75). Because leukotriens have been shown to play an important role in the promotion of inflammation-induced plasma extravasation (81), the above effects of local anesthetics on leukotrien synthesis could be part of their inhibitory effects on edema formation in various inflammatory conditions (82–84).

Histamine

Histamine is synthesized and released by human basophils, mast cells, and neutrophils. Increasing evidence suggest that, in addition to exerting immediate vascular and bronchial responses, histamine might modulate the immune reaction by interacting with T cells, macrophages, basophils, eosinophils, and monocytes (85).

Histamine release from mast cells is effectively and dose-dependently inhibited by lidocaine at concentrations below those used for infiltration anesthesia (Fig. 4) (86). In agreement, latter investigators showed that low concentrations of lidocaine or mepivacaine induced a potent inhibition of histamine release from activated mast cells and that this inhibition increased with higher pH of the medium suggesting it to be primarily mediated by the non-ionized molecules of the local anesthetic agents (87).

Oxygen free radical production

When neutrophils arrive at the site of inflammation, they phagocyte and degrade substances such as bacteria, pathogens, and remnants of damaged tissue. The degradation process is the result of both oxygen-independent mechanisms, which digests bacterial proteins by the action of the enzyme elastase, and oxygen-dependent mechanisms requiring the presence of superoxide anions (88–90).

The inhibition of leukocyte metabolic activity and superoxide anion formation by local anesthetics has been convincingly documented over the years (Fig. 4) (26, 29, 35, 36, 50, 56, 58, 59, 79, 91–100) and shown in several studies to be dose-dependent (34, 56, 98, 101, 102) as shown in clinical studies involving patients with coronary artery disease (103) and diabetes (104) and treated with intravenous lidocaine infusions.

The direct scavenging effects of local anesthetics have been attributed to various mechanisms of action. There is evidence to suggest that once local anesthetics penetrate into the cell membranes, they interact with membrane lipids and proteins to quench oxygen and nitroxide free radical formation (105) or interfere with the Ca^{2+}-induced increase in mitochondrial radical formation (53, 106).

Cytokines

Cytokines produced by the cells of the innate immune system can profoundly influence various steps of the inflammatory response, e.g. phagocytosis, chemotaxis and oxidative metabolic activity (107).

The release of IL-1 by activated human monocytes was dose-dependently inhibited by lidocaine and bupivacaine (Fig. 4) (79). In a study investigating the release of inflammatory mediators after acute lung injury induced by hyperoxia, pre-treatment with an intravenous lidocaine infusion in clinically relevant concentrations, significantly attenuated the release of cytokines (IL-1β, TNF-α) from the injured lung along with reduced influx and metabolic activation of neutrophils (Fig. 4) (108). Several local

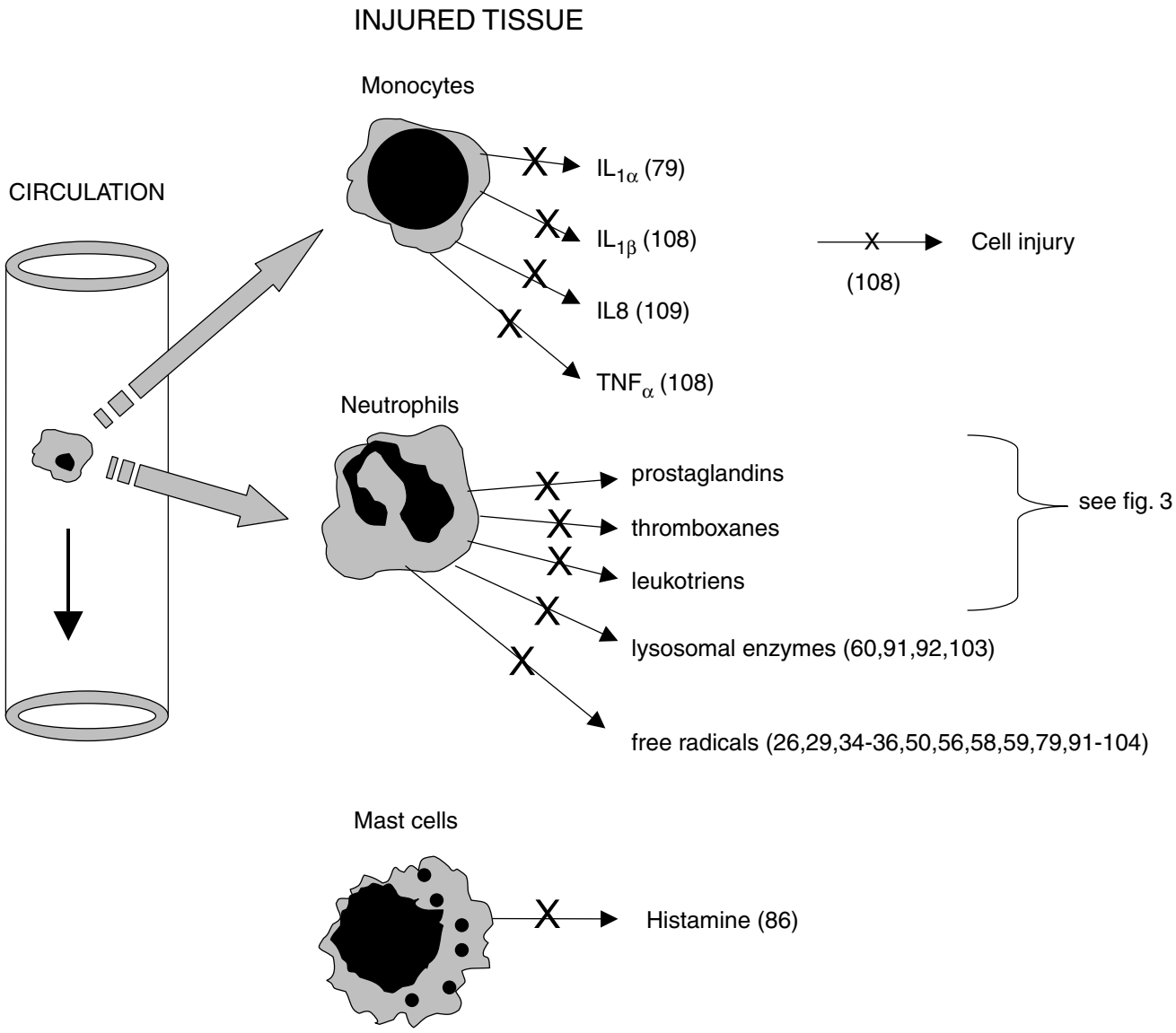

Fig. 4. The extravasation and migration of immune cells from the circulation into the area of injury is followed by activation and release of a large number of potent mediators. The figure illustrates inhibition (X) by local anesthetics of immune cell release of mediators. TNF, tumor necrosis factor; IL, interleukin.

anesthetics (lidocaine, bupivacaine, amethocaine) have been shown to dose-dependently inhibit both the spontaneous and the TNF-α-induced secretion of IL-8 and IL-1β (Fig. 4), whereas lidocaine also proved stimulatory on the secretion of the anti-inflammatory molecule IL-1 RA. The authors ascribed both the inhibitory and stimulatory effects of lidocaine to a possible effect on the regulation of transcription (109). The possible role of local anesthetic agents on cytokine-induced vascular cell injury was recently presented in a study investigating, by use of trypan blue exclusion and lactate dehydrogenase (LDH) release, the survival of rat vascular smooth muscle cells and human microvascular endothelial cells exposed to cytokines (IL-1β, TNF-α, interferon-γ) and pre-treated with lidocaine or tetracaine. Lidocaine, but not tetracaine, was shown to attenuate cytokine-induced cell injury and increase cell survival in both cell types in a dose-dependent manner (110).

Lysosomal enzymes

Granule exocytosis by immune competent cells is a complex process involving membrane signaling that includes Ca^{2+} influx and activation of protein kinase C, fusion of lysosomal vesicles with cell membrane and subsequent release of lytic contents at the site of contact with intruder. This process is, at least in

part, dependent on a functional actin cytoskeleton (111). Several authors were able to demonstrate a dose-dependent inhibition by local anesthetics of the release of lysosomal enzymes, from activated polymorphonuclear leukocytes (Fig. 4) (35, 91, 92, 103). This inhibition is reversible and dose-dependent (60) and most probably mediated by inhibition of the actin microfilaments, being the prerequisite for the fusion between lysosomal vesicles and the cell membrane (91).

Effects on vascular hyperpermeability and edema formation

Local anesthetics have been shown to be potent inhibitors of inflammation-induced edema formation in various conditions. A pronounced inflammation has been shown to take place in the wall of the obstructed small intestine and to be the primary cause for the profuse fluid losses seen with this condition (112). Lidocaine aerosol (20 mg) applied on the serosal surface of the obstructed gut induced a marked inhibition of fluid losses into the intestinal lumen parallel to reduced edema in the gut wall (113). Topical application of lidocaine-prilocaine cream on the burned skin, reduced plasma extravasation to the level of non-burned control animals (114, 115), whereas intravenous lidocaine infusions proved less potent (116). After exposing the colonic peritoneum to hydrochloric acid *in vivo* and subsequently treating it topically with lidocaine or bupivacaine, the resulting edema was significantly inhibited as compared with saline-treated controls (82). Capsaicin-induced extravasation of dextran in the lower airways of guinea-pigs was effectively reduced by topical lidocaine pre-treatment, whereas the mucosal blood flow was unaffected suggesting an action directly on the permeability-regulating endothelial cells rather than on flow regulating pre-capillary resistance vessels (117, 118).

The effects of the local anesthetics on inflammation-induced capillary hyperpermeability could be related to a number of their actions, such as reduced release of histamine from macrophages (86), inhibition of LTB_4, cytokines, and oxidant release from activated granulocytes (79), increased synthesis of prostacyclin (119) and inhibition of the endothelial cell cytoskeleton (120).

Inflammation-related effects

Lung injury

Neutrophils are thought to play a pivotal role in the pathogenesis of lung injury through the release of free radicals, proteases and lysosomal enzymes. This has attracted investigators to test the potential effects of local anesthetics in the treatment of lung injury. Several local anesthetics have been shown to diminish thiourea-induced lung injury in rats as shown by reduced extravasation of radiolabeled protein (121). Similar observations were obtained in reperfused rat lungs, showing that the local anesthetics inhibited lung edema parallel to reduced synthesis of cyclooxygenase products, normally elevated during reperfusion (122). Pre-treatment of *Escherichia coli* endotoxin-induced lung injury with an intravenous infusion of lidocaine (2 mg/kg/min) significantly attenuated lung edema, leukocyte counts and the release of various inflammatory mediators (84, 123). In a study in dogs investigating the effect of lidocaine on the allotransplanted lung, authors showed significantly improved gas exchange paralleled by reduced leukocytes and myeloperoxidase in bronchoalveolar fluid (30). Lidocaine infusion in a clinically relevant concentration was further shown to have a prophylactic effect on hyperoxic lung injury as shown by reduced lung edema and tissue biochemical and histopathological changes (108). Similar results were obtained in a study investigating HCl-induced lung injury in rabbits and showed reduced morphologic and histologic damage in the lidocaine-treated group (124). Acute severe pancreatitis is often associated with acute lung injury possibly by the action of pancreatic enzymes. In a study investigating the effect of pre-treatment of pancreatic enzyme-induced lung injury with lidocaine, the author reported an attenuation of lung injury (125). In bleomycin-induced acute lung injury, lidocaine was able to inhibit the granulocyte colony-induced exacerbation of lung injury and the subsequent lung fibrosis (126). Moreover, lidocaine in a dose of 5 mg/kg significantly attenuated lung edema in the isolated post-ischemic rat lung (127) and significantly reduced HCl-induced acute lung injury when added to the surfactant fluid (128).

Septic shock

In a series of experiments, Fletcher and collaborators studied the effect of lidocaine treatment in different shock models. Intravenous lidocaine infusion at 1 mg/kg/min starting before and lasting 2 h after *E.* coli-induced endotoxin shock, significantly improved survival in dogs (129) and baboons (130, 131), despite that no significant effects on hemodynamic parameters were noticed. The beneficial effects of lidocaine were proposed by the authors to be in part mediated by the agent's effects on eicosanoid

synthesis (132). In a recent study in endotoxemic rats, lidocaine infusion (2 mg/kg/min) was also able to attenuate leukocyte-endothelial adhesion, capillary extravasation (25) and sepsis-induced diaphragmatic dysfunction in hamsters (133). In contrast, lidocaine failed to improve survival when administered as a bolus injection after *E. coli*-induced septic shock in rats (134). Lidocaine was also shown to increase the severity of hypoglycemia and lactic acidosis, although it improved glucose utilization and hepatic pyruvate extraction in septic pigs receiving a continuous intravenous infusion at 2 mg/kg/min (135, 136). In another study investigating the effects of lidocaine infusion (6 mg/kg/min) on septic shock in dogs, the authors reported that lidocaine did not alter hemodynamic variables but induced metabolic acidosis and hypoalbuminemia (137).

Myocardial ischemia

Lidocaine and related local anesthetic agents have been shown to protect against myocardial injury associated with permanent regional ischemia (138, 139), and global (140) or regional ischemia-reperfusion (141–143). Lidocaine also proved beneficial in reducing the size of a myocardial infarction when combined with adenosine treatment (144) or when given alone (145). The beneficial effects of lidocaine could be mediated by the inhibitory effects of the agents on leukocyte recruitment and activation, since mycordial ischemia, and particularly reperfusion injury, is associated with increased neutrophil recruitment and production of free radicals (146). Moreover, agents attenuating leukocyte accumulation have been shown to reduce infarction size (147). In support, lidocaine has been reported to reduce the release of lipid peroxidation products from ischemic-reperfused myocardium (141) and to prevent ion movements associated with tissue damage (140).

Antimicrobial effects

Antibacterial effects

As early as the beginning of this century, several of the local anesthetics used for spinal anesthesia (stovaine, tropacocaine, novocaine) were proposed to possess antibacterial activity (148). Ensuing studies have revealed significant variations in the potency and range of bacterial strains inhibited by the agents, significant dose and structure-dependent differences, pH and temperature variations, as well as differences between individual studies using the same agents (149). In the following, the most significant findings and contradictions will be presented. The observations made by Jonnesco (148) were followed by a number of reports showing that local anesthetics used in ophthalmologic practice inhibited conjunctival flora (150–154). The wide-spectrum antimicrobial actions of most local anesthetics have since been documented by a significant number of publications (58, 153, 155–159, 160–169, 170–179). A number of key references and their effects have been summarized in Table 1.

Accumulating data clearly show that the antimicrobial potency of local anesthetics is primarily related to the concentration of the agent and to a lesser extent to its structure as most local anesthetics, both ester and amide type, can subdue most bacteria in high enough concentrations (180). However, one exception to the rule has emerged, namely ropivacaine. This solitary pure enantiomer (S-form), which has been proven to have weak or no antibacterial actions in clinical concentrations (181–183), has triggered a discussion of whether its use may increase the risk of inadvertent intravascular or intrathecal infections (184, 185). Because ropivacaine also has been proven to be a poor inhibitor of the immune response of granulocytes to foreign agents (58), including bacteria, one could argue that this may compensate for the lack of direct antibacterial effects. Whether these properties of ropivacaine do represent an increased risk for the patient or not will emerge from additional studies addressing the current issue. What is obvious at this stage is that the antibacterial effects of local anesthetics not only depend on the length of the alkyl chain ($-CH_3$) (186), but also on the racemic configuration of the agents with higher potency for the R-isomer over the levoform (187) and poor effects by the S-enantiomer.

The precise antibacterial mechanisms of action are still unclear, but could be related to the interaction of local anesthetics with the bacterial wall (163) or with macromolecules at the cellular surface of bacteria (188). Such electrostatic interactions between cationic local anesthetics and anionic membrane components could induce functional changes by alteration of membrane proteins (189, 190) and by reducing membrane fluidity (191). As a result, various membrane and cell functions (192), such as membrane-bound ATPase activity (193) and the DNA binding properties of the cell (194) may be inhibited. Interestingly, local anesthetics were also reported to potentiate the sporocidal activity of other agents (174) and to enhance the MIC values of several antibiotics up to 10-fold in concentrations lower than those used clinically (195).

Table 1

Summary of the most important inhibitory actions of local anesthetics on various strains of bacteria

Bacterial strain	Local anesthetic	Concentration	Reference
Pseudomonas aeruginosa	Tetracaine	0.5%	152
	Lidocaine	0.25–1%	168
	Procaine	0.5%, 0.25%	155
	Tetracaine	0.5%, 0.25%	155
	Cocaine	4%	155
	Lidocaine	4%	183
E. coli	Bupivacaine	0.5%	165, 180
	Lidocaine	1%, 2%	181
S. aureus	Lidocaine	4%	183
	Bupivacaine, ropivacaine		57
	Bupivacaine	0.5%	165
	Lidocaine	2%	169
	Various		159–161, 170–172
H. influenzae	Lidocaine	4%	183
	Various		162, 163
M. tuberculosis	Various		159–161, 164
S. pneumoniae	Lidocaine	4%	183
	Various		173
S. epidermidis	Bupivacaine	0.5%	165
Campylobacter pylori	Benzocaine		179
Chlamydia trachomatis *Neisseria gonorrhoeae*	Various		175, 176

For additional details see review by Batai et al. (149).

Antiviral effects

In an early study investigating the effects of several local anesthetics (dibucaine, tetracaine, cocaine, lidocaine, and procaine) on bovine kidney cell fusion induced by the herpes simplex virus, the authors reported that all local anesthetic agents induced a significant inhibition of cell fusion in physiologically relevant concentrations and without impairing virus replication. The authors proposed that the local anesthetics exert this inhibition by occupying sites within the plasma membrane, which must be vacant in order for virus-induced membrane fusion to occur (196). In another study (120), the authors suggested that the cell fusion induced by viral infection was related to digestion of the cell surface coat by lysosomal enzymes, and that inhibition of ATPase would prevent fusion. Free radicals have also been shown to play a role in viral cytopathicity as suggested by results showing that the scavenger superoxide dismutase (SOD) was able to protect mice from the lethal influenza virus (197). These infective mechanisms could account for some of the antiviral effects of local anesthetics, as the agents possess the ability to inhibit membrane ATPase (198) as well as the release of lysozymes (35) and free radicals (58). In a study investigating the mechanisms behind local anesthetic-induced inhibition of cell infection caused by vesicular stomatitis virus and other viruses (199), the authors showed the inhibition to take place prior to both primary and secondary RNA transcription but following transfer from the cell surface to an intracellular site, presumably the lysosomes. In a double-blind, placebo-controlled crossover study in patients with verified herpes simplex virus (HSV-1 and HSV-2), administration of a topical local anesthetic cream (lidocaine/prilocaine) in the prodromal stages of the infection resulted in 50% abortion of eruptions and significantly reduced the duration of subjective symptoms and eruptions (200). In accordance, the infectivity of HSV-1 was markedly reduced by treating virions with local anesthetics (lidocaine, dibucaine and tetracaine), possibly by interaction with the physicochemical properties of the virus envelope (201) or by inhibition of viral replication, although this effect was largely dependent on the presence of epinephrine (202).

Antifungal effects

Several local anesthetic agents, including lidocaine, tetracaine, prilocaine and procaine, have been shown to inhibit the growth of *Candida albicans* (151, 169). In a recent study investigating the effect of lidocaine and bupivacaine on 20 Candida strains,

lower concentrations of the agents were found to have fungistatic effects due to yeast metabolic impairment, while higher concentrations were fungicidal, due to direct damage to the cytoplasmic membrane (203). The inhibitory effects of lidocaine, bupivacaine and ropivacaine on germ tube formation by *C. albicans* were suggested to be dose-dependent but not pH-dependent and secondary to blockade of ionic channels, particularly calcium channels (204). Structure-related differences were demonstrated in a study showing ropivacaine to lack antifungal effects on *C. albicans*, with improved effects for bupivacaine and more powerful effects by lidocaine and prilocaine (182). Local anesthetics have also been proven to have fungal sporicidal effects, the potency of which is agent and temperature-dependent (174).

Discussion

General aspects

The first local anesthetic substance in regular clinical use was the ester-type local anesthetic *cocaine*, isolated by Niemann in 1860. The agent became widely used to relieve pain until *procaine* was synthesized by Alfred Einhorn in 1904, being the dominating local anesthetic agent until its era was ended by the synthesis of the first representative of a new group of local anesthetic agents of the amide-type, *lidocaine*, by Löfgren in 1943. Development of new local anesthetic agents has since focused on the potency of their nerve-blocking effects, duration of action and safety and resulted in a substantial number of agents, many of which are currently in clinical use. It is well established and well documented that the nerve blocking effects of local anesthetics are secondary to their interaction with the Na^+ channels thereby blocking nerve membrane excitability and the generation of action potentials. However, accumulating data suggest that local anesthetics also affect K^+ and Ca^{2+} channels and act on intracellular mechanisms at clinically relevant concentrations (205). The wide range and variability of effects induced by local anesthetics on many aspects of activation and response by cells of the immune system, as well as effects on other cells (e.g. microorganisms, thrombocytes and erythrocytes), suggest a more 'global' common pathway of action then simply interaction with Na^+ channels. In his extensive review of the mechanisms of action of local anesthetics, Philip Seeman (206), proposed that local anesthetics 'fluidize and disorder' components within the cell membrane and consequently stimulate or inhibit membrane-associated enzymes and proteins. Current knowledge lends support to Seaman's conclusions that the agents influence a number of important aspects of membrane function, by inducing reversible conformational and functional alterations of the cell membrane. The detailed mechanisms of action are not fully understood but seem to involve interaction with membrane proteins (189, 190) and lipids (207), thus interfering with the function of neighboring ion channels (208), as well as membrane-bound enzyme activity (209) and the cytoskeleton of the cell (60), involved in migration, exocytosis, and phagocytosis. The literature in this area reveals great similarities with respect to the anti-inflammatory and antimicrobial effects of almost all local anesthetic agents, esters and amides alike. Differences in action between individual agents and between groups of agents are overwhelmingly related to differences in potency of action rather than to the nature of action, and by sufficiently increasing the concentration of a local anesthetic, the inhibitory effects will be achieved independent of structure. As discussed above, there is one exception to the rule and that is ropivacaine, which is the first enantiomerically pure local anesthetic of the S-form. Ropivacaine stands out as an agent with weak and, in some cases, complete lack of anti-inflammatory properties (53, 58, 80, 210, 211) and antimicrobial actions (181–183) characteristic of other local anesthetic agents. These differences have prompted researchers to question the clinical potential of ropivacaine in the treatment of inflammatory conditions (211) and point to the risk of inadvertent intravascular or intrathecal infections when using the agent (184, 185). The structural differences between ropivacaine and other local anesthetic agents could perhaps shed some light on the identity of the structures, which enable local anesthetics to exert their broad-spectrum anti-inflammatory and antimicrobial effects.

Clinical implications

Inflammation forms an important part of the pathophysiology of various diseases/conditions, be they related to ischemia, trauma, immunologic disorders or other mechanisms. Although the inflammatory response is a prerequisite for survival in a hostile surrounding, it may at times be exaggerated and inflict additional damage to the affected tissues, jeopardizing their recovery, and in some cases the survival of the individual. Being able to fine-tune the inflammatory reaction without undermining the defensive and reparative functions and with a

minimum of side-effects is highly desirable and could partly be achieved by use of traditional anti-inflammatory agents, e.g. NSAID and steroids. The spectrum of untoward effects characteristic of the latter agents has prompted a search for other anti-inflammatory agents with fewer adverse effects. Substantial evidence has accumulated to support the broad anti-inflammatory properties of local anesthetics, which in some cases may exceed in potency the actions of traditional steroids (24). Although the bulk of data regarding these effects is based on experimental *in vitro and in vivo* studies, clinical studies are emerging to support the potent anti-inflammatory effects of local anesthetics in various clinical conditions.

Local anesthetics are extensively used for analgesic purposes by infiltration into the skin and subcutaneous tissues as well as into joints and the abdominal cavity during laparoscopic surgery. A question which arises is to what extent they exert their potent anti-inflammatory actions in association with such procedures and whether this is beneficial or deleterious to the patient. Experimental studies have clearly shown that instillation of local anesthetics on the abdominal peritoneum can subdue the pronounced inflammatory response to an irritant (hydrochloric acid) (82) and that infiltration of a local anesthetic in a surgical wound will inhibit the migration of leukocytes into the wound and their subsequent release of tissue toxic agents (36). After administration of topical lidocaine in the surgical wound of patients having undergone herniorraphy (212), the authors were unable to detect adverse effects on wound healing 6 months after surgery (213). The studies showing that lidocaine accelerates re-epithelialization (214) and improved wound healing (215) are indicative of a favorable effect. Another interesting aspect is the inhibitory effect of most local anesthetics on a wide range of bacterial strains (149) (Table 1). This could perhaps explain the low incidence of infections reported after administration of local anesthetics into the epidural and spinal cavities of patients.

Interstitial cystitis is a condition characterized by a severe inflammatory reaction in the cystic wall of undefined etiology, but frequently associated with accumulation of mast cells in the detrusor muscle. The symptoms are often severe and disabling, with urinary frequency, urgency and pain (216). Repeated daily instillations of 200 mg lidocaine into the bladder during 2 weeks, was shown in a case report to induce a long-lasting inhibition of edema, ulcerations and mast cell infiltration of the bladder wall, along with improved clinical symptoms (217). In two consecutive studies investigating the effects of intrarectally administered lidocaine gel 2% at a total dose of 800 mg daily during several weeks in patients suffering from ulcerative proctitis (218) or ulcerative colitis (219), the authors were able to show remission of symptoms in a great number of patients paralleled by improved histological and gross appearance of the mucosa. In an open study investigating the effect of 200 mg ropivacaine gel given rectally twice daily during 2 weeks to patients with distal ulcerative colitis, the author reported significant improvement of mucosal inflammation, and paradoxically, an increase in clinical symptoms, such as the number of stools and blood in stools (220). In a recent double-blind and placebo-controlled clinical investigation of patients with distal ulcerative colitis, investigators failed to show any significant inhibition of eicosanoid release from rectal dialysates and several other inflammatory mediators from the rectal mucosa after a single rectal dose of ropivacaine gel (211), which led the authors to question the relevance of using ropivacaine in the treatment of ulcerative colitis.

Major burn injuries are widely recognized to engage most aspects of the immune system and to trigger a pronounced and often exaggerated activation of the inflammatory cascade. Experimental *in vivo* studies in the rat have shown that local anesthetics, both when administered topically(lidocaine-prilocaine cream) and as systemic infusions of lidocaine, induce significant inhibition of burn edema (114–116) and improve blood flow in the burn injury (221). These results were confirmed in latter studies showing that application of a topical lidocaine-prilocaine cream (222) and intravenous lidocaine infusions (40 μg/kg/min) (223) in experimental superficial partial-thickness skin burns in human volunteers, significantly reduced inflammation up to 12 h post-burn as measured by non-invasive digital image color analysis. Because release of pain-inducing inflammatory mediators is a major cause for the severe pain often encountered in burn patients, the above data could offer a rationale for the potent analgesic effects reported in burn patients receiving continuous intravenous infusions of lidocaine at therapeutic doses (72). In a recent case report relating to a patient with a major burn injury, the authors showed that during the initial 48 h post-burn when the patient received a lidocaine infusion, he reported no pain and required no additional analgesics, whereas after ceasing with the infusion, analgesic requirements dramatically increased and ranged from 200 to 600 mg morphine/day during the subsequent 10 days (73).

An estimated 95–98% of the population in the western hemisphere is believed to have antibodies against herpes simplex virus (HSV). Despite being so widespread, we currently lack effective treatment against this life-long infection affecting all categories of the population. In a blinded cross-over study in individuals with clinically manifest recurrent HSV-1 and HSV-2 infection, repeated topical application of lidocaine-prilocaine cream in the prodromal stages of the infection proved to abort 50% of infective episodes and significantly reduce the duration of eruptions and symptoms (200).

In conclusion, although a relatively limited number of inflammatory conditions/diseases have been subject to treatment by local anesthetics in clinical practice, our current understanding and future insights into the mechanisms responsible for the wide range of inhibitory effects by the agents on the inflammatory cascade, may form a platform for the creation of future drugs or treatments of inflammation.

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