



Review

Molecular mechanisms of lidocaine

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ABSTRACT

Lidocaine is an amide-class local anesthetic used clinically to inhibit pain sensations. Systemic administration of lidocaine has antinociceptive, antiarrhythmic, anti-inflammatory, and antithrombotic effects. Lidocaine exerts these effects under both acute and chronic pain conditions and acute respiratory distress syndrome through mechanisms that can be independent of its primary mechanism of action, sodium channel inhibition. Here we review the pathophysiological underpinnings of lidocaine's role as an anti-nociceptive, anti-inflammatory mediated by toll-like receptor (TLR) and nuclear factor kappa- β (NF- κ B) signalling pathways and downstream cytokine effectors high mobility group box 1 (HMGB1) and tumour necrosis factor- α (TNF- α).

1. Introduction

Post-surgery inflammation is characterized by increased blood flow and vascular permeability, the upregulation of inflammatory mediators, and leukocyte accumulation [1]. Cytokines are key modulators of inflammation and can play both pro- and anti-inflammatory roles. A dynamic balance exists between pro- and anti-inflammatory cytokines that affects organ dysfunction, immunity, infection, wound healing, and pain – all of which are associated with surgery [1,2]. Surgical injury induces endogenous mediators and activates hemodynamic, metabolic, and immune responses [1]. This immune response initiates immediately after a surgical injury. Polymorphonuclear leukocytes (PMNs), endothelial cells, macrophages, and lymphocytes are activated by the secretion of pro-inflammatory mediators including cytokines, chemokines, and other molecules including but not limited to reactive oxygen species, nitric oxide, and platelet-activating factor [3]. While essential, when unchecked, excessive inflammation can disrupt the body's immune system, potentially leading to certain inflammation-related conditions and even organ failure [4,5].

Lidocaine was first synthesized by Nils Lofgren in 1935 in the in the Stockholm laboratory of Professor Hans von Euler where Lofgren began tasting the compounds he and his colleagues had synthesized [6]. In

1943, Lofgren found that the 57th compound he tested rapidly numbed his tongue. The patent for Xylocaine® was approved in Sweden on May 11, 1948, based on Goldberg's (toxicology) and Gordh's (clinical results) papers suggesting that lidocaine had a strong and unexpected anesthetic effect. The Food and Drug Administration approved Xylocaine® for usage in the United States in November 1948 [6,7]. Torsten Gordh's clinical testing revealed that lidocaine represented a significant improvement over procaine, the gold standard for managing surgical pain at the time [8,9]. This amide-class anesthetic is still used widely to ease the pain associated with surgery, provide neuropathic pain relief, and treat ventricular arrhythmias [10,11].

In addition to its use as a local anesthetic and anti-arrhythmic agent, lidocaine has analgesic properties for various pain conditions. The nociceptive antagonist effects of intravenous lidocaine have been well established in a variety of acute and chronic pain conditions [7,12]. Moreover, preclinical and clinical data evidence the antihyperalgesic effects of parenteral lidocaine [7]. The recommended initial dose is 1–2 mg/kg administered intravenously followed by a continuous infusion of 2–4 mg/kg/h, resulting in steady plasma concentrations of 1–3 mg/ml [7,13].

The mechanism of action of lidocaine as a local anesthetic is through a blockade of voltage-gated sodium channels (VGSCs) leading to a

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reversible block of action potential propagation [7]. Lidocaine affects inflammatory cells in vitro, for example by inhibiting the priming of human peripheral PMNCs and neutrophils [7,14]. Lidocaine can further reduce the release of pro-inflammatory mediators such as IL-4, IL-6, and tumour necrosis factor- α (TNF- α) [7].

It is well established in the literature that lidocaine exerts its anti-inflammatory effects by inhibiting the expression of pro-inflammatory cytokines, the metabolic activity of leukocytes, and the release of histamine [10,15]. The effects of lidocaine are achieved by preventing NF- κ B activation and its downstream cytokine storm [16]. Specifically, lidocaine significantly reduces TNF- α levels relative to vehicle-treated controls [17]. Therefore, lidocaine's anti-inflammatory mechanism of action at the level of receptor engagement and pro-inflammatory cytokine release in the context of post-surgical injury is the entry point for the present review.

2. Systemic effect of lidocaine in molecular biology

Lidocaine is an amide class of local anesthetics used in medicine to inhibit pain sensations [17,18]. It consists of lipophilic and hydrophilic subunits connected by hydrocarbon chains. The hydrophilic portion is composed of tertiary amines (e.g., diethylamine) while the lipophilic portion is composed of unsaturated aromatic rings [e.g., para-aminobenzoic acid (PABA)] [19,20]. Based on this structure, these local anesthetics can be classified into amino-esters and amino-amides. The lipophilic portion determines the anesthetic activity of the local anesthetic drug [9]. Local anesthetics act on sodium ion channels to reduce the permeability of cell membranes, thereby blocking depolarization and preventing the conduction of the electrical impulse through which pain occurs [21].

Chemically, lidocaine [2- (diethylamino) -N- (2,6-dimethylphenyl) acetamide] contains three basic components: hydrophilic amine groups, aromatic residues, and intermediary groups that connect these two (Fig. 1) [22,23]. The amine group is a tertiary or secondary amine, between an aromatic residue group and an intermediate group connected by an amide bond. Lidocaine is a weak alkaline with pKa of 8, protein binding of 64%, and fat solubility of 1%. Lidocaine remains the drug of choice for a variety of medical procedures due to its strong anesthetic potential, fast onset of action, and wide safety limits [24,25]. Moreover, lidocaine can be administered via many routes, including topical (i.e., skin and airway), subcutaneous, intravenous, perineural, epidural, and intrathecal [22,26,27]. After intravenous administration, peak plasma levels are achieved within 3–5 min with a half-life of 30–120 min [28].

In the liver, lidocaine is dealkylated by dual-function oxidizing enzymes to the pharmacologically active metabolite, monoethylglycinexylidide (MEGX) and then metabolized by the P450 3A4 isoenzyme into N-ethylglycine (NEG) and glycinexylidide (GX). MEGX is 80% as potent as the parent drug, whilst GX is nearly ineffective [29].

In clinical practice, lidocaine is also used as a class IB antiarrhythmic

drug (sodium channel blocker). Sodium channels have three basic states: (1) resting (phase 1), while they await the arrival of an action potential; (2) open/active (phase 0), during which the channel is activated and conducts a sodium current; and (3) inactivated/refractory (phase 2), after the channel has conducted a sodium current but has not yet returned to its resting state. During this refractory period, the sodium channel cannot yet be activated again. Lidocaine occupies receptors on the sodium channel in its open/active (phase 0) and inactivated/refractory (phase 2) states, which lidocaine has a high affinity for its receptors during both phases [30].

Lidocaine's effects on the central nervous system include inhibiting nicotinic and acetylcholine receptors, inhibiting presynaptic calcium channels in the dorsal root ganglion, inhibiting opioid receptors, inhibiting of neurite growth, inhibiting muscarinic cholinergic receptors, and preventing substance P from binding to natural killer (NK) cell receptors [7,31,32].

The anti-inflammatory effect of lidocaine occurs at lower concentrations than required to block sodium channels [33,34]. The effect of lidocaine on inflammation, particularly against inflammatory polymorphonuclear granulocytes (PMNs), macrophages, and monocytes is not due to blocked sodium channels [35,36].

Priming can be described as a process that gives a resting neutrophil a functional response that can be greatly amplified upon exposure to another stimulus [37,38]. The second stimulus is usually considered an activating agent or agonist. The enhanced functional response keeps the neutrophils in an active state. Thus, full neutrophil activation is a two-step process, starting with initial exposure to primary agents such as cytokines (e.g., IL-1 α , GM-CSF, and TNF- α) and antigens (e.g., pathogenic endotoxin). Priming and activation change neutrophils from a resting state to an active state, thus enabling them to perform antibacterial, pro- and anti-inflammatory functions [39]. PMN priming regulates the function of PMNs and is implicated in cases of excessive inflammatory responses that cause tissue damage [39,40]. Some potential mechanisms include local anesthetics inhibiting G-protein-coupled receptors (GPCRs) signals that mediate inflammatory responses such as lysophosphatic acid and thromboxane A2 as well as the M1 muscarinic acetylcholine receptor. GPCRs consist of muscarinic acetylcholine receptors M1-M5, which regulate several functions of the nervous system (Fig. 2) [23]. Furthermore, M1 and M4 receptors are the treatment sites for several central nervous system disorders such as Alzheimer's disease, schizophrenia, and drug addiction [23,41].

3. Lidocaine as an anti inflammatory

Lidocaine is a potent anti-inflammatory agent, whose properties are often compared with steroids and non-steroidal anti-inflammatory drugs (NSAIDs) [42]. The definite anti-inflammatory mechanism of lidocaine remains vague; however, it is presumed that the drug affects a multitude of inflammatory processes such as phagocytosis, migration, exocytosis, and cellular metabolism. In vitro experiments on human polymorphonuclear granulocytes suggest that lidocaine the membrane-ion transporters, thereby, dysregulating cellular pH levels and eventually depressing cytokine release [43].

There is still no universal reference dose for lidocaine administration as an anti-inflammatory agent. Ortiz et al. conducted a double-blind, randomized trial studying the effect of endovenous lidocaine on serum inflammatory cytokine levels using bolus lidocaine of 1.5 mg/kg at the start of the procedure with a maintenance dose of 3 mg/kg/h until 1 h after the end of the surgery [44]. A significant reduction in serum levels of pro-inflammatory markers (IL-1, IL-6, TNF- α , and IFN- γ) was observed in the IV lidocaine group in comparison with a control group [44,45]. In this same study, there were no statistically significant differences regarding the postoperative pain intensity, morphine consumption, ileus, and hospital stay compared with the control group, meaning there were no proven secondary effects at this dose [44].

Multiple, complex mechanisms likely underlie lidocaine's anti-

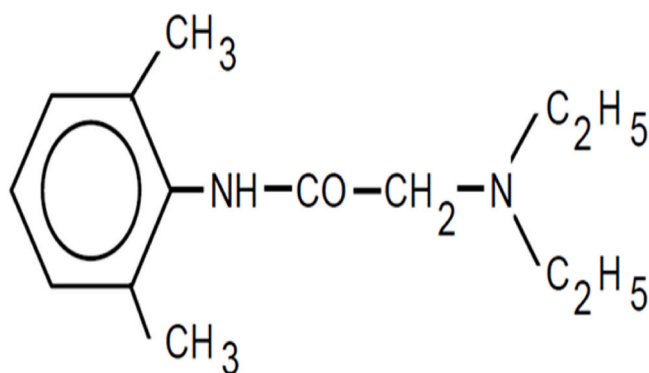


Fig. 1. Chemical structure of lidocaine [21].

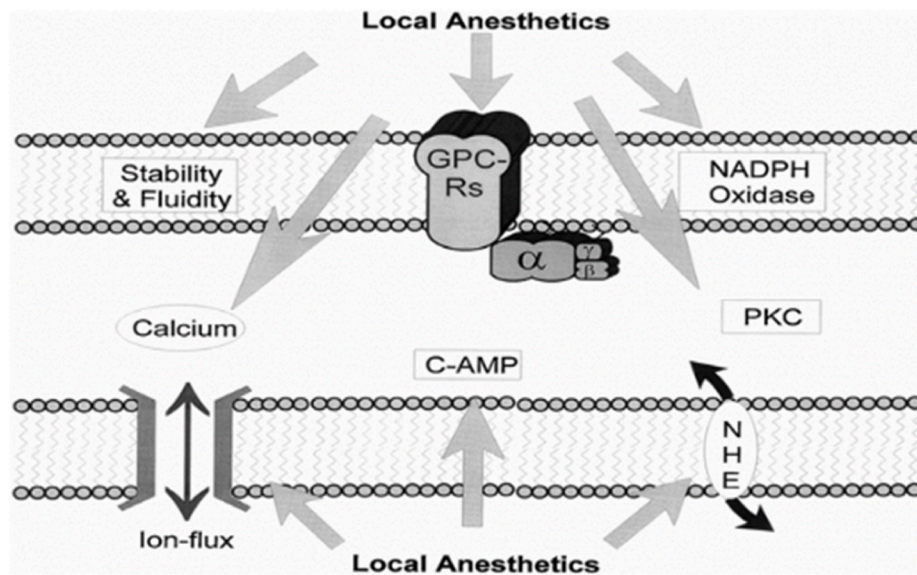


Fig. 2. The mechanism of action of local anesthetics on inflammation [21].

inflammatory effects in a synergy that involves numerous pathways, receptors, cells, and mediators. More specifically, the modulation of high mobility group box 1 (HMGB1), toll-like receptor (TLR), nuclear factor kappa- β (NF- κ B), and TNF- α have been implicated in previous studies.

3.1. High Mobility Group Box 1 (HMGB1) cytokine activity

HMGB1 functions as a pathogenetic cytokine regulator under these conditions. HMGB1 is actively secreted from various cell types including macrophages, NK cells, dendritic cells (DCs), blood vessel endothelial, and platelets [46,47]. HMGB1 is also passively released from necrotic cells, damaged cells, and after extracellular injury [48]. Cells undergoing apoptosis release less HMGB1 than necrotic cells, yet macrophages covered with apoptotic cells can still stimulate the discharge of HMGB1 from WEHI-231, Jurkat, and HL-60 cells. Pyroptosis and caspase-1-associated necrosis are responsible for the continuous discharge of HMGB1 controlled by dsRNA-dependent protein kinase (PKR) and the inflammasome. Pyroptosis follows the activation of inflammasomes, leading to the expression of caspase-1 and its downstream effects, including generation of the cytokines IL-1 β and IL-18 by the cleavage of their precursors [49].

Release mechanisms such as necrosis, macrophage activation, pyroptosis, and apoptosis discharge HMGB1 in various redox forms. Necrotic and pyroptotic cells produce thiol in its reduced form, which then binds to the chemokine CXCL12 and the CXCR4 receptor to stimulate the process of chemotaxis. Pyroptosis and TLR4 stimulation also release reduced HMGB1, disulfide bond HMGB1, C23, C45, and C106, which are all in thiol form. This form of HMGB1 then stimulates cytokine production via TLR4 signaling. Activated macrophages also release the cytokine-inducing form of HMGB1 upon TLR4 activation. Apoptotic cells release HMGB1 that is partially oxidized or completely oxidized at the critical cysteine residues. Completely oxidized HMGB1, with cysteines in the form of sulfonates, is unable to stimulate cytokines or induce chemotaxis; apoptotic cells expressing this form of oxidized HMGB1 can induce tolerance [49].

3.2. Cellular inflammatory response and HMGB1 receptors

HMGB1 is a classic pro-inflammatory mediator because [4]:

- Injuries and infections stimulate its release.

- It causes immuno-competent cells to release TNF- α , IL 1, and other related substances.
- It reduces symptoms of pyrexia, and the sickness syndrome in vivo;
- It is activated by exogenous TLR agonists and other cytokines that stimulate inflammation.
- It can be specifically targeted to therapeutic advantage in sterile and infectious disease syndromes associated with elevated HMGB1 levels.

One difference between HMGB1 and conventional PCs (e.g., TNF- α , IL-1) is it stimulates systemic inflammatory responses through receptors that report and interact with foreign substances [50]. Unlike TNF- α and IL-1, the allied plasma membrane receptor family interacts with HMGB1 and initiates signal transduction through endogenous (RAGE) and exogenous ligands (TLR2, TLR4, and TLR9) [51,52]. These processes show that HMGB1 elicits various inflammatory responses to a diversity of infections and injuries. HMGB1's ability to modulate the magnitude of the inflammatory response in clinical syndromes associated with injury is discussed below. These mechanisms have been explored in loss-of-function-type studies based on HMGB1 antagonists and/or the deletion of receptors via genetic clustering techniques [53].

HMGB1 binding to TLR4-MD2 acts as a measure of surface plasmin resonance and signal transducers that stimulate macrophages to release TNF [4]. These processes require redox-sensitive cysteine 106, which prevents HMGB1 from adhering to TLR4, the endogenous HMGB1 receptor responsible for regulating macrophage activation, cytokine release, and tissue injury repair by activating I κ B kinase (IKK)- β , IKK- α (active endotoxin only IKK- β), and active nuclear translocation NF- κ B [54] [–] [56]. One difference between HMGB1- and endotoxin-mediated signaling, is that the former does not bind to TLR4 as readily as LPS. Another difference is the pattern of gene expression induced upon activation. While both HMGB1 and LPS significantly increase NF- κ B nuclear translocation and Akt/p38 MAPK phosphorylation, LPS increases the production of NF- κ B and TNF more than HMGB1. Furthermore, HMGB1-induced secretion of TNF exhibits a biphasic kinetic profile, while the endotoxin LPS stimulates monophasic TNF release [56].

Animal studies have shown that HMGB1 levels increase during injury due to a lack of oxygen [4]. HMGB1 protein levels rise within 1 h of reperfusion and remain elevated for up to 24 h. Treating wild-type (C3H/HeOuj) mice with anti-HMGB1 antibodies helps to protect them from liver injury, while the TLR4 deficient (C3H/HeJ) mice garner no

benefit from these antibodies [4,16,57]. HMGB1 signaling via TLR4 is an effective target for solid tumors treatment strategies such as antigen cross-presentation or chemotherapy. Renal tubular TLR4 expression in donor kidneys is indicated by HMGB1 immunoreactivity, this reveals its importance in developing kidney graft inflammation and sterile injury [4].

The impact of HMGB1 protein binding on the release of cytokines (e.g., CXCL12, TLR9, thrombospondin, syndecan, TLR2, MAC1, TREM1) in the pathogenesis of sterile infection and injury remains unknown [4]. Furthermore, HMGB1 regulates the body's inflammatory response to sterile threats and infections through TLR4 receptor-mediated signaling [58,59]. HMGB1 then reacts with CD24, a plasma protein working with Siglec-10 to suppress nuclear translocation. This process is controlled by HMGB1 and mediated TLR4 activation, not pathogen-mediated TLR activation, indicating that the outcome of HMGB1 via TLR4 signaling is different from CD24-siglec-10 when it comes to sterile damage [56].

3.3. HMGB1 pathway to NF- κ B

Receptors involved in HMGB1 binding include the receptor for advanced glycation end products (RAGE), a transmembrane, cell surface, multi-ligand member of the large immunoglobulin family (Fig. 3) [4]. Consequently, RAGE-mediate HMGB1 signaling stimulates chemotaxis, cell growth, differentiation, and the migration of immune/smooth muscle cells by engaging with cell-surface moieties such as RAGE/TLR4. Although HMGB1 and RAGE bind to each other, TLR4 still controls the secretion of HMGB1 from macrophages due to the inhibition of RAGE macrophages and the inactivation of TNF-producing macrophages by TLR2. However, TLR4 does not mediate macrophage inactivation [53].

4. TOLL-LIKE receptors (TLRs)

4.1. TLR signaling pathway

The TLR pathways and signals are initiated by a ligand binding to TLRs expressed on the plasma membrane, endoplasmic reticulum, or endosome, which induces the dimerization of the TLRs proteins. Ligand-induced dimerization of TLRs likely transposes the TIR from the cytoplasmic tail of each adjacent protein, followed by a TIR-containing adapter protein that recruits and activates protein kinases to stimulate transcription factors.

Interferon response factor 3 (IRF3), NF- κ B, activation protein 1 (AP-1), and IRF7 are the transcription factors stimulated by TLR signaling pathways upon PAMPs and DAMPs recognition, TLRs recruit TIR domain-containing adaptor proteins such as MyD88 and TRIF [60]. Furthermore, NF- κ B and AP-1 are essential proteins that mediate the gene expression of molecules involved in the inflammatory response such as chemokines (e.g., CCL2, CXCL), cytokines (e.g., TNF, IL-1), and endothelial adhesion molecules (e.g., N-cadherin, E-selectin). Different combinations of ligands and intermediate messengers dictate the shared and unique effects of TLRs. Upon engagement at the cell's surface, dimerized TLRs bind to the MyD88 adapter, which activates NF- κ B, while the signal adapter TRIF (TIR domain-containing IFN- β inducing adapter) activates IRF3. For all TLRs except TLR3, signaling via MyD88 activates NF- κ B and initiates a pro-inflammatory response. Via TRIF, TLR3 activates IRF3 and induces type I interferon expression. Regardless of adapter (i.e., MyD88 or TRIF), TLR-ligand interactions lead to a pro-inflammatory downstream response [61]. TLR7 and TLR9 are abundant within the cytoplasm of dendritic cells and use MyD88-dependent, TRIF-independent pathways to activate NF- κ B and IRFs. TLR7, TLR9, and TLR4 all stimulate reactions against bacterial, single-stranded (ss)RNA from viruses, viral DNA, and bacterial lipopolysaccharide (LPS) [60,62].

There is some evidence of an interaction between lidocaine and TLRs. Lidocaine (50 mM) inhibits the activation of TLR4 and subsequently also NF- κ B and mitogen-activated protein kinases (MAPKs) in LPS-stimulated murine macrophages [7].

5. Nuclear factor kappa- β (NF- κ B)

5.1. NF- κ B in inflammation

Inflammation and the actions of the adaptive and innate branches of the immune system are regulated by NF- κ B [63]. An inflammatory response comprises several activated signaling pathways that modulate the activation of pro- and anti-inflammatory regulators in resident tissue cells and blood-derived leukocytes [64]. Information on inflammation and its underlying signaling pathways is mostly obtained through studies on the IL-1, TNF, and TLR protein families aimed at understanding how microbes in the IL-1R family operate. IL-1 and TNF- α represent a baseline pattern of pro-inflammatory cytokines released rapidly in response to tissue injury and infection. TLR recognizes

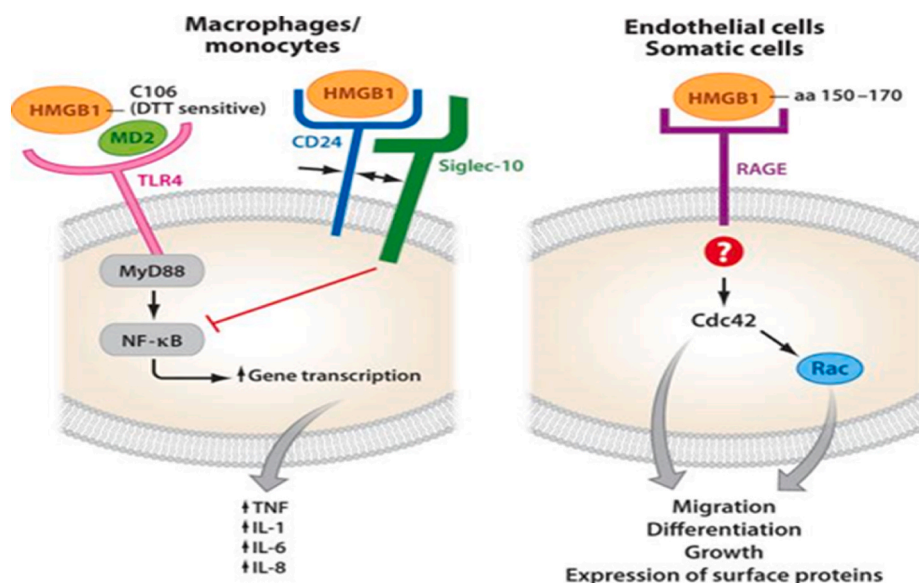


Fig. 3. The relationship between HMGB1, TLR4, and RAGE. TLR4 binding induces cytokine secretion from macrophages and monocytes (left), meanwhile, RAGE modulates endothelial and tumor cell function (right) [3].

microbial molecular patterns and, as such, is known as a pattern recognition receptor (PRR). TLRs represent germline-encoded, non-self-recognition systems poised to induce inflammation [65]. However, endogenous ligands also activate TLR during particular forms of damage, which causes inflammation in the absence of infection. I κ B kinase (IKK) and NF- κ B make use of similar signal-transduction mechanisms even though their structures differ [65,66].

6. Tumor necrosis factor- α (TNF- α)

6.1. Systemic effects of TNF in the inflammatory response

TNF receptors are expressed differently in a variety of cells and tissues; however, the pro-inflammatory effects of TNF occur based on interactions between blood vessel cells and leukocytes. These cells then initiate inflammatory processes with different temporal, spatial, and anatomical presentations using different leukocyte adhesion molecules, including E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [67].

This response, when combined with chemokine release (e.g., IL-8, MCP-1, IP-10) leads to the recruitment of several leukocytes independent of antigen recognition [68,69]. Furthermore, the local effects of TNF on endothelial cells lead to many classic inflammatory features. For example, TNF-induced cyclo-oxygenase 2 expression can increase the EC production of PGI₂, which results in vasodilation, and 'rubor' and 'heat' through increased local blood flow. Swelling is created by edema caused by the accumulation of endothelial fluid and other macromolecules [70]. Furthermore, TNF-induced pro-coagulant protein expression (including tissue-specific factors), anti-coagulant protein regulation, and thrombo modulation can cause intravascular thrombosis [67].

6.2. TNF to NF- κ B family signaling

The NF- κ B pathway is activated by various immunologically-relevant ligands and receptors such as the TNF receptor (TNFR), TLR, IL-1 receptor (IL-1R), and other antigen receptor groups [66,71]. Furthermore, these receptors lack any enzymatic activity, while the results of ligand binding are always relayed through the lipid bilayer and converted into kinases via adapter proteins [66].

The process that holds the ligand bonds also fosters the creation of a receptor oligomer/ligand complex [66]. TNF family signaling via NF- κ B causes several adapter proteins to bind to the ligand-receptor complex, thereby activating IKK [72]. This adapter protein belongs to that protein is well described as the domain of protein interactions participating in the assembly of very complex oligomeric proteins that join ligand-receptor complexes to IKK [66]. Adapter protein domain interactions important for TNF-NF- κ B family signaling include death fold domain (DD), RIP (receptor-interacting protein), homotypic interaction motifs (RHIM), and TRAF (TNF receptor-associated factor) domains [66, 73].

This adapter protein directs signaling to various end pathways. In this case, the functions of transcription factors such as NF- κ B in signaling are discussed. Furthermore, changes in receptor conformation localization and increased avidity are caused by the ligand binding of adapter proteins on cytoplasmic receptor tails [66,74]. This leads to the mobilization of members of the TRAF and RIP families into a complex protein structure. Consequently, the oligomerization of these complexes is sustained by cross-receptors, multimer ligands, and the ability of proteins to form high-order trimers and oligomers [66]. Upstream kinases that control the activation of IKK and NF- κ B signaling through the TNF cytokine family include NIK (NF- κ B inducing kinase) and TAK1 (transforming growth factor- β activated kinase; MAP3K7) [66,71]. Furthermore, NIK controls the stimulation of IKK α and non-canonical pathways. The function of TAK1 in canonical pathways is NEMO-dependent; however, the requirements of TAK1 in all forms of TNF and NF- κ B signaling are not fully understood. After activation, IKK kinase (IKK-K)

triggers a traditional kinase cascade within and outside of the NF- κ B pathway [66].

7. Lidocaine in acute and chronic pain

Lidocaine exerts additional analgesic effects through other pathways. Various studies show the analgesic benefit of systemic lidocaine during surgical procedures, especially during laparoscopic abdominal surgery [75] [–] [80]. Usually, lidocaine is administered initially at doses of 1.5–2 mg/kg BW and maintained by 1.5–3 mg/BW/hr or 2–3 mg/min. This results in serum levels of lidocaine that range from 0.5 to 5 μ g/ml (~2–21 μ M), which is similar to after epidural administration [75,77,78,80,81]. The benefits of lidocaine include a quick recovery, reduced time in the hospital, unaffected bowel movements, and less post-operative pain (Table 1) [7,82].

7.1. Opioid receptors

One study describes the absence of any cellular interaction between lidocaine and recombinant μ -, κ -, and δ -opioid receptors [83,84]. This is because all opioid receptors belong to a family of GPCRs lacking Gaq units, and lidocaine only influences receptors with Gaq. Meanwhile, another study found that when opioids and lidocaine are administered simultaneously, they synergistically potentiate anti-nociception. However, the mechanism underlying this effect, for example, whether occurs at the receptor level (e.g., via TLR4 signaling, Kir, or Ca²⁺ channels) or involves regional/systemic interplay, has yet to be elucidated [7,83].

7.2. Toll-like receptors (TLRs)

Another study describes lidocaine's negligible inhibitory effect on TLRs. However, lidocaine (50 μ M) inhibits the activation of TLR4, along with NF- κ B and MAPKs, in LPS-stimulated murine macrophages. This mechanism is mediated by VGSCs [7].

Intravenous administration of lidocaine in rats with LPS-induced sepsis reduces organ failure significantly compared with control. It was also shown to protect against organ dysfunction through the downregulation of TLR4. The expression of TLR4, NF- κ B, and interleukin (IL)-6 was reduced in the lidocaine group by this mechanism [85]. Nebulized lidocaine prevents the respiratory system of mice from becoming inflamed by reducing TLR2 expression [86]. Further investigation is needed to determine whether these processes can be applied for chronic pain management (Table 2).

8. Lidocaine as an anti arrhythmic agent

In the 1950s, the first case of cardiac arrhythmia treated successfully with intravenous lidocaine was reported: ventricular fibrillation that occurred during cardiac catheterization was successfully reverted to a regular sinus rhythm with electric shock and lidocaine administration [87]. The dose of lidocaine used to treat ventricular arrhythmias

Table 1
The biological effect of lidocaine on various forms of chronic pain [6,81].

Source	Spontaneous pain	Hyperalgesia	Allodynia
Neuropathic pain	Reduced		
Diabetic neuropathy	Reduced		
Peripheral nerve injury	Reduced	Reduced	
Post herpetic neuralgia	Reduced	Reduced	Reduced
Chronic regional pain syndrome	Reduced at high (3 μ g/ml) plasma concentration	Reduced for cold threshold only	Reduced for cold and mechanical thresholds
Central pain	Reduced	Reduced	Reduced

Table 2

Presents the results of studies on the relationship between lidocaine and acute/chronic post-operative pain. Recent reviews highlight differences in the results obtained by these studies [6,76,86].

Perioperative antinociceptive effects	Pain at rest <24 h	Pain during activity	Opioid requirement	PONV
Abdominal surgery	Reduced	Reduced	Reduced	Reduced
CPSP	Odds ratio for incidence of CPSP (4–6 months)		Pain intensity (McGill pain questionnaire score)	
Overall	Reduced		Unchanged (P = 0.06)	
Breast surgery	Reduced			
Non-breast surgery	Reduced			

Abbreviations: CPSP: Chronic post-surgical pain, PONV: postoperative nausea and vomiting.

(tachycardia) is 1–1.5 mg/kg BW administered intravenously followed by an infusion of 1–4 mg/kg BW/hr [28,88].

The mechanism underlying the antiarrhythmic effect appears to be similar to that of procaine. Ventricular excitability is depressed with increasing doses, conduction time is slowed, and the refractory period is prolonged. Cardiac contractility is not diminished in therapeutic dosages [87]. In contrast to procaine and procaine amide, doses of lidocaine that produce comparable increases in the diastolic stimulation threshold cause no fall in blood pressure or decreased myocardial contractility.

Before amiodarone was approved, lidocaine was listed as the primary drug of choice to treat ventricular fibrillation (VF) or Ventricular tachycardia (VT) in the Advanced cardiac life support (ACLS) algorithm. Even though lidocaine had been used to treat VF/VT for years, there was a lack of evidence for its efficacy over other drugs. While lidocaine was since removed from the ACLS Algorithm, it is still considered a suitable alternative if amiodarone is ineffective or unavailable in cardiac arrest from VT/VF [89].

9. Lidocaine and covid-19-associated acute respiratory distress syndrome (ARDS)

9.1. Pathophysiology of COVID-19

COVID-19 is a disease that results from infection with the newly identified SARS-CoV2 virus. Very little has been published to date regarding its pathology and mechanism. Initial pathological changes experienced at the tissue and cellular level include death of alveolar epithelial cells, intraluminal edema, fibrin exudation, hyaline membrane formation, hemorrhage, infiltration of inflammatory cells (e.g., monocytes, macrophages, lymphocytes, and neutrophils) into the alveolar wall and lumina, and elevated levels of serum pro-inflammatory cytokines and chemokines [90].

Other studies show high levels of cytokines and chemokines in blood samples collected during SARS-CoV infections. Kong et al. reported an increase in circulating cytokines, (TNF- α , CXCL-10 [interferon gamma inducible protein 10-strong leukocyte activator], IL-6 and -8) [91]. Other studies confirm these pro-inflammatory cytokine findings [92, 93]. After an initial disruptive phase, the epithelial lining experiences less damage, reduced interstitial and alveolar fibrosis, bronchiolitis obliterans, pneumonia, regeneration of type II pneumocyte hyperplasia (e.g., IL1, IL-6, IL-12, IFN- γ , TGF- β), and chemokines. During this fibrotic phase, interstitial thickening is caused by moderate fibrosis and few inflammatory cells [94].

9.2. Lidocaine, acute lung injury, and ARDS

COVID-19 can progress to acute respiratory distress syndrome

(ARDS), a serious outcome of pulmonary viral infection [95,96]. The primary underlying pathophysiology of ARDS is vascular lung injury [97]. However, local anesthesia addresses the underlying etiology by inhibiting TNF α , which signals to endothelial cells to induce neutrophil binding and increases endothelial permeability [98].

Recently, preliminary studies have explored the anti-inflammatory effects of lidocaine in the context of acute lung injury [43]. The predominant mechanism of action in the specific clinical application remains unclear; however, lidocaine might exert its anti-inflammatory effects by regulating cellular metabolic activity, migration, exocytosis, and phagocytosis by reversibly interacting with membrane proteins and lipids thereby attenuating the inflammatory response by decreasing PMN granulocyte accumulation in the lung [43]. These promising preliminary findings have encouraged pulmonary physicians to introduce lidocaine into their clinical practice.

Nebulized lidocaine appears to be a novel potential treatment for improving COVID-19-related lung injury by reducing the cytokine storms associated with the disease, which would theoretically reverse ARDS. As such, more pre-clinical research and clinical trials are warranted to further define the efficacy and safety of lidocaine for treating patients with severe ARDS due to COVID-19.

10. Conclusions

The analgesic and anti-hyperalgesic effects of systemic lidocaine have served the clinical practice of medicine for 75 years. Prospective clinical investigations have confirmed that lidocaine is a highly safe and effective therapeutic option in cases of acute and chronic pain. The positive effects of incorporating lidocaine into multimodal pain therapy also include acute lung injury applications, based on evidence from experimental animal models.

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Author contribution

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