The Science of Local Anesthesia: Basic Research, Clinical Application, and Future Directions

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Local anesthetics have been used clinically for more than a century, but new insights into their mechanisms of action and their interaction with biological systems continue to surprise researchers and clinicians alike. Next to their classic action on voltage-gated sodium channels, local anesthetics interact with calcium, potassium, and hyperpolarization-gated ion channels, ligand-gated channels, and G protein–coupled receptors. They activate numerous downstream pathways in neurons, and affect the structure and function of many types of membranes. Local anesthetics must traverse several tissue barriers to reach their site of action on neuronal membranes. In particular, the perineurium is a major rate-limiting step. Allergy to local anesthetics is rare, while the variation in individual patient's response to local anesthetics is probably larger than previously assumed. Several adjuncts are available to prolong sensory block, but these typically also prolong motor block. The 2 main research avenues being followed to improve action of local anesthetics are to prolong duration of block, by slow-release formulations and on-demand release, and to develop compounds and combinations that elicit a nociception-selective blockade. (Anesth Analg 2018;126:1381–92)

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Despite being in clinical use for more than a century, local anesthetics (LA) continue to surprise researchers and clinicians alike. They are versatile drugs that have been applied for infiltration, nerve block, for neuraxial anesthesia, and intravenously. Their clinical introduction profoundly changed perioperative medicine. Today, in parallel with advances in neurosciences, our understanding of LA has become much more detailed. The aim of this review is to highlight key aspects of LA pharmacology and toxicology, and delineate current research.

BASIC MECHANISMS OF ACTION

The physiological consequences of LA arise from their interactions with specific ionic channels, receptors, and, possibly, from their more general effects on biological membranes.

Ion Channels: Targets and Physiological Effects

Voltage-Gated Channels. Voltage-gated channels conduct specific ions across membranes and are essential for the generation and propagation of action potentials and for transmitter release and postsynaptic responsiveness.[1]

Na^+ Channels. The 9 isoforms of vertebrate voltage–gated sodium channels are differentially distributed among various excitable tissues, eg, Nav1.5 occurs primarily in cardiac muscle, and Nav1.7 occurs in peripheral nociceptors. Traditional LA show little selectivity for block among voltage-gated sodium channels, although their state-dependent binding (see below) may confer some tissue selectivity. One LA molecule binds to 1 voltage-gated sodium channel, with rates that depend on the state (conformation) of the channel, accounting for the "use-dependent" block of action potentials. Channels in the resting, closed state have slow binding and low affinity, those that are open have a high rate of binding, resulting in a progressive inhibition during rapidly firing trains of action potentials, called "use-dependent block," while the inactivated state channels, resulting from long depolarizations, bind LA most slowly but also have a high affinity.[2]

The binding site for traditional LA is in the aqueous pore of the channel, with different amino acids of the channel's major α-subunit differentially involved in binding to the different states[3] (Figure 1). The ancillary β-units do not directly contribute to the binding, but by modulating the inactivation behavior of the channel, they may indirectly influence binding.[4]

Blockade of voltage-gated sodium channels prevents the generation of action potentials, eg, at nerve endings during an infiltration block, blocks action potential conduction along axons, eg, for peripheral nerve blocks, and inhibits the depolarization-dependent release of transmitters and neuropeptides, eg, at presynaptic terminals, where LA penetrate into the spinal cord during neuraxial blocks.[5] Conduction block is greatest for small myelinated Aδ- and Aγ-fibers,[6] accounting, respectively, for the suppression of "fast" pain conducted by nociceptive afferents and for motor deficits resulting from the loss of tone in muscle spindles innervated by Aγ-efferents.[7] Larger myelinated Aα-(primary motor) fibers and Aβ-(mechanosensory) fibers are less sensitive to block, and nonmyelinated C fibers, which mediate "slow" pain, are least sensitive, contradicting the classical "size principle."[6] Consequently, obtunding Aδ-fiber impulses could cause deficits in pin-prick sensations without preventing C-fiber conduction, allowing the "central sensitization" that is driven by intense, prolonged input from these smaller fiber nociceptors.[8] It should be noted that C fibers are not just A fibers without myelin; neuronal subclasses are characterized by specific neuronal membrane structure and ion channel composition.[9]

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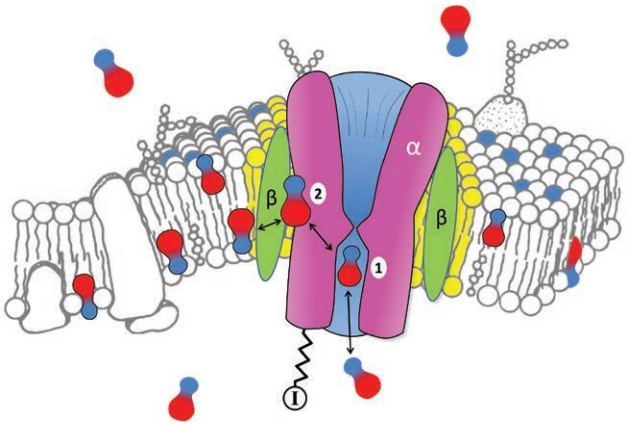


Figure 1. Local anesthetics (LA) may interact with Na+ channels in the nerve membrane in multiple ways. LA molecules (red-blue oblates), because of their amphipathic character, with a hydrophobic (aromatic, red) region and a hydrophilic (polar, sometimes positively charged, blue) region, are adsorbed near the membrane's surface. Adsorption and desorption from the adjacent aqueous solutions to the membrane surfaces occur rapidly, for both charged and neutral LA forms, but transport across the membrane is much slower and is virtually exclusively by the uncharged form. The Na+ channel protein is composed of 1 large α-subunit and 2 smaller β-subunits. Channel opening allows a LA molecule to reach the binding site in the pore of the α-subunit (locus 1) from the cytoplasmic compartment, but a channel that is inactivated when the tethered I particle covers the inner opening has no access to or from this site; in that situation, a LA can reach the inner site from the membrane, albeit much more slowly, via "hydrophobic" pathways (locus 2). Interactions in this domain may also disrupt the association of the α- and β- subunits, and thus alter channel gating. Annular lipids (shown by yellow), that surround the channel proteins and can modify its gating and its association with other proteins, are particularly sensitive to LA present in the membrane.

K^+ Channels. Currents through voltage-gated potassium channels repolarize an excitable membrane after an action potential. Opening more slowly than voltage-gated sodium channels, different isoforms of voltage-gated potassium channels can cause rapid or slow repolarizations, or long after-hyperpolarizations. Importantly, the ability of an excitable membrane to fire action potentials at high frequency depends on both the rapidity of repolarization and the duration of the voltage-gated potassium channel's open state, because the resulting high-potassium conductance renders the membrane refractory to subsequent firing. Structurally homologous to voltage-gated sodium channels, but composed of 4 homo- or heteromeric subunits, the voltage-gated potassium channels are similarly, although less potently, inhibited by LA.[10] By slowing repolarization and thus keeping the membrane depolarized for a longer time during the AP, inhibition of voltage-gated potassium channels potentiates the impulse blocking action that occurs via the blockade of voltage-gated sodium channels.[11] Because there is little affinity difference among different voltage-gated sodium channels to LA, observed differences in functional blockade among different fiber types may arise from the widely varied expression of different types of voltage-gated potassium channels that shape both the individual action potentials and the trains of conducted impulses.[7]

Ca^{2+} Channels. The third major class of voltage-gated cation channels, the calcium channels, are also blocked by LA, although not as strongly as voltage-gated sodium channels.[12] Calcium channels (N-, P-type) are critical for release of neurotransmitters and neuropeptides from presynaptic terminals (and neuroendocrine cells, eg, chromaffin[13]), and also contribute to the impulse-generating depolarizations at the distal neurites of sensory nerves (T-type). Inhibition by LA of voltage-gated calcium channels occurs with about the same potency as for voltage-gated potassium channels, but the physiological effects can be more profound, as noted for the reduction of transmitter release. There the degree of release depends on a higher power of the ionized Ca^{2+} concentration in the presynaptic terminal; for example, doubling this level can increase release by 10-fold or greater.[14] Therefore, a LA concentration that blocks half the calcium current, and thereby halves the elevation of intracellular calcium, could reduce the release by ~90%.

HCN Channels. Hyperpolarization-activated cyclic nucleotide–gated channels are cation-selective channels that open and thus depolarize nerves in response to a membrane hyperpolarization. They are the critical players in oscillatory changes of membrane potential in various neurons (and in the sinoatrial node, where they account for the slow pacemaker current, I_h). These channels are remarkably sensitive to LA; the concentration of lidocaine to inhibit them by 50% is 10–20 μM compared to 100–1000 μM for a 50% inhibition of resting state voltage-gated sodium channels,[15] accounting in part for the antiarrhythmic ability of systemic lidocaine, and, possibly, for some of the antihyperalgesic actions of this drug when infused intravenously to treat chronic pain.[16]

Ligand-Gated Channels. Ligand-gated channels are involved in sensory transduction, eg, transient receptor potential (TRP) receptors, purinergic P2X receptors, and are the primary receptors for ionotropic neurotransmission.

TRP Channels. A variety of sensory information is transduced from the primary stimulus (eg, heat, chemicals) to an electrical "generator current" through transient receptor potential channels. Notable among these are the TRP-vanilloid 1 (TRPV1) and TRP-ankyrin 1 (TRPA1) channels that respond, respectively, to heating and cooling to mediate the sensations of thermal pain and cold pain. Protons shift TRPV1 toward the open state, such that local inflammation, with its acidic environment and elevated temperature, promotes nociceptor activation and pain. LA have a dual action on the TRPV1 channel; at 1 "gating" site, they can open the channel and at another, in the channel's pore, they can pass through it, albeit much more slowly than Na^+.[17] Topical analgesia from LA results partially from actions on TRP channels, and their specific expression in sensory neurons, and particularly TRPV1 channels in nociceptors, sets a scenario for a nociceptive-selective block that is not achieved by voltage-gated sodium channel block alone (see section Recent Advances in Local Anesthesia).

Nicotinic Cholinergic and Glutamatergic Receptors. These channels are gated to an open state, causing the neuronal depolarization of excitatory synapses. The *N*-methyl-D-aspartate class of glutamate receptor is probably involved in local excitation after cutaneous injury, when glutamate is

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released into the skin. These receptors are also an essential feature of excitatory transmission in the spinal cord, where their elevated role in hyperalgesic states has been shown. Thus, both infiltration blocks and neuraxial anesthesia will likely involve the inhibitory actions of LA on these channels.[18]

G Protein–Coupled Receptors

Synaptic cellular communication and hormonal modulation result from the activation of G protein–coupled receptors. These ubiquitous, membrane-intrinsic proteins bind extracellular ligands of a wide chemical variety (small proteins, lipids, and neurotransmitters). Extracellular ligand binding causes conformational changes that result in the intracellular release and dissociation of small "G proteins" into the cytoplasm, with resulting activation of a wide variety of signaling pathways, including pathway-initiating phospholipases and adenylyl cyclases. Not all G protein–coupled receptors are sensitive to LA, but ones that are often experience 50% inhibition in the submicromolar range.[19] In addition to the variety of G protein–coupled receptors contributing to synaptic transmission (and glial activation) in the spinal cord, those in the skin are essential for pain responses after injury. Substance P (NK-1), bradykinin (B2), and endothelin-1 (ETA) receptors have all been implicated in hyperalgesia after cutaneous injury, eg, surgical incision, and inflammation; all 3 are inhibited by LA at concentrations infiltrated perioperatively. Inhibition may result from actions at several sites, but one that seems common to all 3 receptors is at the intracellular locus where the G proteins are bound. Interestingly, G protein–coupled receptors that use the $G_{q/11}$ form of the G protein are most sensitive to LA.

Intracellular Pathways

LA act at a number of locations of intracellular signaling pathways. Both phospholipases and membrane-associated protein kinases, eg, protein kinase C, are inhibited by LA.[20,21] These enzymes' activations result in cytoplasmic signaling that can release Ca^{2+} from intracellular stores,[21] initiate cascades of enzyme phosphorylation that eventual result in both acute changes in cellular activity, through changes in existing proteins, and long-term changes through gene activation and protein synthesis. All these responses occur over minutes to hours and so all can, in principle, be altered by locoregional anesthesia techniques which supply LA for surgical procedures lasting several hours, or administer LA continuously to wound, plexus or neuraxis for days after surgery or trauma. Inhibition may also occur during or after the prolonged intravenous administration of lidocaine, for relief of preexisting, persistent pain.

In a different action, lidocaine, in particular among LA, is known to trigger the release of calcium ions from intracellular stores. Both the endoplasmic reticulum and mitochondria will release stored calcium (by different mechanisms) when cells are exposed to clinical concentrations of lidocaine.[22] Brief exposure, for several minutes, transiently elevates calcium and thereby activates signaling pathways that normally rely on calcium for physiological responses. Longer exposures, however, can lead to pathological results, such as the long-term activation of the mitogen-activated protein kinase p-38, a signaling pathway intermediate whose persistent activity results in cell (neuron) death.[23] This may be one of the mechanisms underlying the well-documented neuropathies caused by high concentrations of lidocaine in the intrathecal space (see section Local Toxicity).

Membrane Properties: Fluidity and Phase Differences

Nonspecific actions, not directly involving proteins, occur when LA interact with lipid bilayer membranes. Because of their amphiphilic character, containing both polar (hydrophilic) and nonpolar (hydrophobic) regions, LA are adsorbed near the surfaces of lipid bilayer membranes, with the polar amine groups closer to the aqueous interface and the aromatic moiety reaching into the lipid interior (Figure 1).[24] The adsorbed LA molecules can modify the membrane's surface electrical charge, and can affect lipid dynamics, changing their lateral mobility in the plane of the membrane, and their rotational mobility as they interact with other lipids and proteins. In mixed lipid bilayers, containing various phospholipids and cholesterol, bulk regions of the membrane are in a more solid, "liquid-ordered" phase, while other regions are in a more "fluid" phase and others in a "gel" phase. LA partition selectively into the gel phase, causing a maximum disordering there; partitioning is lower, and so is the disordering effect, in the more fluid phases.[25] Such a selective disordering can alter the dynamics of the intrinsic membrane proteins that constitute the channels, receptors, and transporters, without a direct binding of the LA molecules to the proteins. "Annular" lipids in biological membranes surround and stabilize membrane-embedded proteins. They are much less mobile than those in the pure bilayer regions, and their motion is most affected by LA, being "fluidized" for greater mobility. Membrane protein activity is affected by these changes in annular lipids, both in their individual behavior, eg, gating of ion channels and rate of energy-dependent ion pumps, and in their interactions with other proteins. Furthermore, it is possible that a LA molecule bound to a site on a membrane protein could reach that site, and dissociate from it, by pathways through the annular lipids (Figure 1).[26] One intriguing possibility is that LA actions on annular lipids alter the association of β-subunits with the pore-forming α-subunit of Na^+ channels and thereby indirectly influence channel inactivation.

NEUROANATOMY

Nerve anatomy, including mechanical barriers to diffusion and the locations of the neural vasculature, greatly influences the actions of LA.[27] Peripheral nerves have 3 connective tissue sheaths. Single nerve fibers are interspersed in the endoneurium, a loose connective tissue which contains glial cells, fibroblasts, and blood capillaries. The cellular perineurium, an endothelial-like structure, encloses bundles of nerve fibers, fascicles, and the outermost epineurium surrounds the peripheral nerve and provides mechanical support during flexing and stretching. The epineurium is collagenous, and gathers together different nerve fascicles along with adipose and connective tissue, and blood vessels. The share of nonneuronal tissue in peripheral nerves can be quite high, at some locations (eg, sciatic nerve in the popliteal fossa) comprising more than half of the nerve's cross-sectional area.[28] Within any

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given nerve, there is a considerable interchange in fibers between different fascicles, often described as an intraneural plexus.[29]

The extracellular fluid around the nerve fibers is the endoneurial fluid, very similar to the cerebrospinal fluid in the central nervous system.[30] Its composition is very tightly controlled, and this is achieved by the blood-nerve barrier.[27] The latter consists of the perineurium and nerve blood vessels.[30] When one looks at the perineurium, the pars fibrosa, responsible for mechanic stability, can be differentiated from the pars epitheloidea, which confers selective permeability.[30] The blood-nerve barrier is supplemented by the myelin sheath in protecting nerve fibers. The perineurium is therefore the major rate-limiting step as LA permeate from the perineural injection site across the nerve structures and finally, across the lipid membrane of the nerve fiber (Figure 2). As LA diffuse toward their site of action, they are taken up by the systemic circulation, and adsorbed into adjacent tissues, eg, fat. The original descriptions of, eg, interscalene block suggested that up to 40 mL of LA be administered.[31] Only a very small share of the LA molecules injected during these blocks would ever take part in sodium channel blockade of the brachial plexus. Most would be lost during diffusion, and taken up into the systemic circulation, where they would exert effects that are now recognized as clinically relevant.[32] Accordingly, it should be noted that the LA injected perineurally has a much higher concentration than necessary for impulse blockade, for example, the critical concentration for lidocaine to block all nerve fibers is approximately 1 mM,[33] while injected solutions range between 37 and 74 mM (for lidocaine 1% and 2%, respectively).

Many diseases change neuronal ion channel composition and function. For example, diabetic neuropathy is associated with altered expression of voltage-gated sodium and potassium channels, leading to a higher sensitivity to LA and a higher stimulation threshold when using a nerve stimulator.[34] Waxman and colleagues[35] have even hypothesized that defects in sodium channel expression may be a contributing factor to, rather than the end-effect of, diabetic neuropathy.

CONTROVERSIES IN CLINICAL USE

Although LA are generally considered safe and reliable drugs, there are some potential limitations to their clinical use. These include allergy, resistance, tachyphylaxis, and the use in inflamed tissue.

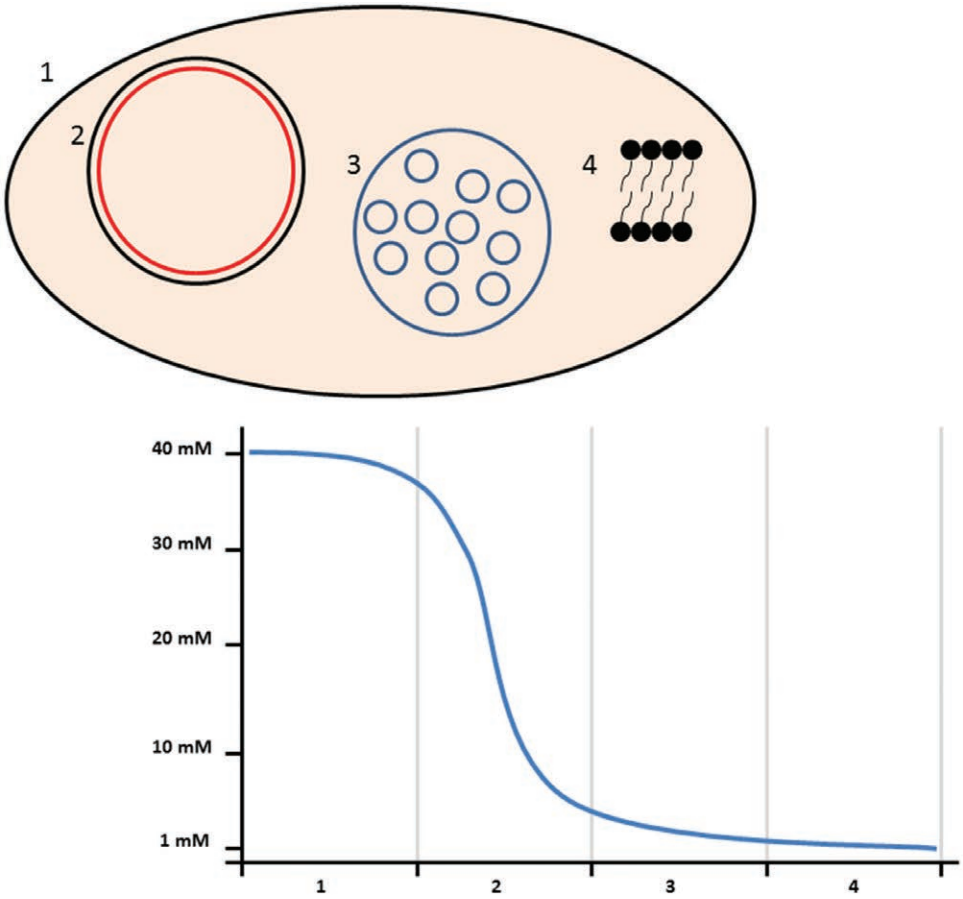


Figure 2. Concept of diffusion of local anesthetics across different barriers of a peripheral nerve. Upper panel, The concentrations of lidocaine (injected at 1%, 37 mM) in the different compartments of peripheral nerve during a functional block. Number under the x-axis refer to the compartments shown by the schematic in the lower panel. Local anesthetic is injected into the region outside the epineurium (1). A slight drop in concentration occurs during passage through this region, but the major reduction in [local anesthetics] occurs at the rate-limiting step, diffusion across the perineurium and blood-nerve barrier (2). Diffusion within the endoneurium (3) results in a shallow gradient of concentration before the local anesthetics molecules reach the neuronal plasma membrane (4), which contains their site of action (see Figure 1).

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Allergy: An Overestimated Event?

LA are highly unlikely to cause allergic reactions. Despite recurring reports of cardiovascular symptoms, such as palpitations, associated with LA administration, true allergy confirmed by standardized tests is exceedingly rare, <1%,[36–38] and worthy of publication as a case report.[39] Patients may report symptoms that may be misconstrued as allergy, but most often these are vasovagal in nature or caused by absorption of adrenaline in the solution, and are not confirmed by skin-prick tests for local reactivity.[37,38]

Most acute or delayed local reactions to LA are thought to result from other substances in the LA solution, or elicited by metabolites. Potential allergenic substances include sulfites, latex particles, or benzoates.[36] The last group has been the focus of attention because *para*-aminobenzoic acid is a metabolite of ester-type LA. Moreover, methylparaben, contained as a preservative in preparations of both amides and esters, may show allergic cross-reactivity with *para*-aminobenzoic acid, and is eventually metabolized to *para*-aminobenzoic acid.[40] It has therefore been suggested that *para*-aminobenzoic acid is the most frequent direct cause of LA-induced allergic reactions.[40] Therefore, ester LA have been considered more prone to elicit allergic reactions than amides, but due to the rarity of allergy, this has not been proven.[41]

Resistance: An Underestimated Phenomenon?

Even though the majority of failed regional anesthetic techniques are caused by technical factors, a small number of patients seem relatively or fully resistant to the numbing effects of LA. Mutations in voltage-gated sodium channels that do not affect their normal function can still affect the efficacy of LA to induce nerve blockade. For example, several mutations in the transmembrane segment IIIS6 of the rat brain α-subunit have been shown to decrease the affinity between sodium channels and LA and anticonvulsants.[42] Similar investigations have also been performed in sodium channel subtypes Nav1.7[43] or Nav1.5.[44] Interestingly, in the study on rat brain channels, different mutations led to differential response of these channels to LA. Similarly, a clinical study showed that some percentage of persons reporting inefficient regional anesthesia demonstrated partial resistance, and some patients had selective resistance against specific LA,[45] potentially since the binding site for LA is made up of multiple residues that have distinct interactions with specific drugs. One caveat in interpreting studies on LA resistance is that patients were tested using 1 clinically relevant concentration of LA, but not in a dose-response fashion, which would allow for the distinction between cases in which a higher dose might yet lead to sufficient analgesia (potency difference) and those in whom increases in dose would not (efficacy difference).

A recent case report and review of the literature established the groundwork to which new studies on this subject will hopefully adhere, including the identification of patients, family investigations, and analysis of genetic variants.[44] In summary, LA resistance does exist, even though the exact incidences for the differing variants are not yet known. While complete resistance to LA is very rare, it appears that subtle differences in reaction to local anesthesia can be discerned in some few out of a hundred patients.

Tachyphylaxis

Even when a satisfactory block is achieved, subsequent redosing can lead to tachyphylaxis. Cohen et al[46] performed the first mechanistic study on dogs in 1968, showing that repeated injection of lidocaine and procaine led to increasing acidification of the cerebrospinal fluid, and hypothesized that this might impair optimal drug access to the site of action. Since then, tachyphylaxis has also been described for peripheral nerve blocks, and the acidification theory has moved to the background. Tachyphylaxis does not invariably follow LA application, since in isolated nerves of rabbits, no tachyphylaxis could be demonstrated (even an enhancement of block was found).[47] Rodent in vivo experiments, however, showed tachyphylaxis after a series of only 3 injections, both for percutaneous peripheral nerve block and infiltration anesthesia. Both pharmacokinetic mechanisms[48] and spinal segmental nitric oxide[49] (the latter potentially effective via pharmacokinetic or dynamic mechanisms) have been implicated but the mechanism of tachyphylaxis remains elusive. Also, the clinical relevance of tachyphylaxis is unclear, and a recent systematic review found 13 clinical studies, of which 5 studies showed tachyphylaxis, 5 studies did not, and 3 studies were inconclusive.[50] In summary, despite basic science evidence, both the mechanisms and clinical relevance of tachyphylaxis are unclear.

LA in Inflamed Tissue

Inflammation may impede LA effectiveness. Clinically, blocks either fail outright or are of short duration. The 3 most commonly cited theories include increased tissue blood flow, the acid environment of inflammation, and increased excitability of nerves in inflamed tissue.[51] What evidence supports these theories, and what can be done to clinically increase LA efficacy? First, increased perfusion is a classic hallmark of inflammation, and seems to play an important role in decreasing the efficacy of LA. One strategy to counter this would be to add epinephrine to the LA, as Harris[52] described for a combination of LA plus epinephrine. A second strategy could be to increase the concentration of LA, as noted in a study by Rood[53], who found satisfactory anesthesia for inflamed gingival tissue with lidocaine 5%, while lidocaine 2% had a high failure rate.[54] The acidic shift seems to be important as well, and it is known that even a small decrease of 0.5 pH unit may shift the balance between charged and uncharged drug by up to 60%, but the human body has a very good buffering capacity,[55] and buffering LA solution does not seem to increase efficacy. Finally, peripheral sensitization may potentially make nerve blockade more difficult.[56] Therefore, it appears that inflamed tissue is harder, but not impossible, to anesthetize. Increasing dose or adding a vasoconstrictor can lead to successful blockade.[51]

Toxicity of LA

Local Toxicity. Direct LA–induced tissue toxicity remains a rare but important clinical concern, and the major obstacle to the development of new LA.[57] All classical LA in current use are potentially neurotoxic,[58] and similar evidence exists to support toxicity on muscles,[59] connective tissue,[60]

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and cartilage.[61] Neurotoxicity is well documented at 5% lidocaine, for spinal and peripheral nerves, and 1%–2% are routinely used clinically, resulting in a relatively poor therapeutic index. To be fair, toxic or growth-inhibitory effects of nonsteroidal anti-inflammatory drugs and opioids on these very tissues have also been demonstrated at concentrations interpreted as clinically relevant.[62,63] Several putative mechanisms for LA neurotoxicity have been investigated, but the "big picture" has not been established. In particular, it is unclear whether the different proposed pathways (eg, mitogen-activated protein kinase p-38, PI3K/Akt, caspase) are activated nonspecifically, eg, by elevated intracellular calcium, or whether they are specifically targeted by LA molecules.[64]

Is there a rank order in tissue toxicity among different LA? Some evidence suggests that equipotent doses of LA are equally toxic,[58,65] but other studies suggest that lidocaine is more toxic than bupivacaine.[66,67] Clinically, there is evidence that spinal anesthesia performed using lidocaine may be more frequently associated with new-onset neurological deficits than when bupivacaine is used.[68] Taking transient neurological syndrome, at least a part of which is drug-specific,[69] as exemplary evidence, lidocaine seems to be more irritating to spinal nerves than mepivacaine or bupivacaine.[70]

The precise incidence of LA-induced neurotoxicity is not known, because in many cases of new-onset neurologic symptoms, there are possible alternative mechanisms of neural damage, including needle trauma, hematoma, abscess formation, tumors, epidural lipomatosis, ossifications, surgical trauma, and positioning.[51] In peripheral nerves, the incidence of new-onset neurological deficits has been estimated in the range of several percent, but most of these resolve over time; permanent damage after peripheral blocks is exceedingly rare.[71] For neuraxial blocks, the major concern is spinal hematoma or abscess, and not toxicity per se, the incidence of which is lower than for peripheral blocks, but the prognosis more somber.[71] It is instructive to remember that, not long ago, hyperbaric 5% lidocaine continuously administered through spinal catheters was linked to cauda equina syndrome and the strategy, as well as 5% lidocaine, was discontinued.[72,73]

Systemic Toxicity. LA invariably end up in the systemic circulation, and the free share, not bound to proteins or red blood cells, determines whether they will cause systemic toxicity.[51] Importantly, LA dissociate relatively rapidly (over a few minutes) from plasma proteins, and are then available to permeate capillary walls and be taken up by perfused tissues, so protein binding is less important after bolus dosing, but becomes more important with continuous administration. Protein binding of LA predominantly involves albumin (high plasma concentration, low affinity) and α-1 acidic glycoprotein (low plasma concentration, high affinity). Fortunately, the acute phase response to surgery and trauma leads to an upregulation of α-1 acidic glycoprotein, thereby reducing the free fraction of LA.[74] There are 3 principal scenarios by which the threshold for toxicity can be exceeded: first, the LA may be overdosed relative to patient weight, metabolizing capacity, plasma protein concentration, or injection site perfusion; this will classically lead to a cascade of central nervous and systemic signs of toxicity as the plasma concentration gradually rises over time. Second, the LA can be injected intravenously; the initial symptomatology then depends on the dose injected, and can range from mild central nervous symptoms to seizure to instant cardiovascular collapse. Third, during nerve or ganglion blocks in the neck, LA may be injected intraarterially; with the small quantities usually injected, this would typically lead to immediate seizures without substantial cardiovascular effects.[51] A review of many cases showed that the symptoms encountered initially vary widely; only 60% of patients actually pass through the classic stages of minor central nervous system symptoms (eg, perioral tingling, metallic taste, tinnitus), followed by major central nervous system symptoms (seizures) and cardiovascular collapse.[75] Many patients either have only central nervous system symptoms or "jump" straight to cardiovascular symptoms. When interpreting symptoms, LA concentration and substance should be considered, because lidocaine and mepivacaine predominantly affect myocardial contractility, whereas the more lipophilic and potent drugs ropivacaine, levobupivacaine, and bupivacaine are both negatively inotropic, and at the same time highly arrhythmogenic.[76]

The incidence of systemic toxicity after regional block is rare, and recent estimates are between 1:1000 for nerve stimulator–guided blockade, and 1:1600 for ultrasound-guided regional anesthesia.[77] Sites et al[78] reported a case series of 12,000 patients with no serious complications. Whether the decrease in toxicity with the use of ultrasound is due to the better visualization of the spread of drugs, or the reduction in required LA is debatable, but most likely it is a combination of both.

The treatment of systemic toxicity is based on supportive treatment and simultaneous application of Intralipid,[79,80] a soybean oil emulsion that is widely used as basis for total parenteral nutrition products.[81] Two prominent pathways have been suggested for the mechanism of action of Intralipid: first, reducing the amount of free LA (the lipid sink theory); second, supporting mitochondrial metabolism by providing a high concentration of free fatty acids.[81] Despite all experimental evidence for these and further beneficial actions of Intralipid, it should be considered that the bulk of experimental evidence is based on rodent experiments, while most porcine experiments do not show the same promising effects.[51] Importantly, even though numerous case reports on successful rescue of patients from systemic LA toxicity have been published, the only human trial to investigate the lipid sink hypothesis was negative.[82] One recent pharmacokinetic simulation indicated that Intralipid may lower the cardiac and cerebral bupivacaine concentrations substantially within several minutes after application.[83] Intralipid is a valuable contribution to, but not a substitute for, careful and meticulous conduct of regional anesthesia.[51]

ADJUVANTS

Adjuvants have long been added to LA to decrease systemic absorption and to prolong blocks. As was the case for novel LA, concerns related to neurotoxicity have decreased enthusiasm for some drugs such as ketamine and midazolam.[84] Others, including epinephrine, clonidine/dexmedetomidine, dexamethasone, and buprenorphine,

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offer prolongation while not causing gross neurotoxicity. Unfortunately, currently used adjuvants prolong both motor and sensory block. Depending on the clinical situation, this may be undesirable, if patients feel uncomfortable about a prolonged paralysis of a limb, if it impedes postoperative monitoring of nerve function, or if it precludes early mobilization.

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Epinephrine

The prototypical adjuvant, epinephrine, has a double mechanism of action. First, it is vasoconstrictive and thereby increases the LA concentration over time in the nerve, leading to a longer block duration.[85] Second, relevant for epidural anesthesia, epinephrine also has α-receptor–mediated analgesic properties,[86] without evidence that it might increase neurotoxicity or cause ischemic injury. Addition of epinephrine to medium-acting LA such as mepivacaine and lidocaine will increase their duration of action by up to 1 hour,[87] while addition to long-acting drugs has little to no appreciable benefit. Usual concentrations in a LA solution range between 1 and 5 μg/mL.

Clonidine and Dexmedetomidine

The α-2 agonist clonidine prolongs block duration by up to 2 hours, both for medium- and long-acting LA.[88] However, sensory and motor block are extended equally, and some studies suggest that the effect may be dependent on the specific situation. A meta-analysis, for example, included 12 negative studies.[89] Adverse systemic events are of concern, including hypotension, bradycardia, and sedation, and limiting the clonidine dose to 0.5–1 μg/kg ideal body weight has been proposed. Next to actions on α-2 receptors, effects on hyperpolarization-induced currents have been conjectured as a mechanism of action.[90] Clonidine on its own will not block conduction.[90]

In contrast to clonidine, dexmedetomidine is a much more specific α-2 agonist, and prolongs both motor and sensory block by long-acting LA by approximately 4 hours[91] beyond that provided by plain LA, and is also more effective than clonidine in prolonging block.[92] A recent meta-analysis focusing on supraclavicular blockade reemphasized the risk of adverse effects from systemic α-2 agonists, as it showed a higher incidence of transient bradycardia and sedation with dexmedetomidine as compared to clonidine.[92] Also, the optimal dose of dexmedetomidine has not been determined; studies included in a recent meta-analysis had used between 3 and 100 μg,[93] and some authors have used up to 150 μg.[94]

Buprenorphine

The partial μ-opiate receptor agonist, buprenorphine, has been extensively studied for prolonging nerve block. Buprenorphine not only acts on κ- and δ-opioid receptors, but also possesses voltage-gated sodium channel-blocking properties.[95] Older reports indicated that buprenorphine might be used instead of LA to provide postoperative analgesia.[96] It is thought to prolong block from long-acting LA by approximately 6 hours, albeit with a significant increase in nausea and vomiting, such that its use has been largely abandoned, and is advised only when accompanied by multimodal prevention of nausea and vomiting.[87]

Dexamethasone

The most effective adjuvant for prolonging block duration with minimal side-effects is dexamethasone. Although the precise mechanism of action has not been elucidated, dexamethasone is in widespread use. Addition of dexamethasone to a LA will increase the block duration, depending on the type of LA, by ~2–3 hours when added to a medium-acting LA, and up to 10 hours when added to a long-acting drug.[97] Unfortunately, as mentioned above, this prolongation is accompanied be prolonged motor block. In clinical practice, between 4 and 10 mg of percutaneously injected dexamethasone are used.[98] Whether intravenous administration is equally effective has been discussed for a long time.[99] A recent meta-analysis suggests that percutaneous administration of dexamethasone is more effective than intravenous administration, by, on average, 4 hours, in prolonging analgesia by long-acting LA.[98]

RECENT ADVANCES IN LOCAL ANESTHESIA

Assuming equal efficacy and safety, the 2 most sought for characteristics of future LA action are controlled duration and selectivity (for pain, with minimal motor/autonomic deficits). Several recent advances in basic research show promise for achieving these characteristics clinically.

Extending the Duration of Action

The duration of LA actions is determined by the degree to which the drugs distribute into neuronal tissues and the speed at which the drugs are removed from those tissues (see section Neuroanatomy). More hydrophobic drugs distribute more strongly into the lipid depots of perineural fat and intraneural membranes, eg, myelin, and are therefore less accessible to the nerve fibers and also slower to be removed by the circulation. Some LA are intrinsically vasoconstrictive, others vasodilatory, and the difference can depend on the local concentration. The rate-limiting steps for removal will vary among specific LA, such that less lipophilic lidocaine's block duration is substantially increased by epinephrine, whereas more lipophilic bupivacaine's is less changed. Recent advances, however, have primarily focused on controlling the rate at which LA are delivered.

Slow-Release Formulations. The advantages of slowly released LA are a prolonged duration of action, which can vary according to the formulation itself, reduction in both local and systemic toxicity, and absence of in-dwelling catheters, with their attendant problems of tip migration and infection.[100] Although the inclusion of LA in lipid-composed multilayers has been studied for decades,[101] more recent formulations of slowly released LA have led to substantive preclinical discoveries. Lidocaine coformulated with the matrix of an absorbable bone wax produced rat sciatic nerve block lasting several days,[102] and, like lidocaine embedded in sheets of polylactic acid:polyglycolic acid,[103] suppressed postincisional pain in the innervated paw for up to 5 days.[104] Bupivacaine embedded in microspheres formulated from polylactic acid:polyglycolic acid also gave several days of sciatic nerve block, although, initially, anti-inflammatory drugs, eg, glucocorticoids, were required to achieve this block duration,[105] since the microspheres appeared to cause local inflammation and thereby limit LA action (see

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section Local Anesthetics in Inflamed Tissue). More recently developed bupivacaine-polylactic acid:polyglycolic acid microsphere formulations also provide long-lasting nerve block and suppress postincisional paw pain without needing an anti-inflammatory agent.[106] Local, preoperative infiltration of this bupivacaine-microsphere formulation at a skin incision site, while anesthetizing the skin for ~24 hours, suppressed both the pain at 4 days after skin incision[107] and the persistent pain after experimental thoracotomy,[108] suggesting that inhibition of some local injury–induced activity for the first few postoperative days suffices to suppress the development of persistent pain for at least 5 weeks. LA dissolved in relatively aqueous-insoluble matrices are also slowly released into the surrounding tissues. Bupivacaine dissolved in a fatty acid–based biodegradable polymer gave 48 hours of mouse sciatic nerve block.[109] In a very recent effort, ropivacaine was dissolved in a mixture of phospholipid and castor oil that has minimal aqueous solubility (proliposomal ropivacaine). When injected into the polar, aqueous environment of tissue, or of saline, the ropivacaine oil vehicle, which is much more stable than liposomal formulations, forms multilamellar particles that only slowly release the LA into the surrounding milieu.[110] The stacks of lipid bilayers in the multilamellar nanoparticles provide a lipophilic environment that is loaded with a high (w:w) proportion of ropivacaine, and when injected preoperatively at an incision site in pigs, delayed the appearance of postoperative pain for 24 hours. Subcutaneous injections of proliposomal ropivacaine in human volunteers gave analgesia to pin prick for twice as long (~24 hours) as that from plain ropivacaine, with resulting plasma concentrations well below the published toxic levels.[111] In contrast to the multilamellar structures of many slow-release liposomal formulations, the "Depofoam bupivacaine" of Exparel is composed of single bilayer lipid membrane "cells" clustered together into a foam-like injectable suspension.[112–114] Because these structures have a much lower lipid:aqueous ratio, the partitioning of LA is far less than in multilamellar liposomes or in the solid polylactic acid:polyglycolic acid microspheres, and the overall duration of experimental sciatic nerve block is only twice that of 0.5% bupivacaine, with greater local perineural inflammation at 2 weeks.[115] Many clinical trials have been published with Exparel but substantial questions have been raised about any increased effectiveness for postoperative pain compared to the far less expensive plain bupivacaine.[116] However, in fairness, none of the other slow-release LA formulations have been examined for clinical postoperative pain, and their eventual cost is unknown.

Photo-Triggered, On-Demand Release. A novel approach to controlling the duration of local anesthesia is to confer external control on the release of LA from internal storage depots. This has been accomplished by using infrared light, that penetrates into tissues to alter the properties of drug-encapsulating liposomes, either by the peroxidation of lipids mediated by a photosensitizer molecule incorporated in the initial formulation[117] or by a light-induced phase transition, mediated by liposome-bound gold nanorods that heat the liposomal membranes, effecting a thermally driven phase transition.[118] The gold nanorod approach appears especially promising, with no covalent chemical reaction needed for the membrane phase transition and with photo-triggered release of the active agent that can double the experimental block duration after paw infiltration in the rat from 12 hours, with no irradiation, to 24 hours, when light pulses are given at times when the block begins to regress. It remains to be shown how effectively a nerve block can be sustained when the drug-containing liposomes are deeply placed, eg, for a femoral nerve block, and light penetration is more challenged. And importantly, all of these studies were conducted using the nontraditional sodium channel blocker, tetrodotoxin, which has yet to be approved for clinical use as a LA.

Modality-Selective Blocks: Targeting Specific Channels

The voltage-gated sodium channels that are the primary targets for LA inhibiting action potentials have 9 mammalian isoforms, which are expressed differently in various tissues. In particular, the channel Nav1.7 has been closely linked to human somatic pain through familial genotyping of inherited hyperalgesia[119] or insensitivity to pain.[120] Interestingly, visceral pain is independent of Nav1.7.[121] This has naturally led to a search to develop Nav1.7-selective blockers, including small organic molecules[122,123] and even a monoclonal antibody.[124] A monoclonal antibody (SVmab1) directed against an extracellular domain involved in voltage-dependent gating of that channel, that is 1000-times more potent on Nav1.7 than on any of the other voltage-gated sodium channel, when given intrathecally or intravenously suppressed formalin-induced acute paw pain and also the persistent tactile hyperalgesia from nerve constriction injury.[124] One expects that analogous antibodies, directed against other voltage-gated sodium channel isoforms, will have selective analgesic actions, eg, targeting Nav1.9 for visceral pain, such as cystitis.[114] Promising preclinical results provide hope that such selective blockers will become effective clinical local analgesics.

Clinical applications may be closer with site 1 voltage-gated sodium channel neurotoxins. The small organic molecules tetrodotoxin and the various saxitoxins (STX) bind at the channel's outer opening (site 1), separate from the traditional LA binding site which is located deeper in the pore.[125] These toxins have high affinity and great specificity for many voltage-gated sodium channels, including Nav1.7, but lower affinity for some neuronal channels (Nav1.8, for example) and, importantly, for the cardiac voltage–gated sodium channel Nav1.5. These features endow site 1 neurotoxins with high potency for nerve block and virtually no cardiotoxicity. In addition, experimental nerve blocks in rats show a long duration and a synergistic action with traditional LA.[126] An exciting development in this field is the synthesis of an acetylated variant of STX that has high affinity for Nav1.7.[127] Clinicians can expect more of these designer toxin approaches, combined with a better understanding of the role of different voltage-gated sodium channels in pain of different tissues, for improved, functionally (analgesic) selective nerve blocks. A recently published phase 1 study reported effective cutaneous analgesia from the STX homologue neosaxitoxin (NeoSTX), with minimum

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systemic toxicity.[128] Subcutaneous delivery of NeoSTX combined with bupivacaine (0.2%) and epinephrine gave analgesia, tested by quantitative sensory testing, for up to 24 hours, far longer than plain bupivacaine or NeoSTX alone. Although some perioral tingling occurred with higher doses of NeoSTX + bupivacaine, these, along with plasma levels of NeoSTX, were reduced by the inclusion of epinephrine.[129]

Modality-Selective Blocks: Targeting Nociceptive Fibers

Peripheral nociceptors show a high expression of TRP channels, including TRPV1 and TRPA1 channels that are critical for pain transduction (see section Transient Receptor Potential Channels). LA can both activate these channels and also pass through their open pores.[17] Traditional LA are tertiary amines, whose neutral species readily permeates the bilayer region of neural membranes to reach the cytoplasmic compartment, from which they enter and block the voltage-gated sodium channel pore (Figure 1). Their permanently charged quaternary derivatives, eg, QX-314, which also block the pore, pass through bilayer membranes poorly. A novel strategy has been developed wherein quaternary LA enter nociceptors through the TRP channel pores, opened by agonists such as capsaicin (for TRPV1),[130] menthol (for TRPA1), or by conventional LA,[131] and produce a nociceptor-selective block. Interestingly, although bupivacaine at high concentrations catalyzes the entry of QX-314 into cells and prolongs the inhibition of the C fiber–related action potentials in isolated sciatic nerve, it does so in the absence of TRPV1 and TRPA1 channels. The basis for this C-fiber selective block is unknown, but regardless of the mechanism, the selective prolongation of peripheral nerve block may hold promise for clinical application.

SUMMARY

The science of LA is an active research field, and LA will continue to be one of the mainstays of contemporary perioperative medicine. It has become clear that LA have many actions aside from blockade of voltage-gated sodium channels. For example, they have strong anti-inflammatory effects mediated by G protein–coupled receptors which may be effected by systemic administration. Partial resistance to LA may be more frequent than previously thought. LA are toxic on many tissues, but clinically apparent nerve damage is very rare, and LA-induced toxicity after peripheral nerve block has a good prognosis overall. Systemic toxicity has become rarer with the introduction of ultrasound. Several adjuvants are used clinically, but they all prolong both motor and sensory block. Current new developments include novel sustained release or controlled release formulations, targeting of nociceptor-specific ion channels, and targeting of nerve fiber subtypes. These research efforts will hopefully lead to new substances with prolonged duration of action while at the same time exhibiting true functionally differential blockade. ■

DISCLOSURES

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