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Novel ideas of local anaesthetic actions on various ion channels to ameliorate postoperative pain

G. R. Strichartz*

Pain Research Center, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115-6110, USA
*E-mail: gstrichz@zeus.bwh.harvard.edu

This review considers the ion channels that underlie transduction of nociceptive energies in the periphery, that are involved in impulse initiation and propagation in peripheral sensory neurones, and that participate in pre- and post-synaptic actions in the spinal cord dorsal horn, in light of their susceptibility to local anaesthetics. Although there are results from experiments on isolated cells and tissues *ex vivo* that support the hypothesized actions, their extrapolation to actions *in vivo* and the consequences for peri- and postoperative pain control are largely speculative.

Postoperative pain arises from the interplay of three factors: (i) impulses generated from injured nerve fibres innervating the site of the incision/retraction/sutures; (ii) inflammatory mediators, such as cytokines, prostaglandins, endothelin-1, and nerve growth factor, which are elevated at the surgical site[14] and which sensitize uninjured and injured nerve fibres; and (iii) a sensitization of the pain-transmitting circuits in the spinal cord that increases their response to noxious stimuli and can introduce their responsiveness to non-painful stimuli, such as light touch or gentle pressure.

There is likely a temporal order that involves these three factors sequentially, with both interaction and overlap. The trauma of incision and of the compression and stretch from surgical retraction, clamping, etc. all will induce impulse firing in peripheral neurones. These discharges will activate central pathways involved in sensitization, but are probably largely restricted to the intraoperative period. Tissue damage, bleeding, and the release of chemoattractants from the injury sites will foster local inflammation.[14] The chemokines/cytokines that are presented by migrating and proliferating immune cells, such as TNF-α, IL-6, and prostaglandin E2 and prostacyclin, are known to enhance the excitability of neurones by enhancing specific inward currents,[4] particularly those expressed on nociceptors [e.g. Na$^+$ (Nav1.8 and Nav1.9)] and also by increasing the activation of the transient receptor potential vanilloid-1 (TRPV-1), which is the receptor for capsaicin (the pungent ingredient of hot peppers) and which is also activated by elevated temperature and protons, both of which occur at the sites of inflammation.[7] The interplay between inflammatory cells and neurones, plus resident cells, such as keratinocytes, the predominant cells of skin that secrete both cytokines and other neuro-active agents and that are activated by tissue damage, constitutes a local positive feedback loop. Mild noxious stimulation results in short-term pain from the transitory discharge of nociceptors, but substantial injury, as occurs in surgery, engages pathways of this positive feedback cascade and thus leads to a prolonged hypersensitivity of peripheral tissues.

Such prolonged peripheral sensitization results in a sufficient barrage of nociceptive impulses into the spinal cord (and, perhaps, the brain) that the properties of the 'receiving circuits' there are sensitized. Central sensitization accounts for the response of spinal 'pain transmitting' cells to normally non-noxious stimuli, such as are conveyed by Aβ-mechanoreceptors, accounting, at least in part, for the postoperative occurrence of tactile allodynia, a common symptom. Central sensitization also spreads beyond the spinal neurones that are normally directly excited from the injured tissue, such that stimulation of adjacent areas, adjacent dermatomes, or even those contralateral to the injury site now cause pain, a phenomenon called 'secondary' hyperaesthesia. Central responses clearly involve both neurones and glia, with resident spinal microglia showing early changes, within minutes after injury, and astrocytes being activated at a later time, and more persistently.[6] Both glial and neuronal involvement in pain are marked by the activation of signalling pathways initiated by MAPkinases; different cell types express different MAPkinase activation patterns at different times.[6] Their functional importance is revealed by inhibitors that prevent MAPkinase activation or action and also suppress the development of postoperative pain or cause a transient reversal of it.

Local anaesthetics can be used perioperatively to affect all three of these contributions.[17] Local infiltration around the wound site, and even deeper in the surgical cavity, can suppress the generation and propagation of injury-induced discharge during surgical manipulations. This action may be due, in part, to inhibition of the transduction and sensitization steps in nociception, for certain local anaesthetics, for example, bupivacaine and amethocaine, have been shown to block a transducing channel, TRPV-1, that plays a key role in the development of hyperalgesia after injury or inflammation.[8] It is noteworthy that lidocaine has been shown to activate this channel, which may account for the stinging pain that accompanies s.c. injection of this local anaesthetic.[10] Continuous delivery of local anaesthetics, from slow-release formulations or temporarily placed catheters, may extend such impulse inhibition for days after surgery. Local anaesthetics can also inhibit inflammatory and local sensitizing responses, by directing suppressing some phases of inflammation, that is, neutrophil priming,[1 2] and by blocking some of the neuronal pathways that are activated by inflammation, that is, protein kinase C, and certain G protein-coupled receptors.[1 12]

Block of peripheral nerves innervating a surgical site, by local or regional anaesthesia, is a traditional approach to perioperative pain control. Even when general anaesthesia is used, the addition of an epidural block can have salutary effects on outcome, perhaps by limiting the afferent impulse activity coming into the spinal cord and thus minimizing central sensitization. In such settings, local anaesthetics are used at concentrations that will prevent impulse transmission in all types of peripheral fibres, large and small myelinated axons, and non-myelinated C-fibres, thus obtunding motor and autonomic physiology and noxious and innocuous sensory inputs. In many cases, this is a desirable condition for surgery, although a persistent postoperative motor block, even of the foot or ankle, presents a serious impediment to the safe mobilization of patients, especially important after 'ambulatory' surgery.

Clinicians should not forget that coordinated motor performance relies on sensory feedback from proprioceptive and kinaesthetic fibres. The literature on local anaesthesia is frequently misleading in this fact, often equating the deficits of motor function with the block of impulses in the large, A-α motor fibres, whereas the sensory components of motor feedback loops are ignored. Indeed, numerous studies in experimental animals have shown that local anaesthetics, for example, lidocaine, are most potent in blocking impulses in small myelinated fibres, including the A-γ motoneurones that drive contraction of the muscle spindles. Block of these axons results in a flaccid spindle, a loss of Ia-fibre afferent activity into the spinal cord and a subsequent, profound reduction in firing of the motoneurone that contracts the muscle, without any requirement for direct effects on the A-α fibres.

Local anaesthetics acting on the spinal cord have been shown to suppress post-incisional pain, when the drugs are focally delivered at the neuraxis (spinal or epidural administration) and when they are present systemically, as the result of vascular redistribution of locally delivered drug or by intentional systemic delivery.[3]

In these various locations, local anaesthetics appear to act on a broad range of targets.[17] All known voltage-gated Na^+ channels that are present in the mammalian nervous system are blocked by local anaesthetics, with some modest differences claimed for potency.[11] In addition, a variety of Ca^{2+} and K^+ channels are sensitive to only slightly higher concentrations than those that block Na^+ channels.[5] TRPV-1 is both sensitized but also blocked directly by local anaesthetics, which also inhibit many G protein-coupled receptors, for example, the NK-1 receptors for substance P. In addition, inotropic glutamate receptors, such as the NMDA type, are sensitized,[13] accounting for part of the anti-hyperalgesic actions of spinal local anaesthetics.[16]

Finally, it is becoming increasingly apparent that local anaesthetics in the systemic circulation can profoundly alter postoperative pain. Plasma lidocaine concentrations of $2–4$ µg ml^{-1} ($\sim 8–15$ µM), during the perioperative period, have been shown to reduce postoperative pain scores and opiate consumption; the presence of these drugs in the circulation for only a few hours can suppress processes that would otherwise elevate pain for days after surgery.[9 15] These concentrations of local anaesthetics in plasma can be reached and maintained not only by continuous i.v. infusions, at safe and effective rates, but also from the vascular uptake of drugs deposited around a peripheral nerve or epidurally for local or regional anaesthesia. How often the benefit of systemically circulating agents follows unintentionally from local administration is an unanswered question.

The mechanisms of action by which systemic local anaesthetics suppress postoperative pain are unknown. At least, some hints may be found in studies of nerve injury-induced pain, where i.v. lidocaine has been shown to reverse mechanical sensitization and thermal hyperalgesia from ischaemia, nerve ligation, or neuroma formation. Recordings of peripheral nerve activity in such animals *in vivo* show spontaneous impulses and repetitive firing patterns that are absent in control animals, and which are transiently abolished by i.v. lidocaine doses such as those that reverse the abnormal pain behaviour.

Spontaneous firing and repetitive bursts of impulses in response to single, brief electrical stimuli can also be produced acutely in isolated peripheral nerves, by manipulation of the gating (opening and closing properties) of a small fraction of neuronal Na^+ channels. Application of the same low concentrations of lidocaine to these nerves also abolishes these aberrant impulses, showing that the block of Na^+ channels alone can account for these unusually potent actions. Perhaps, similar actions occur perioperatively.

One striking feature of reversal of neuropathic pain by lidocaine, seen both clinically and in experimental

animals, is a persistence of pain relief for days and weeks after drug infusions that last for only 30 min to a few hours. For lidocaine, this long-lasting effect is not merely a continuation of the relief that occurs during infusion, for abnormal pain returns quickly at the end of the infusion and then slowly disappears over the next 12–24 h, a time when plasma lidocaine concentration is virtually zero.

These persistent anti-hyperalgesic effects of i.v. local anaesthetics cannot be explained by block of Na^+ channels and are not linked invariably to peri-infusional pain relief, as that acute action is also accomplished by the Na^+ channel blocking drug mexiletine which, nevertheless, effected no long-term pain relief. It would be most useful to know how local anaesthetics prevent postoperative hyperalgesia for days after surgery, in the hope of developing new agents, or applying existing ones targeting this specific mechanism.

The overall effects of local anaesthetics, at the injury site and in the block of afferent impulses, and central effects afforded by drugs delivered intentionally to the neuraxis and incidentally to the systemic circulation[3] have the potential to suppress acute postoperative pain and, hopefully, to minimize the development of more chronic sequelae. Although the primary action of local anaesthetics during a peripheral nerve block is almost certainly by impulse block secondary to the inhibition of neuronal Na^+ channels, many of these other actions are independent of Na^+ channels, involving other known targets or, in other cases, sites of action and mechanisms yet to be identified.

Funding

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