The End of Postoperative Pain—A Fast-Approaching Possibility? And, if So, Will We Be Ready?

Brian M. Ilfeld, MD, MS and Tony L. Yaksh, PhD

The ability to abolish postoperative pain has been a dream of health-care providers for millennia. The quest of a painless postoperative course took an enormous stride forward over a century ago with the discovery of the dense regional anesthesia provided by perineural cocaine.[1] The synthesis of long-acting local anesthetics such as bupivacaine in the 1950s was a further advance in providing prolonged postoperative analgesia, and continuous nerve blocks allowed for an enduring local anesthetic delivery to both neuraxial and peripheral nerves. However, a significant limiting factor for both single-injection and continuous nerve blocks is the lack of affinity that currently available local anesthetics have for any one type of nerve fiber, resulting in a block of motor and proprioception fibers along with the desired sensory fibers.[2] Furthermore, all sensory fibers are affected—as opposed to just pain-conducting fibers—often resulting in an insensate extremity if enough anesthetic is provided in quantities required to reduce pain to a negligible level.[3] So, although great strides in postoperative analgesia have been achieved to date, our ability to provide a pain-free postoperative course remains primarily out of reach. Recently, however, there have been important preclinical advances demonstrating agents that exclusively target pain-conducting nerve fibers, raising the possibility that truly painless surgery may become a reality. This editorial will review the most significant advances in perineural block pharmacology, as well as discuss possible implications for the field of regional anesthesia.

LOCAL ANESTHETIC MECHANISM

Local anesthetics produce their effects by blocking voltage-gated sodium channels and thus inhibiting axon conduction. Importantly, most conventional local anesthetic binds from the intraluminal aspect of the channel and therefore must cross the hydrophobic lipid bilayer to have any effect. Because most local anesthetics currently in use are partly unprotonated at physiological pH, the unionized fraction may diffuse directly across the bilayer. In contrast, protonated molecules cannot readily pass the lipid membrane, will not gain access to the sodium-channel binding sites from the intraluminal side, and do not block the channels. As currently understood, voltage-gated sodium channels are responsible for conduction in all types of nerve fibers—motor, light touch, pain, and so on. The phenomenon of differential block (eg, sensory > motor) produced by various current local anesthetics is explained by the result of varying size and other physical attributes of the different fibers, but not based on a distinction regarding drug preference for the sodium channels in any population of axons. Several recent advances in pain biology demonstrate the ability to target specific axon types, allowing highly specific conduction blockade of subpopulations of nerves, and we will review two of the most significant here.

First, the cloning and characterization of sodium channels have revealed at least 9 structurally-distinct channels (Na_V 1.1–1.9).[4] Significantly, several of these subtypes are unique to small sensory axons and are not found on large afferents (low threshold), motor nerves, or cardiac myocytes. Several molecules have been described that exclusively block the sodium-channel subtype Na_V 1.8, resulting in potent analgesia in preclinical models.[5,6] Importantly, the pharmacology spared motor axons and proved an evident differential effect on sensory and motor function.

Second, various types of sensory afferent fibers display unique channels with unique chemical-gating properties. One such channel is the TRPV1 (transient receptor potential vanilloid 1) found

From the Department of Anesthesiology, University of California, San Diego, CA.
Accepted for publication June 13, 2008.
Address correspondence to: Brian M. Ilfeld, MD, MS, Department of Anesthesiology, UCSD Center for Pain Medicine, MC 7651, 9500 Gillman Dr, La Jolla, CA, 92037-7651 (e-mail: bilfeld@ucsd.edu).
Funding for this project was provided by the Department of Anesthesiology, University of California, San Diego (San Diego, Calif). Dr Ilfeld is supported by NIH grant GM077026 (Bethesda, Md). Dr Yaksh is supported by NIH grants DA002110, DA015353, and NS016541 (Bethesda, Md). The contents of this editorial are solely the responsibility of the authors and do not necessarily represent the official views of these entities.
Reprints will not be available from the authors.

ISSN: 1098-7339
DOI: 10.1097/AAP.0b013e3181962547

predominantly on polymodal nociceptor fibers—nerves activated by high-threshold noxious thermal and mechanical stimuli as well as various inflammatory products such as kinins and protons.[7] This channel is best known for its activation by capsaicin, which results in the opening of the large conductance transmembrane pore. This pore normally allows the influx of calcium, but other relatively large molecules can enter as well when the channel is opened. Last year in the journal *Nature*, Binshtok et al[8] reported using the TRPV1 channel properties to produce potent blockade of pain fibers, while sparing other sensory and motor fibers in rats. In brief, they used the quaternary lidocaine analogue QX-314—basically a charged lidocaine molecule—that blocks sodium channels only when applied intracellularly because it is routinely protonated and does not easily diffuse across the cellular lipid bilayer to reach the sodium-channel binding sites (Fig. 1). By adding capsaicin that opened the TRPV1 channels, the lipophobic QX-314 crossed the lipid bilayer through the TRPV1 channels and terminated the action potential via traditional sodium-channel binding and blockade. Because only this subpopulation of pain-specific nerve fibers contain TRPV1 channels, the lidocaine analogue could not gain entry to other afferent axons, and only those TRPV1-bearing axons (conducting pain sensations) were blocked. When QX-314 or capsaicin were administered alone, little or no effect on sodium conduction or pain behavior was elicited—the combination was required to provide capsaicin that opened the TRPV1 channels and allowed QX-314 cell entry.

These observations provide important direction for producing a targeted and specific block of various subclasses of sensory axons. For example, a specific receptor, TRPM8 (transient receptor potential melastatin 8), helps modulate thermosensation in the peripheral nervous system and mediates the detection of cold thermal stimuli by primary afferent sensory neurons.[9] Others receptor ionophores may be associated with fibers conducting itch/pruritus, stretch, and other sensations. This strategy of targeting specific afferent axons suggests the possibility that the clinician will be able to target the information carried by these functionally distinct subpopulations. Of equal interest is the possibility that such a strategy might serve to produce dense—but selective—blocks after intrathecal delivery.

CAVEATS

Obviously, there is a great deal of progress that must be made in both the preclinical and clinical arenas before making painless surgery a reality. For example, prolonged capsaicin exposure results in irreversible neurotoxicity, and therefore, other TRPV1 channel triggers must be found for use in humans. Interestingly, lidocaine was recently reported to open the TRPV1 channel (the source, in part, of lidocaine's well-known initial sting?).[10] This suggests that some combination of lidocaine analogues and QX-314 might be effective to produce a complete sensory and motor surgical block and a subsequent, persistent pain-specific block.

In addition, what will be the cerebral and cardiac effects of an inadvertent intravascular injection? In the rat model, a QX-314/capsaicin injection does not result in cardiac toxicity at any reasonable dose, as the local anesthetic does not have an entry site to cause cardiac electroconduction abnormalities (personal communication, Clifford Wolf, PhD, December 19, 2007). These considerations, however, should not divert from the significant changes in clinical practice promised by new-found abilities to target functionally defined subpopulations of nerve fibers. Unless some unforeseen and insurmountable technical hurdle arises, it is probable that a pain-fiber–specific sodium-channel blocker will be available for clinical use within the next decade.

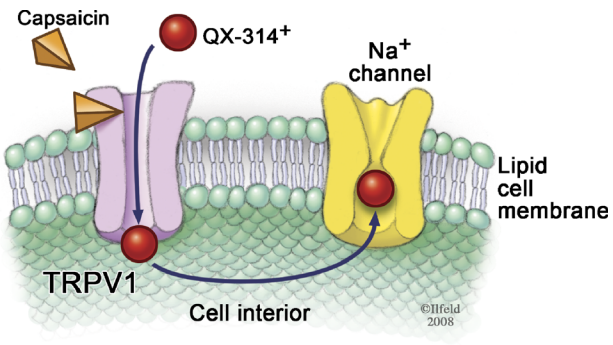

FIGURE 1. A quaternary lidocaine analogue, QX-314, passes the neural lipid bilayer via capsaicin-triggered TRPV1 channels, thus blocking sodium channels and inhibiting nerve conduction. Since TRPV1 channels are found only on pain fibers and not other sensory and motor fibers in rats, the result is a pain-specific neural block.

CLINICAL IMPLICATIONS

If, and when, such a local anesthetic becomes available clinically, will the medical community be able to provide it to patients? Simple wound infiltration would most likely be inadequate to provide complete analgesia: wound infiltration with currently available local anesthetics affecting all neural fibers types may decrease nociceptive transmission, but usually does not provide complete analgesia/anesthesia as do neuraxial and peripheral nerve blocks.[11] There is little reason to believe that using wound infiltration with a new medication that blocks only a small fraction of the nerve fibers would produce results superior to those that are obtained with currently available local anesthetics. Therefore, any new sodium-channel blocking agent will presumably require placement perineurally, much as neuraxial and peripheral nerve block techniques deposit with conventional local anesthetics. Because anesthesiologists are currently the specialists with a predominant role placing percutaneous nerve blocks, they are the most prepared within the medical community to apply newly developed perineural analgesics.

Given that the primary concern of surgical patients is postoperative analgesia,[12] it is difficult to imagine many patients being willing to undergo surgical procedures without a newly available analgesic providing a pain-free postoperative course. To retain their patient base, surgeons worldwide would have little choice but to ensure that their anesthesiology colleagues could and would provide this new perineural anesthetic. Conversely, anesthesiologists would have little choice but to gain the knowledge and skills necessary to provide the new analgesic. And, unlike current practice in which regional analgesia is applied to only a subset of surgical procedures, neuraxial and peripheral nerve blocks would be expected for nearly all surgeries resulting in even a moderate degree of postoperative pain. Are anesthesiologists ready to provide this care?

Currently, many anesthesiology residents—at least in the United States—do not gain enough regional experience to become adept at basic single-injection techniques such as brachial plexus blocks.[13] Even the relatively few individuals who acquire additional skills in regional anesthesia fellowships are often not prepared to provide neural blockade of all peripheral nerves (eg, paravertebral and head/neck nerve blocks).[14] In short, if a pain-fiber–specific sodium-channel blocker becomes clinically available, it is doubtful that current health-care providers will be

able to offer it to patients on a wide-scale basis.[15] Tens of thousands of providers will require relatively rapid training in advanced regional anesthesia techniques. This task would be further complicated if the new medication required prolonged infusion to provide adequate analgesic duration because training in perineural catheter placement and infusion management would also be required. In addition, because many patients now remain hospitalized exclusively to receive potent analgesics, rendering them pain-free would negate the need for a prolonged hospitalization, but would require additional provider training in ambulatory perineural infusion techniques.[16] Associations of regional anesthesia providers such as the American Society of Regional Anesthesia will be best suited to organize and deliver such training; but the enormity of training so many practitioners in a relatively short period would be overwhelming.

Will a pain-fiber–specific sodium-channel blocker become a reality? It already is.[8] Will a medication with similar effects become available for clinical use within the next decade? The odds are probably better than not. Are we ready? Not even close.

REFERENCES

1. Ruetsch YA, Boni T, Borgeat A. From cocaine to ropivacaine: the history of local anesthetic drugs. *Curr Top Med Chem*. 2001;1:175–182.
2. Borgeat A, Kalberer F, Jacob H, Ruetsch YA, Gerber C. Patient-controlled interscalene analgesia with ropivacaine 0.2% versus bupivacaine 0.15% after major open shoulder surgery: the effects on hand motor function. *Anesth Analg*. 2001;92:218–223.
3. Ilfeld BM, Loland VJ, Gerancher JC, et al. The effects of varying local anesthetic concentration and volume on continuous popliteal sciatic nerve blocks: a dual-center, randomized, controlled study. *Anesth Analg*. 2008;107:701–707 .
4. Cummins TR, Sheets PL, Waxman SG. The roles of sodium channels in nociception: implications for mechanisms of pain. *Pain*. 2007;131:243–257.
5. Ekberg J, Jayamanne A, Vaughan CW, et al. muO-conotoxin MrVIB selectively blocks Nav1.8 sensory neuron specific sodium channels and chronic pain behavior without motor deficits. *Proc Natl Acad Sci U S A*. 2006;103:17030–17035.
6. Jarvis MF, Honore P, Shieh CC, et al. A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. *Proc Natl Acad Sci U S A*. 2007;104: 8520–8525.
7. Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. *Annu Rev Neurosci*. 2001;24:487–517.
8. Binshtok AM, Bean BP, Woolf CJ. Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. *Nature*. 2007;449:607–610.
9. Bautista DM, Siemens J, Glazer JM, et al. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature*. 2007;448:204–208.
10. Leffler A, Fischer MJ, Rehner D, et al. The vanilloid receptor TRPV1 is activated and sensitized by local anesthetics in rodent sensory neurons. *J Clin Invest*. 2008;118:763–776.
11. Rowlingson JC. How can local anesthetic in the wound not help? *Anesth Analg*. 2001;92:3–4.
12. Warfield CA, Kahn CH. Acute pain management. Programs in U.S. hospitals and experiences and attitudes among U.S. adults. *Anesthesiology*. 1995;83:1090–1094.
13. Smith MP, Sprung J, Zura A, Ruetsch YA, Gerber C. A survey of exposure to regional anesthesia techniques in American anesthesia residency training programs. *Reg Anesth Pain Med*. 1999;24:11–16.
14. Neal JM, Kopacz DJ, Liguori GA, Beckman JD, Hargett MJ. The training and careers of regional anesthesia fellows-1983–2002. *Reg Anesth Pain Med*. 2005;30:226–232.
15. Hadzic A, Vloka JD, Kuroda MM, Koorn R, Birnbach DJ. The practice of peripheral nerve blocks in the United States: a national survey. *Reg Anesth Pain Med*. 1998;23:241–246.
16. Ilfeld BM, Le LT, Meyer RS, et al. Ambulatory continuous femoral nerve blocks decrease time to discharge readiness after tricompartment total knee arthroplasty: a randomized, triple-masked, placebo-controlled study. *Anesthesiology*. 2008;108:703–713.

