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Acute Pain: Pathophysiology and Clinical Implications

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Progress in postoperative pain management decreases morbidity after surgery.[1] To advance patient care, reduce perioperative morbidity, and decrease healthcare costs, it is critical that we improve acute postoperative pain management. Our armamentarium of drugs for acute pain management has been limited to opioids, controlled delivery of local anesthetics, and nonsteroidal anti-inflammatory drugs or acetaminophen. For acute pain management, we operate using guidelines from the early 1990s that reinforced the generous use of opioids for acute pain even though effective dosing is limited by deleterious side effects. Anesthesia-based acute pain services popularized continuous epidural analgesia, which controls pain better during activities and continuous regional techniques for specific surgeries. If the 1990s assured us opioids should be used with confidence, the last 5 years has demanded efficacious alternatives to opioids with fewer side effects and, perhaps, improved outcome. This is in contrast to patients with rheumatoid arthritis who may be treated with drugs that block the action of inflammatory mediators such as tumor necrosis factor or interleukin-1 (IL-1).[2]

With increasing new knowledge and techniques come important opportunities and challenges for developing insights into the causes, mechanisms, and treatment of human disease. For anesthesiologists, we have an opportunity to treat surgery and trauma as a disease, and this requires investigation into the pathological processes that occur in the perioperative period.[3] One component of the pathophysiology in surgery is acute postoperative pain.

Our long-term goal will be to eliminate postoperative pain. This will require that we develop a better understanding of the mechanisms for surgical pain and prepare to use recent discoveries in biomedical research.[4]

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As we learn more about the etiology for postoperative pain, we will develop mechanism-based, disease-specific treatments. This paper will examine clinical pathophysiology of postoperative pain and recent discoveries about incisional pain.

CLINICAL POSTOPERATIVE PAIN

Most patients have pain at rest after surgery. This is measured using visual or verbal pain scales in the absence of any provocative maneuvers. Pain with activities after

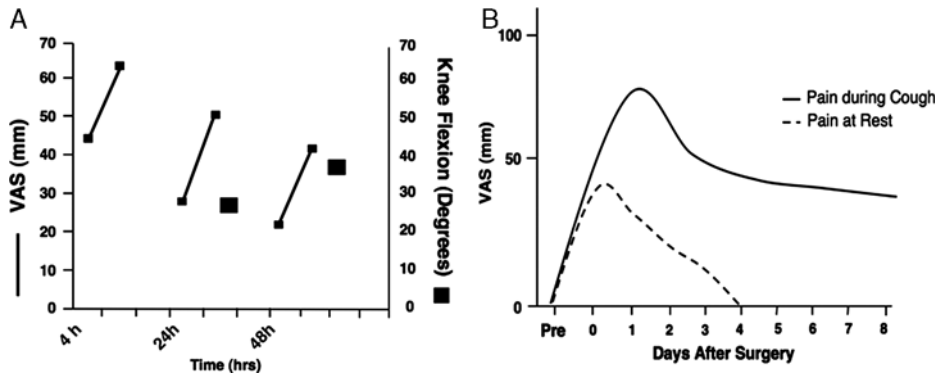

Figure 1. *A*, Pain at rest pain and during flexion after unilateral total knee arthroplasty: visual analog scale (VAS) pain scores at rest and during knee flexion after total knee replacement and optimized pain treatment with patient-controlled analgesia using opioids (Adapted from Singelyn FJ, et al.: *Anesth Analg* 1998; 87:88–92).[5] Small squares connected by lines are VAS scores and large squares are the degree of flexion associated with the pain score. *B*, Pain at rest and during cough after hysterectomy: schematic of VAS pain scores at rest and during cough after abdominal hysterectomy and optimized pain treatment with patient-controlled analgesia using morphine. (Reprinted with permission and adapted from Moiniche S, et al.: *Acta Anaesthesiol Scand* 1997; 41:785–9.)[6]

surgical operations should be measured using functions which are related to morbidity. For example, pain with knee flexion after total knee replacement is a measure of evoked pain (Figure 1A).[5] Early improvement in pain with flexion and improved range of motion have been shown to produce sustained increases in function for weeks to months after surgery.

After abdominal and thoracic surgical procedures, patients complain of pain at rest that is typically present for 3-5 days after surgery (Figure 1B).[6] In some cases, the duration may be greater. Pain measured with activities varies depending on the type of surgery. For abdominal surgical procedures, pain evoked by coughing, movement, and pressure is also present. Such evoked pain is greater than pain at rest, tends to be poorly responsive to opioids, and is present for a longer period of time especially with more extensive upper abdominal and thoracic procedures (Table 1).

Other Pain Measurements

Other pain tests have been explored in patients to attempt to understand sensitization and further quantitate post-operative pain. One of these tests is punctate secondary hyperalgesia, usually mapped or quantified by a small punctate mechanical stimulus applied outside the area of an incision, for example, after nephrectomy[7] or colectomy.[8] In some cases the force required to provoke pain after surgery is quite small indicating a touch stimulus has been converted to pain by the surgery.[7] This remote hyperalgesia is secondary because the test site is outside the area injured by the incision, the area of primary hyperalgesia (Figure 2). Central nervous system sensitization causes pain in the secondary zone because the sensory fibers function normally outside the area of injury.[9] Evidence indicates ketamine administration intraoperatively and in the immediate postoperative period produces sustained inhibition of secondary hyperalgesia after surgery (Figure 2).

In one study of pediatric patients, the primary punctate force for the abdominal flexion reflex was measured in children after herniorraphy.[10] A weak force provoked a flexion response after surgery and the response magnitude was increased as well. Using a different mechanical test after hysterectomy, a blunt probe was applied near or distant to the incision and the threshold pressure that evoked pain was recorded.[6] Again a widespread area of sensitivity can be measured and this persisted for up to 1 week after surgery. These tests have the advantage in that the stimulus intensity can be quantified.

In clinical postoperative studies, analgesics must be available as needed and therefore, superimposed on pain scales and measurements is the patients analgesic consumption, which may confound the detection of a novel treatment. Furthermore, a problem with some evoked pain measures such as pain during cough is that there is difficulty to standardize the effort.

Table 1. Methods to Measure Pain in Patients After Surgery and Example Surgery for Each Measurement

Clinical Postoperative Pain	Clinical Example
Pain at rest	Any surgery
Pain during activities: standing	Hip replacement
Pain during activities: ambulation	Hip replacement
Pain during activities: cough, spirometry	Abdominal or thoracic surgery
Pain during activities: knee flexion/extension	Knee replacement
Pressure pain threshold	Abdominal surgery
Area of mechanical hyperalgesia	Nephrectomy
Flexion response to mechanical stimuli	Pediatric hernia repair
Swallowing	Tonsillectomy

PREEMPTIVE ANALGESIA

The search for preventive analgesic treatments with prolonged benefits continues in part because pain research has

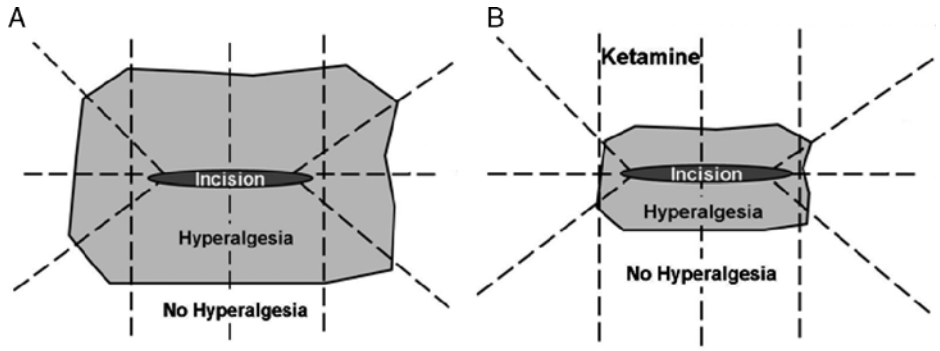

Figure 2. *A*, Area of hyperalgesia to von Frey filament applications in patients after nephrectomy treated with opioids for postoperative pain control. *B*, Area of hyperalgesia in patients after nephrectomy treated with opioids and ketamine infusion for postoperative pain. (Adapted from Stubhaug A., *et al.*: *Acta Anaesthesiol Scand* 1997; **41**:1124–32.)[7]

emphasized the plasticity of the nociceptive system and pain memory. The perioperative period is ideal for translating concepts such as pain memory, plasticity, and preventive treatments because the nature of the injury (surgery), its onset, duration and degree are generally known; in addition, the patients can be assessed before the injury to evaluate the role of predisposing factors (genetic, psychosocial, etc.).

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Thus, an important goal in perioperative medicine is to pretreat postoperative pain so that long-term benefits can be gained.[11] Trials of preemptive analgesia compare the effect of drugs administered before injury with the same treatment administered after injury.

Clinical trials of preemptive analgesia using randomized, controlled protocols strongly indicate that conventional treatments such as local anesthetics and opioids do not exhibit significant preemptive analgesic effects for postoperative pain. Most studies evaluating short-term and long-term effects of local/regional anesthesia largely indicate short-term benefits of regional anesthesia.[12] For example, in a study comparing nerve block to general anesthesia after upper extremity surgery, patients who received nerve block bypassed the postanesthesia care unit more frequently, reported less pain, ambulated earlier, and were ready for home discharge sooner (Figure 3).[13] For follow-up, there was no significant difference between groups in pain scores and medication use.

We must be careful and not conclude that plasticity and pain memory have little role in postoperative pain. It is important to note that clinical plasticity may depend on a variety of issues such as the kind of surgery, the type and duration of the treatment strategy, the analgesic or pain modality tested and the characteristics of the patient before surgery. The exact model for sensitization and plasticity in perioperative care has not been determined. Plasticity may be present on nociceptive nerve terminals producing enhanced responses in these primary afferents–peripheral sensitization. A much greater emphasis has been made on plasticity of pain transmission in the central nervous system. In the future, it is important for anesthesiologists and surgeons to determine how these plasticity models should apply to perioperative care. Furthermore, what treatments are effective and the duration of neuroplasticity treatment must be determined.

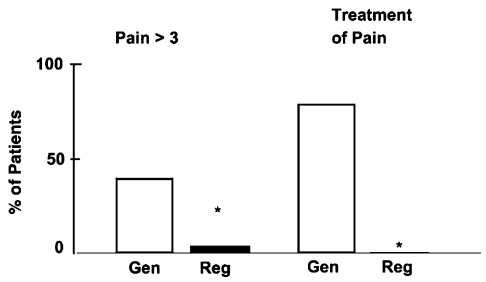

Figure 3. Pain evaluation and treatment of patients undergoing outpatient upper extremity surgery under regional (Reg) or general (Gen) anesthesia. Percent of patients with visual analog scale pain score greater than 3 and percent of patients requiring treatment in the recovery room are shown. Marked short-term benefits in regional anesthesia are noted. Benefits beyond the day after surgery were not apparent.[13] There was no later reduction in pain and opioid use. (Adapted from Hadzic A, et al.: *Anesthesiology* 2004; 101:127–32.)

Acute Opioids Tolerance and Hyperalgesia

Early studies examined preemptive and preventative opioid analgesia for postoperative pain relief after major surgeries. These results largely were lacking in positive results. More recent studies suggest there may be negative effects of early administration of high-dose opioids in the intraoperative period. Some studies indicated that administration of a high but not a low intraoperative opioid dose was associated with either increased pain or greater opioid consumption in the postoperative period. Not all studies are in agreement with these findings. Further studies will be needed to determine whether the development of acute tolerance in patients exposed to a high intraoperative opioid dose occurs and if acute opioid-induced hyperalgesia develops in the postoperative period.

The direction of perioperative medicine must emphasize preventative analgesia studies, and:

- Pretreatment analgesia studies using novel treatment strategies.
- Examine the potential long-term benefits of analgesic treatments by better understanding persistent pain that occurs for up to 6 weeks after surgery.
- Modification of the development of chronic pain after surgery.
- Nonopioid analgesic treatments.
- Therapies that modify the acute and chronic opioids tolerance.

HUMAN MODELS FOR INCISIONAL POSTOPERATIVE PAIN

Kawamata *et al.*[14] subjected volunteers to a small incision in the volar forearm to examine the etiology of pain caused by incisions (Figure 4). Experiments such as these contribute to our understanding of the mechanisms for postoperative pain and make an important link between clinical postoperative pain and basic research in animals on pain mechanisms caused by incisions. Spontaneous ongoing pain was maximal when the incision was made and then it decreased and disappeared within 30 minutes (Figure 4A). There was no sustained spontaneous pain after incision. Primary hyperalgesia was apparent immediately after incision and maintained for several days. This study indicates that small 4-mm incisions in humans produce only transient ongoing pain but persistent hyperalgesia for several days (Figure 4B). The disappearance of pain at rest and maintenance of pain with activities and in response to mechanical stimuli at the wound site is also present in patients after surgery.[6] Furthermore, evoked pain in patients is longer lasting than ongoing pain. Both this translational study and other clinical studies show that pain at rest caused by incisions and evoked pain are likely transmitted by different afferent fiber populations and/or different receptors. For incisions, enhanced responsiveness of central neurons and pain require ongoing afferent input from the incision.

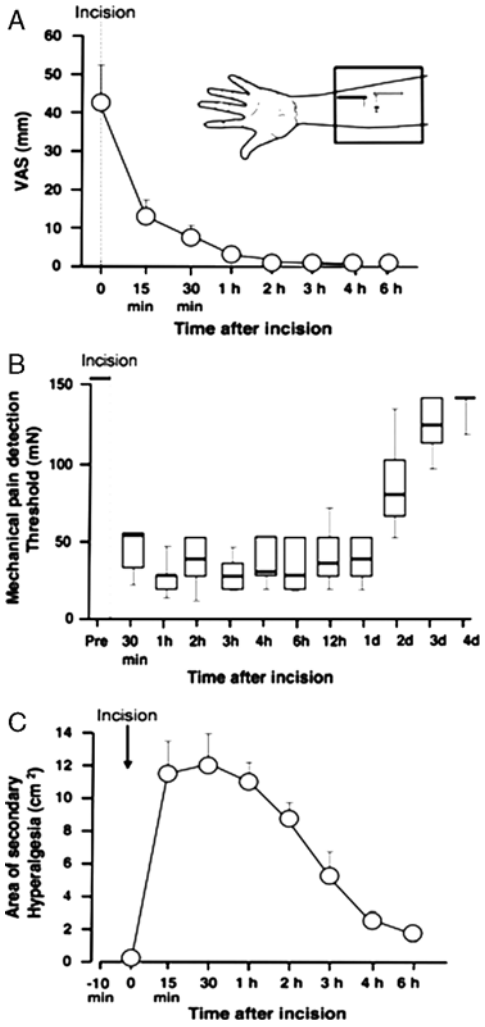

Figure 4. *A*, Pain after skin incision: average visual analog scale pain score at rest after incision in the volar forearm of volunteers. *B*, Primary hyperalgesia after skin incision: pain threshold for primary mechanical hyperalgesia after incision in the volar. Box and whisker plots indicate data expressed as median (horizontal line) with first and third quartiles (boxes), and 10th and 90th percentiles (whiskers). *C*, Areas of mechanical pain after skin incision: average area of hyperalgesia after incision in the forearm. Reprinted with permission from Kawamata M, *et al.*: *Anesthesiology* 2002; **97**:550–9.

Infiltration with a local anesthetic to block the pain before the experimental incision initially prevented ongoing pain and the primary mechanical hyperalgesia. Pain from the incisions was also eliminated when lidocaine was injected after the incision. However, in both cases, as the local anesthetic effect disappeared, the primary hyperalgesia returned, and for the most part, the hyperalgesia was the same in the pretreatment and treatment after incision groups. In patients, local anesthetic injections made before surgery are roughly equivalent for reducing pain to injections made after surgery.

Kawamata *et al.* also mapped the area of hyperalgesia caused by incisions and this area included the uninjured zones as described above (Figure 4C). Secondary hyperalgesia, pain evoked outside the injured area, is one measure of enhanced responsiveness of the central nervous system–central sensitization. As opposed to ongoing pain

and primary mechanical hyperalgesia, the large area of hyperalgesia did not develop when local anesthetic injection was made before the incision. This area of hyperalgesia could not be reversed by local anesthetic injection after incision. In patients after surgery, in some cases, certain treatments greatly reduce the area of hyperalgesia but do not greatly modify clinical measures of postoperative pain such as pain scores and opioid consumption.

MEDIATORS OF PAIN FROM SURGICAL TISSUES

Recent human investigations have measured the release profile of nociceptive mediators from surgical incisions in patients undergoing cesarean section.[15] Wound exudates were collected at 1, 6, and 24 hours after cesarean delivery, and pain scores and analgesic consumption were measured at the same time. Many cytokines were increased after incision. Interestingly, wound prostaglandin E2 and nerve growth factor, known algogenic substances, were increased in incisions. Other pain-related mediators of interest, including IL-1, IL-4, IL-6, IL-8, IL-10, IL-17, and tumor necrosis factor, typically peaked at 6 hours and remained elevated for 24 hours. Analgesic consumption during the first 24 hours was inversely correlated with some cytokines in the incision. The lack of significant correlations between wound and serum levels emphasized the importance of local release and local concentrations contributing to pathophysiology.

From basic science studies, other pain-related mediators present in incisions likely contribute to pain caused by surgery. Tissue pH decreases immediately after incision, is sustained for several days and then recovers by 7 days.[16] During the period of decreased tissue pH, pain behaviors are evident. When the tissue pH returns to normal, wound healing has occurred and pain behaviors are diminished. The decreased pH is localized at the incision site and not to areas surrounding the incision. Further experiments show that incision increases tissue lactate concentrations.[17] The peak increase occurs on postoperative day 4 and returns to the control level between postoperative days 7 and 10. The greatest average concentration was approximately 5 mM.

From studies by others, the facilitation of pH responses by lactate is suggested to be a mechanism for ischemic pain.[18] This mechanism may contribute to pain in the postoperative setting. Lactate is increased in incisions when tissue pH is decreased and therefore pH and lactate together could contribute to pain caused by incisions.

TRPV1/CAPSAICIN RECEPTOR AND POSTOPERATIVE PAIN

Capsaicin is the pungent ingredient in hot peppers. Capsaicin is a specific activator of the transient receptor potential type vanilloid 1 (TRPV1), a nonselective cation channel expressed on nociceptors. TRPV1 is activated by painful stimuli such as heat, acid, capsaicin, and lipoxygenase products.[19] TRPV1 is a molecular integrator of pain transduction and has been identified as a molecular target for the treatment of postoperative pain.

A recent trial tested a TRPV1 antagonist in patients undergoing third molar dental extraction. The appearance of marked hyperthermia at low doses of TRPV1 receptor blockade in humans without evidence of analgesia suggests that systemic TRPV1 blockade elicits undesirable hyperthermia and surgical patients may be highly susceptible to this hyperthermia.[20]

Capsaicin itself has been tested as an analgesic treatment in postoperative patients. Exposure to capsaicin initially causes burning pain. In human volunteer studies using natural capsaicin, there is a late, selective, reversible desensitization of nociceptive C-fibers.[19] This is thought to be the basis of the long-lasting analgesia produced by capsaicin treatments.

A recent clinical study examined the analgesic efficacy of wound instillation of capsaicin during open groin hernia repair (Figure 5).[21] Area under the curve visual analog scale was significantly lower during the first 3 days postoperatively. No clinically significant serious adverse events including abnormal wound healing were observed. In a

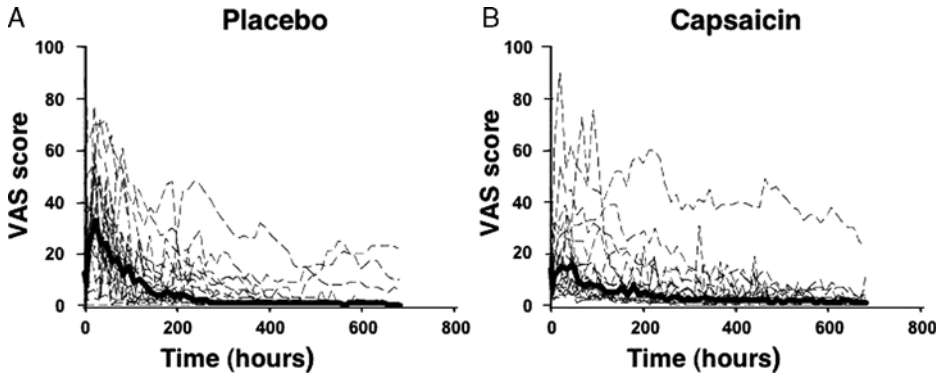

Figure 5. Effect of capsaicin instillation after hernia repair. *A*, Median (solid line) visual analog scale (VAS) pain scores after placebo installation in patients undergoing inguinal hernia repair. *B*, Median (solid line) VAS pain scores after ALGRX 4975 installation for inguinal hernia repair. A significant difference in the area under the curve for VAS was present for the time period from 4 hours until the morning of the third postoperative day. (Reprinted with permission from Aasvang EK, et al.: *Anesth Analg* 2008; 107:282–91.)[21]

recent report, the effect of capsaicin administered into the surgical site immediately before wound closure was examined. Capsaicin significantly reduced postoperative pain after total knee arthroplasty from 4 to 48 hours after surgery. Altogether, these data indicate that capsaicin administered into surgical wounds is a candidate for novel analgesic treatment for postoperative pain. Few side effects may be noted because capsaicin acts on the pain at its origin, has a long duration of action, and produces largely local effects. Clinical barriers still exist in the goal to develop a formulation that would not require general or regional anesthesia before infiltration so that immediate side effects are no longer problematic.

In a recent report, we described the analgesic effects of a TRPV1 receptor antagonist in the plantar incision.[22] Only a small effect on heat hyperalgesia was noted; guarding and mechanical responses were not affected. In agreement, using TRPV1 knockout mice, heat hyperalgesia induced by incision was completely abolished by loss of TRPV1, while guarding pain behaviors and mechanical withdrawal responses, although small in mice, were not affected.[23]

However, pretreatment with dilute capsaicin, either by infiltration or by proximal perineural application, has a differential effect on pain-related behaviors caused by plantar incision.[24] Both heat hyperalgesia and guarding pain behaviors were inhibited by capsaicin treatments. Punctate mechanical withdrawal thresholds were only transiently increased. These results show that dilute solutions of capsaicin are selective for their effects on pain-related behaviors after plantar incision. Altogether, these results indicate that TRPV1-containing afferents are critical for guarding pain but the TRPV1 receptor is not. Other receptors on TRPV1-containing afferents must be important. Furthermore, these data suggest that when evaluating novel treatments for postoperative pain, studies using a single-stimulus modality such as mechanical withdrawal threshold may overlook an analgesic effect by not examining a variety of stimuli. Altogether, these clinical studies and our data suggest that guarding behavior may translate to clinical postoperative pain.

GABAPENTINOIDS

Gabapentin and pregabalin are antiepileptic drugs that have shown antihyperalgesic properties in human pain models. Gabapentinoids are used extensively in chronic pain, especially neuropathic pain. The topic of gabapentinoid use in postoperative pain has been reviewed extensively.[25] In general, postoperative opioid usage, pain scores, and opioid-related side effects were reduced. In some cases, gabapentinoids increased certain side effects such as dizziness and sedation.

Questions concerning gabapentin's use in the perioperative period.

- Is gabapentin analgesic in all postoperative patients or only after selected surgeries?
- Are opioid-related side effects decreased?
- Do gabapentin's effects go beyond opioid sparing?
- Can the perioperative use of gabapentin influence the development of chronic pain after surgery?

The mechanism(s) of action of gabapentin's analgesic effects are not precisely understood. It is well established that gabapentinoids bind the α2δ site of voltage-gated calcium channels.[26] One hypothesis is that their analgesic effects are secondary to the blocking of neurotransmitter release caused by activation of voltage-gated calcium channels. More recently, evidence indicates that gabapentinoids may act chronically by displacing an endogenous ligand that is normally a positive modulator of α2δ subunits.[27] There are various sites at which gabapentin may act on α2δ subunits of the voltage-gated calcium channel. The effect of gabapentinoids may be to displace an endogenous ligand and impair the ability of the α2δ to increase calcium concentration at the plasma membrane. Thus, gabapentin may exert its effect on intracellular α2δ during assembly, trafficking to the plasma membrane and/or binding to the cell surface.

SENSORY-SELECTIVE NEURONAL BLOCKADE

Infiltration or nerve blockade with local anesthetics often produces effective pain relief after surgery. However, in many cases complete sensory loss and motor blockade limit the utility of local anesthetics for postoperative pain control. To improve the duration of analgesia, there has been a marked increase in the use of continuous administration of local anesthetics by perineural catheters in the last 5 years. However, for most cases of nerve blockade, the duration of action of local anesthetics is insufficient given the duration of postoperative pain. A variety of additives to local anesthetics has been tested to attempt to prolong nerve blockade and enhance the sensory specificity of the nerve blockade while sparing the motor effect. Additives also have the potential to reduce the dosage of local anesthetic required.

Recent reports describe drug combinations using capsaicin and local anesthetics in an attempt to produce selective and long-lasting nerve blockade with better antinociceptive and antihyperalgesic effects. It was recently showed that lidocaine derivatives, which are relatively ineffective at producing local anesthesia, can be targeted into nociceptors by the application of TRPV1 agonists (Figure 6).[28] For example, coapplication of the lidocaine derivative, QX-314 with capsaicin restricted the uptake of QX-314 to neurons expressing the TRPV1 receptor. Motor and tactile deficits were not evident with the combination QX-314 and TRPV1 agonist.

This strategy may also be useful to enhance the effect of clinically used local anesthetics. For example, to examine the sciatic nerve block properties of local anesthetic/capsaicin combinations, local anesthetics were followed by injection of capsaicin 10 minutes later.[28] Each of the local anesthetics caused a predominantly pain-related nerve blockade when they preceded the capsaicin injection,

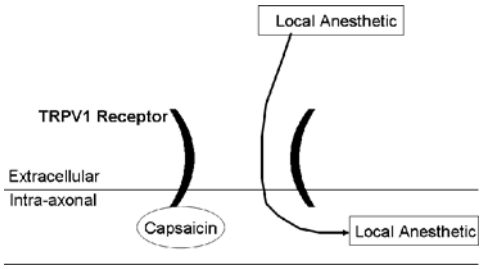

Figure 6. Local anesthetics can produce a predominantly sensory/nociceptor-selective block when administered before injection of capsaicin. Capsaicin facilitates the entry of local anesthetics into pain transmitting sensory fibers. The combined application of capsaicin agonists and local anesthetics or their charged derivatives is a new potential strategy to achieve a long-lasting sensory block for regional analgesia and postoperative pain management. TRPV1 = transient receptor potential type vanilloid 1.

whereas the simultaneous administration of local anesthetics and capsaicin did not. These findings indicate that local anesthetics can be administered before capsaicin perhaps reducing pain in patients caused by capsaicin.

Altogether, these data indicate that combined application of TRPV1 agonists and local anesthetics improve the long-lasting sensory-specific regional nerve blockade compared to the local anesthetic alone.

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Recently, lidocaine has been shown to transiently activate the TRPV1 channel. Therefore, the combination of lidocaine, to transiently activate the TRPV1 receptor, and QX-314 were studied for rodent nerve blockade.[29] Coinjection of QX-314 and lidocaine prolonged the pain-related blockade. Blockade was much longer lasting than the QX-314 or lidocaine administered alone. Altogether, these data suggest that TRPV1 agonists may be used to facilitate entry of local anesthetics to intracellular sites of action. As TRPV1 is sensory neuron-specific receptor, the local anesthetic effect is preferentially sensory-related and in some cases may be prolonged.

CONCLUSIONS

In many cases, our understanding of fundamental pathophysiologic mechanisms provides the rationale for particular therapies in perioperative medicine. However, this is not yet the case for postoperative pain management in which symptom management is the basis for treatments. As new sensitizing chemicals and novel receptors for pain transmission are discovered, our specialty must integrate the knowledge to problems important for our patients. Mechanisms for pain and hyperalgesia from incisions are not well understood but are relevant to all anesthesiologists. Clinical and basic research can unlock the etiology of incisional pain and, direct biomedicine toward treating the problem.

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