Mechanisms Leading to [CHRONIC] Post-Operative Pain: And ways to avoid it.

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Learning Objectives: The goal of this lecture is to present data on the incidence of clinical post-operative pain, discuss some of the known and speculative factors/mechanisms for this pain, and present data on current and potential future drugs for prevention or treatment of this condition.

1. WHEN DOES CHRONIC POST-OPERATIVE PAIN OCCUR?

Chronic post-operative pain often occurs after common surgical procedures, including thoracotomies (Dajczman et al., 1991; Karmarkar and Ho, 2004), breast surgery (lu and Fine, 2005), cholysystectomy and herniorrhaphy (Tverskoy et al., 1990; Bay-Nielsen et al., 2001) (overall, cf. Perkins and Kehlet, 2000; Poobalan et al., 2003; Eisenach 2006a,b; Wilder-Smith et al., 2006). It is characterized by both resting and incident-related pain, the latter most often provoked by pressure or torsion as the patient twists and turns, ambulates or even just sits and breathes, contributing to morbidity and delaying or preventing a return to a full and active life (Macrae, 2001; Pavlin et al., 2002). The single factor that seems to be predictive of the duration and degree of prolonged (several months) or chronic (>6 mos) post-operative pain is the intensity of the acute post-operative pain reported by the patient (Katz et al., 1996; Ochroch and Gottschalk, 2005) which itself can be a response to a high degree of tissue/nerve injury and/or inflammation, or an indication of the individual patient's response to an unexceptional surgical procedure.

2. MODELS FOR POST-OPERATIVE PAIN

Several animal models and a few human surrogate models for post-operative pain have been developed. Animal models, exclusively on rodents, include **a.** skin incision (SI), of the plantar paw skin, sometimes with damage of the underlying muscle (Brennan et al.,1996; Wu et al., 2009), and incision of the hairy skin on the rat's back (Duarte et al., 2005), **b.** incision and retraction of the skin and muscles of the rat's inner thigh (SMIR; Flatters and Strichartz, 2006; Flatters, 2008), entrapping the saphenous nerve and c. thoracotomy with rib retraction (TRR, Buvanendran et al., 2004). Mechanical stimulation reveals heightened pain from these procedures that has distinctly different, procedure-dependent characteristics (Table 1): 1. for both SI procedures, elevated pain is present at the "primary" (1°) area near the incision, with some secondary (2°) allodynia at more distant sites, or 2. for SMIR, pain is characterized by a strong 2o allodynia, in the region innervated by the sciatic n., or 3. for TRR, persistent pain is characterized by profound and extensive 1°and 2° allodynia, rostral and caudal to the wound site. These elevated pain conditions last various times, from 4-6 d for skin incision, with or without intentional muscle damage, ~4 wks for SMIR, and >6 mos for TRR. The latency from the time of surgery to the appearance of heightened pain also varies, with that from skin incision showing up as soon as 30min or less, from SMIR after ~3 d and from TRR after ~6 d. In addition, the percentage of operated animals that develops pain differs: near 100% for skin incision, 75-80% for SMIR and ~50% for TRR. The fact that fewer animals develop the more severe pains, and after a longer time after surgery, may reflect the complex combination of factors that are required for chronic pain to occur.

	Percent Occurence	Induction Stage (latency)	Duration	Modality of Hyperesthesia	Nerve injury
Skin Incision (S.I.)	100%	1-4 hr	4-7 d	Mechanical, heat	yes
Skin Muscle Incision Retraction (SMIR)	75-80%	2-3 d	4-5 wks	Mechanical (2° location)	no
Thoracotomy with Retraction (TRR)	40-50%	5-6 d	>6 mos	Mechanical and Cold	yes

Table 1: Comparative features of three animal models for **Post-Operative Pain.**

3. DO GENETIC FACTORS ACCOUNT FOR THE LARGE VARIATION IN PAIN REACTIONS TO THE SAME PROCEDURE?

How much is due to neuropathic pain due to nerve damage? Although some authors have claimed that genetic factors are likely to account for the large variance in clinical chronic pain development after the same surgical procedures (Kehlet, et al., 2006), the animal data show that the same variance in behavior also occurs with heavily inbred rodent species, where genetic differences are much smaller. Furthermore, there is a widespread notion that chronic post-operative pain is largely neuropathic pain resulting from nerve injury during the surgery, but a recent neurological analysis of post-thoracotomy patients shows that only about half of the chronic pain can be classified as neuropathic (Steegers et al., 2008).

4. PERIPHERAL MECHANISMS THAT CONTRIBUTE TO CHRONIC PAIN.

A. Soluble substances. *Chronic pain is probably initiated by relatively acute (0-24-48 h) pain caused*

by local tissue damage, release of "pro-inflammatory" mediators combined with nerve trauma from surgical manipulations. It is likely that substances released from injured tissue at sites of incision/retraction are essential for establishing the prolonged excitability and neural discharge that drives central sensitization and chronic pain after surgery. Evidence for this hypothesis comes from post-incisional pain studies and from experiments on peripheral nerve activation during inflammation. In the paw incision model, treatments that reduced local **nerve growth factor (NGF)** levels reduced thermal but not mechanical hyperalgesia, whereas treatments that reduced free Tumor Necrosis Factor alpha (TNF-α) affected neither modality (Zahn et al., 2004). NGF content and expression increases in the peri-incisional tissue, as early as 2-4 h after incision, and lasts for ~7d (Wu et. Al., 2007). Pain after paw incision also corresponds to an increase in H+ activity for up to 4d at the incision (Woo et al., 2004), a change that may account for some of the TRPV1-dependent changes in spontaneous activity from afferents at this incision site (Banik and Brennan, 2009; see **TRPV1,** below). These behavioral changes can be ascribed at least in part to peripheral responses, as spontaneous activity and hyper-responsiveness to cutaneous stimuli occur in excised skin-nerve preparations (Banik and Brennan, 2008).

Mechano-allodynia after hairy skin incision of the rat's back is suppressed by inhibitors of ***endothelin-A receptors*** (ETA; Mujenda et al., 2007) for **endothelin-1** (ET-1; cf. Khodorova et al., 2009a for review). However, such inhibition occurs only when the inhibitor is given pre-operatively, during the induction stage (0-4h), implying that ETA receptors are important for induction, not for maintenance of allodynia. In other studies, the subcutaneous injection of micromolar [ET-1] in rats causes allodynia, which is prevented by pre-treatment with antagonists of NMDA-type ***glutamate receptors*** (Khodorova et al., 2009b); the later stage of this allodynia is selectively reversed by inhibitors of ***TRPV1 receptors*** and of ***CGRP1 receptors*** (Balonov et al, 2006; Khodorova et al., 2009b), implicating these receptors in the ET-1-triggered mechano-sensitivity. *Blockade of ETA receptors during the induction stage of post-incisional pain has no effect on primary mechano-hyperalgesia one day later, but totally prevents 2o allodynia measured 24 h after the incision, showing that those peripheral fibers that are activated by ET-1 serve a critical role in central sensitization after incision (Mujenda et al., 2007).*

Injection of 100-fold higher concentrations of ET-1 into the paw causes pain and activates C- and A delta- nociceptors (Gokin et al., 2001a), thus creating an afferent discharge and nociceptive input to the spinal cord that lasts for ~30min. Since ET-1 is synthesized and secreted by keratinocytes that are the major cells of the epidermis, extensive trauma to the skin, e.g., by retraction after incision, will release a large quantity and ET-1 (Khodorova et al., 2009a) which can stimulate nociceptive fibers acutely and directly and, as its concentration falls, will continue to sensitize peripheral fibers to cause allodynia. We intend to measure ET-1 levels in tissues at surgical sites, and also ET receptors, both known to be increased after local injury (Klass et al., 2000).

Glutamate and **calcitonin gene related peptide (CGRP).** Both of these substances are likely candidates to mediate an enhanced responsiveness of peripheral nociceptors, including that caused by ET-1. Glutamate plays an important role in hyperalgesia (Jackson et al., 1995) by participating in both central and peripheral pain transmission (Beirith et al., 2002). Ionotropic glutamate receptors are present on the peripheral terminals of small diameter primary afferents (Carlton et al., 1995; Coggeshall and Carlton, 1998; Kinkelin et al., 2000) and glutamate is released in the plantar skin following high threshold A delta- and C-fiber stimulation of the sciatic nerve (de Groot et al., 2000). Injection of glutamate and of agonists for ionotropic glutamate receptors into the normal rat hind paw (Beirith et al., 2002; Leem et al., 2001) results in acute mechanical hyperalgesia, while local, but not systemic, administration of the NMDA receptor antagonist MK-801 attenuates inflammatory mechanical hyperalgesia induced by Freund's complete adjuvant (Leem et al., 2001). Peripheral metabotropic glutamate receptors also appear to contribute to post-incisional pain, since mechano-induced changes in weight-bearing were significantly prevented or reversed by , respectively, pre- or post-operative intra-plantar injections of an mGluR5 receptor antagonist (Zhu et al., 2005). In contrast, a local antagonist of AMPA/kaianate type glutamate receptors was ineffective on paw incision-induced pain (Lee et al., 2006)

***B. <u>Receptors and Channels</u>*. Changes in Na+ and K+ enhance neuronal excitability.** Impulse firing not only occurs immediately after incision (the "injury discharge" but also persists as spontaneous, ectopic firing from the injured tissue for hours and days afterwards. This hyperexcitability is due to changes in the ion channels that critically determine impulse threshold, notably, neuronal Na+ channels (Devor et al., 1993; Matzner and Devor, 1994,) particularly the nociceptor-expressed Na+ channels Nav1.7, 1.8, and 1.9 (Amir et al., 2006). In cultured neurons the expression of Na+ channels is increased by exposure to NGF (Toledo-Aral et al.,1995), which is known to be released from peripheral tissues by injury (see above). Both threshold and the propensity for repetitive firing are shaped by several types of K+ channels that are known to be down-regulated after procedures that result in hyperalgesia (Ishikawa et al., 1999; Kim et al., 2002; Rasband et al., 2001). And it is further noteworthy that **NGF** has been shown to rapidly modify the gating properties of the delayed-rectifier type of these channels as well as that of a

class of voltage-gated Na+ channels in isolated rat DRG pain neurons.

There is evidence that TRPV receptors, including the classic **TRPV1, capsaicin receptor,** that is activated by chemicals in hot peppers, by H+ that are elevated in the acidic environment of inflammation, and by supra-physiologic temperatures, are involved in a number of responses of skin to damage and inflammation. Mice that are deficient in TRPV1 have lowered hyperalgesic responses to inflammation, although normal heat sensation remains (Caterina et al., 2000). In biopsies of breast skin taken from women with breast pain, TRPV1 is elevated in cutaneous nerve fibers (Gopinath et al., 2005).

Receptors in skin. Activation of TRPV1 in isolated keratinocytes results in the up-regulation of COX-2, with a concomitant increase in PGE2 and in the release of IL-8, a pro-inflammatory interleukin (Southall et al., 2003). This illustrates the point that damaged non-neuronal tissue not only can contribute substances that will excite or sensitize local neurons, but themselves have receptors and pathways that engage in signaling pathways closely associated with pain sensation.

Relating these observations back to the release of soluble factors, nerve growth factor (NGF) increases TRPV1, acting through the trkA receptor (Zhang et al., 2005). In one analyzed pathway PI3Kinase is closely coupled to trkA, with downstream activated Src kinase ultimately binding to and phosphorylating TRPV1, followed by the protein's insertion into the plasma membrane. NGF, which is freed by injured tissues adjacent to peripheral neurons, also can be taken up and transported to sensory cell bodies in the DRG, where it stimulates the MAPKinase p38, leading to an increase in TRPV1 protein (but no mRNA) in these sensory neurons, 24h after injury or inflammation (Ji et al., 2002). So it appears that both local stores at neuron terminals and stores of TRPV1 in the cell soma can be recruited to enhance TRPV1 activity after injury or inflammation.

C. Other peripheral mechanisms. In addition to the actions of chemicals released by incision and trauma (retraction), there are physical actions that can sensitize peripheral nerve. Incision itself, in cutting local blood vessels, reduces blood flow and leads to **local ischemia** (Kim et al., 2007). The pressure from retractors pressing tissues against muscle or, particularly, bone (as in the TRR model), will almost certainly cause local ischemia and hypoxia. In isolated rat sensory neurons, moderate hypoxia has been shown to increase excitability (Gruss et al., 2006). **Stretch of nerve fibers** is known to induce action potentials, perhaps by altering the gating of voltage-sensitive Na+ channels (Morris and Juranka, 2007), and **inflammation,** such as would occur at an incision, or in tissue after retractor-induced ischemia and reperfusion, induces mechano-sensitivity in peripheral nerves (Bove et al., 2003).

5. CENTRAL MECHANISMS CONTRIBUTING TO CHRONIC PAIN.

A. Glial contribution to pain. It has been increasingly apparent that spinal glial cells play an essential role in persistent pain sensitization (reviewed in DeLeo and Yezierski, 2001; Watkins et al., 2001; Ji and Strichartz, 2004; see DeLeo et al., 2007). Spinal glial cells are activated by several different pain-inducing procedures, such as peripheral nerve injury (Garrision et al., 1991), paw incision (Wen et al., 2009), and inflammation (Ragahavendra et al., 2004). Intrathecal injection of glial inhibitors such as fluorocitrate, propentofylline, and minocycline have been shown to reduce pain sensitivity after inflammation and nerve injury . After their activation, spinal glial cells produce various inflammatory mediators, such as proinflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α), NO, and PGE2, to increase spinal cord neuron sensitivity and enhance pain .

Accumulating evidence supports a role for spinal microglia in neuropathic pain, and it seems likely that identical processes will be involved in chronic post-operative pain. Nerve injury induces the expression of microglial markers (e.g. CD11b, TLR4, CD14) within several hours . Specifically, nerve injury upregulates several receptors, such as the chemokine receptors CCR2 and CX3CR1, ATP receptor P2X4, and Toll-like receptor-4 in spinal microglia. Blocking or deleting these receptors results in decreased neuropathic pain (Abbadie et al., 2003; Tsuda et al., 2003; Milligan et al., 2004; Verge et al., 2004; Tanga et al., 2005). A microglial inhibitor, minocycline, has been shown to prevent/delay neuropathic pain, but not to reverse established neuropathic pain .

Less is known about the role of astrocytes in pain regulation. But astrocytes are closely associated with synapses (Haydon, 2001). Astroglial activation is typically preceded by microglial responses (Kreutzberg, 1996). CFA inflammation increases the expression of microglial markers (e.g. Mac-1, TLR4, CD14) in a few hours, but elevates the expression of the astrocyte activation marker GFAP after several days . Microglial activation is known to cause astroglial activation . Further, astroglial activation in the spinal cord is more persistent than that of microglia in several different chronic pain states . Therefore, spinal astrocytes could play a role in the maintenance of chronic pain, due to their delayed and persistent activation characteristic. Intrathecal injection of an astroglial "toxin", alpha-aminoadipate, suppresses nerve ligation-induced mechanical allodynia (Zhuang et al., 2006). We hypothesize that a very similar mechanism occurs during chronic post-operative pain, and that this astrocytes-selective drug will have a similar effect on SMIR- and TRR-induced pain.

B. MAP kinase regulation of glial function and persistent pain. Mitogen-activated protein kinases (MAPKs) play important roles in persistent pain sensitization by regulating intracellular signaling

and neural plasticity (reviewed in Ji and Woolf, 2001). The MAPKs family includes 3 major members: extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK) that represent 3 different signaling cascades. Interestingly, MAPKs are also activated in spinal cord glial cells after tissue and nerve injury and play important roles in regulating the synthesis and release of proinflammatory cytokines (reviewed Ji and Strichartz, 2004; Ji et al., 2009). For example, nerve injury induces a dramatic activation of p38 in spinal microlgia, which plays a critical role in the development of neuropathic pain (Jin et al., 2003; Tsuda et al., 2004; Svensson et al., 2005). Wen et al. have recently shown that p38 activation in spinal microglia after paw incision also contributes to the development of post-operative pain (Wen et al., 2009; see Preliminary Studies, below). Nerve injury induces JNK activation selectively in spinal astroglia (Ma and Quirion, 2002; Zhuang et al., 2006), and this activation is important for the maintenance of nerve injury-induced mechanical allodynia (Zhuang et al., 2006). JNK is also persistently activated in spinal astrocytes after CFA-induced inflammation and contributes to inflammatory pain sensitization (Gao et al., 2007). In contrast, ERK is sequentially and only transiently activated in neurons, microglia, and astrocytes at different times of nerve injury, suggesting distinct role of microglial-ERK and astrocytic-ERK in the early- and late-development of chronic pain (Zhuang et al., 2005).

6. PHARMACOLOGICAL APPROACHES TO POST-OPERATIVE PAIN.

Patients have been variously responsive to the analgesic effects of pre-operative opioids, local anesthetics (neuraxial, peripheral n. block, or wound infiltration), NSAIDs and several less frequently used therapeutics (Wilder-Smith et al., 2003; Ong et al., 2005). Meta-analysis has shown that such "pre-emptive" treatments are, in general, inconsistently effective in reducing post-operative pain, with the exception of peri-operative i.v. lidocaine (see below). Both the initial discharge of local nerves caused by the incision (Yamamoto et al., 1993) and the later, delayed activation of impulses from peripheral nerve, that may be conducted by injured or uninjured fibers (Pogatzki et al., 2001; Hamlainen et al., 2002) probably contribute to the establishment of longer-lasting hyperalgesia, and there is little doubt that changes in the CNS, at least at the spinal cord (and probably also in the brain), are essential for the maintained chronic pain (Dirks et al., 2002; Kawamata et al., 2005; Kehlet et al., 2006).

The differential ability of different drugs, applied at the incision site or delivered systemically, to prevent or reverse post-operative pain supports the concept of at least ***two stages of post-operative pain,*** *an* ***induction stage*** *and a* ***maintenance stage,*** *which involve different mechanisms that occur at different locations.*

A. Intravenous lidocaine. The intentional intravenous delivery of lidocaine has been an effective method for reducing acute post-operative pain (Marret et al., 2008) and also for treating, with some success, existing neuropathic pains arising from various causes (Mao and Chen, 2000). Peri-operative infusions of lidocaine, starting shortly before abdominal surgery, cholesystectomy, or prostatectomy and extending to 1-3 hrs after surgery, have reduced self-reported pain scores (usually as visual-analogue scales, VAS) and post-operative analgesic (opioid) consumption, accelerated return of function and shortened hospital stays (Cassuto et al., 1985; Groudine et al., 1998; Koppert et al., 2004; Kaba et al., 2007) However, there have been no systematic, prospective studies of the effectiveness of i.v. lidocaine for the surgical procedures that frequently lead to chronic pain.

The effect of i.v. lidocaine on experimental pain in humans has been studied using infusion protocols like those for peri-operative administration. In a model of skin incision at the volar forearm, Kawamata et al. (2002) found that systemic lidocaine (delivered over 45 min in pre- and post-incisional periods), transiently suppressed 1° allodynia but persistently suppressed 2° allodynia. In the same study, i.v. lidocaine given 30 min after the incision was effective only during the drug administration period, with allodynia returning quickly after that. Using an almost identical dosing end-point (to give up to 3 ugm/ml plasma), Koppert et al. (1998) found that the elevated pain that occurred during the repeated presentation of a skin pinch was prevented from developing by i.v. lidocaine restricted to the "test arm's" circulation, whereas the pain threshold for heat stimulation was unaffected. These changes did not occur when the same dose of lidocaine was allowed to distribute within the entire circulation, showing that the site of action was peripheral and not central.

Animal studies confirm the pre-emptive actions of i.v. local anesthetics. Although systemic bupivacaine has little effect on the initial post-incisional primary mechanical allodynia and hyperalgesia at the incision site, on the hairy skin of the rat, it can suppress the later components of this pain and virtually abolish secondary allodynia and hyperalgesia (here collectively called secondary "hyperpathia", elevated pain) (Duarte et al., 2005). This therapeutic action will last for the entire hyperpathic period, up to 7d after the incision, even though bupivacaine's half-life in blood is <3 h, showing that the systemic drug is interfering with a key process early in the ***induction stage*** of post-operative pain. Identical delivery of bupivacaine 4-6 h after the incision, when the allodynia had reached a constant value and the ***maintenance stage*** of post-operative pain had been reached, had less than 0.5 the effectiveness in reversing both 1° and 2° allodynia, showing that the mechanisms and pathways for developing pain after

surgery are different from those for maintaining it. These results mirror the findings of Kawamata et al., (2002), who applied local lidocaine before or after experimental skin incision in humans. In that study, pre-incisional block prevented the development of 2° allodynia, but post-incisional block had no effect, implying that the initial afferent impulse activity was essential for causing the central sensitization that underlies 2° hyperesthesia, but was unnecessary for maintaining that sensitization.

A very similar result occurred when bupivacaine was delivered systemically around the time of experimental thoracotomy, such that 3 wks after the procedure those rats that received the local anesthetic were 70% less likely to show mechano-allodynia as those that received no bupivacaine (Shin et al., 2008). Changes in the activity of spinal wide dynamic range (WDR) neurons after skin incision (Kawamata et al., 2005) are transiently suppressed by systemic lidocaine and by its quaternary homologue, QX-314, which does not pass through the blood:brain barrier and so is restricted to peripheral sites. This suggests that some peripheral activity, perhaps other than impulse inhibition, is a factor in central neuron changes, although the role of WDRs in ongoing pain has not been established.

Mechano-allodynia after nerve constriction injury also can be strongly reversed by i.v. lidocaine (Araujo et al., 2003), and the duration of anti-allodynia long outlasts the plasma lifetime of lidocaine; days to weeks of prevention occur although the drug disappears from the circulation in a few hours. The timing of this therapeutic effect is not unlike that for surgical effects; when lidocaine is administered early after the nerve injury the persistent reversal of allodynia is ~75%, but the same dosing one week after injury results in almost none of the persistent effect (Araujo et al., 2003), implying that some virtually irreversible process has occurred in the intervening 5 days, one that precludes the salutary long-lasting action of lidocaine. We think that similar processes occur after surgery, so that peri-operative lidocaine is effective for suppressing post-operative hyperesthesia but delayed, post-operative lidocaine is not

Is impulse blockade the mechanism for i.v. local anesthetic action? Local anesthetic conduction block, e.g. by neuraxial administration, is far less clinically effective than i.v. lidocaine in providing pre-emptive relief of post-operative pain (Moiniche et al., 2002), and the lidocaine plasma concentrations that are reached are inadequate to block conduction of normal nerve impulses (Huang et al, 1997a). However, abnormal impulses, such as arise ectopically at sites of injury or inflammation , or at other locations of affected neurons, can be almost fully suppressed by such low lidocaine concentrations (Devor et al.,1992; Xiao and Bennett, 2008), as can abnormal repetitive impulses that result from an increased expression of atypically gating VGSCs on peripheral nerve fibers (Khodorova et al., 2001; Persaud and Strichartz, 2002).

B. Peripheral nociceptor blockade. Peripheral nerve blockade during surgery is almost always accomplished with local anesthetics (LA). These drugs can be used safely and effectively to abolish sensation from peripheral locations, producing a somewhat selective block of small myelinated (e.g., A-delta) fibers and a significantly less potent block of C-fibers (Huang et al., 1997a; Gokin et al., 2001). Infiltration of a surgical area before an incision (Huang et al., 1997b; Kato et al., 2000) or of the wound after incision (Rosaeg et al., 1998; Gottschlak et al., 2003; Rowlingson and Rawal, 2003) can both be effective for suppressing acute post-operative pain. Evidence from other studies indicates that early afferent discharge is critical for establishing neuropathic pain after nerve injury (Xie et al., 2005). This is also likely to be so for post-incisional pain, where impulse blockade can be accomplished by the less fiber-selective blockade, by LA alone, and by the C-fiber specific blockade afforded by resiniferatoxin (RTX; Kissin et al., 2002) or by LAs plus capsaicin (Gerner et al., 2008). Both of these approaches take advantage of the specific expression of the TRPV1 (vanilloid) receptor on non-myelinated C-fibers to provide a selective blockade, and with RTX one already shown to prevent the short-term allodynia after paw incision (Kissin et al., 2005).

C. Anti-inflammatory actions of local anesthetics. Local anesthetics not only block Na+ channels (and Ca+2 and K+ channels, as well as TRPV1 receptors and other ligand-gated receptors) (cf. Yanagidate and Strichartz, 2006a,b), they also disrupt the coupling between certain G proteins and their associated receptors (Li et al., 1995; Hollmann et al., 2004a, 2005). Through this action local anesthetics exert potent anti-inflammatory effects, particularly on neutrophil priming reactions (Hollmann et al., 2000, 2001). There are, in addition, a variety of other, anti-thrombotic and neuroprotective actions of intravenous local anesthetics (cf. Hollmann et al., 2004b for review) that are independent of Na+ channel blockade but may account for many of the improvements in pain after surgery (Kaba et al., 2005, 2007).

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