Preemptive Analgesia—Treating Postoperative Pain by Preventing the Establishment of Central Sensitization

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Peripheral tissue injury provokes two kinds of modification in the responsiveness of the nervous system: peripheral sensitization, a reduction in the threshold of nociceptor afferent peripheral terminals, and central sensitization, an activity-dependent increase in the excitability of spinal neurons. Together, these changes contribute to the postinjury pain hypersensitivity state found postoperatively, which manifests as an increase in the response to noxious stimuli and a decrease in the pain threshold, both at the site of injury and in the surrounding uninjured tissue. The recent finding that sensory signals generated by tissue damage during surgery can trigger a prolonged state of increased excitability in the central nervous system has encouraged clinical studies to test whether preoperative regional local anesthesia or opioid premedication can preempt postoperative pain by preventing the establishment of central sensitization. Although the results of these first trials are in general very encouraging, therapy limited to the pre- and intraoperative periods alone may be insufficient for many patients, because the inflammatory reaction to tissue damaged during surgery may provide a source of sensory signals postoperatively that could induce central sensitization, even if it had been prevented during the operation. Therefore, the optimal form of pain treatment may be one that is applied both pre-, intra-, and postoperatively to preempt the establishment of pain hypersensitivity during and after surgery. The aim of such treatment would be to minimize patient discomfort while leaving physiologic nociceptive mechanisms intact so that they could continue to function as an early warning system. Preemptive treatment could be directed at the periphery, at inputs along sensory axons, and at central neurons by using nonsteroidal antiinflammatory drugs (NSAIDs), local anesthetics, and opioids, either alone or in combination, applied continuously or intermittently. Different treatment regimes could be used at different times relative to the surgery to maximize the prevention of pain in response to different levels of sensory input. The underlying principle would be that therapeutic intervention is made in advance of the pain rather than in reaction to it. To be maximally effective, some preemptive treatment (possibly in steadily decrementing doses) might be required until the peripheral triggers, which could potentially reinitiate central sensitization, had subsided as a result of normal wound healing. New drugs that block the excitatory amino acid and neuropeptide transmitters that induce central sensitization in the spinal cord may become available in the future, enabling a more direct treatment of injury-induced sensory hyperexcitability. Until then, it should be possible to use existing analgesics to reduce central sensitization by changing the timing of their application.

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The Need for a New Approach for the Treatment of Postoperative Pain

For the treatment of postoperative pain, the conventional therapy of prescribing intermittent doses of analgesics in response to patients' demands is often ineffective (1,2). Breakthrough pain is accepted as normal by many patients, doctors, and nurses after surgical procedures (3). This strategy is now beginning to be recognized as constituting suboptimal management, and more resources are being devoted to acute pain services, including the development of continuous epidural analgesic administration and patient-controlled analgesia (PCA) (4,5). In addition, our knowledge of acute pain mechanisms has advanced sufficiently over the past decade so that rational rather than empirically derived therapy can be used by aiming specifically at interrupting the mechanisms responsible for the generation of clinical pain.

The purpose of our review is threefold: first, we will briefly describe the pathophysiology of postinjury pain

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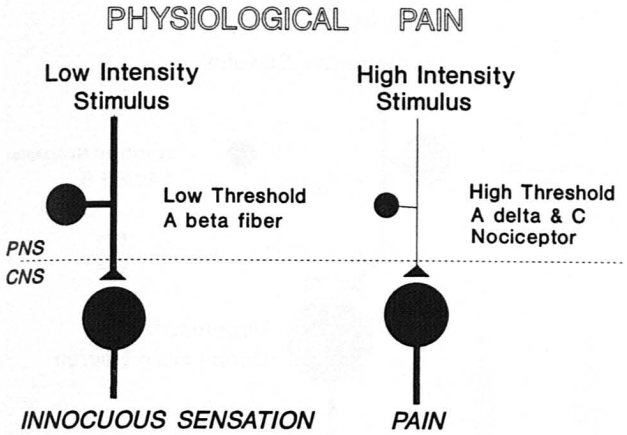

Figure 1. The functional specialization of primary sensory neurons enables, under normal circumstances, the responses to low- and high-intensity peripheral stimuli to be differentiated. The former activate low-threshold receptors generating innocuous sensations, and the latter activate high-threshold nociceptors, which can lead to the sensation of pain. This pain is a physiologic sensation, acting as a warning of potentially harmful stimuli. PNS, peripheral nervous system; CNS, central nervous system.

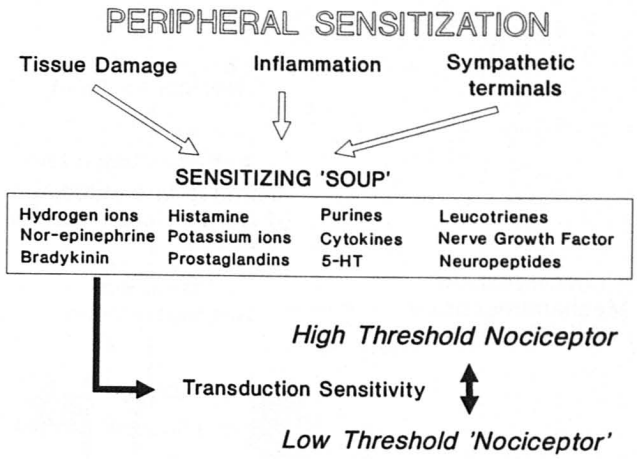

Figure 2. The transduction sensitivity of high-threshold nociceptors can be modified in the periphery by a combination of chemicals that act synergistically as a "sensitizing soup." These chemicals are produced by damaged tissue as a part of the inflammatory reaction and by sympathetic terminals. 5-HT, 5-hydroxytryptamine.

hypersensitivity and show how this has led to the concept of pre-emptive analgesia; second, we will review the efficacy of preemptive analgesia in clinical trials; and third, we will formulate suggestions for optimizing the application of preemptive analgesia in clinical practice by using experimental and clinical data.

Pathophysiology of Postinjury Pain Hypersensitivity

An important conceptual breakthrough in our understanding of pain has been the recognition that the pain we experience in our everyday lives when exposed to noxious stimuli, physiologic pain, is qualitatively quite different from the clinical pain experienced after frank tissue or nerve injury has occurred (6). Physiologic pain has a high threshold, is well localized and transient, and has a stimulus-response relationship similar to that of other somatosensations. Its fundamental role is to operate as a protective system, warning of contact with potentially damaging stimuli. The stimuli required to elicit this pain are sufficiently different from those that produce innocuous sensations that we can reliably predict whether a given stimulus is likely to produce pain or not. This is due to the highly specialized peripheral sensory pathways that subserve these different sensations: the large A β primary sensory fibers for innocuous and the fine A δ and C fibers for noxious stimuli (7,8) (Figure 1).

Clinical pain can be divided into inflammatory and neuropathic pain; the former refers to pain associated with peripheral tissue damage, e.g., that produced during surgery, and the latter refers to damage to the nervous system. Both are characterized by changes in sensitivity, notably a reduction in the intensity of stimuli necessary to initiate pain so that stimuli that would never normally produce pain begin to do so (allodynia). There is also an exaggerated responsiveness to noxious stimuli (hyperalgesia) and a spread of hypersensitivity to noninjured tissue (secondary hyperalgesia) (6,8). Two mechanisms operate to produce these changes in sensitivity found in inflammatory pain. The first is an increase in the sensitivity of the transduction mechanism of high-threshold nociceptor primary sensory neurons at their peripheral terminals when exposed to a cocktail of inflammatory mediators and other chemicals liberated by, or in reaction to, tissue damage (8,9) (Figure 2). This is the phenomenon of peripheral sensitization that contributes directly to changes in thermal sensitivity in the immediate vicinity of tissue injury (8,10,11). Changes in the mechanical sensitivity of high-threshold cutaneous mechanonociceptors have been more difficult to demonstrate (8), but occur in joints (12). Preventing peripheral sensitization has been assumed to be the major action of NSAIDs by virtue of the inhibition of prostaglandin production by the inhibition of the enzyme cyclooxygenase (13). The second mechanism is a change in the excitability of neurons in the spinal cord, triggered by and outlasting nociceptive afferent inputs (14–16). This is the phenomenon of central sensitization (6).

By modifying the response properties of central neurons, central sensitization is responsible for at least some of the changes in mechanical sensitivity that occur at the site of an injury and all the changes in the zone of secondary hyperalgesia outside the site of injury (Figure 3) (10,11,17). The mechanical hypersensitivity resulting from central sensitization is truly pathologic in that it is evoked by A β low-threshold

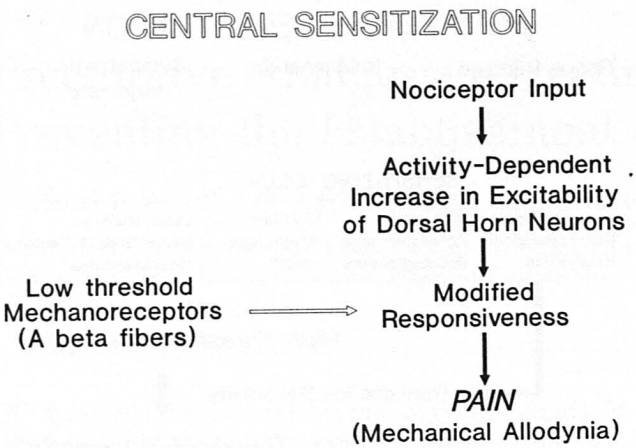

Figure 3. Central sensitization represents a modification in sensory processing within the central nervous system, such that the sensations elicited by low-threshold primary sensory neurons, instead of being innocuous, can become painful. Nociceptor input not only has the capacity to produce pain directly, but in producing hyperexcitability in the spinal cord, it can produce pain indirectly by changing the response to inputs that never normally produce pain.

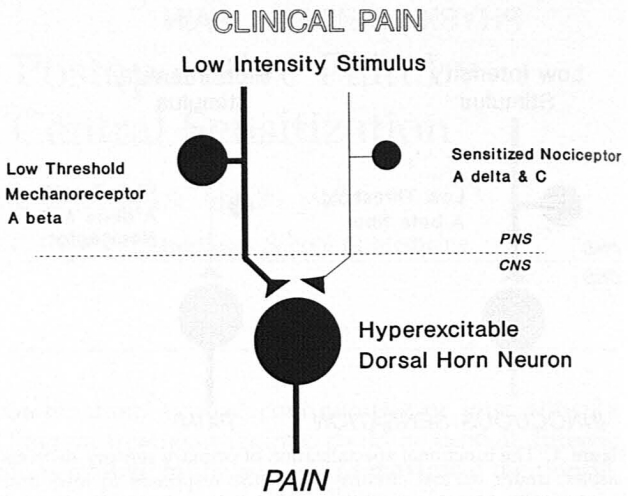

Figure 4. Clinical pain is that pathologic pain that results from abnormal excitability in the nervous system. This involves both central and peripheral changes, and the net result is that a low-intensity stimulus can elicit pain. PNS, peripheral nervous system; CNS, central nervous system.

mechanoreceptors (17–19), which normally do not produce painful sensations (20,21). The fundamental difference between peripheral and central sensitization, then, is that the former enables low-intensity stimuli to produce pain by activating sensitized A δ and C nociceptors, whereas the latter represents an input in normal low-threshold A β sensory fibers producing pain as a result of changes in sensory processing in the spinal cord (Figure 3).

Clinical pain differs from physiologic pain by the presence of pathologic hypersensitivity (Figure 4). The specific involvement of central sensitization in generating abnormal hypersensitivity in humans has been demonstrated in three different circumstances: 1) in volunteers after the application of the chemical irritants capsaicin or mustard oil, where after these intense but short-lasting noxious stimuli, low-threshold A β mechanoreceptors begin to produce pain (11,17,22); 2) in patients in whom a reduction in nociceptive reflex excitability due to central changes has been demonstrated after abdominal surgery (23); and 3) in patients with neuropathic mechanical allodynia, where A-fiber blocks eliminate touch-evoked pain (24–26).

The involvement of central sensitization in clinical pain has three important implications for therapeutic intervention. First, those states of analgesia that eliminate all physiologic and clinical pain need to be differentiated from those in which only abnormal hypersensitivity is eliminated. Although complete analgesia is required intraoperatively in the absence of a general anesthetic, converting clinical pain sensitivity to physiologic sensitivity may be sufficient for many patients postoperatively. Although this may not make the patients totally pain-free, it would eliminate the pain generated by touch or movement, which can be both distressing and disabling. Second, the issue arises over whether the induction or maintenance of central sensitization can be specifically targeted by particular treatments. Third, can a strategy designed to prevent the establishment of central sensitization during elective surgery prevent/reduce postoperative pain? Before addressing these issues, we need to consider the changes in the spinal cord that constitute central sensitization.

Central Sensitization

Sensory processing in the spinal cord can be monitored by studying the receptive field properties of spinal neurons. These are the patterns of neural activity generated by particular stimuli applied to the periphery and include spatial (the size and location of the peripheral receptive field) and threshold (the sensitivity to different intensities of stimuli) components, as well as a temporal (the change in activity in relation to the timing of the stimulus) element, and modality sensitivity (the selective or multiresponsiveness to mechanical, thermal, or chemical stimuli) (7). Recently, it has become apparent that the receptive field properties of dorsal horn neurons are not fixed or hard-wired, but can change (16,19,27). The reason for this is that the synaptic input from primary sensory fibers and interneurons onto spinal neurons is, under normal circumstances, too low in amplitude to generate an action potential discharge in and, therefore, an output signal from, the postsynaptic cell (28). A temporal or spatial summation of postsynaptic excitatory potentials is required to exceed the action potential threshold of the cell, and this is usually only achieved for a small proportion of the total input

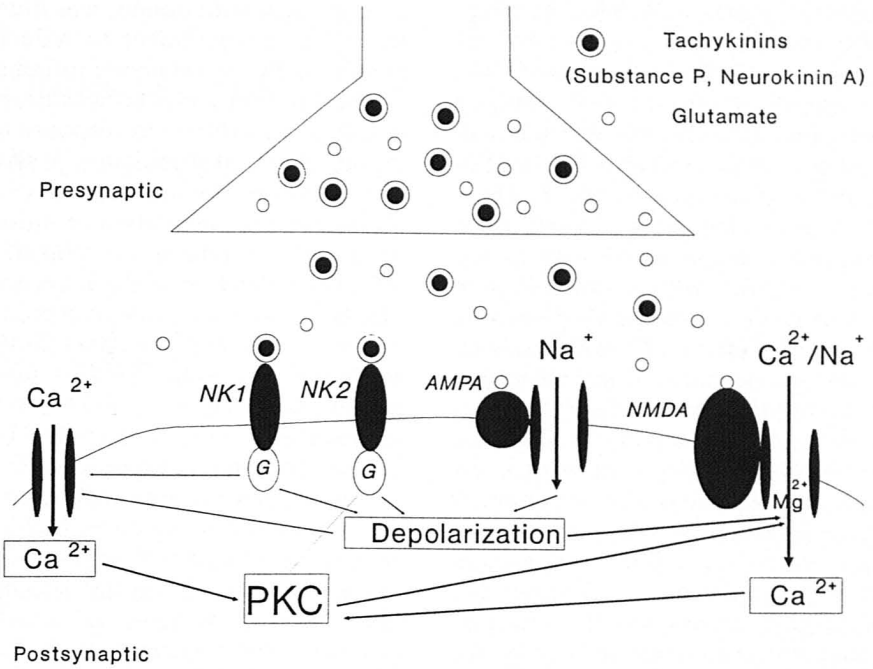

Figure 5. A model of the transmitter and cellular mechanisms that produce central sensitization. C-fiber terminals release both the excitatory amino acid glutamate and neuropeptides such as the tachykinins in the dorsal horn of the spinal cord. Glutamate can act on both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartic acid (NMDA) receptors on postsynaptic membranes on dorsal horn neurons. Normally, the ion channel linked to the NMDA receptor is blocked by a magnesium ion, but the block can be removed by a depolarization of the cell leading to an influx of calcium and sodium ions, which leads to a further depolarization. The tachykinins bind to neurokinin receptors NK_1 and NK_2, leading, via GTP protein activation, to depolarization and to changes in second messengers. The former will directly act on the NMDA ion channel, but the latter acts indirectly via protein kinase C activation. Therefore, there are a number of postsynaptic mechanisms that lead to positive feedforward and feedback changes that increase excitability. Changes in second messengers can also modify immediate early gene expression, potentially producing very prolonged alterations in function.

to the cell. A part of the receptive field, usually the center, constitutes a firing zone where an adequate stimulus will generate an action potential discharge in the cell. Surrounding this is a subliminal zone, where the response evoked in the cell by a peripheral input is subthreshold (28). It is this subliminal input that provides the opportunity for change because an increase in the excitability of a neuron can convert a previously subthreshold input into a suprathreshold response, leading to receptive field plasticity (16). Central sensitization includes those changes in the receptive fields of spinal neurons that follow an increase in excitability produced by peripheral nociceptor inputs, leading to hypersensitivity to subsequent stimuli. Central sensitization can be generated either by electrical stimulation of fine afferent fibers (15,16) or by the activation of nociceptors in response to noxious stimuli or inflammation/tissue damage (14,18,19,27). The resultant increase in excitability produces an expansion of the size of receptive fields, an increase in the magnitude and duration of the response to suprathreshold stimuli, and a reduction in threshold, including a novel response to low-threshold mechanoreceptors in some cells whose receptive fields were originally "nociceptive specific" (16,19). These spatial, temporal, and threshold changes closely parallel the postinjury hypersensitivity changes found in animals and humans.

Cellular Mechanisms of Central Sensitization

The transmitter and postsynaptic mechanisms responsible for central sensitization are unraveling. The first stage depends on the slow synaptic potentials generated by A δ and C fibers in dorsal horn neurons (29). These last up to 20 s, which is about 2000 times longer than the fast synaptic potentials evoked by A β fibers. The slow potentials result from the corelease by nociceptor axon terminals in the spinal cord of the excitatory amino acid transmitter glutamate and of neuropeptides, particularly the tachykinins substance P and neurokinin A (29,30) (Figure 5). The long duration of these slow potentials leads to a summation of potentials during low-frequency repeated nociceptor inputs, thereby generating a progressively increasing and long-lasting depolarization in dorsal horn neurons (29,31). A few seconds of C-fiber input result in several minutes of postsynaptic depolarization. This cumulative depolarization results from the activation by

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glutamate of *N*-methyl-D-aspartic acid (NMDA) receptors (29) and possibly of tachykinin receptors by substance P and neurokinin A (32). The activation of these receptors, both as a result of calcium entry through ligand- and voltage-gated ion channels and the activation of GTP-binding proteins, changes the level of second messengers in the spinal neurons (Fig. 4). These second messengers, in turn, alter protein kinase activity, which, by phosphorylating proteins such as ion channels or enzymes, can alter their function. Protein kinase activation in response to substance P recently has been demonstrated to exert a positive feedback effect on NMDA receptors on spinal neurons, increasing their efficacy by reducing their susceptibility to magnesium block (33). Second messengers can also alter proteins indirectly by changing the level of their expression (34,35) as a consequence of the activation of immediate-early gene products, which are transcription factors that can switch on or off particular genes (36). Although this scenario has evolved from a number of different neurobiological studies, specific relevance to central sensitization has been demonstrated by the capacity of both NMDA and tachykinin receptor antagonists to prevent its development (37–40), and by behavioral studies showing that NMDA-operated calcium channels and protein kinase C contribute to the persistent nociception after application of an acute tissue irritant (41).

Implications of Central Sensitization for Pain Therapy

The function of central neurons can be modified, therefore, by an activity-dependent process triggered by nociceptive afferent input. Because activity is only the initiator of cellular changes, it is not surprising that once central sensitization is established, a local anesthetic to the peripheral trigger site does not immediately eliminate it (14,42). This has been extended in behavioral studies in laboratory animals by showing that pretreatment with intrathecal local anesthetics is more effective than posttreatment in reducing pain-related behavior (43). A similar finding was made in human subjects in whom a local anesthetic applied preinjury had a longer action than the same treatment applied postinjury (44).

Systemic opioids act both presynaptically to reduce neurotransmitter release and postsynaptically to hyperpolarize the membrane of dorsal horn neurons (45). Consequently, these drugs would be expected to prevent buildup of primary afferent-evoked depolarization in dorsal horn neurons and, hence, central sensitization. Low doses of morphine have been shown to prevent the establishment of central sensitization; but once it is established, high doses are required to suppress it (46). This has been confirmed in neurophysiologic recordings from rat dorsal horn neurons where pretreatment with opiates was found to be more effective than posttreatment in reducing the excitability generated by experimental inflammation (47).

The duration of central sensitization in experimental investigations differs in response to different types of inputs; electrical stimulation of skin sensory fibers for 20 s produces several minutes of central hyperexcitability, whereas activation of muscle afferents for the same period produces a central effect of up to an hour (48). The activation of chemoreceptors by chemical irritants for several minutes can produce between 30 and 180 min of central changes (15–19), although in one study, the central changes were found to depend on an ongoing low level of input from the periphery (22). The situation after tissue damage will be more complicated because the afferent input is not transient and because peripheral sensitization will occur so that nociceptors can begin to be activated by low-intensity stimuli. Exactly what amount and what specific types of input are required to initiate central sensitization, the precise time course of changes, and whether more input will produce longer lasting effects have not been adequately studied. It is clear that brief periods of nociceptor input can produce central hypersensitivity changes that alter response to subsequent inputs, which lasts between 10 and 200 times the duration of the initiating stimulus.

One strategy for preventing abnormal sensibility postoperatively could be to prevent or minimize the activation of central neurons by the barrage of afferent activity necessarily evoked during surgery by a pre-/intraoperative treatment. This led to the concept of preemptive analgesia (49).

Models of Preemptive Analgesia

Figure 6 illustrates a simple model of postinjury hypersensitivity. A transient injury initiates central sensitization as a result of excitability increases triggered in spinal neurons by the nociceptors activated by the injurious stimulus. This leads to a hypersensitivity state that outlasts the duration of the injury. Preemptive treatment, i.e., regional local anesthetics at the site of the injury, will prevent the establishment of the hypersensitivity by blocking the sensory input that induces the central sensitization. Postinjury regional anesthesia will have a reduced effect because the central sensitization has already been established. This sort of analysis has provided the theoretical basis for a number of recent clinical trials that have investigated the efficacy of particular preemptive treatments for managing postoperative pain (see below).

Tissue damage, however, will inevitably produce two phases of sensory input. The first will be associated directly with the tissue damaging stimulus, i.e., during surgery. The second will result from the inflammatory

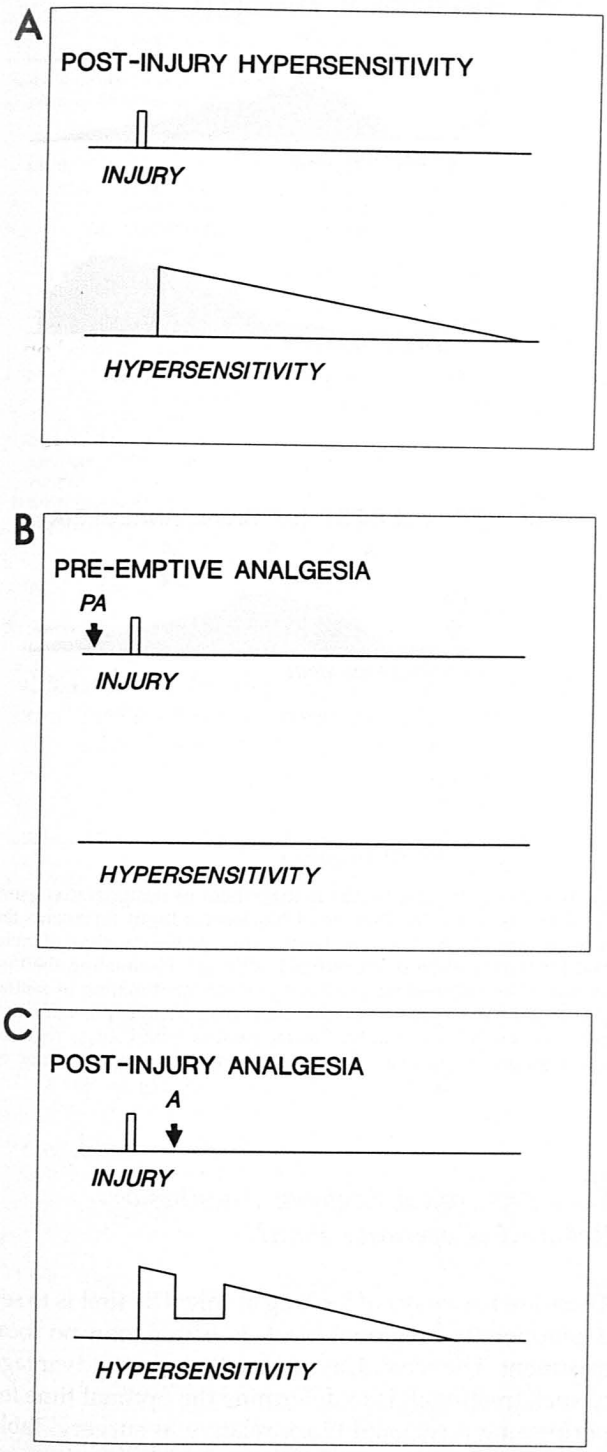

Figure 6. A simple model of the rationale behind single-treatment preemptive analgesia. Injury triggers central sensitization, leading to a prolonged hypersensitivity state (A). A preemptive analgesic (PA) prevents the induction of the central sensitization, preempting the postinjury hypersensitivity (B). Postinjury analgesia (A) has a much diminished effect on an established state of hyperexcitability (C).

reaction to the damaged tissue. This will include the release of a range of chemicals, some which will activate chemosensitive afferents directly, others which will sensitize high-threshold nociceptors (Figure 2). This phase of sensory input will occur postoperatively during the period of wound healing, as illustrated in Figure 7. Here a theoretical measure of the nociceptor input generated during and after surgery is presented. Both phases of nociceptor input have the capacity to induce central sensitization (Figure 7A). The model indicates that a single preemptive treatment may be insufficient to completely eliminate postoperative pain hypersensitivity because it could be induced by the second phase of nociceptor input (Figure 7B). Preemptive treatment in this situation may well be more efficacious than a similar single postoperative treatment (Figure 7, B vs C), but the most optimum form of treatment is likely to be that which is aimed at eliminating the effects of both the first and second phases of afferent input (Figure 7D). This would be a form of continuous preemptive analgesia, continuously preempting the establishment of central sensitization. A number of different options are theoretically available for pre-/intra- and postoperative treatment to achieve this. These include NSAIDs to reduce the activation/sensitization of nociceptors, local anesthetics to block sensory inflow, and centrally acting drugs such as opiates. The merits of using these different approaches and their timing can only be evaluated in the light of clinical experience.

Clinical Trials of Preemptive Analgesia

Trials that specifically have examined whether preemptive analgesia improves the management of postoperative pain are relatively recent and few. There is a fairly large body of clinical data in which incidental comparisons between the pre- and postsurgical administration of different forms of analgesics have been made. Essentially three different general approaches can be discerned. The first has been a comparison between a particular preoperative treatment in one group of patients with another group given no treatment (Table 1) (50–69). The second has consisted of trials comparing the efficacy of a particular treatment if given pre- or postoperatively (Table 2) (70–75). The third has involved the continuous administration of analgesics in the pre- and post-, as well as sometimes intraoperative periods (Table 3) (76–91). Three classes of analgesic drugs have been used: local anesthetics, opioids, and NSAIDs (administered locally, epidurally, intraspinally, or systemically, either alone or in combination). The efficacy of the different treatment protocols have been assessed in a number of ways: the most common being patient report of pain using visual analog scales

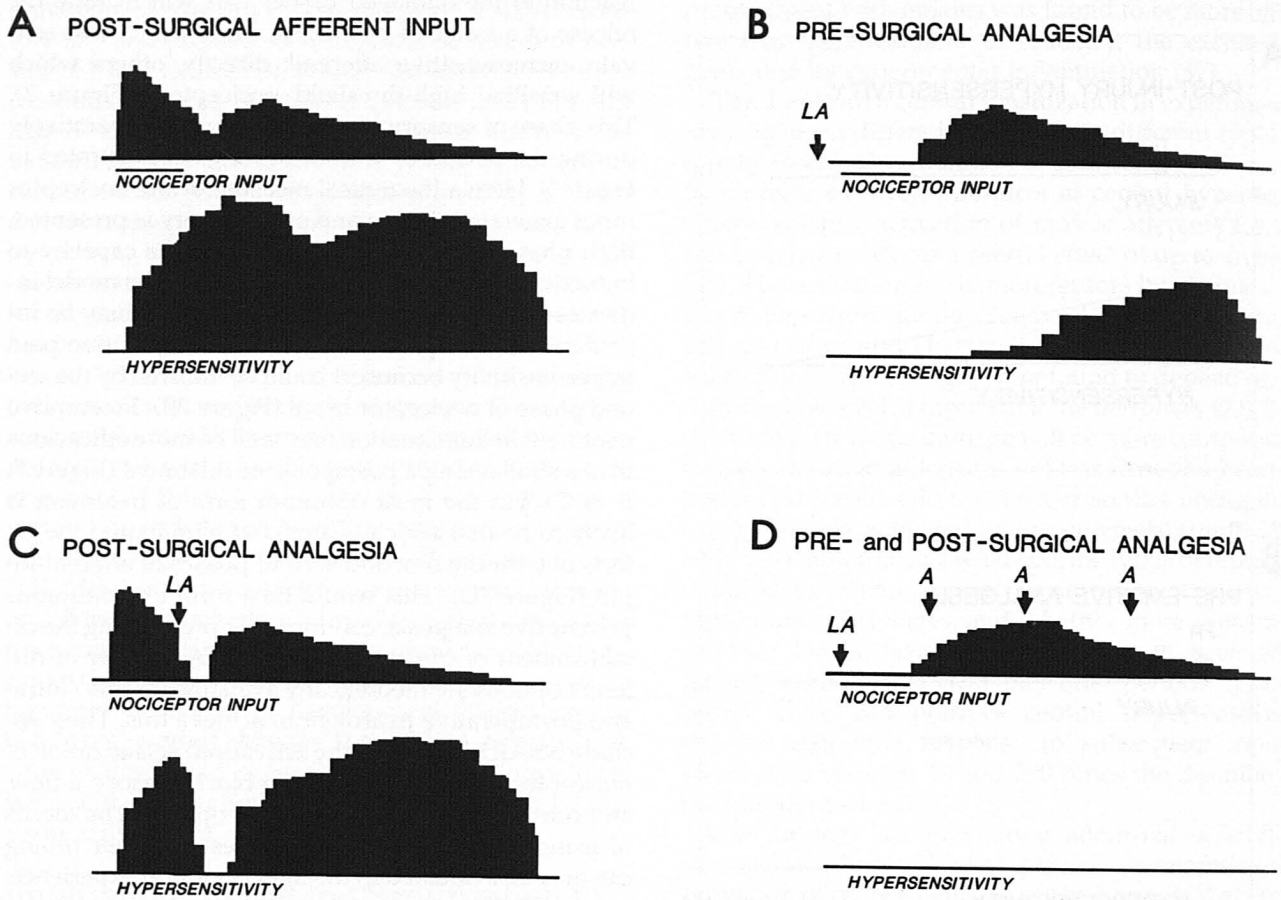

Figure 7. A model illustrating why single-treatment preemptive analgesia may be insufficient for the management of postoperative pain. Surgery leads to a nociceptive input not only during the surgery itself (solid line beneath the drawing of Nociceptor Input represents the duration of surgery), but also postoperatively as a result of the inflammatory response to the damaged tissue. This secondary wave of input can sustain the hypersensitivity state (A). Regional anesthesia administered for the duration of the surgery, although eliminating the first phase of nociceptive input and therefore preempting the first stage of postsurgical hypersensitivity, will not prevent the initiating of central sensitization in response to the second "inflammatory" phase (B), although it might have a greater relative effect than a single postoperative treatment (C). The optimum form of treatment may be one that acts continuously both on the first intraoperative phase (e.g., regional anesthesia or preoperative opioids) and on the afferent activity generated postoperatively (e.g., nonsteroidal antiinflammatory drugs or opioids) (D). LA, local anesthesia.

(VAS), time to first request for an on-demand postoperative analgesic, and total dose of postoperative analgesic. A combination of the differences in the nature, extent, and duration of the surgery, the standard anesthetic procedures used, and the access to and type of demand analgesic make it very difficult to compare individual trials, even if test treatment protocols are similar. An objective measure of patient discomfort is essentially unobtainable, but the total dose of analgesic consumed during a fixed period of PCA may be particularly useful for assessing the efficacy of different treatments, although more subjective measures such as movement-associated pain are valuable for assessing hypersensitivity. From the data presented in Tables 1–3, several general issues related to preemptive analgesia emerge.

Does Presurgical Regional Anesthesia Reduce Postoperative Pain?

There are two ways of looking at this. The first is to see if preoperative regional block is better than no local treatment. The second, assuming there is an advantage to such treatment, is to determine the optimal time for performing a regional block relative to surgery. Table 1A illustrates that in all trials reported to date, preoperative regional local anesthesia by local tissue infiltration or nerve block in patients undergoing surgery under inhalational anesthesia has resulted in less postoperative pain/analgesic requirement than no regional anesthesia. This has been found for a variety of different operations: tonsillectomy (50), inguinal hernia

Table 1. Preemptive Analgesia versus None

	Treatment tested drug/route/dose	Premedication	Anesthetic	Surgical procedure	No. of patients	Assessment	Results	P.A.	Investigators	Ref.
A. Local infiltration with local anesthetics										
DB/R	Bupivacaine 0.25% 3–5 mL/local infiltration	Not stated No opioids	Nitrous oxide/ isoflurane	Tonsillectomy	14	VAS	↓ VAS to day 10	Yes	Jebeles et al., 1991	50
DB/R	Bupivacaine 0.5% or prilocaine + fenylpressin/ local infiltration or nerve block	Temazepam 20 mg/ droperidol 5–10 mg	Nitrous oxide/ enflurane	Molar tooth extraction	84	VAS, A	↓ VAS, ↓ A_D to day 1	Yes	Tuffin et al., 1989	51
	Bupivacaine 0.5% 20 mL/nerve block	Omnopon*	Nitrous oxide/ fentanyl*	Knee joint surgery	100	A	↓ A_D ↑ A_T	Yes	Ringrose et al., 1984	52
DB/R	Bupivacaine 0.25% 40 mL/local infiltration	Promethazine 25 mg	Nitrous oxide/ halothane	Inguinal hernia repair	24	VAS, A	↓ VAS to day 10 ↑ A_T	Yes	Tverskoy et al., 1990	53
DB/R	Bupivacaine 0.5% 20 mL/intercostal nerve block	Diazepam 10 mg	Halothane	Cholecystectomy	30	VAS, A	↓ VAS ↓ A	Yes	Rademaker et al., 1991	54
Retrospective analysis	Local anesthetics block/regional or spinal	No opioid premedication	General anesthetics	Orthopedic procedures	631	A	↓ A_D (30%) ↑ A_T	Yes	McQuay et al., 1988	55
B. Spinal local anesthetics										
DB/R	Bupivacaine 0.5% 12.5 mg/spinal anesthesia	Promethazine 25 mg	Nitrous oxide/ halothane	Inguinal hernia repair	24	VAS, A	↓ VAS to day 2 ↑ A_T	Yes	Tverskoy et al., 1990	53
DB	Lidocaine 5%/spinal	Midazolam 1–2 mg	Nitrous oxide/ isoflurane	Knee surgery	137	VAS	↓ VAS	Yes	Heard et al., 1992	56
C. Systemic opioids										
Retrospective analysis	Opioid premedication		General anesthetics	Orthopedic procedures	830	A	↓ A_D (50%) ↑ A_T	Yes	McQuay et al., 1988	55
	Pethidine 50 mg IM	Flunitrazepam	Nitrous oxide/ halothane/ enflurane or isoflurane/ fentanyl* 2 μg/kg	Lumbar disc surgery	98	A	↓ A_D (50%) to day 2 ↑ A_T	Yes	Kiss and Killian, 1992	57
DB/R	Fentanyl 1 μg/kg IV	Diazepam 10 mg	Nitrous oxide/ halothane	Molar tooth extraction	80	VAS, A	NS	No	Campbell et al., 1990	58
D. Systemic nonsteroidal antiinflammatory drugs										
DB/R	Ibuprofen 400 mg or aspirin 650 mg/oral		Local + IV sedation	Molar tooth extraction	100	VAS, A	↓ VAS, ↑ A_T	Yes	Dionne et al., 1978	59
DB/R	Piroxicam 40 mg/oral	None else	Nitrous oxide/ enflurane	Molar tooth extraction	50	A	↑ A_T ↓ A_D day 1	Yes	Hutchison et al., 1990	60
DB/R	Naproxen 500 mg suppository	Diazepam 10–15 mg	Nitrous oxide/ halothane	Femoral or inguinal herniotomy	60	VAS, A	↓ VAS, ↓ A_T to day 1	Yes	Dueholm et al., 1989	61
DB/R	Diclofenac 1 mg/ kg IM or IV	Diazepam 10 mg	Nitrous oxide/ halothane	Molar tooth extraction	120	VAS, A	↓ A_D ↓ VAS by day 1, IV best	Yes	Campbell et al., 1990	58
E. Combinations										
DB/R	Bupivacaine 0.25% 60 mL/local infiltration	Not stated	Nitrous oxide/ enflurane + morphine*/ bupivacaine epidural	Upper abdominal surgery	50	VAS, A	↓ VAS to day 3 ↓ A	Yes	Mogensen et al., 1992 (Abstract)	62
DB/R	Morphine IV 0.1–0.2 mg/kg indomethacin PR 100 mg/bupivacaine 0.5% nerve block 1 mg/kg	Midazolam	Nitrous oxide/ isoflurane/ fentanyl* 1 μg/kg/h	Thoracotomy	7	VAS, A_{PCA}	↓ A_{PCA} ↓ VAS to 6 h	Yes	Kavanagh et al., 1992 (Abstract)	63
	Morphine 4 mg epidural	Not stated	Bupivacaine 0.5% 16–20 mL epidural	Prostatectomy	30	VAS, A	↓ VAS, ↓ A to 24 h	Yes	Shapiro et al., 1981	64
DB/R	Bupivacaine 0.5% 10 mL/local infiltration and spinal lignocaine	Diazepam 5–10 mg	Spinal, 5% lignocaine	Inguinal hernia repair	45	VAS, A	↓ VAS 48 h ↓ A 24 h	Yes	Bugedo et al., 1990	65

DB, double-blinded; R, randomized; VAS, visual analog scale; A, analgesic; A_D, total dose of analgesics; A_{PCA}, total dose of patient-controlled analgesics; A_T, ime to first postoperative analgesic; *, opioid used as premedication or on induction of anesthesia; P.A., preemptive analgesia demonstrated; Ref., reference number; V, intravenous; IM, intramuscular; postop., postoperatively; PR, through the rectum.

Table 1. *Continued*

	Treatment tested drug/route/dose	Premedication	Anesthetic	Surgical procedure	No. of patients	Assessment	Results	P.A.	Investigators	Ref.
DB/R	Ibuprofen 400 mg ± codeine 30 mg oral and local anesthetics	—	Local anesthetics	Molar tooth extraction	114	VAS, A	↓ VAS ↑ A_T ↓ A_D 40% up to 5 h	Yes	Hill et al., 1987	66
R	Ibuprofen 800 mg or acetaminophen 600 mg/oral and local anesthetics	—	Local anesthetics	Molar tooth extraction	107	VAS	↓ VAS (75%)	Yes	Dionne et al., 1983	67
DB/R	Fenbufen 450 mg oral and local anesthetics	—	Local anesthetics	Molar tooth extraction	38	VAS, A	↓ A_D immediate postop. only	No	Smith and Brook, 1990	68
DB/cross-over	Flurbiprofen 50 mg oral	—	Carbocaine 2%	Molar tooth extraction	20	VAS	↓ VAS, maximal 4–5 h postop.	Yes	Dupuis et al., 1988	69
Retrospective analysis	Opioid premedication with regional/nerve block	—	General anesthetics	Orthopedic procedures	596	A	↓ A_D (50%) ↑ A_T	Yes	McQuay et al., 1988	55

repair (53), cholecystectomy (30), molar tooth extraction (84), and orthopedic procedures (52,55). In all trials, the analgesic effect of the preincisional regional block outlasted the estimated duration of conduction block. A feature of two of the trials was the very long effects of the regional anesthesia, with differences in pain levels between the treated and untreated groups maintained for up to 10 days postoperatively (53). The duration of the effect of maintaining a block of sensory inflow during surgery has not yet been adequately addressed. This will require a complete matching of experimental and control groups in a fully double-blind trial, with accurate and standardized postoperative tests performed at regular intervals for several days. We need to ascertain whether the duration of such "preemptive" analgesia depends on the type and duration of the surgery, the extent of tissue damage produced, and whether a complete conduction block of the surgical field has been achieved. This is essential for considering whether a single treatment strategy is sufficient to produce adequate postoperative pain relief. Given that the experimental evidence in animal models and in human subjects indicates that central sensitization only lasts for several hours after a short triggering input, it is difficult to understand how a short regional anesthetic could produce pain relief lasting 10 days. This may be due to the much more intense input generated during surgery than experimentally, but more clinical data are needed.

Before it can be argued whether the trials in Table 1A constitute proof that by blocking the establishment of central sensitization, preincisional local anesthesia is efficacious in preventing postoperative pain, an obvious question has to be asked. Does the regional block have to be administered preoperatively to produce long-lasting pain relief? One of the earliest trials that supports pre- versus postsurgical treatment found a 50% reduction in opiate requirement in the first 24 h in patients undergoing knee joint surgery if femoral nerve blocks were given before rather than on completion of the surgery (52). More recently, two trials have compared local anesthetic infiltration before or after surgery in patients undergoing inguinal hernia repair. In the first, a reduction in total dose of analgesics and an increased time to first analgesic requirement was found in the presurgery infiltration group compared to the patients who had their regional blocks immediately after the surgery (70). The second trial was of similar design with a comparable number of patients, but no difference in pain score or analgesic requirement was found between the pre- or postlignocaine infiltration group (71). These apparently contradictory findings may relate to the use by the second group of a fentanyl infusion for both of their groups of patients during the surgery. As discussed below, pre-/intraoperative opioids are effective in their own right in preventing/reducing postoperative pain. In the "negative" trial (71), both sets of patients (pre- and postsurgical infiltration) had very low pain scores postoperatively, so that a lack of any difference between the two groups is not too surprising. The nerve blocks were performed under the general anesthesia, and the extent and duration of conduction block was not assessed. In Tables 1–3, all trials in which an opioid was used as part of the standard premedication or intraoperative treatment are identified. Such studies will have to be evaluated separately and differently from those studies in which no routine opioid was administered. More pre- versus postregional anesthetic trails are required; however, regardless of the eventual outcome of such trials, keeping the patient pain-free in the immediate postoperative period is a profound advantage.

The possibility exists that infiltration with local anesthetics have effects other than the block of sodium channels on nerves. An antiinflammatory action of local anesthetic has, for example, been proposed (92), and

Table 2. Pre- versus Postsurgery

Study design	Treatment tested drug/route/dose	Premedication	Anesthetic	Surgical procedure	No. of patients	Assessment	Results	P.A.	Investigators	Ref.
A. Local infiltration with local anesthetic										
DB/R	Lignocaine 1% 40 mL/local infiltration	Diazepam 0.2 mg/kg	Nitrous oxide/ isoflurane	Inguinal hernia repair	37	VAS, A	↓ A_D (50%), ↑ A_T, VAS = NS, up to 6 h	Yes	Ejlersen et al., 1992	70
DB/R	Lignocaine 1% 15 mL, 0.5% 40 mL/local infiltration	Diazepam 10–15 mg	Alfentanyl* 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion Nitrous oxide	Inguinal hernia repair	32	VAS, A	NS to 24 h	No	Dierking et al., 1992	71
	Bupivacaine 0.5% 20 mL/nerve block	Omnopon*	Nitrous oxide/ fentanyl*	Knee joint surgery	20	A	↓ A_D (50%) in 24 h	Yes	Ringrose et al., 1984	52
B. Epidural or spinal local anesthetics										
DB/R	Bupivacaine 7.5 mg/mL + morphine 0.05 mg/mL epidural at 4 mL/h for 72 h	Diazepam 5–10 mg	Nitrous oxide/ enflurane/fentanyl* 0.1–0.2 mg	Colonic surgery	32	VAS, A	NS	No	Dahl et al., 1992	72
DB/R	Bupivacaine 0.5% 15 mL/epidural	Morphine* 7.5–10 mg	Nitrous oxide/ enflurane	Abdominal hysterectomy/ myomectomy	36	VAS, A_{PCA}	NS to 24 h	No	Pryle et al., 1992	73
DB/R	Bupivacaine 0.25% spinal block/ 0.5 mg/kg		Nitrous oxide/ halothane	Herniotomy/ orchidopexy/ hydrocoelectomy	40	VAS, A	NS to 3 h	No	Rice et al., 1990	74
C. Epidural opioids										
DB/R	Fentanyl 4 µg/ kg epidural	Diazepam 10 mg	Nitrous oxide/ isoflurane	Thoracotomy	30	VAS, A_{PCA}	↓ VAS 6 h ↓ A 12–24 h	Yes	Katz et al., 1992	75

DB, double-blinded; R, randomized; VAS, visual analog scale; A, analgesic; A_D, total dose of analgesics; A_{PCA}, total dose of patient-controlled analgesics; A_T, time to first postoperative analgesic; *, opioid used as premedication or on induction of anesthesia; P.A., preemptive analgesia demonstrated; Ref., reference number; IV, intravenous; IM, intramuscular.

consequently, local infiltration may have a theoretical advantage over a nerve block.

Is Local Infiltration/Peripheral Nerve Block More Efficacious Than Epidural/Intraspinal Local Anesthetics in Producing Preemptive Analgesia?

Although two trials have found that intraspinal lidocaine reduced postoperative pain scores compared to patients with no intraspinal treatment (Table 1B) (53,56), when spinal treatment is compared to local infiltration, the latter treatment appears more effective than the former in reducing postoperative pain (53). The addition of local infiltration to patients having spinal treatment, moreover, significantly improves postoperative pain relief (65). No difference in postoperative pain between pre- and postsurgery epidural or spinal blocks has been found in three trials (72–74). This may reflect that regional block is much more effective than a spinal/epidural in producing conduction block (53,65,70) and, therefore, in preventing the production of central sensitization. Certainly at normal doses of epidural or intraspinal local anesthetics, both somatosensory-evoked cortical potentials and afferent-induced stress responses remain present (93). Therefore, short duration epidural/spinal local anesthesia do not seem to be an effective way of preventing postoperative pain, even though they are effective for intraoperative analgesia, as these treatments need to be supplemented either by preincisional regional infiltration or by opioids (53,62,64,65).

Does Preoperative Opioid Administration Diminish Postoperative Pain?

Local infiltration of a local anesthetic is technically not possible or appropriate for all surgical patients. The issue, therefore, arises as to whether other forms of preemptive therapy may be useful. A number of trials have compared the presurgical administration of opioids with nonopiate sedatives (Table 1C). In a large retrospective analysis of patients undergoing orthopedic surgery, the median time to request postoperative analgesics initially was less than 2 h in control patients, whereas with morphine premedication, this was extended to more than 5 h (55). Although this result partially may reflect the pharmokinetics of morphine and the difficulty in using the time to first analgesic as a parameter of pain experienced (94), the trial also reported a reduction in total dose of postoperative analgesia in the opioid premedication group. In another study (57), patients undergoing surgery for lumbar disc prolapse under inhalational anesthesia were randomized to pethidine or flurnitrazepam premedication. The use of opiates produced an increase in the time to demand analgesia and halved the number of patients requesting postoperative analgesia. One study of opiates administered preoperatively for molar tooth surgery

Table 3. Continuous Administration of Analgesics Started Preoperatively

Study design	Treatment tested drug/route/dose	Premedication	Anesthetic	Surgical procedure	No. of patients	Assessment	Results	P.A.	Investigators	Ref.
A. Local infiltration with local anesthetics										
DB/R	Bupivacaine 0.25% 30 mL nerve block + infusion 0.125% at 6 mL/h for 24 h	Temazepam	Fentanyl 1 μg/kg* Nitrous oxide/ isoflurane	Knee replacement	37	VAS, A	↓ VAS (50%) ↓ A (33%) 24 h	Yes	Edwards and Wright, 1992	76
B. Systemic opioids										
DB/R	Fentanyl 50–75 μg/h for 72 h, transdermal	Not stated	G.A. with 0.5 μg/kg sufentanil	Abdominal hysterectomy	20	VAS, A_{PCA}	↓ VAS and A_{PCA} but NS statistically	Yes	Sandler et al., 1991 (Abstract)	77
DB/R	Fentanyl 25–50 μg/h for 72 h, transdermal	Not stated	Nitrous oxide/ isoflurane/ alfentanyl*	Gynecologic surgery	95	VAS, A_{PCA}	↓ VAS and A_{PCA} to day 2 with 50 μg/h fentanyl	Yes	Sevarino et al., 1991 (Abstract)	78
C. Systemic nonsteroidal antiinflammatory drugs										
DB/R	Piroxicam 40 mg for 2 days then 20 mg for 1 day	Temazepam 0.3 mg/kg	Spinal 0.75% bupivacaine 2.75–3.25 mL Midazolam 1–2 mg IV	Hip replacement	24	A_{PCA}	↓ A_{PCA} (50% ↓ in morphine) to 48 h	Yes	Serpell and Thomson, 1989	79
DB/R	Indomethacin 0.8 mg/kg IV then 100 mg TDS for 3 days	Diazepam 0.2 mg/kg	Nitrous oxide/ enflurane	Hysterectomy	41	VAS, A	↓ VAS, ↓ A_T to 72 h	Yes	Engel et al., 1989	80
DB/R	Indomethacin 25–50 mg IV then infusion 5–7.5 mg/h for 20 h	Diazepam 5–15 mg	Spinal bupivacaine 0.5% 3 mL	Orthopedic procedure	54	A	↓ A_T	Yes	Taivainen et al., 1989	81
DB cross-over	Ibuprofen 400 mg TDS beginning evening before surgery for 24 h		Local anesthetics	Bilateral molar tooth cross-over	24	VAS, mouth opening, swelling	↓ VAS + better mouth opening in test group days 1–5	Yes	Lokken et al., 1975	82
DB/R	Indomethacin 100 mg BID for 3 days suppositories	Pethidine* 1–1.5 g/kg Diazepam 5–15 mg	Nitrous oxide/ halothane/ enflurane	Spinal surgery	100	VAS, A	↓ VAS ↓ A_D to day 3	Yes	McGlew et al., 1991	83
DB/R	Diclofenac 50 mg total 200 mg OD for 3 days suppositories	Morphine* 0.15 mg/kg	Nitrous oxide/ fentanyl*/ isoflurane	Uvulopalato-pharyngoplasty	40	VAS, A	↓ A_D (50%) to day 2	Yes	Ejnell et al., 1992	84
DB/R	Indomethacin 100 mg for 2 days/IV or suppositories	Pethidine* 1 mg/kg	Nitrous oxide/ thiopentone infusion	Lumbar disc operation	56	VAS, A	NS 1st 3 h ↓ A_D ↓ VAS to day 2	Yes	Nissen et al., 1992	85
DB/R	Ibuprofen 500 mg TDS for 24 h suppositories	Temazepam 30 mg	Nitrous oxide/ enflurane/ surgery halothane + morphine* 0.2 mg/kg	Abdominal gynecologic procedures		VAS, A_{PCA}	VAS NS ↓ A_{PCA}	Yes	Owen et al., 1986	86
D. Combinations										
DB/R	Bupivacaine (B) 0.125%, 15 mL/h Diamorphine (D) 0.5 mg/h epidural for 24 h	Diamorphine* 5 mg IM	Nitrous oxide/ enflurane or halothane Epidural bupivacaine or morphine alone	Abdominal surgery	60	VAS	↓ VAS in combined treatment compared to either to 24 h	Yes	Lee et al., 1988	87
R	Methylprednisolone 30 mg/kg, indomethacin 10 mg TDS for 96 h Spinal lignocaine during surgery. Epidural bupivacaine 0.25% and morphine 0.3 mg/h at 4 mL/h for 24 h	Diazepam 0.2 mg/kg	Thiopentone, fentanyl, and midazolam G.A.	Colectomy	25	VAS, A, plasma "stress" profile, postoperative pulmonary function and mobility	No pain at rest or mobilization reduction in some stress proteins	Yes	Schulze et al., 1992	88

DB, double-blinded; R, randomized; VAS, visual analog scale; A, analgesic; A_D, total dose of analgesics; A_{PCA}, total dose of patient-controlled analgesics; A_T, time to first postoperative analgesic; *, opioid used as premedication or on induction of anesthesia; P.A., preemptive analgesia demonstrated; Ref., reference number; IV, intravenous; IM, intramuscular; BID, twice daily; TDS, three times a day; OD, every day; G.A., general anesthesia.

Table 3. *Continued*

Study design	Treatment tested drug/route/dose	Premedication	Anesthetic	Surgical procedure	No. of patients	Assessment	Results	P.A.	Investigators	Ref.
DB/R	Morphine 4 mg then 0.5 mg/h for 16 h	Diazepam 0.2 mg/kg	Nitrous oxide/ halothane	Upper abdominal surgery	22	VAS	↓ VAS all those with morphine were pain free	Yes	Scott et al., 1989	89
	Piroxicam 40 mg, then 20 mg OD bupivacaine (B) 0.75% 7 mL + morphine (M) 2 mg then infusion B 0.25%, M 0.05 mg/mL, 4 mL/h	Diazepam 5–10 mg	Nitrous oxide/ enflurane Spinal lignocaine 5% 2 mL	Colorectal surgery	14	VAS	All pain free at rest and on mobilization except one	Yes	Dahl et al., 1990	90
DB/R	Bupivacaine 7.5 mg/mL + morphine 0.05 mg/mL epidural at 4 mL/ h for 72 h	Diazepam 5–10 mg	Nitrous oxide/ enflurane/ fentanyl* 0.1–0.2 mg	Colonic surgery	32	VAS, A	NS	No	Dahl et al., 1992	71
R	Bupivacaine 0.5% morphine 4 mg epidural indomethacin 100 mg IV for 3 days			Cholecystectomy	24	Pain, fatigue score, plasma "stress" profile	No difference at rest but ↓ pain on mobilization	Yes	Schulze et al., 1988	91

has reported no difference between treated and control groups (58). The dose used was, however, very low (intravenous fentanyl 1 μg/kg). In the only reported trial comparing opioids administered pre- and postsurgery (Table 2C), a single dose of epidural fentanyl (4 μg/kg) given presurgery was found to be more effective in reducing pain and analgesic requirement between 12 and 24 h after thoracotomy than when administered after the surgery (75). This important result, which needs to be confirmed, indicates a particular effectiveness of opiates in producing preemptive analgesia and mirrors the experimental findings that preinjury opiates can prevent central sensitization (47). The optimal drug, dose, route, and timing of opioids to prevent postoperative pain requires further investigation as several questions can be raised. Would intravenous opioids administered immediately after induction be as effective as those given by intramuscular injection an hour or so before the operation? If so, this could avoid preoperative sedation/nausea and the need for a painful injection. Can a transdermal application of fentanyl be used? Can opioids be used both to preempt the central sensitization induced by intraoperative sensory input and the effect of any secondary postoperative input; and does this have any implications for single dose versus continuous therapy (see Table 3B). Are the preemptive actions of opioids and local anesthetics synergistic?

Does Preoperative NSAID Administration Diminish Postoperative Pain?

Single doses of NSAIDs administered preoperatively are effective in reducing postoperative pain (Table 1D). This has been studied particularly for ibuprofen for oral surgery (58,59,66–69), but has been demonstrated for abdominal surgery (86) and laparoscopy where preoperative ibuprofen provided longer lasting analgesia than fentanyl administered just before termination of the procedure (95). NSAIDs are usually thought to produce effects by inhibiting the production of eicosanoids from arachidonic acid, which would decrease peripheral sensitization and the activation of nociceptors (96). Although this does occur and may have a useful secondary effect in reducing the sensory inflow from the periphery to the central nervous system that sustains central sensitization in the postoperative period (Figure 7), there is recent evidence that an analgesic action of these drugs occurs centrally (97). NSAIDs may be acting in the spinal cord directly on some of the mechanisms that maintain or induce central sensitization. It is interesting that the converse may also be true: some of the analgesic actions of opioids may arise peripherally (98).

Do Combinations of Analgesic Therapies Offer Any Advantage?

There have been several trials examining the effect of combinations of analgesic agents administered pre-/intraoperatively on postoperative pain (Table 1E). The combinations have included a local infiltration with bupivacaine and epidural bupivacaine and morphine for upper abdominal surgery (62); systemic morphine and indomethacin, a nerve block and a fentanyl infusion for thoracotomy (63); epidural morphine and bupivacaine for prostatectomy (64); regional and spinal bupivacaine for inguinal hernia repair (65); and mixtures of local anesthetics, NSAIDs, and opioids for

molar tooth extraction (66–69). Although all trials demonstrate better postoperative analgesia in the treated compared to the untreated groups (62–69), it is not possible in most cases to establish whether the results achieved are the specific result of the combination used or one particular agent, or whether the effects of the combinations are additive or interact synergistically. No trials using short duration combination therapy have been performed pre- and postoperatively, so that the optimal timing of such treatments is not known. Although these studies appear to support the effectiveness of preoperative treatment in reducing postoperative pain, further trials are needed to assess whether this is actually true. The possibility of incremental risks of side effects by complex combination therapy always needs to be considered, even when combinations may offer the opportunity of decreasing dosage, thereby reducing side effects. When considering the problem of maintaining adequate pain relief after major chest or abdominal surgery, any strategy that results in patients being largely pain-free immediately postsurgery must be advantageous over those in which analgesic treatment is only commenced when the patient begins to complain of pain. Such strategies should, however, be optimized by a proper analysis of what is producing the desired action and when.

Is the Continuous Preemptive Administration of Analgesics an Advantage Over Single Treatment?

The first studies designed to test the preemptive analgesia hypothesis were based on experimental investigations in laboratory animals that had used short-lived sensory inputs to generate central sensitization. The assumption implicit in these studies was that the sensory input generated during the surgery constitutes the major trigger for establishing central sensitization. Eliminating this trigger would substantially reduce or eliminate postoperative pain. Unfortunately, we have no way of measuring the sensory input to the central nervous system generated as a consequence of surgery, but it is most improbable that it ceases on completion of the surgery. It might even rise in the postoperative period as a result of the development of a full-blown inflammatory response (Figure 7). Consequently, therapy limited to the perioperative period may not completely preempt the establishment of central changes. One way of testing this is to compare continuous with single-treatment strategies. Although trials using prolonged/continuous treatments have been performed (Table 3), most have not compared such treatment with treatment limited to the pre/intraoperative period. Although continuous local infiltration, systemic opioids, NSAIDs, and combination therapies have been used successfully to reduce postoperative pain, it is impossible to evaluate whether the results achieved are specifically due to the long duration of the treatment. Only one trial has compared a pre- with a postoperative initiation of the continuous treatment. In 32 patients undergoing colonic surgery, no difference in pain score or supplementary analgesic requirement was found, whether a regime of epidural bupivacaine (7.5 mg/mL) and morphine (0.05 mg/mL) at 4 mL/h for 72 h was started before or on completion of surgery (72). The absence of any difference between the two groups is possibly not too surprising, considering that intraoperative epidural local anesthetic treatment appears to be inadequate to block afferent inputs sufficiently to prevent central sensitization (see above), and that both groups of patients received a preoperative administration of fentanyl. In both groups, pain scores were very low. The study indicates though that there may be an advantage to pre- versus postoperative treatment in the immediate postoperative period when the pain during movement or coughing was less in the pretreatment group.

Continuous treatment appears to offer the possibility of reducing pain after major surgery. Whether this can be improved by strategies designed specifically to prevent the establishment of central sensitization during and after the surgery is not yet known. Treating pain in advance of its manifestation should become a goal for all personnel involved in postoperative pain care.

Assessment of the Efficacy of Preemptive Analgesia

The available data do not provide a definitive answer regarding the efficacy of preemptive treatment and whether it offers any clinically relevant advantage as an analgesic strategy for treating established pain. Although there are sufficient indications that this is likely, further studies are warranted. The aim of preventing central sensitization while leaving physiological pain mechanisms intact has the theoretical advantage that the patient will not be totally analgesic; therefore, postoperative surgical complications should be readily detected, which might not occur with continuous epidurals (99). For example, in one reported trial of continuous administration of epidural bupivacaine and morphine and systemic steroids and nonsteroidal inflammatory drugs after colectomy, an alarmingly high number of wound dehiscence was reported (88). A key issue to consider is the relative duration and extent of the central change produced during and after surgery, because this relates to whether continuous preemptive analgesia has advantages over single preincisional treatments. Although intuitively attractive,

continuously maintaining therapy in advance or anticipation of any request for analgesia has potential risks, particularly when drugs are administered epidurally. Three approaches for minimizing risks and maximizing analgesia are possible. The first is to use a number of different analgesic tactics, local anesthetics, opioids, and NSAIDs aimed at different sites, providing a balanced analgesia (90). The second is to use particular combinations where there is a positive synergistic interaction between the different drugs. Mixtures of opioids and local anesthetics have been shown in several controlled trials to be significantly more effective than either opioids or local anesthetics alone in patients with major abdominal surgery (100). Epidural ketamine combined with bupivacaine has an additive effect (101,102), and continuous ketorolac, an NSAID, has been shown to produce a halving of morphine requirements in patients using PCA (103). The third approach is theoretical. This would be to prevent a state of central sensitization from being established by using suitable pre- and intraoperative analgesic treatments, enabling a lower dose of an analgesic to be effective postoperatively than if the analgesic were administered for the first time postoperatively, when central sensitization was fully evolved. This argument is based on experimental observations that have shown that low doses of morphine prevent central sensitization and that high doses are required to suppress central sensitization once it is already present (46). This argument needs to be examined in appropriate clinical trials. Continuous analgesia might enable continuously decreasing doses of opioids or other analgesics over the postoperative period, as potential peripheral triggers for the induction of central sensitization reduce with time.

Future improvements may be possible in the design of preemptive treatment, based on our increasing understanding of the mechanisms operating in the spinal cord. The induction of central sensitization involves the activation of the excitatory amino acid NMDA receptor in the spinal cord (37). One form of therapy for post-injury hypersensitivity states might therefore be the use of antagonists to this receptor, which has been shown to be highly effective in experimental conditions (37,40). Unfortunately, such antagonists have psychotropic actions in humans. The only NMDA antagonist licensed for use in patients is the dissociative anesthetic ketamine, which is very short acting and unpleasant for most patients. Nevertheless, epidural ketamine produces a potent postoperative analgesia (101,102). Experimentally, NMDA antagonists, in addition to preventing the induction of a state of central sensitization, can reduce it once it is established (37). This appears also to be true for postoperative pain, although the analgesic effect is too short-lived to be useful (104). It is unlikely, therefore, that this drug alone will be suitable for routine preemptive analgesia. However, it does point to new possibilities of treatment if NMDA antagonists with no unacceptable side effects are developed and if they can be administered via the epidural route without systemic actions (105). The clinical use of neuropeptide antagonists is also a possibility.

Possible Risks and Nonanalgesic Benefits of Preemptive Treatment

How preemptive analgesia should be achieved in practice will necessarily depend on the particular circumstances of the patient, the facilities available, and the known or determined risks of side effects or complications from the treatment protocols. This is particularly true if a continuous combination strategy is ultimately demonstrated to be the most effective.

Each of the treatments that has been suggested or used preoperatively has potential risks. NSAIDs are associated with gastrointestinal bleeding (106), a transient impairment of renal function (107,108), and a reduction in platelet adhesiveness (109). These complications, like the antiinflammatory action of the drugs, are related to the block of prostaglandin synthesis. A prolongation of clotting time has been reported after the preoperative administration of NSAIDs (83,84), but no excess bleeding or wound hematoma formation has been found (83–86). The epidural administration of drugs can cause problems arising from the procedure, e.g., chronic back pain (110) or, more seriously, sepsis (111). Problems may arise from the drugs used: opioids can cause respiratory depression (112,113), whereas local anesthetics can produce a profound hypotension, and both may result in urinary retention (4,114,115). Even local anesthetic nerve blocks are associated with nerve damage, and local injections of high concentrations of drugs cause neurotoxicity (116).

Although a reduction in postoperative pain is desirable for the patient and may lead to earlier mobilization (53) and decreased hospital stay (117–119), other benefits may accrue from pre-intraoperative analgesia. These include a prevention of intraoperative hemodynamic reactions (120) and a reduction in respiratory complications (121).

Conclusions

The survival advantage of having a nervous system that sensitizes in the presence of tissue injury, permitting recuperation and recovery by leading to an avoidance of contact with all external stimuli, is sufficiently powerful that it is present in all major animal phyla from invertebrates to humans (122). Although evolution has conserved sensitization in humans, the capacity to inflict "controlled injury" during surgery has clearly not been anticipated. The pain hypersensitivity

state experienced postoperatively has lost its survival value in the context of modern medicine, and consequently, current medical practice should actively anticipate and suppress this defense mechanism which produces discomfort, distress, and pain to millions of patients each year.

Postoperative pain is a multifactorial experience involving ongoing sensory signals generated from damaged tissue and a central nervous system whose function has been modified. Preempting pain must be the goal for all those involved in the postoperative care of patients. Ideally, patients should experience only minimal discomfort in the immediate postoperative period and, potentially, this can be achieved. The process might not simply involve pre- or intraoperative therapy, although this is clearly useful in some situations (50,53,58). Pain should be continuously anticipated and preempted by persisting with preemptive therapy for as long as the abnormal afferent barrage from the wound and surrounding site is present, by using analgesic techniques targeted at three sites: the periphery, sensory inflow in nerves, and cells in the central nervous system.

The validity of preemptive analgesia as a routine treatment strategy can only be evaluated by more clinical trials, particularly those comparing the effectiveness of pre- or postincisional analgesia, and continuous or intermittent administration of analgesic drugs. The pros and cons of this form of therapy must take into consideration the risk of complications, the measures necessary to monitor patients and administer the treatment, as well as the cost of setting up this form of treatment strategy. These will be necessarily complicated by the large individual variations in pain perception and response to treatment, so that carefully designed and conducted trials are needed. Another complicating factor in postsurgical patients is that nerve injuries may be involved which may produce pain by a different pathophysiological mechanism (123,124). Nevertheless, a potential opportunity exists to make a substantial contribution to the management of postoperative pain by using known methods of treatment, but changing their timing or duration of administration.

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