Preemptive Analgesia

Clinical Evidence of Neuroplasticity Contributing to Postoperative Pain

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Recent evidence suggests that surgical incision and other noxious perioperative events may induce prolonged changes in central neural function that later contribute to postoperative pain. The present study tested the hypothesis that patients receiving epidural fentanyl *before* incision would have less pain and need fewer analgesics postoperatively than patients receiving the same dose of epidural fentanyl *after* incision. Thirty patients (ASA physical status 2) scheduled for elective thoracic surgery through a posterolateral thoracotomy incision were randomized to one of two groups of equal size and prospectively studied in a double-blind manner. Epidural catheters were placed *via* the L2–L3 or L3–L4 interspaces preoperatively, and the position was confirmed with lidocaine. Group 1 received epidural fentanyl (4 μg/kg, in 20 ml normal saline) before surgical incision, followed by epidural normal saline (20 ml) infused 15 min after incision. Group 2 received epidural normal saline (20 ml) before surgical incision, followed by epidural fentanyl (4 μg/kg, in 20 ml normal saline) infused 15 min after incision. No additional analgesics were used before or during the operation. Anesthesia was induced with thiopental (3–5 mg/kg) and maintained with N_2O/O_2 and isoflurane. Paralysis was achieved with pancuronium (0.1 mg/kg). Postoperative analgesia consisted of patient-controlled intravenous morphine. Visual analogue scale pain scores were significantly less in group 1 (2.6 ± 0.44) than in group 2 (4.7 ± 0.58) 6 h after surgery ($P < 0.05$), by which time plasma fentanyl concentrations had decreased to subtherapeutic levels (<0.15 ng/ml) in both groups. Patient-controlled morphine usage in group 2 (26.1 ± 5.2 mg) was significantly ($P < 0.008$) greater than in group 1 (11.7 ± 2.2 mg) between 12 and 24 h after surgery, even though visual analogue scale pain scores at these times were not significantly different ($P > 0.05$). The results suggest that *preemptive analgesia* may reduce the central consequences of surgical incision and rib retraction by preventing noxious neural impulses from gaining entry into the central nervous system. (Key words: Analgesia: postoperative. Analgesics, epidural: fentanyl. Anesthetic techniques: Epidural. Pain: neuroplasticity.)

RECENT LABORATORY and clinical studies show that injury produces a prolonged change in central nervous system function that influences responses to subsequent afferent inputs. In rodents, high-intensity electrical stimulation of afferent nerve fibers or injury to nociceptors in skin induces neural and behavioral changes that persist even when inputs from the injured region are later blocked by local anesthesia[1–3] or interrupted by nerve section[4–7] or dorsal rhizotomy.[8] Simply cutting afferent nerve fibers in the absence of a prior noxious conditioning stimulus produces a long-term facilitation in spinal cord cells that persists in the absence of sustaining inputs from the transected nerve.[9] Clinical evidence that central neural plasticity contributes to persistent pain comes from studies of amputees who complain of phantom limb pain that resembles a painful preamputation lesion in the quality of sensation and the location in the limb.[10,11] Taken together, the evidence suggests that noxious stimulus-induced changes in central neural function may contribute to pain long after the offending stimulus has been removed or the peripheral injury has healed.

Physiologic and behavioral studies of animals also show that noxious stimulus-induced neuroplasticity can be prevented or "preempted" by administration of analgesic agents prior to injury. Bathing peripheral nerves in a local anesthetic solution prior to nerve transection reduces the incidence of behaviors indicative of pain in the weeks after the neurectomies.[12,13] Pretreatment with μ-opioid receptor agonists[14,15] or local anesthetic agents[16] prevents development of injury-induced spinal hyperexcitability[14,15] and pain-related behaviors.[16] Conversely, the same treatments are significantly less effective when administered only minutes later, after the prolonged central excitability

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or pain behaviors have been established.[14–16] In one study,[14] the dose of systemically administered morphine needed to prevent the establishment of central hyperexcitability prior to brief noxious electrical stimulation of the gastrocnemius–soleus nerve was one tenth the dose required to abolish the prolonged activity once it had developed.

These results have led to the idea that surgical incision and subsequent noxious perioperative events may also induce prolonged changes in dorsal horn neural processing that later contribute to enhanced postoperative pain.[17,18] Recent clinical evidence shows that a pharmacologic blockade of the somatosensory pathways using local anesthetics before surgery reduces postoperative pain intensity or lowers postoperative analgesic requirements.[19–24] However, the putative importance of *preemptive* blockade has not adequately been assessed: only two studies[23,24] administered a comparable pharmacologic blockade to a group of patients *after* incision, and only one of these was a controlled and randomized trial.[23] Although preincisional blockade was not associated with significantly less postoperative pain at any point in time after surgery when compared with postincisional blockade, fewer patients in the preincisional group required supplemental analgesics, and their demand for analgesics occurred later.[23] Taken together, these studies suggest that administration of local anesthetics before surgical trauma may reduce postoperative pain or analgesic requirements, but more information is required to determine the peripheral sources of central nervous system sensitization and the potential benefit of using other classes of analgesic agents.

The aim of the present study was to evaluate the efficacy of preemptive opioid analgesia and the specific contribution of the surgical incision and rib retraction to postthoracotomy pain. Administration of fentanyl after incision might be expected to result in less postoperative pain intensity than would fentanyl administration before incision because the drug given earlier would be present in smaller concentrations. However, we hypothesized that if the surgical incision and other noxious perioperative events (*e.g.*, rib retraction) sensitize the central nervous system to subsequent afferent inputs, patients receiving fentanyl *before* incision would report lower pain intensity and consume fewer analgesics postoperatively than patients receiving fentanyl *after* incision.

Materials and Methods

Patient Selection and Randomization Procedure

After institutional ethics committee approval and written informed consent had been obtained, 30 adult patients (ASA physical status 2) scheduled for elective thoracic surgery through a posterolateral thoracotomy incision were randomized to one of two groups of equal size and were prospectively studied using a double-blind cross-over design (fig. 1). Exclusion criteria were contraindications to regional anesthesia, ASA physical status > 2, age less than 18 yr or greater than 76 yr, weight greater than 100 kg, incision other than posterolateral thoracotomy, sig-

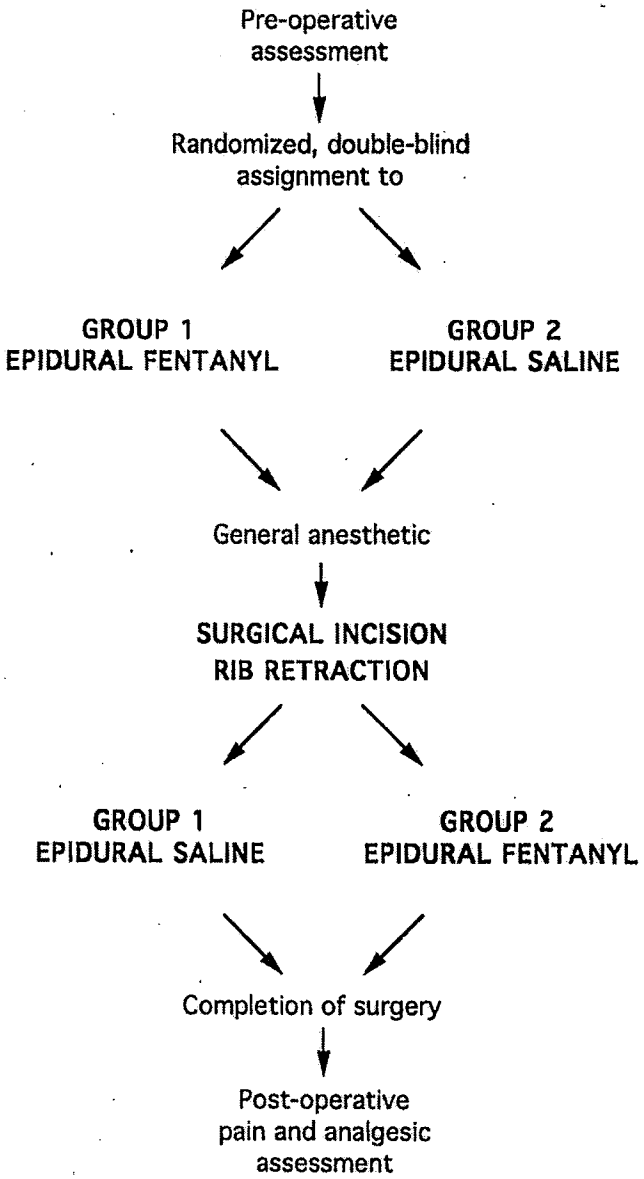

FIG. 1. Flow chart of study design. After obtaining informed written consent, patients were randomly assigned in a double-blind manner to receive an epidural infusion of fentanyl (group 1) or saline (group 2) before surgical incision and an epidural infusion of saline (group 1) or fentanyl (group 2) 15 minutes after surgical incision. Postoperative pain, patient-controlled administration of intravenous morphine, and plasma concentrations of fentanyl were measured after the completion of surgery.

nificant coronary artery disease, congestive heart failure, valvular heart disease, renal disease, hepatic disease, psychiatric history, or history of significant postoperative confusional episodes.

Before the study was begun, a table of random numbers was used to generate a randomization schedule specifying the group (1 or 2) to which each prospective patient would be assigned upon entry into the trial. An envelope containing the group assignment (and the order of fentanyl and saline infusions) was prepared, sealed, and numbered for each prospective patient. On the morning of the surgery, one of the investigators opened the patient's envelope, read its contents, and prepared two identical syringes that were labeled for preincisional and postincisional infusions. One syringe contained fentanyl, and the other contained normal saline. This investigator had no further involvement with the patient. All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been assigned. Although the anesthesiologist in charge of the case also was unaware of the patient's group, he had ready access to this information in the event of an emergency.

Anesthesia

Epidural Analgesia

In all patients, epidural catheters were placed *via* the L2–L3 or L3–L4 interspaces preoperatively. The position of the catheter was confirmed with administration of carbonated 2% lidocaine (5–10 ml). Patients in group 1 received epidural fentanyl by infusion (4 μg/kg in 20 ml normal saline over 30 min) before surgical incision, followed by an infusion of epidural normal saline (20 ml over 30 min) beginning 15 min after incision. Patients in group 2 (n = 15) received an infusion of epidural normal saline (20 ml over 30 min) before surgical incision, followed by an infusion of epidural fentanyl (4 μg/kg in 20 ml normal saline over 30 min) beginning 15 min after incision. All infusions were delivered using computerized infusion pumps (Harvard PCA Pump, Bard, Billerica, MA). No additional preoperative or intraoperative analgesics were administered to patients in either group.

General Anesthesia

Premedication consisted of oral diazepam 10 mg given 1–2 h preoperatively. While patients breathed O_2, anesthesia was induced with thiopental (3–5 mg/kg). Succinylcholine (1.0–1.5 mg/kg) was used to facilitate tracheal intubation with either a double-lumen endotracheal tube or a single-lumen tube with a bronchial blocker. Anesthesia was maintained with O_2/N_2O and halothane or isoflurane. Paralysis was achieved with pancuronium (0.1 mg/kg) and was confirmed with a nerve stimulator in all patients. Neuromuscular blockade was reversed with neostigmine and atropine at the conclusion of surgery. The trachea was extubated after emergence and upon resumption of spontaneous breathing. Patients received supplemental O_2 by mask to ensure Pa_{O_2} greater than 80 mmHg and were transported to the recovery room.

Postoperative Management

After arrival in the recovery room, patients were given access to a patient-controlled analgesia (PCA) pump system (Abbott Life Care II PCA Infuser, Chicago, IL) and given a 2-mg intravenous bolus of morphine by a nurse observer. Every 10 min during the recovery room period, patients were asked whether they needed pain relief. An affirmative response was followed by a 1.5-mg intravenous bolus of morphine administered by the nurse. This procedure was repeated until the patients were alert enough to begin administering the PCA morphine themselves. The PCA pump was set to deliver a 1.5–2.0-mg intravenous bolus dose of morphine, and the lock-out time was set at 7–10 min. This regimen of PCA was continued on the ward for 48 h, during which time no other analgesics were administered.

Blood samples were drawn 2, 4, and 6 h after the completion of surgery. Plasma fentanyl concentrations were determined at these times using a commercial radioimmunoassay kit (Janssen Laboratories, Beerse, The Netherlands). The assay was sensitive to 0.01 ng/ml with intraassay and interassay coefficients of variation of 6.0% and 6.9%, respectively, at 1.0 ng/ml. A 10-cm visual analogue scale (VAS) (with endpoints labeled "no pain" and "worst possible pain") was used to assess pain intensity 2, 4, 6, 12, 24, and 48 h after the completion of surgery. Side effects (nausea, vomiting, pruritus) were recorded if present.

Data Analysis

Before the start of the study, we estimated the sample size[25] required for a test of the hypothesis that postoperative pain would be less in group 1 than in group 2. Based on previous research[26] at our institution using the same outcome measure (*i.e.*, VAS for postoperative pain) and the same surgical population, and posterolateral incision, estimates of the effect size and variance were used to calculate the sample size (n = 15 per group) required to give the study a power of 0.9 (and a type I error rate of 0.05). Demographic and clinical data from groups 1 and 2 were compared using Fisher's exact test (for nonparametric variables) and unpaired, two-tailed *t* tests (for parametric variables).

VAS pain intensity scores and plasma fentanyl concentrations were analyzed by a two-way repeated-measures analysis of variance using group as the independent sam-

TABLE 1. Frequency of Diagnoses and Surgical Procedures for the Two Groups

	Group 1*	Group 2
Diagnosis		
Bronchiogenic carcinoma	12	9
Esophageal surgery (nonmalignant)	1	3
Miscellaneous (pulmonary infarct, bronchiectasis, neurogenic and metastatic tumors)	2	3
Procedure		
Lobectomy	10	9
Wedge resection	3	2
Hiatus hernia repair	1	3
Neurogenic tumor excision	1	1

All procedures involved a full posterolateral thoracotomy.
* Not statistically different from group 2 in diagnosis or procedure ($P > 0.05$ by Fisher's exact test).

ples factor and time after surgery as the repeated-measurements factor. A significant group-by-time interaction term was followed by *post hoc* tests of significance using Tukey's method[27] to compare the two groups at various points in time. Group medians were used to estimate missing VAS pain scores (*e.g.*, when patients were not awakened for pain assessments) for the analysis of variance. Less than 5% of total data were missing. PCA morphine consumption (milligrams) from groups 1 and 2 was compared with unpaired, one-tailed t tests using Bonferroni's type I error rate correction for multiple tests of significance (*i.e.*, α per number of tests). Recent studies[28,29] have shown that VAS pain intensity scores have ratio scale properties, making it appropriate to analyze VAS scores using parametric descriptive and inferential statistical procedures.

Data are presented as frequencies or percentages (for nonparametric variables) or as means ± SEM (for parametric variables). $P < 0.05$ was considered statistically significant for all tests.

Results

Demographics and Clinical Variables

Demographic and clinical variables for the two groups are presented in tables 1 and 2. With the exception of age, the two groups were not statistically different. The significant age difference shown in table 2 is due to two patients in group 2 whose ages were each more than two standard deviations less than the mean age of the entire sample of 30 patients. Removing these two patients from the data set produced a nonsignificant age difference between the groups and did not alter the outcome of the statistical analyses of VAS pain scores or morphine requirements as reported below based on the entire sample of 30 patients. Thus, the observed differences in postoperative pain and morphine consumption reported below are not attributable to the age difference between the groups, and all analyses reported below include the data from the two aforementioned patients.

The mean duration of surgery, blood loss, and the total dose of fentanyl received by each patient did not differ significantly between the groups (table 2). Table 2 shows that the fentanyl infusion in group 1 was started an average of 85 min before surgical incision.

Postoperative Pain and Analgesic Consumption

Figure 2 shows that 6 h after the completion of surgery, VAS pain intensity scores were significantly less ($F(5,140) = 2.40$, $P < 0.04$ for analysis of variance interaction and $Q = 4.88$, $P < 0.05$, for Tukey's test) in the group that received fentanyl *before* incision (2.6 ± 0.44) compared with the group that received fentanyl *after* incision (4.7 ± 0.58), even though patients in group 2 had received the opioid 85 min earlier than those in group 1 (table 2). The significant difference in pain intensity at 6 h could

TABLE 2. Demographic Data and Clinical Variables for the Two Treatment Groups

Variable	Group 1	Group 2	P
Age (yr)	61.9 (2.8)	49.5 (4.7)	0.03
Weight (kg)	70.9 (3.7)	71.1 (3.3)	NS
Males (n)	6	12	NS
Time (min) between start of first infusion and incision*	85 (10.9)	65 (7.7)	NS
Duration of surgery (min)	180 (18.0)	188 (9.0)	NS
Blood loss (ml)	292 (48.3)	287 (29.9)	NS
Total fentanyl dose (μg)	283.5 (14.8)	284.5 (13.2)	NS

Data are presented as means with SEM in parentheses unless otherwise specified.
NS = difference not significant.
* The first infusion contained fentanyl in group 1 and saline in group 2. The second infusion was started 15 minutes after surgical incision in both groups and contained saline in group 1 and fentanyl in group 2.

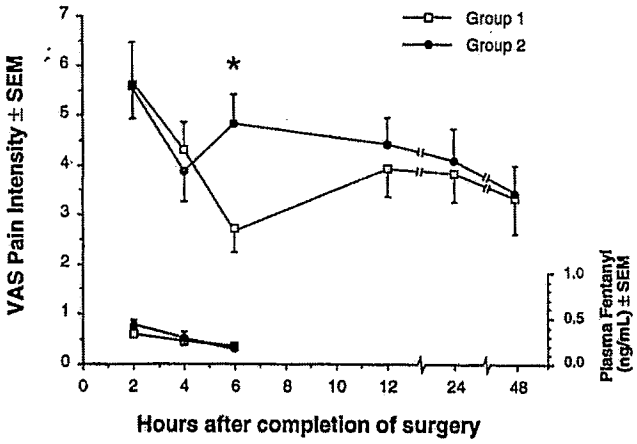

FIG. 2. Mean postoperative visual analogue scale (VAS) pain intensity scores for groups 1 and 2. Zero hours after the completion of surgery corresponds to the time when patients were admitted to the recovery room after the thoracotomy. *$P < 0.05$.

not be explained by lingering plasma concentrations of fentanyl (fig. 2), which, at the time of pain assessment, were subtherapeutic (< 0.15 ng/ml) in both groups ($P > 0.05$), or by PCA morphine consumption, which until this time was virtually identical in group 1 (19.5 ± 2.2 mg) and group 2 (16.8 ± 2.1 mg), as shown in figure 3. However, figure 3 also shows that between 12 and 24 h after surgery, PCA morphine consumption by patients in group 1 (11.7 ± 2.2 mg) was significantly less (t (28) = 2.55, $P < 0.008$, one-tailed) than that in group 2 patients (26.1 ± 5.2 mg), although VAS pain scores at these times were not significantly different ($P > 0.05$). No side effects were observed.

Discussion

The results of the present study demonstrate the benefits of preincisional *versus* postincisional epidural fentanyl on postoperative pain and analgesic consumption using a randomized, double-blind, placebo-controlled crossover design. Six hours after the completion of surgery, patients who received lumbar epidural fentanyl before incision had less pain than patients who received the same dose of fentanyl by the same route 15 min after incision. The finding that intergroup comparisons of VAS pain scores were not different 12 or 24 h after surgery (fig. 2) when PCA consumption in group 2 was more than twice that of group 1 (fig. 3) suggests that the additional morphine used by group 2 reduced their pain to a level comparable to that of group 1. Preemptive analgesia may protect patients from the deleterious effects of surgical incision and other noxious perioperative events (rib retraction) long after the operation has been performed.

The lower postoperative pain intensity ratings and morphine consumption among patients who had received pharmacologic blockade before surgical incision were observed sufficiently long after the administration of fentanyl in both groups to rule out the possibility that residual concentrations of fentanyl in the blood contributed to postoperative analgesia. An extended spinal action of fentanyl also is unlikely because the significant intergroup difference in pain was observed more than 10 and 8 h after fentanyl administration in groups 1 and 2, respectively (table 2), and the difference in morphine consumption was observed more than 30 h later. Finally, a synergistic effect of fentanyl with the test dose of lidocaine is unlikely to have produced extended or enhanced analgesia in group 1, because the addition of a more potent epidural local anesthetic solution does not potentiate the analgesic effects of epidural fentanyl after knee replacement[30] or thoracic surgery.[31]

Skin incision and subsequent transmission of neural impulses from the surgical site to the spinal cord mark the beginning of a process of central neural sensitization that may be enhanced by other noxious perioperative events. In present study, use of rib retractors after incision may have damaged intercostal nerves. In addition, ribs may split or fracture, and the rib periosteum may be denuded.[32] Detectable onset of analgesia after lumbar epidural fentanyl occurs as early as 4 min after injection,[33,34] and peak analgesia occurs approximately 15–20 min later.[34] Because the fentanyl infusion in group 2 was started 15 min after incision, it is reasonable to assume that maximum nociceptive blockade was achieved 20–60 min later so that noxious impulses may have continued to reach the spinal cord for as long as 75 min after skin incision.

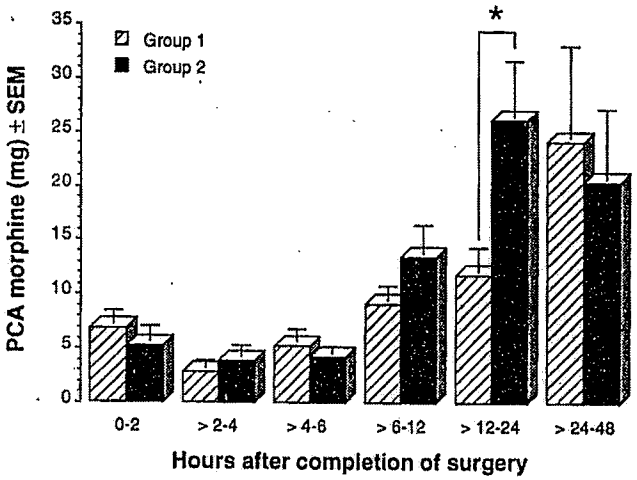

FIG. 3. Mean postoperative PCA morphine consumption for groups 1 and 2. Morphine consumption in the early hours (0–4 h) after the completion of surgery includes both nurse- and patient-administered doses. *$P < 0.008$.

Although preoperative administration of fentanyl resulted in significantly less pain and analgesic use, these effects were limited to the period between 6 and 24 h after surgery. Several aspects of the present design suggest that these effects underestimate the true potency of preemptive analgesia. First, for a given dose of fentanyl, use of lumbar epidural catheters for thoracic surgery may have reduced the degree of analgesia that might have been achieved had thoracic epidural catheters been used.[35,36] Second, use of fentanyl may have only attenuated the noxious effects of surgical incision in group 1, whereas a local anesthetic would have been expected to block it completely. Third, group 2 received the fentanyl 15 min after surgical incision in the course of a 3-h operation. Thus, we did not allow patients in this group to be exposed to the full extent of the surgical trauma. Taken together, these three considerations suggest that the results of the present study provide a conservative estimate of the true effectiveness of preemptive analgesia.

The difference in pain between the two groups did not emerge until 6 h after the completion of surgery. The absence of a difference before this point may reflect the time required for the central effects of the surgical incision to become fully established or the overwhelming contribution of peripheral inputs from the wound, which would mask the central component in the early hours after surgery. This result is not unlike the biphasic pattern of pain behavior exhibited by rats after subcutaneous injection of dilute formalin into the hindpaw.[16] Recent evidence suggests that dorsal horn activity associated with the late phase of formalin-induced pain may be dependent upon spinal activity during the first phase immediately after formalin injection.[15,16,37]

The present results are consistent with recent findings from animal studies[14,15] showing that μ-opioid receptor agonists administered before noxious stimulation can prevent or markedly reduce the prolonged spinal hyperactivity that otherwise develops. The finding that morphine consumption in group 2 was more than twice that of group 1 during the period between 12 and 24 h after surgery parallels the results of a study by Woolf and Wall[14] showing that, in rats, the dose of morphine required to abolish noxious stimulus-induced central hyperactivity was many times that required to prevent these prolonged central consequences when administered before injury. The present data are also consistent with clinical observations that relief of preamputation pain reduces the incidence of phantom limb and stump pain[38] and that pain after surgery[19–24,39,40] and dental work[41,42] is decreased by administering analgesic agents before the surgical trauma.

Although the precise mechanisms by which tissue damage produces prolonged alterations in central neural processing have yet to be fully elucidated, recent evidence suggests that C-fiber excitatory amino acids[43,44] and neuropeptides[44–46] may facilitate plastic changes in spinal cord dorsal horn neurons induced by noxious stimulation. There is evidence that these changes (*e.g.*, central sensitization and windup) are dependent on N-methyl-D-aspartic acid (NMDA) receptor activation[47–49] and that NMDA receptor antagonists may prevent or reverse central sensitization (and behaviors indicative of pain) when administered before[48,50] or after injury[48] even though they do not affect the cell's normal physiologic response to injury.[48] The prolonged changes in nociceptive processing that develop after tissue-damaging injury contrast with the relatively short-lasting postsynaptic actions of C-fiber excitatory amino acids and neuropeptides. Longer-lasting changes in neural function after injury-induced NMDA receptor activation may be brought about by intracellular second messengers[51,52] that would stimulate protein kinases[53] or new gene expression.[54–56] Careful and thorough clinical trials are required to determine whether agents that act at sites on the NMDA receptor (*e.g.*, the noncompetitive antagonist, ketamine, or less potent σ opiates such as pentazocine) also confer protection from needless pain if administered to patients before surgical incision.

In conclusion, epidural administration of fentanyl before surgical incision resulted in lower postoperative pain intensity and reduced postoperative morphine requirements when compared with the same dose and route of fentanyl administered 15 min after incision. The changes in central neural function that are presumed to underlie this effect are induced by surgical incision and other noxious inputs during the surgical operation. One consequence of this central sensitization appears to be an alteration in postoperative pain perception, such that noxious inputs from the surgical wound (*e.g.*, due to mobilization or dressing changes) may be more painful than they would otherwise have been and that innocuous inputs (*e.g.*, gentle touch) may give rise to frank pain. Preemptive analgesia may attenuate or prevent the development of central sensitization induced by surgical incision and later maintained by inputs from the wound.

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