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Long-lasting Hyperalgesia Induced by Fentanyl in Rats

Preventive Effect of Ketamine

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Background: **It has been reported that μ-opioid receptor activation leads to a sustained increase in glutamate synaptic effectiveness at the *N*-methyl-D-aspartate (NMDA) receptor level, a system associated with central hypersensitivity to pain. One hypothesis is that postoperative pain may result partly from the activation of NMDA pain facilitatory processes induced by opiate treatment *per se*. The authors tested here the effectiveness of the opiate analgesic fentanyl for eliciting a delayed enhancement in pain sensitivity.**

Methods: **The consequences of four bolus injections (every 15 min) of fentanyl (20–100 μg/kg per injection, subcutaneously) on immediate (for several hours) and long-term (for several days) sensitivity to nociceptive stimuli in the rat (paw-pressure vocalization test) were evaluated. The effects of the combination of the NMDA-receptor antagonist ketamine (10 mg/kg, subcutaneously) with fentanyl also were assessed.**

Results: **Fentanyl administration exhibited a biphasic time-dependent effect: first, an early response (for 2–5 h) associated with a marked increase in nociceptive threshold (analgesia), and second, a later response associated with sustained lowering of the nociceptive threshold (5 days for the longest effect) below the basal value (30% of decrease for the maximal effect) indicative of hyperalgesia. The higher the fentanyl dose used, the more pronounced was the fentanyl-induced hyperalgesia. Ketamine pretreatment, which had no analgesic effect on its own, enhanced the earlier response (analgesia) and prevented the development of long-lasting hyperalgesia.**

Conclusions: **Fentanyl activates NMDA pain facilitatory processes, which oppose analgesia and lead to long-lasting enhancement in pain sensitivity. (Key words: Glutamatergic transmission; opioid receptors; pain.)**

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IT is generally acknowledged that damage to tissue associated with surgical lesions often produces hyperalgesia (exaggerated nociceptive responses to noxious stimulation), allodynia (nociceptive responses to innocuous stimulation) and persistent spontaneous pain. These enhanced responses to noxious or non-noxious stimuli result from nociceptor sensitization in peripheral tissues or central sensitization.[1–3] Once established, such a central sensitization may become substantially independent of the precipitating event[4,5] and then constitute a pathophysiologic mechanism underlying pain hypersensitivity states, as found in postoperative pain.[2] It is a well-recognized fact that hyperalgesia and allodynia associated with central sensitization after tissue injury and inflammation partly stem from activation of *N*-methyl-D-aspartate (NMDA) receptors.[2,6,7] According to this scenario, laboratory investigations have reported that NMDA antagonists are particularly effective in reducing persistent pain associated with central sensitization in various experimental models.[8–12] Therefore, NMDA-re-

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ceptor antagonists are fruitful molecules for preventing central sensitization induced by tonic nociceptive input associated with surgical lesions. Clinical evidence shows that a subanesthetic dose of a clinically available NMDA-receptor antagonist, such as ketamine, decreases postoperative pain if added to general anesthesia before a surgical procedure.[13-15]

Conversely, electrophysiologic studies have reported that μ-opioid receptor activation by the potent opiate analgesic [D-Ala^2,*N*-Me-Phe^4,Gly-ol^5]-enkephalin also leads to a sustained increase in glutamate synaptic effectiveness at the NMDA-receptor level in neurons of the trigeminal nucleus, a center for processing nociceptive information from the orofacial areas.[16,17] At the behavioral level, we showed recently that a single injection of the μ-opioid receptor agonist heroin induces a delayed enhancement in pain sensitivity (hyperalgesia) for several days in rats.[18] This phenomenon is prevented by the NMDA-receptor antagonist MK-801.[18] On the basis of these data, we hypothesized that the administration of potent opiate analgesics that are widely used for human surgery, such as fentanyl and related compounds, also induces NMDA-dependent central sensitization processes, leading to a long-lasting enhancement in pain sensitivity. To assess whether fentanyl induces pain sensitization on its own, independent of tonic nociceptive inputs, the effects of this opiate on the nociceptive threshold were studied in uninjured rats for several days. We also studied the potential beneficial effect of the clinically available NMDA antagonist, ketamine, on fentanyl effect on nociception.

Materials and Methods

Animals

Experiments were performed on adult male Sprague-Dawley rats (IFFA-CREDO, L'Arbresle, France) weighing 350-400 g that were housed in groups of four or five per cage under a 12-h light-12-h dark cycle (lights on at 7:00 AM) at a constant room temperature of 22 ± 2°C. The animals had access to food and water *ad libitum*. Pharmacologic tests and care of the animals were performed in accordance with the guide for the Care and Use of Laboratory Animals.

Drugs

Fentanyl, naloxone hydrochloride, and ketamine hydrochloride were purchased from Sigma-Aldrich (Saint Quentin Fallavier, France). All drugs were dissolved in physiologic saline (0.9%) and administered subcutaneously (100 μl/100 g body weight). Control animals received an equal volume of saline injections.

Measurement of Nociceptive Threshold

Nociceptive thresholds in rats were determined by a modification of the Randall-Selitto method,[19] the paw-pressure vocalization test, in which a constantly increasing pressure is applied to the hind paw until the rat squeaks. The Basile analgesimeter (Apelex, Massy, France; stylus tip diameter, 1 mm) was used. A 600-g cutoff value was determined to prevent tissue damage.

General Procedure

After arrival in the laboratory, animals were left to become accustomed to the colony room for 5 days. To avoid stress from the experimental conditions, which might affect measurement of the nociceptive threshold, the experiments were performed by the same experimenter in quiet conditions in a test room close to the colony room. For 2 weeks before the experiments, the animals were weighed daily, gently handled for 5 min, and placed in the test room for 2 h (from 11:00 AM to 1:00 PM); then, they were left to become accustomed to the nociceptive apparatus. All experiments began at 1:00 PM and were performed on groups of 8-12 animals during the light part of the cycle. To ensure nociceptive threshold stability, the basal nociceptive threshold was measured twice (with 30 min between the measurements) on the 2 days preceding the planned experimental day (*i.e.*, on D_{-2} and D_{-1}). On the experimental day (D_0), the basal nociceptive threshold also was determined twice before drug injections (30 min between the measurements).

Experiments with fentanyl (or saline) were initiated only if no statistical changes were observed in basal nociceptive thresholds when estimated on days D_{-2}, D_{-1}, and D_0. Two comparisons were performed: between the first and second measurements of the nociceptive threshold performed daily on days D_{-2}, D_{-1}, or D_0 before treatment (Student *t* test, $P > 0.05$) and among the first daily measurements on days D_{-2}, D_{-1}, and D_0 (one-way analysis of variance [ANOVA], $P > 0.05$). The reference value of the basal nociceptive threshold for evaluating the pharmacologic effect of drugs was chosen as the first measurement of the nociceptive threshold performed on day D_0. For the sake of clarity, the nociceptive thresholds on day D_{-2} are not shown in the graphic curves in the figures, and the first measurement is only illustrated on days D_{-1}, D_{+1}, D_{+2}, D_{+3}, D_{+4}, and

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D_{+5}. The rats were assigned randomly to the different experimental groups, and the experimenter was unaware of the treatment used.

Experimental Protocol

In a first set of experiments, we studied the early and long-lasting effects of various doses of fentanyl on nociceptive threshold using a procedure designed to partly mimic its use in surgery. Fentanyl was injected four times (20, 40, 60, 80, or 100 μg/kg per injection, subcutaneously) at 15-min intervals, resulting in total doses of 80, 160, 240, 320, or 400 μg/kg, respectively. The nociceptive threshold was estimated every 30 min for a period of 270–420 min after the fentanyl injections. Subsequent to D_0, the nociceptive threshold was measured twice daily (30 min between both measurements) for 5 days (D_{+1}-D_{+5}). To avoid a delayed decrease in nociceptive threshold caused by an excess of peripheral afferent nociceptive inputs, resulting from the evaluation of the analgesic effect at D_0, an additional experiment was conducted without performing a nociceptive response measurement on the day of fentanyl treatment with four 60-μg/kg doses.

In a second set of experiments, we investigated the effects of the noncompetitive NMDA-receptor antagonist ketamine (10 mg/kg) on early and long-lasting effects induced by fentanyl using the described experimental protocol.

Data and Statistical Analysis

To evaluate the time-course effects of treatments on nociception, ANOVA was performed on the nociceptive threshold value (expressed in grams) and was followed by *post hoc* analysis using the Dunnett test. The Student *t* test was used to assess paired comparisons of nociceptive threshold values.

For further analysis of the overall long-lasting effect of treatments (D_{+1}-D_{+5}), an algesic index (*i.e.*, amplitude of hyperalgesia) was determined for each experimental group. This index was represented by the mean of the surface areas of trapezia evaluated for each rat. Surface areas were calculated by summing the nociceptive threshold values measured every day after the planned experimental day (D_0) according to the formula

$$\text{Surface} = \sum(\text{nociceptive threshold values at } D_{+n}) - \text{basal value} \times n,$$

where n represents the number of days. This total value is proportional to the surface area because the intervals between the successive tests are similar (1 day). Because of the cutoff pressure effect, which does not allow the overall analgesic effect of fentanyl to be estimated by using the trapezia method, the calculation of the analgesic effect duration on day D_0 was used as an analgesic index. Paired saline group–fentanyl group comparisons of analgesic index on day D_0 or algesic index on days D_{+1} to D_{+5} were performed using the Dunnett test, and between-group comparisons were performed by using the Newman–Keuls test. Data were expressed as the mean nociceptive thresholds ± SEM. The statistical significance criterion was $P < 0.05$.

Results

Short-lasting Effects of Fentanyl on the Nociceptive Threshold (D_0)

No statistically significant differences were found between the basal[5] nociceptive threshold value of each experimental group (one-way ANOVA, $P > 0.05$). The mean baseline nociceptive threshold was 307 ± 3 g (n = 60).

The short-lasting changes in nociceptive threshold induced by saline or various doses of fentanyl are shown in figure 1 (D_0). Saline injection did not alter the nociceptive threshold (one-way ANOVA, $P > 0.05$). On the contrary, fentanyl administrations (4 × 20, 4 × 40, 4 × 60, 4 × 80, and 4 × 100 μg/kg, subcutaneously; figs. 1B–F) induced a significant increase in the nociceptive threshold (analgesia). The amplitude and duration of the fentanyl-induced analgesia increased with the dose of fentanyl used. Further analysis by using a calculation of analgesic duration confirmed the previous analysis and indicated that the 4 × 80 and 4 × 100 μg/kg fentanyl analgesic durations were significantly different from analgesic durations of 4 × 20, 4 × 40, and 4 × 60 μg/kg (Newman–Keuls test; $P < 0.01$ for 4 × 80 μg/kg; $P < 0.001$ for 4 × 100 μg/kg).

Long-lasting Effects of Fentanyl on the Nociceptive Threshold (D_{+1}-D_{+5})

The long-lasting changes in nociceptive threshold induced by saline or various doses of fentanyl are shown in figures 1–3 (D_{+1}-D_{+5}). As shown in figures 1A and B, no statistically significant changes in nociceptive threshold were observed for several days (D_{+1}-D_{+5}) in both the saline-treated group and the fentanyl group treated with the lowest dose of the opiate: 4 × 20 μg/kg (one-way ANOVA, $P > 0.05$). On the contrary, a marked decrease

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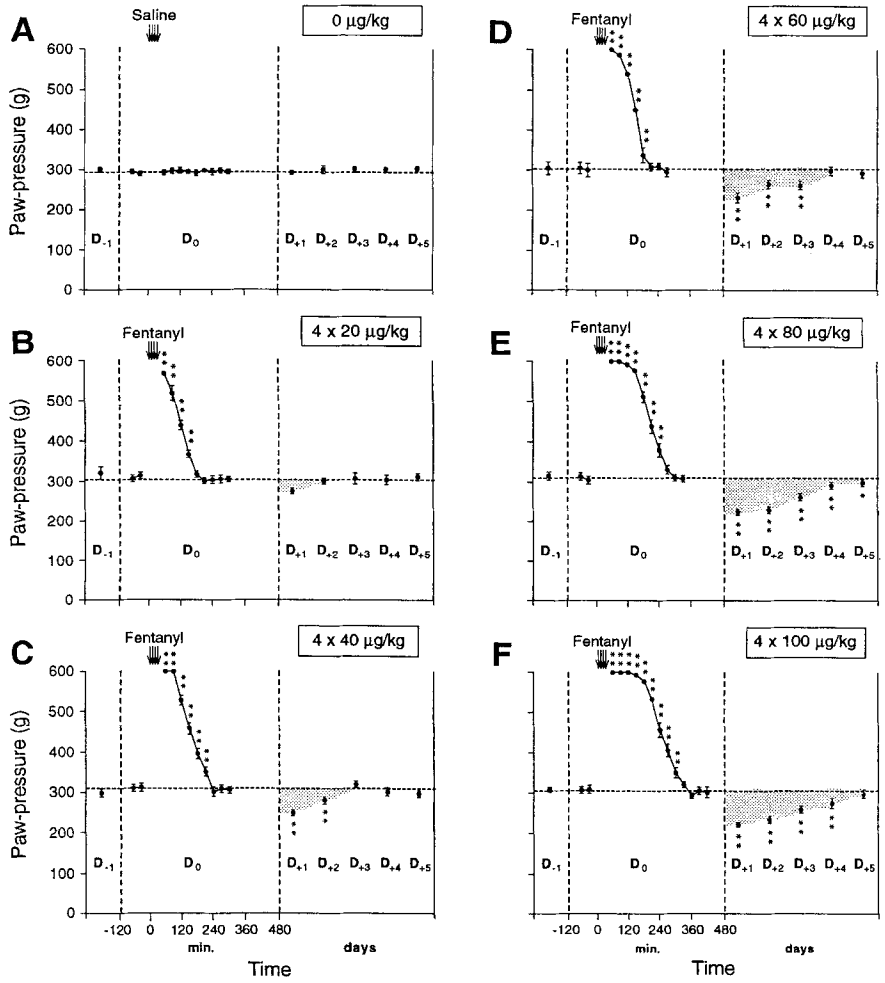

Fig. 1. Biphasic time effect induced by various doses of fentanyl as measured by the paw-pressure vocalization test. The fentanyl or saline injections were performed on the day of the test (D_0). The basal nociceptive threshold was evaluated before any treatment on D_{-1} and D_0 and after treatment for 4–6 h on D_0 and then daily for 5 days (D_{+1}–D_{+5}). Mean nociceptive thresholds (± SEM) were expressed in grams. (*A*) Saline group (n = 9). (*B–F*) Fentanyl groups. For each experiment, saline and fentanyl doses (20, 40, 60, 80, and 100 µg/kg per injection, subcutaneously; n = 10, 10, 9, 12, and 10, respectively) were injected four times at 15-min intervals (arrows), resulting in overall doses of 80, 160, 240, 320, and 400 µg/kg, respectively. The gray shaded surfaces represent the overall long-lasting effect of fentanyl. **P < 0.01 with the Dunnett test compared with the basal nociceptive threshold value.

in the nociceptive threshold was observed on the days after injections of 4 × 40, 4 × 60, 4 × 80, and 4 × 100 µg/kg fentanyl (one-way ANOVA, $P < 0.05$; figs. 1C–F). The decrease durations were 2, 3, 5, and 4 days, respectively. As shown by evaluation of the algesic index (fig. 2), the higher the fentanyl dose used, the more pronounced the delayed effect of fentanyl. Further analysis indicated that the algesic indices obtained with 4 × 60, 4 × 80, and 4 × 100 µg/kg fentanyl were statistically different from the algesic index observed with 4 × 20 µg/kg fentanyl, and the algesic indices obtained with 4 × 80 and 4 × 100 µg/kg fentanyl were statistically different from the algesic index associated with 4 × 40 µg/kg fentanyl (Newman–Keuls test, $P < 0.05$).

A statistically significant decrease in nociceptive threshold was also observed for 3 days in rats in the fentanyl-treated group (4 × 60 µg/kg), which had not received nociceptive inputs associated with the measurement procedure on day D_0 (one-way ANOVA, $P < 0.05$; fig. 3).

No difference in the algesic index was observed compared with the 4 × 60 µg/kg fentanyl group receiving nociceptive inputs on day D_0 (−159 ± 25 *vs.* −175 ± 69; Student t test, $P < 0.05$).

Effects of Ketamine Pretreatment on the Early Analgesic Effect of Fentanyl

If injected 30 min before saline, ketamine (10 mg/kg) had no effect on the nociceptive threshold value measured on D_0 (one-way ANOVA, $P > 0.05$; $n = 10$). Subsequent to ketamine pretreatment, bolus injection of 4 × 60 µg/kg fentanyl induced a significant increase of the nociceptive threshold for 120 min (one-way ANOVA followed by the Dunnett test, $P < 0.05$; fig. 4). The analgesic effect of the combined fentanyl and ketamine was enhanced compared with that observed with fenta-

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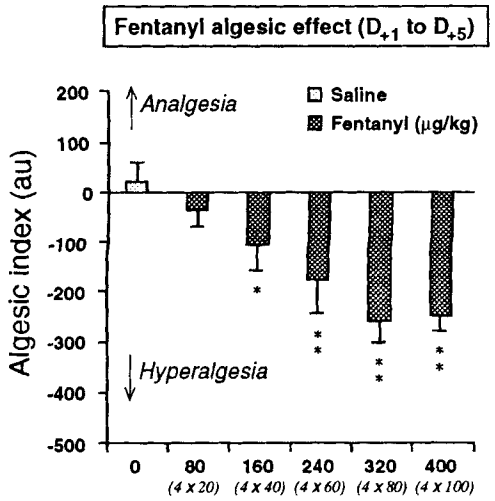

Fig. 2. Dose–response of the fentanyl hyperalgesic effects on the nociceptive threshold as measured by the paw-pressure vocalization test (days 1 through 5 after the treatment [D_{+1}–D_{+5}]). Fentanyl was injected four times (20, 40, 60, 80, or 100 μg/kg per injection; subcutaneously) at 15-min intervals, resulting in overall doses of 80, 160, 240, 320, and 400 μg/kg, respectively. The histogram represents the algesic index determined by the mean of the surfaces (± SEM). *$P < 0.5$, **$P < 0.01$ with the Dunnett test compared with the saline group.

nyl alone (two-way ANOVA, $P < 0.05$). Although a statistical comparison for the whole analgesic effect was not possible because cutoff was observed for 120 min after fentanyl injection in the ketamine-fentanyl group (compared with 60 min only in the saline-fentanyl group), *post hoc* analysis using the Dunnett test indicated significant differences for the later times until 180 min after the opiate administration ($P < 0.01$ for 120 and 150 min and $P < 0.05$ for 180 min).

Effects of Ketamine Pretreatment on the Long-lasting Effect of Fentanyl

As shown in figure 4 (D_{+1}–D_{+5}), the bolus injection of 4 × 60 μg/kg fentanyl produced no long-term changes in nociceptive threshold in ketamine-pretreated rats (one-way ANOVA, $P > 0.05$).

Discussion

The main finding of this study was that the administration of a potent opiate analgesic widely used in human surgery, such as fentanyl, exhibited a biphasic time-dependent effect on nociception: first, an early response (1–5 h) associated with a marked increase in nociceptive threshold (analgesia), as classically described, and second, a later response associated with a moderate but sustained (several days) decrease of the nociceptive threshold below the basal value indicative of hyperalgesia. Of note, the clinically available NMDA-receptor antagonist ketamine, which had no analgesic effect on its own, enhanced the earlier response (analgesia) and prevented the development of long-lasting enhancement in pain sensitivity in fentanyl-treated rats.

Our study showed that the higher the fentanyl dose used, the more pronounced the fentanyl-induced delayed hyperalgesia. From a methodological point of view, the behavioral responses observed in nociceptive tests must be interpreted with caution because an alteration in tail-flick latencies in response to a noxious stimulus may not necessarily be a reliable indicator of changes in pain sensitivity.[20] Thus, it has been postulated that morphine can induce facilitation of the C-fiber reflex by a direct spinal effect.[21] To avoid these difficulties, we chose to use the paw-pressure vocalization test, which provides a more integrated measure of pain involving supraspinal functions. Taking everything into account, we suggest that the delayed decrease in nociceptive threshold observed in fentanyl-treated rats reflects an actual increase in pain sensitivity. Such a de-

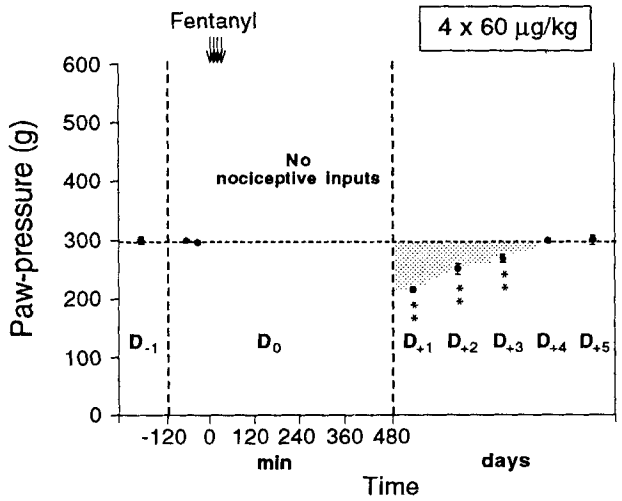

Fig. 3. Long-lasting effect of fentanyl in an experimental group that had not received nociceptive inputs associated with the measurement procedure on the day of the treatment (D_0). The fentanyl injections were performed on D_0. The basal nociceptive threshold was evaluated before any treatment on D_{-1} and D_0 and daily after treatment for 5 days (D_{+1}–D_{+5}). The evaluation of the analgesic effect on day D_0 was not performed. Mean nociceptive thresholds (± SEM) were expressed in grams. Fentanyl was injected four times (60 μg/kg fentanyl per injection, subcutaneously; arrows) at 15-min intervals, resulting in overall doses of 240 μg/kg. The gray shaded surfaces represent the overall long-lasting effect of fentanyl. **$P < 0.01$ with the Dunnett test compared with the basal nociceptive threshold value.

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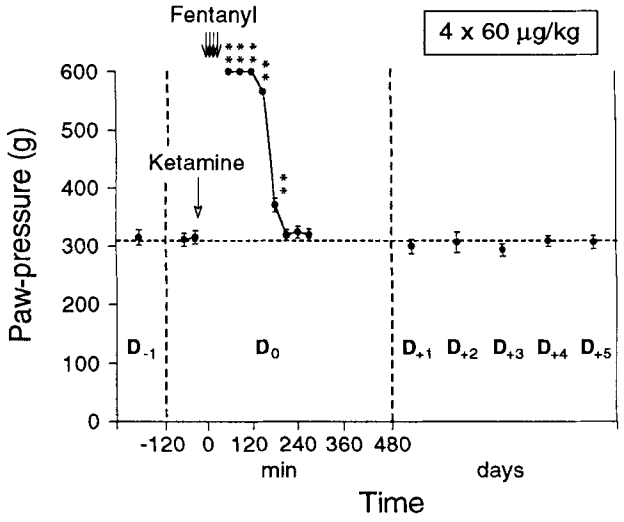

Fig. 4. Effects of ketamine pretreatment on the analgesic and hyperalgesic effects of fentanyl as evaluated by the paw-pressure vocalization test. The basal nociceptive threshold was evaluated before any treatment on the days before and of treatment (D_{-1} and D_0), and after treatment for 4–6 h on D_0 and daily for 5 days (D_{+1}–D_{+5}). Ketamine was administered 30 min before the first fentanyl injection (white arrow) at D_0. Fentanyl was injected four times (4 × 60 µg/kg per injection, subcutaneously) at 15-min intervals (black arrows). Mean nociceptive thresholds (± SEM) were expressed in grams. **$P < 0.01$ with the Dunnett test compared with the basal nociceptive threshold value.

crease cannot be explained by an excess of peripheral nociceptive inputs or by an avoidance response resulting from a conditioned processing associated with repetitive nociceptive stimuli because it was also observed in fentanyl-treated rats unexposed to repeated nociceptive stimuli on the day of fentanyl administration. The finding that no changes in nociceptive threshold were observed in fentanyl-untreated rats indicates that the delayed enhancement in pain sensitivity results from the opiate treatment alone.

Of note is our finding that the delayed fentanyl-induced hyperalgesia was prevented by ketamine. Today, the clinical use of ketamine as a general anesthetic is limited because it produces a trance-like cataleptic state in which the patient appears to be dissociated from the environment ("dissociative analgesia"). Ketamine has been reported to produce not only anesthesia, but also analgesic effects in subdissociative doses.[22] Although this compound interacts with various receptors,[23] it is believed that the analgesic effect of ketamine mainly results from its NMDA-receptor antagonistic properties[22] through prevention of central sensitization associated with repeated nociceptive stimuli.[24,25] In our study, ketamine had no effect on the nociceptive threshold if administered alone, but it prevented the delayed hyperalgesia induced by fentanyl for several days. This suggests that an enhancement of excitatory amino acid neurotransmission at the NMDA-receptor level underlies such an enhancement in pain sensitivity. In agreement with this hypothesis, we recently reported that long-lasting hyperalgesia induced by a single dose of heroin also is prevented by the NMDA antagonist MK-801.[18] A striking feature is that central sensitization triggered by nociceptive inputs also is blocked by NMDA-receptor antagonists.[8–12] It is tempting to speculate that the mechanisms that operate in producing the delayed enhancement in pain sensitivity induced by fentanyl in this study are equivalent to those underlying central sensitization induced by nociceptive inputs. Further studies are needed to ascertain whether fentanyl administration produces an increase in excitability of neurons in the spinal cord as a central sensitization triggered by nociceptive inputs; that is, expansion of receptive fields with a reduction in threshold, an increase in responsiveness and spatial extent, and the recruitment of novel inputs.[1,26]

In this study, we also observed that the NMDA-receptor antagonist ketamine enhanced the analgesic effect of fentanyl. This potentiation was discrete but was probably underestimated because using a cutoff in the experimental procedure did not enable responses to be evaluated with a 600-g stimulus. Although there are conflicting reports of the actions of NMDA-receptor antagonists on the opiate analgesic effect,[27,28] our results are consistent with the majority of previous studies that indicate an enhancement of morphine and heroin analgesic effects by NMDA antagonists.[18,29–36] Two kinds of mechanisms may underlie such potentiation *via* an enhancement in excitatory amino acid neurotransmission at the NMDA-receptor level: The first is a presynaptic mechanism because it was reported recently that intrathecal morphine induces a large increase in glutamate release in the dorsal horn of the spinal cord.[37] The second is a postsynaptic mechanism because it was reported recently that µ-opioid receptor activation by [D-Ala^2,*N*-Me-Phe^4,Gly-ol^5]-enkephalin leads to sustained increase in the NMDA receptor–mediated glutamate response *via* a protein kinase C–mediated removal of the Mg^{2+} blockade of the NMDA-receptor channel. This is a phenomenon observed in the trigeminal nucleus, a center for processing nociceptive information from the orofacial areas.[16,17] These data prompted us and others to hypothesize that a single dose of an opiate in "drug-naive" rats leads to enhanced glutamatergic neurotransmission, which in turn reduces the analgesic effect of the

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drug.[18,31,36,38] Such a suggestion might explain why the blockade of NMDA receptors by ketamine potentiated the analgesic effect of fentanyl.

From a clinical view point, our results indicate that NMDA receptors are involved in a process of enhancement in pain sensitivity after administration of fentanyl, an opiate widely used in human surgery. It is noteworthy that the enhancement in pain sensitivity was observed in the absence of tonic nociceptive inputs. Although speculative, this suggests that preventive administration of clinically available NMDA-receptor antagonists before fentanyl or related opiate compounds in surgical procedures may not only prevent central sensitization induced by tonic nociceptive inputs associated with surgical lesions, as previously described,[22] but also prevent long-lasting enhancement in pain sensitivity induced by opiate treatment *per se*. Our results provide an additional explanation for the beneficial reducing effect of ketamine on postoperative wound hyperalgesia.[13,39-42] Although some studies have reported that a single dose of ketamine administered after fentanyl reduces postoperative pain and morphine consumption after surgery in patients treated by patient-controlled analgesia,[13,42] other studies indicate minimal effect or no effect on pain experience or on morphine use after surgery.[12] By showing that ketamine prevented central sensitization associated with fentanyl administration, our study suggests that ketamine is more effective if it is administered before the opiate. Studies are in progress in our laboratory to test this hypothesis. Because we reported recently that acute tolerance to opiate analgesic effect is associated with NMDA-dependent pain facilitatory systems,[36] the administration of clinically available NMDA antagonists with fentanyl or related compounds may also prevent the development of acute tolerance reported to occur after opiate administration associated with surgery.[43,44] Nevertheless, because the body in pain is not in its normal homeostatic state,[45] further studies of an animal model of surgical pain are needed to test whether a combined fentanyl–NMDA-receptor antagonist therapy has a long-lasting beneficial effect on pain compared with fentanyl monotherapy.

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