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ORIGINAL ARTICLE

Role of gabapentin in preventing fentanyl- and morphine-withdrawal-induced hyperalgesia in rats

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Abstract
Purpose This study was undertaken to examine the effect of gabapentin for preventing hyperalgesia induced by morphine and fentanyl withdrawal in rats.
Methods To induce hyperalgesia, Sprague Dawley (SD) rats were subcutaneously injected with fentanyl four times at 15-min intervals (60 μg/kg per injection), resulting in total dose of 240 μg/kg over 1 h, and morphine 10 mg/kg twice daily for 7 days. The effect of gabapentin was detected with behavioral tail-flick and paw-withdrawal tests.
Results Drug termination produced significant decrease in antinociception thresholds ($P < 0.05$ vs. saline group), indicating that the rats became sensitive to thermal stimuli. In rats that received combined treatment with fentanyl/morphine and gabapentin (25/50 mg/kg), results demonstrated that there were no significant decreases in antinociception thresholds (vs. saline group) after opioid withdrawal. Gabapentin (50 mg/kg) could also prevent morphine tolerance. The 50% effective dose (ED50) value was 12.5 mg/kg in tail-flick and 13.6 mg/kg in paw-withdrawal tests.
Conclusions The study showed that gabapentin can significantly prevented opioid-induced hyperalgesia (OIH) induced caused by fentanyl and morphine, suggesting a role for the addition of gabapentin in the perioperative period and during chronic pain treatment as an effective drug to prevent OIH.

Keywords Gabapentin · Opioid · Morphine · Fentanyl · Hyperalgesia · Tolerance

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Introduction

Opioids are the most commonly used analgesics in pain treatment. However, accumulating evidence suggests that opioids produce not only an antinociceptive effect, but also increase sensitivity to noxious stimulation. The concept of pain sensitization after opioid administration is referred to as opioid-induced hyperalgesia (OIH) [1]. The concept of OIH creates great concern about managing perioperative and chronic pain using opioids [2]. So far, various kinds of opioids have been reported to induce hyperalgesia. Morphine-induced hyperalgesia usually occurs upon drug withdrawal after prolonged administration [3]. Fentanyl has been demonstrated to induce hyperalgesia after acute systemic administration both in uninjured humans and rats [4–7]. The use of alternative analgesics, such as nonopioid drugs, office-based detoxification programs, reduced opioid dose, and multimodal analgesia drugs are viable treatment options for OIH [1].

Neuropathic pain and OIH share common pathophysiologic mechanisms. Underlying mechanisms involve activation of excitatory neurotransmitters, intracellular messenger phosphokinase C (PKC), and *N*-methyl-D-aspartate (NMDA) receptor [8, 9]. Neuropathic pain tends to preferentially

respond to nonopioid medications, such as antidepressants and anticonvulsants.

Gabapentin was originally developed as an anticonvulsant drug. Subsequent studies established that gabapentin shows efficacy in neuropathic pain [10–12]. Gabapentin binds to alpha-2-delta subunit of voltage-dependent calcium channels and inhibits neurotransmitter release [13]. Other mechanisms, including effects on NMDA receptors, sodium channels, and opioid system, have been proposed. Gabapentin cannot only augment the analgesic effect of opioids but reverse morphine-induced tolerance. Field et al. [10] reported that gabapentin prevented the development of allodynia and hyperalgesia in a rat model of postoperative pain. Dirks et al. [14] found gabapentin significantly reduces postoperative morphine consumption after high-dose remifentanil-based anesthesia and suggested gabapentin as a preemptive antihyperalgesic for opioid-withdrawal hyperalgesia. Van Elstraete [15] first reported that gabapentin prevents the development of hyperalgesia induced by systemic exposure to fentanyl. However, few researchers have investigated the effect of gabapentin on both fentanyl- and morphine-withdrawal-induced hyperalgesia.

Our hypothesis was that gabapentin may prevent OIH, and our study therefore tested that hypothesis and explored the utility of systemic administration of gabapentin in rats after drug withdrawal.

Materials and methods

Animals

Male Sprague Dawley rats weighing 200–250 g (Central Animal Facility, Anhui Medical University, China) at the time of testing were housed six per cage in a room at a controlled temperature (22 ± 1°C), humidity (50 ± 10%), and 12-h light/dark cycle. Food and water were made available ad libitum. The protocol was approved by the Ethic Committee of Institute of Clinical Pharmacology, Anhui Medical University.

Drugs

Morphine hydrochloride was purchased from First Shenyang Pharmaceuticals Inc. (Shenyang, China). Gabapentin was provided by Jiangsu Nhwa Pharmaceutical Co., Ltd. (Xuzhou, China). Fentanyl citrate was purchased from Yichang Humanwell Pharmaceutical Co., Ltd (Yichang, China).

Experimental design

In the first part of experiment, according to the study of Celerier et al. [6], to induce OIH, fentanyl was injected subcutaneously (s.c.) (100 μl/100 g body weight) in the back of nonanesthetized rats with a 25-gauge needle. Fentanyl was injected four times (60 μg/kg per injection) at 15-min intervals, resulting in total dose of 240 μg/kg administered over 1 h to induce hyperalgesia. Supplemental oxygen was administered via facemask throughout the procedure. To evaluate the action of gabapentin, separate groups of animals received intraperitoneal (i.p.) injection of gabapentin administered 30 min before the first s.c. injection of fentanyl and 5 h after the last fentanyl injection. The nociceptive threshold was measured every 30 min for 30–240 min after the last fentanyl injection (Fig. 1).

To induce morphine-withdrawal hyperalgesia, rats were injected with morphine hydrochloride 10 mg/kg s.c. twice daily at 8:00 a.m. and 6:00 p.m. for 7 days, as described previously [16]. To investigate the effect of gabapentin on morphine-induced hyperalgesia, rats were administered gabapentin i.p. in doses of 25 and 50 mg/kg 30 min before morphine administration every day (Fig. 2).

To study the effects of various doses of gabapentin on fentanyl/morphine-induced hyperalgesia, rats were divided into four groups ($n = 10$): (1) gabapentin (25 mg/kg) combined with fentanyl/morphine; (2) gabapentin (50 mg/kg) combined with fentanyl/morphine; (3) saline injections of equal volume, and (4) fentanyl/morphine alone. To analyze gabapentin's effect on morphine tolerance, 50% effective dose (ED50) values were calculated using cumulative

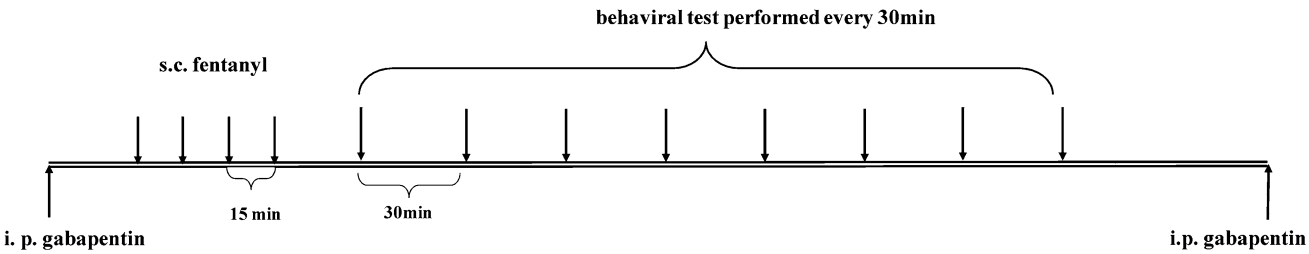

Fig. 1 Experimental design aimed to detect the effect of gabapentin on fentanyl-induced hyperalgesia

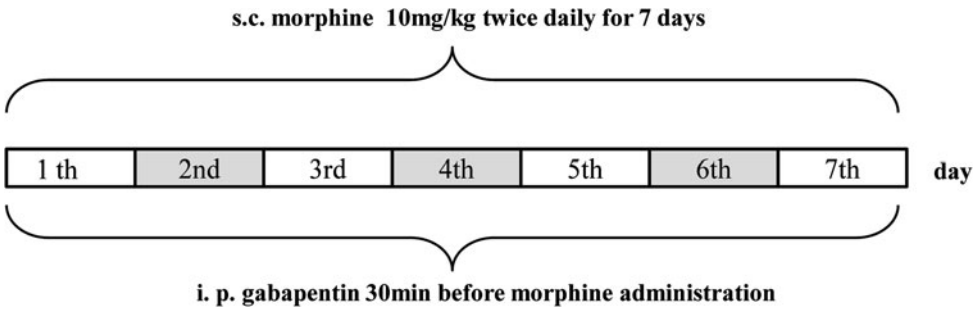

Fig. 2 Experimental design aimed to detect the effect of gabapentin on morphine-induced tolerance and hyperalgesia

dose-response studies on day 8 [17]. On the eighth day, rats ($n = 6$) were injected s.c. with cumulative doses of morphine used for ED50 determination of 0, 2.5, 7.5, 17.5, and 37.5 mg/kg for saline and combined groups (gabapentin 50 mg/kg plus morphine), and 0, 5, 15, 35, 75 mg/kg for the morphine group. Postdrug nociceptive testing was performed 30 min after treatment.

Behavioral test

Nociceptive testing was performed first with the tail-flick test and then with the paw-withdrawal tests. Each test was performed twice, and the average of the two results was recorded. The tail-flick test was performed using radiant heat generated from a bulb applied to the base of the tail, according to the method of Hargreaves et al. [18]. Preliminary experiments established the current needed from the power source to obtain a tail-flick latency of 3–5 s in control rats. The tail-flick latency is defined as the time between onset of heat stimulus and voluntary tail withdrawal. A cutoff time of 10 s is used to avoid tissue injury, in which case, 10 s is recorded. Animals were placed on a 27°C temperature-controlled glass surface inside a cylindrical (20-cm diameter) clear enclosure. After a 20-min period of acclimation, a focused beam of light was directed to the plantar surface of the hind paw immediately distal to the proximal set of footpads. Preliminary test established a paw-withdrawal latency of 5–7 s. Two latency measurements were made per animal approximately 5 min apart. A 15-s stimulation limit (cutoff) was used to avoid tissue damage. The antinociceptive effect was calculated as percentage change of tail-flick latency from baseline level according to the formula:

$$\%\ \text{MPE} = (\text{post-drug latency} - \text{baseline})/(\text{cut-off latency} - \text{baseline}) \times 100.$$

All experiments began at 10:00 a.m. and were performed in groups of ten animals. The basal nociceptive threshold was measured twice on the 2 days preceding the planned experimental day.

Statistical analysis

All results are expressed as mean ± standard error of the mean (SEM). Analysis of repeated measures was accomplished using a two-way analysis of variance (ANOVA) for repeated measures followed by post hoc testing. For parametric data obtained from thermal hyperalgesia test, Dunnett's test was used to detect differences between groups at specific time points. ED50 values were determined using nonlinear regression analysis, followed by one-way ANOVA with a post hoc test for multiple comparisons among groups. Calculations were performed using SPSS statistical package (version 13.0). $P < 0.05$ was considered significant.

Results

Effects of gabapentin on fentanyl-induced hyperalgesia

Figure 3 shows the effects of gabapentin on fentanyl-induced hyperalgesia with the paw-withdrawal test. As shown, administration of a total dose of 240 μg/kg fentanyl (60 μg/kg per injection at 15-min intervals) produced significant decrease in antinociception thresholds ($P < 0.05$ vs. saline group) at about 150 min and lasted till the first day after last fentanyl injection, when the analgesic effect disappeared. Intraperitoneal gabapentin in doses of 25 and 50 mg/kg effectively prevented this hyperalgesia state .

Effects of chronically administered gabapentin and morphine on morphine-withdrawal-induced hyperalgesia

The effect of gabapentin on thermal nociceptive thresholds in rats chronically administered morphine is shown in Fig. 4 with the paw-withdrawal test. Rats receiving morphine 10 mg/kg twice daily for 7 days showed a maximal antinociceptive response on first to third days of treatment ($P < 0.01$). However, there was a decrease in antinociceptive response on the fourth day and almost reached

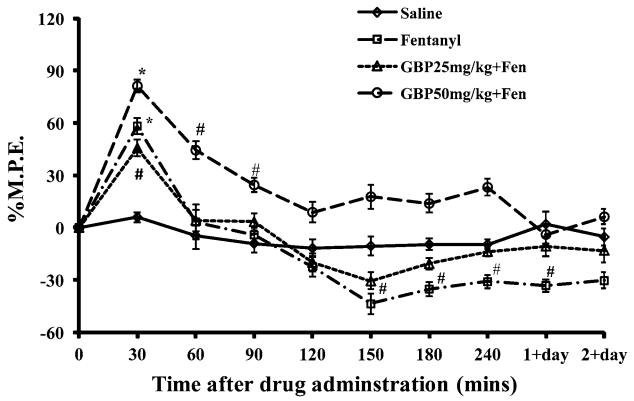

Fig. 3 Effects of gabapentin on fentanyl-induced hyperalgesia in paw-withdrawal test. As shown, administration of a total dose 240 μg/kg fentanyl (60 μg/kg per injection at 15-min intervals) produced significant decrease in antinociception thresholds ($P < 0.05$ vs. saline group) in rats at about 150 min and lasted till the first day after the last fentanyl injection, when the analgesic effect disappeared. Intraperitoneal gabapentin in doses of 25 and 50 mg/kg effectively prevented this hyperalgesic state. *$P < 0.05$ compared with morphine alone. #$P < 0.05$ compared with saline. *Fen* fentanyl, *GBP* gabapentin, *mor* morphine

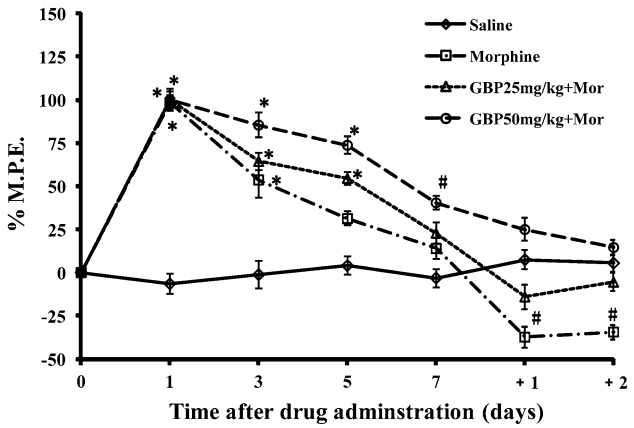

Fig. 4 Paw-withdrawal responses to repeated daily administration of saline, morphine, or morphine plus gabapentin on days 1–7 and days 1–2 after drug withdrawal in rats. Rats receiving morphine 10 mg/kg twice daily for 7 days showed a maximal antinociceptive response on days 1–3 of treatment ($P < 0.01$ vs. saline group). On days 1 and 2 after morphine termination, antinociceptive thresholds decreased compared with the control group ($P < 0.05$ vs. saline), indicating that the rats became sensitive to thermal stimuli. Chronic treatment with gabapentin (25 and 50 mg/kg twice daily) along with morphine prevented morphine-induced hyperalgesia on days 1 and 2. *$P < 0.05$ compared with morphine alone. #$P < 0.05$ compared with saline. *GBP* gabapentin, *mor* morphine

baseline latency by day 7. On the first and second days after morphine termination, antinociceptive thresholds decreased compared with the control group ($P < 0.05$), indicating that rats became sensitive to thermal stimuli. Chronic treatment with gabapentin (25 and 50 mg/kg twice daily) along with morphine prevented morphine-induced hyperalgesia on the first and second day.

Table 1 Effects of gabapentin on 50% effective dose (ED50) values for morphine antinociception after subcutaneous injection of morphine twice daily for 7 days

Group	Tail-flick test (CI)	Paw-withdrawal test (CI)
Saline	3.5 (2.7–4.5)*	3.8 (2.5–5.3)*
Morphine	32.3 (22.4–61.7)	37.1 (21.5–74.1)
Morphine + gabapentin	12.5 (4.6–18.0)*	13.6 (6.2–16.8)*

After the end of the 7-day chronic treatment, cumulative dose-response curves to acute morphine were generated on day 8. ED50 values (reported in mg/kg) were calculated from dose-responsive curves

CI confidence interval

* $P < 0.05$ compared with morphine

On day 8, ED50 values were 3.5, 32.3, and 12.5 mg/kg for morphine alone, morphine plus gabapentin (50 mg/kg), and saline, respectively in tail-flick test (Table 1). As shown, chronically administered morphine produced a significant increase in ED50 values, reflecting the development of tolerance. Gabapentin combined with morphine prevented this increase in both the tail-flick and paw-withdrawal tests, reflecting tolerance inhibition.

Discussion

Our study confirms that systemic use of morphine and fentanyl can induce sustained pain sensitivity indicative of hyperalgesia after drug withdrawal and that systemic gabapentin prevented the hyperalgesia state induced by fentanyl and morphine in normal rats. Results also verified the preventive effect of gabapentin (50 mg/kg i.p.) on morphine tolerance by calculating the ED50 value. Behavioral tests were performed using two tests: the tail-flick test (a spinal reflex test) and the paw-withdrawal test (which involves the higher centers). Gabapentin dosages were chosen according to previous studies in which it was shown to treat neuropathic pain in rats [19, 20]. Gabapentin was injected twice daily considering the elimination half life [21].

Morphine and fentanyl are well known to couple to μ-opioid receptors, inhibit adenylate cyclase (AC) activity, and reduce cyclic adenosine monophosphate (cAMP) levels. Long-term opioid exposure can cause up-regulation of AC activity, resulting in high levels of cAMP [22, 23] and thus cause central sensitization. PKC play a crucial role in the crosstalk between Gi protein subunit–adenyl cyclase–cAMP (Gi-AC-cAMP) pathway and other cellular processes, such as excitatory amino acids (EAA)-NMDA

hyperreactivity [24]. The above mechanisms are involved in both fentanyl- and morphine-induced hyperalgesia [6, 25, 26]. Celerier [27] suggested that both antinociceptive and pronociceptive systems be upregulated after long opioid exposure, and the balance between antinociceptive and pronociceptive systems is broken as opioids are discontinued. Pharmacotherapies focused on inhibiting the facilitatory pathway have been suggested to prevent OIH. Anticonvulsants and antidepressants were suggested as adjuvant drugs. It is not yet clear which pharmacological mechanisms of actions relate to the antihyperalgesic effect of gabapentin. Yannick [28] reported that activation of PKC or AC on glutamate release was blocked by gabapentin. Gabapentin was demonstrated to decrease NMDA-mediated glutamate currents in the superficial lamina of the rat spinal cord [29] and has been shown to inhibit PKC-induced release of glutamate in vitro [30]. Furthermore, the analgesic effects of gabapentin were antagonized by the NMDA receptor agonist [31, 32]. Previous studies have shown additive, or synergistic, interactions between gabapentin and morphine in various conditions. Eckhardt et al. [33] demonstrated that gabapentin increases analgesic effect of morphine in normal volunteers. Gabapentin [34, 35] has also demonstrated to significantly enhance the antinociceptive effect of morphine in neuropathic pain in rats. Hansen et al. [36] reported that, behaviorally, intrathecally administered gabapentin prevents morphine-induced tolerance. The mechanism of this effect might be via suppression of excitatory amino acid release in the spinal cord [37]. Our study confirmed the above effect of gabapentin on fentanyl using tail-flick and paw-withdrawal tests and further demonstrated the similar effect on morphine. Thus, we suggest gabapentin as an auxiliary drug in opioid treatment.

As hyperalgesia includes both thermal and mechanical hyperalgesia, a major shortcoming of this study is that it did not include tests to measure mechanical hyperalgesia to further verify the effect of gabapentin. Results do suggest an addition role for gabapentin in the perioperative period and for chronic pain treatment and indicate that gabapentin may be an effective drug for preventing OIH relate to morphine and fentanyl withdrawal. Further investigations are needed to verify these results in other opioids, such as remifentanil and patient populations, as well as studies to explore the exact sites and mechanisms through which gabapentin exerts its preventive effect on OIH.

Conclusions

In conclusion, this study demonstrated that gabapentin prevents both fentanyl- and morphine-withdrawal-induced hyperalgesia in rats. Further studies are required to confirm the effects in clinical trials and to explore the mechanisms underlying the role of gabapentin in OIH.

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