Acute thermal hyperalgesia elicited by low-dose morphine in normal mice is blocked by ultra-low-dose naltrexone, unmasking potent opioid analgesia

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Abstract

Our previous studies demonstrated that extremely low fM–nM concentrations of morphine and many other bimodally-acting mu, delta and kappa opioid agonists can elicit direct excitatory opioid receptor-mediated effects, whereas higher (μM) opioid concentrations evoked inhibitory effects. Cotreatment with pM naloxone or naltrexone (NTX) plus fM–nM morphine blocked the excitatory effects and unmasked potent inhibitory effects of these low opioid concentrations. In the present study, hot-water-immersion tail-flick antinociception assays at 52°C on mice showed that extremely low doses of morphine (ca. 0.1 μg/kg) can, in fact, elicit acute hyperalgesic effects, manifested by rapid onset of decreases in tail-flick latency for periods greater than 3 h after drug administration. Cotreatment with ultra-low-dose NTX (ca. 1–100 pg/kg) blocks this opioid-induced hyperalgesia and unmasks potent opioid analgesia. The consonance of our in vitro and in vivo evidence indicates that doses of morphine far below those currently required for clinical treatment of pain may become effective when opioid hyperalgesic effects are blocked by coadministration of appropriately low doses of opioid antagonists. This low-dose-morphine cotreatment procedure should markedly attenuate morphine tolerance, dependence and other aversive side-effects.

Theme: Sensory systems

Topic: Pain modulation: pharmacology

Keywords: Acute low-dose morphine hyperalgesia; Bimodally-acting opioid agonists; Tail-flick assay (52°C); Ultra-low-dose naltrexone; Subanalgesic etorphine; Mouse strains 129/SvEv/Tac vs. SW

1. Introduction

Our previous studies demonstrated that cotreatment of mice with ultra-low doses of naltrexone (NTX) markedly enhances the magnitude and duration of antinociceptive effects of morphine and many other opioid agonists [10,34]. This cotreatment paradigm was guided by pharmacologic studies on nociceptive types of mouse dorsal root ganglion (DRG) neurons in culture [7–12]. These in vitro studies showed that low (pM) concentrations of naloxone (NLX) or NTX can selectively antagonize high-efficacy excitatory opioid receptor-mediated effects [e.g., prolongation of the action-potential duration (APD)] elicited by extremely low doses (fM–nM) of morphine (or other mu, delta and kappa opioid agonists) [10,11]. Cotreatment with pM NLX or NTX plus fM–nM morphine unmasked potent inhibitory APD-shortening effects which required μM concentrations of morphine when applied alone. Furthermore, recent evidence indicates that opioid receptors can be interconverted rapidly between an inhibitory (Gi/Go-coupled) and an excitatory (Gs-coupled) mode following physiological alterations in the concentration of a specific cyclic AMP-dependent glycolipid, GM1 ganglioside, in the neuronal cell membrane [11–13,36]. These studies of the bimodal excitatory/inhibitory actions of opioid agonists on DRG neurons in vitro suggested that treatment with morphine in vivo may result not simply in analgesia, but also in anti-analgesic or hyperalgesic effects which would tend to mask the expected analgesia.

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mice carried out at 55°C revealed that morphine does, indeed, elicit anti-analgesic excitatory effects as evidenced by the marked increase in the analgesic potency of moderate doses of morphine (0.1–3 mg/kg) following cotreatment with ultra-low-dose NTX [10,34]. Progressive increases in the magnitude and duration of analgesia were observed in these assays as the dose of morphine alone was increased from 0.1 mg/kg to 10 mg/kg (s.c.) [10,34]. However, tail-flick latencies of mice treated with much lower doses of morphine (ca.1 µg/kg) did not differ significantly from control mice. Because the average control tail-flick latencies were only about 2 s, we realized that possible hyperalgesic effects of low doses of morphine would be difficult to quantify with this type of assay. To determine if low doses of morphine elicit hyperalgesic effects in mice analogous to the excitatory effects evoked in DRG neurons by <nM opioid concentrations, we decreased the temperature of the hot-water bath from 55°C to 52°C.

Tail-flick assays at 52°C showed that 1000-fold lower doses of morphine can, indeed, elicit acute hyperalgesic effects, manifested by rapid onset of opioid-induced decreases in tail-flick latency for periods >3 h after drug administration. Cotreatment with ultra-low-dose NTX blocks this opioid-induced hyperalgesia and unmasks potent opioid analgesic effects. These in vivo results are remarkably consonant with the results of our in vitro studies of the acute excitatory effects of low-dose morphine+ultra-low-dose NTX on DRG neurons [10]. The present evidence indicates that doses of morphine far below those currently required for clinical treatment of pain may become effective when opioid hyperalgesic effects are blocked by co-administration of appropriately low doses of NTX or other opioid antagonists. This low-dose-morphine plus NTX cotreatment procedure should markedly attenuate morphine tolerance, dependence and other aversive side-effects.

2. Materials and methods

2.1. Antinociception assays in mice

Swiss–Webster (SW) male mice (20–25 g, Charles River, NY) and 129/SvEvTac mice (20–25 g, Taconic, Germantown, NY) were housed separately in groups of five, maintained on a 12 h light/dark cycle, and provided water and food ad libitum for 1 to 3 days prior antinociception and withdrawal testing. Antinociceptive effects of opioids were measured on these mice using a warm-water-immersion tail-flick assay similar to methods previously described [10,13,20,34]. Each mouse was permitted to enter into a tapered plastic cylinder (with air holes). The size of the cylinder is a little larger than the animal body size, with the tail hanging out freely from the cylinder. The cylinder provides a secluded environment into which the animal voluntarily enters with no application of any force. During the tail-flick assay only the cylinder is handled without direct contact with the animal. One third of the tail from the tip is immersed into a water bath maintained at 52°C (±0.1°C) with an electronic thermoregulator (Yellow Springs). The latency to a rapid tail-flick was recorded; mice with control latencies >8 s were excluded from these tests and a 10 s cut-off was used to minimize tissue damage. Six sequential control tests were made, each with a 10 min interval. The latencies of the last four tests were averaged to provide a predrug value. Time–effect curves were plotted using tail-flick latencies as the ordinate (see also [13]).

2.2. Animal test groups

Comparative tests were generally carried out on the same day with two or more groups of eight mice receiving a specific cotreatment plus an appropriate control group of eight mice treated with morphine alone. All animal test groups were used for only one assay, except in chronic drug treatment tests.

2.3. Statistical analyses

Differences between treatment groups were examined for statistical significance by means of ANOVA with Neuman–Keuls’ tests or by means of Student’s t-test [35].

2.4. Materials

The following drugs were used: NTX, morphine (Sigma); etorphine (gift from Dr E.J. Simon).

3. Results

3.1. Low doses of morphine elicit acute thermal hyperalgesic effects in normal mice

Antinociception assays at 52°C resulted in control tail-flick latencies >4 s, thereby facilitating detection of experimentally elicited decreases in tail-flick latency, i.e., hyperalgesic effects. Administration of morphine to mice at doses of 0.1, 1 and 10 mg/kg (s.c.) resulted in dose-dependent increases in tail-flick latencies which reached their peak values of about 3–6 s above baseline levels within 30–60 min and returned to baseline levels during the following 1–3 h (Fig. 1A: •, ○). Tail-flick latencies did not return to baseline levels during tests carried out at longer periods after injections of 1–10 mg/kg morphine. Instead, significant decreases in tail-flick latency, ca. 0.5–1 s below baseline levels, were observed at 5–6 h after drug
Fig. 1. Hyperalgesia elicited by low-dose morphine is blocked by cotreatment with ultra-low-dose naltrexone (NTX) unmasking potent opioid analgesia. (A) Time-effect curves show results of hot-water (52°C)-immersion tail-flick tests after injection of morphine (s.c.) at 1 μg/kg (▼), 1 mg/kg (○) and 10 mg/kg (●). Note marked increase in magnitude and duration of antinociception after treatment with 10 μg/kg (●) vs. 1 mg/kg (○) similar to dose-dependent effects of morphine in previous assays using 55°C water bath [31]. By contrast, note significant onset of hyperalgesic effects (manifested by decreases in tail-flick latency) within 30 min after injection of 1 μg/kg morphine (▼) (not detected in previous tests at 55°C [34]). Furthermore, cotreatment of a 4th group of mice with 0.1 ng/kg NTX blocks 1 μg/kg morphine-induced hyperalgesia and unmask a remarkable degree of opioid analgesia comparable to that elicited by a 1000-fold higher dose of morphine alone (○). (B) Cotreatment with 1 pg/kg NTX unmasks the potent antinociceptive effects of a still lower dose of morphine, 0.1 μg/kg (▼), whereas the potential analgesic effect of a much higher dose of morphine alone, 30 μg/kg is almost completely masked (▼) by concomitant excitatory opioid receptor-mediated hyperalgesia. A control tail-flick assay carried out without drug injection (●) shows that sequential tail-immersion in a 52°C water bath does not result in significant alterations in baseline tail-flick latency, in contrast to the typical hyperalgesic effects that are elicited after injection of a low dose of morphine, 0.1 μg/kg (○) or 1 μg/kg morphine (▲). Note: in this and all subsequent figures, n=8 for each curve; error bars indicate S.E.M.

3.2. Ultra-low-dose NTX blocks low-dose-morphine-induced hyperalgesia and unmasks potent opioid analgesia

Cotreatment with 1 μg/kg morphine plus a 10,000-fold lower dose of NTX, 0.1 ng/kg resulted in a remarkable conversion of the hyperalgesic effects elicited by this low dose of morphine alone (Fig. 1A: ▼) to a significant degree of analgesia which lasted for >3 h after dosing (Fig. 1A: ▼). The antinociceptive effect of cotreatment with 1 μg/kg morphine plus 0.1 ng/kg NTX is comparable in magnitude and much longer in duration than that elicited by a 1,000-fold higher dose of morphine alone (Fig. 1A: ▼ vs. ○). Similarly, the hyperalgesia elicited by dosing. These delayed 'hyperalgesic' effects were not detected in our previous assays at 55°C [34].

Administration of 1000 to 10,000-fold lower doses of morphine, e.g., 0.1 and 1 μg/kg (s.c.), resulted in rapid onset of decreases in tail-flick latencies (ca. 1–2 s) which lasted for >3 h after drug injection (Fig. 1A: ▼, Fig. 1B: ○). Preliminary assays indicate that doses of morphine as low as 1–10 ng/kg can elicit significant decreases in tail-flick latencies, but more systematic studies are required to characterize the dose–response properties of the high-efficacy excitatory opioid receptor system mediating these hyperalgesic effects. Interestingly, whereas 100 μg/kg morphine elicited analgesia (slightly weaker than 1 mg/kg morphine: Fig. 1A; time–effect curve not shown for simplicity) and 1 μg/kg morphine resulted in hyperalgesia, injection of an intermediate dose of morphine, 30 μg/kg showed no significant difference from saline (Fig. 1B: ▼). The latter result suggests that about 30 μg/kg morphine elicits equipotent inhibitory/analgesic and excitatory/hyperalgesic effects that effectively neutralize opioid modulation of nociception. In other groups of mice, however, the dose of morphine that elicited equipotent analgesic/hyperalgesic effects appeared to be closer to 5–10 μg/kg (see Section 4.1). In some groups of mice, especially where the mean baseline tail-flick latencies were about 5–6 s (e.g., Fig. 2A), the decreases in tail-flick latencies elicited by 1 μg/kg morphine were larger in magnitude (ca. 2–3 s) and the hyperalgesic effects lasted >6 h. By contrast, in previous assays at 55°C, no significant alterations in tail-flick latency were detected during tests carried out for 4 h after injection of 1 μg/kg morphine [34].

Control assays were carried out in order to evaluate whether the observed low-dose morphine-induced hyperalgesia might be inadvertently exaggerated by the repeated hot-water exposures used in our routine assay procedure. Groups of mice were injected with 1 μg/kg morphine and the initial tail-flick test was delayed until 1, 2 or 3 h after drug administration. Characteristic decreases in tail-flick latency (ca. 1–2 s) still occurred in all three test groups and all showed return to baseline latencies when rested 3 h after the initial test.
3.3. Acute hyperalgesic effects elicited by low doses of morphine do not show desensitization during chronic opioid treatment

Daily injections of low 1 μg/kg doses of morphine for 3 days resulted in maintenance of similar or slightly larger acute hyperalgesic effects (Fig. 2A), whereas daily injections of high doses of morphine result in progressive decreases in analgesia, i.e., tolerance [10,13,34]. Interestingly, the baseline tail-flick latency showed sequential decreases on the 2nd and 3rd days (Fig. 2A). Furthermore, chronic cotreatment of mice with daily injections of 1 μg/kg morphine plus 0.1 ng/kg NTX for 3 days resulted in sustained block of hyperalgesia and maintenance of prominent analgesic effects (Fig. 2B: [in contrast to the marked tolerance observed after three daily doses of 4 mg/kg morphine alone ([13]: Fig. 3]). Acute low-dose morphine-induced hyperalgesia reappeared when the NTX was deleted on the 4th day of drug treatment (Fig. 2B: ▼).

3.4. In contrast to morphine low subanalgesic doses of etorphine do not elicit hyperalgesic effects in mice

Administration of the super-potent opioid analgesic, etorphine [3], at 1 μg/kg resulted in marked antinociception (Fig. 3A: ●) comparable to the effects of >1,000-fold higher doses of morphine (Fig. 1A, B). However, subanalgesic doses of etorphine (ca.1 pg/kg–1 ng/kg) did not elicit hyperalgesic effects (Fig. 3A: ○, ▲ and ▼; see Section 4.1), in contrast to the prominent hyperalgesia evoked by subanalgesic doses of morphine (Fig. 1). The antinociceptive effects of 1 μg/kg morphine that were unmasked by treatment with 1 ng/kg etorphine were even larger in magnitude and longer-lasting than the antinociception evoked by a 1,000-fold higher dose of etorphine alone (cf. Fig. 3B: ○ vs. Fig. 3A: ●).

Interestingly, in a comparative test carried out on three additional groups of mice, the magnitude and the duration of the antinociceptive effects elicited by cotreatment with 1 μg/kg morphine plus 0.1 ng/kg NTX were remarkably similar to those elicited by 1 μg/kg etorphine (Fig. 4).

3.5. Low doses of morphine elicit analgesia rather than hyperalgesia in 129/SvEvTac vs. SW mice

Tail-flick assays were also carried out on 129/SvEvTac mice, which are markedly deficient in excitatory opioid receptor functions in comparison with SW mice [13].

a 10-fold lower dose of morphine (0.1 μg/kg) was blocked by a much lower dose of NTX (1 pg/kg), unmasking prominent opioid analgesic effects (Fig. 1B: ▼).

Comparable hyperalgesia was elicited by low doses of methadone (1 μg/kg) or the much weaker opioid analgesic, tramadol (100 μg/kg) and those effects were also blocked by cotreatment with ultra-low dose NTX, unmasking potent opioid analgesia ([14] and Crain and Shen, in preparation).
Administration of a low 1 μg/kg dose of morphine resulted in analgesic effects in 129/SvEvTac mice in contrast to the hyperalgesia elicited in SW mice (cf. Fig. 5: ● vs. Fig. 1: ▼). In these assays at 52°C, morphine showed remarkably potent antinociceptive effects in 129/SvEvTac mice, comparable to those elicited by a 1,000-fold higher dose of morphine in SW mice (cf. Fig. 5: ● vs. Fig. 1: ○). Furthermore, cotreatment of 129/SvEvTac mice with 1 μg/kg morphine plus 0.1 ng/kg NTX attenuated morphine’s antinociceptive effects (Fig. 5: ○), in sharp contrast to the marked enhancement by low-dose NTX of morphine analgesia in SW mice (Fig. 1: ▼).
4. Discussion

4.1. Acute hyperalgesia elicited by low-dose morphine may be mediated by activation of high-efficacy excitatory opioid receptor functions

The present study demonstrates that extremely low doses of morphine, <1 µg/kg, can elicit acute thermal hyperalgesia in normal, naive mice. Acute low-dose morphine-induced hyperalgesia appears to be mediated by selective activation of excitatory opioid receptor functions because it can be blocked by ultra-low-dose NTX. The mechanism underlying the efficacy of extremely low doses of NTX in selectively antagonizing excitatory opioid receptor-mediated hyperalgesia is unknown. We have suggested that NTX may have higher binding affinity for excitatory vs. inhibitory opioid receptors following conformational changes induced by GM1 ganglioside in the Gs-coupled receptor [11,12].

The present demonstration that morphine can elicit hyperalgesic effects at doses >1,000-fold lower than those required to elicit analgesic effects provides strong support for our hypothesis that nociceptive neurons contain a small fraction of Gs-coupled excitatory opioid receptors which have much higher efficacy than the more abundant fraction of Gi/Go-coupled inhibitory opioid receptors [11]. Furthermore, cotreatment of mice with 1 µg/kg morphine plus ultra-low-dose NTX (0.1 ng/kg) results in a remarkable enhancement of morphine’s antinociceptive potency (Fig. 4). These in vivo results are consonant with our studies showing that cotreatment of mouse DRG neurons in culture with very low (pM) concentrations of naloxone or NTX selectively antagonizes excitatory, Gs-coupled opioid receptor-mediated (‘hyperalgesic’) effects elicited by very low concentrations (fM–nM) of morphine and unmasks potent inhibitory, Gi/Go-coupled opioid receptor-mediated (‘analgesic’) effects of these low morphine concentrations [10].

The absence of acute hyperalgesia after administration of etorphine at doses >1,000-fold lower than analgesic levels (1 pg/kg–1 ng/kg) (Fig. 3A) is consistent with our evidence that subanalgesic doses of etorphine behave like ultra-low-dose NTX in selectively antagonizing excitatory opioid receptor-mediated effects of morphine [34], blocking low-dose morphine-induced hyperalgesia and unmasking potent opioid analgesia (Fig. 3B). Furthermore, the absence of acute hyperalgesic effects in 129/SvEvTac mice after injection of 1 µg/kg morphine and the remarkable degree of antinociception elicited by such low doses of morphine in these mice (cf. Fig. 5 vs. Fig. 1) are readily accounted for by the deficiency in excitatory opioid receptor functions in this mouse strain [13].

In addition to blockade of acute low-dose morphine-induced hyperalgesia by antagonists at recognition sites on putative excitatory opioid receptors, e.g., ultra-low-dose NTX and subanalgesic doses of etorphine [11,34], recent studies suggest that two other agents can attenuate acute opioid hyperalgesia by interfering either with GM1 ganglioside-regulation or Gs-coupling of excitatory opioid receptor functions. (1) Cotreatment of mice with low doses of cholera toxin-B subunit (ca. 10 µg/kg, i.p.), which binds selectively to a putative allosteric GM1 regulatory site on excitatory opioid receptors [12,30,31,37], blocks opioid-induced hyperalgesia and unmasks potent opioid analgesia (Shen and Crain, in preparation), comparable to the effects of ultra-low-dose NTX. (2) Downregulation of the Gsα regulatory protein by intrathecal injection of antisense oligonucleotides in mice also blocks low-dose morphine-induced hyperalgesia [15] (see also Section 4.2). Furthermore, the maintenance of prominent hyperalgesic responses to 1 µg/kg morphine during daily injections for 3 days (Fig. 2A) is consonant with evidence that chronic opioid treatment of DRG neurons in culture results in progressive sensitization of excitatory opioid receptor functions [7,11,31]. This is in contrast to characteristic desensitization of inhibitory opioid receptors [1,5,19] and most other G protein-coupled receptors during sustained agonist exposure (see review in [11]).

We have carried out preliminary assays with NMDA receptor antagonists which show that these agents can also block acute low-dose morphine-induced hyperalgesia. Our analyses suggest that the acute hyperalgesic effects of morphine, as well as other µ and specific kappa opioid agonists, can be most clearly accounted for by a primary action on excitatory Gs-coupled, GM1-regulated opioid receptor functions which are modulated by complex interactions with NMDA- and related excitatory amino acid-receptor functions (Crain and Shen, in preparation). Similar issues have been discussed by Crain and Shen [13] regarding “possible interrelationships between excitatory Gs-coupled opioid receptor functions and excitatory NMDA-receptor functions that may account for the anomalous effects of opioids on 129/SvEv mice”.

4.2. Related studies of acute opioid-induced hyperalgesia

Following submission of the present study for publication we became aware of a preliminary report by Cruciani and Pasternak [15] demonstrating that low doses of morphine (ca. 0.3 µg/kg) elicited similar hyperalgesic effects in another strain of mice and similar unmasking of opioid analgesia following cotreatment with ultra-low-dose NTX (<1 ng/kg). Interestingly, these investigators [15] utilized water-immersion tail-flick assays at a still lower temperature than in the present study: 49°C (vs. 52°C), resulting in baseline tail-flick latencies of 7–12 s (vs. 4–5 s). The excellent agreement between the results of these two studies, notwithstanding significant differences in assay techniques, demonstrates the reliability and reproducibility of these acute low-dose morphine-induced hyperalgesic effects in normal mice.
Two brief earlier reports also indicated that low doses of morphine or other opioid agonists can elicit acute hyperalgesia in normal, naive animals. Kiyatkin [22] showed that a relatively low dose of morphine (0.2 mg/kg) elicited significant hyperalgesic effects in freely moving (but not in restrained) rats assayed by decreases in the vocalization threshold in response to a painful electric stimulus to the tail [22]. This unexpected decrease in vocalization threshold lasted for 3 h after drug administration. By contrast, higher doses of morphine (0.6–6 mg/kg) resulted in dose-dependent increases in pain threshold. Furthermore, Apfel et al. [2] demonstrated that a remarkably low dose of the kappa opioid peptide, dynorphin (0.5 μg/kg, s.c.) injected into normal, naive mice resulted in thermal hyperalgesia measured by a significant decrease in tail-flick latency at 90 min after administration, whereas a 100-fold higher dose (50 μg/kg) elicited analgesia.

Interestingly, in an animal model of persistent pain (arthritic rats) Kayser et al. [21] found that “exceedingly low doses of morphine [3–10 μg/kg, i.v.]... elicit a naloxone-reversible paradoxical hyperalgesia [whereas increased doses are] highly effective in producing analgesia”. However, no significant modification of the pain threshold (measured by the vocalization threshold induced by mechanical paw pressure) was detected in normal rats treated with these low doses of morphine [21]. The low-dose morphine-induced hyperalgesia observed in the present study is also consonant with single-unit recordings from dorsal-horn neurons in normal rats showing that application of low concentrations of mu- or kappa-opioid receptor agonists to the spinal cord produced facilitation of C-fiber-evoked nociceptive responses, whereas higher concentrations resulted in inhibition [23].

Paradoxical hyperalgesia has also been observed within 1 h after i.v. injection of relatively low doses of the kappa opioid agonists, naltbuphine (5 mg) or butorphanol (2 mg) following tooth-extraction surgery in male patients [16,17]. This result is in contrast to moderate analgesia elicited by similar opioid doses in female patients. Furthermore, Gear et al. [18] recently demonstrated that this low-dose kappa opioid-induced hyperalgesia is blocked by cotreatment with 0.5 mg naloxone, unmasking prominent opioid analgesia. Our preclinical studies suggest that low doses of these bimodally-acting kappa opioid agonists may preferentially activate excitatory vs. inhibitory opioid receptor functions in pain patients (as occurs with low concentrations of dynorphin on DRG neurons [7,11,32] and low doses of dynorphin in mice [2]), thereby resulting in acute hyperalgesia similar to that elicited in mice by low doses of the mu opioid agonist, morphine in the present study.

4.3. Opioid hyperalgesia after acute or chronic treatment with high doses of opioid agonists

The delayed onset of hyperalgesia observed in the present study at 5–6 h after injection of 1–10 mg/kg morphine (Fig. 1: ●, ○) is in good agreement with recent reports that administration of high doses of heroin (2.5 mg/kg) or fentanyl (0.1–0.4 mg/kg) in rats results in long-lasting hyperalgesia, for hours or even several days after the initial 2–5 h analgesia [6,24]. Furthermore, many studies have shown that chronic treatment of rodents with high doses of opioid agonists results in the development of hyperalgesia in association with tolerance to opioid analgesic effects (e.g., [25,27,28]). All of these hyperalgesic effects that develop progressively after initial high-dose opioid analgesia may involve much more complex mechanisms than those that underlie the acute low-dose morphine-induced hyperalgesia demonstrated in the present study. Further work is required to determine the degree to which sustained activation of excitatory Gs-coupled opioid receptor functions may mediate some of these complex tolerance and hyperalgesia effects during chronic opioid exposure [7,11,13,31], in addition to the significant roles of excitatory NMDA-receptor functions [25–28].

4.4. Clinical implications

The results of the present study suggest that the clinical use of high mg/kg doses of morphine to inhibit pain are required merely to overcome concomitant activation of excitatory opioid receptor-mediated hyperalgesic effects. Selective blockade of the latter effects by cotreatment with an ultra-low-dose of an opioid antagonist may result in significant analgesia utilizing remarkably lower μg/kg doses of morphine. This novel mode of pain treatment may markedly reduce tolerance, dependence and other aversive side-effects of morphine and similar bimodally-acting opioid analgesics that often require >1,000-fold doses higher when administered alone [29]. The feasibility of treatment of some types of pain with such a low μg/kg dose of morphine plus ultra-low-dose NTX (as suggested by the data in Fig. 4) is supported by the potent analgesic effects elicited by 1 μg/kg etorphine in chronic pain patients [4] (see review [9,33,38]).

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References


