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Antinociceptive activity of combination of morphine and NMDA receptor antagonists depends on the inter-injection interval

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Abstract

The actual time-course of morphine antinociception is shorter than what would be predicted from its elimination kinetics, suggesting the presence of an acute tolerance phenomenon. Since antagonists acting at NMDA subtype of glutamate receptors were repeatedly shown to prolong acute morphine antinociception, acute tolerance may be attributed to hyperactivity of NMDA receptors. The ability of various site-selective NMDA receptor antagonists to affect morphine antinociception (tail-flick test) was assessed in mice 30 and 120 min after acute morphine challenge. Competitive NMDA receptor antagonist 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid (D-CPPene) (SDZ EAA 494; 0.1–1 mg/kg), low-affinity channel blockers 1-amino-3,5-dimethyl adamantane (memantine) (1–10 mg/kg) and 1-amino-1,3,3,5,5-pentamethyl-cyclohexan hydrochloride (MRZ 2/579) (1–10 mg/kg), glycine site antagonists 5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione (ACEA-1021) (5 or 10 mg/kg) and 8-chloro-4-hydroxy-1-oxo-1,2-dihydropyridaliono(4,5-b)quinoline-5-oxide choline salt (MRZ 2/576) (1–10 mg/kg) were administered intraperitoneally (i.p.) 15 or 30 min prior to the tail-flick test (i.e., interval between injections of morphine and NMDA receptor antagonist was either 0–15 or 90–105 min). ACEA-1021, MRZ 2/576 and to the lesser extent, memantine and MRZ 2/579 enhanced morphine antinociception when tests were conducted 120 but not 30 min post-morphine. D-CPPene potentiated morphine antinociception irrespective of the interval between morphine administration and the tail-flick test. The results suggest that NMDA receptor antagonists may restore analgesic activity of morphine in acutely tolerant mice.

Keywords: Morphine; Antinociception; NMDA receptor antagonist; D-CPPene (SDZ EAA 494); Memantine; MRZ 2/579; MRZ 2/576; ACEA-1021

1. Introduction

Vast experimental evidence indicates that antagonists acting at NMDA subtype of glutamate receptors attenuate development of tolerance to analgesic effects of morphine (Bilsky et al., 1996; Dunbar and Yaksh, 1996; Elliott et al., 1994; Kolesnikov et al., 1993, 1994; Marek et al., 1991a,b; Tiseo and Inturrisi, 1993; Tiseo et al., 1994; Trujillo and Akil, 1991). In addition to possible clinical implications, these data suggest that NMDA receptor antagonists may become important research tools in exploring the mechanisms underlying morphine tolerance.

Acute tolerance to morphine antinociception also seems to be affected by NMDA receptor antagonists. Morphine-induced antinociception lasts longer in rats pre-treated with NMDA receptor antagonists (Ben-Eliyahu et al., 1992; Bespalov et al., 1998; Grass et al., 1996). Prolongation of morphine-induced antinociception by NMDA receptor antagonist can be viewed as a sign of retardation of the development of acute tolerance as it was first suggested by Ben-Eliyahu et al. (1992). This hypothesis is based upon experimental evidence indicating that after single morphine injection recovery from antinociception occurred much faster than did the decrease in morphine brain concentration (Kissin et al., 1991).

The present study was designed to test whether NMDA receptor blockade retards development of acute tolerance to morphine antinociception or blocks its expression. To address this issue, we tested the effects of NMDA receptor

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antagonists on morphine-induced antinociception 30 and 120 min after morphine administration, i.e., at the rise and fall of morphine antinociception time-course, respectively. Previous studies have repeatedly addressed the analgesic activity of combined administration of morphine and NMDA receptor antagonist and revealed the importance of both the antagonist used for the study and the species of animals that served as experimental subjects. For NMDA receptor channel blockers, potentiation of morphine analgesia seemed to be more likely in rats (Ben-Eliyahu et al., 1992; Grass et al., 1996) while reduction in morphine activity was more likely to be observed in mice (Lipa and Kavaliers, 1990; Lutfy et al., 1993; Saucier and Kavaliers, 1994). For competitive antagonists, there were reports demonstrating both increase (mice: Saucier and Kavaliers, 1994; Bhargava, 1997; rats: Tiseo and Inturrisi, 1993; Grass et al., 1996) and no changes (mice: Elliott et al., 1994; Bilsky et al., 1996) in acute morphine's analgesic potency. The reasons for such differences between competitive and non-competitive antagonists are not quite clear. However, it is possible to speculate that because of the use-dependency of channel blockers, competitive antagonists may be more effective in tests assessing phasic responses to acute stimuli such as thermally or mechanically induced pain (e.g., Carlsson, 1993).

Therefore, the present study examined a range of NMDA receptor antagonists including a competitive antagonist, 3-(2-carboxypiperazin-4-yl)-1-propenyl-1-phosphonic acid (D-CPPene) (Herrling et al., 1997), as well as structurally unrelated low-affinity channel blockers, 1-amino-3,5-dimethyl adamantane hydrochloride (memantine) (Danysz et al., 1997) and 1-amino-1,3,3,5,5-pentamethyl-cyclohexan hydrochloride (MRZ 2/579) (Parsons et al., 1999), and antagonists acting at the glycine site of the NMDA receptor complex, 5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione (ACEA-1021) (Woodward et al., 1995) and 8-chloro-4-hydroxy-1-oxo-1,2-dihydropyridaliono(4,5-b)quinoline-5-oxide choline salt (MRZ 2/576) (Parsons et al., 1997).

2. Methods

2.1. Animals

Adult male drug and experimentally naive Swiss SHR mice (20–30 g) were purchased from State Breeding Farm ''Rappolovo'' (St. Petersburg, Russia). Animals were maintained with food (standard rodent lab chow; ''Volosovo'', St. Petersburg) and water available ad libitum. All experiments were conducted during the light period of a 12/12 h day–night cycle (lights on at 9:00 a.m.). All tests were performed in accordance with the recommendations and policies of the US National Institutes of Health Guidelines for the Use of Animals. Experimental protocols were approved by the Pavlov Medical University's Ethics Committee.

2.2. Drugs

Morphine hydrochloride (''Endocrinnyj Zavod'', Moscow, Russia), D-CPPene (SDZ EAA 494; molecular weight (m.w.) = 250.2; Novartis Pharma, Basel, Switzerland), memantine (m.w. = 179.3), and MRZ 2/579 (m.w. = 169.3; both from Merz, Frankfurt am Main, Germany) were dissolved in physiological saline. ACEA-1021 (m.w. = 308.1; CoCensys, Irvine, CA, USA) was suspended in 1% Tween-85 in water. MRZ 2/576 (m.w. = 264.6; Merz) was dissolved in sterile water. Morphine and its vehicle were injected subcutaneously (s.c.) while all other drugs and their vehicles were administered intraperitoneally (i.p.). All injections delivered a solution in a volume of 10 ml/kg. Doses are based upon the forms of the drugs listed above.

2.3. Tail-flick test

A mouse's tail (about 1 cm from the base) was exposed to a focused heat source (300 W white bulb). By withdraw-

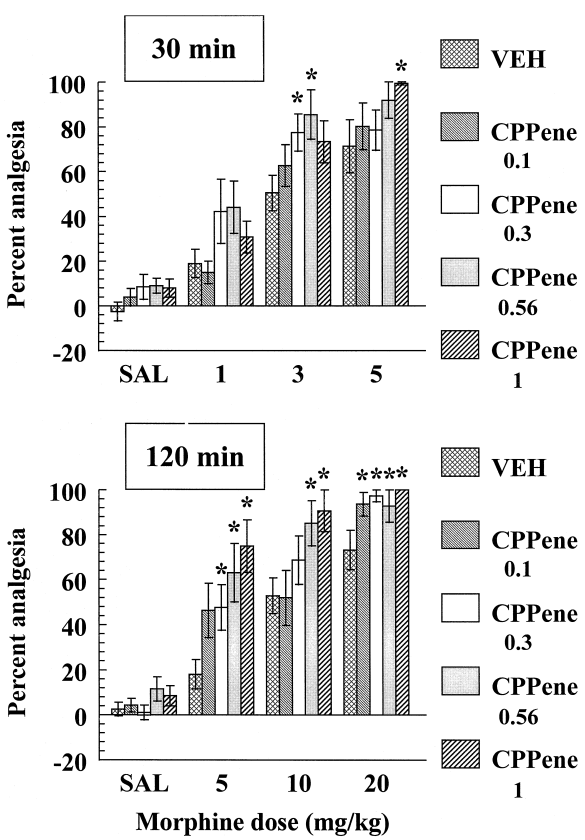

Fig. 1. Effects of D-CPPene on analgesic activity of morphine in mice. Tail-flick latencies were assessed 30 or 120 min after injection of morphine (1–20 mg/kg, s.c.). D-CPPene (0.1–1 mg/kg, i.p.) was administered 30 min prior to the test. Data are expressed as mean (±S.E.M) percent of analgesia. $^{*}P < 0.05$ (Duncan's test), compared to mice treated with vehicle instead of D-CPPene. $N = 10$.

ing or removing the tail from the path of the stimulus and thereby exposing a photocell located in the apparatus (''Farmakolog'', St. Petersburg, Russia) immediately below the tail, mouse could terminate the noxious stimulation and the reaction time was then recorded. An animal that failed to respond before 10 s (cut-off time) was removed from the apparatus and assigned latency of 10 s. Tail-flick latencies were measured twice for each subject — before and after drug treatment. Mice were returned to their home cages after each injection and/or tail-flick test.

2.4. Procedure

After the initial (baseline) tail-flick test, separate groups of mice were treated with the combination of s.c. morphine (vehicle, 1, 3, 5, 10 or 20 mg/kg) and i.p. D-CPPene (0.1, 0.3, 0.56 or 1 mg/kg), memantine (1, 3 or 10 mg/kg, i.p.), MRZ 2/579 (1, 3 or 10 mg/kg, i.p.), ACEA-1021 (5 or 10 mg/kg, i.p.), MRZ 2/576 (1, 3 or 10 mg/kg, i.p.) or their vehicles. The second tail-flick test was held 30 or 120 min after the morphine injection. Except for MRZ 2/576, all NMDA receptor antagonists were administered 30 min prior to the second tail-flick test. MRZ 2/576 is a short acting drug (Parsons et al., 1997) and its pre-test injection time was 15 min. Each treatment group consisted of 9–10 mice.

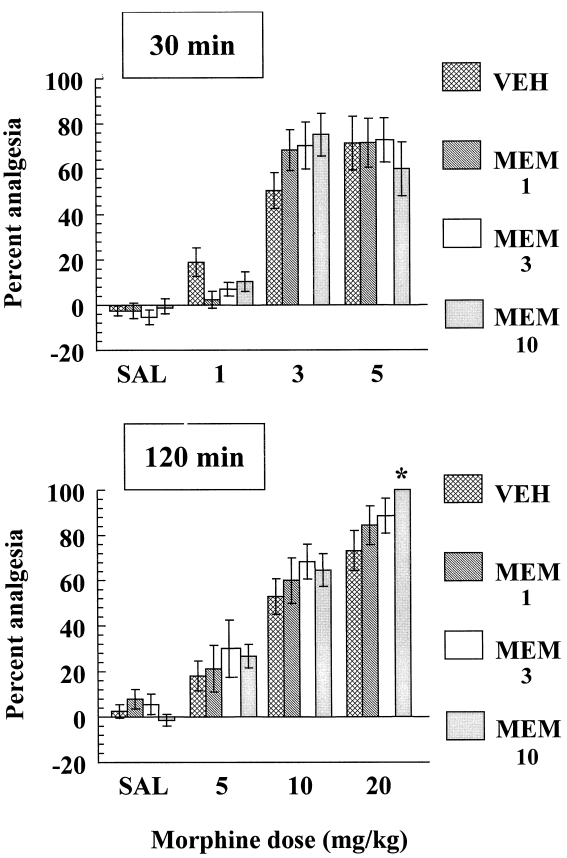

Fig. 2. Effects of memantine on analgesic activity of morphine in mice. Tail-flick latencies were assessed 30 or 120 min after injection of morphine (1–20 mg/kg, s.c.). Memantine (1–10 mg/kg, i.p.) was administered 30 min prior to the test. Data are expressed as mean (±S.E.M.) percent of analgesia. $^{*}P < 0.05$ (Duncan's test), compared to mice treated with vehicle instead of memantine. $N = 9$–10.

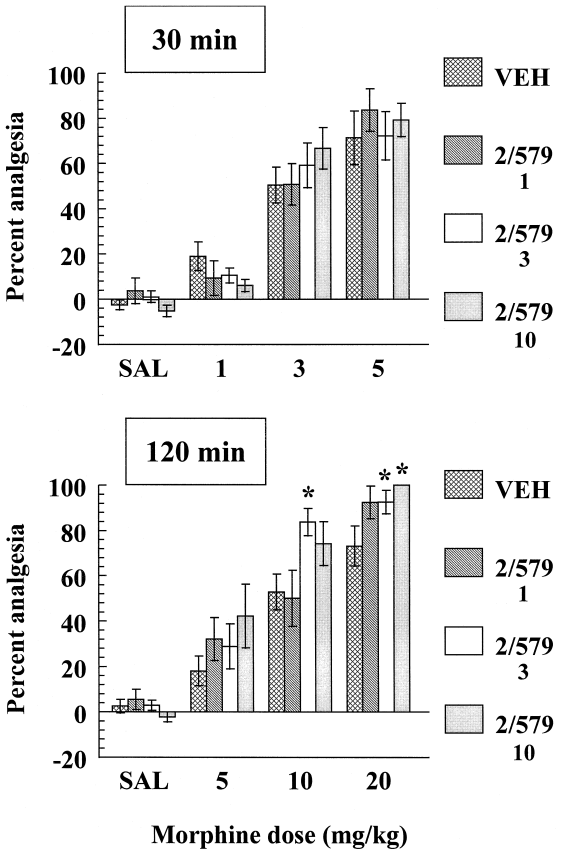

Fig. 3. Effects of MRZ 2/579 on analgesic activity of morphine in mice. Tail-flick latencies were assessed 30 or 120 min after injection of morphine (1–20 mg/kg, s.c.). MRZ 2/579 (1–10 mg/kg, i.p.) was administered 30 min prior to the test. Data are expressed as mean (±S.E.M.) percent of analgesia. $^{*}P < 0.05$ (Duncan's test), compared to mice treated with vehicle instead of MRZ 2/579. $N = 10$.

Because this study involved large number of subjects and treatment groups, during each test day there were at least seven treatment groups tested that always included mice pre-treated with vehicle and all doses of at least one NMDA receptor antagonist.

2.5. Data analysis

Tail-flick latencies were converted to percentage of maximal possible effect. The individual mouse values of the percent of analgesia were calculated according to the formula $(T_{EXP} - T_{BL}) \times 100/(10 - T_{BL})$, where T_{EXP} — test tail-flick latency (s), T_{BL} — baseline latency (s). Data were subjected to the distribution-free two-way analysis of

variance (ANOVA) with Duncan's test for post-hoc between-group comparisons.

3. Results

In drug-naive mice, tail-flick response occurred within 4 s after a mouse's tail was exposed to a focused heat source with an average latency 3.5 s (median = 3.5 s; inter-quartile range = 0.7 s; $n = 1389$; data collected over a period of 4 months).

After the measurement of the baseline ''tail-flick'' latency, separate groups of mice received injections of different doses of morphine (1–20 mg/kg, s.c.). Nociceptive responses were re-tested 30 or 120 min after morphine administration. Morphine dose-dependently increased response latencies (Figs. 1–5, cross-hatched bars; 30 min: $F(3,108) = 75.3$, 120 min: $F(3,108) = 39.6$, $P < 0.01$). Analgesic activity of morphine seemed to be somewhat less pronounced in mice pre-treated with vehicles for MRZ 2/576 (pre-test injection time 15 min) and ACEA-1021

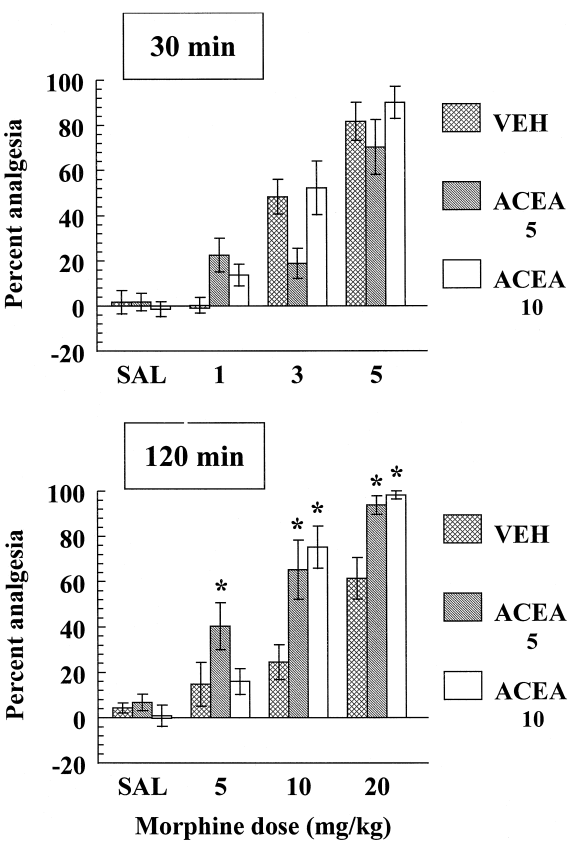

Fig. 4. Effects of ACEA-1021 on analgesic activity of morphine in mice. Tail-flick latencies were assessed 30 or 120 min after injection of morphine (1–20 mg/kg, s.c.). ACEA-1021 (5 or 10 mg/kg, i.p.) was administered 30 min prior to the test. Data are expressed as mean (±S.E.M.) percent of analgesia. * $P < 0.05$ (Duncan's test), compared to mice treated with vehicle instead of ACEA-1021. $N = 10$.

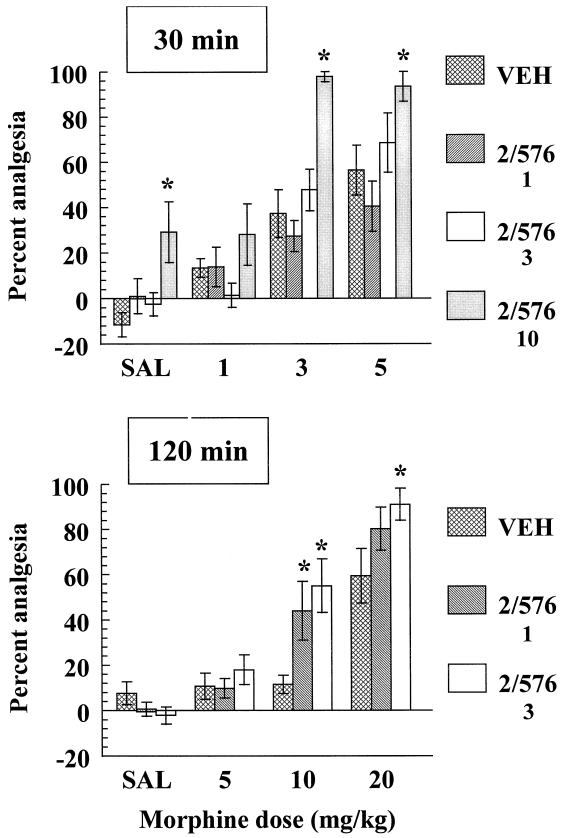

Fig. 5. Effects of MRZ 2/576 on analgesic activity of morphine in mice. Tail-flick latencies were assessed 30 or 120 min after injection of morphine (1–20 mg/kg, s.c.). MRZ 2/576 (1–10 mg/kg, i.p.) was administered 15 min prior to the test. Data are expressed as mean (±S.E.M.) percent of analgesia. * $P < 0.05$ (Duncan's test), compared to mice treated with vehicle instead of MRZ 2/576. $N = 10$.

(Tween-85-containing vehicle; 30 min: $F(6,108) = 2.4$, 120 min: $F(3,108) = 3.9$, $P < 0.05$).

D-CPPene enhanced morphine-induced antinociception irrespective of the interval between morphine injection and tail-flick test (Fig. 1). ANOVA confirmed the significant main effect of D-CPPene dose (30 min: $F(4,180) = 6.0$; 120 min: $F(4,180) = 9.7$, $P < 0.01$).

Memantine (Fig. 2; $F(3,143) = 0.1$), MRZ 2/579 (Fig. 3; $F(3,144) = 0.1$), ACEA-1021 (Fig. 4; $F(2,108) = 1.4$) as well as lower doses of MRZ 2/576 (1 and 3 mg/kg; Fig. 5; $F(3,144) = 14.3$, $P < 0.01$) did not affect significantly morphine antinociception when mice were tested 30 min post-morphine. Meanwhile, the same doses of ACEA-1021 ($F(2,108) = 9.1$, $P < 0.01$), MRZ 2/576 ($F(6,108) = 2.3$, $P < 0.05$) and to the lesser degree, memantine ($F(3,143) = 1.4$) and MRZ 2/579 ($F(3,144) = 2.9$, $P < 0.05$) enhanced analgesic activity of morphine when mice were tested 120 min post-morphine. For memantine, there was no overall effect of the dose ($P = 0.24$) although statistically significant potentiation of morphine antinociception was observed in mice pre-treated with 20 mg/kg of morphine and 10 mg/kg of memantine (Fig. 2, lower panel; $F(3,36) = 3.6$, $P < 0.05$).

4. Discussion

The present study demonstrates that NMDA receptor antagonists may differentially affect morphine-induced antinociception 120 but not 30 min post-morphine. Therefore, it appears that NMDA receptor antagonists are capable of restoring analgesic activity of morphine in acutely tolerant mice. Such conclusions are in line with the existing evidence indicating that (a) after a single morphine injection recovery from antinociception occurred much faster than did the decrease in morphine brain concentration (Kissin et al., 1991) and (b) NMDA receptor antagonists prolong the time-course of morphine antinociception (Ben-Eliyahu et al., 1992; Bespalov et al., 1998; Grass et al., 1996).

Thus, one may argue that NMDA receptor antagonists inhibit expression rather than development of acute tolerance to morphine antinociception. It is noteworthy that these effects occurred at dose levels that did not produce hypoalgesia per se (see also Lutfy and Weber, 1996; Nishiyama et al., 1998 for data on ACEA-1021). It is of particular relevance that one of the compounds used (MRZ 2/576) has a very fast penetration to the brain and short duration of action (Parsons et al., 1997) and therefore, was administered 15 min prior to the tail-flick test. Despite such short pre-test injection time, MRZ 2/576 still enhanced antinociception score in mice pre-treated with morphine 120 min prior to the tail-flick test.

It is well established for several receptor systems that prolonged application of receptor agonists may induce a variety of phenomena such as receptor down-regulation, desensitisation, internalisation, etc. These phenomena may contribute to the acute tolerance observed in the whole animals. Yet, the present experiments may have another plausible explanation. Stimulation of μ-opioid receptors activates protein kinase C that is known to facilitate NMDA-mediated responses possibly via phosphorylation of NMDA receptors (Chen and Huang, 1991; Gerber et al., 1989). Transient facilitation of NMDA receptor function by systemic morphine exposure may later be followed by decreased expression of the mRNA for NMDA receptor subunits (Le Greves et al., 1998). Thus, application of μ-opioid receptor agonists (i.e., morphine) may transiently enhance glutamatergic neurotransmission. Since direct application of glutamate receptor agonists (i.e., intrathecal) can produce specific pain behaviors (Lutfy and Weber, 1996; Urca and Raigorodsky, 1988), one can assume that enhanced NMDA receptor sensitivity may reduce responses to μ-opioid receptor stimulation, that will result in acute tolerance phenomenon.

On the other hand, recent studies showed that acute opioid administration indeed induces NMDA receptor-mediated hyperalgesic state that is masked by the drug's analgesic activity and is explicitly expressed at delayed intervals post-injection (Larcher et al., 1998; Laulin et al., 1998, 1999).

Despite the large number of studies on opioid tolerance, little is known about the temporal characteristics of this process, as well as of opioid dependence. Meanwhile, several studies suggest that some yet unidentified mechanisms occurring few hours after morphine administration contribute to development of morphine tolerance and dependence. For instance, earlier studies demonstrated that NMDA receptor antagonists (dizocilpine, Marek et al., 1991b; MRZ 2/576, Belozertseva et al., 2000) prevented the development of morphine tolerance when applied 2 h after each of the repeated morphine injections. In addition, it is well established that a single morphine injection induces sensitisation to opioid antagonists (i.e., naltrexone) that peaks at 4 h post-morphine (e.g., Young, 1986).

It is not clear whether acute morphine tolerance shares mechanisms with tolerance induced by repeated drug exposures. It is noteworthy, however, that NMDA receptor antagonists including antagonists acting at the glycine site and low-affinity channel blockers attenuate induction of ''repeated injections'' tolerance (Belozertseva and Bespalov, 1998; Herman et al., 1995).

It should also be noted that the present study revealed potentially important differences between tested NMDA receptor antagonists. First, we failed to find a dose of competitive antagonist, D-CPPene, that would selectively affect tail-flick responses 120 but not 30 min post-morphine. Instead, unlike low affinity channel blockers and glycine site antagonists, D-CPPene significantly potentiated morphine antinociception both 30 and 120 min post-morphine. Second, selective facilitation of morphine antinociception 120 min post-morphine was produced by glycine site antagonists and to the lesser degree by channel blockers.

Limited efficacy of NMDA receptor channel blockers is well in line with earlier reports on analgesic activity of combined administration of these compounds and morphine (see Section 1). These results also provide indirect support for the view that the nociceptive responses assessed in this study reflect phasic rather than tonic activation of glutamatergic system elicited by acute thermal pain stimuli.

In conclusion, our data provide direct experimental evidence suggesting that the expression of acute tolerance to morphine antinociception may involve increase in glutamatergic neurotransmission through NMDA receptors. This hyperactivity of glutamatergic neurotransmission may also be implicated in ''repeated injections'' tolerance as well as provide neurochemical basis for counter-response (compensatory reaction) discussed in several modern tolerance theories (Colpaert, 1996; Siegel, 1988).

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