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ORIGINAL PAPER

The effects of serotonin/norepinephrine reuptake inhibitors and serotonin receptor agonist on morphine analgesia and tolerance in rats

Ercan Ozdemir · Sinan Gursoy · Ihsan Bagcivan

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Abstract Several studies have demonstrated that serotonergic and noradrenergic systems have important roles in morphine analgesia and tolerance. However, the exact mechanism underlying the development of morphine tolerance is not fully understood. The aim of this study was to investigate the possible role of serotonin/norepinephrine reuptake inhibitors (amitriptyline, venlafaxine) and serotonin receptor (5-HT_{1A} and 5-$HT_{1B/1D}$) agonist (dihydroergotamine) in morphine analgesia and tolerance in rats. To constitute morphine tolerance, animals received morphine (50 mg/kg; s.c.) once daily for 3 days. After the last dose of morphine was injected on day 4, morphine tolerance was evaluated. The analgesic effects of amitriptyline (20 mg/kg; i.p.), venlafaxine (20 mg/kg; s.c.), dihydroergotamine (100 μg/kg; i.v.) and morphine (5 mg/kg) were considered at 15- to 30-min intervals (0, 15, 30, 60, 90, and 120 min) by tail-flick and hot-plate analgesia tests. In this study, the data obtained suggested that amitriptyline and venlafaxine significantly increased the analgesic effect of morphine and attenuated the expression of morphine tolerance. However, dihydroergotamine significantly increased the analgesic effect of morphine but did not reduce the expression of morphine tolerance. In conclusion, we determined that co-administration of morphine with amitriptyline and venlafaxine increased the analgesic effects of morphine and attenuated the morphine analgesic tolerance.

Keywords Amitriptyline · Dihydroergotamine · Morphine · Morphine tolerance · Venlafaxine

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Introduction

Opioid analgesics are commonly used to treat acute and chronic pain associated with surgical interventions or disease states such as cancer. Opioids produce a diverse spectrum of centrally- and peripherally-mediated responses, including respiratory depression, sedation, nausea, euphoria, and itching [1, 2]. Longterm use of opioids can be problematic due to the rapid development of profound tolerance to the analgesic effects coupled with slow development of tolerance to many of the untoward effects of these agents. It is the inability to tolerate these undesirable side effects that eventually limits dose escalations and analgesic efficacy [2].

Morphine tolerance is a complex phenomena, involving the serotonergic and noradrenergic systems [3, 4]. We have recently demonstrated that the nitric oxide–cGMP signal pathway plays a pivotal role in developing tolerance to the analgesic effect of morphine [5]. The exact mechanisms underlying the development of morphine tolerance remain controversial. Among them, serotonin (5-HT) is particularly well studied, and this transmitter has been shown to widely participate in pain pathways and to play a major role in mediating the analgesic action of morphine [6, 7]. It is well accepted that opioids establish part of their analgesic effect through stimulation of the serotonergic system [8]. It has been

reported that acute morphine administration enhances serotonin turnover as evidenced by an increase in its synthesis, release, and metabolism [8], in particular in projection areas of the dorsal raphe nucleus and median raphe nucleus [9], but upon chronic morphine administration, a decrease in the release of 5-HT from the nerve terminals is observed [10]. There have been controversial results about the role of 5-HT in the development of morphine tolerance. For example, serotonin activity evoked by systemic administration of L-tryptophan or 5-hydroxytryptophan was found to, respectively, accelerate and attenuate morphine tolerance [11].

Tricyclic antidepressants (TCAs) have been used for decades in the treatment of severe pain in non-depressed patients [12, 13]. Nevertheless, their analgesic mechanism of action is still unclear. It apparently involves a direct, central potentiation of the endogenous opioid system [14] or activation of a mixed analgesic effect mediated by serotonergic/noradrenergic pathways [13, 15] or combinations of these mechanisms. Sacerdote et al. [16] concluded that the analgesic effect of clomipramine and amitriptyline, and their potentiation of morphine-induced antinociception, are related to an activation of the endogenous opioid system mediated by serotonin. The TCA amitriptyline has potent serotonin/norepinephrine reuptake inhibiting activity and a potent local anesthetic effect [17, 18]. TCAs produce analgesia by various mechanisms involving *N*-methyl-D-aspartate (NMDA) receptors, opioids, and substance P [19]. Intrathecal amitriptyline injection provides spinal anesthesia in rats [20]. These data suggest that TCAs might be clinically valuable in pain management. Venlafaxine is a structurally novel phenylethylamine antidepressant drug. In vitro, venlafaxine blocks the synaptosomal uptake of noradrenaline and serotonin and, to a lesser degree, of dopamine [21]. Finally, dihydroergotamine mesylate (DHE), a serotonin receptor (5-HT_{1A} and 5-$HT_{1B/1D}$) agonist, has been extensively utilized and studied in the treatment of episodic and chronic migraine [22].

In the light of these data, the present study aimed to investigate the effects of serotonin/norepinephrine reuptake inhibitors (amitriptyline, venlafaxine) and 5-HT_{1A}-5-$HT_{1B/1D}$ receptor agonist (dihydroergotamine) on morphine analgesia and tolerance in rats.

Materials and methods

Animals

Experiments were performed using male adult Wistar Albino rats (weighing 175–190 g). Animals were maintained under standard conditions: 12-h light–dark schedule (lights on at 0800 hours) with ad libitum food and water and constant temperature (21 ± 1 °C). All experiments were carried out blindly between 0900 and 1700 hours. Procedures and animal handling met the guidelines of the National Institutes of Health detailed in the "Principles of animal laboratory care" (National Institutes of Health, 1996). The experimental protocols were approved by the Cumhuriyet University Animal Ethics Committee (licence number: 87/Ethic).

Drugs

Amitriptyline, venlafaxine and dihydroergotamine (Sigma-Aldrich, USA) and morphine sulphate (Cumhuriyet University Hospital, Turkey) were dissolved in physiological saline. Solutions were freshly prepared on the days of experimentation. Subcutaneous (s.c.) morphine (5 mg/kg), amitriptyline (20 mg/kg; i.p.), venlafaxine (20 mg/kg; s.c.), dihydroergotamine (100 μg/kg; i.v.) were administered before the analgesia tests.

Induction of morphine tolerance

The animals were rendered tolerant to morphine using the method by a previous study on the induction of morphine tolerance [23]. For tolerance induction, groups of 6–7 rats were randomly chosen and treated subcutaneously (s.c.) with morphine 50 mg/kg, once a day for 3 days. To evaluate the degree of tolerance, the analgesic effect of the test doses of morphine (5 mg/kg, s.c.) were measured by the hot-plate and tail-flick tests 24 h after the last morphine injection (day 4). In addition, to determine effects of amitriptyline, venlafaxine, and dihydroergotamine on the morphine tolerance, morphine was applied with amitriptyline, venlafaxine, and venlafaxine to the morphine-tolerant animals on day 4.

Antinociception tests

Hot-plate test

In this test, animals were individually placed on a hot-plate (May AHP 0603 Analgesic Hot-plate; Commat, Turkey) with the temperature adjusted to 55 ± 1 °C. The latency to the first sign of paw licking or jump response to avoid the heat was taken as an index of the pain threshold; the cut-off time was 30 s in order to avoid damage to the paw. The antinociceptive response on the hot-plate is considered to result from a combination of central and peripheral mechanisms [24].

Tail-flick test

We used a standardized tail flick apparatus (May TF 0703 Tail-flick Unit; Commat, Turkey) to evaluate thermal nociception. The radiant heat source was focused on the distal

portion of the tail at 3 cm after administration of the vehicle and study drugs. Following vehicle or compound administration, tail-flick latencies (TFL) were obtained. The infrared intensity was adjusted so that basal TFL occurred at 2.8 ± 0.4 s. Animals with a baseline TFL below 2.4 or above 3.2 s were excluded from further testing. The cutoff latency was set at 15 s to avoid tissue damage. Any animal not responding after 15 s was excluded from the study. The hyperalgesic response in the tail-withdrawal test is generally attributed to central mechanisms [24, 25].

Experimental protocols

The analgesic effects of amitriptyline, venlafaxine, dihydroergotamine, and morphine were considered at 30-min intervals (0, 15, 30, 60, 90, and 120 min) by tail-flick and hot-plate test in rats ($n = 6$–7). In the morphine-treated rats after induction of morphine tolerance, analgesic response to the challenge dose was determined again on day 4 at 30-min intervals after the same morphine (5 mg/kg) injection on the first day. To evaluate the effects of amitriptyline, venlafaxine, and dihydroergotamine on development of morphine tolerance, morphine tolerant animals received amitriptyline (20 mg/kg), venlafaxine (20 mg/kg), and dihydroergotamine (100 μg/kg). In the saline-treated group, animals received saline (10 ml/kg) instead of morphine during the induction session.

Data analysis

In order to calculate % maximal antinociceptive effects (% MPE), tail-flick and hot-plate latencies (in seconds) were converted to percent antinociceptive effect using the following equation:

$$\%\text{MPE} = [(\text{Postdrug latency} - \text{Baseline latency})/ (\text{Cutoff value} - \text{Baseline latency})] \times 100.$$

Statistical analysis

All experimental results were expressed as mean ± SEM (standard error of mean). The effect of antinociception was measured and the mean of % MPE in all groups was calculated. The data were analysed by analysis of variance followed by Tukey test. A significant difference was defined as a p value <0.05.

Results

Effect of amitriptyline on morphine analgesia

Obtained data indicated that pretreatment of animals with amitriptyline significantly increased (increased mean of % MPE value) morphine antinociceptive effect in both tail-flick ($p < 0.05$; Fig. 1a) and hot-plate test ($p < 0.05$; Fig. 1b) compared to the morphine administration group. The peak value of this group was observed at 60 min after administration of drugs in analgesia tests (tail-flick: 45.40 ± 6.6; hot-plate: 58.30 ± 6.9). In addition, these data demonstrated that amitriptyline alone has a significant analgesic effect compared to the saline group ($p < 0.01$).

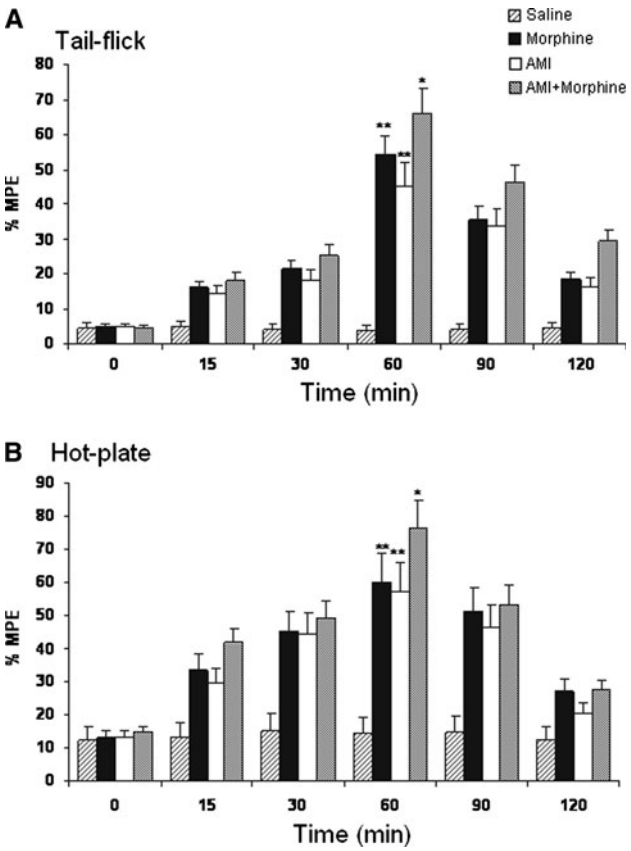

Fig. 1 Effect of amitriptyline (AMI) on the morphine analgesia. **a** Effect of amitriptyline (20 mg/kg) in the tail-flick test, and **b** effect of amitriptyline in the hot-plate test. Amitriptyline in combination with morphine produce a significant increase in % MPE in both the tail-flick ($p < 0.05$; **a**) and hot-plate assays ($p < 0.05$; **b**) as compared to the morphine-treated rats. The maximum % MPE is observed at 60 min after administration of morphine by the tail-flick and hot-plate test. Each point represents the mean ± SEM of percent of maximal possible effect (% MPE) for 6 rats. *$p < 0.05$ compared to the morphine-treated group and **$p < 0.01$ compared to saline-treated group

Effect of venlafaxine on morphine analgesia

Statistical analysis suggested that serotonin/norepinephrine reuptake inhibitor venlafaxine significantly increased morphine analgesic effect in tail-flick ($p < 0.05$; Fig. 2a) and hot-plate tests ($p < 0.05$; Fig. 2b) compared to morphine administration group. The peak value of this group was also

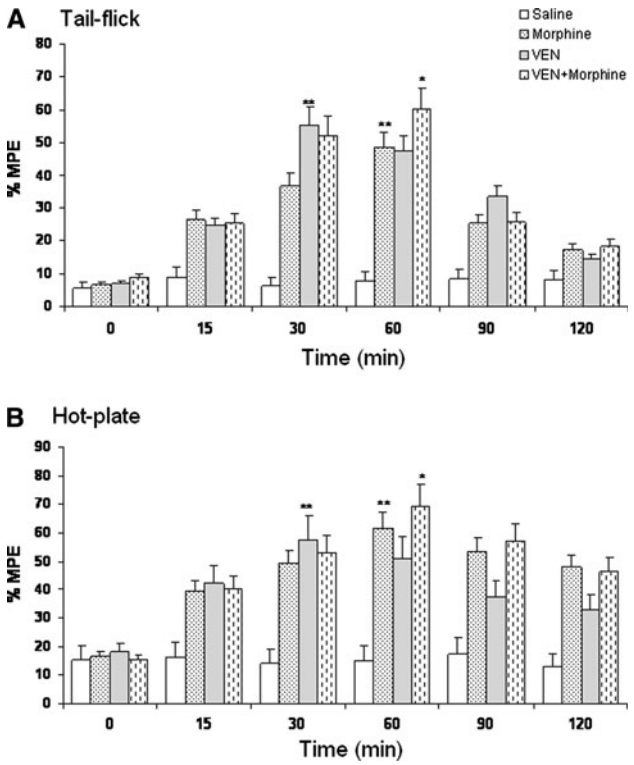

Fig. 2 Effect of venlafaxine (VEN) on the morphine analgesia. **a** Effect of venlafaxine (20 mg/kg) in the tail-flick test, and **b** effect of venlafaxine in the hot-plate test. Venlafaxine in combination with morphine produce a significant increase in % MPE in both the tail-flick ($p < 0.05$; **a**) and hot-plate assays ($p < 0.05$; **b**) as compared to the morphine-treated rats. The peak value of this group was observed at 30 min after administration of morphine in analgesia tests. Each point represents the mean ± SEM of percent of maximal possible effect (% MPE) for 7 rats. *$p < 0.05$ compared to the morphine-treated group and **$p < 0.01$ compared to saline-treated group

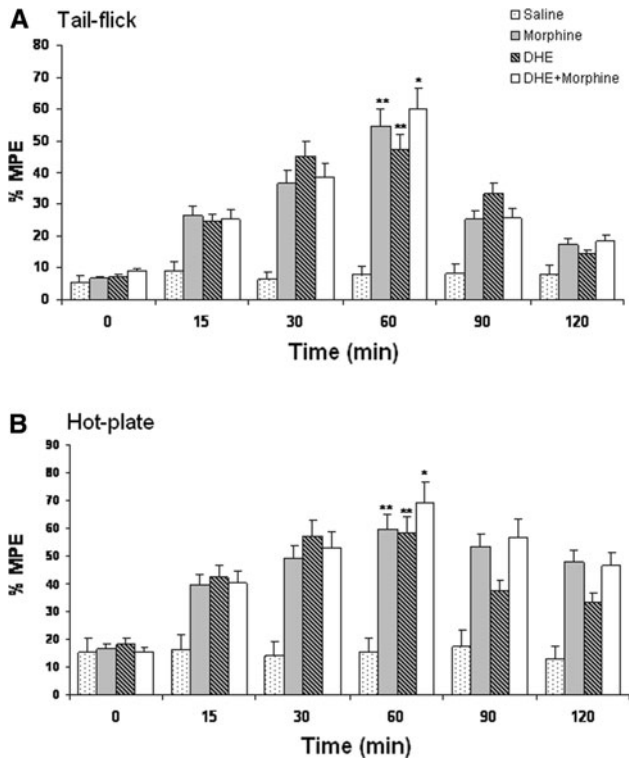

Fig. 3 Effect of dihydroergotamine (DHE) on the morphine analgesia. **a** Effect of dihydroergotamine (100 μg/kg) in the tail-flick test, and **b** effect of dihydroergotamine in the hot-plate test. Dihydroergotamine in combination with morphine produce a significant increase in % MPE in both the tail-flick ($p < 0.05$; **a**) and hot-plate assays ($p < 0.05$; **b**) as compared to the morphine-treated rats. Each point represents the mean ± SEM of percent of maximal possible effect (% MPE) for 7 rats. *$p < 0.05$ compared to the morphine-treated group and **$p < 0.01$ compared to saline-treated group

observed at 30 min after administration of morphine in analgesia tests (tail-flick: 55.2 ± 6.3; hot-plate: 57.40 ± 8.5). Furthermore, these data demonstrated that venlafaxine alone has a significant analgesic effect compared to the saline group rats ($p < 0.01$).

Effect of dihydroergotamine on morphine analgesia

Administration of dihydroergotamine with morphine produced a significant increase in % MPE in both the tail-flick ($p < 0.05$; Fig. 3a) and hot-plate ($p < 0.05$; Fig. 3b) assays as compared to the morphine group rats. In addition, dihydroergotamine alone has a significant analgesic effect compared to the saline group rats ($p < 0.01$).

Effects of amitriptyline, venlafaxine and dihydroergotamine on the tolerance to morphine analgesia

Amitriptyline and venlafaxine in combination with morphine produced a significant decrease expression tolerance to morphine in both the tail-flick (respectively, $p < 0.01$, $p < 0.05$; Fig. 4a) and hot-plate assays (respectively, $p < 0.01$, $p < 0.05$; Fig. 4b) as compared to the morphine-tolerant rats. However, serotonin receptor agonist dihydroergotamine in combination with morphine did not show a significant decrease in morphine analgesic tolerance in the tail-flick (Fig. 4a) and hot-plate assays (Fig. 4b). The maximum % MPE was observed at 60 min after administration of morphine by analgesia tests in administration of the amitriptyline and dihydroergotamine groups.

Discussion

In the present study, co-administration of amitriptyline and venlafaxine with morphine both increased the morphine analgesia and attenuated the morphine analgesic tolerance in the analgesia tests. These results confirm another study that showed amitriptyline suppresses neuroinflammation and up-regulates glutamate transporters in morphine-tolerant rats [26]. Also in this present study, it has been shown

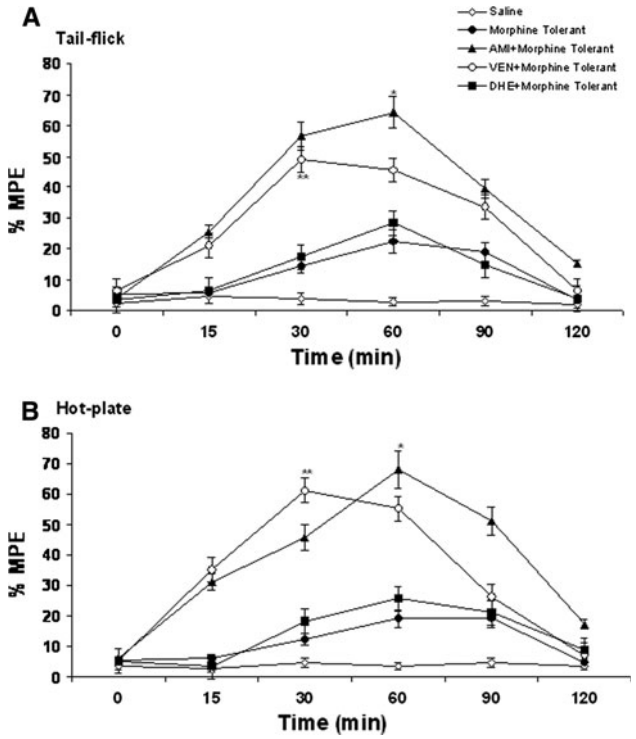

Fig. 4 Effects of amitriptyline, venlafaxine, and dihydroergotamine on the tolerance morphine analgesia. **a** Effects of amitriptyline, venlafaxine, and dihydroergotamine in the tail-flick test, and **b** effects of amitriptyline, venlafaxine, and dihydroergotamine in the hot-plate test. Pretreatment of morphine tolerant animals with amitriptyline and venlafaxine significantly increased % MPE (decrease tolerance to morphine) in both tail-flick ($p < 0.01$; **a**) and hot-plate tests ($p < 0.01$; **b**) compared to morphine-tolerant animals. However, pretreatment of animals with dihydroergotamine showed no significant increase in % MPE in either tail-flick or hot-plate tests. Each point represents the mean ± SEM of percent of maximal possible effect (% MPE) for 6 rats. *$p < 0.01$ and **$p < 0.05$ compared to the morphine-tolerant group

that amitriptyline not only attenuates morphine tolerance but also preserves its antinociceptive effect. Unlike our study, amitriptyline infusion alone has no antinociceptive effect. In addition, our data suggested that serotonin receptor (5-HT_{1A} and 5-$HT_{1B/1D}$) agonist dihydroergotamine did not produce a statistically significant effect on the morphine tolerance. However, co-administration of dihydroergotamine with morphine produced a significant increase in the morphine analgesic effect.

Previous studies have demonstrated that serotonergic pathways play an important role in opioid analgesia [7, 27]. The serotonergic system reduces tolerance to the antinociceptive effect of morphine. However, the exact biochemical and physiological mechanisms underlying this effect are not fully understood. Our recent study suggested that co-administration of morphine with fluoxetine (a specific 5-HT reuptake inhibitor) and LY 367265 (an inhibitor of the 5-HT transporter) increased the analgesic effects of morphine and delayed development of tolerance to morphine analgesia [3]. It has been suggested that chronic morphine administration leads to an increase in GABA tone and subsequently to a decrease in serotonergic activity in the dorsal raphe nucleus [10]. It can be hypothesized that the dorsal raphe serotonergic system has an important role in the manifestation of morphine tolerance. Another study indicates that direct stimulation of 5-HT_{1A} receptors in the dorsal raphe nucleus of the rat prolongs the development of tolerance to the analgesic effect of morphine [28].

Amitriptyline has been found to be an effective antinociceptive agent in various animal models of pain [29]. For example, the hyperalgesia evoked by nerve injury [30] and inflammation [31] was attenuated by amitriptyline. The effects of amitriptyline on the paw formalin test, however, are not consistent. Tai et al. [32] reported that the antiinflammatory effect of amitriptyline on morphine tolerance, probably acting by increasing IL-10 expression, is mediated by p38 mitogen-activated protein kinase heme oxygenase-1 signal transduction cascade. It has been suggested that systemic administration of amitriptyline exerted inhibition, facilitation, or no effect, depending on the type of pain measure and the phase of the formalin test [33, 34]. Co-administration of morphine and amitriptyline demonstrated that the interaction between systemic amitriptyline and morphine is synergistic [35]. In addition, it has been stated that amitriptyline treatment prolonged morphine analgesia and decreased morphine tolerance by increasing the sensitivity of the central nervous system to morphine [36]. Other antidepressants, such as fluoxetine and fluvoxamine, were also found to enhance opioid analgesia in other models [37, 38]. Furthermore, Gray et al. [31] showed that pretreatment with enkephalinase inhibitors potentiated the amitriptyline antinociception against acid-induced abdominal pain. In clinical studies, interactions between opioids and amitriptyline or other tricyclic antidepressants are not consistent. Therefore, systemically administered antidepressants have been shown to potentiate [39], have no effect on [40], or antagonize opioid-induced antinociception [41], depending on the agent, timing of drug administration, and type of pain. However, our data suggested that co-administration of amitriptyline with morphine increased the morphine analgesic effect and attenuated the development of morphine tolerance in the analgesia tests.

It has been suggested that venlafaxine, in addition to its antidepressant profile, could have a therapeutic role in analgesia therapy [42, 43]. The antinociceptive effect of venlafaxine is probably potentiated due to the blockade of somatodendritic 5-HT_{1A} receptors in the same raphe nuclei, facilitating the descending monoaminergic pain control system [44]. Venlafaxine inhibits the reuptake of both 5-HT and noradrenaline, although to varying degrees. It has been shown that venlafaxine preferentially inhibits

the reuptake of 5-HT at low doses, whereas at higher doses it inhibits both monoamine carriers [45, 46]. The findings regarding κ- and δ-opioid receptor involvement in venlafaxine's antinociception are both novel and difficult to interpret. They may involve a significant finding in the preclinical studies of venlafaxine, its effect on β-adrenergic receptors. In the rat pineal model of noradrenergic sensitivity, treatment with venlafaxine caused a subsensitivity of the β-adrenergic-linked cyclic adenosine monophosphate (cAMP)-generating system. Thus, venlafaxine reduced noradrenergic responsiveness after both acute and chronic treatment [47]. This down-regulation of the noradrenergic system, combined with other properties of venlafaxine, may induce an indirect activation of the opioid system supraspinally, even though the κ-opioid system is most active spinally. However, further study is needed to establish the exact location of this interaction. Another explanation may be a dopamine-mediated involvement of the opioid system. Venlafaxine exerts a clear dopamine reuptake inhibitory effect [21]. Increase of the dopamine levels at the synaptic cleft, as well as dopamine D_2 receptor agonists and mixed dopamine D_1/D_2 receptor agonists, were reported to increase dose-dependently the nociceptive threshold of mice. This antinociceptive effect was mediated through the opioid system [48, 49].

Several lines of evidence have suggested that the antimigraine effect of the dihydroergotamine with 5-$HT_{1B/1D}$ receptor agonist properties may result from inhibition of central nociceptive transmission by this drug [50]. In this work, we thus tested the action of dihydroergotamine on morphine analgesia and tolerance. Previous studies showed that 5-HT_{1A} and 5-$HT_{1B/1D}$ receptor agonist dihydroergotamine attenuate hyper-responsiveness to mechanical stimulation of the face in a rat model of trigeminal neuropathic pain, probably by activating 5-$HT_{1B/1D}$-receptors on primary afferent nociceptive fibers [22]. In the present study, we indicated that co-administration of dihydroergotamine with morphine produced a significant increase in the morphine analgesia. However, dihydroergotamine did not show a significant decrease in morphine analgesic tolerance.

In summary, the present study clearly suggests that co-administration of morphine with serotonin/norepinephrine reuptake inhibitors (amitriptyline and venlafaxine) increased the analgesic effects of morphine and attenuated the morphine tolerance. In addition, administration of dihydroergotamine with morphine produced a significant increase in morphine analgesic effect but did not produce a significant effect on the morphine tolerance. Given this information, it can be expressed that serotonin/norepinephrine reuptake inhibitors and 5-HT receptor agonist have important roles in morphine analgesia and/or morphine analgesic tolerance.

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