Role of D_1/D_2 dopamin receptors antagonist perphenazine in morphine analgesia and tolerance in rats

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Abstract

While opioid receptors have been implicated in the development of tolerance, the subsequent mechanisms involved in these phenomena have not been completely understood. The purpose of this study was to investigate effects of D1/D2 dopamine receptors antagonist perphenazine on morphine analgesia and tolerance in rats.

Male Wistar albino rats weighing 190–205 g were used in these experiments. To constitute of morphine tolerance, animals received morphine (50 mg/kg) once daily for 3 days. After last dose of morphine was injected on day 4, morphine tolerance was evaluated by the analgesia tests. The analgesic effects of perphenazine (1, 5, and 10 mg/kg), D1-dopamine receptor antagonist SCH 23390 (1 mg/kg), D2-dopamine receptor antagonist eticlopride (1 mg/kg), and morphine were considered at 30-min intervals (0, 30, 60, 90, and 120 min) by tail-flick and hot-plate analgesia tests.

Obtained data suggested that D1/D2 dopamine receptors antagonist perphenazine was capable of suppressing opioid tolerance, possibly by the mechanism of inhibiting D2-dopamine receptor. Because the data indicated that D2-dopamine receptor antagonist eticloride, but not D1-dopamine receptor antagonist SCH 23390, significantly decreased morphine tolerance in analgesia tests. In addition, administration of perphenazine with morphine increased morphine analgesia.

Results from the present study suggested that dopamine receptors play a significant role in the morphine analgesic tolerance. In particular, D2-dopamine receptor has an important role rather than D1-dopamine receptor in development tolerance to morphine.

KEY WORDS: dopamine receptors, perphenazine, analgesia, morphine tolerance

INTRODUCTION

Opioids are highly efficacious analgesic drugs. However, repeated use of these drugs leads to the development of tolerance, thereby limiting their effectiveness and usage. The mechanisms underlying opioid tolerance are not entirely understood. Up to the present, several studies carried out on the mechanism of morphine tolerance. It has been shown that NMDA receptors [1] and cannaboid receptors [2] are involved in tolerance to opiate-induced antinociception. Tang et al. [3] reported that Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) can modulate opioid tolerance and dependence via its action on learning and memory. Furthermore, it has been suggested that transient receptor potential vanilloid-1 (TRPV1) plays a critical role in morphine tolerance [4]. Recently, we demonstrated that the serotonergic [5, 6] and noradrenergic system [7] play a significant role in the morphine tolerance. The opioid system has close functional links to the dopaminergic system in several brain areas, including the substantia nigra [8], striatum, and mesolimbic projections [9]. Opioids are known to modulate dopamine release in a variety of brain areas [10]. Moreover, some properties of opioids, including hyperlocomotion and reward, are at least partly mediated through dopamine receptors [11], and morphine is reported to increase the metabolism of dopamine in the septum and nucleus accumbens [12]. Dopamine has been implicated in the development of tolerance and dependence to opioids [13]. It has been demonstrated that activation of opioid receptors located on dopaminergic neurones in the striatum and nucleus accumbens may play an important role in mediating tolerance and sensitization to opiates [14].

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Dopamine exerts its action by binding to its specific membrane receptors (DA-Rs) which are subdivided into two subfamilies, D1- and D2-like, on the basis of their biochemical and pharmacological properties [15,16]. The D1-like subfamily comprises D1- and D5-R, while the D2-like subfamily includes D2-, D3- and D4-R [17]. The two DA-R subfamilies differentially couple to adenylate cyclase [18] and exert different effects in many conditions [19]. Dopamine regulates the two major striatal neuronal pathways through differential dopamine receptors. It regulates the striatonigral neurons via D1-dopamine receptors but regulates the striatopallidal neurons via D2-dopamine receptors [19]. In the striatum, dopaminergic and opioidergic neurons display interactions in regulating the function of efferent striatal neurons. For example, morphine acutely increases dopamine release in caudate putamen and nucleus accumbens [20]. Therefore, the D1-like dopamine receptor antagonist SCH 23390 can block a short-term morphine-induced increase in c-fos expression in the nucleus accumbens and caudate putamen [21]. Accordingly, it has been shown that D1- and D2-like dopamine receptors have opposing influences on morphine-induced antinociception [22]. D2-like dopamine receptors, but not the D1-dopamine receptor, exert antinociceptive effects and have a potentiating effect on morphine antinociception [23]. However, the effect of D2-dopamine receptors on the expression of morphine tolerance has not been elucidated. Perphenazine has been used in clinical practice as antipsychotic drugs for more than 60 years, and appears to induce their effects by acting as dopamine receptor antagonist [24]. In this study, we examined effects of D1/D2 dopamin receptors antagonist perphenazine on morphine analgesia and tolerance using the tail-flick and hot-plate tests in rats. In addition, we compared separately the roles of D1- and D2-dopamin receptor in these effects of perphenazine using D1-dopamine receptor antagonist SCH 23390 and D2-dopamine receptor antagonist eticlopride.

MATERIALS AND METHODS

Animals

Wistar Albino rats (weighing 190–205 g) were obtained from the Laboratory Animal Center, Cumhuriyet University School of Medicine (Sivas, Turkey). Rats were maintained under standard conditions: 12-h light–dark schedule (lights on at 8:00 A.M.) with ad libitum food and water and constant temperature (22±2°C). All experiments were carried out blindly between 09:00 and 17:00 h. Procedures and animal handling met the guidelines of the National Institutes of Health detailed in the "Principles of animal laboratory care". The experimental protocols were approved by the Cumhuriyet University Animal Ethics Committee (Licence number: 87/Ethic).

Drugs

Morphine sulphate (Cumhuriyet University Hospital, Turkey), perphenazine, SCH 23390 and eticlopride (Sigma Chemical Co., St. Louis, MO) were dissolved in physiological saline. Solutions were freshly prepared on the days of experimentation. Subcutaneous (s.c.) morphine (5mg/kg), perphenazine (1, 5, and 10 mg/kg; i.p.), SCH 23390 (1 mg/kg; i.p.), eticlopride (1 mg/kg; i.p.) 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 [25]. For tolerance induction, groups of 7-8 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 perphenazine, SCH 23390 and eticlopride on the morphine tolerance, morphine applied with perphenazine, SCH 23390 and eticlopride to the morphine tolerant animals on day 4.

Antinociception tests

Tail-flick test

We used a standardised 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 [26, 27].

Hot-plate test

The antinociceptive response on the hot-plate is considered to result from a combination of central and peripheral mechanisms (26). In this test, animals were individually placed on a hot-plate (May AHP 0603 Analgesic Hot-plate Commat, Turkey) with the temperature adjusted to 54±3°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.

Experimental protocols

The analgesic effects of perphenazine, SCH 23390, eticlo-

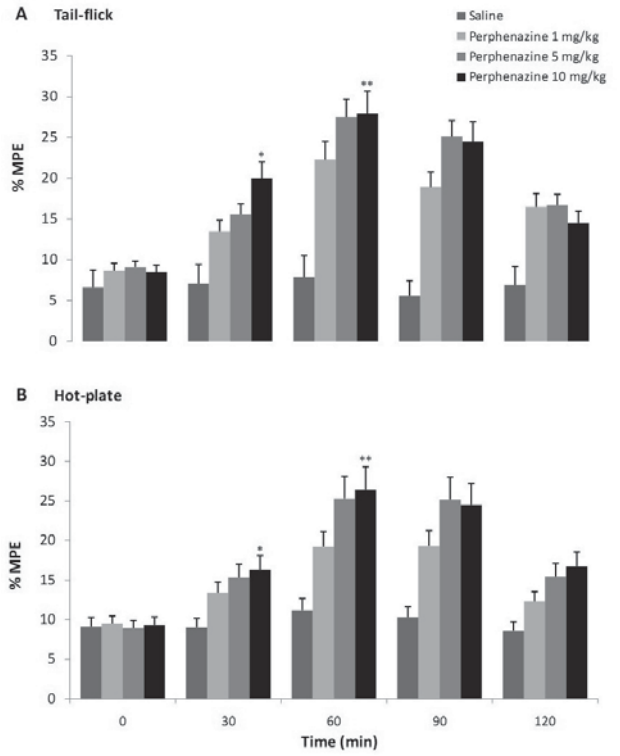


FIGURE 1. The analgesic effects of different doses of perphenazine. (A) shows effect of three different doses of perphenazine (1, 5, and 10 mg/kg) in the tail-flick test, and (B) shows effect of perphenazine in the hot-plate test. Each point represents the mean±SEM of percent of maximal possible effect (% MPE) for 8 rats. *, $p<0.05$ and **, $p<0.01$ compared to saline-treated group.

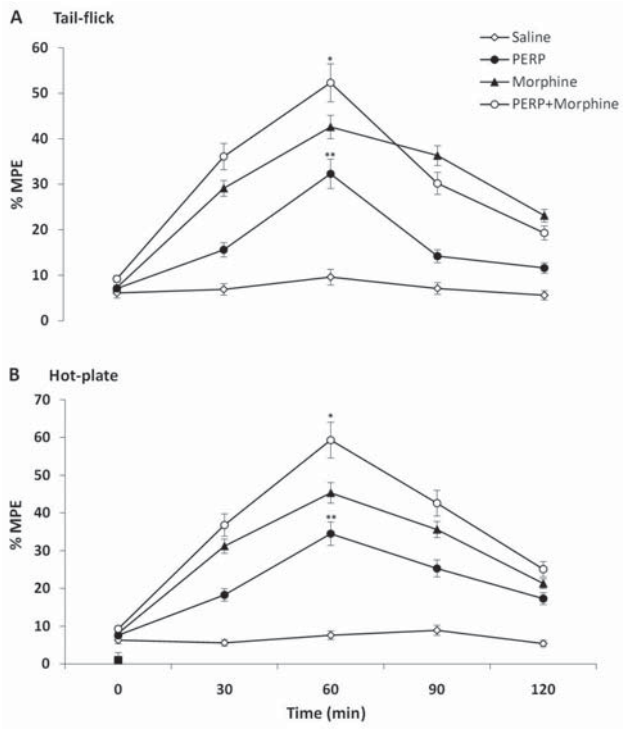


FIGURE 2. Effect of perphenazine on the morphine analgesia. (A) shows effect of perphenazine (10 mg/kg) in the tail-flick test, and (B) shows effect of perphenazine in the hot-plate test. Each point represents the mean±SEM of percent of maximal possible effect for 7 rats. *, $p<0.05$ compared to morphine treated group and **, $p<0.01$ compared to saline-treated group. PERP, perphenazine.

pride, and morphine were considered at 30-min intervals (0, 30, 60, 90, and 120 min) by tail-flick and hot-plate test in rats. To evaluate the effects of perphenazine, SCH 23390, and eticlopride on development of morphine tolerance, morphine tolerant animals received perphenazine (1, 5 and 10 mg/kg), SCH 23390 (1 mg/kg), and eticlopride (1 mg/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: % MPE = [(Postdrug latency – Baseline latency) / (Cutoff value – Baseline latency)]×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 % MPEs 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

The analgesic effects of different doses of perphenazine

To determine the effective dose of perphenazine, the analgesic response were measured for the three different doses of perphenazine (1, 5, and 10 mg/kg) at 30-min intervals (0, 30, 60, 90, and 120 min) by the analgesia tests. The maximum analgesic effect was observed at 60 min after administration 10 mg/kg dose of perphenazine (27.9±5.2 for tail-flick and 26.4±4.8 for hot-plate test). The % MPE produced by perphenazine (10 mg/kg) was significantly higher than in the other groups (1 mg/kg, 5 mg/kg perphenazine, and saline group) in both tail-flick test ($p<0.01$; Figure 1A) and hot-plate test ($p<0.01$; Figure 1B).

Effect of perphenazine on morphine analgesia

Statistical analysis indicated that pretreatment of animals with perphenazine significantly increased morphine analgesic effect in both tail-flick ($p<0.05$; Figure 2A) and hot-plate test ($p<0.05$; Figure 2B) compared to morphine administration group. The peak value of this group was observed at 60 min after administration of morphine and perphenazine in analgesia tests (tail-flick: 52.3±4.6 and hot-plate: 59.3±4.9).

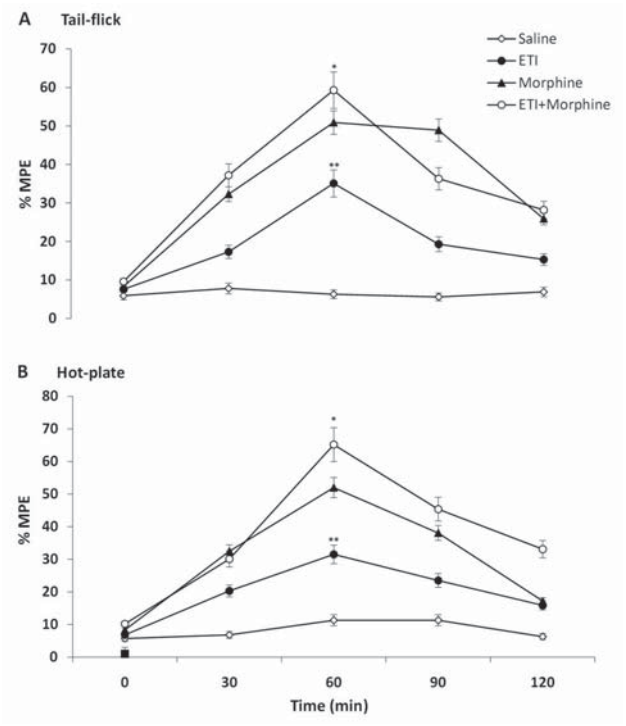


FIGURE 3. Effect of eticlopride on the morphine analgesia. (A) shows effect of eticlopride (1 mg/kg) in the tail-flick test, and (B) shows effect of eticlopride in the hot-plate test. Each point represents the mean±SEM of percent of maximal possible effect for 8 rats. *, $p<0.05$ compared to morphine treated group and **, $p<0.01$ compared to saline-treated group. ETI, eticlopride.

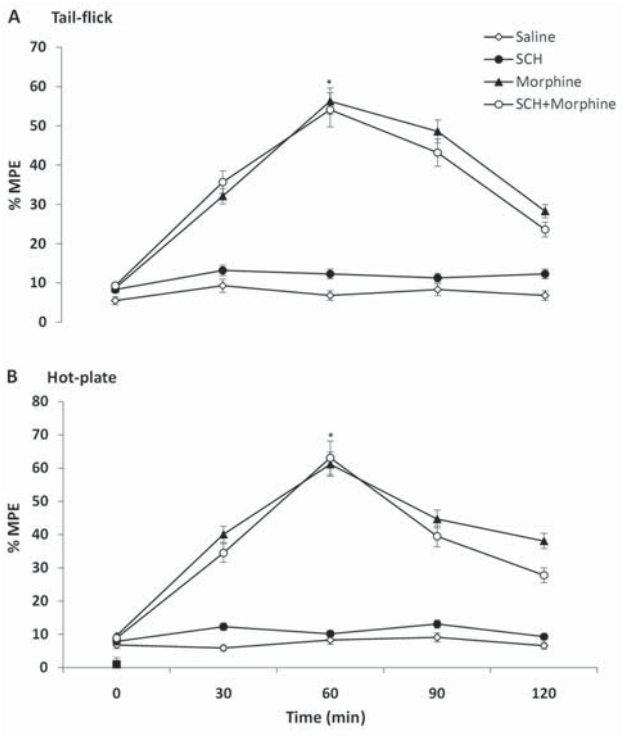
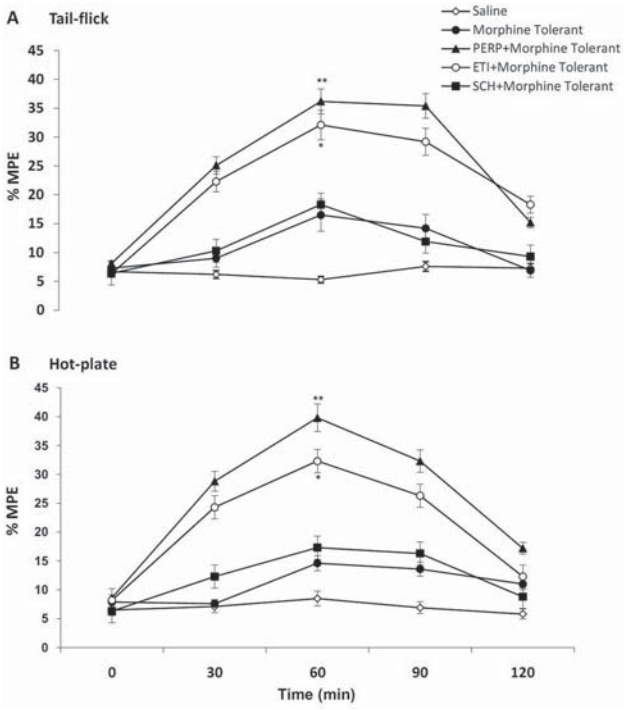


FIGURE 4. Effect of SCH 23390 on the morphine analgesia. (A) shows effect of SCH 23390 (1 mg/kg) in the tail-flick, and (B) shows effect of SCH 23390 in the hot-plate test. Each point represents the mean±SEM of percent of maximal possible effect for 7 rats. *, $p<0.01$ compared to saline-treated group. SCH, SCH 23390.



Effect of eticlopride on morphine analgesia

The findings demonstrated that D2-dopamin receptor antagonist eticlopride significantly increased morphine analgesic effect in tail-flick ($p<0.05$; Figure 3A) and hot-plate test ($p<0.05$; Figure 3B) compared to morphine administration group. The peak value of this group was also observed at 60 min after administration of morphine in analgesia tests (tail-flick: 59.3±4.7 and hot-plate: 65.2±4.8). Furthermore, these data suggested that eticlopride alone has a significant analgesic effect compared to the saline group.

Effect of SCH 23390 on morphine analgesia

Systemic administration of SCH 23390 (D1-dopamin receptor antagonist) with morphine did not significantly increase in % MPE in both the tail-flick (Figure 4A) and

FIGURE 5. Effects of perphenazine, eticlopride, and SCH 23390 on the morphine tolerance. (A) shows effects of perphenazine, eticlopride, and SCH 23390 in the tail-flick, and (B) shows effects of perphenazine, eticlopride, and SCH 23390 in the hot-plate test. Each point represents the mean±SEM of percent of maximal possible effect for 8 rats. *, $p<0.05$ and **, $p<0.01$ compared to the morphine tolerant group. PERP, perhanazine; ETI, eticlopride; SCH, SCH 23390.

hot-plate (Figure 4B) assays as compared to morphine group rats. Also, SCH 23390 alone had no a significant analgesic effect compared to the saline treatment group rats.

Effects of perphenazine, eticlopride, and SCH 23390 on tolerance to the morphine antinociception

Perphenazine and eticlopride in combination with morphine produced a significant decrease (increase in % MPE value) morphine tolerance in both the tail-flick ($p<0.01$, for perphenazine and $p<0.05$, for eticlopride; Figure 5A) and hot-plate assays ($p<0.01$, for perphenazine and $p<0.05$, for eticlopride; Figure 5B) as compared to the morphine tolerant rats. On the contrary, D1-receptor antagonist SCH 23390 in combination with morphine produced no significant effect on morphine tolerance in the tail-flick (Figure 5A) and hot-plate assays (Figure 5B) as compared to the morphine tolerant rats. The maximum % MPE was observed at 60 min after administration of morphine by analgesia tests in all groups rats.

DISCUSSION

In the present study, blockade of D1- and D2-dopamine receptors by perphenazine led to a decreased degree of tolerance to morphine-induced antinociception. Likewise, selective D2-dopamine receptor antagonist eticlopride produced a significant decrease morphine analgesic tolerance. In contrast, D1-dopamine receptor antagonist SCH 23390 in combination with morphine did not significantly decrease morphine tolerance. These findings demonstrate that D2-dopamine receptor has an important role rather than D1-dopamine receptor in morphine analgesic tolerance. The last two decades, many mechanisms have been proposed about the development of morphine tolerance. Recently, one of the discussed topics is the dopaminergic system on the analgesia. Initially, the analgesic effect is caused by inhibition of dopamine receptors [28]. Accordingly, our findings indicate that D1/D2 dopamine receptor antagonist perphenazine and D2-dopamin receptor antagonist eticlopride showed a significant analgesic effect in analgesia tests. The interaction between the dopamine and opiate systems is well recognized [29]. Considerable evidence suggests that dopamine activity affects the opioid system by modulating opiate peptide transcripts [30], synthesis [31], release, and biotransformation [32]. In contrast, opioids modulate the dopamine system by several mechanisms, such as dopamine synthesis [33], release [34], biotransformation [35], and activity of dopaminergic neurons [36]. It has been reported that there is functional interrelationship between morphine and the dopaminergic system [37, 38]. Locomotion induced by morphine [39] and changes in temperature [40] may be mediated via the dopaminergic system. Furthermore, the dopaminergic system also has been implicated in the antinociceptive effect and in the expression of signs of morphine withdrawal [41]. It seems that mesolimbic dopaminergic pathway is essential in the sensitization process. For example, it has been shown that dopamine alters the acquisition of sensitization to the motor effects of morphine in mice [42]. It has been suggested that D2-dopamine receptor antagonist sulpiride decreased the response to morphine (6 and 9 mg/kg) in the formalin test, whereas SCH 23390 did not influence the antinociception induced by morphine [43]. In contrast, our data demonstrated that D2-dopamine receptor antagonist eticlopride significantly increased morphine analgesic effect in the analgesia tests. In addition, several studies have demonstrated that CaMKII has a critical role in opioid tolerance and dependence [44, 45]. Supraspinal and spinal inhibition of CaMKII not only prevented but also reversed opioid-antinociceptive tolerance and physical dependence in several rodent models [3, 45]. Furthermore, it has been reported that dopamin receptor antagonist haloperidol attenuates opioid tolerance and dependence by suppressing CaMKII activity [46]. These data support a critical role of CaMKII in the development and maintenance of opioid tolerance. It has been suggested that cAMP-dependent protein kinase (PKA) signal pathway was involved in dopamine-mediated change of Na^+, K^+-ATPase activity after short-term or long-term morphine treatment [47]. Opioid and D2-dopamine receptors both couple to inhibitory G protein (Gi/o). Activation of both receptors by their agonists inhibits adenylyl cyclase and decreases PKA activation, leading to an enhancement of Na^+, K^+-ATPase activity. Eticlopride only reverses D2- receptor-mediated increase in Na^+, K^+-ATPase activity. Opioid receptor antagonist naltrexone reversed both short-term and long-term morphine-induced changes of Na^+, K^+-ATPase activity. These results suggest that D2-dopamine receptors are implicated in regulating striatal Na^+, K^+-ATPase activity after shorterm morphine treatment, whereas D1-dopamine receptors are involved in regulating striatal Na^+, K^+-ATPase activity upon long-term morphine treatment. Involvement of dopamine receptors in regulating Na^+, K^+-ATPase activity in vivo by morphine is further supported by the observation that eticlopride failed to suppress the enhancement of Na^+, K^+-ATPase activity induced by in vitro direct administration of morphine to isolated striatal synaptosomes [47]. Dopamine is a general dopamine receptor agonist and activates both D1 and D2 dopamine receptors. Activation of D2 dopamine receptors stimulates Na^+, K^+-ATPase activity [48], whereas activation of D1 dopamine receptors inhibits Na^+, K^+-ATPase activity [49]. This dopamine-PKA signal pathway may explain the mechanism of tolerance to morphine. In the same way, dopamin receptor antagonist perphenazine may decrease tolerance to morphine by means of D2-receptor.

CONCLUSIONS

Results from the present study suggested that dopamine receptors play a significant role in the morphine analgesic tolerance. In particular, D2-dopamine receptor has an important role rather than D1-dopamine receptor in development tolerance to morphine. The most important limitation of this study is no adequate data on human study. In the future, dopamin D2-receptor antagonist perphenazine may be used to decrease the development of tolerance to morphine. However, further investigation is needed to explain the mechanism of morphine tolerance.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest in relation to this article.

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