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Morphine modulates the effects of histamine H_1 and H_3 receptors on seizure susceptibility in pentylenetetrazole-induced seizure model of mice

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ABSTRACT

Histamine regulates release of neurotransmitters such as dopamine, serotonin, gamma-aminobutyric acid (GABA), glutamate and also is involved in several functions in central nervous system (CNS). It has been shown that histamine participates in disorders like seizure. It has been well documented that morphine dose-dependently induces anti or proconvulsant effects. In the current study, we firstly showed that morphine (1 mg/kg) exerts anticonvulsant effects which significantly reversed by naltrexone administration. Secondly, we determined seizure threshold for H_1 and H_3 receptors agonists and antagonists in mouse model of pentylenetetrazole (PTZ)-induced clonic seizures. Our results showed that activation of H_1 receptors by 2-(2-Pyridyl)-ethylamine exerts anticonvulsant properties while inhibition of H_1 receptors by pyrilamine maleate induced proconvulsant effects. Furthermore, we showed that immepip dihydrobromide, a H_3 receptor agonist, increased seizure susceptibility to PTZ whereas thioperamide, a H_3 receptor antagonist increased seizure threshold. We also revealed that pretreatment with morphine potently reversed the effects of histaminergic system on seizure threshold suggesting the involvement of opioid system in alteration of seizure threshold by histaminergic drugs.

1. Introduction

Histamine [2-(4-imidazolyl)-ethylamine], an endogenous biogenic amine, mediates pleiotropic functions in the central nervous system (CNS) (Fernandez-Novoa and Cacabelos, 2001). Histaminergic neurons are located in tuberomamillary nucleus of hypothalamus and projects to practically all major brain regions (Haas and Panula, 2003). This neurotransmitter has been implicated in regulation of several CNS activities such as cognition, arousal, circadian rhythms, synaptic plasticity, pain perception, stress, anxiety, and neuroendocrine regulation (Brown et al., 2001). Evidence indicates histamine modulates the release of other neurotransmitters such as dopamine, serotonin, norepinephrine and gamma-aminobutyric acid (GABA) (Flik et al., 2015). Since histamine participates in variety of brain pathologies, it has been suggested that histaminergic system would be an appropriate therapeutic target for treatment of neuropathic pain, sleep-wake disorders, attention deficit hyperactivity disorder, Alzheimer's disease, Parkinson's disease, schizophrenia, migraine and epilepsy (Alstadhaug, 2014; Gemkow et al., 2009; Passani and Blandina, 2011).

Clinical and preclinical studies have suggested the possible involvement of histaminergic system in seizure disorders (Stark, 2003). In this regard, previous research demonstrated that increased level of central histamine acts as an endogenous anticonvulsant agent and exerts an important inhibitory effect during seizure episodes (Bhowmik et al., 2012). Using animal models of electrically/chemically-induced seizure, it has been shown that activation of the histaminergic system, mainly through H_1

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receptor, increase seizure threshold in animals (Hirai et al., 2004; Tuomisto and Tacke, 1986). However, applying H_1 receptor antagonists exhibited proconvulsant effects in animal studies (Cerminara et al., 2013). Moreover, there are pieces of evidence indicating the involvement of H_3 receptors in the seizure activity (Harada et al., 2004; Sadek et al., 2014). A number of investigations have revealed that H_3 receptor antagonists not only mitigate the severity of epileptic symptoms but protect neurons against seizure-associated neurotoxicity through enhancing the release of histamine, GABA and also, histidine decarboxylase activity (Bhowmik et al., 2012; Devi et al., 2011).

On the other hand, evidence suggests that opioids exert both proconvulsant and anticonvulsant effects in different animal models of seizure (Homayoun et al., 2002b; Lauretti et al., 1994). While low doses of morphine have been reported to reduce the seizure susceptibility to picrotoxin, bicuculline and pentylenetetrazol (PTZ), higher doses induce proconvulsant effects that indicating the biphasic effects of morphine on seizure threshold (Frenk, 1983; Lauretti et al., 1994). Considering that opioid receptors possess seizure-modulating properties, they may have functional interactions with other receptor classes involved in seizure activity (Shafaroodi et al., 2004). Considering that both opioid and histamine receptors share physiological properties such as anti-nociception, a possible interaction may exist between these two classes of receptors in controlling seizures. The purpose of the current study is to examine whether opioid system may play a role in mediating the effects of histamine H1 and H3 receptor agonists/antagonists on seizure susceptibility to PTZ.

2. Materials and methods

2.1. Animals

Male NMRI mice weighing 27 ± 3 g (Pasteur Institute, Tehran, Iran) were used in this study. Animals were housed in standard polycarbonate cages (4–5 mice per cage) and under standard laboratory conditions (12-h light/dark cycle, temperature (22 ± 1 °C) and free access to food and water). All behavioral experiments were performed between 10:00 a.m. and 13:00 p.m. All procedures in this study were carried out in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH Publication no. 80-23) and institutional guidelines for animal care and use (Department of Pharmacology, School of Medicine, TUMS). Each mouse underwent treatment only once and also each treatment group was consisted of 8 animals.

2.2. Drugs

The drugs used in this study were as follows: morphine sulfate, pentylenetetrazole (Sigma, U.K.), naltrexone, 2-(2-Pyridyl)-ethylamine, pyrilamine maleate, immepip dihydrobromide and thioperamide maleate (Sigma, St Louis, MO, USA). All drugs were dissolved in 0.9% saline in a volume of 10 ml/kg. In order to assess clonic seizures in experimental animals, PTZ was administered intravenously (0.5%, i.v.) and all other drugs were administered intraperitoneally (i.p.). Doses of each drug were selected based on our previous and pilot studies (Honar et al., 2004).

2.3. Treatment

Experiment 1 examined the effect of morphine (1 mg/kg) on clonic seizure threshold. Animals in this experiment received morphine 30 min before PTZ administration.

In experiment 2 we examined the effect of naltrexone (10 mg/kg) along with morphine (1 mg/kg) on clonic seizure threshold. Animals in this trial received naltrexone 15 min prior to morphine injection and 45 min before the administration of PTZ.

Experiment 3 examined the effect of 2-(2-Pyridyl)-ethylamine (H_1 agonist, 5 mg/kg) alone (30 min before the test) or along with morphine (1 mg/kg, 15 min prior to 2-(2-Pyridyl)-ethylamine) on seizure threshold.

In experiment 4 effect of pyrilamine maleate (H_1 antagonist, 10 mg/kg) alone (30 min before the test) or along with morphine (1 mg/kg, 15 min before pyrilamine maleate) on seizure threshold was determined.

Experiment 5 was designed to examine the effect of immepip dihydrobromide (H_3 agonist, 10 mg/kg) alone (30 min before the test) or in combination with morphine (1 mg/kg, 15 min prior to immepip dihydrobromide) on seizure threshold.

Experiment 6 examined the effect of thioperamide (H_3 antagonist, 10 mg/kg) alone (30 min before the test) or along with morphine (1 mg/kg, 15 min before thioperamide maleate) on seizure threshold.

2.4. Determination of seizure threshold

We assessed the seizure threshold using the method that was previously described in our previous studies (Amiri et al., 2014; Amini-Khoei et al., 2015). To determine the clonic seizure threshold, we inserted a 30-gauge butterfly needle into the lateral tail vein of mice. The needle was then fixed to the tail by a piece of adhesive tape. With the mouse moving freely, the PTZ solution (0.5%) was slowly infused into the tail vein at a constant rate of 1 ml/min, using an infusion pump (NE 1000, New Era Pump System, Inc.), which was connected to the dental needle by polyethylene tubing. Infusion was halted when forelimb clonus followed by full clonus of the body (began with running and then loss of righting ability) was observed. The minimal dose of PTZ (mg/kg of mice weight) needed to induce general clonus was recorded as an index of clonic seizure threshold. In this regard, the seizure threshold is dependent on PTZ dose administered and time-related.

2.5. Statistics

The one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used to analyze the data. Values are expressed as mean $\pm$ S.E.M., a value of $P < 0.05$ was considered as statistically significant in all experiments.

3. Results

3.1. Effects of morphine and naltrexone on seizure threshold

As shown in Fig. 1A, administration of morphine (30 min before the test) significantly increased seizure threshold in animals ($^{**}P < 0.01$). In addition, pretreatment with naltrexone (15 min prior to morphine treatment) significantly decreased seizure threshold ($^{\#\#}P < 0.01$). Furthermore, naltrexone by its own had no effect on seizure threshold ($P > 0.05$).

3.2. Effect of 2-(2-Pyridyl)-ethylamine (H_1 agonist) on the PTZ-induced seizures

Fig. 1B shows the effect of morphine pretreatment on the anticonvulsant effect of 2-(2-Pyridyl)-ethylamine against PTZ-induced seizures. Administration of 2-(2-Pyridyl)-ethylamine significantly increased the seizure threshold in comparison with saline- treated controls ($^{*}P < 0.05$). Moreover, morphine

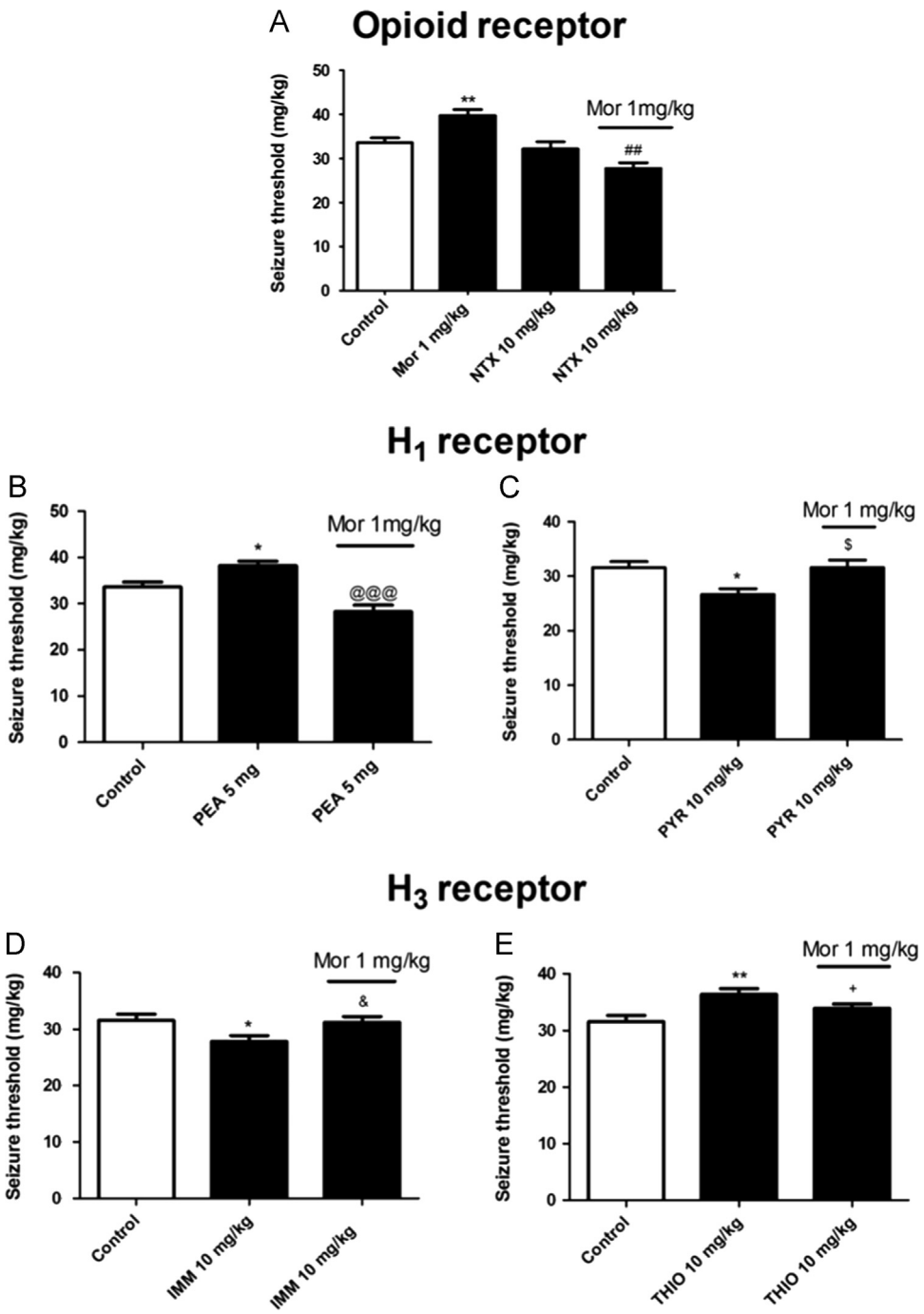

Fig.1. Effects of different treatments on seizure threshold in PTZ model of clonic seizures in mice: (A) Effects of morphine (Mor) and naltrexone (NTX) treatments on seizure threshold. (B) Effects of 2-(2-Pyridyl)-ethylamine (PEA) and morphine on seizure threshold. (C) Effects of pyrilamine maleate (PYR) and morphine on seizure threshold. (D) Effects of immepip dihydrobromide (IMM) and morphine on seizure threshold. (E) Effects of thioperamide maleate (THIO) and morphine on seizure threshold. Data are expressed as mean ± S.E.M. ($n=8$) and were analyzed by one-way ANOVA and Tukey's post-hoc test. $^{*}P<0.05$ and $^{**}P<0.01$ compared with saline-treated controls in each figure. $^{\#\#}P<0.01$ compared with morphine treated group in Fig. 1A. $^{@@@}P<0.001$ compared with PEA treated group in Fig. 1B. $^{\$}P<0.05$ compared with PYR treated group in Fig. 1C. $^{\&}P<0.05$ compared with IMM treated group in Fig. 1D. $^{+}P<0.05$ compared with THIO treated group in Fig. 1E.

pretreatment decreased the anticonvulsant effect of 2-(2-Pyridyl)-ethylamine ($^{@@@}P<0.001$).

3.3. Effect of pyrilamine maleate (H_1 antagonist) on the PTZ-induced seizures

Fig. 1C shows the effect of morphine pretreatment on the proconvulsant effect of pyrilamine maleate against PTZ-induced seizures. Administration of pyrilamine maleate significantly decreased the seizure threshold in comparison with saline-treated controls ($^{*}P<0.05$). As shown in Fig. 1C, morphine pretreatment significantly reversed the proconvulsant effect of pyrilamine maleate ($^{\$}P<0.05$).

3.4. Effect of immepip dihydrobromide (H_3 agonist) on the PTZ-induced seizures

As shown in Fig. 1D, administration of immepip dihydrobromide significantly decreased the seizure threshold in comparison with saline-treated controls ($^{*}P<0.05$). Furthermore,

morphine pretreatment led to an increase in seizure threshold when compared with IMM treated group ($^{\&}P < 0.05$).

3.5. Effect of thioperamide maleate (H_3 antagonist) on the PTZ-induced seizures

As shown in Fig. 1E, administration of thioperamide maleate significantly increased the seizure threshold in comparison with saline-treated controls ($^{**}P < 0.01$). Also, morphine pretreatment reversed the anticonvulsant effect of thioperamide maleate ($^{+}P < 0.05$).

4. Discussion

Results of the present study revealed that H_1 and H_3 receptors play a role in seizure susceptibility to PTZ and also, opioid system is involved in their effects. In contrast to H3 receptors, activation of H1 receptors by its agonists produced anticonvulsant effect and application of H1 antagonists led to a decrease in seizure threshold. In addition, modulatory effects of morphine on histaminergic-induced alterations in seizure threshold suggest the interaction between opioid and histaminergic system in seizure susceptibility to PTZ.

While vast majority of investigations in epilepsy have focused on inhibitory and excitatory neurotransmissions, role of other contributing neurotransmitters, such as histamine and its interactions with other neurotransmission systems have not been studied well. Evidence indicates that histaminergic system has many interactions with excitatory and inhibitory neurotransmission. Once couples to GABAergic and glutaminergic systems, histamine is able to regulate histaminergic activity through interactions with $GABA_A$, $GABA_B$ and NMDA receptors. Moreover, histamine inhibits the release of several neurotransmitters, such as GABA, glutamate, dopamine serotonin, noradrenaline and acetylcholine via H_3 receptors (Brown et al., 2001; Lintunen et al., 2005). There are pieces of evidence suggesting that unlike H_1 receptor antagonists, activation of the central histaminergic system by H_1 receptor agonists positively modifies seizure activity (Kukko-Lukjanov et al., 2012; Miyata et al., 2011).

Our results were consistent with these studies that administration of 2-(2-Pyridyl)-ethylamine led to an increase in seizure susceptibility to PTZ while pyrilamine maleate produced pro-convulsant effect. Considering that H_3 receptors are inhibitory auto-receptors in histaminergic neurons, previous studies have shown that H_3 receptor antagonists are able to mitigate seizure susceptibility by increasing the release of histamine in brain (Bhowmik et al., 2012; Trenité et al., 2013). In this context, thioperamide, a selective H_3 receptor antagonist, has been reported to decrease seizure vulnerability to PTZ via increasing the endogenous histamine levels in brain (Vohora et al., 2000). In agreement with previous investigations, our results corroborated the anticonvulsant properties of H_3 receptor antagonists that mice treated with immepip dihydrobromide exhibited more sensitivity to convulsing effects of PTZ while treating animals with thioperamide induced an anticonvulsant effect. In this context, it has been reported that H3-receptor agonists or H1-receptor antagonists increase seizure susceptibility in different models of seizures including amygdaloid kindling, maximal electroshock, picrotoxin and pentylenetetrazol-induced-induced seizures (Sturman et al., 1994; Vohora et al., 2001).

On the other hand, components of opioid system have been widely distributed in CNS and play an important role in regulation of many behavioral and cognitive processes such as pain, neurotransmission and seizure activity (Akil et al., 1984; Khan et al., 2015). Using different experimental models of seizures, it has been shown that opioids dose- dependently exert anticonvulsant and proconvulsant effects (Gooshe et al., 2015; Homayoun et al., 2002b). Surprisingly, in contrast to higher doses of morphine, lower doses of morphine have anticonvulsant properties (Homayoun et al., 2002a). Morphine in high doses induces excitation and causes myoclonus seizures (Gregory et al., 1992; Hagen and Swanson, 1997). Previous studies suggest that proconvulsant effect of morphine may be associated with production of 3-glucuronide (a morphine metabolite) (Hemstapat et al., 2003), or nitric oxide (Khavandgar et al., 2002). Further investigations have also suggested that multiple receptor systems such as adrenergic and glutamatergic receptors (Homayoun et al., 2002a; Schroeder et al., 1998) or inhibition of GABAergic neurotransmission (Werz and MacDonald, 1982) are involved in triggering opioid-induced seizures.

Focusing on histaminergic system, past studies demonstrated that histaminergic system mediates some of the central effects of morphine and acute treatment with morphine enhances the turnover of neuronal histamine (Karadag et al., 2000). A study by Karadag et al. (1996) has recently showed that H_1-receptor antagonists and naloxone are able to antagonize the anticonvulsant effect of morphine. Moreover, it has been reported that phospholipase C and calcium-linked transduction systems are related to opioid receptor activation which consequently lead to degranulation of mast cell and histamine release (Rehni et al., 2010). Results of the current work showed that Co-administration of morphine with both H_1 and H_3 agonists/antagonists reversed their effects on seizure susceptibility to PTZ indicating the interaction between opioid system and histaminergic system in mediating the seizure activity. Also, these data suggests the involvement of opioid system in different effects of histaminergic system on seizure susceptibility to PTZ as a $GABA_A$ antagonist (Di Capite and Parekh, 2009; Liu and Gintzler, 2006; LÜ et al., 2013). Furthermore, it has been reported that opioid receptor-induced seizures is correlated with a significant increase in histamine release that may mediate the proconvulsant properties of morphine (Zhu-Ge et al., 2007). In this regard, Rehni et al. demonstrated that pro-convulsant effect of amisulpride may be associated with opioid system-induced activation of histamine receptors. They also showed that pretreatment with a H_1 blocker or a mast cell stabilizer significantly attenuated the amisulpride-induced seizures in mice (Rehni et al., 2011).

5. Conclusion

In conclusion, results of our study showed that pretreatment with morphine potently reversed the effects of histaminergic system (H_1 and H_3) on seizure susceptibility to PTZ in mice. Also, our results suggest that opioid system is partially involved in the effects of histamine on seizure activity.

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