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Exacerbation of harmaline-induced tremor by imipramine

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Abstract

Imipramine is a well-established tricyclic antidepressant which was first approved for the treatment of depression in the late fifties. Antidepressant effect of imipramine is attributed to inhibition of serotonin (5HT) and noradrenaline (NA) reuptake in brain. These monoamines have been implicated in a variety of neurological disorders including tremor. In the present investigation attempt was made to study the effect of imipramine on harmaline-induced tremor in rats. Male Sprague Dawley rats weighing 115±2.5 g were given harmaline (10 mg/kg, i.p.) alone or along with imipramine (30 min before harmaline) in doses of 60 and 90 mg/kg respectively. The latency of onset, intensity and duration of tremor and EMG were recorded. To substantiate the role of 5HT in aetiopathology of tremor the above experiment was repeated in the rats pretreated with *P*-chlorophenylalanine (PCPA), a potent 5HT depleter. The levels of 5HT and 5-hydroxyindole acetic acid (5HIAA) in the brain stem were measured using high performance liquid chromatography. Imipramine dose-dependently exacerbated the duration, intensity and amplitude of EMG following harmaline-induced tremor. Imipramine treatment further decreased harmaline-induced 5HT turnover in the brain stem. However, this was statistically insignificant. Depletion of 5HT produced a significant reduction in the intensity and duration of harmaline-induced tremor. In conclusion, this study suggests that imipramine exacerbates harmaline-induced tremor. Clinical use of imipramine for the treatment of depression in patients who also suffer from tremors may require a close monitoring.
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Keywords: Imipramine; Tremor; Harmaline; Serotonin; *P*-chlorophenylalanine; EMG

1. Introduction

Essential tremor (ET) represents a heterogenous group of movement disorder commonly met with in clinical practice for which there is no known underlying cause. It is believed that ET result from very complex physiological and pathological processes and involves the interaction between central and peripheral nervous system (Deuschl and Elble, 2000; Marsden, 1984). According to present belief, a central oscillator at olive cerebellar–thalamic–cortical–spinal level acts as the primary generator of ET, which is modulated by peripheral component (Tapiador et al., 1998). In spite of extensive research, exact nature of neurotransmitters responsible for controlling rhythmicity of these pathways is far from clear. Several studies suggest the involvement of 5HT in regulation of olivary excitability by allowing the membrane potential of neurons to be maintained within a narrow range so as to prevent them from generating uncontrollable rhythmic firing (Barragan et al., 1985; De Montigny and Lamarre, 1975; Sjolund et al., 1977; Welsh and Llinas, 1997; Wilms et al., 1999). These observations are further supported by the findings that the agents with the ability to interfere with endogenous serotonergic pathway may alter the course of clinical and experimentally induced tremor (Arshaduddin et al., 2004; Lin Shiau and Hsu, 1994; McLeod and White, 1986; Mehta et al., 2003).

Imipramine, a prototype tricyclic antidepressant has been frequently used for the treatment of depression for over four decades. It has also been found useful as temporary adjunctive therapy in reducing nocturnal enuresis in children aged 5 years or above (Glazener and Evans, 2000).

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Imipramine exerts its pharmacological effects by inhibiting the reuptake of noradrenaline and serotonin in synaptic cleft in various regions of brain (Mongeau et al., 1977). Clinical studies suggest that drugs affecting both noradrenaline and serotonin display higher antidepressant efficacy than selective serotonin reuptake inhibitors (SSRIS) alone (DUAG, 1988, 1990; Perry, 1996). Since, tremor is one of the neurological adverse effects of imipramine (Zarrindast et al., 2003), it may be hypothesized that use of imipramine as antidepressant in patients who also suffer from tremor may possibly aggravate their tremor. The present study was undertaken to study the effect of imipramine treatment on harmaline-induced tremor in rats.

2. Materials and methods

Male Sprague Dawley rats weighing 115±2.5 g were obtained from the animal care center of the Riyadh Armed Forces Hospital. They were housed under standard conditions at a temperature of 23±1 °C, 12L:12D cycle and had free access to food and water. All animal experiments were done in accordance with animal protection guidelines approved by the Research and Ethics Committee of Riyadh Armed Forces Hospital. In experiment I, the animals were divided into three groups (six rats each). The rats in Groups 1, 2 and 3 were given imipramine in the doses of 0, 60 and 90 mg/kg respectively by gavage 30 min before inducing tremor. Tremors were induced by an intraperitoneal (i.p.) injection of harmaline (10 mg/kg). The selection of doses of imipramine was based on earlier report (Dredge et al., 1999) and results of our pilot studies. In experiment II, a second batch of 4 groups of animals was used to study the effect of imipramine on harmaline-induced tremor in serotonin-depleted animals. The depletion of 5HT was achieved by injecting the rats (Group 1, 2, 3) with *P*-chlorophenylalanine (PCPA) 300 mg/kg i.p., for three days. The fourth group was given saline. The three groups of 5HT-depleted rats received imipramine (0, 60 and 90 mg/kg) by gavage 15 h after the last injection of PCPA followed by harmaline (30 min later) to produce tremor. The occurrence of tremors was rated by an observer blinded to treatment protocol as described earlier (Tariq et al., 2002). The period between the injection of harmaline and the appearance of the first symptoms of tremors was recorded as the time of onset of tremors. The duration of tremors was defined as the time between the onset and complete disappearance of tremors. The intensity of tremors was assessed at regular intervals until the tremors completely subsided and the animals became normal. The clinical grading of the intensity of tremors was done as follows: no tremor=0, mild tremor=1, moderate intermittent tremor=2, moderate persistent tremor=3 and pronounced severe tremor=4. Tremor index was expressed as the total sum of the score for the entire duration of tremor as per the method of Suemaru et al. (2000).

Separate batches of animals were used for neurophysiological (EMG) and neurochemical (5HT, 5HIAA) studies. Ninety minutes after harmaline administration EMGs were recorded by inserting monopolar needle electrodes in the gastrocnemius muscle of the left leg of the rat. EMG signals were filtered from 20 to 10,000 Hz and the amplitude and frequency of tremor were recorded with the help of Medelec MS 92 (Guilford, UK) equipment. The peak amplitudes were measured and averaged from three different recordings of each animal.

For neurochemical studies the animals were killed 90 min after harmaline administration by decapitation and brains were dissected out, frozen in liquid nitrogen and stored at −80 °C. The levels of serotonin (5HT) and its metabolite 5-hydroxy-indoleacetic acid (5HIAA) were determined in the brain stem according to the procedure of Patrick et al. (1991). The tissues were weighed and homogenized in 1 ml of 0.1 M perchloric acid containing 0.05% EDTA for 10 s using a Teflon homogenizer. The homogenates were centrifuged at 10,000 rpm at 4 °C for 10 min. The supernatants were filtered using 0.45 μm pore filters and analyzed by high performance liquid chromatograph (HPLC). The HPLC system consisted of an electrochemical detector Model 656 (Metrohm, Switzerland), autoinjector Waters Model 712, solvent-delivery pump Waters Model 510 and integrator Waters Model 745 (Waters Melford, USA). The mobile phase consisted of 0.1 M citric acid, 0.1 M sodium acetate, 7% methanol, 100 μm EDTA and 0.01% sodium sulfonic acid. The flow rate of mobile phase was maintained at 1 ml/min and the injection volume of sample was 20 μl.

2.1. Statistical analysis

The results are presented as mean±standard error. One way analysis of variance (ANOVA) followed by Dunnett's multiple comparison's test were used to determine the level of significance. Difference with a P value of <0.05 were considered significant.

3. Results

Treatment of rats with harmaline produced characteristic tremors starting within 6.77±0.87 min following harmaline administration and lasted for 111.11±5.63 min. The tremor was more pronounced when the animals were moving or not leaning against the wall of the cage. Although imipramine failed to alter harmaline-induced onset of tremor (data not shown), a significant and dose-dependent increase in the duration (ANOVA $F_{2,12}$=70.50, P<0.000), intensity (ANOVA $F_{2,12}$=14.41, P<0.000) and index (ANOVA $F_{2,12}$=72.98, P<0.000) of tremor was observed in rats treated with imipramine (Figs. 1–3).

The EMG of rats at 90 min after harmaline injection showed a medium range of activity in the gastrocnemius

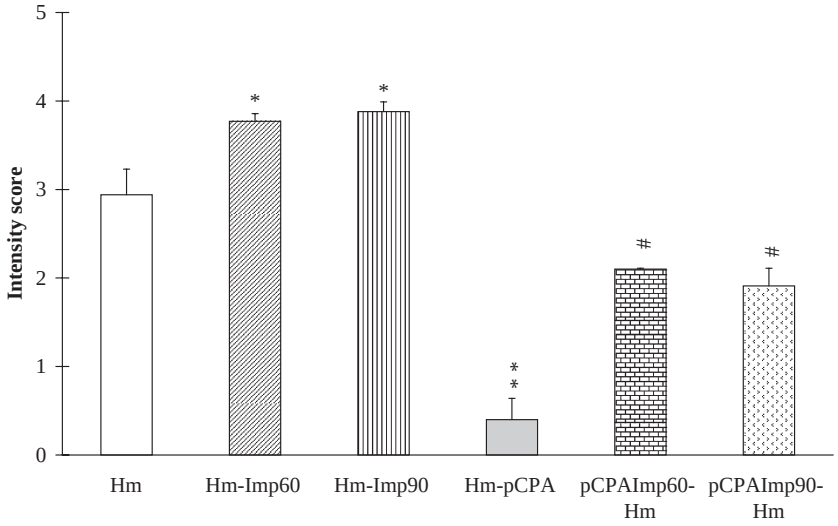

Fig. 1. Effect of imipramine on changes in intensity of harmaline induced tremor in rats. Values are mean±S.E.M. *P<0.01 and **P<0.001 as compared with harmaline alone treated animals and $^{\#}P$<0.001 as compared with pCPA treated animals using ANOVA followed by Dunnett's test. Imp—Imipramine 60 and 90 mg/kg, pCPA—P-chlorophenylalanine.

muscle. A highly significant (ANOVA $F_{5,30}$=31.87, P<0.000) and dose-dependent increase in the amplitude of tremor was observed in imipramine plus harmaline treated animals as compared to harmaline alone treatment (Fig. 4). The amplitude of tremor decreased in 5HT-depleted rats. Imipramine treatment significantly increased the amplitude of harmaline-induced tremor of 5HT-depleted rats (Fig. 4). However, pretreatment with imipramine and PCPA did not change the tremor frequency.

A highly significant decrease in intensity (ANOVA $F_{3,18}$=31.179, P<0.000) and duration (ANOVA $F_{3,18}$= 6.778, P<0.005) of harmaline-induced tremor was observed in 5HT-depleted rats (Figs. 1–3). Imipramine significantly exacerbated the tremor index (ANOVA $F_{3,18}$=39.17, P<0.000), intensity (ANOVA $F_{3,18}$=6.778, P<0.003) and duration (ANOVA $F_{3,18}$=18.69, P<0.000) of harmaline-induced tremors in normal and 5HT depleted rats (Figs. 1–3).

A significant increase in 5HT (ANOVA $F_{5,27}$=26.98, P<0.000) and decrease in 5HIAA (ANOVA $F_{5,27}$=7.826, P<0.000) levels of the brain stem were observed following harmaline administration resulting in a several fold decrease in serotonergic turnover (5HIAA/5HT) (Table 1). Although imipramine alone produced only slight decrease in 5HT and 5HIAA, it significantly (ANOVA $F_{5,27}$=29.68, P<0.000; ANOVA $F_{9,53}$=27.66, P<0.000) decreased the serotonergic turnover in the brain stem at higher dose (90 mg/kg). On

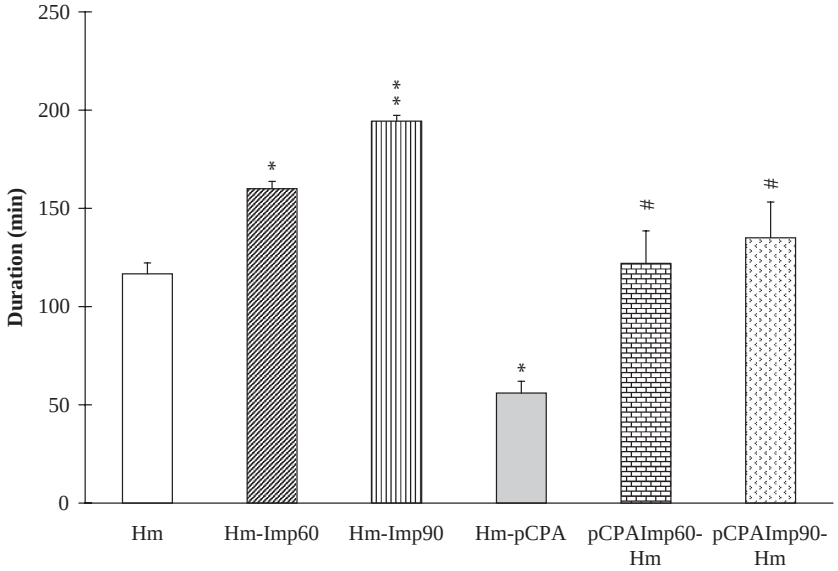

Fig. 2. Effect of imipramine on duration of harmaline induced tremor in rats.Values are mean±S.E.M. *P<0.05 and **P<0.001 as compared with harmaline alone treated animals and $^{\#}P$<0.005 as compared with pCPA treated animals using ANOVA followed by Dunnett's test. Hm—Harmaline 10 mg/kg, Imp—Imipramine 60 and 90 mg/kg, pCPA—P-chlorophenylalanine.

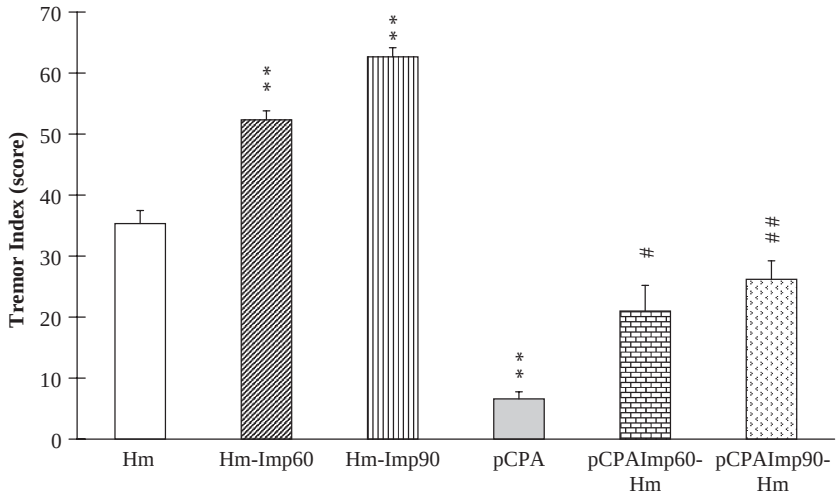

Fig. 3. Effect of imipramine on tremor index of harmaline induced tremor in rats. Values are mean±S.E.M. *P<0.01 and **P<0.001 as compared with harmaline alone treated animals and $^{\#}P$<0.01 and $^{\#\#}P$<0.001 as compared to pCPA treated animals using ANOVA followed by Dunnett's test. Hm—Harmaline 10 mg/kg, Imp—Imipramine 60 and 90 mg/kg, pCPA—*P*-chlorophenylalanine.

the other hand, treatment with PCPA significantly reduced the 5HT and 5HIAA levels in brain stem as compared to control and harmaline alone treated animals (ANOVA $F_{9,53}$=118.33, P<0.000) (Table 1). Administration of imipramine to PCPA treated rats significantly (ANOVA $F_{3,18}$=6.807, P<0.003) reduced 5HT turnover as compared to rats which did not receive imipramine (Table 1).

4. Discussion

The results of this study clearly demonstrated a significant exacerbation of harmaline-induced tremor by imipramine. Potentiation of harmaline-induced tremors was evident from increased intensity and duration of tremors in the rats treated with imipramine (Figs. 1 and 2). Our results support the findings of earlier studies where 5HT uptake inhibitors such as alaproclate (Ogren et al., 1992, 1985) and citalopram (Arshaduddin et al., 2004) were observed to potentiate drug induced tremors. Harmaline-induced tremor was accompanied by an increase in 5HT levels and a decrease in 5HT turnover in brain stem (Table 1). Increase in brain 5HT levels following harmaline administration has been attributed to its ability to inhibit monoamine oxidase (MAO) enzyme (Gerardy, 1994; Kim et al., 1997). Inferior olive located in brain stem has been shown to act as locus that may generate rhythmic components of tremor and myoclonus mediated by 5HT

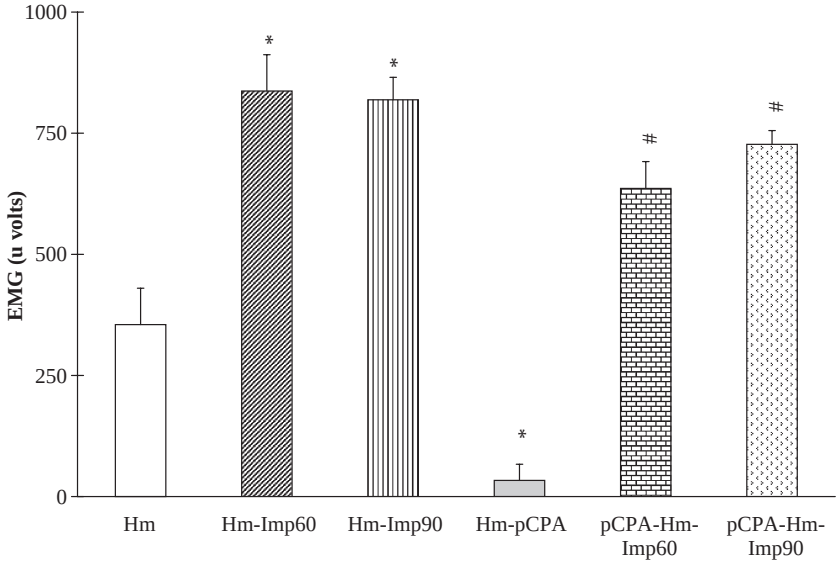

Fig. 4. Effect of imipramine on tremor (EMG) amplitude of harmaline induced tremors in rats. Values are mean±S.E.M. *P<0.001 as compared to harmaline alone treated animals and $^{\#}P$<0.001 as compared to pCPA and harmaline treated animals using ANOVA followed by Dunnett's test. Hm—Harmaline; Imp—Imipramine 60 and 90 mg/kg respectively pCPA—*P*-chlorophenylalanine.

Table 1
Effect of acute imipramine on harmaline (10 mg/kg) and *P*-chlorophenylalanine and harmaline induced changes in the levels of 5HT, 5HIAA and 5HIAA/5HT ratio in the brain stem of rats

Treatment	5HT	5HIAA	5HIAA/5HT
Control	0.693±0.037	0.819±0.098	1.165±0.091
Hm 10 mg/kg	1.268±0.076**	0.514±0.090**	0.395±0.063**
Imp 60 mg/kg	0.663±0.023	0.623±0.060	0.943±0.093
Imp 90 mg/kg	0.709±0.024	0.608±0.054	0.856±0.071*
Hm+Imp 60 mg/kg	1.235±0.079	0.319±0.034	0.256±0.020
Hm+Imp 90 mg/kg	1.106±0.047	0.306±0.020***	0.277±0.0169
Pcp 300 mg/kg	0.107**±0.01	0.044**±0.006	0.41**±0.02
Pcp 300 mg/kg+Hm	0.10±0.011	0.01±0.002****	0.16±0.048****
Pcp+Imp 60 mg/kg+Hm	0.09±0.009	0.02±0.005***	0.20±0.048***
Pcp+Imp 90 mg/kg+Hm	0.11±0.007	0.02±0.003****	0.17±0.02****

Hm—Harmaline (10 mg/kg), Imp—Imipramine, Pcp—*P*-chlorophenylalanine. Each value represents mean±S.E.M. of 5–6 rats.
* $P<0.05$ as compared to control.
** $P<0.001$ as compared to control.
*** $P<0.05$ as compared to Pcp alone treatment by using ANOVA followed by Dunnett's *t* test.
**** $P<0.005$ as compared to Pcp alone treatment by using ANOVA followed by Dunnett's *t* test.

(Welsh et al., 2002). 5HT is a very powerful suppressor of the rhythmic activity of the inferior olive. It acts at multiple subcellular elements to suppress the rhythmic activity of olivary neurons and blocks both subthreshold oscillations and rythmicity of action potentials of inferior olivary neurons (Placantonakis et al. 2000). Without 5HT, olivary neurons are predisposed to oscillate continuously leading to unconstrained rhythmicity resulting in synchronized body tremor (Welsh et al., 2002). Involvement of 5HT in the etiology of tremor is further supported by the fact that agonists of 5HT exacerbate chemically induced tremors (Mehta et al., 2001; Mohanakumar et al., 1990). Treatment of animals with 5HT precursors, L-tryptophan and 5-hydroxy tryptophan produce a typical behavioral syndrome termed as 'serotonergic syndrome'. This syndrome is characterized by tremor, fore paw treading, head weaving and flat body posture (Abdel Fattah et al., 1996, 1997; Biegon et al., 1979). Chlorimipramine, a close derivative of imipramine has also been shown to potentiate 5HT syndrome (Modigh, 1973). We have recently reported augmentative effect of citalopram, a 5HT uptake inhibitor in harmaline-induced tremor (Arshaduddin et al., 2004). Thus, the increased level of serotonin in synaptic cleft due to inhibition of its uptake may lead to uncontrolled rhythmic firing of neurons. Since the therapeutic effect of imipramine is mainly attributed to the inhibition of 5-hydroxytryptamine and noradrenaline uptake in brain (Baldessarini, 2001; Maj et al., 1998), augmentation of harmaline-induced tremor by imipramine may thus be attributed to the altered 5HT and norepinephrine (NE) turnover in the brain.

A decrease in the intensity and duration of harmaline-induced tremor was observed in PCPA pretreated rats (Figs. 1–3). Mehta et al. (2003) also observed inhibition of harmaline-induced tremor in 5HT-depleted rats thus confirming the role of 5HT in the genesis of this motor neuronal dysfunction. Although, imipramine significantly exacerbated harmaline tremor in 5HT depleted (PCPA treated) rats, the intensity and duration of the tremor was significantly less as compared to non-5HT depleted animals. Besides 5HT, a role of NE in the pathophysiology of tremor has also been described by several investigators in humans (Cleeves and Findley, 1988; Rajput et al., 2001) as well as experimental animals (Agarwal and Bose, 1967; Paul, 1986). NE is metabolized primarily by monoamine oxidase type A (Hardebo and Owman, 1980). Since both harmaline (Bucholtz and Boggan, 1977; Gerardy, 1994; Kim et al., 1997) and imipramine (Egashira et al., 1999; Gnerre et al., 2001) have been shown to inhibit monoamine oxidase and may increase the level of NE along with 5HT in synaptic cleft, the augmentation of harmaline-induced tremor by imipramine may be attributed to their additive effect on the bioavailability of NE.

In conclusion, the results of this study suggest that imipramine potentiates harmaline-induced tremor in rats. This synergistic effect to some extent may be attributed to the ability of this agent to interfere with 5HT and NE pathways. The results of this study also suggest a close monitoring of ET patients who are receiving tricyclics for depression therapy.

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