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Metoclopramide attenuates iminodipropionitrile-induced oxidative stress and neurobehavioral toxicity in rats

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Abstract

Metoclopramide (MET) has long been used as a neuroleptic and antiemetic drug in clinical practice. Motor impairment and dyskinesia have been reported in some patients following chronic treatment with MET. Occasionally, the adverse symptoms may appear even after acute exposure to MET in more susceptible population (such as elderly individual) or due to concomitant exposure to MET and certain neurotoxins. Iminodipropionitrile (IDPN), a prototype nitrile toxin, has been shown to produce dyskinetic syndrome in rodents. This study reports the effect of concomitant exposure of rats to MET and IDPN on behavioral abnormalities in rats namely excitation, circling and chorea (ECC) syndrome. Four groups of female Wistar rats (aged 3 months) were given MET (0, 10, 40 and 80 mg/kg, i.p., for 11 days) 30 min before IDPN (100 mg/kg, i.p. for 8 days). Two additional groups of rats were treated with either saline (control group) or 80 mg/kg of MET (drug alone group). The animals were observed for neurobehavioral abnormalities including dyskinetic head movement, circling, tail hanging, air righting reflex and contact inhibition of righting reflex. Horizontal and vertical locomotor activities and fore limbs grip strength were also measured. On day 12, the animals were sacrificed and brains were collected for biochemical analysis. MET significantly and dose-dependently protected the animals against IDPN-induced ECC syndrome, motor impairment and deficiency in grip strength. MET also protected the animals against IDPN-induced oxidative stress.

Keywords: Drug-induced dyskinesia; Neurotransmitters; Free radicals; Oxidative stress

1. Introduction

Adverse interactions between environmental neurotoxins and drugs have been reported by several investigators (Al Deeb et al., 2000; Gao et al., 2003; Llorens and Crofton, 1991; Miller et al., 1991; Noraberg and Arlien-Soborg, 2000; Tang et al., 2003; Tariq et al., 1998). The nitriles are extensively used for the manufacture of synthetic fibers, resins, plastics, dye stuffs and pharmaceuticals, hence, their occupational and environmental exposure is considered to be of potential relevance to human health (Ahmed and Trieff, 1983; Bergmark, 1997; Guirguis et al., 1984; Perbellini et al., 1998). Exposure to propionitrile and dimethylaminopropionitrile may lead to neurobehavioral abnormalities in humans (Scolnick et al., 1993; Spencer and Schaumburg, 1983), whereas, iminodipropionitrile (IDPN), crotonitrile, allylnitrile and acrylonitirle have been shown to produce motor deficits in experimental animals (Gagnaire et al., 1998; Llorens et al., 1993a; Tanii et al., 1989, 1991).

Exposure of rats to the prototype nitrile compound, IDPN, produces a permanent syndrome of motor abnormalities (Al Deeb et al., 2000; Llorens et al., 1993a, 1994; Tariq et al., 1995a,b, 1998, 2002). This syndrome has been designated as excitation, circling and chorea (ECC) syndrome (Selye, 1957). IDPN-induced ECC syndrome is characterized by repetitive head movements, retropulsion, circling, back walking, hyperactivity and swimming deficits (Delay et al., 1952; Selye, 1957). The mechanism of IDPN induced neurotoxicity is complex and multifactorial. Several

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investigators have suggested the role of various neurotransmitters/neuromodulators (Cadet et al., 1987a,b; Gianutsos and Suzdak, 1985; Ogawa et al., 1991; Tariq et al., 1995a, 1998) and oxygen-derived free radicals (Lohr et al., 1988; Tariq et al., 1995a,b, 2002) in IDPN-induced neurotoxicity. However, Llorens et al. (1993a, 1994) have observed a direct correlation between vestibular sensory hair cells degeneration and the severity of IDPN-induced ECC syndrome.

Metoclopramide (MET) is a neuroleptic/antiemetic drug with antagonistic effects on both dopamine (Drew and Glick, 1990; Plaznik et al., 1989) and 5-HT receptors (Li et al., 2000; Takenouchi and Munekata, 1998). Furthermore, several neuroleptics including MET are able to exert antioxidant and/or pro-oxidant action in vivo (Jeding et al., 1995). Administration of MET has been reported to cause tardive dyskinesia and extrapyramidal movement disorders in humans (Ganzini et al., 1993; Sewell et al., 1994). On the other hand, MET has been shown to attenuate drug-induced movement disorders including backward walking (Axon et al., 1987), head twitching (Dall'Olio et al., 1988), circling (Drew and Glick, 1990; Hassan et al., 1986), hyperactivity (Cabib et al., 1991; Chagraoui et al., 1989; Molloy et al., 1986; Robertson and MacDonald, 1985) and stereotypy (Frussa-Filho and Palermo-Neto, 1988; Hassan et al., 1986; Robertson and MacDonald, 1985) in rodents. It is clear from the above literature that both IDPN and MET affect neurotransmitters, alter oxidative stress level in vivo and have potential to interfere with neurobehavior. Neurotoxic effect of both MET (Ganzini et al., 1991) and IDPN (Khan et al., 2003) enhances with age. This investigation was aimed to study the interaction between these two drugs (MET and IDPN) on the resulting movement disorders in rats.

2. Materials and methods

2.1. Animals and drugs

Adult female Wistar rats, approximately 3 months old, weighing 190–215 g were housed in a temperature-controlled room and maintained on 12-h light/dark cycles, with free access to food and water. The development of IDPN-induced ECC syndrome in female rats is more gradual and reproducible as compared to males where the symptoms appear quite abruptly (Moser and Boyes, 1993; Al Deeb et al., 2000). Therefore, female rats were preferred for this study. The protocol of animal studies was approved by Research and Ethical Committee of Armed Forces Hospital, Riyadh, Saudi Arabia. IDPN (Aldrich Chemical, Milwaukee, WI) and MET (Sigma, St. Louis, MO) were dissolved in normal saline (McGraw, USA) and administered intraperitoneally in the volume of 2 ml/kg body weight of animals.

2.2. Dosing and testing

The animals were divided into six groups of eight animals each. The rats in group 1 served as control and received vehicle only, whereas, rats in groups 2, 3, 4 and 5 received MET (0, 10, 40 and 80 mg/kg, i.p.) 30 min before IDPN (100 mg/kg, i.p.), respectively. The animals in group 6 were treated with MET (80 mg/kg) without IDPN, and this group served as MET alone group. The doses of MET (Chagraoui et al., 1989; Wirtshafter and Asin, 1995; Herman and Huzarska, 1993) and IDPN (Al Deeb et al., 2000; Tariq et al., 2002) were selected on the basis of earlier studies in rodents. IDPN was administered daily for 8 days (onset of at least one symptom of ECC syndrome, appeared on 9th day), whereas the treatment of MET was continued till day 11 (until well-developed ECC syndrome in one of the groups).

2.3. ECC Syndrome

Each rat was examined for the presence or absence of the following signs: circling, dyskinetic head movements, tail hanging, air righting reflex and contact inhibition of the righting reflex using previously published behavioral testing battery (Al Deeb et al., 2000). The animals were observed for a period of 2 min to assess the severity of dyskinetic head movements and abnormal circling behavior, whereas the tail hanging and the righting reflexes were tested at least three times for each animal for the grading of their severity (Al Deeb et al., 2000).

2.3.1. Dyskinetic head movements and circling

The animals were placed individually in an observation chamber (50×50 cm), and were observed for dyskinetic head movements (head weaving) and circling for a period of 2 min.

2.3.2. Tail hanging

The rat was lifted by the tail and the response was carefully observed and rated as follows: 0=straight body posture with extension of forelimbs towards the ground (normal), 1=slightly bending the body ventrally (intermediate response), and 2=persistently bending the body, sometimes crawling up towards its tail (severe response).

2.3.3. Air righting reflex

The animal was held supine and dropped from a height of 30–40 cm onto a foam cushion. The response was graded as follows: 0=successful in righting and landing squarely on their feet (normal), 1=poor righting or landing on side (intermediate response), and 2=completely failed in righting and landing on back (severe response).

2.3.4. Contact inhibition of righting reflex

The rat was placed supine on a horizontal surface, and another horizontal surface was slightly placed in contact

with the soles of the supine animal's feet. The rating was performed as follows: 0=animal rights successfully (normal), 1=partial righting, animal does some efforts (intermediate response), and 2=complete loss of righting, animal is facing up the feet and walking with respect to the upper surface (severe response).

2.4. Motor activity

Motor activity was measured using an Optovarimex activity meter (Columbus Instruments, USA). The horizontal motor activity was detected by two perpendicular arrays of 15 infrared beams located 2.5 cm above the floor of the testing area. Each interruption of a beam on *X*- or *Y*-axis generated an electric impulse, which was presented on a digital counter. Similarly the vertical motor activity was recorded using two additional rows of infrared sensors located 12 cm above the floor. Each animal was tested separately and the motor activity was measured for a period of 2 min.

2.5. Grip strength

Fore limbs grip strength was measured using a grip strength meter (UGO Basile, Italy) consisted of a grasping-trapeze attached to a force transducer (Model 7105), peak amplifier (Model 7108) and multifunction printer (Model 2650). After adjusting the height of the grasping trapeze, the animal was allowed to grasp the trapeze and then was pulled by the tail. The peak pulling force (grip strength) was recorded from the digital display on the amplifier.

2.6. Biochemical studies

After behavioral studies on day 12, the rats were sacrificed and cerebrums were isolated from brains for biochemical analysis. Prior to homogenization in a Teflon homogenizer, whole cerebrum was thoroughly minced using a sharp scalpel. The choice of cerebrum for biochemistry was based on earlier studies reporting the effects of IDPN (Al Deeb et al., 2000; Tariq et al., 2002; Llorens et al., 1993b) and MET (Wirtshafter and Asin, 1995; Chang et al., 1988; May and Wightman, 1989; Watson et al., 1992) either on whole cerebrum or regions within the confines of cerebrum.

2.6.1. Analysis of lipid hydroperoxides

The level of lipid hydroperoxides in brain was measured according to the method described by Handelman et al. (1988). Pre-minced cerebral tissue (20–50 mg) was homogenized with 1 ml of ethanol containing 1.2% pyrogallol at 4 °C using a Teflon homogenizer. The homogenate was saponified by adding 150 μl of 10 M potassium hydroxide and acidified to pH 3 using 1 M hydrochloric acid, and extracted with 3 ml of *n*-hexane. One-milliliter aliquot of the *n*-hexane extract was evaporated under nitrogen and reconstituted with 1 ml of a mixture of glacial acetic acid and chloroform (3:2). One hundred microliters of 0.6 g/ml potassium iodide solution was added and the tubes were kept in the dark for 5 min, followed by the addition of cadmium acetate (3 ml of 0.5% solution) and centrifugation. The upper layer was collected and absorbance was read at 353 nm for lipid hydroperoxides determination.

2.6.2. Analysis of α-tocopherol

The levels of vitamin E in cerebrum were analyzed using high performance liquid chromatography (Dexter et al., 1992). Pre-minced cerebral tissue (50 mg) was homogenized using a Teflon homogenizer in a tube containing 1 ml of Tris Buffer (50 mM, pH 7.6) and 3 ml of 1.5% ethanolic pyrogallol. The homogenate was incubated at 70 °C on water bath for 5 min and 150 μl of 10 M potassium hydroxide was added to each tube and further incubation (70 °C) was done for 30 min. The mixture was cooled to room temperature and extracted with 2 ml of hexane. The organic layer was separated after centrifugation and the aqueous homogenate was further extracted with another 2 ml of hexane. The two hexane extracts were combined and evaporated under nitrogen and stored at −70 °C for future analysis.

The HPLC instrument from Waters Associate, Meliford, USA consisted of a solvent delivery pump Model 510, autoinjector Model 712, UV–Visible detector Model 481 and Integrator Model 740. The column was μBondapak C-18 (3.9×150 mm) made of stainless steel. The mobile phase consisted of 95% of chromatography grade methanol in deionized water. All chromatography was carried out at room temperature. The flow rate of mobile phase was adjusted at 1.5 ml/min and the absorbance was measured at 280 nm following a 60-μl injection. The levels of vitamin E were calculated by using a calibration curve.

2.7. Statistics

The incidence of ECC syndrome was evaluated by χ^2 test using EPI-INFO computer software. The results of severity scores of ECC syndrome were analyzed by repeated measures analysis of variance (RM-ANOVA). One-way ANOVA was used to analyze the results of motor activity, grip strength and biochemical parameters using statistical software SPSS version 10. Dunnett's multiple comparison tests determined the significance level between the groups. A value of $P<0.05$ was considered as statistically significant.

3. Results

3.1. ECC syndrome

The signs of ECC syndrome were first noticed in one out of eight rats in IDPN alone group on day 9 and 100%

Table 1
Effect of metoclopramide (MET) on the incidence and severity of IDPN-induced behavioral syndrome in rats

Groups (n=8 per group)	Days			
	9	10	11	12
Incidence of behavioral syndrome (%)				
Control	0.0	0.0	0.0	0.0
MET 80	0.0	0.0	0.0	0.0
IDPN	12.5	37.5	100.0$^{\#\#}$	100.0$^{\#\#}$
IDPN+MET 10	0.0	25.0	50.0*	75.0
IDPN+MET 40	0.0	12.5	37.5**	62.5
IDPN+MET 80	0.0	0.0	0.0***	25.0**
Severity score (mean±standard error)				
Control	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
MET 80	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
IDPN	0.37±0.37	2.62±1.37$^{\#}$	8.12±0.61$^{\#\#}$	8.50±0.65$^{\#\#}$
IDPN+MET 10	0.00±0.00	0.62±0.42	3.87±1.55**	5.75±1.51**
IDPN+MET 40	0.00±0.00	0.25±0.25*	2.37±1.19***	4.25±1.31***
IDPN+MET 80	0.00±0.00	0.00±0.00*	0.00±0.00***	1.50±1.00***

* P<0.05 versus IDPN alone group.
** P<0.01 versus IDPN alone group.
*** P<0.001 versus IDPN alone group.
$^{\#}$ P<0.001 versus control.
$^{\#\#}$ P<0.05 versus control.

of the rats in this group became dyskinetic on day 11 (Table 1). Co-treatment with MET dose-dependently delayed the onset and significantly reduced the incidence and severity of IDPN-induced ECC syndrome (RM-ANOVA F=4.245, P<0.001). Repeated measures analysis for within-subjects (RM-ANOVA F=8.034, P<0.001) and between subjects (RM-ANOVA F=15.878, P<0.001) showed significant effect of time (days 9, 10, 11, 12) and treatments (doses of MET), respectively, on IDPN-induced ECC syndrome (Table 1).

3.2. Motor activity

Administration of IDPN did not affect horizontal motor activity but significantly reduced vertical (rearing) motor activity (ANOVA F=10.20, P<0.0001) (Table 2). Concomitant treatment with MET dose-dependently reduced IDPN-induced motor impairment in vertical activity.

Table 2
Horizontal and vertical locomotor activities and forelimbs grip strength of rats in different treatment groups

Groups (n=8 per group)	Horizontal activity (counts/2 min)	Vertical activity (counts/2 min)	Grip strength (gram force)
Control	1112.88±50.59	59.13±10.89	359.63±22.97
MET 80	1229.62±49.24	67.38±12.30	365.63±21.36
IDPN	1206.63±144.2	7.38±2.69$^{\#\#}$	264.88±20.79$^{\#}$
IDPN+ MET 10	1223.75±87.30	18.88±5.66	299.87±21.22
IDPN+ MET 40	1030.25±59.56	18.38±3.68	329.00±17.48
IDPN+ MET 80	1094.88±48.71	25.75±5.17	341.75±20.10*

* P<0.05 versus IDPN alone group using Dunnett's multiple comparison test. Values are mean±standard error.
$^{\#}$ P<0.01 versus control.
$^{\#\#}$ P<0.001 versus control.

3.3. Grip strength

A significant decrease in fore limbs grip strength was observed in IDPN alone treated rats (Table 2). Administration of MET significantly and dose-dependently attenuated IDPN-induced deficiency in the grip strength (ANOVA F=3.43, P<0.05).

3.4. Cerebral vitamin E

There was a significant depletion of cerebral vitamin E following IDPN treatment (ANOVA F=3.42, P<0.05) (Fig.

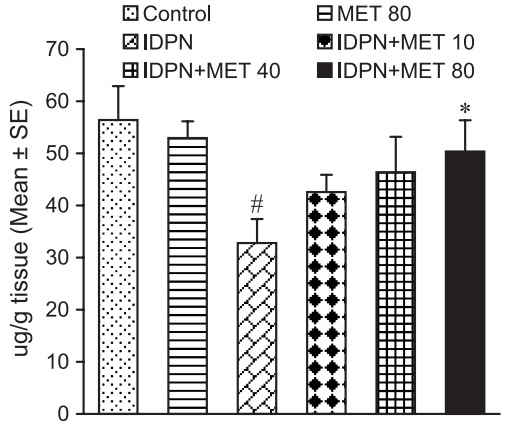

Fig. 1. Effect of metoclopramide (MET) on cerebral vitamin E levels in control and IDPN-treated rats (n=8 per group). $^{\#}P$<0.05 versus control and *P<0.01 versus IDPN alone group using Dunnett's multiple comparison test.

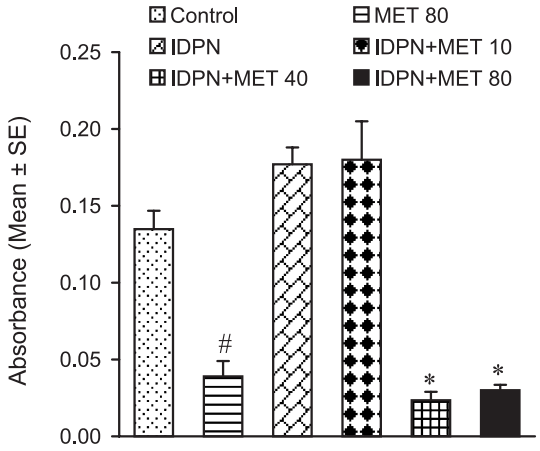

Fig. 2. Effect of metoclopramide (MET) on cerebral lipid hydroperoxides in control and IDPN-treated rats (n=8 per group). $^{\#}P$<0.01 versus control and *P<0.001 versus IDPN alone group using Dunnett's multiple comparison test.

1). Administration of MET dose-dependently reversed the effects of IDPN on cerebral vitamin E (Fig. 1).

3.5. Cerebral lipid hydroperoxides

Administration of IDPN had no significant effect on cerebral lipid hydroperoxides whereas, MET (80 mg/kg) alone significantly decreased their levels (ANOVA F=18.91, P<0.0001). Co-treatment with 40 mg/kg and 80 mg/kg MET significantly reduced cerebral lipid hydroperoxides in IDPN-treated rats (Fig. 2).

4. Discussion

The results of behavioral studies clearly showed the protective effect of MET on IDPN-induced ECC syndrome (Table 1), motor impairment and deficiency of grip strength (Table 2). The mechanism by which MET attenuates IDPN-induced ECC syndrome is far from clear. The results of biochemical studies showed a significant depletion of cerebral vitamin E (Fig. 1) in IDPN-treated rats suggesting the excessive generation of oxygen-derived free radicals (ODFR). Enhanced formation of highly reactive hydroxyl radicals ($OH^{\cdot}$) has been implicated in IDPN-induced neuronal damage (Wakata et al., 2000). The brain is particularly sensitive to oxidative damage because of its high concentration of polyunsaturated fatty acids, high rate of oxygen consumption, higher iron levels, and poor antioxidant defense system (Olanow, 1992). The free radical oxidation of unsaturated fatty acids results in the formation of conjugated dienes that further react with O_2 to produce peroxy radicals ($ROO^{\cdot}$) leading to the propagation (chain reaction) of lipid peroxidation. The $ROO^{\cdot}$ radicals combine with hydrogen atoms to give lipid hydroperoxides (ROOH). On the other hand, vitamin E is a nonenzymatic antioxidant present in biological membranes that acts by terminating the propagation of ODFR-generated chain reaction (Van Acer et al., 1993). The oxidative stress results when pro-oxidative ODFR overwhelm the antioxidant defense mechanism, often leading to irreversible loss of cell viability (Sies, 1985). Pretreatment of animals with ODFR scavengers (Lohr et al., 1988; Tariq et al., 1995b) and vasodilators (Tariq et al., 1995a, 2002) has been shown to protect rats against IDPN-induced neurotoxicity. MET is a powerful scavenger of hydroxyl free radical (Jeding et al., 1995). Furthermore, IDPN-induced neurotoxicity is also associated with cerebrovascular impairment leading to ischemia and hemorrhage (Fiori et al., 1985; Schneider et al., 1980). MET has been shown to protect rats against ischemia (Chiou and Li, 1993) and hemorrhage (Jarrar et al., 2000; Zellweger et al., 1998). Thus, a reduction in oxidative stress (Figs. 1 and 2) and improvement of cerebral perfusion may account for MET-induced protection against IDPN toxicity.

The role of dopamine (DA) and serotonin (5-HT) in IDPN-induced ECC syndrome has been suggested by several investigators (Cadet et al., 1987a, Iida et al., 1998; Langlais and Gabay, 1977; Ogawa et al., 1991). Both DA and 5-HT are localized not only in the central nervous system (Cadet et al., 1987b; Dawson et al., 1998; Gianutsos and Suzdak, 1985) but also in the vestibular labyrinth (Gil-Loyzaga et al., 1997; Hozawa and Takasak, 1993). Whereas, antagonists of DA (Cadet et al., 1987a; Ogawa et al., 1991) and 5-HT (Diamond et al., 1986; Green, 1984) have been shown to attenuate IDPN-induced ECC syndrome. MET has antagonistic effects on both dopamine (Drew and Glick, 1990; Plaznik et al., 1989) and 5-HT receptors (Li et al., 2000; Takenouchi and Munekata, 1998). Thus, the attenuation of IDPN-induced behavioral syndrome by MET may be attributed to its potential antagonistic effects on DA and 5-HT receptors.

Furthermore, the possibility that MET interferes with the pharmacokinetics or metabolism of IDPN may not be ruled out. The antiemetic and gastroprokinetic effects of MET (Scarpignato, 1997; Desta et al., 2002) may affect IDPN absorption from the intraperitoneal cavity causing altered bioavailability of IDPN. It is also known that IDPN needs to be metabolized to a toxic metabolite to exert its neurotoxic effects (Nace et al., 1997). Drugs such as methimazole (Nace et al., 1997) or carbon tetrachloride (Llorens and Crofton, 1991), which interfere with IDPN metabolism, have been shown to significantly affect IDPN toxicity. MET is a potent inhibitor of CYP2D6 (Desta et al., 2002) that may have some implication in MET-induced attenuation of IDPN toxicity.

In conclusion, this study clearly showed the protective effect of MET against IDPN-induced neurotoxicity. Inhibition of oxidative stress and/or antagonism of DA and 5-HT receptors by MET may account for this neuroprotection.

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