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DESENSITIZATION OF METHYLPHENIDATE – INDUCED BEHAVIORAL SENSITIZATION IN RATS TREATED WITH MODAFINIL

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ABSTRACT

Behavioral sensitization is the phenomenon described as the repetitive, infrequent drug administration that leads to a progressive increase in a response to that drug over time and defined as augmented locomotion. Behavioral sensitization can smoothly be measured in animals by defining alternation in their locomotion in a drug response. Methylphenidate is an inhibitor of dopamine transporter and profound for the therapeutics of associated with attention deficit hyperactivity, but it has been reported that long term usage can cause addiction and dependency. It develops locomotor sensitization. Modafinil is an innovative agent that promotes attentiveness and alertness. It localized wakefulness areas concerning drug-induced neuronal activation via an action on oradrenergic neurotransmission. This preclinical work was intended in order to explore the consequences of agents like modafinil pretreatment on methylphenidate influenced behavioral sensitization. The results determined that doses 1, 2 and 4 mg/kg of methylphenidate produce an induction in activity in an activity box and open field as antidepressant-like effect and reduction of anxiogenesis novel environment. Further modafinil pretreatment for two weeks followed by daily co treatment of methylphenidate prevents locomotor sensitization in laboratory animals. Results obtained demonstrated that the increase of modafinil-induced behavioral sensitization is independent on direct neuro adaptive variations in D1 and D2 dopaminergic receptors. This study, therefore establish the correlation between methylphenidate and modafinil and their effect on locomotor sensitization in rats.

Keywords: Behavioral Sensitization, Methylphenidate, Modafinil, Locomotion, Dopaminergic Receptors.

INTRODUCTION

Behavioral sensitization is described as repetitive, irregular drug administration that leads to a progressive increase in a response to that drug over time (Post, 1980; Post and Rose, 1976; Robinson, 1993; Segal and Mandell, 1974). Tolerance is a common physiological response to chronic drug management that is, drug effects commonly reduced with repetitive usage, requiring increasing drug dose to reach the same endpoint (Ramsay and Woods, 1997). Body adapts drug-induced changes by triggering responses that bring all transformed parameters back toward the pre-drug level. The vital principle of homeostasis is these adaptations. The contradictory response pattern occurs regarding sensitization whereby the body's reaction increases with the same dose of drug, or each time involves less drug to reach the same endpoint. This phenomenon seems to be in desecration of homeostatic codes. Behavioral sensitization is dissimilar phenomenon from tolerance, in fact, profligate and non-adaptive (Woods and Ramsay, 2000).

Behavioral sensitization is described as increased in speed, amount and organization of locomotor activity in laboratory animals (Segal and Mandell, 1974). By investigating variations in their induced locomotor activity, behavioral sensitization can smoothly be measured in rodents in response to a drug. Locomotor activity is a consistent and measurable index to quantify sensitization (increased reacting) over the course of drug treatment as it is effortlessly measured in activity observers and demonstrates that a change in behavior has occurred (Eilam and Szechtman, 1989; Einat and Szechtman, 1993).

Methylphenidate is a dopamine transporter inhibitor and used as therapeutic agent for ADHD (attention deficit hyperactivity disorder), however, chronic usage is often reported compulsion and dependence. Methylphenidate develops locomotor sensitization which is a primary effect of drug abuse manifested by psychostimulants. Dopaminergic neurotransmission enhances in the region of brain, neocortex by Methylphenidate (Berridge *et al.*, 2006). It inhibits the dopamine transporter (Ferris and Tang., 1979; Kollins *et al.*, 2001; Barrett*et al.*, 2005) thus increases extra cellular concentration of dopamine and this act initiates molecular episode that strengthens drug seeking behavior, eventually concluding in addiction (Teter *et al.*, 2006; Alizadeh and Ghabili, 2008).

It is reports that the acute dose of Methylphenidate produces hyperactivity in rodents which further sustained with its repeated administration (Castellanos and Tannock. 2002; Rubia *et al.*, 2010; Schecklmann *et al.*, 2010). It has been observed that the behavioral sensitizationis mainly associated with the metabolism of dopaminergic system (Kalivas *et al.*, 1993a, 1993b).The consumption history of psycho stimulant was directly correlated with dopamine release, suggesting an augmented response of dopamine with recurrent use of drug (Cox *et al.*, 2009). For the varied physiological functions regulation, the stimulation of D2 dopamine receptor is critical, like control of locomotor activity (Picetti *et al.*, 1997). Serotonergic neurotransmission has been seen to reduce the effect dopaminergic action in different brain regions like the mid brain and the terminal region (Haleem, 2006).

Modafinil (MOD) is a novel agent promotes surveillance and has been recommended for the treatment of narcolepsy daytime sleepiness by U.S.A (Food and Drug Administration) FDA for. MOD has been considered as an atypical central stimulant compound (Edgar and Seidel, 1997), and is categorized present lyas a Schedule IV controlled substance. As the usage of MOD for nonmedical purposes is being prolonged, it has been considered essential to have additional control of the abusive prospective of this drug. Psycho-activity of MOD is advanced than that of caffeine. Whereas, abused psycho-stimulants, for example, cocaine and amphetamine have more the addictive potential than that of MOD (Dackis *et al.*, 2005; Jasinski, 2000; Karila *et al.*, 2008). The pecific mechanism of this MOD is still unknown despite the escalating clinical indications. By using in vivo and in vitro studies, Number of evidences reported modulation of multiple neurotransmitter systems such as serotonin, catecholamines, glutamate, GABA, histamine and orexine and others are the possible mechanismfor the action of modafinil (Ballon and Feifel, 2006; Wisor and Eriksson, 2005). It has been widely seen that MOD, rather than amphetamine, is more localized in the wakefulness regionsin terms of drug-induced neuronal activation (Scammell *et al.*, 2000).

Many experiments suggest that modafinil stimulates waking via an action on noradrenergic neurotransmission. Certainly, the waking effect of modafinil in cats, mice, and monkeys is prevented or attenuated by pretreatment with α 1 or β antagonists (Battisti *et al*., 1999; Deroche-Gamonet *et al.*, 2002). Modafinil could also induce waking by its action on dopamine transmission. Indeed, it demonstrates weak affinity for the dopamine transporter (DAT)and does not enhance waking in mice with deletion of the DAT gene (Edgar and Seidel, 1997). Modafinil does not induce abnormal behavior alteration, tolerance, sensitization, or reinforcing properties unlike psychostimulants such as amphetamine and methylphenidate that act on dopamine neurotransmission (Chen*et al.*, 2007; Engber *et al.*, 1998). Moreover, modafinil is well demonstrated to induce wakefulness without escalating locomotor activity or consequent hyper-somnolence rebound (Ferraro*et al*., 1996; Goeders, 2003). Therefore, the purpose of the present study was to investigate the effects of pretreatment with modafinil in rats showing methylphenidate induced behavioral sensitization.

METHODS

Animals

The study was conducted on male rats (Albino Wistar), weight of 160±10 grams, were acquired from The Dow University of Heath Sciences Karachi, Pakistan (DUHS). Animals were allowed to acclimatize with their surroundings in individual cages for one week in controlled environment. Animals had free access to normal standard diet and drinking water during this period.

Drugs

Methylphenidate–HCl (Sigma, St Louis, Missouri, USA) was prepared in saline daily before injection and freshly prepared drug were injected in animals subcutaneously. Control animals were administrated with saline (1.0 ml/kg) whereas test animals were administrated with Modafinil, (dissolved in saline) orally (100mg/kg/day).

Experiment # 1: Study of Effects of Methylphenidate on Motor Activity in Rats.

Effects of methylphenidate on motor behavior at dose (1.0, 2.0, and 4.0 mg/kg) were find out in familiar and novel environment test was performed to determine a specific dose that induced a sub-maximal increase in motor activity and can be used to monitor behavioral sensitization and its modulation by modafinil. Animals of respective groups (n=6) were injected subcutaneously with saline or drug. The behavior in an activity cage was monitored for 10 min (5min post-injection) and open-field activity was monitored for 5 min (30 min post-injection); in the period between the two tests (15 min), animals were kept in their home cages.

Experiment # 2: MPD Sensitization in MOD Pre-Treated Animals.

Twenty four rodents with an average weight (160±10) were randomly divided into two equal groups, each groups was contained 12 rats: (a) saline, (b) 100 mg/kg/day modafinil, injected groups. Saline or modafinil was

administered orally at 10:00–11:00 h in the morning. Modafinil administration lasted for 7 days, during which locomotor activity in familiar and novel area was monitored on next day 1st and 7th day of administration. Subsequently, modafinil and methylphenidate (1.0 mg/kg) co-treatment was started on day 9. Animals of each group divided randomly into saline-injected or methylphenidate- injected subgroups were injected accordingly at 11:00–12:00 h immediately after administration of saline or modafinil for next 7 days. Motor activity in was monitored after 24 hrs of of 1st and 7th day of methylphenidate or saline administrations.

Experiment #3: Expression of MPD Sensitization in MOD-Treated Animals

Rats were divided into four groups(eight rats in each group): (a) saline, (b) methylphenidate, (c) modafinil and methylphenidate, and (d) modafinil pre-treated before co-treatment with modafinil and methylphenidate. Animals in the modafinil-pretreated group were administrated with modafinil (100 mg/kg)for 7 days. The other three groups received with saline pretreatment during this period. Subsequently, various groups were treated accordingly with saline, methylphenidate (1.0 mg/kg), or methylphenidate (1.0 mg/kg) plus modafinil (100 mg/kg) daily for 7 days. On 7th day, all groups were injected with methylphenidate (1.0 mg/kg) at 09:00–10:00 h to monitor motor activity in an activity cage (5 min post-injection) and open field (30 min post-injection).

ACTIVITY MONITORING

a. ACTIVITY CAGE TEST (HOME CAGE)

The motor behavior of animal in a familiar environment was assessed by activity box test Activity box was a Perspex square shaped cage of equal dimensions like 26 x 26 x 26 cm. The apparatus floor is bedded with saw dust. Animal was observed in a quiet room under white light. Rats were placed in the activity box for 15 minutes for habituation. Activity was monitored in terms of number of crossing across the cage in all direction with the cutoff time 10 minutes.

b. OPEN FIELD ACTIVTY TEST

To determine the activity of animal in novel environment, open field activity apparatus was used, from which escape is prevented by the surrounding wall. The apparatus of open field used in this experiment was made up of transparent Plexiglas having square area of dimensions 76 x 76 cm with opaque walls of 42 cm height. The floor of the apparatus is divided by lines drawn on the floor into 25 equal squares. For the determination of activity animal was allowed to place in the center squarepart of the apparatus. The time required by rats to move from the center of the apparatus was monitored and the activity (number of square crossed with all four paws) was monitored for 5 minutes.

Statistical analysis

Data on dose-dependent effects of methylphenidate on activity in the activity cage or open field and on methylphenidate induced hyper-locomotion in repeated saline, repeated methylphenidate, and repeated methylphenidate plus modafinil-injected animals were examine by One-Way (ANOVA) SPSS version 15.0.Data on the activity of modafinil administrations for 7daysdetermined by two-way ANOVA (repeated-measures) ANOVA. Data of methylphenidate administration with modafinil and saline pretreated rats were analyzed by three-way repeated-measures ANOVA. For to perform Post-hoc analysis Newman-Keuls test was used.

RESULTS

Figure 1 explains the effect of repeated doseof methylphenidate (1.0mg/kg) onmotor activity in an activity box as well as in open field of Albino-Wister rats. Results of the data(a) on number of cage crossed by one-way ANOVA was showed significant effects of methylphenidate administration ($F=33.125$; $df=3, 20$; $p < 0.01$).Post-hoc analysis by Newman-Keuls test showed that administration of methylphenidate increased the activity in activity box (number of cage crossing) significantly ($p < 0.01$) at all doses 1.0, 2.0 and 4.0 mg/kg as compared to saline injected controls. Analysis of the data (b) on number of square crossed in open filed by one-way ANOVA (repeated measure designing) showed significant effects of methylphenidate ($F=23.669$; $df=3, 20$; $p < 0.01$) on number of square crossed in open field test. Post-hoc analysis by Newman-Keuls test showed that methylphenidate administrated at dose 1.0, 2.0 and 4.0 mg/kg greater the number of square crossings significantly ($p<0.01$) as compared to saline injected controls.

Figure 2 explains the effects of repeated dose of modafinil (100 mg/kg) on activity in a cage box and an open field of male Albino-Wister rats monitored on next day of 1st and 7th day of administrations. Analysis of the data (a)

on number of cage crossed by two-way ANOVA (repeated measure designing) showed significant effects of repeated monitoring ($F=54.33$; $df=1, 22$; $p < 0.01$), effects of modafinil administration ($F=84.26$; $df=1, 22$; $p < 0.01$) and interaction between repeated monitoring and modafinil administration ($F=180.08$; $df=6, 22$; $p<0.01$). Newman-Keuls test showed that number of cage crossed increase in modafinil administrated animals as compare to water administrated animals. The activity was significantly increases ($p < 0.01$) in after 7th day of administration ($p < 0.01$). Modafinil induced sensitization was elevated ($p<0.01$) on repeated doses than single. Data (b) on number of square crossed by two way ANOVA (repeated measure designing) showed significant effects of repeated monitoring ($F=154.36$; $df=1.22$; $p < 0.01$) and effects of modafinil ($F=492.47$;$df=1,22$; $p < 0.01$) were significant. The interaction between modafinil and repeated monitoring ($F=9.070$;$df=1,22$) was non-significant. Newman-Keuls test showed that modafinil administration increased exploratory activity in open field than water administrated control. Significant increase was found after 1st ($p < 0.05$) and 7th ($p < 0.01$) day of administration. Hyper-locomotion effect of modafinil was greater ($p<0.01$) on repeated administrated animals as compared to acute.

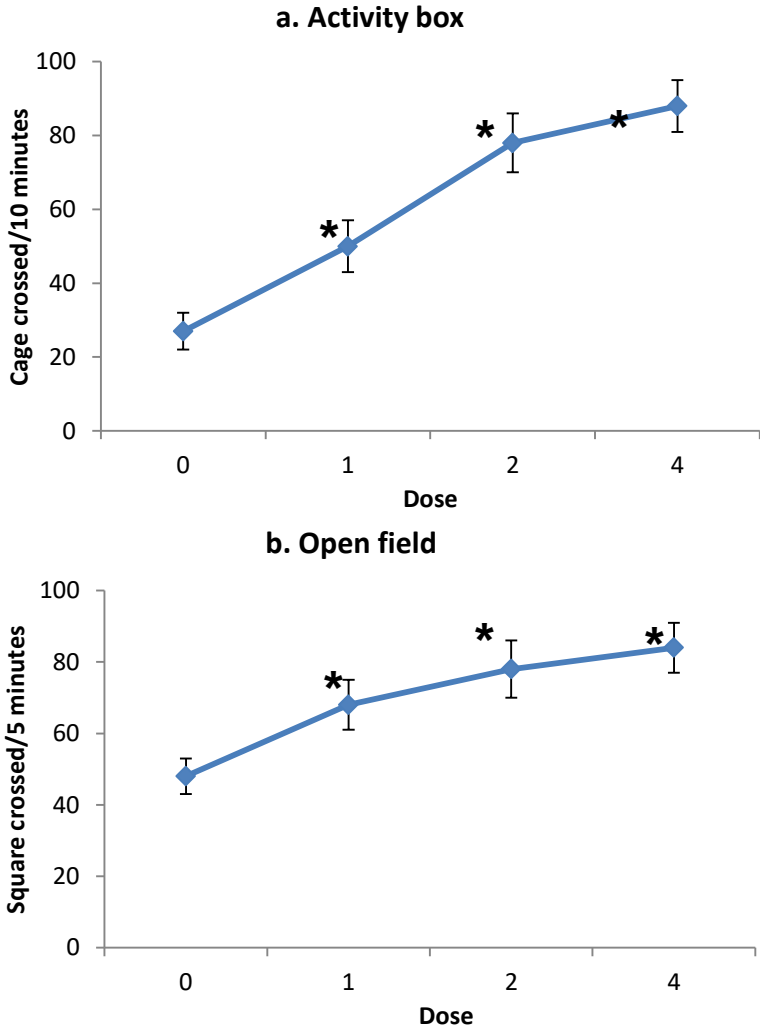

Fig. 1 Dose-related effects of methylphenidate (0-4 mg/kg) on activity in an activity box (a) and an open field **(b).** Values are mean ±SD (n=6); *p<0.01from saline-injected animals following one-way ANOVA.

Figure 3 explains the effect of repeated dose of methylphenidate (1.0mg/kg) on activity in an activity cage box and in open field of rats pre-treated with modafinil for 7 days which were monitored on next day of 1st and 7th day of administrations. Analysis of the data on number of cage crossed by three-way ANOVA (repeated measure designing) showed significant effects of repeated monitoring ($F=196.36$; $df=1, 22$; $p < 0.01$), effects of methylphenidate administration ($F=86.62$; $df=1, 22$; $p < 0.01$) and interaction between repeated monitoring and

modafinil treatment (F=180.08; df=1, 22; p < 0.01). However, the effects of modafinil (F=5.158; df=1, 22) was found non-significant. Post-hoc analysis by Newman-Keuls test showed that methylphenidate at dose 1.0 mg/kg produced behavioral sensitization on repeated administration in saline treated controls as compared to saline administrated animals. Whereas, in modafinil treated animals, sensitization induced by methylphenidate was attenuated. Increased in number of cage crossing was greater after 5th (p < 0.05), 6th and 7th (p < 0.01) days of administration. Hyper-locomotive action of methylphenidate was higher (p < 0.01) after 4th till 7th day of administrations in saline treated controls. In modafinil treated animals, decreased in activity was significant (p < 0.01) from 5th to 7th day of methylphenidate administrations. Analysis of the data (b) on number of square crossed in open filed by three-way ANOVA (repeated measure designing) showed significant effects of methylphenidate (F=71.282; df=1, 22; p < 0.01), effects of repeated monitoring (F=137.169; df=1, 22; p < 0.01) and interaction between repeated monitoring and modafinil administration (F=75.413; df=1, 22; p < 0.01) but the effects of modafinil (F=0.017; df=1, 22) was found non-significant. Post-hoc analysis by Newman-Keuls test showed that methylphenidate induced hyper-exploratory activity was greater after 7th day of administration (p < 0.01) as compared to saline control as well as similarly methylphenidate administrated animals of 1st day administration. In modafinil pre-treated animals, methylphenidate induced hyper exploratory activity was attenuated after single as well as repeated administration. Significant decreased in activity was found after 7th day of administration (p < 0.01).

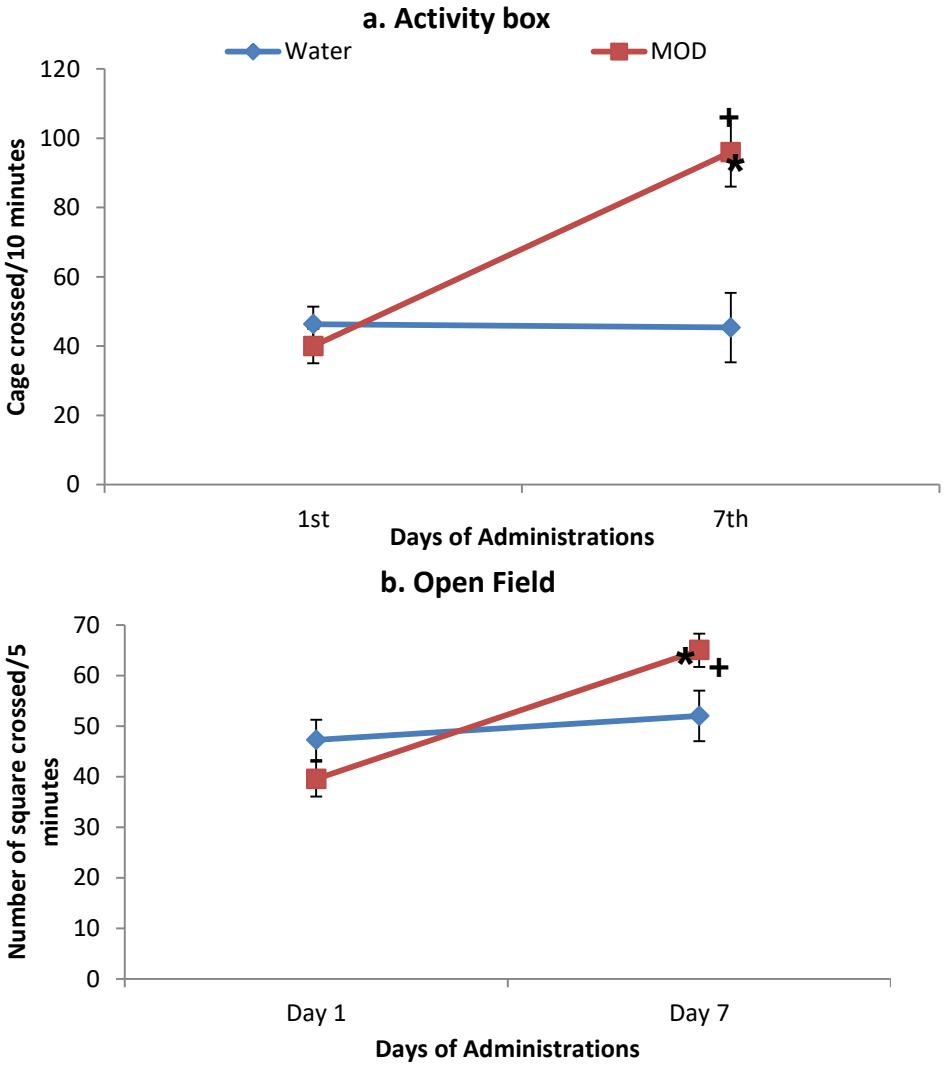

Fig. 2. Effects of administration of MOD (1.0 mg/kg/day) on activity in an activity box (a) and an open field (b). Values are means ± SD (n=12) as monitored on next day of every drug of administration. Significant differences by Newman-Keuls test: * p<0.01 from respective water treated controls; +p<0.01 from respective1y 1st day MOD treated animals, following two-way ANOVA (repeated measures design).

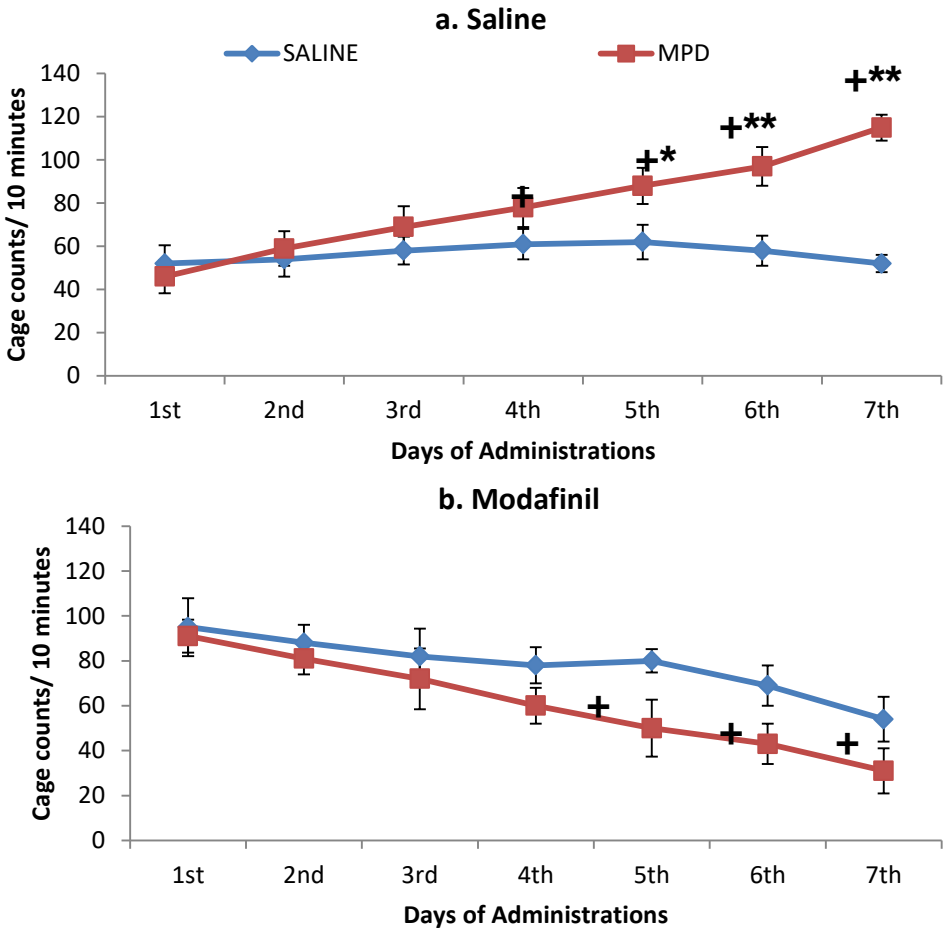

Fig. 3(a). Effects of administration of MPD (1.0 mg/kg) on activity in activity box of MOD pre-treated animal.Values are means ± SD (n=12) as monitored on next day of every drug of administration. Significant differences by Newman-Keuls test: *p<0.05, ** p<0.01 from respective saline injected controls; +p<0.01 from respective1y 1st day MPD injected animals, following the-way ANOVA (repeated measures design).

Figure 4 explains the effect of methylphenidate at dose 1.0 mg/kg on activity in a cage box and an open field of male Albino-Wister rats treated repeatedly with saline, methylphenidate, methylphenidate and modafinil, co-treated with methylphenidate and modafinil following modafinil treatment. Results of data (a) on number of cage crossed by one-way variance (repeated measure designing) showed significant effects of treatment ($F=151.507$; $df=3, 20$; $p < 0.01$) on activity in cage box. Newman-Keuls test indicates that methylphenidate induced hyper locomotion was greater ($p < 0.01$) in repeatedly treated methylphenidate and repeatedly methylphenidate plus modafinil co-treated animals as compared to saline administrated animals. Whereas, decreased in numbers of cage crossed were found in co-treated repeatedly with methylphenidate plus modafinil following modafinil pretreated animals ($p < 0.05$). Methylphenidate administration increased number of cage crossing were smaller ($p < 0.01$) in repeatedly methylphenidate plus modafinil co-treated as well as co-treated repeatedly treated with methylphenidate plus modafinil following pretreated animals. Analysis of the data (b) on number of square crossed by one-way ANOVA showed significant effects of treatment ($F=44.962.507$; $df=3, 20$; $p < 0.01$) on activity in open field. Newman-Keuls test indicates that administration of methylphenidate increased activity in open field was greater ($p < 0.01$) in repeatedly treated methylphenidate animals but decreased activity were found in repeatedly methylphenidate plus modafinil co-treated animals and co-treated repeatedly treated with methylphenidate plus modafinil following modafinil pretreated animals ($p < 0.05$) as compared to saline administrated animals. Methylphenidate induced hyper-exploratory activity were smaller ($p < 0.01$) in repeatedly methylphenidate plus modafinil co-treated as well as co-treated repeatedly treated with methylphenidate plus modafinil following pretreated animals.

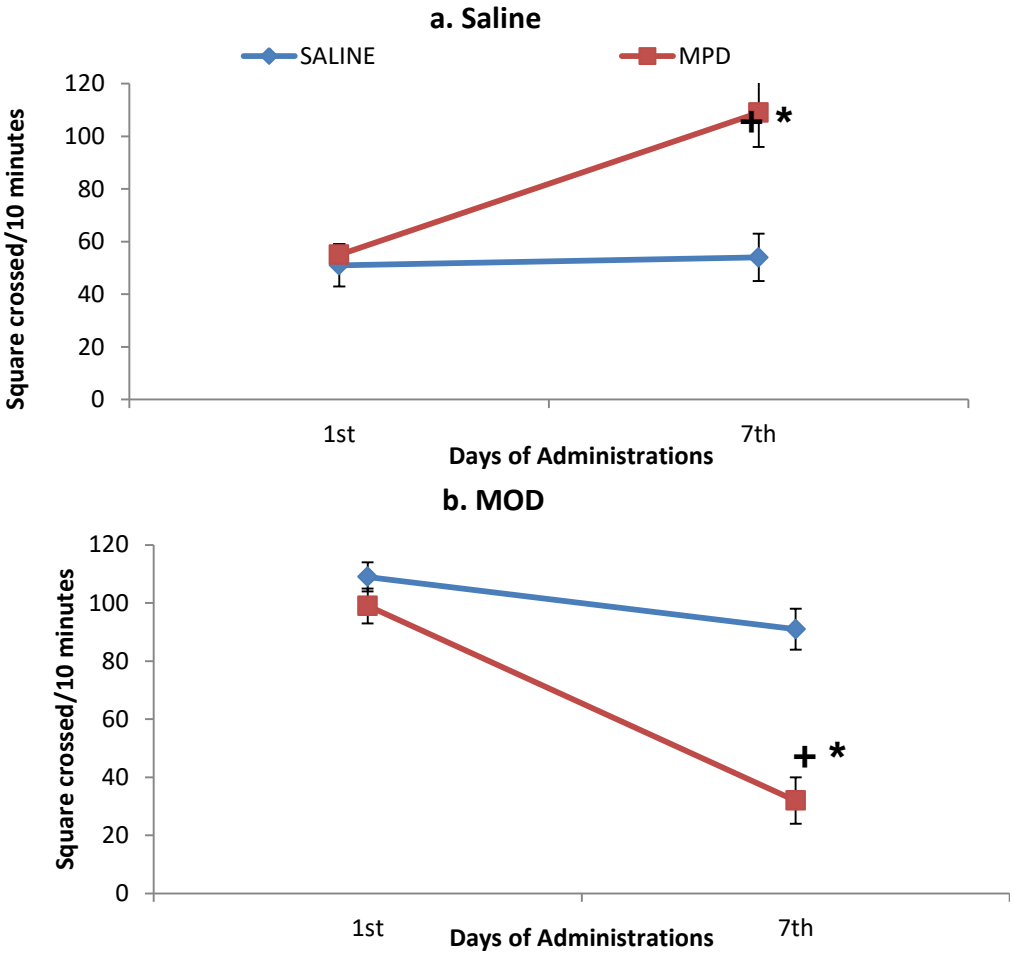

Fig. 3(b). Effects of administration of MPD (1.0 mg/kg) on activity in an open field of MOD pre-treated animal.Values are means ± SD (n=12) as monitored on next day of every drug of administration. Significant differences by Newman-Keuls test: * $p<0.01$ from respective water treated controls; +$p<0.01$ from respective1y1st day MOD treated animals, following two-way ANOVA (repeated measures design).

DISCUSSION

Behavioral sensitization is a condition which is caused by the repeated administration of a drug of abuse to produce continuous increased action in the locomotion of the drug during the repeated exposure phase and in response to acute drug challenge after a drug-free ('withdrawal') period. Induction in locomotor activity which is a consequence of alternating administration of drug abuse. In direct methods of abuse-related characteristics of drugs provide locomotor sensitization and drug differentiation (Neil *et al.*, 2010).The proposed present study suggests that MOD impact was about to change the alteration taking after dull act of dopaminergic D1/D2 receptors. MPD, as other pivotal stimulants, share basic systems of activity. The outcomes confirmed that MOD in vigilance advancing measurements empowered locomotive action of the rat to be sensitized and this was exceptional in contrast to the routine dopaminergic D1/D2 receptor agonist, for example, MPD. MOD refining locomotive exercises in an action encircle and an open field was measured subsidiary. Repeated administrations of both MOD and MPD brought about modification. Cross-sensitization was not observed in MPD experiments in rats that had demonstrated sensitization to MOD. Strikingly, cross-sensitization complications occurred in MOD, rats effectively sensitive to MPD.

From the first part of the present study, the results indicates that recommended doses of MPD increased the behavior of rats in activity and open field apparatus. MPD at different doses) 1.0, 2.0 and 4.0 mg/kg) used in this present study produces comparable effects on motor behavior in different behavioral models in a dose dependent manner (figure 1). It was found that higher (1.0 mg/kg) doses of MPD elicit behavioral sensitization concluding that these doses may exacerbate impulsivity in ADHD patients with chronic treatment of drug.

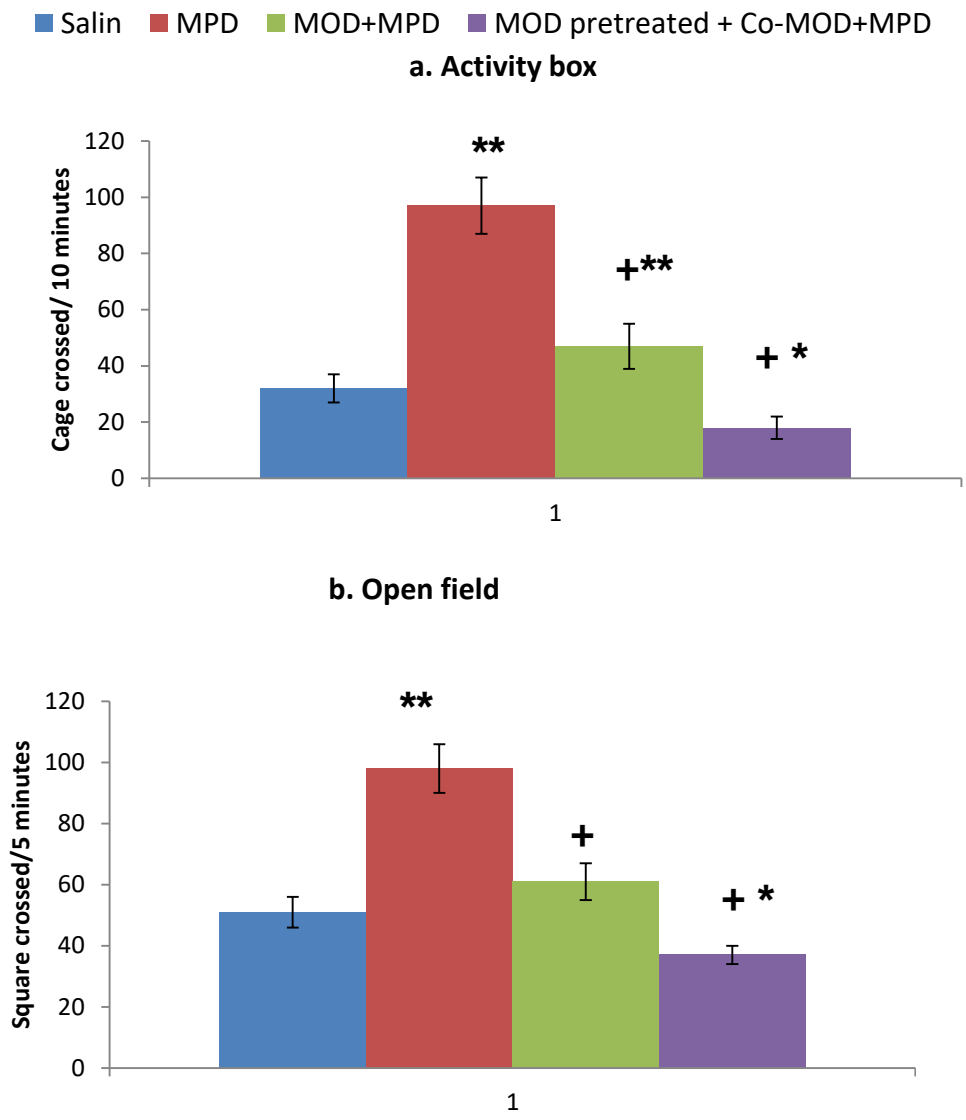

Fig. 4. Effects of administration of MPD (1.0 mg/kg) on activity in an activity box and open field of rats treated with saline, methylphenidate, methylphenidate and modafinil and methylphenidate with co-treated modafinil following modafinil pretreatment. Values are means ± SD (n=6) as monitored on next day of every drug of administration. Significant differences by Newman-Keuls test: *p < 0.05, ** p < 0.01 from respective saline treated controls; +p < 0.01 from respective repeated methylphenidate administrated animals following two-way ANOVA (repeated measures design).

Repeated exposure to psychostimulants elicit behavioral sensitization demonstrated by Behavioral experiments in laboratory. The progressive augmentation of the initial, behavioral responses to a psychostimulantrefers to behavioral sensitization (Leith and Kuczenski, 1982; Kalivas and Stewart, 1991; Wolf 1998). The recurrenttreatment of a low dose of the psychostimulant provoked a sensitized reaction to a psychostimulant, while higher doses produce tolerance (Leith and Kuczenski, 1982; Robinson and Berridge, 1993). Recurring administration of amphetamine, methamphetamine and cocaine stimulates behavioral sensitization (Robinson and Becker, 1986; Segal and Kuczenski, 1987; Pierce and Kalivas, 1997; Crawford *et al.*, 1998). Whereas, outcomes of behavioral sensitization resulted from repeated experience of MPD have been unpredictable (McNamara *et al.*, 1993; Gaytan *et al.*, 1997a; Izenwasser *et al.*, 1999; Kuczenski and Segal, 2002; Yang *et al.*, 2003). Many studies suggest a sensitized locomotor response to methylphenidate take placesucceeding repeated administration (Yang *et al.*, 2007; Wooters *et al.*, 2007). The present work demonstrates the development of a sensitized motor response toMPD inan

activity cage as well as in an open field. The main finding of the present study is the sensitized motor response to MPD was not exerted in animals pretreated and co-treated with MOD. Studies determined that psychostimulants generate variations in the release characteristics of DA (Robinson *et al.*, 1988; Kalivas and Duffy, 1990; Vezina 1993) DA-stimulated signal transduction mechanisms alternations (Steketee *et al.*, 1991; Steketee 1994; Miserendino and Nestler, 1995). Locomotor and neurophysiological sensitization are affected by these drugs changes.

Results from the present study illustrated that the treatment of modafinil for two weeks increased theactivity of rats in activity cage (Figure 2a). The exploratory activity of rats in open field (Figure 2b) exacerbates following repeated administration of MOD. An increase in open field exploration and in an activity box in MOD-treated animals likely indicates an antidepressant-like effect and reduction of novelty-induced anxiety.

The present work demonstrate that the pretreatment of modafinil for 2 weeks followed by daily co-treatment of MPD with MOD actually prevents locomotor sensitization to MPD, rather than MOD merely blocking the expression of motor effects of MPD. This is shown by the absence of a sensitized locomotor response to MPD when these rats received an injection of MPD only (Fig. 4). Interestingly, rats receiving MOD, but without the previous 2 weeks of MOD pretreatment, also showed a sensitized locomotor response on the test for sensitization to MPD (Fig. 4).

In summary, our study demonstrated that MOD-induced behavioral sensitization seemed to be independent on direct neuroadaptive changes in D1 and D2 dopaminergic receptors. The treatment of MOD needs caution because of its potency to develop addiction. MPD-pretreated rats showed cross-sensitization to MOD challenges. However, MOD induced stimulation of behavior was less than that induced by MPD indicates that MOD may be useful for medication of addiction or withdrawal symptoms induced by other psychostimulants.

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