

Depletion of apomorphine induced behavioral sensitization in rats treated with escitalopram

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Abstract: Apomorphine is a classical psychostimulant and used throughout the world as prescribed medicine. Despite of their therapeutic effects, use of psychostimulants is restricted because some psychosis and impulse control disorders are the consequence of their long term use. Studies suggest that serotonin (5-Hydroxytryptamine; 5-HT) has a critical role in psychosis and drug abuse. Center of the present article is to assess the impacts of serotonin in the easing of misuse potential; the sensitization prompted by recommended psychostimulant apomorphine. We researched that whether Escitalopram can weaken apomorphine instigated behavioral sensitization. Rats treated with Escitalopram (10 mg/kg) daily for 7 days followed by apomorphine injections (1mg/kg) for next 7 days. Apomorphine increased motor activity after single injection and repeated injections produced a progressive sensitization of motor activity. Whereas, in rats pretreated with Escitalopram apomorphine induced behavioral sensitization did not occur. In this article, from the results of this study it is concluded that apomorphine induced behavioral sensitization was smaller in rats pretreated with SSRIs. It might be due to the desensitization of somatodendritic 5-HT-1A receptors.

Keywords: Apomorphine, behavioral sensitization, escitalopram, psychosis, serotonin.

INTRODUCTION

Psychostimulants affects transitory change in either mental or physical capacity or both (Haleem 2013). The well known impact induced by psycho stimulants incorporates improved performance, alertness, hypophagia, enhanced alertness (Haleem, 2013). It is effective in the treatment of modulates episodic memory (Montoya *et al.*, 2008), treatment of drug dependence (i.e., to heroin etc), for the treatment of erectile brokenness in males and less active sexual desire disorder in females (Ribaric, 2012). Apomorphine, a non-opiate subsidiary of morphine, is a DA agonist shows proclivity towards D1 and D2 receptors (Wang *et al.*, 2007), is a CNS stimulant (Poewe, 2009). It is a classical psychostimulant and used throughout the world as prescribed medicine (Poewe, 2009).

Despite of its useful effects, its use is limited because of its long term use prompting medication abuse-user drug dependence (Nestler, 2001; Robinson and Berridge, 2000). The drug involved in reward and reinforcing effect produces neurochemical alterations which resultant into an abnormal condition in laboratory animals (Mahmood *et al.*, 2012; Ikram and Haleem, 2011; Marston *et al.*, 2009).

In such manner, one potential target framework is the 5-hydroxytryptamine (5-HT; serotonin) neurotransmitter system is the most potential target. No less than 14 separate types and subtypes of serotonin receptors have been perceived (Hoyer *et al.*, 2002). The 5-HT-1A

receptor subtype which happens on the soma and dendrites of serotonin neurons furthermore postsynaptic ally, has been accounted for to assume a vital part in the fortifying impacts and remunerating of ill-use drugs (Fletcher *et al.*, 2008; Haleem *et al.*, 2002).

Repeated subjection of many psychostimulant drugs leads to a phenomenon termed as behavioral sensitization and due to successive exposures drug response becomes more prominent (Leyton, 2007; Varvel *et al.*, 2007; Robinson and Berridge, 2001). Behavioral sensitization is believed to be a part of the mechanisms involved in a variety of clinical conditions such as addiction (Pacchioni *et al.*, 2002; Robinson and Berridge, 2000), and obsessive-compulsive disorder (OCD) (Dvorkin *et al.*, 2006; Ben-Pazi *et al.*, 2001). The supreme example of behavioral sensitization is locomotor sensitization which can be induced by repeated subjection (Alttoa *et al.*, 2007; Perreault *et al.*, 2006; Przegaliński *et al.*, 2000). Psycho stimulant sensitized rodents exhibit a progressive increase of locomotor behaviors. While the locomotor behaviors which become sensitized are variable, they are most frequently attributed of the acute drug effects (Perrault *et al.*, 2006).

Escitalopram is S-enantiomer of citalopram, therapeutically active, and is a commonly prescribed selective serotonin reuptake inhibitor (SSRI) (Waugh and Goa, 2003). But Escitalopram is found more superior to citalopram in efficacy (Kennedy *et al.*, 2006; Moore *et al.*, 2005). Previous studies have revealed that desensitization of somatodendritic 5-HT-_{1A} receptors can alleviate apomorphine induced behavioral sensitization (Ikram and Haleem, 2011). The purpose of the present study was to

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investigate that whether repeated treatment of Escitalopram could attenuate apomorphine induced behavioral sensitization in rats. Hypothesis of the present study is that, increase serotonin availability in synapse or terminal sites of neuron can desensitize the somatodendritic receptors which can attenuate apomorphine induced behavioral sensitization.

MATERIALS AND METHODS

Subjects

Twenty four male locally bred albino Wistar rats with an average weight of 160 ± 10 grams were purchased from the Dow University of Health and Sciences (DUHS). Each animal as housed in a separate cage with controlled environmental conditions. Room temperature was $22 \pm 2^\circ\text{C}$ and humidity $55 \pm 5\%$ with 12:12 hour light dark cycle. Before experiment, 3 day familiarization period was allowed with free access of food (cubes of standard rodent diet) and water. Each animal examination method, supported by the Institutional Ethics and Animal Care Committee, were coordinated in strict comprehension with the National Institutes of Health Guide for Care and Use of Laboratory Animals. All pharmaceuticals and behavioral weighing were performed in a balanced setup to avoid demand and times wastage.

Experimental protocol

This experimental study is based on two subsequent phases. In 1st phase, 24 male rats were divided into two equal groups, (each contains 12 animals), i) Water treated and ii) Escitalopram treated group. Animals of Escitalopram group were administered orally with drug (10mg/kg) and animals of water treated group were administrated with water for 7 days.

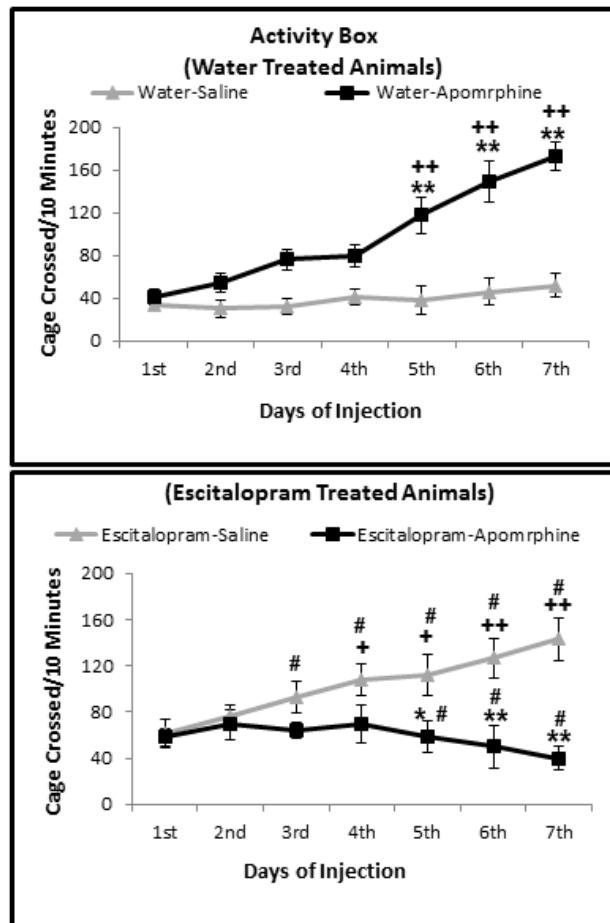
After 24 hours of last (7th) day of administration, (second phase) animals of each group were further divided into two sub groups 1) Water treated Saline 2) Water treated Apomorphine 3) Escitalopram treated Saline 4) Escitalopram treated Apomorphine. Animals of apomorphine administrated group were injected with apomorphine at dose 1.0mg/kg via intra-peritoneal route repeatedly for next 7 days. Animals of saline group were injected similarly with saline. Locomotive activity was monitored in familiar environment (activity box) on next day of each and every injection. Activity in novel environment (open field) was monitored on next day of 1st and 7th day of administration. Anxiolytic behavior of treatment (light dark activity box) was monitored on next day of 1st, 3rd, 5th and 7th day of administration.

Activity monitoring

Activity box

Activity box was used to determine the effects of treatment on locomotor activity of animals. Activity box was a perspex square shaped cage (26 x 26 x 26cm) with a saw dust covered floor. We have monitored no of cage

crossed in all the direction for 10 minutes. Monitoring of activity was performed in a quiet room under weight light as described by Ikram *et al.*, 2011. Control animals show little activity in familiar environment therefore drug induced activity clearly shown in this arena (Haleem 2010).



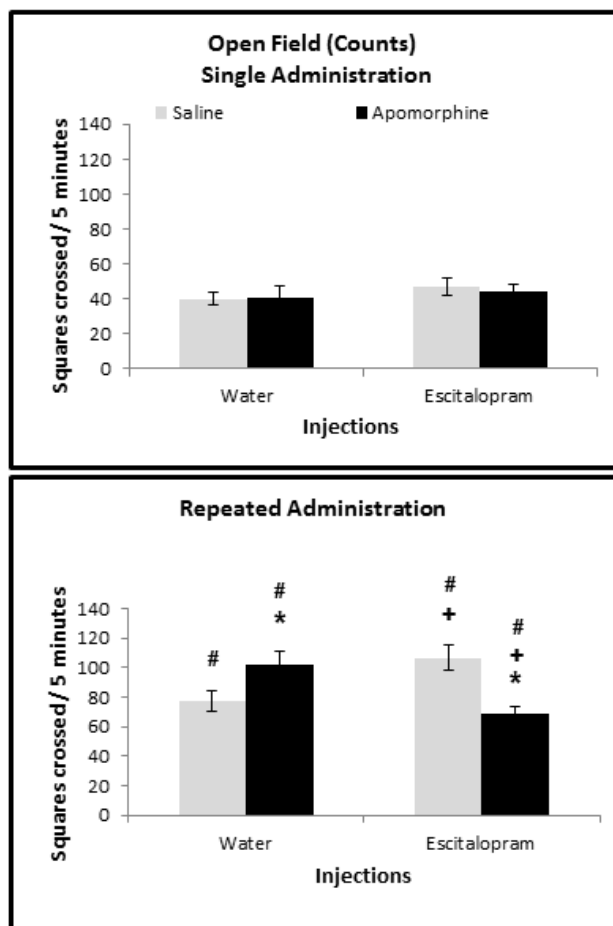
Values are means $\pm$ SD (n=6) as monitored on next day of each injection. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from respective saline injected controls; +p<0.05, ++p<0.01 from similarly injected water or Escitalopram administrated animals from 1st day; #p<0.01 from respective single saline or apomorphine injected water or Escitalopram treated animals following three-way ANOVA (repeated measures design).

Fig. 1: Effects of Apomorphine Injections on Activity in Activity Box of Animals Previously Exposed to Escitalopram

Open field

Open field gives an extensive exploratory range in which depressive like movement of medications can easily monitored (Haleem, 2010). The apparatus of open field used in this experiment was constructed of transparent Plexiglas having square area 76 x 76cm with opaque walls 42cm high. The floor of arena was divided into 25 equal squares. As the test begins, the animals placed in the center of the field to determine the effects of treatment.

Number of squares crossed with all four paws was monitored for 5 minutes (Farhan *et al.*, 2014; Mill *et al.*, 2002; Tang *et al.*, 2002). Latency time is the time to move from the center square in seconds as prescribed by Batool *et al.*, 2011.



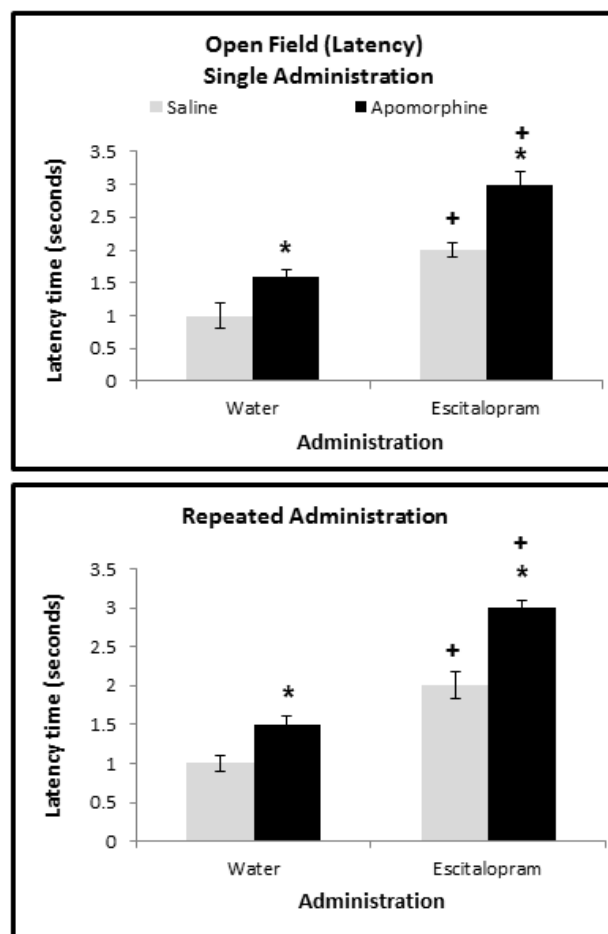
Values are means $\pm$ SD (n=3) as monitored on next day of 1st and 7th injection. Significant differences by Newman-Keuls test: *p<0.01 from saline injected controls; +p<0.05 from similarly injected water or Escitalopram administrated animals; #p<0.01 from respective single saline or apomorphine injected water or Escitalopram treated animals following three-way ANOVA (repeated measures design).

Fig. 2a: Effects of Apomorphine Injection on Activity in Open Field of Animals Previously Exposed to Escitalopram

Light dark box

Light dark activity test can be used significantly to determine anxiolytic effects of drugs (Maldonado and Navarro, 2000). The light dark activity box used in this experiment was locally made and consists of two equal compartments (26 x 26 x 26cm), with an access (12 x 12 cm) between the compartments. Both compartments were different from each others. Walls of one compartment were light (transparent) and other dark (black). Time

spent in light box was monitored for the determination of anxiolytic action of treatment. Cut off time was 5 minutes.



Values are means $\pm$ SD (n=3) as monitored on next day of 1st and 7th injections. Significant differences by Newman-Keuls test: *p<0.01 from saline injected controls; +p<0.05 from similarly injected water or Escitalopram administrated animals; following three-way ANOVA (repeated measures design).

Fig. 2b: Effects of Apomorphine Injection on Activity in Open Field of Animals Previously Exposed to Escitalopram

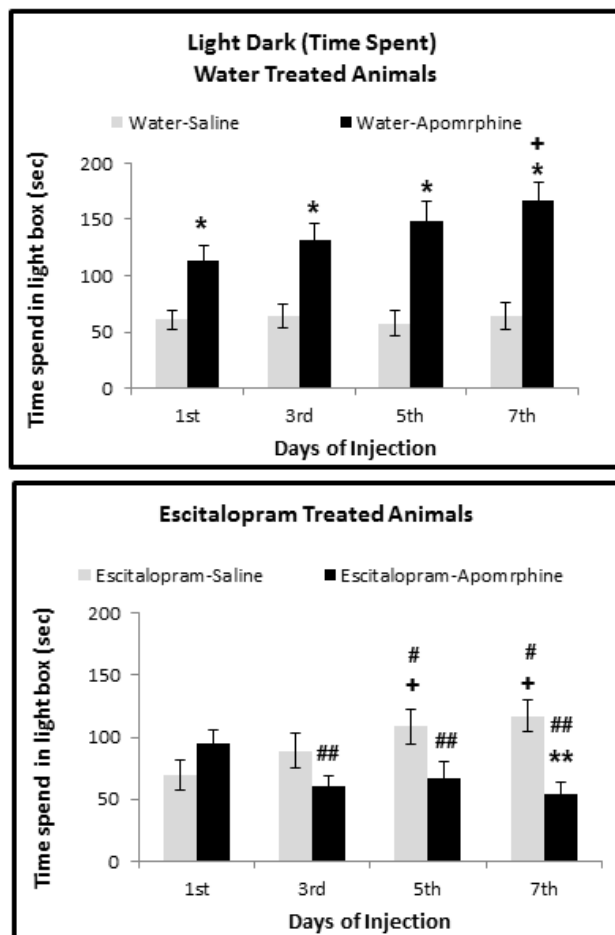
Drugs

Apomorphine-HCl (Sigma, St Louis, Missouri, USA) was dissolved in saline and injected via intra-peritoneal route of administration (Ikram and Haleem, 2011). Drug solutions were prepared daily before injection. Control animals were injected with saline (1.0ml/kg). Escitalopram, dissolved in water, was administered orally at 10 mg/kg. The respective controls were administered water orally.

STATISTICAL ANALYSIS

Behavioral Data of apomorphine administration on rats pretreated with Escitalopram were analyzed by three -

way ANOVA (repeated measure design) (SPSS). Software used for the analysis was SPSS (version 17.0). Individual comparisons were made by Newman-Keuls test. Values of $p < 0.05$ were considered as significant.



Values are means $\pm$ SD ($n=3$) as monitored on next day of 1st, 3rd, 5th and 7th injections. Significant differences by Newman-Keuls test: * $p < 0.05$, ** $p < 0.01$ from saline injected controls; + $p < 0.05$, ++ $p < 0.01$ from similarly injected water or Escitalopram administrated animals; # $p < 0.05$, ## $p < 0.01$ from respective single saline or apomorphine injected water or Escitalopram treated animals following three-way ANOVA (repeated measures design).

Fig. 3: Effects of Apomorphine Injections on Time Spent in Light Box in Light Dark Transition Model of Animals Previously Exposed to Escitalopram

RESULTS

Fig. 1 shows effects of repeated apomorphine injections at dose of 1mg/kg on activity (cage counts) of animals pretreated with Escitalopram in activity box. Activity was monitored on next day of each injection. Change in activity was analyzed by three-way ANOVA (repeated measures design) results showed that effects of Escitalopram [$F(1,20) = 141.335$, $p < 0.01$]; apomorphine [$F(1,20) = 112.119$; $p < 0.01$]; repeated measurements

[$F(6,20) = 212.398$, $p < 0.01$] and interaction between Escitalopram, apomorphine and repeated monitoring [$F(6,20) = 111.414$; $p < 0.01$] were significant. Post-hoc analysis by Newman-Keuls test showed that injections of apomorphine to rats pretreated with water increased ($p < 0.01$) number of cage crossed as compare to saline injected animals. Significant increase was found after 5th, 6th and 7th injections. Injections of apomorphine to rats pretreated with Escitalopram decreased number of cage crossed as compare to saline injected animals. Significant decrease was found after 5th ($p < 0.05$), 6th ($p < 0.01$) and 7th ($p < 0.01$) injections. Number of cage crossed was increased ($p < 0.01$) in water pretreated apomorphine injected animals as compare to similarly injected animals of 1st day administration. Significant increase was found after 5th, 6th and 7th injection. Number of cage crossed was increased in Escitalopram pretreated saline injected animals as compare to similarly injected animals of 1st day administration. Significant increase was found after 4th ($p < 0.05$), 5th ($p < 0.05$), 6th ($p < 0.01$) and 7th ($p < 0.01$) injections. In Escitalopram pretreated animals, saline injections increased ($p < 0.01$) number of cage crossed as compare to respective day effect of water pretreated saline injected animals. Significant increase was found after all injections except 1st injection. In Escitalopram pretreated animals, apomorphine injections decreased ($p < 0.01$) number of cage crossed as compare to respective day effect of water pretreated apomorphine injected animals. Significant decrease was found after 5th, 6th and 7th injections.

Fig. 2 shows effect of repeated apomorphine injections to rats pretreated with Escitalopram on number of squares crossed in an open field model. Activity was monitored on next day of 1st and 7th injection. Analysis of the data (fig. 2a) on number of square crossed by three-way ANOVA (repeated measures design) showed that effects of repeated monitoring ($F = 287.792$; $df = 3, 20$; $p < 0.01$) and interaction among Escitalopram, apomorphine, effects of Escitalopram ($F = 22.120$; $df = 1, 20$; $p < 0.05$) and repeated monitoring ($F = 63.287$; $df = 3, 20$; $p < 0.01$) were significant. However, the effects of apomorphine ($F = 0.354$; $df = 1, 20$; $P > 0.05$) was non-significant. Post-hoc analysis by Newman-Keuls test showed that injections of apomorphine to rats pretreated with water increased ($p < 0.01$) square crossed as compare to saline injected animals. Significant increase was found after 7th day of administration. Apomorphine injections to rats pretreated with Escitalopram decreased ($p < 0.01$) squares crossed as compare to saline injected animals. Significant increase was found after 7th day of administration. Square crossed was increased ($p < 0.01$) in Escitalopram pretreated saline injected animals as compare to water pretreated animals after a week of injections. Square crossed was decreased ($p < 0.01$) in Escitalopram pretreated apomorphine injected animals as compare to water pretreated animals after a week of injections. Number of

squares crossed was increased in water and Escitalopram pretreated animals of saline as well as apomorphine injected animals as compared to 1st day effect, after a week of injections.

Fig. 2b shows effect of repeated apomorphine injections to rats pretreated with Escitalopram on latency time to move in an open field model. Activity was monitored on next day of 1st and 7th injections. Analysis of the data fig. 2b on number of squares crossed by three-way ANOVA (repeated measures design) showed that effects of Escitalopram [$F(1,20) = 61.850, p < 0.01$], apomorphine [$F(1,20) = 151.600, p < 0.01$] and interaction among Escitalopram, apomorphine and repeated monitoring [$F(3,20) = 25.739, p < 0.05$] were significant. However, the effects of repeated monitoring [$F(3, 20) = 13.965, p > 0.05$] was non-significant. Post-hoc analysis by Newman-Keuls test showed that injections of apomorphine to rats pretreated with water and Escitalopram increased latency time to move as compared to saline injected animals. Significant increase was found after 1st and 7th day of injections. Time required to start movement in open field was increased ($p < 0.01$) in Escitalopram pretreated animals of saline as well as apomorphine injected animals as compared to water pretreated animals after 1st and 7th of injection.

Fig. 3 shows effects of repeated apomorphine injections on number of entries in light box in light dark transition box. Activity was monitored on next day of 1st, 3rd, 5th and 7th injections. Analysis of the data by three way ANOVA (repeated measures design) showed that effects of Escitalopram [$F(1,20) = 31.116, p < 0.01$]; apomorphine [$F(1,20) = 63.736, p < 0.01$] and repeated monitoring [$F(3,20) = 16.249, p < 0.05$] were significant. Whereas, the interaction among Escitalopram, apomorphine and repeated monitoring [$F(3, 20) = 5.63, p > 0.05$] was not significant. Post-hoc analysis by Newman-Keuls test showed that injections of apomorphine to rats pretreated with water increased time spent in light box as compare to saline injected animals. Significant increase was found after 1st ($p < 0.05$), 3rd ($p < 0.01$), 5th ($p < 0.01$) and 7th ($p < 0.01$) injection. Apomorphine injections to rats pretreated with Escitalopram decreased time spent in light box ($p < 0.01$) as compare to saline injected animals. Significant decrease was found after 7th injection. Repeated injections of apomorphine to rats pretreated with water increased time spent in light box as compare to first day effect. Significant increase was found after 7th injection. Repeated apomorphine injections to rats pretreated with water increased time spent in light box as compared to its single injection. Increase in time spent was significant ($p < 0.01$) after 7th injection. Apomorphine injections to rats pretreated with Escitalopram decreased time spent in light box as compared to saline injected rats. Decrease in time spent was significant ($p < 0.01$) after 7th injection. Apomorphine injection to rats pretreated with Escitalopram decreased time spent in light box ($p < 0.01$)

as compare to respective day effect of water pretreated apomorphine injected animals. Significant decrease was found after 3rd, 5th and 7th injection. Time spent in light box was increased ($p < 0.05$) in Escitalopram pretreated saline injected animals as compare to respective day effect of water pretreated saline injected animals. Significant decrease was found after 5th and 7th injection

DISCUSSION

Serotonin is accepted to include in the reductions of numerous insane manifestation and abuse potential which are connected with the long-term use of apomorphine (Ikram and Haleem, 2011) and other classical psychostimulants (Steiner *et al.*, 2010; Fletcher *et al.*, 2008). This topic is blessed with the great interest of researchers to alleviate the symptoms of psychostimulants induced disorders (Haleem, 2013). Results from the present study showed that repeated administration of apomorphine induced induction and expression of behavioral sensitization in terms of hyper locomotion is attenuated by Escitalopram, a SSRI with its pretreatment.

Apomorphine, like other traditional psychostimulants are well known to increase motor activity on acute administration. Amphetamines and others activates dopamine receptors indirectly by enhancing the DA concentration in the synapse whereas, apomorphine, a dopamine agonist directly stimulates the Dopamine D₁/D₂ receptors. The present study showed that repeated injections of apomorphine increases the activity of animals in familiar environment of home cage (fig. 1). Pretreatment with Escitalopram also increased motor activity in their familiar environment. While apomorphine injection to Escitalopram pretreated rats reduces the apomorphine induced hyperactivity. These results suggest that Escitalopram (10mg/kg) like fluoxetine (Haleem and Farhan, 2015) reduces the apomorphine (1mg/kg) induced hyperactivity in familiar environment.

Previous study has reported that apomorphine is responsible to enhance exploratory activity in open field (Haleem and Farhan, 2015). Present study revealed that systematic administration of apomorphine and Escitalopram pretreatment increased motor activity in novel environment, whereas apomorphine injections to rats pretreated with Escitalopram reversed the hyperactivity induced by apomorphine (fig. 2a and 2b). These results suggest that apomorphine at dose 1mg/kg is sufficient to induce behavioral sensitization, however; Escitalopram reduces the effects produced by apomorphine.

Results from the present study showed that apomorphine injections to rats pretreated with Escitalopram spent less time in light box as compared to apomorphine injection alone or alone Escitalopram pretreatment. These results indicating that repeated apomorphine injections reverses

the anxiolytic effects of Escitalopram. Escitalopram like fluoxetine and other SSRIs increase 5-HT level in the synapse by two ways; primarily by inhibiting its reuptake and after by causing the desensitization of somatodendritic autoreceptors 5-HT_{1A} in the dorsal striatum and terminal 5-HT_{1B}autoreceptors in different brain regions. As a result of this functional desensitization, negative feedback of these receptors by increased extracellular level of serotonin in disturbed and may results in more efficacy of serotonin (Tao *et al.*, 2002).

From the previous studies it has been reported that adaptations of serotonin neurotransmissions and autoreceptors functions due to pretreatment of SSRIs (Newman *et al.*, 2004; Hensler, 2003), results in the adjustment of dopamine neurotransmission (Haleem, 2013) and is responsible to attenuate apomorphine induced behavioral sensitization. Buspirone administration stimulates somatodendritic 5-HT_{1A} receptors (Haleem *et al.*, 2004; Shireen and Haleem, 2005) results in the functional desensitization of somatodendritic 5-HT_{1A} receptors (Haleem *et al.*, 2007a, 2007b). Systemic administration of buspirone reduces behavioral sensitization induced by apomorphine (Ikram and Haleem, 2011). Inhibition of apomorphine induced hyper-locomotion by pretreatment of fluoxetine (Haleem and Farhan, 2015) also suggests the role of fluoxetine administration on 5-HT_{1A} receptor regulation pathway. The present study is the extra confirmation in the inclusion of 5-HT_{1A} autoreceptors in apomorphine impelled behavioral sensitization.

CONCLUSION

From the results of this study it is concluded that apomorphine induced behavioral sensitization was smaller in rats pretreated with SSRIs. It was also reported previously that SSRIs repeated administration attenuates the CNS stimulant induced sensitization. (Haleem and Farhan, 2015) and, it can be concluded that somatodendritic 5-HT_{1A} receptors might plays a critical role in apomorphine induced psychosis. So escitalopram (or other SSRI) can be used to treat apomorphine induced dependence, psychosis, and addiction

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