Dapoxetine Treatment Leads to Attenuation of Chronic Unpredictable Stress Induced Behavioral Deficits in Rats Model of Depression

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Abstract: Stressful conditions possess a complex relationship with brain and body's reaction to stress and beginning of depression. The hypofunctioning of Serotonin (5-Hydroxytryptamine; 5-HT) is known to be established in unpredictable chronic mild stress exposure. UCMS is broadly taken as the most promising and favorable model to study depression in various animals, imitating many human depressive symptoms. With the class of selective serotonin [5-hydroxytryptamine (5-HT)] reuptake inhibitors (SSRIs) is now considered as the most prescribed antidepressant that can reverse petrochemical and behavioral effects of stresses. The aim of the present study was to investigate whether repeated administration of dapoxetine at dose 1.0 mg/kg could reversed the behavioral deficits induced by UCMS in rat model of depression. Rats exposed to UCMS revealed a significant reduction in food intake as well as growth rate. Locomotive activity in home cage and anxiolytic behavior in light/dark activity box were greater in animals of unstressed group as compared to animals of stressed group. The mechanism involved in the inhibition of serotonin reuptake at pre-synaptic receptors by repeated dapoxetine administration is discussed. The knowledge accumulated may facilitate an innovative approach for extending the therapeutic use of dapoxetine and the interaction between stress and behavioral functions.

Keywords: Unpredictable chronic mild stress (UCMS), Selective serotonin reuptake inhibitors (SSRIs), Dapoxetine, 5-Hydroxytryptamine (5-HT), Depression, Locomotive activity.

INTRODUCTION

Stress is a state of disharmony or threatened homeostasis and is confronted by a complex standard of behavioral and physiological responses of that particular organism [1]. Presently, four renowned aspects of the term stress are known; stress stimulus, stress experience, stress response and the experience of stress response [2]. Most of the animal models possess the common characteristic of stress which was various stress procedures or avoiding events and chronic stress models observed to be more appropriate for the experimental determination of depression as compare to acute stress models [3, 4].

Dapoxetine is an effective antidepressant and has a similar mechanism of action with other SSRIs. It inhibits the serotonin reuptake transporter, with less inhibitory effects at the nor-epinephrine and dopamine reuptake transporters [5]. Dapoxetine binds to 5-HT, norepinephrine and dopamine reuptake transporter. 5-HT> norepinephrine >> dopamine is the order of effectiveness of dapoxetine to inhibit the reuptake of these neurotransmitters [6]. Dapoxetine is an exceedingly effective compound that after dosing attains its peak plasma concentration in about 1.5 hours, which is more rapidly than fluoxetine, paroxetine, or sertraline [7, 8]. It is readily absorbed, followed by a rapid decay in plasma concentrations after oral administration. For on-demand dosing, these pharmacokinetic properties make dapoxetine a first-rate candidate.

Chronic stress models, such as the sustained social stress [9] or unpredictable chronic mild stress (UCMS) [10, 11] have produced the most steady and continuous results of anhedonia and learned helplessness, particularly in rats [12, 13]. Possessing variety of stressors is a vital feature of the UCMS model, as repetition of single or few stressors caused habituation of behaviors rapidly [14]. A rat model of unpredictable chronic mild stress (UCMS) induced a cognitive defect in extra dimensional set shifting capability in an intentional set shifting test, which suggests an alteration in function of the medial prefrontal cortex [15].

The present study was designed to evaluate the proficiency of dapoxetine to reverse UCMS induced behavioral insufficiencies in rats.

MATERIAL AND METHODS

Animals

Albino-Wistar rats (weighing 180-220 grams) provided by The Dow University of health and sciences

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Ojha campus, Karachi. All animals were housed individually in perspex cages under 12-hrs light and dark cycle and controlled room temperature (25±2 ^{o}C) with free access to cubes of standard rodent diet and water, for a period of three days before experimentation to familiarize them with surrounding. All animal experiments, approved by the Institutional Ethics and Animal Care Committee, were conducted in strict accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

Drug

Dapoxetine was acquired from Sigma (St Louis, Missouri, USA) and dissolved in distilled water, 1:1 v/v and was administered orally (to stressed and unstressed rats at a dose of 1mg/kg /ml /body weight for 28 days) by using stainless steel feeding tubes.

Experimental Protocol

Twenty four male Albino Wistar rats were randomly divided into two groups: (i) Unstressed and (ii) UCMS groups. The animals of each group were again subdivided into two further groups each i.e., saline and dapoxetine injected. This resulted in a total of four groups: (i) Unstressed- Saline, (ii) Unstressed-Dapoxetine, (iii) UCMS-Saline and (iv) UCMS-Dapoxetine injected animals. Animals were administrated accordingly with Dapoxetine (1.0 mg/kg) or saline (1.0 mg/ml) 1 hour before of each stress. Stressed group rats were exposed to UCMS schedule for 4 weeks (Table **1**) while animals of unstressed groups remained in their home cages. Food intake and % change in body weight were monitored on next day of 1st and 4th week of treatment. Locomotive activity in home cage (familiar environment) and anxiolytic behavior in light dark transition box were monitored on next day of 1st, 7th, 14th, 21st and 28th day of stress.

Behavioral Assessment

Food Intake

Cumulative food intake was monitored on next day of 7th and 14th day of treatment. In the hooper of every cage, a weighed amount of rodent cubes were placed. Intake of food was monitored by weighing leftover food in the hooper.

Growth Rate

Weekly body weight changes were monitored to find out the effect of treatments on growth of animals. Growth rate changes were calculated as percentage of starting day weight (experiment day body weight/starting day body weight) X 100.

Home Cage Activity Test

Home cage test is used for the determination of locomotors activity in a familiar environment. Using the home cage activity test, the duration of monitoring is of 10 minutes for the study of stress or drug induced activity. Activity cage apparatus was a square Perspex cage (26 x 26 x 26 cm). The floor of the cage is covered with saw dust. For habituation, animal was placed 15 min before the monitoring of the activity [16]. All monitoring was done in balanced design. Observations were recorded simultaneously.

Light-Dark Transition Test

Rats are tending to stay in darker place and feel safer over there. If a choice is given between bright open area and a dark place, rats preferred the dark, enclosed environment. Avoidance of lit space is considered as the reflection of anxiety provoking characteristic of rodents. The apparatus was consisted of two compartments. The boxes are of equal size (26 x 26 x 26 cm), with an opening of (12 x 12 cm) between the boxes. Walls of one compartment were

Table 1: Schedule of CMS

DAYS				UCMS	DISCRIPTION
Day 1	Day8	Day 15	Day 22	Cage agitation (12 rpm)	2 hours
Day 2	Day 9	Day 16	Day 23	Water Deprivation stress	12 hours
Day 3	Day 10	Day 17	Day 24	Noise stress (12 dB)	Alternative noise stimuli pattern for 1 hour
Day 4	Day 11	Day 18	Day 25	Light/Dark inversion cycle	Alternatively for 2 hours
Day 5	Day 12	Day 19	Day 26	Overcrowding stress	Stressed rats in a single cage for 1 hour
Day 6	Day 13	Day 20	Day 27	Cage tilting stress	1 hour (right side) 1 hour (left side)
Day 7	Day 14	Day 21	Day 28	Cold stress	1 hour at 4 ^{o}C

made up of Plexiglas (transparent) and other were painted dark and enclosed (with top). The light dark exploration activity assess the anxiolytic and anxiogenic response of a drug [17]. Rat was placed in the middle of the light box. The procedure was done in balanced design. The parameter observed was time spent in light compartment (the time spent by the animal exploring the light area in 5 minutes).

Statistical Analysis

Results are represented as mean ± S.D. Data of all behavioral models were analyzed by three-way ANOVA (Repeated measure designs). Software used for the analysis was SPSS (version 17). Individual comparisons were made by Newman- Keuls test. Values of $p<0.05$ were considered as significant.

RESULTS

Figure **1** shows effect of UCMS on cumulative food intake in male rats administrated with dapoxetine (1.0mg/kg) as monitored on next day of 1st and 4th week of administration. As the data analyzed by three way ANOVA (repeated measure design) showed that the effect of days ($F=569.839$, $df=1,20$; $p<0.01$), the effect of dapoxetine ($F=273.746$; $df= 1,20$; $p<0.01$), the effect of stress ($F=440.577$; $df=1,20$; $p<0.01$) and the interaction between drug, days and stress ($F=6.166$; $df=4, 20$; $p<0.01$) were significant. Post-hoc analysis by Newman-Keuls test showed that administration of dapoxetine at dose 1.0 mg/kg increased food intake of unstressed as well as UCMS group animals as compared to saline administrated unstressed or UCMS animals. Significant increase ($p<0.05$) in food intake was found after 1st as well as 4th week of administration. The comparison of unstressed group animals to the UCMS group shows decrease in food intake of saline as well as dapoxetine administrated animals. Significant ($p<0.01$) decreased was monitored after 1st and last (4th) week of stress.

Figure **2** shows effect of UCMS on growth rate in male rats administrated with dapoxetine (1.0mg/ml/kg) as monitored on next day of 1st and 4th week of administration. As the data analyzed by three way ANOVA (repeated measure design) showed that the effect of days ($F=5.635$; $df=1,20$; $p<0.01$), the effect of dapoxetine ($F=27.936$; $df= 1,20$; $p<0.01$) and the effect of stress ($F=63.152$; $df=1,20$; $p<0.01$) were significant. Whereas, the interaction between drug, days and stress ($F=1.317$; $df= 4, 20$) was non-significant. Post-hoc analysis by Newman-Keuls test showed that exposure to UCMS decreased growth rate in saline

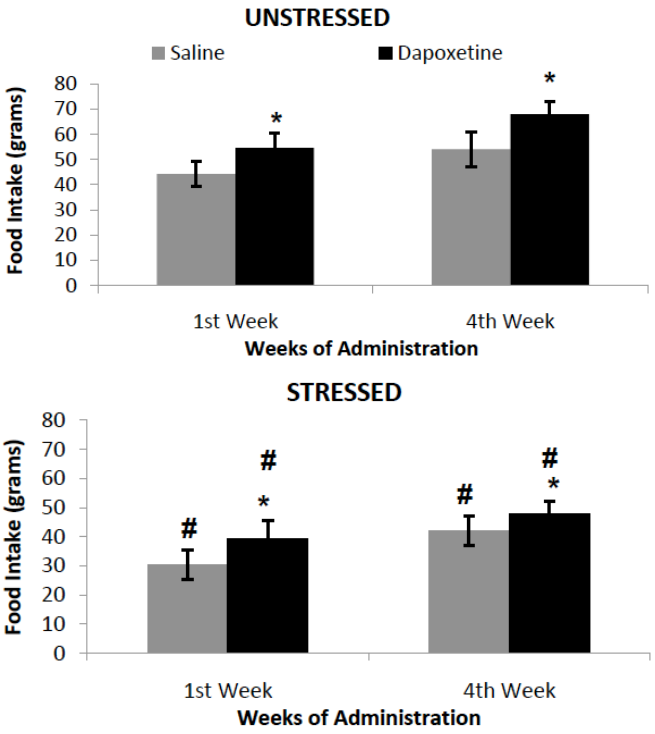

Figure 1: Effects of Dapoxetine on Cumulative Food intake of rats exposed to UCMS. Values are means + SD (n=6) as monitored on next day of first and then weekly drug administration. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from similarly treated saline injected controls; #p<0.01from respective unstressed controls following three-way ANOVA.

administrated animals significantly after 4th week of stress ($p<0.01$) as compared to similarly administrated animals of unstressed group. Administration of dapoxetine at dose (1.0 mg/kg) increased growth rate after 4th week of administration of stressed group ($p<0.01$) and unstressed ($p<0.05$) group animals as compared to similarly treated saline administrated controls. Dapoxetine increased growth rate after 4th ($p<0.01$) week in unstressed as compared to similarly administrated unstressed animals from 1st week administration. Growth rate of stressed group animals decreased after 4th week of saline administration significantly ($p<0.05$) as compared to respectively treated animals from 1st week of saline administration. (Figure **3**) shows effect of UCMS on 1st day and then weekly activity of male rats administrated with dapoxetine (1.0mg/ml/kg) in activity box as monitored on next day of respective administration. As the data analyzed by three-way ANOVA (repeated measured designing) the effect of days ($F=32.572$; $df=4,20$; $p<0.01$), the effect of dapoxetine ($F=340.492$; $df= 1,20$; $p<0.01$) and the effect of stress ($F=203.100$; $df=1,20$; $p<0.01$) were found to be significant. Whereas, the interaction between drug, days and stress ($F=1.767$; $df= 4, 20$) was non-significant.

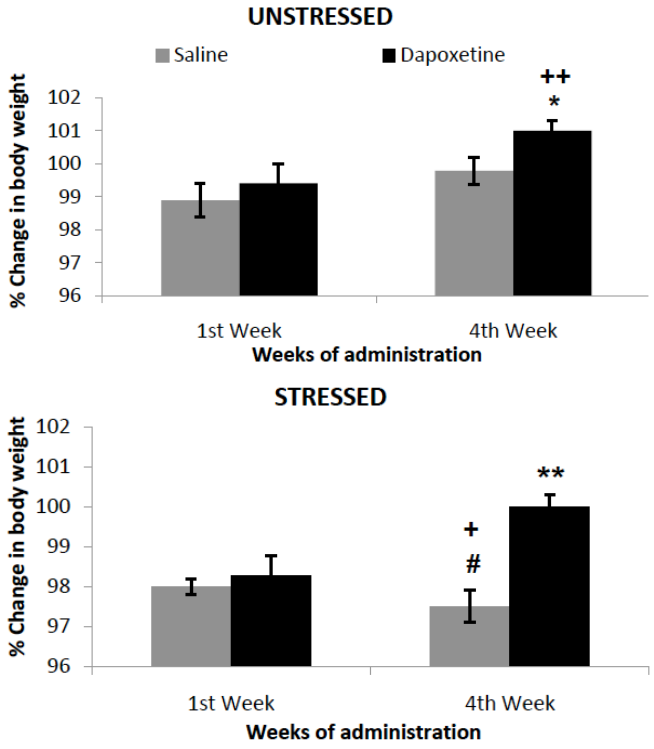

Figure 2: Effects of Dapoxetine on growth rate of rats exposed to UCMS. Values are means + SD (n=6) as monitored on next day of first and then weekly drug administration. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from similarly treated saline injected controls; +p<0.05, ++p<0.01 from respective 1st activity monitored controls; #p<0.01from respective unstressed controls following three-way ANOVA.

Post-hoc analysis by Newman-Keuls test showed that administration of dapoxetine at dose 1.0 mg/kg increased activity in unstressed as well as UCMS animals. In stressed group, significant increase in activity was found after 7th, 14th (p<0.05), 21st and 27th (p<0.01) day of administration. Whereas, activity was found greater (p<0.01) in unstressed animals on repeated monitoring (7th, 14th, 21st and 28th) as compared to saline administrated unstressed or UCMS animals. As compared to activity of unstressed group animals, number of cage counts were decreased of saline as well as dapoxetine administrated animals. Significant (p<0.01) decreased in activity was monitored after 7th, 14th, 21st and 27th day of stress. Repeated administration of dapoxetine increased activity of both unstressed and UCMS animals as compared to similarly administrated animals of unstressed or UCMS from 1st day of administration. In animals of unstressed group, significant (p<0.01) activity was found after 7th, 14th, 21st and 27th days of administration and stressed animals only after 21st and 27th day of administration. Activity of saline administrated animals of unstressed group was decreased significantly after 7th (p<0.01), 14th, 21st and

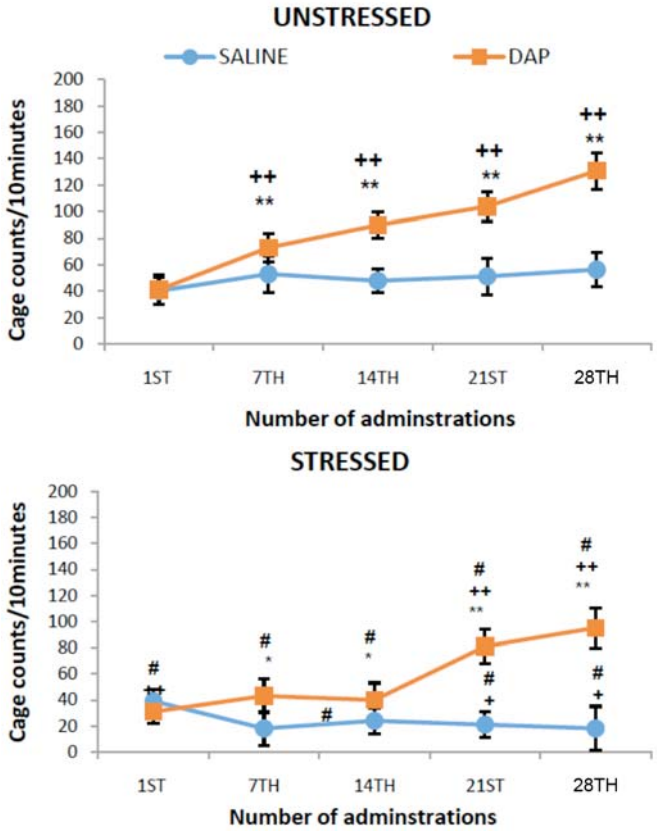

Figure 3: Effects of Dapoxetine on activity in home cage of rats exposed to UCMS. Values are means + SD (n=6) as monitored on next day of first and then weekly drug administration. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from similarly treated saline injected controls; +p<0.05, ++p<0.01 from respective 1st activity monitored controls; #p<0.01from respective unstressed controls following three-way ANOVA (repeated measures design).

27th (p<0.05) day of administration as compared to respectively treated saline administrated animals from 1stday of administration.

(Figure **4**) shows effect of UCMS on 1st day and then weekly activity (time spent in light area) in light/dark transition box in male rats pre-administrated with dapoxetine (1.0mg/ml/kg). As the data analyzed by three-way ANOVA (repeated measured designing) the effect of days (F=61.037, df=4,20; p<0.01), the effect of dapoxetine (F=256.077; df= 1,20; p<0.01) and the interaction between drug, days and stress (F=5.623; df=4, 20; p<0.01) were significant. Whereas, the effect of stress (F=, 0.445; df=1, 20) was found to be non-significant. Post-hoc analysis by Newman-Keuls test showed that dapoxetine increased the time spent in light box of unstressed as well as UCMS treated rat in unstressed animals significant increase was found after 14th day (p<0.05), 21st and 27th day (p<0.01) Whereas, time spent of stressed animals fount greater after 7th

(p<0.05), 14th, 21st and 27th day (p<0.01) from their saline injected controls. The activity of unstressed dapoxetine injected rats was increased on 21stand 27th day (p<0.01) and stressed rats on 7th, 14th, 21st day (p<0.01) from 1st day. Dapoxetine increased activity of stressed rats significantly after 21st and 27th day (p<0.01) of administration from unstressed dapoxetine injected controls.

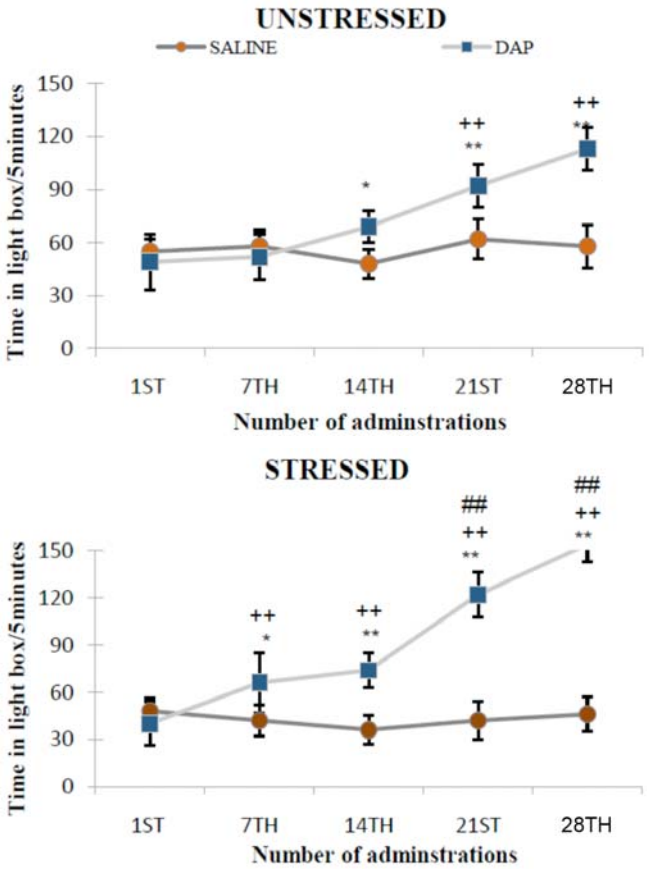

Figure 4: Effects of Dapoxetine on activity in home cage of rats exposed to UCMS. Values are means + SD (n=6) as monitored on next day of first and then weekly drug administration. Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from similarly treated saline injected controls; +p<0.05, ++p<0.01 from respective 1st activity monitored controls; #p<0.05, ##p<0.01from respective unstressed controls following three-way ANOVA (repeated measures design).

DISCUSSION

The aim of the present study was to investigate whether repeated administration of dapoxetine at dose 1.0 mg/kg could reverse the behavioral deficits induced by UCMS in rat model of depression. Stressful conditions possess a complex relationship with brain and body's reaction to stress and beginning of depression. The present study reveals that the long term stress and depression can be attenuate and behavioral deficits due to stressful situations can be inverse by the treatment of antidepressants particularly SSRIs.

This study showed that the growth rate was increased in dapoxetine administered rats in both unstressed and stressed situations where as, decrease in growth rate in saline treated rats in stressful condition has been observed (Figure **2**). Similarly, food intake in dapoxetine treated rats in unstressed and stressed conditions increased rapidly in comparison with saline treated animals but less food intake has been observed in stressful condition in both drug and saline treated rats (Figure **1**). The food intake and growth rate were administered weekly for 4 weeks under the normal and UCMS treated conditions and a distinct difference is observed which shows increase growth rate and appetite in SSRIs treated rats in both unstressed and stressed conditions. Whereas, the food intake level and growth is increased in animals treated with antidepressants particularly SSRIs. Antidepressants particularly SSRIs increases serotonin level in synapses by inhibiting reuptake of 5-HT. High serotonin level causes less food intake and similarly loss in body weight. Commonly, feeding reduces by the agonists at the 5-HT receptors and drugs that inhibit the re-uptake of serotonin [18]. Three 5-HT receptor subtypes (5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C}) have been proposed to mediate 5HT modulation by dapoxetine. The 5-HT_{2C} knockout mouse is hyperphagic and obese due to the fact that the agonist at the 5-HT_{2C} receptor shows inhibition of food intake [19]. The present study showed a significant increase in body weight and food intake in dapoxetine (1.0 mg/Kg) administrated rats in comparison with saline treated rats in unstressed and stressed rats.

One of the important factors that may affect the results is the duration of treatment. A large number of studies found differences among acute and chronic effects of antidepressants on body weight changes. Michelson and his colleagues [20] has found weight loss for patients taking SSRIs (fluoxetine) during the short phase (4 weeks) and weight gain for the same patients in continuing phase. Among different studies, studies considering the time-dependent effects of antidepressants the assortment of acute-chronic and short term long term phases is not similar for interpretation of results.

Home cage activity test determines the locomotors pattern of rats in familiar environment under the influence of stressful or stress-free conditions [21]. The present study shows the decrease in locomotors activity in both dapoxetine (1.0 mg/kg) and saline

treated stressed rats (Figure **3**). Depression and stress cause fatigue, desperation and hopelessness. Stressed rats showed less activity in activity box than unstressed although home cage was a familiar environment for the animal. Whereas, by the treatment of antidepressants particularly SSRIs, the distress can be reverse back. Dapoxetine mainly acts on serotonin receptors 5-HT-1A, 5-HT-1B and 5-HT-2C. 5-HT-1A acts on anxiety and mood behavior [22, 23] whereas, 5-HT 1B acts on anxiety and loco motor behavior [24-27] and 5HT-2C acts on mood anxiety and locomotion [28-30]. It was clearly observed that locomotion in both stressed and unstressed rats was increased in dapoxetine treated rats as compare to saline treated animals. Furthermore, a decrease in dapoxetine treated stressed rats locomotion was observed than in unstressed rats.

The light/dark box test consists on the inborn aversion of rats to the brighter area and on the exploratory behavior in response to light and novelty [31]. Time spent in light area was observed clearly more in Dapoxetine treated unstressed and stressed rats than saline administrated animals. Moreover, Dapoxetine treated stressed rats showed most activity than unstressed rats (Figure **4**). The antidepressants effect of Dapoxetine increased the time duration of rats in illuminated novel area although the entries of SSRIs treated rats were less than saline treated rats. Due to the habituation and adaptations over long time, transformations have found to be an index of exploration activity and the time spent in each compartment is due to aversion [32]. The explorations and percent time spent seems to be best measure in each compartment. The mood, anxiety locomotion and memory are improved by agonist of 5-HT 1A, 5-HT1B and 5-HT 2C receptors and dapoxetine is found to be the best candidate as a SSRIs antidepressant.

CONCLUSION

Long term exposure to stressful situation resultant into several behavioral deficits which can be attenuated by repeated administration of dapoxetine. Dapoxetine produces hyperphagic effect and increase in growth rate was greater in unstressed animals as compared to stressed group animals. Administration of dapoxetine produced continuously increase in activity but this increase was smaller in animals exposed to stress.

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