IMPACT OF EPISODIC TREATMENT OF PAROXETINE ON DEPRESSIVE-LIKE BEHAVIOR AND ANOREXIA IN RAT MODEL OF UNPREDICTABLE STRESS

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ABSTRACT

Paroxetine belongs to the A phenylpiperidine class of selective serotonin reuptake inhibitors (SSRIs). Compared to other SSRIs such as sertraline, fluoxetine, and fluvoxamine, paroxetine, demonstrates greater selectivity as well as potency. Its pharmacokinetic profile makes it highly suitable for clinical application, having a half-life approximately 24 hours and absence of active metabolites. Similar to other SSRIs, it has minimal clinically relevant drug interactions. Stressful conditions exert a complex influence on neural and physiological processes, often contributing to depression and anxiety. Evidence from both clinical and experimental research indicates that paroxetine effectively reduces moderate to acute depression and related anxiety symptoms, with an onset of action comparable to tricyclic antidepressants. To ascertain paroxetine's anxiety-reducing and appetite-enhancing effects in a rat model of unexpected stress. Male adult rats were divided into stressed as well as unstressed groups. Animals received paroxetine (10 mg/kg/day) for a period of 14 days, one hour prior to stress exposure. Behavioral outcomes, including food intake and elevated plus maze performance, were recorded after the first administration and at weekly intervals. The study investigated whether paroxetine could attenuate stress-induced anorexia and behavioral impairments. Prolonged moderate anxiety produced significant changes in the behavior, which were mitigated by recurrent paroxetine treatment. Stressed animals exhibited depressive-like behaviors, attenuated by paroxetine administration. Food intake in unstressed groups treated with paroxetine was significantly higher than in stressed animals treated with saline treatment, demonstrated hyperphagic effects, with food intake being significantly higher in unstressed than in stressed animals. Paroxetine administration produced significant anxiolytic effects in the elevated plus maze, particularly in unstressed animals.

Keywords: Depressed behavior, Anorexia, SSRIs, Serotonin, Paroxetine, prolonged unexpected stress

INTRODUCTION

Neurotransmission of the receptors of serotonin through the brain and spinal cord is crucial for the onset and resolution of depressive disorders (Meltzer, 1989; Risch and Nemeroff, 1992; Spreux-Varoquaux *et al*., 2001). In both human and animal models of depression and stress, decreases in serotonin (5-hydroxytryptamine, 5 HT) and its primary intermediate 5-hydroxyindoleacetic acid (5-HIAA), was most often observed, suggesting serotonergic system dysfunction. Enhancing serotonergic transmission is believed to underlie the therapeutic efficacy of most available antidepressants (Blier *et al*., 1990; Blier and de Montigny, 1994; Byerley and Risch, 1985; Leonard, 1996; Poirier and Boyer, 1999). However, the precise relationship between these neurochemical changes and clinical outcomes remains incompletely understood. Stressful events in life causes disruption of serotonergic neurotransmission. Exposure to persistent stress disrupts serotonergic signaling and contributes to psychiatric conditions such as depression and anxiety. Chronic stress amplifies behavioral, neurochemical, and physiological responses to novel stressors and pharmacological challenges. The concept of using chronic stress paradigms to evaluate antidepressant efficacy was pioneered by Katz and colleagues in the 1980s (Katz *et al*., 1980). Subsequent studies have documented stress-induced phenotypes such as reduced body mass (Muscat *et al*., 1988) and alterations in the levels of monoamine (Rowlett *et al*., 1991). Selective serotonin reuptake inhibitors (SSRIs), a family of antidepressants is commonly given to manage major depressive disorder and various anxiety-related conditions. They function by increasing extracellular serotonin levels, through inhibition of presynaptic reuptake, thereby enhancing serotonergic neurotransmission. SSRIs are frequently recommended for chronic anxiety neurosis, obsessive- compulsive disorder, anxiety disorder associated with panic, eating disorders, stress disorder after trauma, and chronic pain (Preskorn *et al*., 2004). Paroxetine a widely utilized SSRI, is prescribed for major depression and related psychiatric disorders, as well as indications including chronic pain, diabetic neuropathy, and bipolar disorder. The present research sought to investigate the anxiolytic and hyperphagic potential using animal model of persistent, unexpected stress. We hypothesized that chronic administration of paroxetine would alleviate behavioral deficits and anorexia induced by chronic mild stress in rats.

METHODS AND MATERIALS

Animals

Twenty-four Male albino mature (150–200g) Wistar rats acquired via the Ojha Campus of Dow University of Health Sciences in Karachi. All procedures adhered by the Institutional Ethical Committee for Animal Research and compiled with the instructions for the Utilization of Laboratory Animals and their care (Institute of Laboratory Animal Resources, US National Research Council, 1996) (Batool *et al*., 2011). Rats were housed in a temperature-regulated room (25 ± 2°C) with a twelve-hour cycle of illumination and darkness, open access to tap water, and regular rodent food. Animals were allowed three days of acclimatization period before any experimental manipulation.

Drugs and Doses

Paroxetine (Sigma, St. Louis, USA) was made fresh each day in physiological saline (0.9% NaCl) and administered orally at 10 mg/kg/day via a stainless-steel feeding tube. Control animals received an equivalent volume of saline (1Ml/kg).

Experimental Protocol

Two main groups were randomly selected from among the 24 rats: 1. Unstressed and 2. Stressed. The stressed group was subjected to a chronic unpredictable stress (CUS) paradigm for 14 consecutive days. Stressors were applied once daily in a random order and included:

- Cold exposure (4°C)
- Cage agitation
- Loud noise
- Water deprivation
- Reversed light/dark cycle
- Cage tilting
- Crowding
- Light deprivation.

In contrast, unstressed animals stayed undisturbed within their home cages. Both stressed as well as unstressed groups were further subdivided into saline-treated and paroxetine-treated subgroups, yielding four experimental conditions:

1. Unstressed + Saline
2. Unstressed + Paroxetine
3. Stressed + Saline
4. Stressed + Paroxetine

Drug or saline administration was administered daily, one hour prior to stress exposure, for 14 consecutive days. Behavioral assessments were conducted after the first administration and subsequently on days 7 and 14.

Behavioral Assessments

1. Food Intake: Diet consumption has been measured by providing a pre-determined portion of feed to each cage for Twenty-four-hours; the food remaining feed after 24h was weighed to calculate intake.

2. Elevated Plus Maze (EPM): Anxious behavior assessed via standard anxiolytic assessment (Pellow *et al*., 1985; Kulikov *et al*., 1997). Two exposed arms make up the equipment (50cm x 10cm) and two closed arms of the same dimensions, connected by a central platform (5 cm^2) and elevated 60cm over the ground. Every rat was placed in the centre, confronting an exposed arm, and given five minutes to explore while activity was recorded. The amount of duration invested in the exposed arms and the quantity of exposed-arm admissions served as anxiety indicators (Pellow *et al*., 1985; Handley and Mithani, 1984).

Statistical Analysis

The mean ± SD was used to express the data, three-way (ANOVA) with several measurements. For post hoc contrasts, the Newman-Keuls test was employed. P-value < 0.05 were statistically relevant. All analyses were conducted with SPSS version 17.

RESULTS

a. Paroxetine administration's effects on intake of food in unpredictable stress rat model

Figures 1 and 2 illustrate the paroxetine impacts (10 mg/kg/day) on food consumption in rats exposed to chronic unpredictable stress (CUS). Data analyzed using three-way recurrent measures ANOVA showed distinct paroxetine's dosage impacts ($F = 129$, $df = 1, 21$, $p < 0.05$) along with stress exposure ($F = 65.77$, $df = 1, 21$, $p < 0.05$). However, neither recurrent measurement ($F = 6.25$, $df = 2, 21$) nor The relationship amongst stress, days, and drugs ($F = 6.64$, $df = 2, 21$) reached statistical significance. Post hoc Newman–Keuls analysis indicated that paroxetine significantly reduced food intake in unstressed animals on the seventh day ($p < 0.05$) and fourteenth day ($p < 0.01$). In the stressed group, paroxetine also caused hypophagia, with considerable decreases observed on 1st and seventh day ($p < 0.05$), and fourteenth day ($p < 0.01$). When comparing stressed and unstressed groups, paroxetine-treated stressed rats exhibited greater reductions in food intake, with significant differences on day first ($p < 0.01$), day seven ($p < 0.01$), and day fourteen ($p < 0.01$). Moreover, stressed saline-treated animals also demonstrated significantly lower food intake than unstressed saline controls on initial day ($p < 0.05$), seventh day ($p < 0.01$), and fourteenth day ($p < 0.01$).

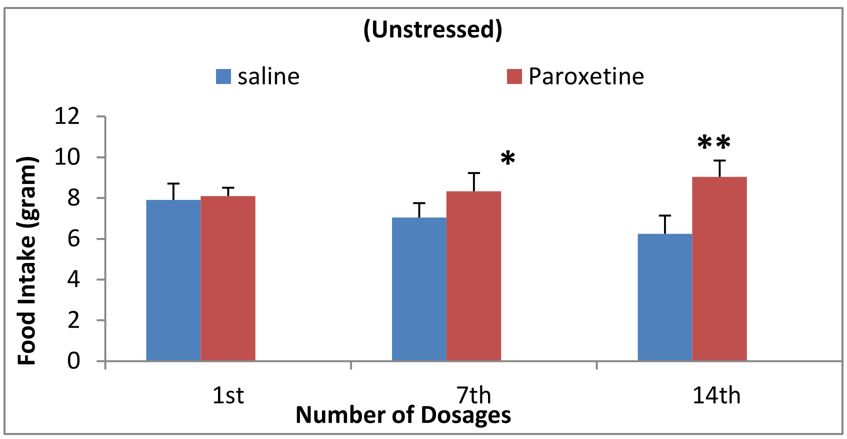

Fig. 1. Effects of paroxetine's administration (10 mg/kg/day) on food intake animals without stress. When measured on days first, seven and fourteen, the values represent the means ± SD (n=06). Newman-keuls test predicted *P<0.05, **p<0.01 in comparison to the corresponding saline-administered animals with or without stress. Considerable variations were predicted by +p<0.05, ++p<0.01 compared to equally saline or paroxetine administered unstressed animals on the same day.

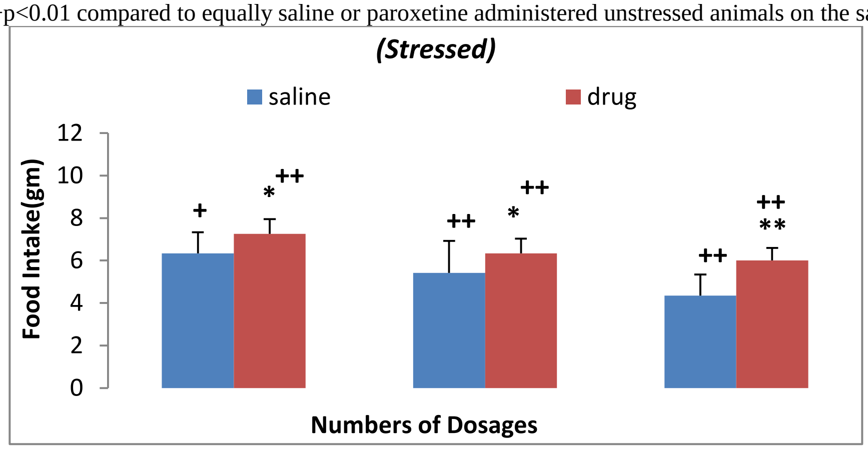

Fig. 2. Paroxetine's administration effects (10 mg/kg/day) on food intake in CMS animals. When measured on days first, seven and fourteen, the values represent the means ± SD (n=06). Newman-keul test predicted *P<0.05, **p<0.01 in comparison to the corresponding saline-administered animals with or without stress. Considerable variations were predicted by +p<0.05, ++p<0.01 compared to equally saline or paroxetine administered unstressed animals on the same day.

b. Paroxetine administartion's effects on time spent in exposed arm in unpredictable stress rat models.

Figures 3 and 4 present the paroxetine impacts (10 mg/kg/day) on exploratory assessment in the anxiolytic activity following CUS. ANOVA revealed significant days effects ($F = 333.36$, $df = 2, 21$, $p < 0.01$), with stress ($F = 157.23$, $df = 1, 21$, $p < 0.05$), and the days × drug association ($F = 249.69$, $df = 2, 21$, $p < 0.05$). Nevertheless, the main effect of the antidepressant alone ($F = 28.97$, $df = 2, 21$) did not reach significance. Post hoc comparisons shows that in unstressed rats, paroxetine significantly increased the duration spent in open arms on day fourteen ($p < 0.01$). In stressed rats, paroxetine produced a modest increase in open-arm activity, it seemed to be statistical insignificant. Relative to unstressed groups, stressed animals displayed significantly reduced open-arm exploration on seventh day ($p < 0.01$) and fourteenth day ($p < 0.01$). The stressed versus unstressed saline controls did not differ considerably.

c. Paroxetine administartion's effects on number of admissions in exposed arm in unpredictable stress models of rats

Figures 5 and 6 demonstrate paroxetine impacts (10 mg/kg/day) on locomotor activity, measured as exposed-arm admissions in the elevated plus maze (EPM). ANOVA indicated no significant days effects ($F = 14.36$, $df = 2, 21$), drug ($F = 8.50$, $df = 1, 21$), with stress ($F = 14.05$, $df = 1, 21$), or their interactions ($F = 9.94$, $df = 2, 21$). Post hoc analysis revealed that paroxetine treatment significantly increased locomotor activity in unstressed rats by day fourteen ($p < 0.01$). Paroxetine also increased activity in depressed animals, with notable increases on day fourteen ($p < 0.01$). When compared with unstressed rats, stressed animals exhibited reduced locomotor activity following paroxetine treatment, with significant decreases detected on day seven ($p < 0.01$) and day fourteen ($p < 0.01$). The stressed versus unstressed controls did not differ considerably.

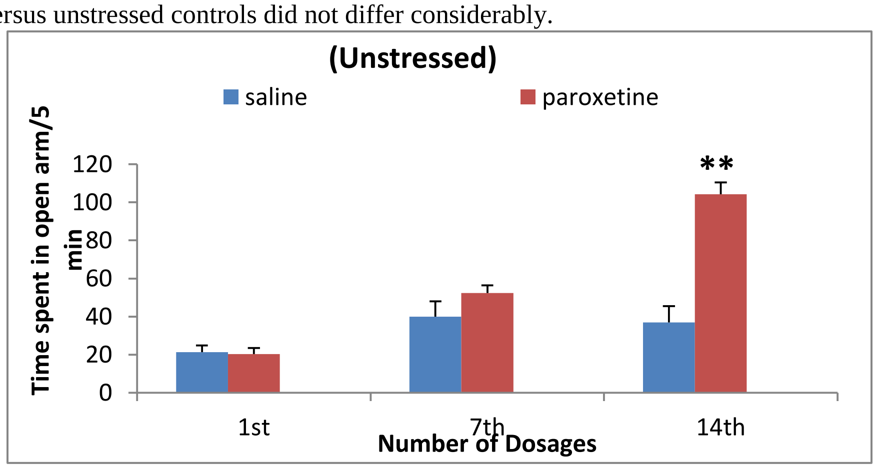

Fig. 3 Paroxetine effects on Time spent in exposed Arm of the anxiolytic activity in rats without stress. When measured on days first, seven and fourteen, the values represent the means ± SD (n=06). Newman-Keuls test predicted *P<0.05, **p<0.01 01 in comparison to the corresponding saline-injected animals with or without stress with considerable variations.

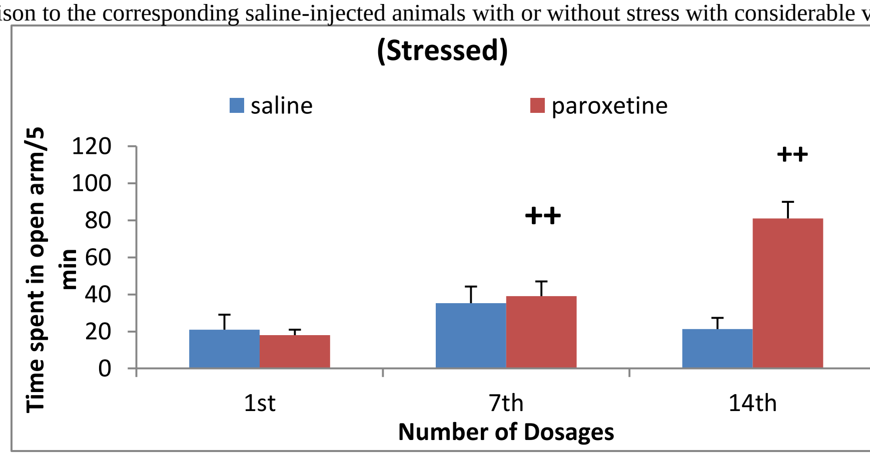

Fig. 4. Paroxetine effects on Time spent in exposed Arm of the anxiolytic activity in rats with stress. When measured on days first, seven and fourteen, the values represent the means ± SD (n=06). Newman-keuls test predicted *P<0.05, **p<0.01 in comparison to the corresponding saline-administered animals with or without stress. Considerable variations were predicted by +p<0.05, ++p<0.01 compared to equally saline or paroxetine administered unstressed animals on the same day.

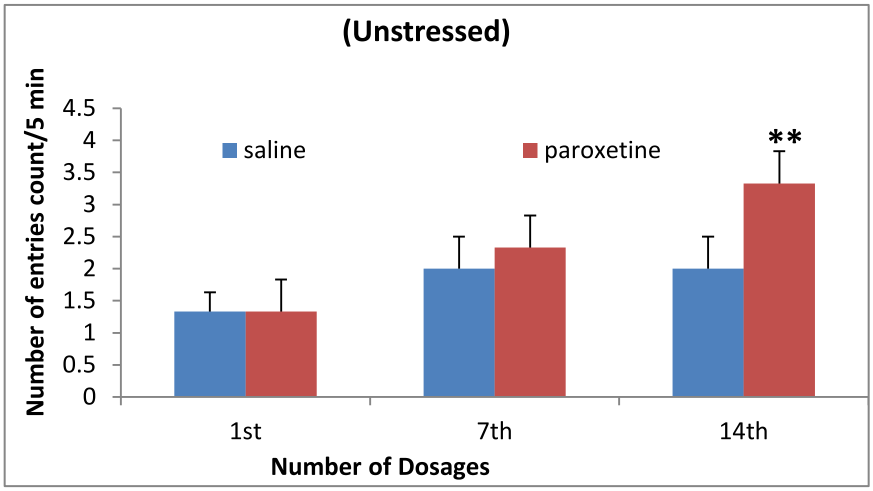

Fig. 5. Paroxetine effects on the Number of Exposed Arm admissions in Open Arm in the anxiolytic activity of unstressed group. When measured on days first, seven and fourteen, the values represent the means ± SD (n=06). Newman-Keuls test predicted *P<0.05, **p<0.01 01 in comparison to the corresponding saline-injected animals with or without stress with considerable variations.

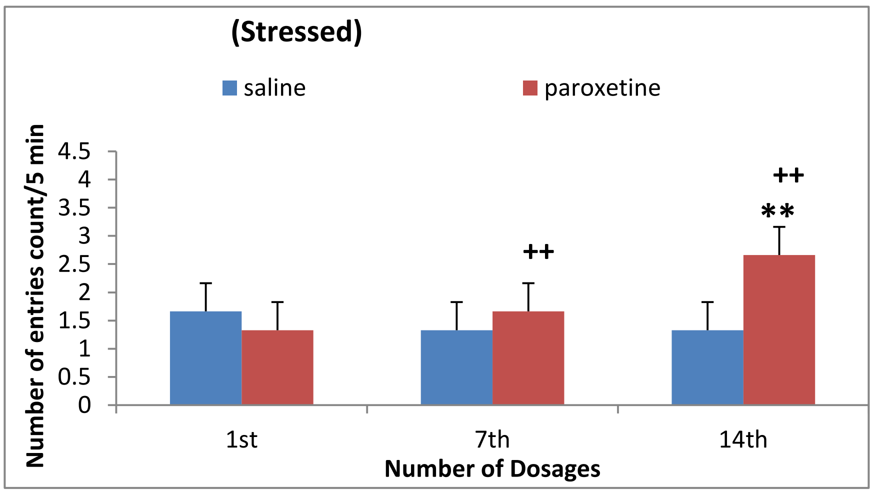

Fig. 6. Paroxetine effects on the number of Exposed Arm activity admissions in anxiolytic activity of stressed group. When measured on days first, seven and fourteen, the values represent the means ± SD (n=06). Newman-keul test predicted *P<0.05, **p<0.01 in comparison to the corresponding saline-administered animals with or without stress. Considerable variations were predicted by +p<0.05, ++p<0.01 compared to equally saline or paroxetine administered unstressed animals on the same day.

DISCUSSION

The present study demonstrates that the model of chronic unpredictable stress (CUS) induces both physiological and behavioral alterations in rats, including reduced food intake and increased anxious responses in the elevated plus maze (EPM). These findings are consistent with earlier studies reporting that repeated exposure to unpredictable stressors disrupts feeding behavior and enhances anxiety in rodents (Willner *et al.*, 1987; Grippo *et al.*, 2002). Importantly, therapy with paroxetine, a selective serotonin reuptake inhibitor (SSRI), attenuated these stress-induced deficits. Stressed rats that received paroxetine displayed significantly greater food intake and improved performance in the EPM compared with saline-treated stressed animals. Although paroxetine did not fully restore behavioral outcomes to the baseline levels of unstressed controls, the partial reversal highlights its efficacy in reducing both hypophagia and anxiety. These results align with previous reports that SSRIs modulate serotonergic transmission to regulate feeding and emotional responses (Blier and de Montigny, 1999; Montgomery, 2001). The absence of significant effects of paroxetine in unstressed animals suggests that its behavioral impact is context-dependent, manifesting primarily under stress-induced conditions. This observation is in agreement with studies showing that

SSRIs exert their most pronounced effects in pathological or stress-exposed models, while their influence on baseline behaviors in healthy animals is limited (Cryan and Holmes, 2005). Stress-induced depression has been widely reported. The mechanisms underlying these findings likely involve serotonergic modulation of neural circuits within the hypothalamus and limbic system, which are critically involved in both appetite regulation and anxiety. Chronic stress has been shown to dysregulate serotonin levels in these regions, while SSRIs restore serotonergic tone and receptor sensitivity (Millan, 2006). Thus, paroxetine's effectiveness in this study may be attributed to its ability to normalize stress-induced disturbances in serotonergic signaling. While the current results are consistent with prior literature, some limitations should be recognized. Because of the sample size, the results may not be as broadly applicable as they may be. Additionally, only male rats were used; sex-related differences in stress responses and antidepressant efficacy should be examined in future work. Finally, biochemical analyses (e.g., serotonin levels, corticosterone assays) were not performed, which could have provided further insight into the neurochemical mechanisms involved. Our finding supports the role of paroxetine in attenuating stress-induced anorexia and anxiety-like behavior in rats, although effects were more pronounced in unstressed animals. Further research incorporating larger cohorts, both sexes, and biochemical markers (including corticosterone and leptin) is warranted to deepen our comprehension of the neurobiological processes behind these results and to better translate preclinical findings into clinical contexts.

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