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# Effects of chronic mild stress on apomorphine induced behavioral sensitization in different brain regions of rats in relation to serotonin change

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## Abstract

**Background:** The impacts of unpredictable stressors have influence on neurochemical and behavioral parameters in laboratory animals. Stress induced behavioral changes particularly those associated with anxiety like behavior may activate topographically organized mesolimbic cortical serotonergic system. This study was designed to investigate the influence of unpredictable stress on behavioral and neurochemical parameters in apomorphine treated rats.

**Methods:** Initially, the animals were divided into two groups as Unstressed and stressed (uncontrollable chronic mild stress or UCMS). Both groups of animals were subdivided into two groups; i.e. saline and apomorphine administrated animals at dose 1.0 mg/kg. Behavioral manipulations was observed by monitoring the locomotor activity and exploratory activity. Neurochemical estimation of 5-hydroxytryptamine (5-HT) was done by High performance liquid chromatography (HPLC). Animals were decapitated 24hr post apomorphine injection and different regions of brain (dorsal and ventral striatum), of animals were collected and stored at -70°C.

**Results:** This preclinical study showed that the UCMS induced hypophagia were promoted in apomorphine administrated animals. Apomorphine induced hyperlocomotion were more prominent in unstressed animals than that of stressed groups. It implies that apomorphine is effective in the retrieval from UCMS induced depressive symptoms in rats. Neurochemical study showed decreased level of 5-HT in unstressed animals than stressed animals in response to apomorphine administration.

**Conclusion:** This study, therefore establish the relation between stress and addiction at behavioral as well as neurochemical level to better understand the idea whether intolerable stress promotes addiction.

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## Introduction

Stressful events in life cause the destruction in serotonergic neurotransmission which in turn appear as disorder like stress and depression. The topographically selective activation of serotonergic neurotransmission suggests that the serotonergic neurons activated by the stress-related stimuli may reside in the median raphe nucleus [1] and caudal dorsal raphe nucleus. Previous study have demonstrated the results which indicates that the inescapable shock positively affects the extracellular levels of 5-hydroxytryptamine (5-HT) in the dorsal raphe nucleus of the rats [2].

Chronic stress potentiates behavioral, neurochemical, and physiological responses to drug challenges and novel stressor. A single session of uncontrollable (inescapable tail shock), but not controllable (escapable tail shock), stress is known to selectively potentiate subsequent morphine-conditioned place preference in a dorsal raphe nucleus, 5-HT dependent manner [2].

Apomorphine is well documented dopamine agonist [3-4] with selectivity towards both D1 and D2 receptors [5]. Apomorphine is reported to produce behavioral sensitization, a phenomenon of progressive increase in locomotor activity on repeated exposure of a substance [6] whereas this sensitization is based on time course between injection and testing. It has been suggested that apomorphine-induced hyperactivity appear to be mediated by dopamine auto-receptor stimulation [7].

Serotonin neurotransmission has been seen to be alters in both acute and chronic stresses. Stressor based on physical and social conditions in repeated manner is reported to increases the density of 5-HT sub type 2A (5-HT2A) receptor in the cortex [8]. Heightened stress sensitivity may be a risk factor in affective disorder onset and susceptibility. Females show an increase in stress response magnitude and recovery time compared to males. Rodent based preclinical studies demonstrated that the females animals are more sensitive to stress it might be due to the increased level of both adrenal corticotropic hormone (ACTH) and corticosterone compared to males as well as the extension of these hormones level in plasma makes it difficult to reverse the stress induced depressive symptoms [9]. Normalized level of 5-HT is demanded to support the intercommunicative neuronal transmission, It optimizes behavioral and neuro modulation during and after different forms of exertions [10]. A variety of stress stimuli increase the synthesis and catabolism of serotonin. It has been reported that different stress conditions such as restraint stress [11] and starvation [12] increase brain 5-Hydroxyindoleacetic acid (5-HIAA) levels. Behavior deficits are also observed following restraint stress [11].

The contradictory effects of dopamine agonists was reported on repeated restrain stress and chronic mild stress as increased and decreased locomotor activity respectively [13-15]. This result raises an idea that antidepressant negatively affects the mesolimbic dopamine system sensitivity as the way of that stress affects, at least as far as the neural circuits mediating locomotor activity are concerned. The changes in a body undergoing due to stress is controlled by the brain serotonergic system [16].

The outcomes of previous studies indicates the enhanced functioning of brain serotonergic system builds a state which cope up with stress as well as prevent the stress-induced disturbances in mood and emotions [17-18]. The present study was designed to monitor the effects of unpredictable chronic stress on the behavioral and neurochemical effects of apomorphine. Apomorphine elicits sensitization on repeated administration. Sensitization is a well-known component of psychostimulant-induced addiction. Uncontrollable stress may lead to depression while prevalence of depression is greater in addicts than normal population.

## Methods

### Animals

Locally bred male Albino-Wister rats weighing 180-220 grams were purchased from The Aga Khan University, Karachi, Pakistan, and housed individually under 12 hrs light-dark cycle and controlled room temperature (25±2) with free access to cubes of standard rodent diet and water, a week. 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.

### Drugs and Doses

Apomorphine-HCl (Sigma, St. Louis, USA) was dissolved in saline (0.9% NaCl) and injected intraperitoneally at a dose of 1.0 mg/kg to the respective group of animals. Drug was freshly prepared before

starting the experiment. Saline (0.9% NaCl solution; 1ml/kg) was injected to control animals.

**Experimental Protocol**

Twenty four (12 male and 12 female) Albino wistar rats were randomly divided into two groups: (i) Unstressed and (ii) Stressed groups. Animals of the stressed group were exposed to a schedule of chronic mild stress (CMS) shown below over a period of 10 days [21]. On the other hand, animals of unstressed groups remained in their home cages. After exposure to CMS the animals of each group were again subdivided into two groups each i.e., saline- and apomorphine injected. This resulted in a total of four groups: (i) Unstressed- Saline, (ii) Unstressed- Apomorphine, (iii) CMS- Saline and (iv) CMS- Apomorphine injected animals. Animals were administrated accordingly with Apomorphine (1.0 mg/kg) or saline (1.0 mg/ml) next 6 days. Daily food intake, change in body weight and activity in activity box was monitored. Activity in open field was monitored on next day of last administration of apomorphine. Animals were sacrificed to collect different brain regions 24 hrs after last apomorphine administration. Samples were stored at -70°C until neurochemical estimations by high performance liquid chromatography with electrochemical detection (HPLC-EC).

**Behavioral Assessment**

*Home cage activity*

The monitoring of locomotion in familiar condition was done by using home cage activity box. Apparatus used in this study was made up of transparent perspex (26 x 26 x 26 cm) with a sawdust covered floor. Testing was done in recommended condition which is quite room under white light [21]. Animals were allowed to habitual in activity box for 15 minutes before monitoring. Number of cage crossing as well as grooming were monitored with the cut off time 10 minutes.

*Open field activity*

Locomotion in novel and exploratory environment was done by open field activity test. Open filed apparatus used in present investigation consisted of a square area (76 x 76 cm) with walls 42 cm high. The floor was divided by lines into 25 equal squares. Procedure was same as described earlier [22-23]. For assessment of exploratory activity animals were individually placed in center of field, time to move from center (latency time) and number of square crossed with all four paw were the measuring during the time period of 5 minutes.

**Neurochemical Assessment**

Decapitation of rat brain Saline or apomorphine injected animals was done 24 hrs post last injections. The collected brains were immediately stored at -70°C for the estimation of 5-HT level using HPLC-EC [24]. Extraction was performed using 70% perchloric acid. 5 times volume of the extraction medium was added to the brain tissues. Samples were homogenized by using electrical homogenizer and subjected to ultracentrifugation at 6000 (rpm). Supernatant was separated and injected to HPLC-EC for neurochemical assay. HPLC-EC estimation was done as described earlier [23]. A 5µ Shimpack ODS separation column of 4.0 mm internal diameter and 150 mm length was used. 0.1 M phosphate buffer (PH 2.9) containing EDTA (0.0035%), methanol (14%) and octyl sodium sulfate (0.023%) was used at an operating potential of 2000-3000 psi on Schimadzu HPLC pump. Electrochemical detection (using Schimadzu LEC 6A detector) was done at an operating potential of +0.8V.

**Statistical Analysis**

Values are presented as means ± SD. All behavioral data on drug administration of unstressed and stressed male and female rats were analyzed by three-way ANOVA. Data of 5-HT level indifferent brain regions were analyzed by two-way ANOVA. Software used for the analysis was SPSS (version 17). Post-hoc comparison was done by Newman-Keuls test. Values of $p<0.05$ were considered as significant.

## Results

**1. Effects of apomorphine on % growth rate of rats exposed to UCMS**

Data as analyzed by three-way ANOVA showed that effects of apomorphine administration ($F=81.025$; $df=1, 22$: $p<0.01$) and interaction among stress, apomorphine and days ($F=49.184$; $df= 1, 22$: $p<0.01$) were significant. However, the effects of days ($F=0.075$; $df=1, 22$) and stress ($F=0.182$; $df=1, 22$), were non-significant. Post-hoc analysis by Newman Keuls test showed that repeated administration of apomorphine at 1.0 mg/kg decreased growth rate in animals of unstressed as well as stressed group. Significant decrease in growth rate was found in both female ($p<0.01$) and male ($p<0.05$) rats of un-

stressed group. In stressed group, significant decrease ($p<0.01$) was monitored only in male rats.

**2. Effects of apomorphine on food intake of rats exposed to UCMS**

Analysis of data on cumulative food intake as analyzed by three-way ANOVA. It showed that effects of stress ($F=9.792$; $df=1, 22$; $p<0.01$), apomorphine ($F=12.37$; $df= 1, 22$; $p<0.01$) and interaction between all three factors ($F=18.86$; $df=1, 22$; $p<0.01$) was significant on food intake. Whereas, the effect of days ($F=0.491$; $df=1, 22$) was non-significant. Post-hoc analysis by Newman Keuls test showed that administration of apomorphine induced decrease in food intake in animals of unstressed as well as stressed group. Apomorphine induced hypophagic condition was significant ($p<0.05$) in both female and male rats of unstressed group but in stressed group hypophagia only developed in female rats ($p<0.05$).

**3. Effects of apomorphine on number of cage crossed in activity box of rats exposed to UCMS**

Data analysis by three-way ANOVA showed significant effect of stress ($F=40.26$; $df=1, 22$; $p<0.01$), apomorphine ($F=985.88$; $df= 1, 22$; $p<0.01$), days ($F=5.56$; $df= 1, 22$; $p<0.01$) as well as interaction among all three factors ($F=36.43$; $df= 1, 22$; $p<0.01$) on cage crossings in activity box. Post-hoc analysis by Newman Keuls test showed that administration of apomorphine at dose of 1.0 mg/kg repeatedly increased the number of cage crossing ($p<0.01$) in activity box of male and female rats of both unstressed as well as stressed group as compared to saline administrated animals. Apomorphine induced hyperlocomotion was greater in female ($p<0.01$) rats on both unstressed and stressed group. Hyperlocomotive response of apomorphine was smaller ($p<0.01$) in stressed animals as compared to unstressed animals.

**4. Effects of apomorphine on number of squares crossed in open field by the rats exposed to UCMS**

Analysis of the data on number of squares crossed by three-way ANOVA showed significant effects of apomorphine ($F=124.63$; $df=1, 22$; $p<0.01$), days ($F=30.02$; $df=1, 22$; $p<0.01$), stress ($F=86.31$; $df=1, 22$; $p<0.01$) and interaction among stress, apomorphine and days ($F=120.00$; $df=1, 22$; $p<0.01$) in open field. Post-hoc analysis by Newman Keuls test showed that apomorphine administration increased exploratory activity in open field area as compared to saline administrated animals. Significant ($p<0.01$) increased in value was found in male and female rats of both unstressed and stressed group. Apomorphine induced hyperlocomotion was smaller ($p<0.05$) in stressed group animals as compared to similarly administrated animals of unstressed group.

**5. Effects of apomorphine on 5-HT Level in Dorsal Striatum of rats exposed to UCMS**

Data on 5-HT level in male and female rats as analyzed by two-way ANOVA showed effects of stress ($F=120.07$; $df=1, 20$; $p<0.01$), apomorphine administration ($F=6.90$; $df= 1, 20$; $p<0.01$) and interaction between stress and apomorphine ($F=36.52$; $df= 1, 20$; $P<0.01$) were significant. Post-hoc analysis by Newman Keuls test showed that level of 5-HT was decreased ($p< 0.01$) in dorsal striatum region of apomorphine administrated male and female rats of unstressed and stressed group. In unstressed group, 5-HT level was less decreased ($p<0.01$) in apomorphine administrated female as compared to male rats. 5-HT level in apomorphine as well as saline administrated female rats of stressed group was less as compared to similarly administrated animals of unstressed group.

**6. Effects of apomorphine on 5-HT Level in Ventral Striatum of rats exposed to UCMS**

Analysis of data on 5-HT level in male and female rats as analyzed by two-way ANOVA showed that effects of stress ($F=45.87$; $df=1, 20$; $p<0.01$), apomorphine administration ($F=62.18$; $df=1, 20$; $p<0.01$) and interaction between stress and apomorphine ($F=20.68$; $df= 1, 20$; $p<0.01$) was significant. Post-hoc analysis by Newman Keuls test showed that level of 5-HT in ventral striatum was decreased in apomorphine administrated animals of unstressed as well as stressed groups as compared to saline administrated animals. In stressed group, the level of 5-HT was significantly ($p<0.05$) smaller in apomorphine and saline administrated animals as compared to similarly administrated animals of unstressed group. Significant value ($p<0.01$) was found in female of saline as well as apomorphine administrated group and only in male rat of saline administrated group.

## Discussion

The present study was aimed to observe the consequences of apomorphine followed by the UCMS

exposure in male and female rats. Subjection of animals to the chronic stress, characterized as a continuous adverse situation which alters the behavior of animals in greater extent [25]. Due to the fact that serotonin neurotransmission alter by stress exposure which in turn produces behavioral deficits, CMS-induced behavioral deficits in animals could be effectively use as an animal model of depression [26]. Decreased serotonergic function might be root cause of the progression of depressive symptoms [27]. In present preclinical study, CMS induced hypophagia was observed to be encourage by repeated administration of apomorphine in animals with both gender. On the other hand, apomorphine lessened induced hypo-locomotion in activity box and open field. The level of the 5-HT was shown to decrease in different brain regions after chronic treatment of apomorphine. Previous Studies have shown that local blockade of striatal DA D2 receptors prevented apomorphine induced increase in dialysate 5-HT level, suggesting that facilitation of 5-HT transmission takes place primarily at the nerve terminal end [28-30]. Present study suggested that the apomorphine decreases the food intake and growth rate of both female and male rats which were previously exposed to CMS. Previously it has been reported that systematic administration of dopaminergic drugs induces significant changes in the behaviors of animal model. From present study, it can be concluded that apomorphine induced changes in behavioral parameter are smaller in CMS animals then unstressed animals. These findings are in agreement with previous study [31], which explained that the repeated administration of apomorphine increased motor activity in familiar as well as in novel environment at dose of 1.0 mg/kg.

The study summarized the effects of apomorphine that is increased locomotor activity of both stressed as well as unstressed animals whereas this apomorphine induced hyperlocomotion was smaller in CMS exposed animals than unstressed animals. Previously, the restraint stress showed increased locomotion and CMS showed decreased locomotion to dopamine agonist respectively. Previous studies had established that effects of exposure to mild stress chronically to an animal model can be altered by antidepressant agents [25,32-33]. Many studies have reported that systematic injections of dopaminergic drugs result in profound changes in the behaviors of the animals [34].

It has been summarized from this study that repeated administration of apomorphine increases the level of 5-HT in the dorsal striatum of both female and male rats of CMS group whereas decreases the 5-HT in ventral striatum of female rats of both CMS as well as unstressed groups. Unstressed Male rats showed decreased 5-HT level in ventral striatum significantly after administration of apomorphine. Studies have shown that local blockade of striatal DA D2 receptors prevented apomorphine-induced increased in dialysate 5-HT level, suggesting that facilitation of 5-HT transmission takes place primarily at the nerve terminal end [28-30]. Present study concluded that the chronic treatment of apomorphine at dose 1.0 mg/kg successfully attenuated UCMS induced depressive behavior. Chronic stress is act as stimulus for the interruption in serotonin neurotransmission. Present study intended to observe the possible outcomes of UCMS exposure in animals which might be able to induce behavioral alterations notably anhedonia, weight loss, loss of appetite, decreased locomotor and exploratory activities. It was observed that apomorphine induced behavioral sensitization was more intensify in unstressed animal than CMS group. Present study will help to emphasis the interaction of stress and addiction at both physiological and neurochemical level in order to understand whether uncontrollable stressful events in life or depression arouse addiction furthermore, whether the use of addictive drugs participate in the progression of depression.

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