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Enhancement and inhibition of apomorphine-induced sensitization in rats exposed to immobilization stress: Relationship with adaptation to stress

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ABSTRACT

Stress increases vulnerability to addiction while drugs of abuse impair coping responses and pre-dispose to depression. Pre-clinical research shows that stress exposure augments locomotor sensitization effects of drugs of abuse and impairs behavioral tolerance to repeated stress. The present study investigates relationship between behavioral tolerance to repeated immobilization stress and apomorphine-induced sensitization. Apomorphine was injected either before exposure or after the termination of immobilization, daily for 5 days, to monitor drug-induced behavioral sensitization and tolerance in immobilization stress-induced anorexia. We find that apomorphine-induced sensitization is enhanced and tolerance to repeated immobilization is impaired if the drug is administered before exposure to stress episode. Conversely, apomorphine-induced sensitization is inhibited and adaptation to stress is facilitated if the drug is administered after the termination of stress episode. It shows that apomorphine, if experienced during stress, produces greater sensitization and impairs stress tolerance. Conversely, sensitization effects of apomorphine are blocked and tolerance to stress is facilitated in animals receiving drug after the termination of stress episode. It is suggested that additive effects of stress and apomorphine on mesocorticolimbic dopamine neurotransmission and 5-HT-1A influences on dopamine neurotransmission may have a role in the modulation of apomorphine sensitization and tolerance to repeated immobilization stress. The results may help develop potential pharmacotherapies when substance abuse/dependence disorder and depression occur together.

1. Introduction

Stress has long been known to increase vulnerability to addiction. Stress-induced changes in brain reward circuits increase the sensitivity to the reinforcing properties of drugs, thereby increasing the motivation to use drugs compulsively (Koob and Le Moal, 1997). Pre-clinical research addressing relationship between stress and addiction support the notion that acute exposure to stress increases initiation and escalation of drug use and abuse. For example, the acquisition of amphetamine and cocaine self-administration was enhanced in rats exposed to a variety of stressors (Kabbaj et al., 2001; Kosten et al., 2000). Exposure to electric foot-shock stress also increased the subsequent reinforcing efficacy of heroin (Shaham and Stewart, 1994) and morphine (Will et al., 1998) in rats.

The likelihood of substance abuse/dependence disorders and depression to occur together in the same individuals is about 5 times greater than would be expected by the prevalence of each disorder alone (Rounsaville, 2004; Volkow, 2004). According to self-medication hypothesis, people use drugs to enhance mood and alleviate emotional distress (Khantzian, 1985). Another, likely explanation for the occurrence of depression and drug addiction together could be that recreational use of drugs of abuse impairs coping responses and pre-dispose to depression. Thus, animals drinking alcohol as the sole source of water for two weeks exhibited impaired tolerance to repeated immobilization stress (Haleem, 1996, Haleem et al., 2002).

Forced immobilization is one of the best explored models of stress in rats. We (Haleem and Parveen, 1994; Haleem, 1999, Haque et al., 2013) and others (Kennett et al., 1985; Calvez et al., 2011, Valles et al., 2000) have reported that exposure to an episode of 2-h immobilization stress decreased 24-h cumulative food intake and body weight in rats. The animals exhibited anxiety/depression like behavior in light dark transition test, elevated plus maze test (Haleem, 2011a,b; Suvrathan et al., 2010, Haque et al., 2013) and forced swimming test (Suvrathan et al., 2010; Snyder et al., 2011). The deficits in food intake and other behaviors no longer persisted upon repeated immobilization (Haleem and Parveen,

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1994; Kennett et al., 1985; Valles et al., 2000; Gil et al., 1992). It was suggested that repeated exposure to the same stressor produces adaptive changes that led to behavioral tolerance (Haleem, 2011a,b).

Repeated exposure to psychostimulant drugs, including apomorphine, induces a progressive enhancement of locomotor activity in rodents. The phenomenon, called 'behavioral sensitization', is thought to underlie certain aspects of drug abuse that lead to drug addiction (Nishikawa et al., 1983; Robinson and Becker, 1986; Vanderschuren and Kalivas, 2000). Drug-induced hypersensitivity of motivational circuitry is suggested to mediate an increase in drug "wanting," shifting recreational drug use to pathological abuse displayed by addicts (Berridge et al., 2009). Although sensitization and reinstatement involve overlapping neuronal circuitry, neurotransmitters and their receptors but the involvement of sensitization in reinstated drug seeking behavior remains controversial (Vanderschuren and Pierce, 2010; Kalivas et al., 2006). Behavioral sensitization however, remains a useful model for determining neural basis of addiction and neuroadaptations associated with the behavioral sensitization are considered as initial step in the drug addiction.

The purpose of the present study was to investigate relationship between tolerance to repeated immobilization stress and sensitization effects of apomorphine. The drug was injected either before exposure or after the termination of immobilization, daily for 5 days, to monitor any change in behavioral sensitization. Effects of apomorphine on immobilization stress induced deficits of food intake and body weight were also determined in both experimental paradigms for an understanding of the relationship between stress tolerance and sensitization.

2. Materials and methods

2.1. Animals

Locally bred male albino Wistar rats, weighing 220–250 g purchased from HEJ Research Institute of Chemistry, Karachi, Pakistan were housed individually under a 12-h light and dark cycle (lights on at 6:00 h) and controlled room temperature (24 ± 2 °C) with free access to tap water and cubes of standard rodent diet, 3 days before the start of experiment so that they could become familiar to the environment. Animals were tested in light phase. Before starting the experiment, rats were accustomed to various handling procedures in order to nullify the psychological affliction of environment. All animal experiments, approved by the Institutional Ethics and animal Care Committee, were performed in strict accordance with National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85–23, revised 1985). All treatments and behavioral monitoring were done in a balanced design to avoid order and time effect.

2.2. Drugs

Apomorphine-HCl (Sigma, St. Louis, USA) was dissolved in saline and injected subcutaneously at a dose of 1.0 mg/ml/kg (Ikram and Haleem, 2011). Drug solutions were freshly prepared before each experiment. Control animals were injected with saline (0.9% NaCl) at a dose of 1.0 ml/kg.

2.3. Experimental protocol

2.3.1. Experiment 1: Behavioral sensitization and adaptation to stress in animals injected with apomorphine 1 h before stress exposure

Twenty four animals were weighed and randomly divided into four equal groups of six each: (i) saline unstressed; (ii) saline stressed; (iii) apomorphine unstressed; (iv) apomorphine stressed groups. The animals placed in the activity box (one in each box) 15 min before injections to get habituated with the experimental arena were injected accordingly with saline or apomorphine between 8:00 and 9:00 h. Activity was monitored for a period of 15 min starting 5 min post-injection. The animals were then placed back to their home cages. One hour after the injection i.e. between 9:00–10:00 h to 11:00–12:00 h, the animals of the stressed groups were immobilized for 2 h by taping their legs to wire grids. Animals of the unstressed groups were left in their home cages during this time. After release from the grids, animals of stressed groups were also placed back in their home cages with free access to food and water. Cumulative food intakes and body weights were monitored next day before injecting the drug. The animals were injected with saline or apomorphine and stressed or left unstressed daily for 5 days. Activity, food intake and body weights were also similarly monitored every day.

2.3.2. Experiment 2: Behavioral sensitization and adaptation to stress in animals injected with apomorphine 1 h after the termination of stress

Twenty four animals were randomly divided into four equal groups of six each: (i) unstressed saline; (ii) stressed saline; (iii) unstressed apomorphine; (iv) stressed apomorphine groups. The animals of stressed group were immobilized on wire grids for 2 h between 9:00–10:00 h to 11:00–12:00 h. After release from immobilization they were placed back in their home cages. The animals of unstressed group were left unstressed in their home cages during this period. Both stressed and unstressed animals exposed to experimental arena 15 min before injection were injected with saline or apomorphine between 12:00 and 13:00 h. Cumulative food intakes and body weights were monitored next day between 8:00 and 9:00 h. The animals were stressed or left unstressed and injected with saline or apomorphine daily for 5 days. Activity, food intake and body weights were also similarly monitored every day.

2.4. Immobilization procedure

The animals were immobilized as described before (Haque et al., 2013). Wire grids of 10 in. × 9 in. fitted with a Perspex plate of 9 in. × 6.5 in. were used. Immobilization was effected by pressing the forelegs of the rat through the gaps in the metal grid and taping them together with zinc oxide plaster. Hind limbs were also taped and the head of the animal rested on the Perspex plate. At the end of the 2 h immobilization period the animals were released and returned to their home cages.

2.5. Monitoring activity in the familiar arena of activity cages

Transparent Perspex cages (26 × 26 × 26 cm) with sawdust covered floor were used to monitor activity in familiar environment. Rats were placed individually in these cages to get familiar with the experimental arena. 15 min later the animals were injected with drug or vehicle. Numbers of cage crossings were counted 5 min post-injection for 15 min (Ikram and Haleem, 2011).

2.6. Food intakes and body weights

Cumulative food intakes (g) were determined by taking the difference of food given on day 1, between 8:00 and 9:00 h, and food left next day and every day (between 8:00 and 9:00 h). Body weights were also monitored at the same time and change in body weights were calculated (body weight on monitoring day / body weight on preceding day) × 100 as reported previously (Haque et al., 2013).

2.7. Statistical analysis

Data were analyzed by three-way analysis of variance (ANOVA) repeated measure design, using SPSS version 15.0. Post-hoc analysis was done by Newman–Keul's test and p values less than 0.05 were taken as significant.