Pharmacological Reports
2011, 63, 1085–1092
ISSN 1734-1140

Locomotor activity changes in female adolescent and adult rats during repeated treatment with a cannabinoid or club drug

Jenny L. Wiley[1,2], Rhys L. Evans[2], Darren B. Grainger[2], Katherine L. Nicholson[2]

[1]RTI International, 3040 Cornwallis Road, Research Triangle Park, North Carolina 27709-2194, USA

[2]Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, Virginia, USA

Correspondence: Jenny Wiley, e-mail: jwiley@rti.org

Abstract:
Adolescents and young adults of both sexes are the primary consumers of "club" drugs; yet, most of the mechanistic preclinical research in this area has been performed in adult male rodents. The purpose of this study was to evaluate the acute and repeated effects of drugs that are commonly abused by adolescents in female adolescent and adult rats in a rodent model of behavioral sensitization. During two five-day periods separated by a two-day break, rats were injected daily with saline or with one of the following drugs: cocaine (7 or 15 mg/kg), ketamine (3 or 10 mg/kg), 3,4-methylenedioxymethamphetamine (MDMA) (3, 10, or 30 mg/kg), or Δ^9-tetrahydrocannabinol (THC) (0.03, 0.1, 0.3 or 1 mg/kg) and their locomotor activity was measured. Cocaine increased activity across days in both age groups. Whereas ketamine produced progressive increases in activity with repeated administration in rats of both ages, MDMA increased, and then decreased, activity in the chronic dosing regimen in female adolescents only. Tolerance to the initial stimulatory effects of low doses of THC was observed at both ages. The results with THC are similar to those obtained for male rats tested under identical conditions in a previous study; however, in contrast with the present results in females, male adolescent rats in the previous study failed to develop behavioral sensitization to ketamine. Together, these results suggest that age and sex strongly influence the progressive adaptive changes that occur with repeated administration of some, but not all, of these commonly abused substances.

Key words:
behavioral sensitization, club drugs, cocaine, female rats, locomotor activity, MDMA, THC

Abbreviations: MDMA – 3,4-methylenedioxymethamphetamine, PN – postnatal, THC – Δ^9-tetrahydrocannabinol

Introduction

Historically, the majority of clinical and preclinical research on substance abuse has focused on the physiological and behavioral underpinnings of this health problem on males. Only relatively recently has attention shifted to include females and examination of sex/gender differences has become increasingly common [36]. With the possible exception of investigation of the effects of substance use on pregnant women and their offspring, however, empirical studies of the specific effects of abused substances in women are still in the minority. Yet, epidemiological studies have shown that the patterns of drug use in women differ from those seen in men [16, 18]. For ex-

ample, while women may initially take lower doses of an abused drug, they tend to become addicted faster and to relapse more frequently following a period of abstinence [2], although gender/sex differences have also been observed during other phases of the substance abuse process [7].

Initial experimentation with illicit drugs for both sexes typically begins during adolescence, a time of neuronal reorganization and receptor pruning in the central nervous system [34]. Consequently, adolescent brains differ from those of adults. Further, these differences are superimposed upon rapid sexual differentiation of the brain and behavior that is induced, in part, by the surge in gonadal hormones that occurs during adolescence [30]. In adult female rodents, hormonal status has been shown to strongly influence responses to drugs of abuse [2, 7]. For example, sensitivity to cocaine's locomotor stimulant effects peaks during proestrus and estrus and plunges during diestrus [32]. The behavioral effects of drugs of abuse in adolescents, and particularly in female adolescents, have not been as extensively investigated.

The purpose of the present study was to examine the effects of selected drugs that are commonly abused by adolescents and young adults in a rodent model of behavioral sensitization. In this context, behavioral sensitization is the phenomenon whereby initial drug-induced stimulation of locomotor activity is enhanced following repeated administration of the drug. It is a robust phenomenon that has been observed with drugs of abuse from several distinct classes, including nicotine [3], but especially with psychostimulants and represents a form of neural adaptation [27, 28]. Because behavioral sensitization is believed to be one of the early processes that may occur in the development of drug dependence [28], examination of this effect in adolescents is particularly important. In a previous report, the effects of cocaine, 3,4-methylenedioxymethamphetamine (MDMA), ketamine and Δ^9-tetrahydrocannabinol (THC: primary psychoactive substitutent of marijuana) in male adolescent and adult rats were described [38]. Cocaine was chosen because it is a prototypic psychomotor stimulant that has often been used in behavioral sensitization studies. In this study, it was intended to serve as a positive control. The other three drugs were chosen because they are illicit drugs that are used recreationally particularly during adolescence/early adulthood. In the present study, these drugs were tested under identical experimental conditions and during the same time period in female adolescent and adult rats as in our previous study with male rats.

Materials and Methods

Subjects

Adolescent female Long-Evans rats used as subjects were bred in house using purchased dams and sires (Harlan, Dublin, VA). After breeding, the individually housed dams were left undisturbed except for providing food, water, and fresh bedding until they gave birth (postnatal day 0, PN0). Sufficient woodchip bedding was available in each cage for nesting. Female pups were randomly selected (one per litter) for each of the drug treatment groups described below. On PN21, pups were weaned and were pair-housed with a same-sex rat from another litter that had been assigned to the same drug treatment group. Male pups from the same litters were used in an identical series of experiments that have already been published [38]. Male and female pups that were not used in either study were assigned to other studies. The rat pups were tested for 10 days between ages PN27–PN38. To provide adult subjects for comparison, drug naive adult female rats were ordered (Harlan) at an age of greater than PN65 and were also pair-housed with another female assigned to receive the same drug treatment. Purchased rats were allowed to acclimate to the animal facility for at least one week before initiating testing. Throughout the experiment, all rats, adolescent and adult, were housed in clear plastic shoebox style cages in a temperature-controlled (20–22°C) environment with a 12-hour light-dark cycle (lights on at 7:00 a.m.). All rats had free access to food and water while in their home cage. The studies reported in this manuscript were carried out in accordance with guidelines published in the *Guide for the Care and Use of Laboratory Animals* [24] and were approved by the Institutional Animal Care and Use Committee at Virginia Commonwealth University.

Drugs

Cocaine HCl [National Institute on Drug Abuse (NIDA), Bethesda, MD, USA] and 3,4-methylenedioxymethamphetamine (MDMA) [NIDA] were dissolved in saline. Ketamine (Phoenix Scientific, Inc., St. Joseph, MO, USA) was diluted with saline from a commercial stock of 100 mg/ml. THC [NIDA] was mixed in a vehicle of absolute ethanol, Emulphor-620 (Rhone-Poulenc, Inc., Princeton, NJ,