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Age-specific behavioral responses to psychostimulants in mice

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Abstract

This study investigated the influence of age on the behavioral responses elicited by psychostimulants in male CD-1 mice. Behavioral activity including locomotion and stereotypy was measured following acute or repeated administration of cocaine, methylphenidate, amphetamine or saline to postweanling (24 days old), periadolescent (33 days old) and adult (60 days old) mice. Postweanling mice exhibited less total and ambulatory activity than periadolescent mice following a single acute injection of cocaine (20 or 30 and 30 mg/kg, respectively). Further, postweanling mice showed less total activity than both periadolescent and adult mice at a dose of 10 mg/kg methylphenidate. Less stereotypy was also seen in postweanling mice when compared to adolescent mice after 30 mg/kg amphetamine. Seven daily injections of cocaine resulted in a heightened behavioral response on day 7 as compared to day 1, indicative of behavioral sensitization in adult and periadolescent, but not postweanling mice. Repeated methylphenidate resulted in increased total activity in adult, but not periadolescent or postweanling mice. None of the animals were sensitized to the behavioral activating effects of amphetamine. The magnitude of behavioral response and the development of sensitization were dependent upon the age of the animal and the agent tested.

Keywords: Cocaine; Methylphenidate; Amphetamine; Mice; Sensitization; Development; Adolescent

1. Introduction

The use of psychomotor stimulants by children and adolescents continues to rise due to both the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and illicit abuse (Cantwell, 1996). Responses to psychostimulants can vary with age. During adolescence and adulthood, stimulants elicit a euphoric response, while they have been described as dysphoric by children (Rapoport et al., 1980). Despite noted differences, few studies have systematically compared the effects of psychostimulants in mice of different ages. This has prompted our study of the effects of both acute and repeated exposure to these drugs in different age groups.

Cocaine, methylphenidate and amphetamine are psychomotor stimulants which all enhance synaptic neurotransmitter concentrations, but with somewhat different mechanisms of action. Cocaine inhibits the reuptake transporters for dopamine, serotonin and norepinephrine, thereby increasing these neurotransmitter concentrations in the synapse (Heikkila et al., 1975a). Methylphenidate also blocks dopamine and norepinephrine reuptake transporters causing an increase in extracellular levels, but exerts a minimal effect on serotonin transporters (Kuczenski et al., 1997). Amphetamine increases dopamine, norepineprine and serotonin in the synapse by increasing their release (Heikkila et al., 1975b; Connor and Kuczenski, 1986). Methylphenidate and amphetamine are used therapeutically to treat common childhood illnesses, whereas all three drugs are used illicitly by adolescents and adults.

Acutely, cocaine, amphetamine and methylphenidate administration can produce dose-dependent behavioral activation (Heffner and Seiden, 1982; Gerasimov et al., 2000; Schramm-Saptya et al., 2004). In adult animals, the repeated administration of psychostimulants can result in an augmentation of the behavioral responses. Behavioral sensitization, or an increased response to subsequent psychostimulant dosing after previous exposure, has been shown to develop to the locomotor-

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stimulating effects of these drugs in rodents (Post and Rose, 1976; Shuster et al., 1982; Stewart and Badiani, 1993). Many neuronal systems including, but not limited to, dopamine, glutamate, serotonin and opioid are thought to be involved in the development of behavioral sensitization (Koe, 1976; Parsons and Justice, 1993; DiChiara, 1995; Wolf, 1998; Vanderschuren and Kalivas, 2000; Everitt and Wolf, 2002; Tzschentke and Schmidt, 2003; Hummel et al., 2004). Specifically, hypersensitization of mesocorticolimbic dopamine neurotransmission is thought to be an integral factor in this phenomenon and has also been linked to drug craving (Robinson and Berridge, 1993). Therefore, if behavioral sensitization is an age-dependent response to chronic psychostimulant administration, it may be indicative of differential sensitivities to the addictive potential of these drugs.

Distinct age-related responses to psychostimulants have been reported. For example, periadolescent rats show an attenuated locomotor response to acute administration of cocaine and amphetamine when compared to adults (Spear and Brake, 1983; Laviola et al., 1999; Adriani and Laviola, 2000). As measured by Cirulli and Laviola, postweanling mice show a heightened sensitivity to amphetamine-induced increases in locomotor and stereotypic activity when compared to preweanling mice (Cirulli and Laviola, 2000). However, it is difficult to generalize the findings following chronic administration of psychostimulants in different ages due to the inconsistencies in the reported results. While some reports show that both periadolescent and adult rodents sensitize to the locomotor-stimulating effects of cocaine, methylphenidate and amphetamine (Laviola et al., 1995; Adriani et al., 1998; McDougall et al., 1999; Shuster et al., 1982), others show that periadolescent rats do not sensitize to the locomotor-stimulating properties of cocaine (Collins and Izenwasser, 2002). Still another group showed sensitization to the locomotor-activating properties of cocaine in periadolescent, but not adult mice if there was no habituation period (Schramm-Saptya et al., 2004). Published data on the behavioral effects of psychostimulants are inconsistent probably due to the use of a variety of experimental paradigms, drug doses, routes of drug administration and strains and species of the animals tested. Therefore, a systematic study to compare the behavioral effects of cocaine, amphetamine and methylphenidate in different age animals was warranted.

Specifically, the present study characterized the acute behavioral effects of several doses of cocaine, methylphenidate and amphetamine, as well as the effects of repeated injections of these agents in postweanling, periadolescent and adult mice within identical treatment paradigms. Mice were chosen for these studies because of the widespread use of genetically engineered mice in neuroscience and addiction research.

2. Methods

2.1. Subjects-housing and treatment

Male CD-1 mice were obtained from Charles River Laboratories. Mice were housed four per Plexiglas cage ($28 \times 18 \times 14$ cm) in a temperature (21 ± 1 °C) and relative humidity ($40 \pm 10\%$)-controlled room and with a 12-h light/dark cycle (lights on at 7:00 a.m.). Animals were housed for five days prior to being tested and had free access to standard laboratory chow and tap water, except during activity monitoring. All experiments were conducted in accordance with the National Institutes of Health guidelines for the Care and Use of Laboratory Animals and with an approved protocol from Temple University School of Medicine Institutional Animal Care and Use Committee.

Animals of each age group, postweanling (24 days old), periadolescent (33 days old) and adult (60 days old), were assigned randomly to a cocaine, methylphenidate or amphetamine treatment group. Each treatment group had an age-matched saline-injected control group.

2.2. Drugs

Cocaine HCl and D-amphetamine, generously supplied by the National Institute of Drug Abuse (NIDA), and methylphenidate (Sigma, St. Louis, MO) were dissolved in sterile saline (0.9% NaCl). Drug or saline was administered intraperitoneally (IP) at a volume of 3 ml/kg body weight.

2.3. Behavioral testing

Activity was monitored in eight identical transparent Plexiglas boxes ($45 \times 20 \times 20$ cm) using Digiscan™ activity monitors (Accuscan, Columbus, OH). The monitors are equipped with 16 infrared light emitters and detectors. The number of times the photo beams were broken was cumulated by a microcomputer. The total number of beam breaks is reported herein as 'total activity', whereas 'ambulatory activity' includes only bouts of successive beam breaks and 'stereotypic counts' include only bouts of repetitive beam breaks. While stereotypic counts cannot directly measure the specific stereotypic activity, repeated breaks of the same beam indicate a stationary animal engaged in repetitive behavior as opposed to locomotion. Animals were placed in the monitors 30 min prior to drug or saline injections. Activity was monitored for 30 min after the injection. All behavioral testing was done between 1:00 and 5:00 p.m.

2.4. Drug administration

For acute drug administration, postweanling (24 days old), periadolescent (33 days old) and adult (60 days old) mice received a single injection of cocaine (0, 10, 20 or 30 mg/kg IP), methylphenidate (0, 5, 10 or 20 mg/kg IP) or amphetamine (0, 2.5, 5 or 10 mg/kg IP) and activity was measured for 30 min post-injection.

In a separate set of experiments, cocaine (20 mg/kg IP), methylphenidate (10 mg/kg IP), amphetamine (5 mg/kg IP) or saline (3 ml/kg IP) was administered to postweanling, periadolescent and adult mice once daily for seven days beginning on postnatal days 24, 33 and 60, respectively.