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Research report

Adolescent exposure to cocaine, amphetamine, and methylphenidate cross-sensitizes adults to methamphetamine with drug- and sex-specific effects

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HIGHLIGHTS

- Early adolescent exposure to stimulants has effects that persist into adulthood.
- Cocaine exposure evidenced drug, but not sex-dependent effects in adult mice.
- High and low amphetamine and methylphenidate doses produced sensitizing effects.
- Low dose amphetamine exposure produces a male-specific sensitizing effect.
- Methylphenidate exposure produces a female-specific sensitizing effect.

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ABSTRACT

The increasing availability, over-prescription, and misuse and abuse of ADHD psychostimulant medications in adolescent populations necessitates studies investigating the long-term effects of these drugs persisting into adulthood. Male and female C57Bl/6J mice were exposed to amphetamine (AMPH) (1.0 and 10 mg/kg), methylphenidate (MPD) (1.0 and 10 mg/kg), or cocaine (COC) (5.0 mg/kg) from postnatal day 22 to 31, which represents an early adolescent period. After an extended period of drug abstinence, adult mice were challenged with a subacute methamphetamine (METH) dose (0.5 mg/kg), to test the long-term effects of adolescent drug exposures on behavioral cross-sensitization using an open field chamber. There were no sex- or dose-specific effects on motor activity in adolescent, saline-treated controls. However, AMPH, MPD, and COC adolescent exposures induced cross-sensitization to a subacute METH dose in adulthood, which is a hallmark of addiction and a marker of long-lasting plastic changes in the brain. Of additional clinical importance, AMPH-exposed male mice demonstrated increased cross-sensitization to METH in contrast to the female-specific response observed in MPD-treated animals. There were no sex-specific effects after adolescent COC exposures. This study demonstrates differential drug, dose, and sex-specific alterations induced by early adolescent psychostimulant exposure, which leads to behavioral alterations that persist into adulthood.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral disorder characterized by symptoms of inattention and/or impulsivity/hyperactivity [1]. It is among the most commonly diagnosed pediatric psychiatric conditions in the world. The current estimated ADHD prevalence rate of 11% in the US for children aged 4–17 years represents a 41% increase in diagnosis over the past decade [2]. Of the 6.4 million children in the US ever diagnosed with ADHD, most are reported to currently have the condition (78%) and

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the majority of these children (66.3%) are receiving medication for its treatment [3]. Stimulant medications, especially amphetamines (AMPH) and methylphenidate (MPD), remain the first line pharmacological treatment for ADHD since they are generally well tolerated and effective in symptom reduction [4–6].

Prescription AMPH preparations include Adderall® (mixed AMPH salts) and Vyvanse® (D-AMPH) and are mainly distinguished by their pharmacokinetic profile [7]. Methamphetamine (METH) is structurally similar to AMPH, but it is more lipid-soluble, which allows for greater access across the blood brain barrier. Despite the similar pharmacokinetic profiles of the two drugs, they exhibit some pharmacodynamic differences resulting in the increased neurotoxic and addictive profile of METH compared to AMPH [8–11]. MPD preparations include Ritalin® and Concerta®. While MPD and COC both target the dopamine (DA), norepinephrine (NE), and, to a lesser extent, serotonin transporters (DAT, NET, and SERT, respectively), MPD is more selective for and many fold more potent at DAT than COC [12].

AMPH and MPD are stimulant drugs with both peripheral and central nervous system effects where they act as indirect agonists for monoamines, especially DA and NE. MPD blocks the monoamine transporters, while amphetamines also induce neurotransmitter release from both synaptic stores and the nerve terminal [13]. The resultant extracellular increases in DA and NE are thought to contribute to the therapeutic effects as well as the reinforcing properties and addiction profiles of these drugs [14]. There are also sex differences in the behavioral response to psychostimulants, which may stem from differences in hormone signaling, pharmacokinetics, DAergic tone (e.g., DAT and DA receptor densities) [15–17] and developmental time frame [18]. However, there is a paucity of literature considering these sex effects in the context of substance misuse and abuse, which have many clinical implications, especially for adolescents.

Children 12 years of age and older have a lifetime prevalence rate of non-medical psychotherapeutic drug use of 19.9%, with 5.7% using in the past year and 2.4% using in the past month [19–22]. Approximately 15% of high school seniors report non-medical prescription drug use with Adderall®, Ritalin®, and COC topping the list [23]. Given their high abuse liability yet limited medical applications, AMPH, MPD, and COC are all Schedule II drugs in the US [13; http://www.deadiversion.usdoj.gov/schedules/]. While there is controversy concerning the state of misdiagnosis/overdiagnosis of ADHD [24,25] and resultant overprescription, in 2011, there were 48.4 million ADHD stimulant prescriptions dispensed in the US representing a 39% increase from 2007 [26]. ADHD stimulant diversion and abuse constitutes a large and growing problem and one that may disproportionately affect adolescents.

Adolescence is a time of continued maturation, especially in forebrain areas, where progressive changes in D1 and D2 receptors, DAergic innervation, and DAT density are evident [27–32]. DA and NE are known tropic and trophic factors during development, which regulate the migration, survival, differentiation, proliferation, and connectivity of both neurons and glia [33]. In addition, an overabundance of stored DA in adolescents compared to adults may serve as a neurobiological explanation for the apparent sensitivity to some drugs of abuse in adolescence via enhanced DA release [28]. DAergic circuitries play heavily into the discussion of both dual-processing models of adolescent risk-taking and incentive salience models of drug addiction as both involve neural plasticity modulated by neurobiobehavioral factors [27,34]. Changes in adolescent DAergic tone are correlated with cortical (e.g., PFC) and subcortical (e.g., basal ganglia and limbic system) development and connectivity between these systems [27,35]. This potentially provides both a neuroanatomical basis for risk-taking behavior and decision-making in adolescence as well as targets for drug-induced circuitry dysfunction during developmental windows with potential long-lasting implications for future substance initiation and abuse [27]. In support of this hypothesis, a recent meta analysis suggests that as many as 1 in 4 are comorbid for ADHD and substance abuse [36].

Given the availability, over-prescription, and misuse and abuse of psychostimulants in adolescent populations, additional studies are warranted to identify potential long-term neural alterations associated with exposure to these drugs. This study utilizes a behavioral cross-sensitization paradigm to assess functional neural alterations induced by adolescent drug exposures and persisting into adulthood. We hypothesized that long-term COC, AMPH, and MPD-induced plastic changes during the key developmental window of early adolescence, evidenced by cross-sensitization to a subacute dose of METH in adulthood, would demonstrate long-lasting, drug-specific, sexually dimorphic locomotor alterations.

2. Material and methods

2.1. Animals

Adult (6–8 weeks) C57Bl/6J mice (Jackson Laboratories, Bar Harbor, ME) were housed in the colony as breeding pairs. The presence of a vaginal plug was used to confirm pregnancy. Dams were singly housed until parturition. Male (n = 72) and female (n = 60) pups were weaned on postnatal day 21 (P21). To address potential litter effects, animals from each treatment, by sex, were group housed (n = 4–6) at weaning by random assignment from multiple litters. All animals were housed in standard caging (Micro-Vent Caging System, Allentown Inc., Allentown, NJ), had free access to food and water, and were maintained on a 12-h light:12-h dark cycle with lights on at 0700 in a temperature (20–22 °C) and humidity (55–60%) controlled colony room. All procedures were conducted according to the *Guide for the Care and Use of Laboratory Animals*. The C57Bl/6J strain of mice used to test pharmacologically-induced behavioral sensitization are less susceptible to a hyperactivity phenotype and do not express the same functional mutations that affect psychostimulant responses as other common strains [37,38].

2.2. Drugs and dosing schedule

2.2.1. Adolescent exposure

Adolescent pretreatments were performed in the animal's home cage in the colony room. P22–31 comprises early adolescence in rodents [28] and is prior to the onset of puberty in female C57Bl/6J [39]. Starting on P22, each mouse received once daily intraperitoneal (i.p.) injections of 1.0 mg/kg (n = 19; female = 10; male = 9) or 10.0 mg/kg (n = 24; female = 9; male = 15) D-amphetamine sulfate, 1.0 mg/kg (n = 24; female = 9; male = 15) or 10.0 mg/kg (n = 21; female = 8; male = 13) methylphenidate hydrochloride, 5.0 mg/kg cocaine hydrochloride (n = 25; female = 14; male = 11), or an equal volume of sterile saline (SAL; n = 19; female = 10; male = 9) for 10 days (P22–31) (Sigma-Aldrich, St. Louis, MO) (Fig. 1). The doses chosen were based on existing pharmacological data [40–44]. Since adolescent exposure to psychostimulants is known to induce acute behavioral sensitization, this behavior was not monitored during pretreatment [28].

2.2.2. Adult challenge dose

Mice were aged for 8 weeks in standard housing conditions following the initial adolescent exposure. After P90, all mice underwent cross-sensitization testing in an open field chamber in a separate behavioral testing room. Female mice were not selected based on estrous cycle phase, since its measurement