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Pretreatment with Δ9-tetrahydrocannabinol (THC) increases cocaine-stimulated activity in adolescent but not adult male rats

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ABSTRACT

Marijuana (*Cannabis sativa*) remains one of the most widely used illegal drugs, with adolescents being particularly vulnerable to its use and abuse. In spite of this, most studies are conducted in adult animals even though the effects might be quite different in adolescents. Additionally, the use of marijuana often precedes the use of other psychoactive drugs including cocaine, especially when marijuana exposure begins during early adolescence. The purpose of this study was to examine the effects of repeated Δ9-tetrahydrocannabinol (THC), the major active ingredient in marijuana, in adolescents compared to adults and to determine its subsequent effects on cocaine-stimulated activity. To this end, adolescent (postnatal day PND 34) and adult (PND 66) rats were administered 3 mg/kg/day THC for 8 days and locomotor activity was measured on days 1, 2, 7 and 8 after dosing. On day 12 (4 days after the last dose of THC), rats were injected with escalating doses of cocaine and behavior was recorded. Results show that THC depressed locomotor activity in adult rats but not in adolescents. However, following a cocaine challenge, adolescents exposed to THC showed increased locomotor responses to cocaine compared to chronic vehicle-injected controls. This was not seen in adults. These results show that the effects of cocaine are enhanced after THC in adolescents, but not adults, and that this might account for the greater transition to cocaine after early, as opposed to later, marijuana use.

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1. Introduction

Marijuana (*Cannabis sativa*) remains one of the most widely used illegal drugs, with adolescents being particularly vulnerable to its use and abuse. The percentage of adolescents reporting lifetime use of marijuana rises steadily from 14.2% in eighth grade to 41.8% by twelfth grade, with a majority of eighth through twelfth graders reporting that they are at a 'great risk' to try marijuana regularly (Johnston and O'Malley, 1997). Both acute and chronic doses of THC have been shown to cause impairment in attention and motor coordination in a maze task in humans (Weinstein et al., 2008), inhibition of movement and basal ganglia neuronal activity in adult rats (Shi et al., 2005), and decreased locomotor activity in rats (Romero et al., 1996; Whitlow et al., 2002). The decrease in locomotor activity after THC administration has been reported in both adult and adolescent rats, with the effect being much smaller in adolescents (Schramm-Sapyta et al., 2007). In addition, it also has been reported that low doses of THC increased activity in adolescence and had no effect in adults (Wiley et al., 2008).

The National Survey on Drug Use and Health showed that adults who initiated marijuana use prior to age 15 were 6 times more likely to be dependent on an illicit drug than adults who first used marijuana at age 21 or older (NSDUH, 2002). In addition, of adults initiating marijuana use prior to age 15, 62% reported lifetime cocaine use, compared to 16% in marijuana users who reported first smoking the drug after age 20 (a four-fold difference) or 0.6% among those who had never used marijuana (a 100-fold difference). These data show that the earlier the first marijuana use, the more likely one is to use other illicit drugs. While these studies do not unequivocally show causality, the data suggest that there may be fundamental differences in the effects of marijuana in preadolescents and young adolescents compared to adults. Laboratory studies show that the adolescent period may in fact be a period of development of increased vulnerability. Earlier studies from our lab and others have shown that drugs such as nicotine (Collins and Izenwasser, 2004; Collins et al., 2004a; Collins et al., 2004b; McQuown et al., 2007) and MDMA (Aberg et al., 2007; Achat-Mendes et al., 2003; Daza-Losada et al., 2008) increase the subsequent response to cocaine in adolescent rats. These studies suggest that it is possible to model and study the effects of drugs during adolescence and to determine whether there are differential effects than during adulthood.

Within the central nervous system, the greatest density of CB1 receptors is found in the cerebellum, basal ganglia and CA1, CA3 and dentate gyrus areas of the hippocampal formation (Herkenham, 1991; Herkenham et al., 1990). Normally stimulated by endogenous cannabinoids (endocannabinoids), the binding of cannabinoids to presynaptic G-protein coupled receptors can alter the release of neurotransmitters at the synapse and is responsible for many of

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the behavioral effects seen with marijuana consumption. Ontogenetic studies show that cannabinoid receptor density in whole brain increases progressively from birth to PND 60 (Belue et al., 1995; McLaughlin et al., 1994). Additionally, although cannabinoid receptors are present in forebrain from PND 10 on, there are regional variations in the ontogeny of these receptors. For example, receptors in the striatum, limbic forebrain and mesencephalon peak between PND 30 and 40 and then progressively decrease to adult levels (Rodriguez de Fonseca et al., 1993). In adults, in the ventral mesencephalon, CB1 receptors are located on GABA terminals and serve to dampen the GABA inhibition of DA firing rates (Szabo et al., 2002; Wu and French, 2000). That is, cannabinoids inhibit GABA's effects on DA neurons in the ventral mesencephalon producing a net increase in firing of the ascending DA projections (Szabo et al., 2002). In striatum in adults, CB1 receptors are co-localized with DA receptors (Herkenham, 1991). Cannabinoids have been shown to inhibit release of DA from striatal synaptosomes (Poddar and Dewey, 1980). Therefore, in striatum cannabinoids appear to directly reduce DA function while in the ventral mesencephalon, cannabinoids appear to enhance DA function. The ventral mesencephalon develops before the striatum and may be selectively activated in adolescents producing enhanced DA function as opposed to dampened DA function in the adult striatum. In addition, these relationships may undergo extensive modification from adolescence into adulthood.

Several groups have examined the effects of chronic THC on behavioral responses to psychostimulants and reported variable results. For example, administration of THC for 14 days led to increased amphetamine-stimulated activity 30 min and 24 h after the last dose (Gorriti et al., 1999). Acutely, CP 55, 940 or THC did not alter the locomotor responses to cocaine (Panlilio et al., 2007) although they did block the development of sensitization to cocaine (Arnold et al., 1998) in adult rats. The present study was done to examine the effects of daily THC in adolescent and adult rats on locomotor activity and on the subsequent response to cocaine. To this end, adolescent (PND 34) and adult (PND 66) rats were injected with 3 mg/kg/day THC for 8 days and locomotor activity was measured on the first two and last two days of the daily dosing. On day 12 (4 days after the last dose of THC) rats were injected with exponentially increasing doses of cocaine and behavior recorded.

2. Materials and methods

2.1. Chemicals

Drugs were obtained from the following sources: Δ9-tetrahydrocannabinol (THC) and cocaine hydrochloride from Research Triangle Institute, Research Triangle Park, NC courtesy of the National Institute on Drug Abuse (Bethesda, MD).

2.2. Treatments

Sprague–Dawley rats (Charles River, NC) were used in these studies. Periadolescent male rats at postnatal day 34 (PND 34) and adult male rats (PND 66) were injected once daily for eight days with i.p. injections of either 3.0 mg/kg THC or vehicle (60% saline:20% ethanol:20% cremophor EL). Periadolescence is a period of early adolescence, which begins in rats at approximately postnatal day 28 and ends at postnatal day 40 (Spear and Brake, 1983). This period of early adolescence was chosen because it is during this stage of development that marijuana use is often initiated (The National Center on Addiction and Substance Abuse at Columbia University, 2003). All rats were housed two per cage in a temperature and humidity-controlled environment under a 12 h light/dark cycle with lights on at 7 a.m. and off at 7 p.m. All behavioral testing was done during the light schedule between 9 a.m. and 4 p.m. with each group tested at the same hour each day and the groups randomized over the course of the day. Food and water were available ad libitum. Administration of THC did not alter body weight compared to vehicle in either adolescent or adult rats.

On day 12 of the experiment, all rats were injected with saline, followed by 1.0, 3.0, 10.0, 20, and 30 mg/kg cocaine (i.p.) in a cumulative dosing regimen (actual injections of 1.0, 2.0, 7.0, 10, and 10 mg/kg cocaine), as described previously (Collins and Izenwasser, 2004). Following each injection, locomotor activity was measured for a total of 10 min for vehicle and for each cumulative dose of cocaine. Thus, there were 10 min between each dose of cocaine and the entire session lasted 50 min. This procedure allows a full dose–response curve to be determined in a single day and greatly reduces the number of animals used, since full curves are determined in each animal.

2.3. Locomotor activity testing

On the first two and last two days (days 1–2 and 7–8) of administration of THC or vehicle, locomotor activity was measured for 30 min. Rats were placed in clear acrylic chambers (16 × 16 in.) inside Digiscan activity monitors (Omnitech Electronics, Columbus, OH) that were equipped with infrared light sensitive detectors mounted 2.5 cm apart along two perpendicular walls. Mounted along the opposing walls were infrared light beams that were directed at the detectors. The pattern of beam breaks provides information on the distance that the animal has traveled. Locomotor activity was analyzed by a three-factor (pretreatment × age × day) analysis of variance (ANOVA) with repeated measures for day. Stereotypy also was measured, both by machine, which measures repeated beam breaks and by experimenter observation. For the cocaine cumulative dosing curve on day 12, a three-way analysis of variance (pretreatment × age × dose of cocaine) with repeated measures for dose was done. Significant interactions were followed by tests for simple treatment (drug) effects. Comparisons of data on individual days were made by one-way ANOVA, and followed by post hoc analysis using Fisher's Protected Least Significant Difference (PLSD) when warranted. P values less than 0.05 were considered significant for all tests.

3. Results

3.1. THC pretreatment (days 1–8)

Locomotor activity: THC (3 mg/kg) decreased activity in adult rats, but not in adolescent rats (Fig. 1). An overall analysis of pretreatment × age × day, with day as a repeated measure, was not significant. However, there was a significant effect of pretreatment ($F[1,52] = 11.29$, $p \leq 0.002$) and a significant pretreatment × age interaction ($F[1,52] = 5.75$, $p \leq 0.02$). Post-hoc tests showed that there were no significant differences in the effect of vehicle on locomotor activity in the adult and adolescent rats. There was, however, a significant difference in the effect of THC, with an overall decrease in activity compared to vehicle in adult ($p \leq 0.0005$) but not adolescent rats. On day 1 of administration, THC did not have a significant effect on activity in either group and on none of the other test days was there a significant effect of THC in adolescents (Fig. 1A). However on days 2, 7, and 8 THC treatment significantly decreased activity in adult rats (Fig. 1B) in response to the THC ($p \leq 0.05$).

3.2. Cocaine-stimulated activity (day 12)

Cocaine increased activity in both adult and adolescent rats and the dose–effect curve for cocaine-stimulated activity was shifted upward in adolescent rats that had been treated previously with THC (Fig. 2A). In contrast, there was no difference in cocaine-stimulated activity in the adult rats that had received THC compared to vehicle. There was a significant pretreatment × age × dose interaction ($F[4,232] = 3.385$, $p \leq 0.01$) on cocaine-stimulated activity on day 12 of the experiment. There was no significant main effect of pretreatment, but there was a significant main effect of age ($F[1,58] = 4.76$, $p \leq 0.03$). There were

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