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Behavioral sensitization to amphetamine follows chronic administration of the CB_1 agonist WIN 55,212-2 in Lewis rats

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Abstract

The extent to which acute and repeated administration of the CB_1 agonist WIN 55,212-2 would affect the stimulatory properties of amphetamine was assessed in Lewis rats. In the first experiment, Lewis rats were treated with either 1 mg/kg of WIN 55,212-2 or vehicle and subsequently treated with 2 mg/kg amphetamine. Acute treatment with WIN 55,212-2 initially increased locomotor activity and then attenuated the stimulating effect of amphetamine on locomotion and exploration (as measured by rears). In a separate experiment, Lewis rats were given daily injections of either WIN 55,212-2 (1 mg/kg) or vehicle for 10 days and the effects of amphetamine were assessed at 1 and 3 days following the last chronic cannabinoid treatment. Those rats, which had been treated with WIN 55,212-2, had an enhanced response to amphetamine with rearing but not with ambulatory movements, suggesting the occurrence of behavioral cross-sensitization to the ability of amphetamine to increase rearing. These data add to the growing evidence that there is at least some overlap between those neural systems acted upon by cannabinoids and those that are believed to be involved in incentive properties associated with other drugs of abuse.

Keywords: Cannabis; Marijuana; Addiction; Drug abuse; WIN 55,212-2; CB_1 receptor; Cross-sensitization

1. Introduction

Marijuana and other *cannabis* products traditionally have been classified apart from other drugs of abuse because of their reputed failure to show high reward value in classic paradigms of reinforcement and reward such as conditioned place preference and drug self-administration (Harris et al., 1974; Leite and Carlini, 1974; Takahashi and Singer, 1979; Wu and French, 2000). Additionally, the lack of a pronounced abstinence syndrome following abrupt withdrawal has reinforced the notion of cannabinoids as non-habit-forming "soft" drugs. However, it is more likely that such findings reflect the unique chemistry and pharmacokinetics of natural cannabinoids rather than their low abuse potential. Because of the high lipophilicity of Δ^9-tetrahydrocannabinol (Δ^9-THC) and its long duration of action, traditional animal models often used to assess abuse liability may be of limited value for evaluating the rewarding properties of cannabinoids. Moreover, studies assessing the hedonic valence of Δ^9-THC may be further confounded by the drug's tendency to be aversive at higher doses (Chaperon et al., 1998; Cheer et al., 2000). Indeed, a recent experiment using lower doses has found Δ^9-THC to support self-administration in primates (Tanda et al., 2000) and conditioned place preference in mice (Valjent and Maldonado, 2000). These data suggest that cannabinoids may indeed have rewarding properties and may pose at least some level of abuse liability.

Exogenous and endogenous cannabinoids act at two major receptor subtypes that have been designated CB_1 and CB_2 (Mechoulam et al., 1998; Pertwee, 1997). Considerable focus has been directed towards the functional role of CB_1 receptors, largely due to the predominance of this receptor subtype in the central nervous system and the availability of relatively selective agonists and, more recently, antagonists. For example, intravenous self-administration of the aminoalkylindole CB_1 agonist WIN 55,212-2 has been described in drug-naïve mice (Martellotta et al., 1998), intracranial self-administration of the bicyclic agonist CP 55,940 has been reported in rats (Braida et al., 2001a,b), and a withdrawal syndrome can be precipitated

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with administration of the CB_1 antagonist SR 141716A following chronic Δ^9-THC or WIN 55,212-2 treatment in rats (Aceto et al., 1995, 1996, 2001; Beardsley and Martin, 2000; Tsou et al., 1995). Recently, a reappraisal of Δ^9-THC withdrawal in humans has exposed a characteristic abstinence syndrome that includes sleeplessness, irritability and increased aggression as well as drug craving (Haney et al., 1999; Kouri et al., 1999). These studies suggest that natural and synthetic cannabinoids are capable of acting on those neural processes associated with drug dependence and that the nature of these actions may be revealed with the appropriate pharmacological manipulation and sufficiently sensitive behavioral assays.

Given that marijuana is the most widely used illicit substance in most Western societies, there has been considerable debate as to whether or not marijuana use can lead to the use of other drugs of abuse. One of the more robust animal models used to describe the development of drug-seeking behavior is the incentive sensitization paradigm, which views drug abuse primarily as a motivational and appetitive phenomenon with the primary locus in the mesolimbic dopamine pathway (Ikemoto and Panksepp, 1999; Robinson and Berridge, 1993). Briefly, this model suggests that all drugs of abuse act on a common neural substrate (i.e., the mesolimbic dopamine system) and that chronic use of drugs of abuse can sensitize these neural systems such that certain stimuli present during drug-taking behaviors will lead to increased drug-seeking behavior in the presence of these incentive stimuli (Robinson and Berridge, 1993; Robinson and Kolb, 1997). Inherent to this approach is the idea that various drugs of abuse will interact in a predictable manner with drugs that act directly on brain dopamine systems and should result in cross-sensitization to direct and indirect dopaminergic agonists. In particular, this model finds that repeated exposures to drugs of abuse result in a progressive increase in amphetamine-induced locomotion and stereotypy (Cador et al., 1999; Pierce and Kalivas, 1997; Robinson and Berridge, 1993; Robinson and Kolb, 1997). This amplified behavioral response is thought to accompany neuroplastic changes in those nuclei believed to elaborate feelings of craving or drug "wanting" (Robinson and Kolb, 1997; Wyvell and Berridge, 2000).

Because electrophysiologic and microdialytic data reveal cannabinoids to be potent activators of mesolimbic dopamine circuitry (Diana et al., 1998a,b; Gardner and Lowinson, 1991; Tanda et al., 1999; Wu and French, 2000), several groups have attempted to show cross-sensitization of cannabinoids to the locomotor effects of amphetamine or cocaine in rats. However, the results have been mixed. Several groups have reported that chronic treatment with Δ^9-THC can result in sensitized responses to either amphetamine (Gorriti et al., 1999; Lamarque et al., 2001) or morphine (Cadoni et al., 2001; Lamarque et al., 2001), suggesting that marijuana use may increase the likelihood of craving for other drugs of abuse. However, repeated administration of synthetic cannabinoids has not always yielded results consistent with those obtained when Δ^9-THC is administered. While repeated administration of the synthetic cannabinoid agonist HU-210 results in a sensitized response to the D_1/D_2 agonist CQP 201-403, a sensitized response to cocaine was not found (Ferrari et al., 1999). An earlier study also found that repeated administration of the synthetic CB_1 agonist CP 55,940 did not yield a sensitized response to cocaine (Arnold et al., 1998). Therefore, while there is reasonable evidence demonstrating cross-sensitization to psychomotor stimulants after chronic treatment with Δ^9-THC, the same cannot be said for more selective agonists.

The purpose of the present study was to further evaluate the extent to which cannabinoids and amphetamine may act on common neural substrates. In the first study, it was determined whether an acute treatment with the selective CB_1 agonist WIN 55,212-2 would interact with the effects of amphetamine in a manner comparable to that reported by Gorriti et al. (1999) for Δ^9-THC. In a subsequent study, the effect of chronic administration of WIN 55,212-2 on amphetamine-induced hyperactivity was assessed in order to determine whether there was clear amplification in behavioral responding to systemic amphetamine.

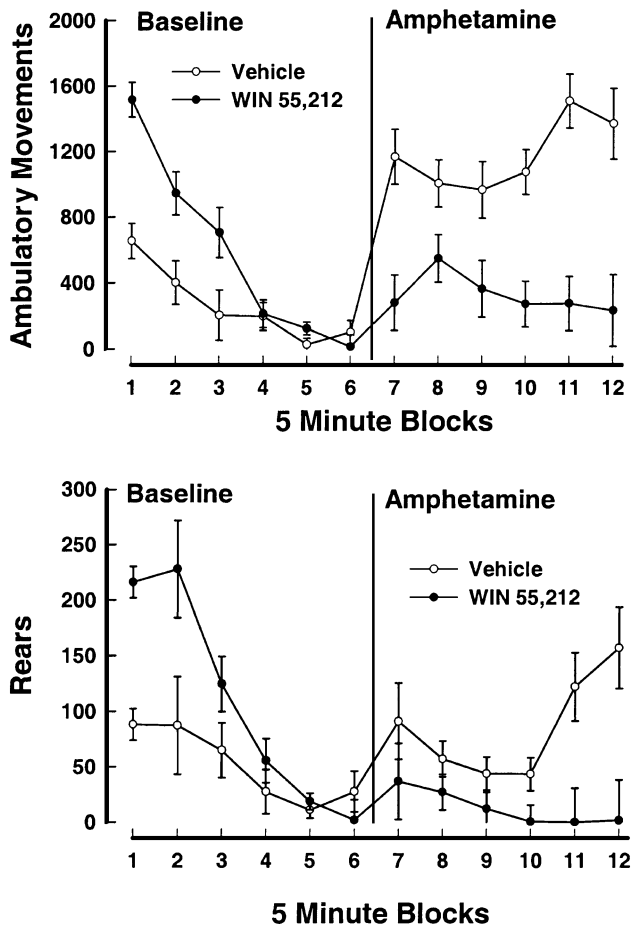

Fig. 1. Mean ± S.E.M. number of ambulatory movements (top) and rears (bottom) in control animals and those treated with 1 mg/kg of WIN 55,212-2 before and after an injection of amphetamine (2 mg/kg).

2. Methods

2.1. Animals

Male Lewis rats obtained from Harlan Sprague–Dawley (Frederick, MD) were used in both experiments. The rats used in Experiment 1 weighed 300 ± 35 g at the beginning of testing, while the rats used in Experiment 2 were younger and weighed 160 ± 30 g at the beginning of testing. All animals were group housed (four per cage) in solid bottom cages (48 × 27 × 20 cm) with food and water freely available. The colony room was maintained at 22 °C and kept on a 15:9 h light/dark cycle (lights on at 8:00 am). Animals were given 2 weeks to acclimate to the colony room prior to any testing. All housing and testing was done in compliance with the NIH Guide for Care and Use of Laboratory Animals.

2.2. Apparatus

Measures of ambulatory and vertical (rearing) activity were made in a 40 × 40 × 50 cm Plexiglas chamber with a white solid bottom under ambient fluorescent illumination during daytime hours. The chamber was placed within the infrared field of an Opto-Varmimex Minor monitor (Columbus Instruments, Columbus, OH). Infrared beam density within the enclosure consisted of two sets of 15 beams spaced 2.5 cm apart and set 6 cm from the floor. Vertical emitters and detectors were placed 13 cm from the floor to detect rearing. Nonrepetitive horizontal beam breaks (ambulatory movements) and vertical beam breaks were recorded on a PC using the accompanying software package.

2.3. Drugs

WIN 55,212-2 (Sigma-RBI, St. Louis, MO) was dissolved in 20 μl of Tween 80 and then diluted with saline to give a final solution of 1 mg/ml WIN 55,212-2 in 4% Tween 80. Amphetamine sulfate (Sigma-RBI) was dissolved in saline. All drugs were injected in volumes equal to 1 ml/kg body weight and all drug solutions were prepared fresh on testing days.

2.4. Procedure

2.4.1. Experiment 1

Immediately before being placed in the activity monitor, animals were injected intraperitoneally (ip) with WIN 55,212-2 ($n = 8$) or vehicle ($n = 8$). Activity counts were

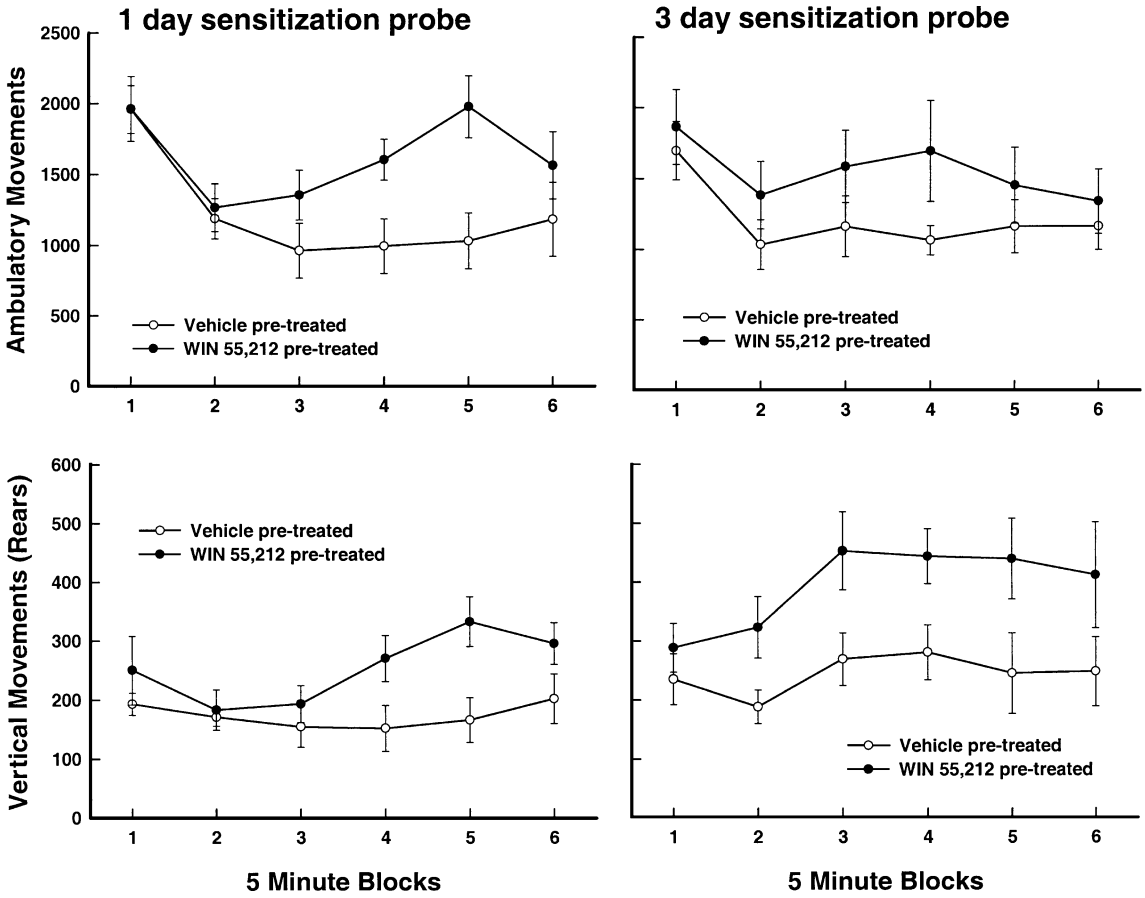

Fig. 2. Mean ± S.E.M. number of ambulatory movements (top) and rears (bottom) after amphetamine (2 mg/kg) in vehicle-pretreated rats and in rats pretreated with 10 daily injections of 1 mg/kg WIN 55,212-2. Rats were tested 1 and 3 days after the last injection of either vehicle or WIN 55,212-2.

recorded at 5 min intervals. After 30 min, all animals were removed from the chamber, given an intraperitoneal injection of amphetamine (2 mg/kg) and returned for a second 30 min observation. As before, activity counts were recorded at 5 min intervals.

2.4.2. Experiment 2

A separate group of animals was injected intraperitoneally with WIN 55,212-2 (1 mg/kg, $n=8$) or vehicle ($n=8$) once a day for 10 days. At approximately 24 h after the final injection, all animals were given amphetamine (2 mg/kg ip) and immediately placed in the activity monitor for a single 30 min observation, with activity recorded at 5 min intervals. Rats were tested with amphetamine again 3 days after the last WIN 55,212-2 or vehicle injection. Seven days after the last chronic injections of WIN 55,212-2 or vehicle were administered, all animals were placed individually in the activity monitor for a 30 min drug-free (no amphetamine) observation.

3. Results

3.1. Experiment 1

An acute injection of WIN 55,212-2 (1 mg/kg) had a significant effect on both ambulatory activity and rearing activity (Fig. 1). Analysis of variance (ANOVA) of the ambulatory activity prior to amphetamine indicated a significant main effect associated with WIN 55,212-2 [$F(1,6)=16.45$, $P<.01$], although this was tempered by a significant Drug×Time interaction [$F(5,30)=7.34$, $P<.001$]. As can be seen in Fig. 1, ambulatory activity was higher for the WIN 55,212-2-treated rats during the first 15 min of testing and then returned to control levels by the fourth 5 min block. A similar pattern was seen with rears, as also indicated by a significant Drug×Time interaction [$F(5,30)=4.41$, $P<.005$].

After 30 min, all of the animals were injected with amphetamine (2 mg/kg) and activity was monitored for an additional 30 min. These data were also analyzed by ANOVA and a significant main effect associated with pretreatment was obtained for both ambulatory activity [$F(1,6)=52.66$, $P<.001$] and rears [$F(1,6)=15.46$, $P<.01$]. The Pretreatment × Time interaction was not significant for either measure. These data indicate that acute pretreatment of the rats with WIN 55,212 attenuated the ability of amphetamine to increase both ambulatory activity and rearing activity, which is consistent with the findings of Gorriti et al. (1999).

3.2. Experiment 2

The data from both sensitization probes (1 and 3 days posttreatment) for ambulatory movements and rears were analyzed by a $2\times2\times6$ ANOVA for each measure, with pretreatment as a between-subjects factor and day of testing and time of testing on each day as within-subjects factors. These data are shown in Fig. 2. Although there was a tendency for amphetamine to have a greater effect on ambulatory movements in those rats pretreated with WIN 55,212-2, this was not robust enough to be sustained over both test days, as supported by the lack of a significant main effect associated with pretreatment group [$F(1,14)=2.85$, $P>.05$]. In addition, none of the interactions involving pretreatment group approached statistical significance for ambulatory movements. A more robust pattern indicative of cross-sensitization emerged for rears. When these data were analyzed as above, the main effect associated with pretreatment group was highly significant [$F(1,14)=11.57$, $P<.005$], with those rats pretreated with WIN 55,212-2 exhibiting more rearing activity after amphetamine than those rats pretreated with vehicle. Although there were more rears on the second day of testing [$F(1,14)=8.82$, $P<.02$], none of the interactions involving either day or group were significant. These data suggest that those rats pretreated with WIN 55,212-2 exhibited a sensitized response to amphetamine for

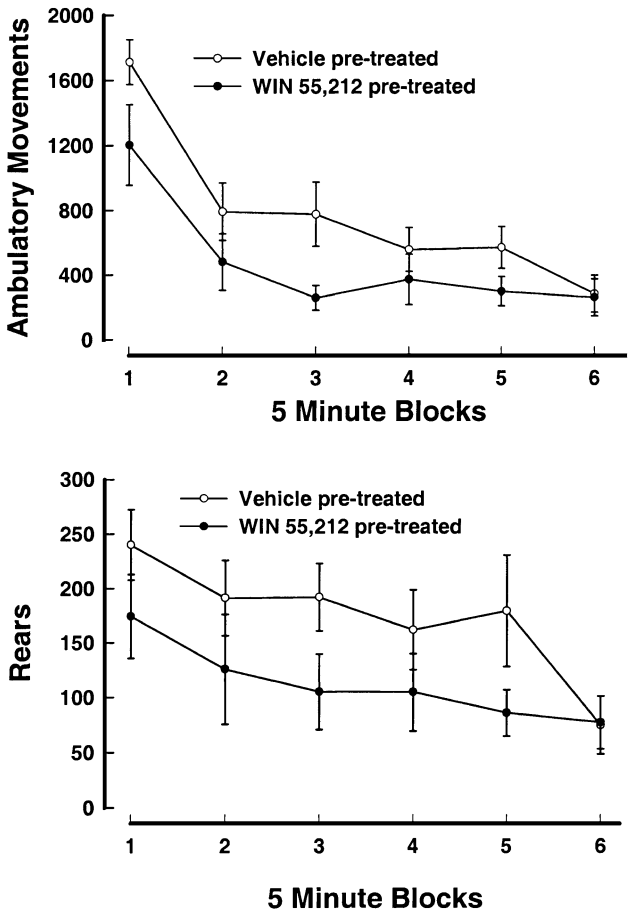

Fig. 3. Mean ± S.E.M. number of ambulatory movements (top) and rears (bottom) in vehicle-pretreated rats and in rats pretreated with 10 daily injections of 1 mg/kg WIN 55,212-2 when placed in an activity monitor 7 days after the last injection of either vehicle or WIN 55,212-2. No injections were given on this test day.

increased rearing that was sustained for at least 3 days after the cessation of treatment.

When activity was assessed 4 days after the second amphetamine probe (7 days after the last treatment with either vehicle or WIN 55,212-2), there was found to be a significant difference between the two groups for ambulatory movements (Fig. 3). In particular, the WIN 55,212-2-treated rats had fewer ambulatory movements across the 30 min test period [$F(1,14) = 5.07$, $P < .05$]. There was also a modest decrease in rearing among the WIN 55,212-2-treated rats, although this did not reach statistical significance [$F(1,14) = 3.40$, $P = .086$].

4. Discussion

It is well established that cannabis administration can influence activity in brain dopamine systems in general and in mesolimbic systems in particular (Diana et al., 1998a,b; Szabo et al., 2000; Tanda et al., 1999). These effects are believed to be associated with presynaptic modulation of transmitter release in neural areas that provide afferent input to the nucleus accumbens (Schlicker and Kathmann, 2001). However, the functional significance of such interactions and the extent to which they may relate to any abuse liability associated with marijuana use remains to be determined.

The results of the present study add to a relatively small body of evidence demonstrating that acute and repeated administration of natural and synthetic cannabinoids can modify the behavioral consequences of other drugs of abuse. The present results demonstrate that acute treatment with the cannabinoid agonist WIN 55,212-2 appears to attenuate the behavioral activating effects of amphetamine (Experiment 1), while chronic 10 day treatment with WIN 55,212-2 can result in selective cross-sensitization to the behavioral activating effects of amphetamine (Experiment 2). In particular, the ability of amphetamine to increase rearing was enhanced in WIN 55,212-2-pretreated rats up to 3 days after the last injection of the cannabinoid. While there was an indication of a sensitized response for ambulatory movements 1 day after the last injection, this effect was not robust enough to be sustained to the third day. Because CB_1 receptor expression is highest in areas of the basal ganglia and cerebellum that control movement (Herkenham et al., 1991a,b; Herkenham, 1992; Mailleux and Vanderhaeghen, 1993; Matsuda et al., 1993), it may be that the motoric activation associated with sensitization is initially subsumed under rebound or "opponent process" effects generated in these brain areas by cannabinoid withdrawal (Gorriti et al., 1999). This may partially account for the short-lived enhancement of amphetamine-induced ambulatory activity when rats were assessed 1 day after the last injection of WIN 55,212-2. However, the sensitized response noted for rearing more likely reflects long-term neuroplasticity in areas of the brain that are perhaps involved with incentive motivation (Robinson and Berridge, 1993; Robinson and Kolb, 1997; Vanderschuren et al., 1999).

Cannabinoids tend to have dose-dependent effects on locomotor activity. While low doses of Δ^9-THC have been reported to uniformly decrease activity, higher doses have biphasic effects over time, with an initial increase in activity followed by a subsequent decrease in activity, as catatonia associated with these doses becomes established (Sanudo-Pena et al., 2000). The pattern of responsiveness observed with WIN 55,212-2 in Experiment 1, as can be seen with the initial increase in activity when compared to vehicle-treated animals (see Fig. 1), would then be consistent with the general pattern for high doses of cannabinoids. It is possible that some degree of catatonia had been established when amphetamine was to be administered. Accordingly, rather than WIN 55,212-2 attenuating the effect of amphetamine, the dose of amphetamine used in the present study may have been insufficient to overcome the hypomotility produced by WIN 55,212-2. In either case, these data are consistent with those of Gorriti et al. (1999) in showing that the behavioral consequences associated with the acute treatment with a cannabinoid and amphetamine can counteract each other.

Relatively few studies have examined the extent to which repeated administration of cannabinoid agonists could result in cross-sensitization to other psychoactive drugs and the results so far have been mixed. To the best of our knowledge, this is the first report demonstrating cross-sensitization of WIN 55,212-2 to a psychomotor stimulant, although chronic administration of WIN 55,212-2 has been reported to yield a sensitized response to morphine (Cadoni et al., 2001). While cross-sensitization between THC and amphetamine has been readily obtained (Gorriti et al., 1999; Lamarque et al., 2001), obtaining cross-sensitization with synthetic cannabinoids has been more problematic (Arnold et al., 1998; Ferrari et al., 1999).

A number of factors may be influencing the extent to which cross-sensitization can be obtained between cannabinoids and psychomotor stimulants, including the type of cannabinoid employed, dose and treatment regimen, the dependent measure used to assess sensitization and individual differences associated with the rats being used. Although different agonists have been used in different studies, there is little reason to believe that these cannabinoids have qualitatively different effects (Chaperon and Thiebot, 1999; Szabo et al., 2000). While dose of the cannabinoid, length of chronic administration and the pattern of administration may all be relevant factors in determining whether or not cross-sensitization is obtained, no studies have systematically evaluated these possibilities. It is also possible that cannabinoid treatment does not cross-sensitize equally to different test compounds. For example, cocaine appears to be relatively resistant to the sensitizing properties of both HU 210 (Ferrari et al., 1999) and CP 55,940 (Arnold et al., 1998), while a sensitized response is more likely to be obtained with amphetamine (Gorriti et al.,

1999; Lamarque et al., 2001). Cross-sensitization to a selective D_1/D_2 agonist has even been observed in the same study where no cross-sensitization was noted with cocaine (Ferrari et al., 1999). Whether these differences between cocaine, amphetamine and selective dopamine agonists reflect either fundamental differences in the sensitivity of these compounds to cannabinoid manipulations or variations in experimental design remains to be determined.

How sensitization is being assessed in the various studies might also influence the extent to which cross-sensitization can or cannot be detected. For example, Gorriti et al. (1999) observed a sensitized response to amphetamine for both locomotion and exploration (including rearing), but only at relatively high doses of amphetamine (≥ 4 mg/kg). Lamarque et al. (2001) obtained a sensitized response in a circular corridor with a smaller dose of amphetamine (1 mg/kg), although rats were given 27 injections of Δ^9-THC. While we obtained a sensitized response with rearing, there was no evidence for cross-sensitization with ambulatory movements. In this sense, the present data are somewhat consistent with those of Arnold et al. (1998) in that these investigators used a measure of activity that would be comparable to ambulatory movements in the present study. Therefore, it is possible that neural areas involved with different types of movement (e.g., mesolimbic vs. nigrostriatal dopamine systems) may be differentially sensitive to the repeated administration of cannabinoids.

Finally, individual differences might also be a relevant factor in determining whether or not cross-sensitization is obtained. Lamarque et al. (2001) used outbred Sprague–Dawley rats but only observed sensitization in those rats that had an enhanced locomotor response to novelty. We specifically used Lewis rats because of the propensity of rats of this strain to self-administer various drugs of abuse as well as demonstrating an enhanced sensitization response to psychomotor stimulants (George and Goldberg, 1989; Kosten et al., 1994; Self and Nestler, 1995). Interestingly, those rats, which show an enhanced response to novelty, have an enhanced response to psychomotor stimulants (Hooks et al., 1991) and are also more likely to self-administer psychoactive drugs as well (Cools and Gingras, 1998). While we were able to obtain sensitization with WIN 55,212-2 in Lewis rats, Arnold et al. (1998) similarly used Lewis rats and found no cross-sensitization between CP55,940 and cocaine. Again, this may be related to the dependent measures being used (locomotion vs. rearing) or may also reflect a differential sensitivity to the two cannabinoids (WIN 55,212-2 and CP 55,940). For example, Lewis rats have also been reported to be less sensitive to the effects of CP 55,940 than the outbred Wistar strain as measured by behavioral indices and the ability of this cannabinoid agonist to induce c-*fos* activation in a wide variety of brain areas (Arnold et al., 2001). Future studies will need to take into account these various factors (cannabinoid agonist, test drug, dependent measure used to assess sensitization and individual differences) in order to better ascertain the full extent to which cannabinoids may influence the subsequent effects of psychomotor stimulants.

One unexpected finding that prompts further study is the lower levels of open-field activity seen 10 days following chronic treatment with WIN 55,212-2 in the absence of amphetamine. This effect may be the result of a general decline in mesolimbic dopaminergic tone following cannabinoid withdrawal (Diana et al., 1998a,b) but may also originate in other areas that control movement. However, incomplete understanding of CB_1 receptor control of extrapyramidal systems precludes further speculation given the systemic route used in these experiments. In any event, this finding suggests that the sensitized response to amphetamine in WIN 55,212-2-pretreated rats is not likely due to an artifact associated with heightened basal activity in these animals.

Given that mesolimbic dopamine activation and sensitization are associated with feelings of "wanting" and drug-seeking behavior (Berridge and Robinson, 1998), the present finding of cross-sensitization to amphetamine may not only speak to a neural basis of marijuana dependence but also for the contention that marijuana is a "gateway drug" that serves as an entrée to the use of other drugs of abuse, such as amphetamine, cocaine and heroin. While recent clinical data do not support the notion of occasional marijuana use (mean use 2.7 days/month) being associated with increased drug use, the opposite appears true of heavy marijuana users (mean use 27.3 days/month) (Kouri et al., 1995). This finding is supported in part by our study, which used Lewis rats, an inbred strain known for its heightened response to drugs of abuse, including Δ^9-THC (Chen et al., 1991), and its propensity to self-administer drugs of abuse and ethanol (Kosten et al., 1994; Kosten et al., 1997; Strecker et al., 1995; Suzuki et al., 1988). Thus, in individuals genetically predisposed to substance abuse, marijuana could become a drug of choice or raise the potential for polydrug abuse.

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