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Discriminative stimulus effects of anandamide in rats

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Abstract

Anandamide (arachidonylethanolamide), a putative endogenous ligand for the cannabinoid receptor, produces a tetrad of behavioral effects in mice characteristic of psychoactive cannabinoids including catalepsy, antinociception, hypothermia, and hypomobility. The present study examined the discriminative stimulus effects of anandamide in rats trained to discriminate Δ^9-tetrahydrocannabinol or the potent cannabinoid receptor ligand CP 55,940 {(−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)-phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol)} from vehicle. Intraperitoneal injections of anandamide substituted for Δ^9-tetrahydrocannabinol and for CP 55,940; however, unlike substitution dose-effect curves with the training drugs, anandamide substitution occurred at a single dose (30 or 45 mg/kg) and was accompanied by severe decreases in response rates. The results of the present study suggest that, although systemic anandamide administration may have cannabimimetic effects similar to those of Δ^9-tetrahydrocannabinol and CP 55,940, some differences in the behavioral effects of anandamide and other psychoactive cannabinoids also are apparent.

Keywords: Anandamide; CP 55,940; Drug discrimination; Δ^9-Tetrahydrocannabinol

1. Introduction

Although the psychoactive and therapeutic effects of *Cannabis sativa* (marijuana) have been recognized since ancient times (see Hollister, 1986, for review), the mechanisms through which cannabinoids produce their pharmacological effects have been elusive. Two recent developments that have increased our understanding of these mechanisms are cloning of the cannabinoid receptor (Matsuda et al., 1990) and discovery of a putative endogenous ligand for this receptor (Devane et al., 1992). This novel compound, arachidonylethanolamide, was isolated in porcine brain and has been named anandamide.

The chemical structure of anandamide (Fig. 1) does not resemble the structure of classical cannabinoids such as Δ^9-tetrahydrocannabinol, or of non-classical cannabinoids, such as CP 55,940 {(−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)-phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol)} (Johnson and Melvin, 1986) and the aminoalkylindoles (Ward et al., 1989, 1991). Nevertheless, recent studies have shown that anandamide binds competitively to the cannabinoid receptor (Childers et al., 1994; Devane et al., 1992; Felder et al., 1993; Vogel et al., 1993) and, similar to other cannabinoids, inhibits adenylate cyclase (Felder et al., 1993; Vogel et al., 1993) and N-type calcium currents (Felder et al., 1993; Mackie et al., 1993). In mice, anandamide produces a tetrad of effects shown to be characteristic of psychoactive cannabinoids (Martin et al., 1991): catalepsy, antinociception, hypothermia, and hypomobility (Crawley et al., 1993; Fride and Mechoulam, 1993; Smith et al., 1994).

Although anandamide has not yet been tested clinically for marijuana-like effects, several investigators (Balster and Prescott, 1992; Järbe et al., 1977) have suggested that Δ^9-tetrahydrocannabinol discrimination in rats represents a preclinical animal model of cannabis intoxication in humans. The purpose of the present study was to examine potential cannabimimetic effects of anandamide in rats trained to discriminate a cannabinoid (either Δ^9-tetrahydrocannabinol or CP 55,940) from vehicle.

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2. Materials and methods

2.1. Subjects

Adult male Sprague-Dawley rats (290–310 g), obtained from Charles River (Wilmington, MA), were individually housed in a temperature-controlled (20–22°C) environment with 12-h light-dark cycle (lights on at 7 a.m.). Rats were maintained at 85% of their free-feeding body weight by restriction of their daily food ration. Rats trained to discriminate Δ^9-tetrahydrocannabinol ($n = 8$) were drug naive at the beginning of the study; those trained to discriminate CP 55,940 ($n = 15$) had been used in previous (unpublished) discrimination studies in which they had been tested with cannabinoid compounds.

2.2. Procedure

Training procedures similar to those previously described were used (Gold et al., 1992; Prescott et al., 1992). Briefly, separate groups of rats were trained in standard two-lever operant chambers to press one lever following administration of Δ^9-tetrahydrocannabinol (3.0 mg/kg) or CP 55,940 (0.1 mg/kg) and to press another lever after injection with vehicle, each according to a fixed-ratio 10 (FR-10) schedule of food reinforcement. During each day of discrimination training, responses on only one of the two levers delivered reinforcement. The position of the reinforced (correct) lever was determined by the type of injection the rat received on a given day. Each response on the incorrect lever reset the ratio requirement on the correct lever. The daily injections for each rat were administered in a double alternation sequence of drug and vehicle. Rats were injected and placed in their home cages for 30 min until the start of the experimental session. Acquisition training for the Δ^9-tetrahydrocannabinol group occurred during 15-min sessions 5 days a week (Monday–Friday) until the rats had met three criteria during ten consecutive sessions: (1) first completed FR-10 on the correct lever; (2) percentage of correct-lever responding $\geq 80\%$; and (3) response rate ≥ 0.5 responses/s. Rats in the CP 55,940 group had completed acquisition training prior to the beginning of the present study.

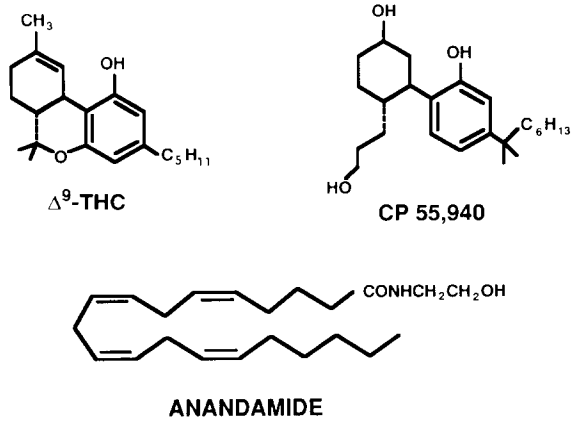

Fig. 1. Chemical structures of Δ^9-tetrahydrocannabinol, CP 55,940 and anandamide.

Substitution tests were conducted on Tuesdays and Fridays with continued training on the double alternation schedule during sessions on Mondays, Wednesdays and Thursdays. During test sessions, consecutive responses on either lever delivered reinforcement according to a FR-10 schedule. In order to be tested, rats must have met the three acquisition criteria (see above) on the day preceding each test session. In the Δ^9-tetrahydrocannabinol-trained rats, 15-min substitution tests were conducted with Δ^9-tetrahydrocannabinol and with anandamide. Tests included in the CP 55,940 dose-effect curve for the CP 55,940-trained rats lasted 2 min (six rats) or 10 min (seven rats). Procedures for these tests have been previously reported (Wiley et al., 1993). Duration of anandamide tests was 15 min. Doses of Δ^9-tetrahydrocannabinol were administered in ascending order; doses of anandamide generally were administered in descending order. Each rat was tested with each dose of the training drug and of anandamide only once. Control tests with vehicle and the training drug were conducted before (Δ^9-tetrahydrocannabinol group) and after (both groups) each dose-effect curve determination.

In order to examine the effect of a shorter pre-session injection interval, rats in the CP 55,940-trained group were given a single injection of 10 mg/kg anandamide 5 min before the start of a test session. To determine whether anandamide would augment the effects of Δ^9-tetrahydrocannabinol, rats trained to discriminate Δ^9-tetrahydrocannabinol were tested with anandamide (10 mg/kg, 15-min pre-session) in combination with subthreshold doses of Δ^9-tetrahydrocannabinol (0.3 and 1.0 mg/kg, 30-min pre-session) that did not substitute for the training dose when tested alone.

2.3. Drugs

Δ^9-Tetrahydrocannabinol (National Institute on Drug Abuse, Rockville, MD) and CP 55,940 (Pfizer, Groton, CT) were dissolved in a 1:1 mixture of absolute ethanol and Emulphor-620 (Rhone-Poulenc, Princeton, NJ) and diluted with saline (1:1:18) to form stock suspensions of 10 mg/ml Δ^9-tetrahydrocannabinol and 1.0 mg/ml of CP 55,940 in a vehicle of emulphor:ethanol:saline (Carney et al., 1977). Lower concentrations were obtained by further dilution with the vehicle solution. Each drug was diluted weekly, as needed. Doses of anandamide (Dr. Raj K. Razdan,

Organix, Woburn, MA) were mixed as needed in a vehicle of 1:1:18 emulphor:ethanol:saline. Injections of Δ^9-tetrahydrocannabinol and CP 55,940 were given 30 min before the start of the session. Anandamide was administered 15 min pre-session, except where specifically noted. Doses of all test drugs were administered intraperitoneally (i.p.) at a volume of 1 ml/kg body weight.

2.4. Data analysis

For each test session, percentage of responses on the drug lever and response rate (responses/s) were calculated. ED_{50}'s (with 95% confidence intervals) were calculated separately for each drug (where appropriate) using least squares linear regression on the linear part of the dose-effect curves (Goldstein, 1964) for percentage of drug-lever responding, plotted against $\log_{10}$ transformation of the dose. (Data on lever selection for rats that had 0.05 responses/s during a test session were excluded from data analysis.) Percentage of drug-lever responding and response rate data for the Δ^9-tetrahydrocannabinol and anandamide combination tests were analyzed with a factorial repeated measures general linear models procedure (SAS Institute, Cary, NC).

3. Results

Acquisition of the Δ^9-tetrahydrocannabinol and CP 55,940 discriminations (see 2.2. for criteria) were achieved within 30 sessions of double alternation training. The two groups did not differ in the average number of sessions to acquisition.

Anandamide fully substituted ($\geq$ 80% Δ^9-tetrahydrocannabinol-lever responding) for Δ^9-tetrahydrocannabinol (Fig. 2, top panel); however, these effects were observed only at a high dose (45 mg/kg) which also severely decreased response rates (Fig. 2, bottom panel). The ED_{50} for anandamide was 36.5 mg/kg (95% CI = 5.3–250.0). Although the combination of 10 mg/kg anandamide and 0.3 mg/kg or 1.0 mg/kg Δ^9-tetrahydrocannabinol slightly increased % Δ^9-tetrahydrocannabinol-lever responding above the level produced by each dose of Δ^9-tetrahydrocannabinol alone in these rats, analysis of the main effect of anandamide in the GLM procedure revealed that this increase was not significant [$F(1,7) = 0.8$, $P = 0.4$]. Anandamide significantly enhanced the response rate decreasing effects of these two doses of Δ^9-tetrahydrocannabinol [main effect of anandamide: $F(1,7) = 39.6, P = 0.004$].

The substitution produced by Δ^9-tetrahydrocannabinol was dose-dependent with mean response rates similar to control test rates, except at the highest (30 mg/kg) dose where responding was decreased (Fig. 2).

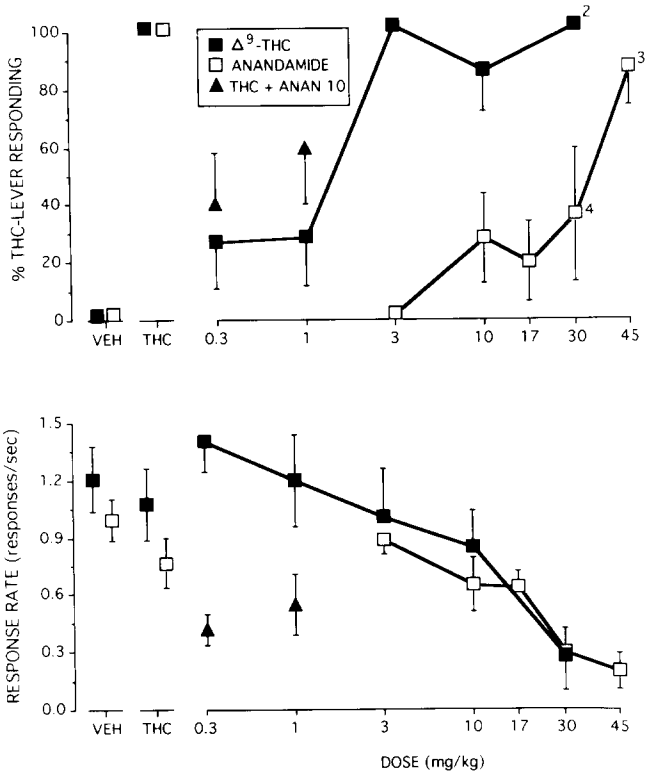

Fig. 2. Mean percentage of Δ^9-tetrahydrocannabinol-lever responding (top) and response rate (bottom) as a function of dose of Δ^9-tetrahydrocannabinol, anandamide, and the combination of 0.3 and 1.0 mg/kg of Δ^9-tetrahydrocannabinol and 10 mg/kg anandamide in rats trained to discriminate 3.0 mg/kg Δ^9-tetrahydrocannabinol from vehicle. Points above VEH and THC represent results of control tests with vehicle and Δ^9-tetrahydrocannabinol (3.0 mg/kg) conducted before each dose-effect curve determination. Values for each dose represent means (+S.E.M.) of data for six to eight rats, except as indicated by numbers beside data points.

The ED_{50} for Δ^9-tetrahydrocannabinol's discriminative stimulus effects was 1.1 mg/kg (95% CI = 0.5–2.8), showing that Δ^9-tetrahydrocannabinol was 30 times more potent than anandamide for this effect. During control tests with vehicle and Δ^9-tetrahydrocannabinol, responding occurred almost exclusively on the appropriate lever.

Similar to the results in Δ^9-tetrahydrocannabinol-trained rats, anandamide fully substituted ($\geq$ 80% CP 55,940-lever responding) for CP 55,940 (Fig. 3, top panel); however, again, these effects were observed only at a high dose (30 mg/kg) which also severely decreased response rate (Fig. 3, bottom panel). The ED_{50} for anandamide's discriminative stimulus effects was 16.3 mg/kg (95% CI = 6.9–38.4). Mean response rates for rats that responded more than 0.05 responses/s (i.e., response rates for data included in the % CP 55,940-lever responding) was 3–4 times lower than mean response rates during vehicle control tests [0.31 (+0.09) vs. 1.07 (+0.11)]; hence, response rates were decreased even for rats that responded enough to

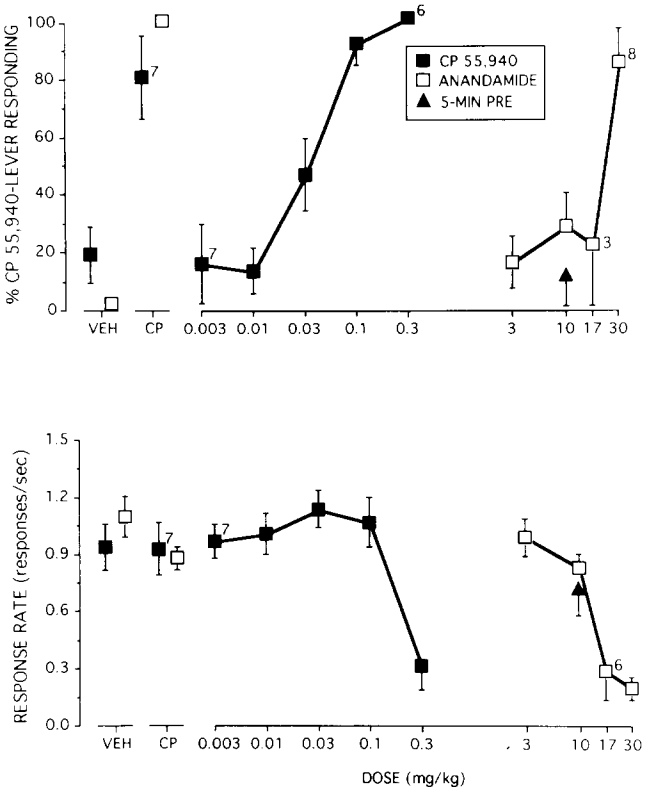

Fig. 3. Mean percentage of CP 55,940-lever responding (top) and response rate (bottom) as a function of dose of CP 55,940 or anandamide (i.p., 15 min pre-session) in rats trained to discriminate 0.1 mg/kg CP 55,940. Points above VEH and CP represent results of control tests with vehicle and CP 55,940 (0.1 mg/kg) conducted before the CP 55,940 dose-effect curve determination and after the anandamide dose-effect curve determination. Triangles represent results of testing 10 mg/kg anandamide injected 5 min before the start of the test session. Values for each dose represent means (±S.E.M.) of data for 12–15 rats, except as indicated by numbers beside data points.

select a lever. An injection of 10 mg/kg of anandamide 5 min prior to the start of a test session did not produce a reliable increase in the level of CP 55,940-lever responding compared to the 15-min pre-session injection of this dose.

CP 55,940 produced dose-dependent substitution with mean response rates similar to control test rates, except at the highest (0.3 mg/kg) dose where responding was decreased (Fig. 3). The ED_{50} for CP 55,940's discriminative stimulus effects was 0.03 mg/kg (95% CI = 0.02–0.04), showing that CP 55,940 was 540 times more potent than anandamide for this effect. During control tests with vehicle and CP 55,940, responding occurred primarily on the appropriate lever.

4. Discussion

Anandamide substituted for Δ^9-tetrahydrocannabinol and CP 55,940 in rats trained to discriminate one of these drugs from vehicle. These results are consistent with those of previous studies which have found that systemic administration of anandamide produces other pharmacological effects typical of cannabinoid drugs, including antinociception, hypothermia, hypomobility and catalepsy (Crawley et al., 1993; Fride and Mechoulam, 1993; Smith et al., 1994). Since the discriminative stimulus effects of cannabinoids and many other drugs are believed to be receptor-mediated (Balster, 1990; Balster and Prescott, 1992), it is not surprising that data from binding assays have verified that, like Δ^9-tetrahydrocannabinol and CP 55,940 (Devane et al., 1988), anandamide binds to the cannabinoid receptor (Devane et al., 1992). In both behavioral and in vitro tests, anandamide generally has been found to be less potent than are Δ^9-tetrahydrocannabinol and CP 55,940 (present results; Smith et al., 1994; Vogel et al., 1993), although there are exceptions (Crawley et al., 1993).

Although anandamide substitutes for Δ^9-tetrahydrocannabinol and CP 55,940 and resembles these cannabinoids in a variety of other tests, examination of the present results reveals some differences between the discriminative stimulus effects of anandamide, Δ^9-tetrahydrocannabinol and CP 55,940. First, only the highest anandamide dose tested in each group (30 or 45 mg/kg) increased percentage of drug-lever responding above chance levels. In contrast, the cross-generalization produced by Δ^9-tetrahydrocannabinol and CP 55,940 is dose-dependent and occurs over a range of doses in animals trained to discriminate either of these drugs from vehicle (Gold et al., 1992; Järbe et al., 1989; Wiley et al., 1993, unpublished observations), as exemplified by the Δ^9-tetrahydrocannabinol and CP 55,940 dose-effect curves in the present study. Second, the dose of anandamide at which maximal substitution occurred in each group of rats was associated with concomittant decreases in response rates. CP 55,940 and Δ^9-tetrahydrocannabinol produce discriminative stimulus effects at doses that do not decrease response rates (Gold et al., 1992; Wiley et al., 1993). This pattern of dose-dependent substitution with response rate decreases only at higher doses is exhibited by Δ^9-tetrahydrocannabinol and CP 55,940 in the present study (see Δ^9-tetrahydrocannabinol and CP 55,940 dose-effect curves in Figs. 2 and 3). Hence, while the discriminative stimulus effects of Δ^9-tetrahydrocannabinol and CP 55,940 are apparent at lower doses than those which decrease response rates, discriminative stimulus and response rate effects of anandamide do not show clear separation.

Other studies also have reported differences between the pharmacological effects of Δ^9-tetrahydrocannabinol and anandamide (Crawley et al., 1993; Smith et al., 1994). Whereas Δ^9-tetrahydrocannabinol consistently produces a characteristic profile of phar-

macological effects (i.e., antinociception, immobility, hypothermia and hypomobility), anandamide's profile of cannabinoid-like effects differs depending upon route of administration (Smith et al., 1994). Anandamide was less potent in all tests, and generally, had a shorter duration of action, although there were exceptions (Smith et al., 1994). Unlike Δ^9-tetrahydrocannabinol, anandamide failed to produce significant effects in tests for anxiolytic activity, feeding and memory (Crawley et al., 1993).

Several alternative explanations could explain the differences in the behavioral effects of anandamide, Δ^9-tetrahydrocannabinol and CP 55,940 observed in the present study. As reported in previous studies, anandamide typically has a shorter duration of action and is less potent than Δ^9-tetrahydrocannabinol (Crawley et al., 1993; Smith et al., 1994). It is possible that anandamide would have exhibited greater substitution at lower doses with a shorter pre-session injection interval; however, probe tests with 10 mg/kg anandamide administered 5 min before testing failed to support this hypothesis. It has been suggested that the biodisposition and metabolic pathways of anandamide and Δ^9-tetrahydrocannabinol are significantly different. Deustch and Chin (1993) have shown that anandamide is metabolized by an amidase, an enzyme that is not involved in the biotransformation of Δ^9-tetrahydrocannabinol or CP 55,940. Additionally, Childers et al. (1994) found that the enzyme inhibitor phenylmethyl-sulfonyl fluoride (PMSF) dramatically increased the binding affinity of anandamide. Smith et al. (1994) also found little pharmacological activity in mice when anandamide was administered i.p., a route likely to result in considerable metabolism. Finally, preliminary studies in our laboratory have shown that [^{3}H]anandamide is rapidly metabolized to arachidonic acid following i.v. administration to mice (unpublished observations). Thus, biodispositional factors may be responsible for differences in the specificity for discriminative stimulus effects of anandamide and standard cannabinoids.

Another possible source of variation among anandamide and Δ^9-tetrahydrocannabinol-like cannabinoids that might have contributed to differences in the dose-responsiveness of their behavioral effects in the present study is the affinity of these drugs for the cannabinoid receptor. Comparison of receptor affinities in a comparable assay revealed that the affinity of Δ^9-tetrahydrocannabinol is approximately 40 nM (Compton et al., 1993) whereas that of anandamide is approximately 100 nM (Childers et al., 1994). It should be pointed out that other low-affinity agonists, such as cannabinol, act as full agonists in the Δ^9-tetrahydrocannabinol drug discrimination procedure (Järbe and Hiltunen, 1987). Although anandamide acts as a partial agonist to inhibit calcium currents in neuroblastoma cells (a procedure in which Δ^9-tetrahydrocannabinol and CP 55,940 act as full agonists) (Mackie et al., 1993), it does not seem probable that anandamide acted as a partial agonist in the drug discrimination procedure. Anandamide showed efficacy in this procedure approximately equal to CP 55,940 and Δ^9-tetrahydrocannabinol. In addition, if anandamide had acted as a partial agonist in the present study, a decrease in Δ^9-tetrahydrocannabinol-lever responding would have been predicted by co-administration of Δ^9-tetrahydrocannabinol and anandamide. Anandamide did not decrease, but rather slightly increased, Δ^9-tetrahydrocannabinol-lever responding when injected following Δ^9-tetrahydrocannabinol administration. Finally, the discriminative stimulus effects of anandamide in rats may be influenced by its actions at receptors other than the cannabinoid receptor.

In summary, while the present results, combined with results of previous studies, suggest that anandamide may produce cannabimimetic effects similar to those produced by other psychoactive cannabinoids such as Δ^9-tetrahydrocannabinol and CP 55,940 and that these effects may be related to anandamide's affinity for the cannabinoid receptor, differences between the pharmacological profiles of anandamide and other cannabinoids should evoke caution in accepting this conclusion. At present, it is unclear whether these differences in the pharmacological profile of anandamide are related to differences in its biodisposition or receptor mechanisms or to other pharmacokinetic factors. Further research with more potent and specific anandamide analogs will be required to answer these questions.

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