Abuse liability and behavior pharmacology profiles of six cannabinoid compounds

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INTRODUCTION

Synthetic cannabinoids are designer drugs that mimic the psychoactive properties of an ingredient in marijuana (Δ9-terahydraocannabinol (Δ9-THC). These newer generation of psychoactive substances (NPS) are marketed as spice drugs with claims to be legal, natural, and safer alternatives to marijuana (Carroll et al. 2012). These drugs are chemically diverse and have a strong affinity to the cannabinoid receptors (Cannaert et al. 2020), however their complex pharmacological action is poorly understood. Significant adverse effects from usage of these drugs include neuropsychological effects, tachycardia, dyspnea, liver damage and deaths (Al-Matrouk et al. 2019; Assi et al. 2020). According to the most recent report from the European Monitoring Center for Drugs and Drug Addiction 790 new synthetic cannabinoids were reported (EMCDDA,2020). Therefore, in a collaborative effort with the DEA, *the purpose of this study was to evaluate six synthetic cannabinoids in a locomotor activity (LMA) assay and to test for substitution for Δ9 -THC in a drug discrimination (DD) assay.* These data were used to determine the preclinical potency and efficacy of these compounds relative to the commonly abused Δ9 -THC.

METHODS

Male Swiss–Webster mice were obtained from Envigo (Indianapolis, IN) at 7-8 weeks of age and tested at approximately 10 weeks of age. The study was conducted using Digiscan (model RXYZCM, Omnitech Electronics, Columbus, OH) locomotor activity testing apparatus (40.5 X 40.5 X 30.5 cm) housed within sound-attenuating chambers. A panel of infrared beams (16 beams) and corresponding photodetectors were located along the sides of each activity chamber. A 7.5-W incandescent light above each chamber provided dim illumination, and fans provided an 80-dB ambient noise level within the chamber. Separate groups of 8 mice were injected i.p. with either vehicle (ethanol/Cremophor EL/0.9% saline 1:1:18) or a cannabinoid: Δ^9-THC (1 - 25 mg/kg), ADB-BUTINACA (0.025 4F-MDMB-BICA (0.025 - 1 mg/kg), 5F-EMB-PICA (2201) (0.1 - 1 mg/kg), 5Cl-AKB-48 (1 - 50 mg/kg), FUB-AKB-48 - 1 mg/kg), (0.1 - 10 mg/kg), or FUB-144 (0.1 – 10 mg/kg) immediately prior to locomotor activity testing. Separate vehicle controls were tested for each test compound. In all studies, horizontal activity (interruption of photocell beams) was measured for 8 hours within 10-min periods, to establish a time-course of locomotor effects. Testing began at 0800 h (1 h after lights on).

Adult male Sprague-Dawley rats were trained to discriminate either methamphetamine (1 mg/kg, i.p.) or cocaine (10 mg/kg, i.p.) from 0.9% saline using a FR 10 schedule of food reinforcement (45 mg food pellets; Bio-Serve, Frenchtown, NJ) with a two-lever choice procedure. A reinforcer was available for every ten responses on a designated injection-appropriate lever. The rats received approximately 60 of these sessions before they were used in tests for substitution of the experimental compounds. Rats were used in testing once they had achieved 9 of 10 sessions at 85% injection-appropriate responding for both the first reinforcer and total session. The training sessions occurred on separate days in a double alternating fashion (drug-drug-saline-saline-drug, etc.). After the until the training phase was complete, after which substitution tests were introduced into the training schedule such that at least one saline and one drug session occurred between each test (drug-saline-test-saline-drug-test-drug; etc.). The substitution tests occurred only if the rats had achieved 85% injection-appropriate responding on the two prior training sessions. Standard behavior-testing chambers (Coulbourn Instruments, Allentown, PA, Model E10-10) connected to IBM-PC compatible computers via LVB interfaces (Med Associates, East Fairfield, VT) were used for testing. Δ^9-THC ((0.01 – 0.1), 4F-MDMB-BICA (0.01 – 0.1 mg/kg), 5F-EM0.1 - 3 mg/kg), ADB-BUTINACA B-PICA (2201) (0.05 – 0.5 mg/kg), 5Cl-AKB-48 (1 - 5 mg/kg), FUB-AKB-48 0.1 - 1 mg/kg), or FUB-144 (0.1 – 5 mg/kg) were tested for substitution in THC trained rats.

ADB-BUTINACA, 5Cl-AKB-4 and FUB-144 was administered 30 min before testing, 4F-MDMB-BICA, 5F-EMB-PICA 15 min before testing, and FUB-AKB48 was administered 60 min before testing.

RESULTS

Locomotor activity time course

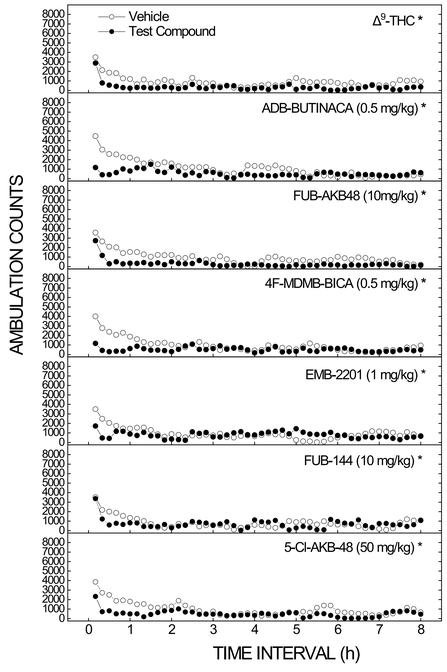

Figure 1. Time course of Δ^9-THC, ADB-BUTINACA, 4F-MDMB-BICA, 5F-EMB-PICA (2201), 5Cl-AKB-48, FUB-AKB-48 or FUB-144 vs vehicle at doses producing maximal effects on horizontal activity (ambulation counts/10min). Time-course data are from independent groups of mice (n=8/test compound, unless otherwise indicated). * indicates p<.05 when compared with vehicle.
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Locomotor activity dose effect

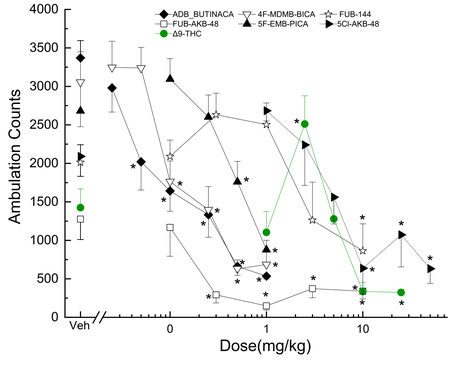

Figure 2. Effect of different doses of : Δ^9-THC, ADB-BUTINACA, 5 4F-MDMB-BICA, 5F-EMB-PICA (2201), 5Cl-AKB-48, FUB-AKB-48 or FUB-144 on locomotor activity. Each data point depicts mean ambulation counts/10min ± SE measured during the earliest 30-min period of maximal effect (ADB-BUTINACA, 5 4F-MDMB-BICA, and 5F-EMB-PICA were 0-30 min; for 5Cl-AKB-48 it was 20-50 min, for FUB-AKB-48 it was 60-90 min and for FUB-144 it was 10-40 min) as a function of dose. Data are from independent groups of 8 mice/dose (unless otherwise indicated). * indicates p<.05 when compared with vehicle.
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Substitution for Δ9 -THC

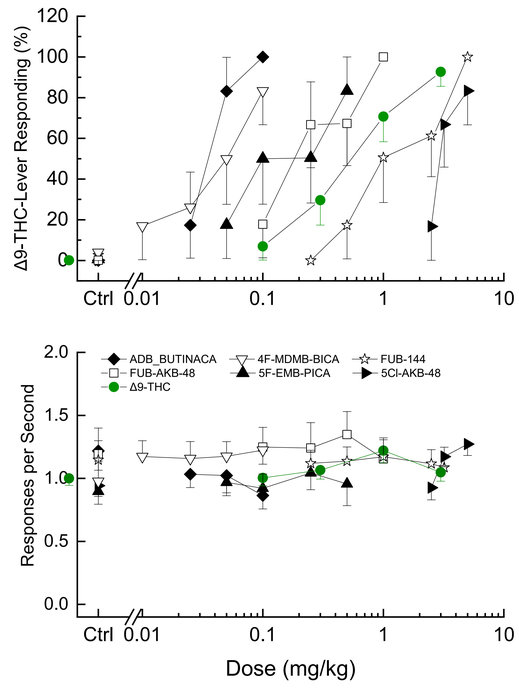

Figure 3. Substitution for the discriminative stimulus effects of Δ9 –THC. **G**raph-Top panel show percentage of total responses made on the drug-appropriate lever. Bottom panels show rate of responding in responses per second (r/s). n=6 unless otherwise shown. Vehicle and training drug controls are pooled averages. Ctrl indicates vehicle and training drug control values.

TABLE-1. Potency of the test compounds compared with that of Δ9-THC in locomotor activity or discriminative stimulus assays.

Test Compound	Locomotor Activity (potency)	THC Discrimination (potency)	Locomotor Activity /Discrimination (ratio)
Δ9-THC	7.51	0.60	12.52
ADB-BUTINACA	0.11	0.04	2.75
FUB-AKB-48	0.17	0.23	0.73
4F-MDMB-BICA	0.20	0.04	5.02
5F-EMB-PICA (2201)	0.66	0.16	4.13
FUB-144	4.86	1.25	3.89
5Cl-AKB-48	6.11	3.21	1.90

RESULTS

- All of the test compounds decreased locomotor activity within 10 – 30 min of administration. Duration of action lasted one to 1.5 h.
  - Most of the test compounds were at least 10-fold more potent than THC. Of the 6 tested compounds, ADB-BUTINACA was the most potent (68 times more potent than THC).
  - FUB-144 and 5Cl-AKB-48 were the least potent, having potencies similar to that of THC.
- All of the test compounds fully substituted for the discriminative stimulus effects of THC.
  - FUB-144 and 5Cl-AKB-48 were less potent than THC
  - The remaining compounds were more potent than THC. ADB-BUTINACA was again the most potent (16-fold more potent than THC).
  - None of the test compounds altered rates of responding at the doses tested.
- All but one of the compounds (FUB-AKB-48) were more potent in producing discriminative stimulus effects than in suppressing locomotor activity.

CONCLUSIONS

- All of the six cannabinoids tested produced behavioral effects similar to those of THC and are likely to share its abuse liability.
- Some of the test compounds are more potent than THC and may pose a public health risk of increased likelihood of overdosing.
- None of the compounds produced the convulsions or lethality observed in other synthetic cannabinoids and may be marginally safer to use.

REFERENCES

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ACKNOWLEDGMENTS

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