CONCLUSIONS

An investigation of the discriminative stimulus and reinforcing effects of cannabidiol in rats

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INTRODUCTION

Cannabidiol (CBD) was recently approved in the USA to treat severe, early-onset, treatment-resistant, epilepsy, i.e. Dravet syndrome and Lennox-Gastaut syndrome. To evaluate its potential for abuse, we have investigated CBD's psychoactive profile in rats trained to discriminate between midazolam and saline, and CBD's reinforcing effect by intravenous self-administration (IVSA) testing in heroin-trained rats.

METHODS

Freely-fed, female, Lister hooded rats were trained to discriminate midazolam (0.5mg/kg ip) from saline in a 2-choice operant test. Lever-pressing was reinforced by sweetened milk rewards on a FR3 schedule in 2hr sessions. The rats were competent in the task (>75% correct responding for each lever) and midazolam (0.5, 1, 1.5 mg/kg po), midazolam (0.25, 0.5, 1.0, 1.5 mg/kg po), diazepam (0.125, 0.25, 0.5, 1.0 mg/kg po).

Mildly food-restricted, male, Sprague-Dawley rats were initially trained to lever-press for food rewards before being surgically implanted with i-v/dawley jugular catheters. Rats were allowed to self-administer heroin (15 mg/kg/po) on a fixed ratio (FR3) schedule of reinforcement in 2hr training sessions. After establishment of consistent heroin self-administration, the rats were subjected to saline extinction. The reinforcing effects of heroin, 100, 500 mg/kg (painless), diazepam (1, 3, 5, 10 mg/kg) and midazolam (0.3, 1, 1.5, 2.25 or 3 mg/kg) were then evaluated on a FR3 schedule in 2hr sessions.

RESULTS

In midazolam-coded drug-discrimination, all CBD doses generalised to saline (maximum generalisation to the midazolam cue: 10.8±4.3% at 20mg/kg ip) (Fig 1). Table 1.

Midazolam and alprazolam given orally dose-dependently generalised to midazolam (91±5%, 89±7%, respectively) (Fig 1 and 2).

Heroin maintained self-administration in rats at levels significantly greater than saline (77.6 ± 0.5 % session, n = 39 vs 37 ± 0.2 % session, n = 39; p<0.001) (Fig 5-7).

One dose of CBD, ie 100 mg/kg ip, maintained a low level of self-administration (6.9±1.8 % session, n=8) at a level that was significantly greater than saline (p<0.001) (Fig 5-7).

The reference comparators, diazepam [3ug/kg/ip] (7.9±2.1 % session, n=9) and midazolam (1.5mg/kg ip) [7.3±1.3 % session, n=16] maintained significantly greater self-administration than saline (p<0.05), and met the criteria for positive reinforcers (Fig 6 and 7).

CONCLUSIONS

This study is the first to investigate systematically the discriminative stimulus and possible reinforcing potential of CBD.

CBD did not generalise to midazolam demonstrating that CBD does not produce benzodiazepine-like psychoactive effects.

CBD served as a weak positive reinforcer at a single dose in heroin-trained rats.

Diazepam and midazolam also served as weak positive reinforcers in this model.

These results predict that CBD poses a very low risk for human abuse.

Consistent with these findings CBD has been recently classified as a Schedule 5 Controlled Drug in the USA.

Table 1: Operant responses of rats receiving cannabidiol (p.o.) (tested 120 min after dosing)

Table 2: Plasma exposure of cannabidiol rats compared with Cmax in human subjects after multiple dosing of cannabidiol

Figure 1: Validation of the model to detect the effects of orally administered drugs by rats trained to recognise midazolam (i.p.)

Figure 2: Effects of alprazolam (p.o.) in rats trained to discriminate midazolam from saline

Figure 3: Effects of cannabidiol (p.o.) in rats trained to discriminate midazolam from saline

Figure 4: Evaluation of cannabidiol on a FR3 schedule of reinforcement compared with heroin and saline

Figure 5: Evaluation of diazepam on a FR3 schedule of reinforcement compared with heroin and saline

Figure 6: Evaluation of midazolam on a FR3 schedule of reinforcement compared with heroin and saline

Figure 7: Evaluation of diazepam on a FR3 schedule of reinforcement compared with heroin and saline

Drugs were evaluated in groups of 7-8 rats. Significantly different from saline *p<0.05, ***p<0.001. Significantly different from heroin ### p<0.001.