EVALUATION OF KETAMINE, AMPHETAMINE AND NICOTINE IN RATS TRAINED TO SELF-ADMINISTER COCAINE

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INTRODUCTION

Detection of abuse liability is becoming an essential component of CNS safety, as recently outlined in guideline documents from the EMA and the FDA. Self-administration (SA) procedures, in which animals are trained to respond for an infusion of test substance, are widely regarded as the most predictive approach to evaluate abuse liability in humans. Self-administration assesses the intrinsic rewarding properties of a substance and is not particularly mechanism-based. It directly evaluates the reinforcing properties of a substance by seeing if animals are prepared to work (typically to lever press) in order to get an injection of the substance (typically by the i.v. route).

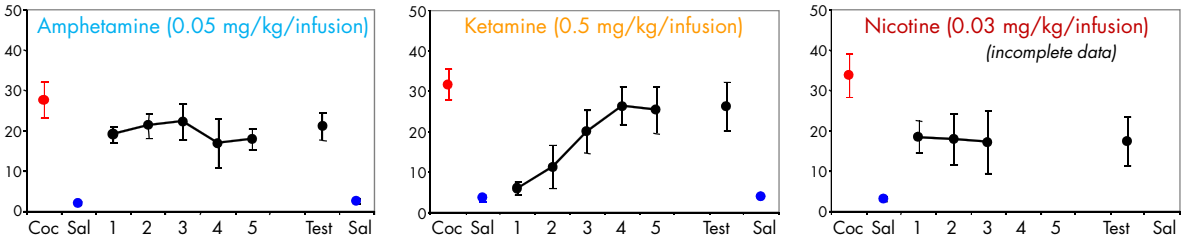
The choice of training substance is rightly highlighted as an important consideration in carrying out SA experiments but with novel test substances, the choice of training substance is not always straightforward. Under these circumstances it is tempting to fall back on readily self-administered substances such as cocaine or heroin. The present study is an initial evaluation of commonly abused substances in rats trained to self-administer cocaine on an FR10 schedule of reinforcement.

METHODS

- All experiments were carried out in operant chambers equipped with a single lever to the right of a food hopper. Experimental events were controlled and monitored, and data collected and stored, by a microcomputer and associated interface (MED Associates, Inc.).
- Following lever-press training, individually housed male Sprague-Dawley rats were prepared with i.v. jugular catheters which could be connected to an infusion pump controlled by computer.
- Beginning at least 3 days after surgery, rats were subjected to daily sessions (typical maximum duration of 120 minutes) during which they could receive a maximum of 50 i.v. infusions of the baseline drug (cocaine, 0.5 mg/kg/infusion) under a Fixed Ratio 5 (FR5) schedule (i.e. they were required to make 5 lever responses to obtain each infusion). Immediately prior to the beginning of daily sessions, rats received 1 non-contingent (i.e., "priming") infusion of the same solution that will be delivered after appropriate responding during the session (baseline drug, saline or test item).
- A distinctive visual stimulus was displayed during periods when i.v. infusions were available and each infusion was followed by a 30-second timeout, during which the chamber was dark and lever presses had no programmed consequence. The infusion duration was approximately 4-6 seconds (infusion rate 2.075 ml/minute) and the infusion volume was 0.519 ml/kg.
- Following acquisition of cocaine self-administration and extinction of responding when saline was substituted, cocaine was retested at 0.25 mg/kg/infusion and the response requirement was increased to FR10 (i.e. under conditions comparable to those evaluating a test substance) and again followed by saline extinction. Each phase was at least three sessions.
- Once all animals had been tested in this way, substitution studies were carried out with ketamine HCl (0.5 mg/kg/infusion), nicotine (0.03 mg/kg/infusion) and amphetamine sulphate (0.05 mg/kg/infusion). Each substance was tested at a single dose that had previously been shown in the literature to support self-administration.

RESULTS

Figure 1. Infusion data for baseline responding and test substance responding



Coc; Sal, Test: Mean of 3 sessions of stable responding for cocaine, saline extinction and test substance respectively.
1-5: Mean per session for each of the first 5 days of test substance availability.

Table 1. First day infusion rates, stable infusion rates and sessions to achieve stable infusion rates for amphetamine, ketamine and nicotine (n=4 or 5)

Substance	Day 1 infusion rate	Stable infusion rates	Sessions to achieve stable rates
Amphetamine	21.4 ± 1.8	24.0 ± 3.8	5.4 ± 0.5
Ketamine	5.2 ± 1.8	29.8 ± 4.2	5.5 ± 0.8
Nicotine	18.5 ± 4.1	16.6 ± 5.6	Not determined

- Cocaine self-administration was immediately acquired under the FR5 schedule and showed good stability over 7 days (mean infusions per session = 22.5 ± 1.9, n=10). Extinction under saline was rapid (7.1 ± 0.9 infusions in 6.6 ± 0.8 sessions). Reinstatement of cocaine under an FR10 schedule at 0.25 mg/kg/infusion resulted in high levels of self-administration (31.2 ± 2.7 infusions per session [mean of three consecutive sessions of stable responding]) within 10.9 ± 1.3 sessions).
- When rats were given the opportunity to self-administer amphetamine, infusion rates were almost immediately at levels similar to those seen with cocaine (Figure 1) and stable rates of responding were obtained within 5.4 sessions (Table 1).
- In contrast, when ketamine was available for self-administration, infusion rates were initially no different to those seen with saline but then rapidly increased to achieve stable rates comparable to cocaine (Table 1).
- Nicotine appeared to behave in a similar way to amphetamine, with most rats showing high levels of self-administration from day 1 (Table 1). Note however that the data presented here for nicotine should be considered as only preliminary data as it is from only 4 animals, over 3 or 4 sessions in most cases, obtained towards the end of their availability for self-administration studies.

CONCLUSION

Rats readily learnt to self-administer cocaine and were then successfully used to demonstrate that cocaine self-administration under an FR10 schedule can be used to detect a broad range of substances with abuse liability, including less overtly stimulant substances such as ketamine. The delayed response to ketamine suggests that care must be taken to ensure that sufficient sessions are run when testing any novel substance in order to avoid false negatives.

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