Relative contributions of drug re-exposure and salient cues in the reinstatement of cocaine and heroin seeking; implications for the treatment of substance use disorders

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INTRODUCTION

The rates of stimulant and opiate abuse have been steadily rising in the USA over the last decade (The Guardian, 2018). Treating drug dependence and addiction are critical areas of unmet clinical need. Persuading subjects to quit substances of abuse is a first step, but helping them to maintain abstinence from drug taking after quitting is a major problem. It is known that reinstatement of drug-seeking can be initiated in humans and experimental animals by salient cues associated with abuse, drug re-exposure, or a combination of both (Gardner, 2011; Bossert et al, 2013). What is less clear is (i) the relative contribution of these triggers to initiating relapse and (ii) whether their contributions are the same for different types of substances of abuse.

RESULTS

Part 1

- Heroin (0.015mg/kg/inj) and cocaine (0.29 and 0.45mg/kg/inj) maintained significantly greater levels of self-administration than saline (**Figure 1A**).
- The break-points for reinforcement of heroin (0.015mg/kg/inj) and cocaine (0.29 or 0.45mg/kg/inj) were not significantly different from one another (**Figure 1B**).
- Therefore, cocaine (0.36 mg/kg/inj) and heroin (0.015mg/kg/inj) were tested at equally reinforcing doses in Part 2.

Part 2

- Cocaine and heroin both served as powerful reinforcers when compared against the appropriate saline control (**Figure 2**).
- Reinstatement of drug-seeking for cocaine or heroin was initiated by presentation of the contingent tone/light cues + drug priming or drug priming alone. The presentation of tone/light cues alone induced reinstatement of cocaine seeking, but not heroin seeking (**Figures 3 & 4**).
- The effects of the contingent cues and drug priming were approximately additive in the reinstatement of cocaine and heroin seeking. However, their relative contributions were very different. Thus, the effects of drug priming and salient cues were equal in the reinstatement of cocaine seeking, but in the case of relapse to heroin seeking the effect of drug re-exposure was 3x greater than that of the salient cues ($p<0.05$) (**Figure 5**).

METHODS

Experiments were conducted in mildly food-restricted, singly-housed, adult, male, Sprague Dawley rats. The investigation was conducted in 2 parts. In Part 1, we explored heroin (0.015mg/kg/inj [injection]) and cocaine (0.29 and 0.45mg/kg/inj) as positive reinforcers by intravenous self-administration (IVSA) on a fixed ratio (FR) schedule in 2hr sessions and then determined their relative reinforcing effects by break-point determination on a progressive ratio (PR) schedule in a single 4hr session.

In Part 2, we used an additional 2 cohorts of rats and trained them to self-administer heroin (0.015mg/kg/inj; Group 1) or cocaine (0.36mg/kg/inj; Group 2) on a FR5 reinforcement schedule in 2hr sessions. Tone + light cues were briefly presented contingently with each drug injection. After robust stable self-administration had been established (≥12inj/session), the responding of the rats was extinguished with saline on FR5 without cues (≤6infusions/session). Reinstatement of drug-seeking was initiated by drug priming (cocaine 1mg/kg i.v. or heroin 0.25mg/kg s.c.), by presentation of tone/light cues, or by drug priming + cues. Results are mean±SEM.

DISCUSSION

The findings reveal that cocaine and heroin both served as powerful reinforcers.

We have previously demonstrated there was no difference between the relative reinforcing effects of cocaine and heroin at the doses used in these experiments (Smith et al, 2018)

At equivalent reinforcing doses which induced a high degree of psychological dependence in the rats, re-exposure to the reinforcing effect of the drug is a much more important factor in the reinstatement of heroin seeking than it is for cocaine.

REFERENCES

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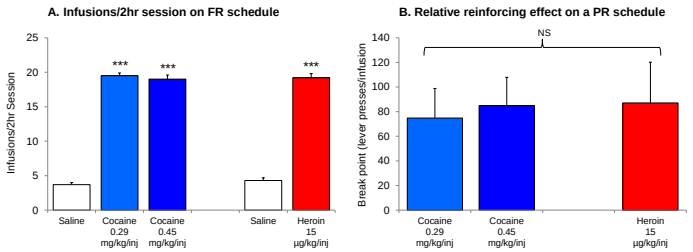
IMPLICATIONS FOR THE TREATMENT OF OPIATE AND COCAINE DEPENDENCE

Substitution therapy is effective for treating dependence to opiates, eg methadone or buprenorphine, but not cocaine; examples of failed interventions in cocaine abuse/dependence include bupropion, vanoxerine (GBR-12,909), methylphenidate and lisdexamfetamine. Our results suggest that one reason for the failure of substitution therapy in cocaine dependence is because contextual cues, eg social situations, drug using friends and locations associated with cocaine taking, have a very important role in triggering relapse to cocaine abuse.

Fig 1: Reinforcing effects of cocaine and heroin



***p<0.001 versus appropriate saline control

NS = Not significantly different

Fig 2: Reinforcing effects of cocaine and heroin on a FR5 schedule of reinforcement

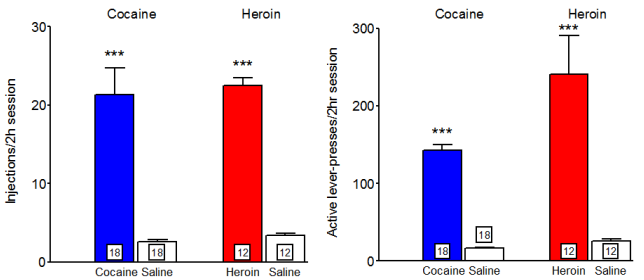


Fig 4: Reinstatement of heroin seeking behaviour

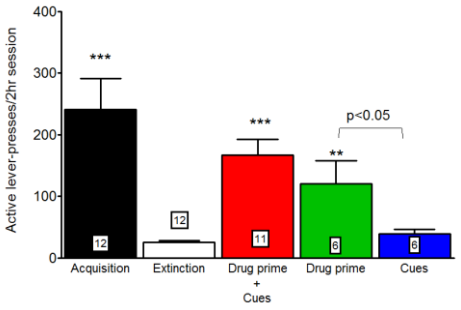


Fig 3: Reinstatement of cocaine seeking behaviour

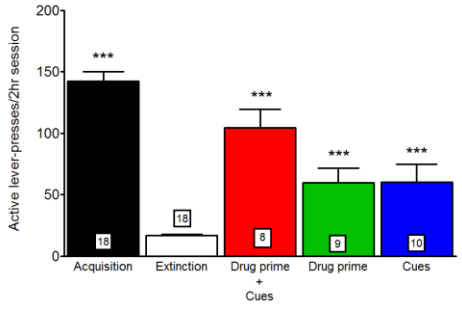
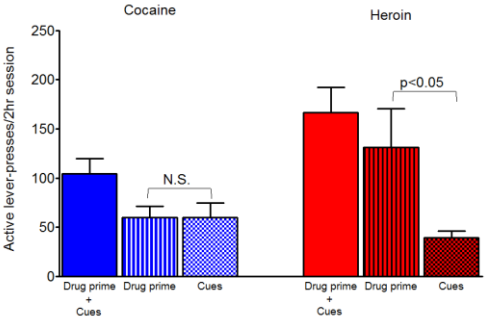


Fig 5: Relative contribution of drug re-exposure and salient cues in reinstatement of drug-seeking



**p<0.01, ***p<0.001 versus saline extinction. N.S. = Not significant

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