CUE-INDUCED VERSUS COCAINE + CUE-INDUCED REINSTATEMENT: TWO DIFFERENT ANIMAL MODELS OF RELAPSE

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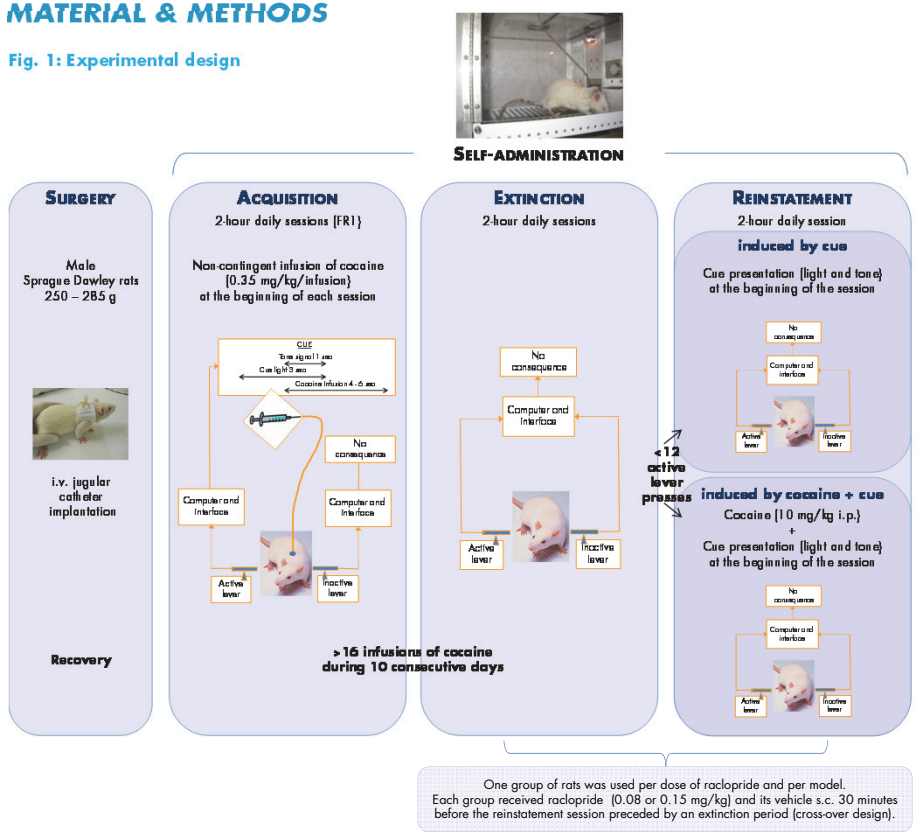
INTRODUCTION

Several animal models of reinstatement that simulate cocaine-seeking behavior or addiction in humans are described in the scientific literature. Reinstatement of cocaine-seeking or relapse-like behavior in animals can be induced by cocaine priming or by the use of cues. The aim of this work was to compare the effects of raclopride (a D2-receptor antagonist) in 2 different models of cocaine (cue alone and cocaine + cue pairing) reinstatement in the rat.

MATERIAL & METHODS

Fig. 1: Experimental design



One group of rats was used per dose of raclopride and per model.
Each group received raclopride (0.08 or 0.15 mg/kg) and its vehicle s.c. 30 minutes before the reinstatement session preceded by an extinction period (cross-over design).

- The number of active lever presses during the reinstatement session, compared to extinction lever responding (mean of the number of active lever presses during the last two sessions of the two extinction periods), was considered as a measure of reinstatement.
- A percentage of inhibition was determined using the following formula:

  [(vehicle - extinction periods) - (test substance - extinction)] x100 / (vehicle - extinction)

  Where vehicle and test substance correspond to the number of presses during the reinstatement session after vehicle and test substance treatment, and extinction corresponds to extinction lever responding as defined above.

RESULTS

Cue-induced reinstatement

Fig. 2: Effects of raclopride (0.08 mg/kg s.c.)

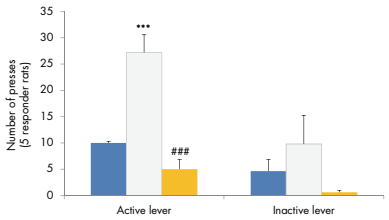
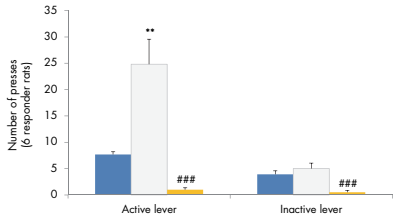


Fig. 3: Effects of raclopride (0.15 mg/kg s.c.)



- Cue-induced reinstatement under vehicle resulted in a significant increase in the number of active lever presses, as compared to extinction lever responding . The number of presses on the inactive lever was stable or slightly increased.
- Raclopride (0.08 mg/kg) significantly decreased the number of active lever presses during cue-induced reinstatement as compared with vehicle with a percentage of inhibition of 129%. The number of presses on the inactive lever was also reduced.
- Raclopride (0.15 mg/kg) significantly decreased the number of active lever presses during cue-induced reinstatement as compared with vehicle with a percentage of inhibition of 139%. The number of presses on the inactive lever was also significantly reduced.

Cocaine + cue-induced reinstatement

Fig. 4: Effects of raclopride (0.08 mg/kg s.c.)

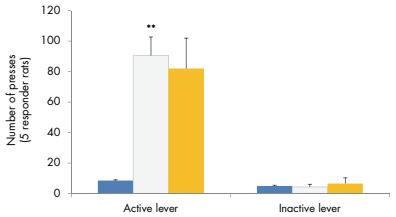
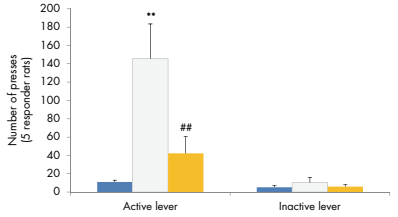


Fig. 5: Effects of raclopride (0.15 mg/kg s.c.)



- Cocaine (10 mg/kg i.p.) + cue reinstatement under vehicle resulted in a significant increase in the number of active lever presses, as compared to extinction lever responding. The number of presses on the inactive lever was stable or slightly increased.
- Raclopride (0.08 mg/kg) did not affect the number of active lever presses during cocaine + cue-induced reinstatement as compared with vehicle with a percentage of inhibition of 11%. The number of presses on the inactive lever was slightly increased.
- Raclopride (0.15 mg/kg) significantly decreased the number of active lever presses during cocaine + cue-induced reinstatement as compared with vehicle with a percentage of inhibition of 77%. The number of presses on the inactive lever was slightly reduced.

Mean of the last two sessions of the two extinction periods | Vehicle (s.c. - 30 min) | Raclopride (s.c. - 30 min)

(*): compared with mean of the last 2 sessions of the 2 extinction periods - (#): compared with vehicle control ** and ## = $p < 0.01$; *** and ### = $p < 0.001$; Fisher's PLSD tests post ANOVA with repeated measures.

CONCLUSION

In rats treated with vehicle, a greater number of active lever presses were observed in the cocaine + cue-induced reinstatement model as compared to the cue-induced reinstatement model. A consistent inhibitory profile on cocaine-seeking behavior was demonstrated for raclopride (0.15 mg/kg s.c.) in both models. However the suppressing effect of raclopride when administered at the lower dose (0.08 mg/kg s.c.) was only observed in the cue-induced reinstatement model.

These data demonstrate that the cocaine + cue-induced reinstatement model induces a higher level of drug-seeking behavior, which is more difficult to reverse than the drug-seeking behavior associated with the cue-induced reinstatement model. However, the cue-induced reinstatement model may be more sensitive for detecting relapse-facilitating or preventative effects with a test substance.

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