

# The orexin-1 receptor antagonist SB-334867 blocks cue-induced reinstatement of cocaine-seeking in rats

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## INTRODUCTION

Previous studies from our laboratory have shown that orexin is involved in the acquisition, expression, and reinstatement of morphine conditioned place preferences (CPP), indicating that orexin is associated with the learning and recall of drug-cue interactions (Harris et al, *Nature* 437:556, 2005; Harris et al, *Behav Brain Res* 183:43, 2007).

Orexin has also been shown to play a role in stress-induced reinstatement of cocaine seeking (Boutrel et al, *PNAS* 102:19168, 2005) and cue-induced reinstatement of ethanol seeking (Lawrence et al, *Br J Pharmacol* 148:752, 2006).

Here, we tested whether the orexin system is involved in drug-cue associations and reinstatement of drug-seeking in a cocaine self-administration paradigm.

## METHODS

### Self-administration

Male Sprague-Dawley rats were trained to lever-press for intravenous cocaine (0.2 mg/infusion) in 2-hour daily sessions in which cocaine infusions were paired with a discrete tone + light cue. Rats experienced 10 self-administration sessions with  $\geq 10$  infusions.

For experiments involving Pavlovian conditioned cues, rats were trained to self-administer cocaine in the absence of cues. After 5 sessions with  $\geq 10$  infusions, a single Pavlovian conditioning session was given, in which no levers were extended and animals received passive infusions of cocaine paired with a tone + light cue. This session was followed by 5 more days of self-administration without cues (See, *Eur J Pharmacol* 526:140, 2005).

### Extinction

During extinction sessions, lever presses had no programmed consequence. Rats experienced  $\geq 7$  extinction sessions, or until the last 2 sessions had  $< 25$  active lever presses each. At least 2 extinction sessions separated each reinstatement test.

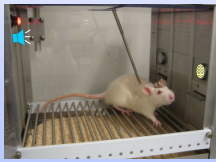
### Reinstatement

For cue-induced reinstatement, active lever presses resulted in presentation of the discrete tone + light cue only. Cocaine was not delivered.

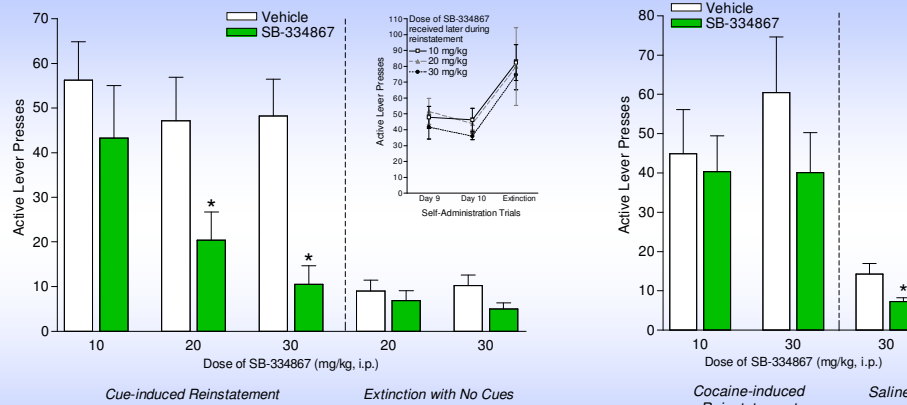
For drug-induced reinstatement, 10 mg/kg cocaine was injected i.p. immediately prior to an extinction session. Lever presses had no programmed consequence.

### SB-334867 administration

The orexin-1 receptor antagonist SB-334867 (10, 20, or 30 mg/kg, i.p.) or vehicle was administered 30 minutes prior to test sessions. SB-334867 was suspended in 2% DMSO and 10% 2-hydroxypropyl- $\beta$ -cyclodextrin in sterile water, and given in a volume of 4 mL/kg.



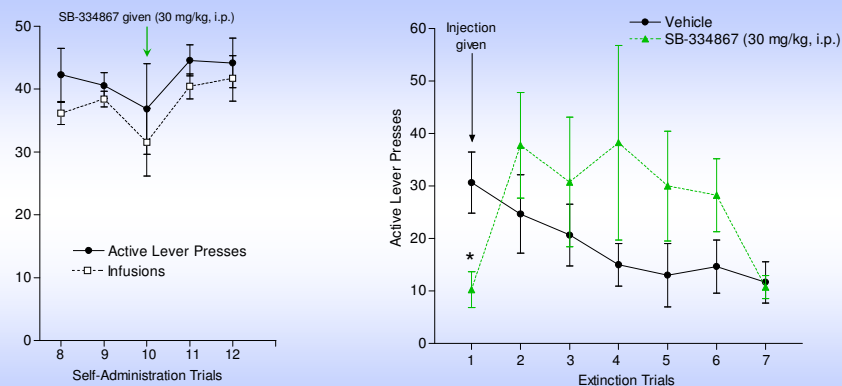
## SB-334867 blocks cue-induced, but not drug-induced, reinstatement of cocaine-seeking



SB-334867 at 20 and 30 mg/kg i.p., but not 10 mg/kg i.p., blocked cue-induced reinstatement as compared to reinstatement sessions with vehicle in the same rats ( $p < 0.01$ ). Doses of 20 and 30 mg/kg had no significant effects on late extinction responding in the same rats. The inset graph shows that prior to reinstatement, groups showed similar lever press activity during the last two days of self-administration and the first day of extinction.  $n = 8$  for 10 mg/kg,  $n = 9$  for 20 mg/kg, and  $n = 8$  for 30 mg/kg.

SB-334867 (10 and 30 mg/kg, i.p.) did not block drug-induced reinstatement as compared to reinstatement with vehicle in the same rats. SB-334867 (30 mg/kg) significantly reduced late extinction responding after a saline injection ( $p < 0.05$ ).  $n = 9$  for 10 mg/kg and  $n = 8$  for 30 mg/kg.

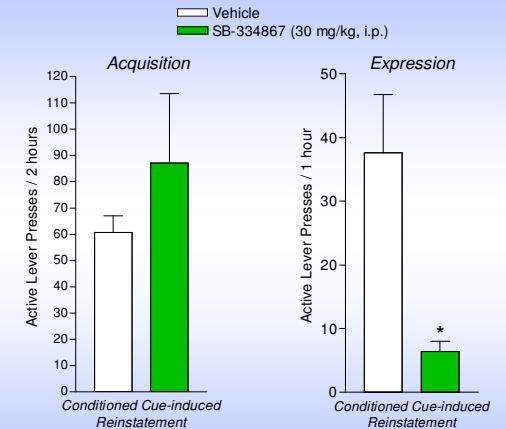
## SB-334867 fails to affect established cocaine-taking, but reduces extinction responding



SB-334867 (30 mg/kg, i.p.) had no significant effects on the number of cocaine infusions or lever presses during the 10<sup>th</sup> day of self-administration.  $n = 7$ .

SB-334867 (30 mg/kg, i.p.) significantly reduced responding on the first day of extinction as compared to vehicle ( $p < 0.05$ ).  $n = 3$  for vehicle and  $n = 4$  for SB.

## SB-334867 blocks expression, but not acquisition, of Pavlovian conditioned cue-reinstatement



Administration of SB-334867 (30 mg/kg, i.p.) prior to a Pavlovian cocaine-cue conditioning trial did not block subsequent conditioned cue-reinstatement ( $n = 7$  for vehicle and  $n = 8$  for SB). However, SB-334867 (30 mg/kg, i.p.) blocked expression of conditioned cue-reinstatement in a subsequent trial ( $p < 0.01$ ,  $n = 8$  for vehicle and  $n = 7$  for SB).

## SUMMARY

- SB-334867 blocks cue-induced reinstatement, but not a Pavlovian acquisition of cocaine-cue associative learning.
- SB-334867 reduces initial extinction responding.
- SB-334867 has no effect on cocaine-induced reinstatement.
- SB-334867 has no effect on maintenance of established cocaine-taking.

*Conclusion: The orexin system is involved in drug-seeking, especially when elicited by discrete cues (reinstatement) or context (initial extinction responding).*

## ACKNOWLEDGEMENTS

Support contributed by grants F31-DA019733, R01-DA017289, and P50-DA015369.