INTRODUCTION

CR845 is a peripherally-acting κ-opioid receptor agonist in clinical development as an injectable drug for the treatment of acute and chronic pain and pruritus. It is a novel, synthetic, peptide (D-Phe-D-Phe-D-Leu-D-Lys-(4-N-piperidinyl)amino carbocyclic acid); molecular weight ~ 880), which is not structurally related to the endogenous κ-opioid agonist, dynorphin-A. CR845’s hydrophilic, unnatural peptide structure greatly limits its entry into the brain. CR845 is not subject to proteolytic degradation or metabolism by CYP enzymes. The compound is ~90% excreted unchanged in urine with ~10% in bile. CR845 is a highly potent, κ-opioid agonist (EC50 = 0.16 nM) with no affinity for either δ- or μ-opioid receptors (Ki > 10,000 nM), and no other detectable off-target activity at other receptors, ion channels or transporters. CR845 exhibits potent analgesic, anti-pruritic and anti-inflammatory properties in preclinical models. Although CR845 is undetectable in the brain at therapeutic doses, a programme of preclinical studies was undertaken to confirm the compound lack potential for recreational abuse in humans. These studies investigated whether CR845 generalised to the discriminative cue elicited by the centrally-acting κ/δ-receptor agonist and μ-receptor partial agonist, (-)pentazocine or substituted as a positive reinforcer in an intravenous self-administration (VSA) experiment in heroin-maintained rats.

METHODS

Female, Lister Hooded rats were trained to discriminate (-)pentazocine (5.0 mg/kg ip) from saline (ip) on a FR5 schedule for sweetened milk rewards. Rats were not food restricted. The potential psychoactive effects of CR845 were evaluated using the clinically relevant intravenous (iv) route of administration. All drugs were dosed as free base. Results are reported as mean ± SD percentage generalisation to the (-)pentazocine cue. Mildly food-restricted, male, Sprague-Dawley, rats were trained to self-administer heroin (0.015 mg/kg/inj) on a FR5 schedule of drug reinforcement. After saline extinction, the positive reinforcing effects of 4 doses of CR845 (0.001, 0.005, 0.025 or 0.125 mg/kg/inj) and 3 doses of (-)pentazocine (0.03, 0.1 or 0.245 mg/kg/inj) were evaluated in separate groups of rats in 2 hr test sessions. Self-administration was limited to a maximum of 20 drug infusions/session. All drugs were dosed as free base. Results are reported as mean ± SEM.

RESULTS

(-)Pentazocine and butorphanol both generalised fully to the cue elicited by i.p. (-)pentazocine validating the model for detecting drugs with μ- and κ-agonist properties (Figure 1A and 1B). CR845 produced low-level, non-dose-dependent, partial generalisation to (-)pentazocine. This result is consistent with the fact that CR845 is a potent κ-opioid receptor agonist with poor brain penetration (Figure 1C).

None of the doses of (-)pentazocine, butorphanol or CR845 suppressed the rate of operant responding in drug-discrimination (Table 1).

The plasma exposure to CR845 in the drug-discrimination test exceeded 3x the maximum clinical exposure in humans (Table 2).

Heroin serves as a powerful, positive reinforcer in rats (Figure 2A and 2B).

(-)Pentazocine (κ-agonist/μ-partial agonist) substituted as a positive reinforcer in heroin-maintained rats at all doses. The numbers of (-)pentazocine infusions/session taken by the rats were significantly greater than saline, but significantly smaller than heroin (Figure 2A).

CR845 did not serve as a positive reinforcer in heroin-maintained rats (Figure 2B).

The plasma exposure to CR845 in the intravenous self-administration test exceeded 3x the maximum clinical exposure in humans (Table 3).

Table 1. Effect of (-)pentazocine, butorphanol and plasma CR845 concentrations on operant responding in drug-discrimination.

Table 2. Toxicokinetic parameters for plasma CR845 concentrations in the drug discrimination experiment.

Table 3. Toxicokinetic parameters for plasma CR845 concentrations in the intravenous self-administration experiment.

CONCLUSIONS

These results are therefore consistent with findings obtained when CR845 was tested in drug experienced human volunteers (CPDD Meeting, 2015). Together, they predict that CR845 is unlikely to be recreationally abused by humans.

INVESTIGATING THE DISCRIMINATIVE AND REINFORCING PROPERTIES OF THE κ-OPIOID RECEPTOR AGONIST CR845 IN RATS

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Figure 1. Effects of intravenously administered (-)pentazocine, butorphanol and CR845 in rats trained to discriminate (-)pentazocine (5 mg/kg ip) from vehicle determined 15 min after dosing

Figure 2. Evaluation of the reinforcing effects of (-)pentazocine and CR845 in rats trained to self-administer heroin

RESULTS

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- The plasma exposure to CR845 in the drug-discrimination test exceeded 3x the maximum clinical exposure in humans (Table 2).
- Heroin serves as a powerful, positive reinforcer in rats (Figure 2A and 2B).
- (-)Pentazocine (κ-agonist/μ-partial agonist) substituted as a positive reinforcer in heroin-maintained rats at all doses. The numbers of (-)pentazocine infusions/session taken by the rats were significantly greater than saline, but significantly smaller than heroin (Figure 2A).
- CR845 did not serve as a positive reinforcer in heroin-maintained rats (Figure 2B).
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