W232

Evaluation of Kappa and Mu Opioid Receptor Occupancy by CVL-354 Using PET in Nonhuman Primates

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INTRODUCTION

- As a key modulator of reward processes and stress responses, the kappa opioid receptor (KOR) is implicated as a mediator in pathways impacted in depression and addiction[1]
- CVL-354 is a selective and short-acting KOR antagonist being evaluated as a potential therapy for major depressive disorder and substance use disorder
- In cell lines expressing KOR or the mu opioid receptor (MOR), CVL-354 demonstrated significant in vitro selectivity for KOR over MOR; additionally, receptor occupancy (RO) studies performed in mice have demonstrated selectivity of CVL-354 for KOR over MOR in vivo
  - In mice, CVL-354 displaced the KOR-preferring radioligand [^{3}H]PF-04767135 with an ID_{50} of 0.1 mg/kg, while CVL-354 displaced [^{3}H]carfentanil (CFN), an MOR-specific ligand, with an ID_{50} of 4 mg/kg

OBJECTIVE

- The objective of this study was to measure the RO of varying doses of CVL-354 at kappa and mu receptors in nonhuman primates using radiotracers [^{11}C]LY2795050[2,3] and [^{11}C]carfentanil ([^{11}C]CFN), respectively
- We hypothesized that CVL-354 would block KOR and MOR in a dose-dependent manner and demonstrate a higher affinity for KOR than MOR

METHODS

STUDY DESIGN AND DRUG DOSING

- For KOR ([^{11}C]LY2795050) imaging, 1 male (~13.7 years old and ~16.7 kg) and 1 female rhesus macaque (~14.9 years old and ~10 kg) were scanned at baseline and several times after administration of varying doses of CVL-354
- For MOR ([^{11}C]CFN) imaging, 2 female rhesus macaques (~14.9 years old and ~10.0 kg; ~14.8 years old and ~13.5 kg) were scanned once at baseline and 1 or 2 times after administration of varying doses of CVL-354
- On positron emission tomography (PET) scan days, a 3-minute bolus of [^{11}C]LY2795050 or [^{11}C]CFN in <10 mL was injected; on blocking scans, a 2-minute bolus of CVL-354 with constant infusion was initiated ~15 min before the start of [^{11}C]LY2795050 or [^{11}C]CFN injection
- Pharmacokinetic sampling was performed throughout the delivery of CVL-354
- The radiotracers [^{11}C]LY2795050 and [^{11}C]CFN were synthesized in the radiochemistry facilities at the Yale PET Center (New Haven, CT)

ANIMAL CARE AND MONITORING

- Rhesus macaques were sedated ~2 hours before the scan using a combination of alfaxalone 1 to 2 mg/kg, dexmedetomidine 0.01 mg/kg, and midazolam 0.3 mg/kg administered intramuscularly; animals were kept anesthetized using isoflurane 0.75% to 2.5%
- Vital signs were monitored at least 4 times per hour, with more frequent monitoring immediately after injection of CVL-354 and radiotracer; animals were also monitored for 2 days post-scan in the housing environment
- All animal procedures were approved before implementation by Yale University's Institutional Animal Care and Use Committee (IACUC)

PET IMAGING

- Data acquisition began simultaneously with tracer injection; the injected tracer mass was limited to 0.8 and 0.03 μg/kg for [^{11}C]LY2795050 and [^{11}C]CFN, respectively
- PET images were acquired using the Siemens FOCUS 220 PET scanner (Siemens Preclinical Solutions, Knoxville, TN) with a reconstructed image resolution of ~2 mm
  - After a transmission scan, the radiopharmaceutical was injected intravenously using an infusion pump
  - List-mode data were acquired for 90 min and binned into sinograms with the following frame timing: 6 × 30 s, 3 × 1 min, 2 × 2 min, and 16 × 5 min

IMAGE ANALYSIS

- Dynamic scan data were reconstructed using a filtered back-projection algorithm with corrections for attenuation, normalization, scatter, and randoms
- Regions of interest (n=17) had previously been manually delineated on a single representative anatomical rhesus macaque magnetic resonance image (MRI) registered to a template image
  - The regions used in this study were the amygdala, brain stem, caudate, cerebellum, cingulate cortex, frontal cortex, globus pallidus, hippocampus, insula, nucleus accumbens, occipital cortex, pons, putamen, centrum semiovale, substantia nigra, temporal cortex, and thalamus

KINETIC ANALYSIS AND BINDING POTENTIAL MEASUREMENT

- Binding potential (BP_{ND}) estimates of [^{11}C]LY2795050 and [^{11}C]CFN were produced using the simplified reference tissue model method with the cerebellum as a reference region
- Apparent percentage RO was computed as

$$r^{A,T} = (BP^{T}_{ND} - BP^{A}_{ND})/BP^{T}_{ND}$$

  where the T and A superscripts indicate values from the test (baseline) and after CVL-354 administration, respectively
- Blood concentration for 50% RO (IC_{50}) was calculated using a 2-parameter maximum effect (Emax) model using plasma concentrations at each dose of CVL-354 and the corresponding RO value

RESULTS

- Minor vital sign changes in heart rate and blood pressure at the lowest doses of CVL-354 were observed in 1 rhesus macaque and were not considered significant
- Representative MRI, baseline, and post–CVL-354 images using [^{11}C]LY2795050 and [^{11}C]CFN are shown in **Figure 1**

Figure 1. Representative images of coronal, transverse, and sagittal views (left to right) summed 15-30 min after radiotracer injection.

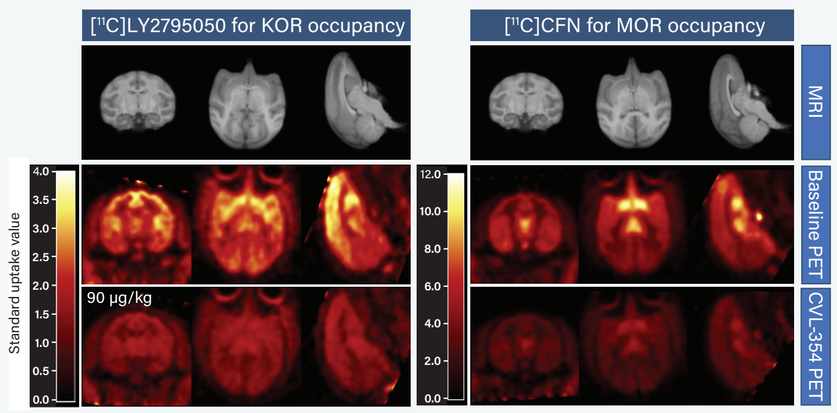
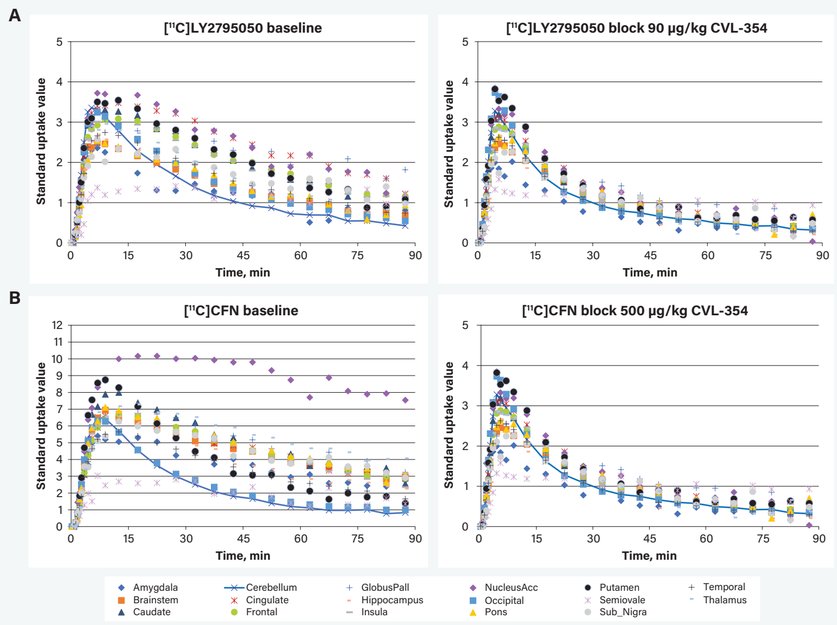


Image scale represents activity concentration normalized by the ratio of injected dose to animal weight. CFN, carfentanil; KOR, kappa opioid receptor; MOR, mu opioid receptor; MRI, magnetic resonance imaging; PET, positron emission tomography.

- Comparisons of representative time activity curves from regions of interest between baseline and post–CVL-354 administration using [^{11}C]LY2795050 and [^{11}C]CFN are shown in **Figure 2**

Figure 2. Comparison of representative time activity curves from individual rhesus macaques at baseline and after delivery of CVL-354 for (A) KOR occupancy using [^{11}C]LY2795050 and (B) MOR occupancy using [^{11}C]CFN.



Solid line is the cerebellum reference region. Scale represents activity concentration normalized by the ratio of injected dose to animal weight. CFN, carfentanil; KOR, kappa opioid receptor; MOR, mu opioid receptor.

- CVL-354 doses affected kappa and mu RO estimates in a dose-dependent manner (**Table**)

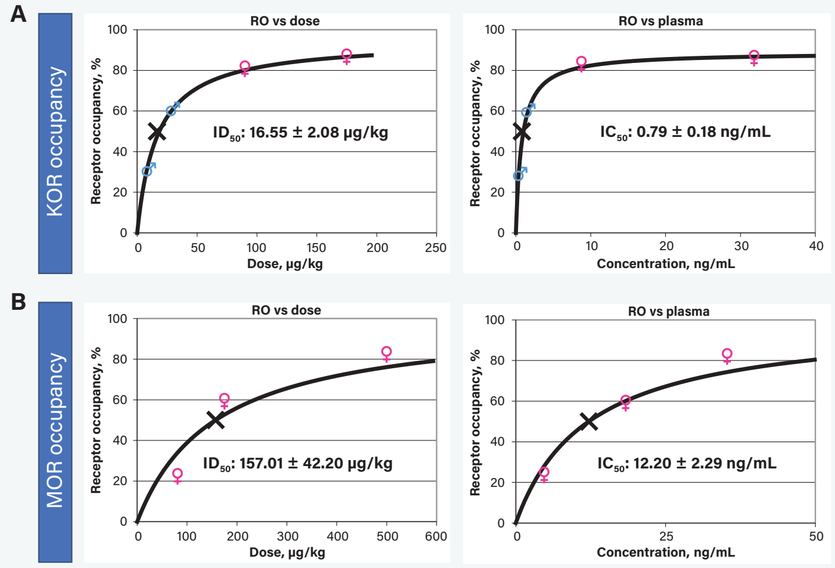
Table. Estimated RO for Kappa and Mu Receptors

CVL-354 dose	Estimated RO
Kappa RO	
7.46 μg/kg	29%
30 μg/kg	61%
90 μg/kg	82%
175 μg/kg	85%
Mu RO	
80 μg/kg	22%
175 μg/kg	59%
500 μg/kg	82%

RO, receptor occupancy.

- The binding affinity of CVL-354 was greater at KOR than MOR
  - The fitted plasma IC_{50} concentration (total; mean ± SE) at KOR was estimated at 0.79 ± 0.18 ng/mL with a maximum RO of 88.9% ± 4.5%; the estimated plasma IC_{50} concentration (total) at MOR was 12.20 ± 2.29 ng/mL with a maximum RO set at 100% (**Figure 3**)

Figure 3. Fit of (A) KOR and (B) MOR occupancy data vs CVL-354 dose (left) and vs CVL-354 PK (right).



IC_{50}, blood concentration for 50% RO; ID_{50}, dose for 50% RO; KOR, kappa opioid receptor; MOR, mu opioid receptor; PK, pharmacokinetics; RO, receptor occupancy.

CONCLUSIONS

- CVL-354 exhibited dose-dependent RO at both KOR and MOR as measured by PET imaging with [^{11}C]LY2795050 and [^{11}C]CFN, respectively, in nonhuman primates
- CVL-354 in vivo selectivity was ~10- to 15-fold greater for KOR over MOR, confirming a 10- to 40-fold greater affinity for KOR compared with MOR across various preclinical evaluations of receptor affinity

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