

NKTR-181: A Novel Opioid With Slowed Brain Entry Shows Low Abuse Liability and Reduced CNS Side Effects

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Abstract

Opioid analgesics represent the mainstay of pain therapeutics, but carry with them severe CNS side effects, including abuse liability, respiratory depression and sedation. Several studies suggest that the rapid rate of entry of opioids to the brain contributes to their addictive properties (1,2), and various formulation strategies have attempted to separate the analgesic properties of opioids from their harmful side effects. Here, we have employed a novel approach using our polymer conjugation technology to create NKTR-181, a novel opioid with slower kinetics of entry to the brain than other opioids, and we demonstrate that this results in a potent analgesic with low abuse liability and reduced CNS side effects.

NKTR-181 is an orally available opioid agonist which binds mu-opioid receptors with moderate affinity (K_i 237 nM) and fully suppresses acetic acid-induced writhing in mice at 100 mg/kg (p.o). Pharmacokinetic studies were performed to compare the brain entry rates of NKTR-181 with those of oxycodone. NKTR-181 demonstrates relatively slow kinetics of entry to the CNS, with a brain entry rate of 0.09 ug/g/h compared with 1.21 ug/g/h for oxycodone, following p.o. dosing in mice (5 mg/kg). These slowed brain uptake properties correlate with dramatically reduced abuse liability and CNS side effects. NKTR-181 shows no reinforcing properties when tested in self-administration studies in rats up to the highest doses studied (3.2 mg/kg/injection), and thus represents a novel opioid analgesic which enters the brain slower than standard opioids, resulting in a significant reduction of CNS side effects.

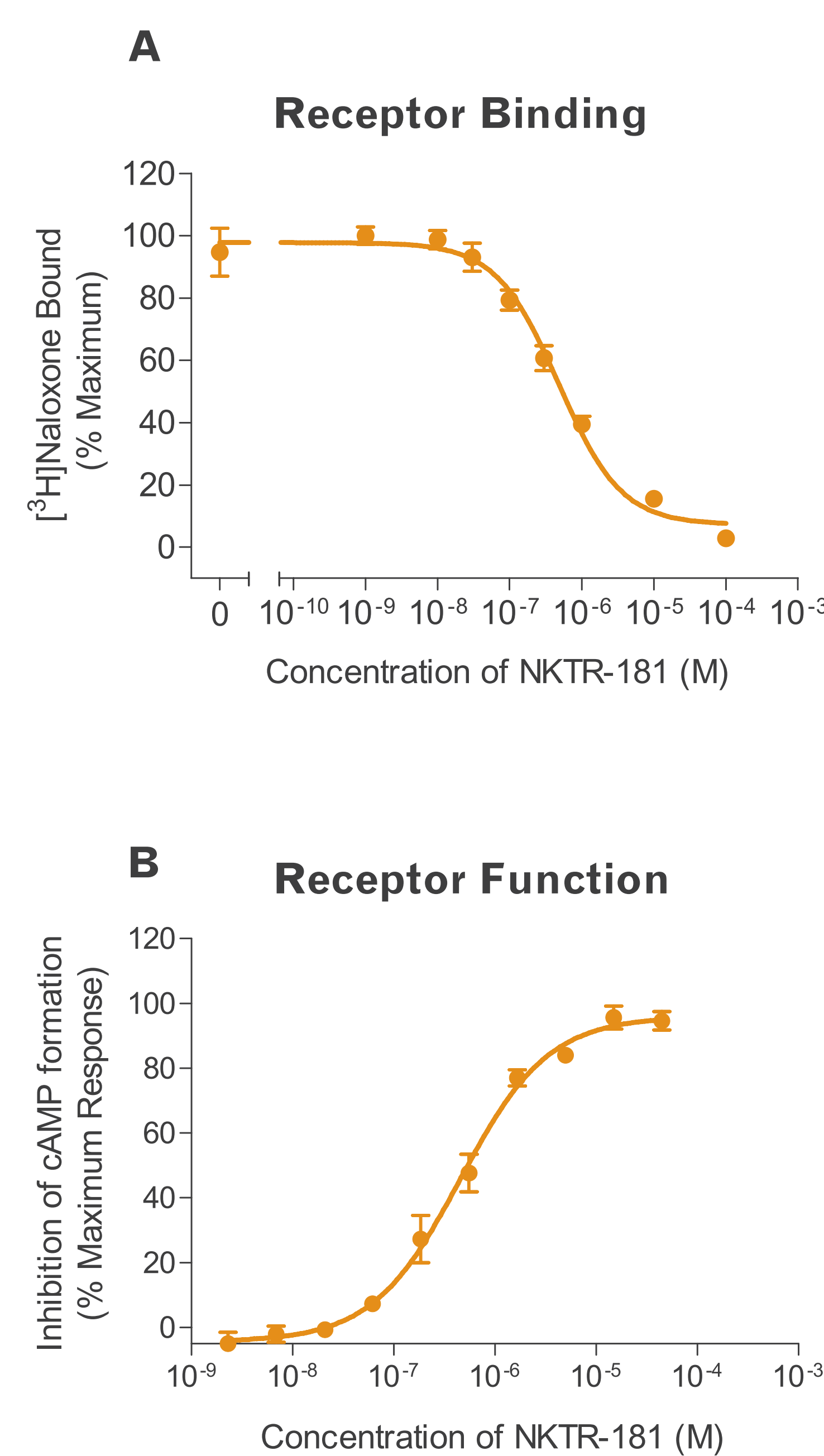
References:

(1)Winger et al. (2002). JPET, 301, 690-697. (2) Marsch et al. (2001). JPET, 299, 1056-1065

Results

NKTR-181 Behaves as a Mu-Opioid Agonist

NKTR-181 binds specifically to the mu-opioid receptor and acts as a full agonist in adenylate cyclase inhibition assays

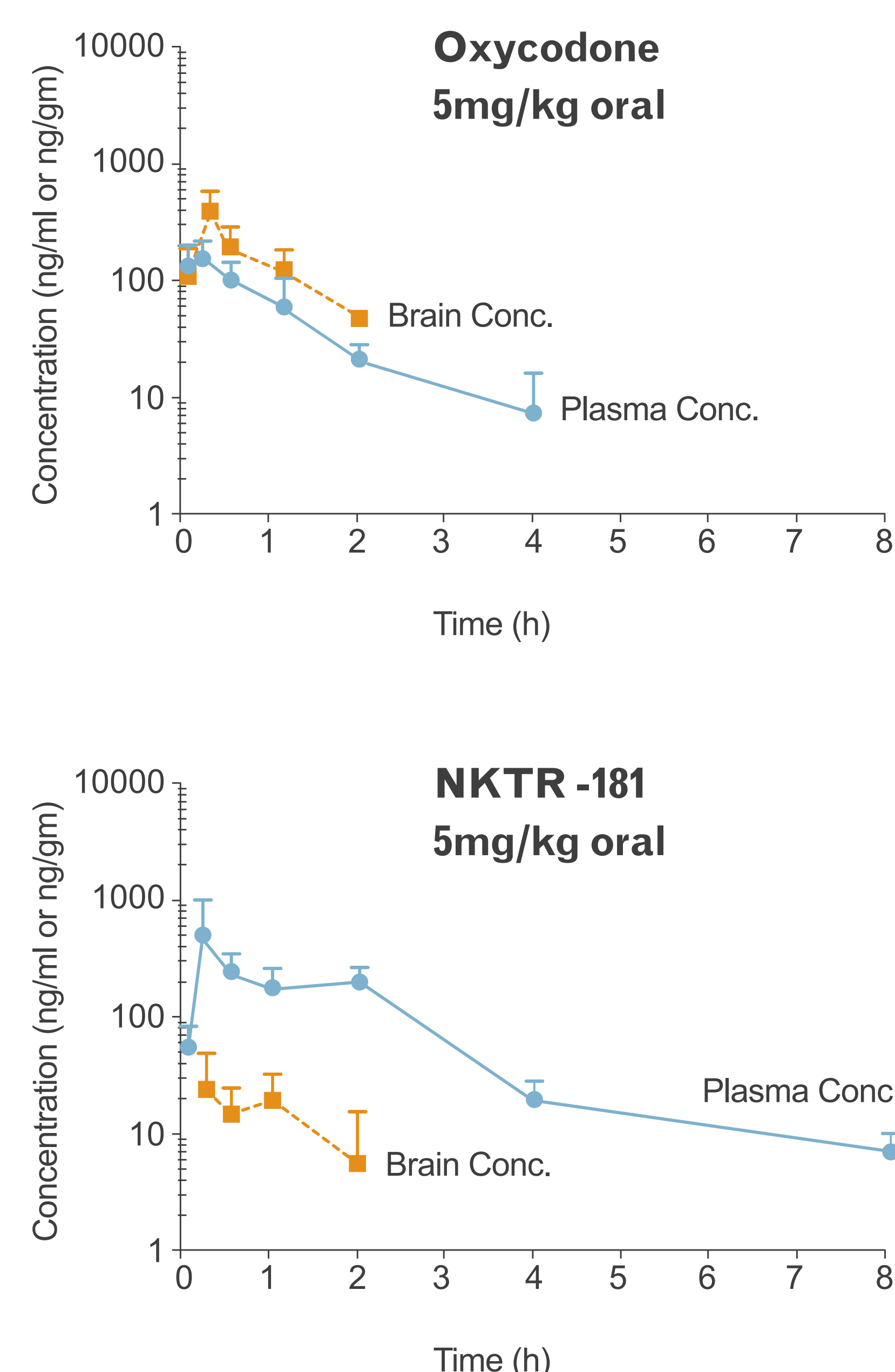


Receptor binding and function studies were performed using CHO cells heterologously expressing the recombinant human mu-opioid receptor. **(A)** Competitive displacement studies were performed on NKTR-181 using the high affinity mu ligand [³H]Naloxone (2nM, K_d : 2 nM). Data shown indicate the mean \pm SEM (n=3) from a representative experiment. **(B)** Adenylate cyclase inhibition studies were performed by incubating NKTR-181 in the presence of forskolin-treated cells for 30 min at room temperature. cAMP levels were quantitated using a competitive immunoassay (Cisbio, Bedford, MA). Data shown represent the mean \pm SEM for three independent experiments.

Results

NKTR-181 Displays Slowed Kinetics of Entry to the Brain Compared with Oxycodone

NKTR-181 displays a dramatically different distribution between brain and plasma following oral delivery in mice

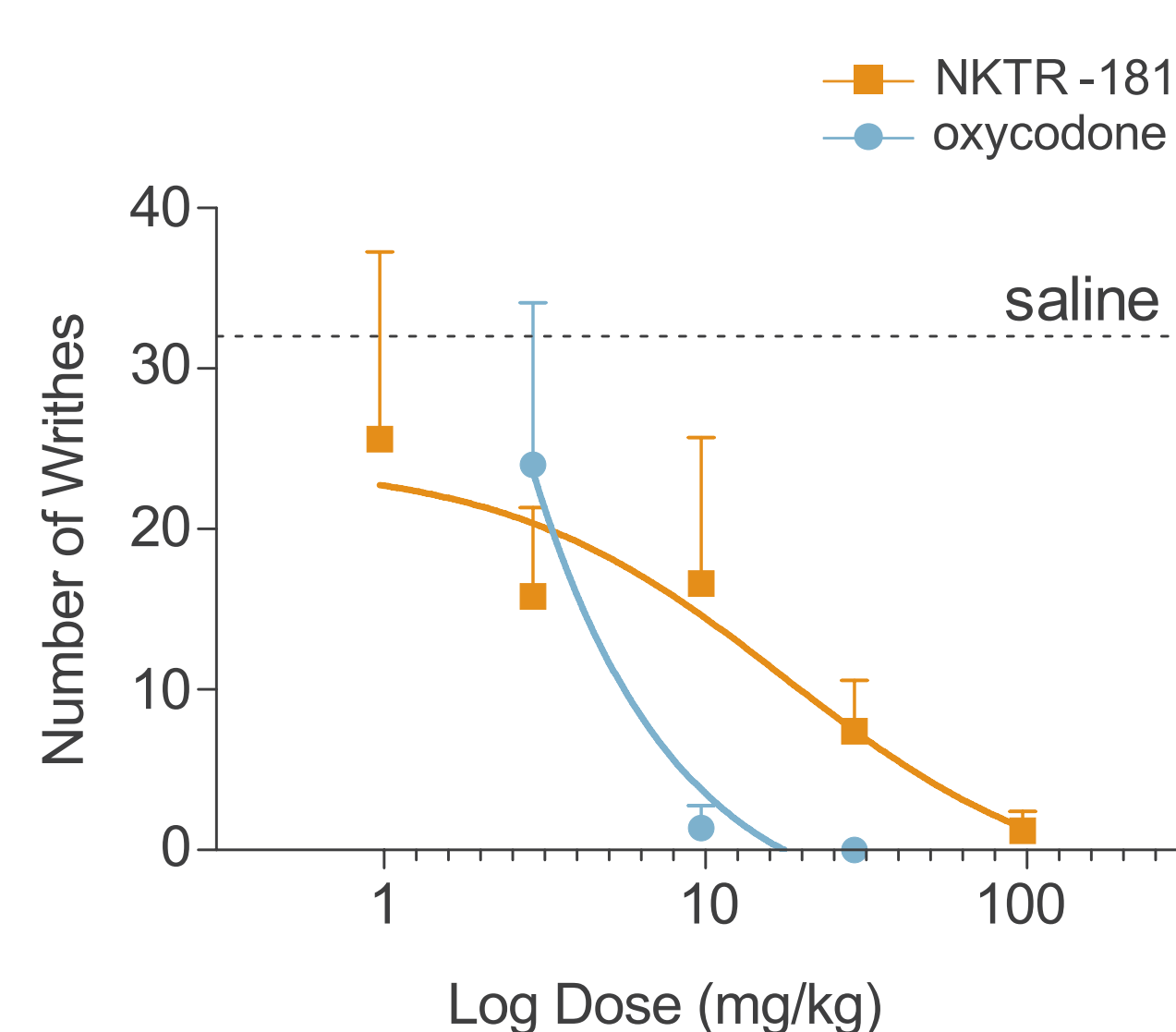


Mice were treated orally with NKTR-181 or oxycodone at 5 mg/kg, and were then sacrificed at the time points indicated. Plasma samples were taken, and, following exsanguination, brains were excised and homogenized. Oxycodone and NKTR-181 were quantitated using LC-MS/MS. Data represent the mean \pm SD (n=3). Rate of entry to the brain was calculated as the ratio of C_{max} : T_{max} for the brain concentrations of the test articles.

	Rate of Brain Entry (C_{max}/T_{max} ; ug/g/hr)
Oxycodone	1.21
NKTR-181	0.09

NKTR-181 Demonstrates Antinociceptive Activity in a Preclinical Model of Pain

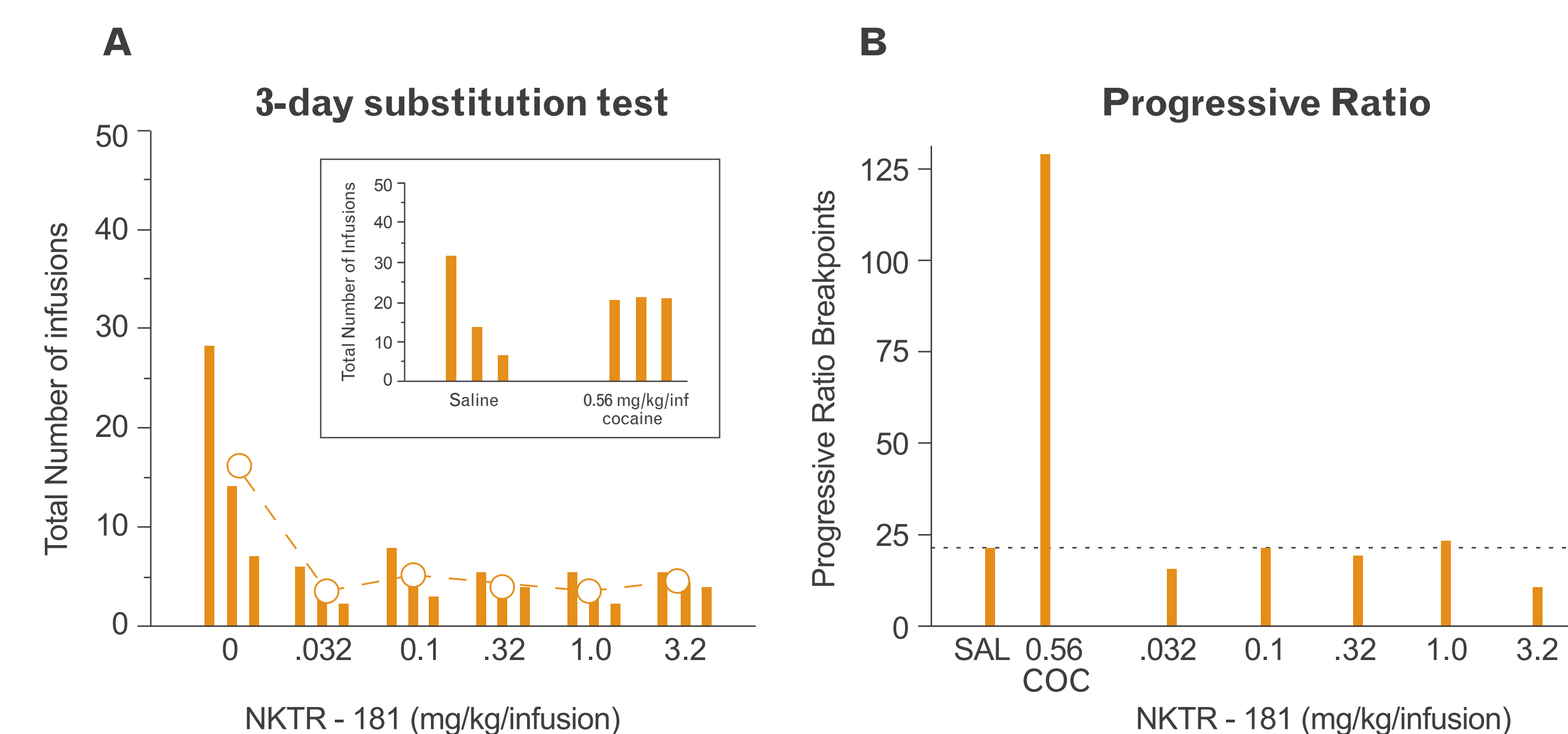
NKTR-181 produces full suppression of acetic acid-induced writhing in mice



CD-1 mice were treated orally with NKTR-181, oxycodone or saline. 30 minutes later animals were given an intraperitoneal injection of 0.5% acetic acid (0.1 mL/10 g body weight). After 5 minutes, writhes were counted over a 20 minute period. Data represent the mean \pm SEM (n=5). The average number of writhes produced by saline is shown by the dotted line.

NKTR-181 Shows Very Low Abuse Liability in Preclinical Studies

NKTR-181 displays no reinforcing properties in self-administration studies in rats, and produces a profile comparable to saline in 3-day substitution and progressive ratio tests



Self-administration studies were performed on cocaine-trained rats, involving intravenous bolus infusions of NKTR-181, cocaine (COC) or saline (SAL) at the indicated unit doses. In the 3-day substitution test (A) a lever-press protocol (FR10) was used in 1 h sessions on 3 consecutive days, with reinforcement defined as <20% variability over 3 sessions. NKTR-181 shows no reinforcing activity up to the highest dose tested. Saline and cocaine (inset) display the expected behavior for negative and positive reinforcement respectively. In the progressive ratio test (B), the number of lever presses required to deliver a unit dose of the indicated value was progressively increased until the breakpoint was reached at which the animal discontinued pressing and no longer would work for reward. Bars represent group means (n = 6).

NKTR-181 Displays No Significant CNS Side Effects at Analgesic Doses in Rats

NKTR-181 produces no significant responses in rats when tested for a range of CNS-mediated behaviors

Evaluation of neurological effects was based on observations collected predose and approximately 0.5, 2, 4, 8, and 24 hours post-dose in a modified Irwin battery in male rats given NKTR-181 orally (n=6/group). Observers were uninformed of each animal's dose level. Data is presented as # of abnormal observations /total # of parameters measured for each type of observation.

NKTR-181 Dose (mg/kg)	Abnormal Observations in Modified Irwin Assay			
	Home Cage	Hand Held	Open Field	Elicited Behaviors
0 (Vehicle)	0/2	0/9	0/8	0/15
50	0/2	0/9	0/8	1/15*
150	0/2	0/9	0/8	2/15**

* 2% increase in mean body temperature noted relative to controls 4 hrs post-dose (0.7°C)
** An abnormal approach response noted in 4/6 animals at 2 hrs post-dose and 5/6 animals 4 hrs post-dose. 2% increase in mean body temperature relative to controls noted 4 hrs post-dose (0.8°C).

Conclusion

- NKTR-181 acts as a mu-opioid agonist and displays antinociceptive activity in preclinical models of pain.
- NKTR-181 is a novel mu-opioid analgesic compound engineered to have a rate of entry into the brain 90% lower than that of oxycodone while producing comparable analgesia to oxycodone in standard preclinical models.
- NKTR-181 displays very low abuse liability in established abuse liability models, and exhibits minimal CNS side effects, including respiratory distress and sedation, in preclinical studies.