

NKTR-192: An Orally Active Opioid Analgesic with Rapid Onset of Activity and Low Abuse Liability

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Conclusions

- NKTR-192 is a novel mu-opioid agonist that demonstrates rapid onset of full analgesia in preclinical pain models with minimal abuse potential.
- In order to reduce abuse potential, NKTR-192 was designed to have a lower rate of entry to the brain than standard opioids.
- In a broad range of preclinical animal pain models, NKTR-192 demonstrates activity through both peripheral and central mechanisms.
- Further tests showed that NKTR-192 did not appear to be highly sedating at doses effective for pain relief.

Introduction

- There are over 250 million prescriptions for opioid painkillers like oxycodone in the US alone each year.¹
- However, opioids are frequently abused, leading to societal costs estimated in the tens of billions in the US annually.²
- The abuse properties of opioid drugs are believed to relate to their rapid entry into the brain.^{3,4}
- In clinical and preclinical studies, polymer conjugation has been shown to control the rate entry of opioids to the CNS.^{5,6}
- Nektar has used its validated polymer conjugation to generate a mu-opioid receptor agonist with slowed brain uptake.
- The resulting molecule, NKTR-192, is an orally active, rapid onset, analgesic that has low CNS side effects and abuse liability in animal models.

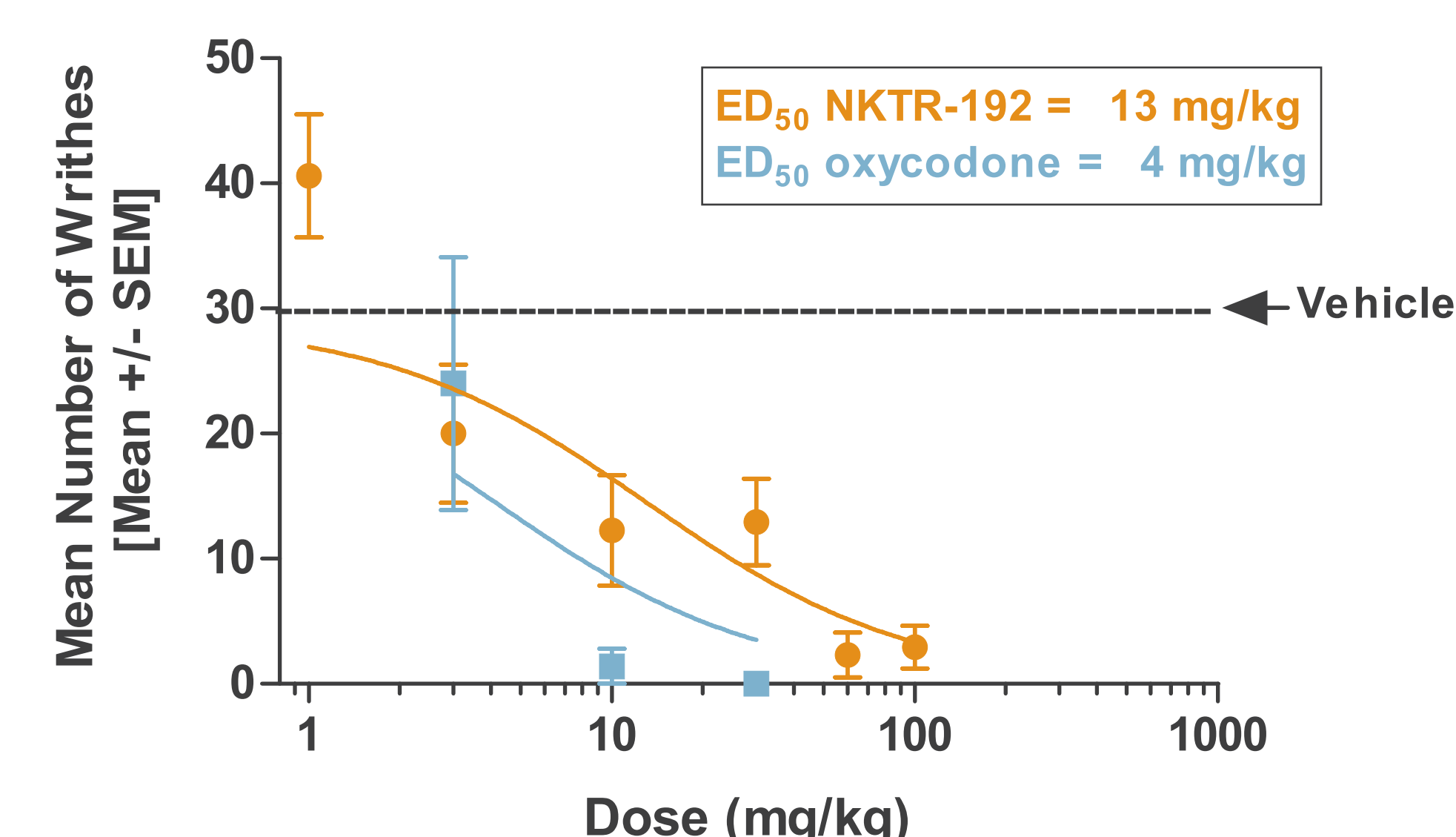
References

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Results

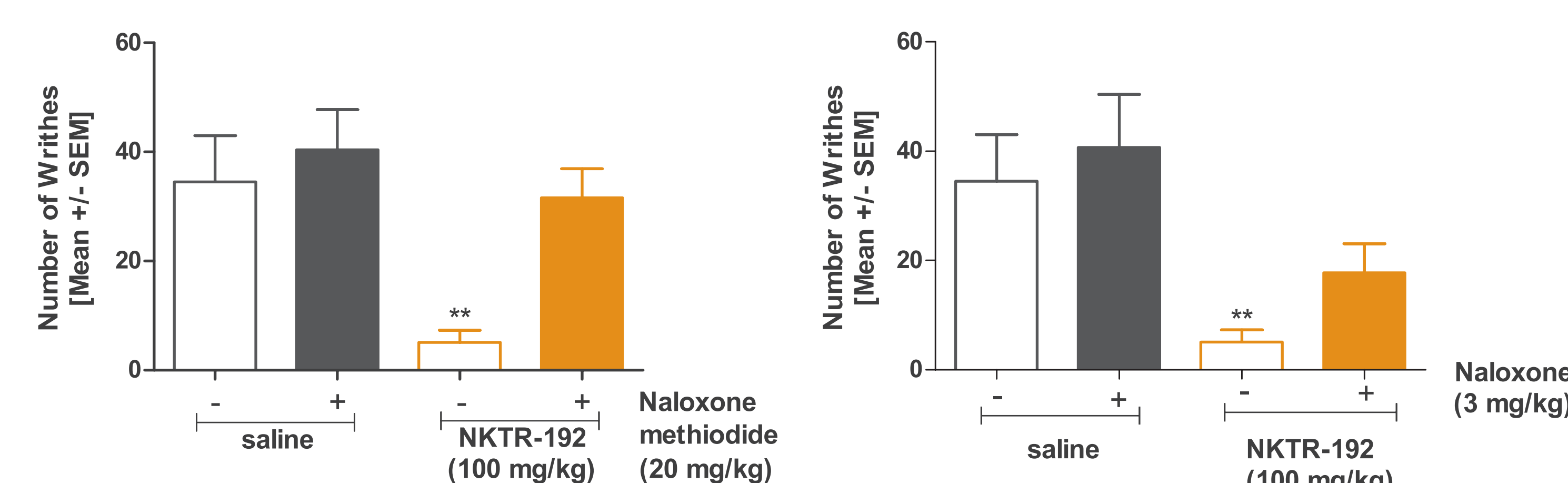
NKTR-192 Demonstrates Analgesic Activity in Animal Pain Models

Orally administrated NKTR-192 produces full analgesic efficacy comparable to oxycodone in the mouse acetic acid writhing model



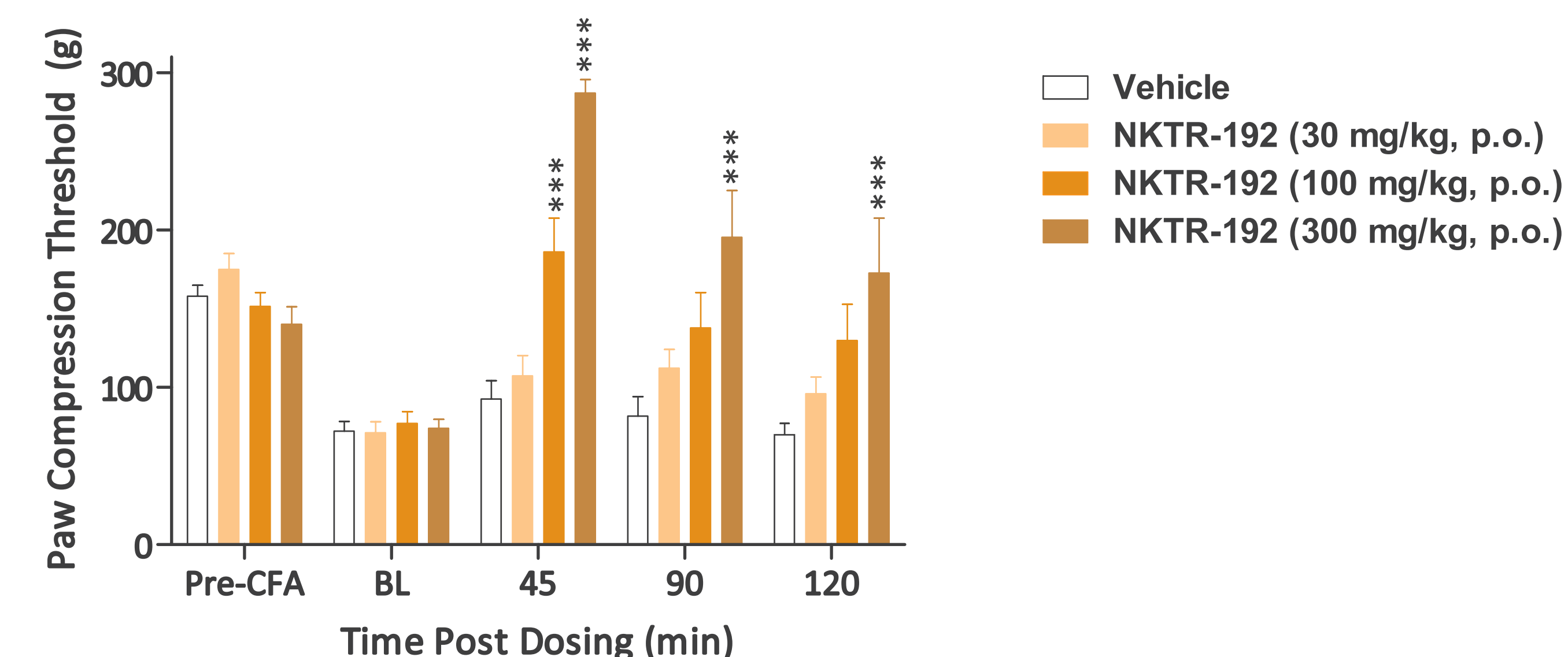
Male CD-1 mice [n = 5-20 per group] were treated orally with either NKTR-192 [1-100 mg/kg], oxycodone [3-30 mg/kg] or vehicle, and 30 min later were injected intraperitoneally with 0.5% acetic acid. After 5 min, writhes were counted over a 20 min period. NKTR-192 produced significant suppression of writhing responses following 10-100 mg/kg oral doses. Oxycodone produced significant levels of suppression following 10 and 30 mg/kg oral doses.

Analgesic effects of NKTR-192 are reversed by pretreatment with opioid receptor antagonists suggesting activity through both peripheral and central mechanisms



Naloxone methiodide [20 mg/kg] or Naloxone [3 mg/kg] were given subcutaneously to mice 15 min prior to treatment with vehicle or NKTR-192 [100 mg/kg, p.o.]. Data were analyzed by One-Way ANOVA using GraphPad Prism and represents an N = 10 per group. **Indicates significant difference vs. vehicle treated animals at the p < 0.01 level of significance.

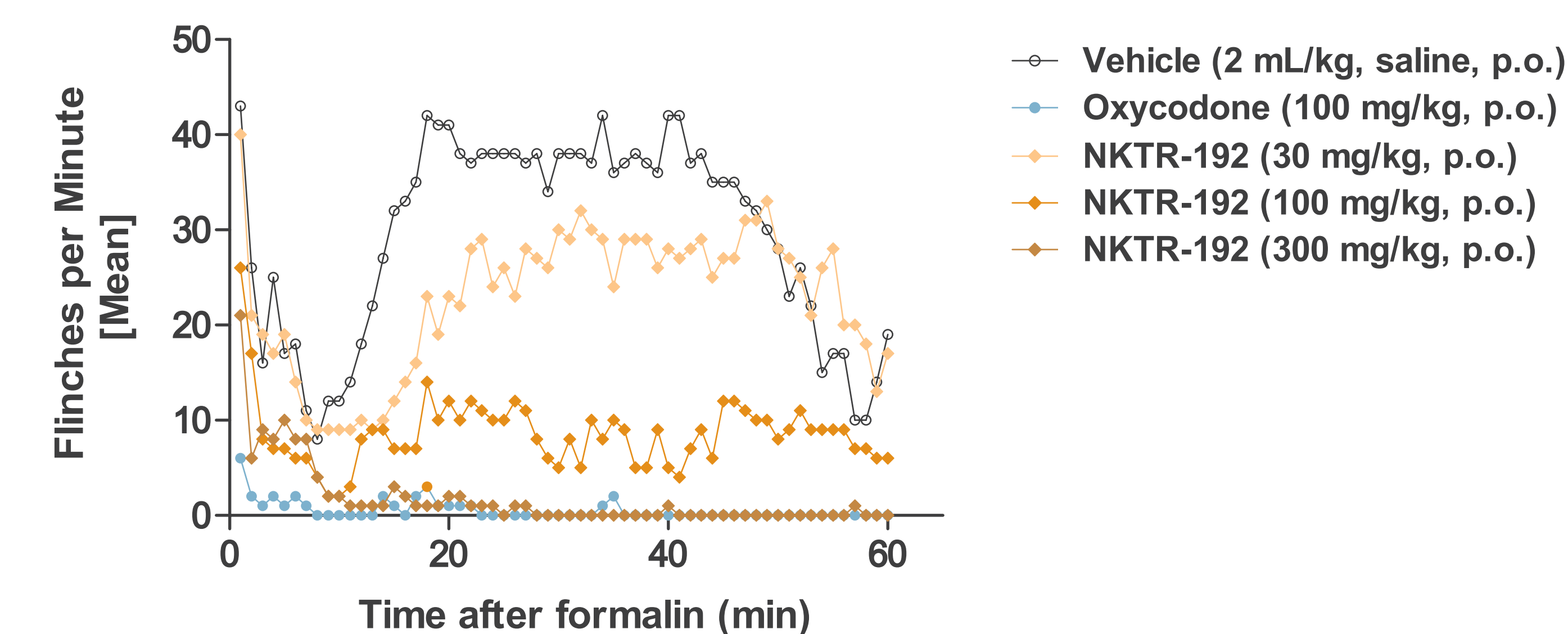
NKTR-192 is effective in a model of inflammatory pain



Inflammatory pain was induced in rats by an intraplantar injection of 50% Complete Freund's Adjuvant (CFA) in a 50 µL volume into the left hind paw. Two days post-CFA injection, rats were evaluated for baseline (BL) paw compression thresholds using a digital Randall-Selitto device (dRS; IITC Life Sciences, Woodland Hills, CA). Fifteen minutes following baseline testing, rats received oral doses of either vehicle or NKTR-192 [30-300 mg/kg] and were returned to their home cages. At pre-determined post-dose timepoints [45 min, 90 min and 120 min], animals were again evaluated for paw compression thresholds in the CFA-injected hindpaw. Data were analyzed by Two-way Repeated Measures ANOVA using GraphPad Prism and represents an N= 10 per group. ***Indicates significance vs baseline at the p < 0.001 level of significance.

NKTR-192 Displays a Rapid Onset of Analgesic Effect

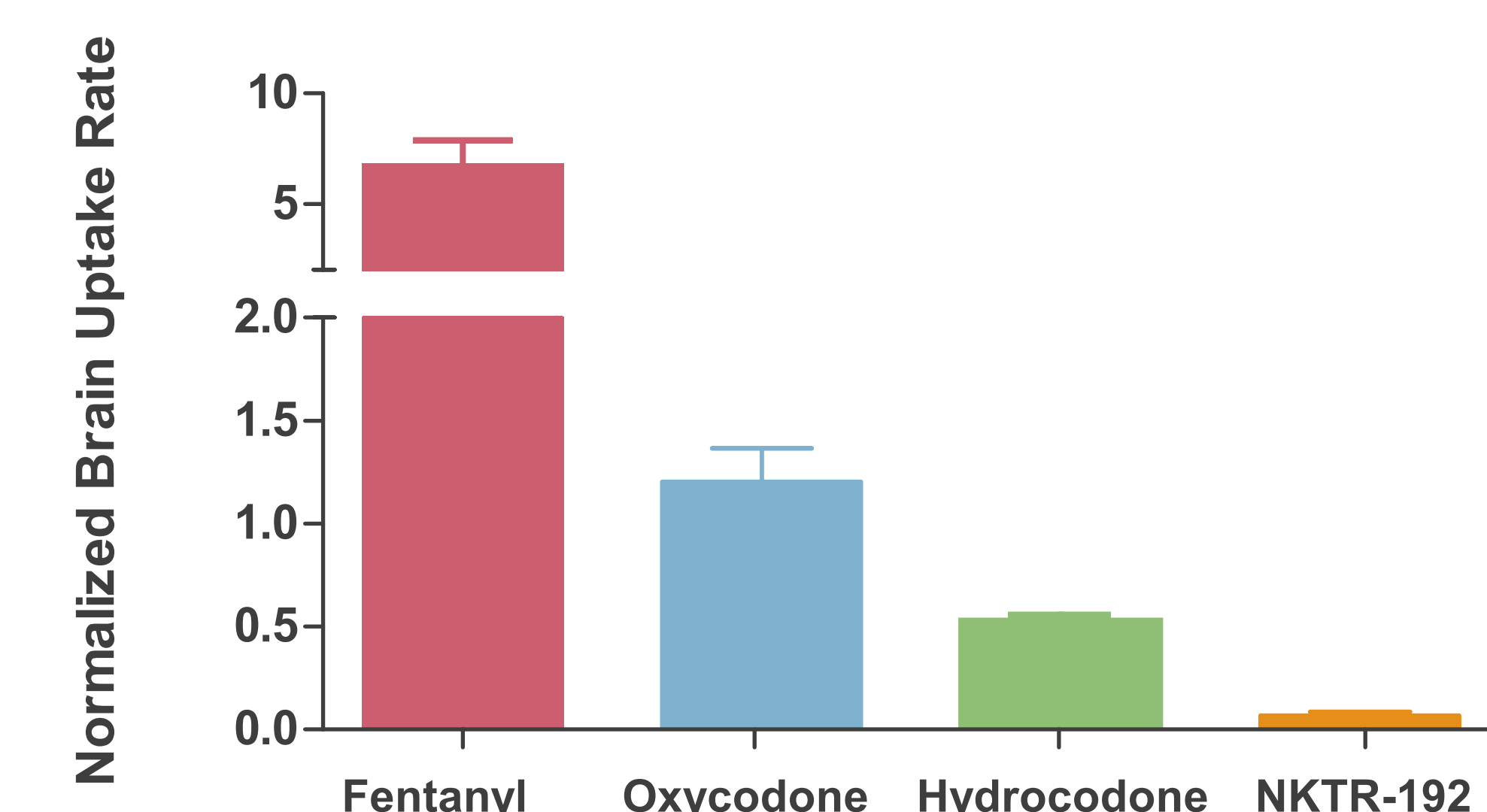
NKTR-192 demonstrates an analgesic effect 5 minutes after oral dosing in rats



Persistent pain was induced in rats (N=10 per group) by a subcutaneous injection (50 µL) of a 5% formalin solution in saline (NaCl 0.9%) into the dorsal surface of the left hind paw. Rats were orally administered vehicle, NKTR-192 [30-300 mg/kg] or oxycodone [100 mg/kg] 5 minutes prior to formalin injection. Paw movements were measured using the Automated Nociception Analyzer (ANA Instrument; University of California, San Diego) following injection of formalin solution. The instrument recorded rapid foot movements, counted in one minute epochs.

NKTR-192 Demonstrates a Significantly Reduced Brain Uptake Rate Compared to Standard Opioids

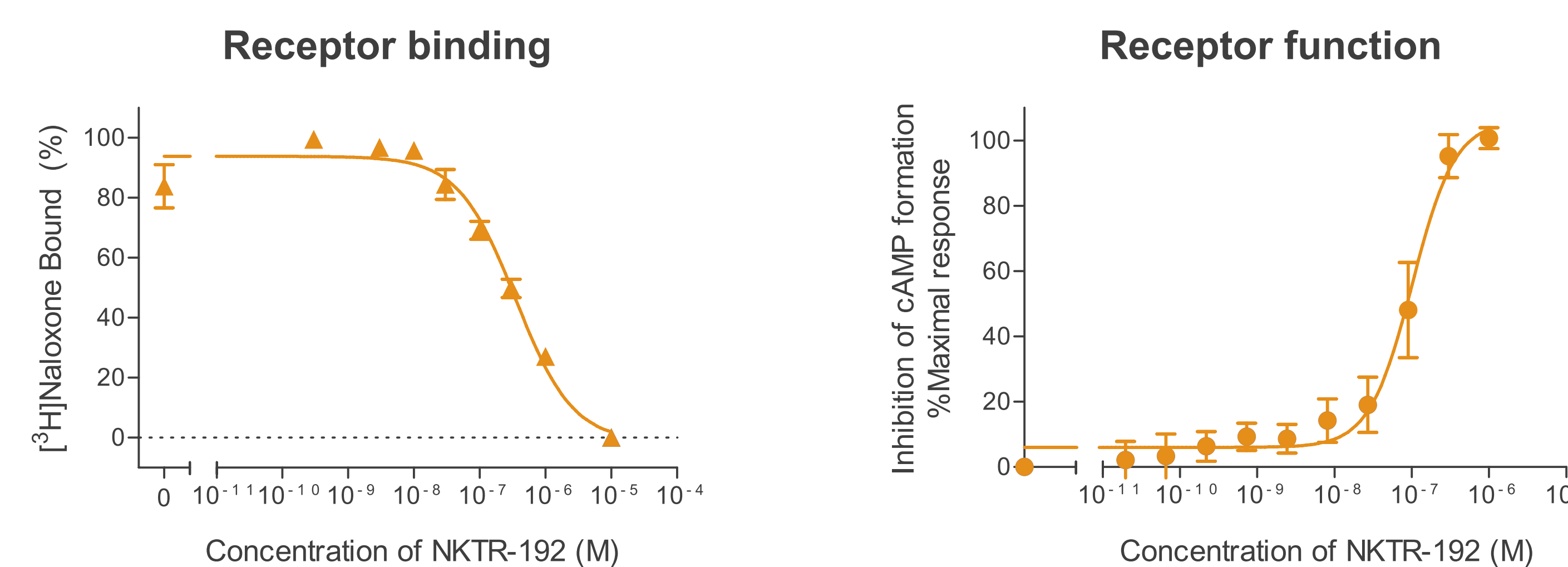
NKTR-192 displays lower rate of brain uptake compared with various opioids as measured using *in situ* brain perfusion studies in rats



The rates of brain uptake of various opioids were measured using the *in situ* brain perfusion model in rats. Rats were perfused for 30 sec with 10 µM of each test compound via the left common carotid artery and concentrations in the brain were measured using LC-MS/MS. The unidirectional permeability constant, Kin (mL/g/min) was calculated for each compound and was normalized to that obtained for the fast permeation reference drug, Antipyrine, that was co-perfused with each test compound. Data are Mean ± SD of 3-4 animals.

NKTR-192 is a Mu Agonist *in vitro*

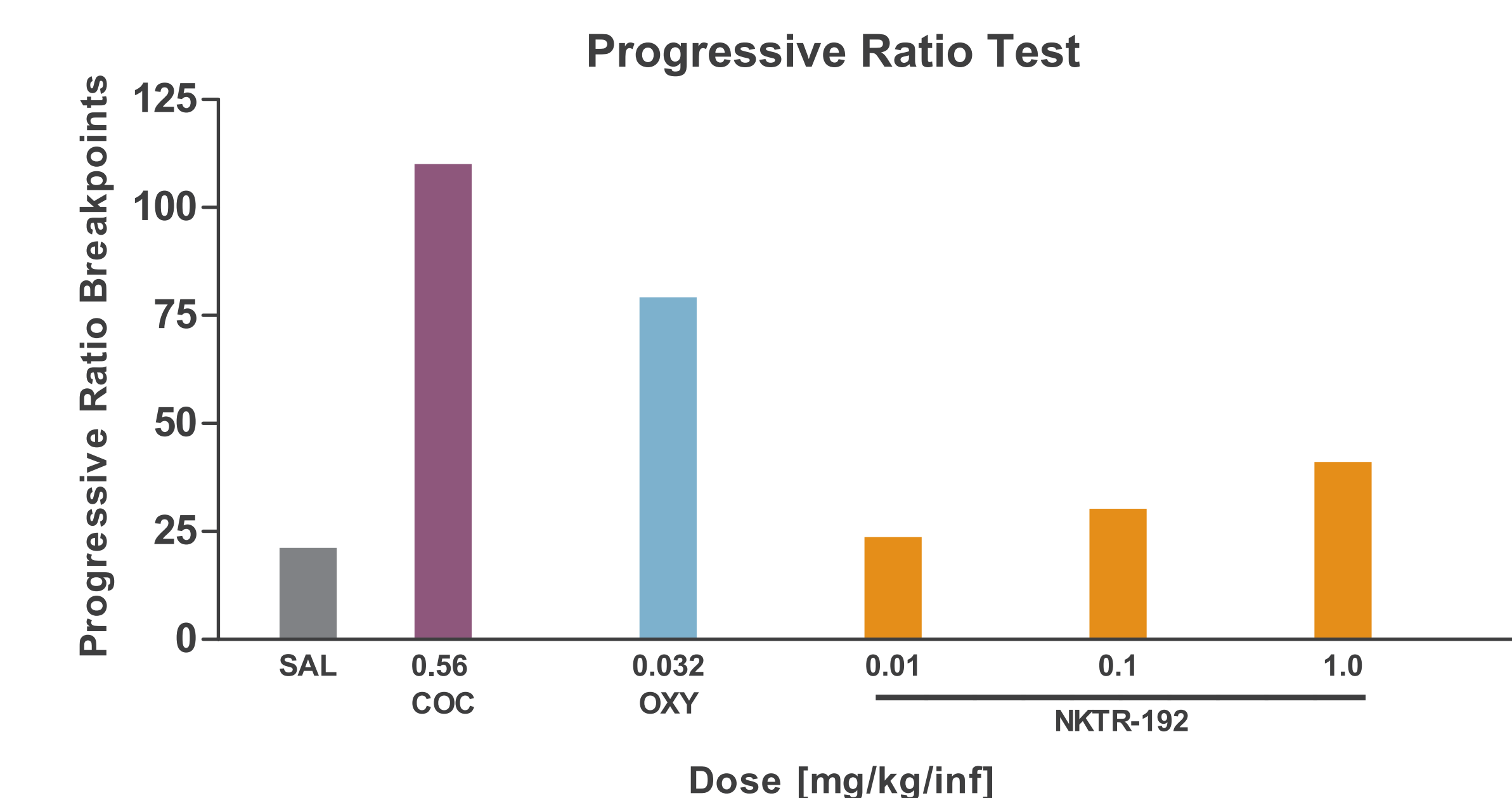
NKTR-192 binds specifically to mu opioid receptors and is a full agonist in adenylate cyclase inhibition assays *in vitro*



***In vitro* binding and function:** Receptor binding and *in vitro* functional assays were conducted using CHO cells expressing the recombinant human mu opioid receptor. Competitive displacement assays were conducted using the high affinity mu ligand, ³H-naloxone (4 nM, K_d : 6.7 nM) and increasing concentrations of NKTR-192. NKTR-192 produced a maximal inhibition of forskolin-stimulated cAMP formation in intact cells. cAMP levels were quantitated using a homogenous time resolved fluorescence assay (Cisbio, Bedford, MA). Data are mean ± SEM of three independent experiments for each study.

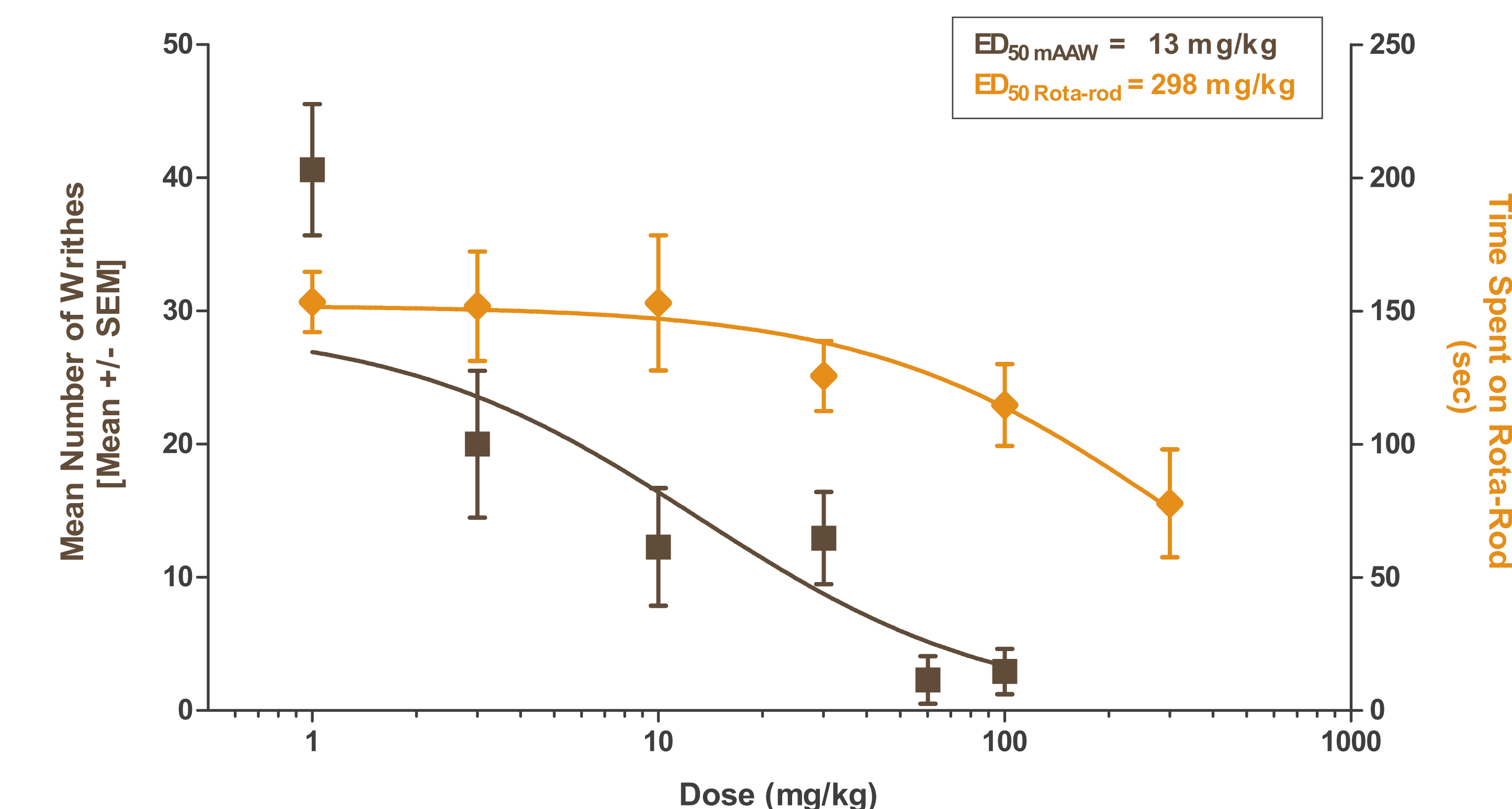
NKTR-192 Displays Low Abuse Liability in Self Administration Studies in Rats

NKTR-192 shows responding rates lower than oxycodone in the progressive ratio test



Self-administration studies were performed on cocaine-trained rats using intravenous NKTR-192, oxycodone (OXY), cocaine (COC) or saline (SAL) [n = 6 for oxycodone and NKTR-192; cocaine n = 38]. For the progressive ratio test, the number of lever presses required to deliver a defined dose was increased until animals no longer worked for reward.

NKTR-192 Demonstrates Reduced CNS Side-Effects within Analgesic Dose Range



Mouse acetic acid writhing was done as described previously. For the rat Rota-Rod, animals (N = 5-10 per group) were trained to run on the treadmill one day prior to the day of study. Animals were trained at a constant speed of 10 RPM and rats that were able to stay on the rod for 300 sec were considered trained. On the day of study, animals were dosed with NKTR-192 [1-300 mg/kg, p.o.] or vehicle and were placed on the Rota-Rod treadmill at 30 min post dose. The treadmill was set at a constant speed of 4 RPM for 15 sec, at this point the timer started (T=0). After this 15 sec period, the rotarod was set to accelerate from 4-40 RPM over a five minute period (using the built in program of the Rota-Rod). The time (in sec) that each animal stopped running was recorded as the animal's run time. Animals that ran for 300 sec were taken off the treadmill and 300 sec was recorded as the run time. Curve fits were done using Nonlinear Regression in GraphPad Prism.