NKTR-181: Relationship Between Mu-Opioid Receptor Binding Kinetics and In Vivo Pharmacodynamics

Laurie VanderVeen, Takahiro Miyazaki, Stephen Doberstein, Jonathan Zalevsky
Nektar Therapeutics, San Francisco CA

BACKGROUND

- NKTR-181 is a novel mu-opioid receptor agonist in clinical development for the treatment of moderate-to-severe chronic low back pain in opioid-naïve adult patients. We have previously reported that the unique physicochemical properties of NKTR-181 result in a slower rate of entry into the central nervous system (CNS) compared with standard opioids.
- Rapid entry into the CNS and the subsequent activation of mu-opioid receptors are important factors that make an opioid attractive for abuse; therefore, NKTR-181 is hypothesized to show less potential for abuse relative to conventional opioids while also achieving meaningful analgesia.
- Here, we compare the temporal effects of NKTR-181 and oxycodone on mu-opioid receptor pharmacology using in vitro kinetic binding and signaling assays as well as in vivo pharmacodynamic studies of neurotransmitter release and antinociception.

RESULTS

NKTR-181 and Oxycodone Binding Kinetics at Mu-Opioid Receptor

NKTR-181 displays slower association kinetics relative to oxycodone.

RESULTS (CONTINUED)

Real-time Functional Effects of Mu-Opioid Receptor Activation by NKTR-181 and Oxycodone

Differential potency and rates of forskolin-induced cAMP inhibition by NKTR-181 and oxycodone.

Figure 2. Onset of mu-opioid receptor activation. CHO cells stably expressing the human mu-opioid receptor were transiently transfected with pGloSensor-225: CAMP plasmid (Promega, Madison, WI). Adenylyl cyclase inhibition studies were performed by incubating cells with 10 μM forskolin for 10 min prior to addition of agonists, then real-time changes in cAMP levels were monitored as luminescence at indicated time points. (A) Kinetic traces of the effect of NKTR-181, oxycodone, and DAMGO on the inhibition of forskolin-induced cAMP. The rates of forskolin-induced cAMP inhibition (k) were calculated from one-phase decay nonlinear regression analysis of time-response curves. (B) Concentration-response data obtained at 10 min were fitted using nonlinear regression analysis.

NKTR-181 Induces Durable Antinociceptive Effect

NKTR-181 peak latency effect delayed relative to oxycodone.

Figure 3. Hot Plate latency time course effect. The time course of hot plate latency was obtained following oral administration of a single dose (50% effective dose) of NKTR-181 or oxycodone in Sprague-Dawley rats. Latency measurements were taken at 0.5, 1, 2, 4, and 6 hours post-dose. Data represent mean ± SEM (n=10). *P<0.05, **P<0.01, ***P<0.001, Two-way ANOVA, Dunnett’s post-test with respect to saline.

CONCLUSIONS

- NKTR-181 exhibits a slower pharmacodynamic profile compared to oxycodone across multiple in vitro and in vivo models.
- These data support a differentiated mechanism of action for NKTR-181 relative to traditional opioids such as oxycodone.

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REFERENCES

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Dopamine Release in the Nucleus Accumbens in Response to NKTR-181 and Oxycodone

NKTR-181 induces slower onset of dopamine release in rat nucleus accumbens.

Figure 4. Extracellular dopamine levels in the nucleus accumbens of awake rats. Test compound was administered as single intravenous doses to male Sprague-Dawley rats. Microdialysates were collected from a probe implanted in the nucleus accumbens shell of awake animals in (A) 90-second or (B) 5-minute intervals, and extracellular dopamine was quantified by HPLC using electrochemical detection.

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