PTI-609, a Novel Strong Analgesic Without Addictive Properties

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Abstract
PTI-609 is a strong analgesic compound that lacks addictive properties compared to morphine. PTI-609 activates the mu opioid receptor (MOR) and also binds the scaffolding protein filamin A (FLNA) with high affinity. This prevents the switch in G protein coupling by MOR (from G/α to Gi) that has been shown to contribute to opioid tolerance, dependence and addictive properties. Here we demonstrate the analgesic efficacy of PTI-609 in the rat hotplate test and its lack of rewarding properties in the conditioned place preference (CPP) paradigm and IV self-administration. The analgesic effects of 2 mg/kg morphine and PTI-609 at 8, 16 and 32 mg/kg were compared in 35 rats using a Latin-Square design. All doses produced significant analgesia versus saline. PTI-609 showed a significant dose-dependent effect; 2 mg/kg morphine produced similar analgesia to 8 mg/kg PTI-609. For the CPP test, rats were divided into 4 dose groups (n=8-9). Each group received three conditioning sessions of saline and, separately, three conditioning sessions of drug. In each 30-min conditioning session, rats were confined to one compartment in a two-compartment apparatus. For the drug-free test, rats were free to move between compartments, and time spent in the drug-paired and saline-paired compartments was compared. Morphine produced a significant place preference; 8 and 16 mg/kg PTI-609 did not. In addition, rats preferred saline to the highest dose of PTI-609. Unlike morphine, PTI-609 was not self-administered. These results suggest PTI-609 is a promising new analgesic candidate without morphine’s addictive properties.

Methods

Animals
Sprague-Dawley rats weighing 270-300 g.

Analgesia Testing
A hotplate apparatus at 50°C was used to assess analgesia, using an 80-sec cut-off to prevent tissue damage. PTI-609 was administered SC (8, 16 and 32 mg/kg) or IV (4, 8 or 12 mg/kg) over 6 min. Morphine (2 mg/kg SC and IV) served as a positive control.

Conditioned Place Preference
On 3 different days, rats received PTI-609 or morphine just prior to a 30-min confinement in one compartment of an apparatus with two visually and tactiley distinct compartments. On three alternate days, the other compartment was paired with vehicle. On a drug-free test day, rats could access both compartments for 20 min, and time spent in each was compared.

Self-administration
Rats were surgically implanted with indwelling jugular catheters and recovered before training in an operant chamber to lever-press for IV infusions in daily 3-hr sessions. In the substitution experiment, rats lever-pressed for morphine (0.32 mg/kg/inf) for 2 days on FR1 (fixed ratio 1; 1 response = 1 infusion) and 3 days on FR3 then were switched to saline, back to morphine, then to PTI-609 (1.6 mg/kg/inf) for 2 days. In the second experiment, separate groups trained on morphine or PTI-609 (0.8, 1.6 or 3.2 mg/kg/inf) on FR3 for 4 days then on FR3 for 3 days.

Results

Fig. 1
A Analgesia
B Conditioned Place Preference

Discussion
PTI-609 is a novel drug candidate with strong analgesic properties and no discernible addictive properties compared to morphine in standard animal models of assessing reward. PTI-609 activates MOR and binds FLNA to control G protein coupling of MOR. Doses of PTI-609 that produced significant analgesia produced no CPP, and rats preferred saline to the highest dose. Rats did not self-administer PTI-609 at equianalgesic doses to morphine. In addition, rats trained to self-administer morphine did not respond when PTI-609 was substituted for morphine. Results suggest PTI-609 is a promising new analgesic drug candidate without addictive potential.