Comparison of morphine, oxycodone and the biased MOR agonist SR-17018 for tolerance and efficacy in mouse models of pain.

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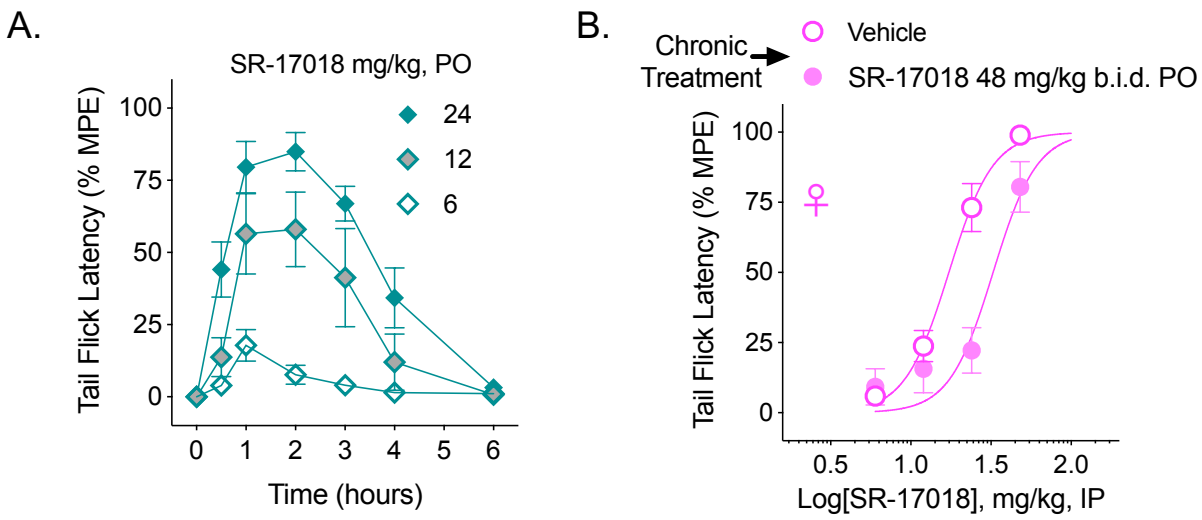
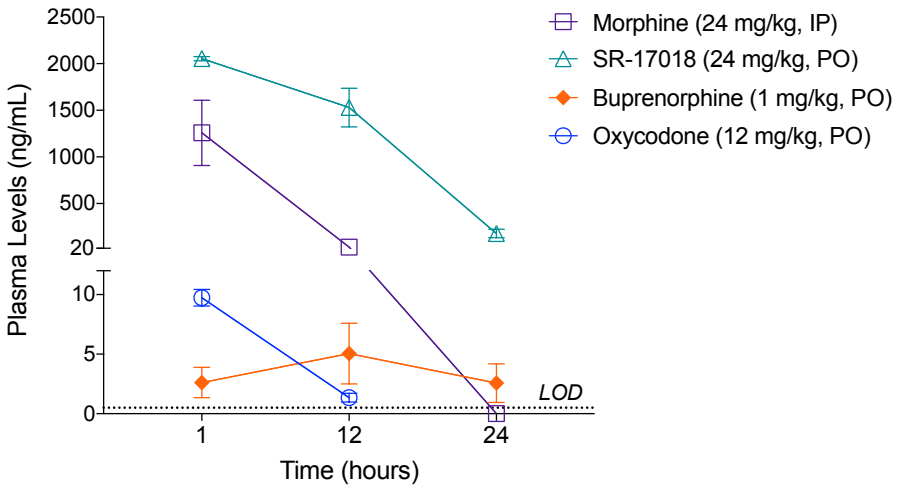
SFigure 1A is provided to demonstrate SR-17018 potency by oral administration in the tail flick test wherein an ED_{50} value is calculated from the response at 1 hour for comparison to other studies in this manuscript. SFigure 1B provides the tolerance data from the SR-17018-treated female mice in the tail flick assay (ED_{50} values included in Table 1). SFigure 2 provides a visual representation of plasma levels measured following the indicated doses of oxycodone, buprenorphine, SR-17018 and morphine at 1, 12 and 24 hours after injection.

Grim, T. W., Schmid, C. L., Stahl, E. L., Pantouli, F., Ho, J. H., Acevedo-Canabal, A., Kennedy, N. M., Cameron, M. D., Bannister, T. D., Bohn, L. M., 2020. A G protein signaling-biased agonist at the mu-opioid receptor reverses morphine tolerance while preventing morphine withdrawal. Neuropsychopharmacology 45, 416-425.



Supplemental Figure 1. A. Male C57BL6/J mice: Dose response over time for oral (p.o.) dosing in the warm water (49°C) tail immersion assay (ED_{50}: 8.5 *(5.2–13.12)* mg/kg, n=5 at 6 & 12; n=13 at 24 mg/kg, PO), %MPE is 100% x [(response sec – baseline sec)/(30 sec – baseline)] where the average baseline was 2.62 ± 0.11 sec (mean with s.e.m.) for this group of mice. **B.** Female C57BL6/J mice were assessed for tail flick response 1 hour following intraperitoneal (IP) injection of SR-17018 following chronic treatment with vehicle (PO., b.i.d.) or 48 mg/kg/day SR-17018 (PO., b.i.d.) for 6 days. The baseline taken 15h after the last dose of vehicle was: 1.65 ± 0.11 sec and after SR-17018: 1.67 ± 0.11 sec. Potencies are provided in Table 1 of the text.



Supplemental Figure 2. C57BL6/J male mouse plasma levels were measured by LC/MS at 1, 12 or 24 hours post drug administration. Shown are means with ± s.e.m. Oxycodone: n=3 (not measured at 24 h); SR-17018: n=3 @ 1, 24h; n=10@ 12 h; buprenorphine: n=7 @ 1, 12 h; n=4 @ 24h; morphine: n=3 @ 1, 12 h; n= 4 @ 24 h. *LOD: limit of detection.* The data for oxycodone is from (Grim et al., 2020); the oxycodone metabolite levels can be found in the reference. For SR-17018, 7 mice from the 12 h point were published in (Grim et al., 2020) while additional mice (n=3) were added for the 1-, 12- and 24-hours points shown here. Morphine levels following SC osmotic pump administration can be found in Grim et al., 2020.