Scientists develop a new non-opioid pain killer with fewer side effects

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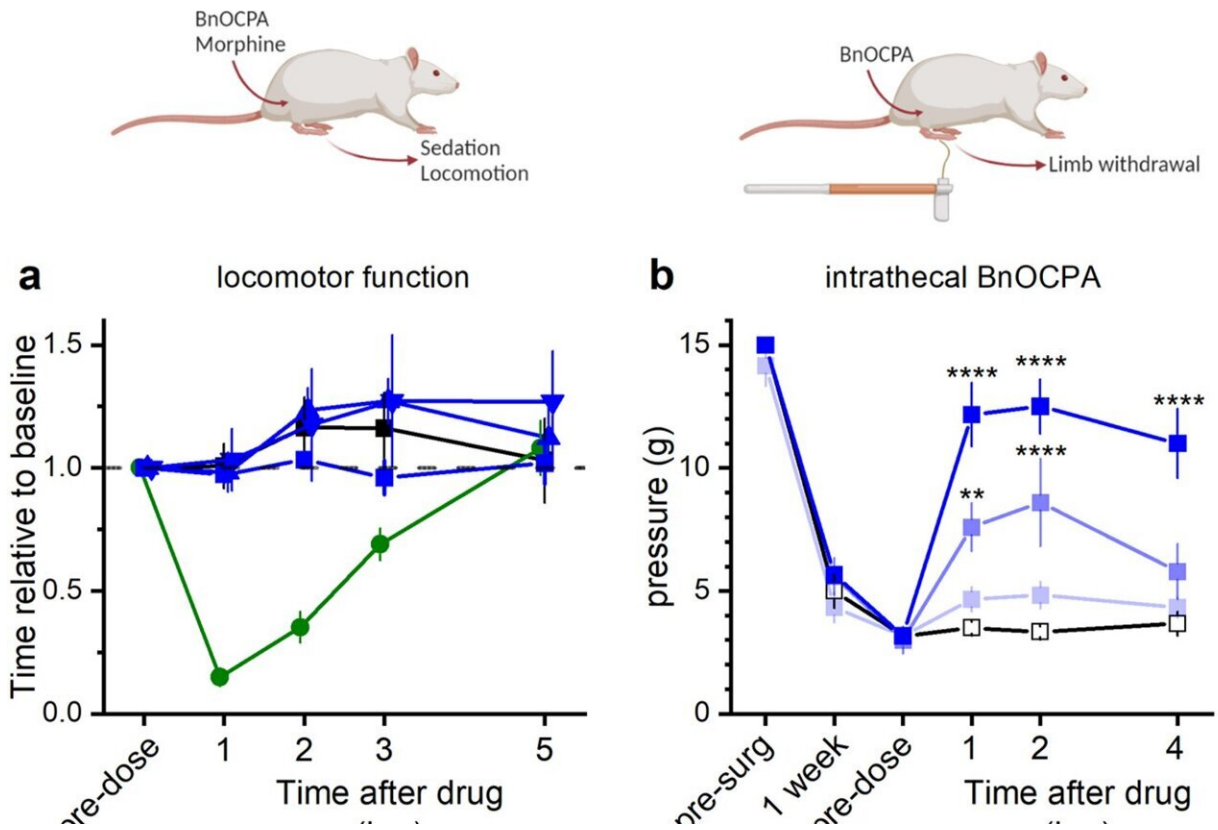

BnOCPA is a potent analgesic without causing sedation or motor impairment. a BnOCPA did not induce sedation or affect motor function when injected intraperitoneally (IP; 10 μg kg^{-1}) or intravenously (IV; 10 or 25 μg kg^{-1}). In contrast, morphine caused sedation and motor impairment (15 mg kg^{-1} subcutaneously, SC). Saline (Veh, SC) did not affect rotarod performance. Data points (mean ± SEM; n = 6 for each compound) are normalized to pre-dose performance and are offset for clarity. b, c BnOCPA alleviates mechanical allodynia in neuropathic pain when administered b via an intrathecal (IT) or c IV

route. Pre-surgery (pre-surg) animals had similar sensitivity to tactile stimulation as assessed by von Frey hair stimulation. Spinal nerve ligation caused hypersensitivity to touch (mechanical allodynia) at 1 week after surgery as evidenced by the reduction in the tactile pressure necessary to elicit paw withdrawal (paw withdrawal threshold; PWT). PWT reaches a similar nadir across all groups prior to the vehicle or BnOCPA infusion (pre-dose). Administration of BnOCPA significantly increased PWT in the limb ipsilateral to the site of injury in a dose-dependent manner (one-way ANOVA (pre-dose, 1, 2 and 4 hrs) for IT BnOCPA $F(3,88) = 21.9$, $P = 1.10 \times 10^{-10}$; for IV BnOCPA $F(3,92) = 18.1$, $P = 2.70 \times 10^{-9}$). Fisher LSD post hoc comparisons showed significant differences at: IT 1 nmol at 1 and 2 hrs, $P = 0.001$ and 4.16×10^{-5}, respectively, and 3 nmol at 1, 2 and 4 hrs, $P = 9.52 \times 10^{-11}$, 1.42×10^{-11} and 1.41×10^{-8}, respectively; IV 3 μg kg^{-1} at 1, 2 and 4 hrs, $P = 0.044$, 0.008 and 0.019, respectively, and 10 μg kg^{-1} at 1, 2 and 4 hrs, $P = 1.37 \times 10^{-8}$, 6.81×10^{-14} and 3.23 × 10⁻4, respectively. b, c n = 6 per treatment, except for 1 nmol BnOCPA, n = 5. d The analgesic effects of BnOCPA (6 μg kg^{-1} IV) were prevented by the A1R antagonist DPCPX (1 mg kg^{-1} IP), but not the A3R-selective antagonist MRS1523 (2 mg kg^{-1} IP). Post hoc LSD comparisons across all four groups and four-time points (pre-dose, 1, 2 and 4 hrs; $F(15,116) = 26.8$, $P = 0$) revealed that BnOCPA at 6 μg kg^{-1} (IV) elicited significant analgesia compared to vehicle-treated animals at 1, 2, and 4 h post-dosing ($P = 4.69 \times 10^{-9}$, 3.50×10^{-16}, 4.69×10^{-9}, respectively), which persisted in the presence of the selective A3R antagonist MRS1523 over the same time period ($P = 4.42 \times 10^{-13}$, 3.38×10^{-14}, 1.81×10^{-10}, respectively). In contrast, the PWT in DPCPX-treated animals did not differ from those in the vehicle group ($P = 0.872$, 0.748, 0.453 at 1, 2, and 4 h, respectively). n = 11 for BnOCPA and vehicle groups; n = 6 for the DPCPX group and n = 5 for the MRS1523 group. Averaged data are presented as mean ± SEM. ns, not significant; *, P