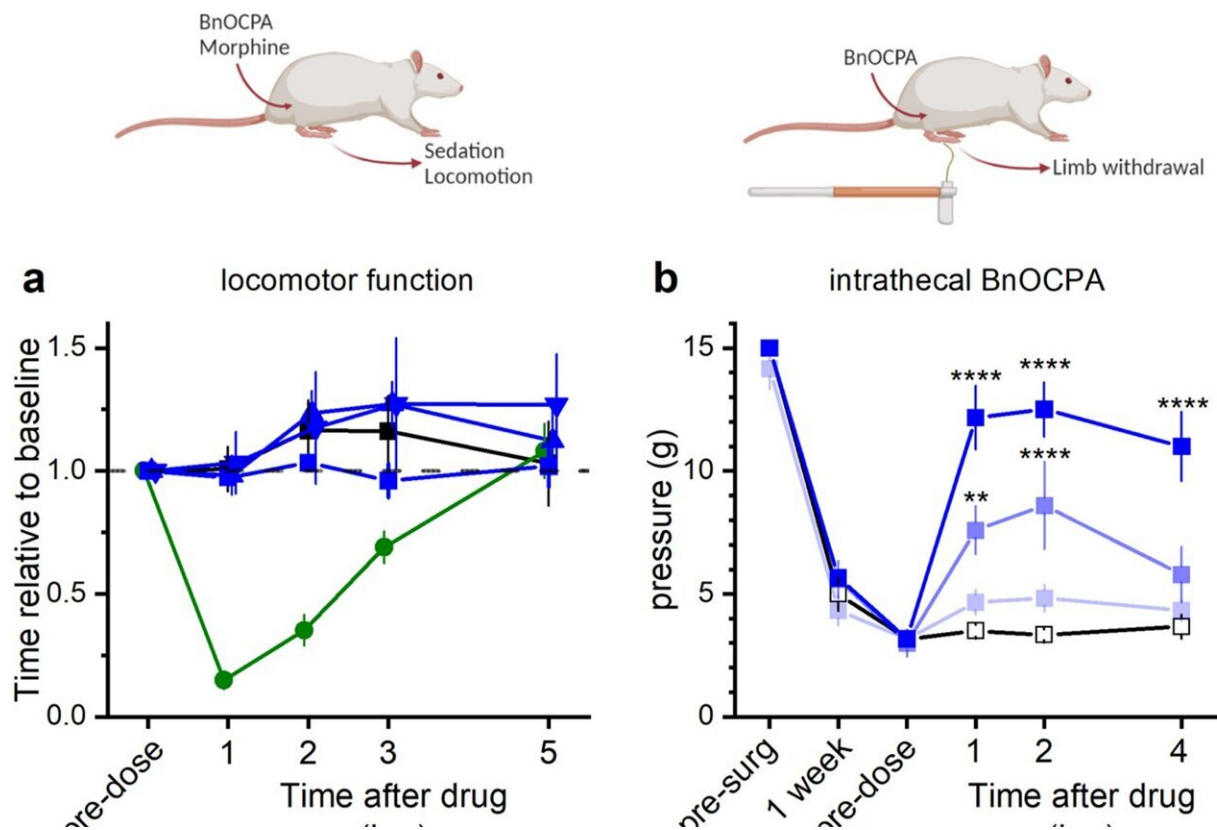


Scientists develop a new non-opioid pain killer with fewer side effects

July 20 2022



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; $10 \mu\text{g kg}^{-1}$) or intravenously (IV; 10 or $25 \mu\text{g kg}^{-1}$). 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 \pm 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 $3 \mu\text{g kg}^{-1}$ at 1, 2 and 4 hrs, $P = 0.044$, 0.008 and 0.019 , respectively, and $10 \mu\text{g kg}^{-1}$ 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 ($6 \mu\text{g kg}^{-1}$ 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 $6 \mu\text{g kg}^{-1}$ (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 \pm SEM. ns, not significant; *, P

Citation: Scientists develop a new non-opioid pain killer with fewer side effects (2022, July 20) retrieved 25 April 2024 from <https://medicalxpress.com/news/2022-07-scientists-non-opioid-pain-killer-side.html>

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