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Enhanced Naloxone-Precipitated Withdrawal-Induced Aversion Following Oxycodone Administration in Zhx2 Knockout Mice

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We mapped a loss-of-function mutation in the transcriptional repressor Zinc-fingers and homeobox 2 (Zhx2), as a candidate variant underlying increased brain oxymorphone (OMOR) concentration and oxycodone (OXY) conditioned reward in BALB/cJ females. CRISPR/Cas9-mediated knockout (Zhx2 KO) in BALB/cByJ mice recapitulated increased brain OMOR and OXY behavioral sensitivity in females. Here, we tested the hypothesis that Zhx2 KO would enhance emotional-affective OXY withdrawal in a conditioned place aversion (CPA) paradigm via increased brain OMOR. On day(D)1, mice received SAL at 0900h and 1300h and were placed in a two-sided chamber to test for initial time(s) on each side. On D2 and D4, OXY/naloxone (NLX) mice received OXY (40 mg/kg, i.p.) in the home cage at 0900h and NLX (1 mg/kg, i.p.) at 1300h in the confined right side. SAL/SAL mice received SAL in the am/pm on all days. On D3 and D5, mice received SAL in the am/pm and were confined to the left side. On D8, mice received SAL in the am/pm and were provided open access to both sides. On D9, OXY/NLX mice received SAL at 0900h and NLX (1 mg/kg, i.p.) at 1300h and were provided open access. Preliminary results indicate robustly enhanced OXY/NLX-CPA in Zhx2 KO mice which we hypothesize is mediated by increased brain concentration of OMOR following OXY administration, due to its increased potency and efficacy at the mu opioid receptor. We will soon assess brain OMOR and eventually expand behavioral analysis to motivational aspects of OXY withdrawal, including shifts in reward threshold.