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Effects of Zhx2 liver and brain overexpression on oxymorphone metabolite levels and state-dependent oxycodone reward learning in BALB/cJ mice with a Zhx2 loss-of-function variant

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Oxycodone **(OXY)** misuse is integral to the opioid addiction epidemic. OXY is metabolized by CYP2D enzymes into oxymorphone (**OMOR**), a much more potent and efficacious mu opioid receptor agonist that could enhance OXY behaviors. We mapped Zhx2 (zinc-finger homeobox 2) as a candidate gene underlying brain [OMOR] in a BALB/c reduced complexity cross. Zhx2 is a transcriptional repressor of CYP450 enzymes. Here, we addressed whether Zhx2 overexpression in Zhx2-deficient BALB/cJ (**J**) mice would decrease CYP2D expression, reduce brain [OMOR], and reduce OXY-induced behaviors. For liver, J mice received retro-orbital AAV (AAV8-TBG-mZhx2-P2A-eGFP) injections. For brain, J females received AAV (AAV/F-CMV-mZhx2-P2A-eGFP.miR122) intracerebroventricular **(ICV)** injections. After 3 weeks, mice underwent OXY-conditioned place preference **(OXY-CPP)**. Following initial preference on Day (**D**) 1, on D2-D5, mice received alternating OXY injections (1.25 mg/kg, IP) and saline (IP). Mice were assessed for drug-free and state-dependent OXY-CPP on D8 and D9. For female Zhx2 liver overexpression, there was increased Cyp2d22 transcript, no effect on brain [OXY] or metabolite levels, and increased time spent on the OXY-paired side on Day 1,8, and 9. For males, there was no effect on Cyp2d transcripts, a decrease in brain [OXY], and no effect on preference. Consistent with our hypothesis, female Zhx2 brain overexpression decreased OXY-induced locomotion during training and state-dependent OXY-CPP. Immunohistochemical analysis showed focal viral spread to brain reward regions, including septal nuclei. Overall, our results support Zhx2 in OXY behaviors. Current data show increased brain CYP2D in Zhx2 loss-of-function mice. We will soon conduct functional analysis of CYP2D6 overexpression in wild-types.