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Functional mechanisms linking Zhx2 loss-of-function with increased brain oxymorphone levels and oxycodone addiction model behaviors

Overprescription of oxycodone (OXY) played a major historical role in the current opioid epidemic and OXY misuse continues to fuel it. OXY is metabolized into oxymorphone (OMOR), a more potent and efficacious metabolite at the mu-opioid receptor, that is associated with increased OXY locomotion and reward in BALB/cJ females vs. BALB/cByJ mice. We previously mapped and validated loss-of-function in zinc-fingers and homeobox 2 (Zhx2) as a quantitative trait gene and genetic mechanism underlying increased brain [OMOR] in BALB/cJ females. We are currently exploring the functional mechanism linking Zhx2 loss-of-function with increased brain [OMOR] and OXY behaviors via in-vivo blood brain barrier (BBB) permeability analysis, in-vivo structural and functional imaging in Zhx2 KO mice, cell-type examination, and liver enzymatic activity. Furthermore, we are assessing multiple OXY withdrawal behaviors in Zhx2 KO mice.

Zhx2 KOs showed increased naloxone-precipitated withdrawal-induced aversion in KOs. Transcriptome analysis of brain tissue identified enrichment of lipid metabolism and cell-to-cell adhesion, as a main effect of genotype. We hypothesize that Zhx2 KO regulates BBB integrity. In support, qPCR analysis for Claudin5 revealed a significant reduction in KO females. Furthermore, preliminary results show increased permeability of sodium fluorescein in KO females, specifically within the hippocampus. In vivo diffusion tensor imaging revealed reduced water diffusion throughout the brain in KO females. KO females also showed increased negative bold signal in midbrain and increased positive bold signal in the brainstem. Moreover, immunohistochemical analysis revealed Zhx2 expression to be restricted to limbic, addiction-relevant regions, with preliminary co-localization analysis indicating that Zhx2 is heavily expressed in neurons (region dependent), including within the hippocampus. Overall, our results suggest Zhx2 loss-of-function compromises BBB integrity which could explain increased brain [OMOR] and increased OXY-addiction model traits. We are currently testing an additional functional mechanism involving increased CYP2D activity from liver microsomes of KO vs. WT mice.

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