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### **Adolescent oxycodone exposure potentiates adult remifentanil self-administration in female mice**

Studies have shown that adolescent use of opioid painkillers predicts later life misuse and transition to illicit opioid drugs, but the causal mechanism for this association is not fully understood. In mice, the Blendy Lab has shown that chronic adolescent oxycodone exposure increases morphine conditioned place preference (CPP) at 28 days of withdrawal, while adult exposure does not. This effect is concomitant with age-specific changes in RNA expression and histone 3 K27 trimethylation (H3K27me3). However, it is not known whether this adolescent oxycodone exposure also increases subsequent intravenous self-administration (IVSA), a model of volitional opioid intake and reinforcement. Adolescent male and female B6 mice (n=12/group) received subcutaneous minipumps delivering 3 mg/kg/day oxycodone (M-OXY, F-OXY) or equal volume saline (M-SAL, F-SAL) for 28 days (post-natal days 28-56). Minipumps were then removed and mice were drug free for 28d prior to starting IVSA. Mice completed IVSA (6d Fixed Ratio [FR] 1, 4d FR2, 1d Progressive Ratio [PR]) using the potent synthetic opioid remifentanil. F-OXY mice had elevated daily intake and cumulative intake during both FR1 and FR2 compared to F-SAL controls. In contrast, M-OXY mice were not different from M-SAL. Mice were sacrificed following the final session of IVSA, and the ventral tegmental area (VTA) and other reward-related brain regions were dissected. An additional cohort was sacrificed at the 28d withdrawal timepoint, corresponding to the first day of IVSA. These samples were processed using single-sample RNA and CUT&RUN-seq (S3EQ) to identify changes in RNA expression, RNA splicing, and H3K27me3. Analysis revealed significant changes in key neural signaling-related genes, including calbindin 1 (Calb1) and a voltage-gated potassium channel family member (Kcna6), between F-OXY and F-SAL mice following remifentanil IVSA. These changes are being validated in ongoing work. Sequencing data from the nucleus accumbens is forthcoming and will also be presented.

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