Exercise Blocks Ethanol-Induced Kappa Opioid Receptor Sensitization in Nucleus Accumbens and Ventral Tegmental Area

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Background

Alcohol Use Disorder (AUD) and Exercise Therapy: Exercise is increasingly utilized in treating AUD, but its impact on mesolimbic circuitry, specifically the Dynorphin-Kappa Opioid Receptor (KOR) system, remains unclear.

Rationale: Alcohol dependence upregulates the KOR system, making it a potential therapeutic target. Understanding these pathways can guide evidence-based integration of exercise into AUD therapies.

Methods

Protocol: Mice were injected twice daily with either EtOH to establish dependence or saline as a control for 2 weeks. During the two weeks, the mice were either given free access to a running wheel or had the wheel restricted with ties to prevent exercise. At the end of the two weeks, the mice were anesthetized, and brain slices were prepared for either fast scan cyclic voltammetry (FSCV) or immunohistochemical (IHC) analysis. Protocol illustrated in figure 1.

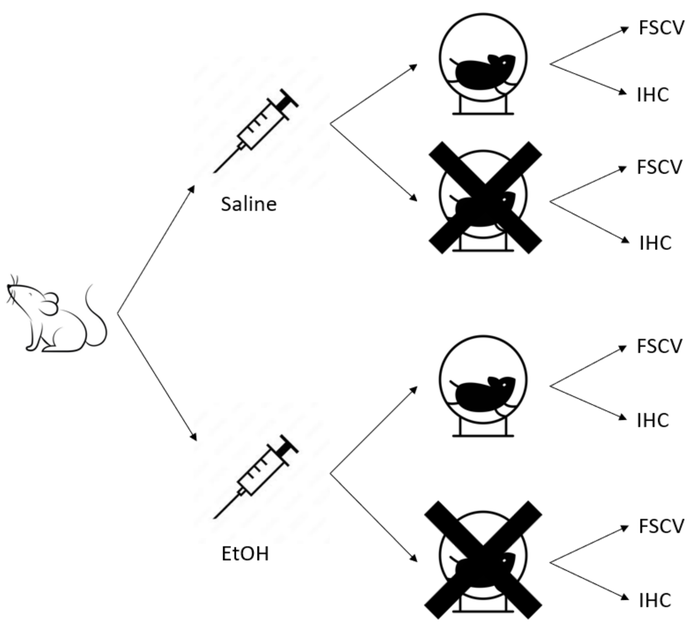

Figure 1: Experimental Design Illustration

Analysis Techniques: Fast scan cyclic voltammetry (FSCV) was used to record dopamine signals from 220 µm-thick coronal slices containing the striatum. Signals were measured at baseline and following bath application of the KOR-agonist U-50488 at 0.3 µM and 1 µM, followed by a reversal dose of the KOR-antagonist nor-BNI at 1 µM.

Immunohistochemical (IHC) analysis of KOR expression was measured under confocal microscopy using anti-KOR antibodies. 30 µm slices of the ventral tegmental area (VTA) and nucleus accumbens (NAc) were used for IHC.

Results

Fast Scan Cyclic Voltammetry (FSCV)

- **EtOH dependent mice:** Dopamine release in the no-exercise group dropped to 82.1% (± 5.5) and 58.7% (± 6.9) of baseline following baths of U-50488 at 0.3 µM and 1 µM respectively. The exercise group dropped to 99.3 % (± 5.2) and 85.1% (±8.9) of baseline following bath administration of U-50488 at 0.3 µM and 1 µM respectively.
- **EtOH non-dependent mice:** Dopamine release in the no-exercise group dropped to 69.1% (± 10.8) and 57.8% (± 13.6) of baseline following baths of U-50488 at 0.3 µM and 1 µM respectively. The exercise group changed to 100.6 % (± 1.2) and 98.6% (±7.5) of baseline following bath administration of U-50488 at 0.3 µM and 1 µM respectively.

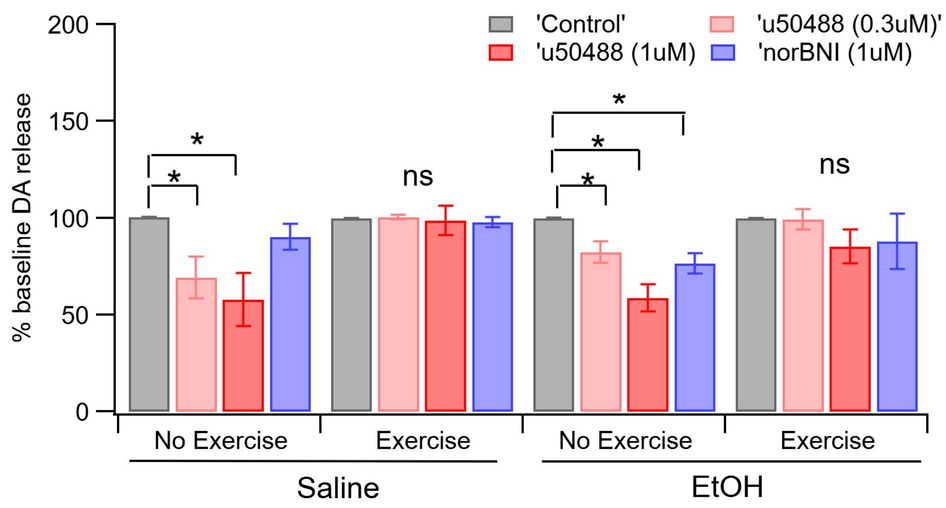

Figure 2: Normalized peak height of evoked dopamine at baseline and following administration of 0.3 µM, 1 µM U50488, or 1 µM norBNI, a KOR antagonist, after EtOH dependence protocol or saline protocol while being with or without access to an exercise wheel for voluntary exercise. Asterisk * indicates significance $p<0.05$.

Immunohistochemistry (IHC)

Exercise decreased the expression of KORs as measured by mean fluorescent intensity (MFI) in both the **ventral tegmental area (VTA)** and **the nucleus accumbens (Nac)** when compared to no exercise mice. These findings applied to both mice that were ethanol-dependent and non-dependent on alcohol.

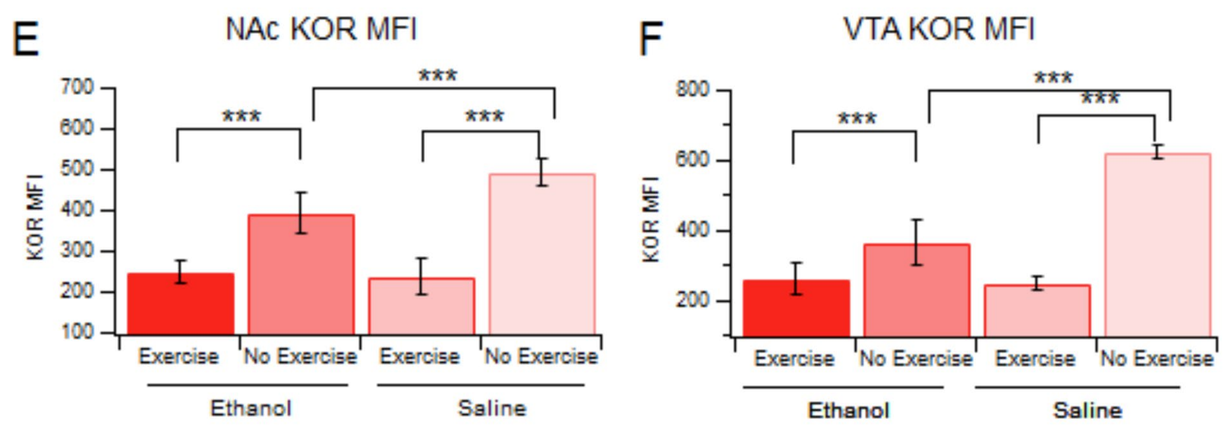

Figure 3: Quantification of mean fluorescence intensity of KOR fluorescence in the NAc (E) and VTA (F) for mice following EtOH dependence protocol or saline protocol, while being with or without access to an exercise wheel for voluntary exercise. Asterisks *** indicates significance $p<0.001$.

Conclusions

Exercise Influence on KOR Expression: Voluntary exercise blunted the expression of KORs in both EtOH dependent and EtOH independent mice.

Therapeutic Insights: Findings suggest a potential mechanism by which exercise contributes to AUD treatment.

Research Gap: Further studies are needed to fully comprehend exercise's role in altering expression and sensitivity of KORs and other opioid receptors impacting mesolimbic circuitry.