Attenuation of Kappa-opioid receptor sensitivity changes after chronic ethanol exposure in response to voluntary exercise

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Introduction

- Exercise has been touted as a viable adjunct therapy for drug abuse disorders. However, the underlying neural mechanisms are unknown.
- K–opioid receptors (KORs) are on presynaptic DA terminals in the nucleus accumbens (NAc) and DA cell bodies in the ventral tegmental area (VTA).

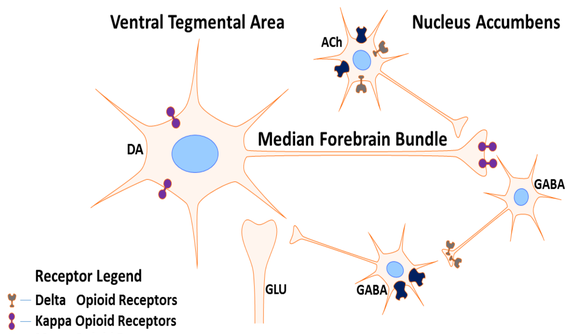


Fig. 1. Location of mu, kappa and delta opioid receptors in the mesolimbic circuitry

- *Chronic ethanol hyper sensitizes KORs.*
- We hypothesize that regular exercise will decrease sensitivity and/or expression of KORs and block chronic ethanol-induced sensitization.

Methods

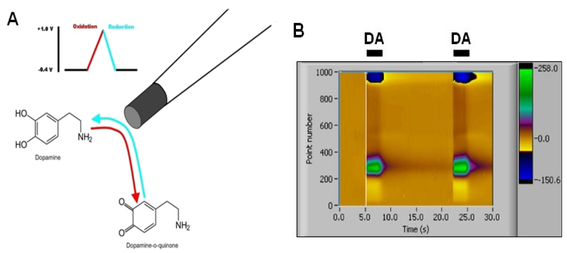


Fig. 2. Dopamine Fast Scan Cyclic Voltammetry. (A) Dopamine is oxidized and reduced at specific voltages. The oxidation/reduction of the reaction is measured by a respective change in current. A triangular voltage waveform is applied to a carbon fiber electrode which oxidizes DA to DA-o quinone. (B) The change in current when DA is released is proportional to the concentration of DA, and can be converted based on specific electrode calibration factors. This graph shows the oxidation and reduction currents associated with two boluses of DA in vitro.

Fig. 3. Explanation of DID and IHC Methods: C57 mice were housed in cages with 24 hour access to a running wheel. They were injected twice daily with 2g/kg EtOH or Saline for two weeks to initiate addiction.

Mice the underwent 4 days of a drinking in the dark (DID) protocol to assess seeking behavior. The water bottle from each cage was replaced with a bottle containing 15 mL of 16% EtOH each day for 2 hours until the last day on which they were left for 4 hours.

Alcohol withdrawal alleviated through exercise induced changes to opiate receptors

Results

Exercise Attenuates EtOH induced Sensitization of KORs

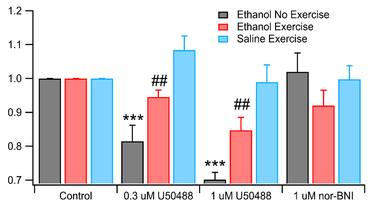


Fig. 4. FSCV Demonstrates that exercise attenuates EtOH induced sensitization. Kappa Opioid Receptors are sensitized by EtOH, as shown by their strong responsiveness to KOR agonists and antagonists. This hypersensitivity is decreased by a regiment of aerobic exercise.

Exercise Increases PPR

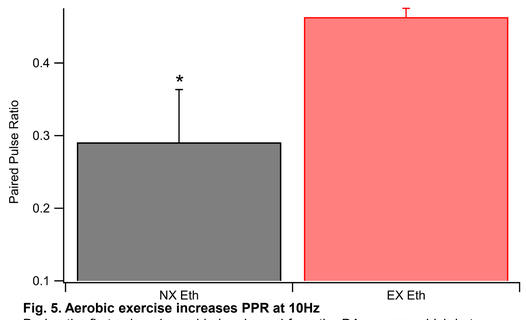


Fig. 5. Aerobic exercise increases PPR at 10Hz During the first pulse, dynorphin is released from the DA neurons which in turn acts on the KORs, decreasing second pulse height. Exercise desensitizes the KORs which in turn leads to a higher second peak.

Exercise Attenuates EtOH induced Sensitization of KORs

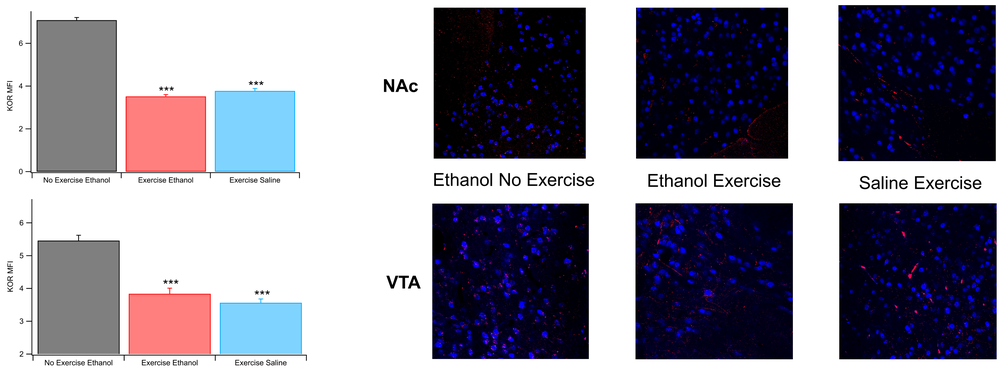
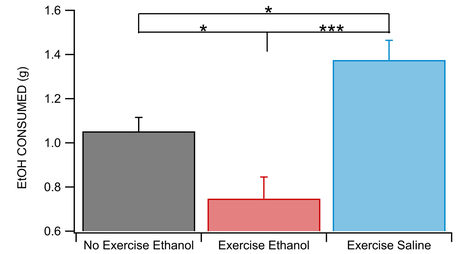


Fig. 6. IHC staining of KORs in the Nacc and VTA. A, B - Exercise attenuates increased chronic ethanol-induced increases in KOR expression in the NAcc and VTA. C,D,E – Representative images from NAcc. F,G,H – Representative images from the VTA. All slices obtained were horizontal in orientation and 30 um thick.

Results Continued



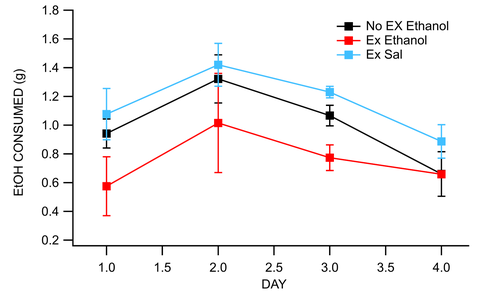


Fig 7. Exercise decreases ethanol drinking. A - Group data summary over 4-days showing a reduction in drinking in the exercise ethanol group when compared to no exercise ethanol. B – Drinking by day in each group.

Conclusions

- **Chronic ethanol increases expression of KORs in the VTA and NAc.**
- **2-weeks of voluntary wheel running concurrent with chronic ethanol exposure reduces ethanol-induced increases in KOR expression.**

Proposed Model

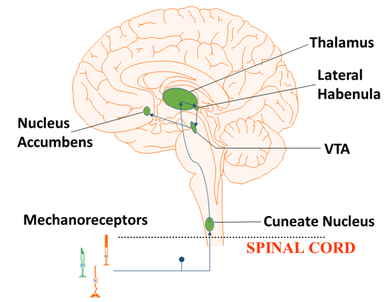


Fig. 9. Proposed model that peripheral mechanoreceptors activate the dorsal column-medial lemniscal pathway, synapse in the cuneate and gracile nuclei, then, progressively, to the VPL thalamus, lateral habenula, DA-ergic projections in the ventral tegmental area which travel to the Nac.

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