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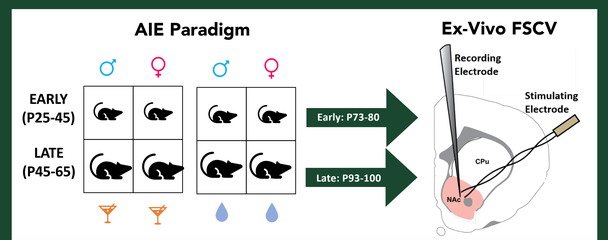
Introduction

Alcohol use generally begins in adolescence, and this early initiation increases risk for affective disorders and alcohol use disorder (AUD). Dopamine and the kappa opioid receptor (KOR) system in the nucleus accumbens (Nac) are involved in reward and emotion processing. Previous studies have shown that chronic ethanol exposure in adult rats reduce dopamine transmission in the NAc. This dopamine transmission is partially regulated by (KORs). Additionally, it has been observed that KOR function is upregulated in alcohol dependent rats. In these previous studies, alcohol exposure occurs in adulthood and dopamine and KOR function were measured during acute withdrawal. However, the impact of adolescent ethanol exposure on dopamine transmission and KOR function following protracted abstinence in unknown. Furthermore this study aims to elucidate the sex differences in dopamine and KOR function.

Methods

Animals: Male and Female Sprague Dawley rats.



Ethanol administration paradigm:

Male and female Sprague-Dawley rats were exposed via orogastric gavage to either water or ethanol every other day during either early (P25-45) or late (P45-65) adolescence for a total of 11 exposures.

***Ex vivo* Fast Scan Cyclic Voltammetry:**

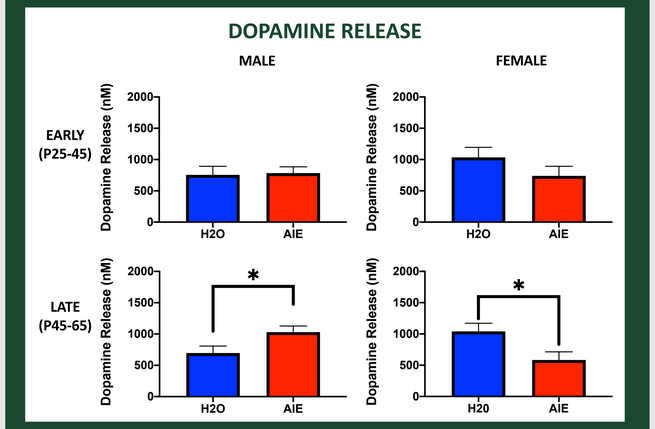
After 28-to-35 days of abstinence, rats were sacrificed via rapid decapitation and coronal sections containing the NAc were harvested for *ex vivo* Fast Scan Cyclic Voltammetry. Dopamine release in the NAc core was evoked by single electrical pulse stimulation (4.0-ms, 3.50 µA, monophasic, inter-stimulus interval: 300 seconds)every five minutes and was measured using a carbon fiber electrode. Dopamine release in the slice before any drug application was measured to obtain baseline measurements. Once stable dopamine release measures were established, cumulative concentrations of KOR agonist U50,488 (10, 30, 100, 300 and 1000 nM) were bath-applied. Dopamine release and uptake were quantified from stabilized signals using a Michaelis-Menten kinetics-based algorithm after the addition of each ethanol concentration.

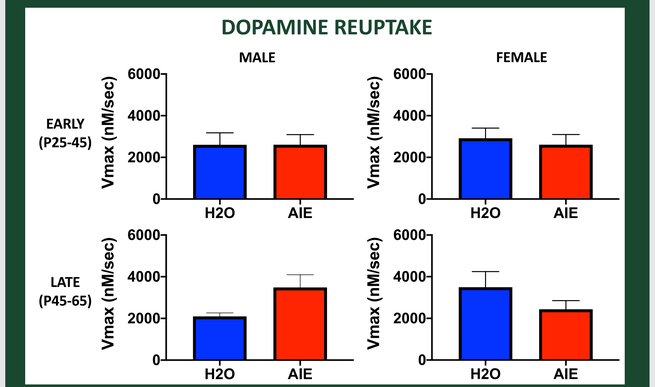
Summary and Conclusions

- Opposing effects on dopamine release at baseline were observed in late AIE animals: late AIE exposure reduced dopamine release in females and increased it in males.
- Early AIE exposure did not have a long-lasting effect on dopamine transmission in adulthood suggesting that adaptation likely occurs in the dopamine system following ethanol exposure during early adolescence.
- The lack of effect on dopamine uptake following early and late AIE exposure in males and females suggests that the changes observed in dopamine release are not driven by the dopamine transporter function.
- Early AIE exposure resulted in augmented KOR function in the NAc in females, while we observed no change in KOR function in males when compared to their respective water exposed controls.
- Surprisingly, late AIE exposure attenuated KOR function in males when compared to water exposed controls. We did not observe any differences in KOR function in late AIE exposed females when compared to water exposed controls.

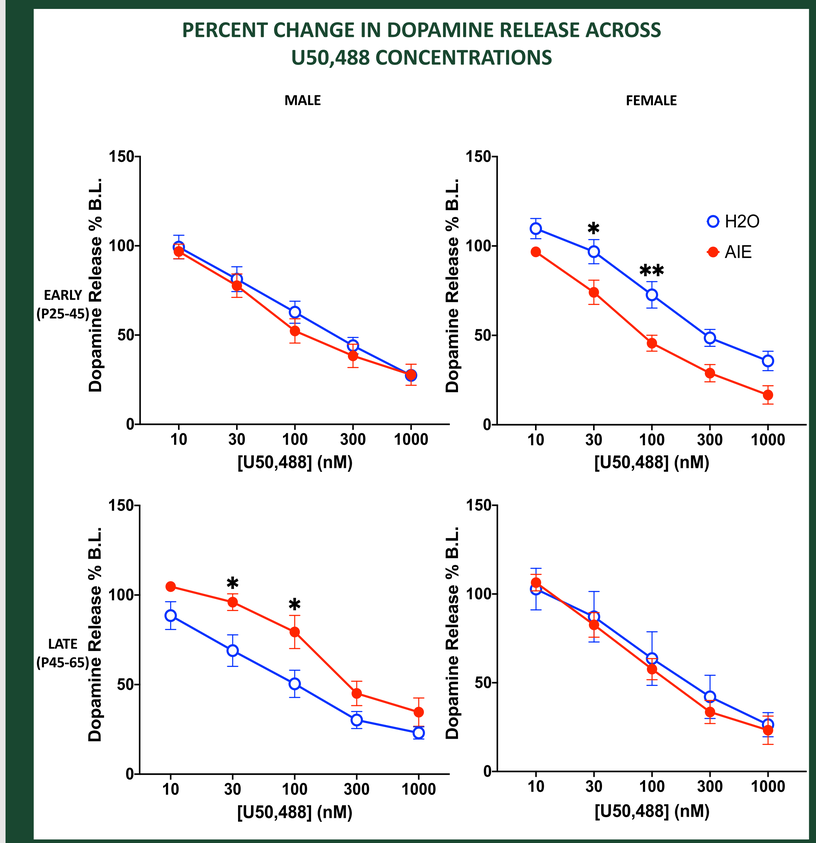
From these observations we can conclude that ethanol exposure during adolescence produces distinctly sex and time specific results in both dopamine transmission and KOR function.

AIE effects on baseline dopamine transmission in an exposure, time, and sex dependent manner

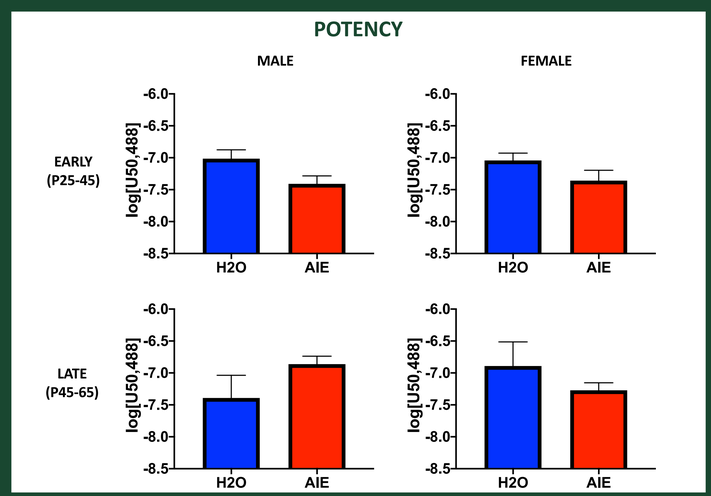


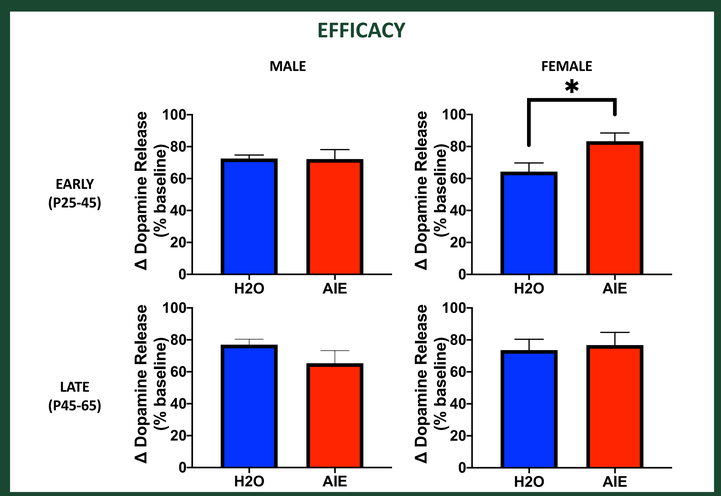


Impact of AIE on kappa opioid receptor mediated inhibition of dopamine release



AIE impact on kappa opioid receptor agonist efficacy and potency on inhibition of dopamine release





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