Interaction Between Estradiol and the Endocannabinoid System: Implications of Addictive Behaviors in Females

Ambrosia M. Smith¹, Brittni M. Peterson²,³, Luis A. Martinez² and Paul G. Mermelstein²,³

¹College of Liberal Arts, University of Minnesota; ²Department of Neuroscience, University of Minnesota; ³Neuroscience Graduate Program, University of Minnesota

INTRODUCTION

Sex differences in addiction
- Women display markedly faster progressions from casual drug use to drug abuse and addiction relative to men
- Female sex steroid, estradiol, appears to mediate this effect

Neural mechanisms of estradiol
- Striatum is an integral brain region in development and expression of addictive behaviors
- Estradiol can impact striatal function via multiple mechanisms:
  - Activation of membrane localized estrogen receptors coupled to mGluR5
  - Stimulation of the endocannabinoid system via mGluR5

Does estradiol modulate expression of components of the endocannabinoid system within the striatum to drive addictive behavior in females? If so, does this effect of estradiol occur via mGluR5?

RESULTS

- Estradiol enhances the expression of endocannabinoid synthesizing enzymes in the caudate putamen
  - This effect occurs via mGluR5
- Estradiol enhances the expression of the cannabinoid receptor in the nucleus accumbens
  - This effect occurs via mGluR5
- Estradiol does not affect the expression of endocannabinoid degrading enzymes in the striatum
- Estradiol may increase endocannabinoid levels and endocannabinoid binding to cannabinoid receptors within the striatum and this may play a role in female responses to drugs

METHODOLOGY

- Intraperitoneal injection of vehicle or mGluR5 antagonist, MPEP (1mg/kg) in OVX female Sprague-Dawley rats
- Subcutaneous injection of cottonseed oil or estradiol (10μg)
- Sacrifice
- Tissue punches of caudate/putamen, nucleus accumbens and hippocampus
- Extract RNA (Qiagen kit)
- Reverse transcribe to cDNA (Roche cDNA synthesis kit)
- qRT PCR (Roche LightCycler 480)
- Analyze stats (independent sample t-tests)

CONCLUSIONS

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  - This effect occurs via mGluR5
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MODEL

- Estradiol (E)
- Increase in CB1R transcription
- Increase in CB1R translation
- Increase 2AG synthesis
- Increase CB1R binding

FUTURE DIRECTIONS

- Directly measure endocannabinoid levels within striatum
- Determine whether this action of estradiol is genomic, non-genomic or both
- Investigate endocannabinoid synthesis, degradation and binding in male brain

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