

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

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INTRODUCTION

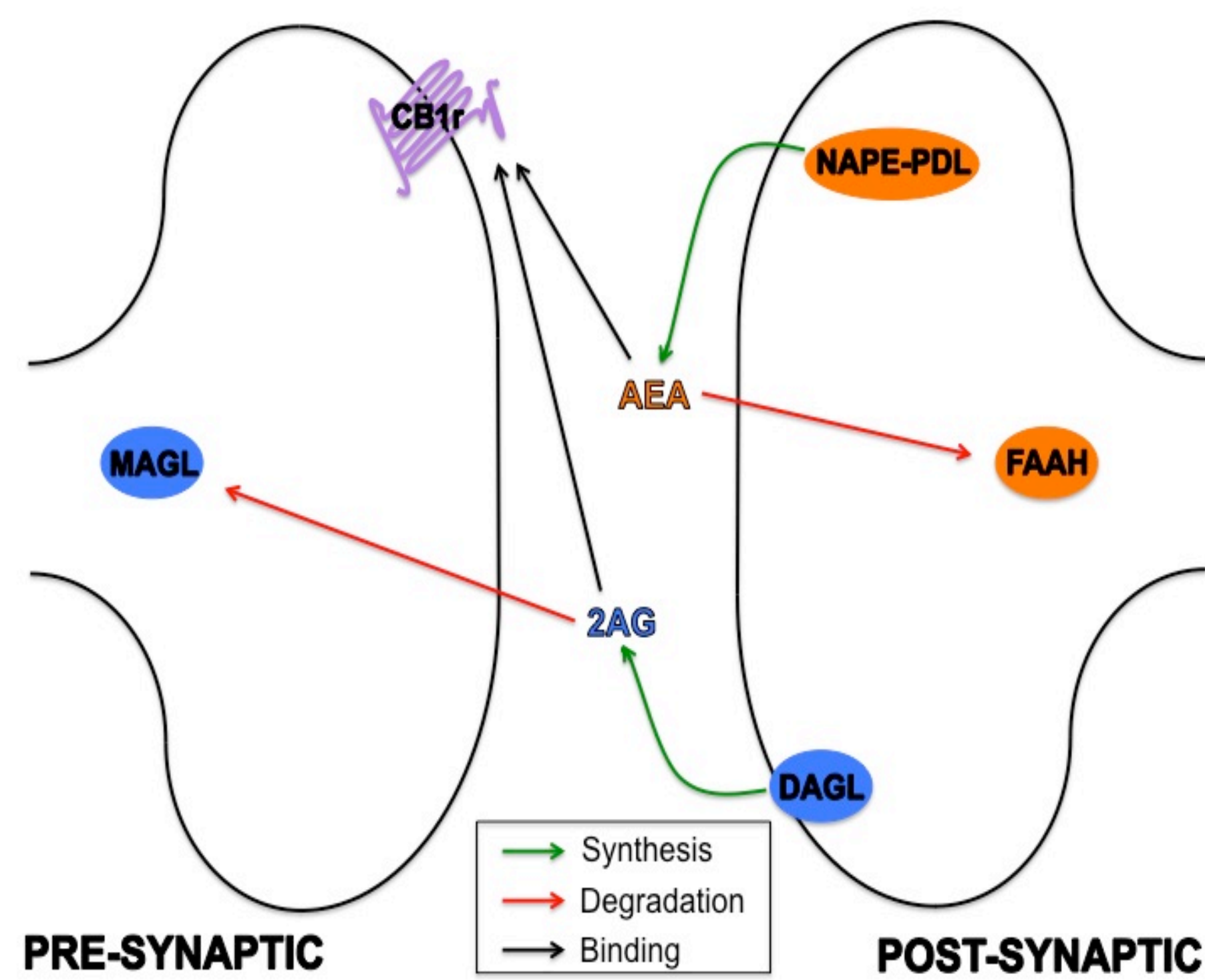
Sex differences in addiction

- 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

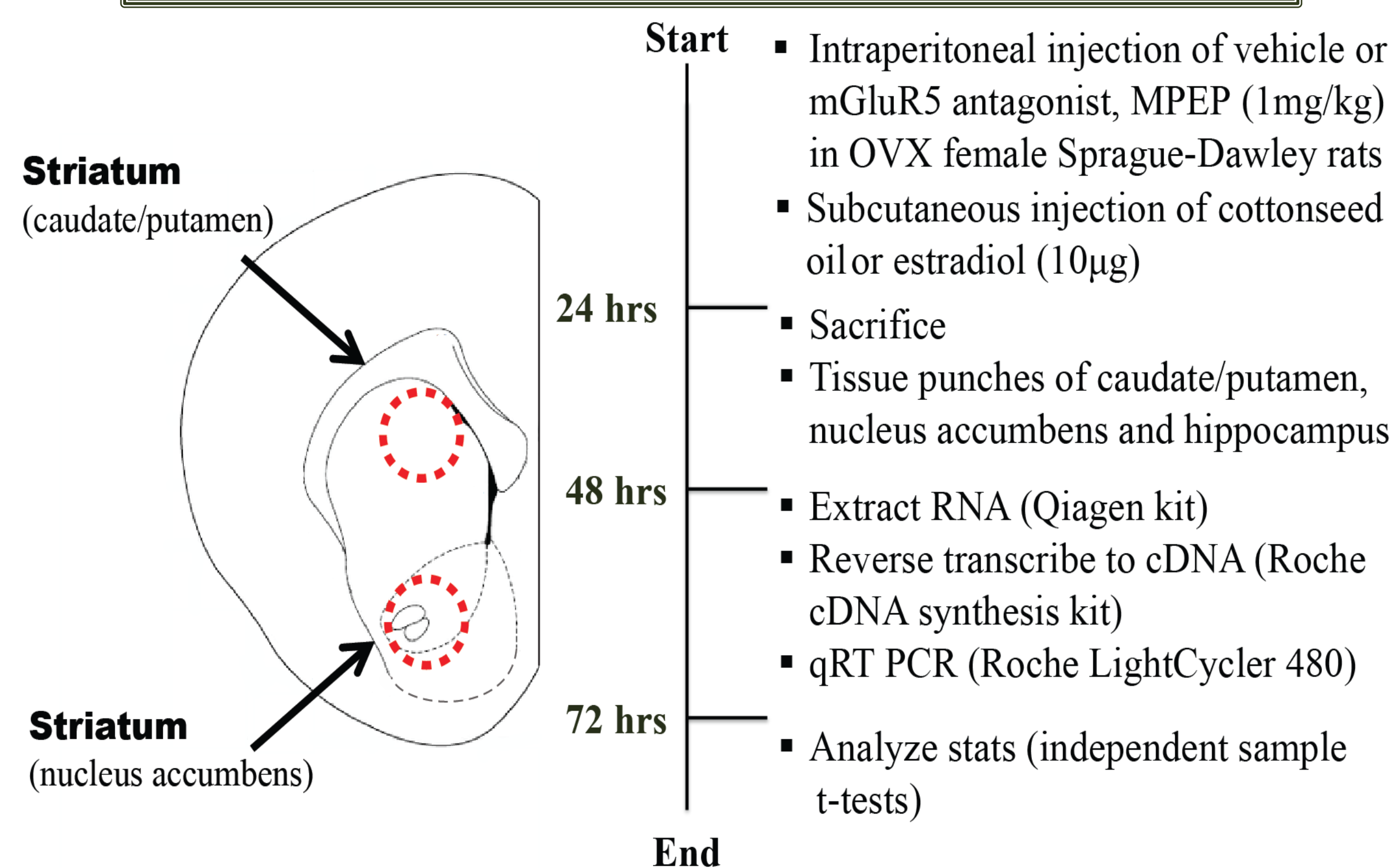
- Striatum is an integral brain region in development and expression of addictive behaviors
- Estradiol can impact striatal function via multiple mechanisms:
 - Activation of membrane localized estrogen receptors coupled to mGluR5
 - Stimulation of the endocannabinoid system via mGluR5

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?

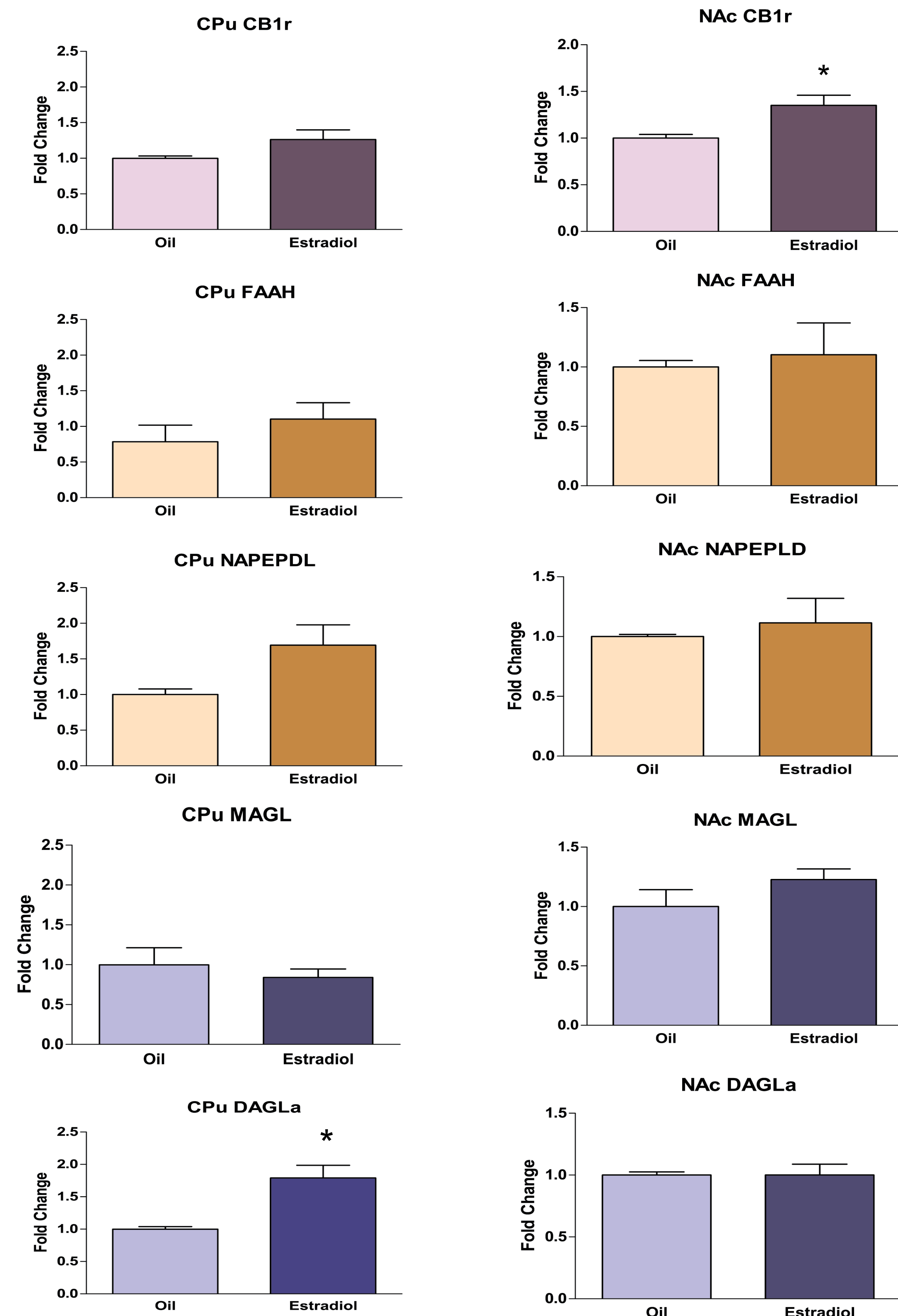


We hypothesized that estradiol mediates the expression of molecules that synthesize, degrade, and bind the two best studied endocannabinoids in the striatum (2AG and AEA) via mGluR5, to ultimately drive addictive behaviors in females.

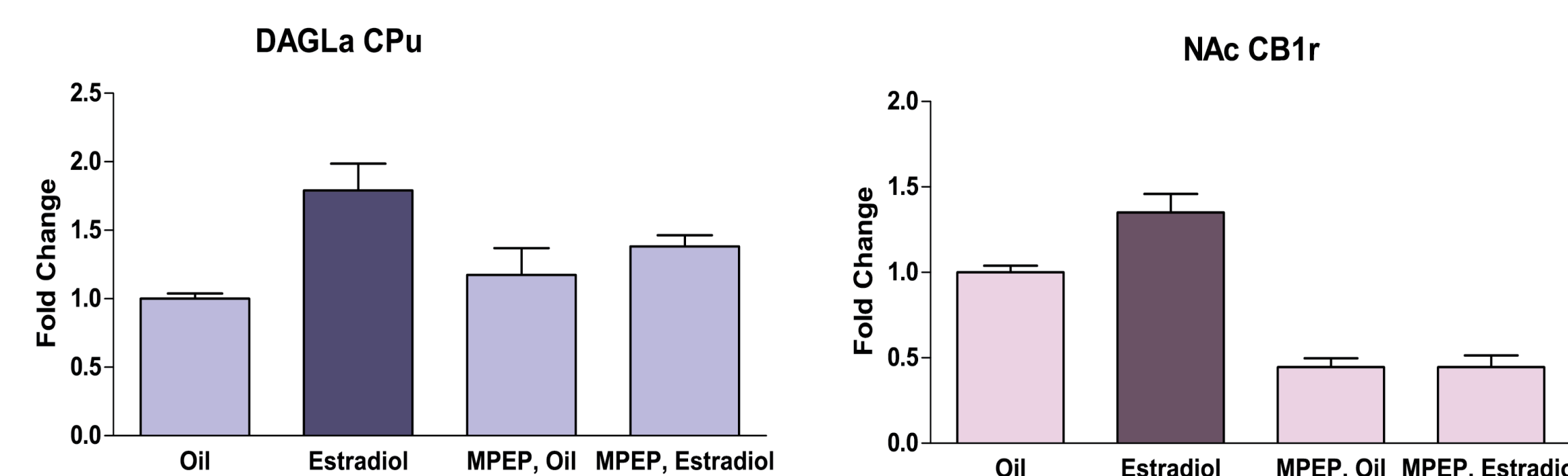
METHODOLOGY



RESULTS



In the caudate putamen, estradiol treatment increases expression of endocannabinoid synthesizing enzyme DAGL, but does not affect expression of endocannabinoid degrading enzymes (MAGL, FAAH) or endocannabinoid receptor CB1. In the nucleus accumbens estradiol increases expression of the endocannabinoid receptor CB1, but has no effect on synthesizing or degrading enzymes. * $p < 0.05$

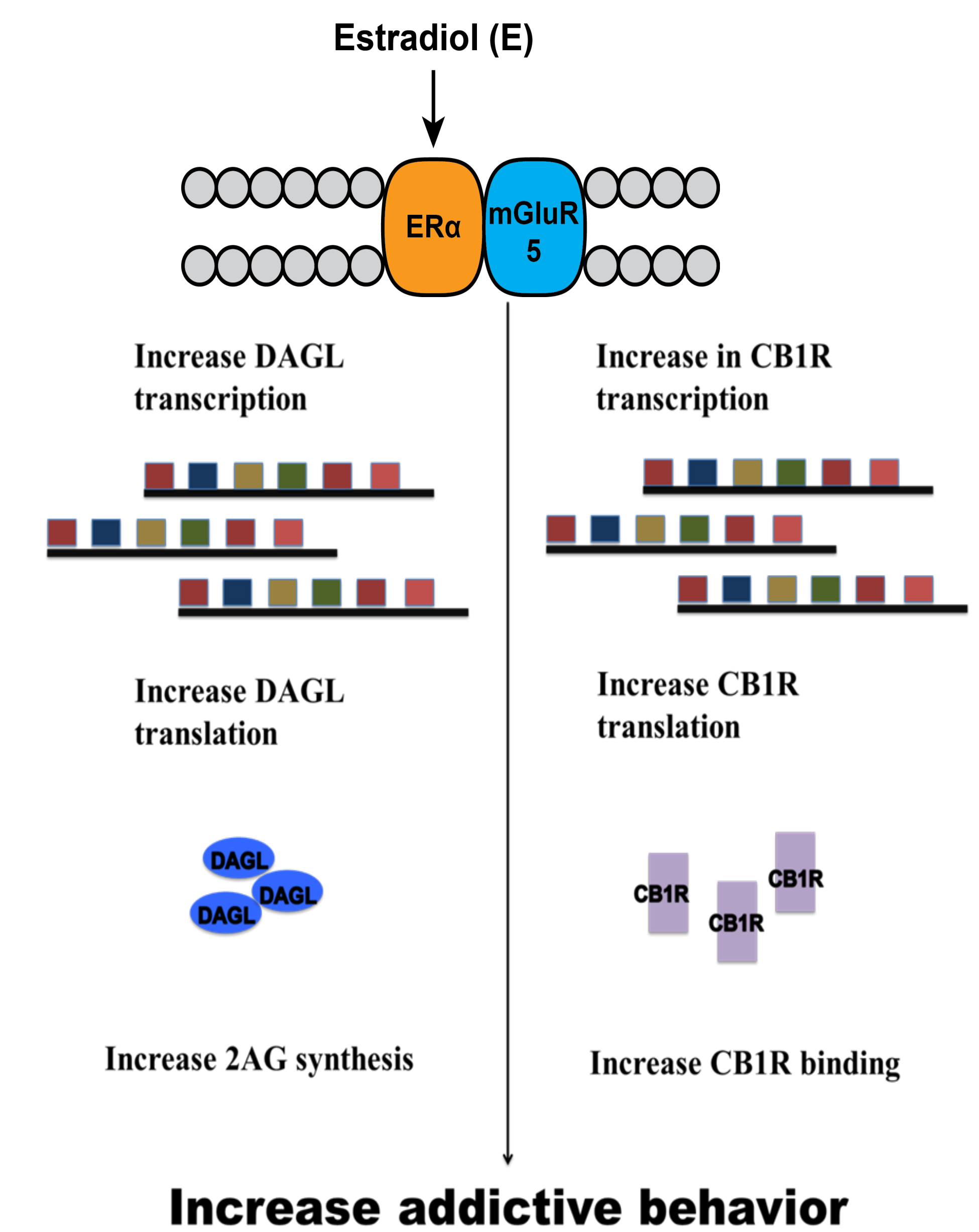


In the caudate putamen, blocking mGluR5 attenuates the estradiol mediated increase in expression of endocannabinoid synthesizing enzyme DAGL. In the nucleus accumbens blocking mGluR5 attenuates the estradiol mediated increase in expression of the endocannabinoid receptor CB1. * $p < 0.05$

CONCLUSIONS

- 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

MODEL



Increase addictive behavior

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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