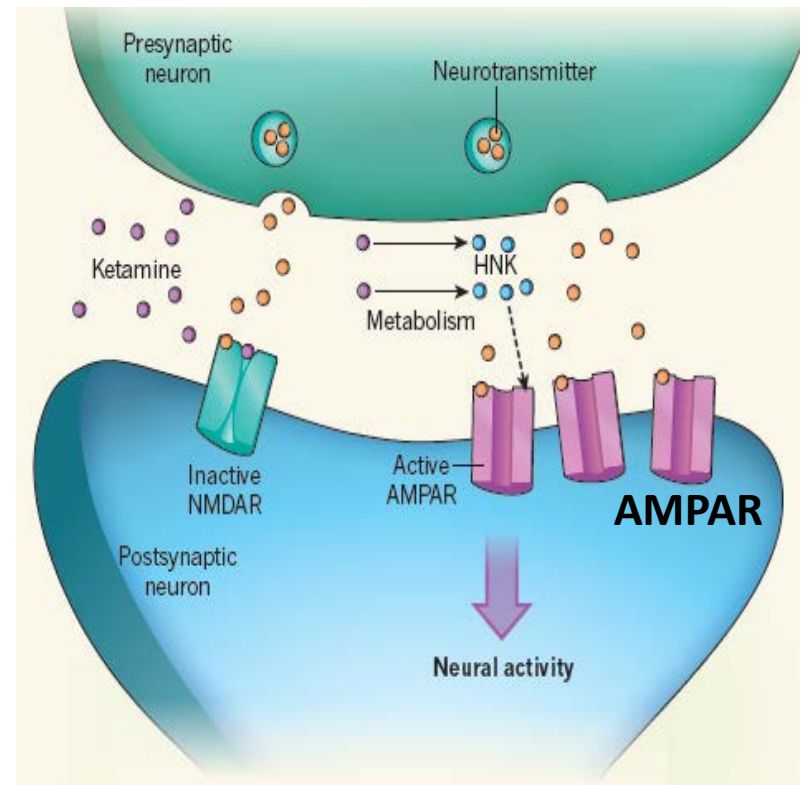


**Ketamine and Ketamine Metabolites as Novel Estrogen Receptor  
Ligands: Induction of CYP2A6, CYP2B6 and AMPA Receptor Subunits—  
genomic links to sex-differences in ketamine response**

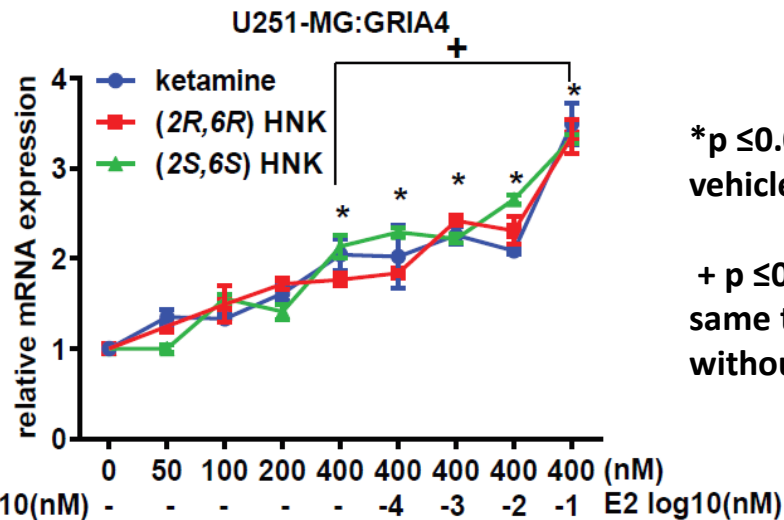
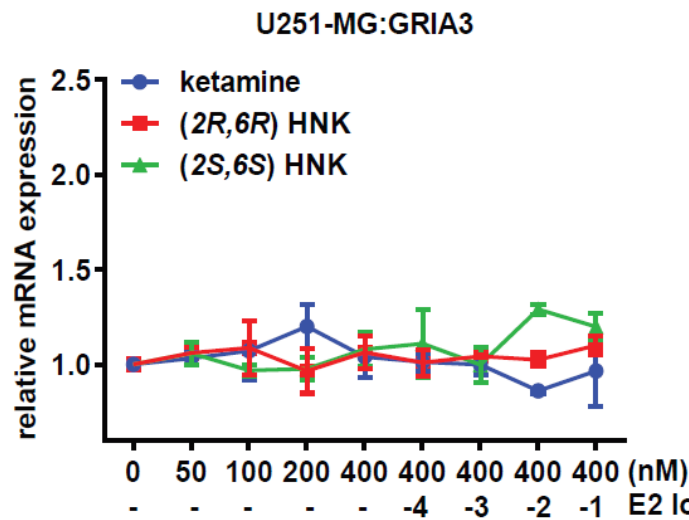
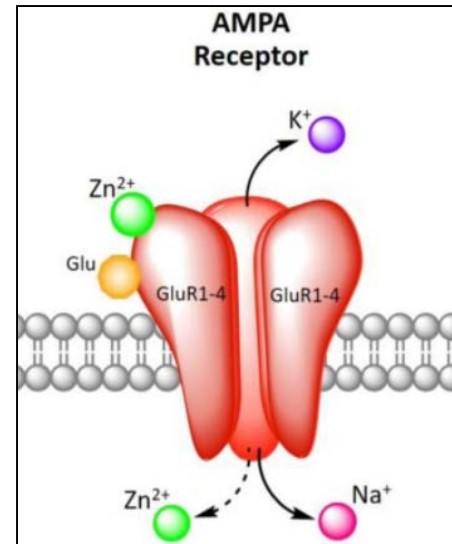
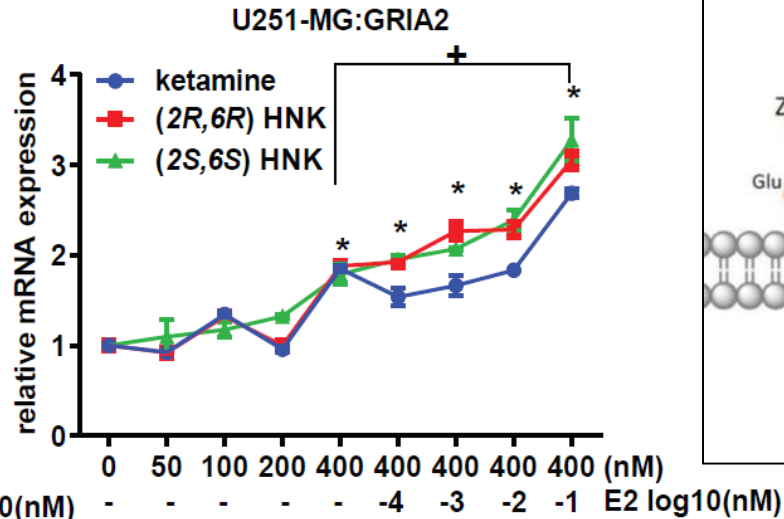
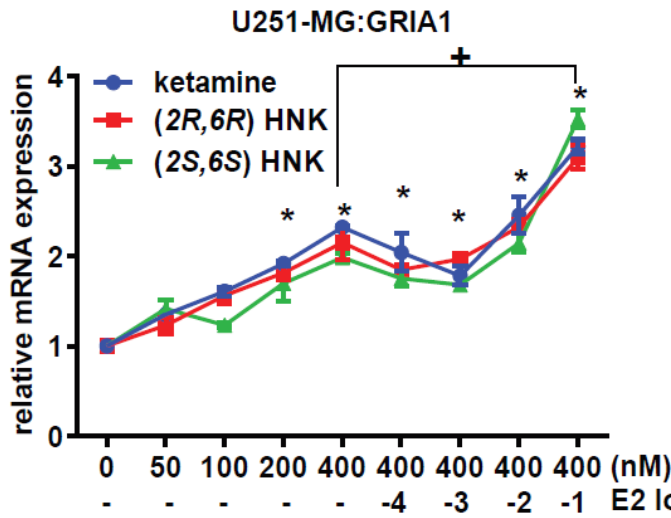
**Ming-Fen Ho Ph.D**

# Ketamine and Depression

- Treatment Resistant Depression.
- ketamine crosses the blood-brain barrier.
- Non-selective NMDA receptor antagonist
- Rapid onset antidepressant effects.
- 2/3 patients are women.
- Sex differences in ketamine treatment response. (Franceschelli et al, Neuroscience 2015; Carrier et al, Neuropharmacology 2013; Sarkar et al, Biological Psychiatry 2016)
- Metabolized by CYP2A6 and CYP2B6.
- Ketamine metabolites (2S,6S;2R,6R)-hydroxynorketamine and AMPA receptors. (Zanos, Nature. 2016)



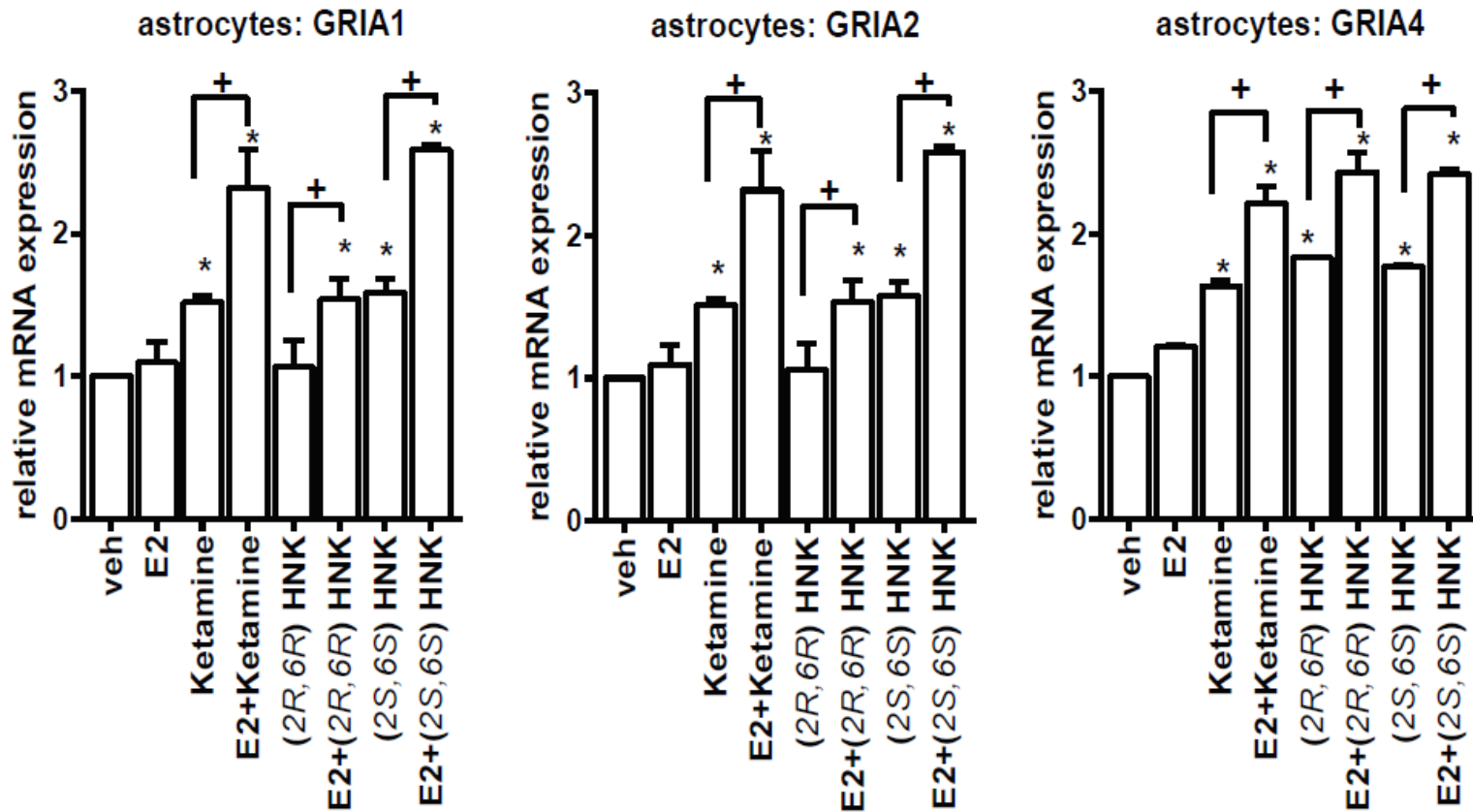
# Estradiol and ketamine act additively to induce AMPA receptor mRNA expression



\*p ≤ 0.05, as compared to vehicle treatment.

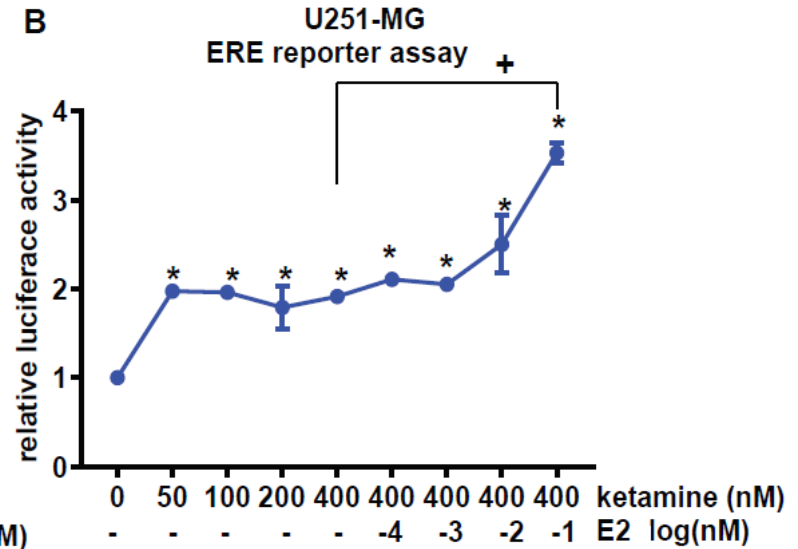
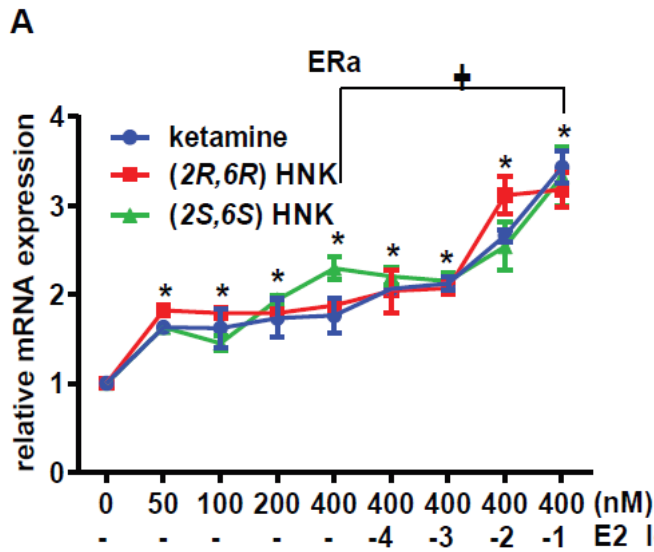
+ p ≤ 0.05 as compared to the same treatment with or without E2

# Human primary astrocytes



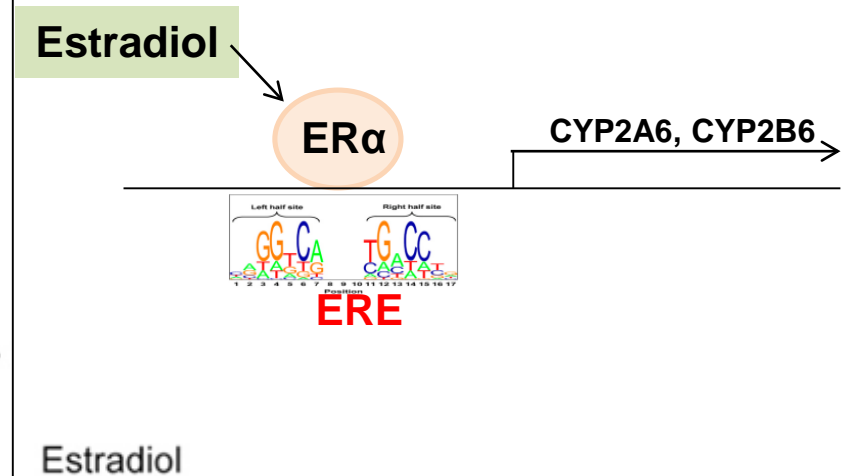
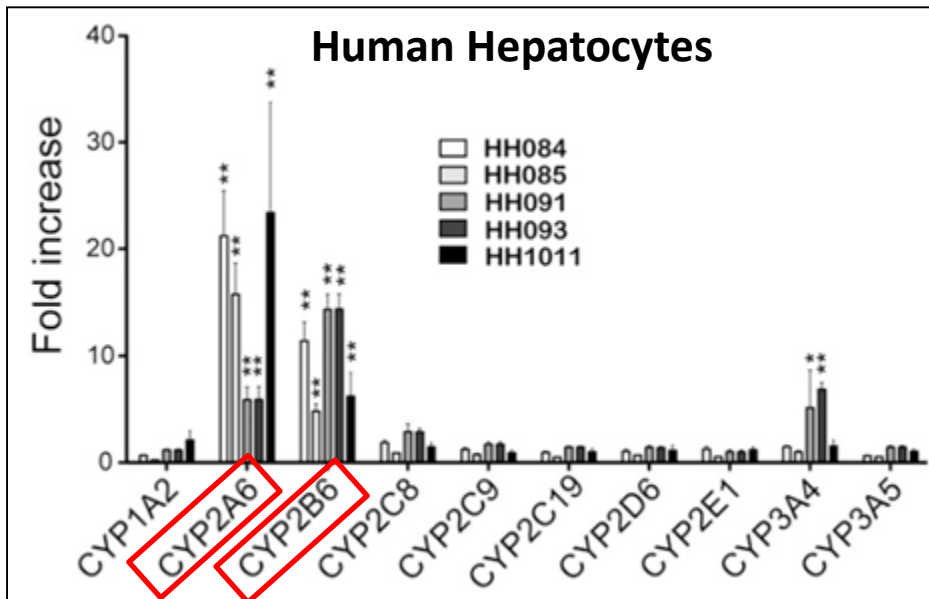
\*p ≤ 0.05, as compared to vehicle treatment.

+ p ≤ 0.05 as compared to the same treatment with or without E2

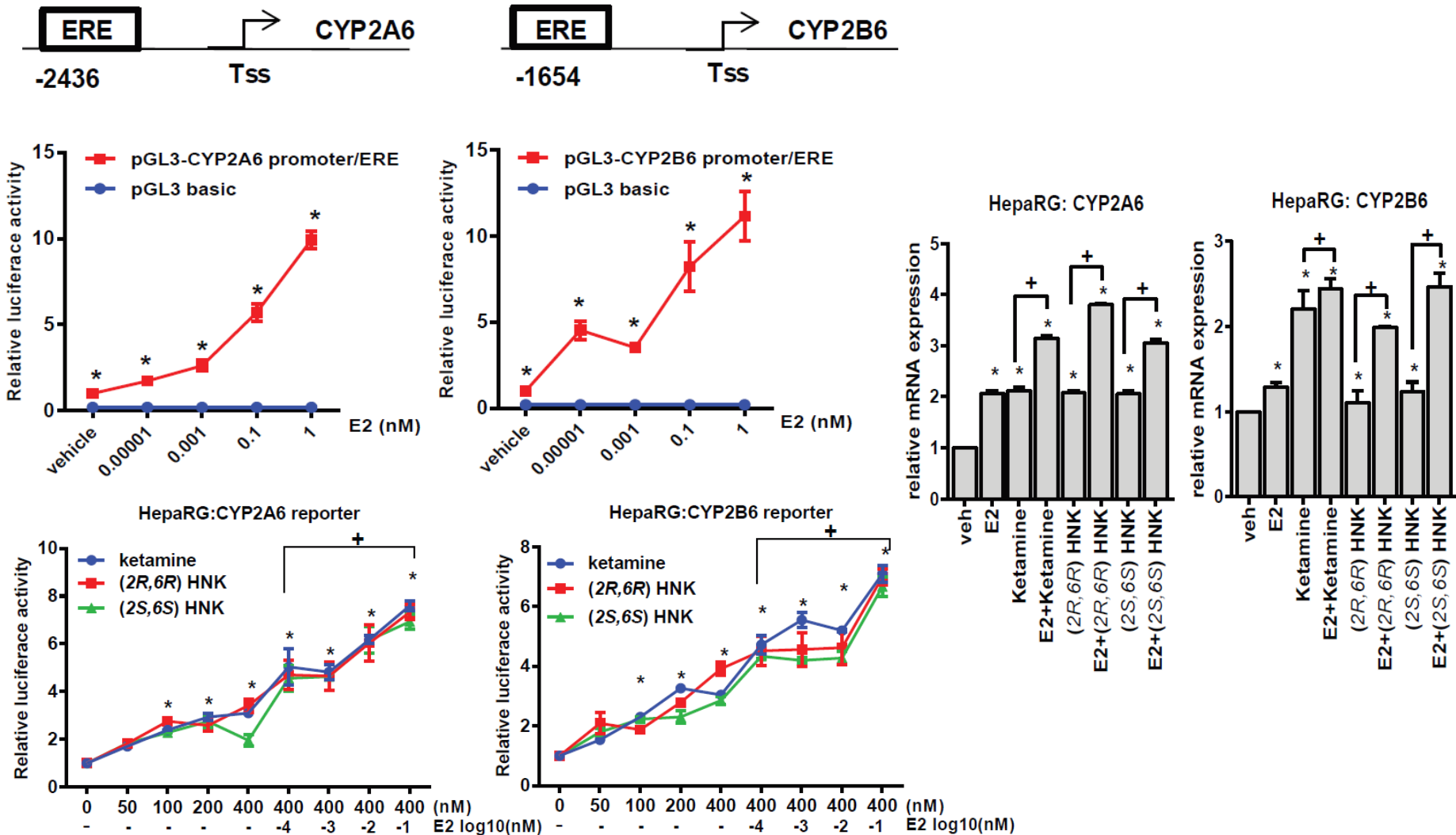


\*p ≤ 0.05, as compared to vehicle treatment.

+ p ≤ 0.05 as compared to the same treatment with or without E2



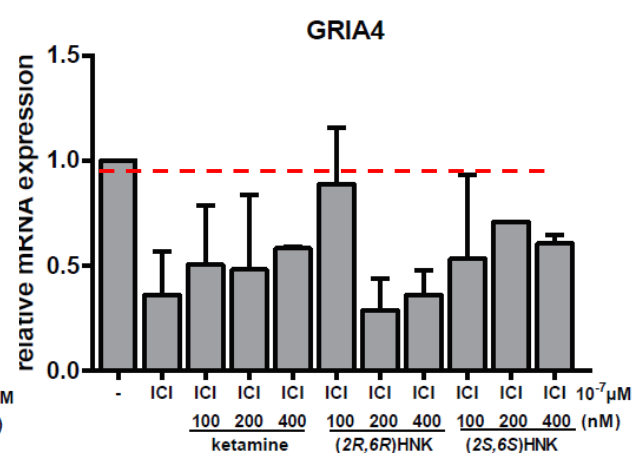
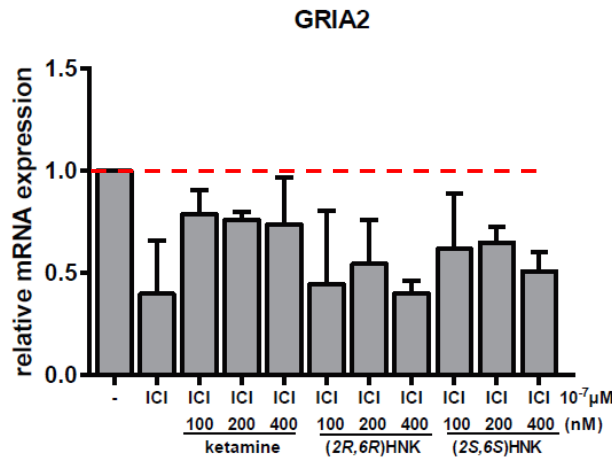
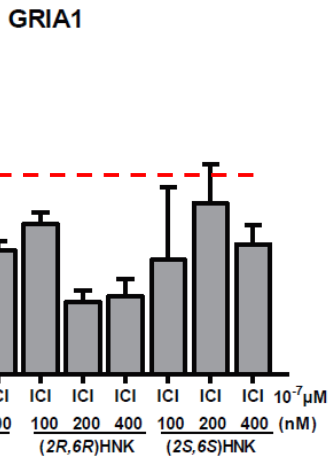
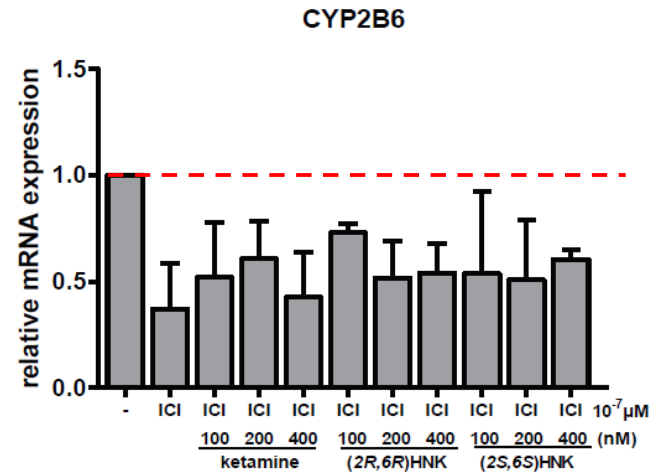
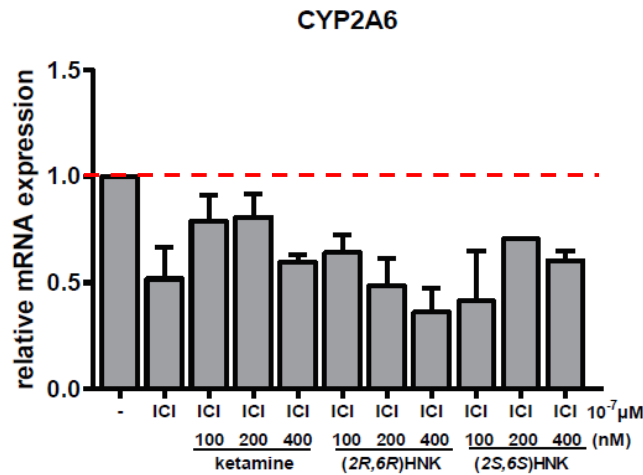
# CYP2A6 and CYP2B6 induction by ketamine and its metabolites



\*p ≤ 0.05, as compared to vehicle treatment.

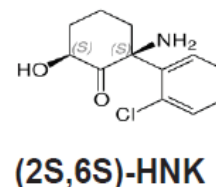
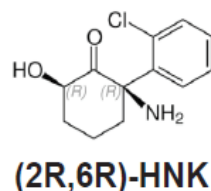
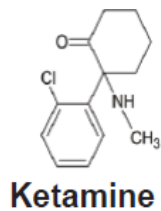
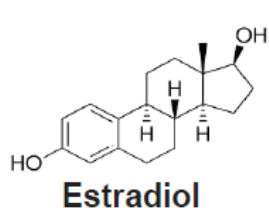
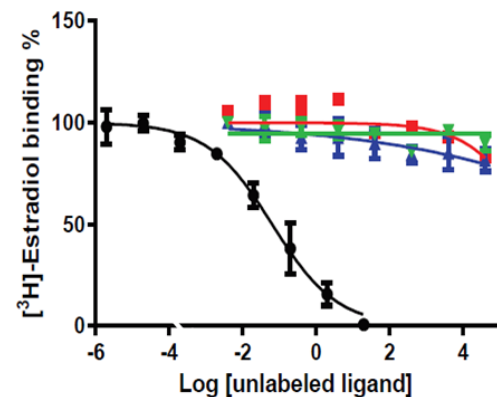
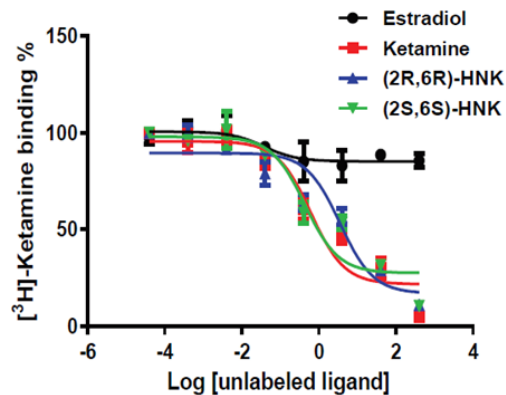
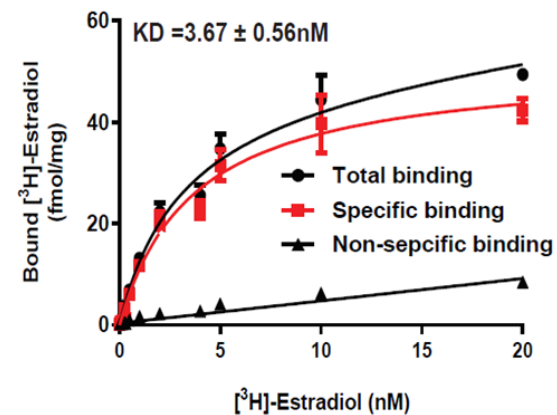
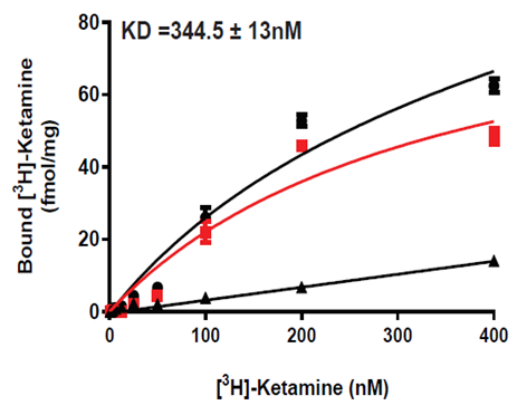
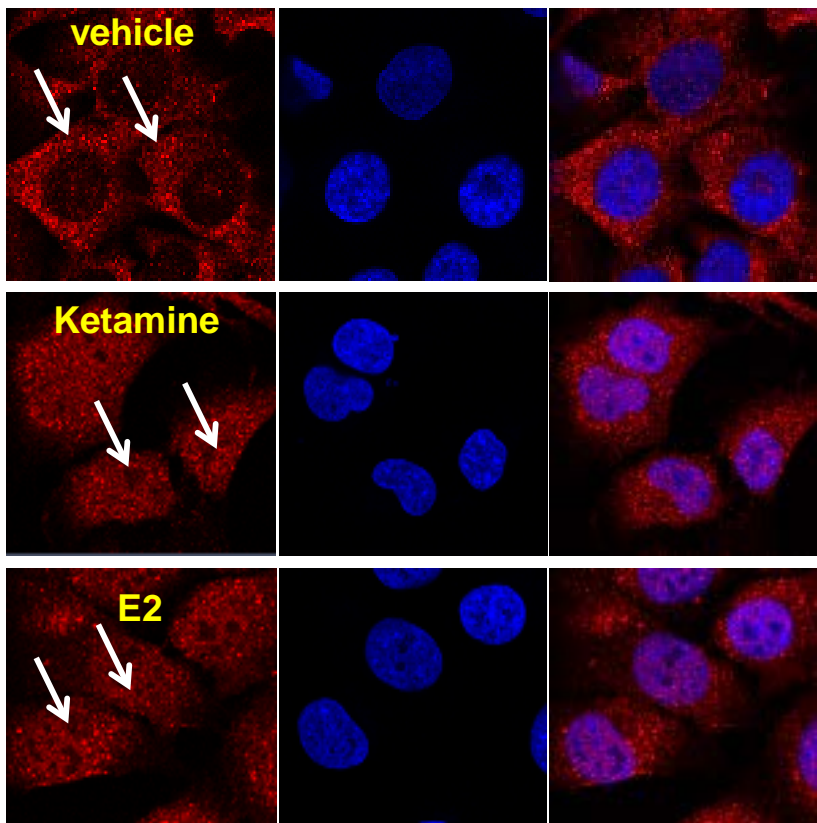
+ p ≤ 0.05 as compared to the same treatment with or without E2

# Induction of CYP2A6, CYP2B6 and AMPARs by ketamine is lost after ER blockade



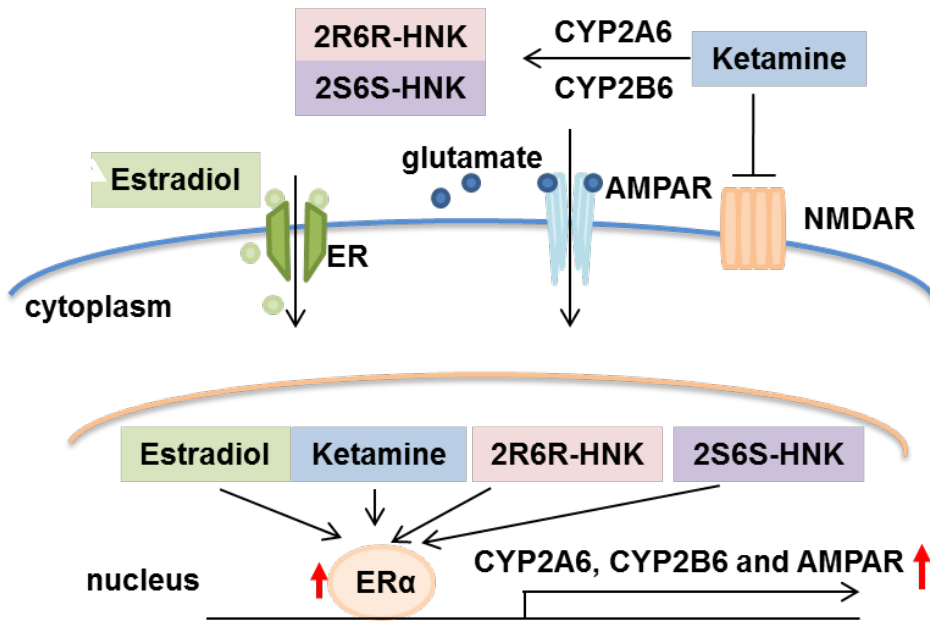
# Ketamine, (2R,6R)-HNK and (2S,6S)-HNK as novel ER $\alpha$ ligands

ER $\alpha$       DAPI      overlay





# Conclusions



- ❑ Ketamine and its (2*R*,6*R*)-HNK and (2*S*,6*S*)-HNK metabolites as novel ligands for ERα.
- ❑ Estradiol (E2) induced CYP2A6, CYP2B6 and AMPARs.
- ❑ E2 and ketamine act additively to induce mRNA expression of CYP2A6, CYP2B6 and AMPARs.
- ❑ Induction of CYP2A6, CYP2B6 and AMPARs was lost when ERα was knocked down or silenced pharmacologically.

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