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

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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

astocytes: GRIA1

astocytes: GRIA2

astocytes: GRIA4

*p ≤0.05, as compared to vehicle treatment.
+p ≤0.05 as compared to the same treatment with or without E2
Estradiol
ERα
CYP2A6, CYP2B6

* 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 (2R,6R)-HNK as novel ERα ligands

**ERα**  |  **DAPI**  |  **overlay**
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Vehicle | [Image] | [Image]
Ketamine | [Image] | [Image]
E2 | [Image] | [Image]

**Graphs:**
- Binding curves for **[3H]-Ketamine** and **[3H]- Estradiol** with KD values.
- Log [unlabeled ligand] vs **[3H]-Ketamine** and **[3H]-Estradiol** binding.

**Chemical structures:**
- Estradiol
- Ketamine
- (2R,6R)-HNK
- (2S,6S)-HNK
Conclusions

- Ketamine and its (2R,6R)-HNK and (2S,6S)-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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