The Role of G-Protein Coupled Estrogen Receptor (GPER) in Early Neurite Development

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Acknowledgement

• Dr. Xu
• Lab Members
  • Brittany Mersman
  • Nicki Patel
  • Pallavi Mhaskar
  • Jason Cocjin

• Committee Members
  • Dr. Christopher Arnatt, Dr. Judith Ogilvie, Dr. Susan Spencer, Dr. Yuqi Wang
Outline

• Introduction
• Methods
• Results
• Future Direction
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Introduction

• G-Protein-Coupled Receptors (GPCR)
  • Membrane receptors
  • Most diverse receptor type in eukaryotes
  • Signals through secondary messenger
  • Drug targets

Estrogen

• Primary female sex hormone

• Heim (1966) showed estrogen increases maturation rate of developing brain

• Estrogen studies on neuron development have been ongoing for decades without controlling for GPER
  • PPT may activate GPER, not as selective for ER<sub>α</sub> as once thought (Srivastava, 2013)

• ER<sub>α</sub> and ER<sub>β</sub> may not play as many roles in estrogen signaling as previously believed
What is GPER

• G-Protein Coupled Estrogen Receptor (GPR30/GPER)
  • Officially named Estrogen receptor in 2007 (Srivastava, 2013)
  • Strongest response to E2 (17β-estradiol)
GPER

- Research has focused on classical estrogen receptors $\text{ER}_\alpha$ and $\text{ER}_\beta$.

- Differs from traditional Estrogen Receptors
  - GPER is largely located in non-nuclear membranes
  - GPER mediates fast, non-genomic action
Previous research about GPER functions in the nervous system

- Evidence of role in neuronal ion channel modulations:
  - Intracellular Ca++ Mobilization from ER (Tran, 2015; Romano, 2008)
  - Regulation of K+ channels (Broselid, 2014)

- Neuroprotective effects in PC-12 cells (Alyea, 2008)

- Increased post stroke recovery in sex specific manner (Gibson, 2016)

- Research almost solely in mature neurons
Previous research: development

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Hypothesis

• Activation of GPER increases neurite outgrowth in early development
Methods: culture

Culture rat embryonic day 18 neurons in estrogen free medium

Each treatment imaged at 8 hours, 20 hours, 48 hours, 72 hours, and 96 hours
Methods: quantifying neurite growth
Methods: quantifying neurite growth
Methods: quantifying neurite growth

Initial Image

Trace Growth

Adjust Image

Introduction

Methods

Results

Future Directions
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Results: cortical neurons
Results: cortical neurons

Neurite outgrowth after 8 & 20 hours

***, p < 0.01 vs. Control

**, p < 0.01 vs Vehicle
Results: cortical neurons

**Neurite outgrowth after 8 – 96 hours**

* *, p < 0.05 vs Control
** **, p < 0.01 vs Control
#, p < 0.05 vs Vehicle
## ##, p < 0.01 vs vehicle
Results

• Hypothesis
  • Activation of GPER increases neurite outgrowth in early development

• In cortical neurons- ❌ ?
  • Activation of GPER has no effect on neurite outgrowth, but blocking the receptor inhibited neurite outgrowth.
Results

• In cortical neurons - ?
  • Activation of GPER has no effect on neurite outgrowth, but blocking the receptor inhibited neurite outgrowth.

• High levels of endogenous E2 in early development may saturate GPER in cortex

• Cell specific co-localization may need activation of partner
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Future directions

• Sub-cellular localization at different developmental times in cortex and hippocampus

• Co-localization of GPER with other growth promoting proteins

• Test other agonists of GPER and other estrogen receptors

• Ca++ mobilization in cortical neuron development

• Investigate second messenger pathways
Literature cited


• LOUISE M. HEIM; Effect of Estradiol on Brain Maturation: Dose and Time Response Relationships, Endocrinology, Volume 78, Issue 6, 1 June 1966, Pages 1130–1134, https://doi.org/10.1210/endo-78-6-1130


Questions?