Sex differences in hippocampal brain-derived steroid contents following hypoxic ischemic encephalopathy

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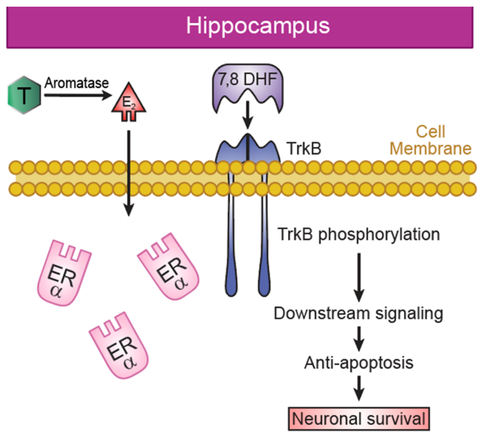
BACKGROUND

Neonatal hypoxia ischemia (HI) related encephalopathy is one of the major causes of developmental disabilities in children. Estrogen receptor alpha (ERα) following HI, gets upregulated in the female hippocampus and confers sex-specific neuroprotection via neurotrophin receptor, tyrosine kinase B (TrkB)[1,2]. This ERα mediated neuroprotection maybe mediated by ligand-dependent way through brain-derived estradiol (E_2) binding to ERα[3]. We hypothesize that E_2 increases post-HI after aromatization of testosterone and acts as a ligand to ERα leading to sex-specific neuroprotection following HI.

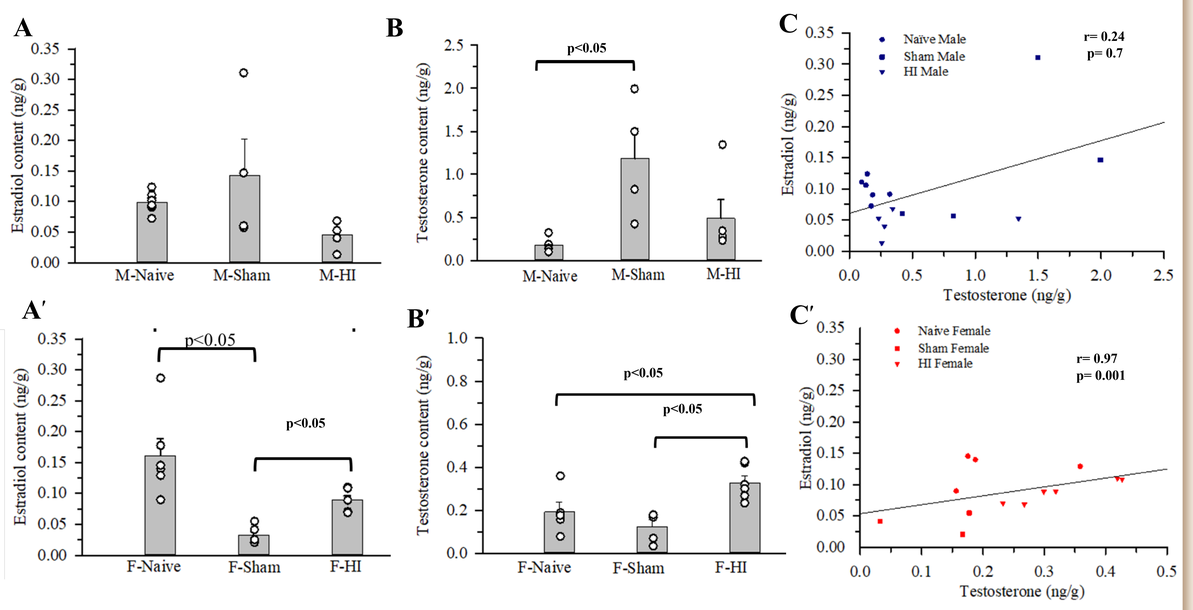
METHODS

HI was induced in P9 C57BL/6J mice by left common carotid artery ligation and exposure of the mice to 10% O_2 using Vannucci's HI model[4]. E_2 and T contents were measured after two IL hippocampi were pooled, homogenized, and analyzed via LC-MS/MS[5,6]. ANOVA was used to compare IL hippocampal E_2 and T contents of sham and HI mice. The lower limit of quantification for E_2 and T were 0.6 pg and 3 pg on column, respectively. The coefficient of variation was determined by analysis of a pool of mouse hippocampi.



- HI induces an increase in testosterone and estradiol contents only in female hippocampi
- Higher estradiol in female hippocampi may be due to aromatization of hippocampal testosterone
- No changes in testosterone and estradiol contents were detected in male hippocampi
- Isoflurane anesthesia maybe altering hormone contents in developing hippocampi

RESULTS



CONCLUSIONS

This data suggests that there is an increase of E_2 and T contents in female hippocampi compared to males post-HI. Increased E_2 in female hippocampi may be due to local aromatization of hippocampal T. Recent studies link the use of aromatase inhibitors (such as letrozole) with a decrease in memory and cognitive impairment. Therefore, we will assess the effects of aromatase inhibition in hippocampal estradiol content post-HI and then investigate its effects on long term memory in mice.

ADDITIONAL KEY INFORMATION

Figure 1. Hippocampal steroid contents 3 days post-HI: (A) Male E_2 contents were not significantly different between sham (0.14± 0.06 ng/g), and HI (0.045± 0.01) **(B)** Male T contents were not significantly different between sham (1.18± 0.35 ng/g), and HI (0.49±0.21). **(C)** No correlation was detected between male E2 and T contents(r= 0.24, p=0.7).**(A′)** Female hippocampal E_2 content was significantly increased in HI (0.09±0.01, n:6) compared to sham (0.03 ± 0.01, n:5) (p<0.001) mice **(B′)** Female hippocampal T content was significantly higher following HI (0.33 ± 032, n:6) compared to sham mice (0.12±0.03, n:5) (p<0.05). **(C′)** Female E_2 contents had a strong positive correlation with the T content (r=0.97, p=0.001)

References

1. Cikla U. et al., eNeuro, 2016. **2.** Cengiz P, et al. Antioxid Redox Signal, 2011. **3.** Vannucci RC, et al. Ann N Y Acad Sci, 1997 **4.** Bertin, J. et al., Steroids, 2015.

Acknowledgements:

Dept of Peds Research and Development Grant, NIH NINDS K08 NS088563, NIH NINDS R01 NS111021, NIH Waisman Core Grant U54HD090256.