Tilting the axis: Devising a conceptual model for early life steroid deprivation and HPA axis programming in rodents

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Introduction

Objective

- To conceptualize a working model that will be employed to evaluate the effects of early life alterations in steroid exposure in select brain areas on development of the hypothalamic-pituitary-adrenal (HPA) response to stress in a sex-dependent manner.
- Brain areas of interest: Hypothalamus-preoptic area (HPOA), amygdala (AMYG), hippocampus (HPC), and frontal cortex (FC).

Methodology

- Several search engines and databases were consulted:
  - PubMed
  - SCOPUS
  - ScienceDirect
  - Scirus

Background

- In rodents, brain sensitivity to steroids is highest during a critical period of central nervous system (CNS) development, which extends from the 18th day of gestation to the 11th postnatal day (PND 11).14

Estradiol

- The initial mode of testosterone (T) action may involve its conversion to estradiol in discrete brain regions.5
- Estradiol receptors in the neonatal rat brain may mediate developmental effects of estrogen, as well as those of T.14

Aromatase activity (AA)

- In both the adult and perinatal rat brain, the aromatase enzyme is phylogenetically conserved in its ability to catalyze the conversion of androgens (testosterone) to estrogens.6,11,13

Best method to inhibit AA involves MS

- Maternal separation (MS) involves deprivation of feeding and warmth (physiological component) + maternal attention (psychological component).1,5
- It has been suggested that MS results in a compromised ability to cope with stressors.8,9
- MS during early postnatal development leads to an enduring dysregulation of HPA axis reactivity to stress.2,3,10

Impact of MS manipulation on AA

- Repeated separations may lead to permanent changes in brain development, as evidenced by behavioral, neurochemical and immunological abnormalities.10

Importance of estradiol and AA

- Brain aromatase hypothesis: The conversion of androgens to estrogens in or around target cells may account for specific neuroendocrine functions, such as brain differentiation.6
- More specifically, this process is important in the differentiation of neural structures in the HPOA and AMYG.14 There is a greater distribution of AA in the hypothalamic and limbic nuclei,11,12
- Androgen-derived estrogens play a physiological role in the organizational actions of T on developing neurocircuity and are necessary in adult male rats for the activation of sexual behavior.1

Methodology

Critical parameters of MS paradigm

1. Frequency: MS on consecutive days (DMS)
   - Repeated MS based on a daily + predictable procedure.10
2. Duration: 3 h
   - A minimum of 2 hours (h) is needed to induce an immediate effect on HPA responsiveness.10
3. Age at separation: PND 1-5
   - Based on findings in early handling (EH) studies, the earlier the manipulation is carried out, the stronger the effects will be.10

Additional parameters

- Litter size: Approximately 10 pups per dam (10 dams in total)
- Litter sex composition: Equal ratios of males to females

Results

Study limitations

I) Statistical power of total sample size.
II) Variability of patterns in maternal response10:
   - Frequency + duration of nursing
   - Licking
   - Nest-building
   - Other activities: Eating, drinking, sniffing, grooming, and undirected locomotor activity.

Advanced search techniques

1. Craft a clear and concise description of the topic of interest.
2. Employ a wide range of relevant search techniques.
   - Appropriate use of synonyms.
   - Employ a wide range of appropriate search techniques.
   - Alternative search operations.
3. Record references in an accurate and consistent manner.
4. Keep a record of each search.
5. Identify gaps in the literature.

Future directions

- Funding has recently been approved for conducting the aromatase assay.
- Following ethics approval, this conceptual model will be carried out in our laboratory setting.

Acknowledgements

The author would like to thank Dr. Konkle and the internal UROP selection committee.

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