Sex Differences in Response to Dihydrotestosterone and Flutamide in Astrocyte Cell Death

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Introduction

- Male sex is an acknowledged risk factor for stroke. Testosterone (T) can be converted to 17 β-estradiol via the aromatase, or metabolized to dihydrotestosterone (DHT) via the enzyme 5α-reductase, a step that then does not permit aromatization to estradiol.
- We previously demonstrated that astrocytic cell death induced by oxygen-glucose deprivation (OGD) is sex-specific (1, 2). However, it is not clear if sex differences in response to T and DHT in astrocyte cell death contributes to the observed sex difference in response to ischemia.
- In the current study, we tested the hypothesis that male (XY) and female (XX) astrocytes are respond differently to T and DHT.

Methods

- Primary sex-specific cultured cortical astrocytes were prepared from 1-3-day old male and female rat pups separately and grown to confluency in steroid-free medium (1, 2).
- Confluent monolayers (10-14 days in vitro) were incubated in anoxia chamber in glucose-, serum-free medium for 6 hours OGD, and then returned to normoxia and glucose-containing medium for 24 hours.
- Cell death was induced by OGD alone, or in combination with T, DHT, or Flutamide (androgen receptor antagonist). These reagents were added 24 hours before OGD, and maintained during OGD and re-oxygenation.
- Cell death was measured at 24 hours after insult by lactate dehydrogenase (LDH) assay.
- Androgen Receptor, 5α reductase 1 and 5α reductase 2 mRNA expression was measured by real time quantitative PCR (qPCR).

Results

Dose Response of Testosterone on Male Astrocyte Cell Death

5α reductase 1 mRNA Expression in Male vs. Female Astrocytes

Higher Androgen Receptor mRNA in Male vs. Female Astrocytes

Conclusion

- Female astrocytes are less sensitive to OGD alone, or in combination with T or DHT than male astrocyte. Androgen receptor antagonist, Flutamide, protect against T or DHT combined with OGD-induced cell death in male astrocytes but not in female astrocytes.
- 5α reductase 1 mRNA expression was not different between male and female astrocytes.
- 5α reductase 2 mRNA level was very low or undetectable both in male and female astrocytes.
- However, androgen receptor mRNA expression was sex difference in male vs. female astrocytes.
- We conclude that there are sex differences in ischemic sensitivity in female and male astrocytes, and male astrocytes (but not female) metabolize testosterone to DHT via the enzyme 5α reductase, resulting in androgen receptor activation and enhanced cell death after OGD.

References