Effect of CYP17A1 inhibitors orteronel & galeterone on adrenal androgen biosynthesis.

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Introduction

The CYP17A1 enzyme, localized in the endoplasmic reticulum, can catalyze both 17α-hydroxylase and 17,20-lyase reactions. In human adrenal glands CYP17A1 enzyme is found in both the ZF and ZR of the cortex and it also has a role in synthesis of cortisol and DHEA. The 17,20-lyase activity of CYP17A1 is key for androgen regulation. Understanding the mechanisms regulating 17,20-lyase activity is important for the understanding of hyperandrogenic disorders such as premature, exaggerated androgenese and the polycystic ovary syndrome, and also for the design of selective 17,20-lyase inhibitors for use in hyperandrogenic states and in sex-steroid dependent cancers. The orteronel and galeterone are known to inhibit 17,20-lyase activity however the detail mechanism of the CYP17A1 inhibition remains unknown. These inhibitors have been developed to treat the castration resistant prostate cancer (CRPC) but little is known about its effect on adrenal androgen biosynthesis. The objective of this project is to study the effect of these inhibitors on CYP17A1 enzyme in adrenal androgen biosynthesis.

Methods

We used the NCI-H295R adrenocarcinoma cell model to study the effect of orteronel and galeterone. We treated H295R cells from 0.2 μM orteronel and galeterone for 24 hours. Steroid production was labeled with [3H] pregnenolone for 90 min. Steroids were extracted and resolved by thin layer chromatography. For specific analysis of the CYP17A1 activities, cells were treated with 1 μM triolostane (a specific blocker of HSD3B) for 90 min before adding labeled with [3H] pregnenolone. To study the effect of these inhibitors on steroidogenic gene expression we performed the relative quantification PCR (qRT-PCR).

Results

1. Role of CYP17A1 in steroidogenesis

![Diagram showing steroidogenesis pathways.](image)

2. CYP17A1 inhibitors

![Diagram showing the effects of CYP17A1 inhibitors.](image)

3. Effect of inhibitors on adrenal steroid profile

![Diagram showing steroid profiles.](image)

4. Effect of inhibitors on CYP17A1 enzyme activity

![Diagram showing enzyme activities.](image)

5. Impact on androgen biosynthesis genes

![Diagram showing gene expression.](image)

6. Effect on CYP19A1 enzyme activity

![Diagram showing enzyme activities.](image)

Conclusions

• Based on our results we can conclude that orteronel is a more potent inhibitor of 17,20-lyase activity than galeterone in H295R cells.

• Additionally, we found slight change in HSD3B2 gene expression especially due to treatment of galeterone but in presence of orteronel no significant change was observed suggesting that it does not affect steroidogenic gene expression.

• We also showed that CYP17A1 inhibitors has no effect on aromatase (CYP19A1) enzyme activity.

• Discovery of these drug actions on specific CYP17A1 17,20-lyase activity would be of great clinical value for understanding adrenal androgen regulation.

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