Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

Androgen Increases the Accumulation of Advanced Glycation End Products in Granulosa Cells by Activating ER Stress in PCOS.

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Polycystic ovarian syndrome (PCOS) is associated with hyperandrogenism. Previously we found that androgen activated endoplasmic reticulum (ER) stress in granulosa cells of antral follicles in PCOS, contributing to ovarian fibrosis (1) and growth arrest of antral follicles (2). In addition, recent studies demonstrated the accumulation of advanced glycation end products (AGEs) in granulosa cells from PCOS patients, which contribute to its pathology. Based on these findings, we hypothesized that androgen upregulates the expression of the receptor for AGEs (RAGE) in granulosa cells of antral follicles by activating ER stress. This in turn, increases the accumulation of AGEs in these cells. In the present study, we found that testosterone induced the expression of RAGE and accumulation of AGE in cultured human granulosa-lutein cells (GLCs). These effects were inhibited with the treatment of tauroursodeoxycholic acid (TUDCA), a clinically available ER stress inhibitor agent. Knockdown of the transcription factor C/EBP homologous protein (CHOP), an unfolded protein response (UPR) factor activated by ER stress, inhibited the testosterone-induced RAGE expression and AGE accumulation. Pretreatment with flutamide, as well as knockdown of androgen receptor decreased the testosterone-induced RAGE expression. Expression of RAGE was increased in GLCs obtained from patients with PCOS. Concomitantly, the expression of RAGE and the accumulation of AGE was increased in granulosa cells of antral follicles from PCOS patients and dehydroepiandrosterone (DHEA)-induced PCOS mice. Administration of the RAGE inhibitor, FPS-ZM1 or TUDCA to PCOS mice, reduced the expression of RAGE and the accumulation of AGE in granulosa cells of antral follicles, accompanied by a reduction of atretic follicles and improvement in the estrous cycle. In summary, our findings indicate that hyperandrogenism in PCOS increases the expression of RAGE and accumulation of AGEs in the ovary by activating ER stress. The potential therapeutic benefit of targeting the AGE-RAGE system, either with a RAGE inhibitor or an ER stress inhibitor agents, may serve as a novel approach for the treatment of PCOS. (1) Takahashi et al. Sci Rep. 2017;7(1):10824. (2) Azhary et al. Endocrinol. 2019;160(1):119–132

Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS II

Uncontrolled Central Precocious Puberty Patient Against GnRH Agonist, After Showing Granuloma Formation and Sterile Abscess to Both Leuprorelin Acetate and Triptorelin Actate

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For more than 30 years, Gonadotropin-releasing hormone (GnRH) agonist has been the treatment of choice for central precocious puberty (CPP) to expect regression of secondary sexual characteristics, delayed menarche, and maximization of linear growth. There are several kinds of GnRH agonists such as leuprorelin, triptorelin, goserelin and histrelin, etc. In Korea, leuprolide acetate and triptorelin acetate are most common used drugs, and a monthly depot preparation is typically used for suppression of the HPG axis. Local complications related to GnRH agonists, including erythematous macules, granulomas, subcutaneous nodules, and sterile abscesses, occur in 10~15% of patients, and sterile abscesses have been known to occur in less than 2~3% of patients. In present case, we would like to introduce a case of CPP patient who was treated with GnRH agonist, but not suppressed and experienced recurrent vaginal bleeding, after showing granuloma formation and sterile abscess to both leuprorelin acetate and triptoreline actate. A 8.9 year-old girl visited our clinic with breast development and vaginal bleeding. On physical examination, she had enlarged breasts (Tanner stage 4) with pigmentation of the areola. Her height and weight was measured as 144.4cm (98th percentile) and 44.2kg (98th percentile) respectively. Her bone age was advanced as 12~12.6 years of age by TW3 method. Therefore, Leuprolide acetate (Lorelin depot®, Dongkook pharm) 3.75mg was administered to the patient every 4 weeks, and until the 6th injection, she exhibited no other complications. However, after 7th injection, the patient presented with granuloma and subcutaneous nodule at the left injection site and elevated hormone levels. Although that we switched to triptorelin acetate from 8th injection, the patient also showed a sterile abscess at the injection site. We switched from triptorelin acetate to leuprolide acetate again, however, after 2 months of the switch, the patient showed abrupt vaginal bleeding and elevated hormone levels. Therefore, after assumption of unsuppression of HPG axis, leuprolide acetate 3.75mg was administered every 2 weeks for 2 months. However, her vaginal bleeding occurred monthly and hormonal level was still unsuppressed, and also, the granuloma appeared again at the injection site. So, we discussed with her parents about her uncontrolled symptoms, and we discontinued the treatment. There are many theories about the cause of local complications of GnRH agonist, but the mechanism has still not been revealed. Further studies are required to identify the mechanism and the relationship between treatment effect and local complications, which could induce uncontrolled CPP.

Pediatric Endocrinology

PEDIATRIC GROWTH AND ADRENAL DISORDERS

The Booster Effect of Aromatase Inhibitor to Overcome Waning Effect of Recombinant Human Growth Hormone

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