Endocrinology-2013

OMICS Group Conferences
Accelerating Scientific Discovery

World Congress on
Endocrinology

August 26-28, 2013 Raleigh, North Carolina, USA

Molecular basis of estrogen enhancement of FSH responsiveness in granulosa cells

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Abstract

Estrogens represent the major class of female sex steroids secreted by the ovary during the follicular phase. Ovarian estrogens exert numerous systemic and local effects that are well established as being crucial for mammalian female reproduction. A particular action of estrogen, which is important to the establishment of dominant follicles, is the enhancement of FSH-induced aromatase activity. This feed-forward attribute of estrogen activity may account for the exponential rise of circulating estradiol which occurs in spite of declining FSH levels during the late follicular phase of the cycle. We have previously reported that the oocyte is obligatory for estrogen to exert its positive effects on FSH activity in rat granulosa cells. Here we have investigated the underlying mechanism. In the presence, but not absent, of oocytes, estrogens enhanced FSH-induced increases in aromatase mRNA expression as well as cAMP production. However, as forskolin did not mimic FSH action this indicated that estrogen/oocytes increase FSH action at a site upstream of adenylate cyclase in granulosa cells. We therefore sought whether the G protein-coupled receptor kinases (GRKs) and ß-arrestins system is involved in the mechanism. We found that estrogens with oocytes suppressed FSH-induced GRK-6 mRNA expression. Moreover, transfecting granulosa cells with GRK6-siRNA significantly increased FSH-induction of aromatase mRNA, suggesting that endogenous GRK-6 plays an inhibitory role in FSH-induced aromatase mRNA expression. These findings strongly suggest that GRK-6 play a critical role in the mechanism by which estrogen and oocytes synergistically augment FSH action in granulosa cells.

Biography

Dr. Shimasaki, Ph.D.is Professor of Reproductive Medicine at University of California San Diego, School of Medicine. He has a long-term interest in the role of growth/differentiation factors in regulating the mammalian reproductive system; specifically the mechanism how they control ovarian follicle development and ovulation. He has more than 170 publications and his research has been continuously funded by NIH grants since 1989.