Proc 3rd Symp Kor Soc Dev Biol, Feb 6, 1998, pp 2-4.

Diverse Functions of Gonadal Hormones.

Byung-Nam Cho*, Yong D. Yoon[a], Kyungjin Kim[b], Kelly E Mayo[c]
*Department of Biology, The Catholic University of Korea, [a]Department of Biology, Hanyang University, [b]Department of Molecular Biology, Seoul National University, Department of Biochemistry, Molecular Biology & Cell Biology, Northwestern University

Introduction

Gonadal hormones including estrogen, progesterone, testosterone, activin, and inhibin as well as the hypothalamic and pituitary hormones play a major role in reproductive physiology. Briefly, estrogen regulates the release of gonadotropin, prolactin and is involved in the growth and development of the uterus and oviduct. Progesterone is associated with the facilitation of implantation and maintenance of pregnancy. Inhibin supresses follicle-stimulating hormone (FSH) synthesis and secretion while activin has stimulatory effects. Despite the antagonistic activities of two hormones, they are composed of three related polypeptide chains (α, βA, and βB). Current studies focus on the influences and pathophysiological roles of gonadal hormones in mammals that are summarized below.

GnRH gene expression by gonadal hormones

The hypothalamic decapeptide, gonadotropin-releasing hormone (GnRH), stimulates pituitary release of LH and FSH. Elucidation of the GnRH gene structure makes it possible to examine the regulation of GnRH gene expression by gonadal hormones despite of a relatively small number of GnRH neurons and their scattered distribution. Treatment with progesterone enhanced the GnRH mRNA level in the hypothalamic tissues derived from ovariectomized, estradiol treated adult rats while progesterone alone revealed inhibitory effect. The stimulatory action of progesterone lasted at least for 9 hours. Treatment with RU486, a progesterone antagonist blocked the stimulatory action of progesterone on the GnRH mRNA level. When the hypophysectomized rats were used to exclude the possible pituitary influence, progesterone also retained its stimulatory effect.

LHβ gene expression by gonadal hormones

The pituitary gonadotropins, LH and FSH play a central role in the mammalian reproductive process including steroidogenesis and gametogenesis. They are glycoprotein hormones consisting of a common α-subunit and a unique β subunit that bestows biological specificity to the hormone. Treatment with progesterone suppressed

the LHβ mRNA level in the pituitary of the same model rats. Estrogen alone decreased LHβ mRNA level, but not below certain level. Progesterone treatment further decreased the estrogen-reduced LHβ mRNA level. The inhibitory action of progesterone on LH β mRNA level was also blocked by RU486 treatment.

Prolactin gene expression by gonadal hormones

The pituitary prolactin is one of the most versatile hormones in terms of biological actions. Various distinct roles of the hormone have been documented ranging from mammary development in mammals to growth in amphibians. Estrogen enhanced the prolactin mRNA level as previously reported while progesterone alone did not reveal any significant effect. However, progesterone combined with estrogen suppressed the estrogen- enhanced prolactin mRNA level at 3, 6, and 9 hours, but not at 36 hours following progesterone administration in our studies. Progesterone can suppress the estrogen-enhanced prolactin mRNA level with the second injection of progesterone at 30 hours. The inhibitory action of progesterone was dose-dependent, and pretreatment with RU486 one hour before progesterone administration partially restored the decreased prolactin mRNA level by progesterone. Experiments are underway to investigate the intervening components of the signaling pathway during LHβ subunit as well as prolactin gene expression by gonadal hormones.

Transgenic mice expressing a gonadal inhibin α subunit gene

Transgenic animal model was used to explore the pathophysiology of the inhibin subunit gene. Several lines of transgenic mice that express a mouse metallothionein I-rat inhibin α subunit fusion transgene have been generated. Mice from two of these lines have revealed the high blood inhibin level and suppressed pituitary FSHβ mRNA and blood FSH levels. Female mice exhibit suppressed fertility, manifested as a reduced litter size, while male mice have reduced testis volume but remain fertility. Interestingly, older female transgenic mice displayed a high incidence of ovarian cyst formation compared to age-matched controls. These very large fluid-filled cysts are of follicular origin, and typically 1-2 such cysts form on each ovary.

Another transgenic animal model was used to investigate the tissue-specific expression of the inhibin α subunit gene. Transgenic mice with a rat α inhibin-β galactosidase fusion gene have been generated and preliminary studies indicated that in a line of mice containing 4 kilobases of the promoter the transgene mRNA is expressed in the ovary. Experiments are underway to define determinants of ovarian and granulosa cell-specific gene expression.

References

Cho BN, Suh YH, Yoon YD, Lee CC, Kim KJ (1993): Progesterone inhibits the estrogen-induced prolactin gene expression in the rat pituitary. Mol Cell Endocrinol 93:47-52.

Cho BN, Seong JY, Cho HS, Kim KJ (1994): Progesterone stimulates GnRH gene expression in the hypothalamus of the ovariectomized, steroid-treated adults rats. Brain Res 652:177-180.

Cho BN, Seong JY, Cho SH, Kang HM, Kim KJ (1994): Progesterone inhibits luteinizing hormone beta subunit (LH β) gene expression in the rat pituitary in a synergic fashion with estrogen. Korean J Zool 37:377-384.

Cho BN, Pei L, Mayo KE (1995): Reproductive deficiencies in transgenic mice that express a rat inhibin alpha subunit fusion gene. The 78th Meeting of the Endocrine Society, Washington, Washington D.C., U.S.A.

Cho BN, Kim KJ (1997): Differential effect of baclofen on hypothalamic GnRH and pituitary LHβ gene expression in steroid- treated rats. Mol Cells 7:605-609.