

This Week's Citation Classic®

Zeleznik A J, Midgley A R & Reichert L E. Granulosa cell maturation in the rat—increased binding of human chorionic gonadotropin following treatment with follicle stimulating hormone in vivo. *Endocrinology* 95:818-25, 1974.
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A primary effect of follicle stimulating hormone on ovarian follicular development is the induction of cell surface receptors for luteinizing hormone on granulosa cells. [The *SCI*® indicates that this paper has been cited in more than 330 publications.]

Heterologous Regulation of Cell Surface Hormone Receptors

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During the ovarian cycle of mammals, many follicles begin to mature, but only a few (one in humans) ultimately will ovulate and release oocytes for fertilization. While studies in the early 1900s documented that the anterior pituitary gland is required for ovarian function, it was not until 1942 that R.O. Greep and coworkers¹ demonstrated that ovarian cyclicity required the synergistic actions of two distinct anterior pituitary hormones—follicle stimulating hormone (FSH) and luteinizing hormone (LH).

The individual roles of FSH and LH in the process of follicular growth and the mechanisms responsible for their synergistic actions remained a mystery during the next 30 years. When I began my doctoral research in the reproductive endocrinology program and the Department of Physiology at the University of Michigan, my thesis adviser, A. Rees Midgley, Jr., suggested that I investigate the biochemical effects of FSH on the developing follicle. Shortly before my arrival, Midgley used his expertise in working with radiolabeled protein hormones to identify receptors for FSH and LH in the ovary. He used an autoradiographical approach with unfixed tissue sections to localize the specific cell types within the ovary that possessed receptors for these hormones. He found that receptors for FSH localized exclusively on the granulosa cells of virtually all follicles while receptors for LH were located primarily on the theca cells, although an occasional follicle contained granulosa cells with LH receptors.

This observation was perplexing because it was known that LH is the principal hormone responsible for ovulation and the transformation of the follicle into a corpus luteum, yet granulosa cells, which are the progenitors of the luteal cells, did not possess LH receptors. Shortly thereafter, the late Cornelia P. Channing demonstrated that LH receptors appear on granulosa cells as the follicle matures.²

Given Greep's observation that FSH is required for LH to induce ovulation, Midgley's observation that only a few follicles possess granulosa cells with LH receptors but all have FSH receptors, and Channing's findings that only mature follicles possess granulosa cells with LH receptors, it didn't take much insight to postulate that FSH might be responsible for the acquisition of LH receptors on granulosa cells.

I set out to repeat Greep's studies using Midgley's autoradiographical technique and purified FSH and LH prepared by Leo E. Reichert, Jr. As expected, granulosa cells from untreated rats did not possess LH receptors while many follicles were evident that contained granulosa cells with LH receptors after the rats were treated with FSH. Subsequent studies using conventional in vitro binding techniques demonstrated that the LH receptor content in granulosa cells is increased more than 50-fold following two days of FSH treatment in vitro. G.F. Erickson and A.J.W. Hsueh later demonstrated that FSH was capable of inducing receptors for LH in vitro in a chemically defined culture medium.³ Recently, it has been shown that FSH increases mRNA levels for the LH receptor in granulosa cells.⁴

The popularity of this manuscript is due not only to the fact that it answered a fundamental question in reproductive biology, but also because it provided a simple system for studying hormone-mediated cellular differentiation. It is now known that FSH induces mRNAs for a variety of proteins, including enzymes involved in steroidogenesis and growth factors.^{5,6} Hopefully this experimental model will continue to provide valuable information on the coordinated regulation of cellular function during hormone-mediated cellular differentiation.

1. Greep R O, VanDyke H B & Chow B F. Gonadotropins of the swine pituitary: various effects of purified thyllakentrin (FSH) and pure metakentrin (ICSH). *Endocrinology* 30:635, 1942. (Cited 305 times since 1945.)
2. Channing C P & Kammerman S. Characteristics of gonadotropin receptors on porcine granulosa cells during follicular maturation. *Endocrinology* 92:531-40, 1973. (Cited 185 times.)
3. Erickson G F, Wang C & Hsueh A J W. The induction of functional LH receptors in granulosa cells cultured in a chemically defined medium. *Nature* 279:336-8, 1979. (Cited 140 times.)
4. LaPolit P A, Oikawa M, Jai X-C, Dargan C & Hsueh A J W. Gonadotropin-induced up-and down-regulation of rat ovarian LH receptor message levels during follicular growth, ovulation and luteinization. *Endocrinology* 126:3277, 1990.
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6. Turner I M, Saunders P T K, Shimaski S & Hillier S G. Regulation of inhibin subunit gene expression by FSH and estradiol in cultured rat granulosa cells. *Endocrinology* 125:2790-2, 1989.

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