Letter to the Editor

To the Editor:

I read the review article by Dr. Elizabeth Stewart entitled "Gonadotropins and the Uterus: Is There a Gonad-Independent Pathway?" with interest.[1] The author concluded that such a pathway involves direct LH and hCG actions in the uterus. However, the conceptual stumbling block that the author faced was how to explain glycoprotein hormone α subunit, FSH, and TSH actions in the uterus, assuming that they also could act through uterine LH and hCG receptors. Because of this dilemma, she speculated that the uterine LH and hCG receptor is either truncated (without specifying the type of truncation) or has an altered extracellular domain or nonhomologous growth factor type kinase receptor.

The recent findings from LH receptor knockout studies are not supportive of these speculations.[2] For example, Zhang et al[3] used the strategy of deleting the transmembrane region to inactivate the LH receptor gene. These animals had the uterine phenotype despite the presence of truncated receptors and elevated LH levels. If the possibility that the uterus contains truncated receptors is correct, then these animals should not have had a uterine phenotype that is related to the loss of uterine LH receptors. Thus these animals should be a good model to test.

Second, the possibility that uterine receptors have an altered extracellular domain that allows them to interact with glycoprotein hormone α subunit, FSH, or TSH is far fetched. Instead, the possibility that the uterus has separate receptors for these hormones or a different mechanism, especially for glycoprotein hormone α subunit, is more realistic.

The author cited two articles for hCG activating TSH receptors and vice versa as a basis to imply that TSH may bind to altered uterine LH and hCG receptors.[4,5] Both those articles report extremely low cross-reactivity. Consequently, activation of heterologous receptors requires high levels of hormones, which are reached for hCG only in normal and molar pregnancies. As a result, hCG can activate thyroid TSH receptors. If TSH were to cross-react with uterine LH and hCG receptors, it must also reach high levels, which is unlikely except in some pathologic conditions.

The third possibility that the uterus contains a nonhomologous growth factor type kinase receptor for LH is a radical speculation without any preliminary evidence. If this type of receptor exists, then uterine phenotype in LH receptor knockout animals should only be due to decreased estradiol and progesterone levels, and their normalization should restore the uterine phenotype, which does not seem to happen (Rao ChV, Mishra S, Zou W, Foltz M, Xu B, Li X, Lei ZM. Targeted disruption of LH receptor gene reveals the importance of uterine LH signaling. J Soc Gynecol Investig 2001; 8 (Suppl), Abstract 7).[6]

In closing, no one knows whether uterine LH receptors are identical to ovarian receptors, and it would be interesting to find this out. In the meantime, it is prudent to assume that they are not identical, but that they are sufficiently similar to mediate biologic actions of LH and hCG in a hormone-specific manner in respective tissues.

Ch. V. Rao, PhD
Department of Obstetrics, Gynecology, and Women's Health
University of Louisville Health Sciences Center
Louisville, KY 40292
PII S1071-5576(02)00160-0

REFERENCES

1. Stewart EA. Gonadotropins and the uterus: Is there a gonad-independent pathway. J Soc Gynecol Investig 2001;8:319–26.
2. Lei ZM, Mishra S, Zou W, et al: Targeted disruption of luteinizing hormone/human chronic gonadotropin receptor gene. Mol Endocrinol 2001;15:184–200.
3. Zhang FP, Poutanen M, Wilbertz J, Huhtaniemi I. Normal prenatal but arrested postnatal sexual development of luteinizing hormone receptor knockout (LuRKO) mice. Mol Endocrinol 2001;15:172–83.
4. Tomer Y, Huber GK, Davies TF. Human chorionic gonadotropin (hCG) interacts directly with recombinant human TSH receptors. J Clin Endocrinol Metab 1992;74:1477–9.
5. Gunji K, Endo T, Ohno M, Minegishi T, Onaya T. Recombinant thyrotropin stimulates cAMP formation in CHO-K1 cells expressing recombinant chorionic gonadotropin receptor. Biochem Biophys Res Commun 1993;197:1530–5.
6. Rao CV, Lei ZM. Consequences of targeted inactivation of LH receptors. Mol Cell Endocrinol 2002. In press.

In Reply:

Dr. Rao and I share a common interest in the mechanisms of action of LH and hCG on human tissue. I am pleased that he feels that the evidence presented is compelling enough to lead to the conclusion that the ovarian and uterine receptors mediating the actions of these hormones are not identical.

While experiments involving knockout animals are of great use in exploring the relevant physiology and its application to human biology, I think care should be exercised in citing a murine model in this instance. As rodents lack a chorionic gonadotropin, I would not expect this model to fully inform this issue.

I, too, would prefer evidence to speculation. My hope in publishing this review was to stimulate others to continue the exploration in this field that is so vital to human reproduction and gynecologic investigation.

Elizabeth A. Stewart, MD
Division of Reproductive Endocrinology
Department of Obstetrics, Gynecology and Reproductive Biology
Brigham and Women's Hospital
Harvard Medical School
Boston, MA 02115
PII S1071-5576(02)00161-2