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Reproductive tract actions of relaxin in models of human pregnancy

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Summary

Elucidating the role(s) of relaxin in women has been greatly hampered by its species specificity. Suitable experimental models of relaxin action in women are limited. We established a non-human primate model of early human pregnancy to study the effects of relaxin in vivo and used three well characterized in vitro models of human endometrial function for study of mechanisms involved. Results from these studies clearly demonstrate that relaxin is an import ant factor in human endometrium which causes accommodation to and maintenance of early pregnancy and uses multiple physiological and biochemical mediators.

Key words

Pregnancy, reproductive tract, endometrium, non-human primate

Although it has been more than thirty-five years since the demonstration that relaxin is a human hormone produced by the corpus luteum of pregnancy (Weiss et al, Science 194:948,1976), understanding of the physiological actions of relaxin and the mechanisms used in the human reproductive tract are still, to date, quite limited. This is due, in large part, to the fact that the sources of production of relaxin, patterns of circulating concentrations of relaxin , and target organs of relaxin vary markedly from species to species. For example, in rodents, relaxin is secreted by the ovary only during second half of pregnancy, and a pre-labor surge in circulating relaxin concentrations occurs. In horses and rabbits, the placenta is the major source of circulating relaxin, and in dogs and cats relaxin secretio n from both the ovary and placenta contribute to circulating concentrations. In women, the corpus luteum of the ovary is the only source of circulating relaxin; levels become detectable during the late luteal phase of the menstrual cycle and will become undetectable if a pregnancy does not ensue. From early pregnancy, circulating relaxin levels increase and peak between the eighth and twelfth week of pregnancy and then decline slightly and remain relatively constant for the entire duration of pregnancy. There is no pre-labor surge as occurs in rodents and pigs. In mice, the major action of relaxin is the formation of an intrapubic ligament to enlarge the diameter of the pubis allowing parturition. This does not occur in women and non-human primates. Thus, the pronounced inter-species differences dictate that improved understanding of the role of relaxin in women requires studies in suitable model systems which are representative of the human.

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Few in vivo studies of relaxin action in women or in appropriate non-human primate models have been performed. We established a non-human primate model of early huma n pregnancy using adult, virgin female rhesus monkeys (*Macaca mulatta)* (Goldsmith et al., PNAS 101:4685, 2004). We choose this species since its physiology has been extensively studied. It is an Old World monkey and therefore has a menstrual cycle, which is well characterized and virtually identical to that of women. Patterns of circulating hormones, feedback mechanisms regulating the menstrual cycle, and tissue responses of women and female rhesus monkeys are totally alike.

To establish this model, animals were ovariectomized, and, due to lack of steroid hormone support, they shed their endometrium within 7 days, as would occur in women. Animals were implanted with silastic capsules containing crystalline estradiol and subsequently capsules containing crystalline progesterone were added, resulting in circulating concentrations of estradiol and progesterone which mimic those of the follicular and luteal phases. Animals were then randomized to receive either human H2 relaxin or vehicle for 21 days, when animals were hysterectomized and tissues retained. Circulating relaxin concentrations achieved in this model closely resembled circulating concentrations occurring during early human pregnancy.

In this rhesus monkey in vivo model, a pronounced uterotropic effect of the physiological levels of circulating human relaxin was demonstrated and definitive actions of relaxin were observed in various reproductive tract tissues. In the endometrium, relaxin significantly increased arteriole number, down regulated progesterone receptor protein expression, and increased numbers of uterine NK cells and macrophages. Relaxin negatively regulated endometrial matrix metalloproteinase expression; decreased proMMP-1 and proMMP-3 and increased TIMP-1. These effects demonstrate that in primate endometrium in vivo, relaxin is uterotropic, angiogenic, regulates resident immune cell number and maintains connective tissue integrity.

In primary human endometrial cell cultures, relaxin stimulated vascular endothelial growth factor (VEGF) and inhibited proMMP-1 expression from stromal and secretory phase epithelial cells. In spontaneously immortalized human endometrial epithelial cells, increased intracellular cAMP (the major biochemical effector of relaxin in endometrium) stimulated PGE2 and PGF2alpha was PKA dependent and MAP Kinase dependent. In telomerase immortalized human endometrial stromal cells, cAMP stimulated VEGF and Interleukin- 11 were both independent of PKA but MAP Kinase dependent.

In women, relaxin is important in the establishment and maintenance of early pregnancy and uses multiple physiological and biochemical mediators.