구두발표-4

Diverse Physiological Roles of Relaxin During Pregnancy

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The protein hormone relaxin was discovered in the mid 1920's when it was found that serum obtained from pregnant guinea pigs contained an active substance that caused elongation of the ligament connecting the pubic portion of the hipbones following its administration into nonpregnant guinea pigs. The isolation of relaxin from the ovaries of rats and pigs about 25 years ago enabled rigorous investigation of the actions of the hormone during pregnancy in these two species. More recently, the actions of relaxin have been investigated in pregnant mice that lack a functional relaxin gene. Because the pregnant rat has received the most experimental attention, the preponderance of this seminar will be an overview of the physiological roles of relaxin during pregnancy in the rat.

Relaxin's actions have been determined by immunoneutralizing the hormone throughout the second half of pregnancy with a monoclonal antibody for rat relaxin. Relaxin has two vital roles in the rat. First, relaxin promotes marked development of the mammary nipples and modest development of the mammary glands. The nipples are so small in relaxin-deficient mother rats that the pups cannot grasp them and obtain milk. Second, relaxin promotes growth and increases the extensibility of the cervix and vagina. Following immunoneutralization of relaxin the durations of labor and delivery are prolonged and there is a marked reduction in live pups on day 1 postpartum. Relaxin's effects on the cervix are likely far more vital than those on the vagina at birth. Relaxin-induced growth of the cervix is attributable, at least in part, to an increase in epithelial and stromal cells during the second half of pregnancy. Recent studies demonstrated that relaxin brings about the

marked accumulation of cervical cells by both promoting cell proliferation and inhibiting apoptosis. A striking feature of relaxin's actions on both the mammary apparatus and the cervix is the reduction in the density of the collagen and elastin fibers within the extracellular matrix. This remodeling of the extracellular matrix is thought to account for the increase in extensibility of the cervix that occurs during the second half of pregnancy.

Relaxin's actions are not confined to reproductive organs during the second half of rat pregnancy. Relaxin acts on the kidneys to bring about changes in their function. Relaxin reduces effective renal vascular resistance, increases effective renal vascular flow and increases glomerular filtration rate. There is evidence that these renal actions of relaxin are attributable to the hormone's vasodilatory actions on small renal arteries. The brain is also a site of action of relaxin during rat pregnancy. Relaxin promotes drinking and there is evidence that the hormones central effects are initiated through actions on the subfornical organ and the organum vasculosum of the lamina terminalis. These two circumventricular organs, which are located on the anterior wall of the third ventricle, have no blood-brain barrier and are accessible to circulating relaxin.

There are differences among species in the actions of relaxin during pregnancy. Whereas the effects of relaxin on the mammary glands and reproductive tract in mice are similar to those in the rat, that is not entirely true for the pig. Unlike in rodents, in pigs relaxin has its most pronounced effects on development of the mammary gland and relatively little effect on development of the nipples. Moreover, relaxin promotes growth of the uterus during pregnancy in pigs but not in rats and mice. The human differs markedly from the rat, mouse and pig. Unlike these latter species, circulating relaxin levels are extremely low during late pregnancy in humans. There is presently no evidence that relaxin has a physiological role during pregnancy in women.