

#### 40. RELAXIN – A REGULATOR OF OESTROGEN RECEPTORS IN THE FEMALE REPRODUCTIVE TRACT?

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The 6 kDa peptide hormone relaxin (RLX) is predominantly produced by the ovaries or placenta of pregnant females and facilitates parturition via its action on the cervix and vagina. Another important biological effect of RLX is its ability to induce uterine growth, similar to oestrogen. These uterotrophic effects of RLX are negated by treatment with an oestrogen receptor (ER) antagonist, implying that RLX is capable of ligand-independent activation of ERs (1). Interestingly, RLX treatment also causes a rapid down-regulation in uterine ER $\beta$ 1 and ER $\beta$ 2 gene expression in immature ovariectomized rats (2). Thus, a RLX-mediated decrease in ER $\beta$  expression may be a prerequisite for oestrogen and other ER activators to exert their effects on target tissues. To study the interactions between RLX and ERs in more detail, we conducted studies in a RLX gene knockout mouse (Rlx<sup>-/-</sup>). The majority of Rlx<sup>-/-</sup> mice are fertile and produce litters of normal size (3). They also appear to have no difficulty giving birth. However, proliferation of the epithelium lining the vagina, cervix and uterus is reduced in Rlx<sup>-/-</sup> mice and there is abnormal accumulation of dense collagen fibre bundles in the stroma of these tissues. These phenotypes can be reversed in late pregnant Rlx<sup>-/-</sup> mice by infusion of 0.05  $\mu$ g/h recombinant human RLX. Our recent studies demonstrate that ER $\alpha$  gene expression increases on day 14.5 p.c. in Rlx<sup>+/+</sup> mice and remains high throughout late gestation. In contrast, ER $\alpha$  mRNA concentrations in pregnant Rlx<sup>-/-</sup> mice are significantly lower compared to Rlx<sup>+/+</sup> mice. Preliminary data in Rlx<sup>+/+</sup> mice show that ER $\beta$  expression is higher in the early stages of gestation, and decreases when RLX concentrations in the plasma start to increase around day 10 p.c. This also coincides with the upregulation in ER $\alpha$  expression. In summary, our data show that RLX positively influences ER $\alpha$  expression in the uterus of pregnant mice. This is due either to a direct stimulatory effect of RLX on ER $\alpha$  transcriptional activity or an indirect effect involving a RLX-mediated down-regulation in ER $\beta$  expression.

(1) Pillai SB *et al.* *Endocrinology* 140, 2426–2429. (2) Pillai SB *et al.* (2002) *Biol. Reprod.* 67, 1919–1926. (3) Zhao L *et al.* (1999) *Endocrinology* 140, 445–453.