

THE ROLE OF PROGESTERONE IN THE REGULATION OF CILIARY ACTIVITY IN THE FALLOPIAN TUBE

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av

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Avhandlingen baseras på följande delarbeten:

- I **Membrane progesterone receptor gamma: tissue distribution and expression in ciliated cells in the fallopian tube.**
Magdalena Nutu, Birgitta Weijdergård, Peter Thomas, Christina Bergh, Ann Thurin-Kjellberg, Yefei Pang, Håkan Billig, D.G. Joakim Larsson
Molecular Reproduction and Development 2007; 74: 843 – 850
- II **Distribution and hormonal regulation of membrane progesterone receptors beta and gamma in ciliated epithelial cells of mouse and human fallopian tubes**
Magdalena Nutu, Birgitta Weijdergård, Peter Thomas, Ann Thurin-Kjellberg, Håkan Billig, D.G. Joakim Larsson
Reproductive Biology and Endocrinology 2009; 7:89
- III **Rapid effects of progesterone on ciliary beat frequency in the mouse fallopian tube**
Anna Bylander*, Magdalena Nutu*, Rikard Wellander, Mattias Goksör, Håkan Billig, D.G. Joakim Larsson
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ABSTRACT

The overall aim of this thesis was to investigate the distribution and regulation of membrane progesterone receptors (mPRs) that may be involved in regulating ciliary activity in the fallopian tube.

The fallopian tube serves to transport the egg and spermatozoa to achieve fertilization. Later, the formation of the pre-embryo is thought to result from the movement of cilia in the epithelium and the muscular activity in the wall of the fallopian tube. The environment in which the gametes exist and develop is greatly influenced by the action of ovarian hormones. Progesterone is essential for many aspects of female reproduction and is also an important regulator of gamete transport and ciliary activity in the fallopian tube. The effects of P_4 in the body are mediated predominantly through the activation of nuclear progesterone receptor (PGR) isoforms. Rapid effects of P_4 in cells and tissues lacking the nuclear receptors indicate that there are other also functional receptors for P_4 in addition to the classical nuclear receptors. In the last four to five years, evidence has been obtained that supports the involvement of mPRs in P_4 signaling in mammalian reproductive tissues and the brain. The mPRs comprise three subtypes (α , β and γ) and belong to the seven-transmembrane domain progesterone adiponectin Q receptor (PAQR) family.

Using antibodies designed to detect specific mPR sequences, we showed that mPRs are present in reproductive and non-reproductive tissues in mice of both sexes. Using mice as well as tissue from healthy fertile women, we have shown that mPR β and γ are expressed in ciliary cells in the fallopian tube epithelium. While mPR β was specifically localized on the cilia, mPR γ was found at the base of the cilia of the same cells. Immunohistochemistry (IHC), confocal microscopy, Western blot, reverse transcriptase PCR and real time PCR were used to detect and confirm the expression and specific cellular localization of the mPRs in the fallopian tube. Treatment with P_4 in a gonadotropin-primed mouse model reduced the expression of the mPR β and γ genes in the fallopian tube, whereas treatment with estradiol rapidly down-regulated both the gene and protein expression of mPR β in immature animals. In humans, the variation in receptor expression over the menstrual cycle showed similarities to the regulation observed in mice before, around and after ovulation. A method based on light reflectometry was designed to study possible rapid effects of P_4 on the tubal ciliary beat frequency (CBF) of mice *ex vivo*. We found a significant and rapid reduction of CBF in P_4 -treated cells compared to controls.

In conclusion, this study demonstrates that mPRs are present in the ciliary cells of mouse and human fallopian tubes and that P_4 can regulate ciliary activity within the fallopian tube.

Keywords: progesterone, progesterone receptor, non-genomic progesterone receptor, ciliated cells, fallopian tube, gamete transport, ciliary activity, ciliary beat frequency, reproduction, fertility.