Corticotropin-Releasing Hormone Receptor 1 (CRHR1) is differentially expressed during human follicle maturation and is up-regulated in ovarian endometriosis

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Introduction

The role of corticotropin releasing hormone (CRH) on ovarian physiology has been reported to be rather inhibitory. Several reports support the thesis that CRH is restricting oocyte maturation, in a CRH receptor 1 mediated fashion. Recently, it was also shown that CRH down-regulates steroidogenesis in an in vitro mouse oocyte model, this being as well mediated by CRH receptor 1.

Endometriosis is a chronic inflammatory condition and thus a potent local stressor for the ovary. It was recently correlated with increased CRH expression at least on the ectopic endometrial sites. Additionally, endometriosis-related infertility has been considered to happen not only due to endometrial receptivity, but also due to poor oocyte quality.

Knowing the negative impact exerted by CRH on ovarian physiology, we investigated whether problematic ovarian function in endometriosis could be explained as well by a derranged ovarian CRH receptor 1 expression.

Population, Materials and Methods

The study was approved by the ethics committee of the Ludwig Maximilians University of Munich. Normal ovaries (n=8) as well as ovaries affected by endo-metriosis (n=14) were retrieved from the archives of the Department of Gynaecology and Obstetrics, LMU, Munich. Formalin fixed paraffin embedded tissue sections were stained for CRHR1 using a standardized immunohisto-chemistry protocol. Appropriate positive (endome-trium, placenta) and negative (isotype matched IgG treated samples) were included in each experiment. CRHR1 immunoreactivity was quantified by two independent observers.

Results

CRHR1 was exclusively expressed in ovarian follicles (n=8) with the ovarian stroma staining negative. Regarding both normal ovaries and cases of ovarian endometriosis (n=14), CRHR1 was identified in primordial, primary and tertiary follicles. The only secondary follicle detected did not show CRHR1 positivity. Regarding normal ovaries the mean fraction of CRHR1 positive follicles was significantly (p<0.01) higher in tertiary follicles (fraction CRHR1 positive = 83±26%) as compared to primordial (fraction CRHR1 positive = 21±22%) or primary (fraction CRHR1 positive = 17±24%) ones. On the contrary CRHR1 was detected to be up-regulated at least threefold (p<0.001) in ovarian endometriosis cases as compared to normal ovaries throughout folliculogenesis. Normal ovaries and ovarian endometriosis samples did not significantly differ regarding mean follicle count or patient age

Figure 1. Presentation of CRHR1 positivity rate of oocytes among different folliculogenesis stages. CRHR1 positivity rates are significantly increased during early folliculogenesis in case of ovarian endometriosis. (*): p<0.05, n.d.: not detected

Discussion

Although derived by a relatively small sample, our results imply that ovarian dysfunction in case of ovarian endometriosis could be at least partially attributed to an up-regulated CRHR1 mechanism. In normal ovaries CRH was reported as a feature of late folliculogenesis, a finding in line with the CRHR1 expression presented herein regarding normal ovaries. Interestingly, in polycystic ovarian syndrome, a situation of increased oocyte atresia, it was shown that CRH is expressed throughout early and late folliculogenesis. We hypothesize that CRH receptor 1 up-regulation in ovarian endometriosis may be stress-mediated, justifying the previously described hormonal misbalance of ovaries affected by ovarian endometriosis. The current findings support further research to verify the working hypothesis of CRHR1 mediated poor oocyte quality in case of ovarian endometriosis. Whether there might be a clinical benefit of blocking CRHR1 signalling in endometriosis patients undergoing controlled ovarian stimulation remains to be also examined.

References