Abstract

The gonadotropin-induced resumption of meiosis and cumulus expansion in preovulatory follicles is preceded by expression of epidermal growth factor (EGF)-like factors, amphiregulin (*AREG*) and epiregulin (*EREG*), in mural granulosa and cumulus cells. *In vitro*, the EGF-like peptides are also produced in cumulus cells upon stimulation by FSH. Both FSH and the EGF-like peptides stimulate resumption of meiosis and cumulus expansion *in vitro* via activation of a broad signaling network in cumulus cells. To define signaling pathways that drive FSH- and AREG-induced cumulus expansion and meiotic resumption, *in vitro* cultured pig cumulus–oocyte complexes (COCs) were treated with specific protein kinase inhibitors. The results document that FSH-stimulated, but not the AREG-stimulated resumption of meiosis, depends on the PKA and MAPK14 activities; both modes of stimulation require activation of EGFR and MAPK3/1. To characterize the effects of FSH and EGF-like peptides on gene expression in cumulus cells, transcriptomes of cumulus cells were analysed using microarray approach. Both FSH and AREG+EREG increased the expression of genes associated with regulation of cell proliferation, blood coagulation and extracellular matrix remodeling. In contrast to AREG+EREG, FSH also increased the expression of genes coding for key transcription factors associated with female fertility. The FSH or EGF-like peptides-induced production of prostaglandin E2 (PGE2) seems to play an important role in the ovulation process. PGE2 was found to stimulate cumulus expansion and meiosis resumption in mice, but little is known about its role in pigs. The data presented in this thesis document that PGE2 is able to upregulate expression of cumulus expansion-related genes and to stimulate meiosis resumption, but less efficiently than FSH. The final aim of this study was to determine whether the resumption of meiosis and expansion of cumulus cells can be blocked by high levels of cGMP. The presented data show that the COCs express *NPPC* and *NPR2* and produced a large amount of cGMP upon stimulation with exogenous CNP. The high levels of cGMP inhibited meiosis resumption, but the inhibitory effect of cGMP was reversed by stimulating the COCs with FSH. The high concentration of intracellular cGMP was not able to suppress FSH-induced activation of MAPK3/1 in cumulus cells, cumulus expansion and expression of expansion-related genes.