Expression of spexin and GALR2/3 receptors in human granulosa cells collected from polycystic ovarian syndrome women and in vitro effect of spexin on steroidogenesis, proliferation and signaling pathways

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Polycystic ovarian syndrome (PCOS) is the most common endocrine pathology in females of reproductive age and characterized by ovulatory dysfunction, polycystic ovaries, increased LH concentrations, insulin resistance and hyperandrogenic symptoms. PCOS women are frequently overweight or obese with increased risk of type – 2 diabetes, endometrial cancer, impaired glucose tolerance and cardiovascular disease. However, the exact pathophysiology of PCOS remains largely unclear, therefore novel insights into the mechanism of PCOS are imperative to identify potential diagnostic markers and therapeutic targets for this endocrine disease. The aim of this study was to characterize the expression of spexin (SPX) and its receptors, galanin receptors 2 and 3 (GALR2/3) in the human ovary and to study it's in vitro effect on granulosa cells (Gc) function. SPX is a novel neuropeptide negatively correlated with obesity and insulin resistance. Follicular fluid (FF) and Gc were obtained from healthy and diagnosed with PCOS women including normal weight and obese. Expression of SPX and GALR2/3 in the ovary was studied by qPCR, western blot, and immunohistochemistry, while level of SPX in FF was assessed by ELISA. The in vitro effect of SPX on Gc steroidogenesis, proliferation, and signaling pathways (MAP3/1, STAT3, AKT, PKA) was analyzed. Moreover, Gc proliferation and estradiol (E_2) secretion were measured with and without an siRNA against GALR2/3 and pharmacological inhibition of the above kinases. The results showed that both the SPX concentration in FF and its gene expression were decreased in Gc of PCOS women, while the protein level of GALR2/3 was increased. We observed that SPX reduced Gc proliferation and steroidogenesis; these effects were mediated by GALR2/3 and kinases MAP3/1, AKT and STAT3 for proliferation or kinases MAP3/1 and PKA for E_2 secretion. The obtained data clearly documented that SPX is a novel regulator of human ovarian physiology and possibly plays a role in PCOS pathogenesis.

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