The Relationship between GSK3β and β-catenin Proteins with Apoptotic Events in Normal and Induced Polycystic Ovaries in Rats

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Abstract

Introduction: Wnt signaling pathway plays an important role in folliculogenesis of rodent ovaries; however, its involvement in ovarian apoptotic events remains undetermined. With respect to the importance of apoptosis in homeostasis and ovarian biological function, this experimental study was conducted to determine the effects of Wnt/β-catenin signaling on follicular growth arrest and apoptosis in polycystic ovary (PCO) models of rats.

Materials and Methods: The experiments were performed in three independent series and with each set of experiments, 8 rats were allocated to the group, half of them as the controls and the other four as the testosterone propionate (TP)-treated rats for the indicated period of time (1 and 4 weeks). Induction of PCO in immature rats was performed by daily injection of testosterone propionate (TP) dissolved in sesame oil over 1 and 4 weeks in the experimental group but to the control group solvent was injected. At the end of the experiments, the ovaries were fixed and sequential paraffin slices were prepared for immunohistochemical analyses of GSK3β, β-catenin and $pGSK3\beta^{ser9}$ proteins. Assessment of Sfrp4 expression as an antagonist of Wnt signaling pathway was performed by Western blot test. Analysis of apoptosis was done by TUNEL staining, followed by quantification of apoptotic follicles in the different groups. The data were analyzed by using Mann-Whitney U-test and a p-value <0.05 was considered significant.

Results: Histological analysis of TP-treated rats showed cystic follicles, absence of corpus luteum and anovulation. GSK3β expression in apoptotic follicles of PCO-induced and control groups was observed. In addition, co-localization of nuclear β-catenin and $pGSK3\beta^{ser9}$ in 1-week-treated rats was detected. In long-term TP-treated rats, there was an increase in apoptosis and GSK3β expression and a 5.1 fold increase in Sfrp4 expression in granulosa cells, compared with the control group, which may explain the absence of nuclear β-catenin in these cells.

Conclusion: The results show testosterone propionate injections induces PCO in immature rats. Furthermore, the increased expression of Sfrp4 and GSK3β in long-term treatment with TP was associated with apoptosis. These results may reveal Wnt signaling inhibition in apoptotic events of rodent ovaries.

Keywords: Apoptosis, GSK3β, Polycystic ovary, Sfrp4, Testosterone, Wnt signaling, β-catenin.

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