REGULATION OF MOUSE MURAL GRANULOSA CELL PROGESTERONE SYNTHESIS BY OOCYTE PARACRINE FACTORS

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Oocytes secrete soluble paracrine factors that play an important role in the growth and development of surrounding follicular cells. It is known that oocytes suppress FSH-induced progesterone production by mural granulosa cells (MGC), however it is unclear which growth factor(s) are involved. Some candidate molecules include growth differentiation factor 9 (GDF9), bone morphogenetic protein 15 (BMP15) and BMP6. The aim of this study was to examine the role of these factors in the regulation of FSH-induced MGC progesterone production. Prepubertal 129/SV mice were primed with eCG and ovaries were collected ~46 h later. MGC from large antral follicles were cultured with either denuded oocytes (DO; 0.25/µl), GDF9 or BMP15 (0.25-4% v/v) or BMP6 (10-200ng/ml), in the absence or presence of FSH. Cells were cultured for 18 h followed by a further 6 h pulse of ^{3}H-thymidine. After 24 h cells and media were harvested for assessment of MGC DNA and progesterone synthesis, respectively. Treatment with FSH increased MGC progesterone production 9-fold, which, as expected, was antagonised by coculture with DO (by 73%). GDF9 and BMP15 both decreased FSH-induced MGC progesterone in a dose dependent manner, significantly reducing control levels (100%) to 17% and 30%, respectively, at doses of 2%v/v. All doses of BMP6 abolished FSH-stimulated progesterone. Even though all treatments inhibited progesterone production, only two of these, GDF9 (0.25%v/v) and DO (0.25DO/µl), stimulated MGC DNA synthesis (2.1 and 3.3 fold above controls, respectively). The BMP receptor type-II (BMPR-II) is a known receptor of several oocyte factors. Treatment with a BMPR-II ectodomain completely antagonised DO- and GDF9-stimualted MGC DNA synthesis, but progesterone levels were only partially restored (by 50%). These data indicate that BMP15 and BMP6 mimic the progesterone-regulating, but not the growth-promoting, activities of oocytes, whereas GDF9 does both. Although the BMPR-II ECD antagonises these oocyte factors, this receptor-signalling system may not necessarily be the means by which oocytes regulate MGC progesterone synthesis.

10.1071/SRB04Ab201