Abstract

Aldosterone (Aldo) is involved in various cardiovascular diseases such as hypertension and heart failure. Aldo levels are known to be increased in patients with polycystic ovary syndrome, and expression of the mineralocorticoid receptor (MR) has also been detected in the ovary. However, the effect of Aldo on reproductive function has yet to be elucidated. Here, we examined the effects of Aldo on follicular steroidogenesis using primary culture of rat granulosa cells by focusing on the ovarian bone morphogenetic protein (BMP) system acting as a luteinizing inhibitor. We found that Aldo treatment increased FSH-induced progesterone production in a concentration-responsive manner. Consistent with the effects on steroidogenesis, Aldo increased mRNA levels of progesterogenic factor and enzymes including StAR and P450scc, whereas Aldo failed to change FSH-induced estradiol and cAMP synthesis or P450arom expression by granulosa cells. Progesterone production and StAR expression induced by FSH and Aldo were reversed by co-treatment with spironolactone, suggesting the involvement of genomic MR action. Aldo treatment attenuated Smad1/5/9 phosphorylation and Id1 transcription induced by BMP-6. Furthermore, Aldo enhanced the expression of inhibitory Smad6 in the presence

of BMP-6. In addition, BMP-6 downregulated MR expression, while Aldo modulated the mRNA levels of endogenous BMP-6 and BMP type-II receptors, indicating the existence of a feedback loop between the BMP system and MR in granulosa cells. Collectively, the results indicated that Aldo predominantly enhances FSH-induced progesterone production by inhibiting BMP-Smad signaling, suggesting a novel role of Aldo in ovarian steroidogenesis and a functional link between MR and BMP pathways in granulosa cells.