

Hormonal Regulation and Function of Progesterone Receptor A and B in the Adult Ovariectomized Mouse Mammary Gland.

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Progesterone (P), an important mitogen in the adult human breast, acts through binding to its cognate nuclear receptor, the progesterone receptor (PR). PR exists as two distinct isoforms, PRA and PRB. Studies using in vitro methods and knockout mice have shown functional differences between these two PR isoforms. In the present study we investigated hormonal regulation of PRA and PRB expression and their functional roles in proliferation in wildtype Balb/c mice. We analyzed PR isoform expression and the proliferative and morphological response in the mammary gland after 3, 5, or 10 days of treatment with control, estrogen (E), or E+P in ovariectomized adult 17 to 20-week-old mice. Ovariectomy did not alter the percentage of PRA positive cells, but decreased PRA expression in PRA positive cells. Treatment with E increased the expression of PRA and proliferation was observed only after 5 days at the distal tips of ducts. Treatment with E+P for 3 days caused sidebranching. After 5 or 10 days of E+P treatment, alveologensis was observed, PRA was significantly decreased, and PRB expression was induced. Proliferation after 3 days of E+P occurred in both PRA positive and negative cells, whereas proliferation after 5 and 10 days of E+P was almost exclusively in PRA negative cells. Additionally, colocalization of cyclin D1 with PRA expression occurred in almost half the PRA positive cells after 3 days of treatment, but the colocalization was dramatically reduced after 5 and 10 days of E+P treatment. These studies suggest that PRA and PRB are regulated differently by E and E+P and regulate proliferation/differentiation through distinct mechanisms.