Progesterone stimulation of proliferation and alveologenesis in adult Balb/c vs. C57Bl/6 mouse mammary glands

Mark D. Aupperlee[1,2,3], Alexis A. Drolet[2,3], and Sandra Z. Haslam[2,3].

[1]Cell and Molecular Biology Program, [2]Department of Physiology, [3]Breast Cancer and the Environment Research Center, Michigan State University, East Lansing, MI.
(517)355-6475 x1384
AUPPERL4@msu.edu

Progesterone (P) acting through the progesterone receptor (PR), which exists as 2 isoforms (PRA, PRB), plays an important role in proliferation and differentiation of the mammary gland. The mitogenic action of P in the mammary gland is hypothesized to depend on estrogen (E) to induce growth factor expression and to upregulate PR. Thus, P treatment without E would not be expected to have any effect. Balb/c and C57Bl/6 strain mice have been used extensively to study P effects in normal mammary gland. However, the 2 strains exhibit significant differences in hormonal responsiveness. In the present study we have compared the effects of E or P alone or in combination (E+P) on mammary gland proliferation and morphology in adult ovarictomized Balb/c or C57Bl/6 mice treated for 3, 5, or 10 days with E, P or E+P. E alone produced similar proliferative and morphological responses in both strains. P alone in Balb/c mice surprisingly induced proliferation, extensive sidebranching by 5 days, and some alveologenesis by 10 days. Notably, P alone in C57Bl/6 mice had no effect on proliferation or morphology. Additionally, C57Bl/6 mice exhibited a delayed morphological response to E+P treatment. The effect of P on PRA and PRB expression was analyzed in Balb/c mice. P alone significantly reduced PRA, but a basal level of PRA expression was maintained. A low level of PRB expression was induced after 10 days of P treatment concomitant with the formation of alveoli. Thus, E is not absolutely required for expression of either PRA or PRB. To determine the mechanism of proliferation

induced by P alone, colocalization of PRA with the proliferation marker BrdU and the cell cycle regulator cyclin D1 were also examined. PRA+ cells did not colocalize with BrdU, indicating that P induced proliferation through a paracrine mechanism. However, nuclear cyclin D1 was expressed in a portion of PRA+ cells, suggesting that although cyclin D1 may be regulated by P, other factors may limit cell cycle progression and proliferation in PRA+ cells. These studies demonstrate that P can have mitogenic activity in the mammary gland in the absence of E. Additionally, Balb/c mice respond to P alone, whereas C57Bl/6 mice do not. Thus, these two strains provide an important model for identifying the mechanism(s) mediating progesterone induced proliferation, in vivo.