Public Abstract
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Graduation Term:FS 2007
Department:Animal Sciences
Degree:MS
Title:The Effects of the Selective Estrogen Receptor Modulators MPP and Raloxifene in Normal and Cancerous Human and Murine Uterine Tissue

Selective Estrogen Receptor Modulators (SERMs) are synthetic compounds that bind with varying affinity to estrogen receptor-alpha and -beta, and for this reason, they are currently used to treat various diseases, including breast cancer and osteoporosis. Due to their antagonistic activity in the uterus, methyl-piperidino-pyrazole (MPP), raloxifene, and ICI 182,780 might be used to treat endometrial cancer in women. The goal of this research was, thus, to discern the in vitro and in vivo effects of the SERMs, MPP, raloxifene, and ICI 182,780, along with 17beta-estradiol, on endometrial carcinoma cells in culture and on murine uterine tissue. The SERMs, MPP and raloxifene, at 1 nM concentrations in vitro, induced significant apoptosis in both endometrial cancer and normal uterine cells when compared to vehicle control alone (P </ 0.0001). These compounds increased uterine wet weight when injected intra-peritoneally (I.P.) (25 to 150 ug doses) into ovariectomized CF1 mice. In addition, our in vivo studies demonstrated that both MPP and raloxifene induce apoptosis in uterine stromal cells rather than luminal epithelium, and cause proliferation of the luminal epithelium. In order to better understand the effect of these SERMs on gene expression in the uterus, microarray experiments were performed by using Affymetrix Mouse Genome 430 2.0 short oligomer arrays. The SERMs, MPP, raloxifene, and ICI 182,780 were employed either alone (50 ug doses) or in combination with 17beta-estradiol (low 1 ug or high 50 ug dose) along with a DMSO vehicle control, which resulted in nine treatment groups. These nine groups organized into two main clusters with MPP, raloxifene, and the high dose of 17beta-estradiol clustering together. Another cluster included the low dose of 17beta-estradiol, ICI + 17beta-estradiol, ICI alone, MPP + 17beta-estradiol, and raloxifene + 17beta-estradiol. Interestingly, the ICI presumably caused competitive antagonism with the 17beta-estradiol treatment and suppressed genes involved in mitosis and cytokinesis. These results provide a framework for the pro-apoptotic, proliferative, and genetic actions of MPP, raloxifene, and ICI 182,780 in the uterus.