Weight change and tumorigenesis in a rat model of menopause

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Background
Menopause, a natural process of ovarian decline, occurs with age, leading to a deficiency in sex hormones including estrogen and progesterone. Although the correlation between menopause and breast cancer is unclear, older women are at greater risk (Howlader). Obesity is another risk factor for women to develop breast cancer (Morimoto). Estrogen (E2) deficiency can increase body weight in both menopausal women and ovariectomized (OVX) rat model. The mammary gland is composed of fat tissue, suggesting a possible link between body weight gain and mammary tumorigenesis. It is unclear whether it is hormonal or body weight change that impacts tumorigenesis at menopause. Using an OVX rat model with E2 deficiency and E2 replacement, we monitored hormone related body weight change and its impact on mammary tumorigenesis.

Methods
The Sprague-Dawley rats used in this study were ovariectomized (OVX) at either 4, 11, or 17 months of age. A capsule containing cholesterol (vehicle, VEH) or 5% estradiol (E2) was implanted during OVX surgery, as shown in Figure 2. Following OVX, body weight was recorded every 5 days for 10 days each month. Ovariectomized rats were monitored from 4 to 20 months of age. Throughout the study the rats were regularly monitored for body weight change that impacts tumorigenesis at menopause.

Results

Figure 3: Body weight changes from young to old age and the influence of OVX and estradiol in rats

Figure 4: 3 month treatment in young and middle-aged OVX rats

Figure 5: 6 month treatment in middle-aged OVX and ovariectomized rats

After OVX the vehicle treated group increased in body weight in both young and ovariectomized groups. The MA-E3 group trends toward the MA-V6 group. The MA-V3E3 trends toward the MA-intact and MA-E6 group. Switching treatment 3 months after OVX altered body weight. The MA-E3V3 group trends toward the MA-V6 group. The MA-E6V3 group did not show any tumor development.

Figure 6: Weight change after 11 and 17 month OVX

Body weight was relatively stable after 11 months of age. All OVX-E2 deficiency increased body weight in MA-V3 and MA-V6.

Figure 7: Tumorigenesis of intact and ovariectomized rats

The timing of OVX and hormone replacement therapy were performed at 4 months, 11 months, and 17 months of age. Group 1 and 2 switched capsule treatment after 3 months of initial treatment in order to compare the data or early exposure to estradiol. The duration of treatment was either 3 months (4-6 months in the middle-aged group) or 6 months (8-10 months in the middle-aged group). The young groups (1 and 2) received hormone replacement therapy at 11 months, and the middle-aged groups (5-7) received hormone replacement therapy at 17 months of age. The timing of OVX and hormone replacement therapy were shown in Figure 2.

Conclusion

• Body weight gain occurs in OVX-VEH treated rats at all ages. Older rats OVX at 17 mo increase in weight when E2 deficient, despite lack of weight change when ovary intact. Body weight of OVX-E2 treated rats are consistent with ovary intact rats.

• The results of tumor incidence indicates that mammary tumorigenesis in rats is related to hormone and ovary status. E2 deficiency had a possible protective effect of tumor incidence for older rats (monitored until 17 mo).

• Tumor incidences was less likely to occur when there is some period of E2 deficiency compared to long term E2 treatment.

OVX induced weight gain does not increase tumor incidence.

Literature Cited


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