75. THE AROMATASE KNOCKOUT (ArKO) MOUSE AS A MODEL TO STUDY THE OESTROGENIC ACTIONS OF TIBOLONE

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Tibolone (ORG OD14) has oestrogenic, progestogenic and/or androgenic activity depending on the tissue. The aromatase knockout (ArKO) mouse provides an ideal model to study the multiple properties of Tibolone given its inability to synthesise endogenous oestrogens. In this study, we examined the effect of Tibolone administration on the ovariectomised (ovx) ArKO mouse. Ovx or sham-operated ArKO and wildtype (WT) mice were orally administered Tibolone (2 μg/g body mass), ethinyl estradiol (EE) (0.05 μg/g body mass) or vehicle once daily for 6 weeks. As expected, ovx increased body weight gain. Tibolone produced a precipitous decline in body mass in ovx ArKO mice. Within 3 weeks of administration, mice lost a mean of 25% of initial body mass, versus 10% for comparative WT mice, likely a reflection of adipose tissue loss. Control EE-induced body mass loss was not as great in ovx ArKO (11.2%). Uterine mass increase was significantly greater in Tibolone-treated ArKO and WT groups compared to EE replacement (13.5- *v.* 7.7-fold increase Tibolone; 3.9- *v.* 2.4-fold increase EE, ArKO *v.* WT respectively, compared to ovx + vehicle). In line with these effects, Tibolone showed an oestrogenic effect on bone yielding an increased bone mineral density in the distal femur. Ovx or intact vehicle-treated ArKO mammary glands were rudimentary, consistent with their oestrogen-naïve background. In contrast, EE-treated ArKO mammary glands had ducts extending from the nipple to beyond the lymph node, relatively small terminal end buds (TEBs), and a bifurcated branching pattern. Tibolone-replaced ovx ArKO mammary glands displayed extensive side branching. TEBs were prominent beyond the lymph node where the duct spread into the fat pad. Clearly Tibolone expresses both oestrogenic and progestogenic activity on breast development. Furthermore it is evident that Tibolone does not need to be aromatised to produce oestrogenic activity as observed on ArKO body-, adipose tissue-, uterine- and bone-mass. The effect is likely being mediated by the two Tibolone metabolites 3α- & 3β-hydroxytibolone. These results demonstrate that the ArKO mouse provides a useful model for assessing the composite steroidal activities of Tibolone.

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