

Defective Folliculogenesis in Leptin Deficient (ob/ob) Mice Does Not Fully Respond to Gonadotropin Administration

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Abstract

The reproductive failure in ob/ob mice may be related to the hypogonadotropic state of the ob/ob animal or leptin may directly modulate ovarian follicle development. The purpose of this study is to determine the site of action of leptin within the hypothalamic-pituitary- gonadal axis. Our hypothesis is that exogenous gonadotropin administration will normalize the effect of leptin deficit in the gonad. Sixteen ob/ob and 16 control mice were studied. At 26 days of age, half of the ob/ob animals and half of the controls were injected sc with 5 IU pregnant mare serum gonadotropin (PMSG) followed 48 hours later with 5 IU of human chorionic gonadotropin (hCG). The remaining half of the animals received vehicle (saline) injections. Animals were killed 24 hours after the second injection. Blood was collected for estradiol and progesterone assay, reproductive organs were weighed and the fallopian tubes were examined for the number of eggs ovulated. Ovaries were paraffin-embedded for hematoxylin and eosin histology and TUNEL assay. Both control and ob/ob mice responded with an increase in ovarian and uterine weights, but this response was attenuated in ob/ob animals. In response to gonadotropin administration 5 of 8 control mice ovulated (12.4 ± 4.2 eggs), but none of the 8 ob/ob mice had ovulated by 24 hours after hCG treatment. Serum estradiol and progesterone levels in the ob/ob animals were higher ($P=0.001$ and $P= 0.0258$, respectively) than the controls and gonadotropin treatment did not alter these values. The number of preantral follicles was higher ($P= 0.0028$) in ob/ob mice than control animals and this number was reduced by gonadotropin treatment in both groups of animals. Neither the leptin deficiency nor gonadotropin treatment altered the number of early antral follicles, but the number of late antral follicles was subnormal ($P=0.0019$) in ob/ob mice and gonadotropin treatment increased ($P=0.01$) the number of these follicles in the controls but not in ob/ob mice. The total number of atretic follicles as documented by TUNEL assay was not different between the ob/ob mice and controls. The number of atretic follicles was reduced by gonadotropin treatment in both the ob/ob and control mice. The data suggest that a leptin deficiency in mice is associated with impaired folliculogenesis that is not fully corrected by gonadotropin administration. The data also suggest that leptin may influence the process of folliculogenesis independent of its ability to alter gonadotropin secretion. The ovarian responsiveness to gonadotropin administration was subnormal in leptin deficient animals (fewer follicles developed to the late antral stage, and animals failed to ovulate), suggesting that leptin may directly alter the process of folliculogenesis at the level of the ovary. Supported by NIH grants: HD41749, RR03024 and GM08248.