

Accelerated Puberty and Late-Onset Hypothalamic Hypogonadism in Female Transgenic Skinny Mice Over-Expressing Leptin

Transgenic skinny mice were generated by causing overexpression of leptin under the regulation of a liver-specific promoter (human serum amyloid P component). In these animals there is chronic hyperleptinemia (81 ng/mL) compared with nontransgenic litter mates (NTLM; 9 ng/mL). Hypophagia is present, white and brown adipose tissue disappears, and insulin sensitivity and glucose metabolism increase (Ogawa Y, et al. *Diabetes* 1999;48:1822-1829).

In the present study by Yura et al, heterozygous males and females with 30 copies of the leptin transgene were mated. *In the female offspring* generated for this study, vaginal opening occurred earlier in the transgenic skinny mice (27.3 vs 29.4 days) than in NTLM ($P < 0.05$). The transgenic animals had larger ovarian follicles but comparable ovarian weights. Uterine weights were significantly increased (22.3 g vs 13.3 g in NTLM; $P < 0.005$). The skinny and NTLM females were comparably fertile at 8 weeks, *but not at 22 weeks*. At that time, the skinny animals were markedly subfertile with markedly reduced ovarian weights, follicular atrophy, decreased basal and gonadotropin hormone-releasing hormone (GnRH)-stimulated serum luteinizing hormone concentrations, and reduced hypothalamic GnRH values compared with NTLM. Gonadotropin administration restored ovarian size and morphology to those of NTLM. In contrast, *in males* there was no significant difference in fertility, testicular weights or morphology, or hypothalamic GnRH content between transgenic mice and NTLM.

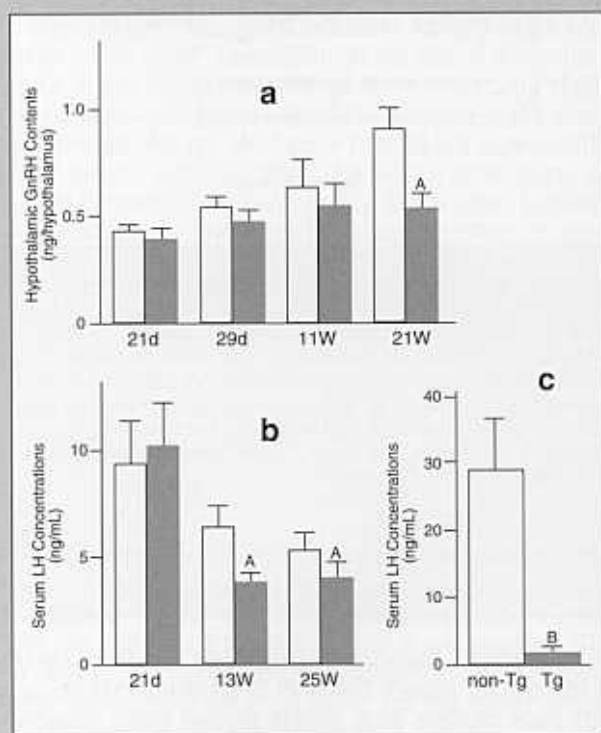
The investigators concluded that transgenic *female mice* with hyperleptinemia undergo earlier pubertal maturation than do NTLM and have comparable fertility at younger ages despite no apparent adipose tissue; when older, however, they develop hypogonadotropism due to decreased GnRH production. The mechanism of the latter effects was attributed to downregulation of "hypothalamic leptin signaling." They suggest that the hypothalamic effects of leptin on feeding and reproduction traverse separate and distinct pathways, and that there also is a gender difference in leptin responsiveness.

Yura S, et al. *J Clin Invest* 2000;105:749-754.

Editor's comment: According to the "critical weight" hypothesis and clinical experience, body fat is extremely important in promoting normal linear growth and sexual maturation in both males and females, but particularly in females. These investigators have developed an animal model in which sexual maturation is normal/accelerated in males and females but that cannot be maintained in older females, probably due to a decrease in hypothalamic GnRH production. The data confirm the significant role that leptin plays in the regulation of the early maturation of the reproductive endocrine system. The data also complement previous studies in which leptin has been administered to normal or leptin-deficient (but responsive) animals. One wonders if the hyperleptinemia of the obese teenage male may sometimes paradoxically delay the onset of puberty. On the other hand, the hypothalamic hypogonadism that may occur in some obese adult women, but seldom in obese adult males, also may reflect an effect of chronic hyperleptinemia.

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Figure



Hormonal profile of transgenic (Tg) skinny mice overexpressing leptin (filled columns) and their nontransgenic (non-Tg) littermates (open columns). (a) Hypothalamic gonadotropin hormone-releasing hormone (GnRH) contents. (b) Serum luteinizing hormone (LH) concentrations 15 minutes after intraperitoneal administrations of GnRH. Procedures were performed on day 21 (21d) (filled columns, $n = 10$; open columns, $n = 8$); on the diestrus day at 13 weeks (13W) (filled columns, $n = 6$; open columns, $n = 4$); and on the diestrus day at 25 weeks (25W) (filled and open columns, $n = 10$) of age. (c) Serum LH concentrations at 2,000 hours on the proestrus day between 13 and 18 weeks of age (filled columns, $n = 6$; open columns, $n = 4$). ^A $P < 0.05$ compared with nontransgenic littermates by ANOVA with Fisher's least significance difference test. ^B $P < 0.005$ by Student's test.

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