Results: On the first injection day, potent increases in serum LH and FSH were observed after sc kisspeptin injection in women with HA (mean maximal increment from baseline within 4 h after injection: LH, 24.0 ± 2.5 IU/liter; FSH, 0.5 ± 0.4 IU/liter). These responses were significantly reduced on the 14th injection day (mean maximal increment from baseline within 4 h postinjection: LH, 2.5 ± 2.2 IU/liter, P < 0.05; FSH, 0.5 ± 0.5 IU/liter, P < 0.05). Subjects remained responsive to GnRH after kisspeptin treatment. No significant changes in LH pulsatility or ultrasound measurements of reproductive activity were observed.

Conclusion: Acute administration of kisspeptin to women with infertility due to HA potently stimulates gonadotropin release, but chronic administration of kisspeptin results in desensitization to its effects on gonadotropin release. These data have important implications for the development of kisspeptin as a novel therapy for reproductive disorders in humans.

The Impact of Exercise Training Compared to Caloric Restriction on Hepatic and Peripheral Insulin Resistance in Obesity

Robert H. Coker, Rick H. Williams, Sophie E. Yeo, Patrick M. Kortebein, Don L. Bodenner, Philip A. Kern, and William J. Evans
(J Clin Endocrinol Metab, 10.1210/jc.2008-2033)

ABSTRACT
Context: It has been difficult to distinguish the independent effects of caloric restriction versus exercise training on insulin resistance.
Objective: Utilizing metabolic feeding and supervised exercise training, we examined the influence of caloric restriction vs. exercise training with and without weight loss on hepatic and peripheral insulin resistance.
Design, Participants, and Intervention: Thirty-four obese, older subjects were randomized to: caloric restriction with weight loss (CR), exercise training with weight loss (EWL), exercise training without weight loss (EX), or controls. Based on an equivalent caloric deficit in EWL and CR, we induced matched weight loss. Subjects in the EX group received caloric compensation. Combined with [6,62H2]glucose, an octreotide, glucagon, multistage insulin infusion was performed to determine suppression of glucose production (SGP) and insulin-stimulated glucose disposal (ISGD). Computed tomography scans were performed to assess changes in fat distribution.
Results: Body weight decreased similarly in EWL and CR, and did not change in EX and controls. The reduction in visceral fat was significantly greater in EWL (–71 ± 15 cm2) compared to CR and EX. The increase in SGP was also almost 3-fold greater (27 ± 2%) in EWL. EWL and CR promoted similar improvements in ISGD [+2.5 ± 0.4 and 2.4 ± 0.9 mg/kg fat-free mass (FFM) 1 min−1], respectively.
Conclusions: EWL promoted the most significant reduction in visceral fat and the greatest improvement in SGP. Equivalent increases in ISGD were noted in EWL and CR, whereas EX provided a modest improvement. Based on our results, EWL promoted the optimal intervention-based changes in body fat distribution and systemic insulin resistance.

Subcutaneous Injection of Kisspeptin-54 Acutely Stimulates Gonadotropin Secretion in Women with Hypothalamic Amenorrhea, But Chronic Administration Causes Tachyphylaxis

Channa N. Jayasena, Gurjinder K. Nijher, Owais B. Chaudhri, Kevin G. Murphy, Amita Ranger, Adrian Lim, Daksha Patel, Amrish Mehta, Catriona Todd, Radha Ramachandran, Victoria Salem, Gordon W. Stamp, Mandy Donaldson, Mohammad A. Ghatei, Stephen R. Bloom, and Waljit S. Dhillon
(J Clin Endocrinol Metab, 10.1210/jc.2009-0406)

ABSTRACT
Background: Kisspeptin is a critical regulator of normal reproductive function. A single injection of kisspeptin in healthy human volunteers potently stimulates gonadotropin release. However, the effects of kisspeptin on gonadotropin release in women with hypothalamic amenorrhea (HA) and the effects of repeated administration of kisspeptin to humans are unknown.
Aim: The aim of this study was to determine the effects of acute and chronic kisspeptin administration on gonadotropin release in women with HA.
Methods: We performed a prospective, randomized, double-blinded, parallel design study. Women with HA received twice-daily sc injections of kisspeptin (6.4 nmol/kg) or 0.9% saline (n = 5 per group) for 2 wk. Changes in serum gonadotropin and estradiol levels, LH pulsatility, and ultrasound measurements of reproductive activity were assessed.
Results: On the first injection day, potent increases in serum LH and FSH were observed after sc kisspeptin injection in women with HA (mean maximal increment from baseline within 4 h after injection: LH, 24.0 ± 3.5 IU/liter; FSH, 9.1 ± 2.5 IU/liter). These responses were significantly reduced on the 14th injection day (mean maximal increment from baseline within 4 h postinjection: LH, 2.5 ± 2.2 IU/liter, P < 0.05; FSH, 0.5 ± 0.5 IU/liter, P < 0.05). Subjects remained responsive to GnRH after kisspeptin treatment. No significant changes in LH pulsatility or ultrasound measurements of reproductive activity were observed.
Conclusion: We identified a novel loss-of-function Q459R mutation in the CaSR gene that exhibits mildly reduced sensitivity to calcium and that is associated with apparent autosomal recessive transmission of FHH. This study demonstrates the importance of genetic testing in FHH to distinguish between de novo and inherited mutations of the CaSR gene and assist in management decisions.

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