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Reproductive Endocrinology

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Reproductive Hormone Secretion is Increased by Intranasal Kisspeptin in Humans

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Background: Kisspeptin is a critical activator of hypothalamic gonadotrophin releasing hormone (GnRH) neurons and has significant potential to treat common reproductive disorders. To date, kisspeptin has solely been administered to humans via the intravenous or subcutaneous routes, however intranasal administration could offer a novel non-invasive delivery route, which is preferred by patients. We therefore sought to determine the effects of intranasal kisspeptin on reproductive hormone release in humans for the first time.

Methods: Randomised, double-blinded, placebo-controlled, cross-over study in 12 healthy men (mean±SEM age 28.3±1.7 yrs; BMI 24.5±0.7 kg/m^2). After monitored self-administration of intranasal kisspeptin-54 (3.2, 6.4, 12.8 and 25.6 nmol/kg) or 0.9% saline, serum reproductive hormone levels were measured every 15 minutes for four hours. Subsequently, four women (mean age 29.8±3.7 yrs; BMI 21.2±1.1 kg/m^2) with hypothalamic amenorrhoea (HA) attended for the same protocol comparing intranasal kisspeptin-54 (12.8 nmol/kg) and 0.9% saline. Mean ±SEM was presented unless otherwise stated. Time profiles of hormone levels during the four-hour study were compared using two-way ANOVA with Bonferroni's multiple comparison test. Multiple means were compared using

one-way ANOVA with Bonferroni's multiple comparison test.

Results: In healthy men, intranasal kisspeptin dose-dependently increased mean luteinising hormone (LH) levels at doses between 3.2-12.8 nmol/kg (p=0.008 and <0.0001 for 6.4 and 12.8 nmol/kg vs saline, respectively), with the maximal rises occurring at 30-45 minutes post-administration. Correspondingly, the area under the curve (AUC) for the LH change was significantly elevated following all doses of kisspeptin compared to saline (saline: -25.4±70.5 h.IU/L; 3.2 nmol/kg: 172.2±64.2 h.IU/L [p=0.03]; 6.4 nmol/kg: 300.2±79.2 h.IU/L [p=0.002]; 12.8 nmol/kg: 595.7±98.3 h.IU/L [p=0.001]; 25.6 nmol/kg: 549.0±108.6 h.IU/L [p<0.0001]). Follicle stimulating hormone (FSH) levels followed a similar trajectory to LH in response to intranasal kisspeptin. Moreover, kisspeptin at 12.8 nmol/kg increased serum testosterone from 120 minutes onwards (p=0.02), with a maximal change from baseline of 4.9±0.7 nmol/L (p=0.03).

In women with HA, intranasal kisspeptin increased mean LH (p=0.002 vs saline), with the peak levels occurring at 30-45 minutes post-administration. The AUC for the LH change was 508.4±77.5 h.IU/L (p=0.02 vs saline AUC for LH). The maximal LH change from baseline was 4.1±0.9 IU/L compared to 0.2±0.4 IU/L for saline (p=0.03). Intranasal kisspeptin increased mean FSH (p=0.01 vs saline). No significant changes in downstream serum oestradiol or progesterone were observed during the acute four-hour study.

Conclusion: We report the first investigation of the effects of intranasal kisspeptin delivery on reproductive hormone release in humans. Our results demonstrate that intranasal kisspeptin robustly and dose-dependently stimulates reproductive hormone release in healthy men and crucially in a patient-group of women with hypogonadism. Given the ongoing development of kisspeptin therapeutics, intranasal kisspeptin therefore offers a novel, safe, effective and non-invasive route of administration for the management of reproductive disorders.

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