

Dynamic Modulation of LH Secretion by Continuous Kisspeptin Infusion in Healthy Men

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Research Article

Keywords: kisspeptin, luteinizing hormone, desensitization, continuous infusion

Posted Date: February 27th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-8942588/v1>

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Version of Record: A version of this preprint was published at Hormones on June 2nd, 2026. See the published version at <https://doi.org/10.1007/s42000-026-00795-y>.

Abstract

Purpose

Kisspeptin stimulates gonadotropin-releasing hormone (GnRH) release and, by extension, gonadotropin secretion. Although continuous kisspeptin administration has been shown to dampen kisspeptin-induced GnRH release in non-human primates [1, 2], this has not been replicated in the limited human studies reported to date. The objective of this study was to examine the effects of continuous kisspeptin administration on GnRH-induced luteinizing hormone (LH) secretion in healthy men.

Methods

Three healthy adult men received a continuous intravenous infusion of kisspeptin-10 at a dose of 12.5 mcg/kg/h for 24 hours and underwent frequent blood sampling to characterize the effect on reproductive hormones.

Results

Continuous administration of kisspeptin resulted in an immediate increase in LH levels, 5 to 10-fold above baseline, which were sustained for several hours. LH levels subsequently began to decline towards the end of the infusion, though they remained above baseline. Continuous kisspeptin induced a modest rise in follicle-stimulating hormone (FSH) levels.

Conclusion

While kisspeptin boluses have been used to probe GnRH pulse generation, continuous infusion of kisspeptin is a complementary physiologic tool to study dynamic changes in GnRH-induced LH secretion. Further studies are warranted to further elucidate the physiologic response of the kisspeptin receptor to non-pulsatile ligand administration.

Clinical Trial Registration: NCT01438073 (August 24, 2011)

Introduction

Kisspeptin plays a central role in GnRH secretion and is thus considered a key regulator of reproductive function. Within the arcuate nucleus, a specialized subset of kisspeptin neurons, known as KNDy (Kisspeptin/Neurokinin B/Dynorphin) cells, functions as a “pulse generator,” coordinating rhythmic bursts of activity that drive the pulsatile release of GnRH [3, 4]. This finely tuned system is obligatory for normal sexual maturation, as evidenced by the consequences of genetic disruptions: loss-of-function mutations in the kisspeptin receptor (*KISS1R*) [5, 6] and kisspeptin gene (*KISS1*) [7, 8] are associated with hypogonadotropic hypogonadism, while gain-of-function mutations are associated with central precocious puberty [9, 10].

Because kisspeptin acts directly upstream of GnRH neurons, exogenous kisspeptin administration has emerged as a valuable tool for probing GnRH neuronal function. Much has been learned about the effects of acute kisspeptin administration in stimulating GnRH-induced LH secretion across a range of conditions including healthy men[11, 12], healthy women[13, 14], individuals with congenital[15–17] or acquired hypogonadotropic hypogonadism[18, 19] and adolescents with delayed puberty[20, 21]. While the effects of kisspeptin administration via long infusion remain less clear, studies using kisspeptin analogs in human have shown that sustained exposure can suppress the reproductive axis[22, 23]. This phenomenon, akin to the downregulation observed with GnRH analogs at the pituitary level, opens the avenues to potential therapeutic applications for hormonal modulation. However, the specific conditions under which a continuous kisspeptin infusion induces receptor desensitization in humans have yet to be fully determined.

This study aims to elucidate the effects of a continuous kisspeptin infusion on GnRH-induced LH secretion in healthy men. Thus, we administered intravenous kisspeptin at 12.5 mcg/kg/h for 24 hours to healthy adult men and performed frequent blood sampling before, during, and after the infusion to characterize its effects.

Materials and Methods

Subjects and eligibility criteria

Three men participated in this study. They met the following inclusion criteria: 21–40 years old; self-reported history of normal timing of puberty and normal erectile and ejaculatory function; no use of prescription medications for at least 2 months before the study; body mass index 18.5–30 kg/m²; blood pressure below 140/90 mm Hg; normal physical examination including testicular volume 15 ml or greater by Prader orchidometer; normal white blood cell and platelet counts, normal hemoglobin; no elevation of creatinine or blood urea nitrogen; aspartate aminotransferase and alanine aminotransferase no more than twice the upper limit of the reference range; and normal TSH, prolactin, FSH, LH, and testosterone.

All protocols were approved by the Institutional Review Board of the Massachusetts General Hospital (MGH) and the Food and Drug Administration, and all subjects gave written informed consent before participation in these studies. This study was registered with ClinicalTrials.gov no. NCT01438073.

Materials and Methods

Kisspeptin 112–121 was provided as kisspeptin-10 under contract to the Eunice Kennedy Shriver National Institute of Child Health and Human Development and was synthesized using good manufacturing practices by PolyPeptide Laboratories (San Diego, CA). Resuspended aliquots underwent additional tests for purity, concentration, sterility, and pyrogenicity.

Study design

Participants were admitted to the Translational Clinical Research Center at MGH for a 36-hour study, with all visits standardized to a 7 a.m. to 7 p.m. schedule to minimize circadian rhythm variations. During hours 0 to 6, subjects underwent q10-minute blood sampling to assess baseline LH levels in the absence of any peptide administration. At hour 6, kisspeptin-10 was administered as a continuous intravenous infusion at a rate of 12.5 mcg/kg/h for 24 hours. At hour 30, the infusion was stopped, but blood sampling q10-minute continued for an additional six hours. To comply with blood drawing safety guidelines, sampling frequency was reduced to once per hour between hours 12 and 24. This approach prioritized frequent blood sampling during initial and end of infusion, which are most informative for assessing attenuation, rather than the mid-infusion rise.

Laboratory assays

During outpatient screening, FSH, LH, and total testosterone (LC/MS) were measured at LabCorp using the Roche Elecsys system. During the research visit, LH was measured from each sample, and FSH and testosterone were measured from 2-hour pooled samples by the MGH Clinical Laboratory Research Core. Pooled samples were constituted from equal aliquots of the 10-min samples over 2 hours. A validated modification of the method of Santen and Bardin was used to identify LH pulses[24].

Statistical analysis

Mean levels of LH, FSH and testosterone were calculated for the three time periods. 'Pre' refers to average hormone values during 0 to 6 hours of the protocol, preceding the infusion. 'Max' levels are the highest average hormone value within a 2-hour window during the infusion: for LH, this was defined as the highest 2-hour rolling average from the 10-minute samples; for FSH/testosterone, this was the single highest value measured in the 2-hour pooled samples. 'End' refers to the average hormone concentrations during the final 2 hours of the infusion.

LH pulsatility was evaluated during the pre-infusion baseline and post-infusion recovery periods. However, because baseline LH levels changed progressively during the infusion, pulse detection during this interval was confounded and likely underestimated pulse frequency; therefore, pulse parameters were not reported for the infusion period.

Results

The three male participants were aged 23 to 32 years and had a BMI ranging from normal weight to overweight (22.5 to 27.5 kg/m²). All participants had normal testicular volume, ranging from 20 to 25 mL, suggesting normal sexual maturation. Testosterone levels ranged from 578.7 to 640.8 ng/dL, within the normal range for men, in the setting of normal LH and FSH levels, indicating an intact hypothalamic-

pituitary-gonadal axis. Baseline clinical and laboratory characteristics for each subject are summarized in Table 1.

Kisspeptin infusion at 12.5 mcg/kg/h led to an increase in LH, FSH, and testosterone concentrations across all subjects, with the individual hormonal profiles shown in Figure 1 and Table 2.

Baseline LH levels ranged from 3.1 to 3.8 mIU/mL during the 6-hour pre-infusion period. LH pulse frequency during this period was 2–3 pulses per 6 hours, which is comparable to that reported in healthy adult men[25]. Following kisspeptin administration, LH levels rose, with maximum levels during the infusion ranging from 17.5 to 30.6 mIU/mL (approximately 5- to 10-fold above baseline) across individuals. The timing of peak LH varied among individuals, occurring at 4 to 16 hours after kisspeptin infusion initiation. LH levels began to decline toward the end of the 24-hour infusion, ranging from 10.7 to 22.8 mIU/mL, but remained elevated compared to baseline.

FSH concentrations demonstrated a more modest increase relative to LH, rising from a baseline range of 1.1–3.2 mIU/mL to 2.9–8.1 mIU/mL (approximately 2- to 3-fold above baseline).

Baseline testosterone levels ranged from 471 to 640 ng/dL, peaking at 847 to 913 ng/dL. Maximal testosterone levels occurred subsequent to the maximal LH levels. By the end of the infusion, testosterone levels remained elevated at 748 to 793 ng/dL by the end of the infusion.

Following the end of kisspeptin infusion, both FSH and LH levels declined toward baseline values within the subsequent 6-hour period. At least one LH pulse was detected in a subject during this recovery window, suggesting the reemergence of endogenous GnRH pulsatility.

Discussion

We have demonstrated that intravenous administration of kisspeptin-10 at 12.5 mcg/kg/h (9.6 nmol/kg/h) over 24 hours in healthy men induced an initial rise in LH levels, followed by a plateau and a subsequent decline towards the end of the infusion across all participants. Notably, while continuous kisspeptin infusion did not suppress LH, the observed changes in gonadotropin secretion suggest that continuous intravenous kisspeptin administration has the capability to modulate GnRH, and by extension LH release.

Fifty years ago, the Knobil laboratory demonstrated that in hypothalamically-lesioned rhesus monkeys, intermittent administration of GnRH reestablished pituitary gonadotropin release, but a constant infusion failed to restore sustained gonadotropin secretion[26]. This seminal work pointed to the importance of the pattern of GnRH delivery, as opposed to simply the dose, in regulating reproductive function. Moreover, it suggested that continuous GnRH administration could result in downregulation of the signaling pathways responsible for gonadotropin release. Over the years, this phenomenon, termed “desensitization”, has been described as a waning of the receptor response in the face of continuous agonist exposure[27].

Subsequent human and animal GnRH infusion studies have provided insights into gonadotropin desensitization. During 72-hour GnRH infusions in healthy men[28] and follicular phase women[29], LH levels peaked at approximately 24 hours, then declined but remained 3–4 times above baseline by the end of the infusion. Following GnRH's discovery, more potent analogues were developed, which, like native GnRH, initially augmented LH but eventually suppressed gonadotroph and gonadal function. In one study of healthy men using chronic buserelin infusion via osmotic minipumps, LH levels sharply declined after the initial peak by the end of first week with further suppression in LH and testosterone over subsequent weeks[30]. Notably, subjects receiving the higher buserelin dose showed signs of desensitization as early as 3 days, with an abolished gonadotropin response to a GnRH bolus during the infusion. Although kisspeptin may not behave identically to GnRH, these studies help contextualize the possible effects of continuous exposure of the kisspeptin receptor to the kisspeptin ligand or an analogue.

Like GnRH, kisspeptin is a hypothalamic peptide derived from a larger precursor molecule[31] and is secreted in pulsatile fashion[32]. Continuous infusion of kisspeptin, as demonstrated in several animal species[1, 33–36], initially induces GnRH-mediated LH release, followed by a progressive decline in LH levels. However, notable differences in the observed patterns across species emphasize the complexity of the mechanisms. The time required for LH desensitization is variable within rats[34, 36], ewes[35] and monkeys[1, 33] ranging from 24 hours to 2–3 days. Variations in kisspeptin response can be partly attributed to differences in experimental design, including kisspeptin peptide formulation, dosing, and duration of exposure. Underlying biological factors may also contribute to variability in kisspeptin response, with notable species differences in kisspeptin cell populations within the hypothalamus[37]. Finally, the response to kisspeptin can change depending on developmental stage and by extension, sex steroid environment[38, 39].

While both GnRH and kisspeptin systems exhibit attenuation with sustained exposure, their desensitization profiles may differ in mechanism. GnRH receptor has a unique physical structure that lacks a cytoplasmic tail, which is typically required for rapid β -arrestin-mediated desensitization. Instead, GnRH receptor desensitization mainly reflects post-receptor adaptations—including diminished calcium signaling and transcriptional responses—during sustained exposure to its ligand[40, 41]. In contrast, the kisspeptin receptor does have a cytoplasmic tail, and its desensitization is mediated by classical G protein-coupled receptor mechanisms[42, 43]—receptor phosphorylation, β -arrestin recruitment, internalization, and receptor downregulation[44, 45]. Internalized receptors may be recycled or degraded, and sustained stimulation increasingly favors degradation, leading to long-term desensitization.

The concept of reduction in LH levels with continuous kisspeptin infusion secondary to desensitization reflects an effect at the level of the hypothalamus rather than the pituitary. Evidence for this comes from studies in rhesus monkeys in which a discrete kisspeptin bolus administered during a continuous kisspeptin infusion failed to elicit an LH rise, while the pituitary remained fully responsive to an exogenous GnRH bolus[1]. This pattern suggests that desensitization reflects reduced stimulatory

kisspeptin input to GnRH neurons; however, it is still not fully understood how this diminished drive affects overall GnRH secretory dynamics.

Human investigations into the downregulation of the reproductive axis in response to continuous kisspeptin administration have been limited and have yielded variable results. Several years ago, an important study demonstrated that twice-daily subcutaneous injections of kisspeptin-54 for two weeks in women with hypothalamic amenorrhea potently stimulated gonadotropin release at the start of study[46]. However, with continued administration, the effect diminished, providing one of the first pieces of evidence in humans that repeated stimulation of the kisspeptin receptor might lead to reduced LH release. Other studies using intravenous kisspeptin administration for shorter durations have revealed different biological responses. For example, an 8-hour continuous infusion of kisspeptin-54 in women with hypothalamic amenorrhea increased LH pulses[47]. Studies examining kisspeptin-10 infusion at 4 mcg/kg/h (3 nmol/kg/h) in both healthy men[48] and men with type 2 diabetes mellitus[49] over 22.5 hours demonstrated an initial rise in LH with increased LH pulsatility, but no decrease in LH levels.

In contrast, clinical studies utilizing oligopeptide analog of kisspeptin, TAK-448, administered subcutaneously (0.01–1 mg/day which is approximately equivalent to 0.05–0.5 pmol/kg/h) resulted in profound downregulation of the reproductive axis. When given to healthy male volunteers for two weeks, LH and testosterone levels fell to below-baseline values by 60 hours and further declined to castration levels by day 8[22]. This evidence for desensitization of the hypothalamic-pituitary-gonadal axis was achieved at all doses tested. Although direct comparisons have not been performed in human subjects to our knowledge, studies in rats have shown that TAK-448 decreases plasma LH and FSH levels more rapidly and effectively compared to the GnRH agonist leuprolide[23].

In summary, while our study reinforces previous observations that kisspeptin-10 infusion initially stimulates the hypothalamic-pituitary-gonadal axis, it remains unclear whether prolonged exposure duration will attenuate kisspeptin receptor signaling in eugonadal male. Modulation of kisspeptin receptor signaling in humans is likely to be both time- and dose-dependent. As previous studies have varied in the isoform of kisspeptin used and their pharmacokinetics[50, 51], it is important to remember that kisspeptin-10 and – 54 may differ with respect to thresholds for receptor saturation and desensitization. Our study was designed as a proof-of-concept experiment to define the physiological response to sustained kisspeptin exposure, which can inform future studies.

Declarations

Competing Interests:

Stephanie Seminara has a financial interest in SeNa Therapeutics, which is developing treatments for reproductive disorders. Dr. Seminara's interests were reviewed and are managed by MGH and Mass General Brigham in accordance with their conflict of interest policies. The other authors have nothing to disclose.

Ethics Approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Mass General Brigham Institutional Review Boards (IRB).

Consent:

Informed consent was obtained from all individual participants included in the study.

Funding:

This work was supported by following grants: S.B.S P50HD104224 from the National Center for Translational Research in Reproduction and Infertility, R37HD043341 from the Eunice Kennedy Shriver National Institute of Child Health and Development and R01FD007843 from the Food and Drug Administration. This work was conducted with support from UL1TR002541 award through Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

Acknowledgements:

This work was supported by following grants: S.B.S P50HD104224 from the National Center for Translational Research in Reproduction and Infertility, R37HD043341 from the Eunice Kennedy Shriver National Institute of Child Health and Development and R01FD007843 from the Food and Drug Administration. This work was conducted with support from UL1TR002541 award through Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

We thank the research subjects, the staff of the Translational and Clinical Research Centers (TCRC) for assistance with the studies; and Min S. Lee, PhD, of the Contraceptive Development Program, Division of Population Health Research, National Institute of Child Health and Human Development (NICHD), for valuable assistance with kisspeptin polypeptide storage.

Data Availability:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

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Tables

Table 1. Baseline Characteristics				
	Subject 1	Subject 2	Subject 3	Reference Range
Age, y	32	23	27	-
BMI, kg/m ²	26.7	27.5	22.5	-
Testicular volume, mL	20	25	25	15-25
Creatinine, mg/dL	0.92	1.0	0.83	0.76-1.27
ALT, U/L	15	34	19	0-55
TSH, µIU/mL	2.7	0.9	3.6	0.45-4.5
Prolactin, ng/ml	9.1	8.1	9.1	4.0-15.2
LH, mIU/mL	3.7	5.0	3.1	1.7-8.6
FSH, mIU/mL	3.7	1.1	1.4	1.5-12.4
Testosterone, ng/dL	641	602	579	348-1197

BMI: body mass index; ALT: alanine transaminase; TSH: thyroid-stimulating hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone

Table 2. Hormonal Pattern During Kisspeptin Infusion									
	LH (mIU/mL)			FSH (mIU/mL)			Testosterone (ng/dL)		
	Pre	Max	End	Pre	Max	End	Pre	Max	End
Subject 1	3.1 ± 0.8	19.9 ± 0.7	10.7 ± 0.8	3.2 ± 0.1	8.1	6.2	471 ± 28	847	772
Subject 2	3.8 ± 0.5	30.6 ± 0.4	22.8 ± 0.6	1.1 ± 0.1	3	2.7	530 ± 38	902	748
Subject 3	3.7 ± 1.1	17.5 ± 0.4	15.4 ± 1.1	1.4 ± 0.1	2.9	2.8	640 ± 26	913	793
Values are given as mean ± standard deviation.									

Figures

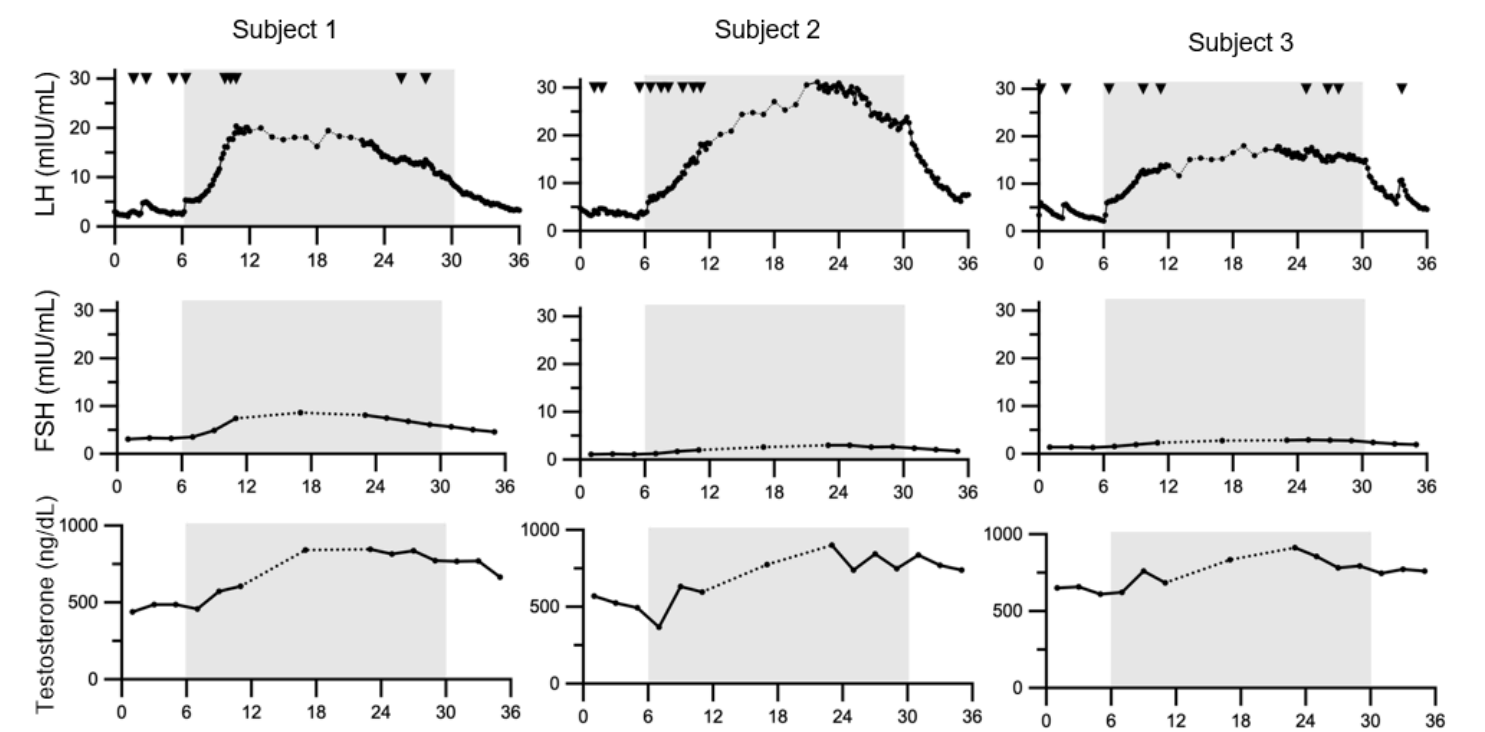


Fig 1. LH, FSH and testosterone levels before, during and after kisspeptin administration. *Shaded box* indicates the 24-hour kisspeptin infusion period (12.5 mcg/kg/h); *arrowhead* indicates peak of LH pulses

Figure 1

See image above for figure legend