Acute and chronic effects of kisspeptin-54 administration on GH, prolactin and TSH secretion in healthy women

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Introduction

- Kisspeptin (KP-54) is a hypothalamic neuropeptide acting on the KISS1R at GnRH neurons to secrete GnRH into the portal circulation (1,2,3).
- GnRH then acts on pituitary gonadotrophs to secrete gonadotrophins.
- Inactivating mutations of KISS1R lead to pubertal failure (4,5).
- KISS1R are found in various tissues including the pituitary (1).
- KP-54 is being used in various clinical trials, including as the trigger for oocyte maturation in IVF.
- There is an ongoing debate due to conflicting animal studies as to whether KP-54 stimulates non-reproductive pituitary hormones.
- There have been no human studies to date looking at the effects of kisspeptin on non-reproductive pituitary hormones

Aim

- To establish whether kisspeptin-54 stimulates non-reproductive pituitary hormones in healthy female volunteers.

Methods

- Post hoc analysis of a prospective, single blinded, placebo controlled, one way cross over study (6).
- 5 healthy women (aged 24-37)
- Month 1 – self administered subcutaneous injections of 0.9% saline twice daily from day 7-14 of the menstrual cycle.
- Month 2 – self administered subcutaneous injections of kisspeptin-54 twice daily from day 7-14 of the menstrual cycle (6.4 nmol/kg).
- Study 1 – acute effects of kisspeptin for 4 hours after 1st injection.
- Study 2 – GH pulsatility 4 days after starting injections. 8 hours of regular blood sampling to review GH pulsatility.
- Study 3 – Chronic effects of kisspeptin at day 14 compared with hormone levels on day 7(first and last day of injections).

Conclusion

- For the first time in humans we have investigated the effects of kisspeptin on non-reproductive pituitary hormones.
- We observed no significant change in GH, TSH or PRL after kisspeptin administration, either acutely or after 7 days.
- It is important to recognise that we cannot exclude that kisspeptin has subtle effects on the secretion of these hormones.
- As kisspeptin is emerging as a possible treatment for certain infertility disorders, our data importantly suggests that at the dose tested, kisspeptin does not cause stimulation of other pituitary hormones.

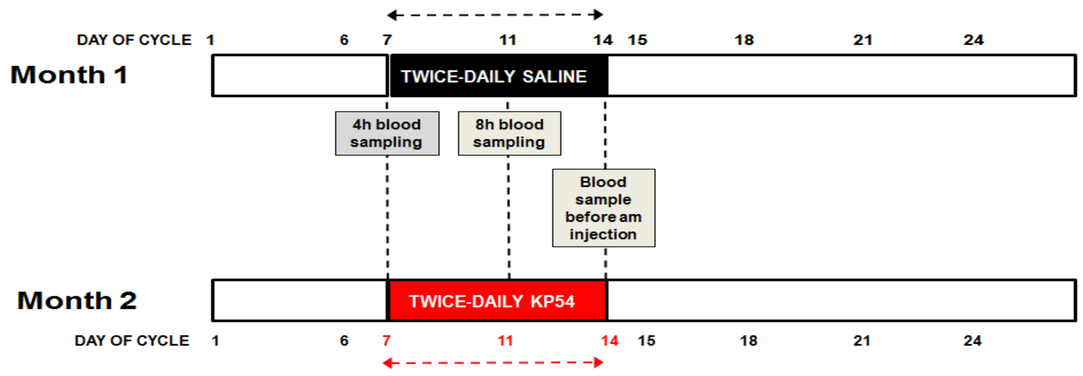

Figure 1: Study protocol diagram. Month 1 – saline injected twice daily on day 7 of menstrual cycle. Month 2 – kisspeptin-54 (6.4 nmol.kg) injected twice daily.

Results – Acute effects

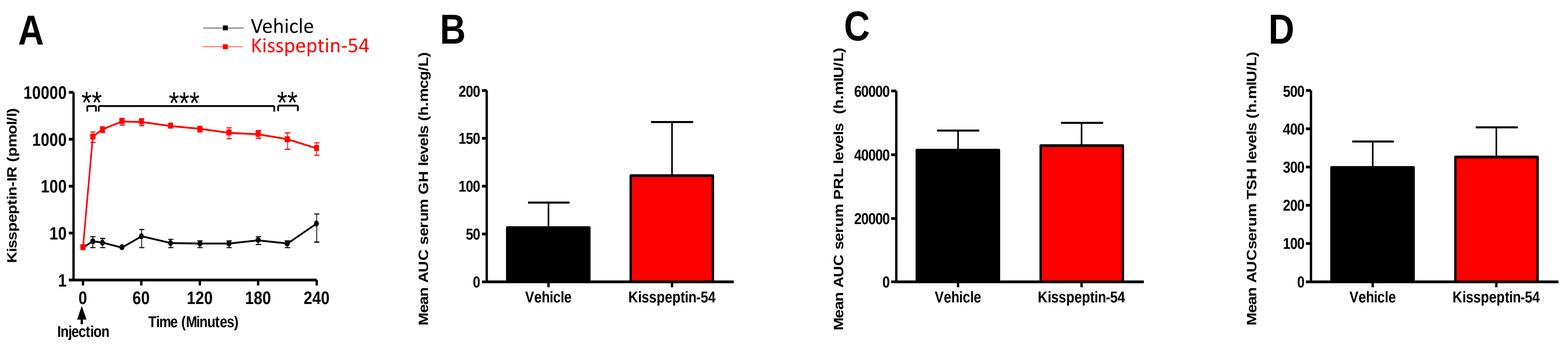

Figure 2: Acute effects of the first injection of vehicle or kisspeptin-54 on GH, PRL and TSH Frequent sampling over 4 hours after the injection (of vehicle in the first month and kisspeptin in the second month on day 7 of the menstrual cycle). Collated results from all participants: **(A)** Time profile of Kisspeptin-IR after injection, **(B)** GH, **(C)** PRL and **(D)** TSH hormone levels presented as AUC. No significant difference in hormone levels between groups.

Results – GH pulsatility

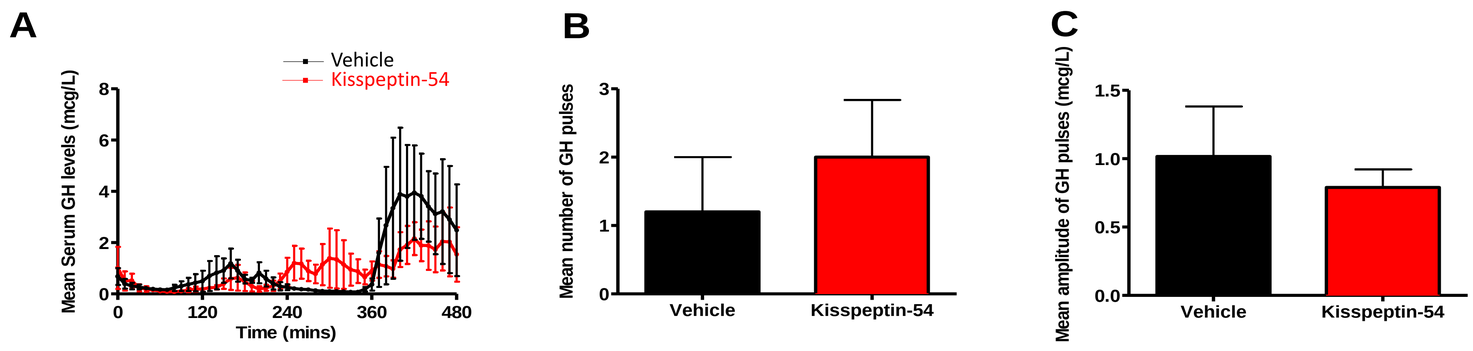

Figure 3: The effects of vehicle or kisspeptin-54 on GH pulsatility.
(A) Grouped mean GH results for each time point of the 8 hour study following 4 days of twice daily injections of vehicle (saline) in month 1 and kisspeptin-54 (6.4nmol/kg) in month 2.
(B) Mean number of GH pulses in the 8 hour period following injection of vehicle or kisspeptin-54 collated for the five participants. **(C)** Mean amplitude of the GH pulses collated for the five participants.

Results – Chronic effects

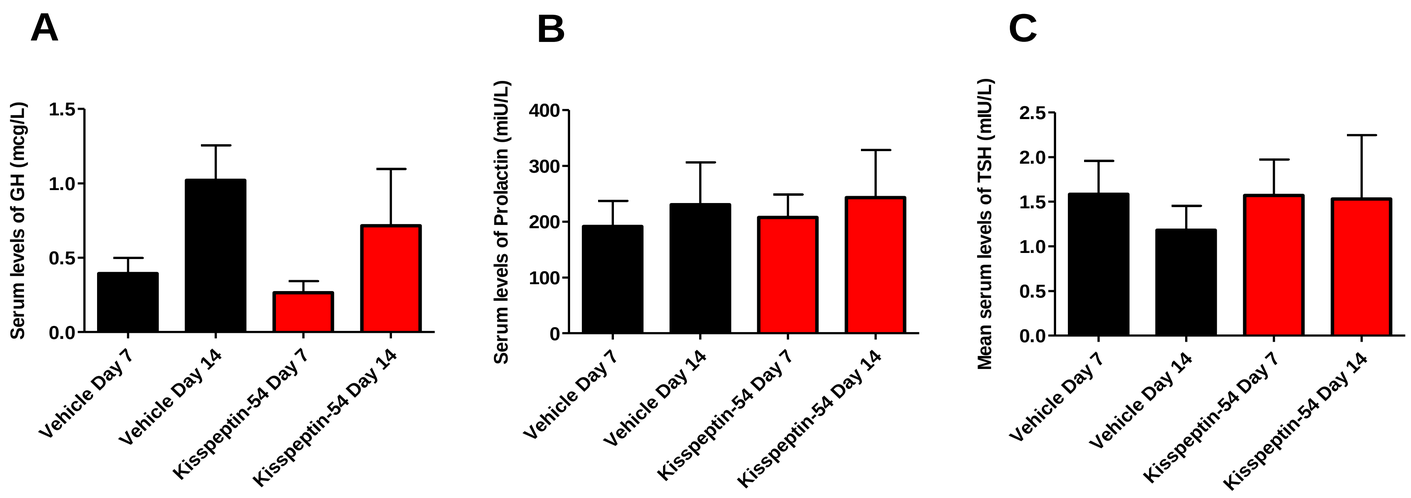

Figure 4: Effects of chronic subcutaneous administration of vehicle or kisspeptin-54. Hormone levels taken prior to the first injection of vehicle (month 1) and kisspeptin-54 (month 2) on day 7 of their menstrual cycle and again on day 14 (after 7 days of twice daily injections of vehicle in month 1 and kisspeptin-54 in month 2). Collated results from all participants and shown for **(A)** GH, **(B)** PRL and **(C)** TSH. No statistical difference in hormone levels between the vehicle and kisspeptin groups or between the day 7 and 14 results.

References
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