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Introduction

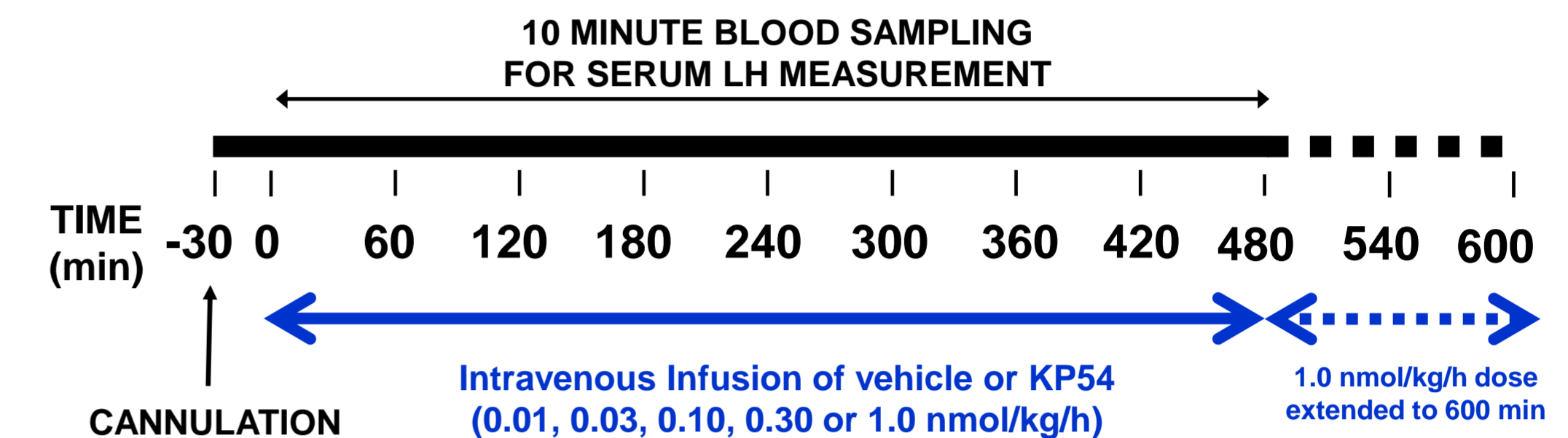
Kisspeptin-54 (KP54) is a recently identified hormone, which potently stimulates gonadotrophin releasing hormone (GnRH) secretion within the hypothalamus. Women with hypothalamic amenorrhoea (HA, hypogonadotrophic hypogonadism associated with low body weight) have reduced luteinising hormone (LH) pulsatility causing amenorrhea and infertility. We have previously demonstrated that exogenous administration of KP54 acutely stimulates gonadotrophin secretion in women with HA, but chronic administration results in tachyphylaxis. However, it is not known whether continuous exogenous administration of KP54 can stimulate LH pulsatility in women with HA.

Aims

To determine whether constant intravenous infusion of KP54 is able to stimulate pulsatile LH secretion in women with HA.

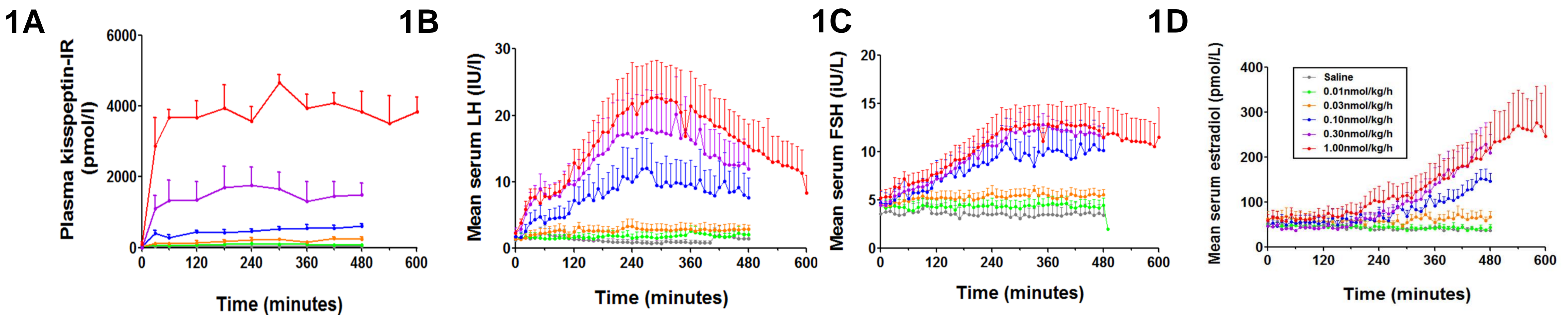
Methods

A single-blinded, placebo-controlled study was performed. Five participants with HA due to low body weight or exercise (mean BMI 18.3) each attended six study visits. Blood was sampled at 10min intervals for measurement of LH. Participants received a continuous intravenous infusion of vehicle or KP54 (doses 0.01, 0.03, 0.1, 0.3 or 1nmol/kg/h) for 8 hours. The 1nmol/kg/h dose was extended to 10h and immediately followed by a 100mcg GnRH test. LH pulsatility was determined by blinded deconvolution analysis.



Results 1: Effect of KP54 infusion on mean LH levels

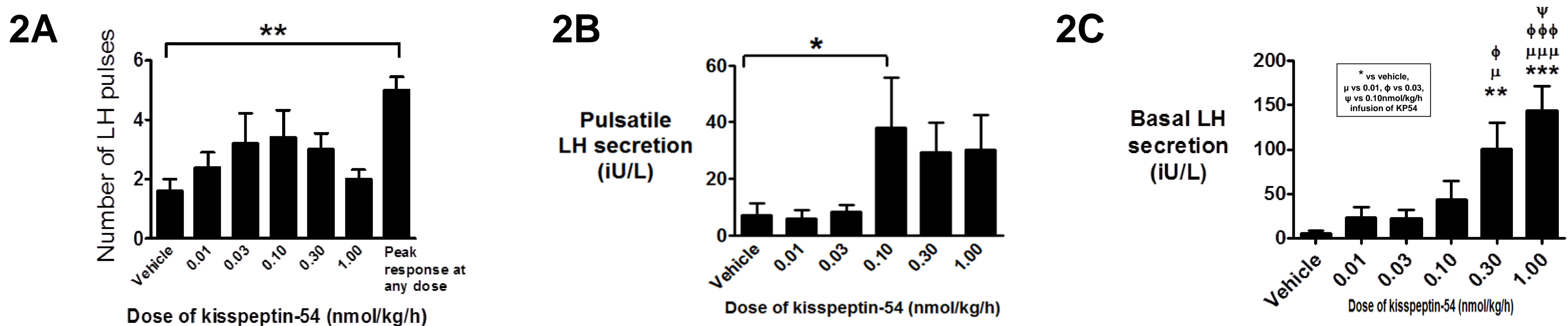
Data presented are mean±SEM during KP54 infusion (0.01, 0.03, 0.10, 0.30, and 1 nmol/kg/h) of 1A kisspeptin (pmol/l); 1B LH (iU/l); 1C FSH (iU/L) and 1D oestradiol (pmol/l)



There was a dose-dependent increase in mean serum LH (iU/L) during KP54 administration. Mean serum LH was increased over 10-fold during infusion of the highest dose of KP54 when compared with vehicle (mean level of serum LH during infusion: 1.26 ± 0.56 , vehicle; 15.42 ± 3.57 , 1.00nmol/kg/h KP54, $P < 0.01$ vs. vehicle).

Results 2: Effects of intravenous KP54 on LH pulsatility

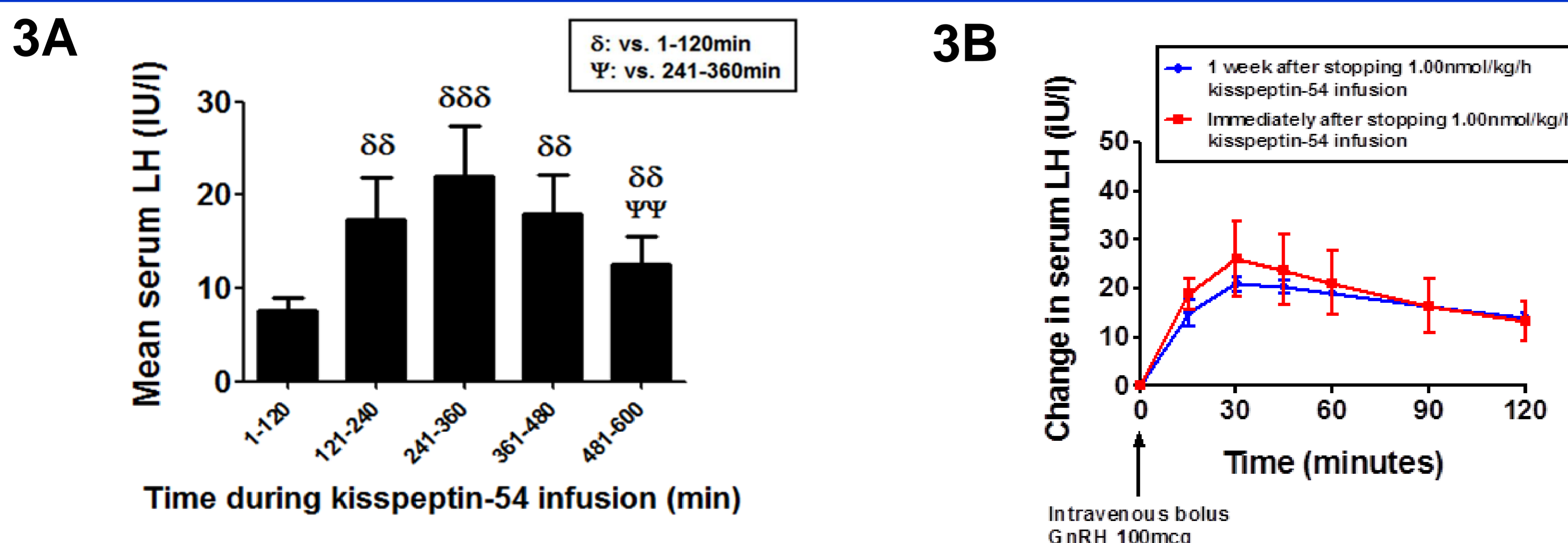
2A number of LH pulses during KP54 infusion by dose; 2B Basal LH secretion (iU/L) during KP54 infusion by dose; 2C Pulsatile LH secretion (iU/L) during KP54 infusion by dose



As expected, very few LH pulses (1.6 ± 0.4 per 8h) were observed during infusion of vehicle in women with HA. KP54 increased LH pulsatility in all patients with HA, with peak responses observed at different doses in each patient. The mean peak number of pulses during infusion of KP54 was 3-fold higher when compared with vehicle (number of LH pulses per 8h: 1.6 ± 0.4 , vehicle; 5.0 ± 0.5 , KP54, $P < 0.01$ vs. vehicle) (figure 2A). Pulsatile LH secretion was increased 4-fold during 0.10nmol/kg/h KP54 when compared with vehicle (mean pulsatile LH in iU/l: 7.0 ± 4.3 , vehicle; 37.9 ± 17.7 , dose of kisspeptin-54 associated with peak number of pulses; $P < 0.05$ vs. vehicle) (figure 2B). Basal LH secretion was increased in a dose-dependent manner during infusion of KP54 (figure 2C).

Results 3: Tachyphylaxis during the highest dose of KP54 (1nmol/kg/h)

3A mean serum LH during infusion of 1nmol/kg/h of KP54 3B mean LH during GnRH test immediately following and 1 week after 1 nmol/kg/h dose of KP54



During the highest dose of KP54 administration mean LH levels peaked at 5h after starting the infusion before gradually falling to levels 50% lower by the end of the 10h infusion when compared with peak levels. Mean LH secretion during a GnRH test immediately following infusion of the 1nmol/kg/h dose of KP54 and one week later was not significantly different suggesting that desensitisation to the stimulatory effects of KP54 did not involve the pituitary gland.

Summary and therapeutic implications

In summary, we demonstrate for the first time that intravenous infusion of KP54 temporarily stimulates LH pulsatility in women with infertility due to HA. Furthermore we have determined that the dosing range of KP54 associated with pulsatile secretion of LH is distinct from higher doses of KP54 associated with tachyphylaxis. This work provides a basis for studying the potential of kisspeptin-based therapies to treat women with HA.