

INTRODUCTION

In rodents, female reproductive behavior is characterized by the lordosis posture when the female is mounted by the male. It has been shown that GnRH can stimulate lordosis behavior suggesting that it might play a role in the brain itself in addition to its well-known role in stimulating the pituitary to release LH and FSH. However, elucidating its functional role in the central nervous system has been difficult because of the difficulty in identifying direct GnRH signaling targets in brain tissue. Previous studies in our laboratory, however, have suggested a role for kisspeptin, an important upstream regulator of GnRH, in lordosis behavior. We further confirmed this by showing that female mice carrying a mutation in the kiss1 gene (Kiss-KO) displayed significantly less lordosis behavior compared to wild-type (WT) females. Interestingly, a peripheral injection with kisspeptin restored lordosis behavior in Kiss-KO mice. To further investigate the functional relationship between kisspeptin and GnRH signaling in lordosis behavior, we focused on neuronal nitric oxide (nNOS)-expressing neurons since nNOS has been shown to co-localize with kisspeptin in the hypothalamus. In this study, we investigate the role of nNOS in the pathway controlling the lordosis using transgenic models knockout models for nNOS and KISS.

METHODS

Transgenic models.

Two transgenic models were used for this study : knockout mice for the neuronal form of nitric oxide synthase (nNOS-KO) and for kisspeptin (KISS-KO).

Surgery.

C57Bl6/J (nNOS KO) and SV129 mice (KISS KO) female mice were ovariectomized and implanted sc with an estradiol capsule in adulthood

Female sexual behaviors.

Female reproductive behaviors were assessed by using two classical paradigms, with a P injection 3h before tests:

Lordosis behavior



Mate preference test



RESULTS

Kiss and GnRH injections do not restore sexual behavior of nNOS null female mice

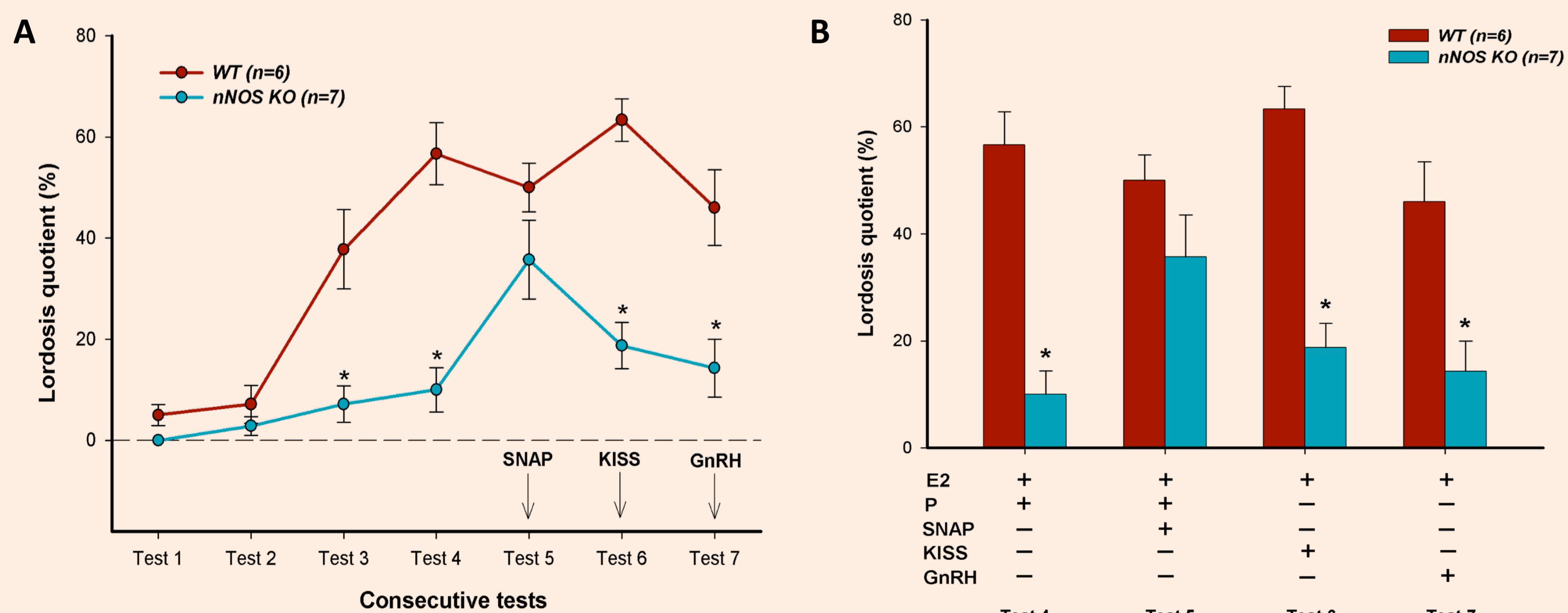


Fig 1. Effect of peripheral injections of SNAP (NO donor), kisspeptin and GnRH in the expression of lordosis behavior in nNOS KO female mice following ovariectomy and treatment with estradiol and progesterone (3h before test). Mean \pm SEM lordosis quotients over (A) consecutive tests or (B) the last 4 tests in WT control and nNOS KO females. * $P < 0.05$, significantly different from nNOS KO females (post hoc tests).

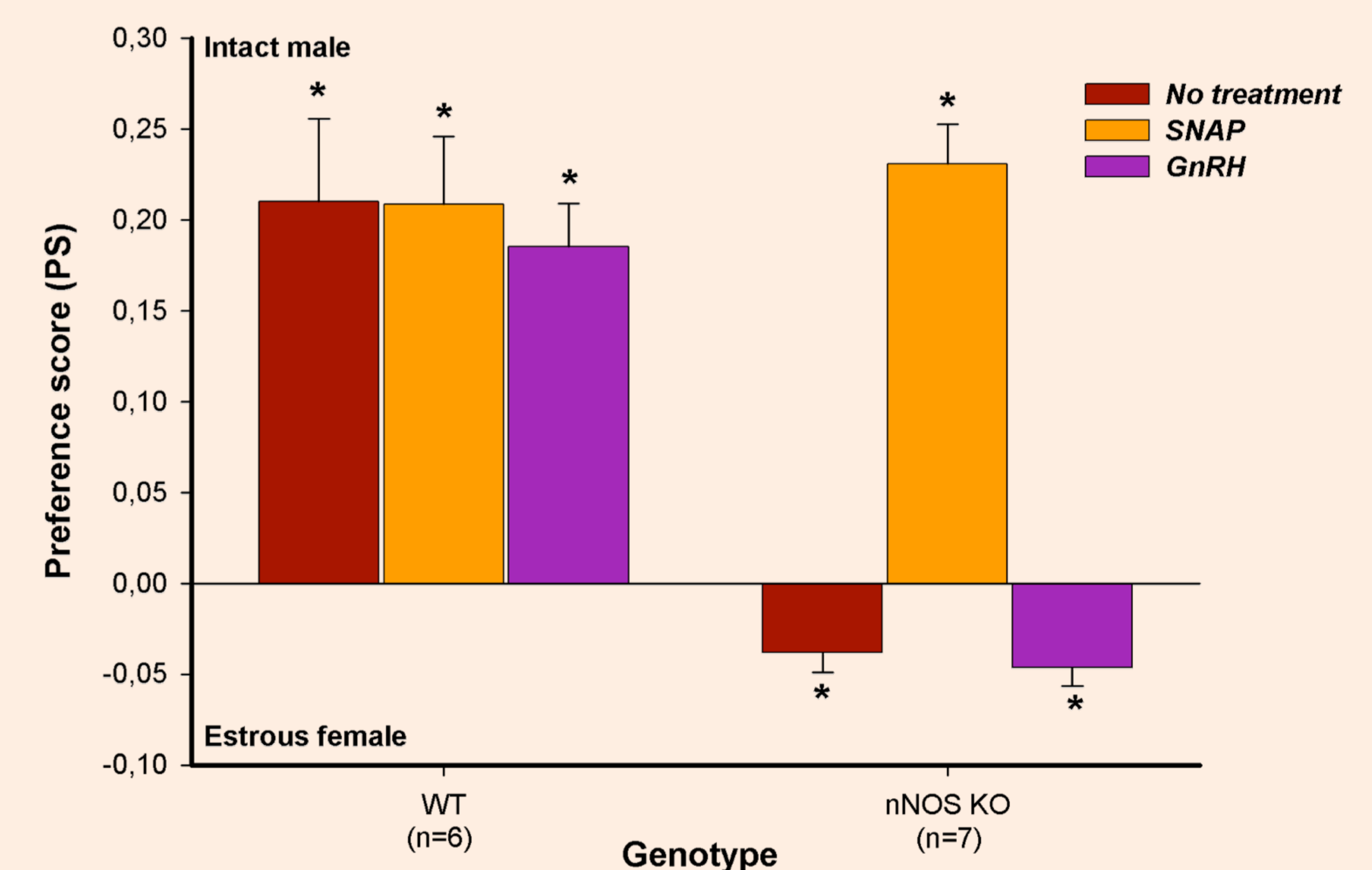


Fig 2. Effect of peripheral injections of SNAP and GnRH on the mate preference of nNOS KO female mice following ovariectomy and treatment with estradiol and progesterone (3h before test). Positive values of the preference reflect a mate preference for stimulus male; negative values reflect a mate preference for the stimulus female. * $P < 0.05$, preference score significantly different from zero (t-test).

Nitric oxide stimulate female sexual behavior in KISS null mice

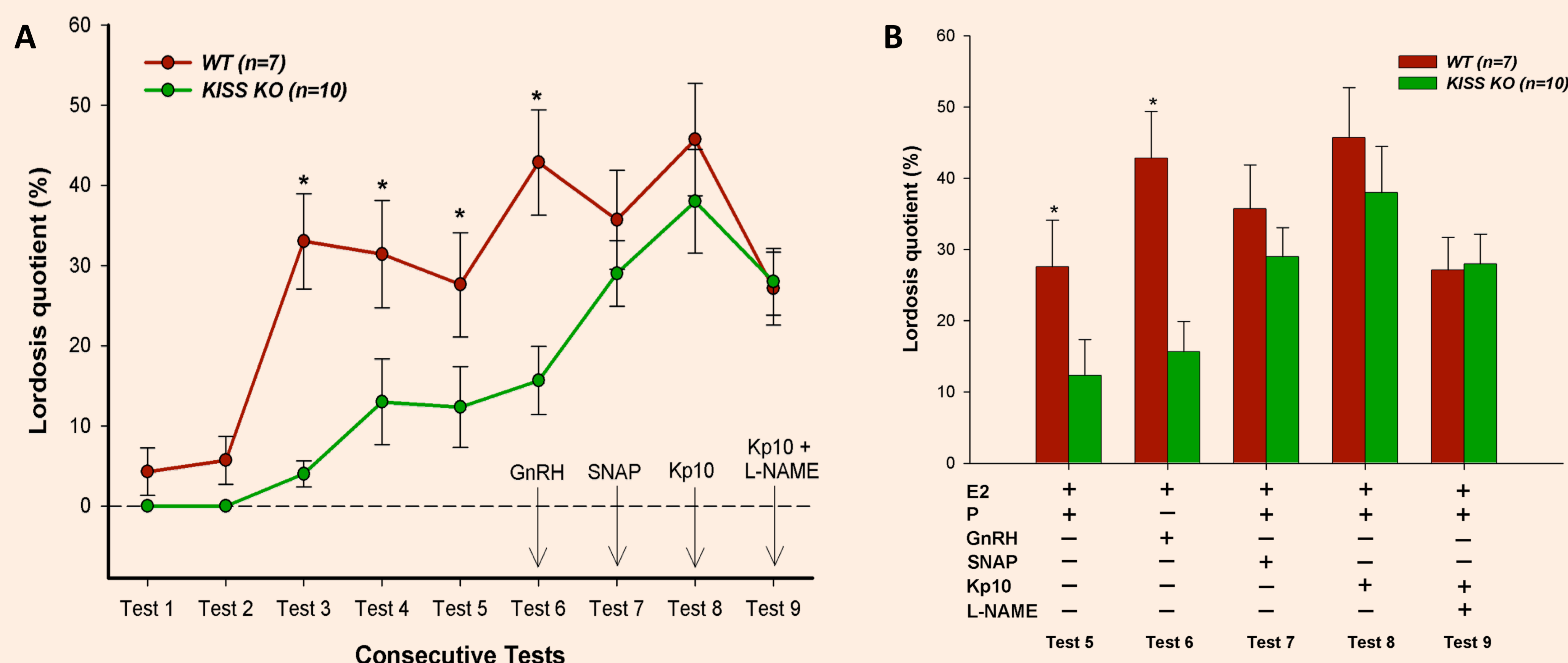


Fig 3. Effect of peripheral injections of GnRH, SNAP (NO donor), kisspeptin L-NAME (nNOS antagonist) in the expression of lordosis behavior in KISS KO female mice following ovariectomy and treatment with estradiol and progesterone (3h before test). Mean \pm SEM lordosis quotients over (A) consecutive tests or (B) the last 5 tests in WT control and KISS KO females. * $P < 0.05$, significantly different from nNOS KO females.

CONCLUSION

nNOS KO and KISS KO mutations in females mice sharply reduce the expression of lordosis behavior and mate preference. However, injections of SNAP, a nitric oxide donor induce an restoration of the sexual behavior and sexual recognition in those models at levels not significantly different from WT mice., indicating that nNOS is important for the establishment of the sexual behavior. On the other hand, peripheral injection of SNAP stimulate the female sexual behavior just like kisspeptin whereas L-NAME and Kiss co-injection cannot sharply reduce the behavior. All these results suggest that nNOS is an important element of the lordosis pathway and that it seems to be the common pathway to the Kiss and GnRH signalling in the hypothalamus to control the lordosis reflex.

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