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Kisspeptin Increases Penile Tumescence and Sexual Brain Processing in Men with Hypoactive Sexual Desire Disorder

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Background: Hypoactive Sexual Desire Disorder (HSDD) is associated with dysfunctional brain activation in regions governing sexual responses, resulting in a deficiency or absence of sexual desire with marked distress. It is of major clinical importance given it affects 8% of men with detrimental effects on quality of life, interpersonal relationships and fertility, but so far has no licensed treatment options. The reproductive neuropeptide kisspeptin offers a putative therapeutic target owing to its emerging role in modulating reproductive behaviour in animal models and healthy men. However, there are no studies examining its effects in HSDD. To address this, we performed the first clinical study of kisspeptin in men with HSDD. **Methods:** We examined the effects of kisspeptin administration (vs placebo) on brain activity during short and long erotic video tasks using functional MRI in 32 men with HSDD (mean ±SEM age 37.9 ±1.5 y, BMI 24.9 ±1.0 kg/m^2). The short video task used 20-second segments of erotic video with non-erotic video as control. During the long video task, participants viewed a continuous eight-minute erotic video. To provide functional and behavioural relevance for the associated fMRI brain responses during the long erotic video, simultaneous penile tumescence and subjective level of arousal were recorded. Participants also completed psychometric and behavioural questionnaires. Standard analysis methods were used for fMRI data from the short videos task, and the long videos task used regressors derived from the subjective arousal and penile tumescence data. The statistical threshold used for both was $Z=2.3$, $p < 0.05$ (cluster-corrected). **Results:** In response to visual erotic stimuli, kisspeptin administration significantly increased penile tumescence during the long video task compared to placebo, with kisspeptin increasing penile tumescence by 56% at six-minutes ($p=0.002$). In addition, kisspeptin increased participant-reported happiness about sex ($p=0.02$). During both video tasks, kisspeptin significantly modulated brain activity compared to placebo in key structures of the sexual-processing network, providing a mechanistic pathway for the increases in physiological and behavioural measures. In response to short erotic videos, kisspeptin enhanced left middle frontal gyrus and left anterior cingulate activity, and decreased activity in bilateral parahippocampus (all $p<0.05$). During the long video task, kisspeptin enhanced right fusiform gyrus and bilateral visual cortex activity, and decreased left frontal pole, right posterior cingulate and bilateral precuneus activity (all <0.05). Additionally, we observed positive correlations between the effects of kisspeptin on aforementioned brain activity and psychometric parameters of sexual desire and arousal (all $p<0.01$). **Conclusion:** Collectively, we demonstrate for the first time that kisspeptin administration in men with HSDD increases penile tumescence and psychometric measures of sexual desire and arousal by modulating sexual brain processing. Taken together, our data suggest that kisspeptin-based therapeutics may offer a novel, effective and much-needed clinical strategy for men with HSDD.

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