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Melanocortin-4 Receptor Agonism Enhances Sexual Brain Processing in Women with Hypoactive Sexual Desire Disorder

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Introduction: Hypoactive sexual desire disorder (HSDD) is characterized by a persistent deficiency of sexual fantasies and desire for sexual activity, causing marked distress or interpersonal difficulty. It is the most prevalent female sexual health problem worldwide, affecting approximately 1 in 10 women, but has limited treatment options despite its substantial health, social, and economic burden. Melanocortin-4 receptor (MC4R) agonists have emerged as a promising therapy for women with HSDD, although, to date, their mechanism of action is unknown. This study aims to use functional MRI to delineate the reproductive neuroendocrine pathways involved and elucidate how MC4R agonists treat HSDD in women. **Methods:** We conducted a randomized, double-blinded, placebo-controlled, crossover clinical study, using psychometric, functional neuroimaging and hormonal analyses, to assess the effects of MC4R agonism on sexual brain processing in 31 premenopausal women with HSDD. Participants attended on two occasions, receiving either a subcutaneous injection of an MC4R agonist (Bremelanotide 1.75 mg), or placebo, at each study visit, thereby acting as their own controls. **Results:** 31 randomized women were included (mean age 32 years, mean duration of HSDD 41 months). MC4R agonism significantly increased self-reported sexual desire for up to 24-hours post administration, compared to placebo ($P=0.007$). During functional neuroimaging, MC4R agonism enhanced cerebellar and supplementary motor area activity, as well as deactivating the secondary somatosensory cortex, specifically in response to visual erotic videos, compared to placebo ($Z=2.3$, $P<0.05$). In addition, MC4R agonism enhanced functional connectivity between the amygdala-insula and amygdala-thalamus during prolonged visual erotic stimuli, compared to placebo ($P=0.025$). MC4R agonism resulted in a mean increase in LH of 1.1 iU/L ($F [1,58] = 13.38$, $P=0.0005$), and FSH of 0.35 iU/L ($F [1,60] = 10.97$, $P=0.0016$) across the 300-minute duration of the study, with no effect observed on circulating estradiol or progesterone levels.

Interpretation of results and conclusions:We demonstrate that MC4R agonism deactivates the secondary somatosensory cortex which can reduce the detrimental self-monitoring process often observed in HSDD, thereby increasing sexual desire. Furthermore, cerebellar and supplementary motor area activation by MC4R agonism are associated with increased sexual arousal and sexual motor imagery respectively. Finally, MC4R agonism enhanced functional connectivity between key limbic structures which can be disrupted in HSDD.

In summary, these data identify the previously undescribed neural substrates and connections through which MC4R agonism modulates sexual brain processing to increase sexual desire. These findings provide mechanistic insight for the action of MC4R agonism in sexual behaviour and are relevant to ongoing therapeutic development for HSDD and for MC4R agonist development more widely.

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