BRAINSTORMS
Clinical Neuroscience Update

Targeting Circuits of Sexual Desire as a Treatment Strategy for Hypoactive Sexual Desire Disorder

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Issue: *Hypoactive sexual desire disorder (HSDD) is hypothesized to be a disorder of the brain's reward circuitry. Neurotransmitters in reward circuits are thus therapeutic targets for improving sexual desire. Novel treatment strategies are to enhance dopamine (DA) actions, reduce serotonin (5-HT) actions, or both.*

What Is Wrong in HSDD?

The circuits thought to mediate normal sexual function are the same circuits that mediate reward in the brain.[1–3] Young women with HSDD viewing erotic videoclips appear to have less subjective sexual arousal than young women without a history of sexual problems, and to overly activate brain areas that hypothetically *suppress* emotions and not those brain areas that hypothetically *experience* emotions.[3–5] It is as though HSDD patients are mentalizing erotic images and not enjoying them, sometimes also called "spectatoring." These neuroimaging studies lead to the question: Is HSDD due to hypofunctional sexual arousal, hyperfunctional sexual inhibition, or some combination of the two?" So far, imaging studies in HSDD are consistent with hyperfunctional inhibition of reward pathways.[3–5] If so, it predicts that treatments that block inhibitory pathways would disinhibit sexual reward and improve sexual arousal in HSDD.

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For reprint and financial disclosure information, go to www.psychiatrist.com/brainstorms.
doi:10.4088/JCP.10bs06117blu

No Approved Pharmacologic Treatments for HSDD Yet

Estradiol and testosterone both are linked to sexual arousal in women.[3] The ability of erotic visual stimuli to activate limbic and cortical areas is reduced in women after menopause but can be restored by hormone treatment with estrogens and androgens, as can sexual desire and number of sexually satisfying events.[3–5] Because of such observations, estrogens, testosterone, and synthetic steroids such as tibolone have all been administered for HSDD, with improvement in the number of satisfying sexual events, especially in postmenopausal women.[3] However, concerns about the long-term safety of this approach have largely caused large clinical trials to be abandoned, and currently no hormone treatment is approved for women with HSDD.

Other pharmacologic approaches to improve sexual interest, libido, and arousal in HSDD are largely anecdotal and based in part upon similarly anecdotal treatments for sexual dysfunction in patients taking selective serotonin reuptake inhibitors (SSRIs).[2,3] These treatments include off-label use of a wide variety of agents that act by enhancing DA activity (eg, bupropion, stimulants, DA agonists, amantadine, buspirone), or by inhibiting 5-HT activity (eg, cyproheptadine, buspirone).[2,3] None of these agents is currently being tested in large scale clinical trials for HSDD, and none will likely ever be formally approved for the disorder for commercial reasons and lack of consistent, robust efficacy.

Novel Targets to Enhance Neurotransmitters of Sexual Arousal

Since DA is generally considered to be the major neurotransmitter that mediates sexual arousal, due to its actions in mesolimbic and hypothalamic circuits, enhancing dopaminergic actions in these brain areas is a logical strategy for improving the symptoms of HSDD.[1–3] In fact, anecdotal evidence suggests that patients who take levodopa or DA agonists (such as drugs given for Parkinson's disease) experience an increase in sexual drive. Additionally, some patients who have been taking antidepressants that lead to increased DA release, such as the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion, can also experience an increase in sexual drive.[1–3] Testosterone may actually enhance sexual interest via a dopaminergic mechanism, namely by interacting with neurons in the hypothalamus and boosting the ability of DA to act in the hypothalamus.[3] Animal models of sexual arousal also strongly support the role of DA in mesolimbic and hypothalamic circuits.[3] However, agents with robust DA actions are often reinforcing, causing the development of addiction, and agents with less robust DA actions are often ineffective, or wear off over time.[2,3] Thus, direct targeting of DA targets has been largely abandoned as a treatment strategy for HSDD.

Take-Home Points

- In HSDD, sexual excitation may be reduced, possibly due to reduced actions of the neurotransmitters dopamine (DA), norepinephrine, oxytocin, or melanocortins in reward circuits.
- Sexual inhibition may be enhanced, which is possibly the cause of the reduced sexual excitation in HSDD. Sexual inhibition may be mediated by the increased actions of the neurotransmitters serotonin (5-HT), opioids, or endocannabinoids in reward circuits.
- Drugs that increase DA directly may enhance sexual excitation in HSDD but risk the development of abuse and addiction due to unwanted actions in reward pathways.
- Increasing DA by indirect means such as disinhibition, thus avoiding direct DA actions in reward pathways, is another strategy for treating HSDD. Thus, drugs that increase DA indirectly by blocking 5-HT actions or that promote oxytocin or melanocortins in reward pathways are promising and novel treatment strategies to enhance sexual excitation in patients with HSDD.

Melanocortins are neuropeptides linked to arousal, especially their actions at 2 different melanocortin receptors (MC_3 and MC_4) in hypothalamus and limbic areas.[1,3,6] The intranasal or subcutaneous administration of the neuropeptide bremelanotide, an $MC_{3,4}$ agonist, improves sexual dysfunction in both men and women.[7–9] However, it also raises blood pressure and has been dropped from further development. Another neuropeptide, oxytocin, well known as the "affinity" neurotransmitter or the "bonding" hormone, can promote sexual arousal,[3] but is difficult to administer and, as a natural product, is not patentable and thus there is not commercial incentive for it to be developed.

Blocking Neurotransmitters of Sexual Inhibition Also Disinhibits Neurotransmitters of Sexual Arousal

More promising is the approach of increasing DA by indirect actions, namely by disinhibiting its release. If sexual dysfunction in HSDD is due to overly active inhibitory 5-HT circuits in reward pathways, DA would be excessively inhibited, both at the brain stem and via prefrontal cortex circuits.[1–3] When such inhibition is blocked, as can occur when the inhibitory 5-HT_{1A} receptor is stimulated while the excitatory 5-HT_{2A} receptor is blocked, DA release is disinhibited.[1–3,10] One drug that has 5-HT_{1A} agonist plus 5-HT_{2A} antagonist actions is flibanserin. This agent not only increases DA and reduces 5-HT in prefrontal cortex,[11] but also is in late-stage clinical development for HSDD, showing a significant increase in sexually satisfying events.[12]

Theoretically, agents that block opiates or block endocannabinoids might also disinhibit sexual inhibitory mechanisms in reward pathways,[3] but there are few trials or agents utilizing this approach yet.

Summary

HSDD may be linked to overactive inhibitory circuits in reward pathways, with excessive activity of 5-HT and diminished activity of DA. Promising approaches to the treatment of HSDD include inhibiting the inhibitory circuits (thus disinhibiting them) by blocking the overly active 5-HT circuits in order to indirectly enhance the underactive DA circuits. Other promising therapeutic targets are enhancing the actions of melanocortins and oxytocin.

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