Illustrating the Circuits of Sexual Desire

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**Issue:** Malfunctioning reward pathways may mediate the reduction of sexual desire caused by depression, sexual disorders, endocrine disorders, hormones, and various psychotropic drugs. Effective treatments for reduced libido target these circuits by enhancing dopamine, reducing serotonin, or both.

**Take-Home Points**

- Reward pathways connect the prefrontal cortex with many key brain regions, including neurotransmitter centers, limbic emotional areas, and the hypothalamus.
- In these circuits, some neurotransmitters, such as dopamine, norepinephrine, oxytocin, and melanocortins, cause sexual excitation whereas other neurotransmitters, such as serotonin, opioids, and endocannabinoids, inhibit sexual excitation in these same circuits.
- Drugs, hormones, and disorders that disrupt sexual desire may either reduce the neurotransmitters of sexual excitation or enhance the neurotransmitters of sexual inhibition.
- Potential treatments for reduced sexual desire are those that promote dopamine, oxytocin, or melanocortins or block serotonin in reward pathways.

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**Figure 1. Circuits of Low Sexual Desire in Hypoactive Sexual Desire Disorder**

1. Prefrontal cortex (PFC) circuits utilizing glutamate as neurotransmitter may be overly active when sexual desire is low.\(^1\)\(^-\)\(^4\)

2. Glutamate neurons in PFC descend to brainstem neurotransmitter centers (raphe) where they directly stimulate serotonin (5-HT) release.

3. When these prefrontal circuits are overly active, they also reduce dopamine (DA) activity.

4. The overly active glutamate pathway reduces DA indirectly by stimulating inhibitory γ-aminobutyric acid (GABA) interneurons in both the ventral tegmental area (VTA) and the zona incerta (ZI) of the hypothalamus (which projects from within the hypothalamus to the medial preoptic area [MPOA]).

5. The net result is excessive 5-HT activity and reduced DA activity.

The behavioral output from this circuit, via the nucleus accumbens back to PFC relayed from the thalamus says “I have a headache,” which in truth is just an excuse, really meaning lack of sexual interest and desire.
Figure 2. Potential Treatments for Low Sexual Desire

The activation of 5-HT receptors in prefrontal cortex enhances dopaminergic activity.

1. Stahl SM. Circuits of sexual desire in hypothalamic dysfunction.

2. Pfau JG. Pathways of sexual desire.

   Women with hypothalamic sexual desire disorder compared to normal females: a functional magnetic resonance imaging study.

   Differences in brain activity in premenopausal women with hypothalamic sexual desire disorder (HSDD) compared to women without sexual dysfunction. Abstracts of the 12th Congress of the European Society for Sexual Medicine (ESSM), November 15–18, 2009; Lyon, France.

5. Stahl SM. Targeting circuits of sexual desire as a treatment strategy for HSDD (hypothalamic sexual desire disorder).

   Observations regarding the possible role of 5-HT(1A) receptors in sexual function.

   Flibanserin, a potential antidepressant drug, lowers 5-HT and raises dopamine and noradrenaline in the rat prefrontal cortex dialysate: role of 5-HT1A receptors.


10. Hadley ME. Discovery that a melanocortin agonist, PT-141, a melanocortin receptor agonist, in healthy male subjects.

    Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal PT-141, a melanocortin receptor agonist, in healthy males and patients with mild-to-moderate erectile dysfunction.

    Evaluation of the safety, pharmacokinetics and pharmacodynamic effects of subcutaneously administered PT 141, a melanocortin receptor agonist, in healthy male subjects and in patients with an inadequate response to Viagra.