Neuroendocrinology of Hypoactive Sexual Desire Disorder (HSDD): The Basics

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Learning Objectives:

Upon completion of this lecture participants should:

- Have a basic understanding of the neuroendocrinology of HSDD.
- Appreciate the potential sites of therapeutic intervention based on our current understanding of that neuroendocrinology.
The Sexual Response Cycle

Modified by Kaplan (1974) and Georgiadis et al. (2012)

Neurobiological & Behavioral Elements of Sexual Response

Processing of Sexual Cues & Stimuli

Cognitive Component
Integration of Signals

Motor Imagery
Appraisal
Attention

Sexual Stimulation

Inhibition / Devaluation / Withholding

Sexual Desire & Appetitive & Consummatory Behavior

Motivational & Emotional
Autonomic & Endocrine
Prefrontal Cortex Controls “Executive Function”

**EXECUTIVE FUNCTIONS**

- forethought
- concentration
- abstract reasoning
- behavioral inhibition
- programming and planning goal-oriented behaviors
- executing a sequence of responses to avoid negative consequences or interactions
- generating alternative socially-adaptive behavioral responses
- learning from experience
  - interpreting social cues
  - problem solving
- verbal ability
- attention

Evolutionary Imperative: 
Peak Desire during Ovulation

Central Regulation of Desire/Arousal

- **Serotonin**
  - (+) Testosterone (in MPOA)
  - (-)
  - (+) Melanocortins

- **Dopamine**
  - (+)
  - (-)
  - (+) Estrogen, Progesterone

- **Estradiol** (classical effects)
  - aromatase
  - (+) Prolactin
  - (-)
  - (+) Norepinephrine
  - (-)

- **Gonadotropin Secretion**
- **Copulatory Behavior**
- **Injury Response** (nerve growth)

Neural Pathways Regulating Sexual Desire in the Brain: Integration of Excitation and Inhibition

Glutamate: 2-Way Communicator in the Brain

Glutamate neurons send signals back and forth between the cortex and other regions of the brain.
Selective Regulation of Glutamate Neurons by 5-HT

Glutamate neurons can be selectively activated or inhibited due to different locations and types of 5-HT receptors on glutamate neurons.

Glutamate Neuron Activity May Be Elevated in HSDD

Preferential stimulation of 5-HT 2A receptors

Increased Glutamate Release

LOW DESIRE
Low DA & NE
High 5-HT

Flibanserin Appears to Work Through This Glutamate Network

Neural Plasticity: Animal Studies

- Adaptive changes in brain structure and function in response to:
  - Stress
  - External environment
  - Hormonal milieu (estrogens, in particular)

- Associated with changes in sexual response
  - Desire & arousal
  - Most data from rodent studies (mating, pregnancy & post-menopausal models)
Neural Plasticity: Estrogens and Neurite Growth

Van der Horst & Holstege. J Neurosci 1997; 17:1122-1136

E_2 \uparrow \text{membrane excitability (rapid effects)}

Similar changes occur with repetitive neural activity (learning/memory)

“Neurons that fire together wire together” – Donald Hebb
Decreased activation, observed primarily in the left hemisphere, is shown in red and increased activation, observed primarily in the right hemisphere, is shown in green. Minimal deactivation was observed in the right hemisphere and minimal activation was observed in the left hemisphere.

Differences in Brain Structure in Women with HSDD
Example of Experience-Based Neuroplasticity?

Alterations in:
- Salience attribution to sexual stimuli
- Perception of bodily sexual responses
- Attentional mechanisms

Decreased Gray Matter

Increased White Matter

- Lower orgasmic function
- Decreased axonal function?
- Increased inhibitory circuitry?

Current Treatments for HSDD and Their Hypothetical Mechanism(s) of Action

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hypothetical Mechanisms of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>psychological therapy (mindfulness, sensate focus, CBT)</td>
<td>trophic (neuroplastic) and functional effects</td>
</tr>
<tr>
<td>experience/behavior</td>
<td>androgenic action</td>
</tr>
<tr>
<td>testosterone</td>
<td>5HT2A receptor antagonist</td>
</tr>
<tr>
<td>fibanserin</td>
<td>5HT1A receptor partial agonist</td>
</tr>
<tr>
<td>buspirone</td>
<td>presynaptic DA receptor antagonist</td>
</tr>
<tr>
<td>bupropion</td>
<td>reuptake inhibitor for NE &amp; DA</td>
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What Is The Neuroendocrinology of HSDD?

Summary and Conclusion

- Sexual desire depends on the activation of neurochemical systems for sexual excitation by erotic cues, driven most directly by dopamine and norepinephrine.

- Sexual inhibition is a normal function of satiety, driven by brain opioid, serotonin, and endocannabinoid systems.

- HSDD may occur if sexual excitation is too weak, or sexual inhibition too strong, or a combination of both.

- Lack of sexual desire can also occur as an adaptation of neural systems to a chronic lack of sexual pleasure (i.e. a learned behavior—"use it or lose it").