Neurobiology and Etiology of Persistent Genital Arousal Disorder (PGAD)

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Masters and Johnson’s (1966) “EPOR” Model, after Moll (1908)

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


Numerous Incentives for Sex

Rewards: Sexual and Non-Sexual

Responsive Desire

Innate Sexual Desire

Sexual Receptiveness

Sexual Stimuli

Sexual Arousal
Definitions

• Sexual Arousal
  Increased genital blood flow; heart rate; sweating, swelling of erogenous tissue; pupil dilation

• Sexual Desire/Interest
  Wanting or craving sexual activity; behaviors aimed at acquiring sex partners or sexual reward

• Sexual Reward
  Pleasure; orgasm; intimacy; bonding; control; other rewards

• Sexual Inhibition
  Satiety; primary aversion; secondary avoidance

Female Sexual Response Cycle Phases
Female Sexual Response Cycle Faces

RESTING  EXCITEMENT

ORGASMIC  PLATEAU

Control of genital blood flow

A

B

C

Glands clitoris
Corpus cavernosum
Crus clitoris
Urethral opening
Vulvar vestibule
Vaginal opening

Dorsal Nerve of Clitoris
Jugal Spine
Pudendal Nerve
Penile Nerve
Inferior Rectal Nerve

NTS
Vagal nerve
Hypogastric nerve
Th10-L1

S2-S4
Sympathetic activation causes blood to accumulate in the spongiosum of the clitoris and labia, increasing the diameter of the glans clitoris, and exposing more tactile sensory nerve endings in both clitoris and labia.

This is normal in women with genital arousal in response to sexual cues and stimulation. If it occurs in a nonsexual circumstance, or if distended (as occurs in men with priapism), it is experienced as intrusive and often painful.
Stimulation of the clitoris, vagina, and cervix activate multiple regions of the brain, including somatosensory cortex, limbic structures, and hypothalamus.

Komisaruk et al., 2011. J Sex Med, 8, 2822-2830

INHIBITION
(Reward/Satiety, Stress, or Aversion)

Opioids- 5-HT- CBs-

Hormones
(Circulating levels/ actions in brain)

Experience/expectation
(Previous sexual encounters)

NE/DA/OT+
Arousal

NE/DA/OT+

DA/MCs+

Sensory input from genitals
(Perception of arousal)

Sensory input from incentives
(Olfactory/visual/auditory)

Net behavioral output
(Interest/solicitation/pursuit/copulation)

DA/MCs+

Attention

Pfaus, Scepkowski, 2005, Curr Sex Health Rep, 2, 95-100
Persistent Genital Arousal Disorder (PGAD)

- Involuntary genital and clitoral arousal that continues for an extended period (hours, days, months).
- No overt cause for the genital arousal can be identified.
- The genital arousal is not associated with feelings of sexual desire.
- The persistent sensations of genital arousal feel intrusive, unwanted, and cause distress.
- After one or more orgasms, the physical genital arousal either does not go away or returns.

PGAD is recommended for inclusion in the ICD-11

Normal engorgement during sexual arousal

Hyperengorgement

Comorbidity associated with PGAD

-- Genital pain
-- Depression and previous antidepressant use
-- Restless leg/overactive bladder syndrome
-- Pudendal neuralgia
-- Inflammation of pudendal/hypogastric nerves
-- Tourette’s/Epilepsy

-- Tarlov’s cysts
-- Interstitial cystitis
-- Pelvic varicies

*Shares similarities with vulvodynia as a neuro-vascular dysfunction, including genital peripheral neuropathy and/or dysfunctional micro-vascular arterio-venous shunting.*
Tarlov cysts

CSF-filled cysts that can form near the spinal cord. If they form in sacral or lower lumbar regions, they disturb incoming neural impulses, leading to local or supraspinal compensation.

↑ DA tone (mPOA)

Muscle spasms
Pain

Neuropathy
Inflammation
Neuralgia
Supraspinal increase in ANS tone

The mPOA is a general neural switch that controls sympathetic and parasympathetic blood flow
Genital tumescence and detumescence

Sensory Input

- mPOA
- Mesolimbic
- Nigrostriatal

Genital Responses
Appetitive Behaviors
Somatomotor Patterns

Serendipitous effect of varenicline

- Varenicline is a partial agonist of the \( \alpha_4 \beta_2 \) nicotinic cholinergic receptor.
- Blocks DA release stimulated by nicotine, BUT causes smaller DA release on its own.
- Immediate relief of PGAD symptoms, which returned when varenicline treatment discontinued.

Site varenicline targets
- mPOA
- VTA
- NAc
... decreased sympathetic to parasympathetic switching

**Serendipitous effect of zolpidem**

Zolpidem is a nonbenzodiazepine compound of the imidazopyridine class that potentiates the activity of GABA by binding to the same moiety on GABA A receptors as benzodiazepines.

King, Goldstein, Pfaus. 2016, ISSWSH abstract 020
Excitation

- Drugs or states that inhibit
  5-HT, opioids, ECBs

+ Drugs or states that activate
  DA, NE, OT, MCs

mPOA DA D1 action
Inhibition

+ Drugs or states that activate
  S-HT
  Opioids
  ECBs

- Drugs or states that inhibit
  DA
  NE
  OT
  MCs

mPOA GABA A action

What is needed?

1. Clear methodical guidelines for hierarchical assessment
What is needed?

2. Comprehensive epidemiological studies

-- Base rates
-- Populations/Cultures
-- Co-morbidities and directionality
-- Etiologies
-- Development of adjective-based screener patterned after McGill Pain Questionnaire and Sexual Arousal and Desire Inventory.

What is needed?

3. “Phase 4” studies of treatment regimens

-- Varenicline and Zolpidem (for starters)
-- Long-term efficacy
-- Who can “live with” PGAD and why?
-- Who cannot? And why?
What is needed?

4. Study of brain activation and deactivation in response to different etiological factors and treatments

-- fMRI/PET studies
-- Predictive validity

What is needed?

5. Animal models

-- Female rat/mouse model of genital hyper engorgement
-- Treatment models
-- Predictive drug effects
-- Effects on behavior (e.g., pain model developed by Farmer et al (2014) *J Neurosci, 34, 5747-5753*).
Will she copulate?

Will she fight?