Control of Ejaculation
What the Rat’s Brain Tells the Clinician

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What is ejaculation?

2 phases:
- Emission
- Expulsion
Seminal emission

- Sperm + fluids from seminal vesicle, prostate, & Cowper’s gland → urethra (in prostate)
- Parasympathetic NS → secretion
- Sympathetic movement
Expulsion, orgasm

- Bulbospongiosus, ischiocavernosus, & pelvic floor muscles contract, bladder neck closes.

- Orgasm: cerebral process; does not require expulsion of semen
How is ejaculation coordinated and controlled?
Neural Control of Ejaculation

- Supraspinal Sites
- Spinal Ejaculation Generator
- Pelvic Organs
Neural Control of Ejaculation

Supraspinal Sites

Spinal Ejaculation Generator

Pelvic Organs

Sensory cues preceding ejaculation
Neural Control of Ejaculation

Supraspinal Sites

Spinal Ejaculation Generator

Pelvic Organs

Sensory cues preceding ejaculation

Descending excitatory and inhibitory signals

Motor/Autonomic

Pelvic Organs
Neural Control of Ejaculation

Supraspinal Sites

Spinal Ejaculation Generator

Pelvic Organs

Sensory cues preceding ejaculation

Sensory signals related to ejaculation

Descending excitatory and inhibitory signals

Motor/ Autonomic
A spinal ejaculation generator
Lumbar spinothalamic (LSt) neurons

Figure 1. Schematic drawing of L4 illustrating the area of analysis (800 × 800 μm) for Fos-IR and activated LSt cells. Gray circles indicate the approximate location of LSt cells. This figure was modified from Paxinos and Watson (1998).

Truitt et al., 2003
LSt neurons

(A) Galanin-containing neurons are Fos-ir after 2 ejaculations,
(B) but not after only intromissions.
(C) They are Fos-ir after 8-OH-DPAT + I ejaculation.
(D) No Fos-ir in a female after she received 1 ejaculation.

Truitt et al., 2003
LSt neurons

- Percentage of galanin cells that were Fos-ir after Home Cage, Anestrous Female, Mounts, M+I, 1 Ejac., 2 Ejacs

Truitt et al., 2003
Destruction of LSt neurons by saporin conjugated to SSP abolished ejac., but mount & intro were normal.

(SSP: analog of SP, agonist at NK1 receptors. Most LSt cells have NK1 rec.)

Truitt et al., 2003
LSt Summary

- LSt neurons are selectively activated by ejaculation and are necessary for ejaculation.
- Receipt of ejaculation by a female does not activate galanin-containing neurons in the same area.
Supraspinal control of ejaculation

Sensory input from genital area

- Cerebral Cortex
- Thalamus
  - SPFp
- Hypothalamus
  - MPOA
  - PVN
- Midbrain
  - PAG
- Pons
  - nPGi
- MeApd
- BNSTpm
- PNpd

Giuliano and Clement, 2005
Supraspinal control of ejaculation

Sensory input from genital area

Cerebral Cortex

Thalamus
SPFp

Hypothalamus
MPOA
PVN

Midbrain
PAG

Pons
nPGi

MeApd

BNSTpm

PNpd

Giuliano and Clement, 2005
Supraspinal control of ejaculation

- Cerebral Cortex
  - Thalamus
    - MeApd
    - Hypothalamus
      - MPOA
      - PVN
        - Midbrain
          - PAG
            - Pons
              - nPGi
                - Motor outputs to spinal nuclei commanding ejaculation

Sensory input from genital area

Giuliano and Clement, 2005
Supraspinal control of ejaculation

- Sensory input from genital area
- Cerebral Cortex
  - Thalamus
    - SPFp
    - Hypothalamus (MPOA, PVN)
      - Midbrain (PAG)
        - Pons (nPGi)
          - Motor outputs to spinal nuclei commanding ejaculation
  - MeApd
  - BNSTpm
  - PNPd

Giuliano and Clement, 2005
Roles of MPOA Dopamine

Dominguez and Hull, 2005
Dopamine is released in MPOA before and during mating

- DA increase from BL was correlated with ability to ejaculate

Hull et al., 1995
Role of MPOA glutamate

- Glut. increased during mating and
- Peaked with ejac.
- Post-ejac. decrease correlated with PEI
- Reverse-dialysis of uptake inhibitors increased ejacs., decreased EL, PEI.

Dominguez et al., 2006
Stimulate MPOA $\rightarrow$ BS firing
PAG lesions abolish the effect

Marson, 2004
Summary of MPOA effects

- High doses of D2 agonists → seminal emission *ex copula*.
- High doses of D2 agonists → ejaculation *in copula*.
- Electrical stimulation → BS firing.
- Lesions of PAG block that effect.
Role of the PVN

Reviewed in Argiolas & Melis, 2004

- D2 agonists, glutamate, NO in PVN $\rightarrow$ ex
copula$\Rightarrow$ erection & seminal emission
- PVN lesions decrease amount of semen in ejaculate.
- Oxytocin fibers $\rightarrow$ lumbosacral cord, as well as hippocampus, other brain areas
- Oxytocin $\rightarrow$ systemic circulation via PP
  - (reviewed in Argiolas & Melis, 2004)
Role of the PVN

Argiolas and Melis, 2004
Role of the PVN

Dopamine
Oxytocin
Excitatory Amino Acids
(+)

Opioids
GABA
(-)

Ca$^{2+}$ $\rightarrow$ NOS $\rightarrow$ NO $\rightarrow$ Oxytocin

(+)

Hippocampus
Pons
Med. Oblongata
Spinal Cord
Role of nPGi

- Lesions of nucleus paragigantocellulararis in medulla: as effective as spinal tran-section at releasing the urethrogenital reflex (model of orgasm) (Marson et al., ‘92).
- nPGi sends 5-HT axons to lower spinal cord; 5-HT lesions disinhibit UG reflex (Marson & McKenna, 1992, 1994).
An ejaculation circuit

- Selective activation (Fos-ir) by ejaculation:
  - Subparafascicular nucleus of thalamus (SPFp)
  - Posteromedial bed nucleus of stria terminalis (BNSTpm)
  - Posterodorsal medial amygdala (MeApd)
  - Posterodorsal preoptic nucleus (PNpd)
Supraspinal control of ejaculation

Sensory input from genital area

Motor outputs to spinal nuclei commanding ejaculation

Giuliano and Clement, 2005
So, what DOES the rat’s brain tell the clinician?
So, what DOES the rat’s brain tell the clinician?

- Premature ejaculation
- Delayed or absent ejaculation

“Can’t you at least wait till I’ve laid the eggs?”
Role of norepinephrine (NE)

- Sympathetic NS transmitter $\rightarrow$ seminal emission & ejaculation; also in CNS.
- Dose-dependent effects of NE drugs
- $\alpha_2$ autoreceptors decrease NE release
  - $\alpha_2$ antagonists (e.g., yohimbine) increase NE release, facilitate copulation in rats
- But too much NE $\rightarrow$ inhibits erection
Role of dopamine (DA)

- **Rats:**
  - Dopamine agonists facilitate copulation and reflexes
  - D2 agonists $\rightarrow$ ejaculation

- **Humans:**
  - DA agonists have been used for erectile dysfunction, but not for ejac. disorder.
  - DA antagonists (antipsychotics) block ejac.
Role of serotonin (5-HT) in rats

- Neurotoxic lesions facilitate copulation
- 5-HT is released in LH at ejaculation
  - SSRI in LH delayed onset of copulation
  - 5-HT in LH decreased DA in Nuc. Accumb.
  - Mechanism for PEI quiescence
- 5-HT1A agonist (8-OH-DPAT) → ejac.
- 5-HT1B agonist inhibits ejaculation
- 5-HT2C agonist → erection, inhibit ejac.
Effects of SSRIs in rats

- Chronic Prozac inhibited ejaculation
  - Systemic oxytocin restored it (Cantor et al., ’99).
  - 8-OH-DPAT (5-HT1A agonist) also restored it (Faulring et al., 2002, SfN).
8-OH-DPAT → ejac.

How does it work?

Autoreceptor on 5-HT somas
Postsynaptic receptor
Uptake inhibitor?
DPAT increased both DA and 5-HT in MPOA. Effects not blocked by 5-HT1A antagonist.

Lorrain et al., 1998
Rat: DPAT in MPOA

Matuszewich et al., 1999
8-OH-DPAT $\rightarrow$ burst firing of rat bulbospongiosus muscle

Clement et al., 2006
8-OH-DPAT $\rightarrow$ burst firing of rat bulbospongiosus muscle

Clement et al., 2006 JPET

- D2 antagonists blocked DPAT’s effect.
  A 5-HT1A antagonist did not.

- D2 agonist $\rightarrow$ more clusters of firing than did DPAT
Therefore, at least some of DPAT’s effects are mediated by D2 receptors.
Effects of SSRIs in humans

- Most SSRIs delay or block ejaculation
- No ejac. delay by some SSRIs
  - Nefazodone: blocks 5-HT2 receptors
  - Mirtazapine: blocks 5-HT2 & α2 autoreceptors
  - Bupropion: inhibits reuptake of DA & NE, also 5-HT1A agonist
How about the little blue pill?

That's odd. This bottle of Viagra was full two days ago.
Effects of nitric oxide (NO) in rats

- NO → GC → cGMP → transmitter release: DA in MPOA, oxytocin from PVN.
- NO → GC → cGMP → vasodilation, erection
  - Parasympathetic, anti-sympathetic
  - NOS antagonist increases seminal emission
Effects of NO in men

- Phosphodiesterase 5 (PDE 5) catalyzes the degradation of cGMP.
- Sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis) inhibit PDE 5 → increase erection (parasympathetic effect)
- But, they also delay/inhibit ejaculation
  - Dilates smooth muscle in vas deferens & seminal vesicles: can’t squeeze fluids
  - Used to treat premature ejaculation.
Summary

- MPOA & PVN $\rightarrow$ ejac.
  - D2 receptors, NO, glutamate
  - Oxytocin from PVN
- NO $\rightarrow$ erection, inhibits ejaculation
- 5-HT inhibits ejac., via 1B, 2C receptors
  - 5-HT1A $\rightarrow$ ejac., partly via D2 receptors
SSRIs inhibit desire, erection, & ejac.

Less inhibition from SSRIs that also inhibit DA & NE reuptake &/or are 5-HT2 or α2 antagonists.

SSRIs and NOS inhibitors used to treat premature ejaculation, but can be TOO effective.
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