Neuromodulatory Therapy for Erectile Dysfunction

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Objectives

ED Treatment Options ➔ Future Strategies
- Ongoing progress in cellular and molecular science

Neurophysiology of Erection
- Have we maximally exploited neurourology potential?

Neuromodulatory Prospects
- Pharmacotherapy
- Mechano-inductive technologies
ED Treatment Options

Education
Sexual education/counseling

Oral Agents
PDE5 inhibitors

Devices
Vacuum constriction devices

Injectable Agents
Intracavernosal injections (alprostadil)
Intraurethral medications (alprostadil)

Surgical Options
Penile implants
Vascular surgery

Therapeutic Targets and Technologies: Future Possibilities

- Pharmacotherapy
- Growth factor therapy
- Gene therapy
- Stem and cell-based therapies
- Regenerative medicine
- Devices

All aim to facilitate mechanisms involved in the erectile response or to revitalize/reconstitute penile erectile tissues toward a functionally intact level in the face of injury or disease.
Radical Prostatectomy and ED

- Surgery offers excellent long-term rates of cancer control\(^1\)
- ED is a historically known significant complication of the surgery
- Cavernous nerve-sparing techniques have reduced ED to 15-40\(\%\)\(^2\)
- Other morbidities largely controlled today

Pathobiology of Traumatic Cavernous Nerve Injury

- **Primary Mechanisms**
  - Contusion
  - Compression
  - Traction
  - Avulsion
  - Transection

- **Secondary Mechanisms**
  - Extracellular Factors, e.g., ischemia, edema, cytokine-mediated inflammation
  - Intracellular Factors, e.g., ischemia-reperfusion, electrolyte imbalance, neurotransmitter excess, lipid peroxidation, reactive oxygen species generation, neurotrophic factor deprivation, apoptosis
Nerve Injury and Recovery

Chemical effect: elevation of intracellular calcium levels and overexcitation/generation of free radicals.

Schwann cell activation: production of extracellular matrix components, axon remyelination, neurotrophin release.

Neurotrophin actions: interaction with cellular receptors, causing trophic (neurite outgrowth) and tropic (neurite directionality).

Neurogenic Dysfunction Treatment: Neurobiologic Strategies

- Neuroprotection
- Nerve regeneration (neurotrophism)
- Inhibition of neuronal programmed cell death
- Combination: procedures to reconnect damaged cavernous nerves and techniques to preserve nerve function

Strategies for Mechanism-Based Neuroprotection

- Anti-inflammatory agents
- Anti-oxidants
- Immune modulators
- Ischemia counteractive agents
- Anti-excitotoxicity agents
- Ionic/Membrane stabilizers
- Anti-apoptotic agents

Strategies for Mechanism-Based Nerve Regeneration

- Neurotrophic factors
- Axonal outgrowth inhibitory neutralizers
- Axonal reconstructive substances
- Tissue engineering/stem cell therapy
- Electrical stimulation

Neurogenic Dysfunction Treatment: Preclinical Investigation

- Experimental rat models of cavernous nerve injury
  - crush
  - transection
  - freezing

- Neurotrophic agents
  - cytokines (IGF-1, TGF-beta 2)
  - growth factors (basic FGF, VEGF, NGF, BDNF)
  - growth hormone
  - gene therapy (BDNF – AA viral vector)
  - immunophilin ligands (FK506, GPI1046, GPI1485)

- Endpoints
  - preserved penile erection
  - protected penile innervation from degeneration

Immunophilin Ligand FK506 is Neuroprotective for Penile Innervation

Immunophilin Ligands

Mechanism: unclear; may involve FK506 binding protein receptors in nerves

Agents: FK506 (Astellas Pharma), GPI-1485 (Guilford Pharmaceuticals/MGI Pharma)

Preclinical work: rat models of cavernous nerve injury\(^1\)\(^{-3}\)

Clinical trials: GPI-1485 and FK506 in Phase II/III trials in men undergoing bilateral cavernous nerve sparing radical prostatectomy – no apparent benefit

Neuromodulatory Molecules as Future Therapeutic Prospects

- Glial cell-line derived neurotrophic factory, e.g. neurturin (Bella AJ et al, J Brachial Plex Peripher Nerve In; 2007 2:5)
- Erythropoietin, via BDNF signaling (Allaf ME et al, J Urol 2005; 174: 2060-4)
- Sonic hedgehog, via BDNF signaling (Bond CW et al, J Sex Med 2013; 10: 730-7)
- Nerve injury – induced protein1 (ninjurin1) via BDNF signaling (Yin GN et al, Proc Natl Acad Sci USA 2014; 111: E2731-40)
Brain-Derived Neurotrophic Factor: Role in the Regeneration of the Cavernous Nerve

Activation of the Janus Kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is a likely major player.

Intracellular Signaling After Erythropoietin Receptor Activation
Erythropoietin Promotes Erection Recovery after Nerve-Sparing Radical Retropubic Prostatectomy: A Retrospective Analysis

Methodology

- Preoperatively potent patients undergoing BNS-RRP from March 2005 to February 2006
- Erythropoietin (Epoietin alpha, 40,000 IU sc) as single injection on preoperative day
- PDE5 inhibitor use permitted “prn” postoperatively
- IIEF-5 monitoring at 3, 6, 12 months postoperatively
- Comparison group declined erythropoietin

Results

- Treatment and comparison groups clinically matched
- No adverse events (e.g. thrombotic events, hypertension)

Neuromodulatory Conduits: Role in Neurotrophic Factor Delivery

- Autologous genitofemoral nerve
- Amniotic membrane
- Silicone nerve tubes
- Schwann cell seeded nerve guidance tubes
- Biodegradable conduit graft/collagen sponge
- Platelet–rich plasma
- Neural embryonic stem cells
- Gene therapy (neurotrophic effectors)

Burnett AL, Lue TF J Urol 2006; 176: 882-7
New Directions
in the Clinical Arena

- Pharmacotherapeutics
- Electrical Stimulation
- Genital Afferent “Technologies”
Objective: To develop and evaluate a neurostimulation system for cavernous nerve electrical stimulation for future use as a chronic implantation device that neurotrophically promotes erectile function recovery after radical prostatectomy.

Method: Temporary placement of electrode array and stimulation (20 Hz, 260 μ sec, 5-60 mA), and measurement of penile circumference in 12 men.

Results: Penile circumference increases demonstrated in 6 of 12 men; array placed with ease and no evidence of neurovascular bundle injury.
Genital Neuromodulatory Therapy

- Theoretically mechano-induces responses via tactile stimuli of the genitalia that reflexively increase erectile physiology and decrease erectile pathophysiology
- Neuromodulation could include genital vibration techniques based on evidence-based protocols
- Role in ED therapy, rehabilitation, prevention
Penile Glans and Afferent Circuitry

- Millions of sensory nerve terminations
- Thin myelinated Aδ and unmyelinated C fibers
- Convergence as the dorsal nerve of the penis, and then the pudendal nerve coursing to the spinal cord
Viberect Therapeutic Stimulation System

- Cleared by the FDA as a medical device to provoke erection in men who experience ED and ejaculation in men with spinal cord injury

- Clinical feasibility demonstrated in producing an erectogenic effect confirmed by Rigiscan and Erection Hardness Scores (Segal RS et al, Can J Urol 2013; 20:6844-7)

Penile vibratory stimulation in the recovery of urinary continence and erectile function after nerve-sparing radical prostatectomy: a randomized, controlled trial

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- Randomized prospective trial involving 30 patients receiving penile vibratory stimulation (PVS) and 38 patients receiving monitoring only
- PVS using FERTI CARE vibrator once daily, beginning 1 week before surgery and continuing 6 weeks afterwards
- At 12 months, 16/30 (53%) of patients in the PVS group and 12/38 (32%) of patients in the control group achieved an IIEF score $\geq 18$ ($p=0.07$)
Conclusions

- Neuromodulatory therapies ranging from pharmacotherapeutics to novel mechano-inductive technologies offer opportunities to manage erectile dysfunction.

- Advances in neuromodulatory therapy rest on research and discovery of mechanisms of genital nerve injury and functional recovery as well as neurobiologic principles relating to the sexual response.