Post prostatectomy erectile function: can we make a difference?

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Disclosure

- I have no relevant financial relationships to disclose.
Erectile dysfunction

- Affects 52% of men 40 to 70
- 82-85% prostatectomy
- 36% recover EF
- PDE5i ineffective in 69%

(Pace et al., 2010)
Prostatectomy damages the cavernous nerve and causes morphological remodeling of the penis.
Upstream: CN injury interrupts communication and transport between the CN and penis.

CN injury interrupts signaling and transport.
Demyelination of CN fibers with injury

Control  Cavernous nerve  CN crush

Pelvic ganglia
Penile remodeling in ED patients

Control | Prostatectomy | Diabetic

1-17P Avg: 6
7-24D Avg: 12

(Angeloni et al., 2013)
Avenues of research

1. Cavernous nerve regeneration
   a. Novel factors involved in nerve regeneration/protection
   b. Neuronal-glial interaction
   c. Delivery strategies to PG/CN

2. Prevent penile remodeling (apoptosis and fibrosis)
   a. Novel factors involved in maintaining CC structure
   b. Delivery strategies to corpora cavernosa
Caspase-3 dependent nitrergic neuronal apoptosis following CNI is mediated via RhoA and ROCK activation in pelvic ganglion
Sci Rep 2016; 6: 29416

Aim/goal: Evaluate role of RhoA/ROCK in CN following injury
Rationale: In peripheral nerves axotomy upregulates transcription and translation of RhoA and ROCK and inhibition increases axonal regeneration. RhoA and ROCK increase in penis after CNI and hamper CN regeneration
Model: 3 15 sec crushes 2-3mm distal to PG
  1.) 2,7,14,21,30,60 day
  2.) Sham, CNI, CNI + ROCK inhibitor (Y-27632)
Methods: RT-PCR, western, IHC, activity, neurite outgrowth, ICP,TUNEL
Results: RhoA/ROCK RNA and protein increased in PG with CNI.
Caspase-3 dependent nitrergic neuronal apoptosis following CNI is mediated via RhoA and ROCK activation in pelvic ganglion


*Sci Rep* 2016; 6: 29416

- TUNEL showed apoptosis as early as 2 days, peaked between 7 and 14 days and was still observable at 60d.

- Caspase 3 mRNA was maximal at 2 days and returned to baseline by 30 days.
- ROCK inhibitor (Y-27632) suppressed caspase 3 in PG, prevented changes in dimer to monomer ratio of nNOS, improved ICP.

**Conclusions:** RhoA/ROCK inhibition can improve EF and suppress the apoptotic response to CNI in the PG.

**Comments:** caspase 3 not present in sham western, GAP43 only at 14d
Pioglitazone enhances survival and regeneration of pelvic ganglion neurons after cavernosal nerve injury


Aim/goal: Mechanism of pioglitazone on PG neurons

Rationale: Thiazolidineodione
  - Neuroprotective effect in sciatic and optic nerve
  - ICP improved 14d post CNI
  - Anti-inflammatory effects

Model: CN crush (84 d SD rat), 3 15 sec crush with forceps

Methods: Presurgery fluorogold as a neuronal tracer of penile neurons
  1. Sham, 2. CNI, 3. CNI + post surgical pioglitazone (6.5mg/kg), 4. CNI + pre (2-5d)/post pioglitazone (oral gavage)
  - RT-PCR, IHC, western nNOS, β-III tubulin, neurturin, glial cell line-derived neurotrophic factor family receptor alpha 2 (GFRα2)
Pioglitazone enhances survival and regeneration of pelvic ganglion neurons after cavernosal nerve injury

**Results:** Fluorogold and nNOS positive cells (IHC) decreased with CNI and increased with pioglitazone.
- However nNOS protein was not different between groups by western.
- GFRα2 expression increased with Pioglitazone.
- β-III tubulin mRNA but not protein were higher with Pioglitazone.

**Conclusions:** Pioglitazone provides a protective effect on PG neurons after CNI. Most effective when given pre and post CNI.
Peptide amphiphile nanofiber hydrogel delivery of Sonic hedgehog protein to the cavernous nerve to promote regeneration and prevent erectile dysfunction
Choe S, Bond C, Harrington DA, Stupp SI, McVary KT, Podlasek CA. *Nanomedicine* 2016 Sep 6; S1549-9634(16)30149-6

**Aim/goal:** Examine how SHH treatment with peptide amphiphile nanofiber hydrogels (PA) promote CN regeneration

**Rationale:** SHH PA treatment of the CN improves ICP/BP 60% at 6 weeks after CNI

**Model:** Bilateral CNI, 30 second crush until indent and discoloration were observed

**Methods:** Examined SHH in normal and CN crushed PG/CN
Reintroduced SHH by PA at time of crush. Examined neuronal/glial signaling.

**Results:** SHH, PTCH1, SMO in PG neurons, glia.
SMO undergoes anterograde transport
With crush injury, PG neurons undergo apoptosis
SHH protein decreases
SMO localization changes to cell surface and anterograde transport stops
Peptide amphiphile nanofiber hydrogel delivery of Sonic hedgehog protein to the cavernous nerve to promote regeneration and prevent erectile dysfunction

Choe S, Bond C, Harrington DA, Stupp SI, McVary KT, Podlasek CA. *Nanomedicine* 2016 Sep 6; S1549-9634(16)30149-6

- SHH is taken up at the injury site
- Undergoes retrograde transport to PG neurons
- Allows SMO transport
- Maintains neuronal-glial interaction
- Prevents apoptosis

Conclusions: SHH treatment prevents neuronal degeneration, maintains neuronal, glial and down stream target signaling, and is significant as a regenerative therapy.
Aim/goal: Review the potential of modulating dopaminergic pathways to improve erectile function

Rationale: PDE5i are insufficient in ED patients

Results:
- Dopamine receptors in the CNS (paraventricular area, medial preoptic area, spinal cord and erectile tissue)
- Dopamine agonists (apomorphine) failed due to less efficacy than PDE5i.
- D2 receptors induce erection in rodents (nausea, emesis)
- D4 receptor agonists were developed and induce erection in rodents. Never introduced clinically
  - Clavulanic acid: arousal and erection
  - Bupropion: reuptake transporter, antidepressant

Conclusions: modulation of dopaminergic pathway as novel avenue for ED treatment strategy
Anti-inflammatory and anti-fibrotic effects of annexin1 on erectile function after cavernous nerve injury in rats

Facio FN, Facio MN, Spessoto LF, Pessutti D, Reis LO, Campos SG, Taboga S
IJIR 25 August 2016

Aim/goal: Effect of annexin1 on erectile function

Rationale: calcium binding protein, anti-inflammatory mediator

Model: 48 Wistar rats, crush injury 3 min with closed hemostat
1. Sham, 2. CNI, 3. CNI /ANX1 50μg/kg, 4. CNI /100μg/kg

AXN1 by IV 30 min before surgery

Methods: ICP/BP at 2 and 7 days, Gomori trichrome and IHC for VEGF and TNF-α

Results: ICP decreased with CNI and increased with ANX1 at 2 and 7 days. VEGF and TNF-α decreased with CNI and improved with ANX1.

Conclusions: ANX1 improves EF possibly through an endothelium dependent mechanism

Comments: Gomori trichrome SM/collagen (high blood cell, no western).
Nanoparticle improved stem cell therapy for erectile dysfunction in a rat model of cavernous nerve injury
*J Urology* 2016; 195: 788-795

**Aim/goal:** Investigate NanoShuttle magnetic nanoparticles to maintain stem cells in the corpora after intracavernous injection

**Rationale:** Most stem cells are washed out immediately after intracavernous injection

**Model:** 56d SD rats, CN crush 2 30 second crushes with ultrafine hemostat

**Groups:** 1. CN crush, 2. Crush with stem cells, 3. Crush with Nano-adipose stem cells, 4. Crush with Nano-adipose stem cells with 2 magnets for 6 hr

**Methods:** ICP (28d), IHC, western
Results: Nanoshuttle magnetic nanoparticles bound to adipose derived stem cells and migrated towards applied magnet in vitro

- In vivo, Nano-adipose derived stem cells were retained in CC for 3-5 days, while those without the Nano-shuttle washed out almost immediately
- ICP, SM and PECAM-1 were higher with Nano-adipose treatment (western and IHC)

Conclusions: Magnetization of adipose derived stem cells with NanoShuttle magnetic nanoparticles improved retention in the CC, EF and penile morphology.

Comment: Stem cells may have an effect on CC if retained
Can we make a difference?

- Therapies targeted to promote CN regeneration
- Prevention of corpora cavernosal remodeling
- Improved/enhanced delivery of factors to CN and penis
- Identification of novel factors
- Translation