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Stress Incontinence in the Era of Regenerative Medicine: Reviewing the Importance of the Pudendal Nerve

Bradley C. Gill, **Margot S. Damaser**, **Sandip P. Vasavada**, and **Howard B. Goldman**
Glickman Urological and Kidney Institute & Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH; Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH; Advanced Platform Technology Center, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH

Abstract

Purpose—Regenerative medicine will likely facilitate improved stress urinary incontinence (SUI) treatment via restoration of its neurogenic, myogenic, and structural etiologies. Understanding these pathophysiologies and how each can optimally benefit from cellular, molecular, and minimally invasive therapies will become necessary. While stem cells in sphincteric deficiency dominate the regenerative urology literature, little is published on pudendal nerve (PN) regeneration or other regenerative targets. The purpose of this review is to discuss regenerative therapies for PN injury in SUI.

Materials and Methods—A PubMed® search for *pudendal nerve* combined individually with *regeneration, injury, electrophysiology, measurement, and activity* produced a combined but non-independent 621 results. English language articles were reviewed by title for relevance, identifying a combined but non-independent 68 articles. A subsequent Google Scholar® searchand review of references in articles obtained aided in broadening discussion.

Results—Electrophysiological studies associate PN dysfunction with SUI clinically and assess PN regeneration functionally while animal models provide physiological insight. Stem cell treatment has improved continence clinically while ex vivo sphincteric bulk and muscle function gains have been noted in the laboratory. Stem cells, neurotrophic factors, and electrical stimulation each benefit PN regeneration in animal models.

Conclusions—Most regenerative work to date focuses on stem cells restoring sphincteric function and bulk, but whether a sphincter denervated by PN injury will benefit is unclear. Regeneration of the PN appears possible through minimally invasive therapies that exhibit significant clinical potential. Treating poor central control and coordination of the neuromuscular continence mechanism remains another challenge.

Corresponding Author: Howard B. Goldman, MD, Cleveland Clinic Glickman Urological and Kidney Institute, 9500 Euclid Ave, Mail Stop Q10, Cleveland, OH 44195, Tel: (216)445-5121 | Fax: (216)445-2267, goldmah@ccf.org.

Keywords

Urethral Sphincter; Neurotrophin; Stem Cell; Neuromuscular Continence; Electrophysiology

BACKGROUND

Many incontinence treatments exist but none target the underlying pathophysiology – failure of the neuromuscular continence mechanism or its coordination. As the era of regenerative medicine dawns, gaining understanding of the etiologies of stress urinary incontinence (SUI) will likely become beneficial, if not necessary for maximizing regenerative treatment efficacy. Structural changes to the pelvic floor, pudendal nerve (PN) injury, and external urethral sphincter (EUS) damage may each necessitate unique therapeutic approaches, while central nervous system etiologies, such as impaired coordination of continence reflexes or storage and voiding may warrant alternative approaches.

Current treatments, largely mechanical, aim to recreate the suburethral vaginal hammock, cause dynamic kinking, reduce hypermobility, mechanically obstruct the urethra, or some combination thereof. Conservative treatments, including physiotherapy and medications, necessitate an intact and coordinated neuromuscular continence mechanism. Regardless of treatment pursued, sphincteric deficiency, whether intrinsic and from muscular injury or due to denervation from nerve injury, challenges the attainment of successful clinical outcomes. Thus, restoring function to the neuromuscular continence mechanism will very likely augment current surgical interventions and provide a potential means of preventing incontinence development.

Investigations of urologic regenerative therapy to date have demonstrated increased EUS muscle in the laboratory and improved continence clinically. However, whether success or failure was associated with a functional EUS gain or simply bulking effect is uncertain. More so, whether EUS function was intact or deficient prior to clinical treatment was unclear. Therefore, more precisely identifying dysfunction of the neuromuscular continence mechanism, whether central or peripheral, may prove crucial in maximizing regenerative treatment efficacy, improving not only muscle size but the ability to use it.

STRESS URINARY INCONTINENCE

Urinary incontinence is a common problem amongst women and poses significant quality of life and economic burdens. Long anecdotally related to childbirth, vaginal delivery is associated with pelvic floor injury and confers at least a 2.5 times greater risk of SUI development.[1] A strong association between antenatal and post-partum SUI in primiparae supports this, as women developing SUI during pregnancy were 5.79 times more likely to have SUI 1 year postpartum, while women with SUI 3 months post-partum were significantly more likely to be incontinent 5 years after delivery.[2,3]

Conceptually, urinary continence is afforded by a mechanism of two major components – one structural and one functional, with central and peripheral nervous system modulation and coordination of the functional components. The structural element is comprised of

pelvic floor musculature and connective tissue, while the functional component is the neuromuscular system of the pudendal nerve (PN) and external urethral sphincter (EUS) it innervates. With vaginal delivery, SUI likely results from injury to both structural and neuromuscular components. Damage to pelvic floor structures, such as connective tissue and the levator ani, can occur during vaginal delivery and is associated with SUI.[4] Likewise, PN injury also can occur during vaginal delivery, according to antenatal and postpartum neurophysiological recordings.[5,6] Direct urethral injury has also been observed after vaginal delivery.[7] Thus, injuries to both structural and neuromuscular components of urinary continence occur with vaginal delivery.

Failures of structural components that maintain continence are well addressed by contemporary treatments. However, failure of the functional, neuromuscular component of continence is not currently attended to clinically, whether of peripheral or central etiology. Persistent PN damage associated with SUI has been noted up to 7 years following delivery.[8,9] Thus, neuroregeneration and recovery of childbirth-mediated PN injury must be insufficient to adequately restore neuromuscular function necessary for maintaining continence – a concept alluded to in colorectal literature highlighting improved surgical outcomes with intact PN function.[10] Basic science studies have confirmed this and identified antagonistic responses between muscle and nerve injury, which likely are implicated in their poor recovery and persistent dysfunction.[11]

CONTEMPORARY TREATMENT OF STRESS URINARY INCONTINENCE

SUI is generally treated initially with symptom management, behavioral intervention, physiotherapy, and occasionally, medications. Minimally invasive treatments, utilized when conservative attempts fail, focus on restoring structural integrity of pertinent tissues and obstructing or bulking the urethra to coaptation – none of which regenerate the neuromuscular continence mechanism. In contrast, Kegel exercises target and strengthen the neuromuscular continence mechanism but rely upon its intactness for success. Thus, utilizing regenerative treatments to facilitate neuromuscular continence mechanism recovery addresses a gap in SUI treatment.

INJURY OF THE NEUROMUSCULAR CONTINENCE MECHANISM: BASIC SCIENCE INSIGHTS

Pudendal Nerve Injury

Crush injury of the PN induces a recoverable model of postpartum SUI in female rats, with a leak-point pressure (LPP) nadir after 4 days and recovery to near-normal levels after 2 weeks.[11] Molecular evidence of PN regeneration supports this, as β_{II}-tubulin, a cytoskeletal protein indicative of neuronal growth and regeneration, is upregulated significantly in motoneuron cell bodies 7 days after injury and normalizes by 2 weeks.[12] Furthermore, levels of brain-derived neurotrophic factor (BDNF) and other regenerative stimuli increase acutely in the EUS after PN injury to facilitate neuroregeneration.[13,14]

The degree of PN injury determines the severity and duration of functional impairment.[11] While these findings may be challenging to translate clinically, electrophysiological studies

of the PN, reflex loops, and EUS in women provide valuable insight into the role of the neuromuscular continence mechanism. Associations between abnormal neurophysiological function and SUI in such studies implicate PN damage as a likely etiologic factor.[15,16]

Direct electrophysiological studies of the isolated PN-EUS system in rats support functional continence outcomes as measured by LPP. Overall muscle activity assessed by electromyography (EMG) nadirs 4 days after PN crush and demonstrated persistent functional impairment with some recovery by 3 weeks.[17] This echoes results of other studies in which LPP recovered 2 weeks after a less intense PN crush.[11] Direct PN electrical activity on electroneurography (ENG) revealed similar findings with impaired function 4 days after crush taking 3 weeks to recover, with PN transection taking longer to recover.[17] Thus, changes in PN activity are linked to those in the EUS, with injury severity determining the magnitude of neuromuscular continence mechanism dysfunction.

External Urethral Sphincter Injury

Vaginal distension (VD) simulates the second phase of labor and damages both the EUS and distal PN branches, as well as sympathetic nerves and smooth muscle within the urethra.[11,18–21] Greater VD duration and extent (controlled by balloon volume) have been associated with more EUS tissue damage, larger and more prolonged LPP deficits, and EUS nerve loss.[18] This parallels a prolonged second stage of labor and macrosomia, which are both associated with postpartum SUI.[7,16] Thus, EUS injury and PN damage are likely etiologic factors in SUI development, along with an element of reduced urethral sympathetic signaling and smooth muscle tone.

Functional studies differentiate VD-induced SUI from that caused by PN injury. Although EUS EMG is reduced 4 days after VD or PN crush, VD produces no ENG deficit.[17] Likewise, LPP took up to 10 days to recover after VD, compared to 21 days after PN crush.[13,17] Thus, VD induces SUI without proximal PN injury via direct sphincteric injury and distal nerve disruption, including adrenergic innervation of urethral smooth muscle.[20,21] This highlights the possibility that birth-induced EUS injury may occur independent of global PN dysfunction, making it an SUI etiology lacking demonstrable PN dysfunction.

Reduced blood flow to the bladder, urethra, and vagina during VD induces hypoxia in both urethral smooth and striated muscle.[18] Thus, the urethra and EUS are susceptible to hypoxic injury and trauma during delivery. These insults impair not only EUS function but also its ability to stimulate PN recovery after VD, as evidenced by sphincteric BDNF downregulation.[13] Such molecular responses to hypoxia and tissue damage have potential as targets for regenerative therapies.[22]

Combined Vaginal Distension and Pudendal Nerve Crush

Combined VD and PN crush is considered a more clinically relevant SUI model. Based upon PN crush severity with VD, LPP deficits can persist beyond 3 weeks.[13,17] Neuroregeneration appeared impaired on EUS EMG and PN ENG after combined VD and PN crush compared to either injury alone, with the largest and longest lasting electrophysiological deficit on PN ENG taking over 3 weeks to recover.[17] This highlights that impaired recovery occurred when both nerve and muscle were injured, suggesting that

EUS and PN childbirth injuries sustained by women play a similar role clinically in SUI by preventing recovery of the neuromuscular continence mechanism.

REGENERATION OF THE NEUROMUSCULAR SYSTEM

Mechanisms

Neurotrophins are cytokines that maintain innervation and neural function as well as stimulate axonal regeneration and neuronal growth.[23] One major neurotrophin is BDNF, which activates JAK/STAT signaling via type-B tyrosine kinase receptors (trkB) to mediate neurite outgrowth, an essential component of neuroregeneration. Evidence of its importance comes from mice carrying a null trkB allele, which regenerate only 50% of motoneurons after nerve transection.[24]

Spinal motoneuron terminals contain trkB receptors while their supporting Schwann cells and innervated skeletal muscles express BDNF, suggesting retrograde signaling occurs.[23] Sciatic nerve injury increases gastrocnemius BDNF expression, which peaks 7–14 days after injury.[25] Upregulation of EUS BDNF occurs within 1 day of PN crush.[13] While BDNF is required for neuroregeneration, when given therapeutically to injury sites it further reduces motoneuron death.[26,27] The necessity of BDNF is further demonstrated by anti-BDNF antibody treatment, which significantly impaired nerve regeneration after injury.[28] Likewise, anti-trkB antibody infusion reduced motoneuron conduction velocity, illustrating the necessity of BDNF-trkB signaling for maintaining neuromuscular function.[27]

While beneficial to neurons, BDNF is inhibitory to and is reduced during neuromuscular junction formation and restoration, as well as myogenic myoblast differentiation.[29,30] Decreased BDNF expression occurs in the EUS following VD-induced injury.[13] Thus, despite neural benefits, BDNF decreases with muscle injury, to likely lessen its negative effects on EUS neuromuscular junction and muscular recovery. As such, concurrent PN and EUS injury likely impairs PN neuroregeneration via downregulation of EUS BDNF to facilitate EUS muscle repair.

Competing Injuries

The more severe functional loss and prolonged recovery in LPP, EUS EMG, and PN ENG from combined PN and EUS injury compared to either injury alone likely results from opposing effects of PN crush and VD on EUS BDNF expression.[13,17,23,24,26] Specifically, VD reduces EUS BDNF while PN crush elevates it, but downregulation induced by EUS injury overcomes the upregulation from PN crush when the injuries are combined.[13] This likely impairs neuromuscular continence mechanism recovery by impeding PN neuroregeneration due to lower EUS BDNF levels.

Another possibility is that muscular and NMJ recovery are impaired. Expression of BDNF remains unchanged after NMJ damage.[31] However, since VD causes EUS and NMJ disruption, it is possible that myocyte loss and NMJ integrity may not recover if BDNF is upregulated in the EUS from PN injury following a combined insult in childbirth.[18,19] Agrin, a proteoglycan that facilitates NMJ restoration by clustering acetylcholine receptors and inhibiting neuronal sprouting, is inhibited by BDNF upregulation.[29] Likewise, since

reduced BDNF levels are necessary for myogenic differentiation of progenitor cells, a phenomenon that can be enhanced by siRNA-induced BNDF suppression, increased EUS BDNF may impair muscle recovery.[30] As such, it is likely that EUS injury leads to EUS BDNF downregulation to facilitate myocyte and NMJ recovery at the expense of PN regeneration in a combined childbirth injury. Therefore, targeting not only the EUS but also the PN with regenerative therapies may be beneficial.

Assessment

The cytoskeletal protein β_{II}-Tubulin, a marker of neuroregeneration, undergoes increased synthesis and anterograde transport from nerve cell bodies to neuronal sprouts at sites of axonal injury, and its quantification approximates the peripheral nerve regenerative response.[32] Levels of β_{II}-Tubulin in the PN correlated with functional recovery after PN injury, with increased expression 7 days after PN crush that normalized by 14 days, echoing temporal trends in LPP after PN crush.[12,13,17] Electrophysiological data further support this, showing gradual PN recovery through 21 days.[17] Thus, it appears the neuroregenerative response precedes, and likely facilitates, functional recovery of the PN and EUS neuromuscular continence mechanism.

NEUROREGENERATIVE THERAPY

Administration of BDNF to the site of nerve transection enhances functional recovery and reduces neuronal death in vivo.[23,28] Various BDNF treatment methods improved cholinergic motoneuron activity, as evidenced by increased choline acetyltransferase.[33] However, neither single injury site injection nor repeated subcutaneous injections improved nerve recovery, but continuous local administration to injury sites did successfully.[23,26,34]

A tibial nerve injury model revealed no acute response to BDNF therapy but showed up to an 83% dose-dependent increase in regenerated motoneurons 2 months later with a 0.5 μg/day 4 week treatment being most effective.[26] Cavernous nerve injury models of erectile dysfunction have also proven the efficacy of BDNF and other neurotrophin treatments, as have studies showing increased sympathetic pelvic ganglion cell sprouting.[35,36] Prolonged-release calcium-alginate hydrogels impregnated with BDNF have facilitated 4-week experimental treatments and may exemplify a clinically relevant drug delivery approach.[34] While a depot approach may be most easily adapted for clinical use, other means of supplying BDNF to PN injury, such as adipose-derived BDNF-secreting stem cells and electrical stimulation warrant further investigation.[37,38]

REGENERATIVE TREATMENTS FOR STRESS URINARY INCONTINENCE

Stem Cell Therapy

Stem cells have been utilized to restore structural integrity in the urogenital organs and bulk the urethral sphincter.[39,40] While successful in small initial clinical trials, little is known about their actual mechanism of action and durability of therapeutic effect.[41,42] Laboratory studies of peri-urethral stem cell injections demonstrate newly formed striated muscle associated with improved continence.[40] Yet functional proof of stronger muscle contraction

was obtained ex-vivo, leaving unanswered whether improved continence was from a functional gain or from bulking a denervated sphincter.[39]

A major uncertainty regarding stem cell therapy results from ex-vivo testing to demonstrate improved muscle function rather than in-vivo electrophysiologic or manometric testing.[39] Nonetheless, when injected peri-urethrally, muscle-derived cells were associated with increased EUS innervation and new striated muscle, but the model utilized urethral rather than proximal PN injury to induce EUS denervation.[43] Thus, while stem cells target the EUS and provide additional bulk through differentiation, the benefit this could provide a denervated sphincter remains unclear.[40,41] As such, utilizing stem cells manipulated to produce BDNF while still differentiating into myocytes may facilitate repair of a denervated EUS and provide a durable therapeutic benefit to sphincter deficiency. A potential alternative treatment with stem cells delivered intravenously, has also shown promise in urological sphincteric and neural injuries with the stem cells homing to both nerve and muscles to facilitate electrophysiological and functional recovery.[22,44]

Cell Signaling Interventions

Like stem cells, certain growth factors improve continence and can lead to improved EUS function. Administration of bFGF after sphincteric denervation with botulinum-A toxin increased LPP and thickened both smooth and striated EUS muscle.[45] However, similar to stem cells, gains in continence were potentially from bulking and not necessarily functional since the EUS was denervated.[45] Although similarly relying upon injection and likewise exerting a probable bulking effect, multipotent lipoaspirate cells provided a measurable benefit to continence thought to be paracrine in nature.[42,46] A study using intramuscular EUS stem cells supplemented with NGF impregnated PLGA microspheres showed improved continence gains with the growth factor compared to stem cells alone, possibly due to improved neuroregeneration as bulking was taken into account with control groups.[47] Lastly, one study of anal sphincter denervation found improved histological PN regeneration with sphincteric IGF-I injection.[48] Despite the beneficial effects of various cytokines, their injection leaves it unclear whether improved continence stems from gains of innervated, functional muscle, or rather a transient bulking effect.

BDNF Therapy

Considering the limitations and uncertainties of cellular and molecular regenerative treatments, understanding of the neuromuscular continence system and its dysfunction provides insight into SUI treatment optimization. Decreased EUS BDNF following VD and EUS injury induced by muscle damage is the dominant effect in a combined nerve and muscle injury model. This likely impairs PN recovery due to insufficient BDNF upregulation in the EUS.[13,23,26] Thus, treating the PN with BDNF is a logical intervention.

Targeted PN treatment with BDNF after PN crush and VD improved LPP, EUS EMG, and was associated with more robust EUS muscle on histological analyses.[49] Unlike EUS intramuscular or peri-urethral injections of stem cells or molecular therapies, no potential for bulking existed. Furthermore, EUS function was assessed in-vivo with both LPP and EUS EMG that demonstrated recovery, indicating a regenerated and intact neuromuscular circuit.

Since both PN and EUS injury likely occur in women, treatments aimed at regenerating the PN nerve may facilitate SUI recovery and even serve as a prophylactic peri-partum therapy to prevent its development. Furthermore, treating the PN itself with BDNF benefits the sphincter, as it is associated with lower EUS BDNF levels, which are detrimental to myocyte and neuromuscular junction recovery.[18,19,29,30,49] Lastly, BDNF has also been shown to increase sympathetic nerve sprouting and enhance sympathetic signaling, which may improve urethral smooth muscle tone, as well.[21,36,50] As such, targeted BDNF treatment can not only overcome EUS BDNF downregulation to facilitate PN recovery, but may also further improve EUS musculature and reinnervation by reducing EUS BDNF as well as maintaining innervation to limit sphincter atrophy.

FUTURE DIRECTIONS

The field of regenerative medicine holds numerous possibilities for incontinence and voiding dysfunction. With the growing focus on regenerative and preventative medicine, a means of not only treating SUI and repairing the neuromuscular continence mechanism, but also preventing SUI development is attractive. Treatment aimed at neuroregeneration of the PN, such as supplemental neurotrophins, may accomplish this. As such, clinically pinpointing the origin of neuromuscular dysfunction, whether central or peripheral and due to nerve and/or muscle injury, may become increasingly crucial in SUI evaluation as the use of regenerative therapy begins.

Direct and continuous neurotrophin treatment to the injured PN facilitates improved functional recovery.[49] In the clinical arena, utilizing degradable materials or formulations such as depot injections for delivery is attractive since they have already shown promise in the laboratory.[34] Similarly, PN electrical stimulation, which can be accomplished transvaginally in the office or at home, increases neurotrophin levels and stimulates PN neuroregeneration according to animal models.[38] Otherwise, stem cells engineered to secrete BDNF could provide supplemental neurotrophins to specific regions and can be harvested from a variety of tissues, including adipose.[37,42] With these possibilities, and a likely number of undiscovered approaches, an exciting challenge for ongoing and future research is exploring PN regeneration and its role in reviving a dysfunctional neuromuscular continence mechanism.

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