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Nerve Growth Factor Modulation of the Cavernous Nerve Response to Injury

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Abstract

Introduction—Surgical therapies for prostate cancer and other pelvic malignancies often result in neuronal damage and debilitating loss of sexual function due to cavernous nerve trauma. Advances in the neurobiology of growth factors have heightened clinical interest for the development of protective and regenerative neuromodulatory strategies targeting cavernous nerve recovery following injury.

Aim—The aim of this review is to offer an examination of current and future nerve growth factor modulation of cavernous nerve response to injury with a focus on brain-derived nerve growth factor, growth-differentiation factor 5, and neurturin.

Methods—Information for this presentation was derived from a current literature search using the National Library of Medicine PubMed Services producing publications relevant to this topic. Search terms included neuroprotection, nerve regeneration, nerve growth factors, neurotrophic factors, brain-derived nerve growth factor (BDNF), growth-differentiation factor 5 (GDF-5), neurturin (NTN), and *cavernous nerves*.

Main Outcome Measures—Basic science studies satisfying the search inclusion criteria were reviewed.

Results—In this session, BDNF and atypical growth factors GDF-5 and NTN, and their potential influence upon cavernous nerve recovery after injury is reviewed, as are the molecular pathways by which their influence is exerted.

Conclusion—Compromised cavernous nerve function is a significant cause of erectile dysfunction development following prostatectomy and serves as the primary target for potential neuroprotective or regenerative strategies utilizing nerve growth factors such as BDNF, GDF-5, and NTN, and/or targeted novel therapeutics modulating signaling pathways.

Keywords

nerve growth factors; neurotrophins; BDNF; GDF-5; neurogenic impotence; animal model; erectile dysfunction

Conflict of Interest: None

INTRODUCTION AND BACKGROUND

Despite advances in operative technique for the management of localized prostate cancer, the majority of men report some degree of compromised erectile function post-prostatectomy or complete loss of potency even with bilateral nerve-sparing modifications to open, laparoscopic, and robot-assisted approaches; the primary pathophysiological mechanism is inadvertent cavernous nerve damage by surgical manipulation [1-3]. Neurogenic erectile dysfunction may also result from surgical management of invasive bladder cancers as well as low pelvic malignancies including colon and rectal cancers [4]. While several management options exist to address the resultant ED, these are limited to interventions which do not directly influence cavernous nerve recovery [5-7]. It is important to note that contemporary data indicates that the probability of erectile dysfunction following radical prostatectomy for clinically localized cancer of the prostate remains 20-90% at 24 months; for cystoprostatectomy, the overall 2-year recovery rate of erectile function (reduced or normal erections) as reported by Kessler et al is 31% using Kaplan—Meier methodology while low anterior or abdominoperineal resection ED rates vary from 10% to 60% [8-11].

MECHANISM OF CAVERNOUS NERVE INJURY AND LIMITATIONS TO RECOVERY

Advances in the neurobiology of growth factors have resulted in a heightened clinical interest for the development of protective and regenerative neuromodulatory strategies for the cavernous nerves as these nerves are inadvertently injured via mechanical stretch or cutting, cautery, ischemia at the time of surgery or post-insult inflammatory changes [4,8]. The translational potential of neuromodulatory therapy is based upon the recognition that although the peripheral nervous system demonstrates an intrinsic ability to regenerate after injury, this endogenous response is somewhat limited and does not usually allow for a full recovery of function as axonal degeneration and loss of neurogenic function occurs [12,13].

Nitric oxide (NO) released from the axonal end plates of the cavernous nerves (CNs) within the corpora cavernosa causes relaxation of smooth muscle, initiating the haemodynamic changes of penile erection as well as contributing to maintained tumescence along with endothelial NO; accumulating evidence suggests that a return to potency following injury to the CNs is dependent, in part, upon axonal regeneration in the remaining neural tissues and successful functional re-innervation of the end-organ (neuronal NO activation) [13].

Well-defined pathobiological changes are observed in animal model studies of the penis following CN compromise which may range from neuropraxia to lethal axonal damage including apoptosis of smooth muscle and endothelium, reduced nitric oxide synthase (NOS) nerve density, up-regulation of fibroproliferative cytokines such as transforming growth factor beta (TGF-β), smooth muscle fibrosis or loss, or pathobiological signaling responses such as altered sonic hedgehog protein (SHH) [13-15]. Additionally, the chronic absence of erection secondary to cavernous nerve neuropraxia during the prolonged recovery phase is thought to increase the potential for further cavernosal smooth muscle structural deterioration due to a failure of normal cavernosal cycling between flaccid and erect state [1]. Due to the extended period of time required for maximal nerve recovery, it is possible that even under ideal non-enhanced conditions for nerve regeneration, functional recovery cannot be completely restored as postinjury tissue alterations may be permanent [13].

NEUROTROPHINS

Endogenous neurotrophins (NTs) play key roles in the survival, development and differentiation of neurons in both the central and peripheral nervous systems; these polypeptides regulate neuronal survival though a series of signaling pathways, including those mediated by G-proteins, MEK, PI3-K, and other signaling cascades [16]. Also, NTs have recently been identified as key factors involved in Schwann cell (SCs) development, as BDNF enhances myelination in SCs through p75NTR and subsequently inhibits migration through the RhoA/Rho kinase pathway [17].

The classical neurotrophins, including BDNF, nerve growth factor (NGF), and neurotrophins 3, 4, and 5, have been the focus of intense investigation because of their central neuromodulatory roles, especially with regards to neuronal survival after injury [18]. NTs bind to two distinct classes of glycosylated receptor: the p75 neurotrophin receptor (p75(NTR)) and tyrosine kinase receptors (Trks). Whereas p75(NTR) binds to all NTs, the Trk subtypes are specific for each NT. For example, BDNF promotes neuronal survival, neurite outgrowth and prevents neuronal death through its interaction with tropomyosin-related kinase B (TrkB) and pan-neurotrophin 75 (p75) receptors and subsequent activation of various putative signaling pathways [4].

Brain-derived Nerve Growth Factor (BDNF)

The ability of BDNF to enhance functional recovery after cavernosal nerve injury has been shown via direct cavernosal injection of neurotrophic factors and gene therapy with adeno-associated virus-mediated neurotrophic factor production in animal models representative of cavernous nerve injury (Table 1) [15,19-21]. The UCSF group, under Dr Tom Lue, was able to demonstrate BDNF-enhanced recovery of erectile function, BDNF and vascular endothelial growth factor (VEGF) putative synergies, and regeneration of NOS-containing nerve fibers using established in vivo rat models of neurogenic impotence [20-22]. Separate studies determined that BDNF-secreting fibroblasts also promote recovery of bladder and hindlimb function following spinal cord contusion [23]. Importantly, BDNF retrograde axonal transport to the cell body was demonstrated by Hiltunen et al, as injected molecules (as well as neurotrophin-3) are taken up by the neural synapses of the corpus cavernosum and travel to the major pelvic ganglion to exert their neuroprotective/regenerative effects; the external location of the penis allows for intracavernous introduction and retrograde transport of potential therapeutic agents to the site of injury [24,25]. Also, BDNF was shown to exert its effects on several classes of neurons, acting in an autocrine or paracrine fashion early after nerve injury when a rapid influx of growth factors occurs distally to the site of trauma (end-organ or end-tissue response) [4].

The need to elucidate the potential pathways responsible for BDNF effects necessitated the development by Lin et al of a cost effective *in vitro* culture system consisting of dorsalcaudal region of the major pelvic ganglion (MPG) and proximal cavernous nerve segment, to study neurotrophic effects of growth factors and resultant erectogenic NOS-containing neurite outsprouting [26]. This advancement allowed for recent identification of the JAK/STAT signaling pathway as the primary mechanism responsible for *in vitro* BDNF-mediated cavernous neurite outgrowth and subsequent observations that CN axotomy up-regulates in *vivo* expression of penile BDNF and leads to endogenous activation of the JAK/STAT pathway in the MPG [12,16,24]. In an accompanying editorial, M.C. Michel remarked upon the potential importance of this new knowledge, as this mechanism is also currently undergoing active investigation as a potential treatment of diabetic nephropathy, inflammatory disease, and a range of malignancies [27].

Subsequently, the membrane receptors JAK1 and JAK2, and downstream molecules including STAT1, 2, 3 and 5 have become key components for further study of the cavernous nerve response to injury; early results demonstrate an age-related decline in the penile BDNF response to cavernous nerve injury in the rat [28] as well as compromised exogenous BDNF-enhanced neurite outgrowth (tissue-culture studies) in Type 1/Type 2 diabetes and metabolic syndrome rat models [29]. Studies of the role of Schwann cells as an intermediary BDNF signaling partner, as well as elucidation of the biphasic activation response of JAK 1 and JAK 2 at 1-2 and 24-48 hours after BDNF treatment, illustrate the importance of not only target-specific approaches to neuromodulation, but also the importance of treatment timing and the remaining gaps in contemporary BNDF knowledge [30].

Growth Differentiation Factor-5 (GDF-5)

GDF-5, a member of the transforming growth factor-beta (TGF-β) superfamily, is a more recently isolated neurotrophic factor [31]. This atypical growth factor is a bone morphogenic protein whose effector pathways include intermediary serine/threonine kinase receptors, namely (bone morphogenic protein) BMP receptor Ib (BMPRIb), BMPR2 and activin receptor 2 (ACTR2) [32]. The principal pathways modulated include Smad and p38 mitogen-activated protein kinase (MAPK) [33-35]. Bone regenerative properties of GDF-5 have been well characterized in animal models and a pilot study of GDF-5 treatment in humans is underway [36].

Pre-clinical central nervous system studies in the rat have demonstrated *in vitro* and *in vivo* neurotrophic and neuroprotective effects of GDF-5 on dopaminergic neurons following intracerebral injection [32,33]. Peripheral nervous system studies focused on sensory nerves identified *in vitro* increases in neuronal survival as well as neuroregeneration [37,38]. Fandel et al have recently published two important studies identifying the effects of GDF-5 following cavernous nerve (CN) injury [39,40]. In the initial pilot, dose-dependent improvements for the recovery of erectile function following bilateral crush injury in the rat were demonstrated, with a maximal treatment benefits doubling the mean peak intracavernous pressures (electrostimulation) compared to controls (Table 2) [39]. Follow-up studies using a novel, slow-release suspension of liquid microparticles have confirmed the neuromodulatory effects of GDF-5, as functional recovery is accompanied by nNOS neuronal preservation and decreased levels of apoptosis (Table 3) [40]. Deleterious effects of TGF-b were diminished by reducing TGF-b mRNA expression [40]. These results are consistent with previous *in vitro* studies, which used diluted GDF-5 concentrations, and suggest an optimal dose-response curve at specific concentrations (similar to BDNF-induced neurite outsprouting) [12,16,24,39,40]. GDF-5 is an atypical neuromodulatory agent with some promise, although to date, neurobiological properties and potential translation impact remain superficially understood; this is not surprising given the fact that GDF-5/receptor binding structures were only first determined in 2005 [35].

Neurturin (NTN)

Glial cell line-derived neurotrophic factors also promote the survival and function of diverse neuronal populations in the peripheral and central nervous systems [4,41]. This nerve growth factor family includes the molecules glial cell line-derived neurotrophic factor (GDNF), neurturin (NTN), persephin, and artemin, representing a class of novel neuroprotective and neuroregenerative agents [42,43]. Initial *in vitro* studies suggested NTN acts as a target-derived survival and/or neuritogenic factor for penile erection-inducing postganglionic neurons [42]. NTN was characterized as a target-derived neurotrophic factor for penile sympathetic neurons and adult rat GDNF family receptor (GFR) alpha-2 and signal transducing receptor kinase Ret were expressed in 98.4 and 100% of penile MPG

neurons [42]. Based on the limited animal model evidence available, NTN neuromodulation appears to occur via a signaling mechanism distinct from other parasympathetic neurons and may be mediated by different cell-surface accessory proteins including the GFRα1, -α2 (predominant), and -α4 mechanisms [44-46].

Bella et al first demonstrated neurturin's ability to confer an *in vivo* advantage for the functional recovery of erectile function following cavernous nerve injury in a randomized, investigator blinded evaluation of NTN in the rat [47]. Neurturin applied directly to the areas of bilateral cavernous nerve injury facilitated the preservation of erectile function as compared to untreated control rats and those treated with extended release neurotrophin-4, with a mean ICP increase of 55% (net increase of 62.0 ± 9.2 cmH2O, $p<0.05$ vs control) (Table 2) [47]. Following this, Kato et al reported improvements for functional recovery after cavernous nerve injury with the use of a viral vector delivery mechanism (herpes simplex) expressing GDNF [48]. As penis-projecting pelvic neurons express neuronal nitric oxide (nNOS) and GFRα2, accumulating tissue culture, cell-line, *in vivo* signaling, and functional evidence suggests that neurturin and GDNF play a role in regeneration, as well as maintenance, of adult parasympathetic neurons.

CONCLUSIONS

Pre-clinical evidence continues to define the role of growth factors in response to cavernous nerve injury. Compromised cavernous nerve function is a major cause of the development of erectile dysfunction after radical pelvic surgery for prostate, invasive bladder or colorectal malignancies, and serves as a primary target for potential neuroprotective or regenerative strategies utilizing nerve growth factors such as BDNF, GDF-5, and NTN, and/or targeted novel therapeutics modulating downstream signaling pathways. Pathologic mechanisms include compromised presynaptic NO synthesis or release (even as regenerated axons express NOS), target-tissue changes, or a combination of these factors. Optimal restoration of erectile function following cavernous nerve injury becomes possible when strategies are available to stimulate nerve growth to re-establish functional penile innervation and surviving or recoverable axons are protected in the post-traumatic period from further deterioration or death. Future treatment options may include signaling pathway modulators, neurotrophic factors, stem cells, immunophilin ligands, or novel combinations of these molecules/agents.

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