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*Review Article*

# Neurobiological insights into lower urinary tract dysfunction: evaluating the role of brain-derived neurotrophic factor

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**Abstract:** Lower urinary tract dysfunction (LUTD) encompasses a range of debilitating conditions that affect both sexes and different age groups. Understanding the underlying neurobiological mechanisms contributing to LUTD has emerged as a critical avenue for the development of targeted therapeutic strategies. Brain-derived neurotrophic factor (BDNF), a prominent member of the neurotrophin family, has attracted attention due to its multiple roles in neural development, plasticity, and maintenance. This review examines the intricate interplay between neurobiological factors and LUTD, focusing on the central involvement of BDNF. The review emphasizes the bidirectional relationship between LUTD and BDNF and explores how LUTD-induced neural changes may affect BDNF dynamics and vice versa. Growth factor therapy and the combined administration of controlled release growth factors and stem cells are minimally invasive treatment strategies for neuromuscular injury. Among the many growth factors and cytokines, brain-derived neurotrophic factor (BDNF) plays a prominent role in neuromuscular repair. As an essential neurotrophin, BDNF is involved in the modulation of neuromuscular regeneration through tropomyosin receptor kinase B (TrkB). Increasing BDNF levels facilitates the regeneration of the external urethral sphincter and contributes to the regulation of bladder contraction. Treatments targeting the BDNF pathway and sustained release of BDNF may become novel treatment options for urinary incontinence and other forms of lower urinary tract dysfunction. This review discusses the applications of BDNF and the theoretical basis for its use in the treatment of lower urinary tract dysfunction, including urinary incontinence (UI), overactive bladder (OAB), and benign prostatic hyperplasia (BPH), and in the clinical diagnosis of bladder dysfunction.

**Keywords:** Brain-derived neurotrophic factor, urinary incontinence, pudendal nerve regeneration, voiding dysfunction, overactive bladder, sphincter function, pelvic muscle, benign prostatic hyperplasia

## Introduction

Neural regeneration poses a challenge to researchers and surgeons. The regeneration of peripheral nerves requires an ideal environment, including one that inhibits inflammation, stressors, apoptosis, and fibrosis, as well as the promotion of immune-regulation, vascularization, cell proliferation and neuro-angiogenesis (**Table 1**). Stem cells [1, 2], biomaterials [3] and growth factors are suitable candidates for promoting peripheral nerve repair since they have some of the effects required to achieve nerve regeneration. Growth factors can exert effects that are beneficial for nerve regeneration, but the best candidate for promoting peripheral nerve regeneration among them has not yet been identified.

Brain-derived neurotrophic factor (BDNF) is an important neurotrophin involved in neural development, neuromuscular function, neural regulation of the lower urinary tract, such as the bladder, urethral sphincter, prostate gland [4]. It is found that BDNF can regulate skeletal muscle including pelvic muscle [5], cardiac muscle [6], airway and vascular smooth muscle [7, 8]. The effects of BDNF include but not lim-

**Table 1.** The principles of peripheral nerve regeneration

| Targets of inhibition | Targets of promotion |
|---|---|
| Nerve injury | Neurogenesis |
| Ischemia | Vascularization |
| Inflammation | Immunomodulation |
| Oxidative stress | Redox effects |
| Apoptosis | Cell proliferation, cell survival |
| Fibrosis | Anti-fibrosis |

ited to mediating depression [9], activating platelets [10], and reducing atrial fibrillation [11]. As a neurotrophin, it has been reported to promote the regeneration of both sensory and motor neurons [12, 13]. Dysregulation of BDNF can contribute to lower urinary tract dysfunction, including urinary incontinence (UI), overactive bladder (OAB) and benign prostatic hyperplasia (BPH). Growth factor therapy is a minimally invasive treatment strategy for neuromuscular injury.

BDNF's role as a targeted neuronal survival factor and its associated effects on neuroplasticity has been well established [14, 15]. Recently, BDNF has been used as a candidate for the treatment of urinary tract dysfunction with encouraging results in neuromuscular tissue regeneration and significant improvement in urethral sphincter function in animal studies [16, 17]. This review briefly discusses the BDNF pathway and its functions in the lower urinary tract system and reviews the application of BDNF and the theoretical basis of its use in the management of UI, OAB and BPH.

## BDNF pathway and its functions in the lower urinary tract system

### *Distribution of BDNF and its receptors*

Brain-derived neurotrophic factor (BDNF) is synthesized by motoneurons and Schwann cells in peripheral nerves. Signaling molecules downstream of BDNF are found in the spinal cord, dorsal root ganglion, pudendal nerve, lower urinary tract, and pelvic muscles. BDNF is synthesized by motoneurons, a subset of the dorsal root ganglion neurons, and Schwann cells. BDNF mRNA is found at low levels in the sciatic nerve, and its expression increased in all neural cell types after nerve transection or injury [18]. BDNF, NGF and associated receptor transcripts have been detected in the urothelium and detrusor smooth muscle of NGF-overexpressing mice [19].

Brain-derived neurotrophic factor is crucial for the development of cranial sensory neurons and several mechanoreceptors innervating the Meissner corpuscles and Pacinian corpuscles [20]. BDNF also affects the development of chemoreceptors innervating taste buds [21]. The majority of BDNF transcripts can be found in the brain and blood cells [22]. BDNF is present in nearly all brain regions and its function is related to the neuronal, glial, and vascular constituents of brain tissue [23, 24].

The role of BDNF in bladder function under normal and pathological conditions has not been well demonstrated yet, and most available studies have used experimental models of bladder dysfunction. It has been suggested that following chronic bladder inflammation or spinal cord injury, the synthesis of BDNF in the urinary bladder is markedly increased [25]. Frias's study further indicated that BDNF seems to protect the central nervous system against detrimental peripheral changes [26].

### *BDNF signaling pathway and regulation*

Neurotrophins are soluble polypeptides that play important roles in neural growth, survival and differentiation in the central nervous system [27]. In addition to BDNF, neurotrophins include nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5) [28]. BDNF was first isolated from the pig brain in 1982 [29] and it is the second most prevalent neurotrophin in the body. BDNF is involved in several neural regulatory processes, such as the neural regulation of bladder storage and emptying, depression, and pregnancy. BDNF activates several important pathways via tropomyosin receptor kinase B (TrkB) to mediate neurite outgrowth, an essential process in neurogenic regeneration. Evidence for the importance of this signaling pathway is based on a study with heterozygous TrkB null mice, in which only 50% of motor-neurons regenerated after nerve transection [30].

Whether neurotrophins are activated depends on their interactions with the tropomyosin receptor kinases (Trks) and the transmembrane receptor p75 neurotrophin receptor (p75NTR). NGF preferentially activates neuro-

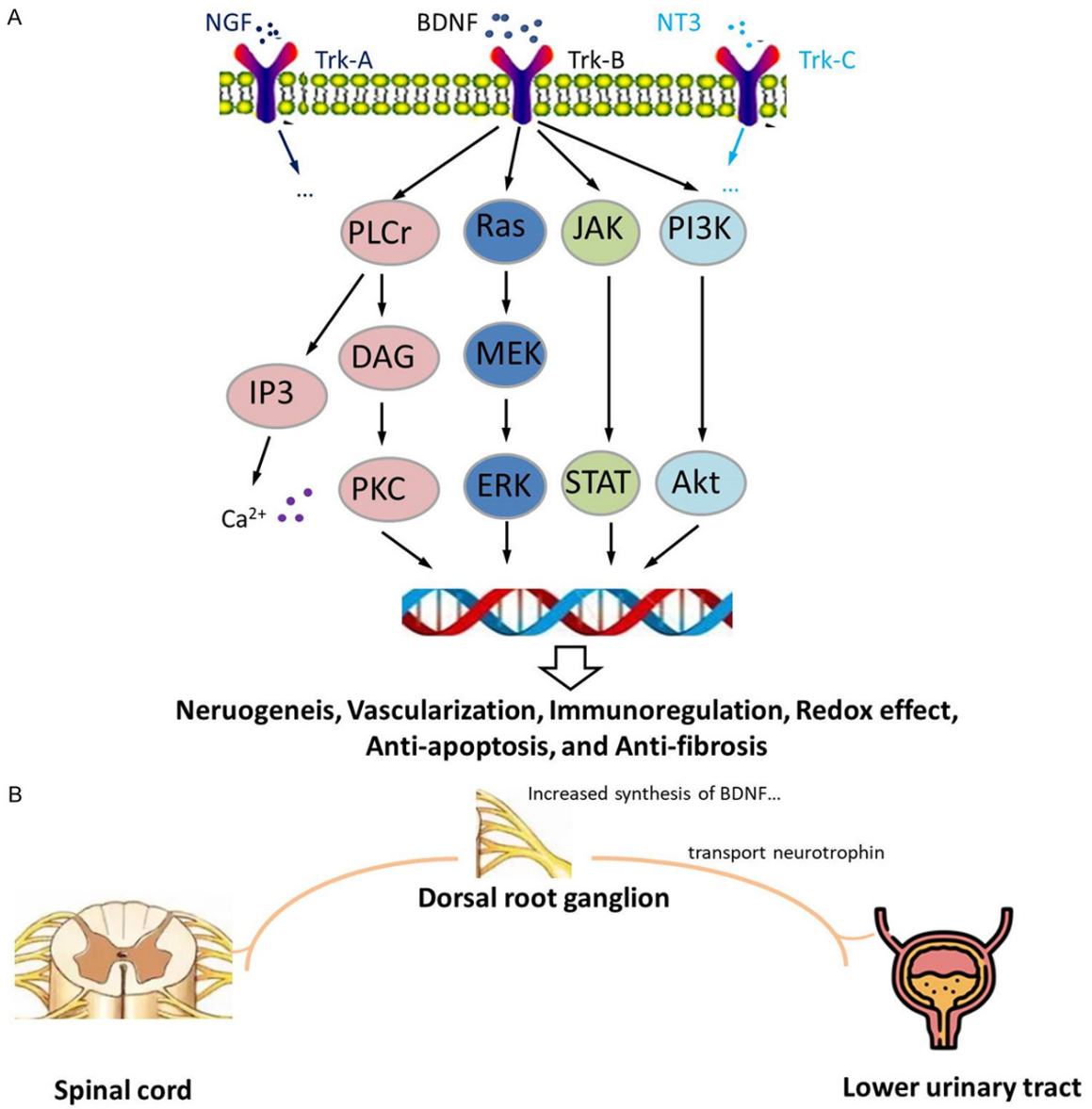


**Figure 1.** Pathway and regulation of BDNF. A. Schematic diagram of the effects of BDNF. BDNF binds to the extracellular domain of the Trk-B receptor, activating an intracellular signaling cascade that includes the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, Ras-mitogen-activated protein kinase (MAPK) pathway, Janus kinase/signal transducer (JAK/STAT) signaling pathway and the phospholipase Cγ (PLCγ)-$Ca^{2+}$ pathway. The effects of BDNF included neruo-genesis, vascularization, immune-regulation, redox effects, anti-apoptosis, and anti-fibrosis. B. Central mechanisms involved in neurotrophin and urinary tract regulation. Upon retrograde transport of neurotrophin along afferent fibers from the urinary tract, dorsal root ganglion neurons increase synthesis of excitatory neuromediators, such as BDNF and voltage-gated ion channels, and these neuromodulators transported anterogradely to primary afferent terminals in the spinal cord.

trophic tyrosine receptor kinase-1 (NTRK1), while BDNF and NT4/5 activate NTRK2, previously known as TrkB. NT3 signals through NTRK3 via NTRK3. Binding of neurotrophins and the phosphorylation of receptors activate three main intracellular signaling pathways: the Ras-mitogen-activated protein kinase (MAPK) pathway, phosphatidylinositol 3-kinase (PI3K)-Akt pathway, and phospholipase Cγ (PLCγ)-$Ca^{2+}$ pathway [31, 32]. Activation of the Ras-MAPK pathway promotes cell survival, differentiation and synaptic plasticity through extracellular signal-regulated kinase and MAPK/ERK kinase [31] (**Figure 1A**).

Lin et al. reported that STAT3/STAT1 is extensively phosphorylated by BDNF in Schwann cells. JAK/STAT pathway activation was found to show an initial peak immediately after BDNF treatment and then a second higher peak at 24-48 hours. This indirect mechanism of BDNF-mediated enhancement of nerve regeneration involving activation of the JAK/STAT pathway in Schwann cells, rather than directly in neurons, represents a novel BDNF signaling pathway [33].

The role of neurotrophins in the central nervous system was established by many researches, and their importance as key regulatory proteins in peripheral tissues had become a recent hotspot. From a clinical standpoint, BDNF was involved in the pathophysiology of various brain diseases through diverse intracellular pathways. Numakawa et al. implied that BDNF was relates to neuronal protection, synaptic function, and morphological changes [34]. As one of the key factors in the brain, BDNF may contribute to different neuronal responses and affect synaptic plasticity [23].

The mechanism by which BDNF expression is regulated in the nervous system is complicated, and both physiological and pathological processes are involved. BDNF expression is regulated by glucocorticoids, which implies that there is a potential connection between the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes. Chow et al. indicated that estradiol is a central regulator of BDNF expression in reproductive tract. Neural excitation, substance abuse and environmental contaminants also act as potential modulators of BDNF gene expression through receptor response elements in different BDNF promoter regions [27].

Although no data have been reported on the effects of exogenous neurotrophin administration on human lower urinary tract function, experimental evidence has shown that neurotrophins such as NGF modulate micturition pathways when applied to the bladder or spinal cord [35]. Infusion of neurotrophin into the bladder wall increases the expression of excitatory neurotransmitters in the lumbosacral spinal cord (**Figure 1B**). This process involves the uptake of peripheral neurotrophins and the retrograde transport to dorsal root ganglion and their spinal projections, which leads to synaptic plasticity in the spinal cord [35].

Frias found that in a model of neurogenic detrusor overactivity (NDO) followed by spinal shock, spinal BDNF expression increased in a time-dependent manner together with NDO emergence. It has also been suggested that BDNF may regulate bladder function after spinal cord injury via inhibition of neuronal sprouting [36].

A relationship between neurotrophic factors and preeclampsia has been suggested by several studies showing that neurotrophic factors are involved in the angiogenesis in the placenta [37, 38]. Vandita examined BDNF levels in both maternal and fetal cord blood in women with preeclampsia, and implied a connection between BDNF and preeclampsia [39].

*Effect of BDNF on peripheral nerve regeneration*

Brain-derived neurotrophic factor has been shown to exert a protective effect on peripheral nerves and neuromuscular junctions. Usually BDNF mRNA is expressed at low levels in peripheral nerves, while BDNF is upregulated in neurons, Schwann cells, and muscles to aid in the survival and repair of injured neurons. Nerve injury upregulates BDNF expression, this effect persists for weeks, and can be attributed to both neuronal and nonneuronal sources. Brain-derived neurotrophic factor is necessary for pudendal nerve regeneration and functional recovery. In facial nerve injury, upregulation of BDNF is correlated with improved functional outcomes [40, 41]. In a pudendal nerve crush model, peripherally administered TrkB was found to bind free BDNF and inhibit the regenerative response [26, 42].

Brain-derived neurotrophic factor also exerts neuroprotective affects by acting on the corticospinal motor system. BDNF has a protective effect and can promote the growth of axons in the corticospinal tract and neurons. It was found that transplanting BDNF-secreting fibroblasts into aspiration lesions increases the survival of motor neurons in the cortical area but does not promote the growth and regeneration of axons [43].

Brain-derived neurotrophic factor can exert protective effects over a long distance, as demon-

strated by studies involving the delivery of BDNF-secreting cells to injury site. One study found that in macaques, following implantation of BDNF- and NT-3-secreting cells into the lesion in the C7 level spinal cord, BDNF had neuroprotective effects on pyramidal neurons approximately 10 cm from the bodies of the BDNF-secreting cells [44]. Recent studies in rodent models determined that BDNF influences the survival of these neurons [44]. In addition to protecting neurons, BDNF promotes the sprouting [45] and increases the remyelination [46] of injured axons in the spinal cord. Several groups have found that BDNF upregulates growth related genes such as T-alpha-1-tubulin and GAP-43 in neurons, while upregulation of these related genes was suggested to promote regeneration [47, 48]. It is also thought that TrkB receptor-mediated activation of TrkB increases the level of cyclic AMP downstream of ERK pathway activation, which may partially contribute to the growth-promoting effects of conditioning lesions in the periphery [49]. Therefore, BDNF may act as a general inducer of sprouting and regeneration [50].

## Overview of urinary incontinence

### *Incidence*

A population-based survey of lower urinary tract symptoms (LUTS), including UI and OAB, in five countries showed that 64.3% of 19,165 individuals reported experiencing LUTS. The overall prevalence of OAB was 11.8% and increased with age. OAB was more prevalent than UI combined with LUTS (9.4%) [51].

Urinary incontinence is a common symptom among different populations, and approximately 50% of adult women may have UI [52]. The reported incidence varies among studies and with patient age. UI may affect about 20% of all women and up to 77% of elderly women [53, 54]. Recent epidemiologic studies suggest an overall prevalence of 17% in women older than 20 years and 38% in women older than 60 years [55].

The different types of urinary incontinence include stress incontinence, urge incontinence, overflow incontinence, functional incontinence and mixed incontinence. The most common type of urinary incontinence is stress urinary incontinence (SUI) [54]. SUI is defined as involuntary urinary leakage on effort or exertion. Sneezing or coughing can also cause SUI. Recent reports indicate that 37.5% of young women between 30 to 50 years in primary care settings report SUI [56]. UI has a reported prevalence of 11% in men aged around 60 and 31% in men over 85 years old. UI affects up to 32% of men with LUTS [57]. The treatment of prostate disease has been associated with an increased risk of UI in men. Long term UI rates following operation are estimated to be between 8-16% [58].

Data from a previous study indicated that the range of UI prevalence in adult women is quite broad. The prevalence rates vary between countries, and cultural differences in the perception of urinary incontinence and willingness to report UI would also affect the acute prevalence. Moreover, methodological differences, including the wording of questionnaire items and the method of administration would affect the outcomes [51, 59, 60]. Several review studies have also emphasized that differences in case definitions may also largely affect the reported incidence of UI [61].

Overactive bladder, which is defined as urinary urgency usually accompanied by frequency and nocturia, may coexist with SUI [62]. The prevalence of OAB is 16.5% in the U.S., but the real number of patients with OAB is probably much larger [63].

Urethral sphincter insufficiency is the main cause of UI following surgery for BPH [64]. BPH is arguably the most common benign disease in humans, and the prevalence of this condition is increasing as the population ages. In the U.S., there are 38.1 million men over 30 years old with BPH pathology, with 12.9 million needing medical services [65]. An epidemiologic study revealed that the prevalence rate of BPH/LUTS ranges from 50% to 75% among men over 50 years old and is 80% among men over 70 years old. The overall incidence rates of BPH ranges from 8.5 to 41 cases/1000 persons [66].

### *Etiology and mechanism*

The mechanism of UI involves structural and functional components [4]. The pelvic floor muscles and connective tissues are the main structural support for maintaining the physio-

logical position of pelvic organs including the urethra. The pelvic floor is a complex anatomical structure with muscles and fascial components regulated by neural signals that consist of the endopelvic fascia, ligaments, perineal membrane, the urogenital diaphragm, levator ani muscles, and superficial perineal muscles [67].

Structural changes due to pregnancy and delivery result in UI. During vaginal childbirth, the pelvic floor, ligaments and pudendal nerve, which passes between the sacrospinous and sacrotuberous ligaments, can be directly compressed [68]. Vaginal childbirth or any other injury to the structural and neuromuscular components of the pelvic floor, such as the and pudendal nerve (PN), can directly result in UI. Childbirth was recognized as a risk factor for the SUI development. It was reported that vaginal delivery is associated with a threefold greater risk of developing SUI than cesarean section [69, 70].

Incontinence after prostate treatment is a common symptom for men. It can result from radical prostatectomy, prostate radiation, and surgery for benign prostatic hyperplasia. All of these factors may increase the risk for UI [71].

The pathogenesis of OAB involves the urothelium, suburothelium, urethra, and central nervous system [72]. All these structures contribute to bladder afferent signaling and affect different functions of the bladder [72]. Endocrine influences have been suggested to play an important role in BPH. Prostatic inflammation is common in adults and is associated with the progression of BPH [73]. Several phenomena involving androgens, estrogens, insulin, inflammation, proliferative reawakening, stem cells and telomerase have been hypothesized to be involved in the pathogenesis of BPH [74]. Although there are many potential mechanisms, the pathogenesis of OAB and BPH is not yet fully understood.

The relationship between neurotrophins and the mechanism of various forms of urinary tract dysfunction including UI, OAB and BPH has not yet been clarified. The neural and pelvic floor muscle would have a recovery in most postpartum women [75]. After pudendal nerve injury caused by delivery, persistently prolonged pudendal motor nerve terminal repair was observed after several years, and partial reinnervation was more obvious in women with SUI.

Modulation and coordination of the functional components of the urinary tract by the central and peripheral nervous systems are directly affected in UI. Dysfunction of neural control may underpin a wide range of clinical urinary tract problems [76]. Neural dysfunction alters reflex activity and influences sensation on the afferent side, while the motor activity of lower urinary tract components can be increased or reduced or become uncoordinated on the efferent side [77]. Although no consensus has been reached about the fundamental causes of UI, existing data suggest that the pathophysiological mechanisms include peripheral nerve dysfunction and weakness of the urethral sphincter and pelvic floor muscles.

Bladder outlet obstruction due to BPH leads to increased urethral resistance, and then induces mechanical stretching of smooth muscle, subsequently increasing neurotrophic factor levels [78]. The increase in neurotrophic factor levels affects bladder afferent neurons, increases excitability and the spinal reflex, and reflexively reduces the threshold for a sensation of urgency to mediate detrusor hyperactivity [79].

Neurotrophins maintain innervation and neural function as well as stimulate axonal regeneration and neuronal growth [80]. Although the mechanism of LUTS is complex, studies on the changes in neurotrophin levels have provided some clues. Several studies have revealed that the expression of neurotrophins such as BDNF and NGF changes after external urethral sphincter (EUS) injury. The levels of BDNF, NT-4, and NGF expression precisely increase in the EUS after pudendal nerve injury to promote neural regeneration [17, 81].

*Treatment strategies and limitations*

Since the pathogenesis of LUTS, such as UI and OAB, is not fully understood, specific medicines are lacking, and many nonsurgical and surgical treatments have been developed to treat LUTS of different severities.

Pelvic floor muscle exercises and behavioral modifications are neuromuscular rehabilitative therapies, and they remain first-line treatments

for SUI. Pharmaceuticals have also been used to treat SUI for many years, but classic alpha-agonists have not been highly successful [82]. However, several studies have shown that pharmaceutical neuromodulation can improve urethral function and alleviate incontinence in SUI patients. The serotonergic (5HT) and noradrenergic (NE) reuptake inhibitor duloxetine was found to increase bladder capacity and EMG activity in an animal model, and a phase 3 study provided further evidence for the efficacy and safety for the SUI treatment [83, 84].

As a minimally invasive therapy, bulking agent injection has been tested for its efficacy in UI treatment. Various agents, such as bovine collagen [85] and carbon-coated zirconium beads [86], have achieved short-term success. Autologous ear chondrocytes were used as bulking agent to treat UI, and the effect was maintained for 3 to 12 months [87]. However, the long-term complications of these treatments include chronic inflammatory and foreign body responses. Erosion of the urethra and bladder, particle migration or even obstruction of the urinary tract were also reported [88]. These complications of injectable agents are not common, but the beneficial effects are not long lasting.

Surgical is currently regarded as the gold standard therapy for SUI and BPH currently. Classic surgical techniques such as Burch colposuspension have evolved into synthetic midurethal sling procedures, which are less invasive [89]. Midurethral slings may be placed in a retropubic fashion or in a transobturator fashion [90]. Novel minimally invasive procedures involving a single vaginal incision, such as tissue fixation and TVT Secure have become common, but their long-term effects remain to be determined. Transurethral resection of the prostate has been the mainstay of surgical treatment for BPH since the early 1900s. Recent modified operations include photovaporization of the prostate and holmium laser enucleation of the prostate [91].

*Regenerative strategy*

Regenerative repair via stem cell therapy has become a novel treatment strategy for LUTS including UI [92]. In a childbirth injury model, mesenchymal stem cells can improve neuroregeneration via their secretions and accelerate the recovery from muscle injury [16]. Stem cell treatments can functionally regenerate the urethral sphincter in patients with suspected intrinsic sphincter deficiency [93]. However, as a result of heterogeneity of preclinical and clinical trials, the best approach to cell-based therapy in SUI is still under investigation [94].

Lee et al. tested the effects of periurethral muscle-derived stem cell treatment on leak point pressure in a rat model of SUI and found that leak point pressure was significantly improved [95]. Several clinical studies have indicated that bone marrow-derived stem cells and adipose-derived stem cells hold promise for improving cure rates with minimal risk. Although different cellular therapies have differences in safety and efficacy, autologous adult stem cells have the potential to treat UI [96]. Kubota et al. reported that stem cell factors in the urinary bladder may act as possible mediators for controlling bladder function by binding to c-kit in an animal model [97]. Many questions regarding the mechanism of secretome from stem cells in regenerative urology require further investigation [2].

## Current applications of BDNF

Controlled release of growth factors may be a promising approach for the treatment of lower urinary tract dysfunction, including urinary incontinence. Our previous studies have shown that the controlled release of various growth factors can stimulate neurovascular and muscle tissue regeneration and repair without causing excessive inflammation or tissue damage [98-104]. This approach may potentially lead to better outcomes for patients with urinary incontinence and reduce the need for repeated treatments. Controlled release of BDNF specifically promotes innervation and skeletal muscle repair in the treatment of lower urinary tract dysfunction.

*Controlled or sustained release of BDNF*

Persistent release of BDNF is important for it to exert a long-lasting protective effect, so many studies have used microbeads or nanoparticles to deliver BDNF. Shi et al. packaged BDNF in poly(D,L-lactide-co-glycolide) (PLGA) microspheres to treat peripheral nerve defects. It was found that BDNF/PLGA sustained-release microspheres decreased the nerve conduction

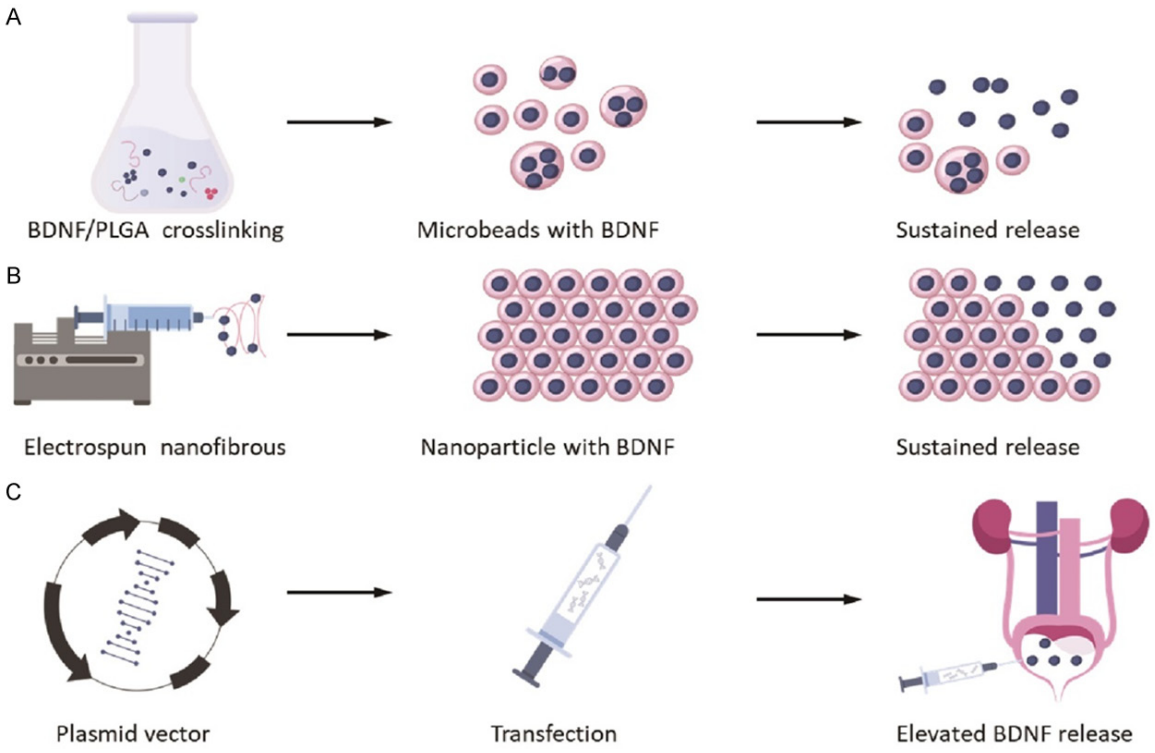


**Figure 2.** Sustained release of BDNF *in vivo*. A. BDNF can be carried by microbeads. PLGA has been widely used in crosslinking with BDNF to produce microbeads. B. Electrospun nanofibrous containing BDNF can be packaged in nanoparticles. Nanoparticles containing BDNF can achieve sustained release in target regions. C. BDNF gene can be transfected and injected into the target tissues to induce BDNF expression.

speed and postponed neuralgic amyotrophy [105] (**Figure 2**).

In a study by Razavi et al., the inner surface of an electrospun PLGA nanofibrous conduit was functionalized with laminin containing BDNF and gold nanoparticles in chitosan nanoparticles. These nanoparticles showed promising effects on peripheral nerve regeneration [106].

Kashyap et al. researched on the impact of BDNF in the rat bladder following bladder wall transfection. Genomic changes in neurons of the bladder were induced by overexpression of BDNF, and a mechanistic link between increased BDNF levels in urine and dysfunctional voiding was observed in an OAB model and OAB patients [107]. In Albukhaty et al. harvested poly-l-lysine-coated superparamagnetic iron oxide nanoparticles (SPIONs-PLL) and used them to deliver BDNF to neural stem cells (NSCs). It was suggested this strategy was an alternative way to obtain BDNF-NSCs by transfection, and could be widely used in regenerative therapy [108].

*BDNF in the treatment of urinary incontinence*

Several drugs and electrical stimulation have been proven to affect the expression of BDNF. Jun et al. implied that caffeine can improve bladder function in diabetic rats, and it was found that the expression levels of BDNF and other factors in the bladder tissues of caffeine-treated rats with diabetes mellitus were increased [109]. In a clinical study, trigonal injection of botulinum toxin A seemed to be an effective treatment for refractory interstitial cystitis/bladder pain syndrome (IC/BPS). A transient but obvious reduction in urinary NGF and BDNF levels was observed in the patients [110].

Electrical stimulation (ES) has been used to restore function and modulate nervous system responses to stimuli. Furthermore, regeneration of injured peripheral or central nerves can be accelerated by regenerative electrical stimulation. ES was implied to increase BDNF expression in injured neurons, activate Schwann cells and promote neural regeneration after nerve injury. In a study by Deng et al., daily

**Table 2.** Main outcomes of recent research on the effect of BDNF on nerve regeneration

| Authors | Model (s) | Usage of BDNF | Main outcomes |
|---|---|---|---|
| JG Boyd, 2002 | Rats [134] | Different doses of BDNF | Low doses of BDNF promoted axonal regeneration of motoneurons; high doses inhibited motor axon regeneration |
| E Vögelin, 2006 | Rats [133] | Calcium alginate prolonged-release capsules | BDNF stimulated faster peripheral nerve regeneration and reduced neuropathic pain |
| J Brock, 2010 | Rhesus monkeys and rats [44] | Lentiviral BDNF injections | BDNF mediated the remote protection of corticospinal neurons in the brain |
| GT Lin, 2010 | Rats [76] | Delivery of BDNF to the major pelvic ganglia | BDNF promoted major pelvic ganglia neurite growth |
| BC Gill, 2013 | Rats [126] | Continuous infusion of BDNF | BDNF accelerated continence recovery after childbirth injury by promoting EUS recovery |
| J Zheng, 2016 | Mice [131] | BDNF injection | BDNF increased neuronal intrinsic growth capacity and promoted behavioral recovery |
| MP Kashyap, 2018 | Rats [107] | Bladder wall transfection | BDNF overexpression induced bladder overactivity |
| S Razavi, 2021 | Rats [106] | BDNF nanoparticles | BDNF led to axonal regeneration and functional recovery after 12 weeks |

bilateral ES of the pudendal nerve was performed, and it was found to accelerate recovery from SUI. This implies that daily ES improves urethral function better than less frequent ES [111].

Balog et al. showed that BDNF expression was significantly increased after electrical stimulation compared with after injury alone [112]. Transgenic mouse experiments have shown that BDNF, NT4 and TrkB expression is important for ES-induced regeneration [113, 114]. BDNF binds to TrkB receptors on the growth cones of neurons or adjacent neurons in a paracrine or autocrine fashion to promote regeneration [115]. Cultured Schwann cells under ES lead to a significant increase in NGF, BDNF, and GDNF levels [114]. Recent studies on the effect of BDNF on nerve regeneration are summarized in **Table 2**.

*Role of BDNF in UI diagnosis and follow-up*

The relationships of UI with clinical and urinary markers such as BDNF have not yet been clarified. Several studies have revealed that symptoms of bladder dysfunction may be associated with changes in urinary marker levels. Soriano et al. studied women with urgency and without incontinence, and univariate analysis revealed that urgency was correlated with elevated levels of NGF and BDNF; however, these relationships did not persist after controlling for confounding factors [116]. Antunes-Lopes et al. tested the urinary levels of these growth factors in women with SUI after a midurethral sling procedure and found that the mean levels of BDNF and NGF had a significant increase in OAB-wet patients. This suggests that increased bladder outlet resistance may play a crucial role in the rise of urinary neurotrophin levels [117].

The urinary BDNF/Cr ratio seems to be a more useful diagnostic marker for bladder dysfunction, such as OAB, than the BDNF level. Kadriye suggested that the urine NGF/Cr and BDNF/Cr ratios would be markers for OAB diagnosis in children. The BDNF/Cr ratio could also be used in monitoring the treatment response [118]. However, Colic's study did not demonstrate that urinary BDNF can be used as a biomarker for monitoring OAB in children [119]. Tsiapakidou et al. reviewed studies on adult women with OAB and found that the BDNF/Cr ratio could be used in the assessment of female OAB patients [120]. Further study showed that urinary BDNF/Cr levels are increased in OAB patients and are significantly correlated with symptom severity. BDNF levels have better sensitivity than NGF levels in detecting OAB in subjects without other LUTS. The results of a recent study suggested a potential role for BDNF as an objective biomarker for OAB diagnosis, and further study is required to identify the relationships of UI with clinical and urinary markers such as BDNF [121].

Wang's study revealed that BPH is associated with increased BDNF levels in urine, and urinary BDNF levels are further elevated by detrusor overactivity. It was suggested that the urinary BDNF level can be used to evaluate the severity of BPH. BDNF was also implied to be a biomarker for the diagnosis of detrusor overactivity with BPH [79]. Bronzetti et al. observed

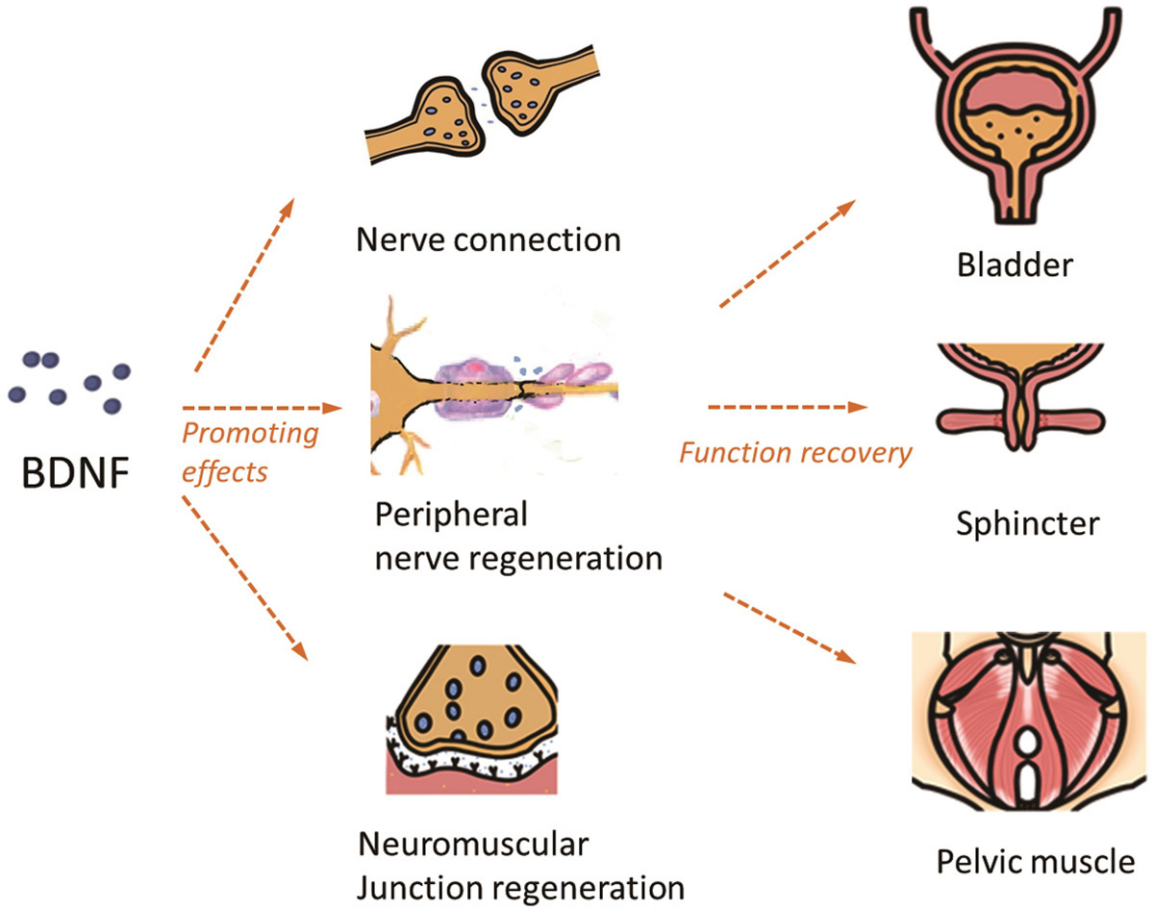


**Figure 3.** Role of BDNF in urinary function regulation. BDNF has promising effects on all types of neural structures such as peripheral nerves and neuromuscular junctions. The regeneration of these neural structures helps to promote functional regeneration of the bladder, sphincter and pelvic muscles.

high expression of BDNF and TrkB in prostate cancer and BPH. This suggests a possible predictive role for BDNF and TrkB in the diagnosis of prostate cancer [122].

*BDNF in urinary function regulation*

The regulatory function of BDNF in UI is complex since it is associated with both the central and peripheral nervous systems. BDNF released into the spinal cord was suggested to control central synaptic plasticity. Potentiation of postsynaptic N-methyl-D-asparate (NMDA) receptors in the CNS might be the possible mechanism [123]. Intravenous injection of recombinant TrkB-Ig2 domain, which was designed to neutralize BDNF but not NGF, reduces the frequency of reflex contractions following treatment with cyclophosphamide [124]. Since TrkB-Ig2 is unlikely to pass through the blood-brain barrier, peripheral uptake of BDNF is suggested to be involved in the regulation of micturition pathway plasticity following cyclophosphamide-induced inflammation [35].

Huang et al. used the translocator protein agonist Ro5-4864 to alleviate mechanical allodynia and bladder dysfunction in a cyclophosphamide model. The results suggested that neuroinflammation could be reduced by inhibiting the elevation of BDNF levels and consequent activation of astrocytes and microglia [125].

Childbirth injury and other structural changes affect BDNF expression. Gill et al. showed that BDNF can accelerate continence recovery after childbirth injury by promoting EUS recovery [126] (**Figure 3**). Singh et al. revealed the effects of BDNF on the internal anal sphincter (IAS) in addition to the urethral sphincter. Aging can result in rectoanal incontinence caused by IAS dysfunction, which is characterized by an

increase in nonadrenergic noncholinergic relaxation and a decrease in IAS tone and contractility [127]. As a growth factor with widespread signaling effects, BDNF may not selectively affect the urinary system, so further research on its safety is needed to support its clinical use.

*Role of BDNF in peripheral nerve regeneration*

Neurotrophins have promising effects on peripheral nerve regeneration, and several researchers have tested the regenerative capacity of BDNF and other factors in different nerve injury models. Compared to other growth factors, such as NGF, IGF1, FGF2, and VEGF, BDNF seems to have greater potential in nerve regeneration. Su tested the biological effects of BDNF in a rat model of sciatic nerve transection with a 10-mm gap and demonstrated that BDNF composite conduits remain bioactive for three months and can promote the neural regeneration [128]. Lin's research indicated that BDNF can promote neurite growth in the major pelvic ganglia (MPG) in a rat model. The ideal dose of BDNF for promoting MPG neurite growth was between 25 and 50 ng/mL [129]. The combination or codelivery of neurotrophins such as BDNF with other particles represents a novel strategy for repairing peripheral nerves after injury. Maliheh prepared gold nanoparticle (AuNP)- and BDNF-encapsulated chitosan in the laminin-coated nanofiber of a poly-lactide-glycolide conduit and contained adipose-derived stem cells suspended in alginate. This method synergistically facilitated nerve regeneration [130].

Zheng et al. tested the expression of several genes related to axonal regeneration and function in a sciatic nerve injury model to determine the potential mechanisms of nerve repair. BDNF was found to promote axonal regrowth by increasing neural intrinsic growth capacity and protection against atrophy of the neural distal portion. BDNF was suggested to promote behavioral recovery after sciatic nerve crush injury [131]. BDNF has been proven to have an influence on cavernous nerve recovery after injury and is regarded as a novel target for modulating cavernous nerve function [132]. Vögelin et al. suggested that BDNF was able to promote the speed of peripheral nerve regeneration while reducing neuropathic pain [133]. The effect of BDNF has been proven to be dose dependent. Low doses of BDNF promote axonal regeneration of motoneurons, while high doses of BDNF significantly inhibit motor axonal regeneration in a rat model [134]. Yuan's study focused on concentrated conditioned media with MSC secretome and found BDNF is one of the key factors for the acceleration of recovery from nerve and muscle injury [16].

Diffusible molecules, such as IGF, VEGF and FGF, are involved in regulating the development and regeneration of the peripheral nervous system. IGF-1 has potent trophic effects on motor and sensory neurons and can promote neuronal development and regeneration. On the other hand, reduced IGF-1 signaling causes microcephaly and mental impairment [135]. Furthermore, IGF-1 plays a role in Schwann cell survival, maturation, and myelination in vitro, and it also exerts beneficial effects in patients with traumatic brain injury by promoting the recovery of neurons. However, the clinical effects of IGF-1 in amyotrophic lateral sclerosis patients are contradictory [136]. Several stuies revealed that IGF-1 has a therapeutic effect on SUI in rats [137, 138]. However, high doses of IGF-1 increase the risk of benign adrenal and epithelial neoplasms, as well as breast neoplasms in rodents [139].

Nishida et al. examined the relationship between peripheral nerve regeneration and angiogenesis in the early stage after nerve transection. Research on a mouse model found that immediate VEGF signaling responses to nerve injury plays an important role in regional angiogenesis, which might trigger the regeneration of nerve fibers [140]. In a rat model, it was found that BDNF combined with VEGF could activate neural regeneration through promoting neurite sprouting from the MPG [141].

Both in vitro and in vivo studies have shown that FGF-2 can promote neuronal survival and neurite outgrowth [142]. FGF-2 mediates the recovery of sensory functions at an early stage and stimulates the long-distance myelination of axons, whereas motor recovery seems to be inhibited. These results may contribute to the development of novel strategies for peripheral nerve regeneration [143].

Exogenous grafts that express and secrete NGF show increased nociceptive axon sprout-

**Table 3.** Comparison of the effect of BDNF with that of other growth factors in the treatment of peripheral nerve regeneration

| GF | Receptor | Biological effect | Applications | Limitations |
|---|---|---|---|---|
| BDNF | Trk-B | Exerts protective effects on almost all types of neurons and axons; regulates inflammation and pain | Nerve regeneration and UI recovery | More clinical data are required |
| NGF | Trk-A | Regulates the survival and function of postganglionic sympathetic neurons and small-diameter primary afferents [50] | Induction of axonal sprouting onto sensory neurons | Dose limitation in clinical study |
| IGF | IGF-R | Has a potent trophic effect on motor and sensory neurons and in neuronal development and regeneration [137] | Beneficial effects in patients with traumatic brain injury | Increased risk of benign and malignant neoplasms |
| VEGF | VEGF-R | Induces angiogenesis to promote nerve regeneration at early stages [140] | Induction of angiogenesis, which may promote the regeneration of nerve fibers in mice | Indirect nerve regeneration |
| FGF | FGF-R | Promotes neuronal survival and neurite outgrowth in vitro and in vivo [148] | Promotion of sensory recovery and elevation of the myelinated axon grade in animals | Motor recovery seems to be inhibited |

Notes: GF-growth factor.

ing [50]. It was also found that exogenous NGF can increase BDNF levels in sensory neurons [144]. Kemp et al. showed that NGF promotes peripheral nerve repair, showing a bell-shaped dose-response curve, and that high-dose NGF inhibits nerve regeneration [145]. Clinical trials testing recombinant human NGF (rhNGF) have shown that sensory function improvements according to physical examinations and average daily pain levels. However, the painful side effects experienced by patients in these studies revealed the dose limit of rhNGF [146].

Compared with other neurotrophins, such as NGF and NT-4/5, BDNF is more abundant and more widely distributed in the central nervous system. BDNF has shown neuroprotective and regenerative effects on a variety of neuronal types after injury. It is found mainly in small to medium sized neurons and has been shown to promote the regeneration of both sensory and motor neurons. There is emerging evidence that BDNF plays crucial roles in the inflammatory process and pain regulation [147]. BDNF is compared with other growth factors in **Table 3**.

## Conclusion

In addition to playing central roles in neural development and cell survival, BDNF appears essential for the function of the lower urinary tract. Recent studies have suggested that BDNF can facilitate external urethral sphincter reinnervation and participate in bladder contraction regulation. It was also revealed that BDNF can be used as a clinical diagnostic tool for bladder dysfunction, and BDNF has more promising effects on peripheral nerve regeneration than other factors. Modulating BDNF could be a new strategy for the treatment of UI and other forms of lower urinary tract dysfunction.

## Future directions

Urinary incontinence is a very common condition, and currently available treatment options mainly involve surgery. Several animal studies have shown that BDNF has promising effects on the urinary and nervous systems, and there is evidence of a positive correlation between BDNF expression and improvements in urinary functional outcomes. Treatments targeting the BDNF pathway and sustained release of BDNF may represent novel treatment options for UI. Further research on animals larger than rodents would help to optimize protocols for the clinical study of BDNF. More data on the optimal dosage and treatment frequency of BDNF-based treatments are needed. Furthermore, growth factor therapy may have inadvertent effects on other organs or systems, and great care needs to be taken when applying BDNF for clinical treatment based on preclinical data. In the future, BDNF may play more important roles in the diagnosis and treatment of UI and other forms of lower urinary tract dysfunction.

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## Disclosure of conflict of interest

None.

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