

## REVIEW ARTICLE

# Partners in Crime: NGF and BDNF in Visceral Dysfunction

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**Abstract:** Neurotrophins (NTs), particularly Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF), have attracted increasing attention in the context of visceral function for some years. Here, we examined the current literature and presented a thorough review of the subject.

After initial studies linking of NGF to cystitis, it is now well-established that this neurotrophin (NT) is a key modulator of bladder pathologies, including Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS). NGF is upregulated in bladder tissue and its blockade results in major improvements on urodynamic parameters and pain. Further studies expanded showed that NGF is also an intervenient in other visceral dysfunctions such as endometriosis and Irritable Bowel Syndrome (IBS).

More recently, BDNF was also shown to play an important role in the same visceral dysfunctions, suggesting that both NTs are determinant factors in visceral pathophysiological mechanisms. Manipulation of NGF and BDNF improves visceral function and reduce pain, suggesting that clinical modulation of these NTs may be important; however, much is still to be investigated before this step is taken.

Another active area of research is centered on urinary NGF and BDNF. Several studies show that both NTs can be found in the urine of patients with visceral dysfunction in much higher concentration than in healthy individuals, suggesting that they could be used as potential biomarkers. However, there are still technical difficulties to be overcome, including the lack of a large multicentre placebo-controlled studies to prove the relevance of urinary NTs as clinical biomarkers.

**Keywords:** NGF, BDNF, urinary bladder, urinary frequency, visceral pain, colon, plasticity, painful syndromes, neurotrophins, biomarkers, spinal cord injury.

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## 1. INTRODUCTION

More than 60 years have passed since the discovery of Nerve Growth Factor (NGF) by Rita Levi-Montalcini and Viktor Hamburger [1-3]. This protein is now acknowledged as the founding member of a well-known family of trophic factors, the neurotrophins (NTs). These highly conserved proteins are produced in peripheral tissues and in the central nervous system and are crucial for neuronal survival, the establishment of neuronal connections as well as regulation of established synaptic structures [4-7]. Along with NGF,

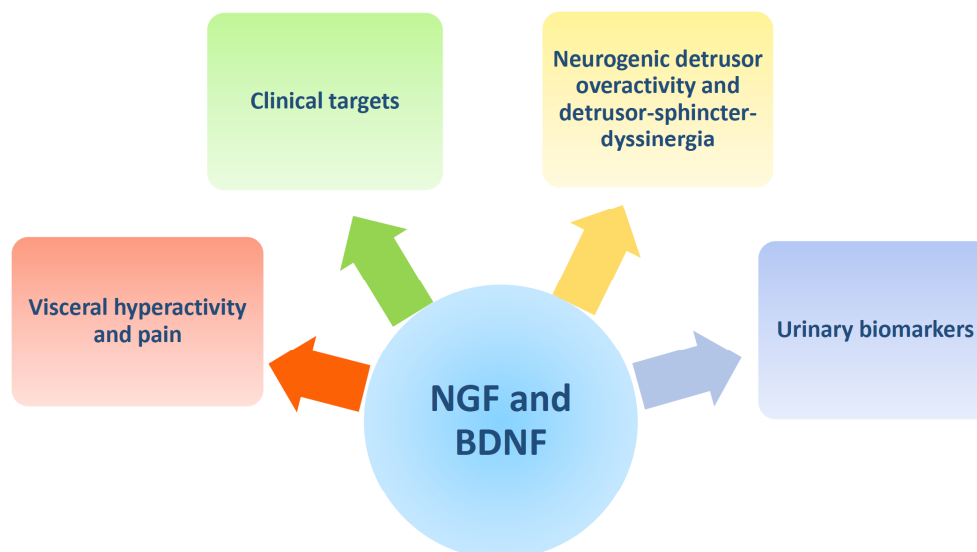
several other proteins comprise the NTs family, including Brain-Derived Neurotrophic Factor (BDNF) and neurotrophins 3, 4 and 5 (NT3 and NT4/5, respectively). All NTs are firstly synthesized as pre-proteins. These immature proteins undergo proteolytic cleavage and extensive post-translational modifications. The mature form of NTs binds to high-affinity Tropomyosin-Related Kinase (Trk) receptors or low-affinity receptor p75 [8]. Dimerization and phosphorylation of such receptors result in downstream activation of signalling pathways [4, 7, 9-11], including the ERK and the Akt pathways. Activation of these pathways eventually results in short-term changes in the activity of cytoplasmic proteins and membrane receptors and, in the long-term, modifications of gene expression [11].

Much has been discussed about the relevance of NTs in regulating neuronal plasticity and they are now well-established mediators of pain, particularly in chronic patho-

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**Fig. (1). Involvement of NGF and BDNF in visceral dysfunction.** NGF and BDNF are two well-known neurotrophic factors, belonging to the large family of neurotrophins (NTs). Several clinical and experimental studies suggest a strong involvement of both NTs in many conditions of visceral hyperactivity and pain and pinpoint them as clinical targets for drug development. NGF and BDNF are also involved in bladder dysfunction arising after spinal cord injury, particularly neurogenic detrusor overactivity and detrusor-sphincter-dyssinergia. Finally, the presence of NGF and BDNF in the urine of patients with several pathologies of the lower urinary tract has sparked a strong debate about their use as putative biomarkers. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

logical conditions [7, 9, 12-14]. More recently, NTs have attracted increasing attention in the context of visceral function. It has been widely demonstrated that visceral organs, such as the urinary bladder and colon, are important sources of NGF and BDNF and tissue concentration of these NTs increase in visceral dysfunction, particularly when associated with chronic pain. Thus, the present review will focus on the role of NGF and BDNF in visceral function in health and disease (Fig. 1).

## 2. NERVE GROWTH FACTOR (NGF)

The ground-breaking studies by Rita Levi-Montalcini and Viktor Hamburger indicated that NGF was essential for the growth and survival of sensory and sympathetic neurons [2-3]. Upon binding to TrkA, activation of intracellular signalling pathways occurs, such as the ERK 1/2 and Akt pathways, resulting in the transcription of pro-survival genes and blockade of cell death pathways [6-7, 11]. This was fully evidenced by the generation of NGF and TrkA-null mice as NGF deletion or its high-affinity receptor results in a very limited lifespan, generally not extending 14 days beyond birth. These animals present a complete loss of postganglionic sympathetic neurons and a significant reduction of sensory neurons in the trigeminal ganglia, dorsal root ganglia (DRG) and basal forebrain cholinergic neurons [15, 16]. In contrast, heterozygous mice have normal growth and development but do present mild neuronal defects in cholinergic forebrain nuclei [17]. Early analysis showed that these transgenic animals present a reduction in pain perception, accompanied by a reduction in the number of small-diameter sensory neurons and defect in peripheral sympathetic innervation [15, 18]. Thus, it is clear that target-derived NGF is crucial to maintain specific neuronal populations and it is important to identify endogenous sources of this NT. After iso-

lation from murine submandibular glands [1-3], several other tissues have been identified as sources of NGF, including adipose endocrine and immune cells [19-21]. Most notably, visceral organs such as the urinary bladder and colon [22] are prominent sources of NGF and their function is highly sensitive to variations in its content.

### 2.1. NGF in the Urinary Bladder

In the 1990s, a series of studies by Steers and co-workers demonstrated the presence of high levels of NGF in the bladder wall of rats submitted to urethral obstruction and showed that this NT regulated survival and neurite expansion of cultured major pelvic ganglia (MPG) neurons [23-26]. The cellular sources of NGF in the bladder were identified and included smooth muscle cells and the urothelial layer. Persson and collaborators cultured Human and rat detrusor cells and demonstrated that these cells were able to release NGF, in a Protein Kinase C (PKC)-dependent manner, following cycles of stretch and relaxation, necessary to maintain their ability to secrete NGF [27-30]. Urothelial cells are also able to produce NGF, although, in normal conditions, its secretion is very low [31, 32]. Urothelial NGF secretion seems to be regulated by oestrogens [33] and bradykinin [34] but it is also increased following bladder ischemia [35], inflammation [36] and stressful conditions [37-39]. While expression of TrkA and p75 in bladder smooth muscle cells is more difficult to confirm, urothelial cells are known to express these receptors [40-42], indicating that like in other systems, NGF may have a pro-survival effect on these cells [33]. NGF has also been detected in the cell bodies of sensory afferents innervating the urinary bladder [43] and in MPG neurons [40], but it remains difficult to ascertain if NGF is produced by these neurons or uptaken from the bladder.

In the bladder, levels of NGF may vary in pathological conditions. Early studies by Lowe and co-workers showed that NGF was overexpressed in bladder biopsies from women suffering from idiopathic sensory urgency and bladder pain syndrome/interstitial cystitis (BPS/IC) [31]. This was accompanied by increased NGF concentration in urine samples [44]. High NGF levels have also been found in urine samples from patients with overactive bladder (OAB) [45-46]. A more recent study compared the urinary NGF concentration between healthy individuals and OAB patients. The authors found significantly higher NGF levels in OAB patients, which were accompanied by high BDNF urinary concentration [47]. Based on results from ten original studies, in 2016 a meta-analysis was published, in which 295 cases of BPS/IC and 290 normal control patients were included, and strengthen the idea that urinary NGF levels are enhanced in BPS/IC patients [48]. Several other studies corroborating such findings can be found in the literature, which will be further discussed below.

Given the limited lifespan of NGF null mice, it is difficult to determine the exact role of this NT in bladder function. Hence, studies aiming to understand the role of NGF in the bladder have chosen one of three paths: exogenous administration of NGF, blockade of NGF in animal models of disease and, more recently, transgenic mice with modified expression of NGF.

### 2.1.1. Exogenous Administration of NGF

Early studies by Dmitrieva and co-workers [49-50] showed that acute intravesical administration of NGF increased the frequency of bladder reflex contractions. Similarly, bladder hyperactivity was also observed in rats following chronic administration of NGF to the bladder *via* osmotic mini-pumps [51], intradetrusor adenovirus-mediated NGF gene transfer [52] and chronic intrathecal administration of NGF at the level of L6/S1 spinal cord [53]. In all cases, bladder hyperactivity resulted from sensitization of bladder sensory neurons.

The effects of NGF upregulation have also been explored using animal models that closely replicate many features of Human pathologies affecting the lower urinary tract, including the upregulation tissue NGF [54-56]. The most commonly used animal models of bladder dysfunction include bladder inflammation induced by intraperitoneal administration of chemical irritants such as cyclophosphamide [36, 40, 57-61], intravesical administration of lipopolysaccharides [62], acetic acid [63] or turpentine [64], urethral ligation to induce bladder outlet obstruction BOO [23, 65-66] and spinal cord injury to induce neurogenic detrusor overactivity (NDO) [67-69]. In all cases, bladder hyperactivity was found to be highly correlated with a significant increase in NGF bladder contents.

### 2.1.2. NGF Blockade

An alternative approach to better understand the effects of NGF on bladder function is to block its activity following experimental upregulation. Several strategies have been used, including NGF scavenging with antibodies or recombinant proteins and antagonists of NGF receptors. The initial studies addressing NGF blockade used BOO rats. The ani-

mals were immunized against NGF and the endogenous anti-NGF antibodies raised were effective in reducing the frequency of bladder contractions and hypertrophy of bladder sensory and MPG neurons [23, 70]. Chronic administration of an exogenous monoclonal antibody against NGF was also effective in improving bladder function in rats with spinal cord injury, with a marked reduction of the frequency of non-voiding bladder contractions, maximal voiding pressure and maximal pressure of uninhibited bladder contractions [67-68].

The same approach of NGF blockade has been widely used in models of chronic bladder inflammation. In this case, NGF activity has been blocked with specific recombinant scavengers [71], antisense oligonucleotides [61, 63, 72], anti-NGF antibodies [32] and antagonists of Trk receptors [32, 73]. The routes for drug delivery varied and included intravenous, intrathecal and intravesical administration. In all cases, studies reported improvement of bladder function and reduction of visceral pain, as shown by the reduction of the frequency of bladder contractions and increased mechanical threshold of the abdomen and hind paws.

Interestingly, almost in an intuitive manner, all of these studies assumed that the main effects of NGF in bladder function were regulated by its activity on TrkA, particularly given the abundance of these receptors in bladder sensory neurons and its upregulation following bladder inflammation and spinal cord injury [40, 74-75]. Thus, the results obtained by modulating the binding of NGF to p75 were unexpected. The expression of the low affinity NT receptors is prominent in bladder afferents and further increased in cases of bladder inflammation [41-42, 76], suggesting that p75 could be involved in inflammatory bladder dysfunction. Surprisingly, intravesical administration of an antibody raised against p75 (PD90780), which prevents NGF binding to p75, worsened bladder dysfunction in CYP-inflamed rats and induced bladder hyperactivity in intact animals, even though the p75 expression was reduced [42]. In addition, a recent study found that the reduction of NGF bladder expression resulted in a downregulation of p75 expression without affecting bladder activity [61]. Taken together, these studies support that modulation of NGF may constitute an effective strategy to treat bladder dysfunction and, if present, visceral pain. However, results obtained with the modulation of p75 expression clearly show that further investigation is needed to fully understand the effect of NGF on bladder physiology and the specific contributions of its binding to either TrkA or p75 in bladder structures.

### 2.1.3. Transgenic Models

To better understand the role of NGF, two transgenic models of NGF overexpression have been generated. In one case, NGF overexpression was restricted to the urothelium as the transcription of the NGF gene is under the control of the uroplakin promotor [58, 77]. These transgenic mice presented morphological bladder changes including bladder enlargement and sensory and sympathetic hyper-innervation [77]. These animals presented increased frequency of bladder contractions but no increase in bladder pressure was observed [77]. Interestingly, NGF overexpression in the urothelium led to a more prominent expression of sensory recep-

tors, such as TRPV4, in the bladder and sensory afferents and changes in the pituitary adenylate cyclase activating polypeptide (PACAP), vasoactive intestinal polypeptide (VIP) signalling system in the bladder [78-80]. A curious, but difficult to explain finding was a significant reduction of BDNF, TrkA and TrkB expression, as it has long been established that BDNF expression is positively regulated by NGF [81-82]. On the other hand, the expression of p75 was upregulated [79], consistent with other studies [63]. Importantly, changes in bladder morphology and function in the NGF overexpressing mice were accompanied by evident signs of visceral pain [77], further confirming that this NT is a key player in bladder dysfunction and pain.

In another genetic model, NGF overexpression was restricted to smooth muscle as the NGF gene was under the control of the  $\alpha$ -actin promoter [83, 84]. In this case, NGF was upregulated in the distal colon and urinary bladder. These studies described robust sprouting of sympathetic and sensory fibres in both visceral organs. Interestingly, the sprouting of sympathetic nerve terminals was also observed in the dorsal root ganglia, surrounding peptidergic/TrkA-expressing neuronal profiles [84]. Importantly, in the absence of p75, sprouting of sensory fibres is exacerbated, suggesting that p75 limits NGF-drive axonal growth [84]. No data regarding the visceral activity or peripheral pain levels were reported in these mice.

## 2.2. NGF in the Colon

It has long been known that in normal conditions, bladder and colon are functionally related. Indeed, micturition and defecation occur in an alternate fashion and bladder reflex activity is inhibited by distension of the rectum or anal canal [85, 86]. This functional relation is particularly evident in the pathological painful condition in which bladder dysfunction is associated with altered colonic activity and vice-versa. Accordingly, one of the most common co-morbidities associated with bladder pain syndrome/interstitial cystitis (BPS/IC) is irritable bowel syndrome (IBS) [87, 88] and BPS/IC is also very prevalent in individuals suffering from IBS [89]. This association of pathologies indicates the occurrence of cross-organ sensitization [90], although it is difficult to ascertain which organ is affected in the first place. Still, colon-bladder cross-sensitization relies on the anatomical organization of visceral sensory innervation. Studies using neuro-tracing techniques showed that sensory afferents innervating bladder and colon either converge in the same spinal neurons or simultaneously innervate both organs [91]. In experimental animals, it has been well-documented that animals with bladder inflammation become hypersensitive to colonic stimulation [92, 93] and colonic inflammation led to a marked increase in the frequency of bladder reflex contractions [92-94]. The underlying molecular mechanisms responsible for pelvic cross-organ sensitization include peripheral and central sensitization of the neuronal pathways regulation bladder and colon function [90]. These neuroplastic changes highly rely on NTs [7], particularly NGF acting on the bladder or colonic sensory afferents.

As in the bladder, NGF is present in the epithelial lining of the colon [22] but recent studies show that it is produced by calretinin-positive myenteric neurons in the murine colon

[95]. In colonic biopsies obtained from IBS patients, NGF levels are upregulated [96-98] and in rodents, NGF was similarly increased following experimental colitis [99-103]. This is accompanied by an upregulation of TrkA expression and cellular translocation in colonic afferent neurons, a process that is blocked by resiniferatoxin, indicating that the ionic channel TRPV1 regulates the increase of TrkA expression [101]. Exogenous NGF administration to the colon induces colonic hyperactivity while its blockade in colitis induced by trinitrobenzene sulfonic acid (TNBS) reduces pain and colonic hyperactivity [102, 103]. Neonatal capsaicin pre-treatment inhibited NGF- and TNBS-induced colonic pain, indicating that capsaicin-sensitive colonic afferents are essential for this type of visceral pain and further stressing the involvement of TRPV1 in colitis [104, 105]. In rodents, colitis-induced increase of NGF levels resulted in the activation of the ERK5 signalling pathway, which activated BDNF transcription [106]. BDNF is now established as a pronociceptive factor and an accelerator of intestinal traffic in experimental models of colitis [101, 106-109] and in IBS patients [110]. In addition, NGF may also contribute to IBS through activation of Acid-Sensing Ion Channels (ASICs), which are proton sensors that participate in the sensitization of visceral sensory neurons, even in non-or-low grade inflammatory conditions [111].

## 2.3. NGF in the Reproductive System

The influence of NGF in other visceral organs, particularly in painful conditions, has been less studied. Still, available studies provide evidence that this NT may play a role in other painful visceral conditions with associated cross-organ sensitization [90], such as testicular pain. A recent study demonstrated that administration of NGF to the testes of adult male rats induced bladder overactivity and behavioural signs of pain, which were abolished by pre-treatment with capsaicin [112].

NGF is also an important mediator of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), a condition that affects a significant percentage of the male population and is characterized by severe pelvic pain. Analysis of gland fluid samples obtained from CP/CPPS patients showed high levels of NGF that directly correlated with pain severity, as assessed by medical examination and validated questionnaires [113, 114]. More recently, in a rodent model of non-bacterial prostatitis, high tissue levels of NGF were found in the prostate where they likely induced sensitization of sensory afferents [115, 116]. This high concentration of NGF was accompanied by signs of evoked pain, expression of nociceptive markers and bladder hyperactivity, suggesting cross-organ sensitization between the prostate and urinary bladder [115, 116].

In females, studies show a connection between NGF and pain caused by endometriosis. Several studies have documented the presence of high levels of NGF and its receptors in tissue samples collected from endometriotic lesions [117-119]. Uterine expression of NGF, TrkA and p75 was decreased following treatment with the levonorgestrel-releasing intrauterine system [120], a therapy commonly used in patients with moderate to severe pain related to endometriosis [121]. NGF was also elevated in the peritoneal fluid obtained

from patients suffering from endometriosis [122]. Interestingly, this fluid was able to promote neurite expansion from cultured sensory neurons, which was reduced by Trk antagonists [122, 123]. This suggests that the increased nerve density observed in endometriotic lesions may be induced by NGF present in peritoneal fluid and reinforces the pivotal role of NGF-dependent nerve fibres in pain arising from endometriosis [124, 125].

Similar findings have been obtained using animal models of endometriosis. In mice, an increase in NGF and TrkA has been observed in the uterus and sensory neurons [126]. The expressions of NGF and TrkA increased with disease progression and were more prominent in the later stages of the disease, suggesting that NGF may be one of the key players in the pathogenesis of endometriosis [126]. This is supported by observations in animals with experimental endometriosis, in which NGF expression was blocked by siRNA [127]. In this study, the authors observed atrophy of endometriotic tissue, pain reduction and decrease of sympathetic and sensory innervation after the suppression of NGF expression, clearly indicating that NGF is at the root of this pathological state and is not only a mere pathophysiological participant [127].

#### 2.4. Is NGF a Clinical Target?

Several studies, both in animals and in humans, clearly show that NGF is a key mediator of pain and hyperalgesia [10]. It comes as no surprise the interest in generating anti-NGF molecules that could inhibit its function. This led to the development of a humanized monoclonal antibody that binds to and inhibits NGF activity [128, 129]. Developed for patients with osteoarthritis, Tanezumab was tested in BPS/IC patients and produced modest results, with some reduction of urgency and frequency and mild improvement in pain scores [130]. Some patients described adverse effects, including paraesthesia, hyperesthesia and migraines [130]. A more recent study reported that Tanezumab was more likely to produce a more pronounced improvement in BPS/IC patients with concomitant non-urolological associated somatic syndromes [131]. However, in men with CP/CPP the reported effects of Tanezumab were not different from placebo, although the reasons for this are still poorly understood and may include hormonal differences between genders [131].

### 3. BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

BDNF is the second most abundant and widely distributed member of the neurotrophins family in the human body. BDNF plays an important role in the development, maintenance and plasticity of the mammalian central nervous system, which include regulation of neuronal survival, regulation of neurite outgrowth and maintenance of synaptic connectivity. It is also involved in the modulation of more complex networks including depression and spatial learning [132].

At the peripheral nervous system, BDNF is synthesized in the cell bodies of small and medium-sized DRG neurons [133], in an NGF-dependent manner [81, 82]. After synthesis, BDNF is packed in large dense core vesicles which also

contain the neuropeptides substance P and CGRP, and anterogradely transported to central terminals terminating in the dorsal horn [13, 134-139]. In the spinal cord, BDNF can be abundantly found in the superficial dorsal horn, laminae I and II, but it is also present in deeper laminae [140]. BDNF has also been found in non-neuronal tissues such as the urothelium, the airway smooth muscle and the colon wall [64, 141, 142]. BDNF acts upon binding to its high-affinity receptor, TrkB, or the non-specific neurotrophin receptor, p75, both present in sensory afferents and spinal cells [11, 13]. Like with NGF, there were attempts to generate a BDNF null-mice but these animals present serious health problems and die shortly after birth [143]. Nevertheless, heterozygous BDNF knockout (+/-) are vital, fertile and present a reduction of approximately 50% of the brain contents of BDNF mRNA and protein in comparison with wild type littermates [144, 145]. Hence, although there are some studies addressing the role of BDNF in visceral function using these transgenic animals [109], the majority of investigators chose to manipulate the visceral levels of BDNF.

#### 3.1. BDNF in the Urinary Bladder

The studies linking BDNF to the activity of the urinary bladder are recent but compelling, particularly in cases of bladder hyperactivity associated with painful states [56, 146, 147]. In the human bladder, the precise location of BDNF or TrkB receptor has never been assessed, although both have been described in bladder cancer cells [148, 149]. BDNF has been found in the urine of healthy individuals but its source has yet to be fully identified [47, 150, 151].

During postnatal development, BDNF mRNA is significantly upregulated in the urinary bladder from day 5 to day 15, decreasing afterward to almost undetectable levels in adulthood, possibly produced by urothelial cells [22, 152-154]. It is thought that these variations in BDNF expression are linked to the replacement of the spinal micturition reflex, responsible for the involuntary voiding in infancy, to the mature spinalbulbosacral micturition pathway, present in adult mammals [22, 152]. This suggests that bladder BDNF is developmentally associated with the neuronal reorganization of micturition pathways.

In pathological conditions such as BOO and BPS/IC, the expression of BDNF strongly increases in the bladder [64, 69, 155, 156]. In the DRG, BDNF is similarly elevated [64, 69, 155, 156], possibly as a result of uptake by sensory neurons and retrograde transport to cell bodies or induced by NGF [82], as this NT is also increased in the bladder in the same circumstances (see above). In addition, expression and activation of TrkB, normally present in approximately one-third of bladder sensory afferents, are also upregulated during bladder pathological conditions [155, 156]. Overexpression of BDNF has been linked to bladder overactivity possibly *via* enhancement of prejunctional cholinergic transmission and mediation of altered gene expression, including TRPV1 and TRPA1 [157].

#### 3.2. BDNF in Animal Models of Bladder Inflammation

Animal models of bladder inflammation, which mimic the clinical symptoms of BPS/IC have been used to study the

role of BDNF in the modulation of bladder activity and sensory input. An early study, dating from 2000, has detected a significant up-regulation of BDNF mRNA and protein in the bladder tissue of rats with CYP-induced bladder inflammation [69]. In studies using the same model of disease, a strong increase in TrkB expression was found in the lumbosacral DRG, where cell bodies of bladder afferents are located [156]. A recent work demonstrated that BDNF synthesis occurs in DRG following depolarization or visceral inflammation [134], suggesting that the presence of this NT in the cell bodies of DRG neurons may represent local production of this NT rather than transport from peripheral tissues. Furthermore, the authors demonstrated that during inflammatory conditions, the mature form of BDNF is released not only from the central sensory terminals but also from peripheral bladder terminals [134]. Overall, this data points out a possible autocrine and paracrine function of BDNF in the bladder during inflammatory events [134, 156].

Other works have further confirmed the importance of BDNF in bladder function related to cystitis. Peripheral scavenging of BDNF reduced CYP-induced bladder hyperactivity and associated pain, as shown by a marked reduction in the spinal expression of c-Fos and phosphoERK [154]. The same treatment was also able to normalize BDNF expression in the urothelial layer, increased by inflammation [154]. Likewise, central BDNF blockade also resulted in an improvement of bladder function and behavioural signs of pain [158]. Moreover, acute intrathecal administration of BDNF induces cutaneous pain and bladder hyperactivity, suggesting that this NT has an excitatory effect on bladder function and nociceptive visceral pathways [158]. Collectively, these data show that bladder inflammation upregulates BDNF and blockade of this NT is beneficial as it reduces bladder dysfunction and associated visceral pain.

### 3.3. BDNF in the Colon

Recent exciting reports have established a connection between IBS and BDNF. The presence of BDNF in the colon, particularly released by epithelial cells, has been established for some time [22, 159]. In biopsies from IBS patients, the levels of BDNF and TrkB were shown to be higher than in controls, correlating with strong abdominal pain and alterations in faecal frequency [106, 160]. In animal models of IBS, such as the TNBS model, BDNF expression was increased in the colon mucosa and TrkB expression and its activation was up-regulated in the lumbosacral DRG where the cell bodies of colonic sensory afferents are located [102, 107-109]. BDNF was also upregulated in DRG, an increase dependent on the activation of the ERK5 pathway via NGF/TrkA-dependent retrograde signalling [101, 106]. Systemic administration of exogenous BDNF induced colonic hypersensitivity in rats confirmed the involvement of BDNF in the modulation of colonic hypersensitivity [102]. In addition, heterozygous BDNF +/- mice showed reduced BDNF expression, colonic activity and pain in response to TNBS-induced inflammation [109], further confirming the involvement of this NT in colonic inflammatory dysfunction [161].

While most of these studies focus either on sensory neurons, epithelial cells or both, enteroglial cells have attracted

attention in the context of IBS [162]. The activation of these cells was found to be increased in colonic biopsies from IBS patients. These cells are in close proximity with the underlying mucosal nerve fibres, suggesting a strong glial-nerve interaction on the colonic mucosa of those individuals [162]. In animals with colonic inflammation, activation of the TrkB receptor in enteroglial cells induces activation of the phospholipase Cy1 pathway, resulting in the heightened activity of these cells [163], which in turn leads to increased activation of the enteric nervous system resulting in heightened peristalsis and colonic pain [163].

Interestingly, it should be noted that many IBS patients also present lower urinary tract symptoms, such as frequency, urgency and, eventually, bladder pain [164, 165]. This likely reflects cross-organ sensitization, with IBS and BPS/IC often coursing together. Accordingly, TrkB expression is increased in peptidergic bladder sensory afferents following TNBS-induced inflammation [107].

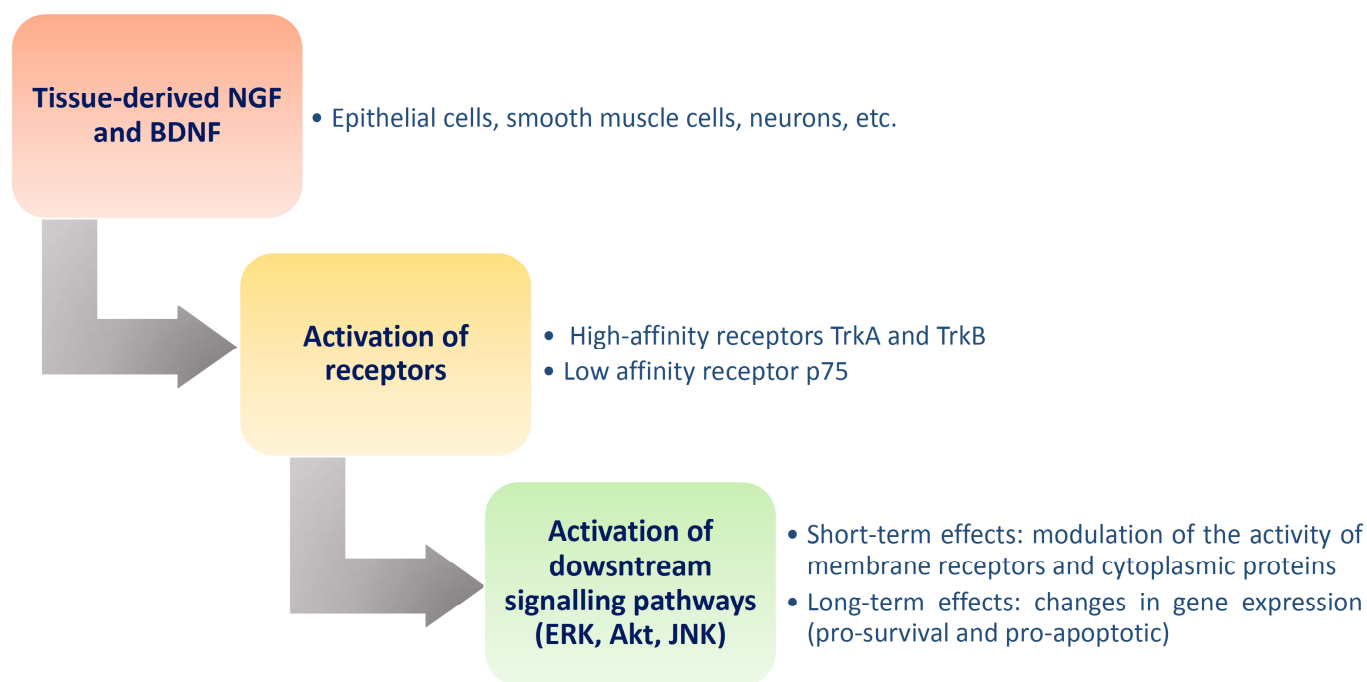
### 3.4. BDNF in the Reproductive System

BDNF and TrkB are present in abundance in the mammalian reproductive system [166, 167]. In the female system, studies showed that BDNF is synthesized by the endometrium [168, 169] supporting a putative involvement of BDNF in gynaecological disorders, particularly those in which pain has a major impact. In biopsies of endometriotic lesions, both BDNF and NT 4/5 were significantly up-regulated when compared to normal tissue, corroborating the hypothesis supporting a link between BDNF and the strong visceral pain reported by patients suffering from endometriosis [168]. Other studies have detected up-regulated levels of this NT in the blood serum of women in early stages of endometriosis suggesting that the serum concentration of BDNF may potentially serve as predicting biomarker of endometriosis [170].

### 3.5. BDNF Val66Met Polymorphism and Painful Visceral Disorders

The occurrence of polymorphisms in the BDNF encoding gene has already been demonstrated. These polymorphisms have attracted attention as some were potentially associated with depressive states, deficits in hippocampal function, learning, and memory. The most well-studied polymorphism (adenine → guanine) resulted in the replacement of the valine amino acid by methionine at position 66 (Val66Met). Since its identification, this polymorphism has been associated with a variety of molecular modifications in the brain that cause deficits in social and cognitive function [171]. In addition, methylation of the BDNF gene, which also alters its epigenetic programming, has linked BDNF to anxiety and mood disorders, aging, cognitive and neurodegenerative diseases [172-174].

In the pain field, Val66Met has been associated with a decreased activity-dependent secretion of BDNF which could affect pain processing at cortical region [175, 176]. Other studies have further suggested that individuals presenting this polymorphism may exhibit increased susceptibility to develop chronic pain induced by peripheral injury [177]. Studies conducted in women at reproductive age found a



**Fig. (2). Mechanisms of action of NGF and BDNF.** These NTs are produced by a wide variety of cells, including epithelial and smooth muscle cells. These NTs bind to high- and low affinity receptors, respectively the Trk and p75 receptors, catalyzing downstream activation of signaling pathways. Ultimately, this results in modulation of cellular elements in the short-term. In the long-term, these signaling pathways may regulate gene expression and cell survival. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

genetic association between symptoms of primary dysmenorrhea and the presence of Val66Met polymorphism [178]. Furthermore, functional magnetic resonance imaging studies detected a positive correlation between diverse functional expressions of descending modulatory pain pathways and the presence of Val66Met BDNF polymorphism in women with and without symptoms of primary dysmenorrhea [179]. A large epigenetic study investigated the presence of the Val66Met polymorphism in women with endometriosis and found an increased frequency of this polymorphism, which was linked to endometriosis-related infertility [180]. Still, available data on this particular field is still poor and more studies are needed to clarify the exact role of BDNF in the modulation of endometrial biology. Taken together, current data support the hypothesis that changes in BDNF transcription and translation may increase vulnerability for chronic pain disorders, though the precise mechanisms by which this may occur remain speculative.

#### 4. DOWNSTREAM TARGETS OF NGF AND BDNF

As in other systems, in the urinary bladder, NGF and BDNF exert their effects on binding to their high-affinity receptors, TrkA and TrkB, respectively, and the same likely occurs in the colon and endometrium. Binding of NGF and BDNF to TrkA and TrkB results in phosphorylation of intracellular domains and downstream activation of the ERK 1 and 2 and Akt signalling cascades [4] Fig. (2). In cystitis, increased activation of ERK 1 and 2 has been described in the bladder and neuronal micturition pathways [60, 154, 158, 181]. Intrathecal administration of a specific ERK inhibitor, BDNF sequestration and intravenous delivery of an NGF a scavenging agent reduced the frequency of bladder reflex

contractions, amongst other cystometric parameters [60, 71, 158]. Increased ERK activation in spinal neurons is thought to lead to bladder hyperactivity and visceral pain *via* modulation of spinal potassium channels, expression of pronociceptive genes and phosphorylation of the N-Methyl-D-Aspartate (NMDA) glutamate receptor [182], all of which participate in the regulation of bladder function at the spinal cord level [183].

In bladder afferents, Transient Receptor Potential Vanilloid 1 (TRPV1) is a probable target of NGF and BDNF-mediated ERK activation. Although not essential for bladder function in normal conditions, TRPV1 plays a fundamental role in inflammatory bladder hyperactivity and visceral pain. Interaction between TRPV1 and NGF has been suggested by *in vivo* somatic pain studies and in *in vitro* studies [184]. This interaction is also important in the bladder. Particularly, it was found that chronic administration of NGF to TRPV1 null mice did not cause any effect on the bladder or cutaneous sensitivity. In contrast, wild type littermates developed bladder hyperactivity and thermal hyperalgesia. Thus, TRPV1 is essential for bladder hyperreflexia and pain associated with chronic inflammatory conditions that lead to NGF upregulation [185]. NGF may also contribute to bladder dysfunction by increasing the levels of BDNF in TrkA-expressing visceral sensory neurons as the expression of this NT is regulated by NGF [81, 82].

While the effects of Trk-mediated effects of NTs have been relatively well explored in the context of visceral regulation, much less is known about the contribution of the low-affinity receptor p75. This receptor is able to bind to NTs and proNTs. In neuronal tissue, recent studies point to direct

influence in enhancing Trk specificity to their NT ligands, improving neuronal survival and differentiation in healthy conditions. In pathological conditions, p75 preferentially binds to pro-NTs, activating apoptotic pathways *via* JNK and NF $\kappa$ - $\beta$  [147, 186], in a process that also requires sortilin [187, 188].

In the context of bladder inflammation and BPS/IC, activation of p75 has been linked to a reduction in bladder reflex activity, in contrast to TrkA-mediated enhancement of bladder [41, 42]. More recently, it was demonstrated that pro-NGF activity on p75 might contribute to detrusor sphincter dyssynergia (DSD) and bladder hyperactivity following spinal cord injury (SCI), suggesting that modulation of the p75 receptor might be of interest for the management of SCI patients [186, 187].

### 5. SPINAL CORD INJURY AND VISCERAL DYSFUNCTION: ARE NGF AND BDNF INVOLVED?

The involvement of NGF and BDNF in chronic visceral pain caused by SCI still needs to be unravelled given the difficulties in evaluation peripheral sensation in animals with spinal lesions. In contrast, available studies support an important contribution of both NTs in visceral dysfunction, such as neurogenic detrusor overactivity (NDO). Spinal cord injury (SCI) is a major cause of autonomic dysfunctions, often resulting in the loss of voluntary control of bladder and bowel [189]. As most lesions occur at cervicothoracic spinal levels, damage to neuronal pathways controlling visceral organs is almost inevitable. After vertebral stabilization, transurethral catheterization is the first measure to be taken during spinal shock, as bladder turns into a flaccid and areflexic organ massively retaining urine [190]. With time, bladder areflexia is overcome and replaced by NDO. It is assumed that this reflects neuroplastic changes occurring at the lumbosacral spinal cord. Type C bladder fibres, which are normally silent and do not respond to bladder filling, greatly expand their central processes at that spinal level, leading to the generation of a new micturition reflex [191-192]. This results in uncontrolled, frequent and strong bladder contractions (NDO) that, together with DSD, result in periods of very high intravesical pressures and episodes of urinary incontinence. In addition to the disruption of neuronal pathways controlling micturition, nerves involved in gut regulation are usually affected after spinal trauma [193]. Loss of neuronal inputs from CNS results in neurogenic bowel that is characterized by situations of faecal incontinence and constipation, but has a major impact on patients' quality of life, requiring strict daily management [189, 194].

While the role of NGF and BDNF in the emergence of neurogenic bladder and bowel after SCI are not fully understood, the contribution of NGF to neurogenic LUT dysfunction has been better explored. NGF is an established peripheral mediator of sensory afferents plasticity [195] and visceral epithelia are major sources of this NT, with secretion occurring, at least in the bladder, in response to tissue stretching [23, 28]. During SCI-induced bladder areflexia, urine accumulation leads to urine retention and consequent tissue stretching. In turn, this results in increased NGF synthesis and release, as in spontaneously hypertensive rats [30, 65, 69]. Bladder NGF overexpression is accompanied by

increased levels of NGF and heightened expression and activation TrkA in the lumbosacral DRG and cord [67, 75]. This leads to cell body hypertrophy, increased production of neuropeptides, including substance P and CGRP, and overexpression and activation of ion channels, such as TRPV1 [196-198]. Treatment of SCI rodents with specific antibodies targeting NGF improved bladder function, with a reduction of non-voiding contractions in these animals [53, 199]. Increased levels of NGF were also linked to the development of DSD. Intrathecal delivery of anti-NGF antibody significantly reduced urethral pressure at the peak bladder contraction, associated with a decrease in NGF expression at L6 spinal cord segments [68].

BDNF has been less studied as an intervenient in NDO emergence after SCI. Like NGF, it is known to be implicated in the regulation of immune responses and neuronal plasticity, but mostly at the CNS level [200]. After SCI, BDNF levels are enhanced in the spinal cord and TrkB expression and activation are also increased in lumbosacral DRG neurons and spinal tissue [74, 75, 201]. The expression of the low-affinity receptor p75 is also altered following SCI and recent studies have demonstrated the importance of this receptor in lower urinary dysfunction following SCI and support the use of p75 antagonists for treatment [187, 202]. Recent findings suggested that this increase in BDNF levels contribute, in an early phase post-SCI, to downregulate abnormal axonal growth and prevent urinary dysfunction [203] possibly by inhibiting NGF-mediated neuronal sprouting [204, 205].

The involvement of NGF and BDNF in bowel dysfunction after SCI remains to be elucidated. It is likely that both NTs should contribute to gut dysfunction but studies are needed, describing the levels of NGF and BDNF and their receptors in the gut and the effects of modulation.

### 6. NGF AND BDNF AS BIOMARKERS OF BLADDER DYSFUNCTION

The National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [206]. Therefore, biomarkers are considered as important tools to identify the causing agent(s) of a specific pathology, establish the prognosis, develop new drugs, obtain information about the effects of a specific treatment and follow disease progression. A vast array of putative biomarker falls within this scope, spanning from data acquired using imaging techniques to biochemical elements present in the serum, cerebrospinal fluid or urine [207, 208]. Urine is currently considered one of the most potentially interesting sources of putative biomarkers. It contains a vast number of peptides, including NGF and BDNF, the concentration of which is thought to reflect ongoing physiological processes in both health and disease. In addition, it can be easily obtained in sizeable quantities, without significant bothersome to the patients, and stored until analysis. Most biomarkers, like NGF and BDNF, can be routinely detected by chromatography and antibody-based assays, among others.



The first study demonstrating the presence of neurotrophic factors in urine dates from 1999 [209]. The authors reported high urinary levels of NGF, neurotrophin 3 (NT3) and glial cell line-derived neurotrophic factor (GDNF) in 4 patients with BPS/IC. Since then, numerous studies demonstrated the presence of other NTs in the urine of patients suffering from various pathologies affecting the lower urinary tract, including BPS/IC and overactive bladder syndrome (OAB). The majority of available studies have focused on NGF and BDNF as studies with experimental animals support their key role in the pathophysiology of many conditions affecting the bladder, as they sensitize bladder afferents, a mechanism associated to the emergence of urinary urgency, frequency and bladder pain [54, 56, 147, 210]. In addition, at least in what concerns NGF, high levels of this NT have been found in the urothelium and detrusor of patients suffering from BPS/IC, idiopathic detrusor overactivity (DO) and BOO due to benign prostate hyperplasia (BPH) [23, 27, 31, 211-212]. The tissue levels of BDNF in these pathologies are still undescribed.

### 6.1. Urinary NGF

It is indisputable that NGF is the most well-studied NT in the lower urinary tract, both in what concerns its physiological action on tissues and as a putative biomarker. In most OAB or BPS/IC patients urinary levels of NGF, normalized against creatinine concentration, were significantly higher when compared with healthy controls [46-47, 150, 213-225]. In OAB, patients with urgency urinary incontinence (OAB wet), most of whom present DO, urinary NGF was higher than patients with OAB dry [46, 214]. Furthermore, the urinary concentration of NGF significantly decreased in responding to OAB patients after lifestyle intervention [47], antimuscarinic drugs [47, 216-217, 219], botulinum toxin and sacral neuromodulation [221]. Likewise, in BPS/IC patients, a significant decline in urinary NGF was reported after cystoscopic hydrodistension, oral pentosan polysulphate [44], botulinum toxin [222] and hyaluronic acid treatment [150]. These results clearly indicate two points: 1) that there is a correlation between the severity of symptoms and the levels of urinary NGF; and 2) urinary NGF varies according to the treatment. These are two desirable characteristics for a biomarker, showing that urinary NGF may be sensitive enough to contribute to the diagnosis and prognosis of diseases of the lower urinary tract.

### 6.2. Urinary BDNF

The interest in urinary BDNF is more recent but a few studies report that it can be found in the urine of OAB [47, 151] and BPS/IC [150, 222, 224] patients and debate its putative role as a biomarker. In OAB, high levels of urinary BDNF were found in OAB patients in comparison with healthy individuals [47]. In patients, those reporting more severe symptoms presented even higher urinary concentration of BDNF [47, 151]. Interestingly, urinary NGF was also measured in the same samples and BDNF concentration was higher and correlated better with the magnitude of symptoms reported, suggesting that urinary BDNF provided better sensitivity and specificity than urinary NGF to diagnose OAB [47, 151].

In BPS/IC, recent studies showed that BDNF was also elevated in the urine of BPS/IC patients and decreased after botulinum toxin [222], but not after treatment with hyaluronic acid [150]. In both studies, a significant reduction in pain levels was reported.

### 6.3. Controversies and Limitations - how useful and Reliable are NGF and BDNF as Biomarkers?

There is a strong debate concerning the use of urinary neurotrophins to complement the diagnosis of bladder disorders or as predictive or prognostic biomarkers [207, 226]. After promising pilot studies, new controversial data and some methodological relevant limitations “dampened the spirits” in the field. A recent study failed to demonstrate a relationship between urinary neurotrophin levels (NGF, BDNF) and OAB in age-matched postmenopausal women [227]. Another recent work, including 45 OAB patients and 45 healthy age-matched controls, reported higher urinary levels of NGF and BDNF in OAB women but questioned the predictive value of these putative markers [228]. They found that after 1-month treatment with solifenacin, urinary levels of NGF and BDNF significantly declined, and the ratio of decrease of these markers was significantly higher in treatment-sensitive patients. However, basal neurotrophin levels did not differ between responder and non-responder groups. This raises the concern about the use of urinary NGF and BDNF as predictive biomarkers to establish the probability of positive response of patients to the treatment.

Other aspects limit the use of urinary NTs as biomarkers for bladder disorders, including technical issues. There is still a lack of a uniform protocol for urine collection and sampling, as well as standardized analysis kits for measuring urinary NTs. Commercial kits also need improvements in terms of variability to reach the required values for clinical use. In addition, the existing studies are small and restricted to single centres and many are no placebo-controlled. Importantly, increased urinary NTs have been found in several bladder disorders, including OAB, BPS/, urolithiasis, urinary tract infections, urothelial neoplasms and in patients with indwelling catheters or who perform clean intermittent self-catheterization [207, 226]. This raises questions about the true specificity and sensitivity of these urinary biomarkers. In many conditions, such as BPS/IC, the diagnosis is based upon the symptoms reported by patients and data collected on examinations. While a urinary biomarker may not contribute to a more accurate diagnosis, one could argue that the variations reported in many studies support the use of urinary NGF and BDNF as a means to describe the progression of the disease.

While the real importance of NGF and BDNF as urinary biomarkers is still debatable, further studies, preferably multicentric, with a placebo arm and a larger number of individuals are warranted to standardize collection and storage of samples, analytic procedures and finally establish the true diagnostic and/or prognostic relevance of urinary NTs. It will be of interest to expand these studies to pathologies with associated high tissue levels of NGF and BDNF, including IBS and endometriosis.

## CONCLUSION

More than twenty years have passed since the original studies demonstrating the presence and synthesis of NGF in the urinary bladder were reported [23]. We now know that NGF is able to strongly sensitize bladder afferents, leading to hyperactivity and pain. Studies blocking its activity, either by scavenging or by using pharmacological antagonists of Trk receptors, further support the role of NGF in bladder dysfunction and raise the possibility of a future translation of NGF modulators. Indeed, Tanezumab, a monoclonal antibody targeting NGF, has already been tested in patients suffering from BPS/IC and CP/CPSP, albeit with not so exciting results as anticipated. Still, it is likely that in the near future this therapy will be improved and become commercially available. Remarkably, the current investigation also points to NGF as an important participant in IBS and endometriosis, further strengthening the importance of NGF as a general mediator of visceral dysfunction and potential therapeutic target.

While we know to accept NGF as a generator of abnormal visceral function and pain, our understanding of the role of BDNF is still in its infancy. Nevertheless, there are already enough published studies pointing to its contribution to the BPS/IC, IBS and endometriosis, in a similar manner to NGF. Thus, it is likely that both NTs act synergistically and thus produce a harmful effect on general visceral reflex activity and pain.

Finally, NGF and BDNF have started to be investigated in recent years as putative urinary biomarkers of bladder dysfunction. Investigators have identified high levels of these NTs in urine samples from OAB, BPS/IC and CP/CPSP patients, which correlated with symptom severity and subsided in responders to treatment. This suggests that urinary NGF and BDNF may serve as putative biomarkers once there is an established standardized procedure to collect and analyse urine samples and large multicentric placebo-controlled studies have provided additional supporting evidence of their true sensitivity and diagnostic value.

From what was discussed here, it is evident that our knowledge of NTs, particularly NGF and BDNF, regarding visceral function has increased almost exponentially in the last quarter of the century. Experimental results are being confirmed by clinical studies and it is very likely that future management of visceral pathologies may include drugs design to modulate the activity of NGF and BDNF.

## LIST OF ABBREVIATIONS

ASICs	= Acid-Sensing Ion Channels
BDNF	= Brain Derived Neurotrophic Factor
BPH	= Benign Prostate Hyperplasia
CP/CPSP	= Chronic Prostatitis/Chronic Pelvic Pain Syndrome
CYP	= Cyclophosphamide
DO	= Detrusor Overactivity
DRG	= Dorsal Root Ganglia

IBS	= Irritable Bowel Syndrome
MPG	= Major Pelvic Ganglia
NGF	= Nerve Growth Factor
NMDA	= N-Methyl-D-Aspartate
NT3 and NT4/5	= Neurotrophins 3, 4 and 5
NTs	= Neurotrophins
OAB	= Overactive Bladder Syndrome
PACAP	= Pituitary Adenylate Cyclase Activating Polypeptide
PBS/IC	= Bladder Pain Syndrome/Interstitial Cystitis
TNBS	= Trinitrobenzene Sulfonic Acid
Trk	= Tropomyosin-Related Kinase Receptors
TRPV1	= Transient Receptor Potential Vanilloid 1
VIP	= Vasoactive Intestinal Polypeptide

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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