Can Botulinum Toxin A Still Have a Role in Treatment of Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia Through Inhibition of Chronic Prostatic Inflammation?

Bing-Juin Chiang 1,2,3, Hann-Chorng Kuo 4,5 and Chun-Hou Liao 1,2,*

1 College of Medicine, Fu-Jen Catholic University, New Taipei City 24205, Taiwan; bingjuinchiang@gmail.com
2 Department of Urology, Cardinal Tien Hospital, New Taipei City 23148, Taiwan
3 Department of Life Science, College of Science, National Taiwan Normal University, Taipei 11677, Taiwan
4 Department of Urology, Buddhist Tzu Chi General Hospital, and Tzu Chi University, Hualien 97002, Taiwan; hck@tzuchi.com.tw
5 School of Medicine, Tzu Chi University, Hualien 97004, Taiwan

* Correspondence: liaoch22@gmail.com; Tel.: +886-2-22193391 (ext. 65278)

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Abstract: Patients with benign prostatic hyperplasia (BPH) can exhibit various lower urinary tract symptoms (LUTS) owing to bladder outlet obstruction (BOO), prostatic inflammation, and bladder response to BOO. The pathogenesis of BPH involves an imbalance of internal hormones and chronic prostatic inflammation, possibly triggered by prostatic infection, autoimmune responses, neurogenic inflammation, oxidative stress, and autonomic dysfunction. Botulinum toxin A (BoNT-A) is well recognized for its ability to block acetylcholine release at the neuromuscular junction by cleaving synaptosomal-associated proteins. Although current large clinical trials have shown no clinical benefits of BoNT-A for the management of LUTS due to BPH, BoNT-A has demonstrated beneficial effects in certain subsets of BPH patients with LUTS, especially in males with concomitant chronic prostatitis/chronic pelvic pain syndrome and smaller prostate. We conducted a review of published literature in Pubmed, using Botulinum toxin, BPH, BOO, inflammation, LUTS, and prostatitis as the key words. This article reviewed the mechanisms of BPH pathogenesis and anti-inflammatory effects of BoNT-A. The results suggested that to achieve effectiveness, the treatment of BPH with BoNT-A should be tailored according to more detailed clinical information and reliable biomarkers.

Keywords: lower urinary tract symptoms; botulinum toxin; benign prostatic hyperplasia; prostatitis; inflammation

Key Contribution: Botulinum Toxin A still have a role in treatment of lower urinary tract symptoms/benign prostatic hyperplasia through inhibition of chronic prostatic inflammation in selected patients.

1. Introduction

Benign prostatic hyperplasia (BPH) is a term exclusively used for describing benign histological patterns in the European Association of Urology (EAU) and the American Urological Association (AUA) guidelines [1,2]. BPH could lead to benign prostatic enlargement (BPE) or benign prostatic obstruction (BPO) resulting in male lower urinary tract symptoms (LUTS). LUTS are grouped into three categories: storage (increased daytime frequency, nocturia, urgency, and urinary incontinence), voiding (hesitancy, slow stream, intermittent stream, straining, and terminal dribble), and post-micturition...
(post-micturition dribble and feeling of incomplete emptying) symptoms [3]. In addition to BPH, other causes of male LUTS include structural or functional abnormalities of the bladder and its surrounding tissues, and some non-urological conditions [4]. Lower urinary tract dysfunction (LUTD) is defined as signs observed by the physician, including simple means, to verify and quantify symptoms [3]. From a clinical perspective, BPH usually refers to LUTD caused by BPE or BPO.

We conducted a review of published literature in Pubmed, using Botulinum toxin, BPH, bladder outlet obstruction (BOO), inflammation, LUTS, and prostatitis as the key words. We reviewed the mechanisms of BPH pathogenesis and anti-inflammatory effects of BoNT-A. We tried to determine the role of botulinum toxin A (BoNT-A) in treatment of LUTS/BPH.

2. Ambiguous Mechanisms of LUTS Related to BPH

Prevalence of LUTS generally increases with age. A large cross-sectional population-based study from the Asia-Pacific region reported LUTS prevalence to be higher in men than women [5]. More men had voiding symptoms (45.3%) than women (31.3%) [5], and the phenomenon could be attributed to BPH. Interestingly, the epidemiologic study showed more storage symptoms (49.9%) in men than voiding symptoms (45.3%). This could be attributed to BOO, which is capable of reducing bladder blood flow and subsequently causes chronic bladder ischemia, as reported by various epidemiologic and clinical studies [6–8]. BOO is also associated with repeated episodes of prolonged detrusor ischemia in pigs with an artificially implanted ring around urethra [9]. BOO causes a reduction in acetylcholine esterase staining nerves in detrusor muscle and expression of hypoxia-inducible factor 1 alpha, a cellular marker of hypoxia [10,11]. Moreover, experimentally, BOO has been shown to exhibit elevated cystometric voiding pressure, reduced urine flow rates, generated bladder hyperactivity, and increased bladder detrusor hypertrophy [12,13]. Further, BOO related bladder ischemia also causes denervation supersensitivity, leading to a fundamental reorganization of the detrusor’s electrical activity and C-fiber mediated micturition reflexes [13–16]. BOO with high bladder pressure could also induce adaptive change of bladder wall, including detrusor muscle hypertrophy, bladder wall fibrosis and reduced bladder compliance [17]. Therefore, besides the preconceived voiding symptoms, BPH also causes varied storage symptoms related to bladder response to BOO. In addition, the prevalence of prostatitis-like symptoms in a community-based study was 11.5% and 8.5% in younger (<50 years) and older (≥50 years) men, respectively [18]. This study also measured irritative and obstructive voiding symptom severity (score, 0 to 10), where men with prostatitis-like symptoms showed significantly higher urinary symptom score. Prostatic inflammation is believed to play an important role in the BPH pathogenesis and progression [19,20]. In brief, most BPH related LUTS arises from BPE/BOO, prostatic inflammation, and bladder response to BPE/BOO. Therefore, it is difficult to distinguish the specific etiology of male LUTS through clinical practice. Although the exact mechanism underlying BPH related LUTS is unknown, its treatment should probably be tailored according to the cause of LUTS.

3. Mechanism of BPH Related to BOO

BPH causes obstruction by inducing functional and morphological changes in the prostate. Functionally, an increase in prostatic smooth muscle tone has been confirmed, which is influenced sympathetically [21]. Moreover, the presence of metabolic syndrome is associated with increased sympathetic nervous system activity and LUTS [22,23]. In such cases, alpha(α)-adrenergic antagonists can improve BPH-induced male LUTS [24]. Morphologically, BPH is characterized by unregulated proliferation of connective tissues, smooth muscles, and glandular epithelium [25]. Tissue proliferation leads to increased prostate volume (PV), subsequently compressing the prostatic urethra. McNeal found that BPH patients had an increase in BPH nodules in the periurethral zone and size of glandular nodules [26]. Further, either epithelium or fibro-muscular stroma proliferation could be found in the resected BPH tissues [27,28].
4. Mechanism of BPH-Imbalance of Internal Hormones

Abundant evidence showed that development of BPH requires testicular androgen [29]. Conversion of dihydrotestosterone (DHT), a metabolite of testosterone, in the prostate is considered as a major factor involved in the BPH pathogenesis. Elevated serum DHT level is associated with larger PV and higher prevalence of BPH [30]. Prostatic DHT and androgen receptor (AR) levels increase with age [31], whereas testosterone level declines with age. Increase in estrogen to testosterone ratio has been recognized as an important factor inducing the development of prostatic inflammation and cytokines [32]. In such cases, administration of 5α-reductase type II inhibitor resulted in increased plasma testosterone levels and further reduced the prostatic inflammation, suggesting the protective effect of testosterone against inflammation compared to that of DHT [33,34]. Imbalance in testosterone and estrogen levels also contributes to decreased activity of some suppressor cells, which maintain tolerance to prostatic antigen and prevent autoimmunity [35,36]. Moreover, the insulin-like growth factor (IGF) signaling pathway has been implicated in BPH development [37]. An IGF receptor antagonist, metformin, has an anti-proliferative effect, which attenuated testosterone-induced BPH in rats by decreasing the expression of estrogen receptor alpha [38]. Furthermore, neurotransmitter serotonin (5-HT) could possibly play a role in the pathogenesis of BPH. 5-HT can downregulate ARs and prevent prostate branching [39]. However, 5-HT depletion contributes to BPH development through modulation of ARs [39]. In summary, imbalance of internal hormones results in the development of BPH and prostatic inflammation.

5. Mechanism of BPH-Chronic Inflammation

A previous clinical study showed that men with prostatitis-like symptoms have significantly higher urinary symptom score [18]. Young-onset prostatitis was positively associated with LUTS [40]. Chronic inflammation along with BPH can coexist in human pathologic specimens [41]. Correlations were found between histopathology of chronic inflammation and severity of LUTS in a subgroup of patients from the randomized REDUCE (reduction in the use of corticosteroids in exacerbated COPD) trial [42]. Moreover, nonsteroidal anti-inflammatory drugs were inversely associated with the onset of LUTS [43]. These clinical results suggested the involvement of prostatic inflammation in the pathogenesis of BPH with LUTS.

The most important cytokine involved in the development of BPH is interleukin (IL)-8, which can directly promote epithelial and stromal proliferation [44]. Plasma IL-8 could serve as a reliable surrogate marker of prostatic inflammatory conditions, including chronic prostatitis and BPH [45]. Moreover, IL-8 can induce stromal cells for the emergence of a reactive myofibroblast phenotype [46]. Human BPH cells, including epithelial and stromal cells, act as antigen-presenting cells (APCs), which can secrete IL-8 and associated cytokines [47]. These cytokines promote prostatic immune cells upregulation for more specific cytokines, which in turn recruit more lymphomononuclear cells. These recruited lymphomononuclear cells express cognate receptors, CXCR1 and CXCR2, which induce proliferation of prostatic cells through autocrine/paracrine effect and generation of fibroblast growth factors [48]. Therefore, the cross-talk between the BPH and immune cells creates a positive feedback loop that can amplify inflammation, and the intraprostatic chronic inflammatory processes are induced and sustained.

6. Etiology of Prostatic Inflammation

The etiology of prostatic inflammatory process remains unclear. It is believed that several possible mechanisms are responsible for triggering a prostatic inflammatory response. Firstly, infection-induced inflammation hypothesis is evidenced by the presence of bacterial and viral strains in BPH tissue specimens [49]. Toll-like receptors (TLRs) expressed by BPH cells recognize structurally conserved molecules derived from pathogens. TLRs-mediated production of proinflammatory cytokines (IL-6) and chemokines (IL-8 and CXCL10) initiate and enhance the inflammatory process [50]. Secondly,
autoimmune responses could be involved in prostatic inflammation. Epidemiologic studies showed that the prevalence of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is eight times more than bacterial prostatitis [51]. Prostate, as well as testes, are considered as immunologically privileged organs [52]; however, self-antigens release following a tissue injury results in autoimmunity [53]. Autoantibodies against prostate-specific antigen (PSA) or prostate acid phosphatase (PAP) were shown to be involved in the prostatic inflammatory process [54]. PSA has been demonstrated to be able to activate CD4+ T cells [55]. In addition, BPH cells, as well as other APCs, produce high levels of IL-12 and IL-23, promoting CD4+ T cell activation and differentiation [47], which in turn, differentiate into interferon gamma-secreting T-helper (Th) type 1 and IL-17-secreting Th17 cells [48]. These downstream pro-inflammatory cytokines manifest a positive feedback signal to inflammatory interaction between BPH and immune cells. Thirdly, neurogenic inflammation plays an important role in chronic prostatic inflammation. Neurotrophin, a nerve growth factor (NGF), is responsible for mediating prostatic neurogenic inflammation. The serum NGF level was found to be correlated with the severity of pain in CP/CPPS [56]. Moreover, damaged tissue has been found to contain higher NGF level [57], which can cause mast cells degranulation [58]. Infiltrating mast cells in BPH tissues can promote BPH development via activation of IL-6/Signal transducer and activator of transcription 3/Cyclin D1 signaling pathway [59]. NGF can also sensitize sensory nerve and induce production of neuropeptides, including substance P and calcitonin gene-related peptide (CGRP) [60]. Further, substance P can stimulate reactive oxygen species generation via its proinflammatory activity [61]. Prostatitis following intraprostatic formalin injection has been reported to induce prostate-to-bladder afferent cross-sensitization, increased urothelial NGF expression, and subsequent bladder overactivity [62]. Fourthly, oxidative stress can be one of the causes of inflammation. Interestingly, the ARR2PB-Nox4(ARR2PB-NADPH oxidase 4) transgenic mice showed increased prostate weight, increased epithelial proliferation, and histological changes, including epithelial proliferation, stromal thickening, and fibrosis through Nox4 promoting oxidative stress [63].

Furthermore, it is believed that chronic pelvic ischemia can generate oxidative stress [64]. Elderly patients with LUTS showed decreased prostate perfusion on transrectal color Doppler ultrasonography [7]. Serum glutathione peroxidase and superoxide dismutase levels, which have antioxidant effects, reportedly declined in dogs with BPH [65]. Oxidative stress also triggers prostate cells proliferation through the activation of cyclooxygenase (COX) pathways [66,67], whereas COX-2 inhibition can induce significant apoptosis in the prostate cell [67]. Fifthly, the autonomic nervous system (ANS) also contributes to prostatic inflammation and growth. Adrenergic innervation plays a role in prostate growth. ANS hyperactivity is significantly associated with LUTS, and serum norepinephrine level increased after tilt predicted prostate size [68]. Moreover, chronic administration of α1-adrenergic agonists induces proliferation of prostatic cells in a rat model [69]. Besides, norepinephrine can stimulate the proliferation of human non-epithelial prostatic cells [70]. α1-adrenoceptors have been linked with inflammatory pathways through activation of transforming growth factor β signaling cascade, regulating various events associated with the BPH development [69,71]. In summary, the major etiology of chronic prostatic inflammation includes prostatic infection, autoimmune responses, neurogenic inflammation, oxidative stress, and autonomic dysfunction.

7. Anti-Inflammatory Effects of Botulinum Toxin A (BoNT-A)

BoNT-A is well-recognized for its ability to block acetylcholine release at the neuromuscular junction by cleaving synaptosomal-associated proteins [72]. Intraprostatic injection of BoNT-A has been shown to induce relaxation of prostatic muscle through downregulation of α-adrenergic receptor expression and reducing smooth muscle contractility [73,74]. On the other hand, BoNT-A also causes morphological atrophy of the glands via chemodenervation and anti-inflammatory effects [75,76]. Clinically, BoNT-A has demonstrated therapeutic anti-inflammatory effects, including the reduction of pain, edema, erythema, and heat emission [77]. A study in a complete Freund’s adjuvant-induced arthritic rat model revealed the anti-inflammatory effect of BoNT-A by attenuating anti-ionized
calcium-binding adaptor molecule 1 and IL-1β immune-reactive cells [78]. Moreover, BoNT-A reduces rosacea-associated skin inflammation by directly inhibiting mast cell degranulation [79]. Intravesical BoNT-A injections plus hydrodistension reduce bladder pain and NGF levels in patients with interstitial cystitis [80], probably through blocking bladder pain responses and CGRP release from afferent nerve terminals, as depicted in a rat model [81]. BoNT-A may also inhibit peripheral and subsequent central sensitizations via suppressing substance P, glutamate, and adenosine triphosphate, showing reduction of somatic and visceral pain [82]. Interestingly, BoNT-A pretreatment could inhibit intraprostatic capsaicin injection-induced COX-2 expression in prostate and spinal cord [83]. Furthermore, BoNT-A also significantly prevented oxidative stress in vascular endothelial cells in cutaneous ischemia/reperfusion injured mouse model [84]. It has been shown that BoNT-A inhibits IL-8/CXCR1 signaling cascade in endothelial cells through inhibiting Rho signaling pathways [85]. In summary, BoNT-A exhibits anti-inflammatory effects by suppressing cytokine generation, mast cell activation, neurogenic inflammation, and oxidative stress in different organs. These reports from the basic research of BoNT-A potentially strengthened evidence for its therapeutic effects in patients with BPH; however, further studies are warranted for some of the proven anti-inflammatory effects on prostatic growth and inflammation.

8. Clinical Perspectives

Although previous single-arm studies showed promising results in improving international prostate symptom score (IPSS), maximal flow rate (Qmax), PV, and post-void residual urine volume (PVR) following intraprostatic injection of BoNT-A, two recent large scale randomized control trials failed to show significant efficacy of BoNT-A on all outcomes [76,86–92]. Moreover, a systematic review including three large randomized placebo-control studies (experimental group, n = 260; control group, n = 262) showed only marginal benefits to IPSS (−1.02; 95% confidence interval: −1.97, −0.07) for the BTX-A versus placebo groups. There were no significant differences in Qmax, PV, and PVR between the two groups, which was attributed to the placebo effect [93]. The EAU guidelines on the management of non-neurogenic male LUTS documented that “Results from clinical trials have shown no clinical benefits for BoNT-A compared to placebo for the management of LUTS due to BPO,” and strongly recommended not to offer intraprostatic BoNT-A injection treatment to patients with male LUTS [1]. Intraprostatic BoNT-A injection is also not listed as one of the treatment choices in the AUA guidelines [2]. However, it is difficult to explain how intraprostatic BoNT-A injection significantly decrease PV, as reported by other meta-analyses [94–96].

Although limited reports are available for the therapeutic effects of BoNT-A on CP/CPPS, several beneficial effects on LUTS have been noted. In an uncontrolled randomized clinical trial conducted in men with refractory CP/CPPS, the patients were classified into two groups according to the route of BoNT-A injection, transurethral or transrectal. After intraprostatic injection of BoNT-A (100 U), Qmax, voiding score, and quality of life (QoL) were significantly improved in both groups during the follow-up period [97], with mean initial PV ranging from 36.4 to 37.9 ml among the groups. Another randomized, controlled study of transurethral intraprostatic injection of BTX-A (100 or 200 U depending on PV) showed significant improvement not only in pain score and QoL but also in the urinary domain of chronic prostatitis symptom index 1-month post-injection [98]. Other outcomes, including IPSS, frequency of diurnal, and nocturnal urination, showed significant reduction compared to baseline at 1, 3 and 6-month after BoNT-A injection. The mean initial PV in the experimental group was 22.27 mL. Chuang et al. reported that 16 men with symptomatic BPH and PV <30 mL were successfully treated with transperineal intraprostatic BoNT-A injection [89], with significant improvement in PV and IPSS following BoNT-A injection. However, the mean PV of men included in the two largest randomized trials failed to show beneficial effects on PV (range, 43.8–48.8 mL) [91,92]. Therefore, these results imply that intraprostatic injection of BoNT-A might be effective in relieving LUTS in patients with small prostate and refractory CP/CPPS. As mentioned above, patients suffering from BPH and CP/CPPS might show overlapping symptoms due to similar etiologies shared by BPH and prostatitis.
9. Conclusions

Based on the current basic and clinical studies, BoNT-A could still be effective in certain subsets of BPH with LUTS, especially in males with concomitant CP/CPPS and smaller prostate. However, this hypothesis requires further validation through randomized controlled clinical studies. In addition, it is imperative to consider exploring biomarkers of BPH, including NGF level, mast cells/distribution of activated subtypes of immune cells in biopsies, inflammatory-associated cytokines, or ANS dysfunction, as determining predictors of the treatment efficacy. Therefore, for effectiveness, the treatment of BPH with BoNT-A should be tailored according to more detailed clinical information and reliable biomarkers.

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References

1. Gravas, S.; Cornu, J.N.; Drake, M.J.; Gacci, M.; Gratzke, C.; Herrmann, T.R.W.; Mamoulakis, C.; Rieken, M.; Speakman, M.J.; Tikkinen, K.A.O.; et al. Management of Non-Neurogenic Male LUTS. Available online: https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/ (accessed on 1 January 2019).
2. Foster, H.E.; Barry, M.J.; Gandhi, M.C.; Kaplan, S.A.; Kohler, T.S.; Lerner, L.B.; Lightner, D.J.; Parsons, J.K.; Roehrborn, C.G.; Welliver, C.; et al. Benign Prostatic Hyperplasia: Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms (2018, Amended 2019). Available online: https://www.auanet.org/guidelines/benign-prostatic-hyperplasia- (accessed on 1 January 2019).
3. Abrams, P.; Cardozo, L.; Fall, M.; Griffiths, D.; Rosier, P.; Ulmsten, U.; van Kerrebroeck, P.; Victor, A.; Wein, A. The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. Am. J. Obstet. Gynecol. 2002, 187, 116–126. [CrossRef] [PubMed]
4. Chapple, C.R.; Wein, A.J.; Abrams, P.; Dmochowski, R.R.; Giuliano, F.; Kaplan, S.A.; McVary, K.T.; Roehrborn, C.G. Lower urinary tract symptoms revisited: A broader clinical perspective. Eur. Urol. 2008, 54, 563–569. [CrossRef]
5. Chapple, C.; Castro-Diaz, D.; Chuang, Y.C.; Lee, K.S.; Liao, L.; Liu, S.P.; Wang, J.; Yoo, T.K.; Chu, R.; Sumarsono, B. Prevalence of lower urinary tract symptoms in China, Taiwan, and South Korea: Results from a cross-sectional, population-based study. Adv. Ther. 2017, 34, 1953–1965. [CrossRef] [PubMed]
6. Ponholzer, A.; Temml, C.; Wehrberger, C.; Marszalek, M.; Madersbacher, S. The association between vascular risk factors and lower urinary tract symptoms in both sexes. Eur. Urol. 2006, 50, 581–586. [CrossRef] [PubMed]
7. Pinggera, G.M.; Mitterberger, M.; Steiner, E.; Pallwein, L.; Frauscher, F.; Aigner, F.; Bartsch, G.; Strasser, H. Association of lower urinary tract symptoms and chronic ischaemia of the lower urinary tract in elderly women and men: Assessment using colour Doppler ultrasonography. BJU Int. 2008, 102, 470–474. [CrossRef] [PubMed]
8. Azadzoi, K.M.; Pontari, M.; Vlachiotis, J.; Siroky, M.B. Canine bladder blood flow and oxygenation: Changes induced by filling, contraction and outlet obstruction. J. Urol. 1996, 155, 1459–1465. [CrossRef]
9. Greenland, J.E.; Brading, A.F. The effect of bladder outlet obstruction on detrusor blood flow changes during the voiding cycle in conscious pigs. J. Urol. 2001, 165, 245–248. [CrossRef] [PubMed]
10. Gosling, J.A.; Gilpin, S.A.; Dixon, J.S.; Gilpin, C.J. Decrease in the autonomic innervation of human detrusor muscle in outlet obstruction. J. Urol. 1986, 136, 501–504. [CrossRef]
11. Koritsiadis, G.; Stravodimos, K.; Koutalellis, G.; Agrogiannis, G.; Koritsiadis, S.; Lazaris, A.; Constantinides, C. Immunohistochemical examination of hypoxia in human obstructed bladder and correlation with clinical variables. BJU Int. 2008, 102, 328–332. [CrossRef]
12. Speakman, M.J.; Brading, A.F.; Gilpin, C.J.; Dixon, J.S.; Gilpin, S.A.; Gosling, J.A. Bladder outlet obstruction—A cause of denervation supersensitivity. J. Urol. 1987, 138, 1461–1466. [CrossRef]
13. Seki, N.; Karim, O.M.; Mostwin, J.L. The effect of experimental urethral obstruction and its reversal on changes in passive electrical properties of detrusor muscle. *J. Urol.* 1992, 148, 1957–1961. [CrossRef]

14. Greenland, J.E.; Hvistendahl, J.J.; Andersen, H.; Jørgensen, T.M.; McMurray, G.; Cortina-Borja, M.; Brading, A.F.; Frokiaer, J. The effect of bladder outlet obstruction on tissue oxygen tension and blood flow in the pig bladder. *BJU Int.* 2000, 85, 1109–1114. [CrossRef] [PubMed]

15. Steers, W.D.; Ciambotti, J.; Etzel, B.; Erdman, S.; de Groat, W.C. Alterations in afferent pathways from the urinary bladder of the rat in response to partial urethral obstruction. *J. Comp. Neurol.* 1991, 310, 401–410. [CrossRef] [PubMed]

16. Harrison, S.C.; Hunnam, G.R.; Farman, P.; Ferguson, D.R.; Doyle, P.T. Bladder instability and denervation in patients with bladder outflow obstruction. *Br. J. Urol.* 1987, 60, 519–522. [CrossRef] [PubMed]

17. Komninos, C.; Mitsogiannis, I. Obstruction-induced alterations within the urinary bladder and their role in the pathophysiology of lower urinary tract symptomatology. *Can. Urol. Assoc. J.* 2014, 8, E524–E530. [CrossRef]

18. Nickel, J.C.; Downey, J.; Hunter, D.; Clark, J. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. *J. Urol.* 2001, 165, 842–845. [CrossRef]

19. Ficarra, V.; Rossanese, M.; Zazzara, M.; Giannarini, G.; Abbinante, M.; Bartoletti, R.; Mirone, V.; Scaglione, F. The role of inflammation in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and its potential impact on medical therapy. *Curr. Urol. Rep.* 2014, 15, 463. [CrossRef]

20. He, Q.; Wang, Z.; Liu, G.; Daneshgari, F.; MacLennan, G.T.; Gupta, S. Metabolic syndrome, inflammation and lower urinary tract symptoms: Possible translational links. *Prostate Cancer Prostatic Dis.* 2016, 19, 7–13. [CrossRef]

21. Lepor, H. The pathophysiology of lower urinary tract symptoms in the ageing male population. *Br. J. Urol.* 1999, 81 (Suppl. S1), 29–33. [CrossRef]

22. Tai, H.C.; Chung, S.D.; Ho, C.H.; Tai, T.Y.; Yang, W.S.; Tseng, C.H.; Wu, H.P.; Yu, H.J. Metabolic syndrome components worsen lower urinary tract symptoms in women with type 2 diabetes. *J. Clin. Endocrinol. Metab.* 2010, 95, 1143–1150. [CrossRef]

23. Soler, R.; Andersson, K.E.; Chancellor, M.B.; Chapple, C.R.; de Groat, W.C.; Drake, M.J.; Gratzke, C.; Lee, R.; Cruz, F. Future direction in pharmacotherapy for non-neurogenic male lower urinary tract symptoms. *Eur. Urol.* 2013, 64, 610–621. [CrossRef] [PubMed]

24. Kuei, C.H.; Liao, C.H.; Chiang, B.J. Significant intravesical prostatic protrusion and prostatic calcification predict unfavorable outcomes of medical treatment for male lower urinary tract symptoms. *Urol. Sci.* 2016, 27, 13–16. [CrossRef]

25. Auffenbarg, G.B.; Helfand, B.T.; McVary, K.T. Established medical therapy for benign prostatic hyperplasia. *Urol. Clin. N. Am.* 2009, 36, 443–459. [CrossRef] [PubMed]

26. McNeal, J. Pathology of benign prostatic hyperplasia. Insight into etiology. *Urol. Clin. N. Am.* 1990, 17, 477–486.

27. Rohr, H.P.; Bartsch, G. Human benign prostatic hyperplasia: A stromal disease? New perspectives by quantitative morphology. *Urology* 1980, 16, 625–633. [CrossRef]

28. Franks, L.M. Benign nodular hyperplasia of the prostate; A review. *Ann. R. Coll. Surg. Engl.* 1953, 14, 92–106.

29. McConnell, J.D. Androgen ablation and blockade in the treatment of benign prostatic hyperplasia. *Urol. Clin. N. Am.* 1990, 17, 661–670.

30. Liao, C.H.; Li, H.Y.; Chung, S.D.; Chiang, H.S.; Yu, H.J. Significant association between serum dihydrotestosterone level and prostate volume among Taiwanese men aged 40–79 years. *Aging Male* 2012, 15, 28–33. [CrossRef]

31. McConnell, J.D. The pathophysiology of benign prostatic hyperplasia. *J. Androl.* 1991, 12, 356–363.

32. Harris, M.T.; Feldberg, R.S.; Lau, K.M.; Lazarus, N.H.; Cochrane, D.E. Expression of proinflammatory genes during estrogen-induced inflammation of the rat prostate. *Prostate* 2000, 44, 19–25. [CrossRef]

33. Zhu, Y.S.; Sun, C.H. 5α-reductase isozymes in the prostate. *J. Med. Sci. (Taipei Taiwan)* 2005, 25, 1–12.

34. Nickel, J.C.; Downey, J.; Pontari, M.A.; Shoskes, D.A.; Zeitlin, S.I. A randomized placebo-controlled multicentre study to evaluate the safety and efficacy of finasteride for male chronic pelvic pain syndrome (category IIIA chronic nonbacterial prostatitis). *BJU Int.* 2004, 93, 991–995. [CrossRef] [PubMed]
35. Kramer, G.; Mitteregger, D.; Marberger, M. Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? *Eur. Urol.* 2007, 51, 1202–1216. [CrossRef] [PubMed]

36. Nickel, J.C. Inflammation and benign prostatic hyperplasia. *Urol. Clin. N. Am.* 2008, 35, 109–115. [CrossRef] [PubMed]

37. Sreenivasulu, K.; Nandeesh, H.; Dorairajan, L.N.; Rajappa, M.; Vinayagam, V. Elevated insulin and reduced insulin like growth factor binding protein-3/prostate specific antigen ratio with increase in prostate size in Benign Prostatic Hyperplasia. *Clin. Chim. Acta* 2017, 469, 37–41. [CrossRef] [PubMed]

38. Mosli, H.H.; Esmat, A.; Atawia, R.T.; Shoieb, S.M.; Mosli, H.A.; Abdel-Naim, A.B. Metformin attenuates testosterone-induced prostatic hyperplasia in rats: A pharmacological perspective. *Sci. Rep.* 2015, 5, 15639. [CrossRef] [PubMed]

39. Carvalho-Dias, E.; Miranda, A.; Martinho, O.; Mota, P.; Costa, A.; Nogueira-Silva, C.; Moura, R.S.; Alenina, N. Serotonin regulates prostate growth through androgen receptor modulation. *Sci. Rep.* 2017, 7, 15428. [CrossRef] [PubMed]

40. Sutcliffe, S.; Giovannucci, E.; De Marzo, A.M.; Willett, W.C.; Platz, E.A. Sexually transmitted infections, prostatitis, ejaculation frequency, and the odds of lower urinary tract symptoms. *Am. J. Epidemiol.* 2005, 162, 898–906. [CrossRef] [PubMed]

41. Nickel, J.C. Prostatic inflammation in benign prostatic hyperplasia—The third component? *Can. J. Urol.* 1994, 1, 1–4. [PubMed]

42. Nickel, J.C.; Roehrborn, C.G.; O’Leary, M.P.; Bostwick, D.G.; Somerville, M.C.; Rittmaster, R.S. The relationship between prostate inflammation and lower urinary tract symptoms: Examination of baseline data from the REDUCE trial. *Eur. Urol.* 2008, 54, 1379–1384. [CrossRef] [PubMed]

43. St Sauver, J.L.; Jacobson, D.J.; McGree, M.E.; Lieber, M.M.; Jacobsen, S.J. Protective association between nonsteroidal antiinflammatory drug use and measures of benign prostatic hyperplasia. *Am. J. Epidemiol.* 2006, 164, 760–768. [CrossRef] [PubMed]

44. Castro, P.; Xia, C.; Gomez, L.; Lamb, D.J.; Ittmann, M. Interleukin-8 expression is increased in senescent prostatic epithelial cells and promotes the development of benign prostatic hyperplasia. *Prostate* 2004, 60, 153–159. [CrossRef] [PubMed]

45. Penna, G.; Mondaini, N.; Amuchastegui, S.; Degli Innocenti, S.; Carini, M.; Giubilei, G.; Fibbi, B.; Colli, E.; Maggi, M.; Adorini, L. Seminal plasma cytokines and chemokines in prostate inflammation: Interleukin 8 as a predictive biomarker in chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia. *Eur. Urol.* 2007, 51, 524–533. [CrossRef] [PubMed]

46. Schauer, I.G.; Ressler, S.J.; Tuxhorn, J.A.; Dang, T.D.; Rowley, D.R. Elevated epithelial expression of interleukin-8 correlates with myofibroblast reactive stroma in benign prostatic hyperplasia. *Urology* 2008, 72, 205–213. [CrossRef] [PubMed]

47. Penna, G.; Fibbi, B.; Amuchastegui, S.; Cossetti, C.; Aquilano, F.; Laverny, G.; Gacci, M.; Crescioli, C.; Maggi, M.; Adorini, L. Human benign prostatic hyperplasia stromal cells as inducers and targets of chronic immuno-mediated inflammation. *J. Immunol.* 2009, 182, 4056–4064. [CrossRef] [PubMed]

48. Fibbi, B.; Penna, G.; Morelli, A.; Adorini, L.; Maggi, M. Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. *Int. J. Androl.* 2010, 33, 475–488. [CrossRef] [PubMed]

49. Sciarrà, A.; Di Silverio, F.; Salciccia, S.; Autran Gomez, A.M.; Gentilucci, A.; Gentile, V. Inflammation and chronic prostatic diseases: Evidence for a link? *Eur. Urol.* 2007, 52, 964–972. [CrossRef] [PubMed]

50. Penna, G.; Fibbi, B.; Amuchastegui, S.; Corsiero, E.; Laverny, G.; Silvestrini, E.; Chavalmane, A.; Morelli, A.; Sarchielli, E.; Vannelli, G.B.; et al. The vitamin D receptor agonist elocalcitol inhibits IL-8-dependent benign prostatic hyperplasia stromal cell proliferation and inflammatory response by targeting the RhoA/Rho kinase and NF-kappaB pathways. *Prostate* 2009, 69, 480–493. [CrossRef] [PubMed]

51. Krieger, J.N.; Lee, S.W.; Jeon, J.; Cheah, P.Y.; Liong, M.L.; Riley, D.E. Epidemiology of prostatitis. *Int. J. Antimicrob. Agents* 2008, 31 (Suppl. S1), S85–S90. [CrossRef] [PubMed]

52. Whitmore, W.F.; Gittes, R.F. Studies on the prostate and testis as immunologically privileged sites. *Cancer Treat. Rep.* 1977, 61, 217–222. [PubMed]

53. Zisman, A.; Zisman, E.; Lindner, A.; Velikanov, S.; Siegel, Y.I.; Mozes, E. Autoantibodies to prostate specific antigen in patients with benign prostatic hyperplasia. *J. Urol.* 1995, 154, 1052–1055. [CrossRef]
54. Motrich, R.D.; Maccioni, M.; Molina, R.; Tissera, A.; Olmedo, J.; Rivero, V.E. Presence of INFγ-secreting lymphocytes specific to prostate antigens in a group of chronic prostatitis patients. *Clin. Immunol.* 2005, 116, 149–157. [CrossRef] [PubMed]

55. Ponniah, S.; Arah, I.; Alexander, R.B. PSA is a candidate self-antigen in autoimmune chronic prostatitis/chronic pelvic pain syndrome. *Prostate* 2000, 44, 49–54. [CrossRef]

56. Miller, L.J.; Fischer, K.A.; Goralnick, S.J.; Litt, M.; Burleson, J.A.; Albertsen, P.; Kreutzer, D.L. Nerve growth factor induces mast cell degranulation without changing intracellular calcium levels. *FEBS Lett.* 1986, 198, 315–320. [CrossRef] [PubMed]

57. Varilek, G.W.; Weinstock, J.V.; Pantazis, N.J. Isolated hepatic granulomas from mice infected with *Schistosoma mansoni* contain nerve growth factor. *Infect. Immun.* 1991, 59, 4443–4449. [PubMed]

58. Mazurek, N.; Weskamp, G.; Erne, P.; Otten, U. Nerve growth factor and chronic prostatitis/chronic pelvic pain syndrome. *Urology* 2002, 59, 603–608. [CrossRef] [PubMed]

59. Ou, Z.; He, Y.; Qi, L.; Zu, X.; Wu, L.; Cao, Z.; Li, Y.; Liu, L.; Dube, D.A.; Wang, Z.; et al. Infiltrating mast cells enhance benign prostatic hyperplasia through IL-6/STAT3/Cyclin D1 signals. *Oncotarget* 2017, 8, 59156–59164. [CrossRef] [PubMed]

60. Lindsay, R.M.; Harmar, A.J. Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons. *Nature 1989*, 337, 362–364. [CrossRef] [PubMed]

61. Chien, C.-T.; Yu, H.-J.; Lin, T.-B.; Lai, M.-K.; Hsu, S.-M. Substance P via NK1 receptor facilitates hyperactive bladder afferent signaling via action of ROS. *Am. J. Physiol. Ren. Physiol.* 2003, 284, F840–F851. [CrossRef] [PubMed]

62. Funahashi, Y.; Takahashi, R.; Mizooguchi, S.; Suzuki, T.; Takaoka, E.; Ni, J.; Wang, Z.; DeFranco, D.B.; de Groat, W.C.; Tyagi, P. Bladder overactivity andafferent hyperexcitability induced by prostate-to-bladder cross-sensitization in rats with prostatic inflammation. *J. Physiol.* 2019, 537, 2063–2078. [CrossRef] [PubMed]

63. Vital, P.; Castro, P.; Ittmann, M. Oxidative stress promotes benign prostatic hyperplasia. *Prostate 2016*, 76, 58–67. [CrossRef] [PubMed]

64. Chiang, B.J.; Chen, T.W.; Chung, S.D.; Lee, W.Z.; Chien, C.T. Synthetic nickel-containing superoxide dismutase attenuates para-phenylenediamine-induced bladder dysfunction in rats. *Oncotarget* 2017, 8, 105735–105748. [CrossRef] [PubMed]

65. Dearakhshandeh, N.; Mogheiseh, A. Changes in the oxidative stress factors and inflammatory proteins following the treatment of BPH-induced dogs with an anti-proliferative agent called tadalafil. *J. Vet. Pharmacol. Ther.* 2019. [CrossRef] [PubMed]

66. Sugar, L.M. Inflammation and prostate cancer. *Can. J. Urol.* 2006, 13 (Suppl. S1), 46–47. [PubMed]

67. Di Silverio, F.; Gentile, V.; De Matteis, A.; Mariotti, G.; Giuseppe, V.; Luigi, P.A.; Sciarra, A. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: A retrospective analysis. *Eur. Urol.* 2003, 43, 164–175. [CrossRef] [PubMed]

68. McVary, K.T.; Rademaker, A.; Lloyd, G.L.; Gann, P. Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J. Urol.* 2005, 174, 1327–1433. [CrossRef] [PubMed]

69. Kim, J.; Yanagihara, Y.; Kikugawa, T.; Ji, M.; Tanji, N.; Masayoshi, Y.; Freeman, M.R. A signaling network in phenylephrine-induced benign prostatic hyperplasia. *Endocrinology* 2009, 150, 3576–3583. [CrossRef] [PubMed]

70. Kanagawa, K.; Sugimura, K.; Kuratsu, K.; Ikemoto, S.; Kishimoto, T.; Nakatani, T. Norepinephrine activates P44 and P42 MAPK in human prostate stromal and smooth muscle cells but not in epithelial cells. *Prostate* 2003, 56, 313–318. [CrossRef] [PubMed]

71. Huang, X.; Lee, C. Regulation of stromal proliferation, growth arrest, differentiation and apoptosis in benign prostatic hyperplasia by TGF-beta. *Front. Biosci.* 2003, 8, s740–s749.

72. Turton, K.; Chaddock, J.A.; Acharya, K.R. Botulinum and tetanus neurotoxins: Structure, function and therapeutic utility. *Trends Biochem. Sci.* 2002, 27, 552–558. [CrossRef] [PubMed]

73. Chuang, Y.C.; Huang, C.C.; Kang, H.Y.; Chiang, P.H.; Demiguel, F.; Yoshimura, N.; Chancellor, M.B. Novel action of botulinum toxin on the stromal and epithelial components of the prostate gland. *J. Urol.* 2006, 175, 1158–1163. [CrossRef] [PubMed]

74. Lin, A.T.; Yang, A.H.; Chen, K.K. Effects of botulinum toxin A on the contractile function of dog prostate. *Eur. Urol.* 2007, 52, 582–589. [CrossRef] [PubMed]
75. Chuang, Y.C.; Tu, C.H.; Huang, C.C.; Lin, H.J.; Chiang, P.H.; Yoshimura, N.; Chancellor, M.B. Intraprostatic injection of botulinum toxin type-A relieves bladder outlet obstruction in human and induces prostate apoptosis in dogs. *BMC Urol.* 2006, 6, 12. [CrossRef] [PubMed]

76. Chuang, Y.C.; Chiang, P.H.; Yoshimura, N.; De Miguel, F.; Chancellor, M.B. Sustained beneficial effects of intraprostatic botulinum toxin type A on lower urinary tract symptoms and quality of life in men with benign prostatic hyperplasia. *BJU Int.* 2006, 98, 1033–1037. [CrossRef] [PubMed]

77. Borodic, G.E.; Acquadro, M.; Johnson, E.A. Botulinum toxin therapy for pain and inflammatory disorders: Mechanisms and therapeutic effects. *Expert Opin. Investig. Drugs* 2001, 10, 1531–1544. [CrossRef] [PubMed]

78. Yoo, K.Y.; Lee, H.S.; Cho, Y.K.; Lim, Y.S.; Kim, Y.S.; Koo, J.H.; Yoon, S.J.; Lee, J.H.; Jang, K.H.; Song, S.H. Anti-inflammatory effects of botulinum toxin type A in a complete Freund’s adjuvant-induced arthritic knee joint of hind leg on rat model. *Neurotox. Res.* 2014, 26, 32–39. [CrossRef] [PubMed]

79. Choi, J.E.; Werbel, T.; Wang, Z.; Wu, C.C.; Yaksh, T.L.; Di Nardo, A. Botulinum toxin blocks mast cells and prevents rosacea like inflammation. *J. Dermatol. Sci.* 2019, 93, 58–64. [CrossRef] [PubMed]

80. Liu, H.T.; Kuo, H.C. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. *Urology* 2007, 70, 463–468. [CrossRef]

81. Chuang, Y.C.; Tu, C.H.; Huang, C.C.; Lin, H.J.; Chiang, P.H.; Yoshimura, N.; Chancellor, M.B. Intraprostatic botulinum toxin A administration produces analgesia against acetic acid induced bladder pain responses in rats. *J. Urol.* 2004, 172, 1529–1532. [CrossRef]

82. Aoki, K.R. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. *Neurotoxicology* 2005, 26, 785–793. [CrossRef]

83. Chuang, Y.C.; Yoshimura, N.; Huang, C.C.; Wu, M.; Chiang, P.H.; Chancellor, M.B. Intraprostatic botulinum toxin A injection inhibits cyclooxygenase-2 expression and suppresses prostatic pain on capsacin induced prostatitis model in rat. *J. Urol.* 2008, 180, 742–748. [CrossRef]

84. Uchiyama, A.; Yamada, K.; Perera, B.; Ogino, S.; Yokoyama, Y.; Takeuchi, Y.; Ishikawa, O.; Motegi, S. Protective effect of botulinum toxin A after cutaneous ischemia-reperfusion injury. *Sci. Rep.* 2015, 5, 9072. [CrossRef]

85. Schraufstatter, I.U.; Chung, J.; Burger, M. IL-8 activates endothelial cell CXCR1 and CXCR2 through Rho and Rac signaling pathways. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2001, 280, L1094–L1103. [CrossRef]

86. Kuo, H.C. Prostate botulinum A toxin injection—An alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology* 2005, 65, 670–674. [CrossRef]

87. Silva, J.; Pinto, R.; Carvalho, T.; Botelho, F.; Silva, P.; Oliveira, R.; Silva, C.; Cruz, F.; Dinis, P. Intraprostatic botulinum toxin type A injection in patients with benign prostatic enlargement: Duration of the effect of a single treatment. *BMC Urol.* 2009, 9, 9. [CrossRef]

88. Maria, G.; Brisinda, G.; Civello, I.M.; Bentivoglio, A.R.; Šganga, G.; Albanese, A. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: Results of a randomized, placebo-controlled study. *Urology* 2003, 62, 259–264. [CrossRef]

89. Chuang, Y.C.; Chiang, P.H.; Yoshimura, N.; Chancellor, M.B. Botulinum toxin type A improves benign prostatic hyperplasia symptoms in patients with small prostates. *Urology* 2005, 66, 775–779. [CrossRef]

90. Brisinda, G.; Cadeddu, F.; Vanella, S.; Mazzeo, P.; Marmiga, G.; Maria, G. Relief by botulinum toxin of lower urinary tract symptoms owing to benign prostatic hyperplasia: Early and long-term results. *Urology* 2009, 73, 90–94. [CrossRef]

91. McVary, K.T.; Roehrborn, C.G.; Chartier-Kastler, E.; Efron, M.; Bugarin, D.; Chen, R.; Patel, A.; Haag-Molkenteller, C. A multicenter, randomized, double-blind, placebo controlled study of onabotulinumtoxinA 200 U to treat lower urinary tract symptoms in men with benign prostatic hyperplasia. *J. Urol.* 2014, 192, 150–156. [CrossRef]

92. Marberger, M.; Chartier-Kastler, E.; Egerdie, B.; Lee, K.S.; Grosse, J.; Bugarin, D.; Zhou, J.; Patel, A.; Haag-Molkenteller, C. A randomized double-blind placebo-controlled phase 2 dose-ranging study of onabotulinumtoxinA in men with benign prostatic hyperplasia. *Eur. Urol.* 2013, 63, 496–503. [CrossRef]

93. Shim, S.R.; Cho, Y.J.; Shin, I.S.; Kim, J.H. Efficacy and safety of botulinum toxin injection for benign prostatic hyperplasia: A systematic review and meta-analysis. *Int. Urol. Nephrol.* 2016, 48, 19–30. [CrossRef]

94. Marchal, C.; Perez, J.E.; Herrera, B.; Machuca, F.J.; Redondo, M. The use of botulinum toxin in benign prostatic hyperplasia. *Neurourol. Urodyn.* 2012, 31, 86–92. [CrossRef]
95. Mangera, A.; Apostolidis, A.; Andersson, K.E.; Dasgupta, P.; Giannantoni, A.; Roehrborn, C.; Novara, G.; Chapple, C. An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. *Eur. Urol.* 2014, 65, 981–990. [CrossRef]

96. Mangera, A.; Andersson, K.E.; Apostolidis, A.; Chapple, C.; Dasgupta, P.; Giannantoni, A.; Gravas, S.; Madersbacher, S. Contemporary management of lower urinary tract disease with botulinum toxin A: A systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). *Eur. Urol.* 2011, 60, 784–795. [CrossRef]

97. El-Enen, M.A.; Abou-Farha, M.; El-Abd, A.; El-Tatawy, H.; Tawfik, A.; El-Abd, S.; Rashed, M.; El-Sharaby, M. Intraprostatic injection of botulinum toxin-A in patients with refractory chronic pelvic pain syndrome: The transurethral vs. transrectal approach. *Arab J. Urol.* 2015, 13, 94–99. [CrossRef]

98. Falahatkar, S.; Shahab, E.; Gholamjani Moghaddam, K.; Kazemnezhad, E. Transurethral intraprostatic injection of botulinum neurotoxin type A for the treatment of chronic prostatitis/chronic pelvic pain syndrome: Results of a prospective pilot double-blind and randomized placebo-controlled study. *BJU Int.* 2015, 116, 641–649. [CrossRef]

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