

- [5] Chuang YC, Chiang PH, Huang CC, Yoshimura N, Chancellor MB. Botulinum toxin type A improves benign prostatic hyperplasia symptoms in patients with small prostates. *Urology* 2005;66:775–9.
- [6] Doggweiler R, Zermann DH, Ishigooka M, Schmidt RA. Botox-induced prostatic involution. *Prostate* 1998;37:44–50.
- [7] Lin ATL, Yang AH, Chen K-K. Effects of botulinum toxin A on the contractile function of dog prostate. *Eur Urol* 2007;52:582–9.
- [8] Dolly JO, Aoki KR. The structure and mode of action of different botulinum toxins. *Eur J Neurol* 2006;13(Suppl 4):1–9.
- [9] Chuang YC, Huang CC, Kang HY, et al. Novel action of botulinum toxin on the stromal and epithelial components of the prostate gland. *J Urol* 2006;175:158–63.
- [10] Chuang YC, Chancellor MB. The application of botulinum toxin in the prostate. *J Urol* 2006;176:2375–82.
- [11] Smith CP, Franks ME, McNeil BK, et al. Effect of botulinum toxin A on the autonomic nervous system of the rat lower urinary tract. *J Urol* 2003;169:1896–900.
- [12] Jones OM, Moore JA, Brading AF, Mortensen NJ. Botulinum toxin injection inhibits myogenic tone and sympathetic nerve function in the porcine internal anal sphincter. *Colorectal Dis* 2003;5:552–7.
- [13] Duggan MJ, Quinn CP, Chaddock JA, et al. Inhibition of release of neurotransmitters from rat dorsal root ganglia by a novel conjugate of a clostridium botulinum toxin A endopeptidase fragment and erythrina cristagalli lectin. *Biol Chem* 2002;277:34846–52.
- [14] Rapp DE, Turk KW, Bales GT, Cook SP. Botulinum toxin type A inhibits calcitonin gene-related peptide release from isolated rat bladder. *J Urol* 2006;175:1138–42.
- [15] Witte LPW, Chapple CR, de la Rosette JJMCH, Michel MC. Cholinergic innervation and muscarinic receptors in the human prostate. *Eur Urol* 2008;54:326–34.
- [16] Pennefather JN, Lau WA, Mitchelson F, Ventura S. The autonomic and sensory innervation of the smooth muscle of the prostate gland: a review of pharmacological and histological studies. *Auton Pharmacol* 2000;20:193–206.
- [17] Dinis P, Charrua A, Avelino A, et al. The distribution of sensory fibers immunoreactive for the TRPV1 (capsaicin) receptor in the human prostate. *Eur Urol* 2005;48:162–7.
- [18] Ramien M, Ruocco I, Cuello AC, St. Louis M, Ribeiro-da-Silva A. Parasympathetic nerve fibers invade the upper dermis following sensory denervation of the rat lower lip skin. *J Comp Neurol* 2004;469:83–95.
- [19] McVary KT, Razzaq A, Lee C, Venegas MF, Rademaker A, McKenna KE. Growth of the rat prostate gland is facilitated by the autonomic nervous system. *Biol Reprod* 1994;51:99–107.
- [20] Anglin IE, Glassman DT, Kyprianou N. Induction of prostate apoptosis by alpha1-adrenoceptor antagonists: mechanistic significance of the quinazoline component. *Prostate Cancer Prostatic Dis* 2002;5:88–95.
- [21] McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349:2387–98.
- [22] Yono M, Foster Jr HE, Shin D, Takahashi W, Pouresmail M, Latifpour J. Doxazosin-induced up-regulation of alpha 1A-adrenoceptor mRNA in the rat lower urinary tract. *Can J Physiol Pharmacol* 2004;82:872–8.
- [23] Apostolidis A, Popat R, Yianguo Y, et al. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol* 2005;174:977–82.
- [24] Schaible HG, Del Rosso A, Matucci-Cerinic M. Neurogenic aspects of inflammation. *Rheum Dis Clin North Am* 2005;31:77–101.
- [25] Di Silverio F, Gentile V, De Matteis A. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. *Eur Urol* 2003;43:164–75.
- [26] Chuang Y-C, Yoshimura N, Wu M. Intraprostatic capsaicin injection as a novel model for nonbacterial prostatitis and effects of botulinum toxin A. *Eur Urol* 2007;51:1119–27.
- [27] Matiyahou A, Rosenzweig N, Golomb E. Rapid proliferation of prostatic epithelial cells in spontaneously hypertensive rats: a model of spontaneous hypertension and prostate hyperplasia. *J Androl* 2003;24:263–9.
- [28] Ullrich PM, Lutgendorf SK, Kreder KJ. Physiologic reactivity to a laboratory stress task among men with benign prostatic hyperplasia. *Urology* 2007;70:487–91.
- [29] Dong M, Yeh F, Tepp WH, et al. SV2 is the protein receptor for botulinum neurotoxin A. *Science* 2006;312:592–6.

Editorial Comment on: Mechanisms of Prostate Atrophy after Glandular Botulinum Neurotoxin Type A Injection: An Experimental Study in the Rat

Riccardo Autorino

Urology Clinic, Second University of Naples, Italy

ricautor@tin.it

Botulinum Neurotoxin Type A (BoNT-A) has recently been proposed as a novel, effective drug in the management of lower urinary tract symptoms caused by benign prostatic enlargement or other urological conditions (ie, neurogenic detrusor overactivity, detrusor-sphincter dyssynergia, motor and sensory urge, or chronic prostatic pain) [1].

BoNT-A's clinical application in urology has been stimulated by a widespread use in other medical fields, but also by some convincing experimental data. Doggweiler et al first demonstrated that BoNT-A injection into the prostate gland induces selective denervation and subsequent atrophy of the prostate [2]. Since that pioneering report, several papers have appeared in the past decade, most of them investigating the effect of

BoNT-A on acetylcholine release from parasympathetic nerves.

In this paper, Dr. Silva and coworkers elegantly provide evidence that adrenergic innervation of the prostate might have an effect on prostatic involution after BoNT-A injection [3]. This interesting new finding indirectly corroborates previous evidence indicating that certain alpha 1 blockers can affect the dynamics of prostate growth by changing the balance between prostate cell proliferation and apoptosis, even if the clinical significance of this evidences remain unclear [4].

Of course, there are two major limitations of this work, as recognized by the authors themselves: the rat prostate is widely different from the human prostate, and the study is performed in a nonpathological experimental model. Thus, many issues regarding the botulinum effect on neuronal pathways of the prostate, and more in general on the lower urinary tract, remain to be addressed. Among them, emerging data suggest an important role of BoNT-A in modulating sensory and antinociceptive mechanisms, which affect bladder urgency, pain, and

inflammation. And we are now well aware of a link between inflammation and benign prostatic hyperplasia [5].

What are the real clinical implications of the findings from Silva et al's paper, then? Well, it is too early to say. But we are on the right path to answering this intriguing question, even though considerable clinical and basic science work still needs to be performed. Currently, all botulinum toxin use for urological conditions is off-label and unlicensed; therefore, caution should be exercised until future studies are reported.

Transforming a lethal poison into a modern, effective, minimally invasive therapeutic weapon remains one of the current exciting challenges of urological research.

References

- [1] Oeconomou A, Madersbacher H, Kiss G, Berger TJ, Melekos M, Rehder P. Is botulinum neurotoxin type A (BoNT-A) a novel therapy for lower urinary tract symptoms due to benign prostatic enlargement? A review of the literature. *Eur Urol* 2008;54:765–77.
- [2] Doggweiler R, Zermann DH, Ishigooka M, Schmidt RA. Botox-induced prostatic involution. *Prostate* 1998;37:44–50.
- [3] Silva J, Pinto R, Carvalho T, et al. Mechanisms of prostate atrophy after glandular botulinum neurotoxin type A injection: an experimental study in the rat. *Eur Urol* 2009;56:134–41.
- [4] Tahmatzopoulos A, Kyprianou N. Apoptotic impact of alpha1-blockers on prostate cancer growth: a myth or an inviting reality? *Prostate* 2004;59:91–100.
- [5] Sciarra A, Di Silverio F, Salciccia S, et al. Inflammation and chronic prostatic diseases: evidence for a link?. *Eur Urol* 2007;52:964–72.

DOI: [10.1016/j.eururo.2008.07.004](https://doi.org/10.1016/j.eururo.2008.07.004)

DOI of original article: [10.1016/j.eururo.2008.07.003](https://doi.org/10.1016/j.eururo.2008.07.003)