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Apostolidis A[1], Popat R[2], Yiangou Y [3], Dasgupta P[4], Anand P[3], Fowler C J[2]
1. The National Hosp for Neurology and Neurosurgery,UCLH & The Hammersmith Hosp, Imperial Coll, 2. The National Hosp for Neurology and Neurosurgery,UCLH , 3. The Hammersmith Hosp, Imperial College London, 4. Guys' and St. Thomas' Hosp

A POSSIBLE EXPLANATION FOR THE EXCEPTIONAL EFFICACY OF BOTULINUM TOXIN TREATMENT FOR DETRUSOR OVERACTIVITY

Hypothesis / aims of study

Improved cystometric parameters of patients with intractable detrusor overactivity (DO) successfully treated with intra-detrusor injections of botulinum toxin type A (BoTx/A) are accompanied by an early and significant reduction in their sensations of urinary urgency. This suggests an effect of BoTx/A on afferent bladder pathways and animal studies of BoTx/A have recently shown that it inhibits the release of sensory neurotransmitters from dorsal root ganglia and has an anti-nociceptive effect in an animal pain model. A suppression of ACh release by BoTx/A has also been shown in rat detrusor strips.
We focused our investigation on the possible mechanism of action of BoTx/A on the bladder afferents, studying the changes in the suburothelial innervation of patients with neurogenic or idiopathic DO (NDO/IDO) treated with BoTx/A, using the pan-neuronal marker PGP9.5, the afferent markers TRPV1 and $P2X_3$, and acetylcholinesterase (AChE).

Study design, materials and methods

Flexible cystoscopic bladder biopsies were obtained from 38 patients, 22 with NDO and 16 with IDO, who were treated with intra-detrusor injections of BoTx/A. Biopsies were taken at baseline and at 4 and 16 weeks post treatment. All patients responded to treatment, showing sustained clinical and urodynamic improvement at 16-week follow-up. The improvement in sensation of urgency, quantified as change in number of micturition episodes associated with urgency per 24 hours, was dramatic at 4/52 (8.77 ± 0.73 baseline vs 2.76 ± 0.69, P<0.0001) and sustained at 16/52 (2.63 ± 0.55, P<0.0001).
Control tissue was obtained from 13 subjects with no symptoms of bladder overactivity. Specimens were fixed in 4% w/v paraformaldehyde and sections were incubated with specific antibodies to PGP9.5, AChE, TRPV1 and $P2X_3$. PGP9.5 immunoreactivity (IR) was quantified by image analysis and expressed as % red area. A scale of nerve fibre density ranging between 0-3 was used for AChE, TRPV1 and $P2X_3$ fibre staining. The paired t test and Mann Whitney test were used for statistical analysis, with significance determined at P values <0.05.

Results

An increase in suburothelial fibres expressing TRPV1 and/or $P2X_3$ in patients with NDO has previously been reported and this observation was confirmed in the present study; the density for $P2X_3$-IR fibres being 1.35±0.13 (mean ± SEM) in NDO bladders compared to 0.86±0.17 (P=0.037) in patients with IDO and 0.47±0.09 (P<0.0001) in controls (Figure 1), and TRPV1-IR fibres being 0.555 ± 0.130 compared to controls (0.166 ± 0.09), although this was not statistically significant (P=0.17) (Figure 2). No difference in AChE (+) nerve fibre density was found between control (0.72 ± 0.25) and overactive bladders (0.93 ± 0.12).

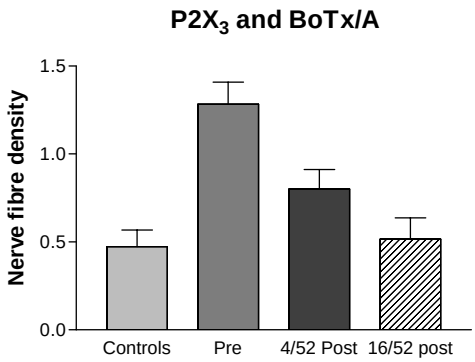

Figure 1.

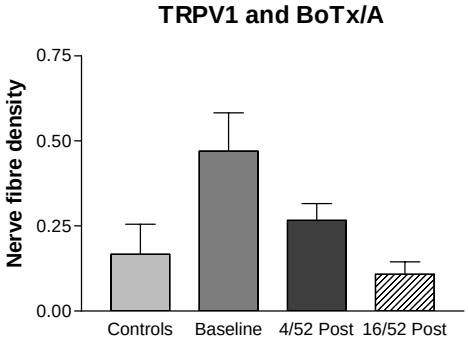

Figure 2.

Four weeks (4/52) after treatment with BoTx/A, PGP9.5 values remained unchanged in n=27 available follow-up biopsies (2.04 ± 0.24 vs 1.85 ± 0.22, *P*=0.39), and also at 16/52 (1.63 ± 0.22 vs pre: 1.98 ± 0.33, *P*=0.35, n=19 available biopsies). No change was found in AChE-IR nerve fibres at 4/52 follow-up (0.91 ± 0.15) compared to baseline values (0.96 ± 0.14; *P*=0.84) for 30 subjects, or at 16/52 follow-up for 20 available biopsies (0.68 ± 0.16 vs 0.97 ± 0.14, *P*=0.18). However, a significant decrease was noted for $P2X_3$-IR suburothelial fibres at 4/52 (1.28 ± 0.13 vs 0.80±0.11, *P*=0.01, n=29), with a further decrease at 16/52 (0.51±0.12, *P*=0.006, n=19)(Figure 1). TRPV1-expressing fibres showed a trend to decrease at 4/52 post-BoTx/A (0.47 ± 0.11 vs 0.27 ± 0.05), which became significant only at 16/52 (0.11 ± 0.04, *P*=0.0004) (Figure 2).

Interpretation of results

Our findings suggest that successful BoTx/A treatment of overactive bladders is not associated with substantial suburothelial neuronal or cholinergic fibre degeneration or sprouting. However intra-detrusor BoTx/A injections do result in a significant decrease in TRPV1 and/or $P2X_3$ expressing fibres, or at least in the level of expression of these receptors. This effect may be secondary to a reduction in the efferent input to the detrusor, reducing overactivity and the production/uptake of neurotrophic factors, which regulate the expression of TRPV1 and/or $P2X_3$. However, this decrease taken in conjunction with the clinical reduction in urinary urgency and the emerging knowledge about the effect of BoTx/A on afferent signalling mechanisms, suggests that a direct effect of BoTx/A on the afferent bladder innervation is responsible for the exceptional efficacy of the treatment.

Concluding message

The clinical response of patients with DO to BoTx/A may be partly the result of alterations in the afferent bladder mechanisms.

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