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BOTULINUM TOXIN A DETRUSOR INJECTIONS REDUCE MUSCULAR M2, P2X2 AND P2X3 RECEPTORS IN CHILDREN AND ADOLESCENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY

Hypothesis / Study Objectives

Post-intervention receptor analyses after botulinum toxin type A (BoNT/A) detrusor injections have previously focused primarily on neurogenic changes. We analyzed the effect of botulinum toxin type A (BoNT/A, preparation onabotulinum toxin A (Botox®)) detrusor injections on muscular receptors in children with neurogenic detrusor overactivity.

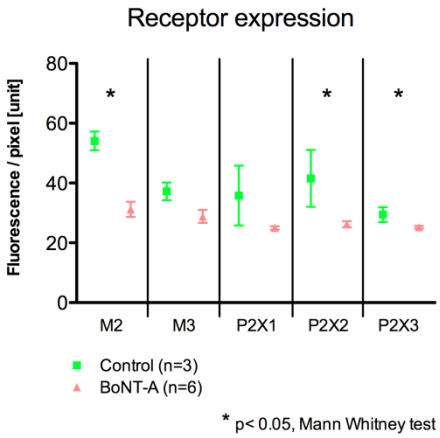
Study Design, Materials and Methods

A bladder augmentation became necessary in 9 children and adolescents (7m, 2f, median age 12 years) with conservatively treated neurogenic detrusor overactivity. 6 children had previously received between 1 and 8 (∅ 4) BoNT/A detrusor injections, the last one always being 300 U Botox®; however, the detrusor pressure values could not be maintained at tolerable values anymore with this therapy due to a low-compliance bladder. The last injection session had been completed 3 months previously (1.5 - 3.5) on average. 3 patients had never received such a therapy (controls). The bladder dome resections were placed into a 4% buffered paraformaldehyde solution; afterwards, a specific receptor analysis (muscarinic M2 and M3, purinergic P2X1, P2X2, P2X3) via confocal immunofluorescence was performed and the nerve fiber density was analyzed via light-microscopic DAB-immunohistochemical staining.

Results

The receptor analysis showed a tendency towards downregulation of all examined receptors after BoNT/A injections, whereas M2, P2X2 and P2X3 receptors reached a significance level of $p<0.05$ (Mann-Whitney test). The relationship of medians (BoNT/A vs. control) was: 0.53 (M2); 0.71 (M3); 0.93 (P2X1); 0.68 (P2X2); 0.94 (P2X3). The innervation density, however, was not influenced.

Fig.1: receptor expression of M2, M3, P2X1, P2X2 and P2X3 in patients without (green) and with (red) BoNT/A pretreatment.



Interpretation of Results

Several actions of BoNT/A, once applied to the urinary bladder, have yet been examined, e.g.: BoNT/A blocks the presynaptic release of acetylcholine into the synaptic gap [1]; BoNT/A also decreases sensory nerve fiber receptors P2X3 and TRPV1 in the suburothelial layer with no influence on the total number of neurons [2]; and BoNT/A inhibits calcitonin-gene related peptide release from afferent nerve terminals [3]). These findings, exclusively investigated on the neurogenic site, might in part explain the clinically detectable reduction of detrusor overactivity and sensory perception in patients with OAB, and relief of pain in patients with, e.g., interstitial cystitis. Our study elucidates, that BoNT/A also decreases the density of the M2, P2X2 and P2X3 receptors on the muscular site of the neuromuscular junction. This might also contribute to the reduced force development of the detrusor muscle after BoNT/A injections, that on its part leads to incomplete bladder emptying up to urinary retention. As was shown before [2], also in our study the innervation density remained unchanged.

Concluding Message

BoNT/A detrusor injections lead to a significant reduction in muscular M2, P2X2 and P2X3 receptors without influencing innervation density. With this study, the influence of BONT/A on the muscular receptor level has been verified for the first time. The reduction of these receptors probably has an impact on the force generation of the urinary bladder and could explain the clinically seen increase of residual urine.

References

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Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**