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Everaerts W[1], Gevaert T[1], Van Leuven L[1], Hutchings G[1], de Ridder D[1]
1. University Hospitals KU Leuven

THE EFFECT OF BOTULINUM TOXIN A ON AUTONOMOUS CONTRACTIONS DIFFERS BETWEEN NORMAL AND SPINALISED RAT BLADDERS.

Hypothesis / aims of study

Botulinum toxin A (Btx) is successfully being used in clinic to treat patient with neurogenic bladder overactivity. These clinical finding are supported by animal research, showing that Btx injections in the detrusor muscle of rats significantly decreases frequency and amplitude of uninhibited bladder contractions in SCI rats.[1] It is assumed that botulinum toxin A not only inhibits the release of Ach by the efferent nerve endings, but also affects local mechanisms modulating afferent nerve activity.[2] As autonomous bladder contractions are the result of local mechanism, we hypothesized that Btx can influence autonomous contractions in the isolated (denervated) bladder model.

Study design, materials and methods

Female Whistar rats (200-250 mg) were randomly allocated into 4 groups: group 1 (n=5) underwent sham operation followed by saline injection (0,250mL) in the detrusor 3 weeks later, group 2 (n=4) underwent a sham operation followed by injection of Btx (5U, 250mL) in the detrusor. Group 3 (n=6) underwent spinal cord transection (T8-T9) followed by saline injection after 3 weeks. Group 4 (n=3) underwent spinal cord transection followed by Btx (5U) 3 weeks later.
Two weeks after the injection, bladders were excised and autonomous bladder contraction were recorded in an organ bath filled with heated Krebs.

Results

None of the rats developed urine retention after injection of Btx and autonomous contractions were present in all bladders examined. Btx reduced amplitude of bladder contractions in both neurogenic and non-neurogenic bladders, without significantly influencing bladder weight. In neurogenic bladders, Btx significantly reduced the number of spikes (saline 83,1 ± 31,7, botulinum toxin 39,3 ± 12,9 p= 0.048). Bladder response to carbachol was also influenced by Btx and the effect was the opposite in neurogenic vs control bladders. In neurogenic bladders Btx strongly inhibited the increase in phasic (amplitude of macro transients) and tonic (baseline pressure) bladder activity induced by admission of cumulative doses of carbachol (10^{-9} to 10^{-6} M). In non-neurogenic bladders however, there was a stronger phasic and tonic response to carbachol than in the saline treated group.

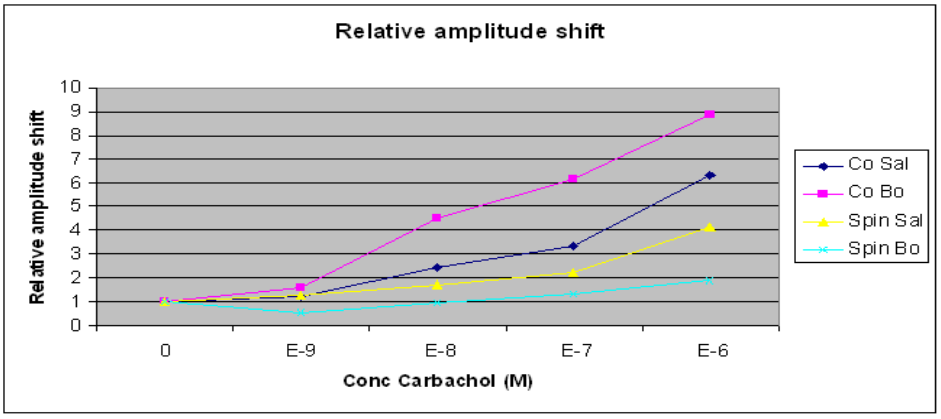

Fig 2. Relative shift in amplitude of autonomous contractionin response to cumulative doses of carbachol.

Interpretation of results

As Btx influences autonomous contractions, without completely inhibiting them, this model can be used to test the effect of botulinum toxin on local bladder mechanisms. Local mechanisms influencing afferent activity are affected by Btx as spikes were significantly reduced in neurogenic bladders. Surprisingly Btx has an opposite effect on changes of bladder contractions in response to carbachol, in neurogenic and non- neurogenic bladders. A possible explanation could be that Btx affects the muscarinic pathways in a different way in normal or neurogenic bladders.

Concluding message

Botulinum toxin A significantly decreases the number spikes in neurogenic autonomous bladders and changes the response to carbachol compared to non-neurogenic autonomous bladders. Since the autonomous bladder model is a denervated model, these findings suggest that Btx interferes with non-neuronal intrinsic bladder wall mechanisms and that these mechanisms undergo important changes after spinalisation.

References

1. J Urol (2005)174(6);2393-6.
2. Urology (2005)66; 208-12.

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