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THE USE OF THE NEUROTROXINS IN THE PREVENTION OF NEUROGENIC DETRUSOR OVERACTIVITY

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ABSTRACT

Bladder dysfunction is one of the most perturbing consequences of **spinal cord injuries** (SCI) and a top priority in SCI management. **Neurogenic detrusor overactivity** (NDO) affects about 80% of SCI patients and occurs due to the development of a **spinal micturition reflex** at the lumbosacral spinal cord level mediated by **type C bladder sensory afferents**. NDO is characterized by **frequent and strong bladder contractions** and, together with detrusor-sphincter dyssinergia (DSD), leads to frequent episodes of **urinary incontinence** and periods of **very high intravesical pressures**.
Currently, treatment is only initiated when NDO is stable-fixed, reducing the chances of NDO effacement and preservation of upper urinary tract. Here, we tested a **preventive strategy** with resiniferatoxin (**RTX**) and botulinum toxin A (**BoNT/A**) aiming to effectively block the emergence of NDO.

METHODS

Female Wistar rats were divided into 5 groups, submitted to spinal cord transection at T8/T9 level or sham surgeries and treated as following:

Group	Surgery	Treatment
A, n=5	Sham	No treatment
B, n=5	SCT	SCT + intravesical vehicle (ethanol 10% in saline), 3 and 9 days post-SCT
C, n=5	SCT	SCT + intravesical RTX 50 nM diluted in vehicle, 3 and 9 days post-SCT
D, n=5	SCT	SCT + intradetrusor injections of 100 µL of saline, 3 days post-SCT in 10 bladder locations
E, n=5	SCT	SCT + BoNT/A 10 U/100 µL of saline, injected as in group D

Four weeks after surgery animals were anesthetized with urethane and underwent 1 hour-cystometry followed by collection of L5-S1 spinal cord segments and bladder tissue. Immunohistochemistry and Western immunoblotting techniques were used to investigate changes in sprouting pattern of peripheral and central neuronal fibres related to treatment.

CONCLUSIONS

Early treatments after SCI with RTX and BoNT/A resulted in a significant improvement on bladder function in a rat model of NDO. Both RTX and BoNT/A lead to significant decrease in the amplitude of bladder contractions but only RTX was capable of preventing high intravesical pressures. Therefore, we suggest that a restricted modulation of bladder sensory afferents at early stages of disease progression might be a useful strategy in the prevention of NDO development.

RESULTS

Early administration of RTX and BoNT/A after spinal cord injury: Effects on bladder function

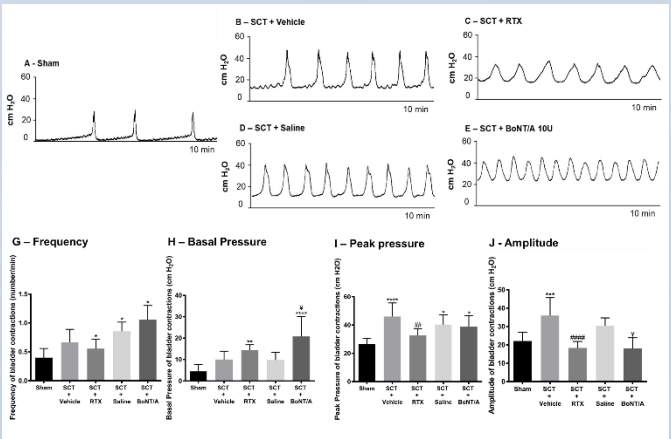

Figure 1: Urodynamic effects of early intravesical RTX and intradetrusor BoNT/A. Cystometograms from sham-operated rats **(A)** and 4 weeks post-SCT rats treated with **vehicle (B)**, **RTX (C)**, **saline (D)** and **BoNT/A 10U (E)**. Graphic representation of averaged **frequencies (G)**, **minimal pressures (H)**, **maximal pressures (I)** and **amplitude (J)** of bladder contractions from all experimental groups. Data represent Mean+SD. Statistical analysis: One-way ANOVA followed by Tukey's multiple comparisons test. *p≤0.05, **p≤0.01, **p≤0.001 ****p≤0.0001 compared to Sham (A); ##p≤0.01, ####p≤0.0001 compared to SCT+Vehicle (B); ¥p≤0.05 compared to SCT+Saline (D).

Early administration of RTX and BoNT/A after spinal cord injury: Effects on bladder tissue

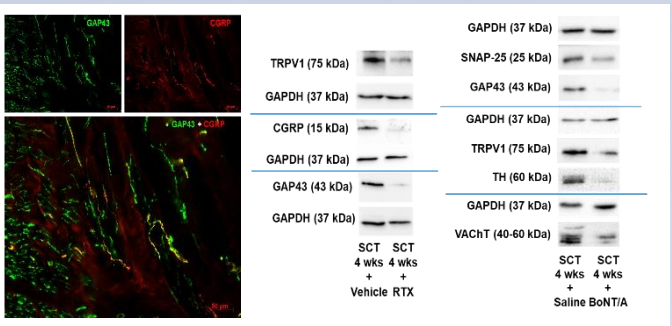

Figure 2: Effects of early intravesical RTX and intradetrusor BoNT/A on bladder tissue 4 weeks after SCT. (A) Immunostaining against the neuronal growth marker **GAP43 (green)** and the marker of peptidergic sensory fibres **CGRP (red)** in the bladder shows an extensive sprouting of bladder fibres that occurs in the totality of peptidergic sensory nerves (yellow). (**B**) Representative Western immunoblot bands show a **reduction** in the relative expression of **TRPV1**, **CGRP** and **GAP43** in the bladder after early treatment with RTX, suggesting a desensitization effect on bladder sensory fibres and a decrease in their growth. (**C**) Western immunoblot bands show a **reduction** in the bladder relative expression of **TRPV1**, **SNAP-25** and **GAP43** after **early** treatment with 10 U of **BoNT/A**. These results suggests that BoNT/A has a broader effect, acting on all bladder nerves and suppressing their growth. Proteins relative expression were normalized against GAPDH.

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