EFFECT OF INTRATHECAL BOTULINUM TOXIN TYPE A IN PAIN ASSOCIATED WITH CHEMICAL-INDUCED CYSTITIS

Hypothesis / aims of study
Bladder Pain syndrome/Interstitial Cystitis (BPS/IC) is a debilitating condition characterized by urinary urgency, frequency and intense pelvic pain that negatively impacts the quality of life of the patients. Botulinum toxin type A has been used as a treatment for many bladder pathologies as it relieves lower urinary tract symptoms (LUTS). Previous studies performed in BPS/IC patients showed that detrusor injection of botulinum toxin has an antinociceptive effect, reducing pain as shown by a pronounced reduction in the visual pain analogue scale. This suggests a possible antinociceptive effect of the toxin, along with the known beneficial effects on bladder function (1). Currently, botulinum toxin administration protocols are restricted to bladder intramural injections. Recent studies, however, suggest that the intrathecal (IT) route may also be advantageous and possibly allow the use of a smaller dose of toxin.

In the present work we addressed this issue by using an animal model of BPS/IC to determine the effects of IT administration of botulinum toxin A.

Study design, materials and methods
Female rats were separated into four experimental groups, (1) IT saline, (2) 48H cyclophosphamide (CYP) 150mg/kg and IT saline, (3) IT Onabot/A, (4) 48H CYP plus IT Onabot/A. All animals were deeply anaesthetized and a laminectomy between T9/T10 performed. A silicone catheter was inserted under the subarachnoid space until the L6 segment and externalized in the forehead. Animals were left to recover for 4 days before any procedure. 5U of Onabot/A diluted in 50μl of saline were administered through the catheter 48H after intraperitoneal injection of CYP. Mechanical allodynia was assessed using the Von Frey test in the hind paws and abdomen before surgical placement of the intrathecal catheter and after CYP, and reassessed 24H after Onabot/A treatment. At the end of the experiment, animals were perfusion-fixed through the ascending aorta, bladders and spinal cord collected and processed for light and fluorescence immunohistochemistry using antibodies against cleaved SNAP-25 and p-ERKS.

Results
CYP-induced bladder inflammation caused the emergence of cutaneous hypersensitivity in the lower abdomen and hindpaws. This hypersensitivity was observed in the abdominal region as early as four hours after CYP injection and later in hindpaws. IT administration of Onabot/A significantly reduced mechanical hypersensitivity of the hindpaws and abdomen induced by CYP. Accordingly, immunoreactivity (IR) for the neuronal marker of activation p-ERK was also decreased by neurotoxin administration. Improvement of pain levels and reduction in p-ERK expression were accompanied by expression of the cleaved form of SNAP-25 (cSNAP-25) observed in the spinal cord and urinary bladder of rats treated with Onabot/A. In the spinal cord, IR-fibers were present throughout the segments L5-S1 with higher abundance of IR fibers in the peripheral area. In the urinary bladder, a few varicose fibers were found between detrusor muscle bundles.

Interpretation of results
These findings showed that the IT route of Onabot/A administration is effective on the relief of pain symptoms associated with BPS/IC. This effect is possibly associated with a reduction of the activity of the nociceptive pathways. The presence of cSNAP-25 in the spinal cord attests the effect of Onabot/A. Surprisingly, the presence of cSNAP-25 was also observed in nerve fibers coursing the urinary bladder suggesting an axonal transport of the toxin from the central to the peripheral nervous system.

Concluding message
Intrathecal administration of botulinum toxin type A is an effective route to treat pain symptoms associated with BPS/IC. The toxin is axonally transported and, like in the spinal cord, also cleaves SNAP-25 in the urinary bladder.

References

Disclosures
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