

DRAMATIC EFFECTS OF A SELECTIVE BETA3-ADRENERGIC AGONIST ON INDICES OF NEUROGENIC BLADDER OVERACTIVITY ASSOCIATED WITH SUPRASACRAL SPINAL CORD INJURY

Hypothesis / aims of study

Suprasacral spinal cord injury (SCI) results in neurogenic detrusor overactivity, a condition characterized by low bladder compliance and numerous high pressure non-voiding contractions (NVC). The resultant high intravesical pressures not only damage the bladder itself, but can also ultimately result in renal failure.

It is generally assumed that the NVC in SCI are the result of uninhibited spinal reflexes driving aberrant parasympathetic activity. However, recent results from our laboratory using spinally intact animals have demonstrated that purely myogenic NVC may also attain similarly dramatic pressures. In these animals, myogenic NVCs were amplified by autonomic ganglionic blockade and were inhibited by beta2-3 adrenergic agonists. Beta3-adrenergic receptor agonists (B3-ARA) are known to relax detrusor smooth muscle directly, but do not eliminate strong parasympathetic-driven contractions.

The SCI rat affords us a model of NVCs during filling together with a spinal voiding reflex, similar to the situation of SCI patients with Blaivas Type II detrusor-sphincter dyssynergia [1]. The present study utilized such a rat model to examine whether NVCs associated with SCI also have a strong myogenic component that may be blocked by a B3-ARA, thereby potentially reducing their deleterious effects on the upper tracts.

Study design, materials and methods

Chronic SCI rats (n=13, T9-10 transection with at least 4 weeks recovery) underwent cystometric evaluation under conscious, restrained conditions. Following a 60 minute control period and a vehicle challenge, escalating doses of the rat specific B3-ARA, CL-316,243 (at 1, 10 and 100 ug/kg), were administered every ~30 minutes.

Evaluated cystometric parameters included true and functional bladder capacity (TBC; FBC), compliance (C), NVC number (#) and maximum amplitudes (MA), voiding pressure parameters, voided volumes (VV) and voiding efficiency (VE). Data were analyzed using Friedman nonparametric ANOVA with Dunn's multiple comparison post-test. P<0.05 was considered statistically significant

Results

Urodynamic parameters were significantly improved in a dose-dependent fashion (Figure 1). FBC and C were markedly increased by ~60% and ~150%, respectively. NVC # and MA were reduced by ~70% and ~25%, respectively, although the NVC MA reduction did not achieve statistical significance (P=0.08). During spinal reflex-driven micturition, both opening and voiding pressures were reduced by ~15%, with no change in either closing pressures or VE (n=4 for the latter). TBC (n=4) and VV (n=13) tended to increase (mean ~50%), but these were not statistically significant

Interpretation of results

B3-ARA stimulation selectively reduces the hallmark characteristics of detrusor overactivity associated with suprasacral SCI (low compliance, NVCs), without adversely affecting the spinal micturition event. These findings suggest that a strong myogenic component may contribute to the neurogenic detrusor overactivity. The drop in opening and voiding pressures may suggest facilitation of voiding during the spinal micturition reflex, although the limited voiding efficiency data were unable to support this.

Concluding message

B3-ARA are capable of discriminating between high amplitude, non-voiding contractions during filling and the spinal micturition reflex-driven voiding contractions in chronic SCI rats, resulting in a dramatic reduction of the former with little adverse effect on the latter. These results are reminiscent of those from systemic vanilloid treatment [2]. While one is apparently targeting smooth muscle (B3-ARA), the other is directed at C-fiber nociceptors. This disparity may be explained by the generation of high amplitude NVC as a two part mechanism, that of low amplitude myogenic filling contractions from the bladder base resulting in high amplitude, C-fiber mediated reflex contractions of the bladder dome. Thus, B3-ARA may eliminate NVC by eliminating the initiating event, while vanilloid treatments eliminate the reflex response – the end result is similar for two entirely different mechanisms of action. These findings also support a clinical use of B3-ARA for the treatment of detrusor overactivity in patients with suprasacral SCI.

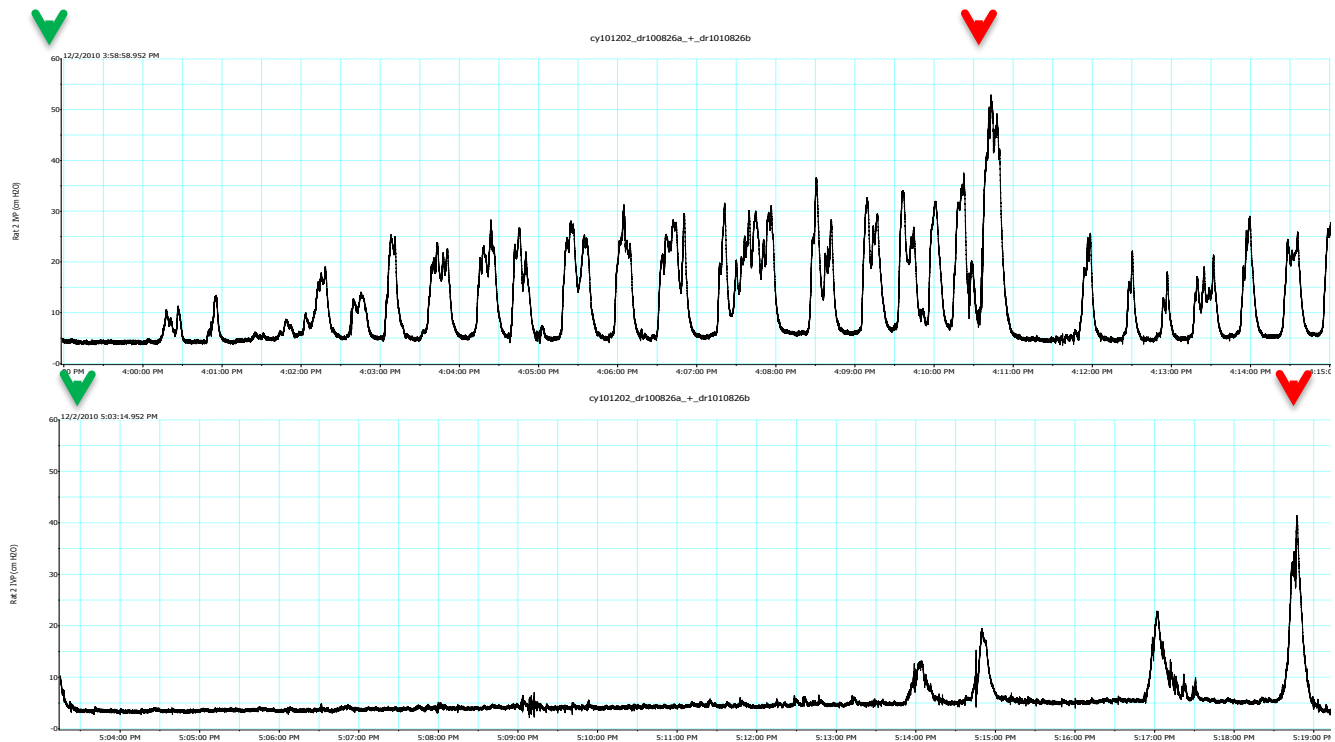


Figure 1 - Cystometric traces during conscious, restrained cystometry in a chronic SCI rat – The top trace is from the vehicle control period, while the bottom trace is following 100 $\mu\text{g}/\text{kg}$ of CL-316,243. Green arrows indicate the beginnings of micturition cycles, red arrows indicate voiding contractions. Note both the dramatic reduction in the number of NVC and the increase in bladder capacity.

References

1. Fraser MO. 2011. New Insights into the Pathophysiology of Detrusor-Sphincter Dyssynergia. *Current Bladder Dysfunction Reports*, 6: 93-99.
2. Cheng CL, de Groat WC. 2004. The role of capsaicin-sensitive afferent fibers in the lower urinary tract dysfunction induced by chronic spinal cord injury in rats. *Experimental Neurology*, 187: 445-54.

Disclosures

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