EFFECTS OF INTRATHECAL BACLOFEN ON BLADDER PAIN REFLEX RESPONSES IN THE HYPERSENSITIVE RAT

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INTRODUCTION:

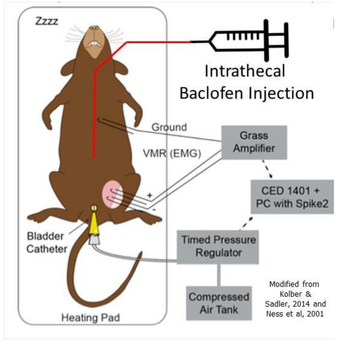
- Chronic pelvic pain syndromes (CPPS) such as painful bladder syndrome (PBS) are prevalent, often debilitating and difficult to treat.
- In many cases, pelvic floor dysfunction (hypertonia/spasticity) is a major contributor to the pathophysiology of these conditions.
- Therapies for CPPSs in general have targeted the peripheral organ, i.e., bladder or prostate, with limited efficacy.
- Central sensitization may contribute to pain and inflammation.
- Intrathecal baclofen (ITB) is an effective clinical treatment for severe spasticity, spasticity-related pain and neuropathic pain in animal models.
- This study examines the efficacy of ITB in a rat model of bladder pain.

METHODS:

- The bladder pain model was produced by intravesical zymosan (1%) administered to isoflurane-anesthetized female neonatal Sprague-Dawley rat pups. When adults (12-16 weeks), intravesical zymosan (Z) under isoflurane anesthesia was repeated 24 hours before testing.
- All rats were treated with urethral betadine and SQ ampicillin to minimize infection risk.
- In addition to the PBS treatment group (ZZ), three control groups were evaluated (n = 6-10 rats/group):

Group (designation)	Early-in-Life Treatment	Later-in-Life Treatment
Treatment (ZZ)	Anesthesia, urethral betadine swab, intravesical zymosan and SQ ampicillin (Z)	Z
Control 1 (ZA)	Z	Anesthesia, betadine and ampicillin (A)
Control 2 (AZ)	A	Z
Control 3 (AA)	A	A

- IT catheters were introduced into the cisterna magna and the tip advanced to the lumbar enlargement. All IT treatments were administered in 10 mcL saline followed by a 10 mcL catheter flush.
- EMG electrodes were placed in external oblique or pubococcygeus muscles (pelvic floor) to measure visceromotor responses (VMRs) to 20-sec urinary bladder distension (UBD) under isoflurane-urethane anesthesia. Preparation is depicted below:
- Cumulative ITB dose-responses were determined to graded UBDs (10-60 mm Hg,10 mm Hg increments, 20 s, 1 min between UBDs) and to repeated administrations of IT saline.
- In some ZZ rats, vasopressor responses to UBD were also measured directly via an indwelling femoral arterial cannula.



METHODS (CONT.):

- Using single ED_{50} doses (40 ng), the duration of ITB-induced VMR inhibition was assessed and the $GABA_B$ antagonist, CGP35348 (Tocris, Bristol, UK), evaluated on UBD-induced VMRs before and after ITB.

RESULTS:

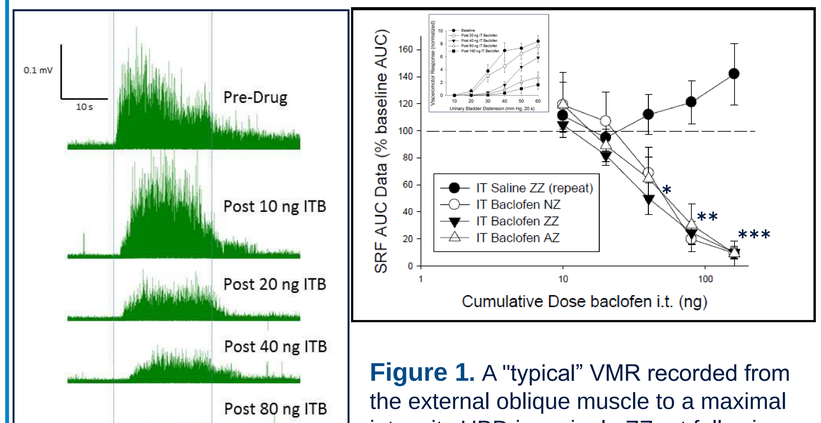


Figure 1. A "typical" VMR recorded from the external oblique muscle to a maximal intensity UBD in a single ZZ rat following cumulative dosing of IT baclofen is depicted on the left. The graph on the right depicts stimulus-response functions (SRFs) to cumulative ITB doses. Each point represents the mean ± SEM of the area measured under the graded stimulus-response curves (AUC) for a given ITB dose as a percent of the AUC for the baseline stimulus-response curve in the absence of baclofen (insert). In ZZ rats, ITB produced significant inhibition vs. IT saline at the three highest cumulative doses (ANOVA with post hoc comparisons, p<.05*, < .01**, <.001***). Both figures demonstrate the dose-dependent inhibitory effects of ITB on UBD-evoked VMRs in hypersensitized (ZZ) rats. The graph on the right shows that ITB is equally effective in control rats; results were similar in AA control rats (data not shown). Repeated IT saline produced no inhibition of VMRs.

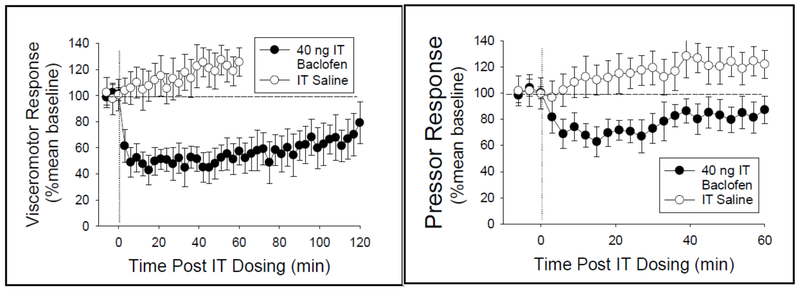


Figure 2. Left and right panels depict the onset and duration of a single 40-ng dose of ITB on repeated UBD-evoked VMRs and arterial blood pressure responses, respectively, over time compared to IT saline. UBDs were performed using a stimulus intensity of 60 mm Hg for 20 s repeated every 3 min. For both types of UBD-evoked responses measured with repeat IT saline, response magnitude increased over time. On the contrary, ITB inhibited VMR and pressor responses relative to baseline for at least 120 and 30 min, respectively.

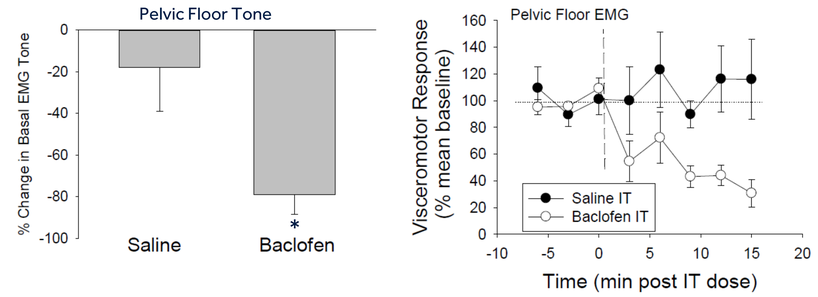


Figure 3. In ZZ rats, an ED_{50} dose of ITB (40 ng) significantly reduced baseline pelvic floor tone relative to IT saline (left panel). Hypersensitized ZZ rats (model of human PBS) are unique from all control rats in displaying increased pelvic-floor but not abdominal-muscle tone. The right panel shows the rapid onset and significant effect of ITB (40 ng) to inhibit UBD-evoked VMRs in comparison to IT saline for at least 15 min.

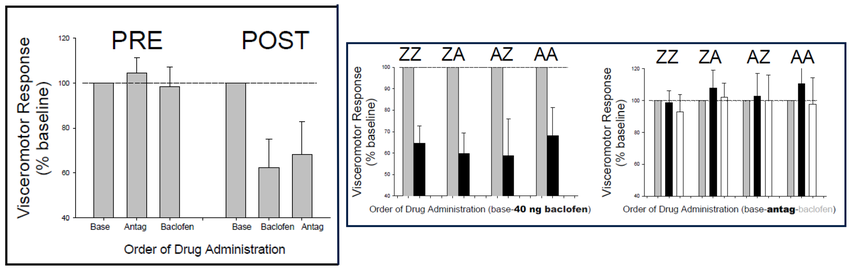


Figure 4. Effects of the selective, competitive $GABA_B$ antagonist, CGP35348 (30 mcg IT), on 40 ng ITB-induced inhibition of UBD-evoked VMRs. The left panel shows that pretreatment but not post treatment with the antagonist completely blocks inhibition of the pain response by baclofen. The right panel shows the same effect in the control groups when CGP35348 is administered before ITB.

CONCLUSIONS:

1. ITB dose-dependently inhibits reflex pain responses evoked by bladder distension in a rat model of PBS.
2. In the PBS rats, ITB significantly reduced baseline tone and evoked-pain responses recorded from the pelvic floor in response to bladder distension.
3. CGP35348 experiments demonstrate that baclofen effects are mediated at the level of the spinal cord via $GABA_B$ receptors.
4. Encouraging results in this rat model of PBS together with the proven clinical safety and efficacy of ITB infusion for severe spasticity suggest that clinical research of ITB in pelvic pain patients is warranted. Patients with concomitant pelvic floor hypertonia may be ideal.

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