

EFFECTS OF INTRAVESICAL INSTILLATION OF RESINIFERATOXIN ON BLADDER FUNCTION AND NOCICEPTIVE BEHAVIOR IN FREELY MOVING, CONSCIOUS RATS

Hypothesis / aims of study

Interstitial cystitis/painful bladder syndrome (IC/PBS) is an inflammatory disease characterized by bladder pain related to bladder filling, often coupled with urinary frequency. Therefore we tried to establish a new animal model that can evaluate bladder function and nociceptive behavior concurrently using freely moving, non-catheterized conscious rats, and evaluated the correlation of two symptoms (pain and frequency) following intravesical instillation of resiniferatoxin (RTx).

Study design, materials and methods

Female SD rats were used. Care and handling of animals were in accordance with institutional guidelines and approved by the Institutional Animal Care and Use Committee. RTx (0, 0.3 and 3 μ M) was instilled via a polyethylene catheter temporarily inserted into the bladder through the urethral orifice in a restraining cage. The rats were placed individually in a transparent metabolic cage, and then the incidence of nociceptive behavior (lower abdominal licking and freezing) was scored every 5 seconds for 15 minutes after intravesical instillation of RTx. Voided urine was collected continuously using a cup specially fitted to a force transducer for the measurement of bladder capacity. Fifteen minutes before collecting urine, distilled water (30mL/kg, po) was administered in order to increase urine production. In some animals, the bilateral pudendal nerves were transected in order to eliminate urethral sensory transmission two weeks before the experiment.

Results

Intravesical instillation of RTx decreased bladder capacity and, at the same time, increased licking and freezing behaviours although licking behaviour was more frequently observed compared to freezing. Whereas RTx-induced reduction in bladder capacity was unaffected by pudendal nerve transection, the immediate phase (0-5 min) of RTx-induced licking behavior was decreased in pudendal nerve-transected rats. However, the late phase (5-15 min) licking behavior still remained in pudendal nerve-transected rats. This late phase licking was attenuated in pudendal nerve-transected rats without water-loading although licking behavior was still enhanced after RTx stimulation compared with RTx-untreated, pudendal nerve-transected rats. Reduced bladder capacity and nociceptive behaviors after RTx treatment were also individually plotted in order to clarify their relationship. There was an apparent negative correlation between bladder capacity and licking behavior in pudendal nerve transected rats ($r=0.85$, $p<0.01$, $n=11$) whereas the correlation was not clearly observed in normal rats ($r=0.48$, $p>0.05$, $n=15$).

Interpretation of results

These results indicate that intravesical instillation of RTx decreases bladder capacity associated with increased licking behavior in freely moving, conscious rats. It seems likely that bladder afferent nerves control licking behavior and bladder capacity after pudendal nerve transection whereas an early phase of licking behavior appears to be induced by activation of urethral afferent nerves in the pudendal nerve in normal rats. Thus, at least three components are involved in the different steps of RTx-induced pain behavior; (1) the immediate response mediated by urethral afferents in the pudendal nerve, (2) the late-phase response evoked by direct stimulation to C-fiber afferents in the bladder and (3) gradual facilitation due to bladder wall distension induced by bladder filling.

Concluding message

Late-phase pain behavior (licking) enhanced by bladder filling and decreased bladder capacity after RTx treatment seem to well represent clinical symptoms found in patients with IC/PBS, such as bladder pain related to bladder filling and urinary frequency. Thus, simultaneous recordings of bladder activity and nociceptive behavior during bladder irritation with RTx in conscious rats could be a useful method for the study of mechanisms inducing bladder pain and the evaluation of new treatments of bladder hypersensitive disorders such as IC/PBS.

References

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ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by University of Pittsburgh Institutional Animal Care and Use Committee