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COMPARISON OF RAT CYSTITIS MODELS IN FREELY MOVING, CONSCIOUS CONDITIONS; CYCLOPHOSPHAMIDE AND ACETONE INDUCED ALTERATIONS IN VOIDING FUNCTION AND PAIN BEHAVIOR

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. However, it is not well characterized how these two symptoms (pain and frequency) are correlated following bladder inflammation. Therefore, we sought to establish a new animal model that can evaluate bladder function and pain behavior concurrently using freely moving, non-catheterized conscious rats, and examined nociceptive behavioral responses and their correlations with bladder dysfunction in two cystitis models, which were induced by cyclophosphamide (CYP) or intravesical instillation of acetone.
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. Cystitis was induced by interperitoneal injection of CYP (0, 100 and 200mg/kg) or intravesical instillation of acetone (0, 10, 30 and 50%) via a polyethylene catheter temporarily inserted into the bladder through the urethral orifice in a restraining cage. The rats were then placed individually in a transparent metabolic cage, and the incidence of nociceptive behavior such as freezing and lower abdominal licking was scored every 5 seconds. Voided urine was collected continuously using a cup specially fitted to a force transducer for the measurement of bladder capacity (voided volume per micturition). Before collecting the urine, distilled water (30mL/kg, po) was administered in order to increase urine production. After physiological measurements, plasma extravasation in the bladder was evaluated by measuring the content of Evans Blue that was injected intravenously (50 mg/kg) 15 min prior to removal of the bladder. In some animals, capsaicin (125mg/kg, sc) was injected in order to desensitize C-fiber afferents one week before the experiment.
Results
CYP (100mg/kg, ip) induced freezing behavior, but had no effect on bladder capacity or plasma extravasation. A high concentration of CYP (200mg/kg, ip) decreased bladder capacity and increased plasma extravasation as well as freezing behavior. In contrast, intravesical instillation of acetone (30%) decreased bladder capacity and increased plasma extravasation, but evoked freezing behavior less frequently compared with CYP-treated animals. A high concentration of acetone (50%) was needed to evoke obvious freezing behavior. In capsaicin pretreated rats, freezing behavior induced by CYP or acetone was similarly reduced. Furthermore, the decrease in bladder capacity in capsaicin-pretreated rats was attenuated when comparing with normal rats, although both groups exhibited equivalent plasma extravasation. Interestingly, the normalizing effects of C-fiber desensitization on bladder capacity appeared to be clearer in the CYP-group than the acetone-group.
Interpretation of results
CYP is known to be metabolized to acrolein and excreted into bladder. Acrolein seems to not only induce tissue injury, but also directly stimulate C-fibers because rats treated with low concentration CYP exhibited C-fiber-mediated freezing behavior without increasing plasma extravasation. In contrast, intravesical instillation of acetone is more likely to cause bladder tissue injury to induce inflammation and edema, resulting in urinary frequency and pain behavior. Thus, multiple factors, such as C-fiber stimulation, inflammation and edema seem to be involved in the development of urinary frequency, while freezing behavior appears to be more simply due to C-fiber activation.
Concluding message
There is a difference in the onset of urinary frequency and pain behavior such as freezing following two different types of bladder irritation. Simultaneous recordings of bladder activity and nociceptive behavior during bladder irritation could be useful for the study of mechanisms inducing bladder pain and the development of new treatments of bladder hypersensitive disorders such as IC/PBS.
References

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