Pharmacological modulation of urinary bladder inflammation in a rat model of cyclophosphamide-induced acute bladder pain

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Objectives

Cyclophosphamide (CYP)-induced cystitis is a well characterized model of subacute, inflammatory visceral pain in rats and mice1-3. This model is widely used and is considered one of the closest experimental model to bladder pain syndrome/interstitial cystitis.

Recently, we showed that a single injection of CYP induces visceral pain in female rats, characterized by both referred mechanical allodynia and hyperalgesia. Aspirin, ibuprofen, 2 non steroidal anti-inflammatory drugs (NSAIDs), and morphine, an opioid agonist, were able to reverse referred visceral pain induced by CYP4.

Our main objectives were to identify and quantify different key inflammatory mediators in urinary bladders and urines which may contribute to the antinociceptive effects of these drugs.

Methods

Animals: female Sprague Dawley rats (225-250 g)

Chemical cystitis: single intraperitoneal (i.p.) injection of CYP at a dose of 150 mg/kg in saline (5 mL/kg)

Pharmacological treatment:
- Aspirin - 300 mg/kg p.o.; Ibuprofen - 300 mg/kg p.o.; Vehicle (5% Na₂CO₃) - 5 mL/kg p.o.
- Morphine: 3 mg/kg s.c.; Vehicle (saline); 5 mL/kg s.c.

Macroscopic inflammatory parameters:
- Urinary bladder weight and wall thickness
- Macroscopic analysis (edema & hemorrhage)4)

Quantification of inflammatory mediators:
- Urinary bladders (Multiplex technology): pro-inflammatory cytokines (IL-1β and IL-6), monocytic chemotactic protein-1 (MCP-1) and vascular cell adhesion molecule (VCAM)
- Urines (enzyme immunoassays): prostaglandin E2 (PGE2), lipoxin A₄ (LXA₄) and 15-epi lipoxin

Schematic protocol:

Pharmacological treatments

Metabolic cages for urine collection

T = 5 min

T = 0

T = 4h

CYP or Saline i.p.

Sacrifice & Urinary bladder analysis

Conclusions

A single i.p. injection of CYP induces an acute inflammation in the urinary bladder 4h post-administration. This reaction is confirmed by high levels of pro-inflammatory cytokines, IL-1β and IL-6, and an increase in chemokine and adhesion molecules, suggesting a strong recruitment of monocytes/macrophages. High levels of lipid-derivated mediators are also present in urines. These metabolites play a key role in the regulation and resolution of acute cystitis. In summary, altered visceral sensation following CYP seems to be mediated by inflammatory reactions in the urinary bladder. Antinociceptive effects of NSAIDs are associated with a decrease in key inflammatory mediators such as IL-1β, IL-6 and PGE2, known to promote the sensitization of bladder nociceptors. In contrast, reversal of bladder pain by morphine may not be linked to a direct modulation of bladder inflammation.

References

(3) Lluel et al, ICS meeting, Toronto Canada, 2010.