N° 420

DEVELOPMENT AND VALIDATION OF A CLINICALLY-RELEVANT CHRONIC MODEL OF INTERSTITIAL CYSTITIS / BLADDER PAINFUL SYNDROME

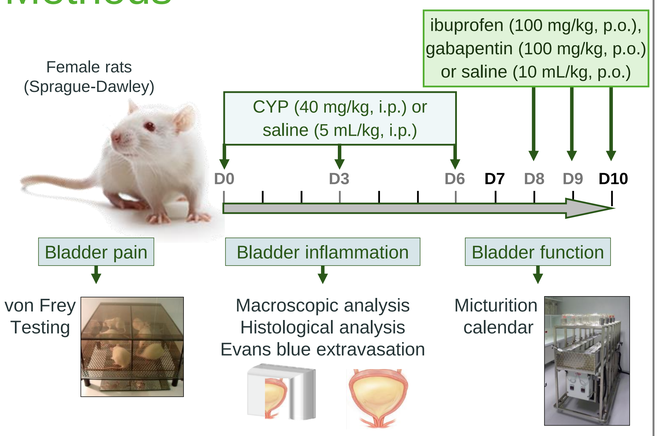
Sophie Chabot[1], Céline Augé[1], Murielle Méen[1], Véronique Guilloteau[1], Nathalie Vergnolle[2], Xavier Gamé[3, 4] and Philippe Lluel[1]

[1] Urosphere, Toulouse, France; [2] INSERM UMR1220, IRSD, Toulouse, France; [3] Urology Department, CHU Rangueil, Toulouse, France; [4] INSERM I2MC-UMR1048, CHU Rangueil, Toulouse, France

Objective

Interstitial cystitis / bladder painful syndrome (IC/BPS) is a chronic inflammatory disease characterized by visceral pain and urinary symptoms. A main limitation in IC/BPS understanding is the lack of appropriate preclinical model. Cyclophosphamide (CYP) is commonly used as an experimental model for IC/BPS in rodent. However, the proposed models are mainly acute and very aggressive, contrasting with what occurred in clinic, and often associated with severe toxicity. In addition, only few of them recapitulate the 3 hallmark symptoms of IC/BPS: bladder inflammation, pain and dysfunction. **Our aim was to develop and validate a chronic model of CYP-induced IC/BPS in rats that would share key features of the human disease**.

Methods



Nociceptive response was assessed by von Frey testing by applying, close to bladder, 8 von Frey filaments of increasing forces from 1 to 60 g. Scoring was as follows: 0 = no response; 1 = abdominal retraction; 2 = change of position; 3 = licking of the stimulated area.

Nociceptive threshold was defined as the von Frey force (in grams) at which a first response was obtained (stimulus perceived as painful).

Area Under the Curve (AUC) between 1-60 g is calculated by plotting individual score (in %) against each force from 1 to 60 g.

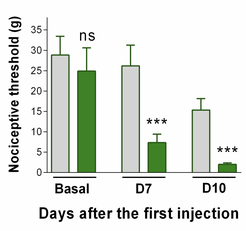
Bladder inflammation was evaluated by macroscopic analysis (weight, wall thickness and edema scores), histopathology (HE staining) and bladder vascular permeability measurement by quantification of extravasated Evans blue dye into the bladder 30 min after its injection (50 mg/kg, i.v.).

Bladder function was evaluated in metabolic cages. Number of micturition was recorded continuously overnight (which corresponds to the active phase in rodent) to establish micturition calendar.

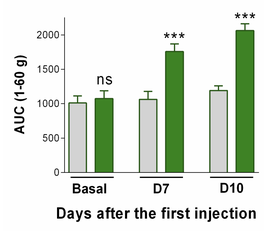
Results

Bladder pain

Allodynia



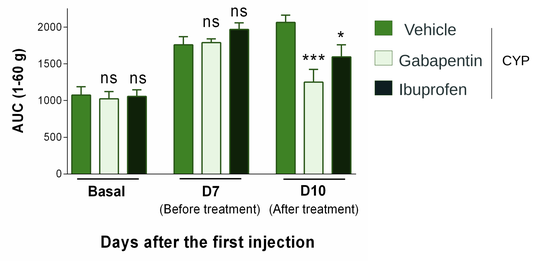
Hyperalgesia



Saline CYP

Values represent mean ± s.e.m. (n=11-12/group).
ns p>0.05, *** p<0.001, *vs* Saline (Mann Whitney test or Unpaired t-test)

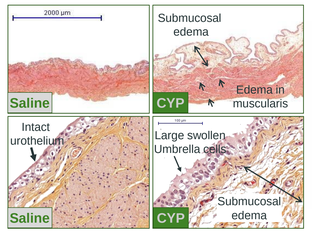
Validation with clinically relevant compounds



Values represent mean ± s.e.m. (n=11-12/group).
ns p>0.05, * p<0.05, *** p<0.001, *vs* Vehicle (Unpaired t-test w/ or w/o Welch's correction)

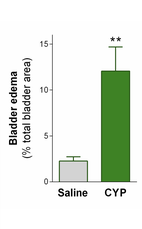
Bladder inflammation (at D10)

Histological characteristics

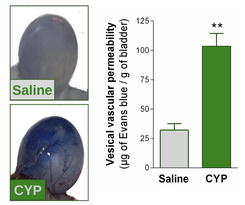


Representative pictures of HE-stained bladder. Histological features in CYP-injected rats are: strong edema, focal urothelium damage and absence of massive infiltrate.

Vesical vascular permeability

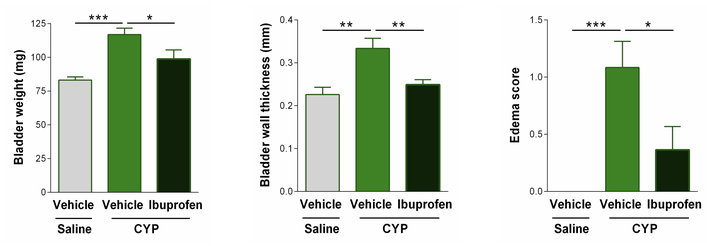


Values represent mean ± s.e.m. (n=10/group).
** p<0.01 (Unpaired t-test w/ Welch's correction)



Representative bladder after Evans blue i.v. injection. Values represent mean ± s.e.m. (n=5-7/group).
** p<0.01 (Mann Whitney test)

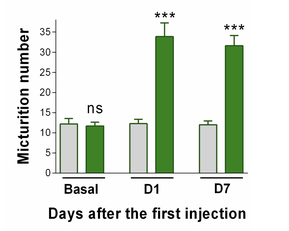
Validation with clinically relevant compound



Values represent mean ± s.e.m. (n=11-12/group).
* p<0.05, ** p<0.01, *** p<0.001 (Unpaired t-test w/ or w/o Welch's correction or Mann Whitney test)

Bladder dysfunction

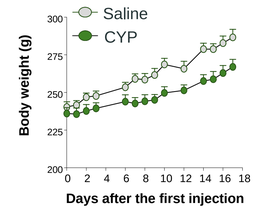
Voiding frequency (12h recording)



Saline CYP

Values represent mean ± s.e.m. (n=9-11/group).
ns p>0.05, *** p<0.001, *vs* Saline (Unpaired t-test)

Protocol is well tolerated by rats



No mortalities occurred in this protocol. Values represent mean ± s.e.m. (n=9-12/group).

Conclusions

We developed and validated a new chronic model of IC/BPS in female rat. **This model recapitulates the key features of human non-ulcerative IC/BPS**, which accounts for more than 80% of IC patients. These include **sustained visceral pain** and **mild inflammatory response in bladder tissue** characterized by edema, focal urothelium injury and absence of massive infiltrate or tissue hemorrhage. In accordance with the human situation, bladder pain and inflammation are **associated with urinary frequency**.

This new model is of significant value for better understanding pathophysiological mechanisms and evaluating new therapies for IC/BPS.

31st Annual EAU Congress, 11-15 March 2016, Munich, Germany