Experimental evidence of the effect of the inhibition of phosphodiesterase type 4 by rolipram in conscious rat with bladder outlet obstruction.

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MATERIALS & METHODS

Partial bladder outlet obstruction

Female Wistar rats weighing 200-225 g were anesthetized with isoflurane. The bladder and the proximal urethra of all rats were exposed through a lower midline abdominal incision. An extraperitoneal metal rod with an external diameter of 1 mm, was placed around the urethra to provide a calibrated loop for a single 4-0 silk suture inducing a partial BOO. The metal rod was removed after calibrated urethral ligature and the abdominal wall was closed. Non-obstructed control rats underwent the same surgical procedure than obstructed rats without inserting a proximal urethral ligature.

Cystometry

Six weeks after the first surgery, animals were anesthetized with isoflurane (1-1.2%). A trumpet tip polyethylene catheter (PE50), filled with saline, was inserted through the dome into the bladder and secured with a suture. The urinary bladder was slowly filled to check eventual leakage. The abdominal wall was then closed. Cystometry was then performed in conscious rats. Rats were placed in a diuresis cage for freely moving animals. The bladder catheter was connected to a pressure transducer (Elcomatic EM 750, UK) and a syringe-pump KD5-200 (Kd Scientific, Phymep, Paris) with a T-tube, allowing simultaneous bladder perfusion and bladder pressure monitoring. The intravesical pressure was recorded continuously using an acquisition card (DAIS, 1000, Computer Boards, hyperscience, Paris) and a specific data acquisition software (Ephy, CNRS, France).

RESULTS

Bladder outlet obstruction (BOO) is a common etiology of overactive bladder (OAB). BOO may result from benign prostatic hyperplasia, urethral stricture or congenital abnormality. The functional changes that develop in response to BOO include detrusor instability, elevated voiding pressure and the presence of a residual urine volume. The morphological changes associated with BOO are smooth muscle hyperplasia and hypertrophy developed to produce the elevated pressures necessary to maintain effective bladder emptying.

The BOO model in rats mimics the voiding patterns of patients with severe bladder outlet obstruction in that animals develop an increased bladder capacity, high voiding pressures, residual urine volume and detrusor instability. The intensity and the duration of the cAMP second messenger signalling within the detrusor smooth cells is partly regulated by phosphodiesterase type 4 (PDE4) enzymes. Increase in cAMP levels by PDE4 inhibition has been reported to relax various types of smooth muscle cells.

We aimed to investigate the effect of the selective inhibition of PDE4 activity by an archetypal PDE4 inhibitor, rolipram, in an experimental model of OAB induced by partial BOO in conscious rats.

The bladder was continuously infused (50µl/min) with saline (at room temperature). After a stabilization period of 30 min to check the quality of the recording and the frequency of micturition, the bladder was emptied before the 30 min control period cystometry. For each group, the treatment (rolipram, 3 mg/kg or vehicle DMSO 30 % IP) was delivered at the end of the control period and before the beginning of the 60 min cystometry recording. During cystometry, the animals were continuously observed by the experimenter to discriminate between moving artefacts and bladder contractions. Voiding and non voiding bladder contractions were noted.

Effect of rolipram on urodynamic parameters in sham rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of non voiding contractions</th>
<th>Amplitude of non voiding contractions (mmHg)</th>
<th>Intravesical pressure (mmHg)</th>
<th>AUC of non voiding contractions (mmHg.s)</th>
<th>Duration of non voiding contractions (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle group (n=6)</td>
<td>7.0 ± 1.7</td>
<td>8.5 ± 0.8</td>
<td>0.1 ± 0.2</td>
<td>158.0 ± 7.9</td>
<td>26.1 ± 1.7</td>
</tr>
<tr>
<td>Treated period</td>
<td>7.0 ± 1.7</td>
<td>8.5 ± 0.8</td>
<td>0.1 ± 0.2</td>
<td>158.0 ± 7.9</td>
<td>26.1 ± 1.7</td>
</tr>
<tr>
<td>Rolipram group (n=6)</td>
<td>6.7 ± 1.7</td>
<td>4.3 ± 1.3</td>
<td>1.2 ± 0.8</td>
<td>77.5 ± 3.3</td>
<td>26.1 ± 3.3</td>
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</tbody>
</table>

**Note:** after rolipram administration, no voiding contractions were observed in sham group.

CONCLUSIONS

- Partial BOO elicited bladder hypertrophy and an increase in non voiding contractions. In BOO rats with a marked bladder hypertrophy, rolipram, a specific PDE4 inhibitor, reduced detrusor hyperactivity. Confirmation of these results would indicate that there is a potential for PDE4 inhibitors in the treatment of OAB.