Role of the Autonomic Nervous System in Catheter-Induced Urethral Inflammation

Key Words
Catheters
Urethra
Autonomic nerves
Inflammation

Abstract
We have studied role of the autonomic nervous system on experimentally induced urethral inflammation in the rat. Urethral inflammation was produced by inserting latex strips into the urethra. The effects of different experimental procedures were assessed by using a 4-grade inflammation scale based on histological findings. Rats pretreated with the nonspecific catecholamine depleters reserpine or quinethidine had a significantly less severe urethral inflammation than vehicle-treated controls. The severity of urethral inflammation was increased in spontaneous hypertensive rats, which have an increased sympathetic tone as compared to the normotensive rats. Propranolol, a nonselective β-adrenergic receptor antagonist reduced and butoxamine, a β2-antagonist, significantly reduced the urethral inflammation. Neither phenoxybenzamine (nonselective) nor prazosin (α1) or yohimbine (α2), α-adrenergic receptor antagonists, affected the degree of urethral inflammation. These data taken together indicate that the autonomic innervation of the urethral mucosa is critically involved in the inflammatory reaction and that the use of β2-antagonist may be a treatment alternative in the future for the treatment of catheter-induced inflammation.

During the last years, much attention has been paid to the catheter material and its role in urethral inflammation [1–2]. Experimental findings have shown that the degree of catheter-induced inflammation is related to the chemical composition of the catheter material [3–5]. It is possible that substances released from the catheter material trigger processes which involve the activation of the peripheral nervous system. In recent studies, we have shown that the sensory [5, 6] and the autonomic innervation [5] of the urethral mucosa is involved in the inflammatory reaction. In the present study, we have more in detail investigated the role of the autonomic nervous system in catheter-induced urethral inflammation.

Materials and Methods
The study was carried out on Sprague-Dawley female albino rats weighing 220–260 g (Anticimex, Sollentuna, Sweden). The rats were anaesthetised with chloral hydrate (0.4 g/kg) and positioned supine with the legs extended. A lower midline incision was made and a
cystotomy performed. Strips (1-mm wide) of the surface of the mid-section of the latex catheter to be tested were inserted into the urethra as far as the external meatus. The bladder was closed around a catheter of similar material and the proximal end cut flush with the skin to which it was fixed with black silk. The rats received strips of the same latex catheter brand and batch after different treatments. Ten rats underwent cystotomy (group 1) and 10 rats serving as controls were tested with latex strips (group 2). The influence of the autonomic nervous system on urethral inflammation was evaluated by sympathectomy using guanethidine as well as reserpine (groups 3–6). Guanethidine produces a depletion of catecholamines by destroying the sympathetic postganglionic neurons without injuring catecholaminergic neurons of the CNS [7]. Guanethidine (5 mg/day) was administered to 10 rats for 6 weeks before the latex strip was given (group 3). As a control, guanethidine vehicle without guanethidine was given (group 4). Since guanethidine may activate the immune system, another group of rats received a daily subcutaneous injection of another catecholamine depletor, reserpine (0.25 mg/kg/day), starting 2 days before the induction of urethral inflammation (group 5). As a control, reserpine vehicle without reserpine was given (group 6). To further study the influence of the sympathetic nervous system, a strain of rats having an abnormally high activity in the sympathetic nervous system [spontaneously hypertensive (SH) rats] was used. These SH rats derive from the original pedigreed NIH strain which has a tonically increased tone [9]. Ten SH rats were given latex strip (group 7). The normotensive Wistar-Kyoto (WKY) rat which derives from the same pedigree strain was used as a control (group 8). Ten rats were treated with propranolol (20 mg/kg, 3 times/day) to obtain a nonselective β-adrenergic blockade (group 9). To produce a nonselective α-adrenergic blockade, phenoxybenzamine (30 mg/kg, once daily) was used (group 10). For β-receptor blockade, M32 MTC (80 mg/kg, 3 times/day) was used (group 11), and for β2-blockade, we used butoxamine (50 µg/kg, 3 times/day; group 12). For α1-receptor blockade, prazosin (2 mg/kg, 5 times/day) was used (group 13), and for α2-receptor blockade, we used yohimbine (3 mg/kg, once daily; group 14). After 72 h of latex strip administration, the bladders were perfused with 5% glutaraldehyde in a 300-mosm phosphate buffer also containing 0.1 M sucrose, the rats were then sacrificed. Cystourethrectomy was carried out and a 5-mm long segment was dissected out. The specimens were postfixed in a glutaraldehyde, osmicated (2% osmium tetroxide in phosphate buffer for 4 h), rinsed in buffer, dehydrated in acetone and embedded in Vestopal W. Semithin longitudinal sections were cut on an LKB ultratome. The sections were stained with toluidine blue and used for light microscopy. The effect of different experimental procedures on the rat urethra was assessed using a 4-graded scale: 1 = no edema or other inflammatory sign; 2 = mild edema and loss of surface epithelium, no inflammatory exudate; 3 = inflammatory infiltrate, epithelial loss; 4 = inflammatory infiltrate, epithelial loss, exudate and hemorrhage (fig. 1). For the statistical analysis of degrees 1–4 of inflammation between the different groups, the Kruskal-Wallis test with multiple comparisons was used.

Results

The results of the present study are summarized in table 1. In the rats undergoing cystotomy only, the degree of inflammation was minimal. In the rats to which the latex strip was applied, the degree of inflammation was
Table 1. Inflammatory effect on the urethral mucosa assessed by a 4-graded scale

<table>
<thead>
<tr>
<th>Group</th>
<th>Experimental procedure</th>
<th>Sample size</th>
<th>Median</th>
<th>Min.</th>
<th>Max.</th>
<th>Sum</th>
</tr>
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<tr>
<td>1</td>
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<td>10</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>latex</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>guanethidine + latex</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>vehicle + latex</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>reserpine + latex</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>vehicle + latex</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
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<td>10</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>37</td>
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<tr>
<td>8</td>
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<td>10</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>29</td>
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<td>9</td>
<td>phenoxybenzamine</td>
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<td>3</td>
<td>3</td>
<td>4</td>
<td>33</td>
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<td>3</td>
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<td>3</td>
<td>2</td>
<td>4</td>
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<td>2</td>
<td>1</td>
<td>3</td>
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<td>10</td>
<td>3</td>
<td>2</td>
<td>4</td>
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</tr>
<tr>
<td>14</td>
<td>butoxamine</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>21</td>
</tr>
</tbody>
</table>

Scale 1 = No edema or other inflammatory sign; 2 = mild edema and loss of surface epithelium; 3 = inflammatory infiltrate, epithelial loss; 4 = inflammatory infiltrate, epithelial loss, exudate and hemorrhage.

1 vs. 2: p < 0.01; 1 vs. 10: NS; 2 vs. 10: NS; 3 vs. 4: p < 0.001; 5 vs. 6: p < 0.002; 7 vs. 8: p < 0.02; 2 vs. 9: NS; 2 vs. 14: p < 0.02.

Discussion

The degree of experimentally induced urethral inflammation reflects changes in the activity of the autonomic nervous system. Reduction of urethral inflammation was produced by sympathectomy prior to inducing urethral inflammation by application of the latex strip. This is in accordance with our previous study [6]. The results of the present study show that selective blockade of β-adrenergic, but not α-adrenergic receptors reduced the catheter-induced inflammation. Since the β₂-antagonist butoxamine reduced the catheter-induced inflammation, the anti-inflammatory effect of the nonselective β-adrenergic antagonist was likely mediated by its β₂-receptor blocking effect. The contribution of the β₂-agonists to urethral inflammation is possibly mediated by the release of vasoactive amines, adenosine triphosphate and neuropeptide Y from sympathetic postganglionic neurons. In several studies, it has been shown that especially the vasoactive amines have a major influence on the immune system [9-11]. It is, therefore, likely that the effect of β₂-agonists is due to the inhibition of the release of any or all of these compounds.

The similarities of the results obtained in the present study on catheter-induced urethral inflammation and the results obtained by Levine, Basbaum et al. [10-12] in experimental and clinical arthritis indicate that β₂-agonists may be tried in the treatment of catheter-induced inflammation.

Acknowledgements

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References


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Congress Calendar

22.10.-23.10.1992
Munich
FRG

20th Munich Endourological Symposium

5.11.-7.11.1992
Vienna
Austria

1st International Symposium on Microsurgery in Urology

4.12.-5.12.1992
Berlin
FRG

8th Intern. Steglitz Paediatric Surgical Congress 1992

4.6.-5.6.1993
Rome
Italy

5th International Meeting of Andrology: Corporal Veno-Occlusive Dysfunction, Diagnosis and Treatment
The invited speakers will be: G.M. Coli (I), A. Isidori (I), K.P. Junemann (D), T.F. Lue (USA), G.F. Menchini Fabbri (I), G. Papp (H), A. Pereira da Silva (P), D. Pozza (I), P. Rigatti (I), M. Rosello Barbara (E), I. Saenz de Tejada (USA), W. Stackl (A), C. Stief (D), L. Subrini (F), P. Torreclla (E), S. Toldo (IT), K. Virag (F), L. Wagenknecht (D), E. Wespes (B).

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Information:
Dr. Leyh, Dr. Hofmann, Dr. Pickl
Department of Urology, Technische Universität München
Klinikum rechts der Isar, Ismaningerstrasse 22
D-W-8000 München 80 (FRG)
Tel.: 89-4140 2577

Information:
Drs. Dr. Schramek
c/o Wiener Medizinische Akademie
Vienna (Austria)
Tel.: 43-1-4271.65
43-1-42.13.84
Fax: 43-1-42.13.83.6

Information:
Dr. F. Schier
Kinderchirurgie, Univ. Klinikum Steglitz
Hindenburgdamm 30
D-W-1000 Berlin 45 (FRG)
Tel.: 030/7964181
Fax: 030/7964141

Information:
Dr. Diego Pozza
Centro di Andrologia e di Chirurgia Andrologica
to Flaminia Nuova 280
I-00191 Roma (Italy)
Tel. + Fax: +39-6-3270741