Epinephrine Reduces the Severity of Catheter-induced Urethral Inflammation by Action at the $\alpha_2$-adrenoceptors

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Summary—We have studied the contribution of epinephrine to experimentally induced urethral inflammation in the rat. Inflammation was induced by inserting latex strips into the urethra. The effects of various experimental procedures were assessed according to a 4-point scale based on histological findings. The results showed that 0.5 mg/kg epinephrine decreased the severity of catheter-induced urethral inflammation. This effect was blocked by the $\alpha_2$-adrenergic agonist, yohimbine, but not by $\alpha_1$ (prazosin), $\beta_1$ (M32 MTC), or $\beta_2$ (butoxamine) antagonists. The results suggest that the suppressive effect of epinephrine is mediated by action at the $\alpha_2$ adrenergic receptor.

The use of urethral catheters may lead to urethritis with subsequent stricture formation (Edwards et al., 1983). Factors influencing inflammation and stricture formation are trauma during insertion, duration of use, infection and individual patient response. Cytotoxic substances released from the catheter material may also exacerbate the urethritis and thus the stricture formation (Engelbart et al., 1978; Graham et al., 1983). We have shown that the autonomic nervous system may contribute to the severity of catheter-induced urethral inflammation in the rat (Nordling et al., 1990, 1992a). The release of catecholamines from sympathetic efferent neurons produces physiological changes associated with inflammation (Levine et al., 1988), while the destruction of efferent sympathetic neurons by chemical sympathectomy is associated with decreased inflammation. Nordling et al. (1992b) reported that adrenal medullectomy significantly reduced the severity of experimental urethritis in the rat, and that infusion of epinephrine or the $\beta_2$-agonist salbutamol reproduced the severity of catheter-induced urethral inflammation to the degree observed in non-medullectomised catheter-induced inflammation. Neither epinephrine nor salbutamol, however, could induce urethral inflammation in rats which had undergone adrenal medullectomy and sympathectomy. These data suggest that a low dose of epinephrine contributes to catheter-induced urethral inflammation through action at the $\beta_2$-adrenoceptors, whereas a high dose reduces the severity of this inflammation.

The aim of the present study was to establish the site of action of epinephrine when administered at a high dose.

Material and Methods

The study was carried out on female albino rats, Sprague-Dawley, weight 220–290 g (ALAB, Stockholm, Sweden). The rats were anaesthetised with chloralhydrate (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) from the surface of the midsection of a latex catheter 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 only (group 1) and 10 rats serving as controls were tested with latex strips only (group 2). To elucidate the effect of epinephrine on catheter-induced urethral inflammation it was co-administered with a receptor selective adrenergic antagonist ($\alpha_1$, $\alpha_2$, $\beta_1$ or $\beta_2$). The effect of epinephrine was also compared with that of various receptor selective adrenergic agonists ($\alpha_1$, $\alpha_2$, $\beta_1$, or $\beta_2$).

The effect of epinephrine on urethral inflammation was evaluated by the administration of epinephrine (0.5 mg/kg) (group 3); vehicle (control) (group 4); epinephrine (0.5 mg/kg) and vehicle (group 5); epinephrine (0.5 mg/kg) and prazosin ($\alpha_1$-antagonist) (10 mg/kg) (group 6); epinephrine (0.5 mg/kg) and yohimbine ($\alpha_2$-antagonist) (15 mg/kg) (group 7); epinephrine (0.5 mg/kg) and M32 MTC ($\beta_1$-antagonist) (80 mg/kg) (group 8); or epinephrine (0.5 mg/kg) and butoxamine ($\beta_2$-antagonist) (25 mg/kg) (group 9). Catheter-induced urethral inflammation was also assessed in rats treated with phenylephrine ($\alpha_1$-agonist) (1 mg/kg) (group 10); clonidine ($\alpha_2$-agonist) (0.1 mg/kg) (group 11); isoproterenol ($\beta_1 + \beta_2$ agonist) (0.25 mg/kg) (group 12); salbutamol ($\beta_2$ agonist) (0.5 mg/kg) (group 13); or epinephrine (low dose) (0.05 mg/kg) (group 14). Epinephrine and the adrenergic agents were dissolved in 0.2% ascorbic acid, then mixed in a slow release preparation with paraffin oil and arlacel (4:25:5.0:0.75 V/V/V) as previously described (Borkowski and Quinn, 1985). This preparation was administered subcutaneously every 3 days starting 6 days before and ending 3 days after induction of the catheter-induced inflammation. All surgery was performed by one of the authors to avoid differences related to technique.

After 72 h of latex strip administration the bladder was perfused with 5% glutaraldehyde in a

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**Fig.** Effect of experimental procedures on the rat urethra assessed on a 4-point scale: 1—no oedema or other inflammatory sign; 2—mild oedema and loss of surface epithelium; 3—inflammatory infiltrate, epithelial loss; 4—inflammatory infiltrate, epithelial loss, exudate and haemorrhage.
300 mM phosphate buffer also containing 0.1 M sucrose; the rats were then sacrificed. Cystoureterectomy was carried out and a 5-mm segment was dissected. The specimens were post-fixed in glutaraldehyde, osmicated (2% osmium tetroxide in phosphate buffer, 4 h), rinsed in buffer, dehydrated in acetone and embedded in vestopal W. Semi-thin longitudinal sections were cut on an LKB ultratome. The sections were stained with toluidine blue and used for light microscopy. The effect of the experimental procedures on the urethra was assessed with a "blind" observer using a 4-point scale: 1 = no oedema or other inflammatory sign; 2 = mild oedema and loss of surface epithelium, no inflammatory exudate; 3 = inflammatory infiltrate, epithelial loss; 4 = inflammatory infiltrate, epitelial loss, exudate and haemorrhage (Fig.). For statistical analyses of degrees 1–4 of inflammation between different groups the Kruskal-Wallis test with multiple comparisons was used.

Results

The results are summarised in the Table. In the rats undergoing cystotomy only, the degree of inflammation was minimal. In rats to which the latex strips were applied the degree of inflammation was significantly increased (P < 0.001). Epinephrine produced a significant (P < 0.02) reduction in inflammation when compared with the vehicle treated. The severity of urethral inflammation in the epinephrine-treated rats was significantly antagonised (P < 0.001) by co-administration of yohimbine but unaffected by prazosin, M32 MTC or butoxamine. In comparison with vehicle-treated controls, clonidine significantly (P < 0.001) reduced urethral inflammation, whereas phenylephrine, isoprotenerol or salbutamol had little or no effect.

Discussion

The results of the present study show that epinephrine in a high dose (0.5 mg/kg) reduces the severity of catheter-induced urethral inflammation. This reduction was significantly antagonised by the selective α2-adrenergic antagonist, yohimbine, but not by selective α1 (prazosin), β1 (M32 MTC) or β2 (butoxamine) antagonist. In addition, repeated infusion of the α2-adrenergic agonist clonidine but not selective α1 (phenylephrine), β1 + β2 isoprotenerol) or β2 (salbutamol) agonists, resulted in decreased severity of the urethral inflammation. The results indicate that at low doses, epinephrine contributes to urethral inflammation by the release

<table>
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<tr>
<th>Group no.</th>
<th>Experimental procedure</th>
<th>Sample procedure</th>
<th>Median</th>
<th>Min</th>
<th>Max size</th>
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Kruskal-Wallis test with multiple comparisons. The calculated P values are based on the rank sum differences between the groups.

1 versus 2 = P < 0.001
3 versus 4 = P < 0.001
3 versus 10 = P < 0.001
3 versus 11 = P < 0.001
3 versus 12 = P < 0.005
4 versus 10 = NS
4 versus 11 = NS
4 versus 12 = NS
5 versus 6 = NS
5 versus 7 = NS
5 versus 8 = NS
5 versus 9 = NS

1 = no oedema or other inflammatory sign; 2 = mild oedema and loss of surface epithelium; 3 = inflammatory infiltrate, epithelial loss, 4 = inflammatory infiltrate, epithelial loss, exudate and haemorrhage.
of pro-inflammatory non-catecholaminergic factors from sympathetic postganglionic terminals. This effect would be mediated by action at the presynaptic β2-adrenergic receptors (Nordling et al., 1992b). On the other hand, a high dose of epinephrine would inhibit this release through action at the presynaptic α2-adrenoceptors. Increased knowledge of the contribution of the autonomic nervous system to catheter-induced inflammation may lead to the development of new and effective drugs, thus preventing catheter-induced urethritis, pain and stricture formation.

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References

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