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EFFECT OF PROTAMINE PRETREATMENT ON DETRUSOR HYPERACTIVITY INDUCED BY INTRAVESICAL CAPSAICIN IN ANAESTHETIZED GUINEA-PIGS.

Aims of Study

Protamine complexes glycosamminoglycan mucosal layer and can destroy bladder urothelium facilitating the penetration of bacteria and irritants within the bladder wall (1, 2). However, it has been recently shown that, beyond the above-mentioned barrier function, the urothelium could have a role in the modulation of both afferent and efferent neurotransmission (3, 4). Functional TRPV-1 (capsaicin) receptors are expressed on urothelial cells and their stimulation induce the release of nitric oxide and ATP from these cells (3, 4). In turn, both nitric oxide and ATP could exert a variety of effects on smooth muscle cells, efferent and sensory nerve terminals. In this study we investigated the effect of protamine pretreatment on capsaicin-induced bladder hyperactivity in anaesthetized guinea-pigs.

Methods

Male Dunkin-Hartley guinea-pigs (400-500 g) were anaesthetized with urethane (1.6 g/kg, sc). A double-lumen polyethylene catheter was inserted into the bladder dome for intravesical administrations, liquid infusion, and pressure recordings. Following a baseline cystometry performed with saline (100 µl/min for 90 min, Period 1), protamine sulphate (15 mg in 1.5 ml) (Group 2), or saline (Group 1) were instilled intravesically and kept for 30 min. Urethral leakage of solutions was avoided by clamping the preputium during the treatment. Afterwards, the clamp was removed and the cystometry was repeated by infusing saline (100 µl/min for 90 min, Period 2); the solution for intravesical infusion was then changed, and capsaicin (10 µM) was infused for 90 min (Period 3). The following urodynamic parameters were evaluated in each period (mean±s.e.m. of n experiments): bladder capacity (BC, µl), mean amplitude of micturition contractions (MAC, mmHg), pressure threshold for micturition reflex (PT, mmHg), and duration of micturition (MD, s). Results were analyzed through Student's t test for unpaired or paired data, when applicable.

Results

Basal urodynamic parameters were similar in both groups. Protamine treatment did not change urodynamic parameters as compared to saline. In controls (Group 1), the PT for the activation of micturition reflex decreased during the 2nd Period as compared to baseline. Capsaicin infusion induced bladder hyperactivity in both protamine- and saline-pretreated animals; although this hyperactivity was more prominent in saline-pretreated guinea-pigs, the difference was not significant. The MD increased in both groups although not significantly, wheras other urodynamic parameters did not change following capsaicin, as compared to baseline values.

Table

		Period 1	Period 2	Period 3
Group	Parameter	Baseline (n)	Saline (n)	Capsaicin (n)
1	BC (µl)	1802±167 (11)	2047±233 (12)	883±105** (12)
2	BC (µl)	1620±252 (12)	1357±193 (10)	845±73* (9)
1	MAC (mmHg)	24±4 (11)	24±5 (12)	26±6 (12)
2	MAC (mmHg)	22±4 (12)	29±6 (10)	24±4 (9)
1	PT (mmHg)	9.3±1.6 (11)	5.7±1.2** (12)	5.2±1.3 (12)
2	PT (mmHg)	7.8±1.8 (12)	7.8±1.9 (10)	6.2±1.6 (9)
1	MD (s)	58±20 (11)	33±4 (12)	57±12 (12)
2	MD (s)	36±4 (12)	35±5 (10)	46±6 (9)

*P<0.05 and **P<0.01 vs previous period.

Conclusions

Intravesical capsaicin elicits bladder hyperactivity in guinea-pigs, as previously assessed in both rats and hamsters (5). In a previous study in guinea-pigs, intravesical capsaicin induced an inhibition of the micturition reflex, however cystometries were carried out at high flow rates, where excitatory effects could not be highlighted (6). The urodynamic changes accompanying capsaicin-induced hyperactivity vary in different species, possibly reflecting both the nature and the amount of neurotransmitters contained in TRPV-1-expressing neurons and the differential expression of receptor types at the post-junctional level. In the guinea-pig bladder TRPV-1-expressing neurons contain significant amounts of both tachykinins and CGRP, and both excitatory tachykinin NK1 and NK2, and inhibitory CGRP receptors are expressed on detrusor muscle and postganglionic fibers (5, 7). Because of this arrangement, it is likely that a compensation between excitatory and inhibitory signals occurs, and capsaicin does not change the MAC. In rats, where both detrusor muscle and postganglionic fibers express tachykinin but not CGRP receptors, capsaicin increases the MAC, whereas in hamsters the same stimulus decreases the MAC, possibly because of the paucity of tachykinins in this species (5). Protamine neither changed the urodynamic parameters during cystometries, nor significantly altered capsaicin-induced bladder hyperactivity, suggesting that transmitters released by the urothelium do not affect neurotransmission in this paradigm. Despite this, a decrease in the PT during the 2^{nd} period was observed in controls but not in protamine-treated animals. This decrease in the PT could be interpreted as the animal correlate of the sensitization that occurs in humans following repeated bladder distensions (8), therefore mediators released by the urothelium (prostanoids?) might be involved in this effect.

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