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Title (type in CAPITAL LETTERS, leave one blank line before the text) CHARACTERIZATION OF ACROLEIN-INDUCED URINARY BLADDER OVERACTIVITY IN ANAESTHETISED RATS

Aims of Study Cyclophosphamide, an anti-neoplastic agent, produces severe haemorrhagic cystitis in humans via a metabolite, acrolein, that is excreted in urine (1). Cyclophosphamide induced cystitis in rats is characterised by detrusor hyperactivity and oedema (2). Since bladder hyperactivity results from *in vivo* metabolism of cyclophosphamide to acrolein, urinary bladder acrolein concentrations may vary, depending on the strain of rat as well as factors that modulate liver microsome activity, hydration and renal blood flow. In order to minimise the effects of such variables, a model in which acrolein is infused directly into the bladder was developed.

Methods: Female Sprague Dawley rats were anaesthetised with isoflurane (2.5% at 2 L/min) and urethane (1.2 g/kg, s.c.). The dome of the bladder was cannulated with fluid-filled PE-50 tubing and a venous port was established. Rats were then placed on a heating pad (37°C) and the bladders were perfused with saline or acrolein in a buffer containing citric acid (50 mM, pH 5.2) at a rate of 100 µl/min for up to 6 h. Bladder pressure was monitored using a Gould polygraph and Power Lab data acquisition system.

Results: During baseline saline infusion, the mean urinary bladder contraction amplitude was 24.5 ± 1.9 mmHg (n = 66) and the bladder inter-contraction interval was 6.3 ± 0.36 min (n = 66). Direct infusion of acrolein (100, 200, 300 and 600 µM) into the bladder produced a dose-dependent increase in contraction amplitude and decrease in inter-contraction interval. Significant changes ($p < 0.01$) in steady state amplitude and inter-contraction interval readings were achieved after 2 h of acrolein (200 or 300 µM) infusion. The effects of a 1 h acrolein (200 or 300 µM) infusion into the

bladder were not reversed by a subsequent 3-h saline infusion. Acrolein-induced changes in amplitude and inter-contraction interval were modulated by administration of test compounds. Atropine (1 mg/kg, i.v.) significantly ($p < 0.01$) decreased amplitude without affecting inter-contraction interval. The ganglionic blocking agent, hexamethonium (0.03, 0.3, 3 mg/kg, i.v.) significantly ($p < 0.05$) decreased both amplitude and inter-contraction interval. By contrast, the cyclooxygenase inhibitor, indomethacin (0.3, 1, and 6 mg/kg, i.v.), significantly ($p < 0.01$) decreased contraction amplitude while significantly increasing inter-contraction interval. Upon histopathological examination of the urinary bladder, there was diffuse, transmural acute inflammation characterised by severe oedema, venular congestion, urepithelial ulceration and minor inflammatory cell infiltration.

Conclusions Acrolein infused directly into the urinary bladder of anaesthetised rats produces a dose-dependent decrease in bladder inter-contraction interval and an increase in bladder contraction amplitude. The effects of acrolein last for at least 3h following cessation of acrolein administration. Administration of atropine, hexamethonium or indomethacin differentially affected acrolein-induced changes in bladder activity. These results suggest that a model of acrolein-induced urinary bladder hyperactivity in anaesthetised rats may be useful in evaluating novel pharmacologic agents for treatment of overactive bladder.

References

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