Human detrusor muscle

Role of inflammatory mediators in interstitial cystitis

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ABSTRACT

This PhD dissertation is based on investigations carried out at Smooth Muscle Laboratory, Departments of Urology and Pathology, Herlev Hospital, University of Copenhagen, Denmark, first as a research fellow granted by the University of Copenhagen and later as a research fellow at the Department of Urology, Herlev Hospital, Denmark.

Interstitial cystitis (IC), a great enigma of urology today, is a chronic sterile inflammatory disease of the bladder of unknown etiology characterized by urinary frequency, urgency, nocturia and suprapubic pain. Although there are many theories, the etiology of the condition remains unknown. Current evidence from clinical and laboratory studies confirms that mast cells play a central role in the pathogenesis and pathophysiology of IC. Cysteinyl leukotrienes (CysLTs) are potent proinflammatory mediators released by mast cells upon activation. CysLTs have a wide range of biological effects, including ability to evoke smooth muscle contraction. It was the aim of this dissertation to investigate whether CysLTs receptors were expressed in the human detrusor and to functionally characterize these receptors. CysLTs induced increase in cytosolic free Ca^{2+} in cultured human detrusor smooth muscle cells (HDSMC) and increase in contractile force in human detrusor preparations. Leukotriene D4 enhanced histamine induced increase in cytosolic free Ca^{2+} and contractile force. Patients with IC and detrusor mastocytosis had increased levels of urinary leukotriene E4. In a pilot study, oral treatment of IC patients with montelukast, a CysLT1 antagonist, reduced urinary frequency, nocturia and pain thus supporting the role of CysLTs in IC. Finally, the studies included investigations on the factors responsible for the migration of mast cells to the detrusor in IC. Stem cell factor and cytokines are possible candidates. Human detrusor smooth muscle cells cultured under inflammatory conditions express and secrete several cytokines and growth factors including MCP-1, RANTES, eotaxin, IL-8, IL-6 and SCF. HDSMC secretory function is likely to influence mast cell number and migration to the detrusor in IC.