ABSTRACT

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Title of Doctoral Thesis **On Purinoceptors in the Rat Urinary Bladder**

Both divisions of autonomic nervous system regulate the urinary bladder function. In addition to the classical autonomic neurotransmitters, noradrenaline and acetylcholine, other autonomic transmitters and signalling molecules play important roles in the physiology and pathophysiology of the lower urinary tract. Interstitial cystitis (IC) is a chronic inflammation of the bladder of non-infectious origin and unclear etiology and pathophysiology, characterized by urinary frequency, urgency and sharp pelvic pain that fade away while urinating. Non-adrenergic, non-cholinergic (NANC) systems influence functional responses in the inflamed bladder. The aim of this study was to investigate purinergic and nitrergic mechanisms involved in the IC pathogeneses and in urodynamic dysfunction.

Methods: A single dose of i.p. injection of cyclophosphamide caused CYP-induced cystitis; a condition very similar to IC and for that property was used as a model of the inflamed bladder throughout our experiments. The organ bath set was employed in investigation of functional responses. The expression of the receptors was studied by immunohistochemistry and the degree of the inflammation was studied macroscopically and microscopically as well as according to mast cell infiltration into detrusor muscle.

Key findings: The studies showed that both contractile and relaxatory functions are altered in the state of inflammation. ATP- and acetylcholine-evoked contractions are reduced in cystitis. The reduction of P2X purinoceptor response does not depend on the increased level of nitric oxide (NO) while the reduction of the muscarinic receptor response does. The β-adrenoceptor relaxations of the bladder are reduced in cystitis but they did not seem to be involved with NO. The ATP-evoked relaxations are increased in cystitis, but only the purinergic response in the bladder body involves NO. It has been shown that P1A1 purinoceptors are expressed in the urinary bladder in all parts of the bladder wall; the expression was especially intense in the urothelium and detrusor. An activation of those purinoceptors causes bladder relaxation. During the CYP-induced cystitis the amount of purinoceptors seemed to be decreased, affecting also the bladder function. P1A3 proved to be a contractile purinoceptor while P1A2B seemed to be relaxatory. Pre-treatment with a nitric oxide synthase (NOS) inhibitor prevents many of the changes induced by CYP-treatment. A muscarinic receptor-NO coupling seems to be absent in the regulation of the inflammation development in contrast to its control of function in cystitis.

Conclusions: NANC mechanisms play significant roles in IC development and in the control of the disease. ATP, adenosine and NO are of great importance in the inflammation progression and potential drug targets.

Key words: urinary bladder, purinoceptor, ATP, adenosine, nitric oxide, cyclophosphamide-induced cystitis, inflammation, rat