Purinergic Effects in the Rat Urinary Bladder

Functional Studies of Cyclophosphamide Treatment on Afferent and Efferent Mechanisms

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 15 mars 2013 kl. 13:00.

av

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I. **Aronsson P**, Carlsson T, Winder M & Tobin G.
A novel *in situ* urinary bladder model for studying afferent and efferent mechanisms in the micturition reflex in the rat. *Submitted.*

II. **Aronsson P**, Andersson M, Ericsson T & Giglio D (2010).
Assessment and characterization of purinergic contractions and relaxations in the rat urinary bladder.
Basic & clinical pharmacology & toxicology 107(1): 603-613.

III. Giglio D, **Aronsson P**, Eriksson L & Tobin G (2007).
In vitro characterization of parasympathetic and sympathetic responses in cyclophosphamide-induced cystitis in the rat.
Basic & clinical pharmacology & toxicology 100(2): 96-108.

IV. **Aronsson P**, Carlsson T, Winder M & Tobin G.
Studies of the micturition reflex initiated by stretch stimulation of the urinary bladder wall in normal and cyclophosphamide-treated anaesthetized rats. *Manuscript*.

V. **Aronsson P**, Johnsson M, Vesela R, Winder M & Tobin G (2012). Adenosine receptor antagonism suppresses functional and histological inflammatory changes in the rat urinary bladder.
Autonomic neuroscience: basic & clinical 171(1-2): 49-57.

VI. **Aronsson P**, Vesela R, Johnsson M, Tayem Y, Wsol V, Winder M & Tobin G.
Inhibition of nitric oxide synthase prevents muscarinic and purinergic functional changes and development of cyclophosphamide-induced cystitis in the rat. *Submitted*.

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ABSTRACT

Pathological conditions in the lower urinary tract are common and have a great impact on the quality of life for the patients suffering from such disorders. In this thesis cyclophosphamide (CYP)-induced cystitis, a well-established rat model of inflammatory bladder diseases such as bladder pain syndrome/interstitial cystitis (BPS/IC), has been employed to study the role of purinergic transmission in the normal and inflamed state. The main focus was to characterize purinergic functional contractile and relaxatory parameters, studied *in vitro*, *in vivo* and *in situ*, for which the latter a novel method was developed and validated. The P2X1 purinoceptor was, in concordance with previous studies, found to be the major contractile subtype, whereas P2Y purinoceptor(s) with different sensitivities to the purinergic agonists ADP/ATP and UDP/UTP were shown to be relaxatory. Furthermore, the adenosine $P1A_{2B}$ purinoceptor was demonstrated to play a functional relaxatory role.

Using the novel *in situ* experimental setup presented in this thesis it was concluded that stretch-evoked contralateral contractions, mediated by afferent nerve fibers, were increased during cystitis. This was in contrast to most other contractile studies, in which the response in the inflamed bladder was generally decreased. This enlargement to stretch stimulus was found to be due to both cholinergic and purinergic factors, of which the latter were more pronounced at lower stimulation intensities.

Since the purinoceptors are often mentioned in the context of inflammation, studies were also conducted to investigate the role of purinergic, as well as of cholinergic and nitrergic, blockade in the development of cystitis. It was concluded that blockade of the $P1A_1$ purinoceptor or inhibition of nitric oxide synthase can alleviate the change in contractile function to CYP-induced bladder inflammation, which was confirmed by the study of several inflammatory findings common in cystitis.

Taken together, the purinergic transmission is altered during cystitis, and the changes are likely predominantly on the afferent side of the micturition reflex arc. The novel *in situ* setup can be modified and used to study various afferent factors, without interfering with the contractility of the bladder. Future therapeutic drugs targeting purinoceptors on afferent neurons may provide a valuable addition to the currently used medicines. The fact that blockade of purinoceptors at the same time may have a beneficial impact on the inflammation itself may prove to be useful in the treatment of inflammatory conditions in the lower urinary tract.

Keywords: purinoceptor, cystitis prevention, detrusor, bladder function, ATP, adenosine, nitric oxide
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