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.

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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 P1A2B 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 P1A1 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