

FUNCTIONAL RELEVANCE OF P2X4 RECEPTOR IN THE BLADDER

Hypothesis / aims of study

Purinergically mediated neurotransmission contributes significantly to the initiation of bladder smooth muscle (BSM) contractions in many animal models and becomes prominent in patients under certain pathologic conditions. The P2X1 receptor is the most abundantly expressed purinergic subtype in the bladder and is responsible for ATP mediated detrusor contractions. The P2X4 receptor expression has also been identified in the detrusor, although little is known about its distribution or functional relevance. In the present study, the role of P2X4 receptor activation in mediating BSM contractile responses was determined and the expression of this purinoceptor in bladder tissue was examined.

Study design, materials and methods

Longitudinal rat bladder strips without mucosa were mounted in organ baths containing Krebs's solution at 37°C and were stretched to 1.5 grams of tension. After equilibration, the amplitude of bladder contractions induced by either electrical field stimulation (EFS) or by exogenous administration of α - β -methylene ATP ($\alpha\beta$ meATP) was measured before and after sequential incubation of P2X1 receptor antagonist NF449 and P2X4 receptor antagonist 5-BDBD. In addition, the amplitude of EFS-induced contractions, as well as the level of bladder spontaneous activity (SA), was measured before and after the administration of ivermectin (IVC), a positive modulator of P2X4 receptor. P2X4 receptor expression was determined by western blotting in BSM tissue and isolated BSM cells.

Results

Bladder contractions induced by $\alpha\beta$ meATP that persisted after P2X1 receptor inhibition were abolished in the presence of P2X4 receptor antagonist 5-BDBD. Administration of IVC significantly increased the amplitude of EFS induced contractions, while 5-BDBD decreased both the total and the purinergic component of nerve-mediated bladder contractions. EFS-induced contractions that were resistant to atropine and NF449 were eliminated by subsequent treatment with 5-BDBD. Exposure to IVC significantly increased the amplitude of bladder SA however, the increase in amplitude of SA induced by IVC was prevented by pre treatment with 5-BDBD. Western blot analysis detected P2X4 receptor expression in lysates from both detrusor tissue and cultured BSM cells.

Interpretation of results

P2X4 receptor expression in BSM and the functional effects of P2X4 receptor modulators are consistent with a role in modulating mechanical responses to purinergic stimuli in the bladder. The activation of P2X4 receptor may enhance purinergic neuromuscular transmission and promote the generation of SA.

Concluding message

This study suggests that changes in P2X4 receptor expression or in its signaling may contribute to the development of pathologic conditions which are associated with alterations in purinergic responses.

Disclosures

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