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PROPIVERINE AND OXYBUTYNIN INHIBIT CA2+ INFLUX MEDIATED BY THE ACTIVATION OF A SPECIFIC RECEPTOR, TRANSIENT RECEPTOR POTENTIAL VANILLOID SUBTYPE 1 (TRPV1)

Hypothesis / aims of study

Detrusor overactivity is a widespread clinical problem and difficult to treat. For over a decade, intravesical vanilloids such as capsaicin and resiniferatoxin have been used as promising agents in the treatment of neurogenic detrusor overactivity. Vanilloids exert their activity through the transient receptor potential vanilloid subtype 1 (TRPV1), a nonselective cation channel. In the bladder TRPV1 has been shown to be localized in various cell types, including the urothelium, detrusor muscle and fibroblasts [1]. TRPV1-positive afferent neurons have been shown to perform an active role in decreasing the micturition threshold in neurogenic detrusor overactivity [2]. Thus, TRPV1 may play a significant role in the pathophysiology of bladder. Anticholinergic agents such as oxybutynin and propiverine are widely used for the treatment of overactive bladder. Oxybutynin and propiverine are metabolized in the intestine and liver to form active metabolites, N-desethyl-oxybutynin (DEOB) and its N-oxide metabolites (1-methyl-4-piperidyl diphenylpropoxyacetate N-oxide: P-4(N→O), 1-methyl-4-piperidyl benzilate N-oxide: DPr-P-4(N→O)), respectively. These metabolites are suggested to contribute to pharmacological effects of parent compounds. The effects of anticholinergic agents on the afferent neurons have become of interest in recent years. Thus, this study was conducted to clarify the effects of oxybutynin, propiverine and their metabolites on the TRPV1 function in HEK293VR11 cells expressed heterologously this receptor.

Study design, materials and methods

The measurement of Ca^{2+} influx in HEK293VR11 cells expressing TRPV1 was performed as previously described [3].

Results

Capsaicin (1-1000 nM) increased the Ca^{2+} influx in HEK293VR11 cells in a concentration dependent manner. This effect was effectively antagonized by capsazepine, a specific antagonist of TRPV1, indicating the mediation by TRPV1. Notably, propiverine at concentrations of 50, 100 and 300 μM inhibited concentration-dependently capsaicin-induced Ca^{2+} increase in HEK293VR11 cells (Fig. 1). Similar effect was also observed by oxybutynin at concentrations of 30-300 μM. On the other hand, DEOB, P-4(N→O) and DPr-P-4(N→O) had little effect on the capsaicin-induced Ca^{2+} increase in these cells. To further confirm antagonistic effects of anticholinergic agents, their direct binding activities of TRPV1 by radioligand binding assay using [^{3}H]resiniferatoxin are now under investigation.

Interpretation of results

The major findings of this study are that 1) capsaicin-induced Ca^{2+} influx through the activation of TRPV1 has been developed in HEK293VR11 cells expressing this receptor subtype and 2) anticholinergic agents, propiverine and oxybutynin widely used in the treatment of overactive bladder, are able to antagonize the capsaicin-induced Ca^{2+} influx in the concentration dependent manner. On the other hand, their metabolites had little inhibitory effects on the TRPV1-mediated Ca^{2+} increase in these cells.

Concluding message

The present study has firstly demonstrated that propiverine and oxybutynin may inhibit the activation through TRPV1 in the bladder. Thus, we believe that this work will contribute significantly to the further understanding of therapeutic effects of propiverine and oxybutynin in patients with overactive bladder.

References:
[1] Proc Natl Acad Sci USA (2001) 98; 13396-13401.
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[3] Life Sci (2006) 79; 2303-2310.

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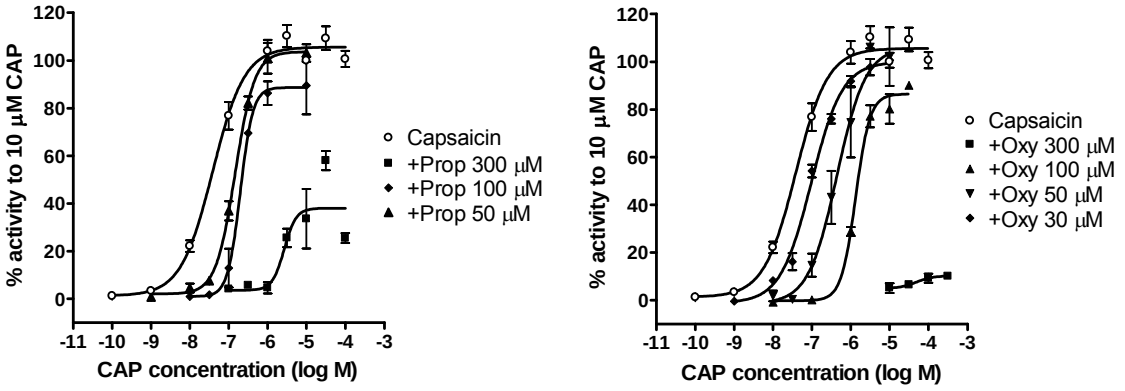

Fig. 1. Inhibitory effects of propiverine (50-300μM□) and oxybutynin (30-300 μM) on the capsaicin (CAP)-induced Ca^{2+} increase in HEK293VR11 cells expressing TRPV1

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