

Fig. 1. Effect of quinpirole in the absence & presence of remoxipride. * $p < 0.001$; † $p < 0.01$.

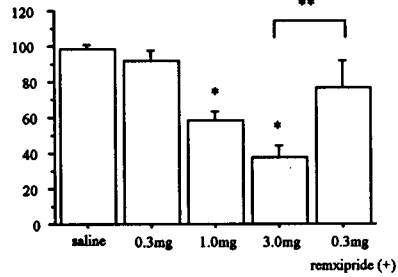


Fig. 2. Effect of MPTP in the absence & presence of remoxipride. * $p < 0.001$; ** $p < 0.05$.

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| H. Seshita, M. Yoshida, A. Inadome, M. Yono, Y. Miyamoto, S. Ueda |
| Department of Urology, Kumamoto University School of Medicine, Kumamoto, Japan |
| THE EFFECT OF A NOVEL PYRROLE DERIVATIVE POTASSIUM CHANNEL OPENER, NS-8 ON THE HUMAN BLADDER. |

Aims of study

Potassium channels play a role in the physiologic and pathophysiologic regulation of detrusor smooth muscles (1). It is known that some reports have investigated the effects of ATP-dependent potassium channel openers, cromakalim and pinacidil on human bladder (2). These drugs have been shown to induce hyperpolarization of the cell membrane which leads to smooth muscle relaxation. Potassium channels except ATP-sensitive channels also have been confirmed the existence in various tissue. NS-8 is a newly synthesized pyrrole derivative designed as a high conductance calcium sensitive potassium channel opener. Large conductance calcium dependant potassium channels have been reported in various tissues including detrusor (3). Previously, it has been reported that the effects of NS-8 were caused opening of potassium channels and subsequent hyperpolarization in isolated rat detrusor strips. In this study, We evaluated the effects of NS-8 on the isolated human detrusor smooth muscles.

Methods

Human detrusor strips were obtained from 11 male and 2 female patients (mean age; 68.5 years) undergoing cystourethrectomy because of bladder malignancy. The detrusor strips were mounted in thermostatically controlled organ baths filled with oxygenated Krebs-Henseleit solution for isometric tension recordings. And the relaxant effects of NS-8 were investigated for the contractile responses induced by KCl (20 mM and 100 mM), carbachol (0.01 μ M-100 μ M), and 5 mM CaCl_2 , electrical field stimulation (EFS; 3 sec trains, supra maximal voltage, duration 0.3 msec, main interval 120 s, frequency 2-60 Hz) were observed. The effects of pretreatment with various potassium channel blockers, glibenclamide, iberiotoxin, on inhibitory response induced by NS-8 were also evaluated.

Results

NS-8 (0.01 μ M-10 μ M) caused a concentration-dependent decrease in contraction induced by KCl in human detrusor smooth muscle. The relaxant effect was greater in 20mM KCl than in 100mM KCl. Pretreatment with 0.1 μ M iberiotoxin, a high conductance calcium-sensitive potassium channel blocker significantly inhibited the effects of NS-8, but 0.1 μ M glibenclamide, an ATP-sensitive potassium channel blocker little inhibited the effects of NS-8. NS-8 (0.1 μ M-10 μ M) had an inhibitory effect on contraction induced by EFS. The inhibitory effect of NS-8 on EFS induced contraction was greater in the presence of atropine than in the absence of atropine. NS-8 (0.1-10 μ M) had little inhibitory effects on contractions induced by carbachol (0.01 μ M-100 μ M) and 5 mM CaCl_2 .

Conclusions

The present data suggests that the actions of NS-8 are associated with an efflux of potassium channel on human detrusor smooth muscles, and that NS-8 may be an useful agent for atropine-resistant bladder instability.

References

1. J. Urol., 155, 1454-1458, 1995.
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3. J. Pharmacol. Exp. Ther., 283 : 1193-1200, 1997.

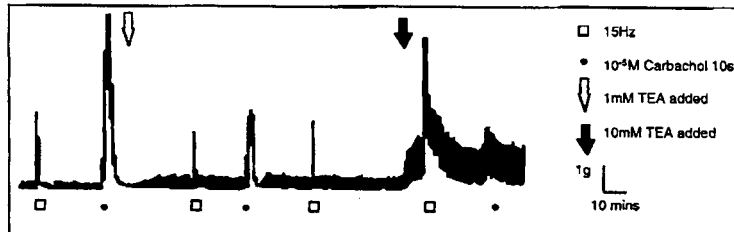
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| R. McCoy, G. McMurray, M.J. Drake and A.F. Brading |
| University Department of Pharmacology, Oxford, UK |
| EFFECT OF TETRAETHYLAMMONIUM CHLORIDE ON ISOLATED HUMAN DETRUSOR SMOOTH MUSCLE STRIP RESPONSES TO CARBACHOL AND ELECTRICAL STIMULATION. |

Aim of the study: The blockade of potassium channels in smooth muscle should increase the response of events mediated by action potentials, such as neurotransmitter release and excitation-contraction coupling. The aim of this study was to investigate the role of potassium channels in the contractile responses evoked by carbachol and intrinsic nerve stimulation in isolated human detrusor smooth muscle strips, with the use of, the nonspecific potassium channel blocker, tetraethylammonium chloride (TEA).

Methods: Whole normal human detrusor (N=4) was obtained from cadaveric organ donors and transported to the laboratory in cold Krebs solution (ca 4°C). The dome region of the detrusor was selected for study. The mucosa was carefully removed and smooth muscle strips (1x1x5mm) dissected with the aid of a binocular dissection microscope. The strips were mounted in 0.2ml superfusion organ baths at an initial tension of one gram. The organ baths were constantly perfused with carboxygenated Krebs solution (37±0.1°C, pH 7.4) and the strips were allowed to equilibrate for ninety minutes. Repeatable control responses to both 10⁻⁵M Carbachol and 15Hz stimulation were obtained and the mean result determined. Subsequently, responses to carbachol and 15Hz stimulation were determined in the presence of 1mM and 10mM TEA added in a cumulative manner. Responses are expressed in g/mg of tissue and as a percentage of the control tissue response to contractile agents. A paired t-test was used to establish statistical significance of the results, a value of p<0.05 proving significance.

Results: An example of an experimental trace is shown below for reference.



A concentration dependent increase, both in frequency and magnitude, of spontaneous contractile activity was observed in all strips studied upon addition of TEA. In addition, an increase in intrinsic tone of a magnitude of 0.15g/mg was observed in only one strip upon addition of 1mM TEA, whereas an increase in tone of 0.29±0.06g/mg was recorded in 44.8% of total strips upon addition of 10mM TEA.

As shown in the table below, isolated human detrusor smooth muscle strip responses to carbachol was significantly reduced during TEA-sensitive potassium channel blockade. In contrast, the responses to intrinsic nerve stimulation were potentiated substantially under the same conditions (10mM TEA present).