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S. Seki, Y. Igawa, K. Kaidoh, O. Ishizuka, O. Nishizawa and K.-E. Andersson*

Department of Urology, Shinshu University School of medicine, Matsumoto, Japan and Department of Clinical

ROLE OF DOPAMINE D2 RECEPTORS FOR MICTURITION AND MPTP (N-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine) - INDUCED BLADDER HYPERACTIVITY IN CONSCIOUS RATS

AIMS OF STUDY

Previous studies using anesthetized animals have suggested that dopamine D2 receptors are involved in facilitation of the micturition reflex. [1-2] However, anesthesia itself may affect the results of such studies. No studies on the role of dopamine D2 receptors for micturition in conscious animals have been reported. By administration of MPTP, which is known to cause degeneration of dopaminergic neurons in the substantia nigra, an experimental model of Parkinson's disease has previously been developed in primates.[3-4] The aims of the present study were to investigate in conscious rats; 1) the effects of selective D2 receptor agonism and antagonism on micturition; 2) whether acute administration of MPTP had any effects on micturition; and if so, 3) whether D2 receptors may be involved in the effects of MPTP.

METHODS

Female Sprague-Dawley rats were used. A catheter was implanted into the bladder through the dome and a separate catheter into a jugular vein under general anesthesia. Three or four days after the operation, cystometric investigations were performed without any anesthesia before and after intravenous (i.v.) administration of quinpirole (D2 receptor agonist; 0.01-0.1mg/kg) and MPTP (0.3-3mg/kg) in the absence and presence of remoxipride hydrochloride (D2 receptor antagonist; 1mg/kg). Analysis was performed for a 20-minute period before and after drug administration, and the percentage change of urodynamic parameters (micturition volume, micturition intervals, and micturition pressure) were calculated. All results are expressed as means ± SE. Student's t-test was used to determine the significance of differences between the baseline and post-administration values. Mann-Whitney test was used to determine the significance of differences between the absence and presence of remoxipride.

RESULTS

Quinpirole 0.01mg/kg (n=8) did not cause any significant change in micturition. Quinpirole 0.03mg/kg (n=8) significantly ($p<0.05$) decreased micturition volume (73 ± 8.2 % of the base-line value) and tended to decrease micturition interval (82 ± 7.7 %, $p=0.05$; Fig. 1.). When given at 0.1mg/kg (n=8), the effects of quinpirole on these parameters were more pronounced (10 ± 1.8 % and 14 ± 1.5 %, $p<0.001$; Fig. 1.)

Remoxipride (0.1,0.3,1.0mg/kg, n=6 in each) did not cause any significant change in micturition parameters. Pretreatment with remoxipride (1mg/kg i.v, n=6) significantly ($p<0.05$) attenuated the effects of quinpirole (0.1mg/kg) on micturition volumes and intervals (96 ± 11.4 % and 96 ± 12.0 %, respectively; Fig. 1.).

MPTP 0.3mg/kg (n=9) significantly ($p<0.05$) decreased micturition volume (83 ± 4.6 % of the base-line value) and increased the micturition pressure (113 ± 3.6 %), but did not affect micturition interval (91 ± 5.9 %; Fig. 2.). MPTP 1 mg/kg (n=9) significantly ($p<0.05$) decreased micturition volumes (57 ± 5.5 % of the base-line value) and micturition intervals (59 ± 4.9 %; Fig. 2.) and increased the micturition pressure (by 114 ± 3.7 %). When given at 3 mg/kg (n=9), the effects of MPTP on these parameters were more pronounced (36 ± 5.7 %, 38 ± 6.4 % and 129 ± 15.4 %, respectively; Fig. 2.). Pretreatment with remoxipride (1mg/kg, n=7) significantly ($p<0.05$) attenuated the effects of MPTP (3 mg/kg) on micturition volumes and intervals (82 ± 16.5% and 77 ± 14.5 %, respectively; Fig. 2.).

CONCLUSIONS

The present results obtained in conscious rats with quinpirole and remoxipride support the view suggested by previous studies in anesthetized animals that dopamine D2 receptors are involved in facilitation of the micturition reflex. The present results also suggest that acute administration of MPTP can induce bladder hyperactivity in conscious rats, involving activation of D2 receptors. This model may be useful for studies of drug effects on bladder hyperactivity.

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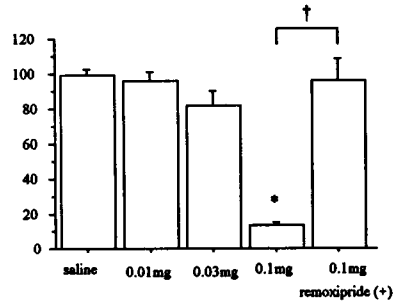

Fig. 1. Effect of quinpirole in the absence & presence of remoxipride. * p<0.001; † p<0.01.

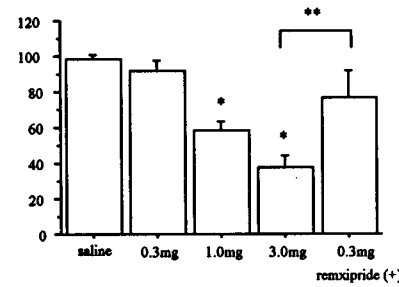

Fig. 2. Effect of MPTP in the absence & presence of remoxipride. * p<0.001; ** p<0.05.

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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 pinancidil 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 μM-100 μM), 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 inhibtory responce induced by NS-8 were also evaluated.

Results

NS-8 (0.01 μM-10 μM) caused a concentration-dependent decrease in contraction induced by KCl in human detrucer smooth muscle. The relaxant effect was greater in 20mM KCl than in 100mM KCl.

Pretreatment with 0.1 μM iberiotoxin, a high conductance calcium-sensitive potassium channel blocker significantly inhibited the effects of NS-8, but 0.1 μM glibenclamide, an ATP-sensitive potassium channel blocker little inhibited the effects of NS-8. NS-8 (0.1 μM-10 μM) had a 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 μM) had little inhibitory effects on contractions induced by carbachol (0.01 μM-100 μM) and 5 mM $CaCl_2$