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NICORANDIL, A KATP CHANNEL OPENER AND NITRIC OXIDE DONOR, WAS EFFECTIVE TO REDUCE THE BLADDER OVERACTIVITY.

Hypothesis / aims of study

ATP-sensitive potassium-channel (K_{ATP} channel) openers have been shown to inhibit unstable bladder contractions without affecting the normal voiding reflex (1). Nicorandil, which has been used for angina, has a unique feature as a K_{ATP} channel opener and nitric oxide (NO) donor. The purpose of this study was to investigate the activity of nicorandil on murine models of overactive bladder. The efficacy of nicorandil on bladder overactivity was compared with that of an another K_{ATP} channel opener which also acts as a nitrate, KRN2391 (2), a prototypical K_{ATP} channel opener, pinacidil and with the antimuscarinic drug, oxybutynin. In addition to the conventional overactive bladder models such as ones with C-fiber mediated bladder overactivity and partial urethral obstruction, the experiment was done on the nNOS deficient mice. The mice with targeted disruption of nNOS gene (nNOS KO) result in voiding abnormalities (3). nNOS KO develop bladder hypertrophy due to the deficient outflow relaxation. nNOS KO has urinary frequency presumably due to the decreased threshold of afferent firing of the bladder detrusor. These features of the abnormal urination propose that nNOS KO is a plausible model of human overactive bladder.

Study design, materials and methods

1. C-fiber mediated bladder overactivity model. Female Wistar rats were preemptively treated intravesically with nicorandil (10 g/kg/min or 30 g/kg/min), KRN2391 (100 g/kg/min), or pinacidil (30 g/kg/min) prior to the intravesical administration of acetic acid. 2. Partial urethral obstruction model. Female Wistar rats were created the urethral obstruction by approximating urethra by 1mm in a diameter. Fifty days after obstruction, rats were treated with nicorandil (1mg/kg p.o.), KRN2391 (1 mg/kg p.o.), or vehicles for a week. Micturition profiles were compared among the 3 groups. 3. nNOS KO. Micturition profiles were compared during the observation periods (210 min.) among the 5 groups of nNOS KO (8-13 weeks old); groups treated with vehicle, nicorandil (1mg/kg p.o.), nicorandil (3mg/kg p.o.), KRN2391 (1 mg/kg p.o.), and oxybutynin (30 mg/kg/ p.o.). nNOS KO was obtained from Jackson lab (Maine, USA). All experiments followed the institutional and national guidelines for the care and use of laboratory animals.

Results

1.Cystometric investigations showed that preemptive intravesical instillation of nicorandil, KRN2391, and pinacidil successfully inhibited the overactive bladder induced by the intravesical instillation of acetic acid ($p<0.05$). 2. In the urethral obstruction model, both nicorandil and KRN2391 significantly reduced the frequency of urination as compared with untreated obstructed rats (vehicle:12.6±2.2 vs. nicorandil 5.2±1.0, $p<0.01$, vehicle 10.2±2.1 vs. KRN 2.4±0.8, $p< 0.05$) . 3. In nNOS KO, mean total urine volume and mean voided volume did not differ among 5 groups. Nicorandil (3mg/kg p.o.) and KRN2391 (1 mg/kg p.o.) significantly reduced the frequency of urination during the observation periods.

Table 1 Results of medication on the urination of nNOS KO

	vehicle	nicorandil (1mg/kg)	nicorandil (3mg/kg)	KRN-2391 (1 mg/kg)	oxybutynin (30 mg/kg/)
Urination/day	11.4±4.4	8.7±3.1	7.4±2.7	4.8±1.5	11.8±3.7
p		0.205	0.044	0.003	0.840
urine output/day	1.45±0.38	1.19±0.09	1.18±0.29	0.73±0.19	1.34±0.09
p		0.395	0.417	0.036	0.701
n	8	7	8	6	6

Oxybutynin did not affect both the urinary frequency and daily urinary output in nNOS KO. One mg/kg of KRN2391 was more effective in reducing urinary frequency than 3mg/kg of nicorandil, although KRN2391 significantly decreased the daily urine output whereas nicorandil did not.

Interpretation of results

We investigated the efficacy of nicorandil on the three kinds of functional *in vivo* animal models of overactive bladder. Nicorandil significantly reduced the frequency of urination in the conventional models of overactive bladder and in nNOS KO.

Concluding message

Concluding message: Our *in vivo* results indicated that nicorandil, a K_{ATP} channel opener and nitric oxide donor, is a promising drug for clinical application in patients with overactive bladder.

References

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FUNDING: **Chugai Pharmaceutical, Japan**
DISCLOSURES: **NONE**
ANIMAL SUBJECTS: **This study followed the guidelines for care and use of laboratory animals and was approved by Teikyo University School of Medicine**