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ALPHA-1D ADRENOCEPTOR ANTAGONIST INHIBITS PREMICTURITION CONTRACTIONS IN RATS WITH BLADDER OUTLET OBSTRUCTION

Aims of Study

Lower urinary tract symptoms associated with bladder outlet obstruction include storage and voiding symptoms, and the most bothersome in men with benign prostatic hyperplasia (BPH) is predominantly storage rather than voiding symptoms.[1] Detrusor overactivity, a major cause of irritative symptoms is a common phenomenon in those with BPH. However, the pathophysiology of this detrusor dysfunction remains to be elucidated. Now alpha 1 adrenoceptor (AR1) antagonists are widely used to treat LUTS suggestive of BPH, and this therapeutic agent relieves voiding as well as storage symptoms.[3] The relaxtant effect of AR1 antagonists on the smooth muscle tone in prostatic tissue has been well documented, and this effect is predominantly mediated by AR1a. Because a highly selective AR1a antagonist did not appear to relieve irritative symptoms in patients with BPH despite of a significant increase in urinary flow rate,[4] the role of another distinct subtype of adrenoceptor, especially AR1d adrenoceptor, in the development of storage symptoms has been focused on. Aims of this study was to clarify the effects of a selective AR1d antagonist, naftopidil,[5] on the micturition reflex in rats with bladder outlet obstruction.

Methods

Female Wistar rats were used. Partial urethral obstruction was created by wrapping the proximal urethra by a polyethylene catheter with an inner diameter of 1.40mm. Six weeks after obstruction, a catheter was inserted through the bladder dome, and the femoral artery and vein were cannulated for the measurement of arterial blood pressure and intravenous drug administration, respectively. Two days after catheterization, conscious cystometry was performed. To evaluate the effect of an alpha 1d adrenoceptor antagonist, cumulative doses of naftopidil (0.1-1.0mg/kg.) were injected intravenously. Before drug administration baseline urodynamic parameters were measured, and then control injection of vehicle (0.2ml of 100% DMSO) was tested to evaluate possible injection artifacts. During cystometric evaluations, each dose of nafopidil was given 20 min before the first test and 3 to 4 cystometries were recorded after each dose.

Results

Vehicle did not affect both cystometric parameters and arterial blood pressure. Administration of 0.1mg/kg or 1.0mg/kg of naftopidil had no significant effect on bladder capacity, voided volume, residual volume and micturition pressure or mean arterial pressure (table). Naftopidil of 1.0mg/kg dose decreased voided volume and increased residual volume without a significnant difference, however, a significant decrease in voiding efficiency was noted at a dose of 1.0mg/kg of naftopidil (64.9±5.1% at control, 49.0±8.8% at 1.0mg/kg, $p<0.05$) (table).

	Naftopidil		
	Control	0.1mg/kg	1.0mg/kg
Bladder Capacity (ml)	2.49±0.26	2.61±0.47	2.40±0.37
Voided Volume (ml)	1.61±0.19	1.58±0.33	1.14±0.37
Residual Volume (ml)	0.94±0.15	1.04±0.32	1.31±0.33
Micturition Pressure (cmH_2O)	33.2±3.3	35.9±4.7	27.3±3.1
Voiding Efficiency (%)	64.9±5.1	61.1±7.6	49.0±8.8*
Blood Pressure (mmHg)	95.6±6.1	95.5±11.6	82.3±11.5

*:Significant difference vs. control, $p<0.05$.

Interestingly premicturition contractions were inhibited in a dose dependent manner by administration of naftopidil. A significant decrease in the amplitude of premicturition contractions was noted at 0.1mg/kg. or 1.0mg/kg of naftopidil (7.2±0.9cmH_2O at control, 5.1±0.8 cmH_2O at 0.1mg/kg; $p=0.0495$, 1.0±0.7cmH_2O at 1.0mg/kg; $p=0.0192$). The frequency of premicturition contractions was also significantly reduced by 1.0mg/kg of

naftopidil (2.6±0.5 times /min at control, 1.8±0.4 /min. at 0.1mg/kg; $p<0.1$, 0.3±0.2 /min. at 1.0mg/kg; $p=0.0171$).

Conclusions

Naftopidil, a selective AR1d antagonist, inhibited the premicturition contractions during conscious cystometries in obstructed rats. These data suggest that premicturition contractions associated with bladder outlet obstruction is at least partially mediated by AR1d in rats. Recent study indicated that bladder outlet obstruction induces a remarkable increase in bladder AR1d mRNA and protein expression in rats.[6] Taken together, it is possible that up-regulated AR1d secondary to bladder outlet obstruction plays a certain role in the development of detrusor overactivity in men with BPH.

References

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