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EFFECTS OF SAW PALMETTO EXTRACT ON URODYNAMIC PARAMETERS, BLADDER PHARMACOLOGICAL RECEPTORS AND URINARY CYTOKINES IN RATS WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

Hypothesis / aims of study

There are many reports about the efficacy and safety of phytotherapeutic compounds for BPH and LUTS. The most commonly used phytotherapeutic is an extract of the berry of saw palmetto plant, a dwarf palm tree native to the southeastern U.S. Saw palmetto extract (SPE) is composed of both saturated and unsaturated fatty acids, more than 90% of which are present in a mixture of free and esterified forms. Numerous proposals for the mechanism of SPE's effect have been made, including inhibition of 5□-reductase [1]. Previously, we showed that SPE significantly improved urodynamic symptoms in the hyperactive bladder of rats by increasing bladder capacity and prolonging the micturition interval [2,3]. Such an improvement of urodynamic symptoms by SPE arises partly from its binding to pharmacologically-relevant receptors (□$_1$-adrenergic, muscarinic) in the lower urinary tract. Since the effect of SPE on cystitis has not been clarified, the current study aimed to characterize pharmacological effects of SPE on urodynamic parameters, bladder muscarinic and purinergic receptors, and urinary cytokines in rats with cyclophosphamide (CYP)-induced cystitis.

Study design, materials and methods

SPE (60 mg/kg/day) was administered orally twice a day for 7 days to rats. The urodynamic parameters in CYP (150 mg/kg i.p.)-treated rats were monitored by a cystometric method under anesthesia. The muscarinic and purinergic receptors in the bladder and submaxillary gland were measured by radioreceptor assays using [N-methyl-^{3}H] scopolamine chloride ([^{3}H]NMS) and αβ-methylene-ATP [2,8-^{3}H] tetrasodium salt ([^{3}H]αβ-MeATP), respectively. Urinary cytokines (interleukin-1β [IL-1β], IL-6 and L-17) were measured with ELISA kits.

Results

Micturition interval and micturition volume were significantly decreased and the frequency of micturition and basal pressure were significantly increased in CYP-treated rats compared with sham-operated rats. Orally administered SPE (60 mg/kg/day) significantly increased the micturition interval and micturition volume and decreased the frequency of micturition and basal pressure (Fig. 1). The maximal number of sites (B_{max}) for specific binding of [^{3}H]NMS and [^{3}H]αβ-MeATP was significantly decreased in the bladder of CYP-treated rats. The decrease in these receptor densities (Bmax) was attenuated by repeated treatment with SPE (Fig. 2). An elevation in urinary cytokine (interleukin-1□□and interleukin-17) levels was seen in the urine of CYP-treated rats, and this increase was effectively suppressed by SPE treatment.

Interpretation of results

In CYP-treated rats, there was a significant decrease in micturition interval and mean micturition volume and significant increase in the frequency of micturition and basal pressure. These results reflect the detrusor overactivity in CYP-treated rats. The repeated oral administration of SPE in CYP-treated rats resulted in a significant increase of micturition interval and micturition volume and a significant decrease in the micturition frequency and basal pressure. Previously, we showed that SPE attenuated the acetic acid-induced increase of micturition frequency and decrease of voided volume of urine in rats [2.3]. The present study is the first to demonstrate that SPE improves bladder overactivity in rats with CYP-induced cystitis. Furthermore, down-regulation of muscarinic and purinergic receptors in the bladder and an elevation of cytokines in urine of rats with cystitis in CYP-treated rats were effectively attenuated by repeated treatment with SPE at a pharmacological dose. Therefore, SPE may be a viable alternative in the pharmacological treatment of cystitis.

Concluding message

SPE attenuates the alteration of urodynamic parameters, pharmacologically relevant receptors, and urinary cytokines in CYP-treated rats. Therefore, SPE may be a potential therapeutic agent for improving clinical symptoms of cystitis.

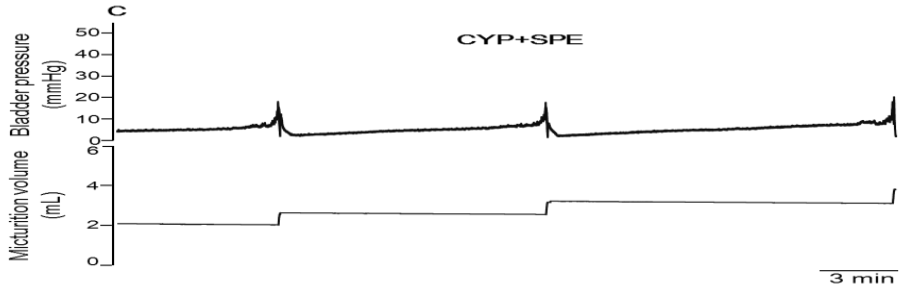

Fig. 1. Representative cystometric traces of bladder pressure and micturition volume for sham-operated(A), CYP-treated (B) and CYP+SPE-treated (C) rats.

Table 1. Dissociation constant (K_d) and maximal number of binding sites (B_{max}) for specific binding of [^{3}H]NMS and [^{3}H]αβ-MeATP in sham-operated, CYP-treated and CYP + SPE-treated rats

Variable	K_d			B_{max}		
[^{3}H]NMS binding	(pM)			(fmol/mg protein)		
Bladder						
Sham	296	±	26	246	±	21 (1.0)
CYP	274	±	12	158	±	11 (0.64)*
CYP + SPE	324	±	13	228	±	17 (0.93)†
Submaxillary gland						
Sham	228	±	12	198	±	10
CYP	255	±	19	197	±	17
CYP + SPE	242	±	15	208	±	10
[^{3}H]αβ-MeATP binding	(pM)			(pmol/mg protein)		
Bladder						
Sham	868	±	155	10	±	0.4 (1.0)
CYP	860	±	182	4.9	±	0.6 (0.49)***
CYP + SPE	872	±	101	6.9	±	0.4 (0.69)***,†

Each value represents the mean ± SE (n=7-9). *P<0.05, ***P<0.001 significantly different from sham-operated rats. †P<0.05, significantly different from CYP-treated rats.

References
1. 1 Iehle C et al. J. Steroid Biochem. Mol. Biol. 54: 273-9 (1995).
2. 2 Oki T et al. J. Urol. 173:1395-9 (2005).
3. 3 Suzuki M et al. Urology 69: 1216-20 (2007).

Disclosures
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