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ALPHA-AMINO-3-HYDROXY-5-METHYL-4-ISOXAZOLEPROPIONATE (AMPA) GLUTAMATE RECEPTOR ANTAGONIST CAN INHIBIT PREMICTURITION CONTRACTIONS IN RATS WITH BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

Detrusor overactivity (DO), a major cause of filling symptoms is a common phenomenon in men with bladder outlet obstruction (BOO) due to benign prostatic hyperplasia. Proposed mechanisms of DO associated with BOO include myogenic as well as neurogenic origin. However, neural mechanisms of DO still remain unclear. In rats BOO produces premicturition contractions (PMCs) during the filling phase that are assumed to be equivalent to DO in humans. Our previous study showed that of glutamate receptors that have an essential role in the micturition reflex pathway in normal rats, NMDA receptor is not involved in the pathogenesis of DO in BOO rats [1]. In this study we explored the possible involvement of AMPA glutamate receptor in bladder dysfunction associated with BOO using a specific antagonist.

Study design, materials and methods

Under halothane anesthesia, BOO was created by implanting a polyethylene catheter (inner diameter of 1.40 mm) around the urethra in female Wistar rats. Six weeks after obstruction, a catheter was inserted through the bladder dome to evaluate conscious filling cystometry. A specific AMPA receptor antagonist 1-(4'-aminophenyl)-3,5-dihydro-7,8-dimethoxy-4H-2,3-benzodiazepin -4-one (CFM-2) was injected intravenously (i.v.) (0.003-3mg/kg) or intrathecally (i.t.) (0.01-10μg) in sham operated and obstructed rats.

Cystometric parameters including bladder capacity, micturition pressure, threshold pressure, voiding efficiency, amplitude and number of PMCs were measured before and after administration of CFM-2. PMCs were defined as spontaneous detrusor contractions with amplitude of 4 cm of water or more that were not associated with micturition.

Results

The cystometric data in BOO rats are summarized in the following figures. I.v. administration of of CFM-2 (0.3 mg/kg or more in sham operated rats and 0.03 mg/kg or more in BOO rats) decreased voiding pressure significantly (Figure 1). Threshold pressure was slightly but significantly decreased only in BOO rats (Figure 1). The most remarkable findings were that i.v. administration of CFM-2 in BOO rats significantly and dose dependently decreased the amplitude and number of PMCs (Figure 1, 2). The highest dose of CFM-2 almost completely eliminated PMCs (Figure 1). As shown in Figure 3, no significant changes in cystometric parameters were observed after i.t. administration of CFM-2 except the highest dose (10 μg) that increased bladder capacity and decreased voiding efficiency. I.t. administration of CFM-2 did not have a significant effect on PMCs (Figure 3).

Interpretation of results

Previous studies indicate that AMPA glutamate receptor plays an important role in the reflex control of micturition in rats [2]. However, AMPA receptor has never been nominated as one of neural mechanisms of bladder dysfunction associated with BOO. Although PMCs in BOO rats were assumed to be mainly of myogenic origin [3], PMCs were suppressed by i.v. administration of CFM-2 in the present study. Thus, we believe that PMCs are at least partly of neurogenic origin that is linked with AMPA receptor. In the present study, i.v. but not i.t. administration of CFM-2 suppressed PMCs, suggesting peripheral and/or supraspinal sites of inhibitory action of CFM-2 for PMCs. Interestingly, in BOO rats, i.v. administration of CFM-2 decreased voiding pressure without changes in voiding efficiency, suggesting that this effect of CFM-2 might be mediated through the action on the urethral sphincter activity rather than the detrusor activity. This is in accordance with previous findings that AMPA receptor antagonist had preferential site of action on the urethral sphincter activity. Intrathecal administration of CFM-2, in general, was not effective in changing cystometric parameters in either sham operated or BOO rats. Only the extremely highest dose (10μg) produced the increase in bladder capacity and decrease in voiding efficiency that were associated with overflow incontinence in some rats. Thus, this may be non-specific suppressing effect of CFM-2.

Figure 1. The effects of CFM-2 (i.v.) on cystometric parameters in BOO rats (*<0.05, **<0.01).

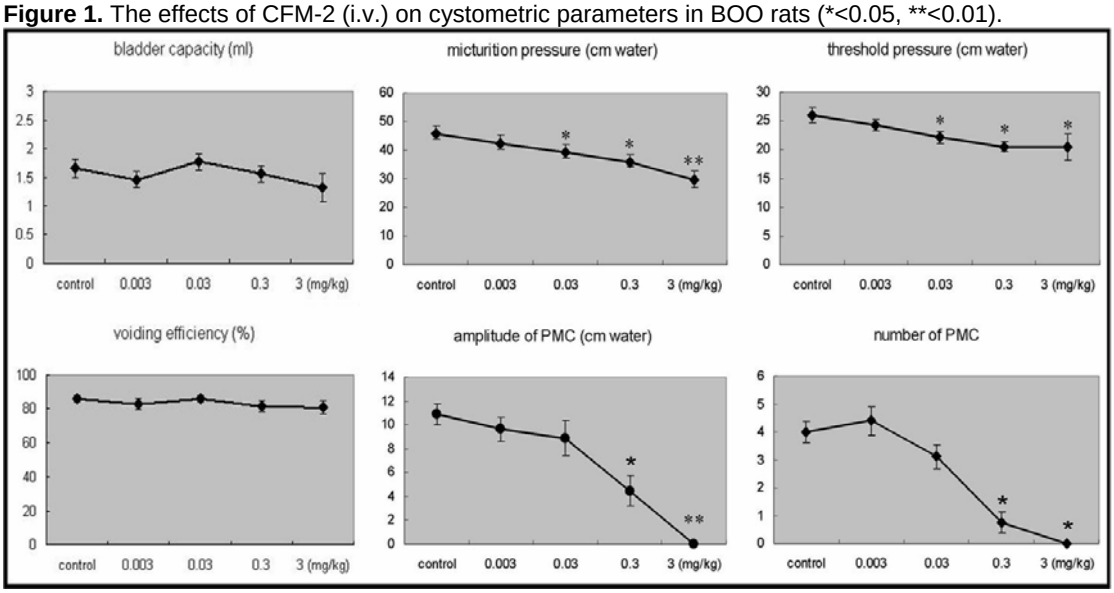


Figure 2. Typical cystometry recording after i.v. injection of CFM-2

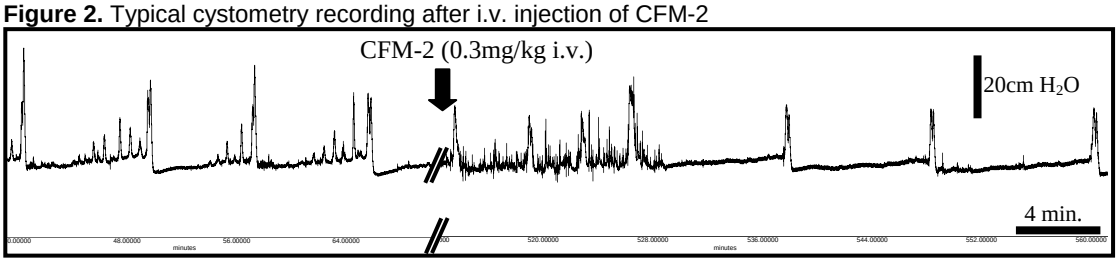
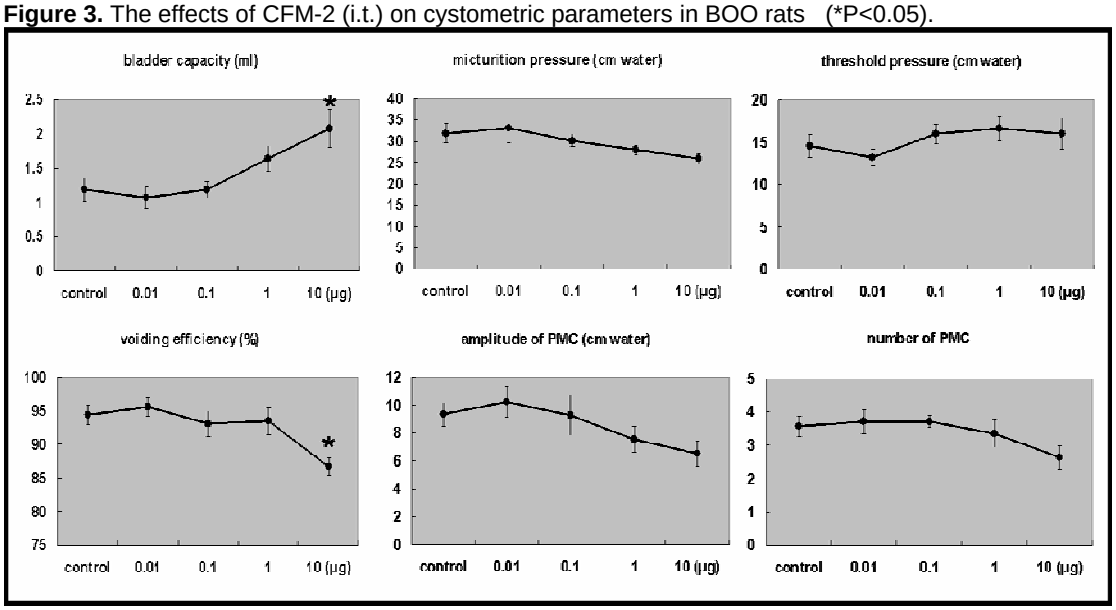


Figure 3. The effects of CFM-2 (i.t.) on cystometric parameters in BOO rats (*P<0.05).



Concluding message

PMCs in BOO rats were inhibited by i.v. administration of specific AMPA glutamate receptor antagonist. The present findings indicate that DO associated with BOO might be at lease partly mediated by AMPA glutamatergic transmission. Further studies will be warranted to provide direct evidence to support the inhibitory effect of AMPA glutamate receptor antagonist on PMCs.

References: [1] J Urol, 170: 1427-1431, 2003 [2] J Pharmacol Exp Ther, 280: 894-904, 1997 [3] J Urol, 151: 244-249, 1994

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