

BLOCKADE OF NEURAL TRANSMISSION VIA METABOTROPIC GLUTAMATE RECEPTOR SUBTYPE 5 FACILITATES URINE STORAGE WITHOUT IMPAIRING BLADDER CONTRACTILITY AND MICTURITION IN MICE

Hypothesis / aims of study

These studies were undertaken to examine whether metabotropic glutamate receptor subtype 5 (mGluR5) antagonist, 6-methyl-2-(phenylethynyl)pyridine (MPEP) can increase volume threshold for inducing micturition without impairing bladder contractility and efficiency of voiding in decerebrate unanesthetized mice and to explore possible site(s) of action for the drug.

Study design, materials and methods

Thirty-four C57BL/6 mice (12-13 week-old, n=17 for each sex) were used in these studies.

Cystometrograms (CMGs): All mice were decerebrated under sevoflurane anesthesia and intravesical pressure was recorded via a PE-50 tube inserted into the bladder dome. CMG recordings were conducted under unanaesthetized conditions by continuously infusing saline (10 μ l/min) at room temperature. MPEP (30 mg/kg i.p.) solution or its vehicle was administered via a PE-10 tube. Evaluated parameters are: voided volume (VV), postvoiding residual volume (RV), volume threshold for inducing micturition (VT), voiding efficiency (VE), pressure threshold for inducing micturition contraction (PT), maximal voiding pressure (MVP, mmHg), bladder compliance (BCP, μ l/mmHg), bladder contraction duration (BCD).

Real time RT-PCR: A real time RT-PCR was used to quantify the expression of mGluR5 gene in urothelium, detrusor, urethra, L6 and S1 dorsal root ganglia (DRG), L6/S1 spinal cord and brainstem in mice.

Data analysis: All values are expressed as mean \pm S.E.M. Two-way repeated measures ANOVA or unpaired *t*-test were used when applicable, and $p < 0.05$ was considered significant ($*p < 0.05$, $**p < 0.01$, ns: not significant).

Results

CMGs: Mice that received a systemic injection of MPEP (30 mg/kg) had markedly larger VV and VT, as compared with mice treated with the vehicle, in the female and male (Table 1); however, MPEP did not affect RV, VE, PT, MVP, BCP, and BCD (Table 1 and Figure 1) in both sexes.

Real time RT-PCR: mGluR5 genes were expressed in L6 and S1 DRG, L6/S1 spinal cord segments, pons, and midbrain, whereas they were not detected in urothelium, detrusor and whole urethra (Table 2).

Interpretation of results

CMGs: Systemic administration of MPEP markedly increased VV and VT without affecting the other CMG parameters evaluated in this study (Table 1), suggesting that neural transmission via mGluR5 is essential in sensory afferent/ascending limb from the bladder. The effects of the antagonist were exerted similarly in both sexes.

Real time RT-PCR: No mGluR5 mRNA expression was found in urothelium, detrusor and urethra. In contrast, mGluR5 mRNA were expressed in L6 and S1 DRG, L6/S1 spinal cord segments, pons, and midbrain (Table 2)

Taken together, it is suggested that an increase of bladder capacity by MPEP is due to mGluR5 antagonism in DRG, spinal cord, pons, and/or midbrain in the sensory pathway.

Concluding message

Blockade of bladder sensory pathway by mGluR5 antagonist can be a useful pharmacological treatment to increase bladder capacity in urine storage with no disturbance in voiding. Possible sites of action for the antagonism are in afferent/ascending limb including L6 and S1 DRG, L6/S1 spinal segments, and/or brainstem. The mGluR5 antagonist may become an alternative choice for the treatment of bladder hyperactivity because it has the mechanism different from M2/M3 antimuscarinic drug or β 3 agonist for which a main site of action is in detrusor.

Table 1 Effects of MPEP 30 mg/kg i.p. on storage and voiding functions in mice

	Female				Male			
	VV (μ l)	RV (μ l)	VT (μ l)	VE (%)	VV (μ l)	RV (μ l)	VT (μ l)	VE (%)
Vehicle	156 \pm 27	6 \pm 2	162 \pm 28	97 \pm 1	94 \pm 16	7 \pm 2	101 \pm 18	93 \pm 1
MPEP	226 \pm 11*	6 \pm 1	232 \pm 11*	97 \pm 0	172 \pm 19*	7 \pm 2	179 \pm 20*	96 \pm 1

* $P < 0.05$, statistical difference from vehicle (by unpaired *t*-test).

Table 2 mGluR5 mRNA expression (GAPDH normalized expression; $\times 1,000$) in mice

	urothelium	detrusor	urethra	L6 DRG	S1 DRG	L6/S1 spinal	pons	midbrain
Female	0	0	0	0.18 \pm 0.01	0.18 \pm 0.04	19.6 \pm 0.8	13.6 \pm 1.1	25.3 \pm 2.5
Male	0	0	0	0.12 \pm 0.01	0.15 \pm 0.01	19.2 \pm 0.8	17.3 \pm 0.9	26.4 \pm 2.2

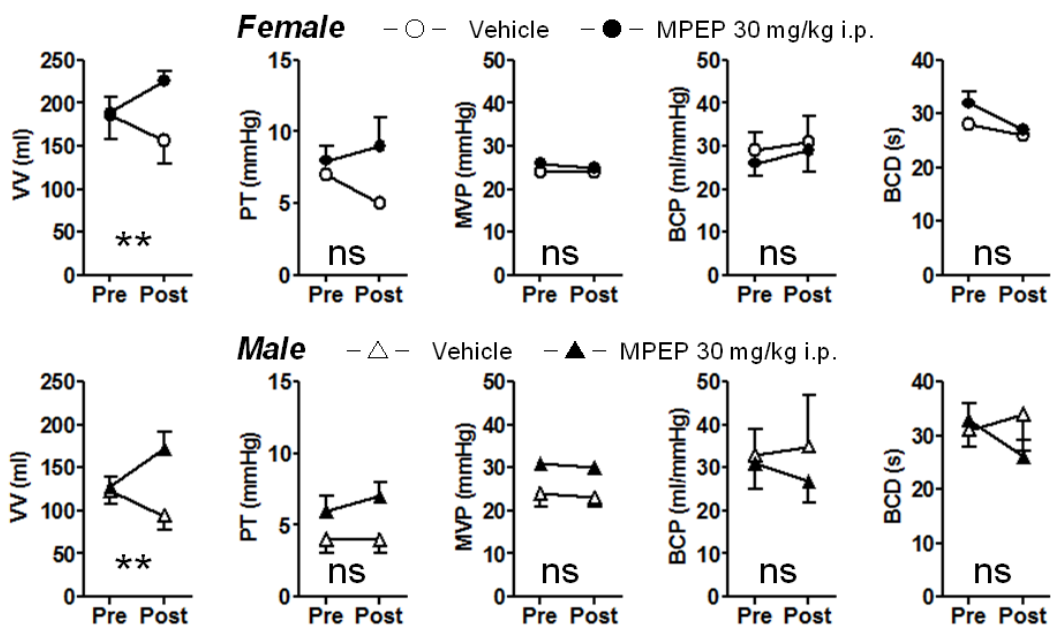


Figure 1

** $P < 0.01$, statistical difference between vehicle and MPEP (by Two-way repeated ANOVA).

Disclosures

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