

ARE METABOTROPIC GLUTAMATERGIC RECEPTOR SUBTYPES 1 AND 5 (MGLUR-1 AND -5) INVOLVED IN AFFERENT PROCESSING OF DETRUSOR OVERACTIVITY INDUCED BY CHEMICAL IRRITATION IN MICE?

Hypothesis / aims of study

Glutamate receptors consist of two major classes, the ionotropic receptors which form ligand-gated channels and metabotropic receptors (mGluR) which are G-protein coupled receptors including eight subtypes (mGluR-1 to -8). The former which include *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), receptors have essential roles in the control of micturition and in the processing of nociceptive input from the lower urinary tract (LUT) to the central nervous system [1]; however less is known about the function of mGluR. Recent studies suggested that the peripheral mGluR-1/-5 had a functional role in inflammatory pain as well as normal nociception in the skin [2]. In the present study, we examined whether mGluR-1, -5, or both played a significant role in afferent processing of the reflex micturition during intravesical infusion of chemical irritant or normal saline in decerebrate, unanesthetized mice.

Study design, materials and methods

Animal preparations: Experiments were performed on a total of 26 female null mutant (mGluR-1 knockout, KO) mice and their wild type (WT) littermates (12-14 week-old) under decerebrate, unanesthetized conditions. All surgical procedures were conducted under sevoflurane anesthesia (2-3% in oxygen 0.2 ml/min flow). A precollicular decerebration was performed using scalpel and blunt spatula after skull being removed with a fine rongeur. A transvesical bladder catheter connected to a pressure transducer was used to record bladder pressure during continuous infusion cystometrograms (CMG) (0.01 or 0.03 ml/min) with physiological saline or 0.1 % acetic acid (A.A.) [3]. Experiments were performed 2 hours after decerebration.

Experiment #1: Voided volume (VV), residual volume (RV), volume threshold for micturition (VT), and voiding efficiency (VE) were evaluated to compare between WT and mGluR-1 KO mice during saline infusion CMG (0.01 ml/min).

Experiment #2: To examine whether blockade of mGluR-5 or mGluR-1 KO could antagonize the hyperreflexic voiding induced by acute intravesical infusion of chemical irritant, WT or KO mice received MPEP (mGluR-5 antagonist) (30 mg/kg) or vehicle intraperitoneally 40 min before CMG with A.A. The inter-micturition interval (IMI) was evaluated during continuous CMG with normal saline and the following A.A. infusion (0.03 ml/min) in each animal.

Evaluations and statistics: All values are expressed as mean \pm S.E.M. Unpaired *t* test or two-way ANOVA was applied, and $P < 0.05$ was considered significant.

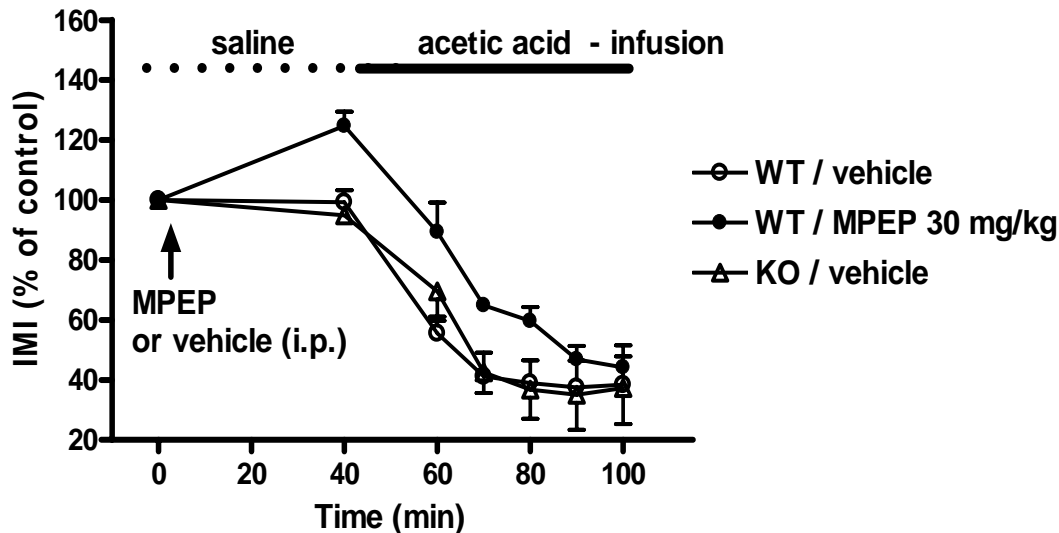
Results

Experiment #1: Values in the parameters evaluated during CMG are presented in Table 1. No difference was found between WT and KO in each parameter.

Table 1

	VV (μ l)	RV (μ l)	VT (μ l)	VE (%)
WT ($n=7$)	173 \pm 16	4 \pm 1	176 \pm 15	98 \pm 1
KO ($n=6$)	176 \pm 13	8 \pm 2	184 \pm 14	96 \pm 1

Experiment #2: The control IMIs in the 3 groups, WT/vehicle ($n=4$), WT/MPEP ($n=5$), and KO/vehicle ($n=4$), were similar (337 \pm 61, 318 \pm 48, and 382 \pm 44 sec, respectively). In WT mice, MPEP (30 mg/kg i.p.) significantly increased the IMI by 25 \pm 5 % during intravesical saline infusion, whereas vehicle had no effect (Fig. 1). In the 3 groups, A.A. intravesical infusion started 40 min after MPEP or vehicle i.p. injection decreased the IMI for 40 min in a similar fashion (Fig. 1). As shown in Fig. 1, the effect of MPEP on the IMI lasted for 80 min.



Interpretation of results

MPEP (30 mg/kg i.p.) increased the IMI during saline infusion CMG in WT mice, demonstrating that the mGluR-5 was involved in the afferent processing under non-noxious bladder-filling condition. Blocking neural transmission via mGluR-5 with MPEP could not antagonize the A.A.-induced hyperreflexic voiding, revealing that mGluR-5 were less important in the regulation of afferent signalling induced by noxious stimulation in the LUT. However, it should be noted that the IMI of MPEP-treatment group was larger than that of vehicle group, because blockade of mGluR-5 inhibited the neural transmission conveying non-noxiously-induced signals in the afferent pathways. WT and mGluR-1 KO mice were similar in cystometric properties such as VT, VV, RV, VE, and IMI during saline or A.A. infusion CMG, suggesting that mGluR-1 did not play a significant role in bladder afferent pathways.

Concluding message

The mGluR-5 is involved in the afferent processing of reflex micturition induced by non-noxious (mechanical) stimulation in the LUT and can be a potential target for the treatment of the overactive bladder syndrome. On the other hand, in the female mouse, the mGluR-1 is less likely to have a significant role in the urine storage function whether under normal or pathophysiological condition.

References

1. Annu. Rev. Pharmacol. Toxicol. 41:691-721, 2001.
2. Trends in Neurosci. 24:550-552, 2001.
3. Neurosci. Lett. 313:57-60, 2001.

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