

BLOCKADE OF METABOTROPIC GLUTAMATERGIC PATHWAYS WORSENS VOIDING DYSFUNCTION IN MICE WITH CHRONICALLY-TRANSECTED SPINAL CORD

Hypothesis / aims of study

In rats, group I metabotropic glutamate receptors (mGluRs) (i.e., mGluR1 and mGluR5) are found in Onuf's nucleus [1]. Previous study demonstrated that spinal cord intact mice lacking mGluR1 exhibit facilitated external urethral sphincter (EUS) electromyogram (EMG) activity with a prominent tonic component superimposed on bursting activity during voiding (i.e., detrusor-sphincter dyssynergia, DSD), suggesting that at least mGluR1 plays an inhibitory role in modulation of EUS activity to obtain efficient voiding [2]. The aims of the present study using mGluR1-knockout (KO) mice were: (1) to determine the contribution of mGluR1 in voiding function of wild-type (WT) phenotypes after chronic spinal cord transection (SCT), and (2) to further examine, by using a mGluR5 antagonist, the possible involvement of mGluR5 in voiding of the spinal cord-transected mice.

Study design, materials and methods

Twenty-four female C57BL/6 mice were used for this study. All surgical procedures were conducted under sevoflurane anesthesia. Spinal cord transection (SCT) was performed in 12 mice at 9 week-old by sectioning at the T9-10 level, and experiments on the spinalized mice were performed 4 weeks post-spinalization. Simultaneous recordings of continuous infusion CMG (30 μ l/min) and EUS EMG were conducted in 13 week-old mice under decerebrate, unanesthetized conditions. A mGluR5 antagonist, 2-methyl-6-(2-phenylethynyl)pyridine (MPEP) (30 mg/kg) or the vehicle (diluted HCl) was administered i.p., and changes in patterns of voiding and EUS EMG activity after the drug were evaluated. Evacuation of intravesical fluid occurred during a descent phase of sudden decrease of bladder contraction pressure presented as a notch on cystometrogram chart (Fig. 1, from a SCT-WT mouse). The number of notches (# Notches) and sum of evacuation duration (SED) per each bladder contraction were evaluated. All values are expressed as means \pm SEM. Unpaired t-test and repeated measures two-way ANOVA followed by Sidak's multiple comparisons test were used for statistical analysis, if applicable. For all analyses, P values of <0.05 were considered significant.

Results

SCT mice exhibited DSD and periodical detrusor-sphincter 'synergistic' (DSS) pattern during each bladder contraction (Fig. 1). Fluid was evacuated at the DSS, which is presented as a notch on cystometrogram chart. Before MPEP injection, there were marked differences between SCT-WT and SCT-KO mice in the number of notches and the SED ($P < 0.0001$ for each). MPEP produced greater decrease in the number of notches in both SCT groups (Fig. 2). Meanwhile, MPEP markedly decreased SED in SCT-WT mice, whereas it had no effect on SED in SCT-KO mice (Fig. 2).

Interpretation of results

The results showed that mGluR1 and mGluR5 are involved in urethral relaxation during a bladder contraction, indicating that mGluR1 and mGluR5 participate in an inhibitory control of external urethral sphincter activity during bladder contraction in SCT mice.

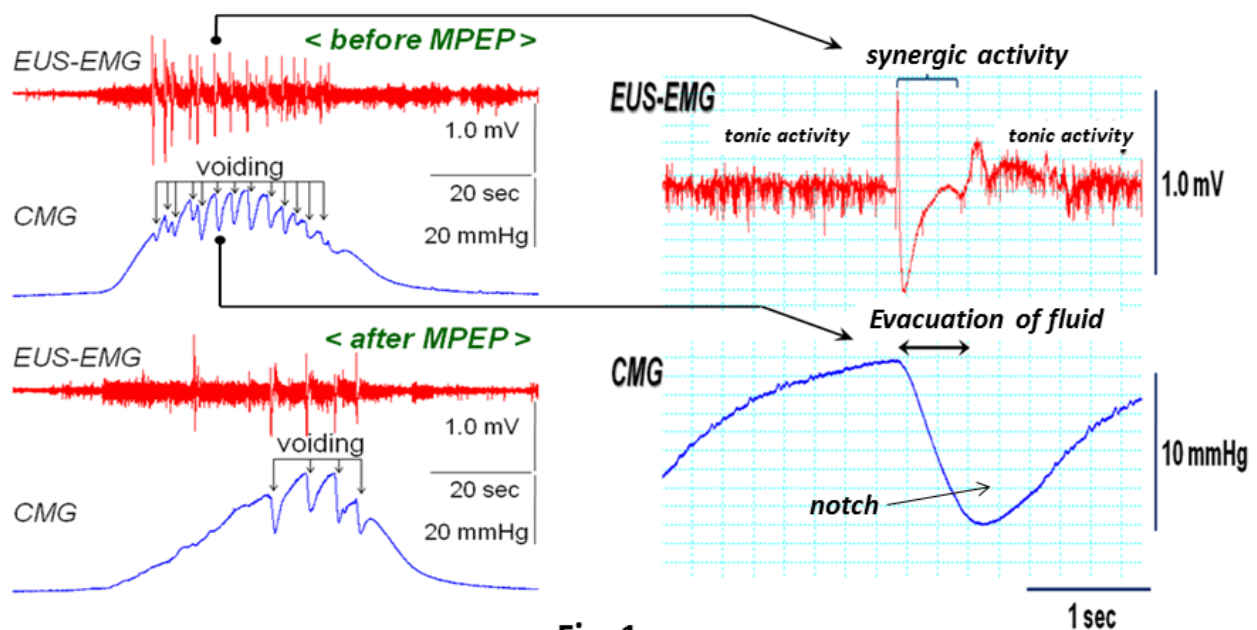


Fig. 1

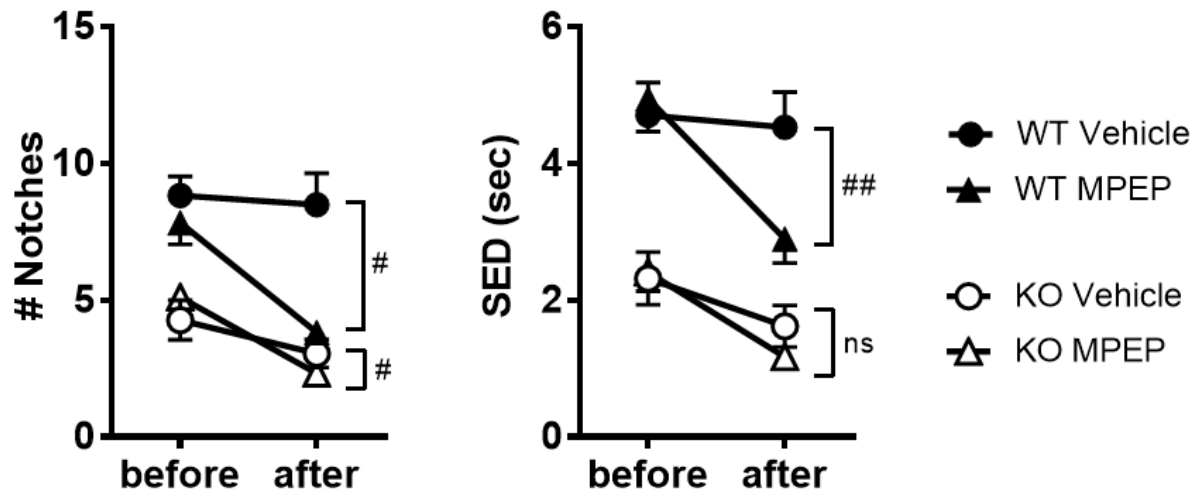


Fig. 2

Concluding message

Both mGluR1 and mGluR5 are important in relaxation of external urethral sphincter of SCT mice. The present results suggest the possibility that dysfunction of these metabotropic glutamatergic transmission in the spinal cord underlies a mechanism exacerbating DSD subsequent to spinal cord injury.

References

1. Alvarez et al., J. Comp. Neurol. 422 (2000) 464-487.
2. Yoshiyama et al., ICS Meeting (2006) Abstract No. 210.

Disclosures

Funding: JSPS KAKENHI for Scientific Research (No. 25462507 & No. 16K11042) (to M. Yoshiyama) **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Mouse **Ethics Committee:** The Institutional Animal Care and Use Committee of the University of Yamanashi (Chuo, Yamanashi, Japan)