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EFFECTS OF A METABOTROPIC GLUTAMATE RECEPTOR SUBTYPE 5 ANTAGONIST ON LOWER URINARY TRACT FUNCTIONS IN MICE WITH NORMAL OR TRANSECTED SPINAL CORDS

Hypothesis / aims of study

A selective metabotropic glutamate receptor subtype 5 (mGluR5) antagonist, 6-methyl-2-(phenylethynyl)pyridine (MPEP) increased the inter-micturition interval (IMI) during continuous infusion cystometrograms (CMGs) in unanesthetized decerebrate mice, suggesting that the drug could facilitate the urine storage function [1]. On the other hand, an immunohistochemical study revealed mGluR5 and mGluR1 immunoreactivity in region of external urethral sphincter (EUS) motor nucleus (ie, Onuf nucleus) in the rat spinal cord [2]. I.t. injection of an mGluR group I/II (ie, mGluR1 and 5/2 and 3) antagonist facilitated EUS EMG activity during micturition in unanesthetized decerebrate rats [3]. It is also known that mGluR1 knockout mice exhibited detrusor-sphincter dyssynergia (DSD) during voiding [3]. The present studies were conducted to determine if mGluR5 was also involved in the uncoordinated activity of bladder and EUS, and to examine if MPEP disturbed efficient voiding.

Study design, materials and methods

Animal preparations: Twenty two female C57BL/6 mice were used for these studies. All surgical procedures were conducted under sevoflurane anesthesia (2-3% in oxygen 0.2 ml/min flow). Spinal cord transection was performed in 5 mice at 9 week-old by sectioning at the T9-10 level, and the experiments on spinalized mice were performed 4 weeks post-spinalization. CMGs were conducted in 12-13 week-old mice under decerebrate, unanesthetized conditions. A transvesical bladder catheter connected to a pressure transducer was used to record intravesical pressure during continuous infusion CMG (10 or 30 µl/min) with physiological saline. To examine the EUS EMG activity, epoxy-coated stainless steel wire (50 µm) EMG electrodes were placed percutaneously in regions adjacent to the EUS. Experiments were performed 2 hours after precollicular decerebration. MPEP (30 mg/kg) or the vehicle was administered i.p. *Protocol #1:* Effects of MPEP were examined in mice with normal (NSC, n=5) or transected (TSC, n=5) spinal cords during continuous infusion (30 µl/min) CMG in combination with EUS EMG recording. *Protocol #2:* Urodynamics parameters during CMG (10 µl/min) were evaluated 40 min after administration of MPEP (n=6) or the vehicle (n=6).

Results

Protocol #1: TSC mice exhibited a prominent tonic EUS EMG activity during a bladder contraction (ie, DSD), which was not detected in NSC mice (Figs. 1 and 2). MPEP reduced amplitudes and numbers of EUS EMG bursting activity during a bladder contraction in NSC (Fig. 1) and TSC (Fig. 2) mice, respectively. MPEP increased the IMI in NSC mice (260 ± 34 sec to 354 ± 35 sec, $p<0.001$) but decreased that in TSC mice (349 ± 35 sec to 221 ± 39 sec, $p<0.01$), whereas the drug had no effect on the maximal voiding pressure (MVP) in either mice.

Protocol #2: The results are presented in Table below.

	Pressure threshold (mmHg)	Maximal voiding pressure (mmHg)	Volume threshold (µl)	Residual volume (µl)	Voiding efficiency (%)
Vehicle	4.7 ± 0.4	26.0 ± 0.9	162 ± 28	6 ± 2	96.5 ± 0.5
MPEP	10.2 ± 1.7*	25.5 ± 1.0	232 ± 11*	6 ± 1	97.4 ± 0.4

*$p<0.05$

Interpretation of results

In NSC mice, MPEP reduced the amplitude of EUS EMG bursting activity and increased the pressure and volume thresholds for inducing micturition (and IMI) without affecting maximal voiding pressure, residual volume and voiding efficiency. On the other hand, in TSC mice, MPEP decreased the IMI suggestive of the approximate voided volume. It was speculated that the decreased IMI by MPEP in TSC mice was due to the reduction in numbers of EUS bursting activity which promoted efficient voidings.

Concluding message

This is the first report which shows EUS EMG activity concomitant with a bladder contraction in the chronically spinal cord transacted mouse. The mGluR5 antagonist can increase bladder capacity without affecting the efficient voiding when the spinal cord is normal. Thus, the micturition reflex pathways *via* mGluR5 can be targets for the treatment of urine storage dysfunctions.

References

[1] ICS 36th Annual Meeting (2006) Abstract No. 213.
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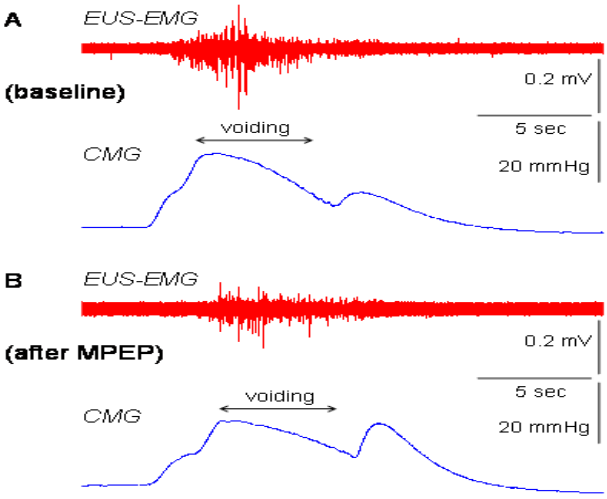

Fig. 1

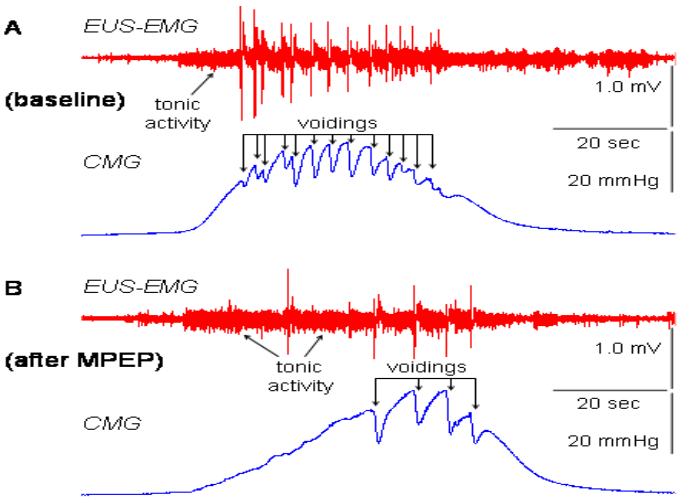

Fig. 2

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**The University of Yamanashi Institutional Animal Care and Use Committee**