260

Yoshiyama M[1], Araki I[2], Zakoji H[2], Kobayashi H[2], Du S[2], Aiba A[3], Takeda M[2]
1. Yamanashi Rehabilitation Hospital, 2. Department of Urology, University of Yamanashi Faculty of Medicine, 3. Div. of Cell Biology, Dept. of Mol. Cell. Biology, Kobe Univ. Graduate Sch. Med.

ADDITIVE CONTROL BY METABOTROPIC GLUTAMATE RECEPTORS 1 AND 5 IN BLADDER AFFERENT MECHANOSENSORY TRANSMISSION

Hypothesis / aims of study

Glutamate receptors consist of two major classes, the ionotropic glutamate receptors which form ligand-gated cation channels and the metabotropic glutamate receptors (mGluRs) which are a family of G-protein coupled receptors activating distinct signal transduction pathways in neurons. The former includes *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-lisoxazole-4-propionic acid (AMPA), and kainite receptors, which have been revealed to play essential roles in the control of micturition reflexes [1]. The latter, on the other hand, mGluRs are constituted of eight subtypes (mGluRs1 to 8) which are placed into three groups (group I to III) on the basis of sequence homology, transduction mechanism, and agonist pharmacology [2]. Recent studies suggested that mGluR1 and mGluR5 (i.e., group I mGluRs) were involved in afferent mechanosensory from the bladder [3]. In the present study, we examined whether mGluR1 and mGluR5 produced an interaction in the effect on afferent processing of the reflex micturition during cystometrograms in decerebrate, unanesthetized mice.

Study design, materials and methods

Animal preparations: Experiments were performed on 12-14 week-old female C57BL/6 mice (wild type, WT, *n*=20; mGluR1 knockout, KO, *n*=12) 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 a scalpel and a 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 (CMGs, infusion rate at 0.03 ml/min) with physiological saline. Experiments were performed 2 h after decerebration.
Drug, evaluations and statistics: Effects of 6-methyl-2-(phenylethynyl)pyridine (MPEP, 0.3-30 mg/kg i.p.), a selective mGluR5 antagonist, or the vehicle on inter-micturition interval (IMI) were evaluated during continuous CMGs. IMI was defined as a time between peaks of two consecutive bladder contractions. All values are expressed as mean +/- S.E.M. Two-way analysis of variance was used for statistical analysis when applicable. $P<0.05$ was considered significant.

Results

Baseline values of IMI measured before drug injection was: 268 +/- 21 sec in WT (*n*=20) and 385 +/- 27 sec in KO (*n*=12), demonstrating the significant difference between WT and KO (*P*=0.002). As shown in Figure 1A, in WT mice, MPEP (0.3-30 mg/kg i.p.) dose-dependently increased the IMI. The 30 mg/kg dose increased the IMI in KO mice (*P*=0.0004) by the same degree as in WT mice (Figure 1B). The effect of the 30 mg/kg on the IMI persisted for at least 2 hours in both WT and KO mice (Figures 1A and 1B).

Interpretation of results

IMI is reflected by a functional bladder capacity. Therefore, the baseline values measured from WT and KO mice suggested that KO mice had larger functional bladder capacities than WT did, implying that mGluR1 was involved in afferent mechanosensory. In WT mice, MPEP (0.3-30 mg/kg) increased the IMI in a dose-dependent fashion, suggesting that mGluR5 also participated in afferent signalling transmission. In KO mice, MPEP (30 mg/kg) could increase the IMI by the same degree as in WT mice, suggesting that the mGluR5 antagonist blocked afferent signalling transmission regardless of mGluR1.

Concluding message

These studies demonstrated that both mGluR1 and mGluR5 are involved in afferent mechanosensory transmission from the bladder, and revealed that these mGluRs additively interacted to transmit the afferent signal. Thus, they are expected that a group I mGluR antagonist, which blocks both mGluR1 and mGluR5, would exert the effect more potently than a drug targeting at either mGluR1 or mGluR5 does and that it can be a promising drug to treat overactive bladder.

References

[1] Neuroscience 132:1017-1026 (2005).
[2] Trends Pharmacol. Sci. 22:114-120 (2001).
[3] ICI 2006 Abstract No. 213 (2006).

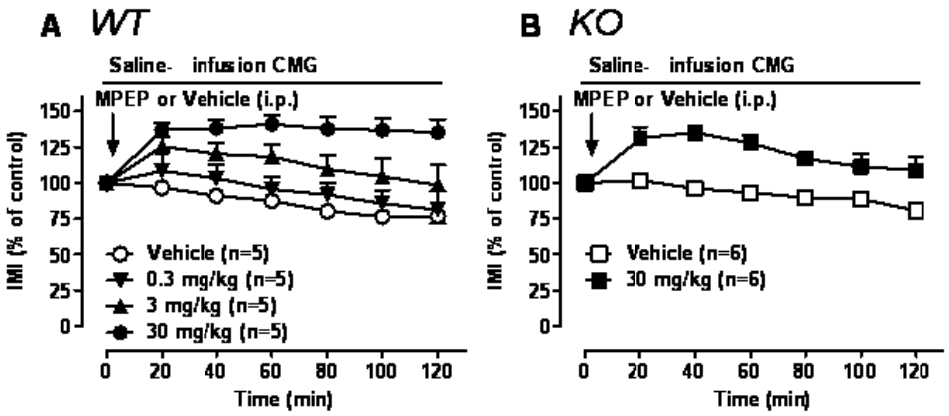

Figure 1

FUNDING: None

ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by The Institutional Animal Care and Use Committee, University of Yamanashi