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METABOTROPIC GLUTAMATERGIC RECEPTOR SUBTYPE 1 (MGLUR-1) KNOCKOUT MICE EXHIBIT DETRUSOR-SPHINCTER DYSSYNERGIA DURING MICTURITION

Hypothesis / aims of study

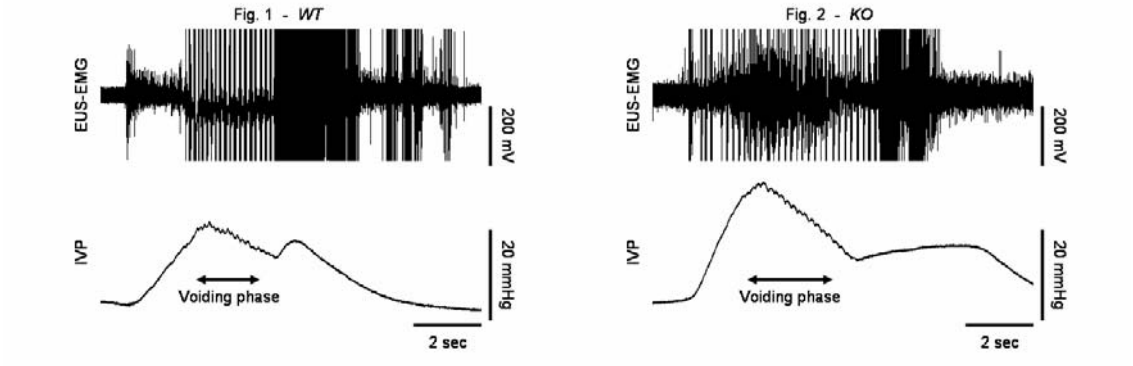
Previous studies demonstrated that the metabotropic glutamatergic receptor subtype 1 (mGluR-1) was expressed in the Onuf's nucleus [1] and that intrathecal injection of mGluR groups I and II (subtypes 1/5 and 2/3, respectively) antagonist facilitated the external urethral sphincter (EUS) EMG activity in unanesthetized rats [2]. The present study was conducted using decerebrate, unanesthetized mGluR-1 knockout mice to further examine the role of mGluR-1 in the lower urinary tract function. This is the first study which recorded EUS EMG activity concomitant with reflex bladder contractions in mice under unanesthetized condition.

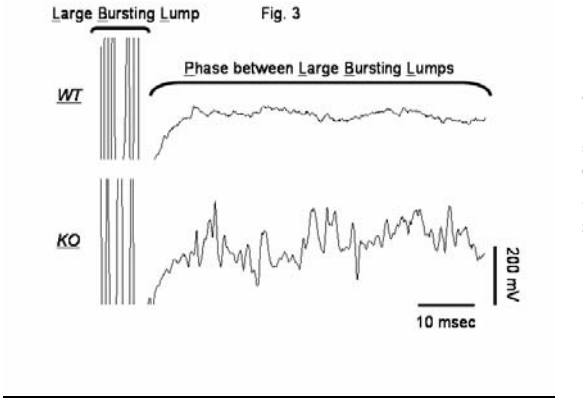
Study design, materials and methods

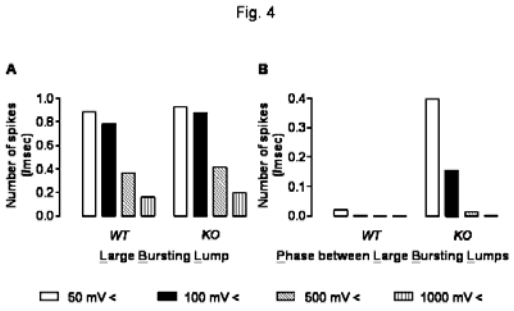
Animal preparations: Experiments were performed on a total of 20 male and female null mutant (mGluR-1 knockout, KO) mice and their wild type (WT) littermates (12-14 week-old) under decerebrate, unanesthetized conditions. All surgical procedures were conducted under sevoflurane anesthesia (2-3% in oxygen 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 intravesical pressure (IVP) during continuous infusion cystometrograms (CMG) (0.01 ml/min) with physiological saline. To examine the EUS EMG activity, epoxy-coated stainless steel wire (50 µm) EMG electrodes were placed percutaneously in the striated muscle of the EUS or its adjacent region. The EUS EMG activity was amplified 1,000-fold and filtered (high frequency cut-off at 10,000 Hz and low at 10 Hz) by a preamplifier, and the data were collected in a recording system at sampling rate of 10,000 Hz. Experiments were performed 2 hours after decerebration.
Evaluations and statistics: The amplitudes of EUS EMG spikes were measured and divided into the following groups: 10 mV <; 50 mV <; 100 mV <; 500 mV <; and 1000 mV <. All values are expressed as mean +/- S.E.M. For statistical analysis, two-way ANOVA was applied, and $P<0.05$ was considered significant.

Results

Male: The EUS EMG activity concomitant with a bladder contraction in a WT mouse was recorded as shown in Fig. 1, exhibiting the single voiding contraction accompanied by coordinated EUS activity which consisted of 'large bursting lumps' (LBL) and the silence at 'phases between LBL' (PLBL) during evacuation. On the other hand, the EUS EMG in a KO mouse contained the periodic occurrence of LBL and irregular 'uninhibited small bursting' (USB) activity at PLBL (Fig. 2). Extended EUS EMG charts at middle point during voiding of WT and KO mice (Fig. 3) further revealed the marked difference between the two groups at PLBL. Between WT (*n*=5) and KO (*n*=5) mice, the numbers of EMG spikes in time (per msec) at LBL were similar, whereas those at PLBL were significantly different (Fig. 4).
Female: The EUS EMG spikes (at both LBL and PLBL) in female mice of both WT (*n*=5) and KO (*n*=5) was much lower in average amplitude (mV) compared to that in male mice: a majority of spikes was less than 50 mV. The numbers of the USB spikes in time at PLBL (in 10 mV <, 50 mV <, and 100 mV <) in female mice were: 0.088 +/- 0.029, 0.024 +/- 0.022, and 0.012 +/- 0.012 per msec in WT; and 0.394 +/- 0.069, 0.092 +/- 0.054, and 0.018 +/- 0.018 per msec in KO, respectively, which were statistically different between the two groups.







Interpretation of results

Mice lacking mGluR-1 exhibited the facilitated EUS EMG activity (i.e., USB) at PLBL during voiding, whereas WT mice did not show such activity. The results suggest that mGluR-1 has an inhibitory role in the control of EUS activity during micturition in both male and female mice.

Concluding message

In the mouse, mGluR-1 is involved in tonic inhibition of the excitatory pathway (e.g., glutamatergic transmission *via* AMPA and/or NMDA receptors) to the EUS, raising the possibility that removal of the mGluR-1 inhibitory mechanism may participate in the uncoordinated activity of bladder and EUS (i.e., detrusor-sphincter dyssynergia) that occurs after spinal injury.

References

1. J. Comp. Neurol. 422:464-487, 2000.
2. ICS 34th Annual Meeting, Paris, France, Abstract #252, 2004.

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