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ROLES OF METABOTROPIC GLUTAMATE RECEPTOR SUBTYPE 1A IN LOWER URINARY TRACT FUNCTION OF MICE

Hypothesis / aims of study

Glutamatergic mechanisms have been implicated in control of lower urinary tract (LUT) activity [1]. Glutamate receptors are constituted of two major classes: the ionotropic glutamate receptors and the metabotropic glutamate receptors (mGluRs). We conducted this study using mice lacking mGluR1a, one of the mGluR subtypes, to examine if neural transmission *via* mGluR1a is involved in LUT function in mice.

Study design, materials and methods

We used 12-14 week-old female mGulR1a-knockout (KO) mice that were backcrossed on a C57BL/6N background as well as wild-type (WT) littermates. In this study, we employed a dual analysis of voiding behaviour and reflex micturition to examine lower urinary tract function in these mice. For evaluating micturition behaviour, conscious mice were individually placed in metabolic cages, and frequency-volume charts (FVCs) were measured. For assessing reflex micturition, mice were decerebrated under sevoflurane anaesthesia and cystometrogram (CMG) recordings were conducted under unanaesthetized conditions by continuously infusing saline (10 µl/min). Evaluated parameters are: water intake (ml/day), urine output (ml/day), urinary frequency (voids/day), and urine volume/void (µl) for metabolic cage study; and bladder compliance (BCP, µl/mmHg), volume threshold for inducing micturition (VT, µl), voiding efficiency (VE, %), and maximal voiding pressure (MVP, mmHg) for CMG study. All values are expressed as mean ± S.E.M. Statistical analyses were made using Mann-Whitney test and $p < 0.05$ was considered significant (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

Results

The FVC showed that KO mice void less frequently and release larger urine volume per voiding, as compared to WT mice (Fig .1 and Table A). Meanwhile, no differences were found between KO and WT in the water intake and urine output per day. The CMG revealed that KO mice have larger VT, BCP and MVP, but show lower VE than WT mice (Fig. 2 and Table B). Thus, the differences between the two groups were found not only in storage phase parameters (i.e., BCP and VT) but also in voiding phase parameters (i.e., VE and MVP).

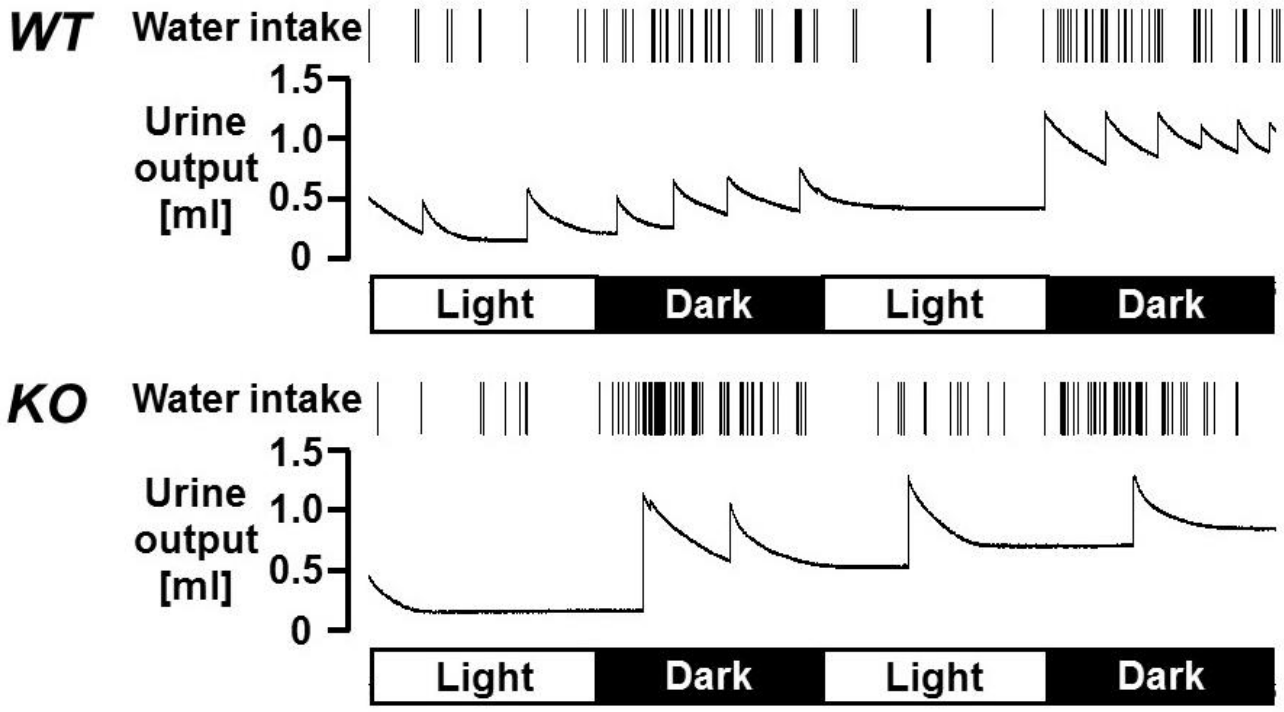

Fig. 1

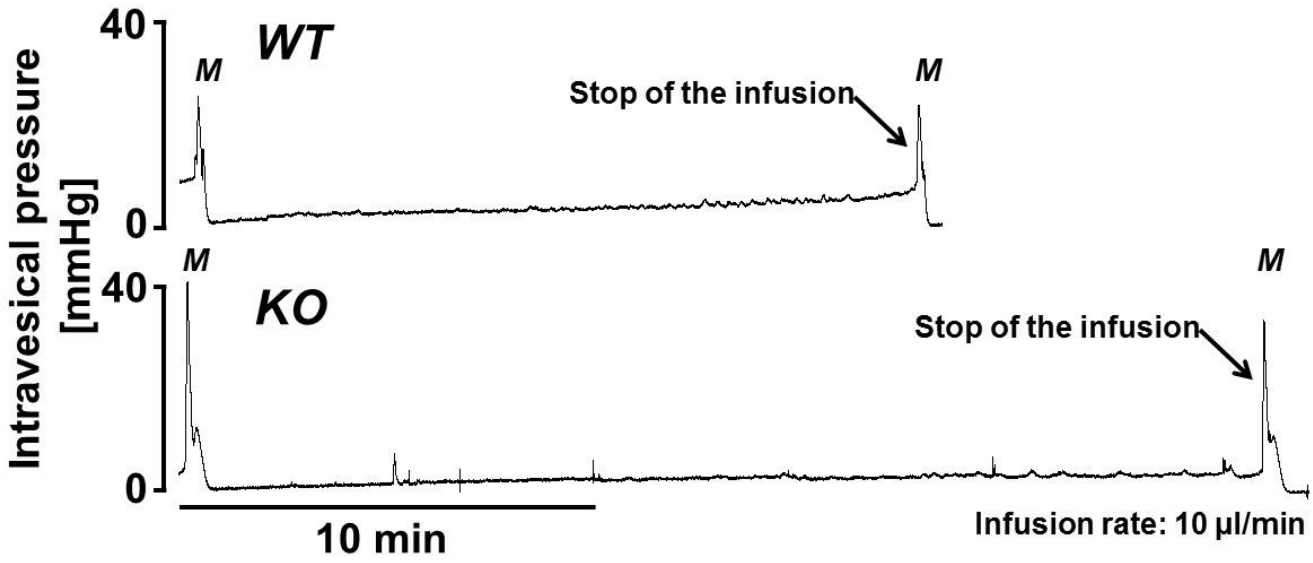

Fig. 2

A. Frequency-volume chart (in voluntary 'voiding behaviour')				
	Water intake (ml/day)	Urine output (ml/day)	Frequency (voids/day)	Volume/void (µl)
WT (n=8)	2.9 ± 0.3	1.6 ± 0.1	7.3 ± 0.8	255 ± 39
KO (n=8)	2.7 ± 0.2	1.6 ± 0.1	3.7 ± 0.3**	458 ± 48**
B. Cystometrogram (in involuntary 'reflex micturition')				
	MVP (mmHg)	BCP (µl/mmHg)	VT (µl/)	VE (%)
WT (n=10)	27.3 ± 1.1	26.4 ± 3.3	167 ± 12	97.2 ± 0.6
KO (n=10)	32.1 ± 1.1*	78.5 ± 8.8***	328 ± 59***	93.8 ± 1.3*

Interpretation of results

Increases of volume/void in FVC and of VT in CMG in KO mice suggest the possibility that neural transmissions *via* mGluR1a are involved in the bladder afferent excitatory transmission in storage phase. Lower VE and higher MVP in KO mice, as compared to those in WT mice, are likely to be due to higher urethral resistance. This hypothesis is supported by the results of the previous two studies: (i) an i.t. injection of a mGluR antagonist produced a significant facilitation of peak firing in the EUS EMG activity [2], and (ii) mice lacking mGluR1a genes showed the EUS EMG activity during voiding exhibiting a prominent tonic component superimposed on bursting activity [3].

Concluding message

These studies suggest the possibility that mGluR1a mechanism is involved in the afferent excitatory transmission from the bladder during bladder filling and the inhibition of the excitatory pathway to the external urethral sphincter during voiding.

References

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Disclosures

Funding: Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research (C) No. 25462507 (to M. Yoshiyama) **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Mouse **Ethics Committee:** University of Yamanashi Institutional Animal Care and Use Committee