Acute unilateral ureteral distension inhibits glutamate-dependent spinal pelvic-urethra reflex potentiation via GABAergic neurotransmission in anesthetized rats

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Chen K-J, Peng H-Y, Cheng C-L, Chen C-H, Liao J-M, Ho Y-C, Liao J-T, Tung K-C, Hsu T-H, Lin T-B. Acute unilateral ureteral distension inhibits glutamate-dependent spinal pelvic-urethra reflex potentiation via GABAergic neurotransmission in anesthetized rats. Am J Physiol Renal Physiol 292: F1007–F1015, 2007. First published November 22, 2006; doi:10.1152/ajprenal.00256.2006.—The effects of an acute increase in intraureteral pressure (IUP) on pelvic-urethra reflex potentiation were examined in urethane-anesthetized rats by recording the external urethral sphincter electromyogram activities evoked by the pelvic afferent stimulation. Compared with a single action potential elicited by the test stimulation (TS; characterized by an intensity that evoked a constant reflex response without facilitation, 1/30 Hz, 1.03 ± 0.12 spikes/stimulation, n = 7), the repetitive stimulation [RS; identical stimulation intensity as the TS (1 Hz)] significantly induced spinal reflex potentiation (SRP; 16.90 ± 0.20 spikes/stimulation, P < 0.01, n = 7). Such SRP was significantly attenuated by intrathecal 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo (F) quinoxaline [NBQX; a glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionat (AMPA) receptor antagonist] and n-2-amino-5-phosphonovalerate [APV; a glutamatergic N-methyl-d-aspartate (NMDA) antagonist]; the spike number per stimulation: 11.0 ± 0.70 for NBQX, 1.01 ± 0.30 for APV, and 16.90 ± 2.0 for RS, respectively, n = 7, P < 0.01]. Acute stepwise elevations of IUP gradually attenuated and eventually abolished the RS-induced SRP (16.80 ± 1.30, 17.00 ± 1.30, 16.30 ± 1.30, 10.50 ± 1.80, 8.80 ± 1.90, 3.50 ± 1.60, 0.80 ± 0.20, 0.70 ± 0.20, and 0.20 ± 0.10 spikes/stimulation at intrabecal pressure of 0, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, and 20 cmH2O, respectively, n = 7). Intrathecal NMDA (a glutamatergic NMDA receptor agonist) and bicuculline (a GABA receptor antagonist) both reversed the abolition of RS-induced SRP caused by unilateral ureteral distension (14.0 ± 4.04 and 8.00 ± 1.53 spikes/stimulation, respectively, n = 7, P < 0.01). All the results suggested unilateral ureteral distension might compensatorily relax the urethra via GABAergic inhibition of NMDA-dependent SRP.

intrabecal pressure; unilateral ureteral obstruction; spinal reflex potentiation; N-methyl-d-aspartic acid

ACTIVITY-DEPENDENT REFLEX plasticity means that the efficacy of a reflex can vary depending on the patterns of ongoing activities (29). Long-term potentiation (LTP) (3, 4) is a long-lasting enhancement of the efficacy of excitatory synapses following a strong brief stimulation. Investigations of LTP have focused on the CA1 area of the hippocampus (25, 45) and suggested LTP is involved in the laying down of memory traces, partly because the CA1 area is known to be necessary for the formation of declarative memory and partly because LTP fulfills the requirements of Hebb’s model of memory (26, 36, 37). It is clear, however, that LTP occurs not only in the hippocampus but also in the central nervous system, including the dorsal horn neurons in the spinal cord (32).

Glutamate is widely utilized in the spinal cord for primary afferent neurotransmission (34). The glutamatergic receptors can be classified as metabotropic and ionotropic receptors. Metabotropic glutamatergic receptors that couple to the G protein may initiate intracellular messengers. On the other hand, ionotropic glutamatergic receptors are classified into three subtypes, including N-methyl-d-aspartate (NMDA), α-aminooxyhydroxy-5-methyl-4-isoxazolepropionat (AMPA)/quisqualate (QA), and kainate receptors. Ionotropic glutamatergic receptors directly regulate the permeability to sodium and potassium ions and, in the case of NMDA receptors, calcium ions as well (28). It is widely accepted that glutamatergic NMDA-dependent neural transmission underlies LTP (38). In NMDA-dependent LTP, the repetitive stimulation (RS) to the afferent fibers produces a surge of glutamate release and leads to a depolarization on the postsynaptic membrane. This subsequently removes the blockage of magnesium to the NMDA receptors and makes NMDA receptors permeable to calcium ions and therefore induces a series of cellular reactions (35). In the field of plasticity induction, the activation of NMDA receptors plays a key role in most synapses of nerve tissues because the intracellular biochemical cascades are triggered by the calcium ion influx gated by NMDA receptors (27).

GABA is an inhibitory neurotransmitter in the nervous system, including brain areas and the spinal dorsal horn (7). Investigations of the regulation of LTP in the CA1 area of the hippocampus have demonstrated that activation of a GABAergic system may attenuate the induction of LTP in brain slice preparations via its inhibitory effect on glutamatergic NMDA receptors (8, 16) and therefore indicated an impor-

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tart role of GABAergic neurotransmission in the modulation of LTP.

Urine storage is one of the important functions of the urinary bladder. During the storage phase of a micturition cycle, sensory impulses induced by bladder distension transmit centripetally onto the dorsal horn neurons through the pelvic efferent fibers (13). After sensory impulses have been integrated within the spinal cord, motor impulses travel centrifugally through the pudendal efferent fibers and finally cause external urethral sphincter contractions (19). Such a pelvic-urethra reflex is essential for the urethra to develop sufficient resistance to maintain urine continence during the storage phase of a micturition cycle (14). Our laboratory has recently reported that pelvic efferent nerve RS may elicit an activity-dependent spinal reflex potentiation (SRP) in pelvic-urethra reflex (PUR) activity (9, 22, 23). In addition, by using pharmaco-logical manipulations, we have demonstrated that such a SRP, similar to the LTP, is glutamatergic receptor dependent (23, 24).

An elevation in intravesical pressure (IUP) caused by a partial or complete obstruction in the lower urinary tract is seen in various pathological conditions. Many studies investigating lower urinary tract obstruction have shown that unilateral ureteral distention as well as subsequent hydroureret and hydronephrosis can have an effect on kidney function due to chronic fibrosis (11, 17, 21) and infiltration of inflammatory cells (42, 43). Chronic ureteral obstructions have an impact on the formation of urine due to tubuloglomerular feedback (44). In addition to the investigations of the pathophysiological mechanisms in ureteral obstruction, there are studies about the alternations in the spinal neurotransmission caused by a lower urinary tract obstruction. Results of these studies suggest that spinal glutamatergic NMDA-dependent neurotransmission is modulated by a lower urinary outlet obstruction (39, 47). Therefore, whether such a change in spinal NMDA neurotransmission caused by ureteral distension secondary to ureteral obstruction may affect the NMDA-dependent SRP is an interesting question to be answered. In the present study, we investigate whether acute unilateral ureteral distension may affect the RS-induced SRP and the possible neurotransmitter involved to clarify the effects of ureteral distension on micturition functions.

EXPERIMENTAL PROCEDURES

Animal preparation. Adult female Wistar rats, weighing 200–250 g, were anesthetized with urethane (1.2 g/kg ip). The animal care and the experimental protocol were in accordance with the guidelines of the National Science Council of Taiwan (NSC 1997) and the guidelines of the National Institute of Health’s Care and Use of Laboratory Animals (NIH Publication No. 80–23; revised 1996). All efforts were made to minimize both animal suffering and the number of animals used throughout the experiment. The trachea was intubated to keep the airway clear. A PE-50 catheter (Portex, Hythe, Kent, UK) was placed in the left femoral vein for administration of anesthetic to keep the airway clear. A PE-50 catheter (Portex, Hythe, Kent, UK) was placed in the left femoral vein for administration of anesthetic when needed. Body temperature was kept at 36.5–37.0°C by an infrared light and was monitored using a rectal thermometer. A midline abdominal incision was made to expose the pelvic viscera. Both the proximal and the distal ends of the right ureters were ligated tightly. A small opening for drainage was made using a microscissor on the ureter above the site of the proximal ligation to avoid hydro-nephrosis and kidney damage. The right pelvic nerve was dissected carefully from the surrounding tissues and was then transected as distally as possible for performance of the stimulations. The rats were monitored for the corneal reflex and a response to noxious stimulation to the paw throughout the experiment. If either was present, a supplementary dose (0.4 g/kg) of anesthetic was given through the venous catheter. At the end of the experiment, the animals were killed by an intravenous injection of potassium chloride saturation solution under deep anesthesia.

IUP. A catheter connected to a volume reservoir was inserted to the proximal end of the right ureter below the site of ligation. In experiments testing the effects of various IUP levels on the SRP, the position of the volume reservoir was changed sequentially at levels that were 0, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, and 20 cmH2O higher than in the right ureter and maintained, respectively. In our preliminary experiments, we found that the inhibitory effect on the SRP showed no further increase when the IUP was >20 cmH2O. Besides, an irreversible change would appear in the reflex activity if the IUP was maintained above 20 cmH2O for longer than 10 min. Therefore, we tested the effect of an IUP increase at the range below 20 cmH2O. IUP recording. In animals in which IUP was recorded, two 4-0 nylon threads were placed around the bladder trigone and ligated. IUP was continuously recorded on an oscilloscope (Tectronics TDS 3014, Wilsonville, OR) and the recording system (Biopac, MP30, Santa Barbara, CA) through a preamplifier (Grass 7P1, Grass, Cleve-land, OH) by an intrarethral catheter (PE-50), which was inserted into the urethra from the urethral opening.

Intrathecal catheter. An intrathecal catheter was inserted according to the technique described by Yaksh and Rudy (46). In short, the occipital crest of the skull was exposed and the atlantooccipital membrane was incised at the midline using the tip of an 18-gauge needle. A PE-10 catheter was inserted through the slit and passed caudally to the sixth lumbar level of the spinal cord. The volume of fluid within the cannula was kept constant at 10 μl in all experiments. Each single 10-μl volume of drug solution was administrated, followed by a 10-μl flush of artificial cerebrospinal fluid (18). At the end of the experiment, a laminectomy was performed to verify the location of the cannula tip.

Electromyogram recordings. Epoxy-coated copper wire (50 μm; Giken, Tokyo, Japan) electromyogram electrodes were placed in the external urethral sphincter using a 30-gauge needle with a hooked electromyogram electrode positioned at the tip. The needle was inserted into the sphincter ~1–2 mm lateral to the urethra and then withdrawn, leaving the electromyogram wires embedded in the mus-

Fig. 1. Schematic diagram for recording the external urethral sphincter electromyogram (EUSE) activity evoked by the electric stimulation (stim) at the central stump of the pelvic nerve. The fluid within the bladder cavity was drained free with a catheter on the bladder dome. The right ureter was ligated proximally (near the hilus of the right kidney, marked by a cross) and distally (near the bladder, marked by another cross). A small hole was made on the ureter at the site rostral to the proximal ligation. A catheter connected to a pressure transducer and a volume reservoir (VR) was inserted carefully into the right ureter at the site caudal to the proximal ligation to record and to manipulate the intraurethral pressure (IUP).
The electromyogram activity was amplified 20,000-fold and filtered (high frequency cutoff at 3,000 Hz and low at 30 Hz, respectively) by a preamplifier (Grass 7P1) and then was continuously displayed on an oscilloscope (Tectronics TDS 3014) and the recording system (Biopac, MP30). The dissected nerve and the stimulating/recording electrodes were bathed in a pool of warm paraffin oil (37°C) to prevent drying.

Application of drugs. Drugs dissolved in artificial cerebrospinal fluid with the pH value adjusted to 7.4 were used for intrathecal injections. Drugs used in the experiment were 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo (F) quinoxaline [NBQX; a glutamatergic AMPA receptor antagonist; 100 μM, 10 μl, Sigma], D-2-amino-5-phosphonovalerate (APV; a glutamatergic NMDA receptor antagonist; 100 μM, 10 μl, Sigma), L-glutamate (100 μM, 10 μl, Sigma), NMDA (100 μM, 10 μl, Sigma), and bicuculline (a GABA receptor antagonist; 100 μM, 10 μl, Sigma). These selected drug doses were used because previous studies showed that glutamate and NMDA induced, while NBQX and APV attenuated, spinal LTP in anesthetized rats at these doses (32). Therefore, we adopted these effective doses without obtaining a dose-response curve in our study. Artificial cerebrospinal fluid, of identical volume to the tested agents, was dispensed intrathecally to serve as a vehicle. At the end of the experiment, the location of the injection site was marked by an injection of Alcian blue (2%, 10 μl). The volume of drug injected into the spinal cord in such an experiment was reported to spread 0.5–1.5 mm from the site of injection (9). Therefore, a cannula positioned >0.5 mm away from the intended site of injection was not included in the statistical analysis.

Experimental arrangement. Recording the numbers of action potentials evoked by the electric shocks assessed PUR activity. The schematic arrangement of external urethral sphincter electromyogram (EUSE) recordings as well as the pelvic afferent nerve stimulation are shown in Fig. 1. Once the electrodes’ positions were optimized, recording of EUSE activity was started. An electric current of a square-wave pulse with pulse duration of 0.1 ms was applied from a stimulator (Grass S88) through a stimulus isolation unit (Grass SIU5B) and a constant-current unit (Grass CCU1A). The protocol for assessing the effects of electrical stimulations, different kinds of reagents, and different levels of IUP on PUR activity was as follows. 1) For test stimulation (TS), single shocks repeated at intervals of 30 s (1/30 Hz, lasting for 30 min; this frequency of stimulation did not result in response facilitation) were given through the stimulation electrodes to standardize the baseline reflex activity. 2) For RS, after the baseline reflex activity had been established by the TS, RS (1 Hz, lasting for 30 min, with intensity identical to the TS) was applied to induce SRP. 3) For agonist/antagonist tests, after a 30-min equilibrium period, the TS was once again applied for 30 min to establish a...
baseline reflex activity. In the agonist tests, NMDA or glutamate was tested intrathecally after the baseline reflex activity had been established. In the antagonist tests, RS was used to produce SRP once more after a vehicle flush (10 μl) that was followed by 30-min equilibrium. Then, NBQX or APV was tested via the intrathecal catheter after SRP had been established. 4) For IUP manipulations, after another vehicle flush (10 μl) with a 30-min equilibrium, RS (1 Hz) was tested once again at the IUPs of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, and 20 cmH2O, respectively. There was a 30-min equilibrium period between each two tests of different IUP levels.

Statistics. Results were analyzed by an SPSS package (SPSS/PC+; SPSS, Chicago, IL). All data in the text and figures are expressed as means ± SE. Because of the limited numbers in the experiment, nonparametric tests were used: the Wilcoxon signed rank test for comparison within groups and the Kruskal-Wallis test for comparison between groups. A P value of <0.05 (2-tailed) was considered statistically significant.

RESULTS

Baseline reflex activity. As shown in Fig. 2A, a single pulse of pelvic afferent nerve TS (1/30 Hz) evoked a single action potential in EUSE at the baseline IUP (i.e., 0 cmH2O). The mean latency for the TS to induce an action potential in the EUSE was 68.3 ± 0.5 ms (n = 7). The reflex activity evoked by the TS varied little over the test period; i.e., the mean spike numbers elicited by the TS showed no statistical difference throughout the period of stimulation (Fig. 2B, P > 0.05, n = 7).

RS-induced potentiation. As shown in Fig. 3A, at the baseline IUP (0 cmH2O), the pelvic nerve TS evoked a single action potential in EUSE, while RS induced SRP; i.e., the number of action potentials in EUSE evoked by each shock increased by 10.220.33.5 on June 22, 2017 http://ajprenal.physiology.org/ Downloaded from

Fig. 4. Effects of glutamatergic agonists/antagonists on pelvic-urethral reflex activities. A: single action potentials in EUSE were evoked by the TS (1/30 Hz) at the pelvic afferent nerve. Intrathecal glutamate (TS + Glu; 100 μM, 10 μl) and N-methyl-D-aspartate (NMDA; TS + NMDA; 100 μM, 10 μl) both potentiate the reflex activities evoked by the TS. On the other hand, a longer-lasting reflex potentiation was induced by the RS. Intrathecal 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo (F) quinoxaline (NBQX; RS + NBQX; 100 μM, 10 μl) attenuated, and intrathecal D-2-amino-5-phosphonovalerate (APV; RS + APV; 100 μM, 10 μl) abolished, the reflex potentiation caused by the RS. B: summarized data (means ± SE) show the potentiation in the reflex activity caused by glutamate (RS + Glu) and NMDA (RS + NMDA) as well as antagonism on the RS-induced reflex potentiation caused by NBQX (RS + NBQX) and APV (RS + APV). **P < 0.01 for the TS group. ##P < 0.01 for the RS group, n = 7.
gradually following the onset of stimulation and obtained a rather constant level at ~30 s until the cessation of stimulation. The summarized data in Fig. 3B showed that the mean spike numbers in EUSE elicited by RS were significantly higher than that done by the TS (*P < 0.01, **P < 0.01, n = 7).

**Glutamatergic agonists and antagonists.** As shown in Fig. 4A, RS on the pelvic afferent nerve induced SRP at the baseline IUP (RS). Intrathecal NBQX, a glutamatergic AMPA receptor-selective antagonist (100 μM, 10 μl, bolus), exhibited inhibitory effects on the RS-induced SRP (RS+NBQX, P < 0.01, n = 7). Intrathecal APV, a glutamatergic NMDA receptor antagonist (100 μM, 10 μl, bolus), elicited more pronounced inhibitory effects than did NBQX (RS+APV, P < 0.01, n = 7). On the other hand, the TS on the pelvic afferent nerve evoked a single action potential in EUSE at the baseline IUP (TS). Intrathecal glutamate and NMDA both exhibited excitatory effects on the TS-elicited reflex activities (TS+Glu and TS+NMDA, respectively). Figure 4B summarizes the data obtained by intrathecal application of glutamatergic receptor agonists and antagonists. Intrathecal glutamate and intrathecal NMDA (TS+Glu and TS+NMDA) both significantly produced excitatory effects on the TS-elicited reflex activities (counted at 30 min following the stimulation onset, both P < 0.01, n = 7). On the other hand, both intrathecal NBQX and

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**Fig. 5. Effects of increased IUP on the RS-induced potentiation of pelvic-urethral reflex activity.** A: a longer-lasting reflex potentiation was induced by the RS at baseline IUP (trace 1). The RS-induced reflex potentiation was gradually attenuated (traces 2 and 3) and eventually abolished (traces 4 and 5) when the IUP was stepwise increased. B: summarized data (means ± SE) show spike numbers evoked by the RS dropped steeply when the IUP was increased to >5 cmH₂O and reached a constant level when the IUP was again increased to >15 cmH₂O (n = 7).
intratheal APV (RS+NBQX and RS+APV) elicited significantly inhibitory effects on the RS-induced SRP (counted at 30 min following the stimulation onset, $P < 0.01, n = 7$).

**Effects of IUP increment.** As shown in Fig. 5A, when SRP had been established by the RS at the baseline IUP (trace 1), elevations in the IUP gradually attenuated (traces 2 and 3) and eventually abolished (traces 4 and 5) the RS-induced SRP. Mean spike numbers counted at 30 min following the stimulation onset at various IUP levels are summarized in Fig. 5B. When the IUP was below 5 cmH$_2$O, the RS-induced SRP was not affected by the IUP increment. However, when IUP was increased within the range 7.5–12.5 cmH$_2$O, the RS-induced SRP was significantly inhibited in association with the IUP increase. Besides, when the IUP was >15 cmH$_2$O, the inhibitory effects on the RS-induced SRP kept relative constant ($n = 7$).

**Changes in intraurethral pressure.** As shown in Fig. 6, A and B, TS evoked a single action potential, while RS produced SRP in the reflex activity at the baseline IUP (0 cmH$_2$O). The contraction wave of intraurethral pressure (IUUtP) secondary to the reflex activity was therefore elongated in parallel to the potentiate reflex activity produced by the RS, despite that the peak pressure was almost not affected. Figure 6C shows, as described in the above, an elevation in IUP (16 cmH$_2$O) abolished the RS-induced SRP. Furthermore, the elongation in IUUtP secondary to the potential reflex activity was also abolished by the elevation in IUP.

**Effects of NMDA.** As shown in Fig. 7A, compared with the TS-evoked single action potential, RS induced SRP that is abolished by the elevation in IUP caused by ureteral distension (RS+Dis). Intrathecal NMDA reversed such abolition of the RS-induced SRP caused by the ureteral distension (RS+Dis+NMDA). Figure 7C summarizes the spike numbers, counted 30 min following stimulation onset, evoked by TS, RS, and RS under ureteral distension without/with NMDA injections (RS+Dis and RS+Dis+NMDA, respectively). NMDA significantly reversed the blocking effect caused by the elevation in IUP ($+P < 0.01, n = 7$).

**Effects of bicuculline.** Figure 7B showed, quite differently from TS-evoked baseline reflex activity, that RS induced SRP that is abolished by the elevation in IUP caused by unilateral ureteral distension. Pretreated bicuculline, a GABAergic receptor antagonist, reversed the abolition caused by the IUP elevation. Figure 7D summarizes the spike numbers, counted 30 min following stimulation onset, evoked by TS, RS, and RS under ureteral distension without/bicuculline injections (RS+Dis and RS+Dis+Bicuculline, respectively). Bicuculline significantly reversed the blocking effect caused by the elevation in IUP ($+P < 0.01, n = 7$).

**DISCUSSION**

The results in the present study demonstrate a glutamatergic NMDA-dependent RS-induced SRP in PUR activity in in vivo animal preparations. In addition, acute increase in the IUP inhibited the glutamate-dependent RS-induced SRP and the elongated urethra contraction wave. Furthermore, a GABAergic antagonist, bicuculline, reversed the inhibition of the RS-induced SRP caused by ureteral distension.

PUR is physiologically important because it produces urethral contraction and therefore results in sufficient resistance for urine continence during the storage phase of a micturition cycle (14). Our laboratory has recently demonstrated an activity-dependent SRP in PUR activity, and suggests it may be physiological relevance to the urine continence and/or pathological relevance to hyperalgesia or allodynia (23, 24). In addition, using glutamatergic agonists/antagonists, we have suggested a spinal glutamate-mediated mechanism that is similar to the induction of LTP in the hippocampal CA1 area may underlie this SRP (9, 22).

Glutamate is widely utilized in the spinal cord for the primary afferent neurotransmission (34). In glutamate-mediated LTP, tetanization of the afferent fibers leads to depolarization in the postsynaptic membrane and therefore subsequently removes the blockade of magnesium to the NMDA receptors and makes NMDA receptors permeable to calcium ions (35). In the field of LTP induction, the rise of cytoplasmic calcium caused by calcium ions influx mediated by the activation of the NMDA receptor is a key factor in most synapses of nerve tissues because the intracellular biochemical cascades are triggered by the surge of free calcium ions (27). In addition to the excitatory neurotransmitters, such as glutamate, there are also inhibitory neurotransmitters involved in the spinal cord.
GABA and glycine are readily accepted as a vital inhibitory transmitter at the spinal cord level (7). GABA elicited an inhibitory effect on the superficial dorsal horn neurons through activation of the chloride-permeable GABA_A receptors (41) or G protein-coupled GABA_B receptors (6). It is widely accepted that GABAergic neurons in the spinal network provide pre-/postsynaptic inhibition of the primary afferent fibers and interneuronal axons (1, 2, 15). In studies investigating LTP, pre- and postsynaptic inhibitions of glutamatergic transmission by GABA receptors were observed in rat hippocampal neurons (16). In addition, an in vivo study has demonstrated that activation of GABA_A or GABA_B receptor activity might induce inhibition of spinal responses to primary afferent inputs via an inhibition of NMDA and metabotropic glutamate receptors-mediated synaptic transmission (8). All these reports imply that GABAergic neurotransmission may exhibit inhibitory effects on the glutamatergic system pre- or postsynaptically via an inhibition on glutamatergic NMDA receptors and/or metabotropic glutamate receptors and therefore abolished the NMDA-mediated LTP. Previous immunohistochemical investigation has demonstrated that the sacral GABA immunoreactive neurons, which are innervated by the descending control from the pontine micturition center, may produce urethral sphincter relaxation (5). In addition, GABA is the widely utilized neurotransmitter which mediates the sensory afferent fiber arising from the abdominal and pelvic viscera, including Fig. 7. NMDA and bicuculline reversed the inhibition of the RS-induced reflex potentiation caused by unilateral ureteral distension. A: TS evoked a single action potential in EUSE activity at baseline IUP (i.e., 0 cmH2O). RS produced a potentiation in the reflex activity that is abolished by an elevation of IUP caused by unilateral ureteral distension (RS+Dis). Intrathecal NMDA reversed such abolition of the RS-induced spinal reflex potentiation caused by the ureteral distension (RS+Dis+NMDA). B: pretreated bicuculline also reversed such abolition of the RS-induced spinal reflex potentiation caused by the ureteral distension (RS+Dis+Bicuculline). C and D: summarized data (means ± SE) show that NMDA and bicuculline reversed the inhibition of the RS-induced reflex potentiation caused by unilateral ureteral distension.
the ureters and rectum (7, 30). In the present study, a pretreated GABAergic antagonist reversed the blocking effect on the RS-induced SRP caused by unilateral ureteral distension. This result suggested unilateral ureteral distension may reflexively inhibit the RS-induced SRP via GABAergic neurotransmission. However, with the limitations of multiple unit recording techniques used in this study, the detailed mechanism involved in this inhibition still needs further investigations to be elucidated.

Obstruction of the urinary tract is a relatively common disease and thus has been the subject of intensive investigation (11, 17, 20, 21, 42, 43). The unilateral ureteral ligation, which caused ureteral distension, has emerged as an important model for the study of urinary tract obstruction. Many investigators have reported a ureteral obstruction, and the subsequent ureteral distension may lead to ureteral and kidney damage (10–12, 31, 40). In view of neural control in the lower urinary tract, the effects exerted by unilateral ureteral distension that mimics the pathological condition during ureteral obstruction have been less examined so far. Niedzielski (31) described significantly decreased numbers and distribution of nerve structures in the muscular layer of the ureteral wall and subsequently decreased innervations of the ureteral wall in children aged 3–12 yr with obstruction of the ureteropelvic junction and formation of hydrenephrosis (31). However, the effects of acute increase of IUP caused by the unilateral ureteral obstruction on bladder and urethral activities have not been intensively investigated. In the human being, the range of the IUP was reported to be within 9.7–22 cmH2O under physiological conditions and could be as high as 40–60 cmH2O under conditions of ureteral obstruction (33). The normal range of IUP in rats was estimated to be within 25 cmH2O. The IUP in the present study is, therefore, within the physiological range of IUP in rats. However, since the compliance of the ureter allows its filling volume without a significant pressure increase, the possibility that the inhibition of SRP caused by ureteral distension is involved in pathological conditions such as ureteral obstruction cannot be excluded.

In conclusion, our study has demonstrated that acute unilateral ureteral distension inhibits glutamate-dependent spinal PUR potentiation via GABAergic neurotransmission in anesthetized rats. However, two points remain to be answered. First, whether such an inhibition of the ureter-urethra reflex pathway is physiologically relevant to the micturition function or provides a protective mechanism to facilitate fluid elimination when the IUP is increased secondary to the obstruction occurring in the lower urinary tract needs further investigation. Second, whether such an inhibition of the ureter-urethra reflex pathway is purely via GABAergic systems or via other pathways needs further evaluation.

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