Effect of a 5-HT\textsubscript{1A} receptor agonist (8-OH-DPAT) on the external urethral sphincter activity in the rat

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**KEYWORDS**
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**Background/Purpose:** This study examined the effects of a 5-HT\textsubscript{1A} receptor agonist (8-OH-DPAT) on external urethral sphincter (EUS) activity in urethane-anesthetized rats.

**Methods:** An EUS electromyogram (EMG) and intravesical pressure (IVP) were simultaneously recorded during continuous cystometrographic monitoring, to provide a quantitative evaluation of EUS activity and urethral urodynamics of voiding.

**Results:** When examining the EUS burst activity, durations of the active (AP) and silent periods (SP) as a function of the time axis, respectively, exhibited concave- and convex-shaped curves. The burst discharges of the EUS-EMG were divided into nonvoiding and voiding burst activities based on the oscillation waves of the IVP, which were located in Phases 1 and 2 of the IVP. After 8-OH-DPAT treatment, the entire burst period in Phases 1 to 2 of the IVP was significantly prolonged. The average SP in both Phases 1 and 2 significantly increased but the average APs were not affected. Urodynamic results showed decreases in the volume threshold, contraction amplitude, and residual volume as well as an increase in the contraction duration. In addition, the amplitude of bladder high-frequency oscillatory waves in the IVP and the average urethral flow rate were reduced, but the entire voiding efficiency increased.

**Conclusion:** The influences of 8-OH-DPAT on EUS burst activity and urodynamics were exactly detected by the sophisticated EMG analytic design, and the results could be a reference for the pharmacological treatment of patients with lower urinary tract dysfunction.

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Introduction

Stress urinary incontinence (SUI) is one of the most common forms of incontinence among middle-aged women. Serotonergic agents (e.g., Duloxetine) are used to treat SUI in patients. However, recent studies continue to investigate the effects of serotonergic ligands on the bladder activity in animals. Serotonin (5-hydroxytryptamine, 5-HT) was characterized into 14 structurally different 5-HT receptors in mammalian species, which are divided into seven subfamilies (5-HT1 to 5-HT7). Studies indicated that some 5-HT receptors, i.e., 5-HT1, 5-HT2, and 5-HT3 receptors, are involved in the control of lower urinary tract (LUT) function. These 5-HT receptors and terminals are located on spinal cord areas that contain afferent and efferent components of LUT neural control centers. These receptors seem to modulate all of the pathways involved in the control of micturition, including the parasympathetic, sympathetic, and somatic pathways.

The 5-HT1A receptor is one of the most extensively investigated agents and has been used in various animal pharmacological experiments including the rat, guinea pig, and cat. However, contradictory results spurred various interpretations of the function of this receptor subtype in different animal species. A great deal of our original understanding of 5-HT mechanisms involved in controlling micturition came from cat experiments. For example, 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) significantly increased both the bladder volume threshold and the intercontraction interval, and thus moderately inhibited bladder activity in cat experiments. However, the bladder-inhibition effect is exactly the opposite of the bladder-excitatory effects of 8-OH-DPAT reported in rats. As the rat model has now become the main species for investigating urine storage and micturition reflexes, it is essential to precisely define the regulatory functions of 5-HT1A receptors in the LUT of rats.

Although recent studies continue to investigate the effects of 5-HT ligands on bladder activity, most rat studies focus on measuring urodynamic parameters, to detect the volume threshold (VT), changes in the VT, bladder pressure, voided volume (VV), and residual volume (RV). As external urethral sphincter (EUS) burst activity plays an important role in the micturition reflex in the rat, the electrophysiological effects of 5-HT on EUS activity require further investigation. In our recent studies, we developed a novel experimental design to analyze EUS burst discharges in urethane-anesthetized rats after nerve damage. In the present study, we continue exploiting this method to examine the role of the 5-HT1A receptor in controlling the micturition reflex by activating 5-HT1A receptors with 8-OH-DPAT (a 5HT receptor agonist) in urethane-anesthetized female rats. In addition, a new experimental design was used to analyze patterns of the external urethral sphincter electromyographic (EUS-EMG) burst discharges in time domain. Both EUS-EMG and intra-vesical pressure (IVP) were measured during continuous cystometry (CMG) to provide a quantitative evaluation of interactions between EUS activity and urodynamics during micturition.

Materials and methods

General preparation

A total of 21 female Sprague-Dawley rats (weighing 290–360 g) were used in this study. All rats were anesthetized with urethane (1.2 g/kg, s.c.). Body temperature was maintained at 36–38°C by a heating lamp. In addition, the femoral vein was catheterized for fluid and drug administration. The entire procedure was approved by the Institutional Animal Care and Use Committee of Taipei Medical University.

The urinary bladder was exposed via a midline abdominal incision. Two insulated silver wire electrodes (0.05 mm in diameter) with exposed tips were inserted into the lateral sides of the mid-urethra, where the muscle fibers of the EUS were identified. The recorded EUS-EMG was similar to that recorded from electrodes implanted into the exposed EUS via a pubic symphysis incision and was also completely blocked after neuromuscular blockade with pancuronium bromide (1.0–1.5 mg/kg i.v., pancuronium, Organon, Istanbul, Turkey), which confirmed that the EMG activity originated in striated sphincter muscles. A polyethylene (PE) tube 60 (1.0 mm ID and 1.5 mm OD) was then inserted into the bladder lumen for bladder pressure measurements. The bladder end of the PE tube was heated to form a collar and then passed through a small incision at the apex of the bladder dome. After the collar of the tube was tightened, the abdominal wall was closed with nylon sutures. The PE tube was in turn connected via a three-way stopcock to an infusion pump for filling with physiological saline and to a pressure transducer to monitor bladder pressure. The rats underwent urodynamic and EUS-EMG examinations that usually began 3–4 hours after the induction of anesthesia. The bladder pressure and EUS-EMG were first amplified and sampled at 12-bit resolution using a biological signal acquisition system (Biopac MP 150, BIOPAC Systems, Santa Barbara, CA, USA).

Physiological investigations

In the experiments, 8-OH-DAPT (0.3 mg/kg dissolved in saline, Sigma, St. Louis, MO, USA) was administered by an intravenous injection based on previous studies. Different doses of 8-OH-DPAT injected into the same animal were at approximately 40–60-minute intervals from each other. All rats underwent urodynamic and EUS-EMG examinations after the vehicle or drug dosing. The first post-treatment urodynamic and EUS-EMG examinations were usually completed within 30–45 minutes after drug administration. Transvesical cystometry was performed at an infusion rate of 0.123 mL/minute with physiological saline at room temperature. The urethra was opened to allow elimination of fluid during micturition. The infusion pump was turned off after three voiding contractions.

Various cystometric parameters were measured: (i) the micturition VT, which is the volume of saline sufficient to induce the first voiding contraction; (ii) contraction amplitude (CA), which is the maximal pressure during voiding; and (iii) bladder contraction duration (CD) during voiding, as shown in Fig. 1A. Additional urodynamic
Figure 1  Typical pattern of intravesical pressure (IVP) (upper traces) and external urethral sphincter electromyography (EUS-EMG) recorded during a continuous transvesical infusion cystometrographic (CMG) measurement in the anesthetized rat. (A) Bladder micturition contractions were measured with a constant rate (0.123 mL/minute) of the intravesical saline infusion, which was accompanied by large-amplitude EUS-EMG activity. The CMG parameters include micturition volume threshold (VT), contraction duration (CD), intercontraction interval (ICI), and contraction amplitude (CA). (B), (C), (D), and (E) are expansions in the time scale of the recording in (A). The parentheses indicate the recording periods in (B), (C), (D), and (E), respectively, at faster time scales. A micturition contraction was divided into the three phases of bladder activity in (B). The burst period (BP) in the EUS-EMG can be clearly observed in (C), which lasted from the end of Phase 1 throughout the entire duration of Phase 2. The BP in (D) could be divided into nonvoiding and voiding burst activities, which were located in Phases 1 and 2, respectively. The voiding burst activity was accompanied by the IVP superimposed with a series of high-frequency oscillations (HFOs) but the nonvoiding bursts did not cause any oscillation waves in the IVP. (E) Individual bursts were composed of active (APs) and silent periods (SPs).
parameters were obtained: RV, VV, and voiding efficiency (VE). RV is the volume of saline withdrawn through the intravesical catheter after micturition. The collection of fluid was facilitated by manually pressing on the abdominal wall. VV is represented as the VT minus the RV, and the ratio between VV and VT is computed as VE. The person conducting the EMG activity analysis was blinded to the status of the rat. As described in earlier papers, a single micturition contraction of the bladder can be divided into three phases of IVP (Fig. 1). Various EUS-EMG parameters in Phases 1 and 2 of IVP were measured including the average duration of the burst period (BP), the silent period (SP), the active period (AP), the number of SPs (Num), the frequency of the burst discharge (FB), and the average urethral flow rate (the ratio of the VV to the BP, VV/TSP). All data obtained from three micturition contractions were averaged for each animal with the aid of Acqknowledge software (BIOPAC Systems).

**Statistical analysis**

All parameters obtained from CMGs and EUS-EMG are presented as the mean value ± standard deviation (SD). The parameters obtained after vehicle and drug administration were statistically compared using the Student t-test. A p value <0.05 was considered statistically significant.

**Results**

**Typical pattern of bladder activity and EUS-EMG during CMG**

Typical IVP and EUS-EMG measurements are depicted in Fig. 1A. The rat after vehicle treatment exhibited micturition contractions during the continuous intravesical infusion of saline. EUS-EMG exhibited low-amplitude tonic activity during the initial filling phase of CMG or between micturition contractions but it markedly increased in amplitude during bladder contractions. According to Maggi et al., a single micturition contraction of the bladder can be divided into three phases of IVP: Phase 1, rising phase; Phase 2, high-frequency oscillation (HFO) phase; and Phase 3, rebound and failing phase, as shown in Fig. 1B. During a single micturition contraction, the EUS-EMG clearly shows a long BP, which lasted from the end of Phase 1 throughout the entire duration of Phase 2, as depicted in Fig. 1C. In most cases (n = 18 of 21 rats), the BP could be divided into nonvoiding and voiding burst activities, which was characterized by HFO waves in the IVP (Fig. 1D). The nonvoiding burst activity at Phase 1 usually appeared for a short period (for < 1 second) and was not accompanied by any oscillation waves in the IVP. However, the voiding burst activity at Phase 2 usually lasted 3–5 s and was accompanied by the IVP superimposed with a series of HFOs. Burst discharges in the BP were characterized by clusters of high-frequency spikes (AP) separated by periods of quiescence (SP), as shown in Fig. 1E.

**The effect of 8-OH-DPAT on the three phases of micturition contractions**

Similar to the control CMG, the rat after 8-OH-DPAT treatment still exhibited regular voiding contractions during the recordings. Typical patterns of the IVP and EUS-EMG activity during the three phases of micturition recorded from the same rat after vehicle and drug treatments are compared in Fig. 2A and 2B, respectively.

After vehicle treatment, EUS-EMG gradually increased its tonic discharge during Phase 1, in parallel with the sharply increased IVP (Fig. 2A,C). At approximately the end of Phase 1, EUS-EMG with a short period of a nonvoiding burst discharge (approximately 1 second) was recorded, as depicted in Fig. 2C. During this period, no apparent urination was found as the bladder neck or proximal urethral sphincter was still closed (no HFOs in the IVP). During Phase 2, a series of HFOs was superimposed on the IVP. The HFOs were correlated with the voiding burst discharge of EUS-EMG. Meanwhile, HFOs were commonly accompanied by the emission of fluid in a stream-like manner. During Phase 3, the IVP initially appeared as a rebound pressure, followed by a rapid fall in the IVP (Fig. 2E). The EUS-EMG converted to tonic-type activity during Phase 3. No urine was expelled during this phase.

After 8-OH-DPAT treatment, the pattern of micturition contractions prominently altered the IVP of all three phases. In Phase 1, the IVP slowly increased (compared to that in Fig. 2C) with a prolonged duration of the rising phase, as shown in Fig. 2D. As a result, the maximal amplitude of the IVP was dramatically reduced compared to the controls. In addition, during this phase, almost the entire tonic EUS-EMG was transformed into nonvoiding burst activity (approximately 3–5 s) until the end of Phase 1, as shown in Fig. 1D. This phenomenon should not have been due to an overdose of the drug, as it can be produced in anesthetized rats even at low doses of 8-OH-DPAT. During Phase 2, the entire period of the burst discharge was significantly prolonged, which is in parallel with the occurrence of HFOs in IVP (Fig. 2B,D). Observations at the urethral outlet showed that urine was emitted in a long stream-like pattern during this phase. By contrast, the amplitude of HFO waves in the IVP during this phase was significantly reduced compared to the controls, as shown in Fig. 3. In Phase 3, the voiding burst activity of EUS-EMG was transformed into a tonic

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*Figure 2* Comparison of the intravesical pressure (IVP) (top traces) and external urethral sphincter electromyographic (EUS-EMG) activity (bottom traces) of the three phases of micturition after administration of vehicle and 0.3 mg/kg of 8-OH-DPAT to an anesthetized rat. Typical patterns of micturition contraction recorded from one rat after vehicle and drug treatments are shown in (A) and (B), respectively. The parentheses in (A) indicate the recording period micturition in (C) and (E) at faster time scales. Similarly, (D) and (F) are expansions of plots in (B) marked with parentheses. Comparing the phase durations before and after 8-OH-DPAT treatment, the duration of nonvoiding burst activity was elongated in Phase 1 (compare C with D), and the duration of burst activity was elongated in Phase 2 (shown in A and B). In Phase 3, the rebound pressure of the IVP almost completely disappeared (compare E and F).
discharge, and gradually decreased (Fig. 2F). Similar to Phase 1 of the IVP, bladder contractions showed a prolonged and slowly descending IVP. But the rebound pressure detected in control rats had almost disappeared or was unclear after drug administration.

The pattern of burst activity

The 5-HT receptor agonist (8-OH-DPAT) induced a long BP lasting from Phases 1 to 2 (Fig. 2B). When examining the distribution of the duration of the burst discharges in detail, the burst discharges were transformed into two curves: SP and AP curves. The curves are the function of the durations of the AP and SP to the corresponding time axis which was represented as the middle of the duration of each AP or SP, as shown in Fig. 4A. Typical patterns of SP and AP curves after vehicle and 8-OH-DPAT treatments are, respectively, shown in Fig. 4B and 4C. In most cases (n = 17 of 21 rats), vehicle treatment, the AP curve exhibited a concave-like shape whereas the SP curve showed a convex shape (Fig. 4B). During the nonvoiding burst activity in Phase 1, the AP and SP curves showed an asymptotic decrease (starting from 100 ms) and increase (starting from 60 ms), respectively, until the end of Phase 1. At the beginning of Phase 2 or the middle of Phase 2, the AP and SP curves almost reached the bottom around 60 milliseconds and a plateau around 100 milliseconds, respectively. Finally, the AP curve at the end of Phase 2 asymptotically ascended to around 80 milliseconds, whereas the SP curve asymptotically descended close to the initial value of the curve.

After 8-OH-DPAT (0.3 mg/kg) treatment, the entire AP and SP curves were both elongated approximately 2.5-fold that of the control (Fig. 4C). The initial value of the AP curve was elevated to 150 milliseconds, and then the AP curve exhibited an asymptotic decrease to the end of Phase 1 and reached the bottom around 60 milliseconds to the end of Phase 2. In contrast to the control AP curve, AP after treatment did not show an ascending phase at the end of Phase 2. The SP curve showed a sharply increasing curve which soon formed a plateau at the beginning of the curve. The plateau was elevated up to around 150 milliseconds and lasted from Phase 1 to the end of Phase 2. During the plateau period, there were several sporadic SPs with very long durations which reached 300 milliseconds in some cases.

Measurements of EUS-EMG and bladder activity parameters

The drug effects on the relationship between bladder activity and EUS-EMG parameters were determined during continuous CMGs in rats. The summary of changes in the urodynamic and EUS-EMG parameters in rats (n = 12) after intravenous administration of vehicle and 8-OH-DPAT is tabulated in Tables 1 and 2, respectively.

During the CMGs, the average VT for stimulating voiding significantly decreased after 5-HT treatment compared to that of the vehicle (Table 1). Moreover, the average maximal CA during voiding was significantly reduced after 5-HT treatment. 8-OH-DPAT slightly reduced the average VV from 0.44 to 0.39 mL, but there was no significant difference compared to the vehicle. In addition, the CD significantly increased after administering the 5-HT receptor agonist (23.94 ± 2.40 vs. 31.92 ± 7.63 seconds, p < 0.05). The RV significantly decreased in rats with 5-HT treatment (0.05 ± 0.02 mL) compared to values (0.19 ± 0.03 mL) in vehicle. The average VE, i.e., the ratio of VV to VT, in rats after 5-HT treatment had markedly increased from approximately 68% to 88%.

By contrast, EUS-EMG measurements in rats with vehicle treatment, the average duration of the BP in Phase 1 (0.86 ± 0.47 seconds) was much shorter than that in Phase 2 (3.91 ± 0.50 seconds) (Table 2). In addition, the SP in Phase 1 (69.1 ± 5.4 milliseconds) was much shorter than that in Phase 2 (98.5 ± 3.4 milliseconds), but the AP in Phase 1 (99.4 ± 3.8 milliseconds) was much longer (65.6 ± 2.9 milliseconds) than that in Phase 2. After 8-OH-DPAT treatment, the average durations of the BP in Phases 1 and 2 had
significantly increased by approximately 4- and 2-fold of the vehicle, respectively. Moreover, the average durations of the SP were significantly increased in Phase 1 (by approximately 1.8-fold that of the vehicle) and in Phase 2 (by approximately 1.7-fold that of the control), but no significant difference was found in the average durations of the AP in Phases 1 or 2 compared to the vehicle. In addition, the average frequency of bursting discharge (FB) and the ratio of the Num to the BP significantly decreased in both Phases 1 (from 5.95 to 4.48 Hz) and 2 (from 6.05 to 4.19 Hz). The averaged urethral flow rate (VU/TSP) in Phase 2 was significantly reduced by 8-OH-DPAT.

Discussion

The present results indicate that activation of 5-HT_{1A} receptors by 8-OH-DPAT significantly affected the pattern of EUS-EMG burst activity and urodynamic parameters in female urethane-anesthetized rats. In control EUS-EMG, we detected a short period of burst discharges before the oscillation waves of IVP, called the nonvoiding burst activity. After drug administration (0.3 mg/kg, i.v.), the entire tonic EUS-EMG in Phase 1 of the IVP was almost completely transformed into nonvoiding burst activity in which the duration of the SP increased. EMG activity occurring during bladder filling would originate from striated muscles rather than smooth muscles as noted in our previous studies, because EMG activity was eliminated after acute nerve transection or administration of a neuromuscular blockade agent.EMG activity occurring during bladder filling would originate from striated muscles rather than smooth muscles as noted in our previous studies, because EMG activity was eliminated after acute nerve transection or administration of a neuromuscular blockade agent.14 Other studies showed that 8-OH-DPAT acts on at least two different and independent sites of the central nerve system (CNS): one at the spinal cord and the other at the supraspinal level.15 Recent studies indicated that burst activity was detected in rats with acute and chronic spinal cord injuries after giving 8-OH-DPAT via i.v. administration.18 Therefore, the possible action site for initiating nonvoiding burst activity is located at the spinal cord level, but determining the involved segments of the spinal cord requires further experiments. In general, our results show that 8-OH-DPAT might have an excitatory effect on somatic pathways in the spinal cord and may trigger the generator of EUS burst activity early during voiding.

We examined the pattern of burst activity by observing the SP curve as a function of its time course. In control data, the SP curve exhibited a convex-like shape during the BP. It asymptotically increased at the beginning of the BP and decreased at the end of the BP. Interestingly, this pattern is similar to that indicated by previous studies of the urethral flow rate of female rats gradually increasing at the beginning and declining at the end of the voiding curve exhibited a concave-like shape, whereas the SP curve showed a convex curve in (B). At the end of Phase 1, the AP and SP curves asymptotically reached the bottom and plateau, and then at the end of Phase 2 the curves gradually increased and decreased, respectively. (C) After the administration of 8-OH-DPAT, both the AP and SP curves were prominently elongated. The AP and SP curves reached the bottom and plateau prior to the end of Phase 1, and then remained at the bottom and plateau until the end of Phase 2, respectively.
Therefore, the duration of the SP rather than the AP is an important factor influencing bladder emptying.

By contrast, the asymptotical increase at the beginning of the BP (approximately 1 second in most rats) is located in Phase 1, which is prior to the appearance of bladder high-frequency oscillation waves in the IVP. We think this phenomenon might be due to the EUS burst activity appearing before bladder neck opening. Therefore, it cannot detect any fluid drops around the urethral outlet during this period or oscillation waves in the IVP. Hence, the nonvoiding burst activity was markedly prolonged by up to approximately 3.6 s after 8-OH-DPAT treatment. The entire tonic EUS-EMG activity for the entire Phase 1 was transformed into burst discharges. However, the actual role of nonvoiding burst activity requires further explanation. Previous studies indicated that the EUS acts as a valve which permits fluid to escape from the bladder and accelerates the flow that generates the fast flow rate peaks. These nonvoiding bursts might act as a warm-up period for EUS activity to make micturition more efficient in Phase 2.

In our results, the general effect of 8-OH-DPAT enhanced the VE in anesthetized female rats. This could be accounted for by several mechanisms. First, the burst activity of EUS-EMG in Phase 2 reflects the rhythmic opening and closing of the outlet to produce the pulsatile flow of urine that is common in rodents. Electrophysiological studies showed that the EUS-EMG in normal control rats exhibits a 4–8-Hz BP during voiding. The EUS-EMG bursting, particularly occurring during the SP, represents the relaxation and opening of the outlet which is essential to achieve efficient voiding. Our previous study showed that rats with pudendal nerve injury exhibited a decreased duration of the SP as well as an increased frequency of EUS-EMG bursting, and thus a decreased duration of urethral opening which caused voiding inefficacy. On the contrary, our current results indicated that 8-OH-DPAT increased the duration of the SP of EUS-EMG bursting. Thus, the urethra was open for a longer period permitting urine evacuation from the urethra which may have partially contributed to the increased voiding efficiency.

Another possibility is that 8-OH-DPAT might alter bladder activity (decreased VT but increased CD) during the CMG measurements. Our results indicated that 8-OH-DPAT decreased the VT but did not significantly decrease the value of the VV. In addition, 8-OH-DPAT increased the bladder CD supporting the fact that the drug enhances bladder contractile ability to maintain the same level of VV as in the controls. Above all, results indicated that 8-OH-DPAT could enhance bladder evacuation by decreasing the VT and improving bladder contractions. It is also noteworthy that 8-OH-DPAT increased the duration of both the SP and CD. Studies reported that stimulation of urine flow to the urethra could excite afferent nerves and in turn facilitate reflex bladder contractions. This facilitative urethra-to-bladder reflex could promote complete bladder emptying. This assumption was supported by our present results. The increase in the duration of the SP represented an increased duration of urine flow stimulation to the urethra. Thus, the urethra-to-bladder reflex was enhanced and sustained for a longer duration of bladder emptying. By contrast, 8-OH-DPAT decreased the bladder CA during CMG. This result seems to be inconsistent with the consensus that 8-OH-DPAT enhances bladder CA and thus improves VE. This might be attributed to 8-OH-DPAT affecting EUS-EMG activity during the burst period (by increasing the SP). The increase in the duration of the SP in Phase 2 of the BP indicated that the rat had longer relaxation and opening durations in the urethral outlet as well as lower urethral outlet resistance during bladder evacuation. This assumption, supported by recent studies, indicated that 8-OH-DPAT increased bladder CA during transurethral CMG with the ligation of bladder outlet. Therefore, 8-OH-DPAT markedly decreased the amplitude of the bladder contraction that occurred with longer SPs.

In contrast to the amplitude of bladder contractions, the amplitude of HFO waves in the IVP during burst activity was significantly reduced by 8-OH-DPAT (Fig. 3). Intuitively, this implies that 8-OH-DPAT reduced the pulsatile effect, which is adverse for efficient urine expulsion during voiding. Surprisingly, 8-OH-DPAT treatment did not reduce the bladder’s voiding function but produced a positive effect on VE. This might be attributed to improved bladder contractions and lengthened urethral opening periods induced by the drug to compensate for the lower urethral flow rate. However, further experiments are needed to quantify the roles of detrusor contractions and EUS burst activity in VE.

In this study, the average urethral flow calculated by the ratio of void volume to burst period (VV/TSP) might not exactly reflect the real flow velocity, because the real urethral flow in the rat should be a nonlinear transformation pattern due to the intermittent EUS activity. However, the experimental design could be useful to determine the relationship between urodynamics and EUS-EMG. The urethral flow rate was reduced by 8-OH-DPAT, which is reasonable as the drug simultaneously lengthened the urethral opening periods (silent period, see Table 2).

| Parameters of bladder activity after administration of vehicle and 8-OH-DPAT in the rat. |
|-----------------------------------------------|---------------|---------------|---------------|
| VT (mL)                                      | CA (cm H2O)   | CD (s)        | VV (mL)       |
| Vehicle                                     | 0.64 (±0.10)  | 24.98 (±1.22) | 23.94 (±2.40) |
| 8-OH-DPAT (0.3 mg/kg)                       | 0.44* (±0.10) | 20.24* (±1.96)| 31.92* (±7.63)|

Values are Mean ± SD.

* A p-value < 0.05 indicates a statistically significant difference compared with vehicle treatment.

CA = contraction amplitude; CD = contraction duration; RV = residual volume; VE = voiding efficiency; VV/VT; VT = volume threshold; VV = voided volume.
In summary, the present results indicate that the typical pattern of EUS-EMG burst activity in urethane-anesthetized rat exhibited a concave and a convex waveform in AP and SP curves, respectively. The burst activity was markedly prolonged by the activation of 5-HT$_1A$ receptor with 8-OH-DPAT treatment. Moreover, the drug also altered voiding efficiency due to a longer excitation of bladder activity coinciding with prolonged urethral opening periods during micturition. These results provide a more detailed understanding of the properties of the relationship between urodynamics and EUS-EMG after 8-OH-DPAT treatment that could promote the development of pharmacological-based treatments for lower urinary tract dysfunction.

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