Improving voiding efficiency in the diabetic rat by a 5-HT1A serotonin receptor agonist

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Introduction
Bladder dysfunction in patients with chronic diabetes mellitus (DM) is characterized by impaired bladder sensation, increased bladder capacity, decreased bladder contractility and increased residual urine. Diabetic cystopathy has been attributed primarily to peripheral neuropathy, involving autonomic and somatic sensory and motor nerves. However, DM also impairs the innervation of the urethra and directly impairs urethral Closing and opening. The resulting diabetic urethra pathology could degrade voiding function by impairing outlet function and urethra-to-bladder reflexes. The voiding phase in rats is associated with intraluminal pressure high frequency oscillations (IPHOs) and pulsatile flow of urine. The IPHOs consist of a series of urethral openings and closures, believed to create a “wirling action” of the urethra. Without the IPHOs the bladder does not empty effectively. The IPHOs are thought to arise from contractions of the sphincter and spread by a pressure pulse backwards to the bladder. In normal rats, this alternating EUS activation and relaxation occurs at about 6 Hz during voiding. Voiding efficiency is reduced when this phase EUS activity during voiding is prevented. The bulbar and parasympathetic, as well as the sphincter motoneuronal network (SNc of the nucleus), receive a dense serotonergic input, and the descending bulbo-splanchnic pathway to the lower urinary tract is an inhibitory circuit, with 5-HT as a key neurotransmitter. Ligands acting at 5-HT1A receptors modify lower urinary tract function and have effects on both the external urethral sphincter (EUS) and external anal sphincter.

Materials and methods
A total of 18 adult female Sprague-Dawley rats initially weighing 250 to 275 g were used. DM was induced by intraperitoneal injection of STZ (65 mg/kg) after 18 hours of fasting. Rats were considered diabetic when blood glucose was 300 mg/dl or greater. Rats were anesthetized with urethane. A polyethylene catheter (PE-50) was placed in the left jugular vein for i.v. drug administration. The urinary bladder was exposed via a midline abdominal incision, a polyethylene catheter (PE-50) with a flared end was inserted through the bladder dome, and a suture was tightened around it. The other end of the bladder catheter was connected to a microinfusion pump for continuous infusion of saline and to a pressure transducer for intravesical pressure monitoring. The 5-HT1A antagonist WAY-100635 was administered after each 8-OH-DPAT dose-response curve. To record the EUS-EMG, two fine insulated silver wire electrodes (0.05 mm diameter) with exposed tips were inserted into lateral sides of the urethra, where muscle fibers of the EUS were identified. EUS-EMG was recorded and analyzed using laboratory data acquisition system. All data are expressed as the mean ± SD. Fisher’s test was used to determine the statistical difference of proportions between groups. The paired Student t test or 1-way ANOVA followed by the Bonferroni correction was used for statistical comparisons within and between groups with p <0.05 considered significant.

Methods

**Results**

**General Characteristics of Control vs DM Rats**

DM rats body mass was significantly less than that of controls, whereas the DM rat blood glucose level, bladder capacity, and bladder mass were significantly increased above those of controls (Table 1).

**Cystometric variables**

Normal control rats (n=7). In the normal animals, mean micturition volume was 0.44 ± 0.07 ml, bladder capacity 0.54 ± 0.07 ml, residual volume 0.12 ± 0.00 ml, peak intravesical pressure 21.8 ± 8.92 cm H2O, and voiding efficiency 81 ± 3.0%. With increasing doses of 8-OH-DPAT, bladder capacity and micturition volume decreased significantly (Figure 1).

**EUS-EMG**

Normal control rats and DM rats exhibit different types of EUS-EMG activity during bladder contractions under urethane anesthesia; normal control rats show heightened tonic activity interrupted by phasic relaxations, whereas DM rats show shorter periods of alternating bursts and pauses, including decreases of the number of the pauses and/or the length of individual pause (EUS dysfunction), which consequently result in voiding dysfunction. Intravenous administration of 8-OH-DPAT to both normal control rats and DM rats resulted in dose-dependent increasing of phasic EUS relaxations, including the number of the pauses and/or the length of individual pause, and this increasing was reversed with WAY-100635 (Figure 3).

**Conclusions**

Both the bladder voiding efficiency and the period EUS activity were decreased in DM rats. 5-HT1A receptor agonist promoted period EUS activity, thereby improving voiding efficiency. Whether or not these results may have implications for the future treatment of voiding dysfunction in DM patients remains to be studied.

**Literature cited**

Dobler PC, Gu B, Zhang X, et al. 2007. Activation of the external urethral sphincter central pattern generator by a 5-HT1A receptor agonist in rats with chronic spinal cord injury. Am J Physiol Regul Integr Comp Physiol 292:R169–76. Gu B, Fraser MO, Thor KB, et al. 2004. Induction of diabetic urethropathy could degrade voiding function by impairing outlet function and urethra-to-bladder reflexes. The vesicourethral phase in rats is associated with intraluminal pressure high frequency oscillations (IPHFOs) and pulsatile flow of urine. The IPHFOs consist of a series of urethral openings and closures, believed to create a “wirling action” of the urethra. Without the IPHFOs the bladder does not empty effectively. The IPHFOs are thought to arise from contractions of the sphincter and spread by a pressure pulse backwards to the bladder. In normal rats, this alternating EUS activation and relaxation occurs at about 6 Hz during voiding. Voiding efficiency is reduced when this phase EUS activity during voiding is prevented. The bulbar and parasympathetic, as well as the sphincter motoneuronal network (SNc of the nucleus), receive a dense serotonergic input, and the descending bulbo-splanchnic pathway to the lower urinary tract is an inhibitory circuit, with 5-HT as a key neurotransmitter. Ligands acting at 5-HT1A receptors modify lower urinary tract function and have effects on both the external urethral sphincter (EUS) and external anal sphincter.

**Fig. 1.** Dose–response curves for the effects of i.v. 8-OH-DPAT on cystometric variables and EUS-EMG pauses/micturition in DM rats. Asterisks indicate significant increases in micturition volume, voiding efficiency, EUS-EMG pauses/micturition and decreases in residual volume, bladder capacity, and peak intravesical pressure relative to vehicle values (V).

**Fig. 2.** Dose-response curves for cystometric variables in DM rats are shown in Figure 2.

**Fig. 3.** Effect of increasing doses of 8-OH-DPAT on EUS-EMG activity in normal control rats and DM rats.

**For further information**

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