Research report

Role of spinal $\alpha_1$-adrenergic mechanisms in the control of lower urinary tract in the rat
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Abstract

The role of spinal $\alpha_1$-adrenergic mechanisms in the control of urinary bladder function was examined in urethane (1.2 g/kg s.c.) anesthetized and decerebrate unanesthetized female Sprague–Dawley rats (250–320 g). Bladder activity was recorded via a transurethral catheter during continuous infusion (0.21 ml/min) cystometrograms or under isovolumetric conditions. All drugs were administered intrathecally at the L–S segmental level of spinal cord. During cystometrograms, 3 or 30 nmol of phenylephrine ($\alpha_1$-adrenergic agonist) did not alter bladder activity; whereas 300 nmol increased the intercontraction interval by 98% and pressure threshold for inducing micturition by 115%, but did not change bladder contraction amplitude. A large dose of phenylephrine (3000 nmol) completely blocked reflex voiding and induced overflow incontinence at a high baseline pressure (mean: 33 cmH$_2$O; range: 28–42 cmH$_2$O). Under isovolumetric conditions, 3–30 nmol of phenylephrine abolished bladder activity for 22–45 min; whereas smaller doses (0.003–0.3 nmol) were inactive. Doxazosin (50 nmol), an $\alpha_1$-adrenergic antagonist, decreased intercontraction intervals but did not change bladder contraction amplitude during cystometrograms. Under isovolumetric conditions this dose of doxazosin increased bladder contraction frequency and decreased bladder contraction amplitude. Smaller doses (5 or 25 nmol) of doxazosin did not alter bladder activity. These studies suggest that two types of spinal $\alpha_1$-adrenergic mechanisms are involved in reflex bladder activity: (1) inhibitory control of the frequency of voiding reflexes presumably by regulating afferent processing in the spinal cord and (2) facilitatory modulation of the descending limb of the micturition reflex pathway.

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1. Introduction

Interest in the role of central noradrenergic pathways in the control of micturition was stimulated by the report of Dahlström and Fuxe [1] that sympathetic and parasympathetic nuclei in the lumbosacral cord receive inputs from noradrenergic neurons in the brainstem. A significant proportion of these inputs arise in the locus coeruleus (LC) [1,14,20,21,23], which has been implicated in the supraspinal control of micturition [3,26,27]. In rats, destruction of bulbospinal noradrenergic pathways with 6-hydroxy-dopamine did not depress voiding [14,20,21]; however, studies in anesthetized cats, revealed that electrical stimulation of the LC induced bladder contractions that were blocked by the intrathecal (i.t.) injection of prazosin, an $\alpha_1$-adrenergic antagonist [26,27]. In addition, destruction of noradrenergic cells in the LC by microinjection of 6-hydroxy-dopamine produced a hypoactive bladder, and this effect was partially reversed by the i.t. injection of phenylephrine (an $\alpha_1$-adrenergic agonist) suggesting that bulbospinal noradrenergic pathways are involved in the micturition reflex. It is noteworthy, however, that iontophoretic application of norepinephrine to bladder preganglionic neurons (PGNs) did not excite but rather inhibited synaptic and amino acid...
evoked firing [18]. This finding is consistent with the electrophysiological data indicating that the descending noradrenergic excitatory pathway from the LC terminates on interneurons in the region of the sacral parasympathetic nucleus rather than PGNs and that the interneurons make excitatory synaptic contacts with the PGNs to complete the descending pathway [28]. Iontophoretic application of prazosin blocked the excitatory effect of LC stimulation on interneurons but did not block the excitation of PGNs. In contrast to these results in anesthetized cats, experiments in conscious cats did not reveal an inhibitory effect of i.t. prazosin on voiding [6]. However, 6-hydroxy-dopamine treatment did increase bladder capacity.

Pharmaceutical studies in rats have also used adrenergic drugs to determine the function of bulbospinal noradrenergic pathways in the regulation of micturition [4,25]. Kontani et al. [12] reported that in anesthetized rats, i.t. administration of phenylephrine abolished bladder activity; whereas prazosin did not alter bladder contractions during continuous infusion cystometrograms (CMGs). On the other hand, Ishizuka et al. [10] noted that pressure during a CMG when the bladder was filled with a transducer was used to record the bladder pressure isovolumetrically with the urethral outlet ligated or to record activity; whereas prazosin did not alter bladder contractions during voiding [6]. However, 6-hydroxy-dopamine treatment did increase bladder capacity.

In the present studies, the involvement of spinal $\alpha_1$-adrenergic pathways in the regulation of micturition was examined in anesthetized and decerebrate unanesthetized rats by studying the effects of drugs administered intrathecally on reflex bladder contractions recorded under isovolumetric conditions or during continuous infusion CMGs. Our results revealed two types of spinal $\alpha_1$-adrenergic mechanisms involved in reflex bladder activity: (1) inhibitory control of the frequency of reflex bladder contractions, presumably due to modulation of afferent processing in the spinal cord and (2) excitatory modulation of the amplitude of bladder contractions, presumably due to regulation of the descending limb of the spinobulbospinal bladder reflex pathway.

A preliminary account of this work has been presented in abstract form [5,30].

2. Materials and methods

2.1. Animal preparation

Experiments were performed on urethane anesthetized (1.2 g/kg s.c.) or decerebrate unanesthetized female Sprague–Dawley rats weighing 250–300 g. The trachea was cannulated with a polyethylene tube (PE-240, Clay Adams, Parsippany, NJ, USA) to facilitate respiration. An i.t. catheter was inserted according to the technique of Adams, Parsippany, NJ, USA) to facilitate respiration. An
the electrical activity of the striated muscle. A 30-Gauge needle with a hooked EMG electrode positioned at the tip was inserted into sphincter approximately 5–10 mm lateral to the urethra and then withdrawn leaving the EMG wires embedded in the muscle [13]. The EMG activity was passed through a discriminator/ratemeter and recorded on chart recorder. The peak firing rate during each micturition contraction was measured.

The protocols in these studies were approved by the Animal Care and Use Committee of the University of Pittsburgh. All efforts were made to minimize animal suffering, to reduce the number of animals used, and to utilize alternatives to in vivo techniques, if available.

2.2. Drugs

Drugs used in these studies included urethane (ethyl carbamate, Sigma, St. Louis, MO), phenylephrine (Sigma) and doxazosin (a gift from Roche Bioscience). Phenylephrine was dissolved in artificial CSF [9,16] to prepare 0.3–3000 μM solutions. Doxazosin was dissolved in 100% dimethyl sulfoxide to prepare a 20-mM solution, which was diluted to 10 mM with artificial CSF. Drug doses were calculated for the base of each compound.

2.3. Evaluation and statistical analysis

The effects of phenylephrine and doxazosin were evaluated on various parameters of bladder activity including: the amplitude and frequency of reflex bladder contractions under isovolumetric conditions and the bladder contraction amplitude (BCA), pressure threshold for inducing micturition (PT, the intravesical pressure required to trigger a reflex voiding contraction) and ICI during continuous CMGs. All values are expressed as mean±S.E.M. Analysis of variance (ANOVA), the paired t-test and Dunnett’s multiple comparison test were used when appropriate for statistical data analysis. For all statistical tests, P<0.05 was considered significant.

3. Results

3.1. Effects of i.t. phenylephrine on the lower urinary tract during continuous CMGs

As shown in Figs. 1 and 2, high doses (300 and 3000 nmol) of phenylephrine increased the ICI and PT during continuous CMGs; whereas small doses (3 and 30 nmol) occasionally increased the ICI but in most experiments were inactive. The 300 nmol of the drug prolonged the intervals between the contractions, and the 3000 nmol induced long-lasting elevation of the intravesical pressure (Fig. 1). The increase in intravesical pressure is presumably due to overdistension of the bladder by continuous infusion of saline after drug-induced suppression of voiding. A high dose (300 nmol, n=5) consistently increased the PTs and the ICIs (Fig. 2). In one rat, this dose produced an initial decrease in the ICIs accompanied by a slightly higher baseline pressure (3 cmH₂O higher). This effect persisted for 20 min after which the ICIs increased as in other experiments. The dose–response curves in Fig. 2 were constructed from data obtained at least 30 min after drug administration.

![Graph](Fig. 1. The effects of phenylephrine (30, 300 and 3000 nmol i.t.) on bladder activity during continuous CMG. Note that the intercontraction interval and pressure threshold for micturition were increased by 300 nmol in this animal and the overflow incontinence was induced by 3000 nmol; whereas 30 nmol had little effect. The rise in intravesical pressure after 300 and 3000 nmol is presumably due to overdistension of the bladder during continuous infusion of saline following drug-induced suppression of voiding. The pattern of oscillatory changes prior to peak intravesical pressure by these doses varied between animals. Phenylephrine (3, 30, 300 and 3000 nmol) was injected at 30–45-min intervals. (The effects of 3 nmol are not presented.)}
The largest dose (3000 nmol) of phenylephrine completely blocked reflex voiding and induced the overflow incontinence in all animals (n=5). After this dose, the intravesical pressure gradually increased (Fig. 1) and reached peak pressures ranging from 28 to 57 cmH₂O (mean: 45 cmH₂O) within 5–8 min (mean: 6 min). Overflow incontinence then persisted for 15–40 min (mean: 25 min, n=4) at intravesical pressures ranging from 28 to 42 cmH₂O (mean: 33 cmH₂O). In four of five rats, partial recovery of bladder activity occurred within 50 min. In these animals, the activity consisted of small amplitude contractions (10–22 cmH₂O) with higher baseline pressures and shorter ICIs, implying inefficient voiding and increased residual volumes. In one rat, partial recovery of bladder activity occurred within 10 min. Phenylephrine (3000 nmol) administered to decerebrate unanesthetized rats (n=2) also produced overflow incontinence.

The effects of increasing doses of phenylephrine on EUS EMG activity were examined in two animals. In one rat, doses of 3–300 nmol of phenylephrine decreased the EMG activity by 26–62%; whereas in the other rat these doses had no effect. During the overflow incontinence induced by a higher dose (3000 nmol), EUS EMG activity was totally suppressed in both rats. In another group of animals (n=4), a single dose (300 nmol) of phenylephrine was given. In three rats, EUS EMG activity was suppressed 41–62%; while ICIs increased 42–111% (from 169±26 to 306±70 s) and PTs increased 141–419% (from 6±1 to 25±7 cmH₂O). However, the BCA was not changed. In one rat, the EUS EMG was not affected by this dose of phenylephrine.

3.2. Effects of i.t. phenylephrine on urinary bladder activity under isovolumetric conditions

Cumulative doses of phenylephrine ranging from 0.03 to 30 nmol were also administered while recording bladder activity under isovolumetric conditions. As shown in Figs. 3 and 4, low doses of phenylephrine (0.03 and 0.3 nmol) had little effect on the frequency and amplitude of bladder contractions; whereas higher doses (3 and 30 nmol) completely eliminated bladder contractions for 19–35 min. In this paper, the period of complete inhibition will be termed ‘disappearance time’ (Fig. 4). Recovery from inhibition was usually characterized by the abrupt appearance of large amplitude bladder contractions that were very similar to those occurring before the drug (Fig. 3). In two animals, a second administration of phenylephrine (3 nmol) produced a similar depressant effect.

3.3. Effects of i.t. doxazosin on the lower urinary tract during continuous CMGs

Doxazosin was administered in 25 nmol doses at 30-min intervals to construct a cumulative dose–response curve. A small dose (25 nmol) was inactive, whereas 50 nmol significantly decreased the ICI (58% reduction) without altering BCA or PT (Fig. 5 and Table 1). The 100 nmol dose of doxazosin slightly suppressed the BCA (from 34±1 to 26±2 cmH₂O, 24% reduction, P=0.081, n=4) and reduced the ICI (from 150±43 to 34±14 s, 77% reduction, P=0.062, n=4). Injections of vehicle (50% dimethyl sulfoxide in saline) did not affect bladder activity.

3.4. Effects of i.t. doxazosin on urinary bladder activity under isovolumetric conditions

Small doses of doxazosin (5–25 nmol) did not alter isovolumetric bladder contractions however, 50 nmol significantly decreased the BCA (55% reduction) and increased the bladder contraction frequency (69% increase) (Fig. 6, Table 2). After the injection of 50 nmol, bladder

Fig. 2. These graphs show the effects of phenylephrine (3–3000 nmol i.t.) on bladder contraction amplitude (A), pressure threshold for inducing micturition (B), and intercontraction intervals (C), during continuous CMGs. ** P<0.01 (Dunnett’s multiple comparison test following repeated measures ANOVA, n=5). C=control (artificial CSF) injection. O.I.=overflow incontinence.
Fig. 3. The effects of phenylephrine (0.03 and 3 nmol i.t.) on bladder activity under isovolumetric conditions. Multiple doses of phenylephrine could be injected in this animal. (The effect of 0.3 nmol is not presented in this figure.) Note that the 0.03 nmol of the drug produced decrease of bladder contraction ‘frequency’ whereas artificial CSF had little effect on the parameter, and that the 3 nmol eliminated bladder activity for 15 min and bladder activity recovered with the intravesical pressure almost as high as control values.

Table 1
Effects of doxazosin (i.t.) on bladder activity during continuous infusion CMGs

<table>
<thead>
<tr>
<th>Dose of doxazosin (nmol)</th>
<th>Bladder contraction amplitude (cmH₂O)</th>
<th>Intercontraction interval (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 nmol (n=6) Before</td>
<td>34±2 (30–39)</td>
<td>152±42 (42–366)</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>31±3 (25–38)</td>
</tr>
<tr>
<td>50 nmol (n=7) Before</td>
<td>34±3 (25–50)</td>
<td>124±28 (39–225)</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>30±2 (18–38)</td>
</tr>
</tbody>
</table>

**P<0.01 (paired t-test, in comparison with before). Values in parentheses are the ranges measured in the present studies.

activity completely recovered to control values within 30 min.

3.5. Interactions between phenylephrine and doxazosin on the micturition reflex

When phenylephrine and doxazosin were administered in the same experiments (n=10) in an attempt to demonstrate antagonistic interactions, the results were variable. In

Fig. 4. The graph shows the time of disappearance induced by phenylephrine (0.03–30 nmol i.t.) of bladder activity under isovolumetric conditions. DT=disappearance time, the interval until the 90% of bladder contraction amplitude recovered after the inhibition by phenylephrine. Values at each dose were obtained from five to seven experiments.

Fig. 5. The effects of doxazosin (50 nmol i.t.) on bladder activity during continuous CMG. Note that the drug markedly decreased intercontraction intervals but had no effect on other parameters.
two anesthetized rats during continuous CMGs, 300 nmol of phenylephrine elicited a significant increase in ICI and PT. Thirty min later while the effects of phenylephrine still persisted, administration of doxazosin (50 nmol) reversed the effects of phenylephrine. A second injection of phenylephrine 30 min after doxazosin, did not alter bladder activity. In another anesthetized rat, doxazosin (50–100 nmol) did not reverse the overflow incontinence induced by a large dose of phenylephrine (3000 nmol, n = 1). In unanesthetized decerebrate rats (n = 2), doxazosin (50 nmol) reversed the overflow incontinence induced by phenylephrine (3000 nmol) in one rat but not the other rat.

Under isovolumetric conditions, the effect of phenylephrine (3 nmol) to reduce the frequency or completely inhibit bladder contractions was blocked or markedly reduced by doxazosin pretreatment (50 and 10 nmol, respectively) in two experiments after the administration of doxazosin in doses (50 nmol) that depressed the BCA. In two other experiments the inhibitory effects of phenylephrine (3–30 nmol) were not altered.

### Table 2

<table>
<thead>
<tr>
<th>Dose of doxazosin</th>
<th>Bladder contraction amplitude (cmH2O)</th>
<th>Contraction frequency (contractions/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 nmol (n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>46±4</td>
<td>0.45±0.06</td>
</tr>
<tr>
<td></td>
<td>(37–64)</td>
<td>(0.21–0.65)</td>
</tr>
<tr>
<td>After</td>
<td>45±5</td>
<td>0.47±0.07</td>
</tr>
<tr>
<td></td>
<td>(32–62)</td>
<td>(0.20–0.63)</td>
</tr>
<tr>
<td>50 nmol (n=7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>53±2</td>
<td>0.55±0.05</td>
</tr>
<tr>
<td></td>
<td>(44–56)</td>
<td>(0.40–0.79)</td>
</tr>
<tr>
<td>After</td>
<td>24±4***</td>
<td>0.93±0.17*</td>
</tr>
<tr>
<td></td>
<td>(11–38)</td>
<td>(0.55–1.88)</td>
</tr>
</tbody>
</table>

* P<0.05, *** P<0.001 (paired t-test, in comparison with before). Values in parentheses are the ranges measured in the present studies.

4. Discussion

The present studies revealed that α1-adrenergic receptor mechanisms in the spinal cord may have a complex role in the neural control of voiding function in the rat. Intrathecal administration of phenylephrine, an α1-adrenergic agonist, decreased the frequency and increased the intravesical pressure threshold for inducing reflex voiding; whereas doxazosin, an α1-adrenergic antagonist, increased the frequency but decreased the amplitude of reflex bladder contractions. These findings raise the possibility that activation of α1-adrenergic receptors can inhibit spinal sensory mechanisms that trigger voiding, but also facilitate the parasympathetic efferent pathways that induce bladder emptying. Thus, brainstem noradrenergic neurons which project to the lumbo sacral spinal cord may exert two opposing influences on the lower urinary tract: (1) enhancement of urine storage by delaying the initiation of the micturition reflex and (2) facilitation of voiding by increasing the excitatory neural input to the urinary bladder. These effects on the parasympathetic outflow to the bladder are likely to work in concert with other spinal adrenergic mechanisms that regulate the sympathetic and somatic neural pathways to the urethra and EUS, respectively [2,6,17].

The function of central noradrenergic pathways in the control of micturition has been a subject of controversy for many years. Early studies in anesthetized cats showed that norepinephrine applied iontophoretically to bladder parasympathetic PGNs suppressed firing induced synaptically or by a glutamatergic receptor agonist [18]. Other experiments in anesthetized cats revealed that descending noradrenergic projections from the LC provided an excitatory input to bladder PGN via activation of interneurons in the spinal cord [28]. However, subsequent studies in unanesthetized cats were unable to demonstrate this excitatory pathway [6,8]. Experiments in rats have also yielded variable results. In anesthetized rats, i.t. administration of phenylephrine depressed reflex micturition, whereas prazosin, an α1-adrenergic antagonist, was inactive [12]. On the other hand, in unanesthetized rats, some studies were unable to demonstrate an involvement of spinal α1-adrenergic receptors in micturition [7], but other investigations revealed that doxazosin, an α1-adrenergic antagonist, depressed the intravesical pressure during voiding [10]. Based on the latter finding, it was suggested that α1-adrenergic receptors have a facilitatory role in micturition. Our present data support such a conclusion.

The variability in the results of different studies are very likely due to multiple factors including: the presence in the spinal cord of both inhibitory and facilitatory adrenergic mechanisms which control the bladder and the urethral...
outlet, as well as the different experimental conditions for each of the studies. For example, during continuous infusion CMGs, intravesical voiding pressures are dependent not only on the amplitude of bladder contractions but also on urethral outlet resistance. Thus, adrenergic blocking agents that can alter urethral as well as bladder activity might lower voiding pressure by several actions [2]. In the present study, the contribution of the urethra was eliminated in some experiments by recording under isovolumetric conditions. In these experiments, doxazosin suppressed bladder contraction amplitudes, indicating that the drug acted by depressing the parasympathetic excitatory input to the bladder. During continuous infusion CMGs, this effect was not detected, suggesting that a simultaneous action on the neural control of the urethra or rapid distension of the bladder negated the inhibitory effect on the parasympathetic reflex pathway. Alternatively, it is possible that during rapid filling of the bladder, the spinal α1-adrenergic excitatory mechanisms do not make an important contribution to micturition.

However, during both isovolumetric recording and constant infusion CMGs, doxazosin did increase the frequency of voiding reflexes, indicating that an α1-adrenergic inhibitory pathway was tonically controlling the triggering mechanism for voiding. The micturition reflex is initiated by afferent receptors in the bladder wall, which respond to distension. These afferents travel in the pelvic nerve to the sacral spinal cord, where they activate a long ascending supraspinal pathway that projects to an area in the dorsolateral pons known as the ‘pontine micturition center’ (PMC). The PMC provides the on–off switching function, which generates the rhythmicity of reflex bladder contractions. A descending pathway then projects from the PMC back to the parasympathetic PGNs in the lumbosacral cord and axons which in turn provide excitatory input to the bladder [4]. Because voiding is activated by afferent input from the bladder, it is reasonable to speculate that the adrenergic inhibitory pathway regulates afferent processing in spinal cord. The finding that phenylephrine increased the ICIs during continuous CMGs, supports this speculation. The action of phenylephrine to completely inhibit voiding under isovolumetric conditions indicates that this adrenergic inhibitory mechanism has the potential to exert a powerful influence on micturition. However, as evidenced by the modest effect of doxazosin on voiding frequency (i.e. approximately two-fold increase) this inhibitory mechanism is only submaximally active under normal conditions.

The effect of phenylephrine to increase the intravesical PT for initiating voiding, also implies that α1-adrenergic inhibitory mechanisms can modulate the spinal processing of afferent input from the bladder. Reflex voiding is triggered by afferent input from bladder mechanoreceptors that are sensitive to bladder wall tension and indirectly to intravesical pressure. Afferent activity is transmitted through spinal pathways to the switching circuitry in the PMC [4]. If it can be assumed that i.t. administration of phenylephrine does not act in the periphery to alter afferent activity, then it seems reasonable to conclude that it acts centrally to reduce the transmission of afferent activity to the PMC. The effect of doxazosin to increase the frequency of reflex bladder contractions under isovolumetric conditions is consistent with this concept. On the other hand, doxazosin did not alter the PT during continuous CMGs. This might be attributable to the fact that the control PTs were very low (1.5–3 cmH2O) and therefore it is technically difficult to detect a further reduction after doxazosin.

In some but not all experiments, doxazosin antagonized the inhibitory effect of phenylephrine, suggesting that the latter effect is due to activation of α1-adrenergic receptors. The reason for the variable effects of doxazosin is unknown. However, it should be noted that the doxazosin–phenylephrine interaction studies are difficult to conduct because both agents have inhibitory actions. For example, the inhibitory effect of doxazosin on bladder contraction amplitude limited the dose that could be tested. In addition, this inhibitory effect could have interfered with the ability of doxazosin to reverse the phenylephrine inhibition of afferent mechanisms; because a doxazosin-induced decrease in bladder contraction amplitude would reduce afferent input from the bladder and in turn indirectly enhance the inhibitory effects of phenylephrine.

In summary, the present results indicate that two types of spinal α1-adrenergic mechanisms are involved in the control of reflex bladder activity in rats: (1) inhibitory control of afferent processing in the spinal cord and (2) excitatory modulation of the descending limb of bladder reflex pathway (Fig. 7). These two mechanisms acting in concert would facilitate urine storage by increasing bladder capacity and also enhance voiding efficiency by increasing parasympathetic nerve activity and the amplitude of bladder contractions. Although it might seem paradoxical that bulbospinal noradrenergic pathways would promote opposing activities of the bladder (i.e. storage and voiding), it should be noted that activation of central and peripheral α1-adrenergic receptors also facilitates other urine storage (e.g. reflex control of the urethra and external urethral sphincter [2,6,17]) and voiding mechanisms (e.g. cholinergic transmission in bladder ganglia [11] and acetylcholine release from parasympathetic nerves in the bladder [22]). Thus, it might be appropriate to consider that bulbospinal noradrenergic projections to the sacral parasympathetic nucleus are just one component of a broadly distributed noradrenergic system that is responsible for maintaining normal excretory functions and in turn body homeostasis. It will be important in future experiments to determine whether different subtypes of α1-adrenergic receptors are involved in the various modulatory mechanisms that regulate the activity of the lower urinary tract.
Fig. 7. Scheme showing putative $\alpha_1$-adrenergic mechanisms in the L6-S1 spinal cord that contribute to the control of reflex activity of the urinary bladder in the rat. PGN, preganglionic neurons; PMC, pontine micturition center. Descending noradrenergic pathways from the brainstem may excite inhibitory interneurons to regulate the sensory pathways from the bladder and excitatory interneurons to regulate the efferent pathway to the bladder.

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References