Effect of Memantine on Overactive Detrusor in Rats With Spinal Cord Injury

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The aim of this study was to determine the effect of memantine on overactive detrusor (OAD) 15 days after spinal cord injury (SCI) in rats. Twenty-eight adult Wistar rats were used in this study. Fourteen animals served as normal controls, while 14 underwent spinal cord transection (clip compression technique) at the 10th thoracic vertebra. Fifteen days after SCI, all animals underwent urodynamic testing to confirm OAD. Memantine (16 mg/kg) was injected intraperitoneally into rats with SCI and OAD. Parameters measured included voiding volume, micturition pressure, resting bladder pressure, the period between micturitions and the maximum pressure of the OAD during the filling period. Results have showed that OAD developed in 8/14 animals (57.1%). OAD was resolved in 5/8 (62.5%) of these animals after memantine administration. Resting bladder pressure was significantly different in dependent groups ($p < 0.05$). Micturition pressure increased after SCI but decreased in rats with SCI after memantine injection. However, the period between micturitions was prolonged in both SCI and memantine groups, compared with normal rats. These results show that memantine could be useful for treating neurogenic OAD after SCI by modulating the micturition reflex pathway. Memantine may also provide an alternative treatment option for OAD in the future.

Key Words: memantine, overactive detrusor, rats
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Overactive bladder (OAB) is described as urinary urgency, with or without urge incontinence, and usually with frequency and nocturia if there is no proven infection or other obvious pathology [1]. Anticholinergic agents are the most widely used drugs for the management of neurogenic and idiopathic overactive detrusor (OAD). The limitations of the current drugs for the treatment of OAB have lead to a focus on new targets for pharmacologic intervention and on the physiologic basis for lower urinary tract function and dysfunction.

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The micturition reflexes involve several transmitters and transmitter systems that may offer therapeutic targets to control micturition, including γ-aminobutyric acid, opioids, serotonin, noradrenalin, dopamine and glutamatergic receptors [2,3]. Glutamate is probably involved as an excitatory transmitter in the supraspinal control pathway between the pontine micturition center and the preganglionic neurons [4].

Spinal cord injury (SCI) results from secondary damage via the excitatory amino acid cascade (i.e. glutamate) or via direct injury to the spinal cord [5]. Glutamate acts on spinal neurons through a variety of glutamatergic receptor subtypes, including the N-methyl-D-aspartate (NMDA) subtype, that control the urogenital reflex pathways at the lumbosacral levels [6]. Memantine is a specific, noncompetitive NMDA-receptor antagonist with moderate affinity [7]. Here, we evaluated the effect of memantine on OAD in rats with SCI.

Methods

Animals

Twenty-eight adult Wistar rats weighing 140–210 g were used in this study. The University Committee on Laboratory Animals approved the experimental protocol.

SCI

Fourteen rats served as normal controls and 14 underwent spinal cord transection at the 10th thoracic vertebra. The animals were anesthetized by intramuscular injection of ketamine (20 mg/kg body weight). A midline dorsal incision was made about 2 cm over the subcutaneous trunk to expose the vertebral spine and paraspinous muscles. These muscles were split from their attachment to the spinal processes and retracted laterally. After laminectomy, a 5-mm gap was created between the proximal and distal ends. The spinal cord was compressed by extradural application of an aneurismal clip (Technomedical TK 25132.00) for 1 minute. All muscles and skin were closed using 4-0 catgut sutures. The animals were treated with intramuscular ampicillin (150 mg/kg) for 10 days. The bladders of the SCI rats were emptied manually two times every day.

Urodynamic testing

Fifteen days after SCI, 14 rats underwent a filling cystometrogram to confirm OAD, while another 14 served as normal controls. The animals were anesthetized with ether inhalation and the bladder was exposed by a midline abdominal incision. A 6-Fr double-lumen cystometry catheter (DLC-6P; Life-tech, Urolab Primus, USA) was implanted into the bladder through the dome and a suture was tightened around the collar of the catheter. The anatomic layers were closed using 4-0 catgut sutures. Cystometry was started 30 minutes after the surgery to allow the rats to recover from the ether anesthesia, which provides a shorter duration of recovery compared with other anesthetics.

A computer-assisted unit (Life-tech) was used for urodynamic testing. Cystometric recordings were performed by continuously infusing physiologic saline (6 mL/hr, Abbott Lifecare infusion pump, Abbott Lab, Chicago, IL, USA) at room temperature into the bladder to elicit repetitive voids. After the urodynamic recordings were completed in the normal and SCI rats, memantine (16 mg/kg) was administered intraperitoneally. The effect of memantine on OAD was observed urodynamically at 40 minutes after injection.

The parameters measured included voiding volume, micturition pressure (MP), resting bladder pressure (RBP), the period between micturitions (PM), and the maximum pressure of the OAD during the filling period.

Statistical analysis

Data were analyzed using Friedman's test for three dependent groups. Wilcoxon signed-rank test was performed to determine the significance of differences among groups (Bonferroni correction). All data are shown as mean ± standard deviation and values of $p < 0.05$ were considered statistically significant.

Results

Normal rats

The mean RBP was 7.25 ± 3.61 cmH_2O (range, 4–15 cmH_2O) and the mean MP was 22.75 ± 9.66 cmH_2O (range, 11–39 cmH_2O). PM and voiding volume were 35.75 ± 6.60 seconds (range, 29–49 seconds) and 50–100 μL, respectively (Table). However, the measurement of voiding volume was not reliable due to technical problems, including leakage of the small reservoir placed under the cage. None of these animals showed OAD (Figure 1A).

SCI rats

Eight of 14 (57.1%) SCI rats had OAD (Figure 1B). Impaired detrusor contractility was seen in the other five rats and one rat had hypo-compliant bladder. The mean RPB in SCI rats with OAD was 14.75 ± 8.24 cmH_2O (range, 6–29 cmH_2O) 15 days after inducing SCI. Mean MP was 44.37 ± 21.89 cmH_2O (range, 20–91 cmH_2O) and PM was 48.25 ± 41.32 seconds (range, 15–140 seconds). The maximum OAD pressure ranged from 20 to 92 cmH_2O in the SCI rats with OAD.

Memantine

After memantine administration, OAD disappeared in five of the eight SCI rats with OAD (62.5%) (Figure 1C). The maximum OAD pressure decreased in the remaining three animals. The RBP values were significantly different among the three groups ($p < 0.05$), but

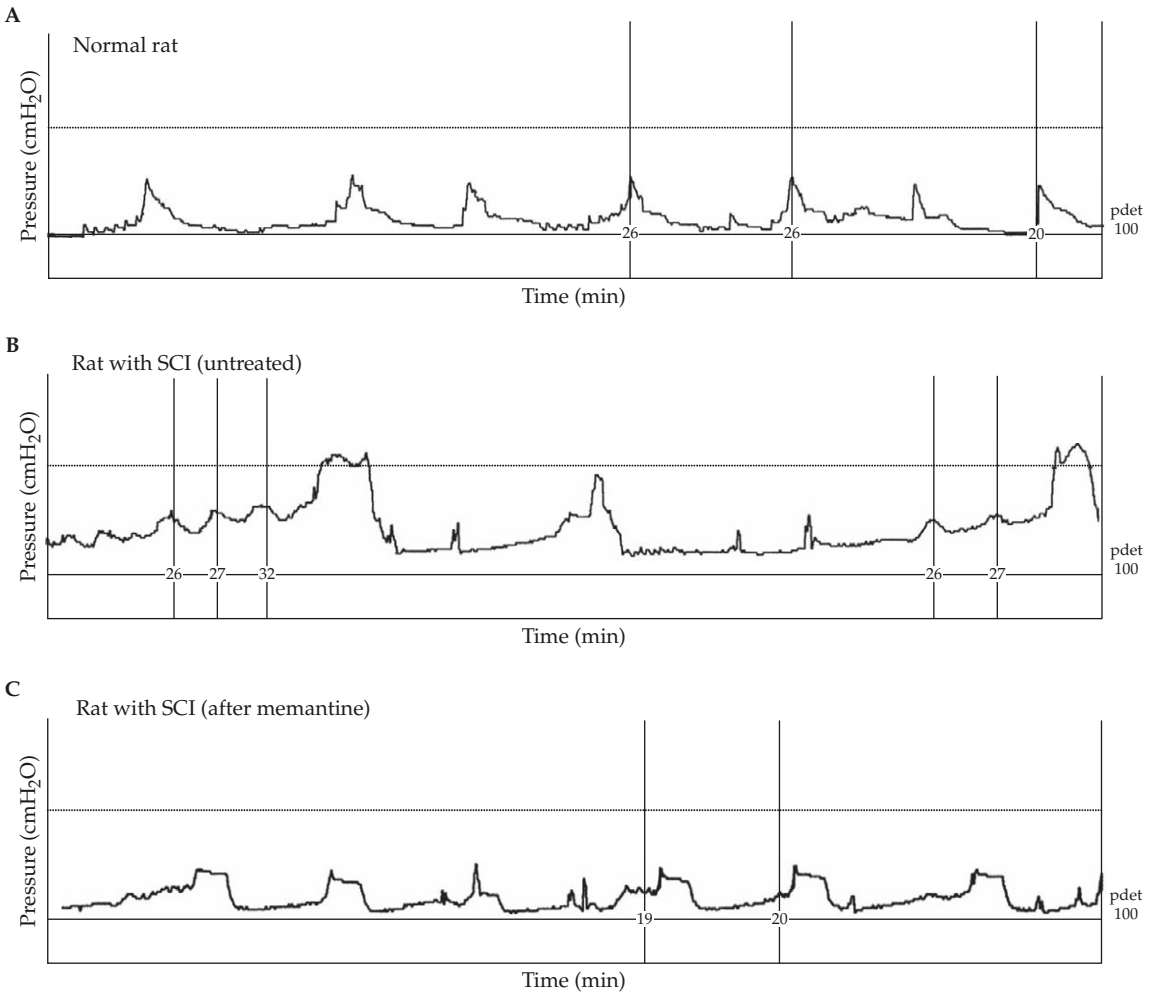

Figure 1. *Typical cystometrograms in (A) normal control rats showing no detrusor overactivity; (B) untreated rats with spinal cord injury showing detrusor overactivity; and (C) rats with SCI after memantine administration showing decreased detrusor pressure. SCI = Spinal cord injury.*

Table. Cystometric parameters in control rats and rats with spinal cord injury before and after memantine treatment

	Control group	Spinal cord injury group	
		Before memantine treatment	After memantine treatment
Mean MP (cmH_2O)	22.75 ± 9.66	44.37 ± 21.89	30.87 ± 14.74
Mean RBP (cmH_2O)	7.25 ± 3.61	14.75 ± 8.24	10.12 ± 7.37
Mean PM (sec)	35.75 ± 6.6	48.25 ± 41.32	65.37 ± 31.25

MP = Micturition pressure; RBP = resting bladder pressure; PM = period between micturitions.

there were no statistically significant differences in terms of MP and PM among the three groups according to the results of the Friedman test. RPB and MP were significantly lower in the memantine group than in the SCI group according to the Wilcoxon test. The mean MP, RBP and PM values for each group are shown in the Table and Figure 2.

Discussion

Memantine has been marketed in Germany since 1982, and was initially indicated for various neurological syndromes and cognitive dysfunction. This agent is an adamantine derivative and blocks ligand-gated Ca^{2+} channels, such as the NMDA-type glutamate receptor

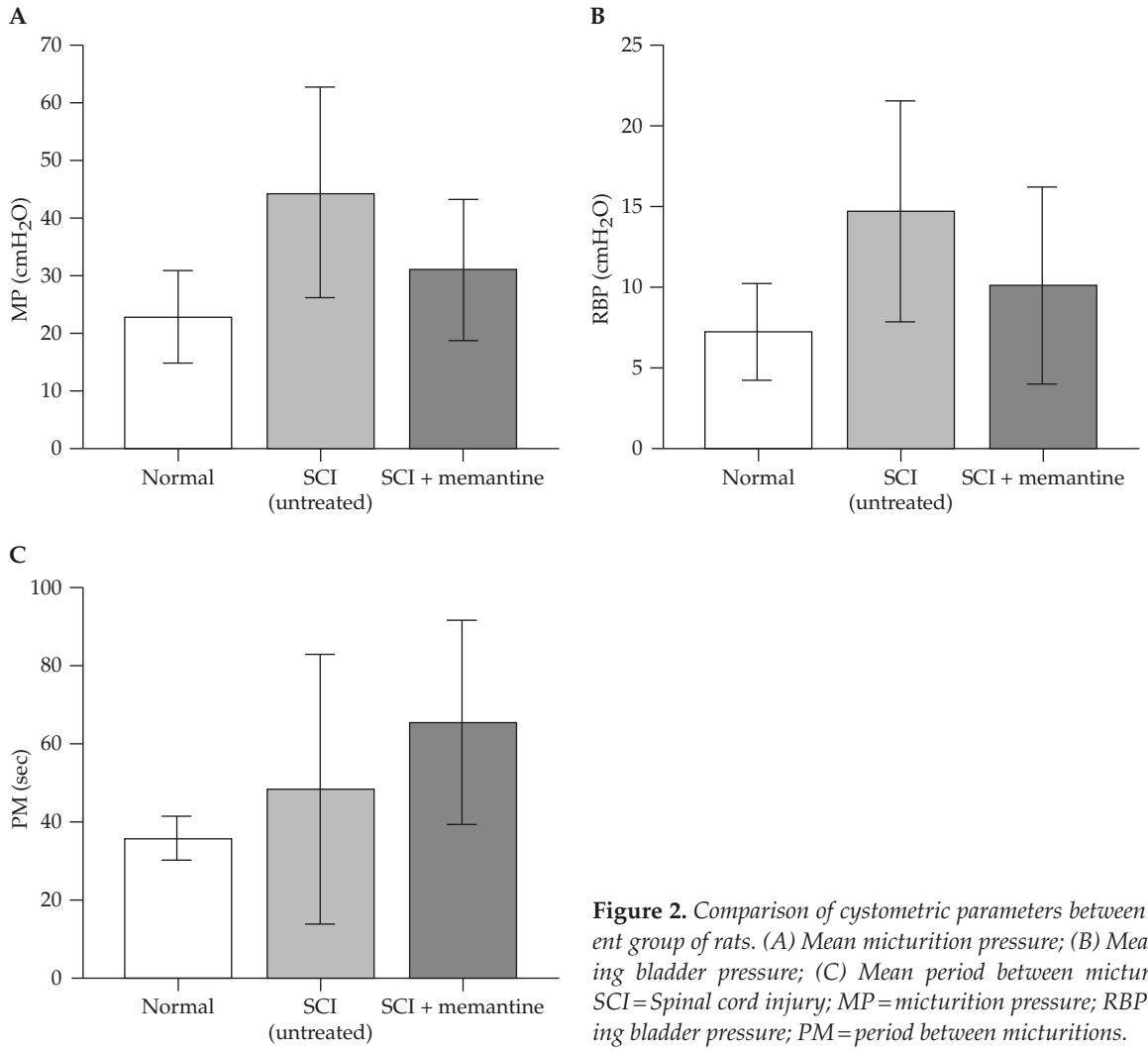

Figure 2. *Comparison of cystometric parameters between different group of rats. (A) Mean micturition pressure; (B) Mean resting bladder pressure; (C) Mean period between micturitions. SCI = Spinal cord injury; MP = micturition pressure; RBP = resting bladder pressure; PM = period between micturitions.*

[7,8]. Glutamate is a major excitatory neurotransmitter in the mammalian central nervous system. There are two major classes of glutamate receptors: ionotropic and metabotropic. The ionotropic glutamate receptors are classified into three types: NMDA, α-amino-3-hydroxy-5-methyl-lisoxazole-4-propionic acid (AMPA) and kainate receptors [9]. NMDA is a large protein complex, consisting of an ion channel, a number of binding sites for glutamate, glycine and polyamines, and a channel blocking site [10].

The function of the NMDA receptor in the micturition reflex pathway has been extensively studied in recent years. AMPA/kainate and NMDA glutamate receptor antagonists decreased the amplitude, frequency and duration of reflex bladder contractions. In our study, the PM was prolonged after memantine administration, consistent with these earlier findings [11]. Conversely, changes in NMDA receptor function were reported to be involved in the recovery of detrusor–external urethral sphincter coordination after incomplete SCI [12]. Yokoyama et al showed that NMDA receptors play an essential role in the development of OAB and that AMPA receptor antagonists temporally inhibited OAB after cerebral infarction [13].

In the present study, 57.1% of the SCI rats exhibited OAD 15 days after SCI. This rate is similar to another study [14]. We observed that OAD was ameliorated by memantine treatment in 62.5% of these SCI rats. MP was significantly lower after memantine treatment compared with that seen before memantine administration in the SCI rats. These results imply that memantine plays a role in decreasing detrusor contractility. This effect may be due to blocking the ligand-gated Ca^{2+} channels that decrease intracellular Ca^{2+} levels [15,16].

Anticholinergic agents are currently recommended as first-line therapy for OAB. Although anticholinergic

agents are clinically effective for the relief of OAB symptoms, their use has been associated with adverse effects such as dry mouth, constipation and blurred vision [17]. Furthermore, these agents can have a negative effect on cognitive function, particularly in the elderly [18]. For these reasons, other agents with fewer adverse effects are needed for the treatment of OAB. Although the effect of memantine on OAB is not fully understood, our study showed that memantine has a positive effect on OAB. Conversely, adverse effects of NMDA receptor antagonists, such as locomotor stimulation, ataxia, cognitive impairment and psychotomimetic actions, have been described [19]. Nevertheless, these effects of memantine occur at much higher doses [20].

In conclusion, the administration of memantine reduced bladder contraction pressure in rats. Thus memantine offers an effective treatment for OAD after SCI. This drug may provide alternative options for the treatment of OAB. Further studies are now needed to confirm the effect of memantine on OAB in clinical trials.

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