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Tanaka H, Kakizaki H, Takashi S, Mitsui T, Ameda K, Koyanagi T
Hokkaido University Graduate School of Medicine

EFFECTS OF ACUTE AND CHRONIC BLOCKADE OF NMDA GLUTAMATERGIC RECEPTORS BY MK-801 ON THE MICTURITION REFLEX IN RATS WITH BLADDER OUTLET OBSTRUCTION

Aims of Study

Bladder outlet obstruction (BOO) produces bladder overactivity as well as sensory alterations manifested by urinary frequency, urgency, and urge incontinence. In the rat, partial urethral obstruction induces neuroplasticity in the bladder afferent pathways and facilitates the spinal micturition reflex [1,2]. Increased bladder afferent activity is believed to be one of the major causes of these functional changes following partial urethral obstruction. On the other hand, NMDA glutamatergic receptors play a key role in the bladder afferent pathways [3], and are implicated in the development of sensory alterations following peripheral nerve injury or noxious stimulation of the viscera [4,5]. Thus, we investigated the effects of MK-801, a noncompetitive NMDA receptor antagonist, on the micturition reflex in rats with BOO. Chronic blockade model was adopted to evaluate the possible involvement of NMDA receptors in the development of bladder functional changes following BOO, while acute blockade was used to examine their ongoing role during the micturition reflex in obstructed rats.

Methods

Female Wistar rats were used. In chronic blockade model (BO/MK:n=9), MK-801 (1.0 mg/kg) was injected intramuscularly once a week just before the creation of partial urethral obstruction until 5 weeks after the obstruction. Five to 7 days after the last injection of MK-801, conscious filling cystometry was performed and compared to obstructed rats treated with vehicle (saline) (BO/V:n=8). In addition, the results of cystometric evaluations were also compared between sham operated rats treated with MK-801 (Sham/MK: n=9) or vehicle (Sham/V: n=7). In acute blockade model, the effects of intravenous (i.v.) administration of MK-801 (0.01-1.0 mg/kg) on the micturition parameters were investigated 6 weeks after the obstruction (n=6).

Results

Partial urethral obstruction led to a significant increase in bladder weight (362.5±22.6mg in obstructed rats vs. 154.0±6.4mg in sham rats, $p<0.01$). However, the mean bladder weight was not significantly different between BO/MK vs. BO/V (389.3±34.6mg in BO/MK vs. 338.6±24.3mg in BO/V) and Sham/MK vs. Sham/V (161.6±8.9mg in Sham/MK vs. 144.3±8.1mg in Sham/V). Conscious cystometry in obstructed rats revealed that chronic blockade of NMDA receptors significantly increased bladder capacity (2.29±0.12ml in BO/MK vs. 1.73±0.16ml in BO/V, $p<0.01$) and voided volume (2.00±0.10ml vs. 1.56±0.17ml, $p<0.05$), without changes in voiding efficiency (87.5±1.6% vs. 87.8±1.7%) or micturition pressure (55.8±2.3cmH_2O vs. 56.4±3.0cmH_2O). Interestingly, neither frequency nor amplitude of pre-micturition bladder contractions was different in both groups. For sham operated rats, chronic blockade of NMDA receptors had no significant effect on bladder capacity (0.73±0.06ml in Sham/MK vs. 0.64±0.05ml in Sham/V) or voided volume (0.62±0.06ml vs. 0.59±0.06ml). In obstructed rats, acute blockade of NMDA receptors by i.v. administration of MK-801 significantly reduced bladder capacity in a dose dependent manner.

Conclusions

Although the development of bladder instability following partial urethral obstruction could not be prevented, chronic blockade of NMDA receptors by repeated injections of MK-801 induced a significant increase in bladder capacity, without changes in micturition pressure or voided efficiency in obstructed rats. Theses effects were not observed in sham operated rats. On the other hand, acute blockade of NMDA receptors facilitated the micturition reflex in obstructed rats, which is consistent with the acute effects of MK-801 in conscious unobstructed rats [6]. These data suggest that BOO might cause an NMDA receptor-mediated neuroplasticity in the bladder afferent pathways and that NMDA receptors also have inhibitory actions on the ongoing bladder afferent activity during the micturition reflex irrespective of BOO.

References

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