

THE THERAPEUTIC EFFECT OF ORAL ADMINISTRATION OF L-ARGININE ON VOIDING DYSFUNCTION IN DIABETIC RATS

Hypothesis / aims of study

We have previously reported the therapeutic effect of L-arginine, a precursor of nitric oxide, on urethral dysfunction in streptozotocin-induced diabetic rats. In this study, we investigated whether the oral L-arginine treatment can improve bladder dysfunction in diabetes mellitus (DM).

Study design, materials and methods

Five weeks after the induction of DM with streptozotocin (65 mg/kg, intraperitoneally), the effect of oral administration of L-arginine (150-200 mg/day) for one week on bladder function were evaluated by the following three methods: (1) cystometry in an awake condition, (2) measurements of nerve growth factor (NGF) levels in the bladder, and (3) in vitro organ bath study of bladder muscle strips. In the organ bath study, longitudinal strips were removed from the dorsal detrusor from normal rats and diabetic rats with or without L-arginine treatment, and contractile responses to electrical field stimulation (EFS) and potassium chloride (KCl) were evaluated.

Results

(1) In awake cystometry, the mean inter-contraction interval (ICI) was significantly longer in diabetic rats than in normal rats. In addition, the mean amplitude of the first peak of bladder contractions (BC), which corresponded to urethral opening pressure at the starting point of voiding, was significantly higher in diabetic rats than in normal rats. However, in L-arginine-treated diabetic rats, ICI was significantly shorter in L-arginine-treated diabetic rats than in untreated diabetic rats, but still significantly longer than in normal rats (1816 ± 153.8 , 2657 ± 329.1 , and 951.1 ± 54.4 seconds, respectively). In addition, BC was significantly reduced compared with untreated diabetic rats, and not significantly different from BC in normal rats (31.2 ± 1.9 , 46.5 ± 2.8 , and 26.0 ± 1.3 cmH₂O, respectively). (2) In ELISA measurements, NGF levels in the bladder in untreated diabetic rats (13.4 pg/ μ g protein), which was significantly lower than in normal rats (47.3 pg/ μ g), was significantly increased after L-arginine treatment (21.1 pg/ μ g). (3) In the muscle strip study, all detrusor strips exhibited tetrodotoxin (TTX)-sensitive contractions in response to EFS. Detrusor strips from untreated diabetic rats required higher frequency (10 and 30 Hz, respectively) of EFS to obtain 60% and 90% of maximum contractions than those from normal rats (2 and 10 Hz, respectively). In diabetic rats treated with L-arginine, EFS frequency to obtain 60% and 90% of maximum contractions was lowered to 5 and 20 Hz, respectively. However, the contractile response to KCl (100 mM), which was significantly reduced in untreated diabetic rats compared with normal rats (tension/weight: 0.20 ± 0.02 versus 0.37 ± 0.04 g/mg), was not changed (0.25 ± 0.03 g/mg) in diabetic rats by L-arginine treatment.

Interpretation of results

The oral administration of L-arginine reduced ICI as well as urethral opening pressure in cystometry, and increased NGF levels in the bladder in diabetic rats. Since a previous study has indicated that a reduction in bladder NGF levels is correlated with bladder sensory dysfunction inducing diabetic cystopathy, these results suggest that oral L-arginine treatment can improve afferent nerve activity to restore bladder function by increasing bladder NGF levels in DM. In addition, oral L-arginine restored decreased detrusor contractility in response to EFS, but not to KCl, in DM, suggesting that oral L-arginine treatment improved efferent nerve activity inducing bladder contractions. Taken together, it is assumed that exogenous L-arginine administration can restore decreased NGF expression in the bladder and bladder afferent/efferent nerve function, thereby improving bladder function in DM.

Concluding message

The oral L-arginine supplement therapy may be useful for treating voiding dysfunction in DM.

References

1. Urethral dysfunction in diabetic rats. *Journal of Urology*, 171, 1959–1964, 2004.
2. Diabetic cystopathy correlates with long-term decrease in nerve growth factor (NGF) levels in the bladder and lumbosacral dorsal root ganglia. *Journal of Urology* 168:1259-1264, 2002.