

NITRERGIC AND ADRENERGIC MECHANISMS INDUCING DIABETIC URETHRAL DYSFUNCTION IN RATS

Aims of Study

Diabetes mellitus (DM) is a global health problem. As many as 80% with non-insulin-dependent DM have cystopathy, which is characterized by impaired sensations of bladder fullness, increased bladder capacity, reduced bladder contractility and elevated volume of post void residual. However, little is known about diabetic urethral dysfunction in DM, which may also contribute to voiding symptoms in DM. Thus, we investigated DM-induced alteration in urethral function, focusing on nitrergic and α -adrenergic mechanisms.

Methods

Adult female Sprague-Dawley rats weighing 200 to 300g were used. Five to eight weeks after streptozotocin injection (65mg/kg, i.p.), the effects of DM on urethral functions were evaluated in comparison with normal rats using simultaneous recordings of urethral perfusion pressure and isovolumetric intravesical pressure under urethane anesthesia. After the control periods of the recordings, α -bungarotoxin (BGT; a neuromuscular nicotinic receptor antagonist), L-arginine hydrochloride (L-arginine; the substrate of nitric oxide [NO] synthase), terazosin (an α_1 -adrenoceptor antagonist), or N ω -Nitro-L-arginine methyl ester hydrochloride (L-NAME; an analogue of arginine that inhibits NO production) were intravenously administered to investigate the effects on urethral activity.

Results

In diabetic rats, the lowest urethral pressure during reflex bladder contractions and intravesical pressure thresholds inducing urethral relaxation were significantly higher by 145% and 68%, respectively, than in normal rats while baseline urethral pressure was not significantly different between two groups. The mean amplitude and rate of high frequency oscillation of urethral striated muscles observed during bladder contractions were significantly smaller in diabetic rats by 64% and 29%, respectively, than in normal rats. In addition, following the blockade of striated muscle activity by BGT, diabetic rats exhibited "urethral instability" characterized by fluctuation of baseline urethral pressures (i.e., higher standard deviation values of averaged baseline urethral pressures between reflex bladder contractions), which was not observed in normal rats.

In both normal and diabetic rats, intravenous administration of L-arginine (200 mg/kg) reduced the lowest urethral pressure during reflex bladder contractions by 29% and 55% reduction, respectively, as well as bladder pressure thresholds inducing urethral relaxation by 28% and 95% reduction, respectively, indicating that L-arginine-induced urethral relaxation is greater in diabetic rats than in normal rats. Intravenous administration of terazosin (0.4 mg/kg) reduced the value of the lowest urethral pressure by 33% and 38% reduction, respectively, and bladder pressure thresholds inducing urethral relaxation by 42% and 38%, respectively, indicating that terazosin-induced urethral relaxation is similarly observed in normal and diabetic rats. In addition, urethral instability in diabetic rats was significantly reduced by terazosin. Urethral smooth muscle relaxation during reflex bladder contractions after the administration of terazosin and L-arginine was abolished by intravenous application of L-NAME (40 and 100 mg/kg, respectively).

Conclusions

It is concluded that in diabetic rats, relaxation mechanisms of both striated and smooth muscles of the urethral sphincter during reflex bladder contractions are impaired. Therefore, the association of bladder hypoactivity and urethral relaxation incapability could result in higher degrees of inefficient voiding and bladder overdistention in DM. Moreover, fluctuated urethral activity that can be suppressed by terazosin was found in diabetic rats, raising the possibility that α -adrenergic mechanisms are enhanced to induce urethral instability in DM. The L-arginine supplement therapy, which can augment urethral relaxation by increasing NO

release, as well as the terazosin treatment, which can increase urethral relaxation and normalize urethral instability, may be useful for the treatment of urethral dysfunction in DM.