

DIFFERENTIAL ROLES OF CENTRAL AND PERIPHERAL NITRIC OXIDE MECHANISMS IN THE REGULATION OF LOWER URINARY TRACT FUNCTION IN THE RAT

Hypothesis / aims of study

Previous studies have suggested that nitric oxide (NO) released in the bladder and the spinal cord plays an important role in the regulation of the micturition reflex. It has been reported that intravesical administration of NO scavenger decreased bladder capacity inducing bladder contractions in rats, suggesting a local inhibitory effect of NO on bladder activity (1). In contrast, NO centrally released in the spinal cord can induce detrusor overactivity because cystitis-induced detrusor overactivity was reportedly suppressed by intrathecal (i.t.) injection of NO synthase (NOS) inhibitor in rats (2). Thus it seems that NO release in the bladder suppresses the micturition reflex, while NO in the spinal cord facilitates the reflex. However, it is not known how these local and spinal NO mechanisms interact to modulate bladder activity in conscious voiding. Therefore, we examined the effects of NOS inhibition at different sites on bladder activity in rats under an awake condition. We also investigated the involvement of C-fiber afferent pathways in the NO mechanism using awake rats with C-fiber desensitization.

Study design, materials and methods

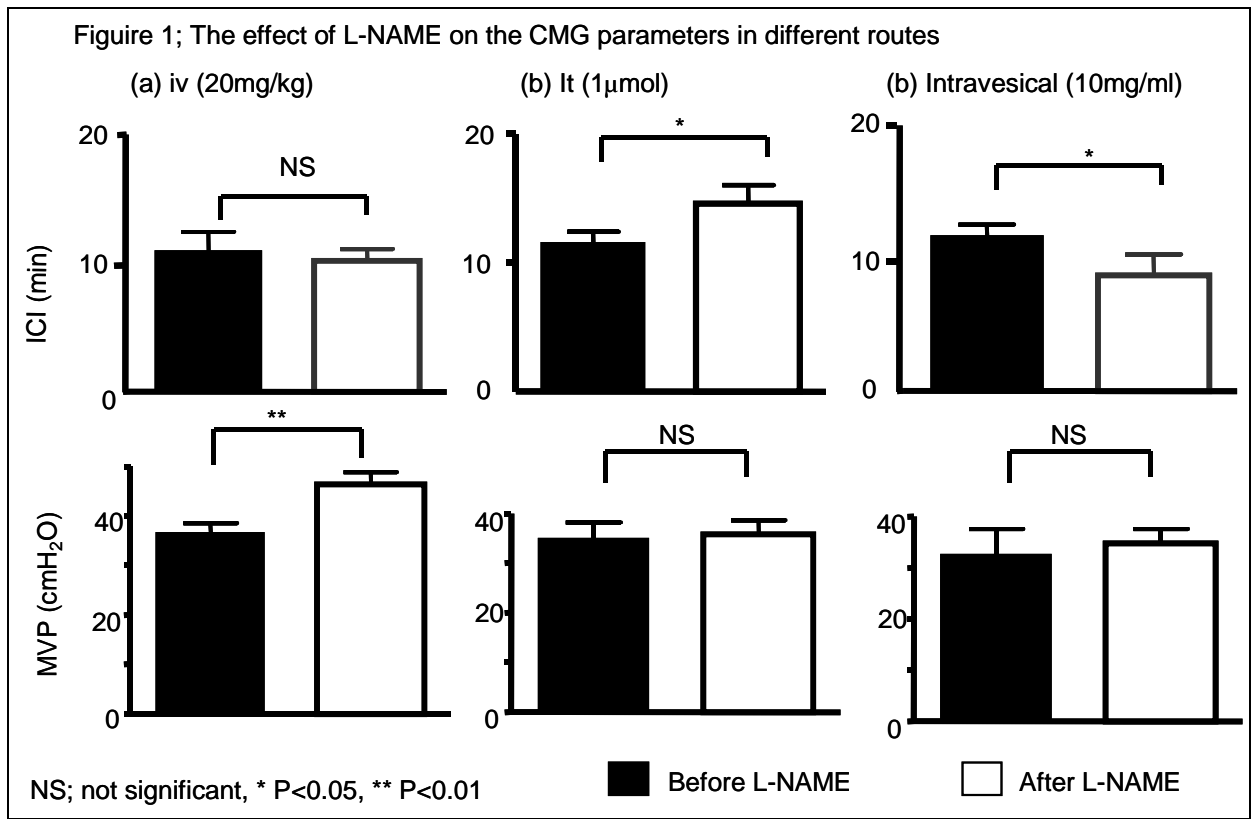
Adult female Sprague-Dawley rats (200-230g) were used. An intrathecal (i.t.) catheter was implanted at the level of the L6-S1 spinal cord following a laminectomy at the Th11 vertebra under halothane anesthesia 3 days before continuous cystometry (CMG). Resiniferatoxin (RTX, 0.3mg/kg), a very potent C-fiber afferent neurotoxin, administered s.c. was used for C-fiber desensitization 5 days before CMG recordings. An NO synthase inhibitor, N-nitro-L-arginine methyl ester (L-NAME), was given intravenously (i.v.), i.t. or intravesically during CMG recordings (infusion rate; 0.04 ml/min) in untreated and RTX-pretreated rats under an awake condition. Intercontraction interval (ICI), maximum voiding pressure (MVP) and pressure threshold (PT) were measured.

Results

In untreated rats, i.v. injected L-NAME (20 mg/kg) did not affect the ICI or PT (n=9), while, i.t. injected L-NAME (1 μ mol) significantly ($P<0.05$) increased the ICI and PT (n=7). In contrast, intravesical instillation of L-NAME (10 mg/ml) decreased the ICI significantly ($P<0.05$, n=6). D-NAME, an inactive stereoisomer, had no effects in all routes (n=5 in each route). In RTX treated rats, i.v. or i.t. injected L-NAME had no effect on ICI or RT in CMG (n=7 in each). In addition, i.v., but not i.t., injected L-NAME increased the MVP in rats with or without RTX pretreatment, due to increased outlet resistance induced by suppression of NO mediated relaxation of the urethra. (See Figure 1)

Interpretation of results

These results indicate that NO released in the spinal cord facilitates the micturition reflex and that this facilitatory effect in the spinal cord is masked by local inhibitory effects of NO on the micturition reflex in the bladder. In addition, these spinal and local effects of NO seem to be predominantly mediated by activation of mechanoreceptive C-fiber bladder afferents because both effects were negligible after RTX treatment.



Concluding message

Central and peripheral NO mechanisms have differential roles in the regulation of conscious voiding. Thus it is assumed that imbalance of these two NO mechanisms might be involved in the emergence of detrusor overactivity in pathological conditions.

References

1. J Urol 164: 545-550, 2000
2. J Urol 155: 355-360, 1996

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