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LOCAL NITRIC OXIDE PRODUCTION IS INVOLVED IN SUPPRESSION OF CAPSAICIN-INDUCED DETRUSOR OVERACTIVITY IN THE RAT

Hypothesis / aims of study

Functional TRPV-1 receptors are expressed in urothelial cells and afferent nerves, and their stimulation can induce the release of nitric oxide (NO) (1, 2). However, the functional role of NO at these sites is uncertain. It has been reported that intravesical administration of NO scavenger decreased bladder capacity inducing bladder contractions and that intravesical NO donor application suppressed bladder overactivity induced by a chemical irritant, cyclophosphamide (3). These findings suggest that NO might have a depressant effect on afferent activity in the bladder. Therefore, we examined the role of locally released NO in capsaicin-induced detrusor overactivity.

Study design, materials and methods

Adult female Sprague-Dawley rats (200-230g) were used under urethane anesthesia (1 g/kg, s.c.). 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). A double-lumen catheter was inserted into the bladder from the bladder dome for intravesical drug administration and pressure recordings during CMG. Intraarterial (i.a.) and intravenous (i.v.) catheters were inserted through femoral artery and jugular vein, respectively. Following baseline CMG recordings with saline (0.04ml/min for 120min), the solution containing capsaicin (30μM) was infused for 90 min. N-nitro-L-arginine methyl ester (L-NAME), an NO synthase inhibitor, was given i.v., i.a. or i.t. to the animals before or during capsaicin instillation.Urodynamic parameters such as intercontraction interval (ICI), maximum voiding pressure (MVP) and pressure threshold (PT) were measured.

Results

During saline infusion, i.v. (20 mg/kg), i.a. (10 mg/kg) and i.t. (1 μmol) administration of L-NAME significantly increased the ICI. L-NAME administered i.v. and i.a., but not i.t., increased the MVP. Capsaicin instillation into the bladder induced detrusor overactivity evidenced by a significant reduction in the ICI, and i.v. and i.a. administration of L-NAME further decreased the ICI. I.v. (200mg/kg) and i.a. (100mg/kg) administration of L-arginine reversed this facilitatory effect of L-NAME on capsaicin-induced detrusor overactivity. Moreover, pretreatment with i.v. and i.a. administered L-NAME (20 min before capsaicin instillation) enhanced capsaicin-induced overactivity. However, i.t injection of L-NAME (1 μmol) had no effect on capsaicin-induced detrusor overactivity.(See Figuire 1 and 2)

Interpretation of results

The difference between i.a. and i.t. administration of L-NAME during capsaicin instillation suggested that capsaicin induced NO from peripheral tissues acts as an inhibitor of bladder overactivity. The different effects of i.t. administered L-NAME during saline and capsaicin infusion suggest that NO-mediated facilitatory mechanisms in the spinal cord are involved in the normal micturition reflex, but not in capsaicin-induced bladder overactivity.

Concluding message

It is conceivable that there is an inhibitory effect of locally released NO on bladder overactivity induced by capsaicin-mediated C-fiber activation, and that modulation of local NO levels in the bladder could be a potential therapeutic modality for bladder overactivity.

References

1. PNAS 98: 13396-13401, 2001.
2. Nature Neuroscience 5: 856-860, 2002.
3. J Urol 162: 2211-2216, 1999.

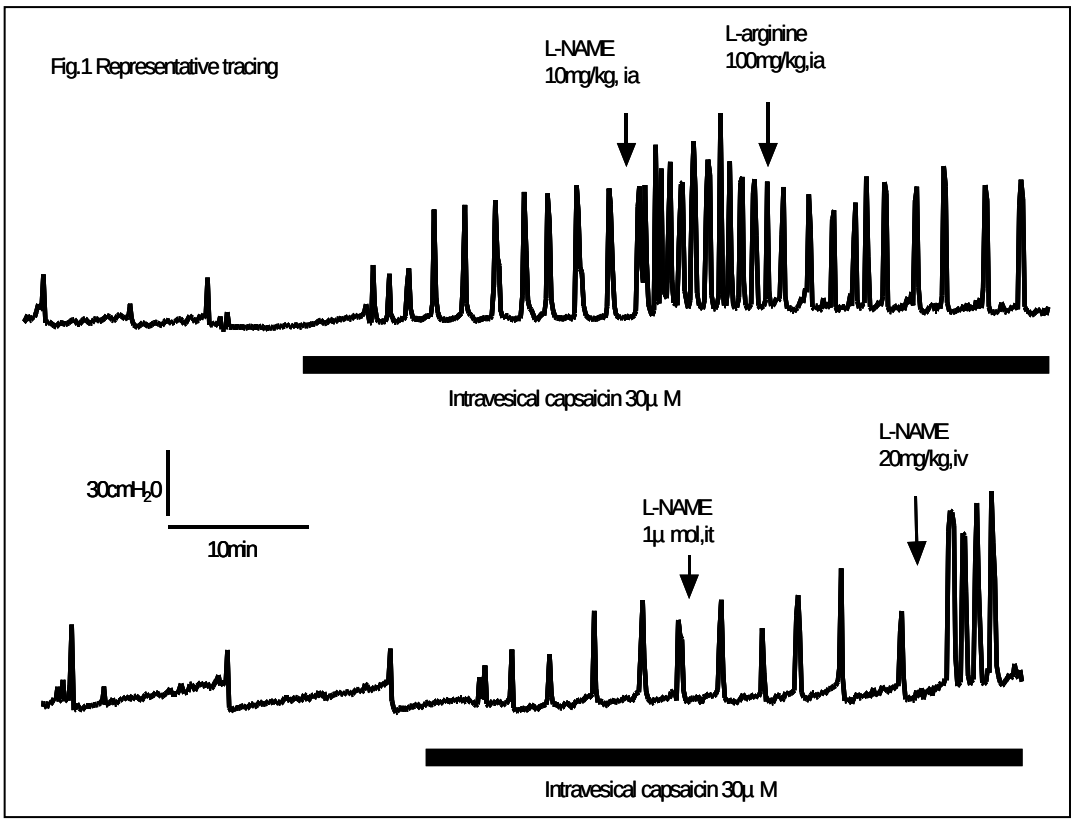
Fig.1 Representative tracing
L-NAME
10mg/kg, ia
L-arginine
100mg/kg,ia
Intravesical capsaicin 30μ M
L-NAME
20mg/kg,iv
30cmH2O
10min
L-NAME
1μ mol,it
Intravesical capsaicin 30μ M

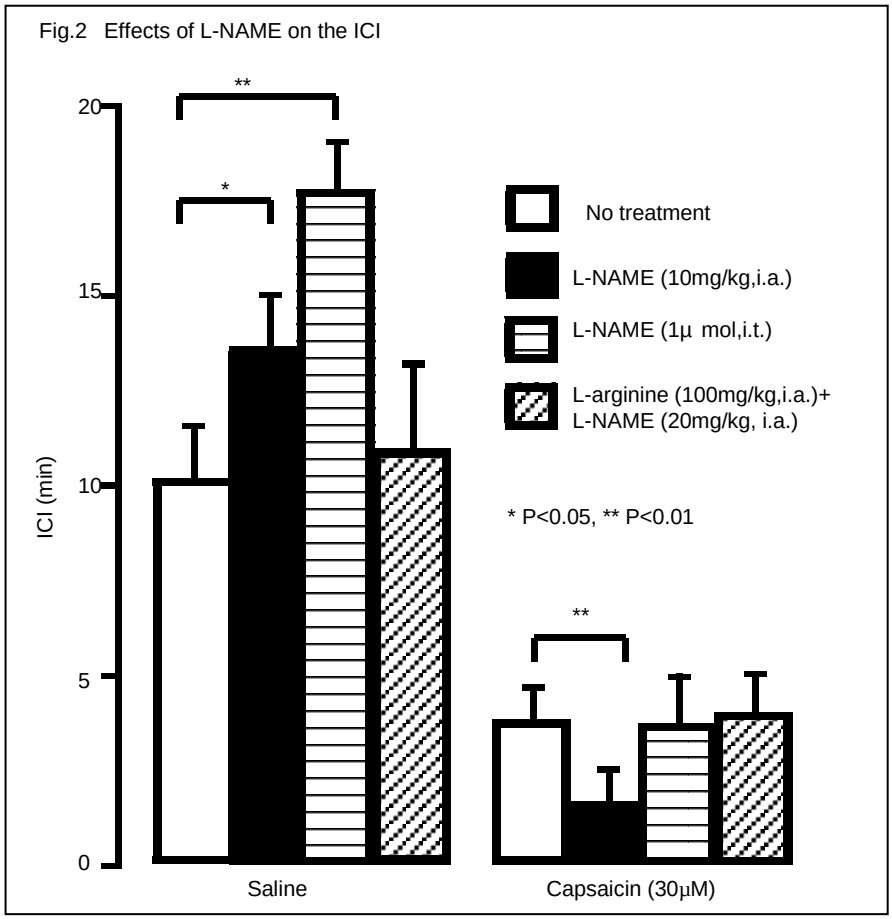
Fig.2 Effects of L-NAME on the ICI
ICI (min)
20
15
10
5
0
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*
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No treatment
L-NAME (10mg/kg,i.a.)
L-NAME (1μ mol,i.t.)
L-arginine (100mg/kg,i.a.)+
L-NAME (20mg/kg, i.a.)
* P<0.05, ** P<0.01
Saline
Capsaicin (30μM)

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