

ARGINASE INHIBITION SUPPRESSES BLADDER OVERACTIVITY IN RATS WITH CHRONIC SPINAL CORD INJURY BY ENHANCING NO PRODUCTION

Hypothesis / aims of study

It has been reported that nitric oxide (NO) in the bladder can inhibit bladder afferent activity to suppress bladder overactivity and nociceptive responses (1,2). NO production can be controlled not only by activities of constitutive and inducible NO synthase isozymes but also by arginase activity (3). However, little is known about the contribution of changes in arginase activity to bladder overactivity. Therefore, we investigated the effects of an arginase inhibitor, which enhances NO production, on bladder overactivity and measured the bladder arginase I & II levels using quantitative real-time polymerase chain reaction (qRT-PCR) in rats with spinal cord injury (SCI).

Study design, materials and methods

The spinal cord of female Sprague-Dawley rats was transected at the level of Th 8-9. Awake cystometrograms were performed 3-4 weeks after spinal cord transection. Cystometric parameters such as mean amplitudes of non-voiding contractions (NVCs), the number of NVCs, voided volume, voiding efficiency, and micturition pressure were evaluated before and after intravenous (i.v.) injection of an arginase inhibitor (nor-NOHA: N^ω-Hydroxy-nor-L-arginine dihydrochloride) in SCI rats. The effects of a NOS inhibitor (L-NAME: N^ω-Nitro-L-arginine methyl ester hydrochloride) were also examined to determine whether suppression of bladder overactivity by arginase inhibition is mediated by increased production of NO. In addition, at 3-4 weeks after spinalization, mRNA levels of arginase I & II in the bladder were measured using qRT-PCR.

Results

nor-NOHA (10 mg/kg, i.v.) significantly decreased the amplitudes of NVCs from 42.4 ± 2.3 cmH₂O to 31.8 ± 3.6 cmH₂O ($p < 0.01$, $n=6$) and the number of NVC from 5.8 ± 0.6 to 4.5 ± 0.7 ($p < 0.05$, $n=6$) whereas vehicle or a lower dose of nor-NOHA (1.0 mg/kg, i.v.) did not affect the amplitude and/or number of NVCs. There were no significant changes in pressure thresholds, maximum voiding pressure, voided volume or voiding efficiency before and after administration of vehicle or nor-NOHA at any dose. When L-NAME (20 mg/kg, i.v.) was administered prior to nor-NOHA injection (10 mg/kg, i.v.), nor-NOHA-induced inhibition of NVCs was prevented (Fig.1). The relative expression levels of both arginase I & II mRNA in the rat bladder were significantly higher in SCI rats compared to spinal cord intact rats (4-5 fold increase) ($p < 0.05$, $n=7$).

Interpretation of results

These findings indicate that arginase inhibitor can suppress bladder overactivity induced by spinal cord injury and that suppression of bladder overactivity by arginase inhibition is mediated by increased production of NO. Furthermore, arginase expression is increased in overactive bladders from SCI rats.

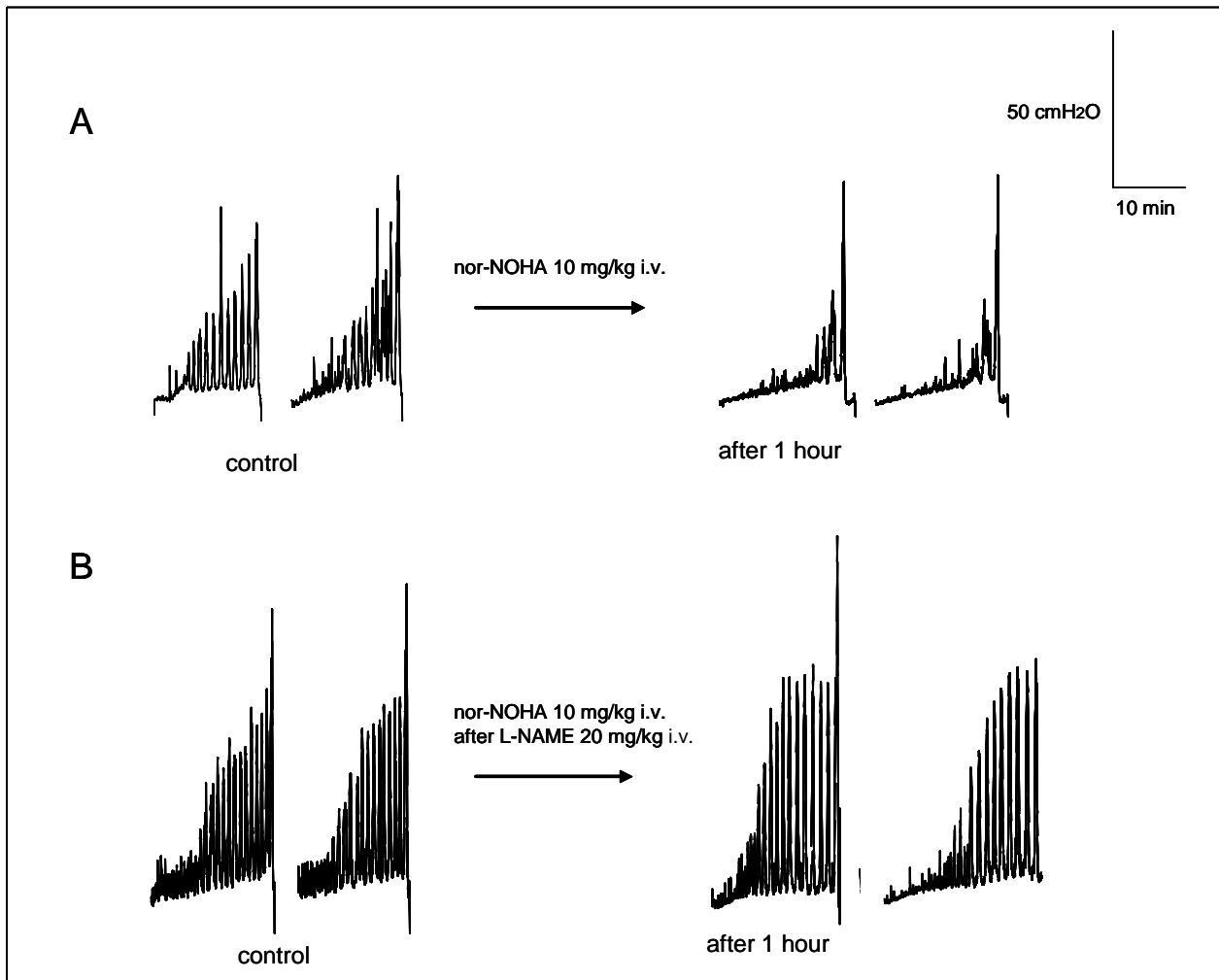
Concluding message

These results suggest that upregulation of arginase I & II is involved in the mechanism inducing bladder overactivity in chronic SCI rats and that arginase inhibition can suppress SCI-induced bladder overactivity as indicated by a reduction in NVCs. Thus, arginase inhibition could be an effective treatment for neurogenic bladder overactivity in pathological conditions such as spinal cord injury.

References

1. J Urol (1999) 162: 2211-2216.
2. J Neurophysiol (2001) 86: 304-311.
3. Nitric Oxide; San Diego, 2000 (199-208)

Fig. 1. Effects of i.v. administration of (A) nor-NOHA alone and (B) nor-NOHA after i.v. injection of L-NAME on NVCs in SCI rats.



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ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by University of Pittsburgh Institutional Animal Care and Use Committee