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THE EFFECT ARGINASE INHIBITOR ON THE LOWER URINARY TRACT

Aims of Study

Nitric oxide (NO) is synthesized by nitric oxide synthase (NOS) and is involved in the micturition reflex. Arginase is an enzyme that shares a common substrate, l-arginine, with NOS and may downregulate NO production by competing with NOS for this substrate. This study attempted to determine whether selective inhibition of arginase can affect bladder and/or urethra function.

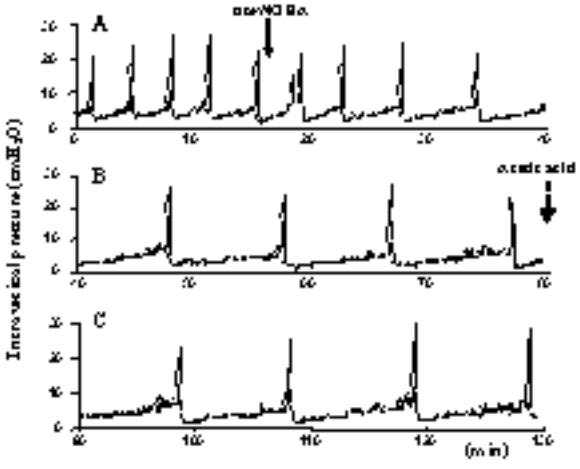
Methods

Awake continuous cystometrogram (CMG) was performed with and without the presence of the arginase inhibitor N-ω-Hydroxy-nor-L-arginine (nor-NOHA, 6 mg/kg) in adult female Sprague-Dawley rats. Under halothane anesthesia, the bladder was exposed with a lower midline abdominal incision, and PE-50 tubing with a cuff at the end was inserted into bladder dome. A PE-50 cannula was also placed in the external jugular vein in animals to deliver the drug. The intravesical catheter was connected via a 3-way stopcock to a pressure transducer and a syringe pump for recording intravesical bladder pressure and infusing saline into the bladder, respectively. Saline at room temperature was infused at a rate of 0.04 ml/min to elicit repetitive bladder contractions. The saline infusion was continued for at least 2 hours before application of any agent to the animal. Reduction in voiding intercontraction interval (ICI) was attempted by intravesical instillation of acetic acid solution (AA, pH 4.0) after intravenous injection of nor-NOHA. In another group, the bladder and urethra were isolated separately using the 2-way catheter system and changes in urethra pressure was measured after injection of nor-NOHA (6mg/kg). Blood pressure was also measured throughout the experiments.

Results

In awake CMG, intravenous nor-NOHA increased ICI by 57% compared with the control period and changes in ICI after intravesical AA was prevented under the presence of nor-NOHA. These changes were seen for more than 90 minutes after injection (figure). There was only a mild and transient (1-2 minutes) decrease in both urethra and blood pressure after nor-NOHA injection.

Figure - Continuous CMG recordings after intravenous application of an arginase inhibitor nor-NOHA . A-C: in awake rats. A. Before and after nor NOHA i.v. (black arrow indicates nor-NOHA 6.0 mg/kg i.v.), B. After nor-NOHA i.v. administration (broken arrow indicates the starting point of intravesical instillation of acetic acid 0.1%), C. After acetic acid instillation.



Conclusions

This study provides evidence for the first time *in vivo* that arginase inhibitor affects voiding function. It shows that arginase inhibition can suppress bladder activity and bladder nociceptive responses induced by bladder irritation. These results demonstrate another possible route for pharmacological manipulation of the nitric oxide pathway and may contribute to reduction of detrusor overactivity in painful bladder syndrome.