609

Caremel R[1], Oger S[2], Behr-Roussel D[2], Grise P[1], Giuliano F[3]
1. *Charles Nicolle Hospital,* ***2.*** *Pelvipharm,* ***3.*** *Raymond Poincare Hospital; Université Versailles Saint Quentin*

NITRIC OXIDE/CGMP SIGNALING MEDIATES AN INHIBITORY ACTION ON SENSORY PATHWAYS OF THE MICTURITION REFLEX IN THE RAT

Hypothesis / aims of study
Overactive bladder (OAB) can be associated with an hyperexcitability of bladder afferent fibers. In particular, C-fibers, normally silent, can become hyperexcitable under pathophysiological conditions and therefore could be responsible for inducing bladder hyperactivity. Several studies have suggested that nitric oxide (NO) or its downstream signalling could modulate the micturition reflex by reducing the excitability of bladder afferents. We have evaluated the role of the NO/cGMP signalling pathway on the micturition reflex in an acute model of bladder hyperactivity associated with C-fiber excitability in rats induced by acute intravesical capsaicin.
Study design, materials and methods
Cystometry experiments were performed in isoflurane-anesthetized adult female rats. Sodium nitroprusside (SNP) 0.1mg/kg, a NO donor; 8Br-cGMP 10mg/kg, a cGMP analogue, sildenafil 3 mg/kg and vardenafil 1 mg/kg, two phosphodiesterase 5 inhibitors (IPDE5); N^G-nitro-L-arginine methyl ester (L-NAME) 10mg/ml, a NO synthase inhibitor; LY-83583 1mg/kg, a guanylate cyclase inhibitor, were administered 45 min after the beginning of intravesical capsaicin (30µM) instillation. All drugs or vehicle were injected by intravenous route except for L-NAME intravesically administered. Cystometrogram was recorded 1 hour after drug administration. Each group of treatment included 8-12 animals. Urodynamics parameters related to the sensory component of the micturition reflex: intercontraction interval (ICI), micturition pressure threshold (MPT), baseline pressure (BP), and parameters related to the motor component: maximal pressure (MP) and voided volume (VV) were analyzed. Statistical analysis was performed using two-way ANOVA.
Results
SNP, 8Br-cGMP, and IPDE5 increased ICI by 83, 44, 39 and 43% respectively. In contrast, L-NAME decreased ICI by 16%. SNP, IPDE5 and 8Br-cGMP increased MPT by 35, 40, 25 and 11% respectively. In contrast, L-NAME and LY-83 583 decreased MPT by 55% and 10% respectively.
8Br-cGMP decreased MP by 24% whereas L-NAME and LY-83 583 increased MP by 131% and 29% respectively. SNP, and IPDE5 did not exert any effect on MP. SNP increased VV by 46%. 8Br-cGMP, and IPDE5 also increased this parameter albeit not significantly. In contrast, L-NAME tended to decrease the VV. 8Br-cGMP decreased BP by 22% whereas LY-83 583 increased it by 18%. SNP, IPDE5 and L-NAME did not exert any effect on BP.
Interpretation of results
Compounds activating NO/cGMP pathway inhibited bladder hyperactivity induced by capsaicin whereas compounds inhibiting NO/cGMP pathway increased it. These results indicate that the NO/cGMP signalling pathway is involved in the regulation of the micturition reflex in a pathophysiological model of bladder hyperactivity with a mechanism of action on both the sensory and the motor components of the micturition reflex.
Concluding message
The present study could support the potential development of NO/cGMP pathway modulators for the treatment of OAB.

Specify source of funding or grant	**"Grants from Coloplast fundation and from the association francaise d'urologie" were obtained**
Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**All procedures were performed in accordance with the legislation on the use of laboratory animals (NIH publication N°85-23, revised 1996) and Animal Care Regulations in force in France as of 1988 (authorization from competent French Ministry of Agriculture – Agreement No. A91-471-109, May 2009).**