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EFFECT OF NITRIC OXIDE DEPLETION IN THE BLADDER AND URETHRAL FUNCTION

Hypothesis / aims of study

Urinary frequency, urgency and urge incontinence are common in men with bladder outlet obstruction (BOO) due benign prostatic enlargement (BPE). These symptoms develop in 50-75% of patients with BPE and correspond to detrusor overactivity (DO).

Animal with BOO, caused by urethral obstruction has DO, evidenced by non voiding contractions (NCVs) during filling phase of cystometry. However, this animal model does not evaluate the urethral function.

Nitric oxide (NO) has been implicated as a neurotransmitter or neuromodulator at various sites in the mammalian nervous system, including the peripheral synapses in the urogenital tract (1).

Pharmacological studies have provide evidence that NO is a transmitter mediating relaxation of the bladder and urethral smooth muscle (2). The N-nitro-L-arginine methyl ester (L-NAME) is a potent nitric oxide synthase (NOS) inhibitor, the enzyme responsible for NO synthesis, thus it could be used to evaluate experimentally the effects of NO depletion on voiding function.

This study was undertaken to examine the role of NO depletion in the lower urinary tract of rats chronically treated with L-NAME.

Study design, materials and methods

A total of 16 adults male Wistar rats weighting 200 to 300g were used. The rats were divided into two groups, eight in untreated group (Group 1) and the others treated 30 days with L-NAME (60mg/kg/day) in the water (Group 2). All animal underwent to urodynamic evaluation.

The animals were anesthetized with intraperitoneal injection of urethane (1.2 g/Kg; Sigma Chemical Co., St Louis, Missouri). An abdominal midline incision was done to expose the bladder. To perform continuous cystometry a catheter with steel needle 18 G was inserted into the bladder dome. After emptying the bladder, it was waited 30 minutes to detrusor equilibrium before start physiological saline infusion into the bladder at 4 mL/h with an infusion pump. The intravesical catheter was connected via a three way stopcock to a pressure transducer for recording intravesical pressure and a syringe pump for infusion.

The frequency of NVCs per minute, maximal detrusor pressure during the NVCs (Pdet.Max NCVs) and volume threshold (VT), pressure threshold (PT) and peak pressure (PP) for voiding, frequency of micturition per minute (FM) and maximal detrusor pressure during voiding (Pdet.Max V) were determined from cystometograms (CMG). NVCs were defined as contractions of > 4 cmH2O occurring during filling phase. VT was calculated as follows: time required for first micturition (min) x 4 (ml) / 60 (min).

All values were expressed as mean and ± the standard deviation of the mean. Student's paired t test was used for comparison of CMG parameters during saline infusion. For all statistical tests, $p < 0.05$ was considered significant.

Results

During the filling phase, the mean rate of NVCs per minute in the Group 1 was 1.17 (±0.79) and in the Group 2 was 2.61 (±0.88), it was significant (P=0.004). The VT was 1.25 (±0.31) and 2.82 (±1.64) in the Group 1 and 2, respectively (P=0,019). The mean rate of FM was 1.01 (±0.66) and 1.97 (±0.77) in the Group 1 and 2, respectively (P=0.02). The rats of the Group 2 have large bladders and ureterohydronephrosis. There is no statistical difference comparing the other variables (Table).

The rats treated chronically with L-NAME present more involuntary detrusor contractions, reduced bladder emptying, consequently, resulting large bladders and ureterohydronephrosis.

Table – Cystometograms parameters during continuous saline infusion

	Control (N=8)	L-NAME (N=8)	P
NVCs/min	1.17 (±0.79)	2.61 (±0.88)	0.004
Pdet.Max NVCs	21.38 (±3.39)	16.68 (±6.83)	0.1
VT	1.25 (±0.31)	2.82 (±1.64)	0.019
TP	18.38 (±2.12)	19.13 (±2.89)	0.5
PP	20.47 (±2.46)	20.05 (±2.92)	0.7
FM/min	1.01 (±0.66)	1.97 (±0.77)	0.02
Pdet.Max V	24.82 (±2.81)	22.21 (±1.94)	0.07

Interpretation of results

In the present study, the cystometograms data of rats chronically treated with L-NAME was compared with control group. The L-NAME is a potent inhibitor of the enzyme responsible for NO synthesis, so it can be used in an experimental model to evaluate the effect of NO depletion in the lower urinary tract. L-NAME effects were exhaustively study in the cardiovascular system impairing NO-dependent vasodilatation and enhanced sympathetic vasoconstriction. In consequence of hypertension there are intrarenal vascular, tubular and glomerular lesions and reduction in renal. However, only partial improvement in renal function may be achieved when arterial pressure is fully controlled and several reports indicate that the L-NAME-induced renal structural changes were independent of blood pressure (3). Previous studies in vitro report that NO induce relaxation of urethral smooth muscle and this results in vivo show that the inhibition of NO synthesis result in detrusor overactivity and reduced bladder emptying, similar to bladder outlet obstruction due benign prostatic enlargement. Another important observation was that all rats treated have ureterohydronephrosis, so the renal failure may be at least partly due impairment of bladder emptying transmitting pressure to kidney lowing ultrafiltration pressure, causing glomerular damage.

Concluding message

The inhibition of nitric oxide synthesis results in detrusor hyperactivity and reduced bladder emptying. Therefore, depletion of NO is primarily involved in mechanisms that promote detrusor and urethral muscle exacerbated activity and may play role in the physiopathology of detrusor overactivity as well functional bladder outlet obstruction. The reduction on renal function may be at least partly mediated by alterations of lower urinary tract.

References:

1- Pharmacol Rev. (1991) 43:109-42.
2- J Pharmacol Exp Ther. (1993) 265:713-9.
3- J Cardiovasc Pharmacol. (2001) 38 Suppl 2: 65-70.

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