THE LOSS AND PROGRESSIVE RECOVERY OF VOIDING AFTER SPINAL CORD INTERRUPTION IN RATS IS ASSOCIATED WITH SIMULTANEOUS CHANGES IN AUTONOMOUS CONTRACTILE BLADDER ACTIVITY

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Introduction & Objectives: Autonomic contractile activity (AA) is a well-known phenomenon in isolated bladders from different species. It is thought that such AA is important in the physiology of both normal and dysfunctional voiding. Here we studied AA in bladders excised from paraplegic rats at different times post-surgical spinal cord transection (day 1, day 7, day 14, day 21, day 28, day 56) and in sham-operated animals (day 56). AA was measured by recording the duration of spontaneous contractions (SPC) from the bladder using transducer catheters (day 56). We found that AA increased with time after surgery and was associated with changes in the bladder mass and weight. The results suggest that AA is an important factor in the development of bladder dysfunction after spinal cord injury.

Material & Methods: Paraplegic rats were randomly assigned to one of the following groups: sham-operated group (n=18), 1 day surgical spinal transection (day 1, n=18), 7 days surgical spinal transection (day 7, n=18), 14 days surgical spinal transection (day 14, n=18), and 28 days surgical spinal transection (day 28, n=18). The bladders were removed at the time of sacrifice and the duration of SPC was measured. The results were analyzed using ANOVA and post-hoc tests.

Results: The duration of SPC was significantly shorter in the sham-operated group compared to the other groups (p<0.05). The duration of SPC was also shorter in the day 1, day 7, and day 14 groups compared to the day 28 group (p<0.05). The duration of SPC was not different between the day 1, day 7, and day 14 groups.

Conclusions: The results suggest that AA is an important factor in the development of bladder dysfunction after spinal cord injury. Further studies are needed to understand the mechanisms underlying this phenomenon.

VARDENAFIL IMPROVES BLADDER COMPLIANCE IN MEN WITH SPINAL CORD INJURY: RESULTS FROM A SINGLE DOSE, PILOT STUDY

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Introduction & Objectives: To evaluate, by urodynamical assessment, bladder compliance changes after a single 20 mg vardenafil administration in male Spinal Cord Injured (SCI) patients under oxybutynin treatment.

Material & Methods: We performed a single centre, randomized, double-blind, placebo controlled trial on 25 SCI patients with erectile dysfunction and urological disorders. A baseline urodynamic test and, later, a second urodynamic test 1 to 3 hours after administration of vardenafil 20 mg (15 cases) or placebo (10 cases) were performed. In all patients, standard oral oxybutynin administration was discontinued. Urodynamic assessment included maximum cystometric capacity (MCC) and maximum detrusor pressure during voiding (MDP) to calculate bladder compliance.

Results: Placebo administration did not significantly affect either MDP and MCC, with no change in compliance. After vardenafil administration, maximum cystometric capacity was considerably improved (233.5 vs. 272.0 ml, p<0.001), while maximum detrusor pressure during voiding was significantly reduced (59.3 vs. 52.1 cmH2O, p<0.001). These changes generate a remarkable improvement in bladder compliance (4.3 vs. 6.2 cmH2O/ml, p=0.003). Only 1 patient retained the same bladder compliance after vardenafil administration (4 ml/cmH2O), while 24 patients reported a compliance decrease.

Conclusions: We demonstrated that, in SCI patients, a single 20mg vardenafil administration achieves a remarkable increase of bladder compliance. This trial reveals, for the first time, a urodynamically recordable activity of PDE5i on human bladder. Further studies are necessary to investigate the potential role of PDE5i for neurogenic overactive bladder.

VARDENAFIL RELAXES PRE CONTRACTED RAT DETRUSOR PARTIALLY THROUGH UROTHELIAL-DEPENDENT MECHANISMS

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Introduction & Objectives: Nitric oxide and cGMP- mediated mechanisms have been proposed to be involved in sensory functions of the bladder and inhibition of PDE5 has been demonstrated to cause relaxation of rat detrusor smooth muscle with outflow obstruction. The objective of the current investigation was to study effects of vardenafil on isolated detrusor preparations from rats devoid of resiniferatoxin-sensitive afferent nerves or with partial outflow obstruction.

Material & Methods: Female Sprague Dawley rats were divided into 3 groups: 1) animals subjected to partial outflow obstruction for 14 days (n=10), 2) animals treated with 0.3 mg/kg (s.c.) of resiniferatoxin (n=6), 3) control rats (n=6). Bladder preparations were mounted in organ baths and effects of increasing concentrations of vardenafil (1 nM - 100 μM) were studied on carbachol (1µM)-activated preparations, and on contractions induced by transmural activation of nerves. Levels of cGMP were determined using radioimmunoassay.

Results: Vardenafil caused concentration-dependent relaxations of the carbachol-contracted rat bladder, which at 100 μM amounted to 88 ± 8 % in control rats and 100 % in obstructed rats. -Log IC50 values amounted to 4.407 ± 0.06 and 4.734 ± 0.05, respectively (p<0.01). No difference in the vardenafil-induced increases in cGMP levels in control rat bladder strips (2.5 ± 0.6 to 5.0 ± 0.8 pmol/mg protein) compared to strips from obstructed bladders (1.4 ± 0.2 to 7.2 ± 1.3) were detected. Removing the urothelium increased the relaxant effect of vardenafil at 1-0µM (p=0.05) but -log IC50 values were unaffected compared to controls. Resiniferatoxin treatment had no significant effect on vardenafil-induced relaxations (-log IC50: 4.392 ± 0.886, n=6). Vardenafil concentration-dependently inhibited nerve-induced contractions. At 100 μM 19 ± 3 % of the control contraction remained compared to 8 ± 1 % for preparations from obstructed rats.

Conclusions: The current results support that vardenafil can modify rat detrusor smooth muscle tone and suggest that this effect may partly be mediated by urothelium-dependent mechanisms but does not appear to involve resiniferatoxin-sensitive nerves.

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EFFECT OF PHOSPHODIESTERASE TYPE 4 INHIBITOR ROLIPRAN ON CYCLOPHOSHAMIDE-INDUCED BLADDER OVER ACTIVITY

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Introduction & Objectives: Cyclophosphamide (CYP) induces a severe haemorrhagic cystitis characterized by bladder over activity. The study was conducted to examine effects of a PDE4A inhibitor rolipram on bladder over activity in rats with CYP treatment.

Material & Methods: 42 Female Wistar rats were used. 30 rats received a single i.p. injection of CYP (150 mg/kg) whereas the others received saline. After 72 h, bladder function was evaluated by (1) in vitro preparations of whole bladders (n=24) and (2) cystometry with continuous saline infusion under urethral anesthesia (n=18). The spontaneous contractile activity of isolated whole bladder was quantified by calculation the maximal amplitude (cmH2O), its frequency (contractions/min) and the area under the curve of spontaneous contractions. Carbachol (1 µM) elicited spontaneous contractions superimposed on a tonic contraction in CYP-treated rats. Rolipram (5-80 µM) caused a relaxation on the tonic contraction whereas it could not suppress the spontaneous contractions induced by carbachol. During continuous infusion cystometry, intercontraction interval (ICI) the time between two voiding cycles, pressure threshold (bladder pressure immediately prior to micturition) and basal pressure (the lowest bladder pressure during filling) were analyzed by Student’s t-test.

Results: CYP-treatment dramatically potentiated the basal spontaneous contractions of isolated whole bladders compared to control rats. An adrenergic neuron blocker guanethidine (2 µM), a cholinergic neuron blocker atropine (2 µM) or a purinergic antagonist suramin (100 µM) was ineffective on the spontaneous contractions whereas a L-Type calcium channel blocker nifedine (1 µM) completely abolished. Rolipram (5-80 µM) induced a significant concentration-dependent suppression on the amplitude, frequency (contractions/min) and area under the curve of spontaneous contractions. Carbachol (1 µM) elicited spontaneous contractions superimposed on a tonic contraction in CYP-treated rats. Rolipram (5-80 µM) caused a relaxation on the tonic contraction whereas it could not suppress the spontaneous contractions induced by carbachol. During cystometry, intercontraction interval (ICI) was significantly shorter in CYP-injected rats than in control rats. Rolipram at 540 µM has no significant effect on the ICI and contraction pressure while it significantly decreased these parameters at 80 µM. Rolipram at 20-80 µM caused a significant decrease on the pressure threshold in a concentration-dependent manner. After washout of rolipram, pressure threshold increased to the previous level before rolipram application. At 10-80 µM, rolipram tended to decrease baseline pressure but these changes were not statistically significant.

Conclusions: PDE4A inhibitor rolipram caused a significant suppression of the basal spontaneous contractions in CYP-treated rats, at doses that have no effect on the carbachol-induced spontaneous contractions and cystometric parameters. PDE4 inhibitors may be considered as an attractive strategy for the treatment of CYP-induced bladder over activity.