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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: Autonomous 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 periods post spinal cord injury (PSCI): during spinal shock (2 hours PSCI), during detrusor areflexia (24 hours PSCI), during the onset of non-voiding contractions (NVC) without spontaneous voiding (1 week PSCI) and finally during the onset of neurogenic detrusor over activity (NDO, 3 weeks PSCI). Our aim was to investigate whether SCI induced alterations in the behaviour of AA which could be involved in the evolution from detrusor areflexia towards NDO.

Material & Methods: Female Wister rats were made paraplegic by spinal cord interruption at the vertebral level T8-T9 and sacrificed at different time periods PSCI (2 hours, 24 hours, 1 week and 3 weeks). Each bladder was excised and placed in an organ bath where intravesical pressure changes were measured. The effects of intravesical volume load and muscarinic (M) agonists (non-selective and M2-selective) were studied. The behaviour of AA was analysed as pressure transients and statistically compared between all groups. Such transients were defined as pressure changes of at least 0.5 cmH20, lasting between 5 and 30 sec and ending when the pressure level had fallen to 25% of its original height. All p-values shown are compared to controls.

Results: Following SCI a clear evolution in AA was observed. During spinal shock (2 hours PSCI) we observed increased amplitude of transients ($p<0.05$), normal compliance and increased response to non-selective muscarinic agonists ($p<0.05$). 24 hours PSCI the behaviour of AA only showed moderately decreased frequency of transients ($p<0.05$). With the appearance of NVC (1 week PSCI) we observed a strongly decreased frequency of transients ($p<0.01$) associated with highly increased compliance ($p<0.01$) and contractile response to selective M2-agonists ($p<0.01$). AA in bladders from SCI rats with renewed voiding reflexes (3 weeks PSCI) showed a decreased frequency of transients ($p<0.05$), together with a normal compliance and a moderately increased sensitivity for M2-agonists ($p<0.05$).

Conclusions: From these observations it is apparent that SCI leads to alterations in the behaviour and muscarinic response of AA in the isolated bladder. Besides being essential for the aetiology and symptoms of NDO, such changed AA might also offer new therapeutic approaches. Interacting on local targets could be promising in new treatments for NDO, due to the possible advantage of fewer side effects and less disturbance of normal voiding pathways. Based on the present data it might then be interesting to further explore M2 as a possible (early) local therapeutic target in neurogenic bladder.

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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 urodynamic 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 micturition 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 not 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 ml/cmH2O, $p=0.003$). Only 1 patients retained the same bladder compliance after vardenafil administration (4 ml/cmH2O), while no patients reported a compliance decline.

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.

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VARDENAFIL RELAXES PRECONTRACTED RAT DETRUSOR PARTIALLY THROUGH UROTHELIUM-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 shown to decrease non-voiding contractions of rats with outflow obstruction. The objective of the current investigation was to study effects by vardenafil on isolated detrusor preparations from rats devoid of resinferatoxin-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 resinferatoxin (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 to 100 % in obstructed rats. –Log IC50 values amounted to 4,407 ± 0,08 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 1-10μM ($p<0.05$) but –log IC50 values were unaffected compared to controls. Resinferatoxin treatment had no significant effect on vardenafil-induced relaxations (-log IC50: 4,392 ± 0,889, 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 associated with urothelium-dependent mechanisms but does not appear to involve resiniferatoxin-sensitive nerves.

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EFFECT OF PHOSPHODIESTERASE TYPE 4 INHIBITOR ROLIPRAM ON CYCLOPHOSPHAMIDE-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 PDE4 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 urethane anesthesia (n=18). The spontaneous contractile activity of isolated whole bladder was quantified by calculation the maximal amplitude (cm H2O), the frequency (contractions per min) and the area under the curve (AUC). The cystometry parameters evaluated were amplitude (maximum bladder pressure during micturition), 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). Data 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 receptor antagonist atropine (2 μM) or a purinergic antagonist suramin (100 μM) was ineffective on the spontaneous contractions whereas a L-Type calcium channel blocker nifedipine (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. In anesthetized rats, during continuous infusion cystometry, intercontraction interval (ICI) was significantly shorter in CYP-injected rats than in control rats. Rolipram at 5-40 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: PDE4 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.