

models the effects of indomethacin (1.0 mg/kg iv, bolus) were investigated on bladder contractions induced either by activation of the pre-ganglionic efferent pathway (ESPR) or through the activation of afferent and efferent pathways, induced by bladder filling (VIBC).

Results:

In vitro, indomethacin (1 μ M) reduced basal tone of bladder preparations and reduced, or in some cases entirely eliminated, spontaneous myogenic activity of the smooth muscle preparations.

In vivo, indomethacin (1.0 mg/kg) had no effect on bladder contractions induced by pre-ganglionic efferent nerve stimulation (ESPR model), while in the VIBC model frequency of contraction was reduced (6.17 ± 0.75 to 2.33 ± 0.33 contractions, per 10 min interval,) with no alteration in amplitude of the contractions.

Conclusions:

These data suggest that prostanoids act at several levels in the micturition reflex. The *in vitro* studies suggest a degree of prostanoid-induced basal tone and spontaneous myogenic activity of urinary bladder smooth muscle. Data from the VIBC studies suggest that prostanoids are involved in the neuronal control of micturition. The fact that the frequency rather than the amplitude of volume-induced bladder contractions were altered by indomethacin suggests an involvement of prostanoids at the afferent level of the micturition reflex. The lack of effect of indomethacin in the spinally-stimulated pithed rat studies (ESPR model) further supports the notion that prostanoids modulate the micturition reflex at the level of the bladder afferents or the central nervous system.

References:

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BLADDER INSTABILITIES AND ADRENERGIC SUPERSENSITIVITY OF DETRUSOR SMOOTH MUSCLE IN FEMALE AGED RAT

Disturbances of bladder function are common in the elderly. Despite the extensive use of the rat in research on aging, the effects of senescence on urinary bladder function are not yet well characterized. Particularly, there is no report on urinary bladder function in conscious aged animals and the consequences of aging on the adrenergic neurotransmission to the detrusor smooth muscle are still debated.

Aims. To characterize the consequences of aging on micturition profiles in conscious female rats and the associated modifications in adrenergic responses *in vitro*.

Methods. *In vivo* experiments were performed in 10 and 30 months old female Wistar/Rij rats chronically instrumented with an intra-vesical catheter. The bladder was perfused at a rate of 6ml/h and intravesical pressure and urinary volume recorded. Five reproducible micturition cycles were analyzed and means of the different cystometric parameters calculated. *In vitro*, two detrusor strips and the bladder neck were isolated from each animal and placed in 20 ml glass organ baths containing a modified Krebs solution with 1 μ M propranolol, maintained at 37° C and aerated with 95% O₂ and 5% CO₂. After a contractile response to 80 mM KCl, cumulative concentration-response curves to noradrenaline (NA) (0.01-100 μ M) were performed and results were expressed as % of the contraction to KCl.

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Results. The percentage of vesical weight vs body weight was identical in 30 and 10 months old rats, indicating that aging does not induce vesical hypertrophy in this strain of Wistar rats. Cystomanometrical data are shown in the table.

	10 months n=13	30 months n=14
Micturition pressure, (cmH ₂ O)	46±3	63±6 *
Threshold pressure, (cmH ₂ O)	13±2	13±1
Basal Pressure, (cmH ₂ O)	12±3	15±3
Micturition duration, (sec.)	8±1	12±2 *
Interval between micturition, (min.)	3.2±0.5	3.6±0.3
Micturition volume, (mL)	0.19±0.02	0.27±0.03
Residual Volume, (mL)	0.13±0.04	0.12±0.02

* Statistically different from 10 months, unpaired t-test, $p < 0.05$

In the aged rats, micturition pressure and duration were significantly higher (about 40-50%) whereas, bladder capacity, as reflected by interval between micturition, micturition volume and residual volume were not modified. Most of the aged rats (60%) showed a pronounced bladder instability during cystometry. Moreover, some aged rats (4/18), exhibited unstable bladder contractions, associated with urinary leakage, in the absence of micturition.

In vitro, the intrinsic contractility of the detrusor muscle was unaffected by age since no difference was found in the magnitude of the contraction induced by 80 mM KCl (1.94 ± 0.12 g and 1.79 ± 0.13 g in 10 and 30-month-old rats, respectively).

Conversely, maximal contractile responses to NA were 2 times greater in detrusor from older rats ($E_{max} = 53.6 \pm 4.1\%$ vs $28.4 \pm 6.3\%$, $p < 0.05$).

In the bladder neck, however, no difference was observed in the contractile response to NA between 10 and 30 month old rats, as evidenced by similar pD_2 or E_{max} responses.

Conclusions. Micturition profiles in aged rats were characterized by a higher peak micturition pressure, longer duration of micturition and in most cases a pronounced spontaneous activity during the filling phase. These altered micturition profiles appeared to have common features with those recently reported in an experimental model of bladder instability in female rats (1). In contrast, the intrinsic contractility of the detrusor muscle seems unaffected by age as indicated by similar responses to KCl. The higher sensitivity to NA, specific of the bladder dome, may explain both the increased micturition pressure and the bladder instabilities observed. These results are in accordance with a previous report in rats (2) and could be due to denervation supersensitivity subsequent to damage of sympathetic nerves of the detrusor smooth muscle (3).

- (1) : Experimental bladder instability following bladder outlet obstruction in the female rat, *J. Urol.*, **160**: 2253-2257, 1998.
- (2) : Age-related change in α -adrenergic responsiveness of the urinary bladder of the rat is regionally specific, *Neuropharmacol.*, **25**:1335-1340, 1986.
- (3) : Sympathetic and sensory innervation of the urinary tract in young adult and aged rats : a semi-quantitative histochemical and immunohistochemical study, Warburton and Santer, *Histochemical Journal*, **26**:127-133, 1994.