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Altered neural control of micturition in the aged F344 rat

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Abstract The purpose of this study was to determine whether micturition reflexes are altered in aged rats. Voiding frequencies and awake cystometrograms (CMGs) were measured in young (3–5 months old) and aged (24 months) F344 male rats. Bladder contractions induced by subcutaneous apomorphine and intravesical capsaicin stimulation were measured using awake CMGs. Urodynamic parameters were compared. Aged rats voided less frequently (4.1 vs 6.9 times/18 h, $P = 0.006$), with a higher volume per void (1.1 vs 0.7 ml, $P = 0.02$) and had a higher micturitional threshold pressure (8.7 vs 4.6 mmHg, $P = 0.0001$) than the young rats. Apomorphine induced a higher frequency of bladder contractions in aged animals compared to young animals (5.5 vs 3.1 contractions/min, $P = 0.03$). Intravesical capsaicin caused a lower pressure bladder response in the aged rats (38.5 vs 70.6 mmHg, $P = 0.01$) compared to the young rats. Bladder afferents and central micturition pathways may be altered in aged rats. Impaired bladder contractility in the elderly may be exacerbated by reduced sensory input, whereas the propensity for detrusor instability could result from altered central processing. This study demonstrated the utility of the F344 animal model to study micturitional changes resulting from aging.

Key words Aging · Micturition reflex · Apomorphine · Capsaicin · Rat model

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Introduction

Various investigators have examined the effects of aging on the bladder by studying bladder smooth muscle in rats. The bladder mass, voiding frequency and intravesical pressure at micturition are increased in aged animals compared to young controls [4]. In vitro experiments examined the responses of the aging bladder muscle to pharmacologic agents or mechanical stretch [5, 17, 22, 29, 30, 32]. However, the potential contribution of changes in neural pathways to voiding dysfunction with aging has not been examined.

Baseline bladder function was determined by measuring voiding frequency and performing in vivo awake cystometrograms (CMGs). To assess whether alterations exist in the central neural pathways controlling micturition, subcutaneous apomorphine, a dopamine agonist that stimulates the supraspinal centers, was used to initiate a micturition reflex [20, 36]. Furthermore, at the peripheral level, the afferent limb of the micturition reflex was probed by infusion of intravesical capsaicin. Capsaicin is a chemonociceptive agent, which triggers an afferent evoked micturition reflex [16, 21]. The bladder hyperactivity elicited by apomorphine and capsaicin was measured using awake CMGs. Our results reveal that baseline micturition behavior and voiding reflexes elicited by both apomorphine and capsaicin in aged animals differed significantly from the young controls. This animal model may prove useful in addressing clinical voiding problems in the elderly, which range from overactive detrusor to urinary retention.

Materials and methods

Animals

Ten 3- to 5-month-old male F344 rats (National Institutes of Aging stock, Harlan Sprague-Dawley, Indianapolis, Ind.), weighing 200–300 g, were used as the young controls. Ten 24-month-old male F344 rats, weighing 360–420 g, were used as aging models. The rats were housed in a vivarium with free access to water and food. Surgeries and pharmacologic treatments were approved by the Animal Research Committee of University of Virginia and principles of laboratory animal care were followed.

Voiding frequencies

Prior to any surgical or pharmacologic manipulations, all animals were placed in metabolic cages (Nalgene, Rochester, N.Y.) with free access to food and water for the 18-h period between 1500 h and 0900 h the next day. The light was off between 1700 h and 0800 h the next day to maintain a consistent dark cycle. Urine was collected in a tube fashioned from a polypropylene centrifuge tube, which was connected to a Grass FT-03 force transducer (Grass-AstraMed, Warwick, R.I.). Voids were recorded on a Grass Model 79 polygraph recorder (Grass-AstraMed). Voids were defined as a volume greater than 0.1 ml and occurring in a period greater than 2 min from the previous void. Voiding frequency was determined on two separate occasions for each animal. Urine osmolality was measured using an osmometer (Wescor, Logan, Utah). Water consumed during the 18 h was also measured.

Awake CMGs

The method of bladder tube placement for the awake CMGs has been previously described [25]. An awake CMG was measured by placing an unrestrained rat in the metabolic cage used for voiding frequency measurements. The polyethylene tube (PE-50) was connected to a Harvard pump (Harvard Apparatus, S. Natick, Mass.) and a pressure transducer (P23XL, Spectramed, Oxnard, Calif.) via a 2-way stopcock. The bladder was filled with room temperature normal saline at a rate of 0.072 ml/min. The volume and pressure measurements from the first void were not used. Each subsequent void was collected and weighed during the course of the CMG to calculate the volume voided. Intravesical pressures were recorded on a Gould multichannel polygraph (Gould Electronics, Cleveland, Ohio). Four voiding contractions were elicited and recorded per animal. The intravesical pressure prior to micturition, peak micturition pressure and volume per void were determined from the each contraction.

Apomorphine treatments

Rats were injected subcutaneously with 0.125, 0.25 or 0.50 mg/kg of apomorphine (Sigma Chemical, St. Louis, Mo.) dissolved in sterile normal saline at a concentration of 1 mg/ml. Two to three minutes after injection of apomorphine, both the young and old animals exhibited similar behavioral changes, including sniffing, rotational movement and yawning. An awake CMG was performed to assess the effect of the particular dose of apomorphine on bladder behavior. Voided volumes were not measured because the rats did not always void with every bladder contraction. The CMG data were analyzed over a 10-min interval, 10 min after apomorphine injection. This interval was chosen because it represented the most dramatic response of the bladder to apomorphine. Mean peak pressures represented the average of the peak pressures during this 10-min interval. The peak pressure was defined as maximum amplitude for that contraction without subtraction of the baseline. The pressure transducer was zeroed to air prior to apomorphine injection. Mean frequencies of contractions were determined by the number of bladder contractions per minute during this 10-min interval. A detrusor contraction was defined as a change in intravesical pressure, ≥15 cmH_2O (≥11.03 mmHg). The animals recovered from the effects of apomorphine within 1 h. Animals received the three doses of apomorphine with a recovery period of 2 h after each dose.

To confirm that the effect of apomorphine on the micturition reflex was mediated via the central and/or peripheral nervous system, and not in the peripheral smooth muscle or due to motion artifact, one animal underwent denervation of the bladder at the time of initial CMG tube placement. Denervation was accomplished by bilateral removal of the major pelvic ganglia (MPG). The CMG tube in this animal was not sealed to allow for urinary drainage. After 2 days recovery, an awake CMG after a 0.25 mg/kg apomorphine injection was performed.

Capsaicin treatments

Capsaicin was made as a 10 mM stock in 100% ethanol and stored at −20 °C until needed. The stock capsaicin was diluted to 30 or 100 μM with saline and infused at a rate of 0.072 ml/min into the bladder via the same protocol as performing the awake CMGs. The capsaicin experiments were performed after 24 h of recovery from the last dose of apomorphine. The rats all exhibited licking of their lower abdomen after 30 min of infusion with capsaicin. The CMG tracings were analyzed during the peak effect of capsaicin, which occurred after 30 min from the start of the infusion. Mean peak bladder pressures and mean frequency of bladder contractions were calculated from the CMG curves, as described above. Voided volumes were not measured because the rats did not necessarily void with each bladder contraction. Each animal received 30 and 100 μM capsaicin intravesically with a 1-day recovery period in between.

Statistical analysis

Two-tailed Student's *t*-test was used to compare the means obtained for each of the parameters measured. Difference in means were considered statistically significant for $P < 0.05$.

Results

Voiding frequency and awake CMG

The aged rats voided less often than the young controls over the 18-h period (4.1 ± 0.5 vs 6.9 ± 0.7, $P = 0.006$) (Fig. 1A). However, the mean voided volume in the aged rats was significantly higher (1.1 ± 0.1 vs 0.7 ± 0.08 ml, $P = 0.02$) (Fig. 1B). The urine was significantly less concentrated in the aged rats (1480 mOsm vs 1999 mOsm, $P = 0.00007$). There was no significant difference between the water consumed over the 18-h period between the two groups of animals (results not shown) and the product of voiding frequency times the volume per void, which reflects an estimation of the total voided volume, was almost identical. The aged rats were significantly heavier than their younger counterparts (393 vs 255 g, $P < 0.05$).

Baseline parameters were measured with the awake CMG (Fig. 2). Threshold pressure at micturition and voided volume were the two parameters that were statistically different between the aged and young rats. The aged rats had a higher threshold pressure at micturition

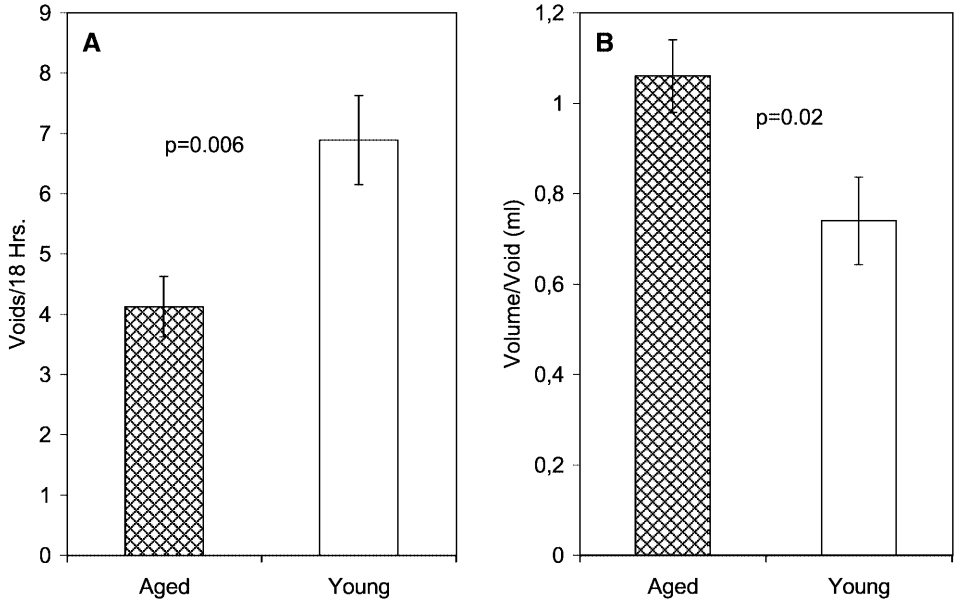

Fig. 1A, B Baseline voiding parameters in aged and young rats. **A** Aged rats voided significantly less ($P = 0.006$) than young rats. Data represent mean ± SEM. **B** Aged rats had a larger bladder capacity than young rats ($P = 0.02$). Data represent mean ± SEM

and a significantly higher volume per void when compared with the young controls (Fig. 2A, B). Peak micturition pressure was not statistically different between the two groups (Fig. 2C).

Apomorphine treatments

After subcutaneous apomorphine, the young and aged rats exhibited detrusor hyperactivity (Fig. 3A, B). The aged rats had consistently higher frequency of contractions than the young animals at all doses of apomorphine. At a dose of 0.25 mg/kg, the difference was statistically significant (Fig. 4A). The mean peak bladder pressures were not significantly different between the two groups of rats at any dose of apomorphine, but there was a trend of the young rats having higher bladder pressures throughout the dose range (Fig. 4B). The bladder contraction pressures induced by apomorphine were lower than the baseline micturition pressures at all doses used in both the aged and young animals. Because most of the contractions elicited by apomorphine did not result in a voided volume, these contractions were termed peak bladder pressure rather than micturition pressure. In the one animal with bilateral MPGs removed (see Material and methods), apomorphine did not cause any bladder contractions (Fig. 3C).

Capsaicin treatments

Capsaicin instilled into the bladder induced frequent bladder contractions in both aged and young rats (Fig. 5A, B). Similar to apomorphine injections, not all bladder contractions resulted in voided urine. We again analyzed frequency of bladder contractions and mean peak bladder pressure. There were no statistical differences between the aged and young rats in the frequency of bladder contractions elicited by capsaicin at either dose (Fig. 6A), but again the frequency was higher than baseline in both sets of animals. The mean peak bladder

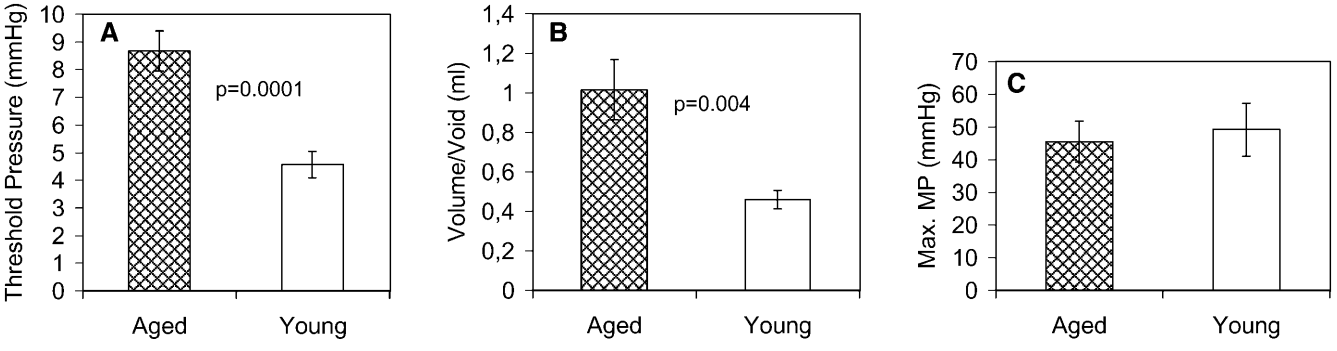

Fig. 2A-C Baseline awake CMG parameters measured in aged and young rats. **A** The micturitional threshold pressure was significantly higher ($P = 0.0001$) in the aged rats. Data represent mean ± SEM. **B** The bladder capacity as determined by an awake CMG was also significantly higher in the aged rats (compare with Fig. 1B). Data represent mean ± SEM. **C** Maximal micturition pressure was not different between the two groups of animals. Data represent mean ± SEM

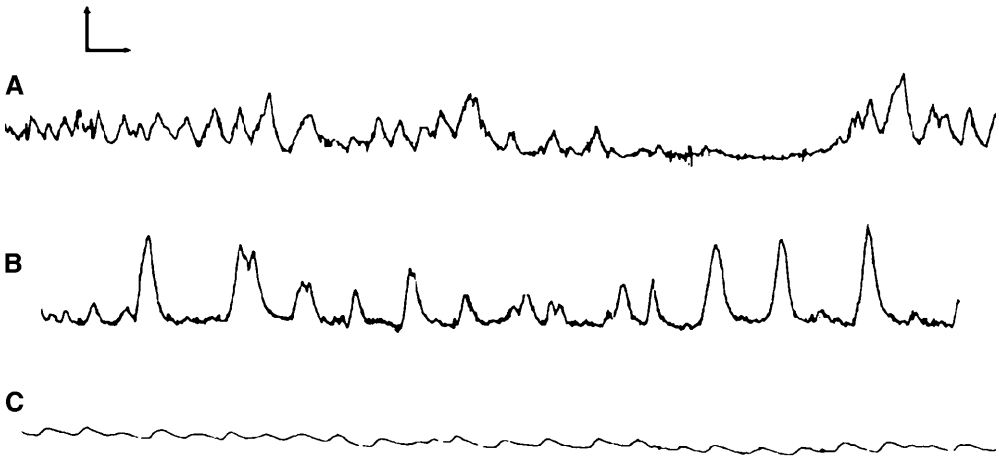

Fig. 3A, B Awake CMG 10 min after 0.25 mg/kg subcutaneous apomorphine. *Vertical arrow* equals 20 mmHg; *horizontal arrow* equals 0.2 min. **A** Representative curve in aged F344 rat. **B** Representative curve in young F344 rat. **C** Curve of animal with bilateral MPG removal

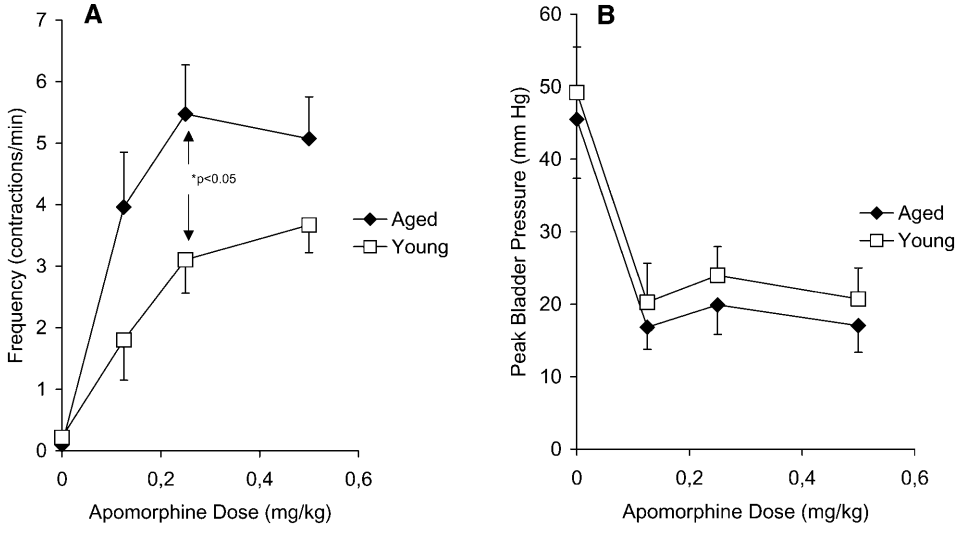

Fig. 4A, B Bladder responses (frequency and pressure) to subcutaneous apomorphine measured by an awake CMG. Note that 0 mg/kg apomorphine data points are bladder frequency and pressure responses to saline infusion in animals without subcutaneously injected apomorphine. **A** At dose of 0.25 mg/kg, the aged rats had a significantly higher frequency of bladder contractions compared with young rats. Note that at all doses, aged rats had higher mean frequencies. Data represent mean ± SEM. **B** No significant differences in peak bladder pressures were found between young and aged animals. Data represent mean ± SEM

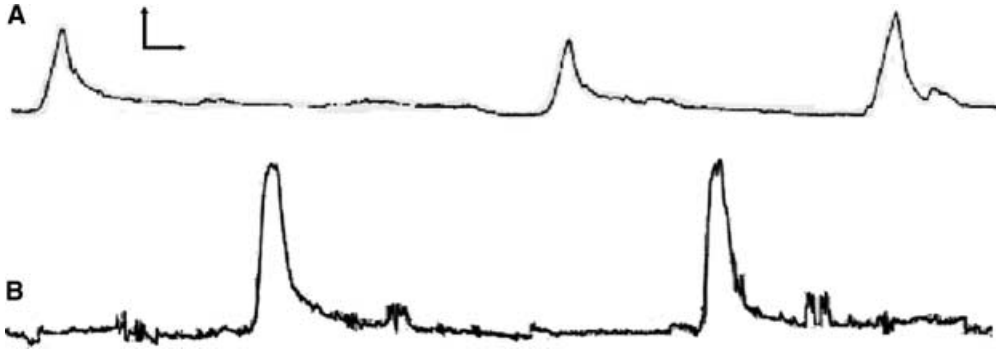

Fig. 5A, B Awake CMG recordings after 100 μM intravesical capsaicin infusion. *Vertical arrow* equals 20 mmHg; *horizontal arrow* equals 0.2 min. **A** Representative curve in aged F344 rat. **B** Representative curve in young F344 rat

pressure response to 100 μM capsaicin was significantly higher in the young rats (Fig. 6B).

Discussion

Previous aging studies have focused on bladder smooth muscle physiology, anatomy and pharmacology. Investigators studying ultrastructural changes in the aged bladder have theorized that aging's effect on voiding dysfunction was primarily due to altered structure of bladder smooth muscle [8, 9]. Since there is ample evidence that aging causes changes in peripheral autonomics [2, 10, 12, 26, 27, 33, 34], it is not unreasonable to consider that age-related changes in autonomic innervation of the bladder may result in altered micturition.

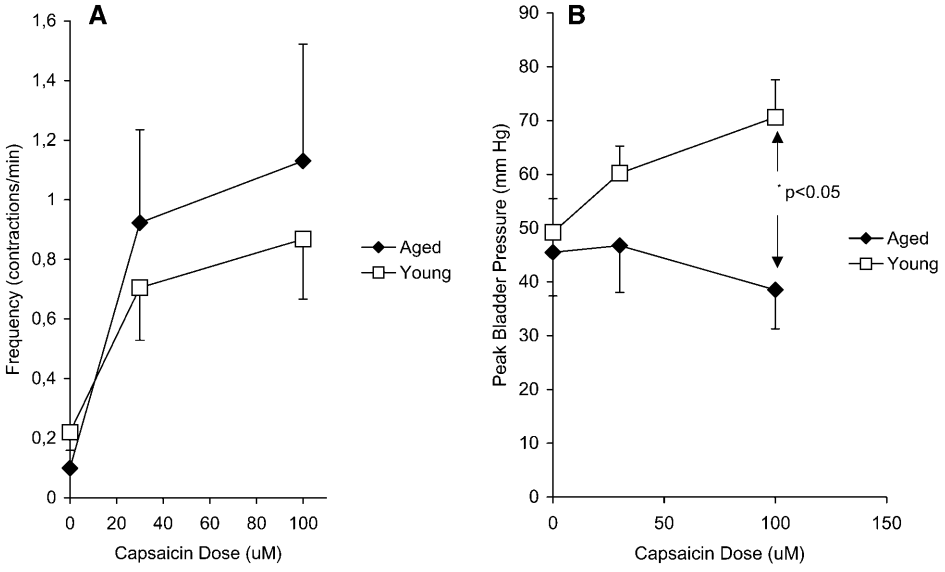

Fig. 6A, B Bladder responses (frequency and pressure) to intravesical capsaicin measured by awake CMG. Note that 0 μM capsaicin data points are bladder frequency and pressure responses to saline infusion alone without capsaicin. **A** No significant differences in frequency of bladder contractions were found between the young and aged animals. Data represent mean ± SEM. **B** 100 μM intravesical capsaicin resulted in a significantly greater bladder pressure in the young rats compared to the aged rats. Data represent mean ± SEM

Responses to central (apomorphine) and peripheral (capsaicin) neural stimuli suggest that there may exist altered neural control of the micturition reflex in the aging F344 rat.

The finding of decreased voiding frequency in aged rats is in contrast with previous results [4]. In this previous study [4], voiding frequency determinations were determined over only 4 h. It is known that the micturition behavior of the rat follows a circadian rhythm. Bladder weights were not measured because of edema induced by the CMG tube; however, it has been shown previously that the bladder in the aged F344 rats is significantly heavier and has a significantly larger bladder capacity than its younger counterparts [4]. These findings imply that the lower urinary frequency in aged rats reflects, in part, an increased voided volume secondary to a larger bladder capacity.

There was no significant difference between the maximal micturition pressure generated by the aged and by the young bladder (Fig. 2C). This is in contrast to an earlier study [4] in which CMGs were performed on anesthetized animals. The awake CMG data also showed a two times higher threshold pressure at micturition in the aged rats (Fig. 2A). These findings are in agreement with the notion that differences in micturition behavior between these animals are due to alterations in neurogenic rather than myogenic mechanisms. Whether the higher pressure needed to trigger a micturition reflex in the aged animal is due to intrinsic myogenic (increased bladder tension) and/or neurogenic (afferent threshold) processes is uncertain.

Apomorphine has also been used to stimulate supraspinal and spinal centers in producing micturition [19, 36] and detrusor hyperactivity. We confirmed that apomorphine's action on the bladder was indeed central because a decentralized bladder did not respond to apomorphine (Fig. 3C). Furthermore, there is no evidence that dopamine acting through peripheral receptors can trigger a reflex micturition. The finding that the aged rats reacted to apomorphine with a significantly higher frequency of bladder contractions than young rats (Fig. 4A) was surprising, given that the micturition threshold pressure was higher in the aged bladder. Because apomorphine acts at central sites, alterations may exist in central dopamine neural pathways regulating the micturition reflex in aged rats. A possible difference in the effect of apomorphine on the outlet (urethra) between the aged and young rats may also have contributed to our findings. Dopamine or its agonists have been reported to increase, decrease or have no effect on urethra contractility [1, 11, 15]. However, because the rats did not void with the majority of the bladder contractions, it is impossible to perform pressure–flow studies to ascertain effect of apomorphine on outlet resistance. Additionally, due to the high frequency of contractions elicited by apomorphine, when micturition did occur it would be difficult to ascertain which voiding contractions resulted in urinary flow.

Several studies have reported associations between aging and decreased numbers or function of dopamine receptors, and also with decreased dopamine levels, in the central nervous system (CNS) [7, 31, 37–40]. These observations imply a general loss of dopamine neural pathways over time. Possibly, the aged F344 rats have increased sensitivity to dopamine agonists because of a central "denervation supersensitivity" due to loss of dopamine and/or dopamine synapses at the supraspinal or spinal micturition center. Therefore, exogenous dopamine agonists, such as apomorphine, caused an exaggerated response in the aged rats, which was reflected in the higher frequency of bladder contractions. However, other differences, such as bioavailability of apomorphine, may explain the differences in response between the aged and young animals.

Capsaicin triggers a chemonociceptive micturition reflex, presumably by the release of sensory neurotransmitters such as substance P or calcitonin gene-related peptide (CGRP) [16, 21]. The mechanism of this

reflex involves the C-afferent fibers in the bladder wall, whereas the normal micturition reflex is triggered through Aδ-afferent fibers. It has been shown that the bladder receptor mediating a C-fiber reflex, such as in a cooling reflex, is different compared to the mechanoreceptor mediating the Aδ-fiber reflex [13, 14]. Input from the CNS or spinal cord is still required for capsaicin to induce a micturition reflex because hexamethonium, a ganglionic blocker, abolished capsaicin-induced bladder contractions [23, 24].

At a dose of 100 μM capsaicin intravesically, the young rats responded with a higher peak bladder pressure than the aged rats (Fig. 6B), possibly due to altered afferent function in the aged animal. It is known that the afferent input from the bladder and the urethra reinforce the micturition reflex to ensure that bladder emptying is complete [3]. This concept is further supported by the comparison of mean peak bladder pressures in both aged and young rats elicited by saline filling (Fig. 2C), apomorphine (Fig. 4B) and capsaicin (Fig. 6B). Capsaicin induced, in both sets of animals, peak bladder pressures similar to the pressures from saline filling. However, apomorphine, which presumably did not affect afferent signaling, induced much lower bladder pressures than either saline filling or capsaicin. The lesser response of aged bladders to capsaicin in conjunction with the finding that aged bladders have a higher micturition threshold pressure (Fig. 2A) imply that the function or impact of both the Aδ- and C-afferents are diminished in the aged rats. The finding that there was no difference in the frequency of bladder contractions in response to capsaicin between the aged and young animals (Fig. 6B) could be explained by the fact that capsaicin acted only peripherally within the bladder when infused intravesically. Therefore, only afferent nerves within the wall of the bladder mediated its action.

Sensory changes in somatosensory systems secondary to aging have been studied extensively. However, very little has been described regarding sensory changes in visceral organs as a result of aging. Changes in afferent nerve function in the aging digestive tract have been studied. Aged rats had decreased ability to increase gastric mucosal blood flow in response to capsaicin compared to young rats [28, 35]. Additionally, it has been shown there is a decrease in CGRP immunoreactivity in the mesenteric resistance vessel, suggesting possibly decreased afferent function [18].

It would be tempting to conclude that the aged rats have decreased afferent input at the peripheral level, leading to a higher threshold pressure to initiate a micturition reflex and a lower peak bladder pressure in response to capsaicin. At the level of the CNS, the aged rats have an increased sensitivity to dopamine agonists. This balance can be easily tipped by either endogenous or exogenous dopamine and/or dopamine agonists, resulting in bladder hyperactivity. Indeed, this hypothesis of impairment of central and peripheral neural responsiveness of aging F344 rats has been recently described in the catecholaminergic system of the hypothalamus–pituitary–adrenal axis [6].

This paradigm of decreased peripheral afferent signaling coupled with altered central input into the micturition reflex may also explain incontinence secondary to detrusor instability without urge sensation, as seen in the elderly. This has been described as detrusor hyperreflexia with impaired contractility (DHIC) by Resnick et al. [8, 9]. Finally, elderly patients may be more prone to developing hyperactive voiding in response to centrally acting drugs, injury or some minor stimuli because of increased sensitivity at the level of the supraspinal micturition centers.

References

1. Araki S, Kato M, Kase H, Okada K (1995) Hyper-dopaminemia may produce an increased outlet resistance of the prostatic urethra: a case report of malignant pheochromocytoma. J Urol 153: 1614
2. Baker DM, Santer RM (1988) Morphometric studies on pre- and paravertebral sympathetic neurons in the rat: changes with age. Mech Ageing Dev 42: 139
3. Barrington F (1931) The component reflexes of micturition in the cat. Brain 54: 177
4. Chun AL, Wallace LJ, Gerald MC, Levin RM, Wein AJ (1988) Effect of age on in vivo urinary bladder function in the rat. J Urol 139: 625
5. Chun AL, Wallace LJ, Gerald MC, Wein AJ, Levin RM (1989) Effects of age on urinary bladder function in the male rat. J Urol 141: 170
6. Cizza G, Pacak K, Kvetnansky R, Palkovits M, Goldstein DS, Brady LS, Fukuhara K, Bergamini E, Kopin IJ, Blackman MR, Chrousos GP, Gold PW (1995) Decreased stress responsivity of central and peripheral catecholaminergic systems in aged 344/N Fischer rats. J Clin Invest 95: 1217
7. Dobrev D, Bergstrasser E, Fischer HD, Andreas K (1995) Restriction and functional changes of dopamine release in rat striatum from young adult and old rats. Mech Ageing Dev 80: 107
8. Elbadawi A, Yalla SV, Resnick NM (1993) Structural basis of geriatric voiding dysfunction. II. Aging detrusor: normal versus impaired contractility. J Urol 150: 1657
9. Elbadawi A, Yalla SV, Resnick NM (1993) Structural basis of geriatric voiding dysfunction. 3. Detrusor overactivity. J Urol 150: 1668
10. Felten SY, Bellinger DL, Collier TJ, Coleman PD, Felten DL (1987) Decreased sympathetic innervation of spleen in aged Fischer 344 rats. Neurobiol Aging 8: 159
11. Gahlin K, Sparf B (1978) Differences in postsynaptic alpha-adrenoceptor populations between isolated cat urethra and various other isolated tissues. Acta Pharm Tox 43: 48
12. Gavazzi I, Andrews TJ, Thrasivoulou C, Cowen T (1992) Influence of target tissues on their innervation in old age: a transplantation study. Neuroreport 3: 717
13. Geirsson G (1993) Evidence of cold receptors in the human bladder: effect of menthol on the bladder cooling reflex. J Urol 150: 427
14. Geirsson G, Lindstrom S, Fall M (1993) The bladder cooling reflex in man – characteristics and sensitivity to temperature. Br J Urol 71: 675
15. Harada T, Kumazaki T, Kigure T, Etori K, Tsuchida S (1989) Effect of adrenergic agents on urethral pressure and urethral compliance measurements in dog proximal urethra. J Urol 142: 189
16. Ishizuka O, Igawa Y, Mattiasson A, Andersson KE (1994) Capsaicin-induced bladder hyperactivity in normal conscious rats. J Urol 152: 525

17. Johnson JM, Skau KA, Gerald MC, Wallace LJ (1988) Regional noradrenergic and cholinergic neurochemistry in the rat urinary bladder: effects of age. J Urol 139: 611
18. Kawasaki H, Saito A, Takasaki K (1990) Age-related decrease of calcitonin gene-related peptide-containing vasodilator innervation in the mesenteric resistance vessel of the spontaneously hypertensive rat. Circ Res 67: 733
19. Kontani H, Inoue T, Sakai T (1990) Dopamine receptor subtypes that induce hyperactive urinary bladder response in anesthetized rats. Jpn J Pharm 54: 482
20. Kontani H, Inoue T, Sakai T (1990) Effects of apomorphine on urinary bladder motility in anesthetized rats. Jpn J Pharm 52: 59
21. Lecci A, Giuliani S, Garret C, Maggi CA (1993) Evidence for a role of tachykinins as sensory transmitters in the activation of micturition reflex. Neuroscience 54: 827
22. Longhurst PA, Eika B, Leggett RE, Levin RM (1992) Comparison of urinary bladder function in 6 and 24 month male and female rats. J Urol 148: 1615
23. Maggi CA, Santicioli P, Borsini F, Giuliani S, Meli A (1986) The role of the capsaicin-sensitive innervation of the rat urinary bladder in the activation of micturition reflex. Naunyn-Schmiedebergs Arch Pharm 332: 276
24. Maggi CA, Santicioli P, Meli A (1984) The effects of topical capsaicin on rat urinary bladder motility in vivo. Eur J Pharm 103: 41
25. Malmgren A, Sjogren C, Uvelius B, Mattiasson A, Andersson KE, Andersson PO (1987) Cystometrical evaluation of bladder instability in rats with infravesical outflow obstruction. J Urol 137: 1291
26. Martinez JL Jr. Vasquez BJ, Messing RB, Jensen RA, Liang KC, McGaugh JL (1981) Age-related changes in the catecholamine content of peripheral organs in male and female F344 rats. J Gerontol 36: 280
27. McLean MR, Goldberg PB, Roberts J (1983) An ultrastructural study of the effects of age on sympathetic innervation and atrial tissue in the rat. J Mol Cell Cardiol 15: 75
28. Miyake H, Inaba N, Kato S, Takeuchi K (1996) Increased susceptibility of rat gastric mucosa to ulcerogenic stimulation with aging. Role of capsaicin-sensitive sensory neurons. Dig Dis Sci 41: 339
29. Munro DD, Wendt IR (1993) Contractile and metabolic properties of longitudinal smooth muscle from rat urinary bladder and the effects of aging. J Urol 150: 529
30. Ordway GA, Esbenshade TA, Kolta MG, Gerald MC, Wallace LJ (1986) Effect of age on cholinergic muscarinic responsiveness and receptors in the rat urinary bladder. J Urol 136: 492
31. Roth GS, Joseph JA (1994) Age-related changes in transcriptional and posttranscriptional regulation of the dopaminergic system. Life Sci 55: 2031
32. Saito M, Kondo A, Gotoh M, Kato K, Levin RM (1993) Age-related changes in the response of the rat urinary bladder to neurotransmitters. Neurourol Urodyn 12: 191
33. Schmidt RE, Chae HY, Parvin CA, Roth KA (1990) Neuroaxonal dystrophy in aging human sympathetic ganglia. Am J Pathol 136: 1327
34. Schmidt RE, Plurad SB, Modert CW (1983) Neuroaxonal dystrophy in the autonomic ganglia of aged rats. J Neuropathol Exp Neurol 42: 376
35. Seno K, Lam K, Leung JW, Leung FW (1996) Aging impairs afferent nerve function in rat intestine. Reduction of mesenteric hyperemia induced by intraduodenal capsaicin and acid. Dig Dis Sci 41: 346
36. Sillen U (1980) Central neurotransmitter mechanisms involved in the control of urinary bladder function. An experimental study in the rat. Scand J Urol Nephrol Suppl 58: 1
37. Valerio A, Belloni M, Gorno ML, Tinti C, Memo M, Spano P (1994) Dopamine D2, D3, and D4 receptor mRNA levels in rat brain and pituitary during aging. Neurobiol Aging 15: 713
38. Wang HY, Bashore TR, Friedman E (1995) Exercise reduces age-dependent decrease in platelet protein kinase C activity and translocation. J Gerontol 50A: M12
39. Woods JM, Ricken JD, Druse MJ (1995) Effects of chronic alcohol consumption and aging on dopamine D1 receptors in Fischer 344 rats. Alcohol Clin Exp Res 19: 1331
40. Zhang L, Ravipati A, Joseph J, Roth GS (1995) Aging-related changes in rat striatal D2 receptor mRNA-containing neurons: a quantitative nonradioactive in situ hybridization study. J Neurosci 15: 1735