Asian Journal of Urology (2017) xx, 1–6

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Review

The aging bladder insights from animal models

Lori A. Birder [a,b], Aura F. Kullmann [b], Christopher R. Chapple [c,*]

[a] University of Pittsburgh School of Medicine, Department of Pharmacology, Pittsburgh, PA, USA
[b] University of Pittsburgh School of Medicine, Department of Medicine, Pittsburgh, PA, USA
[c] Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Received 10 March 2017; received in revised form 20 March 2017; accepted 20 March 2017

KEYWORDS
Lower urinary tract symptoms;
Aging;
Etiology of lower urinary tract symptoms;
Bladder function

Abstract Alterations in bladder function with aging are very common and are very likely to represent an increasing healthcare problem in the years to come with the general aging of the population. In this review the authors describe the prevalence of lower urinary tract symptoms (LUTS) and comment upon potential mechanisms which may be responsible for the increasing prevalence of lower LUTS with increasing age, based on laboratory studies. It is clear that there is a complex interplay between the various components of the neural innervation structure of the bladder in leading to changes with age, which are likely to underpin the LUTS which are seen in the aging bladder.

1. Introduction

Current demographic forecasts have predicted a worldwide increase in the proportion of the population aged 65–80 years. It is well recognized that the urinary bladder appears to be particularly susceptible to aging. The prevalence of both storage and voiding lower urinary tract symptoms (LUTS) increases significantly over the age of 65 years in patients of both sexes [1]. It is well recognized that overactive bladder (OAB) symptom syndrome and urodynamic evidence of bladder overactivity which is seen in a proportion of these patients increases in both sexes with increasing age as does detrusor underactivity and indeed both can co-exist in the same patient [2]. Furthermore there is a clearly increasing prevalence of bladder outflow obstruction in the aging male population. Furthermore disorders such as diabetes, cerebrovascular accidents and neurological disease all exert an increasing influence with increasing age. Understanding how physiological and pharmacological mechanisms function alters as we(who, please check the confirmation) age is now vital to ensure the progress of drug discovery and treatment of diseases in an aging society.

* Corresponding author.
E-mail address: c.r.chapple@shef.ac.uk (C.R. Chapple).
Peer review under responsibility of Second Military Medical University.

http://dx.doi.org/10.1016/j.ajur.2017.03.004

Please cite this article in press as: Birder LA, et al., The aging bladder insights from animal models, Asian Journal of Urology (2017), http://dx.doi.org/10.1016/j.ajur.2017.03.004

Although functional lower urinary tract conditions pose limited risks to life expectancy, they severely impair patients' quality of life, in particular OAB, leading to depression, sleep deprivation, embarrassment and fatigue. Bladder and continence conditions therefore place a huge burden on global healthcare resources which is likely to become even more of an issue as the population continues to age. While our understanding of the basic physiology of the bladder is expanding, the underlying pathophysiological processes are poorly understood, although there is an increasing emphasis on the importance of both peripheral afferent mechanisms in the lower urinary tract as well as altered central transmission and processing of neural information from the bladder and lower urinary tract.

Normal bladder function is dependent on the integration of autonomic and somatic mechanisms which coordinate a complex cycle of filling and emptying. In the first phase of this cycle, the filling phase, the bladder is relatively quiescent as filling ensures. The sensory (afferent) nerves detect changes in bladder volume and distension and convey information to the central nervous system (CNS). Sensory information is integrated in the brainstem micturition centre and when the bladder is full or when it is convenient to void the second phase, the voiding phase, is initiated. During voiding motor (efferent) nerves are activated, resulting in relaxation of the urethral sphincters and concomitant contraction of the detrusor smooth muscle.

Sensory innervation from the bladder is carried via pelvic and hypogastric afferent nerves whose cell bodies lie in the dorsal root ganglia (DRG). These nerves consist of myelinated Aδ fibers and unmyelinated C fibers which have polymodal sensitivity responding to a host of mechanical and chemical stimuli. Deformation of the bladder wall and therefore mechanical stimulation of the sensory nerve terminal (mechanosensitivity) results in the formation of an action potential. This is the basis by which the afferent nerves detect bladder filling and convey the extent to which the bladder is full to the brain. Interestingly however, sensory information from the bladder does not arise from the afferent nerves alone. It has been suggested that the epithelial lining of the bladder, the urothelium can actively participate in sensory transmission [3]. The current theory is that as the bladder fills, urothelial cells detect the degree of stretch and release a host of excitatory and inhibitory chemical mediators. These mediators act on nearby afferent terminals to modulate and tune the excitability of the nerves. Therefore, sensory information from the bladder is a result of both the stimulation of the nerve terminal and the modulation of the nerves by the urothelium. This review will detail some of the contemporary developments in this field based on contemporary animal models.

2. *In vivo* evaluation of age related changes in bladder function in rodents

The effects of aging on bladder structure and function have been investigated using both *in vivo* and *in vitro* methodology in a variety of rodent models. These models include C57BL6 mice (male and female, 22—25 months old [4—6]), the senescent-accelerated prone SAMP8 mice (36—38 weeks old [7]), Fisher 344 rats (male, 22—28 months old [8—10], female, 24 months old [11]), Fischer/Brown Norway rats (male, 28—30 months old [12]), Wistar rats (male or female, 22—37 months old [13—15], Sprague Dawley (SD) rats (male, 18—24 months old [16,17]). Other species included dogs [18,19] and guinea pigs [20,21]. Similar to results from human studies, the rodent models revealed complex and interdependent changes that varied with species, strain and sex. *In vivo* metabolism cage studies have shown increased voiding frequency in mice and rats, as well as in rats with chronic bladder ischemia (a risk factor in aging) [4,7,9,22,23]. Cystometry yielded somewhat more variable results likely due to species and gender differences and/or anesthesia. For example, voiding frequency increased with age in awake male Fischer/Brown Norway rats [12], while it decreased in anesthetized female mice [6]. Several studies reported an increase in bladder capacity and post-residual voiding volume associated with decreased voiding efficiency [10,12,24]. Pressure threshold for voiding increased regardless of species and gender [10,11,16,24], suggesting disturbances of the afferent system. Baseline intravesical pressure also increased [12,16], suggesting changes in the smooth muscle/bladder wall that may impact storage function. Spontaneous non-voiding contractions, considered the hallmark of detrusor overactivity were also reported [10,12,14,16]. Together, these studies suggest that in animal models, a mixture of "detrusor overactivity and underactivity"-like bladder behavior can be found, and more detailed investigations are needed. Ischemia, which is a main risk factor in aging, has shown to result in dynamic changes, resembling in the initial phase detrusor overactivity (e.g., increased non-voiding contractions, increased voiding frequency and decreased voided volume), and progressing with time to detrusor underactivity (e.g., decreased voiding frequency) [25]. Thus, depending on the underlying risk factors, aging may have variable effects on bladder function. Data from animal models, which seem to be as variable as the data from human studies in different clinical, may be useful for understating the progression of bladder function with aging.

3. *In vitro* evaluation of age related changes in micturition reflex components in rodents

Changes observed in overall bladder function are the result of both structural and functional alterations in each component of the bladder and its controlling nervous system. *In vitro* studies were employed to elucidate how each component of the micturition reflex, including the afferent nerves, spinal cord, brain, efferent nerves, smooth muscle, urothelium, extracellular matrix and immune system components, were affected by aging.

3.1. Afferent systems

The peripheral afferent limb of the micturition includes the urothelium and afferent nerves. Although the urothelial functions and urothelial-afferent nerve interactions play an important role in bladder sensations [26], little is known about the influence of aging on these components.

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Structural studies have shown urothelial thinning (male Fischer/Brown Norway rats) [12], granular appearance of umbrella cell layer, discoidal vesicles, electron dense bodies and vacuoles in umbrella layer, often containing what appears to be cellular debris in all layers [27]. These could be the result of oxidative stress and altered mitochondrial function. In support, increased reactive oxygen species (ROS) in cultured urothelial cells, associated with upregulation of transient receptor potential cation channel subfamily M member 8 (TRPM8) [28], decreased total antioxidant capacity and significantly increased levels of lipid peroxides, malondialdehyde (MDA) and inducible nitric oxide synthase (iNOS) (markers of oxidative stress) as well as ultrastructural alterations in mitochondria with accumulation of lipofuscin [29] have been reported. Changes in the urothelium can affect afferent neuronal input. It has been shown that in aged mice the activity of afferent nerves is augmented during bladder filling (male C57BL6, 3–4 *vs.* 24 months [4]). This could be due to increased stretch-induced release of acetylcholine (ACh) from non-neuronal cells, possibly from the urothelium [30], and/or increased adenosine 5′-triphosphate (ATP) and ACh bioavailability in the urothelium, as inferred from measurements of transmitter levels in the lumen [4]. If these findings are similar in humans, they could represent underlying mechanisms for bladder overactivity in the elderly. Studies in rats indicated that the density of Calcitonin gene-related peptide (CGRP) fibers was unchanged [31] and conduction velocity of myelinated and unmyelinated fibers did not appear to change with age; however, there was a reduction in the number of small diameter (predominantly unmyelinated) fibers [15]. These changes, if occurring in humans, may account for alterations in bladder sensations in the elderly. Further investigation of urothelial signaling properties (e.g., receptors, transmitters, intracellular pathways) and the influence on afferent nerve activity are still needed.

3.2. Central micturition pathways

The influence of an aging on central micturition pathways is far less understood. Imaging studies in elderly women with normal bladder function revealed activation of different brain areas depending on the bladder fullness. For example, when the bladder was filled from an empty state, activity was observed near the periaqueductal gray, an area important for reflex voiding, and was thought to reflect unconscious monitoring and relaying of ascending bladder signals. In contrast, when the bladder was full, further filling activated cortical areas associated with sensations, such as regions near the insula, the dorsal anterior cingulate cortex and supplementary motor area [32]. Systematic investigation of CNS centers involved in micturition in animal models of aging remains to be done.

3.3. Efferent system (sympathetic, parasympathetic and smooth muscle)

The efferent system includes the sympathetic and parasympathetic nerves and the smooth muscle. The sympathetic system is thought to be tonically active during filling phase, releasing Norepinephrine (NE) to relax the bladder smooth muscle. The parasympathetic system is active during voiding and releases ACh to contract the bladder and nitric oxide (NO) to relax the urethra. Although not systematically investigated, gross anatomical observations have shown axonal degeneration in human bladders [33], and bladder from rats with induced ischemia [25]. Cystometry studies in rodents have shown increased intravesical pressure [12,16], suggesting changes in the sympathetic output and/or the smooth muscle/bladder wall that may impact storage function. Accordingly, histological studies have found a reduction of the sympathetic fibers in the aging rat bladder body [31]. On the postsynaptic site, responses to NE are mediated by β-adrenergic receptors (β-ARs). In human, β_3-AR are the predominant subtype, while in animals all β-ARs 1–3 subtypes are present [34,35]. Studies assessing β-ARs expression yielded inconsistent results (possible due to species/strain/sex differences), showing a decrease in β-ARs in aged male Fischer 344 rats [36], no change in male SD rats and female Wistar/Rij [14,16], or increase in rabbit [37]. Similarly, there is some variability in human data, with some studies showing a decrease in overall β-AR density [38], while more detailed investigations revealed no changes in β_3-AR expression but small decreases in β_2-AR in the urothelium of the trigone [39]. *In vitro* smooth muscle strips showed weaker smooth muscle response (relaxation) to β-AR agonists (noradrenaline, isoproterenol or the β_3-AR agonist BRL37344) in male Wistar rats [13] and human strips [38]. Though changes in β-AR function in the elderly cannot be excluded, the β_3-AR agonist (mirabegron) is efficacious and well tolerated in these patients [40].

Cystometry studies reported variable changes in micturition pressure, which is a measure of the efferent parasympathetic nerves and smooth muscle contractility [6,16], suggesting changes in more than one component of the efferent system. Bladder strips using electric field stimulation (EFS) to activate parasympathetic nerves, which then release ACh and ATP to contract the smooth muscle, have shown a general decrease of the EFS-induced contraction, associated with loss of the atropine resistant component in some studies [12,16,41]. This correlates with structural changes that indicated a decrease (~40%) in the number of acetylcholinesterase (AChE)-positive neurons in the intramural plexus in guinea pigs [42]. These alterations may impact the strength of the contraction and may lead to changes in voiding function that could account for the underactive bladder condition. Numerous studies tested the responsiveness of the smooth muscle to agonists for muscarinic and purinergic receptors. Again, variability was present. Muscarinic receptor mediated contraction has been reported to increase (male Fischer 344 rats [43], male mice [4]), decrease (male SD rats [16,43,44], male Fisher/Brown Norway [12] and male mice [5] or remain unchanged (male Wistar [45] and female Wistar/Rij rats [14]). A systematic study in rats with induced bladder ischemia (a risk factor in aging) has shown differential expression pattern for different subtypes of muscarinic receptors depending on the time after inducing ischemia. In the early stages of ischemia (8 weeks), M2 expression was increased and this was associated with detrusor overactivity (evaluated by cystometry). In the late stages of ischemia (16 weeks) M2

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expression remained elevated, M3 expression decreased, M1 expression increased, and these were associated with detrusor underactivity (evaluated by cystometry) [25]. Regardless of pharmacological studies in animals, which seem to be species/strain/sex dependent and many lack detailed receptor subtype investigation and/or detailed location of different receptor subtypes (e.g., dome, trigone, smooth muscle, urothelium in humans, clinical effectiveness of muscarinic antagonists does not seem to be age related [46–48]. Patients with OAB discontinue treatment mainly due to lack of efficacy (i.e., refractory overactive bladder) and unpleasant side effects. A better understanding on the alterations of specific muscarinic receptor subtypes may help design better antimuscarinic therapies for the elderly.

The purinergic component of the efferent transmission has been shown to be upregulated in conditions associated with overactive bladder [49], including aging [50,51]. It is believed that increased of ATP release from parasympathetic nerves with aging [51] may result in decrease expression of P2X1 mRNA expression in the smooth muscle (in human tissue) [52]. In aging rodents, the purinergic component was also upregulated likely due to increased purinergic receptor sensitivity [5]. This was associated with overexpression of P2X3 receptor in the urothelium (male mice C57BL6 [4]), suggesting differential changes in receptor expression/function/subtypes the smooth muscle versus urothelium and perhaps afferent nerves. Further detailed studies of the purinergic component are needed.

In addition to possible changes in receptor expression and/or function (muscarinic, β-AR and purinergic), aging impairs calcium handling in the smooth muscle. Strips from the aged rats were more susceptible to a calcium channel antagonist and to reduced extracellular calcium [17,44], aged dissociated smooth muscle cells showed differences in mobilization of intracellular calcium [5]) while responses to KCl were variable [4,5,14,16]. Thus, intracellular pathways involved in smooth muscle contractility may decline with aging and this set up the stage for overactive or underactive muscle.

Structural changes in the bladder wall, including widespread degeneration of muscle cells and axons [33,53] and decrease in the area density of smooth muscle to connective tissue ratio [53], indicate that fibrosis develops in aged human bladder. Similarly, in aged rodents fibrosis (increased collagen deposition) was reported in various studies [12,16], and was to some extent alleviated by caloric restriction [41] (obesity is a risk factor for LUTS) or testosterone supplementation therapy [54] (age dependent hormonal changes are a risk factor). Recent studies have found changes in collagenases (matrix metalloproteinase-13 (MMP-13)) [10] in aging rat bladder.

Collagen and elastin fibers provide structural support as bladder smooth muscle stretches during bladder filling. Not only is the amount of these fibers important for proper bladder function, but also their orientation, conformation and recruitment during bladder filling. Collagen type III fibers (found in flexible and distensible tissues) display specific orientations with different bladder volumes, that also differ according to bladder location [22]. For example, when empty, fibers appear as loose (wavy) networks with random orientation. When full, fibers appear long and thin and lie parallel to urothelium and smooth muscle. This arrangement likely allows maximal bladder storage without imposing strain on the wall. In aging bladders, changes in the smooth muscle/collagen ration and possibly extracellular matrix composition [10] likely impair the orientation, conformation and recruitment of collagen fibers. New studies (unpublished data, Robertson et al.), using a combination of biaxial stretch and multiphoton imaging, have shown that fibers in the lamina propria start to flatten (be recruited to bladder stretch) at lower strains, which may be equivalent to lower volume, in aging bladders compared to controls. This suggests that additional tension/stretch may be imposed on the urothelial cells and/or smooth muscle as the bladder fills. This can impair the communication between the urothelium and other cells in the bladder wall and account for symptoms of the aging bladder. Further studies are necessary to evaluate fibrosis and its impact on the bladder biomechanics and sensory signaling in the bladder wall, as well as mechanisms underlying fibrosis and possible venues for treatment.

4. The immune system

The influence of immune system in aging bladder is far less understood; however, it is conceivable that age decreases in the ability of the immune system to react to insults (e.g., urinary tract infections). Recent studies have found changes in genes involved in the immune response, including protease granzyme (Gzm) (Gzma, Gzmb, Gzmc) [55]. These results suggest that voiding dysfunctions are associated with immune and inflammatory related responses in the bladder and afferent system (DRG).

5. Conclusion

There are a number of limitations associated with animal models, both in terms of the particular importance of the non-adrenergic non-cholinergic innervation seen in rodents and the limitations of the model systems as proxies for the human condition. Allowing for these clear limitations there is however no doubt that such data gives us insight into potential avenues for further research and the potential development of new therapies. Clearly both myogenic and neurogenic changes are found in rodent aging bladder. The structural and functional changes observed in animal models are somewhat similar to those observed in humans. Clearly there is significant variability in the data obtained from different species, strains of animal, their gender and the methodology utilized. Based on our review we believe the translational importance of future work will be increased if both *in vivo* and *in vitro* parameters could be studied in the same animal species.

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