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Review

The aging bladder insights from animal models

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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.

Q4 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 symptom syndrome (OAB) 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.

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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 (males 22–28 months old [8–10], females 24 months old [11]), Fischer/Brown Norway rats (males, 28–30 month old [12]), Wistar rats (male or female 22–37 month old [13–15], Sprague Dawley (SD) rats (male 18–24 months old [16,17]). Other species included dogs [18,19] and guinea pigs [20,24]. 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) [25,9,4,26,7]. 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 [27,10,12]. Pressure threshold for voiding increased regardless of species and gender [16,11,10,27], suggesting disturbances of the afferent system. Baseline intravesical pressure also increased [16,12], 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 [12,16,14,10]. 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) [28]. 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 [29], little is known about the influence of aging on these components.

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