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The Aging Overactive Bladder: A Review of Aging-Related Changes from the Brain to the Bladder

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Abstract

Purpose of review—To understand the current literature on age-related neural and detrusor changes associated with overactive bladder symptoms.

Recent findings—Recent functional magnetic resonance imaging (fMRI) studies have unveiled an age-related decrease in the neural control of continence, represented in the insula, anterior cingulate cortex (ACC) and prefrontal cortex (PFC). Older individuals with overactive bladder symptoms also demonstrate heightened activation of the ACC with low volumes, representing increased bladder sensitivity or sense of urgency. At the level of the bladder, age-related changes in the urothelium, neurotransmitters/receptors (both muscarinic and purinergic), and inflammation [including nerve growth factor (NGF), monocyte chemoattractant protein-1 (MCP-1) and oxidative stress] are also associated with overactive bladder.

Summary—Overactive bladder among older adults is a complex condition incorporating physiologic age-related changes from the brain to the bladder and beyond.

Keywords

Detrusor overactivity; geriatric; inflammation; neurotransmitters; white matter disease

Introduction

Overactive bladder is a common problem among older adults, affecting up to 40% of men and 30% of women ages 75 years and older.[1] This condition is defined by the International Continence Society as a *symptom complex* of urinary urgency, usually with frequency and nocturia, in the absence of other pathology such as infection or stones.[2] As a *symptom complex*, overactive bladder is considered to have no singular cause and can be influenced by comorbidities, environmental factors, medications, prior surgeries and age.[3]

While there are many known changes in the bladder associated with normal aging, such as a reduction in bladder capacity[4,5] and increased bladder sensation,[5] our understanding of how

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Suskind has no conflicts of interests to declare

Human and Animal Rights and Informed Consent

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aging affects the development and progression of overactive bladder remains in its infancy. Recent advances in functional magnetic resonance imaging (fMRI) of the brain and in the cellular and contractile properties of the bladder itself are adding to our current understanding of the relationship between aging and overactive bladder. This review article will serve to summarize recent advances in our knowledge behind the physiologic underpinnings of overactive bladder associated with aging from the brain to the bladder.

Neurologic

Normal neurologic control of the bladder

In normal lower urinary tract function, neural control of the bladder can switch between storage and voiding via the spinobulbospinal voiding reflex. During storage, as the bladder fills, it sends afferent (sacral) signals to the periaqueductal gray (PAG) in the brainstem. In the absence of any inhibition, the reflex fires and sends a signal to the pontine micturition center (PMC) or “Barrington’s nucleus”, which initiates relaxation of the urethral sphincter and bladder contraction resulting in voiding. In isolation, this reflex would be activated when the bladder volume reaches a certain threshold resulting in involuntary voiding, or urinary incontinence. However, continent adults have the ability to postpone voiding until a socially appropriate, safe and desired time and location is reached.[6] Furthermore, there are additional higher brain functions at play that contribute to continence.

Our current understanding of the brain regions that govern normal storage and emptying have been investigated via functional magnetic resonance imaging (fMRI) and are currently described by a working model depicting 3 neural circuits: (1) frontal, (2) midcingulate and (3) subcortical (Figure 1).[7]

1. Frontal—The frontal circuit is the primary target of ascending signals from the PAG and includes the thalamus, insula, lateral prefrontal cortex (lPFC) and medial prefrontal cortex (mPFC). The insula is considered to be the homeostatic afferent cortex and registers visceral sensations,[7] providing important information and contextualization of bladder sensory information to help make decisions on whether or not to void.[8] In healthy controls, the insula becomes more and more activated with bladder filling and with the desire to urinate.[9,10]

2. Midcingulate—The midcingulate circuit is responsible for registering bladder sensory information such as urgency and includes the supplementary motor area (SMA) and dorsal anterior cingulate cortex (dACC). The ACC determines how much attention to give to afferent signals coming from the bladder and how to react to them.[11] This sensation triggers activation from the dACC to the SMA to tighten the pelvic floor and urethral sphincter as a “back-up” continence mechanism.[6]

3. Subcortical—The subcortical circuit serves as a further “back-up” mechanism for continence and consists of the hippocampal and paralimbic regions. These regions correspond to the limbic system and are thought to permit voiding only if it is judged to be “safe” to do so.[11]

Changes in neurologic control of the bladder with age

Several neurologic changes occur in older individuals, which may predispose them to overactive bladder. Functional MRI images taken in older continent healthy women during bladder filling and emptying demonstrate that activation of the insula, ACC and mPFC decreases with age, weakening the ability of the brain to control for leakage.

Furthermore, with increasing age there seems to be weaker signals in the bladder control network, both via the frontal and midcingulate circuits, that may predispose an individual to symptoms of overactive bladder.[12] Functional MRI data on older women with detrusor overactivity to the contrary, demonstrate strong activation of the ACC with low bladder volumes and more moderate responses at higher bladder volumes. This recruitment of the ACC even at low volumes indicates the abnormal sensation of urgency and may also indicate the recruitment of this alternate pathway (described as midcingulate circuit above) to prevent leakage, suggesting that the frontal circuit may not be working optimally.[13]

It is difficult to know for certain whether these changes truly reflect changes of the aging brain itself, or whether they reflect a more peripheral etiology consisting of decreased bladder afferent input. Additionally, it is unknown whether these changes in the brain may alternatively represent undiagnosed or undetected pathology as opposed to normal aging.[12]

White matter disease

Cerebral white matter disease, caused by small vessel disease of the brain, is a common condition among older individuals and can lead to vascular dementia, vascular parkinsonism and “vascular incontinence.” Vascular dementia may include mild cognitive impairment and sometimes occurs as a stepwise progression; vascular parkinsonism is marked by gait disorder, easy falls, slow, short stepped, often wide-based gait, and typically lacks tremor and rigidity of the hands; and vascular incontinence is marked by urinary frequency and urgency. All white matter disease demonstrates diffuse abnormalities in the small deep perforating vessels of the hemispheric white matter, basal ganglia, and brain stem and can be associated with atherosclerotic risk factors such as dyslipidemia, diabetes, obesity, metabolic syndrome, hypertension, and smoking.[14]

It is thought that white matter disease may contribute to overactive bladder. A study of older individuals with varying degrees of white matter disease demonstrated that worsening white matter disease was associated with worsening overactive bladder symptoms. This study also found that urinary dysfunction was more common than cognitive and gait disorders among study participants, suggesting that bladder symptoms may serve as an early and predictive sign of this condition.[15]

While white matter disease is a diffuse cerebral process, it has been shown that the frontal lobe can be the most severely affected area. This explains why affected individuals may have a combination of urinary and gait disturbance[16,17] as well as dementia.[18] One study looking at fMRI imaging of older women with urgency urinary incontinence found a strong correlation between the burden of white matter disease and urgency urinary incontinence. This study further revealed that with increasing white matter disease, certain areas of the brain were activated during bladder filling (medial/superior frontal gyrus adjacent to the

dorsal ACC and right anterior insula) while other areas were deactivated during filling (ACC and parahippocampal complex).[19]

Parkinson's Disease

Parkinson's Disease is induced by dopamine depletion in the substantia nigra, leading to bradykinesia, akinesia, and overactive bladder symptoms in 50–70% of individuals.[7,20] A study of 9 male patients with Parkinson's Disease who underwent positron emission tomography (PET) during bladder filling via a catheter found significant activation of the PAG, SMA, cerebellum, insula, putamen and thalamus associated with detrusor overactivity. Compared to healthy volunteers, individuals with Parkinson's Disease did not demonstrate activation of pons or the ACC, which the authors speculate may be related to overactive bladder symptoms.[21] Further investigation is needed to confirm and explore this relationship.

Cerebral infarction and brain injury

Approximately 20–50% of individuals with focal brain lesions, including cerebral infarction, experience voiding dysfunction. This dysfunction most commonly manifests as detrusor overactivity.[22] Studies using PET and fMRI suggest that these findings may be attributable to impaired striated sphincter control and lack of appreciation of bladder filling and contraction.[23] However, the specific mechanism underlying detrusor overactivity in the setting of cerebral infarction remains unclear.

Studies in cerebral-infarcted rats demonstrate decreased bladder capacity and lower voided volume compared to non-infarcted rats.[24,25] Further studies in cerebral-infarcted rats show an up-regulation of detrusor muscarinic receptors compared to sham rats, which may also contribute to detrusor overactivity and symptoms overactive bladder.[26]

Bladder; Detrusor and urothelium

The normal aging bladder consists of increased collagen content, changes in gap junctions, increased space between myocytes and changes in the sensitivity of sensory afferents.[27] Studies on 86 human bladders demonstrate that there is a decrease in the area density of smooth muscle to connective tissue ratio in both older males and females, resulting in an increase in detrusor fibrosis.[28] This fibrosis may be related to an observed decrease in bladder compliance seen with aging[29] and may also be related to detrusor irritability and symptoms of overactivity.[30]

Once thought to be merely a passive barrier, our current understanding of the bladder urothelium indicates a more complex sensory organ that receives, amplifies, and transmits information about the bladder to the environment.[31] Specifically, the bladder epithelium is adept at responding to stretch during bladder filling, neural innervation of the bladder, and to bladder pain and substances in urine (e.g. bacteria).[32,33] The urothelium also produces neurotransmitters and mediators including ATP, neuortrophins, nitric oxide and cytokines.[31]

Neurotransmitters

Neurotransmitters are an essential component to bladder contraction, and further, to overactive bladder. Data from electrical field stimulation performed on cystectomy specimens indicate that there is a significant positive correlation between age and acetylcholine (ACh) (r=0.97) and a significant negative correlation between age and adenosine triphosphate (ATP) (r=−0.98). While the mechanisms behind these correlations are not well understood, it is postulated that changes in the amounts of ACh and ATP released from intrinsic nerves may be, at least in part, responsible for overactive bladder in older adults.[34]

Changes in muscarinic receptors in the bladder have also been demonstrated with normal aging. Radioligand-binding studies have been conducted in human bladder specimens of individuals with normal bladder function. One study found that in the normal aging bladder, the number of all muscarinic receptors (M_1–M_5), and particularly M_3 receptors, declines with age. This finding, however, would advocate for underactive, rather than overactive, bladder symptoms among the older population.[35]

Additional studies in bladder tissue specimens from women with idiopathic detrusor overactivity demonstrate a significant increase in purinergic $P2X_2$ receptors in addition to increased nerve-mediated ATP contractions, pointing to abnormal purinergic transmission in the bladder of individuals with detrusor overactivity.[36]

Inflammation

The association between inflammation and aging is an emerging topic and active area of research. Inflammation is a key function responsible for cellular repair from both injury and old age,[37] and markers of elevated inflammation have been associated with frailty and disability among older individuals.[38] A study of urine samples from individuals with overactive bladder found that older age was associated with increased levels of nerve growth factor (NGF) and monocyte chemoattractant protein-1 (MCP-1).[39]

NGF is a protein that influences neuronal development, function and response to injury.[40] Its age related increase among individuals with overactive bladder may represent a homeostatic response to increase the trophic support to help combat the progression of overactive bladder into detrusor hyperactivity with impaired contractility (DHIC).[41] It has also been shown that NGF increases with increased severity of overactive bladder symptoms and decreases in patients receiving treatment for these symptoms.[42]

Like NGF, levels of MCP-1 have been shown to increase with age among individuals with overactive bladder.[39] MCP-1 is a chemokine that activates the recruitment of monocytes and macrophages in response to cellular injury and serves to sustain the on-going inflammatory process associated with aging. The age-related increased in MCP-1 is likely linked to other age-related changes in body composition by which a portion of detrusor myocytes are gradually replaced by adipocytes.[43] This also explains the tendency for older bladders to become stiffer and trabeculated, which unresolved, can progress from overactive bladder to DHIC.

In addition to these specific markers of inflammation, the aging body and bladder are also affected by oxidative stress. Free radicals stimulate the NF-κb signal transduction cascade leading to the synthesis of inflammatory mediators. With aging, there is a decrease in enzymes, such as superoxide dismutase, that suppress this pathway, resulting in an age-related increase in inflammation.[44]

Conclusions

Research on overactive bladder in older adults is fertile with new knowledge spanning from the brain to the bladder, as summarized in Table 1. Based on our current understanding, age-related changes in the brain illustrated by fMRI and other imaging modalities, demonstrate a new understanding of how different parts of the brain change with age. In particular, normal aging is associated with a decrease in activation of regions of the brain associated with control of continence (e.g. insula, ACC and PFC) and at the same time an increase in the ACC with low bladder volumes, which promotes a heightened sense of bladder sensation or urgency. In the bladder, changes in neurotransmitters and increases in inflammation and oxidative stress also contribute to symptoms of overactive bladder among the older population.

These fascinating discoveries about the physiology of overactive bladder associated with age, however, are still in their infancy. The relationship between the brain and the bladder are likely far more dynamic than our current understanding and a future model that incorporates the interrelationship between the brain, the bladder and the multifaceted components of aging (e.g. frailty, function, comorbidity, and environmental factors) is necessary to better understand this complex relationship.

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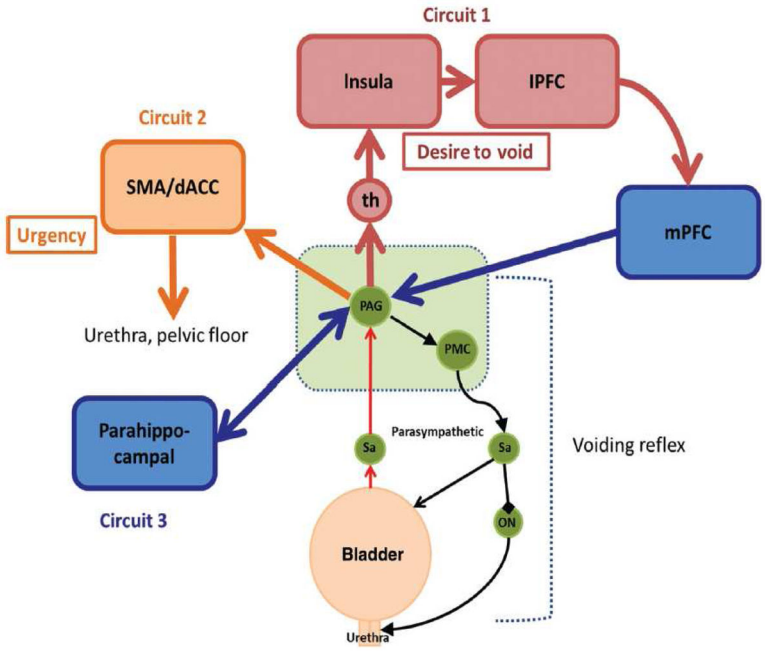

Figure 1.

Working model of lower urinary tract control. Green represents the voiding reflex and brainstem and circuits 1, 2, and 3 are represented by red/blue, orange, and blue, respectively. ***Reproduced with permission by Wiley. De Groat, William C., et al. "Neural Control of the Lower Urinary Tract." Comprehensive Physiology. Vol 5. Jan 2015. Copyright © American Physiological Society.***

PAG=periaqueductal gray; PMC=pontine micturition center; th=thalamus; mPFC=medial prefrontal cortex; lPFC=lateral prefrontal cortex; SMA=supplementary motor area; dACC=dorsal anterior cingulate cortex

Table 1

Summary of changes in the brain and bladder associated with aging.

Brain • Decreased activation of insula, ACC and PFC • Increased activation of ACC with low bladder volumes • Increased burden of white matter disease • Decreased activation of pons and ACC with Parkinson's Disease • Up-regulation of detrusor muscarinic receptors among cerebral infarcted rats
Bladder • Increase of ACh and decrease of ATP • Increase of P2X2 receptors • Increase of NGF and MCP-1 in urine • Increase of free radicals/oxidative stress

ACC=anterior cingulate cortex; PFC=prefrontal cortex; ACh=acetylcholine; ATP=adenosine triphosphate; NGF=nerve growth factor; MCP-1=monocyte chemoattractant protein-1