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Review

Sensory and circuit mechanisms mediating lower urinary tract reflexes

Zachary C. Danziger [a,*], Warren M. Grill [a,b,c,d]

[a] Department of Biomedical Engineering, Duke University, Durham, NC, USA
[b] Department of Neurobiology, Duke University, Durham, NC, USA
[c] Department of Surgery, Duke University, Durham, NC, USA
[d] Department of Electrical and Computer Engineering, Duke University, Durham, NC, USA

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ABSTRACT

Neural control of continence and micturition is distributed over a network of interconnected reflexes. These reflexes integrate sensory information from the bladder and urethra and are modulated by descending influences to produce different physiological outcomes based on the information arriving from peripheral afferents. Therefore, the mode of activation of primary afferents is essential in understanding the action of spinal reflex pathways in the lower urinary tract. We present an overview of sensory mechanisms in the bladder and urethra focusing on their spinal integration, identify the cardinal spinal reflexes responsible for continence and micturition, and describe how their functional role is controlled via peripheral afferent activity.

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1. Introduction

The work of storing and expelling urine is done by the urinary bladder, which acts as a repository and pump, and the urethra, which functions as an outlet to transfer urine out of the body. These seemingly straightforward tasks, however, are controlled by numerous parallel neural systems that interact in local, spinal, and supraspinal organizations to produce a range of sophisticated behaviors. For example, the primary afferents of the lower urinary tract consists of at least four distinct types of fibers, may terminate in local ganglia to coordinate reflex integration, project to spinal interneurons that modulate numerous reflexes, or travel to executive centers to inform voluntary supervision. Further, these afferents can be differentially activated by pressure, stress, or toxins, be parasympathetic, sympathetic, or somatic, and even be subject to regulation by non-neural cells lining the bladder or urethra.

The complexity of the neural regulatory mechanisms controlling continence and voiding render the system vulnerable to a host of disorders that present with myriad and overlapping symptoms, making the identification of specific etiologies difficult. The principle challenge to neurourology is, therefore, to understand the mechanisms of the neural circuitry and associated regulators in sufficient detail to ascertain the

* Corresponding author at: Duke University/Hudson Hall Box 90281/Durham, NC 27708, USA.
E-mail address: zd10@duke.edu (Z.C. Danziger).

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causes of lower urinary tract diseases and identify potential treatments. This review examines our understanding of how primary afferents mediate the many reflexes that control the lower urinary tract, and how those reflexes affect the detrusor, urethral sphincters, and their synergistic cooperation.

2. Primary afferent nerves

2.1. Pelvic

The pelvic nerve carries "pressure-related" sensory information from the bladder to spinal centers, and conveys excitatory efferent signals to the detrusor. Early neurophysiological investigations discovered that distention of the detrusor muscle could reliably elicit afferent firing in *in vivo* preparations across animal models (Evans, 1936; Talaat, 1937). The pelvic afferents burst in response to onset of bladder filling, given that it occurs with sufficient pressure (Talaat, 1937), track intravesical pressure as it rises during artificial bladder filling with physiological saline, and persist after filling has ended, provided that bladder pressure remains high (Evans, 1936; Talaat, 1937). These early studies also showed that if filling is paused at low to mid-volumes the bladder pressure slowly drops, along with pelvic afferent activity, but that at high volumes bladder pressure persists during pauses in filling. This provided indirect evidence that the bladder wall is elastic up to a point, and that pelvic afferents encode bladder pressure or detrusor stretch rather than fill volume. Corroborating studies have since shown directly that the completely denervated bladder does not exhibit a rise in intravesical pressure at low volumes and slow filling rates (Klevmark, 1977), and that passive isovolumetric stretching *in vivo* or stretching bladder strips *in vitro* also generate afferent responses (Iggo, 1955). This provides strong evidence that the bladder's intrinsic mechanical properties, and not inhibitory efferent neural control, are primarily responsible for pressure accommodation during urine storage, and enforces the supposition that pelvic afferents report stimuli related to detrusor stretch, as opposed to bladder volume, which is intimately tied to bladder elasticity and conformation (Sasaki, 1998).

More recently, this picture of pelvic afferent sensitivity has been complicated by single unit recordings from the nerve or its associated local ganglia. These data indicate that some neurons are activated selectively by different types of mechanical perturbation, while some respond exclusively to chemical irritation. Perhaps the clearest distinction is between the mechanosensitive and mechanoinsensitive afferent types. Electrophysiological studies of unmyelinated afferents located in the dorsal and ventral roots show that afferent fibers that were unresponsive to mechanical stimulation of the detrusor did respond to the chemical irritant mustard oil (Häbler et al., 1990), capsaicin (Shea et al., 2000), or cold (Bors and Blinn, 1957). These afferents are commonly referred to as 'silent' because they are not active under physiological continence or micturition conditions. Complicating a bipartite distinction, however, is the fact that some unmyelinated chemosensitive fibers also respond selectively to high bladder pressures (Häbler et al., 1990), opening the possibility that these fibers could be multi-sensory in nature or that chemosensitive fibers can locally influence the action of mechanosensitive afferents at high pressures. More evidence against strictly separate classes of chemosensitive and mechanosensitive pelvic afferents emerged when it was found that following chemical irritation of the bladder with 300 mM KCl (and subsequent 0.9% NaCl cleansing) a subgroup of fibers that had previously not responded to either bladder distention or the KCl irritant became responsive to bladder distention (Shea et al., 2000). The finding is reproducible with mustard oil (Häbler et al., 1990) and other irritants (Rong et al., 2002), suggesting that irritants are able to induce latent mechanosensitivity in this subgroup of afferents. Therefore, a straightforward classification of activation modes of pelvic sensory neurons may not be possible and more research is needed to develop a complete picture of the response of these afferents. Such investigations could also inform theories of overactive bladder that posit a transformation in the role of capsaicin-sensitive pelvic afferents leading to chronic irritability of the bladder (Fowler et al., 2008; Yoshimura and de Groat, 1999).

Another set of pelvic afferents has been classified by the pressure or volume at which they become active, as opposed to the sensory modality of their activation. It has been noted that there is a relatively small subset of pelvic afferents (both myelinated and unmyelinated) that track bladder pressure in exclusively high pressure regimes, and are quiet at low pressures (Bahns et al., 1987; Häbler et al., 1990; Shea et al., 2000; Zagorodnyuk et al., 2006). The pressure regimes at which these so called "high-threshold" fibers respond (in cats) (Häbler et al., 1990) correspond to the pressures at which humans report painful sensations (Torrens and Morrison, 1987), providing circumstantial evidence that these fibers are responsible for the sensation of pain associated with hyperdistention of the detrusor (Kanai, 2011). To show this conclusively, experiments are needed that directly link these fiber types with pain, either through recording in known pain centers during periods when the high threshold afferents are active or with other quantitative measures of visceral pain such as the visceral motor response (Ness and Gebhart, 1988). Another potential role for the range of pelvic afferent pressure thresholds is to ensure that bladder pressure is effectively conveyed to spinal centers across a full range of pressures, which may not be possible using homogeneous thresholds because afferent activity for some low threshold units plateaus at intermediate pressures (Shea et al., 2000).

A mechanistic basis for the difference in sensitivity between high and low threshold afferents has yet to be established, and several observations suggest that the development of such an explanation will be challenging. Most notably, there are a range of thresholds in the high and low threshold fiber populations rather than two clearly separated groups, and unmyelinated and myelinated fiber types comprise both populations (Sengupta and Gebhart, 1994; Shea et al., 2000). Further, most chemical blocking studies of pelvic afferents, for example administering an extracellular ATP antagonist to inhibit ligand-gated ion channels in mechanosensitive afferents in the bladder (Rong et al., 2002), affects both populations, making it difficult to study each group in isolation. One study did observe that low-threshold afferents in TRPV1 knockout mice saturated at lower firing rates than in wild type mice, while there was no difference in firing rates between high threshold afferents in wild type and TRPV1 knockouts (Daly et al., 2007). Although these data suggest a mechanistic difference between populations, the firing rates of high-threshold units in wild type and knockout mice were compared before their saturation points, a regime where there was also no distinction between firing rates of low-threshold units in the two groups. Moreover, another study in TRPV1 knockout mice found a 40% reduction in sensitivity to pain compared to wild type mice (Jones et al., 2005), which would not be expected if high-threshold afferents are not responsive to TRPV1 and primarily code nociceptive states.

Classification of fibers by global bladder pressure thresholds is also confounded by the local stress to which their receptive fields are exposed. Relating intravesical pressure to afferent activation could generate the appearance of many activation thresholds because at any given pressure, fibers innervating different regions of the bladder would be exposed to different stresses. For instance, during bladder filling there will be significant distention of the bladder dome, moderate distention in the region of the bladder being fed by the ureters, and little distention near the bladder neck, which remains largely undeformed across physiologic bladder volumes. The geometry of this distention over the course of a filling cycle has been observed *in vivo* using magnetic resonance imaging (Lotz et al., 2005), and modeled in three-dimensions using a completely stationary bladder neck position (Fig. 1C) (Tziannaros et al., 2013). Therefore, afferents innervating the dome will register large distention, while, at the same pressure there will be little distention of the bladder neck, potentially resulting in minimal discharge from afferents innervating the bladder neck. Further, an