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Review

Mucosal signaling in the bladder

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ABSTRACT

The bladder mucosa is comprised of the multilayered urothelium, lamina propria (LP), microvasculature, and smooth muscle fibers (muscularis mucosae). The muscularis mucosae is not always present in the mucosa, and its presence is related to the thickness of the LP. Since there are no mucus secreting cells, "mucosa" is an imprecise term. Nerve fibers are present in the LP of the mucosa. Efferent nerves mediate mucosal contractions which can be elicited by electrical field stimulation (EFS) and various agonists. The source of mucosal contractility is unknown, but may arise from the muscularis mucosae or myofibroblasts. EFS also increases frequency of mucosal venule contractions. Thus, efferent neural activity has multiple effects on the mucosa. Afferent activity has been measured when the mucosa is stimulated by mechanical and stretch stimuli from the luminal side. Nerve fibers have been shown to penetrate into the urothelium, allowing urothelial cells to interact with nerves. Myofibroblasts are specialized cells within the LP that generate spontaneous electrical activity which then can modulate both afferent and efferent neural activities. Thus mucosal signaling is defined as interactions between bladder autonomic nerves with non-neuronal cells within the mucosa. Mucosal signaling is likely to be involved in clinical functional hypersensory bladder disorders (e.g. overactive bladder, urgency, urgency incontinence, bladder pain syndrome) in which mechanisms are poorly understood despite high prevalence of these conditions. Targeting aberrant mucosal signaling could represent a new approach in treating these disorders.

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1. Introduction

The human bladder's main purpose is to store and expel urine, efficiently and without distraction or bother to the person. Bladder function can be analogized as a neuromuscular reflex: during storage of urine, the bladder smooth muscle is quiescent, and as bladder fills to a certain volume of filling, ever increasing afferent signals ultimately trigger efferent signals to induce smooth muscles to contract. Furthermore psychological factors including cognition, emotion, stress, mood and behavior also modulate bladder function, thus increasing the complexity of bladder control.

The bladder wall is organized into these histologic compartments: urothelium, lamina propria (LP), muscularis mucosae (smooth muscle bundles within the LP) and serosa, muscularis propria (main smooth muscle layer deep to the LP). A histologic image of the full thickness of the human bladder wall with these compartments is shown (Fig. 1). The LP contains microvasculature (capillaries, venules and arterioles), specialized "pacemaker cells", or myofibroblasts, and nerve fibers

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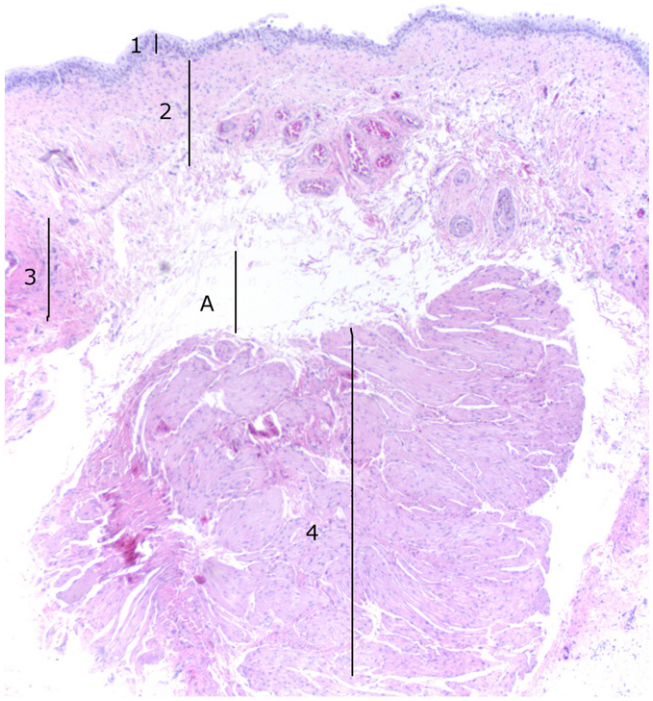

Fig. 1. Human bladder full thickness bladder, H&E staining, 40× magnification. 1 = urothelium, 2 = lamina propria, 3 = muscularis mucosae, 4 = muscularis propria, A = separation artifact, 1 + 2 + 3 = mucosa.

(motor and sensory). Because of multiple specialized cells within the LP, some have proposed to analogize the LP as the "functional center" of the bladder (Andersson and McCloskey, 2014). The term "mucosa" refers to the tissue that is easily dissected off the muscularis propria. The mucosa contains urothelium, LP and muscularis mucosae (though smooth muscle is inconsistently present in the mucosa). Because there are no specialized mucous secreting cells in the mucosa, the term "mucosa" is inaccurate. But in order to be consistent with published literature, and to be able to denote to the compartments of urothelium, LP and muscularis mucosae unambiguously as one tissue, we maintain the use of the term "mucosa" throughout this review.

Since the mucosa contains both sensory and motor nerves, the autonomic nervous system must play a role in mucosal function. However, what function can we ascribe to the mucosa? Traditionally, the working model for bladder mucosal function (and more specifically, urothelial function) is providing an impermeable layer to protect the bladder from urinary waste, toxins and microbes. However, there is a growing body of literature suggesting that the mucosa can modulate non-barrier functions such as urinary storage and emptying, which requires nervous system input. In this review, we will define mucosal signaling as any interactions between autonomic nerves and other mucosal specialized cells (e.g. myofibroblasts, urothelial, endothelial, detrusor and vascular smooth muscle cells). Because of interactions between multiple cell types, mucosal signaling is complex, but this complexity offers increased or finer control of urinary storage and emptying functions that has been under appreciated.

A common clinical problem of urinary storage dysfunction is characterized by hypersensory symptoms (urinary urgency, urgency incontinence, frequency, and nocturia) also called lower urinary tract symptoms (LUTS). While clinical "labels" have been used as diagnostic terms for patients with LUTS (e.g. overactive bladder, interstitial cystitis/painful bladder syndrome, benign prostatic hypertrophy), the common theme in these conditions is augmentation of bladder afferent pathways (Clemens, 2010). A better understanding of mucosal afferent signaling could lead to new treatment modalities of hypersensory symptoms. Bladder emptying dysfunction has been coined "detrusor underactivity" (or underactive bladder). While this condition could be an efferent problem, it can also be lack of afferent input (Osman and Chapple, 2014) to induce a motor response. Though speculative, augmentation of afferent signaling could trigger an underactive bladder to contract. This method could allow bladder contraction to be synchronized with bladder outlet relaxation which is less likely to occur if treatments focused only on augmenting the bladder motor outflow.

This review will discuss issues related to dissecting mucosa and results obtained from these dissections. Results from published data in mucosal afferent and mucosal efferent signaling will be reviewed. The overarching goal for this review is to present a contemporary framework to understand how mucosal signaling can modulate urinary storage and emptying functions.

1.1. Can the mucosa be further dissected with separation of the urothelium apart from the LP?

The two major components of the mucosa are the urothelium and the LP. Ideally, one needs to be able to separate these compartments apart from each other to understand each compartment's unique contribution to overall mucosal signaling. However, is this possible? An example of confusion within the literature is the apparent interchangeable use of the terms "mucosa" and "urothelium" (Zagorodnyuk et al., 2007). In this paper, the investigators performed two different procedures: "removal of urothelium" and "mucosal stroking". No histologic images were shown of the "urothelium" obtained during "removal of urothelium". It is likely that the "urothelium" removed is the "mucosa". The ability to remove a pure urothelium without the underlying LP has been demonstrated in mice (Lu and Chai, 2014), but it is uncertain whether pure urothelial tissue can be dissected off other species such as guinea pigs or pig. Photomicrographs obtained after muscle organ bath experiments of porcine mucosal strips showed the presence of smooth muscle, but interestingly, loss of urothelium (Sadananda et al., 2008).

Pig mucosal strips dissected off the luminal surface of the bladder were histologically examined and shown in Fig. 2a and b (two separate strips). The pig mucosa strip contained urothelium, LP, and smooth muscle. A possible source for mucosal contractility is the presence of smooth muscle in the mucosal dissections. Because of the presence of muscularis mucosae in porcine mucosa, mucosal contractions could be due to the presence of smooth muscle.

The mouse bladder wall is much thinner and the LP is much less prominent without evidence of muscularis mucosae (Fig. 3). A technique was recently described to dissect only the urothelium off the underlying LP in mice bladders (Lu and Chai, 2014). Fig. 4 shows the histology of a pure sheet of mouse urothelium dissected off the LP. Furthermore, investigators were able to patch clamp urothelial cells in situ from the dissected urothelial sheet, preserving the location of the cell within the stratified urothelium. This technique could be used to help clarify unique and separate functional roles between the urothelium and the underlying LP.

1.2. Innervation of mucosa

In the classic paper by Gosling and Dixon (Gosling and Dixon, 1974), mucosa innervation was described using technology available at that time. It should be noted that these authors stated "In the present paper, attention had been focused on the subepithelial connective tissue, termed 'submucosa' for brevity, between the base of the epithelium and the inner aspect of the muscular coat." Thus, 'submucosa' was synonymous to LP and their entire study focused on studying innervation