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Urothelial Targets in the Overactive bladder

C.-H. Fry, A. Roosen

The bladder wall contains three layers: the urothelium, the lamina propria, and the submucosa. The bladder urothelium, or transitional epithelium, forms a distinctive interface with the underlying bladder wall tissues and can be divided into three main layers: the superficial layer, the intermediate layer, and the basal layer. The superficial layer is composed of umbrella cells, the intermediate layer contains cells that form a distinctive interface with the urine, and the basal layer provides attachment to the basement membrane. The urothelium acts as a physical barrier separating urine from underlying bladder wall tissues and plays a crucial role in the bladder's functions, including sensation and micturition. Changes in urothelial transport properties can influence afferent nerve function and thereby modulate bladder sensation. This review discusses the functional understanding of the urothelium, with a focus on recent advances in the field.

Structure of the urothelium

In recent years, the focus of activity in searching for causes of bladder overactivity has shifted from the detrusor smooth muscle layer to the urothelium. There are several layers that form the urothelium: the superficial layer, the intermediate layer, and the basal layer. The superficial layer is composed of umbrella cells, which form a distinctive interface with the urine. The intermediate layer contains cells that are separate by tight junctions, thus limiting diffusion of solutes and forming an effective barrier between urine and suburothelial tissue. Below are several further layers of urothelial cells that provide a supportive layer opposed to a basement membrane. The suburothelial layer is the site of several other distinctive cells that include: nerve-endings, a rich capillary network, and a layer of myofibroblasts connected by gap junctions to form a syncytium.

Urothelial transport

Finite transport of solutes (e.g., Na+, urea) and water across the urothelial barrier is possible. The best characterised is Na+ transport, mediated in part by epithelial Na-channels (ENaC) in turn inhibited by amiloride [5]. As discussed below Na+ transport is implicated in the release of other activators from the urothelium that can influence afferent nerve function. Thus changes to urothelial transport would be expected to alter sensory responses from the bladder wall. A number of urinary constituents, for example reduced pH and kallikrein (secreted from the distal tubule), decrease transport. Barrier function is also compromised by urinary tract infections [6], pathological conditions such as spinal cord injury [7], inflammation and irradiation-induced cystitis [8] through a mechanism that is now only being fully understood. Intestinal cystitis is an inflammatory-like response to mechanical stretch following rising intravesical pressure with Na+ transport being the main intracellular mechanism. Via purinergic receptors, ATP acts on afferent nerve fibres and myofibroblasts in the suburothelial space; these form a functional syncytium and modulate so the afferent Erregung. Vom Urothel freigesetztes Stickstoffmonoxid und Acetylcholin wirken ebenfalls auf suburothelale Myofibroblasten, die die korrespondierenden Rezeptoren exprimieren. P2X Knockout Mäuse und Biopsien von Patienten mit hyperaktivem Detrusor belegen klar die Bedeutung von urothelialen Vanilloid-Rezeptoren, urothelial freigesetztem ATP sowie von P2X-Rezeptoren im Suburothelium für die Entstehung des Blasentüllungsgefühls. Viele Miktionsstörungen wie die Interstitielle Zystitis, die idiopathische oder neurogene Detrusorüberaktivität zeigen eine Dysbalance im Transmitter- und Rezeptorstatus des Urothels und Suburotheliums. Das bessere Verständnis dieser Prozesse eröffnet eine Vielzahl neuer medikamentöser Therapieoptionen.

Correspondence to: Prof Christopher Fry, BSc BA PhD DSc, Institute of Urology and Nephrology, UCL, 48 Riding House Street, London W1W 7EY, UK, E-mail: c.fry@ucl.ac.uk

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Figure 1. Schematic representation of the urothelial/suburothelial layer of the bladder wall. The urothelium has a surface layer of umbrella cells with basal and intermediate cells below. This is separated by a basement membrane from a suburothelial layer that contains blood vessels, small unmyelinated fibres, and myelinated fibres, as well as a syncytium of myofibroblasts. Many of these cells are concentrated towards the urothelial layer.
condition that manifests as reduced bladder capacity, frequency and painful micturition and is associated with a loss of barrier function [9]. IC patients have a raised urine level of an antiproliferative factor [10] that may attenuate urothelial proliferation and hence reduce barrier function. Thus, several factors modulate urothelial integrity, transport properties and release of agents from the urothelium that can influence sensory function.

**Sensory functions of the urothelium**

The urothelium responds to many chemical and mechanical stimuli by releasing agents such as ATP, acetylcholine, nitric oxide, cytokines and prostanoids, that in turn may initiate sensory responses. Urothelial cells are also the locus of many receptors (including cholinergic, purinergic and vanilloid receptors), that in turn may mediate the effect of these exogenous stimuli. There is thus extensive cross-talk between urothelial cells and exogenous agents that will modulate their secretory and sensory functions. Because of the close proximity of afferent nerve fibres to urothelial cells, the urothelium has the capability to act as a sensitive transducer to external stimuli.

**Purinergic signalling in the urothelium**

This is the most intensively studied chemical transduction pathway, since the original observation that deformation of the urothelium, through alteration of the transurothelial hydrostatic pressure gradient, releases ATP on the basolateral surface. Release was presumed to be mediated by Na+ transport through ENaC, as it was attenuated by amiloride [11]. In a number of pathologies, including interstitial cystitis, stretch-induced release of ATP from the urothelium is increased [12, 13] and provides a potential pathway to explain the symptoms associated with this condition. Stretch-induced ATP release is also raised in ageing bladders [14], although its significance is not yet clear.

The mechanism whereby ATP elicits sensory responses has not been fully evaluated. The most straightforward explanation is that urothelial-derived ATP stimulates directly suburothelial afferents. This has been given credence by the explanation is that urothelial-derived ATP stimulates directly suburothelial afferents. This has been given credence by the fact that P2X, knockout mice have a damped micturition reflex and reduced afferent firing on bladder filling [15, 16]. Iontropic P2X receptors have been located on suburothelial afferents [17] so that ATP binding would depolarise directly the nerve endings to elicit action potentials.

However, purinergic receptors have been located at several other sites in the urothelial layer. The urothelium itself displays a variety of ionotropic (P2X subtype) and metabotropic (P2Y subtype) receptors [18]. This implies considerable feedback control of urothelial ATP release, although such a process has not been fully characterised. In addition there is a layer of suburothelial myofibroblasts that form a functional syncytium, and make close contact with afferent nerves [19, 20]. These myofibroblasts label for P2Y6 receptors [21], and because of their intermediate position between the urothelium and afferent nerves they are in an ideal position to modulate the sensory process by modulating afferent function upon their own activation.

Regulation of ATP release therefore represents a potential pathway to modulate sensations from the bladder wall. Botulinum toxin (BoTox) has been shown to be very effective in reducing symptoms associated with the overactive bladder [22]. Originally it was presumed to reduce transmitter release from motor nerves, however a urothelial site of action should also be considered as: application of BoTox to the mucosa, not the detrusor layer, is equally effective in human of reducing symptoms; and it is effective in the filling phase of the micturition cycle. A recent study showed that BoTox A reduced ATP release evoked by artificial induction of inflammation and also reduced non-voiding contractions in experimental animals [23].

Thus, although the precise purinergic pathways in the urothelium remain to be characterised there is strong evidence that ATP can act as a chemical mediator between the urothelium and afferent activation.

**Cholinergic mechanisms in the urothelium**

The bladder wall has also been shown to release acetylcholine: it was insensitive to the neurotoxin tetradotoxin, and hence non-neuronal, and was increased by stretch. Moreover, this TTX-insensitive fraction was much
greater if the urothelium was present in the preparation, and the effect was enhanced in the ageing bladder [24]. Unlike the situation with ATP far less is understood about the action of this non-neuronal, urothelial release of acetylcholine, however it provides a rationale for the effectiveness of antimuscarinic agents during bladder filling. A recent report has shown that local application of carbachol will initiate propagating electrical and Ca** waves that were confined initially to the suburothelial space of the bladder wall before passing to the detrusor layer only after a delay [25] (figure 2). This implies that acetylcholine acts on targets in the suburothelial space to initiate propagating activity over a significant area. These cellular targets are unknown but the fact that suburothelial myofibroblasts are connected by gap junctions makes them a possible site. A recent report has demonstrated M2 receptor labelling in these myofibroblasts, and that such labelling is significantly increased in bladder wall samples from patients with painful bladders and idiopathic detrusor overactivity [26].

Muscarinic receptors of subtypes M2 and M3 have been labelled in human urothelium [27]. The latter is of significance because the urothelium releases a diffusible agent that exerts a negative inotropic effect on the detrusor layer [28]. Release of this unknown agent is mediated by M2 receptors, so that one role of urothelial-derived acetylcholine may be to exert a suppressant action on detrusor contractility [29]. In this respect a study with an animal model of bladder outflow tract obstruction, that is associated with bladder overactivity, showed that the inhibitory effect of an intact urothelium on detrusor contractility was absent [30, 31].

Acetylcholine also acts via nicotinic receptors and a recent report has demonstrated their presence on urothelium. Functional experiments indicated that nicotine may activate both excitatory and inhibitory pathways in this tissue, but the precise significance of these findings remains to be determined [32].

**Vanilloid receptors**

The transient receptor vanilloid-type (TRPV) channels form a large family of sensor molecules that respond not just to ligands such as capsaicin and resiniferatoxin, but also to conditions such as altered temperature and pH. One subtype, TRPV1, is located on urothelial cells and its activation modulates bladder function, as knockout mice for the receptor show decreased voiding reflexes [33]. Activation of these channels may interact with urothelial purinergic pathways as stretch-evoked ATP release was reduced in this knockout strain. If so their activation would enhance chemically mediated sensory pathways from the urothelium.

Several lines of evidence indicate that TRPV1 channels are associated with some pathological bladder responses. With tissue from patients with neurogenic detrusor overactivity (NDO), urothelial TRPV1 labelling was increased compared to control [34]. In the same study NDO patients who responded to resiniferatoxin showed a decrease of TRPV1 labelling. TRPV1 labelling may also be seen on associated afferent nerve fibres, and a study from the same group as above found that treatment with botulinum toxin A also reduced TRPV1 (and P2X) labelling here [35]. In the case of P2X1 labelling the reduction significantly correlated with the number of urgency episodes, and there was a similar trend with TRPV1 labelling. Of interest was that urothelial labelling was unaffected in this study. TRPV channel activity is also likely on other cells. Suburothelial myofibroblasts respond to low pH interventions by generating increases of intracellular [Ca**]i, and associated tonic currents, in the same way as they respond to exogenous ATP. During filling local changes to bladder wall blood flow has been recorded [36] and it may be hypothesised that such local changes will generate acidosis and also act as a stimulus on conditions when relative tissue blood flow was reduced, as may occur during bladder wall hypertrophy or arterial disease.

**Nitric oxide (NO) release from the urothelium**

NO generation is hastened by NO synthases (NOS), and this signalling molecule exerts many of its effects by raising intracellular cGMP. NOS and cGMP immuno-reactivity have been located in many sites in the bladder wall including the urothelium and suburothelial nerve fibres and myofibroblasts [37]. NO release may suppress bladder activity [38], in particular overactivity associated with inflammation [39], and in patients with interstitial cystitis NO levels are reduced [40]. In addition, NO is produced from the mitochondria of urothelial umbrella cells, via a specific mitochondrial NOS, and such production can be raised during irradiation [41]. The consequent damage to the barrier function of the urothelium will contribute to bladder dysfunction associated with this condition. Adrenergic-receptor agonists (both alpha and beta) can also modulate NO production [42, 43], and influence bladder function. The α1A receptor is located on the urothelium and α receptor antagonist reduce distension-evoked afferent activity and ATP release [44].

**Summary**

The past few years have shown that the urothelium exerts functions more than merely acting as a barrier between urine and underlying tissues. The ability of the tissue to secrete agents in response to stimuli associated with bladder filling, and also the ability of the urothelium to respond to agonists, implies a central role in the initiation of sensory responses that record bladder volume and composition. Furthermore, these functions may be altered in certain symptomatic lower urinary tract conditions and this implies a role for the urothelium. The particular cell-to-cell and intracellular reactions in the urothelium and suburothelial space that transduce physiological or pathological signals remain to be ascertained but their evaluation should identify a number of novel targets to regulate lower urinary tract function.

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Christopher Henry Fry, BSc, BA, PhD, DSc


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