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Urothelial Targets in the Overactive bladder

C.-H. Fry, A. Roosen

Das funktionelle Verständnis des Urothels hat sich durch intensive Erforschung in den letzten Jahren grundlegend geändert. Die Vorstellung einer reinen Barrierefunktion zwischen Harn und Blasenwand ist dabei dem Konzept eines dynamischen Transportes von Wasser und löslichen Substanzen (Natrium, Harnstoff) gewichen. Darüber hinaus gilt das Urothel als Ausgangspunkt und Zielort zahlreicher Botenstoffe und spielt somit eine entscheidende Rolle in der Vermittlung der Blasenempfindung. Zu den auf Urothelzellen beschriebenen Rezeptorklassen gehören purinerge (P2X, P2Y), cholinerge (M2, M3) und Vanilloid-Rezeptoren (TRPV₁). Letztere werden durch Temperatur- und pH-Änderung aktiviert und scheinen somit unmittelbar in den sensorischen Prozeß eingeschaltet zu sein. Purinerge und cholinerge Rezeptoren haben möglicherweise eine modulatorische oder rückkoppelnde Wirkung. Das Urothel sezerniert Acetylcholin, Stickstoffmonoxyd und ATP. Letzteres wird auf mechanische Dehnung als Folge eines intravesikalen Druckanstieges hin freigesetzt. Dabei gilt der Na⁺-Transport als wesentlicher intrazellulärer Mechanismus. Über purinerge Rezeptoren wirkt ATP auf afferente Nervenendigungen und Myofibroblasten im Suburothelium; diese bilden ein funktionelles Synzytium und modulieren so die afferente Erregung. Vom Urothel freigesetztes Stickstoffmonoxyd und Acetylcholin wirken ebenfalls auf suburotheliale Myofibroblasten, die die korrespondierenden Rezeptoren exprimieren. P2X₃-Knockout-Mäuse und Biopsien von Patienten mit hyperaktivem Detrusor belegen klar die Bedeutung von urothelialen Vanilloid-Rezeptoren, urothelial freigesetztem ATP sowie von P2X₃-Rezeptoren im Suburothelium für die Entstehung des Blasenfüllungsgefühls. 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.

Extensive research during the past few years has completely remodelled the functional understanding of the urothelium. Rather than being a mere barrier between urine and underlying tissues, the urothelium provides a dynamic transport of solutes (Na⁺, urea) and water. Moreover, it has been identified both as target and origin of a number of activating chemical signals and thus may play a pivotal role in the process of bladder sensation. Among the receptors detected on urothelial cells are purinergic (P2X, P2Y), cholinergic (M2, M3), and vanilloid (TRPV₁) receptors. While the latter are activated by altered temperature and pH and therefore seem to be directly involved in sensory signalling, purinergic and cholinergic receptors might play a role in modulating secretory functions or feedback control. In turn, the urothelium releases acetylcholine, NO, and ATP. ATP is secreted in 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, the latter forming a functional syncytium and thus modulating afferent nerve stimulation. Urothelial-released NO and acetylcholine might also stimulate suburothelial myofibroblasts which express the corresponding receptors. P2X₃ knockout mice and biopsies from patients with detrusor overactivity clearly demonstrate the importance of urothelial-based vanilloid receptors, of urothelial-released ATP, and of P2X₃-receptors in the suburothelial space for the process of bladder sensation. Many micturition disorders like Interstitial Cystitis, idiopathic or neurogenic detrusor overactivity show imbalances in receptor and transmitter status of the urothelial and suburothelial layer. The better understanding of these processes provides a variety of new possible drug targets. *J Urol Urogynäkol* 2007; 14 (1): 20–23.

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 a number of reasons for this: the urothelium is no longer regarded as merely a physical barrier separating urine from the underlying bladder wall tissues [1], it can respond to physical stretch or changes in urine composition by releasing chemical signals [2]; the urothelium changes its properties during pathological conditions associated with bladder overactivity [3]; and many therapeutic agents used in the treatment of bladder overactivity are effective in the filling phase, rather than the contractile phase, of the micturition cycle [4]. For the purposes of this discussion the urothelium will also encompass the immediate suburothelial layer as it is likely that the entire structure forms a functional unit. A schematic of this region of the bladder wall is shown in figure 1. The superficial layer of urothelial cells, the umbrella cells, form a distinctive interface with the urine. They are separated by tight junctions thus limiting paracellular movement of solutes and form an effective barrier between urine and suburothelium. Below are several further layers of urothelial cells, intermediate cells and a basal 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. Perhaps 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 mechanism that are only now being fully understood. Interstitial cystitis is an inflammatory-like

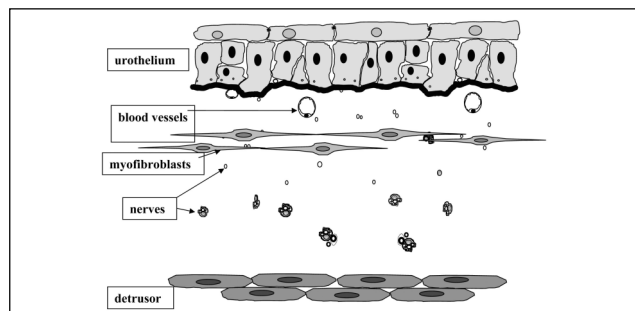


Figure 1. Schematic representation of the urothelial/suburothelial layer of the bladder wall. The urothelium has a surface layer of umbrella cells with basal and intermediate cells below. This is separated by a basement membrane from a suburothelial layer that contains blood vessels, small unmyelinated and myelinated fibres, as well as a syncytium of myofibroblasts. Many of these cells are concentrated towards the urothelial layer.

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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 baso-lateral 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 fact that P2X₃ knockout mice have a damped micturition reflex and reduced afferent firing on bladder filling [15, 16]. Ionotropic P2X₃ 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 tetrodotoxin, and hence non-neuronal, and was increased by stretch. Moreover, this TTX-insensitive fraction was much

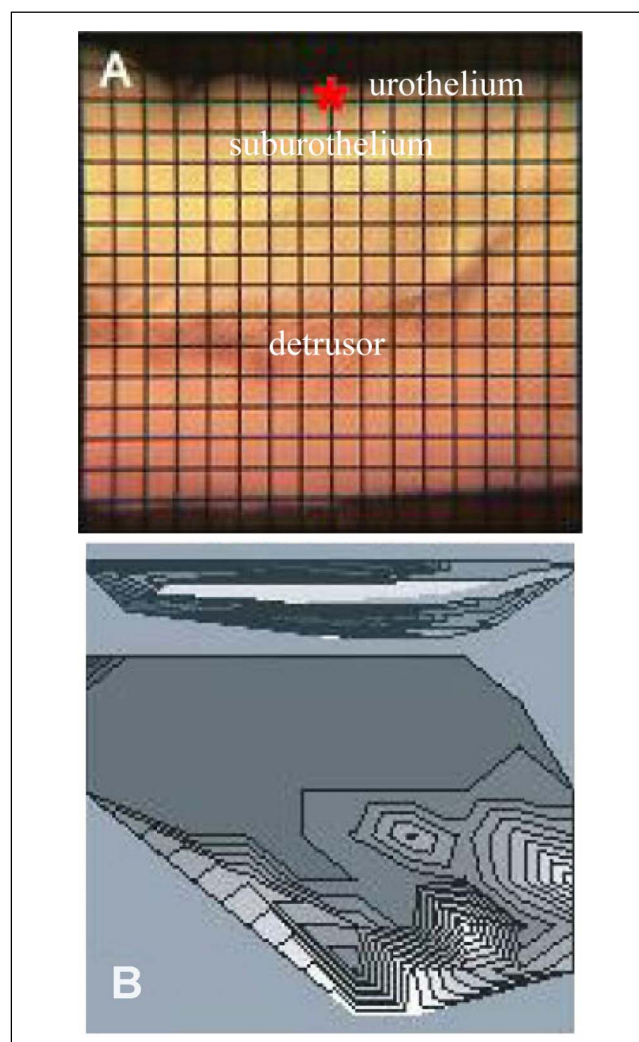


Figure 2. A map of Ca²⁺ waves originating after focal application of 50 nM carbachol (star). **A:** micrograph of a cross-section of the bladder wall with the urothelium uppermost (mucosa). The superimposed grid represents the squares from which separate Ca²⁺ transients were measured in order to construct isochronal maps. **B:** isochronal map of Ca²⁺ transients after application of 50 nM carbachol to the suburothelial layer. The darker colours represent longer delays. An initial transient spreads across the suburothelial layer but does not penetrate to the detrusor layer. A separate Ca²⁺ transient originates from the serosal surface in this instance. From [25], used with permission (copyright © The American Physiological Society).

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^{2+} 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 at present 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 P2X₃) labelling here [35]. In the case of P2X₃ 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 $[\text{Ca}^{2+}]$, and associated ionic 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 immunoreactivity 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 α_{1D} 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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