5 Spontaneous Activity and the Urinary Bladder

Christopher H. Fry and Karen D. McCloskey

Abstract

The urinary bladder has two functions: to store urine, when it is relaxed and highly compliant; and void its contents, when intravesical pressure rises due to co-ordinated contraction of detrusor smooth muscle in the bladder wall. Superimposed on this description are two observations: (1) the normal, relaxed bladder develops small transient increases of intravesical pressure, mirrored by local bladder wall movements; (2) pathological, larger pressure variations (detrusor overactivity) can occur that may cause involuntary urine loss and/or detrusor overactivity. Characterisation of these spontaneous contractions is important to understand: how normal bladder compliance is maintained during filling; and the pathophysiology of detrusor overactivity. Consideration of how spontaneous contractions originate should include the structural complexity of the bladder wall. Detrusor smooth muscle layer is overlain by a mucosa, itself a complex structure of urothelium and a *lamina propria* containing sensory nerves, micro-vasculature, interstitial cells and diffuse muscular elements.

Several theories, not mutually exclusive, have been advanced for the origin of spontaneous contractions. These include intrinsic rhythmicity of detrusor muscle; modulation by non-muscular pacemaking cells in the bladder wall; motor input to detrusor by autonomic nerves; regulation of detrusor muscle excitability and contractility by the adjacent mucosa and spontaneous contraction of elements of the *lamina propria*. This chapter will consider evidence for each theory in both normal and overactive bladder and how their significance may vary during ageing and development. Further understanding of these mechanisms may also identify novel drug targets to ameliorate the clinical consequences of large contractions associated with detrusor overactivity.

Keywords

Urinary bladder · Overactive bladder · Spontaneous contractions · Detrusor smooth muscle · Mucosa · Trigone

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5.1 Introduction: The Filling and Voiding Cycle of the Bladder

The urinary bladder has two functions: to store urine, normally up to a maximum of about 500 mL; and periodically to completely void this content. Bladder filling is achieved with a small change of intravesical pressure, up to 10–15 cm H_2O, i.e. the bladder is compliant. This is necessary to minimise increases of pressure in the upper urinary tract (ureters and renal pelvis) that would damage renal function. Several times per day urine is completely expelled from the bladder, a process that is under conscious control. This is achieved by active contraction of detrusor smooth muscle, the major tissue component of the bladder wall, to raise intravesical pressure with concomitant reduction of bladder outlet resistance; co-ordinated by central control of sacral and thoraco-lumbar centres [1]. The latter is achieved by relaxation of smooth muscle, comprising an internal sphincter, in the urethra and bladder neck, as well as cessation of contractile activity in skeletal muscle forming the external sphincter (rhabdosphincter). This enables intravesical pressure to be raised to a sufficient level to overcome the fluid resistance offered by the outflow tract.

The periodic rise of intravesical pressure for voiding is achieved by generating co-ordinated contractions of detrusor smooth muscle, principally mediated by activation of post-ganglionic parasympathetic nerve fibres. However, it is not accurate to view the bladder as completely inactive during filling: continuous asynchronous movements of regions of the bladder wall occur that can manifest themselves as small variations of intravesical pressure. This chapter is concerned with the origin of these small movements, what their physiological functions may be and if they change under pathological conditions. These movements are often called spontaneous, in that they are autonomous, with a non-neurogenic origin and so are intrinsic to detrusor smooth muscle itself, modulated or initiated by local factors or nearby tissue. It has been implicitly assumed by some that spontaneous contractions are random and therefore have no role in co-ordinated voiding and filling cycles of bladder function. However, this may not be an accurate description of their role and others consider that spontaneous contractions should be regarded as an integral part of bladder function that may become aberrant during ageing or disease and contribute to pathological activity.

5.2 The Structure of the Bladder Wall

A description of the tissue components of the bladder wall is integral to understand the nature of spontaneous contractions. It is convenient to describe four layers of the bladder wall: an outer serosa; a detrusor (smooth) muscle layer; a *lamina propria* or suburothelium; and uroepithelium (urothelium). The *lamina propria* and urothelium are collectively described as a mucosa as these two layers have an integrated activity in the context of spontaneous activity (Fig. 5.1a).

The serosa protects the underlying tissue and is a reflection of the visceral peritoneum that covers only the superior and upper lateral walls of the bladder. The remainder of the bladder wall is protected by an adventitia that merges with other pelvic floor organs. The detrusor muscle layer comprises most of the bladder wall and consists of detrusor smooth muscle in muscle bundles that can combine in circular and longitudinal directions, although distinct circular and longitudinal muscle layers are not as evident as they would be in the G-I tract or the urethra.

The mucosa is the most complex region of the bladder wall and provides protective and sensory functions, and in regard to spontaneous activity has an intimate relationship with the detrusor muscle layer. The urothelium separates underlying bladder wall tissues from urine and consists of a tight epithelium [2] whose transport characteristics will not be considered further in the context of spontaneous activity. However, it also has the capacity to release bioactive small molecules that are regarded as serving a sensory function in

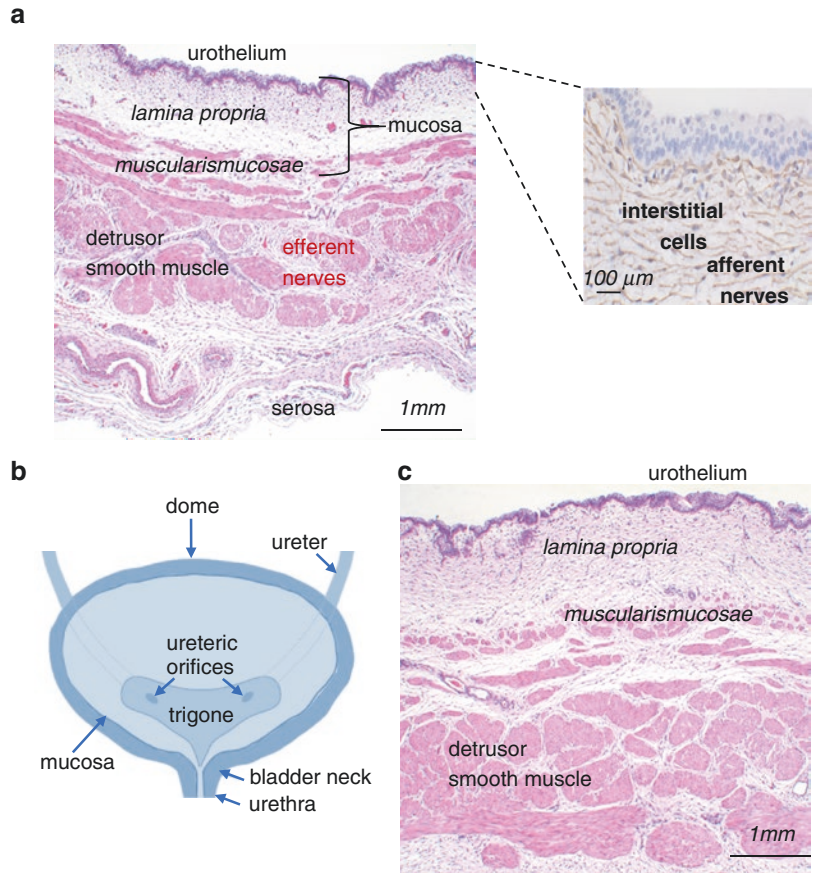

Fig. 5.1 Cross section of the sheep bladder wall; haematoxylin and eosin stain. (**a**) Full thickness section from a normal bladder showing the urothelium, *lamina propria* with *muscularis mucosae*, detrusor layer and serosa. The inset shows the urothelium and *lamina propria* lying immediately below. (**b**) Schematic structure of the lower urinary tract. (**c**) Section from a bladder with outflow obstruction

co-ordination with the *lamina propria*. The *lamina propria* itself consists of numerous interstitial cells (ICs), interspersed with afferent nerve fibres, blood vessels and in some larger species a separate muscle layer—the *muscularis mucosa*.

This basic structure is maintained throughout the bulk of the bladder wall, called the dome. A small triangular region of the bladder, between the ureteric orifices and the bladder neck, is called the trigone. This consists of a superficial layer of trigonal smooth muscle overlaying deeper detrusor contiguous with the dome, and in the guinea pig bladder the two may be separated by blunt dissection. The trigone and bladder neck are regarded by some as part of the outflow tract with characteristic high levels of spontaneous activity that will be described separately. The bladder dome and trigone are conventionally understood to have separate embryological origins, derived, respectively, from the endodermal urinogenital sinus and mesoderm-derived Wolffian (mesonephric) ducts. However, this model has been modified recently with the view that the eventual trigone musculature largely derives from bladder detrusor muscle, with mesodermal tissue confined to the ureteric openings [3].

Pathological conditions such a bladder outflow obstruction, as occurs in men with benign or malignant prostate growth, cause changes to the bladder wall, most evident in an increase of wall thickness (Fig. 5.1c). Not only does the muscle layer undergo cellular hyperplasia and hypertrophy, but the *lamina propria* also thickens with a significant increase of interstitial cell number, an aspect that has consequences for generation of spontaneous activity, as will be discussed in following sections.

5.3 Demonstration of Spontaneous Activity

Overactive bladder syndrome (OAB) is an age-related clinical condition characterised by nocturia, urgency and frequency [4] and occurs in 12–18% of Western populations [5]. A further study showed that about 12% of OAB patients have a condition of detrusor overactivity (DO [6]), i.e. over 1% of the total population. DO is characterised by large, spontaneous contractions of the bladder that are not possible to defer whilst the bladder is being filled. It not only decreases the quality of life for patients, but also can lead to involuntary loss of urine (incontinence) and if persistent a rise of pressure in the ureters that may lead to renal failure, especially if it associated with bladder outflow tract obstruction and detrusor sphincter dyssynergia. Figure 5.2a shows a clinical urodynamic record of a patient with DO. Prior to the voiding contraction associated with flow, there are three greater overactive contractions with no associated voiding, as presumably there is no co-ordinated reduction of outflow tract resistance. One applied objective of fundamental research into the origin of bladder spontaneous activity is to explain the pathophysiology and inform the clinical management of DO.

In vivo, small oscillatory bladder wall movements and intravesical pressure changes have been measured in animals and humans during the filling phase (Fig. 5.2b). Whilst some are associated with respiratory movements [7], others are independent and can coincide with sensations arising from the bladder itself [8, 9]. Bladder wall movements are asynchronous in different parts of the bladder wall, suggestive of localised, independent movements. Because the variations of pressure are lower than those observed in DO, voiding is not generally initiated and so are termed non-voiding contractions. Amalgamation of these localised spontaneous contractions could however generate larger DO contractions, and this raises two questions: what are the origins of spontaneous contractions; and how might they coalesce into larger ones?

Ex vivo, asynchronous, localised micromotions of the bladder wall or pressure transients are also measured (Fig. 5.2c) [10–13], which makes it unlikely they are derived only from external, nervous influences. These are modulated by increased stretch of the bladder wall [14] low concentrations of muscarinic agonists [11, 15] or pathological conditions such as bladder outflow obstruction [10]. Analogous transient electrical events also show limited propagation across the bladder wall [16]. The above observations are mirrored by isometric tension and electrophysiological events from in vitro bladder sheets (Fig. 5.2d), bladder wall strips (Fig. 5.2e) and even isolated detrusor myocytes from several animal and human sources (Fig. 5.2f) [17–22].

Overall, spontaneous contractile and electrical activity is a feature of the intact bladder and associated isolated preparations and is generally enhanced in bladders demonstrating pathological overactive behaviour in vivo. Some of this activity will derive from detrusor myocytes themselves but, as shown below, this activity crucially can be initiated or modulated by external influences.

5.4 Significance of Spontaneous Activity

Spontaneous contractions in the normal bladder wall are generally of small amplitude and occur at multiple sites across the bladder wall. Associated intracellular Ca^{2+} and membrane potential waves do not propagate significant distances in relation to the size of the bladder itself [11, 16, 23]. Such low level, but relatively frequent (2–3 min^{-1}) activity would be suitable to set a background, low level of tension in the bladder wall. When nerve-mediated activation of the detrusor occurs for voiding, the increased muscular contraction would raise wall tension, and hence intravesical pressure, more quickly than if the initial muscle work had to overcome a fully flaccid structure.

Changes to passive and active tension of the bladder wall are proposed as a sensory transduc-

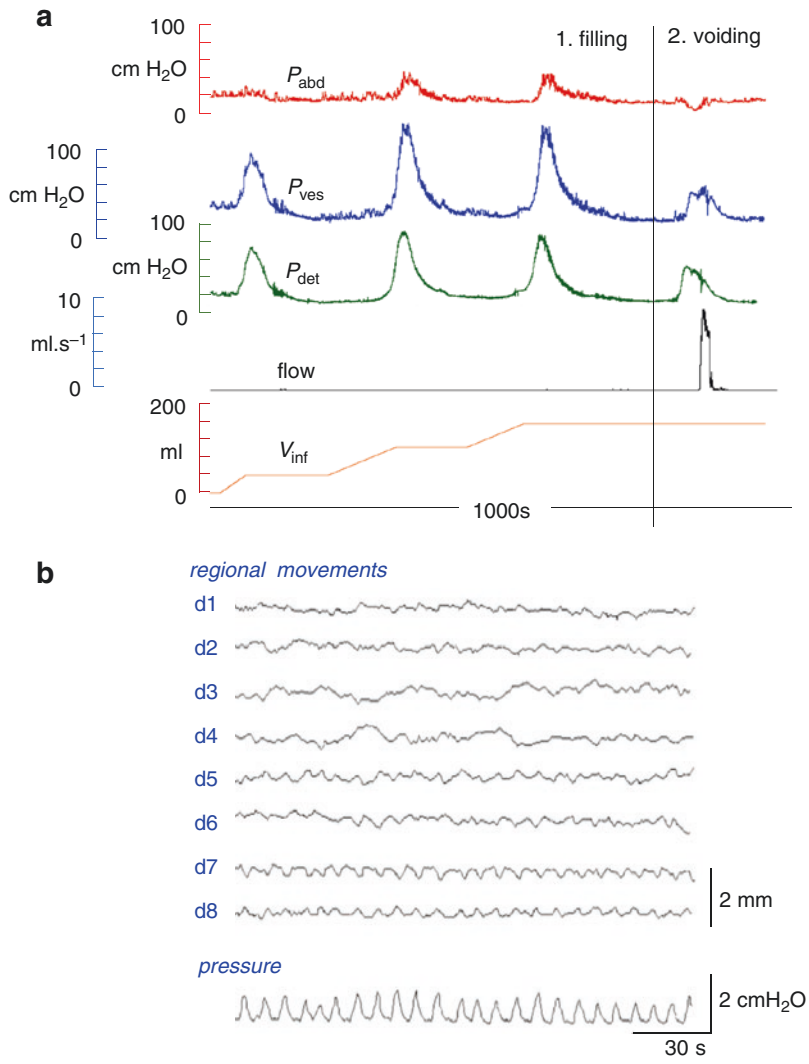

Fig. 5.2 Spontaneous contractions from in vivo, ex vivo and in vitro recordings. (**a**) Urodynamic traces from a patient with detrusor overactivity. Traces, top to bottom, are from catheters in the rectum, to measure abdominal pressure, P_{abd}, and the bladder lumen, to measure vesical pressure, P_{ves}. Detrusor pressure, P_{det}, is obtained from P_{ves}—P_{abd}. The trace below shows urine flow from the bladder. The volume infused, V_{inf}, is shown at the bottom. The vertical line divides the system into filling (left, 1) and voiding (right, 2) periods. The filling period shows three uninhibited P_{det} contractions in the absence of flow, evoked at the end of three periods of infusion. With no further filling a voiding contraction occurs, i.e. a rise of P_{det} accompanied with flow (data courtesy of the Bristol Urological Institute). (**b**) Regional movements of different regions of the bladder wall in vivo (d1–d8) and simultaneous measurement of intravesical pressure [9]. (**c**) Micromotions of an ex vivo perfused pig bladder. Carbon particles are placed on the bladder surface and the scalar distance between pairs were measured from video recordings. Examples of three distances (a, b, c) are shown with time, as well as simultaneous measurement of intravesical pressure [12]. (**d**) Spontaneous isometric contractions from a superfused rat bladder sheet for methods [10]. (**e**) Spontaneous isometric contractions from a superfused guinea pig strip with an intact mucosa [48]. (**f**) Isolated human detrusor myocytes; left, intracellular Ca^{2+} transients, right, spontaneous action potentials for methods [19]

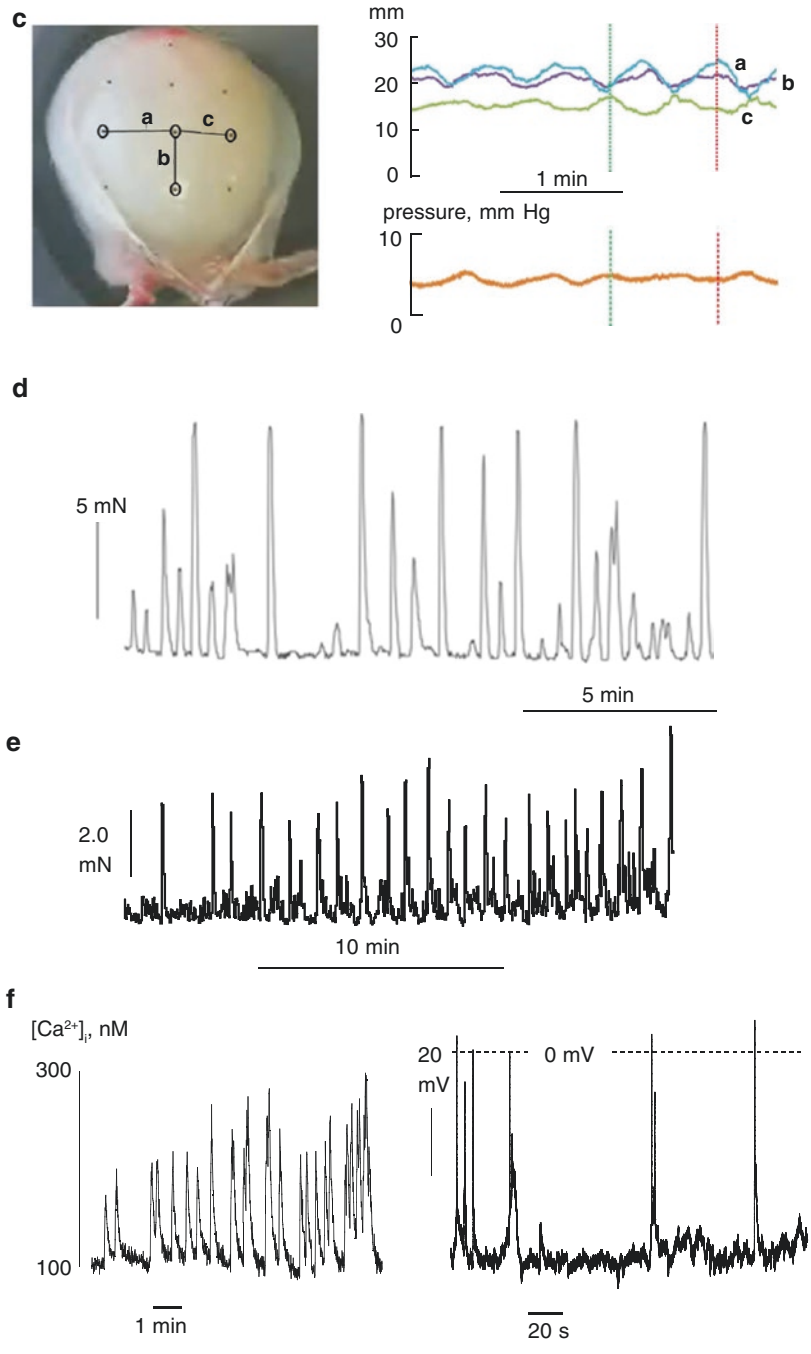

Fig. 5.2 (continued)

tion mechanism to convert bladder filling to sensory signals. An increase of passive wall tension by filling or artificial stretch is associated with augmented afferent nerve activity [24, 25]. Stretch of the bladder wall releases neuromodulators such as ATP and acetylcholine (ACh) that are proposed to activate afferents. It has also been hypothesised that added gain to the system may be provided by spontaneous contractions that will generate additional, transient changes in wall tension. Indeed, increased bladder filling raises the amplitude and frequency of spontaneous contractions [14, 26]. In part, increased spontaneous contraction amplitude on bladder filling will be due to muscle cells adjusting to a new position on their length-tension relationship, but frequency alterations suggest an additional mechanism [26], which might include activation of local nervous reflexes upon neuromodulator release. The important role of spontaneous contractions contributing to afferent activation is gleaned from the fact that afferent firing is dependent not only on static changes to wall tension, but also the rate of change of tension [27]. The mode of transduction of a transient tension/pressure signal to afferent nerve activation is unclear and may involve intermediate cellular responses from *lamina propria* cells (see below). However, the significance of the study is that alteration to spontaneous contractile activity can modulate afferent nerve activity during bladder filling.

5.5 Spontaneous Activity and Detrusor Overactivity

Detrusor overactivity is an involuntary rise of intravesical pressure, interpreted as a contraction of the bladder, measured during the filling phase of a urodynamic investigation [4, 28]. Such contractions are transient, cannot be suppressed by the patient and may be spontaneous or provoked by filling. It is tempting to hypothesise that these transient changes to intravesical pressure are a result of abnormal spontaneous contractile activity of smooth muscle in the bladder wall. However, it must be remembered that spontaneous contractions in isolated preparations are brief and of high frequency whereas overactive bladder contractions are less frequent with very much longer durations. Nevertheless, this hypothesis is consistent with observations made from in vitro preparations from overactive bladders where the amplitude and frequency of spontaneous contractions and action potentials are augmented [22, 23, 29, 30]. Optical imaging experiments show that in rat bladder preparations spontaneous contractions from in vitro bladder sheets, or pressure variations from ex vivo whole bladders, are associated with multiple sites of locally propagating Ca^{2+} and membrane potential transients [11, 23]. With similar preparations from rats that have overactive bladders, there are fewer originating sites, but these propagate more extensively over the bladder wall [11, 23]. Such rises of intravesical pressure can be greater than those achieved during normal voiding and sufficient to overcome the resistance of a still-contracted outflow and so cause urinary leakage. What is unclear is the origin of the overactive bladder contractions. Before pathological mechanisms can be proposed, it is first necessary to consider how bladder contractions arise and whether they are spontaneous or evoked by nervous stimulation of detrusor smooth muscle.

5.6 Generation of Detrusor Contractions

Only a brief description of how detrusor contractions are generated is given, with more detailed descriptions elsewhere [31, 32]. Detrusor contractions are generated by a transient rise of the intracellular Ca^{2+} concentration ($[Ca^{2+}]$), initiated

by intracellular release of Ca^{2+} from stores and/or Ca^{2+} influx via L-type and T-type Ca^{2+} channels. Co-ordinated contraction of the bladder is evoked by parasympathetic post-ganglionic fibres releasing ACh and ATP, and driven by descending fibres, emerging at sacral levels S2-S4. ACh and ATP bind, respectively, to metabotropic M_3 and ionotropic $P2X_1$ receptors. Detrusor muscle is a phasic type and can generate action potentials with a depolarising phase driven by L-type and T-type Ca^{2+} channels and repolarisation driven by K^+ channels, predominantly but not exclusively large conductance Ca^{2+}-activated K^+ (BK) channels [33–35]. It should be noted that with normal human and old-world monkey bladders ACh is the sole functional transmitter, whilst with most other species and also with human detrusor from pathological bladders both ACh and ATP support nerve-mediated contractions [36]. This may be explained by greater extracellular ATP hydrolysis in normal human bladder so that released ATP from motor nerves does not reach the muscle membrane [37].

Between the muscle bundles is a network of detrusor interstitial cells (IC_{det}) that develop Ca^{2+} transients [38, 39]. There is a debate if they contribute a pacemaking mechanism to drive detrusor myocytes, like their counterparts in the G-I tract [40, 41]. However, Ca^{2+} imaging studies show that IC_{det} transients are out of phase with those in detrusor myocytes [39, 42] and it is suggested that they may co-ordinate activity between adjacent muscle bundles. A subset of IC_{det} label for platelet-derived growth factor receptor-α (PDGFRα) [43, 44]. They respond to purines via P2Y receptors, mainly $P2Y_2$ receptors, to generate membrane hyperpolarisation by Ca^{2+}-induced activation of small conductance K^+ (SK) channels. It is proposed that they hyperpolarise adjacent detrusor muscle cells via gap junctions [45], but there is as yet little evidence for direct intracellular coupling between detrusor myocytes and ICs. However, if such coupling is demonstrated this provides a mechanism whereby cyclical variation of ATP release from urothelium and/or *lamina propria* cells would also generate cyclical variation of tension in the detrusor smooth muscle layer, through a direct activating response on detrusor via $P2X_1$ receptors and tempered by the indirect effect via P2Y receptors on PDGFRα-labelled IC_{det}.

5.7 Influence of the Mucosa on Spontaneous Activity

Several groups have reported that the mucosa from pig, guinea pig and rat bladder is capable of developing spontaneous contractile [46–48] or electrical [49] activity independent of detrusor smooth muscle, although others report that contractile activity is absent from rat and mouse isolated mucosa preparations (Hashitani, personal communication). Moreover, when the mucosa and detrusor components are not separated the amplitude of spontaneous contractions is greater than that developed by the two components separately. Figure 5.3 describes the basic phenomenon in guinea pig tissue: Fig. 5.3a (top) shows spontaneous activity in an isolated preparation of the bladder wall with the mucosa dissected away as much as possible (in all species the mucosa may be removed by sharp or blunt dissection), spontaneous activity is present but is relatively low in amplitude. In this example, spontaneous activity is very small but in other publications [50] this may be greater, but still smaller than in intact strips as described below. If the dissected mucosa is similarly attached to an isometric force transducer spontaneous activity is also recorded of equivalent or even greater amplitude (Fig. 5.3a, middle). However, if the mucosa is left intact on the detrusor preparation a proportionately much greater amplitude of spontaneous contractions is measured (Fig. 5.3a bottom), note also the change of vertical calibration bar). Thus, the mucosa itself is capable of spontaneous contractile and electrical activity in many animal species, and in addition there is synergistic enhancement when the two layers of the bladder wall are in contact. The significance of the contribution of the mucosa to bladder spontaneous contractile activity is that the *lamina propria* thickens in many pathological conditions asso-

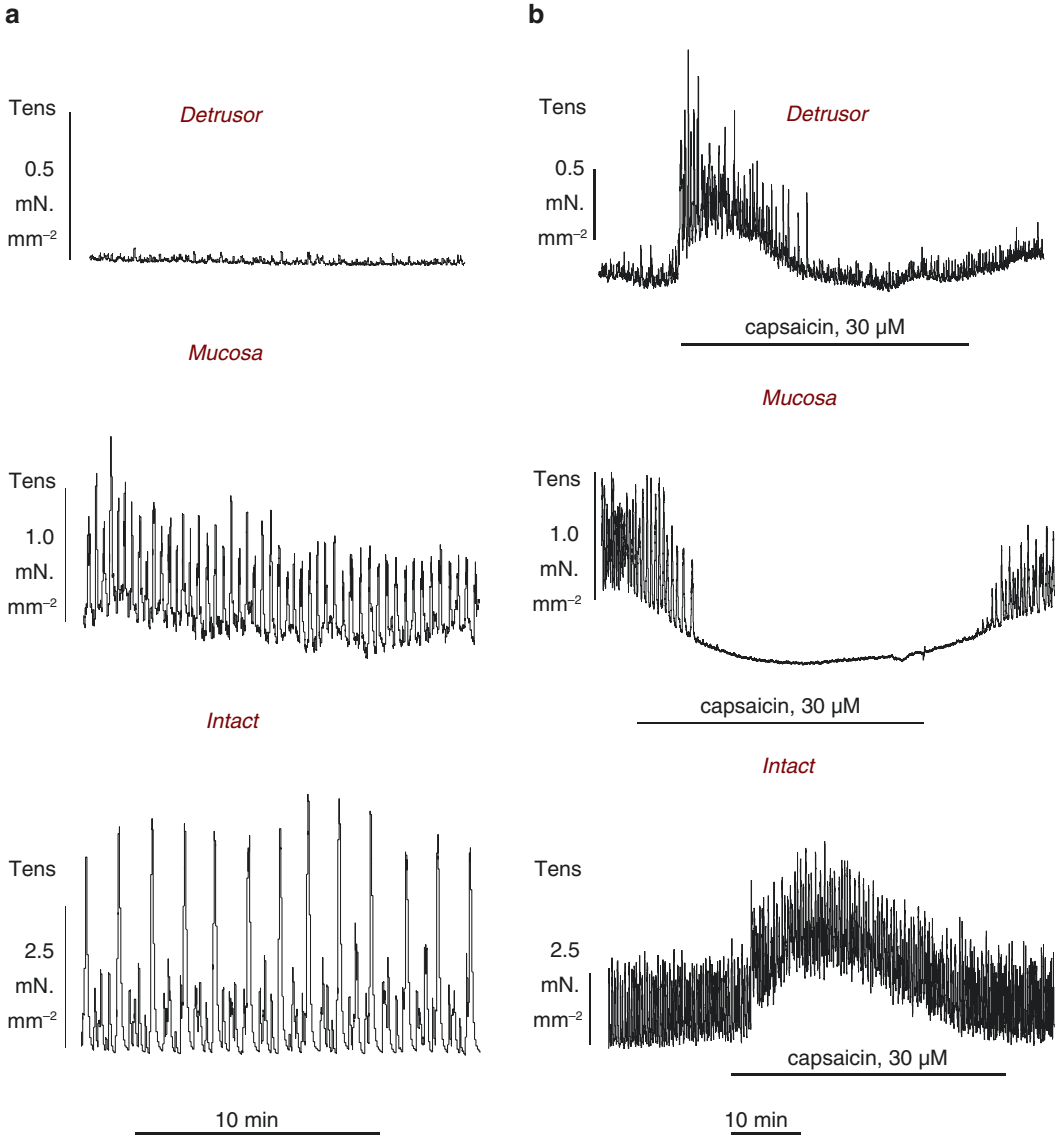

Fig. 5.3 Spontaneous contractions from isolated bladder wall preparations. (**a**) Guinea pig bladder. Baseline spontaneous contractile activity from a detrusor strip with the mucosa removed (upper); a mucosa preparation dissected from detrusor muscle (middle); an intact preparation of detrusor and mucosa (lower). (**b**) Spontaneous contractile activity on addition of 10 μM capsaicin in: a detrusor preparation (upper); a mucosa preparation (middle); an intact preparation (lower). Note the different calibration bars for the three preparations. Adapted from [48]

ciated with neurogenic or idiopathic detrusor overactivity [51, 52]. The particular cells contributing to mucosa spontaneous activity is considered in more detail below (Sect. 5.8) and may be from the *muscularis mucosa*, with contributions also from smooth muscle cells and/or pericytes around blood vessels or even ICs.

5.8 The Origins of Mucosa Spontaneous Activity

The mucosa itself has contractile properties and electrical field stimulation (EFS) can elicit contractions that are abolished by tetrodotoxin, implying they are nerve-mediated. The fre-

quency dependence of EFS detrusor vs. mucosal contractions is different in pig preparations [53], but similar in other species such as guinea pig [49, 54], highlighting the fact that mucosal contractile function can have different properties from detrusor. Moreover, mucosal spontaneous activity demonstrates different pharmacological characteristics whereby: capsaicin augments detrusor activity but inhibits that of the mucosa (Fig 5.3b); extracellular acidosis initially suppresses detrusor activity but has a much smaller effect on isolated mucosa; and the $P2X_1$ agonist α,β methylene ATP, (ABMA) enhances detrusor but attenuates mucosa activity [48]. Moreover, although α- and β-adrenoceptor-dependent modulation of spontaneous activity in the mucosa is evident, the functional receptor subtype populations involved show differences from the detrusor [55]. The actual cell type(s) contributing to mucosa contractions are unknown but may be from several sources, including *muscularis mucosae*, abundant ICs and pericytes around blood vessels. All these cells label for smooth muscle actin [56, 57].

Muscularis mucosae generates bursts of spontaneous action potentials (APs) with a depolarising phase supported by L-type Ca^{2+} channel activity. BK and SK channels, as well as Kv7 K^+ channels which all modulate the bursting characteristics of the AP trains and hence the excitability of the tissue [58]. The current density of K^+ currents in the *muscularis mucosae* is much lower than in detrusor [59] and may contribute to increased electrical excitability. In addition, TRPV4 channels are also present in *muscularis mucosae* and their activation generates a sustained contraction and reduction of spontaneous activity, possibly by Ca^{2+} influx opening BK channels [60]. Overall this might suggest that *muscularis mucosae* can exhibit a phasic contractile response and a background tonus to the bladder wall.

Vascular smooth muscle cells and/or pericytes surround suburothelial blood vessels, generate intracellular Ca^{2+} transients and also generate circular and longitudinal contractions [61, 62]. The physiological properties of these cells will be covered in a separate chapter. Longitudinal contractions would contribute to mucosal force generation, although the proportional effect they have remains to be ascertained.

ICs are the most numerous type of cell in the *lamina propria*; the ratio of ICs to smooth muscle cells in the *muscularis mucosae* in six sheep bladders was 5.1 ± 0.7 (n = 6, Fry, Nyirady, unpublished data). They are especially abundant near the urothelium (see Fig. 5.1a, b) and often appose and even surround the terminals of afferent nerves [63], so that they probably have synapse-like relations. They are electrically excitable, generating transient depolarisations via a Ca^{2+}-activated Cl^- channel, the rise of intracellular Ca^{2+} mediated by release from intracellular stores after membrane receptor activation via, for example, purines acting on P2Y receptors [64]. Moreover, these ICs are coupled by connexin43 (Cx43) gap junctions suggesting they form a functional electrical syncytium [65]. Their excitatory responses to purines are consistent with activation by ATP and its metabolites that may be released from the overlying urothelium in response to stretch. Moreover, some ICs have a myofibroblast-like morphology where they contain myofilaments that form cytoplasmic stress fibres [66]. IC number increases significantly as the *lamina propria* thickens in conditions associated with detrusor overactivity, such as bladder outflow obstruction (Fig. 5.1b), [67] and spinal cord injury [51] when they could augment indirectly mucosal spontaneous activity.

Overall it may be concluded that the mucosa has distinct contractile properties from detrusor with potential contributions from the three major cell types described above. The proportion of mucosal tissue occupied by *muscularis mucosae* is about 4.5% in guinea pig bladder, compared to 73.4% occupied by detrusor in the muscle layer [48] to produce broadly comparable magnitudes of spontaneous contractile activity. Thus, if *muscularis mucosae* solely contributed to spontaneous contractile activity, its unit contractile properties would have to be substantially greater than detrusor.

5.9 Interactions Between Mucosa and Detrusor and the Generation of Spontaneous Activity

Augmentation of spontaneous activity by retaining a mucosa-detrusor structure implies there is interaction between the two layers. This may be though diffusion of chemical modulators or cell-to-cell signalling (Fig. 5.4a, b). One observation to suggest diffusional coupling (Fig. 5.4a) shows that simple placement of mucosa on detrusor muscle rapidly increases the amplitude and frequency of spontaneous contractions. Augmentation of spontaneous activity is not suppressed by atropine implying that ACh is not the diffusible active

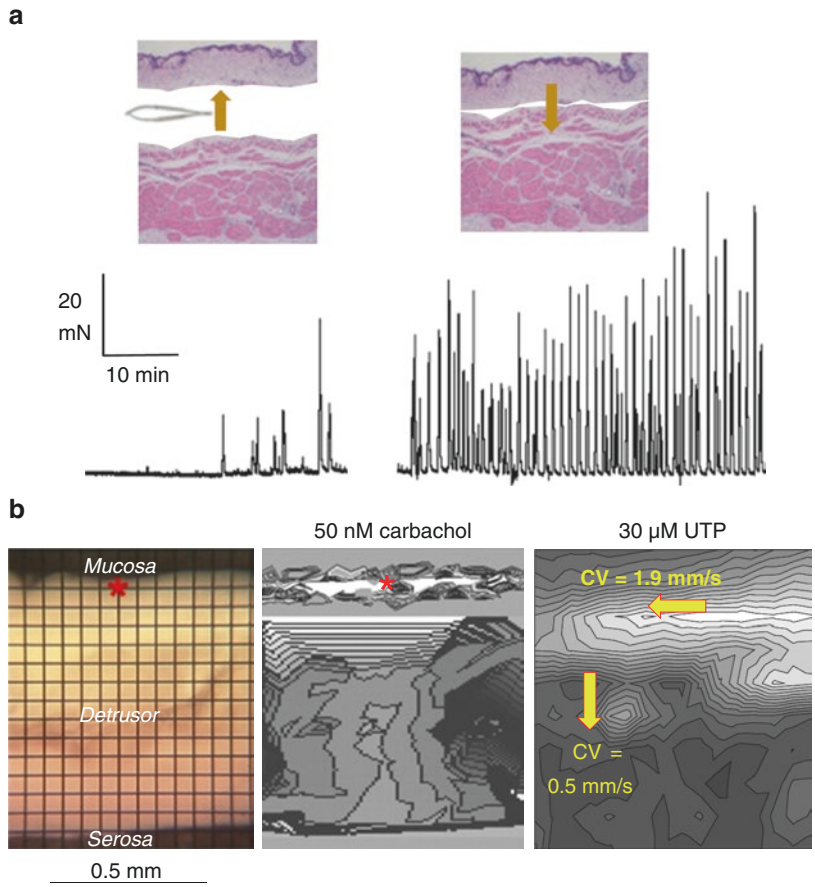

Fig. 5.4 Interaction between mucosa and detrusor in the generation of spontaneous contractions. (**a**) Evidence for non-cell-to-cell contact. Spontaneous activity in a detrusor preparation with the mucosa dissected away as a sheet (left) and when the mucosa was subsequently placed on the detrusor preparation (right): Kitney and Fry, unpublished data. Pig bladder, a schematic of the experiments is shown above the experimental tracings. (**b**) Evidence for cell-to-cell contact. Left, a cross section of a rat bladder used for optical imaging experiments, the superimposed grid delineates separate pixels from which Ca^{2+} waves were recorded to construct conduction maps. Middle, a conduction map constructed from the latencies of Ca^{2+} transients from each pixel on injection of a low carbachol concentration at the *lamina propria* (red star)—increasing delays are designated by areas of greater darkness. Thus, the initiation of a signal propagates transversely in the mucosa before propagating laterally to the detrusor layer. Right: a conduction map again showing rapid transverse propagation and slower invasion of the detrusor after application of UTP, a purine that excites *lamina propria* interstitial cells. Adapted from [11, 23]

agent. However, many other agents are released by mucosal cells that can have local paracrine, contractile effects on detrusor muscle including ATP, prostaglandins and nitric oxide [68]. In particular, it has been shown in guinea pig bladder that spontaneous activity goes through cyclical variations in magnitude that coincides with background release of ATP, after consideration of diffusion times for ATP in the tissue [48]. However, Fig. 5.4b shows evidence also for intercelluar coupling from the mucosa to the detrusor layers. Direct evidence that spontaneous activity can result from localised release of ATP from detrusor or mucosa is shown below (Fig. 5.5b, see Sect. 10.2 below). Although some will be broken down by ecto-ATPases, some ATP undoubtedly persists to generate contractile events. Moreover, ecto-ATPase activity is reduced in bladder wall tissue from overactive bladders that would exacerbate the contractile effects of ATP released from tissue [37].

There are also data to suggest there is cell-to-cell coupling between the mucosa and detrusor. With intact or detrusor-only preparations, gap junction blockers including 18-β glycyrrhetinic acid, carbenoxolone or heptanol attenuate spontaneous activity, especially in animals where activity was increased by spinal cord injury or inflammation [51, 69]. However, it should be cautioned that there is evidence to show some gap junction blockers also block voltage-gated Ca^{2+} channels [70] which would also explain why these agents may reduce spontaneous activity. However, it remains to be shown whether this blockade is occurring solely between detrusor muscle cells or also in the *lamina propria* at the interface between the two layers. There are also optical signalling data that indicate that Ca^{2+} waves and electrical signals can pass within the *lamina propria* and across to the detrusor layer. Ca^{2+} signals, propagating at 60–70 μm.s^{-1} have been measured in isolated *lamina propria* preparations. These were augmented by ATP and TRPV4 agonists and attenuated by the Ca^{2+}-ATPase inhibitor cyclopiazonic acid, implying an intracellular source of Ca^{2+} [71]. Optical imaging of the rat bladder wall, with an absent *muscularis mucosae*, reveals that spontaneous waves of intracellular Ca^{2+} or changes to membrane potential originate not in the detrusor, but in the *lamina propria* where they propagate laterally within this layer before invading the detrusor [10]. Signal propagation velocity is about 0.3 cm s^{-1}, faster than in *muscularis mucosae* [23, 59]. Overall it is possible that the two cellular elements exert different influences over the detrusor layer, with *muscularis mucosae* setting a background tonus and an IC layer providing a more dynamic response to changes of neuromodulator released from the urothelium.

Although the mucosa enhances spontaneous activity in the bladder this has to be set against the observation that it also suppresses contractions evoked by muscarinic receptor agonists, but not when depolarised by raised extracellular [K] [72]. Exhaustive studies by the original authors did not reveal the intermediate diffusible agent, nevertheless the augmentation of spontaneous activity must be offset by this observation.

5.10 Theories for the Origin of Spontaneous Activity in Normal and Pathological Bladders

In principle normal and overactive spontaneous activity may arise from several, not mutually conflicting, mechanisms:

- A myogenic origin
- A neurogenic origin
- A urotheliogenic origin

5.10.1 Myogenic Spontaneous Activity

Isolated detrusor myocytes can develop spontaneous action potentials and intracellular Ca^{2+} transients, the frequencies of which are greater in cells isolated from overactive human bladders (Fig. 5.2f) [22]. The depolarising phase of the action potential is supported by L-type and T-type Ca^{2+} currents; the latter are activated at potentials near to the membrane potential and so in princi-

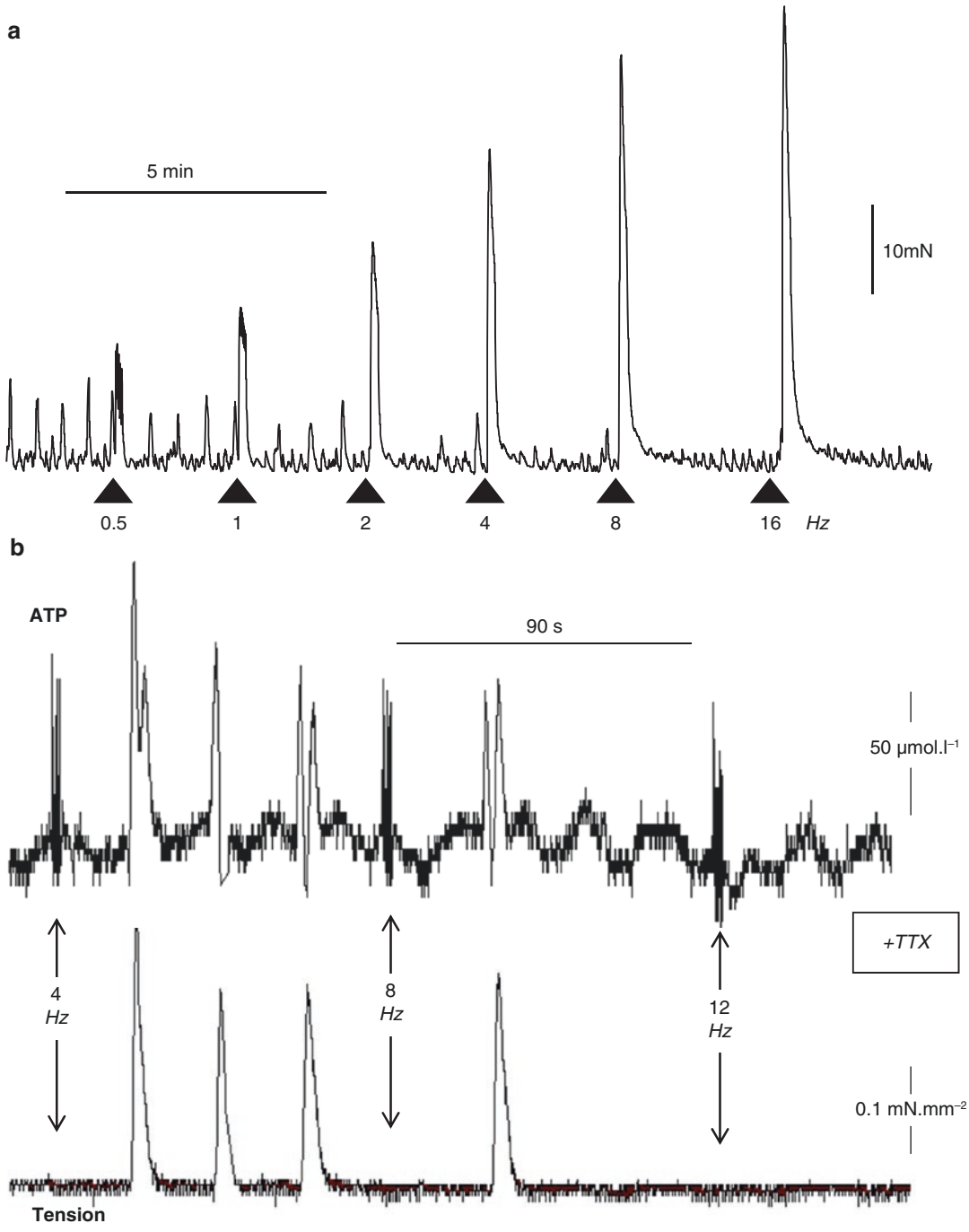

Fig. 5.5 Appearance of spontaneous contractions with absence of nerve-mediated activity. (**a**) Nerve-mediated contractions stimulated by tetanic stimulus with frequencies between 0.5 and 16 Hz. Note the greater spontaneous activity as stimulus frequency decreases. (**b**) Spontaneous contractile activity (lower trace) during abolition of nerve-mediated contractions with 1 µM tetrodotoxin. Upper trace: Extracellular ATP transients accompany spontaneous contractions. Note the stimulus artefacts on the ATP electrode trace co-incident with stimulation at 4, 8 and 12 Hz. Trace in panel **a** adapted from [120]

ple could serve as a pacemaker current. Moreover, the density of T-type Ca^{2+} current is greater in myocytes from overactive human bladders and this could account for the increased frequency of spontaneous action potentials [73]. Detrusor myocytes are connected by connexin45 (Cx45) gap junctions so that electrical activity generated in a cell, or group of cells, could spread to adjacent tissue. However, the expression of Cx45 protein is reduced in human detrusor from overactive bladders, corroborated by an increased electrical resistance between adjacent myocytes. This would limit the speed and extent of spread of electrical signals across the bladder wall [74]. Thus, although localised electrical activity may be generated more in detrusor from overactive bladders, these signals would be confined to a smaller region of the wall bladder. These data do not support the ability of electrical signals to spread across larger regions of the bladder wall that would form the basis of an overactive bladder contraction [23].

It may be hypothesised that during an overactive bladder contraction, detrusor contractility may be greater than that during normal voiding. An estimate of true bladder contractility may be obtained from transformation of the isovolumic phase of detrusor pressure rise during voiding or overactive contractions. However, an overactive contraction does not represent a state of enhanced contractility compared to that for a nerve-mediated voiding contraction, which does not support this hypothesis [75].

Overall, although myogenic activity does occur in detrusor smooth muscle, there is no evidence that the greater frequency and larger amplitude of spontaneous activity in detrusor from overactive bladders is a significant basis of pathological detrusor overactivity.

5.10.2 Neurogenic Detrusor Overactivity (NDO) and Spontaneous Activity

A subset of patients with DO have associated neurological deficits such as spinal cord injury or Parkinson's disease. This subgroup is described as suffering from NDO but whether or not the pathophysiology of the condition is different from that of the majority of DO patients remains unclear at present. However, isolated detrusor preparations from NDO bladders are associated with greater spontaneous contractile activity [76, 77]. Spontaneous contractions from isolated multicellular detrusor preparations obtained from normal or DO bladders are insensitive to application of tetrodotoxin (TTX)—to block nerve action potentials—or atropine—to block the action of Ach that might be released or simply leaks from motor nerves [78]. This implies that intrinsic motor nerves do not generate autonomous activity resulting from release of neurotransmitter. Moreover, nerve-mediated contractions of isolated human detrusor preparations from DO bladders are similar in magnitude or decreased compared to those from normal bladders [36, 78]. This implies that the functional innervation by postganglionic fibres to DO bladders is similar or even reduced compared to normal bladders.

The role of several detrusor K^+ channels in modulating spontaneous activity and their role in the aetiology of NDO in particular has been studied. These channels include small, intermediate and large conductance Ca^{2+}-activated K^+ channels (SK, IK and BK channels, respectively), as well as ATP-dependent K^+ channels. Openers of both BK and SK/IK channels (NS-1619 and SKA-31/NS-309, respectively) reduce spontaneous contractions in rat and human detrusor. These actions are reversed by their respective channel blockers iberiotoxin and apamin [79–82]. IK channels have not been implicated as the IK blocker, TRAM-3K, had no effect [81]. However, with human detrusor samples from NDO patients NS-1619 and iberiotoxin had no effect on spontaneous activity, unlike the situation with detrusor from normal human bladders [76, 77]. This latter result was corroborated by demonstrating a reduced iberiotoxin-sensitive K^+ current and expression of the α-subunit of BK channels, the β1 and β4-subunits were not significantly different [76]. Thus, increased spontaneous activity in isolated detrusor strips from NDO patients may be due, at least in part, to a myogenic response through reduced BK channel density.

An indirect role for motor nerves involvement to generate some spontaneous activity may be inferred from the observation that an increase of nerve stimulation to isolated detrusor samples, with an intact mucosa, leads to a decrease of activity (Fig. 5.5a) [54]. Not only is spontaneous activity resistant to atropine but persists also in the presence of PPADS, an antagonist to most P2X receptors, including $P2X_1$ expressed in detrusor smooth muscle [54]. However, Fig. 5.5b shows an experiment after nerve-mediated contractions had been abolished by addition of TTX where spontaneous activity was also evident and accompanied by transient increases of ATP, as measured by an amperometric ATP-selective sensor placed on the surface of the preparation (McCarthy and Fry, unpublished data). These observations are consistent with the presence of spontaneous transient depolarisations in mouse detrusor that were abolished by the $P2X_1$ receptor antagonist NF449 and increased by latrotoxin [83], a venom that acts on presynaptic nerve terminals and secretory cells to release transmitters [84]. However, the inability of PPADS to diminish spontaneous activity requires explanation.

5.10.3 Mucosal Modulation of Spontaneous Activity and its Significance in Overactive Bladder

The term *Urotheliogenic* derives from the observation that spontaneous contractions are greater when in vitro detrusor preparations retain their covering of mucosa [49]. Although the term implies that it is the urothelium itself that augments detrusor contractions, in fact control may derive from any of the cell types in the mucosa, either singly or in combination. It has been discussed above that diffusional and/or cell-to-cell contacts between mucosa and detrusor layers could generate the augmented spontaneous activity observed when the two layers of the bladder wall are in contact. Moreover, in bladder pathologies thickening of the mucosa occurs, accompanied by an increase in the population of ICs and these are associated with larger amplitude spontaneous contractions that propagate across greater areas of the bladder wall [48]. It is suggested that *lamina propria* IC fall into two subtypes [85], a more abundant population near the urothelium that express α-smooth muscle actin and PDGFRα and not CD34, and a population nearer the detrusor layer that had an inverse expression of these epitopes. It is not clear what are the functional distinctions between these subtypes but any study with isolated ICs is more likely to use the former due to their greater abundance.

With this caveat the pharmacological properties of *lamina propria* ICs can give insight into the interaction between mucosa and detrusor in generating spontaneous activity. Firstly, enzymatically dispersed *lamina propria* ICs do not respond to exogenous cholinergic agonists to generate an intracellular Ca^{2+} transient or electrophysiological responses [64]. However, very low concentrations of carbachol do augment spontaneous activity and Ca^{2+}-wave propagation in isolated bladder sheets with an intact mucosa [11], a potential resolution to this apparent paradox is discussed below. However, ICs respond in a complex way to purines as they generate large inward currents to exogenous ATP, ADP and UTP that suggests that they act via P2Y receptors [64]. This is corroborated by immunohistochemistry that shows an abundance of $P2Y_6$ receptors, with only sparse labelling for $P2X_1$, $P2Y_2$ and $P2Y_4$ receptors on these cells [86]. The inward current is through a Ca^{2+}-activated-Cl^- channel in response to a rise of the intracellular $[Ca^{2+}]$ after purine application. Application of ADP or UTP to bladder sheets with an intact mucosa greatly increases the magnitude of spontaneous contractions, especially in bladders that are already overactive with a thickened mucosa [23]. With these intact bladder sheets, application of P2Y agonists greatly enhances the velocity at which membrane transients or Ca^{2+} waves propagate, as well as increases the area of that bladder wall over which they spread.

The urothelium releases a number of bioactive molecules when subjected to chemical or physical interventions, which include ATP, acetylcholine, prostaglandins and nitric oxide. Most is known about stress-activated ATP release and it is noteworthy that release is augmented from

urothelium obtained from bladders that exhibit overactive pathologies [87–91]. Released ATP is rapidly broken down by ectoATPases to ADP and other metabolites that would have a paracrine effect on the increased numbers of ICs, one result of which would be to upregulate spontaneous activity.

An allied observation is that ACh release from urothelium occurs at much lower levels of physical stress and in much greater quantities compared to ATP release [92]. Moreover, muscarinic receptor agonists augment ATP release from urothelium via M2 receptors [93, 94]. This interaction between muscarinic receptor activation and urothelial ATP release provides a sensory transduction pathway for bladder filling or other stresses to activate suburothelial afferents as well as modulate spontaneous contractions via the above urotheliogenic mechanism. Moreover, the increase of ATP release in pathological bladders provides an understanding of how sensory pathways as well as spontaneous activity is increased in these pathologies.

A final consideration is the range of physical and chemical stressors that can release bioactive molecules. Urothelial cells express purinergic, muscarinic, nicotinic and adrenergic receptors [95–98] among others, which can respond in an autocrine/paracrine mode or to circulating catecholamines. Moreover, a variety of transient receptor potential (TRP) channels [99–101] and piezo-channels [102] have been identified that allow urothelial cells to respond to environmental changes such as low pH, changes to ambient temperature and physical stress or strain changes. This variety of receptor molecules ensures that the urothelium is a sensitive and multimodal sensory structure that provides the link to sensation and outputs such as spontaneous activity and afferent nerve activation.

5.11 The Trigone

Because of its structural connection to the intravesical portion of the ureter, and its potential role as part of the outflow tract, the trigone may play a role in regulating the opening and closure of the ureteric orifices to prevent vesicoureteral reflux. Whilst the main mechanism to prevent reflux is the oblique angle of the insertion of the ureter through the bladder wall, providing a compression valve as the bladder fills, periodic contractions of the trigone may support opening of ureteral orifices to facilitate filling and may also assist compression during voiding contractions of the bladder.

Spontaneous phasic contractions have been recorded in 71% and 89% of trigone strips from pigs and humans, respectively, compared with only 20% in muscle strips from the dome [17]. Moreover, in the trigone spontaneous contractions arise purely from the smooth muscle component, as removal of the mucosa has no effect on their amplitude and frequency [46]. This is in contrast to the situation with tissue from the bulk of the bladder body—the dome—where the presence of the mucosa is crucial to maintain spontaneous activity. The cellular pathways underlying spontaneous contractions have been studied in the superficial trigone of the guinea pig bladder, where the majority of muscle strips also generate spontaneous phasic contractions [103] (Fig. 5.6a). Trigone smooth muscle generates spontaneous bursts of action potentials [104], similar to detrusor from the bladder dome. However, electrical stimulation of this region of the bladder elicits action potentials [105] which do not occur when the dome of the bladder is similarly excited. This demonstrates that the trigone exhibits greater excitability than the bladder dome and that smooth muscle in the two regions are functionally separate. This latter observation is corroborated by the fact that spontaneous electrical activity in the trigone is generated independently from that in the bladder dome [106]. The greater excitability of a functionally independent trigone arises from the fact that its smaller muscle mass, compared to detrusor in the bladder dome, means that the overall electrical resistance of the tissue is greater. Thus, ionic current generated in the tissue will generate larger local potential fields as observed above [105]. The separateness of trigone and detrusor is also indicated by spatiotemporal mapping techniques that show propagating patches of

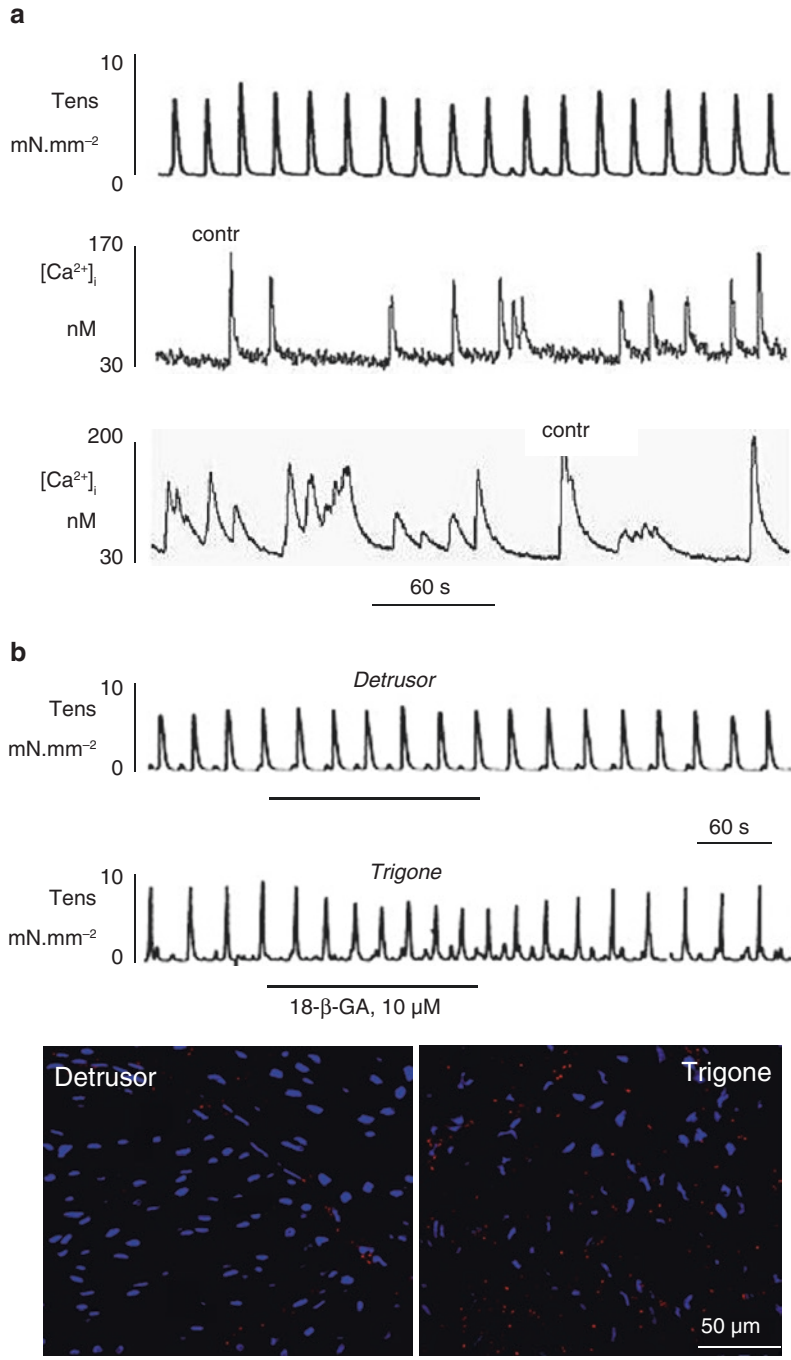

Fig. 5.6 Characteristics of spontaneous activity in trigone. (**a**) Isolated trigone tissue showing regular spontaneous contractions (upper trace). Different patterns of intracellular Ca^{2+} transients in isolated trigone myocytes (middle and lower traces). (**b**) Spontaneous activity and gap junction blockers. Effect of 18-β-glycyrrhetinic acid (GA) on regular spontaneous activity recorded in isolated detrusor (upper trace) or trigone (lower trace) smooth muscle. The two images below are of the muscle layer and are labelled for connexin proteins (red) and nuclei (blue); sections are from detrusor (connexin45, left) and trigone (connexin43, right). (**c**) Effect of a 0-Ca solution (upper panels) on spontaneous contractions (left) and intracellular Ca^{2+} transients (right). Effect of a niflumic acid (100 μM) on spontaneous contractions (middle panel) and intracellular Ca^{2+} transients (lower panel). (**d**) Effect of carbachol (carb, 1 μM) in the absence or presence of 10 μM phenylephrine on tension (upper panel) and intracellular [Ca^{2+}], lower panel. Adapted from [8, 103]

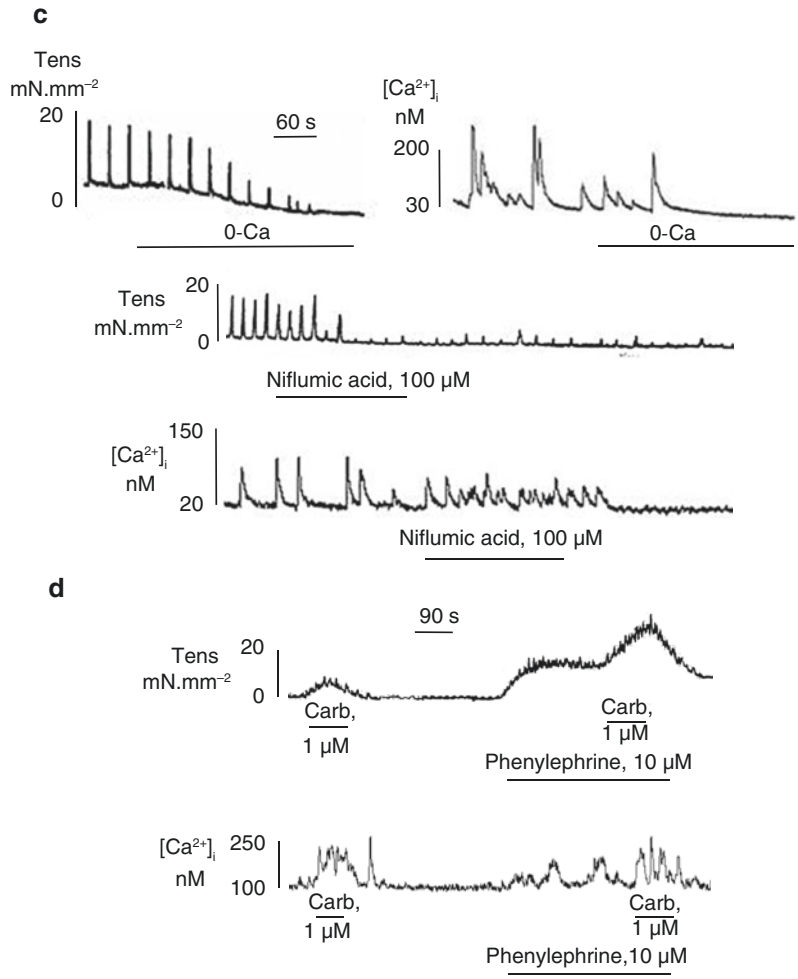

Fig. 5.6 (continued)

contraction in the dome travel mainly along the anterior and lateral surface of the bladder and do not traverse the trigone [107].

The relative ease of electrical transmission in the trigone compared to detrusor is mirrored by a greater abundance of connexin-labelling gap junctions, as determined by immunolabelling [103]. Moreover, the connexin subtype between smooth muscle cells in the trigone is Cx43, rather than Cx45 as in the dome [51], which is of significance as Cx43 gap junctions have a greater unit electrical conductance compared to those formed with Cx45. 18-β glycyrrhetinic acid, a gap junction blocker, reduces the amplitude but increases the frequency of spontaneous contractions in the trigone, whereas under similar conditions it has little effect on detrusor spontaneous activity (Fig. 5.6b). The appearance of less well-coordinated activity in 18-β glycyrrhetinic acid suggests that intercellular communication plays a role in developing such contractions.

The upstroke of the action potential is mainly mediated by Ca^{2+} influx through L-type Ca^{2+} channels as intracellular Ca^{2+} transients are abolished by either an L-type Ca^{2+} channel inhibitor or Ca^{2+} free solution, but not by a T-type Ca^{2+} channel inhibitor. Furthermore, neither thapsigargin, an inhibitor of SR Ca^{2+} uptake, nor FCCP, a mitochondrial uncoupler, are inhibitory, also sug-

gesting the importance of Ca^{2+} influx rather than intracellular Ca^{2+} stores to support contraction [103]. Niflumic acid, a blocker of Ca^{2+}-activated Cl^- channels, also attenuates Ca^{2+} transients and spontaneous contractions of the trigone [103]. At membrane potentials near the resting value such channels would pass inward current which would activate L-type Ca^{2+} channels. Thus L-type Ca^{2+} channel antagonists inhibit both spontaneous contractions and intracellular Ca^{2+} transients (Fig. 5.6c). Carbachol increases intracellular $[Ca^{2+}]$ and thus muscarinic receptor activation would initiate the process of augmenting spontaneous activity.

The trigone is unusual in that both cholinergic and adrenergic agonists augment spontaneous activity, however the rise of intracellular $[Ca^{2+}]$ is greater with carbachol than with the non-selective α-adrenoceptor agonist, phenylephrine. Moreover, phenylephrine increases the cholinergic contractile responses independent of a further rise of intracellular $[Ca^{2+}]$, suggesting that an important action may be to increase the Ca^{2+}-sensitivity of the contractile proteins [108] (Fig. 5.6d). Synergy between cholinergic and adrenergic pathways is also suggested by the fact that a muscarinic receptor antagonist reduces contraction generated by adrenergic agonists [109]. Such synergy between cholinergic and adrenergic pathways allows the autonomic nervous system to regulate spontaneous activity with a high degree of gain and suggests that the trigone exhibits such activity in the filling and voiding phases of bladder activity.

Suppression of spontaneous contractions can be achieved by activation of K^+ channels. However, in contrast to dome detrusor smooth muscle, ATP-dependent K^+ (K_{ATP}) channels appear to have important roles in membrane repolarisation rather than BK and SK channels as is the case in bladder dome detrusor [46].

The greater contractile spontaneity and excitability of the trigone and its functional separation from the bladder dome implies that spontaneous contractions may serve separate purposes. During bladder filling, maintained tonus by the trigone could contribute to the resistance offered by the internal sphincter. Micromotions in the dome of the bladder, which help to keep bladder shape and offer a low tonus, would also not propagate to the trigone as this region of the bladder is fairly rigidly fixed to the bladder base. Thus, the different functions of the two regions of the bladder are reflected in the separate processes that generate and propagate spontaneous activity.

5.12 Changes to Spontaneous Activity in Development and Ageing

Spontaneous contractions develop in the first few post-natal weeks in the neonatal bladder, as exemplified by studies in rats and pigs [11, 110–112]. These are greater in amplitude and less frequent than in the adult bladder, reminiscent of the pattern observed in adult animals with spinal cord injury, an example of pathophysiology recapitulating ontogeny. In the rat, where much work has been done, large bladder contractions may be evoked by mechanical stimulation of the perineum and help to empty the bladder, exemplified by maternal grooming of pups. This indicates the activity of local spinal reflexes when supraspinal pathways are not yet fully developed [113]. Their suppression upon establishment of supraspinal control is supported by the fact that GABA antagonists increase the amplitude of spontaneous contractions in developing animals [114]. Because they have been observed in isolated preparations and intact bladders it is proposed that they result from intrinsic processes in the bladder wall. Such activity is enhanced by low concentrations of muscarinic receptor agonists that initiate excitatory signals that originate in the *lamina propria* and propagate to the detrusor layer [11, 114], potentially mediated by activation of detrusor T-type Ca^{2+} channels [115]. However, the cellular pathways whereby large, infrequent spontaneous contractions in the neonatal bladder change to smaller more frequent ones in the adult bladder remain to be elucidated and have important implications to understand the origin of large contractions in the neurogenic bladder.

An increase of spontaneous activity is also recorded in ageing rats [111, 116] but not mice [117]. However, the pattern is different from that observed in neonatal bladders, consisting of numerous, short-duration events that might imply a different origin. A uniform description of alteration to bladder function with ageing is difficult to describe, as a variety of changes have been observed that may depend on the extent of ageing, as well as the experimental model. However, a number of changes to purinergic and cholinergic signalling systems have been reported in human and animal models. In particular, there is an increased dependence on purinergic signalling during nerve-mediated voiding responses and urothelial transmitter release during filling [117–119]. However, cholinergic signalling changes with age are more variable with a reported decrease [117] or increase [118, 120] of non-neuronal ACh release during filling or supporting nerve-mediated contractions. In view of the association of purinergic signalling with spontaneous activity, or overactive bladder in human detrusor, such a linkage may contribute to increased activity with ageing.

An increase of bladder afferent firing and spontaneous contractions accompanies bladder filling, a phenomenon augmented by administration of P2X receptor agonists or irritants such as cyclophosphamide into the bladder lumen [121]. The induction of spontaneous contractions by raised afferent firing could involve spinal or supraspinal reflexes. A decrease of bladder compliance would therefore be expected to increase bladder afferent firing and hence increase spontaneous activity. Ageing is associated with a spectrum of changes to bladder compliance with reports of it being decreased [122], increased [123] or unchanged [116]. This will reflect various changes that may impact on determining bladder compliance, ranging from altered central or peripheral nervous control that determines detrusor tone during filling [124, 125], or deposition of excess collagen [126] that would reduce bladder compliance. Overall, a number of factors determine how ageing impacts on the biomechanical properties of the bladder during filling, so that there is no single way spontaneous activity may be impacted (see also Sect. 5.14). An additional confounding factor when studying how ageing may impact on any biological function is the range of actual ages that are used for animal models. The life expectancy of a mouse is 2–3 years and for a rat up to 5 years [127], so that many animal models of ageing to date merely reflect middle-aged rather than the aged human for comparison.

5.13 External Influences on the Bladder and Spontaneous Activity

The urinary bladder, due its position immediately above the pelvic floor, is especially prone to external influences that affect its function, particularly in the exacerbation of spontaneous activity and the development of detrusor overactivity. For example, the bladder is prone to irritation by exposure to urinary tract infections or noxious agents, as well as damage from irradiation to treat pelvic organ malignancies which may affect spontaneous activity. Cyclophosphamide or acetic acid are examples of noxious agents often used experimentally to induce bladder pain and inflammation, as well as generate increased spontaneous activity [121, 128]. Cyclophosphamide is a cytotoxic drug with a major side effect of haemorrhagic cystitis mediated importantly through its metabolite acrolein [129]. Acrolein itself has multiple effects including urothelial damage through generation of reactive oxygen species and exposure of the deeper bladder layers to urine [130]. Acetic acid will also reduce urothelial permeability with similar consequences [131]. In consequence, cyclophosphamide or acetic acid infusion into the bladder lumen increases ATP release [132, 133], as well as inducing an overactive bladder as measured by cytometry [132]. Cyclophosphamide-induced detrusor overactivity may be reduced by blocking urothelium receptors to prokineticin 2, a chemokine-like peptide implicated in the development of inflammatory and pain responses in the bladder [128]. The important role of the mucosa has also been implicated in radiation-induced cystitis

and its regulation of bladder contractions [54]. Radiation-treatment increased detrusor contraction after application of contractile agonists such as carbachol; however, this was not observed in mucosal-intact preparations. Radiation cystitis is also associated with increased fibrosis in the bladder wall, a consequent decrease of compliance and development of spontaneous non-voiding contractions with urinary leakage. Resolution of the fibrosis by post-irradiation treatment with the hormone relaxin in rat bladder not only normalised the fibrosis but reversed the decrease of compliance and development of spontaneous non-voiding contractions [134]. Various noxious interventions will impact differently on bladder function, one of the final common pathways being the development of spontaneous contractions, but potentially by different processes. Thus, it is important to characterise the fundamental pathways altered by different interventions to able to ameliorate the consequences to lower urinary tract function by these different processes.

5.14 The Clinical Consequences of Bladder Spontaneous Activity in Health and Disease

Spontaneous contractile activity is a fundamental feature of bladder function and is reflected in recordings from the intact bladder to isolated myocytes. It occurs not just in the smooth muscle layer but also in the *lamina propria*. The physiological functions are postulated to add a resting tone to the bladder wall to enable the bladder itself to efficiently raise detrusor pressure during initiation of voiding and also to affect the gain of signal transduction to afferent nerve activation during bladder filling. Two pathological states may reflect a failure of this basic system: (i) bladder underactivity, when the increase of detrusor pressure is insufficient to completely void the contents of the bladder and (ii) detrusor overactivity when large, uncontrollable contractions during modest bladder filling leads to sensations of urgency and sometimes incontinence. However, whether changes to the processes generating normal spontaneous contractions results in pathological states remains to be answered.

Detrusor underactivity (DU) is a relatively new term to describe poor voiding performance and various publications have attempted to define a clinical picture [135, 136]. However, the clinical criteria used to define DU are currently empirical and do little to identify fundamental causes of the symptom complex. There is no evidence that DU results from contractile failure of detrusor muscle [74], but more likely is due to a replacement of muscle with extracellular matrix. This has relevance to the role of spontaneous activity in symptoms associated with DU. If the extracellular matrix is predominantly of collagen the bladder wall will be stiffer and hence a spontaneous contraction will transmit more energy to afferent transducing mechanisms and so increase a sense of urgency without a powerful contraction [137]. If the extracellular matrix is composed more of a gel-like ground substance of glycosaminoglycans and glycoproteins, then bladder compliance will increase, and transmission of forces depressed [138]. Both states have been reported in failing bladders [139] and the pathways that lead from one state or another have yet to be determined.

Detrusor overactivity has been better described (Fig. 5.2a) and occurs during filling. Again, the precise aetiology is unknown and several theories have been advanced, which need not be mutually exclusive: altered central control of the normal voiding reflex [140]; a myogenic hypothesis of increased detrusor excitability and spontaneous activity [74, 141]; enhanced spinal reflexes; greater urotheliogenic interaction within and between *lamina propria* and detrusor, for example from enhanced stretch-activated ATP release and enhanced spontaneous activity [89].

The uncertainty in characterising, by fundamental research, the extremely common condition of DO, and the recent description of DU, underlies the continuing need to interweave investigative and clinical research to explain how normal spontaneous activity can manifest itself as pathological entities.

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