The integrative physiology of the bladder

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ABSTRACT

Normal bladder function is complex, resulting from the co-operative interaction of numerous regulatory cell types, of which the interstitial cells and the peripheral neurones are particularly interesting. Collectively, these comprise the myovesical plexus, which appears to confer structural and functional characteristics on the bladder loosely akin to those of the gut. These include functional modularity, which gives rise to the potential for localised and propagating peristalsis-like movements in the bladder wall according to the prevailing physiological conditions. Localised modular activity during filling may contribute to normal generation of sensation and exaggerated modular activity may give rise to urinary urgency. Enhanced co-ordination of modular activity occurs in various models of detrusor overactivity; it leads to surges of contraction over a large part of the bladder wall, generating phasic changes in intravesical pressure. During voiding, the myovesical plexus sustains detrusor contraction at the behest of the brainstem, monitoring state of bladder fullness as it does so, as a guide to the required duration for which it has to keep up the effort. Accordingly, the bladder wall itself may house structures which render the bladder the effector level in a hierarchy of lower urinary tract regulation. Dysfunction in these vital regulatory structures is an underestimated factor in the pathophysiology of clinical bladder problems.

KEYWORDS

Bladder function – Myovesical plexus – Detrusor contraction – Lower urinary tract regulation – Clinical bladder problems

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Some years ago, a drug was available for use in patients who failed to pass urine after a catheter was removed, in the hope that it would aid return of normal voiding. The drug, bethanechol, was a logical choice in this context, because the parasympathetic nerves supplying the bladder release acetylcholine to make the detrusor muscle contract. Giving a drug that stimulates the detrusor muscle in the same way, it was thought, should increase bladder tone and so re-establish voiding. Sadly, the clinical outcome was usually disappointing, resulting in suprapubic discomfort and a stubborn persistence of urinary retention. The experience with bethanechol is illuminating, as it illustrates a failure to grasp the fundamental complexity of bladder function; the specific weakness lies in the fallacy that whole bladder function can be extrapolated from any individual cell type (in the case of bethanechol, the smooth muscle). Integrative physiology, the study of how intact tissue behaves, focuses on the cellular interactions; these appear to be fundamental to a clear understanding of normal bladder function and the pathophysiological changes underpinning clinical lower urinary tract problems.

The clinical setting

The normal bladder has storage and voiding phases, the onset of the latter being determined by the pontine

micturition centre in the brainstem. Clinical problems affecting urine storage are highly prevalent, and result in urinary urgency, frequency and urgency incontinence. They are commonly associated with detrusor overactivity (DO), which is the presence of inappropriate detrusor contractions detected during pressure cystometry while the bladder is being filled. Voiding problems also show a high prevalence, and result in a weak urinary stream and incomplete bladder emptying, the latter detectable as the presence of a post voiding residual volume (PVR). Improved understanding of the mechanisms underlying these problems is desirable, as current management options available are only effective in a proportion of cases and can carry significant risk of adverse effects.

Cellular phenotypes present in the bladder

Understanding cell interactions is a challenge, because the bladder wall, perhaps a little unexpectedly, has quite a complicated structure. Two particularly interesting cell classes are the interstitial cells (ICs) and the peripheral neurones. The existence of bladder ICs was only recently established, but they have spawned much interest, since they appear to share some of the properties of the interstitial cells of Cajal (ICCs) in the gut. Since the ICCs

appear to be the gastrointestinal pacemaker cells, the presence of similar cells in the bladder is potentially highly significant. A few groups have already demonstrated striking structural characteristics and functional potential of bladder ICs.¹⁻³ Nerve ganglia in the bladder wall and in the pelvic plexus contain multitudinous connections, and express a diverse range of putative transmitters;⁴⁻⁶ current understanding of their functional properties is limited.

Most people studying ICs and ganglia have become convinced of their likely importance to bladder function and dysfunction. Nonetheless, to understand how the bladder functions as an organ, and the potential functional contribution of these complex cell types, requires evaluation of how the cell types interact. However, there is little scientific evidence as to what the bladder does. In fact, there is a tacit assumption that it probably does not do very much, beyond the obvious functions of storage and emptying, giving the impression that the only really important regulatory structure in bladder function is the brainstem. It is assumed that the bladder is a mere slave of the CNS of no great regulatory consequence. Notwithstanding, recent work suggests that when cellular components of the bladder wall are studied as they behave *in situ*, there is an unrecognised potential for crucial contributions to physiological function, and a likely basis for clinical problems of the lower urinary tract.

The myovesical plexus

In the gut, ganglia and ICCs make up the myenteric plexuses; these, therefore, are a fair place to start when attempting to understand the similar structures in the bladder, known as the myovesical plexus by analogy. The myenteric plexuses are crucial in regulating gut peristalsis, which, broadly speaking, takes two forms. First, the segmentation contractions, where a back-and-forth squeezing mixes the gut content with the digestive enzymes. These arise because the gut wall is arranged in functional modules,⁷ which are areas capable of independent, localised contraction. After mixing is complete, the myenteric plexuses change the peristalsis to propulsive contractions, where a contraction wave propagates along the gut wall to push the contents to the next part of the bowel. Effectively, the myenteric plexuses determine the existence of the modules, and they facilitate co-ordination between modules.

In the bladder, spontaneous localised and propagating contractions can be observed, somewhat similar to gut peristalsis.⁸ This observation led to a proposal that, like the gut, the bladder might be modular – functionally rather than anatomically.⁹ The bladder might then be regarded as vaguely reminiscent of a football, in that it is made up of modules, equivalent to the patches of the football, joined in such a way as to make a spherical organ; under certain cir-

Figure 2 Localised movement in an isolated mouse bladder. Measurements of separation between two pairs of points; in one pair (above) the points periodically got closer together, in the other, separation increased at the same time as the shortenings in the neighbouring pair.

cumstances, the modules might contract independently (equivalent to segmentation), in others activity in neighbouring modules may become co-ordinated (propagating peristalsis). This similarity to the gut suggests a new interpretation of how the bladder might work, which can be summarised in the following key points:

1. The myovesical plexus, made of bladder interstitial cells and nerve ganglia, determines the functional behaviour of the bladder wall.
2. The basic functional unit is a circumscribed area of muscle, known as a module.
3. Each module can contract independently in the right circumstances.
4. Activity in neighbouring modules can be co-ordinated so that a large proportion of the bladder wall becomes synchronously active.
5. In detrusor overactivity, the modules are abnormally active and better co-ordinated.
6. Excessive localised contraction is likely to cause distortion of the bladder wall, which will enhance bladder sensations and might underlie urgency.⁸

Experimental evidence

These above concepts allow derivation of predictions, which can be tested experimentally:

1. The existence of localised and propagating movement should be observed in the bladder wall. It is comparatively straightforward to isolate the rodent bladder and maintain it in a 30-ml organ bath. Using the apparatus illustrated in Figure 1, it is possible to observe movements in the bladder wall, while simultaneously measuring

intravesical pressure. Under these conditions, localised contractions in the form of phasic twitches do indeed arise (Fig. 2);¹⁰ confirmation of their localised nature is given by the fact that neighbouring (or sometimes distant) areas elongate at the same time, meaning that effects of each twitch on intravesical pressure is slight. Once the bladder has been distended slightly, or exposed to a low concentration of a muscarinic acetylcholine agonist, bladder wall movements take the form of waves of contraction propagating over varying distances across the bladder surface.¹¹

2. Exaggerated, co-ordinated bladder wall movements should be apparent in DO; the co-ordinated activity in a substantial proportion of the bladder wall will predictably result in more considerable effects on the intravesical pressure. Examining the rat bladder after a period of outlet obstruction is a recognised animal model of DO. When the bladder is subsequently removed and placed in the organ bath, localised movements are visibly more active and more widely dispersed than in normal bladders.¹² Furthermore, following distension, each bolus of fluid elicits exaggerated co-ordination contractions across great swathes of the bladder wall in the animal model (Fig. 3).
3. The suggestion that distortion in the bladder wall might result in exaggerated sensation, and hence urgency, means that increased localised movements should be apparent in people with urgency. This obviously cannot be tested in an isolated organ. However, it is possible to correspond bladder wall movement with reported sensation using balloon-mounted intravesical electrodes in women during urodynamic studies. Symptomatic women with increased filling sensation do indeed show exaggerated localised wall movements which are more

clearly apparent than asymptomatic women,¹⁵ though the method used to test this is invasive and could have interfered with bladder behaviour.

4. Finally, the purported properties of myovesical plexus suggest they are responsible for generation of the bladder wall movements. Several lines of evidence suggest this is the case. For example, when exposed to a nitric oxide (NO) donor, the only cells in the mouse bladder showing a response by generating increased intracellular cGMP are ICs; the same NO donor powerfully inhibits autonomous bladder activity.¹⁴ Likewise, glivec, another agent capable of affecting IC function, alters spontaneous bladder activity.¹⁵

The voiding phase

The myovesical plexus is a remarkable structure, yet current understanding suggests it is down to the brainstem to determine the micturition cycle and provide the efferent drive powering the motor nerves responsible for the detrusor contraction in voiding. Nonetheless, careful consideration suggests that for the brainstem alone to drive voiding would be improbably inefficient. Because the brainstem is a long way from the bladder, signals would

have to pass back and forth along the spinal cord and through the pelvic plexus, using considerable amounts of energy. First of all, signals reporting high intravesical volume would have to come up from the bladder, eliciting the motor commands to instigate the detrusor contraction of voiding, passing back down to the periphery. Because voiding is only finished when the bladder is empty, the afferents would have to bring information about the state of bladder fullness back up to the brainstem, ensuring the contraction is sustained while urine is still in the bladder. Back-and-forth signalling, across this considerable distance, would have to be sustained until emptying is complete.

A comparable situation exists in aircraft, where the tailfin is a long way from the cockpit. In the latter, fly-by-wire technology means that when a turn is planned, the cockpit computer calculates the tailfin angle needed. It sends a signal the length of the aircraft to the tailfin servo motor with the angle required. As the servo motor moves the tailfin, sensors detect the angle of the tailfin; this is fed back to what engineers call a comparator, in the tailfin assembly. The comparator compares the actual angle with the required angle. When the actual angle reaches the required angle, the servo's job is done, and only then does a return signal go back to the cockpit computer. Thus the tailfin servo does the job of deflecting the tailfin; it knows when it has finished, thanks to the comparator, but it is subordinate to the cockpit computer, which ensures the tailfin behaves in line with safe function of the entire aircraft.

The aircraft tailfin arrangement may be analogous to the relationship between the brainstem and the myovesical plexus; the plexus may supply servo-assistance to the brainstem by driving the detrusor contraction of voiding, and doing so until the lumen is empty (Fig. 4). In this model, the pontine micturition centre sends an instruction down the spinal cord to a comparator in the myovesical plexus, in effect saying that 'desired volume is now empty'. The myovesical plexus makes all modules active in a co-ordinated manner; the detrusor contracts accordingly, and does so for as long as the actual state of bladder fullness is not equal to the desired state of emptiness.

For a servo function to be correct, it is necessary to demonstrate that the myovesical plexus is aware how full the bladder is – in other words, that the servo has a comparator. Two suggestive lines of evidence lend support to the possibility. First, the nerves which run close to the ICs in the bladder wall characteristically express transmitters typical of sensory nerves.¹⁶ Second, the response to acetylcholine in an isolated bladder is very strongly affected by how full the bladder is (Fig. 4). At low volume, the extent to which a muscarinic agonist elicits autonomous bladder activity is minimal, while at high volume the phasic activity is substantial.¹⁷

Hierarchical control of bladder function

A servo-assistance function places the bladder as the effector level in a hierarchy of regulatory structures. Functioning of the hierarchy can be envisaged by summarising possible stages in the micturition cycle. After voiding, the bladder is empty, so the level of sensory activity is minimal, and level of excitation throughout the hierarchy is low. As the bladder starts to fill, afferent activity increases; clearly, this is relayed to the brainstem, allowing the pontine micturition centre to determine progress of bladder filling. In addition, afferent collaterals feed into the myovesical plexus, in which the level of excitation increases as a result, leading to localised modular contractions, which serve to help signal the degree of bladder fullness. With further filling, these collaterals render the myovesical plexus increasingly active, as if it is gearing itself up for the task ahead. When the 'void' command finally comes from the brainstem, it instructs the comparator in the myovesical plexus that the desired state is bladder emptiness. The ICs of the myovesical plexus then drive detrusor contraction, sustaining it until the comparator reports completion of bladder emptying. Accordingly, lesions at several levels of the central and peripheral nervous system can have similar effects on lower urinary tract function.¹⁸

Clinical lower urinary tract dysfunction

In normal functioning, the myovesical plexus generates modular contractions; a small area of the bladder contracting has little effect on pressure, but the resulting distortion may contribute to generation of sensation. Structurally, the relevant structures are complex; in particular, they have a considerable number of nervous inputs characterised by a range of transmitters. Intuitively, it is quite easy to envisage such a complex structure being at risk of damage. For example, a subclass of the nervous inputs may have an inhibitory role and, should these nerves be at greater risk of damage, the effects can be predicted at a theoretical level. First, the modular activity may be enhanced, which would potentially exaggerate the distortion associated with localised contractions, leading to excessive bladder sensation, hence urinary urgency. If at the same time, the loss of inhibitory nerves allowed the modules to become better synchronised, a substantial part of the bladder wall could contract, leading to DO. The clinical experience with bethanechol alluded to above is relevant here; its use resulted in urinary urgency, rather than voiding. Experimentally, similar drugs cause a tremendous degree of localised contraction and hence extreme distortion, when applied to the isolated bladder.¹¹

During the voiding phase, the myovesical plexus sustains detrusor contraction so long as the comparator tells it

this is necessary, *i.e.* up until completion of bladder emptying. Functionally this is important, because the conditions of voiding vary ('noise' in engineering parlance). For example, in men with bladder outlet obstruction due to benign prostate enlargement, a greater amount of work has to be done by the detrusor to overcome the increased outlet resistance. However, if the myovesical plexus fails to work properly, detrusor contraction may no longer be adequately sustained, so that there will be a post void residual volume due to incomplete bladder emptying. This may explain how increasing age, which is known to lead to bladder denervation, is associated with fundamental changes in the autonomous activity of the isolated bladder.¹⁹

Conclusions

The control of the bladder is hierarchical, but the level at which bladder function is executed is within the bladder wall itself. It is the myovesical plexus which underpins the behaviour of the bladder; during filling, it generates a certain amount of localised activity, which may contribute to normal generation of sensation. Exaggerated modular activity may contribute to urinary urgency, while enhanced co-ordination of modular activity occurs in various models of DO. During voiding, it sustains detrusor contraction at the behest of the brainstem, monitoring state of bladder fullness as it does so, as a guide to the required duration for which it has to keep up the effort. The myovesical plexus is a very complex structure, with various cell types and subtypes; this complexity renders it susceptible to damage, the effects of which can be predicted according to how they influence excitability or co-ordination of modules, and the comparator.

The bladder is not an obedient slave of the CNS, but stands in its own right in the hierarchy of lower urinary tract control. Understanding of myovesical plexus function is currently rudimentary, but the theoretical benefits of studying the underlying mechanisms might encompass a large part of bladder pathophysiology.

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