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LOWER URINARY TRACT

THE ACTIVATION OF BLADDER WALLafferent
nerves

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AFFERENT MECHANISMS

The functional state of the lower urinary tract is monitored more or less continuously by
afferent nerves, which provide a sensory input in the control of the bladder and the external
urinary sphincter. The functional state of the former is regulated by the autonomic nerves to
the bladder, principally the parasympathetic (pelvic) nerves, which cause the detrusor muscle
to contract, and possibly also by the sympathetic (mainly hypogastric nerve) innervation,
which may reduce the resting tone of the smooth muscle. Continence is normally maintained
by the resistance of the urethral sphincters; the tone generated by the skeletal muscle external
sphincter is under the control of the somatic α-motoneurones running in the pudendal nerve,
and possibly some somatic afferents in the pelvic nerve of some species.

The afferents monitor the volume of the bladder and the amplitude of bladder contraction;
these two factors are important in the regulation of bladder function, the former of relevance
particularly to the physiology of the filling phase, and the latter to maintenance of voiding
contractions of the detrusor muscle. In the pelvic and hypogastric nerves of cats, various
authors have described ‘in-series’ tension receptors in the detrusor muscle with Aδ afferent
fibres (Iggo, 1955; Floyd et al. 1976; Habler, 1993) that respond to distension or contraction
of the bladder, but cannot distinguish between them; these afferents, at least those in the pelvic
erve, are believed to play a part in the regulation of the amplitude of micturition contractions
by providing a sensory input that is used as positive feedback to maintain the contraction of
the viscus (Morrison, 1995). But the absence of volume receptors in these descriptions has
always been an intellectual problem because there are some aspects of neural control that
cannot be performed just by in-series receptors. For example, the ability to remain continent
at high bladder volumes depends on sensing a large volume in the bladder, and suppressing
the micturition reflex. Current thinking states that the ‘in-series’ tension receptors are involved in
a positive feedback that facilitates and coordinates the micturition contraction, and it seems
unlikely that a single type of sensory receptor can undertake both contrasting functions
(Morrison, 1995). Indeed there is evidence that the sympathetic activity may be switched on at
high bladder volumes (Gjone, 1966; Edvardsen, 1967), and may oppose the contraction
induced by the micturition reflex.

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There are two examples of inhibitory influences on the micturition reflex. In the rat, Lumb (1986) and Chandler et al. (1994) described excitation of raphe–spinal neurones by bladder distension. These neurones are believed to inhibit bladder motility. The second example of an inhibitory pathway that would be activated by vesical distension is the nucleus reticularis pontis oralis, where Kimura et al. (1995) identified a urethral storage centre. It would be surprising if the very receptors that initiated or facilitated the micturition reflex were also responsible for inhibitory phenomena such as suppression of the desire to void or facilitation of urine storage.

This separation into volume receptors and tension receptors has not been a feature of the scientific literature until recently, because most authors have used the cat as an experimental model, and others have been particularly keen to differentiate between receptors that subserve innocuous and noxious sensations.

Sengupta & Gebhart (1994) have described bladder nociceptors in an experiment where, on average, ten afferents per animal were studied whilst undergoing repeated distensions of the bladder to 80 mmHg; a proportion of these afferents became desensitized. However, it would be desirable not to subject the bladder to repeated distensions of these pathophysiologically pressures. In studies from this laboratory that will be described below, bladder pressures never exceeded 40 mmHg. The bladder of each animal was cannulated and kept empty until the start of the recording. One unit per animal was studied. Distension was effected with saline at 37 °C. Potentially sensitizing solutions were introduced into the bladder once only per experiment, after a series of control measurements during saline distension. Great care was taken not to overdistend the bladder at any stage, and this was confirmed at the end of the experiment by the lack of trauma to the viscus, i.e. no evidence of haematuria, thus ensuring that the properties of the units could not have been altered by previous manipulations of the viscus.

The sampling procedure for isolation of the units depends on finding a filament of the dorsal roots containing afferents that respond to stimulation of the pelvic nerve at the bladder base; this procedure eliminates any sampling bias associated with searching for units using mechanical stimuli.

In the rat, conduction velocities greater than 1.3 m s⁻¹ are classified as Aδ-units (Waddell et al. 1989). Sengupta & Gebhart (1994) described a population of C fibres in the rat whose mean conduction velocity was 1.7 m s⁻¹. Clearly there is some incompatibility between the definitions. In the cat, C-afferents are generally accepted as having conduction velocities of less than 2 m s⁻¹. Some authors (e.g. Häbler et al. 1990) have described cat C fibre afferents which are normally insensitive to distension and have been called ‘silent’ afferents; some of these afferents may be sensitized by various forms of chemical inflammation of the bladder mucosa (Häbler et al. 1990).

In the rat there is now evidence that many C-afferents with conduction velocities of less than 1.3 m s⁻¹ do respond to slow distension of the viscus with physiological volumes; some of these are ‘volume’ receptors that do not respond to contractions of the bladder. Twenty-three percent of Aδ fibres and 64 % of C fibres studied during bladder contractions induced by ventral root stimulation behaved in this way; so the volume receptor afferents are mainly C fibres that discharge during a normal cycle of distension of the bladder, but with higher thresholds than those of the Aδ ‘in-series’ tension receptors.

Many C fibres which can be seen in the mucosa of the bladder contain peptides, and it may be that the receptors that do not respond to detrusor contractions may have endings in the mucosa. If these peptides were released into the interstitial fluid around these mechanosensitive endings, they would be bathed in a cocktail of endogenously active agents arising from the nerve itself and the surrounding tissue. The ability to transduce mechanical signals depends on
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Fig. 1. This diagram shows a sensory ending associated with smooth muscle and monitoring forces generated in the bladder wall. The membrane proteins in the ending include receptors, and those shown are receptors for neurokinin A (the NK-2 receptor), inflammatory mediators (such as bradykinin), and trophic agents (such as nerve growth factor).

membrane proteins such as the mechanogated channel, which is a membrane protein transported from the nucleus of the cell along an intracellular network of neurotubules. These proteins impart specific sensitivities to the nerve ending and Fig. 1 shows just some of the types of membrane protein on which the nerve ending depends to perform its function. These include not only the mechanogated channel, but also a series of pharmacological binding sites, and some neuropeptides that can be released as neurotransmitters or neuromodulators. The latter include substance P, neurokinin A (NKA) and calcitonin gene-related peptide (CGRP), while the membrane sensitivity depends on receptors for inflammatory mediators, neurochemical mediators such as NKA and nerve growth factor (NGF) (Su et al. 1986; Persson et al. 1995; Steers et al. 1991, 1996). This review will consider briefly the effects of neurokinin A and NGF.

SENSITIZATION

The relationship between volume and spike rate is not constant in many small fibre afferents, and the threshold or slope of the relationship or gain can be adjusted or modulated in various ways. Figure 2 shows the process called sensitization, in which at a given bladder volume the frequency of action potential in the afferent fibres is increased. This can be achieved either by reducing the volume at which afferent firing is initiated or by increasing the slope of the volume–frequency relationship. Consider how the brain would interpret a particular spike rate, such as that shown by the horizontal dashed line in Fig. 2. In the normal bladder that amount of neural activity might be associated with a full bladder. However, after sensitization, the subject would think that the bladder was fuller than it actually is. This will give rise to the clinical symptom of frequency.

It has been known for some time that some of these endings are sensitive to inflammatory mediators such as bradykinin (Floyd et al. 1977), and what is becoming clearer is that some membrane proteins present in the sensory endings, such as the NK-2 receptor, which respond
to the presence of chemicals such as neurokinin A in the local micro-environment of the nerve ending, can alter the transduction process, possibly through interference with second messenger systems such as inositol 1,4,5-trisphosphate (IP$_3$). Another aspect of sensitization is that the afferent neurone may become spontaneously active at rest, even when the bladder is empty.

Changes in urinary composition have been shown to influence the sensitivity of bladder afferent endings (Jiang & Morrison, 1995, 1996), possibly by acting on intraepithelial or submucosal nerve endings. The stimuli are alterations to the composition of normal constituents of urine found in extreme physiological states in man, e.g. a pH of 4.5 (the lowest urinary pH, such as might occur during a diabetic ketoacidosis), a high potassium concentration (about 300 mM) or high osmolality (2000 mosmol kg$^{-1}$, consistent with the urinary concentration during dehydration, or diabetic ketoacidosis).

Lowering urinary pH to 4.5 sensitizes pelvic afferent endings in the bladder, increasing the slope of the pressure–response curve, and inducing a resting discharge (Jiang et al. 1994). Sensitization would predispose to lowering the sensory threshold to distension and sensory urgency, and to reflex hyperactivity of the detrusor.

Raising the potassium concentration of the fluid in the bladder also sensitizes primary afferents in the pelvic nerve; about one-third of those tested were sensitized by 300 mmol K$^+$; about two-thirds were sensitized by 400 mmol K$^+$ and all were sensitized by 500 mmol K$^+$ (Jiang & Morrison, 1995). The sensitization consisted of (a) the development of a resting discharge significantly greater than that present when the bladder was empty in the control part of the experiment, (b) a reduction in the threshold of the afferents, (c) an increase in the slope of the pressure–response curve, and (d) the development of mecanosensitivity in ‘silent’ C-afferents. Similarly hyperosmolality (2000 mosmol kg$^{-1}$) achieved by increasing NaCl or glucose concentrations in the intravesical fluid also caused sensitization.

Fig. 2. The changes occurring in the spike frequency–volume relationship during sensitization include a reduction in threshold (the volume at which spike discharge increases), an increase in the slope of gain of the relationship, and the occurrence of resting discharge.

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It is known that neurogenic extravasation occurs as a result of stimulation of afferents innervating the bladder (Koltzenburg & McMahon, 1986; McMahon & Abel, 1987), and it is probable that neuropeptides present in the afferent innervation are responsible for these changes. The tachykinins substance P and neurokinin A, and CGRP appear to be released from afferent nerve terminals during stimulation of the unmyelinated afferent fibres. We have previously found that neurokinin-2 binding sites, which have a high affinity for neurokinin A, are present on afferent nerves in the bladder mucosa (Nimmo et al. 1992, 1993); we also tested the hypothesis that neurokinin A may play a part in the sensitization of mechanoreceptive afferents in the rat bladder. It is suggested that NK-2 binding sites are autoreceptors on sensory endings: Kibble & Morrison (1996a) found that the NK-2 agonist $\beta$-Ala$^8$-NKA(4–10) sensitized many mechanosensitive afferents in the rat bladder. Furthermore the NK-2 receptor antagonist SR48968 was able to block the action of the agonist, suggesting that the sensitizing effect was mediated by an NK-2 receptor mechanism (Kibble & Morrison, 1996b).

Finally, the possibility exists that part of the normal response of the afferent to distension may be mediated by the NK-2 receptor. One might hypothesize that NKA release begins once a threshold level of afferent discharge is achieved, and that sensitization is a physiological process thereafter. The hypothesis was tested by comparing the responses of afferents to distension before and after treatment with the NK-2 antagonist SR 48968: about 30% of the normal mechanoreceptor activity seen at 30 mmHg intravesical pressure can be blocked by the NK-2 antagonist (Kibble & Morrison, 1996b). This finding suggests that release of NKA and sensitization of afferents may be a physiological process; furthermore it demonstrates a potential target for modulating afferent sensitivity.

As stated previously, nerve growth factor is released from smooth muscle cells and appears to influence the sprouting of afferents in the hypertrophied bladder. It is also postulated that the hyperactivity of the hypertrophied bladder is due to an increase in afferent sensitivity that may be due to NGF. Dmitreva & McMahon (1996) have indeed demonstrated that NGF can sensitize afferents in the bladder wall. Thus NGF and NKA may both be involved in sensitization phenomena in the bladder.

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