Handbook of Experimental Pharmacology 202

Karl-Erik Andersson
Martin C. Michel
Editors

Urinary Tract

Springer

Handbook of Experimental Pharmacology

Volume 202

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Urinary Tract

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ISSN 0171-2004 e-ISSN 1865-0325
ISBN 978-3-642-16498-9 e-ISBN 978-3-642-16499-6
DOI 10.1007/978-3-642-16499-6
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2011921350

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Cover design: deblik, Berlin

Printed on acid-free paper

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This book is dedicated to the memory of the late Prof. Alison Brading who passed away while this book was being produced.

Preface

Functional disorders of the urinary tract are common and in many cases have major adverse effects on the quality of life of the afflicted patients. These include disorders of the ureters, the bladder, the urethra, the prostate and the pelvic floor. For a long time, only surgical approaches and conservative treatment could be offered for such disorders. The last two decades have seen an amazing proliferation of knowledge in the field of anatomy, physiology and pharmacology of the urinary tract. Several major new treatments have emerged from such research and are benefitting millions of patients. However, therapeutic needs remain and only a profound knowledge on the underlying tissue, cell and molecular processes is likely to provide novel treatments addressing such needs. Therefore, we are very happy that internationally leading experts have contributed to the writing of this book and we thank all of them for their efforts. Their combined insight provides a comprehensive overview of the state of knowledge regarding the pharmacology of the urinary tract. Therefore, we trust that this book will become a valuable source of information for basic and clinical researchers alike in a dynamically growing field.

Winston-Salem, NC, USA — Karl-Erik Andersson
Amsterdam, The Netherlands — Martin C. Michel
September 2010

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Overview on the Lower Urinary Tract

Christopher Chapple

Contents

Abstract This chapter overviews our current knowledge on the subject of the urinary tract, whose fundamental role is to transport urine from the kidneys and then store it at low pressure in the lower urinary tract until it can be voided at a socially convenient time. Current understanding of lower urinary tract function and dysfunction is summarized, with reference to anatomy, innervation, and function. The importance of the neurological system in the normal function of the lower urinary tract is emphasized, with a brief overview of the consequence of neural injury at different levels within the central nervous system. The role of urodynamics in the evaluation of lower urinary tract symptoms is discussed with particular reference to the currently recommended terminology advocated by the International Continence Society and The International Urogynaecological Association.

Keywords Bladder · Physiology · Pharmacology · Neuro-urology · Urodynamics

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K.-E. Andersson and M.C. Michel (eds.), *Urinary Tract*,
Handbook of Experimental Pharmacology 202,
DOI 10.1007/978-3-642-16499-6_1, © Springer-Verlag Berlin Heidelberg 2011

1 Introduction

The urinary tract consists of two mutually dependent components:

- Upper tract (kidneys and ureters)
- Lower tract (bladder and urethra)

This provides a highly sophisticated system of conduits that converts the continuous involuntary production of urine by the kidneys into the intermittent, consciously controlled voiding of urine (micturition) in appropriate circumstances.

Both kidneys continuously produce greater than 0.5 ml of urine per kg of body weight per hour (i.e. >35 ml per hour in a 70 kg man) when functioning properly and adequately hydrated. This urine empties into the kidney's collecting systems that then drain via the ureters.

The ureters function as low-pressure distensible conduits with intrinsic peristalsis, which transport urine from the kidneys to the bladder. The urine drains into the bladder at the vesico-ureteric junction (VUJ) at the lower end of each ureter. Each junction, if correctly functioning only, allows the one way flow of urine and contains a mechanism to prevent retrograde transmission of urine back into the ureters from the bladder. This serves to protect the upper tract from the high pressures encountered within the bladder during voiding and to prevent infection entering the upper tracts.

The bladder has two main functions:

- Collection and low-pressure storage of urine
- Expulsion of urine at an appropriate time and in an appropriate place

Urinary continence during bladder filling, urine storage in the bladder, and the efficiency of subsequent voiding all depend upon accurate coordination of the opposing forces of:

- Detrusor contraction
- Urethral closure pressure

Symptomatic evaluation of urinary tract dysfunction is difficult because the bladder often proves to be an "unreliable witness", not only because of subjective bias but also because there is considerable overlap between the symptoms for different disorders.

1.1 Innervation

Before considering the clinical investigation and treatment of disorders of micturition, it is first essential to consider the neural mechanisms controlling urinary tract function. Although most contemporary knowledge is based on studies with experimental animals, it is difficult and often misleading to relate the findings from such animal models directly to man (Michel and Chapple 2009; Fry et al. 2010). However, data for

humans are limited as they can only be obtained from studying clearly defined clinical syndromes and isolated spinal cord lesions (Wyndaele et al. 2010).

The pioneering neurophysiologist, Barrington, initially described five reflexes associated with micturition in the cat, to which he added a further two after further study. Two of these reflexes had reflex centres in supraspinal sites (medulla and pons) and caused strong and sustained contractions. He considered that these were essential for normal micturition because bladder contraction and urethral relaxation are not coordinated after experimentally produced high spinal transection. The remaining five reflexes appeared to be confined to the spinal cord. More recently, it has been proposed that many interrelated reflexes act upon the sacral micturition centre, exerting both excitatory and inhibitory effects (Drake et al. 2010a, b; Fowler et al. 2008).

The detrusor muscle is controlled by the autonomic nervous system and is richly innervated by three groups of nerves:

- The principal population comprises presumptive cholinergic nerves (identified by their content of the enzyme acetylcholinesterase and demonstrated by the use of electron microscopy to lie in close apposition to muscle cells) – by releasing the neurotransmitter acetylcholine, they provide the major motor control of the detrusor muscle
- The sympathetic innervation comprises a sparse distribution of noradrenergic neurones, which occur in greatest concentration towards the bladder base and are thought to be of principal importance in contracting the outlet of the bladder to facilitate storage
- The third population of nonadrenergic noncholinergic (NANC) sensorimotor nerves contains a variety of putative neurotransmitters (principally peptides), which can be identified by immunofluorescent techniques

The close juxtaposition of these neural populations allows them to interact. To facilitate this, there are potential neural links via ganglia at every level from the spinal cord to the target organs (prostate, bladder, sphincters), particularly between the parasympathetic and sympathetic nervous systems.

The spinal segments S2–S4 act via efferent parasympathetic cholinergic neurones to initiate and maintain detrusor contraction. Damage to these spinal segments abolishes the micturition reflex.

After leaving the sacral foramina, the pelvic splanchnic nerves containing the parasympathetic innervation to the bladder pass lateral to the rectum to enter the inferior hypogastric or pelvic plexus. They are joined by the hypogastric nerve containing efferent sympathetic nerve fibres originating from the spinal cord segments T10–L2. When combined, they form a plexus at the base of the bladder.

It has been suggested that:

- The pelvic nerves provide the main afferent pathway of the micturition reflex – there is now increasing evidence to suggest that the urothelium and its associated afferent innervation has an important role in the normal control of micturition

- Sympathetic neuronal pathways in the hypogastric nerves (innervating the trigone) passing to the spinothalamic tracts (bladder and urethral sensation) provide additional afferent information

The sympathetic nerves provide the main motor control for urethral and prostatic smooth musculature. The somatic pudendal nerve contributes an additional component to the striated sphincter mechanism.

1.1.1 Disruption of Normal Peripheral or Central Nervous System Control Mechanisms

A neurological classification is invaluable for counselling and can be of useful prognostic significance. Certain characteristic patterns – peripheral denervation, suprasacral spinal cord lesions, and cerebral (suprapontine) lesions – can be identified (see below).

Peripheral Denervation

The clinical picture of peripheral denervation depends upon the extent of denervation. Complete lesions decentralize the lower urinary tract, and although ganglionic activity may persist, an acontractile bladder will result with an inactive urethra. Subsequent continence is governed by the functional competence of the bladder neck mechanism. The urethra has a fixed resistance, and bladder emptying depends upon abdominal straining or manual compression. Partial lesions often result in detrusor hyperreflexia.

Suprasacral Spinal Cord Lesions

If the spinal cord is transected above the fifth lumbar segment, a "cord bladder" develops. A principal feature of this lesion is loss of coordinated detrusor–sphincter behaviour, which results in simultaneous contraction of the detrusor and urethral sphincter (detrusor–sphincter dyssynergia). Sphincter contractions are not usually prolonged throughout the period of detrusor action, so there is intermittent voiding as well as urine retention. Voiding function can be particularly ineffective in people who have lesions of the thoracolumbar cord, and in these people, low compliance is an important feature.

Cerebral (Suprapontine) Lesions

Lesions of the midbrain rarely result in disturbances of continence and micturition. It is likely that this is due to

- The bilateral representation of nuclei at this level
- The poor prognosis of patients who have extensive lesions

Damage to the basal ganglia results in a reduced threshold for the transmission of impulses through the reticulospinal tracts controlling micturition. The typical picture is therefore of involuntary bladder contractions, which occur in people who have Parkinson's disease and following cerebrovascular thrombosis or haemorrhage.

Lesions of the cerebral cortex, particularly involving the inner surface of the cerebral hemispheres or the frontal cortex, can result in incontinence. It is felt that these patients lose the centrally mediated inhibition of the pontine voiding reflex, resulting in involuntary bladder contractions and urgency incontinence.

Many urinary disorders seen in clinical practice may have a neurological cause, but a classification based on specific abnormalities and particularly the site of a neurological lesion is not practical because

- The aetiology and pathogenesis of many disorders is at present unclear
- Lesions are often difficult to locate, and once located, can be difficult to relate to the neurological signs (e.g. multiple sclerosis)
- Different lesions can produce identical functional changes in the lower urinary tract

1.2 Sphincteric Mechanisms

Apart from the obvious anatomical differences (the longer urethra and presence of a prostate gland in men), there are important differences in the histological structure, innervation, and function of the outflow tract between males and females.

1.2.1 Males

In the male, there are two important sphincteric mechanisms:

- A proximal "bladder neck mechanism"
- A urethral mechanism lying at the apex of the prostate (the "distal sphincter mechanism")

The male bladder neck is a powerful sphincter subserving both the urinary and genital roles, the latter function being of primary importance in preventing retrograde ejaculation. Ultrastructurally, in males, the bladder neck consists of two muscular layers – a powerful inner layer of muscle bundles arranged in a circular orientation containing a rich adrenergic sympathetic nerve supply and an outer layer contiguous with the detrusor muscle and receiving both a cholinergic and adrenergic innervation.

The distal sphincteric mechanism is also extremely important as evidenced by its ability to maintain continence even when the bladder neck has been

rendered totally incompetent by bladder neck incision or prostatectomy. Conversely, in patients who have a damaged distal urethral sphincter (e.g. as in pelvic fracture-associated urethral disruption), continence is maintained by the bladder neck mechanism.

The prostate is made up of smooth muscle and glandular tissue, the proportion of smooth muscle being increased in benign prostatic hyperplasia. This muscle is controlled by the sympathetic nervous system, which acts by releasing noradrenaline onto α_{1A} adrenoceptors located on prostatic smooth muscle cells.

1.2.2 Females

The female bladder neck is a far weaker structure than the male bladder neck. It is poorly defined with the muscle fibres having a mainly longitudinal orientation and the predominant innervation being cholinergic and can be incompetent, even in nulliparous young women.

Urinary continence in women usually relies upon the integrity of the intrinsic urethral sphincteric mechanism. This is composed of intrinsic urethral smooth muscle and extrinsic striated muscle components and extends throughout the proximal two-thirds of the urethra, being most developed in the middle one-third of the urethra, particularly dorsally. The efferent innervation of the striated muscle of the extrinsic component of the urethral sphincter arises predominantly from cell bodies lying in a specific area of the sacral anterior horn known as Onuf's nucleus. Various aspects of the innervation of this sphincter are controversial – not only the neural pathways involved but also the relative contribution of somatic and autonomic nerves. The limited knowledge available suggests that the pudendal nerve transmits urethral mucosal sensation.

Damage to the innervation of the urethral sphincter (particularly the pudendal nerve) by obstetric trauma predisposes to urinary stress incontinence.

1.3 Lower Urinary Tract Symptoms

The term "the bladder is an unreliable witness" was first coined with the recognition that lower urinary tract symptoms (LUTS) were not disease- or gender-specific, could be reported inaccurately by the patient, or be poorly documented by the investigator (Chapple and Roehrborn 2006). In recent years, attempts have been made to quantify the symptoms by the use of disease-specific symptom scores and quality of life measures. Well-known examples include the International Prostate Symptom Score (IPSS) for suspected prostate and the King's Health Questionnaire for incontinence-related problems. Currently, internationally acceptable questionnaires are being evaluated for incontinence (http://www.iciq.net/).

LUTS are best subdivided into *storage* of urine (also "irritative"), *voiding* (also "obstructive"), and post-micturition symptom groups (Tables 1 and 2).

Urine storage and voiding are two interrelated yet distinct phases of lower urinary tract function. The bladder and urethra possess intrinsic tone produced by the muscle and connective tissue they contain. At rest, the urethral tone keeps the walls in apposition and aids continence. During filling, the walls of the bladder exhibit receptive relaxation (i.e. the vesical lumen expands without resulting in a concomitant rise in intravesical pressure). Once a threshold level of filling has been achieved (which will depend upon circumstances and vary between individuals), increasing afferent activity will start to impinge on consciousness, resulting in awareness that the bladder is filling up. Except during infancy, in health, there is complete volitional control over these reflex pathways, and voiding will be initiated in appropriate circumstances.

1.3.1 Storage Phase

During the storage phase, the bladder is filled with urine from the ureters. For the majority of the time (greater than 99%), the lower urinary tract will be in the storage phase, whilst less than 1% of time is spent voiding. The bladder needs to accommodate to the increase in volume without an appreciable rise in bladder (intravesical) pressure. The extent to which a change in volume (V) occurs in relation to a change in intravesical pressure (P) is known as the bladder compliance (V/P).

Factors that contribute to compliance are:

- The passive elastic properties of the tissues of the bladder wall
- The intrinsic ability of smooth muscle to maintain a constant tension over a wide range of stretch or "tonus"
- The neural reflexes, which control detrusor tension during bladder filling

During bladder filling, afferent activity from stretch receptors increases and passes via the posterior roots of the sacral cord and the lateral spinothalamic tracts to the brain, thereby mediating the desire to void. Activity within the striated component of the urethral sphincter is increased, and the local spinal reflex activity enhances the activity within striated muscles of the pelvic floor and sphincter to tighten up the bladder outlet mechanisms and so augment continence.

Table 1 LUTS

Storage	Voiding	Post-micturition
• Urgency	• Hesitancy	• Feeling of incomplete emptying
• Increased daytime frequency	• Intermittency	• Post-micturition dribble
• Nocturia	• Slow stream	
• Urinary Incontinence	• Splitting or spraying	
• Altered bladder sensations	• Straining	
	• Terminal Dribble	

Table 2 Lower urinary tract symptom terminology

	Terminology	Definition	Notes
Storage symptoms	*Increased daytime frequency*	The complaint by the patient who considers that he/she voids too often by day	Term is equivalent to pollakiuria used in many countries
	Nocturia	The complaint that the patient has to wake at night one or more times to void	
	Urgency	A sudden compelling desire to pass urine, which is difficult to defer	
	Urinary incontinence (*UI*)	Any involuntary leakage of urine	
	Stress urinary incontinence (*SUI*)	Involuntary leakage on effort or exertion, or on sneezing or coughing	
	Urge(*ncy*) *urinary incontinence* (*UUI*)	Involuntary leakage accompanied by or immediately preceded by urgency	Urge urinary incontinence is a misnomer since it is urgency that is associated with this incontinence and we therefore believe it should in fact be called "urgency incontinence" and not urge incontinence
	Mixed urinary incontinence (*MUI*)	Involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing	A mixture of urgency urinary incontinence and stress urinary incontinence symptoms
	Mixed urinary symptoms	Involuntary leakage associated with exertion, effort, sneezing or coughing, but not associated with urgency	
	Enuresis	Any involuntary loss of urine	Similar to definition of urinary incontinence
	Nocturnal enuresis	Loss of urine occurring during sleep	Involuntary symptom; as opposed to "nocturia", which is a voluntary symptom
	Continuous urinary incontinence	The complaint of continuous leakage	
	Other types of urinary incontinence	May be situational	For example, incontinence during sexual intercourse, or giggle incontinence
	Normal bladder sensation	Aware of bladder filling and increasing sensation up to a strong desire to void	

Bladder sensations during storage phase	*Increased bladder sensation*	Feels an early and persistent desire to void	
	Reduced bladder sensation	Aware of bladder filling but does not feel a definite desire to void	
	Absent bladder sensation	No sensation of bladder filling or desire to void	
	Non-specific bladder sensation	No specific bladder sensation but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity	These are most frequently seen in neurological patients, particularly those with spinal cord trauma or malformations of the spinal cord
Voiding symptoms	*Slow stream*	The perception of reduced urine flow, usually compared to previous performance or in comparison to others	
	Splitting or spraying	Description of the urine stream	
	Hesitancy	Difficulty in initiating micturition, resulting in a delay in the onset of voiding after the individual is ready to pass urine	
	Intermittent stream (Intermittency)	Urine flow, which stops and starts, on one or more occasions, during micturition	
	Straining	The muscular effort used to either initiate, maintain or improve the urinary stream	
	Terminal dribble	A prolonged final part of micturition, when the flow has slowed to a trickle/dribble	Compare to post-micturition dribble
Post-micturition symptoms	*Feeling of incomplete emptying*	A feeling experienced by the individual after passing urine	
	Post-micturition dribble	The involuntary loss of urine immediately after an individual has finished passing urine, usually after leaving the toilet in men, or after rising from the toilet in women	Compare to Terminal dribble
Other symptoms	*Symptoms associated with sexual intercourse*	E.g. dyspareunia, vaginal dryness and incontinence	Should be described as fully as possible. It is helpful to define urine leakage as: during penetration, during intercourse, or at orgasm
	Symptoms associated with pelvic organ prolapse	E.g. “something coming down”, low backache and dragging sensation	May need to digitally replace the prolapse in order to defaecate or micturate

(*continued*)

Table 2 (continued)

	Terminology	Definition	Notes
	Genital and lower urinary tract pain	Pain, discomfort, and pressure may be related to bladder filling or voiding or may be felt after micturition, or even be continuous	The terms "strangury", "bladder spasm", and "dysuria" are difficult to define and of uncertain meaning and should not be used, unless a precise meaning is stated Dysuria literally means "abnormal urination". However, it is often incorrectly used to describe the stinging/burning sensation characteristic of urinary infection (UTI)
Painful bladder syndrome symptoms	*Painful bladder syndrome/ interstitial cystitis (PBS/IC)*	Subrapubic pain associated with other LUTS, usually increased frequency (but not urgency)	Diagnosed only in the absence of UTI or other obvious pathology Interstitial Cystitis is a specific diagnosis usually confirmed by typical cystoscopic and histological features. If these features are not present, then the term PBS is preferable

Important local factors facilitating bladder filling include both receptive relaxation and the passive viscoelastic properties of the bladder wall. Conditions that contribute to poor bladder compliance and detrusor overactivity include:

- Abnormal bladder morphology resulting from collagenous infiltration, hypertrophy, or altered muscle structure (e.g. obstructed bladder)
- Abnormal detrusor smooth muscle behaviour, either primary or secondary to neural dysfunction

During the storage phase, the urethra and sphincteric mechanisms should be closed, thereby maintaining a high outlet resistance and continence. Storage symptoms (nocturia, frequency, urgency, and urge incontinence – the so-called frequency urgency syndrome/overactive bladder syndrome) may arise from failure of the bladder to store urine. This may be due to a reduced anatomical capacity (shrunken bladder after surgery/radiotherapy/infections such as tuberculosis) or a reduced functional capacity resulting from abnormally increased bladder sensation (e.g. interstitial cystitis/painful bladder syndrome – beware the need to exclude carcinoma in situ – or bladder overactivity). Non-urological conditions (e.g. diabetes mellitus, diabetes insipidus, polydypsia) can also present with frequency and nocturia.

Urgency is often considered to be a pivotal symptom in the genesis of overactive bladder syndrome and is defined as a sudden compelling desire to pass urine, which is difficult to defer. It may arise as a consequence of disordered peripheral afferent function or central interpretation of afferent symptoms (Griffiths and Tadic 2008; Birder 2010; Roosen et al. 2010).

Frequency is a very troublesome symptom and is the complaint by the patient who considers that he/she voids too often by day. A frequency of voiding of more than eight times per day is usually taken to be abnormal.

Nocturia (sleep-disturbing voiding) is an interesting symptom since it may result from changes in bladder function as well as a harbinger of other physiological disorders such as cardiac failure. By the age of 65, a nocturia rate of once a night is taken to be the norm. Indeed, in many elderly patients, a reversal of the normal diurnal voiding pattern is seen, with more than 30% of the 24-h urine volume being produced overnight. In these cases, a frequency–volume chart (measuring and timing fluid intake and output and incontinence episodes for a minimum of 3 days) is essential in both investigation and treatment.

Incontinence. Urinary incontinence is the involuntary loss of urine. This can be constant or intermittent, and with (urgency) or without (stress) a detrusor contraction.

Enuresis, which represents incontinence occurring at night, can be associated with severe detrusor overactivity, but is also a classical symptom seen in association with chronic retention. Overflow incontinence is the classical cause in elderly men presenting with enuresis. The bladder has become acontractile and overfills, and empties only when the volume exceeds the anatomical capacity, under the influence of the elastic forces in the bladder wall. These patients pass small volumes of urine, frequently without any control. Chronic retention is an important condition to consider in any patient as many will present with renal impairment.

1.3.2 Voiding Phase

The bladder must cease relaxing and instead contract to expel the urine, and the urethra and sphincteric mechanisms must "open" to decrease the outlet resistance and allow passage of urine. Voiding should be efficient, and there should be minimal or no urine remaining in the bladder at the end of the voiding phase.

Micturition initiated by the cerebral cortex is likely to involve a complex series of bladder–brain stem reflexes. During voiding, the following mechanisms occur:

1. The urethral relaxation precedes detrusor contraction.
2. Simultaneous relaxation of the pelvic floor muscles occurs.
3. "Funnelling" of the bladder neck occurs to facilitate flow of urine into the proximal urethra.
4. Detrusor contraction occurs to forcefully expel urine.

The underlying mechanism includes:

- Increased activity within parasympathetic neurones results in the removal of the central inhibitory influences acting on the sacral centres
- Voiding is initiated under the influence of pontine medullary centres

There is, therefore, a parasympathetically controlled detrusor contraction associated with a corresponding relaxation of the urethra/prostate/bladder neck complex resulting from reciprocal nerve-mediated inhibition of the sympathetic nerve-mediated outflow.

In addition to these primary actions, other important secondary events are:

- Contraction of the diaphragm and anterior abdominal wall muscles
- Relaxation of the pelvic floor
- Specific behavioural changes associated with voiding

At the end of voiding, the proximal urethra is closed in a retrograde fashion, the "milkback" seen at videocystometry. Once these events have been completed, the sacral centres are re-inhibited by the cortex and the next filling cycle starts.

During the voiding phase, the reverse activity to the storage phase must occur. Voiding symptoms (poor stream, hesitancy, interruption, and straining) are either due to the loss of detrusor power or progressive outflow obstruction, which, it is presumed, may progressively lead to detrusor failure and retention.

1.3.3 Return to Storage Phase

At the end of voiding, the proximal urethra is closed in a retrograde fashion, thus milking back the urine into the bladder. This "milkback" is seen during contrast studies of the lower urinary tract when the patient is asked to stop voiding. Following this, the bladder returns to a state of relaxation.

1.4 Urodynamic Parameters

1.4.1 Normal Function

Normal function of the human lower urinary tract depends upon integrated coordination of the neural control of the bladder and outflow tract, for which an intact spinal cord is essential.

Under normal circumstances:

- Bladder capacity is approximately 500 ml and the bladder empties, leaving no residual urine
- Males void at a pressure of 40–50 cm H_2O and a maximum flow rate of 30–40 ml/s
- Females void at a pressure of 30–40 cm H_2O and a maximum flow rate of 40–50 ml/s

The difference between males and females is a consequence of the higher outflow resistance exerted by the male urethra.

1.4.2 Abnormal Function

Disordered lower urinary tract function can result from:

- Disruption of the normal peripheral or central nervous system (CNS) control mechanisms
- Disordered bladder muscle function, either primary (of unknown aetiology) or secondary to an identifiable pathology such as prostatic-mediated bladder outflow obstruction

Patients who have disordered lower urinary tract function in routine clinical practice represent a heterogeneous collection for most of whom there is no identifiable neurological abnormality. Some of these patients will have a primary neural or muscular disorder (e.g. primary idiopathic detrusor overactivity) in contrast to postobstructive secondary detrusor overactivity where the major aetiological factor is likely to be peripheral disruption of local neuromuscular function.

It is essential to use well-calibrated equipment with the technique being performed in an appropriate fashion (Schäfer et al. 2002). It is essential that standardized terminology is used when discussing LUTS and the results of urodynamic investigations, to allow accurate exchange and comparison of information for clinical and research purposes. The official terminology is as suggested by the International Continence Society (ICS) in 2002 (http://www.icsoffice.org; Abrams et al. 2002) and there has been a recent update of this for women (Haylen et al. 2010). The management of lower urinary tract dysfunction lies outside the remit of this chapter, and the interested reader is directed to recent reviews on the subject (Abrams et al. 2008, 2009, 2010; Andersson et al. 2009).

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Animal Models in Overactive Bladder Research

Brian A. Parsons and Marcus J. Drake

Contents

Abstract Overactive bladder syndrome (OAB) is a symptom-based diagnosis characterised by the presence of urinary urgency. It is highly prevalent and overlaps with the presence of bladder contractions during urine storage, which characterises the urodynamic diagnosis of detrusor overactivity. Animal models are needed to understand the pathophysiology of OAB, but the subjective nature of the symptom complex means that interpretation of the findings in animals requires caution. Because urinary urgency cannot be ascertained in animals, surrogate markers such as frequency, altered toileting areas, and non-micturition contractions have to be used instead. No model can recapitulate the subjective, objective, and related factors seen in the clinical setting. Models used include partial bladder outlet obstruction, the spontaneous

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K.-E. Andersson and M.C. Michel (eds.), *Urinary Tract*,
Handbook of Experimental Pharmacology 202,
DOI 10.1007/978-3-642-16499-6_2, © Springer-Verlag Berlin Heidelberg 2011

hypertensive rat, the hyperlipidaemic rat, various neurological insults and some gene knock-outs. Strengths and weaknesses of these models are discussed in the context of the inherent difficulties of extrapolating subjective symptoms in animals.

Keywords Adenosine triphosphate · Animal models · Detrusor overactivity · Knock-out studies · Nitric oxide · Oestrogen · Overactive bladder syndrome · Prostaglandin · Transgenic · Urgency · Uroplakin

Abbreviations

ATP	Adenosine triphosphate
BOO	Bladder outlet obstruction
BPE	Benign prostatic enlargement
COX	Cyclooxygenase enzyme
DO	Detrusor overactivity
DSD	Detrusor sphincter dyssynergia
EAE	Experimental autoimmune encephalomyelitis
EP	Family of G-protein coupled receptors
ER	Oestrogen receptor
ICS	International Continence Society
MCA	Middle cerebral artery
MPTP	Neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	Multiple sclerosis
NANC	Non-cholinergic non-adrenergic
NMDA	N-methyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
OAB	Overactive bladder syndrome
P_2X	Purinergic receptor
PD	Parkinson's disease
PGE_2	Prostaglandin E_2
SHR	Spontaneous hypertensive rat
VR-1	Vanilloid receptor type 1

1 Introduction

Overactive bladder syndrome (OAB) is a clinical diagnosis based on the presence of the symptom of urinary urgency. The subjective nature of the defining symptom is a crucial consideration since it is therefore not possible to ascertain the syndrome's presence or otherwise in an animal. The discussion below must be read with the

consideration of the inherent limitations of relying on surrogate markers to infer a situation akin to the clinical scenario. Seemingly more objective is the concept of detrusor overactivity (DO), the urodynamic observation of phasic bladder contractions during the filling phase. On the face of it, this represents a more sound foundation for developing animal models. However, such contractions appear to be normal in many animal species. Indeed in humans, contractions that would be labelled as DO during conventional urodynamics are often observed when people with normal lower urinary tracts are studied with ambulatory urodynamics. Accordingly, the use of terms such as OAB and DO in animal contexts risks misinterpretation of the underlying processes. Nonetheless, animal models are an essential adjunct in endeavouring to address the considerable clinical challenges of OAB.

2 The Problem

OAB is a symptom-based diagnosis defined by the International Continence Society (ICS) as urgency with or without urgency incontinence usually with daytime frequency and nocturia (Abrams et al. 2002a). This definition presumes that infection and other causes for the storage symptoms have been excluded. The key symptom of OAB is urgency, defined as a sudden compelling desire to void, which is difficult to defer (Abrams et al. 2002b). Urgency with at least one of the other storage symptoms listed above is essential for the diagnosis of OAB to be made. Synonyms for the condition include urgency syndrome and urgency–frequency syndrome. OAB is a diagnosis of exclusion as there is no pathognomonic criterion available to confirm the diagnosis.

It is a common condition with an estimated overall prevalence of 11.8%, comprising 10.8% of men and 12.8% of women (Irwin et al. 2006a). Although the condition affects all ages, the prevalence of OAB increases with ageing (Irwin et al. 2006a). OAB symptoms have been shown in numerous studies to have a significant negative impact on the health-related quality of life, emotional well-being and work productivity of affected individuals (Abrams et al. 2000; Irwin et al. 2006b). OAB can be socially disabling as it foments low self-esteem and embarrassment, which can in turn lead to depression and withdrawal from social activities. Increased night-time voiding may cause significant sleep pattern disturbances, resulting in fatigue. Urgency incontinence is associated with an increase in the number of falls and fractures in the elderly population (Brown et al. 2000).

DO is a urodynamic observation characterised by involuntary contractions during the filling phase of cystometry and these can be spontaneous or provoked (Abrams et al. 2002b). Although the symptom of urgency described by OAB patients often correlates with DO seen on cystometry, it must be emphasised that the two terms are not synonymous with each other. A retrospective study published in 2006 found that only 64% of patients diagnosed with OAB using the new ICS definition had DO demonstrable on urodynamics (Hashim and Abrams 2006). The study also showed that more than 30% of patients with DO did not have OAB