The basis for drug treatment of the overactive bladder

Abstract The normal bladder functions, storage and elimination of urine, are dependent on neural circuits in the brain and spinal cord that coordinate the activity of the detrusor and that of the smooth and striated muscles of the outflow region. Disturbances at different levels may cause the overactive bladder (OAB) syndrome, characterized by urge, frequency and urge incontinence. Knowledge about the mechanisms controlling both normal and abnormal micturition is mandatory for the detection of targets for pharmacological intervention. Such targets may be found in the central nervous system (CNS) or peripherally. Several CNS transmitters can modulate voiding, but few drugs with a defined CNS site of action have been demonstrated to be clinically useful. Traditionally, drugs for treatment of OAB have had a peripheral site of action. Antimuscarinics are still the gold standard, but their well-known side effects have focused interest on other modalities of treatment. Promising preclinical results have been obtained for some principles, but so far there are few positive clinical proof of concept studies available.

Key words urinary incontinence · bladder contraction · micturition reflex · neurotransmitters · muscarinic receptors · sensory mechanisms

Introduction

Failure to store urine can be due to involuntary detrusor contractions which may or may not be associated with symptoms of urge, frequency and urge incontinence, the components of the overactive bladder (OAB) syndrome. OAB is a common and underreported problem, the prevalence of which has only recently been assessed. Milsom et al. (2001) determined the population-based prevalence of chronic and debilitating symptoms of OAB, defined as the presence of chronic frequency, urgency and urge incontinence (either alone or in any combination), and presumed to be caused by involuntary detrusor contractions. They used a survey of men and women aged 40 years and above selected from the general population in France, Germany, Italy, Spain, Sweden and the United Kingdom, using a random stratified approach. They found that the overall prevalence of OAB was 16.6%, and that frequency (85%) was the most commonly reported symptom, followed by urgency (54%) and urge incontinence (36%). The prevalence of OAB symptoms increased with advancing age. Only a minority of patients were receiving treatment for their symptoms.

Knowledge about the mechanisms controlling both normal and abnormal micturition is mandatory for the detection of targets for pharmacological intervention. Below we briefly review the central and peripheral mechanisms which control bladder function and which are the basis for current pharmacological treatments. We also summarize the recommendations from the International Consensus Meeting held at the beginning of July in Paris 2001 (Andersson et al. 2001) relating to contemporary pharmacological agents.

Central nervous control

The normal micturition reflex in the adult individual is mediated by a spinobulbospinal pathway, passing

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through relay centres in the brain. Micturition occurs in response to afferent signals from the lower urinary tract, and distension of the bladder wall is considered the primary stimulus (de Groat and Yoshimura 2001; de Groat et al. 1999).

During bladder filling, once threshold tension is achieved, afferent impulses conveyed by the pelvic nerve reach centres in the CNS. It has been proposed that the afferent neurons send information to the periaqueductal grey (PAG), which in turn communicates with the pontine tegmentum, where two different regions involved in micturition control have been described (Griffiths et al. 1990). One is a dorso-medially located M-region, corresponding to Barrington’s nucleus or the pontine micturition centre (PMC). A more laterally located L-region may serve as a pontine urine storage centre (PSC), which has been suggested to suppress bladder contraction and regulate external sphincter muscle activity during urine storage. The M- and L-regions may represent separate functional systems, acting independently (Blok and Holstege 1999).

The micturition reflexes use several transmitters and transmitter systems that may be targets for drugs aimed at controlling micturition, including γ-aminobutyric acid (GABA), opioid, serotonin, noradrenaline, dopamine, or glutamatergic receptors and mechanisms (de Groat and Yoshimura 2001). Still, no drug with a clearly defined central mode of action has been developed for OAB treatment.

**Peripheral nervous control**

Bladder emptying and urine storage involve a complex pattern of efferent and afferent signalling in parasympathetic, sympathetic and somatic nerves. These nerves are parts of reflex pathways which either maintain the bladder in a relaxed state, enabling urine storage at low intravesical pressure, or which initiate micturition by relaxing the outflow region and contracting the bladder smooth muscle. Contraction of the detrusor smooth muscle and relaxation of the outflow region result from activation of parasympathetic neurons located in the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2-S4 (de Groat et al. 1993). The post-ganglionic neurons in the pelvic nerve mediate the excitatory input to the human detrusor smooth muscle by releasing acetylcholine (ACh) acting on muscarinic receptors. However, an atropine-resistant component has been demonstrated, particularly in functionally and morphologically altered human bladder tissue (see below). The pelvic nerve also conveys parasympathetic fibres to the outflow region and the urethra. These fibres exert an inhibitory effect and thereby relax the outflow region. This is mediated partly by release of nitric oxide (NO) (Andersson and Persson 1993), although other transmitters might be involved (Bridgewater et al. 1993; Hashimoto et al. 1993; Werkstrom et al. 1995).

Most of the sympathetic innervation of the bladder and urethra originates from the intermediolateral nuclei in the thoracic-lumbar region (T10-L2) of the spinal cord. Sympathetic signals are conveyed in both the hypogastric and pelvic nerves (Lincoln and Burnstock 1993). The predominant effects of the sympathetic innervation of the lower urinary tract in humans are inhibition of the parasympathetic pathways at spinal and ganglion levels, and mediation of contraction of the bladder base and the urethra. However, in several animals, the adrenergic innervation of the bladder body is believed to inactivate the contractile mechanisms in the detrusor directly (Andersson 1993).

Most of the sensory innervation of the bladder and urethra reaches the spinal cord via the pelvic nerve and dorsal root ganglia. In addition, some afferents travel in the hypogastric nerve. The sensory nerves of the striated muscle in the rhabdosphincter travel in the pudendal nerve to the sacral region of the spinal cord (Lincoln and Burnstock 1993). At least two types of afferent neurons innervate the urinary bladder. One type is mechano-sensitive, with myelinated axons, and is activated by both low (non-nociceptive) and high (nociceptive) intravesical pressure (A δ-fibres). The second type of afferents (C-fibres) do not respond to bladder distension, possess unmyelinated axons, and are activated by cold or chemical irritation of the bladder mucosa. These latter afferents are believed to have primarily nociceptive functions (de Groat et al. 1999), but to contribute to micturition in the fetus and neonatally, and also when the bladder and/or the micturition reflex is damaged in adult life.

**Pathogenesis of bladder control disorders**

Bladder storage problems can occur as a result of weakness or anatomical defects in the urethral outlet, causing stress urinary incontinence, which may account for one-third of cases. Failure to store also occurs if the bladder is overactive, and this may affect > 50% of incontinent men and 10-15% of incontinent young women. OAB can occur as a result of sensitization of afferent nerve terminals in the bladder or outlet region, changes of the bladder smooth muscle secondary to denervation, or to damage to CNS inhibitory pathways as can be seen in various neurological disorders, such as multiple sclerosis, cerebrovascular disease, Parkinson’s disease, brain tumours, and spinal cord injury. OAB may also occur in elderly patients due to changes in the brain or bladder during aging.

**Bladder contraction**

Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle. Atropine resistance, i.e. contraction