Basic Terminology

Overactive bladder (OAB) was defined by the International Continence Society (ICS) in 2002 as urinary urgency with or without incontinence, usually with increased daytime frequency and nocturia, in the absence of proven pathological or metabolic disorders (such as lower urinary tract infection, bladder cancer, benign prostatic enlargement) or other obvious pathology [1].

The definition of overactive bladder (OAB) has changed over the years, from regarding it only as a symptom to understanding it as a complicated pathophysiological syndrome. The most common definition of OAB was established in 2002 by the International Continence Society (ICS) as urinary urgency with or without incontinence, usually with increased daytime frequency and nocturia, in the absence of proven pathological or metabolic disorders (such as lower urinary tract infection, bladder cancer, benign prostatic enlargement) or other obvious pathology [1].

However, a review of the ICS 2002 terminology report, published in 2006, recommends replacing certain terms in the definition given above. The revision suggests that “urge incontinence” should be replaced with “urgency incontinence” to emphasize the fact that the incontinence is due to urgency and not an urge; and that the word “frequency” should be substituted by the term “increased daytime frequency”. Thus, the revised OAB definition is urgency with or without urgency incontinence (UI), usually with increased daytime frequency and nocturia. “Urgency” is defined as “the complaint of a sudden compelling desire to pass urine, which is difficult to defer” [2, 3]. Thus, “urgency urinary
The Epidemiology and Social Impact of Overactive Bladder

OAB is a common clinical entity, with global prevalence ranging from 3% to 43%, depending on the population studied, sex, age, and differences in the accepted definition of OAB. Generally, the frequency of OAB increases with age and is more common in women than men. Two large population-based studies conducted in Europe and the USA revealed a similar prevalence of approximately 17% of the general adult population [3]. Data from the European study indicated that the overall prevalence of OAB among the adults studied (18 years or older) was 16.6%, with slightly lower frequency in men (15.6%) than in women (17.4%) [5]. The US study was performed by the National Overactive Bladder Evaluation Program (NOBLE) and the results indicated that OAB is noted in 16% of men and 16.9% of women, and that 37% of the patients who met OAB criteria experience incontinence, while 63% do not. Dry OAB is more common in men than in women (13.6% vs. 7.6%); wet OAB is found mainly in women (9.3% vs. 2.4%) [6].

One of the latest studies estimating OAB epidemiology is the EPIC study, based on current ICS guidelines. Conducted in Canada, Germany, Italy, Sweden and the UK, it revealed a prevalence of OAB in 11.8% of the adults participants (10.8% in men and 12.8% in women). OAB was more common in men than in women after the age of 60, while under age 60 it was more common in women. Incontinence was reported in 49.2% of the women with OAB and 28.7% of the men [7].

The impact of OAB on quality of life (QoL) is considerable: OAB contributes to QoL limitations and impairment of physical activity, psychological well-being, social and sexual activity, occupational productivity and domestic habits [6, 8].

The results of the NOBLE study suggest that some risk factors can be distinguished. Age, diabetes, urinary tract infections and early menopause have been suggested [6]. Moreover, in female, abdominal hysterectomy predisposes to urinary incontinence, especially the development of urge incontinence [5]. In both sexes, obesity was reported as an important OAB risk factor [5, 8]. Most diet and lifestyle factors were not found to be associated with OAB [5].

Lower Urinary Tract Anatomy and Physiology

The lower urinary tract (LUT) is composed of the urinary bladder, the urethra, the internal and external urinary sphincter, the bladder outlet and the striated muscles of the pelvic floor. Additionally, in men, the prostate gland and rhabdosphincter make the urinary bladder neck stronger. In females, the primary additional elements contributing to normal bladder functioning are the levator ani muscles. The bladder wall contains smooth muscle fibers forming the detrusor muscle. The internal urinary sphincter consists of the bladder neck and the proximal urethra, and is surrounded by striated muscle fibers, producing the external urinary sphincter. The bladder outlet is composed of both internal and external sphincters with the additional support of the pelvic floor muscles [4].
An important element of bladder anatomy and physiology is the bladder urothelium, composed of three cell layers. The basal cell layer (inner layer) contains cuboidal cells that coat the lamina propria. The intermediate layer is built up of "club-shaped" cells, while the superficial apical layer contains hexagonal cells called umbrella cells, covered by proteins called uroplakins. In the past, the urothelium was viewed simply as a barrier between urine and the detrusor muscle. Nowadays it is regarded as a structure involved in the micturition reflex, metabolic secretion and inflammatory regulation. The suburothelial localization of afferent endings makes the urothelium a highly specialized sensory site, reacting to thermal, mechanical and chemical stimuli, and a transducer, able to release various neurotransmitters and alter afferent excitability (Table 1).

Urothelial cells release adenosine triphosphate (ATP), acetylcholine (Ach), nitric oxide (NO), prostaglandins and substance P by a calcium-dependent mechanism, similar to neurotransmitter release from nerve endings. These chemicals allow reciprocal communication with neighboring cells and with sensory nerves and other cells located in the detrusor muscle. These findings are of special interest because they offer potential pharmacological targets for future OAB medical agents [9, 10].

The LUT is innervated by a complex of afferent and efferent neurons, including both sympathetic, parasympathetic, NANC and somatic pathways. Generalizing, the sympathetic nervous system nerves originating from spinal segments T11-L3 control the inter-micturition periods, leading to urethral sphincter closure and to detrusor relaxation, enabling the bladder to fill. The parasympathetic nerves, arising from segments S2-S4, are responsible for the relaxation of urethral sphincter and simultaneous detrusor contraction during micturition. Somatic motoneurons come from spinal segments S2-S4, contributing to resting pelvic floor muscle tone and controlling the external urinary sphincter. The LUT is also supplied with afferent nerves, which are an element of the voiding reflex and organize micturition. Normal micturition occurs in response to an afferent signal from the LUT and is under the control of brain and spinal centers. A general conviction exists that pontine circuits are responsible for the shift from the filling (storage) phase to the emptying (voiding) phase. In adults, voiding is under the influence of central nervous mechanisms, and therefore also under voluntary control [4, 11].

Normal voiding is preceded by bladder filling, which entails the accommodation of an increasing volume of urine with little or no change in intravesical pressure, with a closed sphincter and the absence of involuntary bladder contractions. When the bladder is empty, its wall is folded and has high viscoelasticity, enabling it to preserve relatively low and constant pressure during the filling phase by expanding the smooth muscles and stretching the bladder. The progressive distension of the bladder wall is the primary excitation that starts the micturition reflex. There are at least two afferents innervating the bladder: myelinated, mechanosensitive Aδ neurons, activated in response to both low (non-nociceptive) and high (nociceptive) pressures; and unmyelinated C-fibers, which respond to cold, heat or chemical irritation of bladder mucosa. Aδ fibers play the main physiological role in the voiding reflex, whereas C-fibers are regarded as primary nociceptive neurons and as the main fibers responsible for controlling micturition in fetuses, neonates and in adults with LUT damage. During bladder filling, when threshold pressure is achieved, afferent impulses conducted by the pelvic nerve are sent via dorsal root ganglia (DRG) and the spinal cord to the periaqueductal gray matter (PAG). This center plays a crucial role in the voiding reflex, communicating with the suprapontine regions. The central suprapontine voiding regulatory mechanisms are poorly understood, but some positron emission tomography (PET) studies suggest that the inferior frontal gyrus and anterior cingulated gyrus are involved. These regions are parts of the limbic or emotional nervous system and are associated with the affective aspects of voiding. On the one hand, voluntary control over voiding is responsible for the motivation to empty the bladder before it becomes overfilled; but on the other hand, is also responsible for making decisions to abstain from voiding if there are not social grounds to do so.

The ascendant PAG neurons project to the pontine tegmentum, where two different regions involved in the micturition reflex are located: the dorsomedially located M region (Barrington’s nucleus), which is also named the pontine micturition center (PMC), and the more laterally located L region, which is regarded as a pontine storage center (PSC). Electrical stimulation of the PMC leads to urethral sphincter relaxation, following transient detrusor contraction; thus, the PMC organizes the normal voiding coordination of these structures. This results from the course of fibers originating from the PMC — some of them synapse in the sacral parasympathetic outflow spinal region, which provides excitatory innervations to the detrusor. Other fibers conduct stimulatory signals to the urethral sphincter synapse on the sacral Onuf spinal nucleus, causing the sphincter relaxation.

The second pontine L-region (PSC) acts as a central control to keep the individual dry be-
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<th>Activator (Activator)</th>
<th>Ion channel or receptor (Kanal jonowy lub receptor)</th>
<th>Blocker (Bloker)</th>
<th>Modulator (Modulator)</th>
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<td>Catecholamines</td>
<td>α- and β- subtypes</td>
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<td>urothelium nerve endings</td>
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<td>Cold (Niska temperatura)</td>
<td>ENaC</td>
<td>amiloride</td>
<td>aldosterone, CAP-1, Trypsin pH, Na⁺, Ca²⁺</td>
<td>urothelium nerve endings DRG</td>
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<td>urothelium nerve endings</td>
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<td>Low pH (Niskie pH)</td>
<td>ASIC</td>
<td></td>
<td>Zn²⁺, neuropeptide FF</td>
<td>urothelium nerve endings</td>
</tr>
<tr>
<td>Heat ~ 43°C (Wysoka temperatura ~ 43°C)</td>
<td>TRPV1</td>
<td></td>
<td>Na⁺, Ca²⁺, Mg²⁺, adenosine</td>
<td>urothelium nerve endings DRG detrusor myofibroblasts</td>
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<td>Low pH (Niskie pH)</td>
<td>ASIC</td>
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Table 1. Targeted receptors in the urothelium and on sensory neurons [9, 10] – cont.

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<th>Activator (Activator)</th>
<th>Ion channel or receptor (Kanal jonowy lub receptor)</th>
<th>Blocker (Bloker)</th>
<th>Modulator (Modulator)</th>
<th>Location (Umiejscowienie)</th>
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<tr>
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<td>TRPA1</td>
<td>Ca(^{2+}), voltage</td>
<td>urothelium nerve endings</td>
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<tr>
<td>Mechanical (Czynniki mechaniczne)</td>
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<td>DRG</td>
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<td>Cinnamaldehyde (Aldehyd cynamonowy)</td>
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<td>Isothiocyanate (Izotiocyjanek)</td>
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<td>Bradykinin (Bradykinina)</td>
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| Cold (Niska temperatura)                                   | TRPM8                                                | pH, Ca\(^{2+}\)   | urothelium nerve endings |
| Icilin (Syntetyczny super agonista TRPM8-icilin)           |                                                      |                  | DRG                    |

| Cold (Niska temperatura)                                   | TREN-K1                                               | scorpion toxin    | detrusor               |
| Heat (Wysoka temperatura)                                 |                                                      | arachidonic acid  | DRG                    |
| Mechanical (Czynniki mechaniczne)                          |                                                      | Na\(^{+}\) ether  |                         |
| Voltage – leak current (Czynniki elektryczne)              |                                                      | halothane         |                         |

ENaC – Epithelial Na\(^{+}\) Channel.
CAP-1 – Channel Activating Protein-1.
DRG – Dorsal Root Ganglion.
ASIC – Acid-Sensing Ion Channels.
TRPV – Transient Receptor Potential Vanilloid.
TRPA – Transient Receptor Potential Ankyrin.
TRPM – Transient Receptor Potential Melastatin.
TREK – Tandem P domain weak inwardly rectifying K\(^{+}\) channel (TWIK).
– related K\(^{+}\) channel (a subfamily of the K2P channel).
tween voiding, maintain tonic sphincter contraction during periods of urine storage and relax the detrusor (see Figure 1) [4, 11, 12].

The final activation of muscarinic receptors results in bladder contraction. There are at least three subtypes of muscarinic receptors: M1, M2 and M3. M1 receptors appear to facilitate the further release of acetylcholine. M2 and M3 types act synergistically. The activation of M2 receptors, which predominate in the bladder, leads to inhibition of detrusor relaxation by diminishing sympathetic activity. This enhances the detrusor response to M2 receptor activation, although direct partial stimulation of bladder contraction by M2 subtypes also seems possible [4, 13]. Studies by Matsui et al. [14] and Stengel et al. [15] with M2 and M3 knockout mice demonstrated that M2 receptors also play a role in contraction, but not the most important one. In M2/M3 double knockout animals, responses to muscarinic agents in vitro were eliminated, suggesting that these two receptors are involved in contraction. M3 subtypes are regarded to be essential in mediating cholinergic-induced contractions of the detrusor. It is generally believed that contraction of the detrusor smooth muscle is a consequence of the activation of M3 muscarinic receptors due to acetylcholine release from efferent endings. The results of studies concentrating on the molecular mechanisms of muscarinic receptor activation in the bladder are also ambiguous. M3 receptors act by producing inositol triphosphate (IP3) and diacylglycerol (DAG) as second messengers, while M2 receptors are thought to mediate a reduction in cAMP level (thus, the effect is the opposite of beta-adrenergic relaxation). Recent studies suggest that after the administration of muscarinic receptor agonists, other pathways may be involved: inhibition of po-

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**Fig. 1.** Storage reflexes: During bladder filling, increasing afferent activity (the dotted line; 1) occurs. There is no parasympathetic efferent drive (the bold line; 2) organizing bladder contractions. The sympathetic outflow (the double line; 3) to the urethral smooth muscle and the somatic outflow (the single continuous line; 4) to urethral and pelvic floor striated muscles are increased, keeping the outflow region closed [4, 5]. Voiding reflexes: During bladder emptying, an increased parasympathetic efferent drive occurs (the bold line; 2), organizing bladder contractions. The sympathetic outflow (the double line; 3) to the urethral smooth muscle and the somatic outflow (the single continuous line; 4) to urethral and pelvic floor striated muscles are turned off, enabling the outflow region to relax [4, 5]

**Ryc. 1.** Okres międzymikcyjny: podczas wypełniania pęcherza dochodzi do wzrostu impulsacji aferentnej (przerywana linia; 1). W tym okresie brak eferentnej impulsacji parasympatycznej (gruba linia; 2), kontrolującej skurcze pęcherza. Aktywność włókien sympatycznych mięśniówki gładkiej cewki moczowej (podwójna linia; 3) oraz włókien somatycznych unerwiających mięśnie poprzecznie prążkowane cewki i dna miednicy (cienka linia; 4) jest zwiększona, co powoduje zamknięcie drogi odpływu moczu [4, 5]. Okres mikcyjny: podczas opróżniania pęcherza występuje wzrost eferentnej impulsacji parasympatycznej (gruba linia; 2), odpowiedzialnej za skurcze pęcherza. Dochodzi do zahamowania aktywności włókien sympatycznych mięśniówki gładkiej cewki moczowej (podwójna linia; 3) oraz włókien somatycznych unerwiających mięśnie poprzecznie prążkowane cewki i dna miednicy (cienka linia; 4), co umożliwia relaksację drogi odpływu moczu [4, 5]
tassium channels or activation of calcium influx via L-type channels with subsequent activation of the Rho kinase system [13].

Additionally, spontaneous contractile activity in the bladder is observed, called “micromotions”. It was formerly believed that any bladder contractions prior to voiding are inappropriate and are indicative of bladder overactivity. Nowadays it is agreed that a “normal” bladder exhibits some spontaneous activity, but also that an exaggeration of micromotions during filling-phase contractions may be attributed to detrusor overactivity. There are still questions about which cells generate spontaneous phasic activity. Detrusor myocytes are known to be among the cells that have contractile activity. However, most studies indicate that interstitial myofibroblasts are pacemakers [13]. These cells are similar to the interstitial cells of Cajal, located in the digestive tract, which are responsible for its basic electrical rhythm, organizing motor activity. Other researchers favor the opinion that the interstitial cells in the detrusor modulate the spread of action potentials along the muscle bundles rather than being pacemakers of spontaneous activity [10]. In any case, there is no doubt that bladder micromotions are an important element in physiological voiding as well as being one of the possible elements of bladder overactivity [10, 13].

Summarizing, the efferent loop driving the normal voiding reflex includes the PAG with the suprapontine controlling centers, the M-region of the pontine micturition center, the lumbar and sacral spinal cord, the bladder and the urethra, with activation of the M3/M2 muscarinic receptors.

Theories Regarding the Pathophysiology of Overactive Bladder

The pathophysiology of OAB may be neurogenic, myogenic or – in the case of symptoms that cannot be explained – idiopathic.

The Neurogenic Theory of OAB: Disturbances of Central Mechanisms

Because the bladder is under nervous control, it is obvious that pathological changes affecting the central or peripheral nervous system can result in voiding disturbances. The mechanisms responsible for neurogenic OAB include decreased suprapontine inhibition of micturition, damage to the axonal paths in the spinal cord, a loss of peripheral inhibition or enhancement of excitatory neurotransmission in the voiding reflex. Common disorders that are associated with OAB via these disturbances include stroke, spinal cord injury, Parkinson’s disease (PD) or multiple sclerosis [8, 11].

The prevalence of post-stroke incontinence is from 57% to 83% [11, 16]. In patients with cortical lesions, urinary incontinence results from uninhibited detrusor contractions due to damage to the cerebral inhibitory centers, and does not involve detrusor-sphincter dyssynergia. According to Sakakibara et al. [16], the anteromedial frontal lobe and its descending tonic inhibitory pathways are responsible for micturition dysfunction in stroke patients. An animal model of stroke also confirmed that cortex ischemia plays a role in stroke-associated OAB: detrusor overactivity was observed in rats 30 minutes after experimental occlusion of the middle cerebral artery with subsequent putamen and cortex ischemia [17]. This pathomechanism of post-stroke OAB may be related to several neurotransmitter disturbances, including glutamate (with NMDA receptors), dopamine, GABA or nitric oxide (NO). It was found that overactivity can be reversed by NMDA receptor antagonists, selective D2 receptor blockers or GABA-ergic agents [11].

In spinal cord injury, urinary dysfunction is related to the severity and area of the spinal cord affected by the disease. OAB symptoms develop days to weeks after spinal damage, and spinal lesions above the sacral level lead to detrusor overactivity. The most important role in this pathomechanism is apparently played by capsaicin-sensitive C-fibers that can fire at low intravesical pressures. The increased mechanosensitivity of C-fibers may arise from synaptic reorganization of the dorsal root ganglion (DRG) supplying the bladder. This phenomenon is manifested by neuron enlargement and electrical instability, and a high expression of low-threshold tetrodotoxin-sensitive sodium channels [11, 18].

Voiding dysfunction is often observed in the course of Parkinson’s disease (PD). Detrusor overactivity occurs in up to 90% of patients with the later stages of this disease [11]. In men, an additional factor in OAB symptomatology may be benign prostatic hyperplasia (BPH) [11]. Urinary symptoms in PD include both storage disturbances (frequency, urgency, incontinence) and obstructive ones (hesitancy, weak urinary stream). It has been suggested that substantia nigra may be involved in an inhibitory effect on micturition [11]. Experimental administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) demonstrated that D1 receptors have an inhibitory effect on the micturition reflex. Thus, in PD, neurogenic
detrusor overactivity may be related to a lack of D1 receptor activation [19, 20].

In multiple sclerosis, voiding disturbances are mostly due to spinal lesions, and arise from demyelinating plaques of white matter, especially in the posterior and lateral columns of the cervical cord. As in PD patients, symptoms of voiding dysfunction include frequency, urgency, incontinence and poor urinary stream [11, 21].

The neurotransmitter and receptor abnormalities implicated in the central nervous system diseases mentioned above may be glutamatergic (both NMDA and AMPA), dopaminergic, cholinergic and abnormalities of the GABA system [11]. There are some studies that attach importance to serotoninergic abnormalities, because there is a link between decreased serotonin levels (depression, anxiety) and OAB occurrence [11].

Additionally, serotonin reuptake inhibitors and selective 5HT1A/5HT2 receptor agonists have been found to improve nervous control of the urethral outlet [11].

**The Neurogenic Theory of OAB: Disturbances of Peripheral Afferent Control**

In current OAB pathophysiology, a great deal of attention is devoted to afferent elements of the micturition arc. As described above, mechanical stimuli trigger myelinated Aδ fibers and transmit impulses via the sacral spinal cord to the brainstem and then to periaqueductal gray matter, terminating in the pontine micturition center. Unmyelinated C-fibers appear to be responsible for signaling irritation and noxious stimuli, and are also capable of triggering the voiding reflex.

In OAB, interruption of descending spinal pathways leads to a reorganization of afferent fibers, and the C-fibers become predominant. Sensitization of these fibers increases bladder excitability and lowers the pain threshold. This is supported by the desensitizing effect of capsaicin. This compound is neurotoxic, and when administered intravascularly, it ameliorates OAB symptoms without impairing normal micturition, proving that C-fibers are involved in bladder overactivity.

In subcutaneous administration in rats, capsaicin also increased the volume threshold for initiating voiding [22]. Resiniferatoxin is considered 1000 times more potent an agent than capsaicin, and is able to develop C-fiber desensitization in lower concentrations that do not produce nocius side effects. It has been stated that resiniferatoxin stimulates the vanillloid receptors and inhibits tachykinin release [22]. These local mechanisms seem interesting in terms of future pharmacological studies seeking agents to ameliorate OAB.

Several other factors may be related to neurogenic OAB pathomechanisms associated with disturbed afferents activity, such as bradykinin, histamine, nitric oxide (NO) or substance P (SP), vasoactive intestinal peptide (VIP), calcitonin-gene related peptide (CGRP) and other peptides. There is evidence that chronic inflammatory bladder is characterized by overexpression of nitric oxide synthase and NO release from capsaicin-sensitive afferents [22, 23]. NO is a molecule that relaxes the smooth muscles around the bladder outlet and thus contributes to the urethral pressure drops that precede involuntary bladder contraction. VIP seems to be an inhibitory agent in efferent parasympathetic pathways and – along with SP – an excitatory factor in bladder afferents. It has been discovered that the VIP concentration in overactive bladder smooth muscles is reduced when compared to a normal bladder, leading to the conclusion that a loss of the inhibitory impact of VIP may promote bladder overactivity. These findings are also promising for future therapies to ameliorate OAB [22, 23].

The role of calcium influx in unstable myocytes is also emphasized in current OAB pathophysiology. In addition to the neurotransmitter disturbances mentioned above, poor calcium ion regulation has been proposed as another potential mechanism leading to increased cells depolarization and detrusor instability. Verapamil was the first calcium channel blocker that was shown to reduce detrusor contractility and increase the intravesical pressure at which micturition is induced, although potential cardiovascular side effects limit the usage of verapamil as an OAB drug [24]. Another effective agent in calcium channels blocking is propiverine, which also has antimuscarinic properties, inhibiting bladder overactivity in rats more effectively than oxybutynin, the classic cholinolytic [25]. Agents affecting calcium influx are also expected to be introduced in future OAB treatment.

OAB may be also related to an exaggerated response to muscarinic agents. In vitro, these agents provoke a greater bladder response in comparison to normal detrusor muscle, probably suggesting denervation. Although it has not been established for all types of OAB, in some conditions associated with bladder outlet obstruction, enhanced sensitivity to cholinergic agents was found [13].

**The Myogenic Theory of OAB**

The normal bladder wall is composed of many contractile and noncontractile elements. According to some studies, structural and ultrastructural
changes in the detrusor smooth muscle may be a key factor in the development of OAB [22]. The normal bladder has high compliance during the filling phase, while an overactive one exhibits some structural changes when observed under microscope. An increased density of elastin and collagen within smooth muscle bundles has been reported as a change that may affect electrical conduction and reduce compliance and emptying. A clinical entity associated with bladder wall reconstruction and its reduced compliance is bladder outflow obstruction. In an experimental rat model of bladder outflow obstruction, detrusor muscle hypertrophy, spontaneous electrical activity, partial denervation and abnormal cell junction were observed. Obstruction has also been shown to increase spinal reflexes involving C-fibers [22]. Elbadawi et al. [26] studied structural abnormalities in geriatric patients with OAB, using electron microscopy. They found that overactive detrusor muscle contained widened intercellular spaces, an abundance of protrusion junctions and ultraclose abutments, which may result in a “chainlike linkage” of cells. This finding corresponds to the theory of abnormal electrical cell excitation. In the normal bladder, the foci of electrical activity are spread across a small number of coupled neighbouring cells. This means that, physiologically, excitatory nerve input must be delivered to a large number of smooth cells to trigger an organized bladder contraction. In OAB muscle, dysfunctional electrical coupling between smooth muscle cells enables small foci of electrical impulses to be propagated beyond their normal range. As a consequence, it can be concluded that the normal bladder is characterized by scattered contractions which appear locally, while in an overactive bladder these local activities are more prone to be global. The electrical abnormalities may be due to the distinctive structural changes mentioned above [13, 22].

**The Autonomous Bladder Theory**

There is also a relatively new hypothesis that posits that the detrusor is modular – made up of distinct separate areas of muscle. Each module is supplied by one intramural ganglion or by a node of interstitial cells called a myovesical plexus. During normal bladder functioning, autonomous electrical activity of various modules is observed, which does not lead to micturition contractions. In pathological conditions there can be a synchronization of activity between modules, which may be propagated through a network of intramural ganglia or myovesical plexuses. These changes may result in excessive excitatory input or a failure of inhibitory input, thus predisposing to bladder overreactivity. Obviously, one can classify this hypothesis as special kind of myogenic OAB theory, although it is less specific with respect to the mechanism [3, 27–29].

**A Unifying Theory: A Compromise View**

The most widely accepted theories of the pathophysiology of OAB are the neurogenic and myogenic ones. They are not mutually exclusive, and can be regarded as complementary. The basic mechanisms underlying these two concepts interact to produce the clinical manifestation of overactive bladder [22]. It remains uncertain whether it is neurogenic or myogenic disturbances that initiate involuntary detrusor activity and affect the second component. For example, smooth muscle changes may be responsible for promoting the pathological spread of electrical activity and inducing the emergence of pathological nerve pathways. This is suspected to be mediated by nerve growth factor (NGF), which is synthesized by the structurally altered bladder wall. NGF concentration was significantly higher in specimens of overactive bladders than in normal ones; however, the role of this molecule in OAB pathomechanisms is unknown so far and requires further study [30, 31]. On the other hand, neurologic changes (sensitization of peripheral afferent pathways with enhanced neuroendocrine activity of these fibers, and reduced activity of central inhibitory nerves supplying the muscles) may contribute to alternations in the sensitivity of the detrusor. Thus, determining which changes are the cause and which are a secondary consequence requires further study [22, 32].

Undoubtedly, further progress in understanding the pathophysiology of overactive bladder, with a focus on the various neurotransmitters contributing to disturbed central and peripheral innervation, is a promising area of research for future OAB pharmacotherapy.

**Conclusions**

Overactive bladder affects millions of individuals and has a negative influence on their quality of life. Neurogenic disturbances – especially those involving an afferent component – and myogenic ones play a significant role in the pathogenesis of OAB. Continued study of OAB pathomechanisms may open new therapeutic options in the near future.
References


Address for correspondence:
Łukasz Dobrek
Department of Pathophysiology
Jagiellonian University Medical College
Czysta 18
31-121 Kraków
Poland
E-mail: lukaszd@mp.pl

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