Overactive bladder syndrome (OAB) – the future of pharmacological treatment

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Abstract:
OAB is a social disease, and its frequency increases with age. Most of the currently-prescribed medications, used in the pharmacotherapy of this syndrome, have a peripheral action. They function by affecting the sensory nerves and by reducing the contractibility of the detrusor urinae muscle. However, the clinical application of such medicines is limited due to their low efficiency and intensified adverse effects. The efficacy of OAB treatment depends on the precise identification of the potential targets for pharmacotherapy. Below the authors have presented an update on the potential targets and mechanisms that could form the basis for synthesising new substances which would be effective in OAB pharmacology. Some of the compounds shown have already passed the proof-of-concept stage of development and are deemed to have the therapeutic potential to play a crucial role in the future of OAB pharmacotherapy. By describing the mechanisms of medicines’ impact on the voiding cycle, the review indicates the possibility of their use in specific groups of patients.

Key words: overactive bladder syndrome, pharmacological treatment

OAB is a social disease which substantially affects people’s quality of life. Anticholinergics remain the first-choice pharmacological treatment for OAB. However, their unsatisfactory tolerance profile and limited clinical effectiveness create the need to seek new OAB treatment options. The mechanisms of the action of compounds currently subject to clinical trials are based on neurotransmitters and specific receptors which have a vital function in the voiding reflex regulation. Their distinctive feature is increased receptor and organ specificity. Many of them have a therapeutic potential, which gives them the real possibility to shape the future of OAB pharmacotherapy. Due to the complex etiopathogenesis of the syndrome, it seems important that the new treatment methods be “tailor-made”, and have an impact on pathophysiological mechanisms which induce OAB symptoms and not only treat the symptoms by reducing the contractibility of the detrusor urinae muscle. The below-mentioned short review of the potential OAB treatment options focuses on compounds subject to preclinical and clinical trials, at the same time suggesting that it is possible to apply them to specific patient groups.

A very interesting option is the possibility to influence the dopaminergic system, which serves both as an inhibitor (through D₁ receptors) and as an activator (through D₂ receptors) on the voiding cycle. Detrusor overactivity (DO) symptoms in the course of Parkinson’s disease stem from insufficient D₁ receptor activation. In cerebral infarction, in turn, DO symptoms are caused by increased D₂-type receptor density and a decrease in D₁ receptors. Thus, the selective antagonists of D₂ receptors could be used in OAB pharmacology in patients after cerebral infarction. It seems that the stimulation of D₁-type central dopamine receptors with the simultaneous blocking of D₂ receptors can prove to be an interesting alternative in OAB pharmacology [1].

It has been indicated that the GABAergic system inhibits the voiding reflex at both the peripheral and central levels. GABA₉ receptor agonists (e.g. baclofen) are now used to treat patients with OB or DO secondary to spinal cord damage. GABA transporter inhibitors (e.g. tiagabine) are also under clinical trials. Tiagabine inhibits voiding, leading to a decrease in the micturition pressure, a decrease in the post-void residual volume, and an increase in the functional capacity of the bladder [2].

An interesting alternative to OAB pharmacotherapy might be treatment with TRPV₁ receptor antagonists. It has been proven that they block the release of ATP from urothelium, which is induced by bladder wall stretching. Also, they do not induce adverse effects typical of TRPV₁ agonists. Capsazepine happens to be an effective agent in reducing detrusor contractions induced by the administration of cyclophosphamide [3].
The compound which is currently subject to clinical trials is nociceptin – an agonist of OP₄ opioid receptors. The intravesical administration of this compound increases the functional capacity of the bladder in patients with neurogenic incontinence. It seems likely for OP₄ receptor agonists to become an interesting pharmacological option in the pharmacotherapy of the neurogenic bladder and an alternative to bladder instillation using vanilliods [4].

Much attention is given to cannabinoid receptors (CB₁, CB₂), whose presence was detected in neurons of the dorsal root. It was determined that CB₁ receptor stimulation inhibits DO induced by the intravesical administration of NGF. Clinical trials in the group of patients with multiple sclerosis and related symptoms of OAB confirmed the efficacy of treatment with the cannabis extract containing delta-9 tetrahydrocannabinol [5].

The disturbance of the HPA axis as a common element for the etiopathogenesis of OAB and depression drew scientists’ attention to CRF hypersecretion. It was found that this hormone, through the CRF₁ receptor, lowers the threshold for the afferent impulsion of the voiding reflex and increases the contraction activity of the detrusor muscle. The brain areas which are characterised by high CRF₁ density, such as Barrington’s nucleus, the prefrontal cortex and hippocampus play an important role in voiding control. Preclinical studies have confirmed that CRF has a simulative effect on micturition and that CRF₁ antagonists are effective in the reduction of DO symptoms. Therefore, the antagonists of this receptor can become an attractive option for the treatment of OAB, especially in patients with accompanying depression [6].

The presence of receptors for vitamin D₃ was detected in the lower urinary tract. Its analogues used in clinical trials appeared to have an effect on the voiding cycle through the up-regulation of L-type Ca²⁺ channels and the inhibition of Rho-kinase. Elocalcitol administered to patients with the clinical symptoms of OAB and the urodynamic diagnosis of DO resulted in a decrease in the number of incontinence episodes and an increase in voiding volumes, but had no effects on the objective symptoms of DO visible in the urodynamic test. However, it possesses a huge potential to become an alternative to antimuscarinics, especially in persons with wet OAB [7].

An extremely important role in the proper functioning of the urinary bladder is played by β₂-adrenergic receptors (β₂AR). Their agonist – mirabegron – is currently used as a second-line medication in OAB pharmacotherapy. Acting through M₂ and M₃ receptors, antimuscarinics inhibit detrusors’ contractions which are independent of the will and can lead to an increase in the post-void residual volume, whereas β₂AR stimulation causes bladder relaxation during the urine collection stage but has no impact on the voiding stage. It was confirmed that, apart from β₂AR stimulation, mirabegron also shows a slight agonistic effect on β₁AR and β₃AR. Blood pressure and heart rate increases after treatment with β₂AR are associated with reversible effects, and recede after the discontinuation of treatment, having no significant adverse effects on the cardiovascular system. Treatment with mirabegron is now contraindicated in patients with acute uncontrolled hypertension. As β₂AR agonists and ROCK inhibitors have different mechanisms of action, their joint use might possibly improve the effectiveness of OAB treatment and minimise side-effects. Polypharmacotherapy with gradual dosage reduction might improve the tolerance profile when compared to monotherapies [8].

The role of Rho-kinase in the smooth muscle contraction mechanism (including detrusor muscle contraction) is well-documented. Its metabolic pathway modifies the level of phosphorylation of light myosin chains, mainly through the inhibition of myosin phosphatase. The results of preclinical studies show that it has a key role in DO. It seems that Rho-kinase inhibitors, such as fasudil, might prove to be an effective group of medications in overactive bladder treatment. These medications will be designed to affect the urine collection stage, but they will not interfere with the bladder’s physiological functions.

P₂X₃ and P₂X₇ receptors also seem to constitute an important element in voiding control. It was found that P₂X₃ receptor blocking leads to a rise in the bladder irritability threshold. High density of those receptors was found in nociceptive IB₄ fibres. Moreover, cytotoxins which selectively destroy IB₄-positive neurons lead to a reduction in bladder overactivity induced by ATP. It therefore seems that those fibres might be an attractive target for OAB pharmacotherapy and that the medications affecting P₂X receptors might become an interesting alternative, especially in respect of persons with neuropathies, or elderly patients due to increased purinergic transmission [9].

The preclinical and clinical trials helped to identify new options for OAB pharmacotherapy. It appears that they will allow the adoption of patient-appropriate treatment based on the etiopathogenetic mechanisms which lead to the development of disease symptoms.
References


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