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Review article

Pharmacotherapy in detrusor underactivity: A new challenge for urologists and pharmacologists (from lab to clinic)

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ABSTRACT

Higher incidence of functional urinary bladder dysfunction (detrusor overactivity – DO and detrusor underactivity – DU) occurs in elderly people. Effective therapy is widely used in patients with DO, in contrast DU seems to be a serious burden for the older population due to the lack of successful treatment. The aim of the study was to review the potential pharmacological targets in DU treatment in the animal model. This review is based on systemic literature research. The Medline/Pubmed, Scopus, Embase, and Web of Science databases were searched in order to identify original and review articles, as well as editorials relating to underactive bladder, detrusor underactivity. The following Medical Subject Headings (MeSH) terms were used to ensure the sensitivity of the searches: urinary bladder, animal models, humans and therapy. 19 papers met the criteria and were included for this review. 19 papers met the criteria and were included for this review. The pathophysiology of DU and its animal models were described. Moreover, the potential pharmacological targets in DU therapy were discussed, such as bombesin receptors, prostaglandin-, ATP-, NO-, CGRP-, SP-, Dopamine-, NGF-, M2-, and agrin-dependent pathways. In conclusion, due to the lack of effective treatment strategies in DU, further research is necessary. Close cooperation between urologists and pharmacologists should be maintained for optimal research on DU pharmacotherapy.

Contents

Introduction

Higher incidence of functional urinary bladder dysfunction (detrusor overactivity – DO and detrusor underactivity – DU) occurs in elderly people. Effective therapy is widely used in

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patients with DO [1,2]. In contrast, DU seems to be a serious burden for the older population due to the lack of successful treatment. DU affects more and more patients due to the ageing population and number of comorbidities affecting urinary bladder function. Underactive bladder (UAB) is strictly linked with DU. Epidemiological data show that DU is not an uncommon disease. Urodynamic study in patients with non-neurogenic LUTS confirmed DU in about 9–48% men and 12–45% women [3]. Although these data do not contain in themselves information about whether DU is clinically significant, or is only urodynamic findings. International Continence Society (ICS) defines DU as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span [4]. Chapple et al. [5] proposed the definition of UAB as a symptom complex suggestive of DU and is usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream. On the other hand post-void residual should be considered in all cases suspected for DU. Repetitive post-void residual is a characteristic feature of DU. Etiopathogenesis of overactive bladder/detrusor overactivity (OAB/DO) is well described. Available therapeutic methods allow to achieve a good response of the patient and alleviate LUTS associated with OAB. In contrast to OAB/DO, little is still known about UAB/DU. Moreover it is postulated that long-lasting OAB due to DO may result in DU in the future (Fig. 1). In the course of OAB/DO the urinary bladder wall thickens. The alteration in the urinary bladder wall structure (muscles, connective tissue) may affect proper detrusor contractility. The aim of the study was to review the potential pharmacological targets in underactive bladder treatment in the animal model. This review is based on systemic literature research. The following databases such a Medline/Pubmed, Scopus, Embase, and Web of Science were searched in order to identify original papers, review articles, as well as editorials relating to detrusor underactivity. Additionally, we used the following Medical Subject Headings (MeSH) terms to ensure the sensitivity of the searches: urinary bladder, animal models, humans and therapy. 19 papers (2 review and 17 original) met the criteria and were included for this review. A small number of publications on DU seems to be due to the fact that DU is not fully known disease. Probably the complex ethiopathogenesis of DU make difficult to find satisfactory results worth publishing. Many studies in animal models published recently may allow research on a large scale in humans.

Pathophysiology of the detrusor underactivity (DU)

The three main theories underlying DU were defined: (1) neurogenic, (2) myogenic and (3) integrative. The neurogenic theory suggests that DU results from the damage of either peripheral innervations of lower urinary tract (afferent and/or efferent nerves) or of spinal and/or supraspinal micturition control systems. The myogenic theory describes the direct defect of urinary bladder muscles leading to diminished cells excitability and loss of intrinsic contractility of the muscle cells of the urinary bladder driving spontaneous detrusor contraction. The third promising integrative theory combine factors (*muscles*, *connective tissue*, *urothelium*, *afferent and efferent innervations*) which are responsible for the physiological generation of localized spontaneous muscle activity (micromotions – localized contractions and stretches). Lack of proper interaction of these factors can lead to DU. The most common causes of DU include diabetes mellitus, bladder outlet obstruction and ageing. In addition, other risk factors of DU have been described, such as: (1) neurogenic disorders (*e.g.* multiple sclerosis, Parkinson disease, cerebrovascular events), (2) spinal cord, cauda equina and pelvic plexus injury (*e.g.* pelvic surgery, pelvic fractures, herniated disc, pudendal nerves lesions, radical prostatectomy), (3) infective disorders affecting the nervous system (*e.g.* AIDS, syphilis, herpes zoster and herpes simplex infection, Guillain–Barre syndrome), (4) drugs (neuroleptics, Ca^{2+}-channel antagonists, *etc.*). With ageing the neurotransmitter release from the urothelium and coupling of the interstitial cells in suburothelial space with afferent nerves endings are significantly changed [6–9]. Additionally it is worth nothing that long lasting DO may lead to DU. In patients with OAB the urinary bladder wall thickens and also the urine concentration of nerve growth factor (NGF) increases. These facts indicate that during OAB the bladder components (connective tissue, muscle) may be affected, which leads to impaired detrusor activity [10].

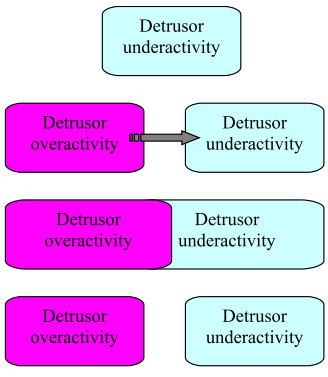

Fig. 1. Potential clinical relationship between detrusor underactivity and overactivity.

Animal models of DU

Many similarities in the physiology of urinary bladder and its neural control in rodents as in humans were observed. Therefore, animal models of DU are appropriate experimental tools for research of underlying pathomechanisms of DU development. Several animal models of DU were developed as follows: (1) diabetes bladder dysfunction model (DBD), (2) neurogenic model, (3) ageing models, (4) ischaemia model, (5) obstructive model, (6) urinary bladder overdistension model, and (7) oxidative stress model. DBD, neurogenic and ageing models are widely used. Most of the aforementioned models depend on myogenic and neurogenic mechanisms of DU development. DBD is induced by the intraperitoneal administration of streptozotocin in dose of 65 mg/kg [11]. The neurogenic model of DU is due to bilateral pelvic nerves damage. Ageing animals (over 12–24 months) present urinary bladder dysfunction similar to DU due to ischaemia, neuronal damage and sacropenia with accumulation of connective tissue [12].

Potential pharmacological targets in DU therapy

A wide range of neurotransmitters control urine storage and voiding such as acetylcholine (ACh), norepinephrine (NE), dopamine, serotonin, excitatory and inhibitory amino acids, adenosine triphosphate (ATP), nitric oxide (NO) and neuropeptides. ACh *via* detrusor muscarinic receptors remains the primary neurotransmitter affecting bladder emptying. The storage phase is mediated by NE released from sympathetic nerve endings. Moreover during voiding NO is released from parasympathetic nerve terminals within urethra providing relaxation of urethral smooth muscles [13]. The armamentarium of DU management is sparse. Still indwelling or intermittent catheterization remain recommended and a conventional option. Standard pharmacotherapy includes