Update on Basic Science Studies of Overactive Bladder

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INTRODUCTION

Overactive bladder syndrome is a common and distressing condition with a significant impact on the quality of life of many people. Antimuscarinics have been the mainstay of pharmacotherapy, however the usage of these agents is hampered by adverse effects and limited efficacy. Developing a new, more effective agent is, therefore, a goal of the research community, and thus basic science studies of overactive bladder (OAB), especially the underlying pathophysiology, have become increasingly important. Currently, there has been a shift towards targeting a novel pathway which is considered to play a role in detrusor overactivity (DO). This review is aimed at providing insight into the latest developments in basic research on OAB.

THE GAP BETWEEN BASIC STUDIES AND CLINICAL ASPECTS

The fact that OAB is a clinical and symptomatic diagnosis prevents development of reliable animal models because animals are not able to report symptoms of OAB. DO is defined as urodynamically demonstrable involuntary contractions of the detrusor during filling cystometry and is considered an equivalent of OAB in basic studies using animal models. However, not all patients with OAB have detrusor overactivity, and not all patients with detrusor overactivity have OAB. For instance, in a retrospective study of 1076 patients with OAB [1], the authors found that only 64% of the patients had DO. In addition, more than 30% of patients had no OAB but had DO on a filling cystometrogram. This can be interpreted to mean that the bladder is not a very " reliable witness", but it also shows that there are many unknowns about the bladder itself deserving further basic research. The precise causes of OAB and DO have not yet been identified. The reason is that current understanding of lower urinary tract signals based on behavioral traits is inadequate and research using the most reliable animal models is pending. Hence, basic science studies have had to focus on abnormalities of afferent signaling and the underlying mechanisms of detrusor overactivity, and then translate the scientific findings to the clinical setting through hypothetical inference.

THEORIES OF OVERACTIVE BLADDER AND DETRUSOR OVERACTIVITY

Over the last century, three main causes of OAB and DO have been proposed. The first is the myogenic theory, suggesting that detrusor smooth muscle changes are necessary for generating an involuntary detrusor contraction [2]. A local contraction taking place in any part of the detrusor can spread over the entire bladder wall and result in coordinated muscle contraction of the entire bladder. Detrusor overactivity is also associated with some characteristic changes in the ultra-structure, including increased numbers of gap junctions, which could enhance spreading of the contraction over a wider than normal part of the body of the detrusor. This has been observed in the bladder as part of aging and in bladder outlet obstruction leading to detrusor hypertrophy [3,4]. The second theory, the neurogenic theory, suggests that damage to central pathways in the brain or spinal cord or sensitization of peripheral afferent nerves in the bladder can induce primitive voiding reflexes which trigger detrusor overactivity [5]. Damage to both the central and peripheral nervous systems could arouse DO via different mechanisms, including reduction of suprapontine inhibition, expression of primitive spinal bladder reflexes, synaptic plasticity, and sensitization of peripheral afferent terminals in the bladder. The third theory is the autonomous bladder theory, which is a relatively new hypothesis that suggests the detrusor is modular [6]. Each module is a circumscribed area supplied by an individual bladder ganglia or by a node of interstitial cells which are collectively termed the myovesical plexus. This theory says that during normal bladder filling, there is autonomous activity with non-micturition contractions and phasic sensory discharge. In pathological conditions, the basic mechanism can be modified, resulting in a shift in balance leading to inappropriate augmentation of autonomous activity, and then detrusor overactivity. Moreover, all factors enhancing communication between modules can predispose to DO. To sum up, the pathophysiology of OAB/DO includes damage to afferent and efferent pathways to and from the bladder [7]. The true etiology of OAB/DO may be different in different individuals and may consist of one or more of the above theories and probably other mechanisms which are yet to be elucidated.

THE ROLE OF THE UROTHELIUM AND SUBUROTHELIUM AND THE MECHANOSENSORY BASIS IN OVERACTIVE BLADDER

Since the advent of the 21st century, there have been many basic science studies of OAB focusing on the role of the urothelium and suburothelium and the mechanosensory mechanism, because the muscarinic receptors only can not fully provide a significant contribution in normal bladder contraction. The urothelium is now not thought to be just an inert lining. Urothelium and suburothelial tisuues have been found to be the site of action of various transmitters and play a potential mechanosensory role in peripheral control mechanisms of bladder activity. For example, a substance called urothelium-derived

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inhibitory factor, which is released from the urothelium by muscarinic or histamine receptor stimulation, can inhibit detrusor contractions in the pig and human bladder [8-10]. In addition, in the presence of ATP released by the urothelium in response to stretch, suburothelial interstitial cells may contribute to a modifiable sensory feedback mechanism [11].

Over the last few years, it has been realized that suburothelial nerves, interstitial cells, neurotransmitters and receptors may play a more important role than previously recognized in the pathogenesis of OAB/DO. Following the current direction of basic research, we are going to provide an update on this subject, which may lead to new approaches to the treatment of OAB [12].

UPDATE ON MUSCARINIC RECEPTORS

M2 and M3 receptors are the main subtypes found in the bladder. The M2 receptors predominate in number, while the M3 receptors directly play a key role in mediating detrusor contraction. The M2 receptor is traditionally thought to play a minor role in normal bladder contraction via inhibition of detrusor relaxation. However, changes in the function and expression of M2 receptors have been implicated in the pathogenesis of neurogenic bladder dysfunction both in early animal studies and studies using human tissues [13,14]. Nonetheless, a 2007 study revealed that contractions of bladders from patients with idiopathic detrusor overactivity(IDO) and NDO were mediated exclusively by M3 receptors [15]. The role of M2 receptors in human disease has yet to be clarified.

The current focus has shifted to the muscarinic receptors in the urothelium. In 2000, it was found out that stimulation of these urothelial muscarinic receptors causes the release of urothelium-derived inhibitory factor which can regulate detrusor contraction [8]. Another study found that M2-mediated contractions in normal bladders from organ transplant donors were found to be associated with an increased density of urothelial muscarinic receptors, implicating a possible role of the urothelium in controlling signal transduction of M2-mediated contractions [16].

Similarly, a study disclosed that spontaneous activity in the whole rat bladder originates from the urothelium and suburothelium following stretch and may be due to urothelial acetycholine release, implicating the role of urothelial muscarinic receptors in OAB syndrome [17]. In the diabetic rat, bladder M2 receptor mRNA and protein were increased in both the urothelium and detrusor muscle, suggesting motor and sensory mechanisms [18]. In another study, increased immunostaining for M2 and M3 receptors in suburothelial myoblast-like cells from patients with IDO and painful bladder syndrome was found to correlate with clinical scores of urgency [19], supporting the idea of a sensory basis for the pathophysiology of OAB.

Based on recent research, a putative sensory mode of action for antimuscarinics seems to be emerging and prevailing. At least part of the therapeutic effect could be through modulation of sensory pathways. One current interesting question is whether antimuscarinic drugs have motor or sensory actions in DO/OAB [20].

UPDATE ON ALPHA-1 ADRENOCEPTORS

Previously, α1-antagonist effects on the prostate were thought to be mediated via α1A-adrenoceptors and effects on storage symptoms mediated through α1D [21]. In a rat model of bladder outlet obstruction, tamsulosin has recently been shown to improve both storage and emptying symptoms [22]. However, a selective α1A-antagonist (KMD-3213) could decrease DO in a rat model of benign prostatic hyperplasia, suggesting that DO appears to be mediated via the α1A-adrenoceptor in this model [23]. Therefore the α1-adrenoceptor subtypes involved in OAB/DO remain to be clarified.

It is evident that α1-antagonists seem to influence bladder storage symptoms through mechanisms other than their effects on the prostate. It was postulated that these agents act on sensory neurons in the bladder by a rat model in a study investigating the role and location of α1-adrenoceptors in mediating neurogenic inflammatory responses [24]. These receptors were found on sensory neurons, and upon activation were involved in the release of substance P and in conveying signals of irritative responses.

A further study supporting a sensory mechanism of action of tamsulosin also showed that it has an inhibitory effect on C-fiber urethral afferents, improving bladder storage function in rats [25]. This may partly explain why these agents can exert benefits on storage symptoms in the lower urinary tract. However, we should be cautious about extrapolating these data to humans because of species differences in α1-adrenoceptor subtype and function.

UPDATE ON TACHYKININS

Tachykinins belong to a family of peptides, consisting of substance P, neurokinin A, and neurokinin B. They are found in both the central and peripheral nervous systems. Tachykinins are released from capsaicin-sensitive afferent nerves in the bladder and are involved in the sensory part of the micturition cycle. They are also found to have some local effects in the bladder wall including facilitation of neurotransmitter release, neurogenic inflammation, and smooth muscle contraction [26].

Increased afferent nerve activity may play a partial role in the pathophysiology of OAB/DO. In the human, bladder neurokinin-1 (NK1) receptors have been found on the vascular endothelium in the detrusor and suburothelium, while neurokinin-2 (NK2) receptors have been found in the detrusor muscle [27].

A 2006 study found impaired neurokinin-mediated in-vitro responses in bladders from IDO but not NDO patients [28]. These contradictory results have raised doubt s about the feasibility of tachykinin receptor antagonists in the treatment of OAB/DO and have implied that targeting the detrusor itself may not be the best choice. On the contrary, NK1 found in the suburothelium may highlight a brand-new therapeutic approach which deserves monitoring in the near future.

UPDATE ON VALLINOIDS

The transient receptor potential (TRP) family of nonselective cation channels has long been noted to play an important role in many physiological processes. The vallinoid receptor TRPV1 is found in the suburothelial sensory nerves and urothelium of the bladder. It has recently been related to the pathophysiology of OAB/DO. TRPV1 expression was increased in the trigone mucosa of women with sensory urgency, but this phenomenon was not observed in the bladder body or bladders of women with IDO [29], implicating the importance of targeting the urothelium in the investigation of the pathogenesis of and

therapeutic approaches for OAB/DO.

Recently, resiniferatixin (agonist of TRPV1) has been shown to have novel effects on autonomous contractile activity in the rat bladder independent of its effects on the afferent pathway. This may contribute to the beneficial effects of this agent in OAB/DO [30].

A new vallinoid receptor in bladder sensory neurons, TRPA1, was found to be involved in normal contraction of the rat bladder through sensory fiber stimulation. It may offer an additional new target for the treatment of OAB/DO [31].

UPDATE ON POTASSIUM CHANNELS

Potassium channels are essential in the regulation of cellular excitability. Efflux through these channels results in decreased influx of calcium, thus relaxing the detrusor muscle. Expression of K_{ATP}, BK_{CA}, and SK potassium channels has been found in human, pig, rat, and mouse bladders. Potassium channel openers have also been demonstrated to inhibit detrusor contractility with evidence from in-vitro studies and animal models [32].

Given that first-generation K_{ATP} openers were unsuccessful in the treatment of OAB/DO due to lack of bladder selectivity, several new "uroselective" second-generation compounds have been developed. Although researchers have not yet proved their clinical efficacy, potassium channel openers are worthy of further basic studies as therapeutic targets in the treatment of OAB.

UPDATE ON BETA-ADRENOCEPTORS

Beta-adrenoceptors are found in the body of the bladder and can mediate detrusor relaxation to noradrenaline that is released from the sympathetic nerve system. The distribution of beta-adrenoceptor subtypes in the bladder is species dependent. The β3-adrenoceptor subtype was found out to be predominant in pig and human bladders [33]. An in-vitro study comparing the effects of β-agonists on human detrusor muscle confirmed that β3-adrenoceptor agonists play a major role in mediating relaxation of the human detrusor [34].

The target of β3 agonists has long been considered to be the detrusor muscle. However, a putative role was suggested for urothelial beta-adrenoceptors in the modulation of bladder function of the rat. Stimulating these receptors induces release of nitric oxide modulating the activity of afferent nerves [35].

In 2007, an animal model using a pig bladder was designed to investigate the mechanism of action of beta-adrenoceptor agonists. The authors found that β-agonists can induce the release of a urothelium-derived inhibitory factor from the urothelium which is not nitric oxide, but can inhibit detrusor muscle contraction [36]. Therefore the exact role of these beta-receptors requires further research, but they may offer a novel target for beta-adrenoceptor agonists.

CONCLUSIONS

Based on recent advances in the basic science of OAB syndrome, it is clear that the control mechanism of bladder functioning is much more complex than previously recognized. The urothelium and suburothelial tissues are currently the putative target for development of novel treatments for patients with OAB/DO. In addition, the concept of a variety of neurotransmitters working together in the bladder and changes in mainstream basic science studies of the mechanosensory pathways have led to anticipation of an exciting new era.

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