Selective β_3-Adrenoceptor Agonists for the Treatment of Overactive Bladder

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Purpose: The bladder effects of isoprenaline, and selective β_1 and β_2-adrenoceptor agonists reported in early studies suggest that bladder β-adrenoceptors are atypical. Since there is a lack of alternatives to antimuscarinics in the treatment of overactive bladder symptoms, there has been an intensive search for new drug targets. Discovery of the β_3-adrenoceptor with high expression in the bladder suggested that this receptor, which mediates detrusor relaxation, could be a target for overactive bladder symptoms.

Materials and Methods: An overview of the published literature on β-adrenoceptor and the bladder was performed using MEDLINE®. The United States Food and Drug Administration website, clinicaltrials.gov and controlled-trials.com online trial registries were searched for English language articles containing the terms β_3-adrenoceptors and β_3-adrenoceptor agonists. In addition, abstracts from recent international scientific meetings were searched for randomized, controlled trials of β_3-adrenoceptor agonists.

Results: Stimulation of β_3-adrenoceptors relaxes detrusor smooth muscle, decreases afferent signaling from the bladder, improves bladder compliance upon filling and increases bladder capacity. Randomized, controlled trials show that the selective β_3-adrenoceptor agonist mirabegron, for which most information is available and which is approved in Japan, the United States and Europe, decreases the number of micturitions and incontinence episodes in a 24-hour period compared with placebo. The most common adverse effects recorded are dry mouth (placebo level) and gastrointestinal disturbances, rated as mild to moderate. Small increases in mean heart rate (1 beat per minute) and blood pressure (1 mm Hg) were noted in patients with overactive bladder.

Conclusions: Available information suggests that β_3-adrenoceptor agonists may be a promising alternative to antimuscarinics in the treatment of overactive bladder. However, further clinical experience outside clinical trials and information on long-term use in terms of efficacy, safety and tolerability are warranted to optimally characterize the position of β_3-adrenoceptor agonists in the treatment algorithm for overactive bladder.

Key Words: urinary bladder, overactive; muscle, smooth; receptors, adrenergic; mirabegron; solabegron

Abbreviations and Acronyms

AR = adrenoceptor
DO = detrusor overactivity
OAB = overactive bladder

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In 1948 the existence of 2 broad subtypes of ARs (α-ARs and β-ARs) was first reported.[1] Two subtypes of β-ARs (β_1 and β_2) were identified and characterized in the late 1960s,[2] while in 1989 a third (β_3) was isolated and

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cloned.[3] β_3-ARs are widely distributed in the body, including adipose tissue, the heart and vascular system, and the bladder, although distribution is highly species dependent.[4,5] In the isolated human bladder nonsubtype selective β-AR agonists such as isoprenaline have a pronounced inhibitory effect and administering such drugs can increase bladder capacity in humans.[6] Early functional studies in the bladders of cats and humans suggested that such effects may be mediated by an atypical β-AR since β-ARs have functional characteristics typical of neither β_1 nor β_2-AR.[7,8] Thus, effects could be blocked by propranolol (nonsubtype selective) but not by practolol (β_1), metoprolol (β_1) or butoxamine (β_2).

Despite these functional data, it was suggested based on receptor binding studies using subtype selective ligands that human detrusor β-ARs are primarily of the β_2 subtype.[6] Favorable effects in patients with DO were reported in open studies with selective β_2-AR agonists such as terbutaline.[9] However, further series did not show that nonsubtype or β_2-AR selective agonists represent an effective therapeutic principle for OAB.[10]

All 3 β-AR subtypes (β_1, β_2 and β_3) were identified in the detrusor of most species, including humans.[11] In addition, human urothelium contains the 3 receptor subtypes.[12] Real-time reverse transcription-polymerase chain reaction revealed predominant expression of β_3-AR mRNA in the human detrusor muscle.[11,13] As pointed out by Frazier et al, studies at the protein level have been difficult to interpret because no available radioligand is suited to detect β_3-ARs.[14] However, the preclinical functional evidence for an important role of β_3-ARs in normal and neurogenic bladders is convincing.[15] The human detrusor also contains β_2-ARs and most probably the 2 receptors are involved in the physiological detrusor effects (relaxation) of noradrenaline.[11]

RATIONALE FOR USING SELECTIVE β_3-AR AGONISTS FOR OAB

Several factors may contribute to OAB, whether defined based on symptoms (OAB syndrome) or urodynamics (DO). Various theories were put forward and previously discussed in detail.[16] OAB is a filling disorder and recent research focused on afferent bladder function. Two signaling pathways (myogenic and urothelial) were defined by which afferent information is generated and conveyed to the central nervous system (figs. 1 and 2).[17]

It is well established that β-AR stimulation has relaxant effects on the detrusor muscle in terms of basal tone or when contracted by KCl or various agonists.[15] However, 2 types of detrusor contraction can be observed. One type is the voiding contraction, which is a well coordinated bladder contraction caused by the release of acetylcholine and other contractant transmitters, eg adenosine triphosphate, from cholinergic nerves. This contraction requires parasympathetic output from the sacral spinal cord. The other type of contraction is spontaneous (autonomous) contractile activity, which occurs during bladder filling and was demonstrated in vitro and in vivo.[18] Preclinical and clinical studies showed that β_3-AR agonists have no significant negative effect on voiding contraction,[15] suggesting a more limited potential for urinary retention.

The normal stimulus for activating the micturition reflex is considered to be bladder distention, which initiates activity in in-series coupled, low threshold mechanoreceptive (Aδ) afferents.[19] It is obvious that if this response to distention is decreased by the detrusor muscle being relaxed and more compliant, the afferent activity needed to initiate micturition will be delayed and bladder capacity will be increased. Such an effect may be achieved by stimulating β_3-ARs on the detrusor muscle. There are reasons to believe that the spontaneous contractile, phasic activity of detrusor smooth muscle during filling can create tone in the detrusor muscle and also generate afferent input (afferent noise), contributing to OAB/DO. In fact, Aizawa et al noted in rats that the β_3-AR agonist CL316,243 could inhibit filling induced activity not only in mechanosensitive Aδ fibers but also in C-fiber primary bladder afferents, provided that these fibers were stimulated by prostaglandin E_2.[20] A more recent study by the same group confirmed similar findings for mirabegron.[21] β_3-AR agonists showed a pronounced effect on spontaneous contractile activity in the detrusor muscle in vitro (fig. 3),[22] which may be an important basis for their clinical effects.

Changes in urothelial receptor function and neurotransmitter release may lead to changes in bladder contraction.[23,24] The urothelium interacts closely with underlying structures, eg interstitial cells and afferent nerves, which appear to work together as a functional unit.[23,24] The detrusor muscle, urothelium, interstitial cells and afferent nerves contain β_3-ARs,[12,25,26] which may be targeted and, when stimulated, may contribute to the effects of β_3-AR agonists.

The possible role of urothelial β_3-ARs in bladder relaxation was investigated by several groups.[12,25] Murakami et al found that the presence of urothelium in human bladder strips caused a parallel right shift of the concentration-response curve to isoprenaline.[25] They suggested that urothelial β_3-AR stimulation could induce the release of a urothelium derived factor that inhibited the β_3-AR agonist induced relaxation of detrusor smooth muscle. However, the extent to which a urothelial