available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Voiding Dysfunction

Antimuscarinic Mechanisms and the Overactive Detrusor: An Update

Karl-Erik Andersson *

Wake Forest Institute for Regenerative Medicine, Wake Forest University Medical School, Medical Center Boulevard, Winston Salem, NC 27157, USA

Article info

Article history:
Accepted November 30, 2010
Published online ahead of print on December 8, 2010

Keywords:
Acetylcholine release
Muscarinic receptors
Urine storage
Urothelium
Overactive bladder (OAB) syndrome

Abstract

Context: Antimuscarinics are the drugs of choice for the treatment of detrusor overactivity (DO) and overactive bladder (OAB) syndrome. However, the mechanisms for their beneficial effects have not yet been definitely established.
Objective: Literature available on the pathophysiologic aspects of storage symptoms and of antimuscarinic actions on the bladder was reviewed.
Evidence acquisition: Medline was searched for the period ending October 2010 and included studies on human and animal tissues and animal models. Clinical studies exploring mechanisms involved in the effects of antimuscarinics were included. Searches were limited to the English language.
Evidence synthesis: Evidence for release of acetylcholine (ACh) from non-neuronal as well as neuronal sources during bladder filling has been demonstrated in isolated animal bladders as well as the human bladder. Urothelially derived ACh, probably via release of adenosine triphosphate, may stimulate afferent activity (“afferent noise”) from the bladder contributing to OAB and DO. Afferent noise may also be generated by local ACh release within the detrusor muscle. This afferent activity can be inhibited by antimuscarinics at the low concentrations obtained with doses recommended for clinical use in OAB/DO. Within this therapeutic window, antimuscarinics may decrease OAB symptoms and DO without affecting the voiding contraction. Changes in muscarinic receptor functions have been demonstrated with aging and in different disorders associated with OAB/DO.
Conclusions: ACh, derived from non-neuronal as well as neuronal sources and during bladder filling, directly or indirectly stimulates afferent activity from the bladder, contributing to OAB and DO. By inhibiting this effect, antimuscarinics may decrease OAB symptoms and DO without affecting the voiding contraction. Even if changes in muscarinic receptor functions may occur with aging and in different disorders associated with OAB/DO, such changes have not been shown convincingly to modify the beneficial effect of antimuscarinics in OAB/DO.

* Tel. +1 336 713 1195; Fax: +1 336 713 7290.
E-mail address: Karl-Erik.Andersson@med.lu.se.

0302-2838/$ – see back matter doi:10.1016/j.eururo.2010.11.040

1. Introduction

Antimuscarinics are still the first-line pharmacologic treatment of overactive bladder (OAB) syndrome and detrusor overactivity (DO) [1]. The classical view of their mode of action is that in OAB/DO, the drugs act by competitively blocking the muscarinic receptors on the detrusor muscle, which are stimulated by acetylcholine (ACh), released from activated cholinergic (parasympathetic) nerves. They thereby decrease the ability of the bladder to contract [2]. However, the detrusor contracts in different ways: (1) During filling, it shows "spontaneous contractions" that are the result of the intrinsic (myogenic) activity of the myocyte or of small units of smooth muscle cells, and (2) during voiding, there is a coordinated contraction of all the muscle units. This coordination is produced by the parasympathetic outflow from the spinal cord via cholinergic nerve terminals reaching each of the units [3]. The nerves may act in concert with the interstitial cells within the detrusor. This coordinated contraction empties the bladder, and if it is reduced, the ability to empty will be impaired, eventually leading to urinary retention.

Because antimuscarinic drugs act mainly during the storage phase, increasing bladder capacity and decreasing urgency [4], there must be a release of ACh somewhere in the bladder during this phase. Clinically used antimuscarinics are competitive antagonists, so the massive release of ACh from neurons initiating the micturition contraction overcomes most of the effects of the drugs, which are present only in low concentrations with recommended doses. At high doses, the antimuscarinics influence the voiding contraction, eventually leading to urinary retention. However, with clinically recommended doses, this risk seems to be low, even in the presence of outflow obstruction [5].

Our knowledge about the muscarinic receptor mechanisms in the bladder has increased during the last decade [6,7]. However, questions remain to be answered: (1) Which structures in the bladder contain muscarinic receptors, the blockade of which can contribute to the beneficial effects of antimuscarinics in the treatment of OAB/DO? (2) In which mechanisms for initiation of symptoms and micturition reflex activation are antimuscarinics involved? (3) Are there changes in the muscarinic receptor functions in OAB/DO and in disorders where storage symptoms are common that can influence the response to antimuscarinics?

In the present review these questions are discussed with a focus on recent advances in the field and on the impact these advances have had on the pharmacologic management of OAB/DO.

2. Evidence acquisition

Data for this review were identified by searches of PubMed for the period ending October 2010 and references from relevant articles. Numerous articles were also identified through searches of the extensive files of the author. The search terms *muscarinic receptors*, *overactive bladder*, and *antimuscarinics* were used. References were grouped into studies exploring sites of action and studies on mechanisms involving the urothelium lamina, propria, and detrusor muscle. Abstracts and reports from meetings were included only when they related directly to previously published work. Searches were limited to the English language.

3. Evidence synthesis

The muscarinic receptors, their distribution and function in different bladder structures, and the possible receptor changes in diseases associated with OAB/DO are reviewed and discussed.

3.1. Generation and release of acetylcholine in the bladder

ACh is the main contractile transmitter in the human bladder [3,7]. It is released from postganglionic efferent cholinergic (parasympathetic) nerves, acts on muscarinic receptors, and produces the contraction that empties the bladder. However, there is also a non-neuronal release of ACh that may be involved in other bladder functions. Lips et al. [8] analyzed the content of ACh in the urothelium and characterized the molecular components of its synthesis and release machinery. They found ACh to be present in the urothelium in a nanomolar range per gram of wet weight. Real-time reverse transcription–polymerase chain reaction (RT-PCR) data supported the presence of the ACh-generating enzyme carnitine acetyltransferase but not choline acetyltransferase. The vesicular ACh transporter, used by neurons to transport ACh into synaptic vesicles, was detected by RT-PCR or immunohistochemistry in suburothelial cholinergic nerve fibers but not in the urothelium. Lips et al concluded that the urothelial non-neuronal cholinergic system differs from that of neurons with respect to molecular components of the ACh synthesis and release machinery. Hanna-Mitchell et al. [9] arrived at a similar conclusion. Because this means the urothelium is a source of ACh, it also implies that muscarinic receptors within the urothelium and underlying structures can be targets for antimuscarinic drugs.

3.2. Muscarinic receptors

In humans, as well as in most animals, muscarinic receptors are the physiologically most important mechanisms to elicit contraction of the urinary bladder, and the messenger RNAs (mRNAs) and proteins of all defined muscarinic receptor subtypes (M_1–M_5) have been demonstrated in different bladder structures [10,11]. Although there is a predominance of M_2 receptors in the detrusor, the M_3 receptors are mediating the main part of the contraction [3,7]. Muscarinic receptors are functionally coupled to G proteins, but the signal transduction systems vary. M_1, M_3, and M_5 receptors are excitatory, whereas M_2 and M_4 receptors are inhibitory [7,12]. It was originally thought that the M_3 receptor–mediated contractile response in the bladder is mediated by intracellular calcium mobilized by inositol phosphates that are generated following activation of phospholipase C [13,14]. However, in the human detrusor, it has been suggested that muscarinic agonist–induced contraction is mediated via M_3 receptors and largely depends on Ca^{2+}